



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

Enalapril oral solution (Epaned) and lisinopril oral solution (Qbrelis) were approved via the 505(b)(2) pathway, in which at least some of the information required for approval comes from studies not conducted by or for the applicant.<sup>17</sup>

## 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.<sup>18</sup> The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) suggests most patients require two medications for adequate control of hypertension.<sup>19</sup>

Drug	Manufacturer
<b>ACE Inhibitors</b>	
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
<b>Renin Inhibitor</b>	
aliskiren/HCTZ (Tekturna HCT®)	Novartis

## OVERVIEW

Hypertension affects over 33.5% of adult Americans (≥ 20 years of age) and is an independent risk factor for the development of cardiovascular disease.<sup>20</sup> Hypertension can increase the risk of myocardial infarction (MI), stroke, heart failure (HF), 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 diabetes, the current goal for blood pressure therapy is less than 140/80 mm Hg, but lower systolic targets, such as < 130 mmHg may be appropriate for certain individuals, such as younger patients, if it can be achieved without undue treatment burden<sup>21,22</sup> Only about half of patients diagnosed with hypertension have their disease under control.<sup>23</sup> Attainment of blood pressure goals results in a reduced risk of cardiovascular events.<sup>24</sup> 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.<sup>25,26,27</sup>

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).

First-line therapy for HTN according to The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7), published in 2003, is diuretics.<sup>28</sup> Angiotensin-converting enzyme (ACE) inhibitors may be used as first-line therapy for treatment of essential hypertension when a diuretic cannot be used or when a compelling indication is present. According to the JNC-7 guidelines, compelling indications for ACE inhibitors are: congestive heart failure (CHF), post-myocardial infarction (MI), high-risk coronary disease, diabetes mellitus, chronic kidney disease, and recurrent stroke prevention.<sup>29</sup> 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.<sup>30,31,32,33,34</sup>

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.<sup>35</sup> 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.

ACE inhibitors are a cornerstone in the treatment of CHF according to the 2009 focused update of the 2005 American College of Cardiology Foundation/American Heart Association (ACCF/AHA) Heart Failure Guidelines.<sup>36</sup> Benefits of ACE inhibitor therapy are seen in patients with both mild and severe disease and are independent of CHF etiology. ACE inhibitors improve symptoms, slow disease progression, and decrease mortality in heart failure.<sup>37</sup> The evidence suggests the benefit of ACE inhibitors in CHF is a class effect.<sup>38</sup> 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.<sup>39</sup> 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.<sup>40</sup>

Beneficial effects of ACE inhibitors are demonstrated in diabetic and nondiabetic nephropathies beyond those expected from lowering blood pressure.<sup>41</sup> 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.<sup>42, 43</sup>

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.<sup>44</sup> 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% or less and for those with hypertension, diabetes, or chronic kidney disease unless otherwise contraindicated.<sup>45</sup> ACE inhibitors are also considered a reasonable option in patients who are at lower risk.<sup>46</sup> Patients recovering from unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI) with LVD (LVEF less than 40%), hypertension or diabetes mellitus, unless contraindicated, should receive ACE inhibitors indefinitely.<sup>47</sup>

In AMI, ACE inhibitors reduce 30-day mortality when therapy is initiated within 36 hours of the acute event.<sup>48</sup> 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.<sup>49,50</sup>

The Agency for Healthcare Research and Quality (AHRQ) has published a comparative effectiveness report for the ACE inhibitors and ARBs.<sup>51</sup> The ACE inhibitors 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 ACE inhibitors versus ARBs on these serious outcomes. ACE inhibitors have been shown to have a greater risk of cough than ARBs and the direct renin inhibitor.<sup>52,53,54,55</sup>

A renin inhibitor, aliskiren (Tekturna), is approved for the treatment of hypertension.<sup>56</sup>

## 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.<sup>57</sup> 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.<sup>58</sup>

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).<sup>59</sup>

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.<sup>60</sup> 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.

## PHARMACOKINETICS

Drug	Absorption (%)	Half-Life (hr)	Metabolism	Elimination (%)
<b>ACE Inhibitors</b>				
benazepril (Lotensin) <sup>61</sup>	37	10-11	Yes - to active benazeprilat	Renal: 88 Biliary: 11-12
captopril (Capoten) <sup>62,63</sup>	75	< 3	Yes	Renal: > 95
enalapril (Vasotec, Epaned) <sup>64, 65</sup>	60	11	Yes - to active enalaprilat	Renal: 60-78 Hepatic: 33
fosinopril (Monopril) <sup>66</sup>	36	11.5 in HTN 14 in CHF	Yes - to active fosinoprilat	Renal: 44-50 Hepatic: 46-50
lisinopril (Prinivil, Qbrelis, Zestril) <sup>67,68,69</sup>	25 (varies between 6-60)	12	None	Renal: 100
moexipril (Univasc) <sup>70</sup>	13	2-9	Yes - to active moexiprilat	Renal: 13 Feces: 53
perindopril (Aceon) <sup>71</sup>	75	0.8-1	Yes - to active perindoprilat	Renal: 100

## Pharmacokinetics (continued)

Drug	Absorption (%)	Half-Life (hr)	Metabolism	Elimination (%)
<b>ACE Inhibitors</b>				
quinapril (Accupril) <sup>72</sup>	60	3	Yes - to active quinaprilat	Renal: 61 Hepatic: 37
ramipril (Altace) <sup>73</sup>	50-60	13-17	Yes - to active ramiprilat	Renal: 60 Feces: 40
trandolapril (Mavik) <sup>74</sup>	80	22.5	Yes - to active trandolaprilat	Renal: 33 Hepatic: 66
<b>Renin Inhibitor</b>				
aliskiren (Tekturna) <sup>75</sup>	2.5	24	None	Renal: 25
<b>Diuretic</b>				
HCTZ <sup>76</sup>	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.<sup>77</sup> 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<sub>max</sub> 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.<sup>78,79,80,81,82,83,84,85</sup>

## CONTRAINDICATIONS/WARNINGS<sup>86,87,88,89,90,91,92,93,94,95,96,97,98,99,100</sup>

Aliskiren and aliskiren-containing products are contraindicated with angiotensin II receptor blockers (ARBs), or angiotensin converting enzyme inhibitors (ACE inhibitors), in patients with diabetes due to increased risk of renal impairment, hyperkalemia, and hypotension. ACE inhibitors are contraindications in combination with a neprilysin inhibitor (e.g., sacubitril); do not administer within 36 hours of switching to or from an ACE inhibitors.

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 ACE inhibitor is not recommended in patients with glomerular filtration rate (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.

ACE inhibitors have been associated with a hepatic syndrome that often may begin with cholestatic jaundice or hepatitis and may progress to fulminant hepatic necrosis and even death. The mechanism of this is not understood. If a patient develops these initial symptoms, the ACE inhibitor should be discontinued and appropriate medical treatment should be administered.

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

## **DRUG INTERACTIONS<sup>101,102,103,104,105,106,107,108,109,110,111,112,113,114</sup>**

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 (P-gp) 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<sup>®</sup>) (50% reduction in aliskiren concentrations), atorvastatin (Lipitor<sup>®</sup>) (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<sup>®</sup>), 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 ACE inhibitors, 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.<sup>115</sup> 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 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
<b>ACE Inhibitors</b>						
benazepril (Lotensin) <sup>116</sup> n=964	6.2 (4.2)	3.6 (2.4)	2.4 (2.2)	1.2 (1)	reported	0.5
captopril (Capoten) <sup>117, 118</sup>	0.5-2	0.5-2	0.5-2	reported	4-7	< 1
enalapril (Vasotec, Epaned) <sup>119, 120</sup> 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 <sup>121</sup> n=688	> 1 (> 1)	1.6 (0)	> 1 (> 1)	2.2 (0)	0.2-1 (reported)	0.2-1
lisinopril (Prinivil, Qbrelis, Zestril) <sup>122,123,124</sup> 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) <sup>125</sup> n=674	> 1 (> 1)	4.3 (2.2)	2.4 (1.8)	6.1 (2.2)	1.6 (0.9)	< 0.5
perindopril (Aceon) <sup>126</sup> n=789	nr	8.2 (8.5)	nr	12 (4.5)	reported	0.1
quinapril (Accupril) <sup>127</sup> n=1,563	5.6 (10.9)	3.9 (2.6)	2.6 (1)	2 (0)	1.4 (1)	0.1
ramipril (Altace) <sup>128</sup> n=651	5.4	2.2	2 (1)	12	< 1	0.3
trandolapril (Mavik) <sup>129</sup> n=832	> 1 (> 1)	1.3 (0.4)	> 1 (> 1)	1.9 (0.4)	0.3-1	0.13
<b>Renin Inhibitor</b>						
aliskiren (Tekturna) <sup>130</sup>	> 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.

## SPECIAL POPULATIONS<sup>131,132,133,134,135,136,137,138,139,140,141,142,143</sup>

### 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.<sup>144</sup>

Aliskiren (Tekturna) has not been studied in patients less than 18 years of age.<sup>145</sup>

### 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.<sup>146,147,148,149</sup> In compliance with the Pregnancy and Lactation Labeling Rule (PLLR), Qbrelis (lisinopril oral solution) does not have a Pregnancy Category. 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

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.<sup>150,151,152</sup>

Patients with severe renal impairment were excluded from clinical trials of aliskiren (Tekturna) in hypertension.<sup>153</sup> 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.

## DOSAGES

Drug	Hypertension (Adult)	Hypertension (Pediatric)	CHF	Post-MI	Diabetic Nephropathy	Reduce risk of CV outcomes	Stable CAD – reduce CV mortality/ nonfatal MI	Availability
<b>ACE Inhibitors</b>								
benazepril (Lotensin) <sup>154</sup>	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) <sup>155, 156</sup>	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) <sup>157, 158</sup>	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
fosinopril <sup>159</sup>	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) <sup>160,161,162</sup>	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) <sup>163</sup>	7.5-30 mg daily	--	--	--	--	--	--	7.5, 15 mg tablets
perindopril (Aceon) <sup>164</sup>	4-16 mg daily	--	--	--	--	--	4 – 8 mg daily	2, 4, 8 mg tablets
quinapril (Accupril) <sup>165</sup>	10-80 mg daily	--	5-20 mg twice daily	--	--	--	--	5, 10, 20, 40 mg tablets
ramipril (Altace) <sup>166</sup>	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) <sup>167</sup>	1-4 mg daily	--	1-4 mg daily	1-4 mg daily	--	--	--	1, 2, 4 mg tablets

**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
<b>Renin Inhibitor</b>								
aliskiren (Tekturna) <sup>168</sup>	150-300 mg daily	--	--	--	--	--	--	150, 300 mg tablets

RETIRED

## 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
<b>ACE Inhibitors/HCTZ</b>	
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	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
<b>Renin Inhibitor/HCTZ</b>	
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<sup>2</sup> (serum creatinine >3 mg/dL), the recommended initial dose is benazepril 5 mg once daily.<sup>169</sup>

captopril (Capoten) – For patients with creatinine clearance 10-50 mL/min/1.73 m<sup>2</sup>, the initial dose should be reduced by 25%. For patients with creatinine clearance less than 10 mL/min/1.73 m<sup>2</sup>, the dose should be reduced by 50%.<sup>170</sup>

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.<sup>171,172</sup>

fosinopril (Monopril) – No dosage adjustments are necessary for renal impairment.<sup>173</sup>

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.<sup>174,175,176</sup>

moexipril (Univasc) – For patients with creatinine clearance < 40 mL/min/1.73 m<sup>2</sup>, an initial dose of moexipril 3.75 mg once daily should be given cautiously.<sup>177</sup>

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.<sup>178, 179</sup>

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.<sup>180</sup>

ramipril (Altace) – In patients with creatinine clearance < 40 mL/min/1.73 m<sup>2</sup> (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.<sup>181</sup>

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.<sup>182</sup>

## 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.<sup>183</sup> 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.<sup>184</sup>

## 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.

## 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.<sup>185</sup>

Leonetti and colleagues reviewed ACE inhibitors to determine which agent should be used for specific patients.<sup>186</sup> 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.<sup>187</sup> 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.<sup>188</sup> The authors concluded the overall mortality results were consistent with those of two major trials, SOLVD and CONSENSUS.<sup>189</sup> An extension of the SOLVD trial demonstrated enalapril used for three to four years extended median survival by 9.4 months.<sup>190</sup>

Numerous studies cite underutilization of ACE inhibitors in the treatment of CHF and acute MI.<sup>191, 192, 193, 194</sup> 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.<sup>195</sup> 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).<sup>196</sup>

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.<sup>197</sup> Captopril and losartan improved systolic and overall LVD function, but greater benefit was observed with captopril.<sup>198</sup>

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.<sup>199, 200</sup>

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.<sup>201</sup> 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).<sup>202</sup> 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.<sup>203</sup> 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.<sup>204</sup> Ramipril (Altace) reduced mortality in patients with heart failure following acute MI.<sup>205</sup>

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.<sup>206</sup> 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.<sup>207</sup> 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.<sup>208</sup> 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.<sup>209</sup> 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.<sup>210</sup> 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.<sup>211</sup> 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

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.<sup>212</sup> 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.<sup>213</sup> 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.<sup>214</sup> 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.<sup>215</sup> 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.

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,  $p=0.037$ ).<sup>216</sup> 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<sup>2</sup> 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.<sup>217</sup> 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.<sup>218</sup> Greater blood pressure reductions were achieved with combination therapy compared with monotherapy.

Aliskiren was studied in obese patients (body mass index  $\geq 30$  g/m<sup>2</sup>) with hypertension.<sup>219</sup> 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.

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.<sup>220</sup> 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.<sup>221</sup> 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  $\geq 30$  kg/m<sup>2</sup>) was performed.<sup>222</sup> Aliskiren monotherapy provided significantly greater BP reductions than HCTZ at week 12 (-16.7/-12.3 versus -12.2/-9.1 mm Hg,  $p \leq 0.001$ ) 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.<sup>223</sup> Patients ( $n = 722$ ) with mean sitting diastolic BP  $\geq 90$  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

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.<sup>224</sup> 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.<sup>225</sup> 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.<sup>226</sup> 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.<sup>227</sup> 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<sup>2</sup> were randomized to receive aliskiren 300 mg, losartan 100 mg or the combination of both for nine months.<sup>228</sup> Add-on therapy, with the exception of other inhibitors of the renin-angiotensin-

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<sup>2</sup> 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.<sup>229</sup> 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.<sup>230</sup> 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.<sup>231</sup> 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

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 ( $\geq 65$  years of age) patients with SBP  $\geq 140$  mm Hg.<sup>232</sup> 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.<sup>233</sup> Treatment with aliskiren and amlodipine resulted overall in significantly greater reductions in diastolic and systolic blood pressure compared to the respective monotherapy components.

### **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.<sup>234</sup> 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.<sup>235</sup>

## **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.

The 2009 ACCF/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 sulphhydryl side chain.

Aliskiren (Tekturna) offers an alternative in the treatment of hypertension, but at this time, evidence does not support a clear advantage over ACE inhibitors and ARBs. Based on the halted ALTITUDE study, aliskiren containing drugs are contraindicated in combination with an ACE inhibitor 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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## Angiotensin Modulators: Angiotensin II Receptor Blockers Therapeutic Class Review (TCR)

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## FDA-APPROVED INDICATIONS

Drug	Manufacturer	Indication(s)
<b>Angiotensin II Receptor Blockers: Single Agents</b>		
azilsartan (Edarbi®) <sup>1</sup>	Arbor	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
candesartan (Atacand®) <sup>2</sup>	generic, Ani/AstraZeneca	<ul style="list-style-type: none"> <li>Hypertension (including ages 1 to &lt; 17 years)</li> <li>Heart failure – (LVEF &lt;40%, NYHA II-IV) to reduce risk of CV death and reduce hospitalizations for HF (in addition to ACE inhibitors or when ACE inhibitors are not tolerated)</li> </ul>
eprosartan <sup>*3</sup>	Mylan	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
irbesartan (Avapro®) <sup>4</sup>	generic, Sanofi-Aventis	<ul style="list-style-type: none"> <li>Hypertension</li> <li>Nephropathy in type 2 diabetic patients</li> </ul>
losartan (Cozaar®) <sup>5</sup>	generic, Merck	<ul style="list-style-type: none"> <li>Hypertension (including ages 6 to 16 years)</li> <li>Nephropathy in type 2 diabetic patients</li> <li>Reduce the risk of stroke in hypertensive patients with LVH (not in African American patients)</li> </ul>
olmesartan (Benicar®) <sup>6</sup>	generic, Daiichi Sankyo	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
telmisartan (Micardis®) <sup>7</sup>	generic, Boehringer Ingelheim	<ul style="list-style-type: none"> <li>Hypertension</li> <li>80 mg tablets only: risk reduction of myocardial infarction (MI), stroke, or death from CV causes in patients ≥ 55 years at high risk of developing major CV events who are unable to take ACE inhibitors</li> </ul>
valsartan (Diovan®) <sup>8</sup>	generic, Novartis	<ul style="list-style-type: none"> <li>Hypertension (in adults and children ≥ 1 year of age)</li> <li>Treatment of HF (NYHA II-IV) to reduce hospitalizations for HF</li> <li>Reduction of CV mortality in clinically-stable patients with left ventricular failure or left ventricular dysfunction following MI</li> </ul>

ACE inhibitors = angiotensin converting enzyme inhibitors; CV = cardiovascular; HCTZ = hydrochlorothiazide; HF = heart failure; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association Classification

\*In March 2020, the FDA announced that Mylan plans to discontinue eprosartan mesylate 600 mg tablets. No other strengths or formulations will be commercially available.<sup>9</sup>

## FDA-Approved Indications (continued)

Drug	Manufacturer	Indication(s)
<b>Angiotensin II Receptor Blockers: Combination Products</b>		
azilsartan/chlorthalidone (Edarbyclor®) <sup>10</sup>	Arbor	<ul style="list-style-type: none"> <li>Hypertension (first-line therapy in patients requiring multiple agents)</li> </ul>
candesartan/HCTZ (Atacand HCT®) <sup>11</sup>	generic, Ani/AstraZeneca	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
irbesartan/HCTZ (Avalide®) <sup>12</sup>	generic, Sanofi-Aventis	<ul style="list-style-type: none"> <li>Hypertension (first-line therapy in patients requiring multiple agents)</li> </ul>
losartan/HCTZ (Hyzaar®) <sup>13</sup>	generic, Merck	<ul style="list-style-type: none"> <li>Hypertension (first-line therapy in setting of prompt BP reduction)</li> <li>Reduce the risk of stroke in hypertensive patients with LVH (not in African American patients)</li> </ul>
olmesartan/HCTZ (Benicar HCT®) <sup>14</sup>	generic, Daiichi Sankyo	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
sacubitril/valsartan (Entresto®) <sup>15</sup>	Novartis	<ul style="list-style-type: none"> <li>Reduce the risk of CV death and hospitalization for HF in patients with chronic heart failure; its benefits are most clearly evident in patients with left ventricular ejection fraction (LVEF) below normal; clinical judgment is needed in deciding whom to treat</li> <li>Treatment of symptomatic HF with systemic left ventricular systolic dysfunction in pediatric patients ages ≥ 1 year</li> </ul>
telmisartan/HCTZ (Micardis HCT®) <sup>16</sup>	generic, Boehringer Ingelheim	<ul style="list-style-type: none"> <li>Hypertension</li> </ul>
valsartan/HCTZ (Diovan HCT®) <sup>17</sup>	generic, Novartis	<ul style="list-style-type: none"> <li>Hypertension (first-line therapy in patients requiring multiple agents)</li> </ul>

ACE inhibitors = angiotensin converting enzyme inhibitors; CV = cardiovascular; HCTZ = hydrochlorothiazide; HF = heart failure; LVH = left ventricular hypertrophy; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association Classification

## OVERVIEW

### Hypertension

Approximately 45% adults in the United States (US) have hypertension. Prevalence of high blood pressure is higher in the non-Hispanic Black population; approximately 54% of these men and women have high blood pressure, compared to about 46% of White men and women, 39% of non-Hispanic Asians, and 36% of Hispanics.<sup>18</sup> It is estimated that hypertension is controlled in only 24% of patients with the condition. Hypertension is an independent risk factor for cardiovascular disease and can lead to heart failure (HF) and stroke if uncontrolled for a prolonged period.<sup>19</sup> Angiotensin receptor blockers (ARBs) are indicated for the treatment of hypertension either alone or in combination with other antihypertensive medications.

The 2014 Eighth Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-8) in general recommends to start antihypertensive therapy in patients at least 60 years of age when systolic blood pressure (SBP) is ≥ 150 mm Hg or diastolic blood pressure (DBP) is ≥ 90 mm Hg, with a goal of SBP < 150 mm Hg and DBP < 90 mm Hg.<sup>20</sup> For patients younger than 60 years and adults with chronic kidney disease (CKD), therapy should be initiated when SBP ≥ 140 mm Hg and DBP ≥ 90 mm Hg, and target blood pressure is less than 140/90 mm Hg. In the non-African American population, initial treatment should include a thiazide-type diuretic, calcium

channel blocker (CCB), angiotensin-converting enzyme (ACE) inhibitor or ARB. For African Americans, initial treatment should include a thiazide-type diuretic or CCB. In patients with CKD treatment should include an ACE inhibitor or ARB to improve kidney function, regardless of race or diabetes status. If blood pressure goal is not reached within 1 month of starting treatment, the dose should be increased or a second a drug from another class should be added; a third drug can be added if needed.

In 2017, The American College of Cardiology (ACC) and American Heart Association (AHA) released joint guidelines on the prevention, detection, evaluation, and management of high blood pressure (BP) in adults.<sup>21</sup> The guideline revised the classification system for blood pressure. The initiation of drug therapy should be based on a combination of average BP, atherosclerotic cardiovascular disease (CVD) risk, and comorbid conditions. For high-risk (pre-existing CVD or estimated 10-year risk of  $\geq 10\%$ ) adults with stage 1 hypertension, defined as average SBP of 130 to 139 mm Hg or DBP 80 to 89 mm Hg, treatment should be initiated in patients with a BP of  $\geq 130/80$  mm Hg (class I recommendation). For lower-risk adults, ACC/AHA specifies the threshold BP for drug treatment at  $\geq 140/90$  mm Hg (class I recommendation). Regardless of risk, the goal BP after initiating treatment is  $< 130/80$  mm Hg. First-line therapy recommendations include thiazide diuretics, CCBs, and ACE inhibitors or ARBs (class I recommendation). Patients in stage 2 hypertension (SBP  $\geq 140$  mm Hg or DBP  $\geq 90$  mm Hg) should be initiated with 2 first-line treatment agents with differing mechanisms of action (class I recommendation). For hypertension in adults, the ACC/AHA notes that simultaneous use of an ACE inhibitor, ARB, and/or renin inhibitor is potentially harmful and is not recommended. For resistant hypertension, AHA provides additional guidance with an initial focuses on optimizing first-line therapies, including ARBs.<sup>22</sup>

The American College of Physicians (ACP) and American Academy of Family Physicians (AAFP) published evidence-based recommendations on the benefits and harms of higher ( $< 150$  mm Hg) versus lower ( $< 140$  mm Hg) SBP targets in the treatment of hypertensive adults ages 60 years and older.<sup>23</sup> The ACP and AAFP recommend initiating antihypertensive therapy in adults 60 years and older with SBP  $\geq 150$  mm Hg with a target SBP  $< 150$  mm Hg to reduce the risk of mortality, stroke, and cardiac events (strong recommendation, high-quality evidence). A stricter goal of SBP  $< 140$  mm Hg may be considered in older adults with a history of stroke or transient ischemic attack to reduce the risk for recurrent stroke (weak recommendation, moderate-quality evidence). A stricter goal, SBP  $< 140$  mm Hg, may also be considered in older adults at high cardiovascular (CV) risk to reduce the risk of stroke or cardiac events (weak recommendation, moderate-quality evidence). The clinician and patient should discuss the risk versus benefit when determining the most appropriate blood pressure goal. The ACP and AAFP also state that providers should consider treatment with nonpharmacologic options (e.g., weight loss, diet, exercise), as well as pharmacologic therapy. Treatment burden (e.g., total number of drugs prescribed, drug interactions, adverse effects), given the potential for other comorbid conditions, should also be taken into consideration when treating hypertensive older adults. If pharmacologic therapy is chosen, generic formulations should be prescribed, when available, to reduce cost and thereby aid treatment adherence.

It is estimated that 3.5% of children and adolescents have hypertension.<sup>24</sup> In 2017, American Academy of Pediatrics (AAP) published guidelines on diagnosis, evaluation, and treatment of high blood pressure in children and adolescents. The goal of treatment is to achieve a blood pressure that decreases the risk for organ damage in youth and decrease the risk of hypertension in adulthood. For children and adolescents on treatment for HTN, the blood pressure goal is  $< 90^{\text{th}}$  percentile and  $< 130/80$  mmHg. Lifestyle modifications such as diet and physical exercise are recommended for the potential benefit to

reduce blood pressure. First line therapy options include an ACE inhibitor, ARB, long-acting calcium channel blocker, or thiazide diuretic; treatment should begin a low dosage and titrate as needed; a second agent may be added if needed. Beta blockers are not recommended as initial pharmacologic treatment in children due to the side effect profile and to follow the therapy recommendations of beta blockers in adults. Long-term studies on the safety of antihypertensive medications in children and their impact on future cardiovascular disease are limited.

ARBs are available as fixed-dose combinations with a diuretic to treat hypertension.

## Heart Failure

According to the 2017 American College of Cardiology (ACC) and American Heart Association (AHA) focused update of the 2013 consensus guidelines for the management of HF, routine combined use of an ACE inhibitor or angiotensin receptor blockers with a beta-blocker is recommended in all patients with reduced ejection fraction heart failure (HFrEF), unless contraindicated.<sup>25</sup> Drugs with an indication for HF include many ACE inhibitors and some beta-blockers. ARBs that are indicated for HF when a patient is intolerant to an ACE inhibitor include candesartan (Atacand) and valsartan (Diovan). In addition, for patients with HFrEF, diuretics are recommended if fluid retention is present; aldosterone antagonists (spironolactone [Aldactone<sup>®</sup>] and eplerenone [Inspra<sup>®</sup>]) are recommended in patients who also have adequate renal function; and digoxin can be beneficial to decrease hospitalizations due to HF. The combination of hydralazine and isosorbide dinitrate is recommended in African Americans with HFrEF 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 and in patients with HF following a non-ST-elevated myocardial infarction (NSTEMI) or ST-elevated myocardial infarction (STEMI).<sup>26,27</sup>

In 2015, the Food and Drug Administration (FDA) approved sacubitril/valsartan (Entresto), the combination product of a neprilysin inhibitor and an ARB, also called an angiotensin receptor-neprilysin inhibitor (ARNI), which has demonstrated greater efficacy than enalapril in patients with HFrEF.<sup>28</sup> In the 2017 ACC/AHA/Heart Failure Society of America (HFSA) Focused Update on New Pharmacologic Therapy for Heart Failure, which updates the 2013 ACCF/AHA guideline on the management of HF, the role of sacubitril/valsartan (Entresto) has been addressed.<sup>29</sup> The guidance recommends an ACE inhibitor, ARB, or ARNI in addition to a beta-blocker and aldosterone (in select patients) in patients with chronic HFrEF (Class I, Level A [ACE inhibitor, ARB] and B-R [ARNI] evidence). Patients with chronic symptomatic HFrEF 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) was found to be superior to enalapril in reducing the risks of death and hospitalization for heart failure.<sup>30</sup> In 2021, the ACC published an update to The Expert Consensus Decision Pathway for Optimization of Heart Failure Treatment in 2017, which reiterates the recommendation in the 2016 update regarding the use of ACE inhibitors, ARBs, and an ARNI in the treatment of patients with chronic HFrEF.<sup>31</sup> The consensus pathway also provides guidance on initiating beta-blockers which may be used at onset instead of ACE inhibitors or ARBs in select HF patients. Guidance is also provided for initiation and/or titration of diuretics, aldosterone antagonists, vasodilators, such as hydralazine and ivabradine.

## Nephropathy

Approximately 25% of patients with diabetes will develop microalbuminuria during the 10 years after diagnosis and 25% to 40% will develop diabetic nephropathy over 20 to 25 years after diabetes onset.<sup>32</sup> Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the US, accounting for 40% of all the patients with end-stage renal disease (ESRD) who are on dialysis.<sup>33</sup> Type 1 and 2 diabetes increase the risk for nephropathy and follow the same progression to renal insufficiency and failure. Guidelines by the American Diabetes Association (ADA; 2021), American Association of Clinical Endocrinologists/American College of Endocrinology (AACE/ACE; 2015/2020), the AHA/American Stroke Association (ASA; 2014), and the JNC-8 suggest that all patients with diabetes should receive an ACE inhibitor or ARB for the treatment of hypertension to reduce the risk of stroke and to delay the progression of diabetic nephropathy.<sup>34,35,36,37,38,39</sup>

In patients with type 1 diabetes, hypertension and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy, hypertension, and microalbuminuria; both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria in patients with type 2 diabetes. In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine > 1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. Irbesartan (Avapro) and losartan (Cozaar) are approved to slow the progression of nephropathy in type 2 diabetic patients. Prevention of nephropathy progression is associated with reduced healthcare costs and improvement in mortality. ACE inhibitors have clearly shown to prevent early death in diabetic patients. Telmisartan (Micardis) and ramipril (Altace®) were similar in reducing cardiovascular (CV) mortality in patients with vascular disease or high-risk diabetes; however, the combination of telmisartan and ramipril resulted in more adverse events without increased benefit.<sup>40</sup>

The 2021 Kidney Disease Improving Global Outcomes (KDIGO) guidelines for blood pressure management in patients with CKD recommend the use of ARBs or other renin-angiotensin-system inhibitors for patients with CKD, diabetes, hypertension, and moderately to severely increased albuminuria (1B), but they recommend avoiding the combination of an ACE inhibitor, ARB, or direct renin inhibitor in patients with CKD, regardless of diabetes diagnosis (1B).<sup>41</sup>

## Myocardial Infarction

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.<sup>42,43</sup> 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 CKD, unless otherwise contraindicated. ACE inhibitors are also considered a reasonable option in patients who are at lower risk. ARBs are recommended in place of ACE inhibitors in those who are intolerant to ACE inhibitors.

The Agency for Healthcare Research and Quality (AHRQ) has published a comparative effectiveness report for the ACE inhibitors, ARBs, and aliskiren.<sup>44</sup> 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. ACE inhibitors have been shown to have a greater risk of cough than ARBs and the direct renin inhibitor.<sup>45,46,47</sup>

## PHARMACOLOGY<sup>48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67</sup>

All ARBs are available as single agents and in combination with a thiazide diuretic such as hydrochlorothiazide (HCTZ) or chlorthalidone. Valsartan is also available in combination with a neprilysin inhibitor, sacubitril.

ACE inhibitors do not completely block the renin-angiotensin-aldosterone system (RAAS). ACE inhibitors are competitive inhibitors of angiotensin-converting enzyme, which converts angiotensin I to angiotensin II, a potent vasoconstrictor. Angiotensin II causes vasoconstriction, release of aldosterone and antidiuretic hormone, sympathetic activation, and constriction of the efferent arterioles of the glomerulus in the kidneys. ARBs block the vasoconstrictive and aldosterone-secreting effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor found in many tissues, such as vascular smooth muscle and the adrenal gland. Non-ACE pathways also produce angiotensin II. ARBs do not inhibit ACE (kinase II, the enzyme that converts angiotensin I to angiotensin II and degrades bradykinin).

Angiotensin receptor-neprilysin inhibitors (ARNIs) increase levels of natriuretic peptides that are degraded by neprilysin through inhibition of neprilysin and simultaneously inhibit the effects of angiotensin II. The ultimate result of sacubitril's neprilysin inhibition is vasodilation, natriuresis, and diuresis.

Thiazide diuretics, such as HCTZ, exhibit its pharmacological effects by blocking the reabsorption of sodium and chloride leading to diuresis and a reduction in intravascular volume. Consequently, there are increases in plasma renin activity and aldosterone secretion. Concurrent administration of an ARB and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.

Chlorthalidone, a thiazide-like diuretic, produces diuresis with increased excretion of sodium and chloride. The site of action appears to be the cortical diluting segment of the ascending limb of Henle's loop of the nephron. The diuretic effects of chlorthalidone lead to decreased extracellular fluid volume, plasma volume, cardiac output, total exchangeable sodium, glomerular filtration rate, and renal plasma flow. Although the mechanism of action of chlorthalidone and related drugs is not fully clear, sodium and water depletion appear to provide a basis for its antihypertensive effect.

## PHARMACOKINETICS<sup>68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84</sup>

Drug	Prodrug	Time to Peak (h)	Bioavailability (%)	Food – Peak Levels	Food – AUC	Elimination Half-life (h)	Elimination Altered in Renal Dysfunction	Elimination Altered in Hepatic Dysfunction
<b>Angiotensin II Receptor Blockers</b>								
azilsartan (Edarbi)	Yes*	1.5–3	60	No effect	No effect	11	No	No
candesartan (Atacand)	Yes <sup>†</sup>	3–4	15	--	No effect	9	Yes	No
eprosartan	No	1–2	13	< 25%	< 25%	20	Yes	Yes <sup>§</sup>
irbesartan (Avapro)	No	1.5–2	60–80	No effect	No effect	11–15	No	No
losartan (Cozaar)	Yes <sup>‡</sup>	1 / 3–4	33	Decreased	↓ 10%	2 / 6–9 <sup>‡</sup>	No	Yes
olmesartan (Benicar)	Yes	1–2	26	No effect	No effect	13	Yes <sup>§</sup>	Yes <sup>§</sup>
telmisartan (Micardis)	No	0.5–1	42–58 dose dependent	--	↓ 6–20%	24	No	Yes
valsartan (Diovan)	No	2–4	25	↓ 50%	↓ 40%	6	No	No
<b>Components in Combination Products</b>								
chlorthalidone	No	1.5–6	65	No effect	No effect	40–60	Yes	No
HCTZ	No	1–5	65–75	↓ 20%	--	5–18	Yes	No
sacubitril	No	0.5–2	≥ 60	No effect	No effect	1.4–11.5 (metabolite)	Yes	Yes <sup>§</sup>

\* azilsartan medoxomil – active metabolite is azilsartan

† candesartan cilexetil – active metabolite is candesartan

‡ losartan – active metabolite is EXP3174

§ dosage adjustments are not necessary

## CONTRAINDICATIONS/WARNINGS<sup>85,86,87,88,89,90,91,92,93,94,95,96,97,98,99,100,101</sup>

Hypersensitivity, including angioedema, to any angiotensin-converting enzyme (ACE) inhibitor or angiotensin II receptor blocker (ARB) is a contraindication to use of the class. The HCTZ component in the combination agents is contraindicated in patients with anuria or a sulfa allergy. Azilsartan/chlorthalidone (Edarbyclor) is contraindicated in patients with anuria.

An ARB or an ARNI (Entresto) should not be prescribed with an ACE inhibitor. Aliskiren and aliskiren-containing products are contraindicated with ARBs, or ACE inhibitors, in patients with diabetes due to increased risk of renal impairment, hyperkalemia, and hypotension. Do not co-administer aliskiren with an ARB in patients with diabetes. Avoid use of aliskiren with ARBs in patients with renal impairment (estimated glomerular filtration rate [GFR] < 60 mL/min/1.73 m<sup>2</sup>).

ARBs should be used with caution in patients that are volume and salt depleted, have hyperkalemia, or have unilateral and bilateral renal artery stenosis. Volume or salt depletion should be corrected prior to administration. Concomitant use of an ARB with drugs that may increase potassium levels may increase the risk of hyperkalemia; serum potassium should be monitored periodically.

The FDA evaluated data from 2 clinical trials in which patients with type 2 diabetes taking olmesartan (Benicar) had a higher rate of death from a cardiovascular (CV) cause compared to placebo.<sup>102</sup> In both the Randomized Olmesartan and Diabetes Microalbuminuria Prevention (ROADMAP) and Olmesartan Reducing Incidence of End Stage Renal Disease in Diabetic Nephropathy Trial (ORIENT) trials, patients with type 2 diabetes were given either olmesartan or placebo to determine if treatment with olmesartan would slow the progression of kidney disease. An unexpected finding observed in both trials was a greater number of deaths from a CV cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The FDA has completed its safety review of patients with type 2 diabetes taking olmesartan and found no clear evidence of a higher rate of CV risk as compared to placebo.<sup>103</sup> The FDA reminds practitioners that numerous clinical trials with olmesartan, as well as trials with other ARBs, have not suggested an increased risk of CV-related death. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks.

Sprue-like enteropathy has been reported in patients taking olmesartan months to years after the start of the drug. Severe, chronic diarrhea with substantial weight loss has been reported and, if a patient develops these symptoms while on olmesartan, other etiologies must be excluded. Discontinuing olmesartan in cases where no other etiologies are identified should be considered. In July 2010, the FDA announced that they were conducting a review of ARBs after a meta-analysis including data from over 60,000 patients suggested that ARBs may be associated with a small increased risk of cancer.<sup>104</sup> In June 2011, the study was complete, and the FDA concluded that treatment with an ARB does not increase cancer risk.<sup>105</sup> To draw this conclusion, the FDA conducted a trial-level meta-analysis of 31 clinical trials in which patients were randomized to treatment with an ARB (n=84,461) or a non-ARB (n=71,355). The meta-analysis evaluated the association between ARBs and the risk of incident (new) cancer, cancer-related death, breast cancer, lung cancer, and prostate cancer. The rate of cancer events in the ARB group was 1.82 per 100 patient-years compared to 1.84 per 100 patient-years in non-ARB comparators. The relative risk of cancer in patients taking ARBs was 0.99 (95% confidence interval [CI], 0.92 to 1.06). The FDA also found no evidence of association between ARBs and cancer-related death (relative risk, 1.04; 95% CI, 0.96 to 1.13), breast cancer (odds ratio [OR], 1.06; 95% CI, 0.9

to 1.23), lung cancer (OR, 1.07, 95% CI, 0.89 to 1.29), or prostate cancer (OR, 1.05; 95% CI, 0.95 to 1.17).

Another meta-analysis assessed the association between antihypertensive drugs and cancer risk.<sup>106</sup> It included 70 randomized controlled trials with 324,168 participants and recorded no difference in the risk of cancer with ARBs. There was an increased risk with the combination of ACE Inhibitors plus ARBs (OR, 1.14; 95% CI, 1.02 to 1.28); however, this risk was not apparent in the random-effects model (OR, 1.15; 95% CI, 0.92 to 1.38).

Thiazide diuretics which are commonly used in combination with ARBs may cause exacerbation or activation of systemic lupus erythematosus. Thiazide diuretics may also cause electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended.

Hydrochlorothiazide can cause an idiosyncratic reaction, resulting in acute transient myopia and acute angle-closure glaucoma. It can also cause elevated intraocular pressure with or without a noticeable acute myopic shift and/or choroidal effusions. 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. Risk factors for developing acute angle-closure glaucoma may include a history of sulfonamide or penicillin allergy.

Hydrochlorothiazide is associated with an increased risk of non-melanoma skin cancer. The Sentinel System study found an increased risk for squamous cell carcinoma (SCC) particularly in Caucasian patients taking large cumulative doses. The increased risk for SCC in the overall population was approximately 1 additional case per 16,000 patients per year, and for Caucasian patients taking a cumulative dose  $\geq$  50,000 mg, the risk increase was approximately 1 additional SCC case for every 6,700 patients per year.

In 2019, numerous pharmaceutical manufacturers voluntarily recalled select lots of agents within this class, specifically losartan-, irbesartan-, and valsartan-containing products due to the detection of trace amounts of N-Nitroso N-Methyl 4-amino butyric acid (NMBA) and N-nitrosodiethylamine (NDEA) that are possible process impurities or contaminants in the active pharmaceutical ingredient.<sup>107</sup>

## **DRUG INTERACTIONS**<sup>108,109,110,111,112,113,114,115,116,117,118,119,120,121,122,123,124</sup>

Significant drug interactions have not been reported with ARBs; however, use with potassium-sparing diuretics, potassium supplements, or other drugs that may increase potassium levels can lead to hyperkalemia. Potassium levels should be monitored in these patients. Increases in serum lithium concentrations and lithium toxicity have been reported with concurrent use of lithium and ARBs. Serum lithium levels should be monitored with concurrent use. In addition, diuretics, including hydrochlorothiazide (HCTZ) reduce the renal clearance of lithium and greatly increase the risk of lithium toxicity. These agents generally should not be given concurrently.

Administration of a nonsteroidal anti-inflammatory drug (NSAID) can reduce the diuretic, natriuretic, and antihypertensive effects of HCTZ and ARBs. Cholestyramine and colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract. Also, the HCTZ dose should be staggered (4 hours prior or 4 to 6 hours after) from resin administration. Dosage adjustment of the antidiabetic drug

may be required if given with HCTZ. Administration of carbamazepine and HCTZ may lead to symptomatic hyponatremia. In patients who are elderly, volume-depleted (including those on diuretic therapy), or who have compromised renal function, co-administration of NSAIDs, including selective COX-2 inhibitors, with ARBs, may result in deterioration of renal function, including possible acute renal failure. These effects are usually reversible. Monitor renal function periodically in patients receiving ARBs and NSAID therapy. Concomitant use of steroids or adrenocorticotrophic hormone (ACTH) with HCTZ may lead to hypokalemia.

In addition, HCTZ may increase the hyperglycemic effect of diazoxide and decrease the renal excretion of methotrexate and cyclophosphamide resulting in an increased myelosuppressive effect. Cyclosporine, when used with HCTZ, may increase the risk of hyperuricemia. HCTZ may decrease arterial responsiveness to norepinephrine, but this does not preclude its use if a pressor is needed.

Drug interactions with the combination product sacubitril/valsartan are the same as those described above due to the ARB component and effect of neprilysin inhibition.

Dual blockade of the renin-angiotensin-aldosterone system (RAAS) with ARBs, angiotensin-converting enzyme (ACE) inhibitors, or aliskiren is associated with increased risks of hypotension, hyperkalemia, and changes in renal function (including acute renal failure) compared to monotherapy. Closely monitor blood pressure, renal function, and electrolytes in patients on an ARB and other agents that affect the RAAS.

The ALTITUDE study, a phase 3, 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.<sup>125</sup> 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 to 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 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<sup>126,127,128,129,130,131,132,133,134,135,136,137,138,139,140,141,142</sup>

All ARBs have been well tolerated in clinical trials, with an incidence of adverse effects comparable to placebo. Cough and hyperkalemia, which have been problematic with angiotensin-converting enzyme (ACE) inhibitors, do not appear to occur as frequently with the ARBs.

Angioedema has been reported with all ARBs; the risk appears to be lower than with ACE inhibitors.<sup>143</sup>

Drug	Dizziness	Angioedema	Back Pain	URI	Discontinuation Rate
azilsartan (Edarbi)	≥ 0.3	reported	nr	nr	2.2–2.7 (2.4)
candesartan (Atacand) n=3,260 (n=1,106)	4 (3)	< 1	3 (2)	6 (4)	3.3 (3.5)
eprosartan	≥ 1	reported	< 1	8 (5)	4 (6.5)
irbesartan (Avapro)	≥ 1	< 1	nr	nr	3.3 (4.5)
losartan (Cozaar) n=1,075 (n=334)	3 (2)	< 1	2 (1)	8 (7)	2.3 (3.7)
olmesartan (Benicar)	3 (1)	reported	> 1	nr	2.4 (2.7)
sacubitril/valsartan (Entresto)	6	reported	nr	nr	reported
telmisartan (Micardis) n=1,455 (n=380)	≥ 1	reported	3 (1)	7 (6)	nr
valsartan (Diovan) n=2,316 (n=888)	> 1	reported	> 1	> 1	2.3 (2)

Adverse effects are reported as a percentage. Adverse effects data are obtained from prescribing information and are not meant to be comparative or all inclusive. Incidences for the placebo group are indicated in parentheses. nr = not reported. URI = upper respiratory infection

Adverse reactions commonly reported with chlorthalidone and hydrochlorothiazide (HCTZ) include hyperuricemia and electrolyte abnormalities (e.g., hypokalemia, hyponatremia). Other adverse effects reported with chlorthalidone and HCTZ may occur when used as a fixed-dose combination product with an ARB, as found in this class.

## SPECIAL POPULATIONS<sup>144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161</sup>

### Pediatrics

Losartan (Cozaar) and olmesartan (Benicar) are indicated for the treatment of hypertension in children ages 6 to 16 years. Candesartan (Atacand) and valsartan (Diovan) are indicated for the treatment of hypertension in children ≥ 1 years old, although neither agent has been assessed in pediatric patients with a glomerular filtration rate < 30 mL/min/1.73 m<sup>2</sup>. Safety and effectiveness in the pediatric population have not been established for the other ARBs.

Sacubitril/valsartan (Entresto) is indicated to treat symptomatic HF with systemic left ventricular systolic dysfunction in patients ages ≥ 1 year.

Safety and efficacy of azilsartan (Edarbi), azilsartan/chlorthalidone (Edarbyclor), and hydrochlorothiazide (HCTZ) have not been established in children.

## Geriatrics

In general, no relevant pharmacokinetic differences for any drug in this review have been observed in geriatric patients (age  $\geq 65$  years) compared to younger adults; however, caution should be used in this population due to the blood pressure lowering effects of these agents. In addition, a greater sensitivity of this population cannot be ruled out.

## Pregnancy

All products in this review 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, particularly during the second and third trimesters.

## Race

Losartan (Cozaar) and losartan/hydrochlorothiazide (Hyzaar) are both indicated for the reduction of the risk of stroke in hypertensive patients with left ventricular hypertrophy. However, beneficial effects have not been seen in the African American population. In general, antihypertensive benefits may be smaller in the African American population, as they are often a low-renin population.

## Renal Impairment

Renin-angiotensin-aldosterone (RAAS) system blockers, including ARBs, may cause renal failure in susceptible patients, such as those with renal artery stenosis.

No specific dosage adjustments are recommended for ARBs in patients with renal impairment for most agents, but lower starting doses and maximum may be considered. However, data are limited in severe renal impairment. Patients should be monitored for potentiation of effects. The maximum dose of eprosartan in severe renal impairment is 600 mg/day. In addition, dosage adjustment is required for sacubitril/valsartan with severe renal impairment.

Chlorthalidone and HCTZ should be used with caution in renal impairment as they may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

## Hepatic Impairment

No specific dosage adjustments are recommended in patients with hepatic impairment for most agents, but lower starting and maximum doses may be considered. However, data are limited in severe hepatic impairment. Patients should be monitored for potentiation of effects. Losartan and telmisartan should be started at a lower dose in patients with hepatic impairment. In addition, dosage adjustment is required for sacubitril/valsartan with moderate hepatic impairment; use is not recommended in patients with severe hepatic impairment.

Thiazide diuretics should be used with caution in patients with impaired hepatic function since minor fluid and electrolyte imbalances may precipitate hepatic coma.

## DOSAGES<sup>162,163,164,165,166,167,168,169,170,171,172,173,174,175,176,177,178</sup>

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
<b>Angiotensin II Receptor Blockers: Single Agents</b>								
azilsartan (Edarbi)	80 mg once daily	40 mg to 80 mg once daily	--	--	--	--	no dosage recommendation	40 mg, 80 mg tablets
candesartan (Atacand)	16 mg once daily; Pediatrics: 1 to < 6 years: 0.2 mg/kg once daily; 6 to < 17 years: < 50 kg weight: 4 mg to 8 mg once daily; > 50 kg weight: 8 mg to 16 mg once daily*	8 mg to 32 mg; Pediatrics: 1 to < 6 years: 0.05 to 0.4 mg/kg daily; 6 to < 17 years: < 50 kg weight: 4 mg to 16 mg daily; > 50 kg weight: 4 mg to 32 mg daily May give doses divided once or twice daily	--	--	4 mg to 32 mg once daily	--	no dosage recommendation <sup>†</sup>	4 mg, 8 mg, 16 mg, 32 mg tablets
eprosartan	600 mg once daily	400 mg to 800 mg per day; divided doses once or twice daily	--	--	--	--	no dosage recommendation <sup>†</sup>	600 mg tablets
irbesartan (Avapro)	150 mg once daily	75 mg to 300 mg once daily	300 mg once daily	--	--	--	75 mg once daily	75 mg, 150 mg, 300 mg tablets
losartan (Cozaar)	50 mg once daily Pediatrics (6 to 16 years): 0.7 mg/kg/day (or 50 mg daily)	25 mg to 100 mg per day; divided doses once or twice daily Pediatrics (6 to 16 years): 0.7 mg/kg/day (or 50 mg daily) to max of 1.4 mg/kg/day or 100 mg daily	50 mg to 100 mg once daily	Reduction of stroke risk with HTN and LVH: 50 mg to 100 mg daily	--	--	25 mg once daily	25 mg, 50 mg, 100 mg tablets
olmesartan (Benicar)	20 mg once daily Pediatrics (6 to 16 years): < 35 kg 10 mg once daily; ≥ 35 kg 20 mg once daily*	20 mg to 40 mg once daily Pediatrics (6 to 16 years): < 35 kg 10 to 20 mg once daily; ≥ 35 kg 20 to 40 mg once daily*	--	--	--	--	no dosage recommendation <sup>†</sup>	5 mg, 20 mg, 40 mg tablets

\* Pediatric suspension may be compounded for pediatric patients.

† Manufacturer recommends correcting condition prior to initiating treatment, or that therapy is initiated under close medical supervision with consideration given to administration of a lower dose of the ARB.

**Dosages (continued)**

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
<b>Angiotensin II Receptor Blockers: Single Agents (continued)</b>								
telmisartan (Micardis)	40 mg once daily	20 mg to 80 mg once daily	--	CV risk reduction: 80 mg once daily	--	--	no dosage recommendation <sup>†</sup>	20 mg, 40 mg, 80 mg tablets
valsartan (Diovan)	80 mg to 160 mg once daily Pediatrics (≥ 1 to 16 years): 1 to 2 mg/kg once daily*	80 mg to 320 mg once daily Pediatrics (≥ 1 to 16 years): 1 to 4 mg/kg once daily (40 mg to 160 mg)*	--	--	40 mg to 160 mg twice daily	20 mg to 160 mg twice daily	no dosage recommendation <sup>†</sup>	40 mg, 80 mg, 160 mg, 320 mg tablets
<b>Angiotensin II Receptor Blockers: Combination Products</b>								
azilsartan/chlorthalidone (Edarbyclor)	40/12.5 mg once daily	40/12.5 mg to 40/25 mg once daily	--	--	--	--	--	40/12.5 mg, 40/25 mg tablets
candesartan/HCTZ (Atacand HCT)	16/12.5 mg once daily	16/12.5 mg to 32/25 mg per day	--	--	--	--	--	16/12.5 mg, 32/12.5 mg, 32/25 mg tablets
irbesartan/HCTZ (Avalide)	150/12.5 mg once daily	150/12.5 mg to 300/25 mg once daily	--	--	--	--	--	150/12.5 mg, 300/12.5 mg tablets
losartan/HCTZ (Hyzaar)	50/12.5 mg once daily	50/12.5 mg once or twice daily or 100/25 mg once daily	--	--	--	--	--	50/12.5 mg, 100/12.5 mg, 100/25 mg tablets

\* Pediatric suspension may be compounded for pediatric patients.

† Manufacturer recommends correcting condition prior to initiating treatment, or that therapy is initiated under close medical supervision with consideration given to administration of a lower dose of the ARB.

### Dosages (continued)

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
<b>Angiotensin II Receptor Blockers: Combination Products (continued)</b>								
olmesartan/ HCTZ (Benicar HCT)	20/12.5 mg once daily	20/12.5 mg to 40/25 mg once daily	--	--	--	--	--	20/12.5 mg, 40/12.5 mg, 40/25 mg tablets
sacubitril/ valsartan (Entresto)	--	--	--	--	<b>Adults</b> - Initial: 49/51 mg twice daily; Range: 24/26 mg to 97/103 mg twice daily <sup>‡</sup> <b>Pediatrics (ages ≥ 1 year)*</b> <i>Body weight &lt; 40 kg:</i> initial: 1.6 mg/kg twice daily; range: 2.3 to 3.1 mg/kg twice daily <sup>§</sup> <i>Body weight 40 kg to &lt; 50 kg:</i> initial: 24/26 mg twice daily; range: 49/51 mg to 72/78 mg <i>Body weight ≥ 50 kg:</i> initial 49/51 mg; range: 72/78 mg to 97/103 mg	--	--	24/26 mg, 49/51 mg, 97/103 mg tablets
telmisartan/ HCTZ (Micardis HCT)	40/12.5 mg once daily	40/12.5 mg to 160/25 mg once daily	--	--	--	--	--	40/12.5 mg, 80/12.5 mg, 80/25 mg tablets

\* Pediatric suspension may be compounded for pediatric patients.

‡ For sacubitril/valsartan (Entresto), a reduced starting dose of 24/26 mg twice daily is recommended for patients not currently taking an ACE inhibitor or ARB or previously taking a low dose of these agents; patients with severe renal impairment; and patients with moderate hepatic impairment.

§ The mg/kg dose range is based on the combined amount of sacubitril and valsartan

**Dosages (continued)**

Drug	Initial hypertension dosage	Hypertension dosage range	Type 2 diabetic nephropathy dosage range	Risk Reduction	CHF	Post MI	Dose for volume- or salt-depleted patients	Availability
<b>Angiotensin II Receptor Blockers: Combination Products (continued)</b>								
valsartan/HCTZ (Diovan HCT)	160/12.5 mg once daily	80/12.5 mg to 320/25 mg once daily	--	--	--	--	--	80/12.5 mg, 160/12.5 mg, 160/25 mg, 320/12.5 mg, 320/25 mg tablets

Maximal clinical effects of combination therapy are seen 2 to 4 weeks after a dosage adjustment.

## CLINICAL TRIALS

### Search Strategy

Studies were identified through searches performed on PubMed and review of information sent by manufacturers. Search strategy included the FDA-approved use of all drugs in this category. Randomized, controlled trials comparing agents within this class for 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 and/or funding must be considered, the studies in this review have also been evaluated for validity and importance.

Some antihypertensive comparative trials of short duration have been conducted between the ARBs. Long-term clinical outcomes trials have not directly compared the agents in this class. Cardiovascular outcomes data are available from large clinical trials comparing an ARB to another type of antihypertensive agent.

### Hypertension

#### ***azilsartan (Edarbi) versus olmesartan (Benicar)***

In a randomized, double-blind, placebo controlled trial of 1,275 patients, azilsartan was compared to olmesartan.<sup>179</sup> The primary endpoint was change from baseline in mean 24-hour ambulatory systolic blood pressure (SBP) after 6 weeks of treatment. Patients had an initial SBP of 130 mm Hg to 170 mm Hg. Treatment arms included: placebo, azilsartan 20 mg, 40 mg, and 80 mg, and olmesartan 40 mg. Reduction in 24-hour mean SBP was greater with azilsartan 80 mg than olmesartan 40 mg (-2.1 mm Hg,  $p=0.038$ ), while azilsartan 40 mg was found to be non-inferior to olmesartan 40 mg.

#### ***azilsartan (Edarbi) versus valsartan (Diovan) versus olmesartan (Benicar)***

A randomized, double blind study compared 2 doses of azilsartan (40 mg and 80 mg) with valsartan 320 mg, olmesartan 40 mg, and placebo<sup>180</sup>. The primary endpoint was change from baseline in 24 hours mean SBP. This study included 1,291 patients with baseline 24 hour mean SBP of 145 mm Hg. Azilsartan 80 mg demonstrated superior efficacy to both valsartan at 320 mg (-10 mm Hg,  $p<0.001$ ) and olmesartan at 40 mg (-11.7 mm Hg;  $p=0.009$ ). Safety and tolerability among placebo and the 4 active treatment groups were similar.

#### ***azilsartan/chlorthalidone (Edarbyclor) versus olmesartan (Benicar) and hydrochlorothiazide***

A randomized, double-blind, 12-week, forced-titration trial of 1,071 patients compared the effect of azilsartan/chlorthalidone (40/12.5 mg or 40/25 mg) to olmesartan medoxomil/HCTZ (40/25 mg) in reducing SBP in patients with moderate to severe hypertension.<sup>181</sup> Both doses of azilsartan/chlorthalidone lowered blood pressure more effectively ( $p<0.001$ ) versus olmesartan

medoxomil/HCTZ at each hour of the 24-hour interdosing period as measured by ambulatory blood pressure monitoring (ABPM). Similar results were observed in all subgroups, including age, gender, or race.

### ***candesartan (Atacand) versus losartan (Cozaar)***

Candesartan was compared to losartan in the treatment of essential hypertension in 334 patients using a multicenter, double-blind, placebo-controlled study design.<sup>182</sup> A placebo run-in period was completed for the first 4 weeks of the study. If the patients' sitting diastolic blood pressure (DBP) was between 95 to 114 mm Hg at the end of the placebo run-in, the patient was randomized to candesartan 8 mg (n=82), candesartan 16 mg (n=84), losartan 50 mg (n=83), or placebo (n=85) given once daily for 8 weeks. Blood pressure and heart rate measurements were completed with a fully automatic device during the morning clinic visit and approximately 24 hours after intake of the study drug. The DBP decreased by -8.9 mm Hg with candesartan 8 mg, -10.3 mm Hg with candesartan 16 mg, -6.6 mm Hg with losartan 50 mg, and increased slightly with placebo. The active medications reduced sitting DBP to a greater extent compared to placebo. There was no difference between candesartan 8 mg and losartan 50 mg in reduction in blood pressure. The mean difference between the sitting DBP with candesartan 16 mg and losartan 50 mg was -3.7 mm Hg (p=0.013).

Candesartan (16 mg to 32 mg daily) and losartan (50 to 100 mg daily) were compared in 332 patients.<sup>183</sup> In an 8-week, randomized, double-blind, parallel group study, patients had a mean trough DBP of 90 mm Hg or greater following at least 4 weeks of treatment with candesartan 16 mg or losartan 50 mg daily. Doses were then doubled in both groups. Candesartan (-11 mm Hg) provided significantly greater reduction in trough sitting DBP than the losartan regimen (-8.9 mm Hg). Achievement of sitting DBP of less than 90 mm Hg or reduction in BP of greater than 10 mm Hg, defined as a responder, was reported in 64% and 54% of the candesartan and losartan groups, respectively. Discontinuation rate due to adverse effects or lack of efficacy was higher in the losartan group (1.9% for candesartan versus 6.5% for losartan).

Another double-blind, randomized, forced-titration study compared candesartan and losartan in 611 patients with essential hypertension.<sup>184</sup> Patients had DBP of 95 to 114 mm Hg prior to enrollment. Patients were randomized to candesartan 16 mg once daily or losartan 50 mg once daily. After 2 weeks, doses were doubled. Candesartan reduced blood pressure (BP) at trough (24 hours post-dosing), 6 hours (peak effect), and 48 hours after a dose to a significantly greater degree than losartan (p<0.05). The 24-hour trough BP values were reduced by -13.4/-10.5 mm Hg with candesartan and -10.1/-9.1 mm Hg with losartan. Response rates did not differ between the 2 treatments (58.8% for candesartan and 52.1% for losartan). Adverse events were similar between the groups.

A similarly designed study also evaluated candesartan and losartan in 654 hypertensive patients.<sup>185</sup> Trough BP reductions were significantly greater in the candesartan group (-13.3/-10.9 mm Hg) than in the losartan group (-9.8/-8.7 mm Hg, p<0.001). Significantly more patients were responders in the candesartan group (62.4 and 54% for candesartan and losartan, respectively; p<0.05). Both treatments were well tolerated.

A double-blind, randomized, placebo-controlled study compared candesartan 8 mg to losartan 50 mg once daily for 6 weeks in 256 patients with mild to moderate hypertension.<sup>186</sup> Ambulatory BP measurements were completed every 15 minutes for 36 hours. The mean change in DBP over hours zero to 24 hours after the dose were significantly greater with candesartan (-7.3 mm Hg) compared to

losartan (-5.1 mm Hg;  $p < 0.05$ ) and placebo (0.3 mm Hg,  $p < 0.001$ ). The mean change in SBP was also greater with candesartan (-10.8 mm Hg) compared to losartan (-8.8 mm Hg) and placebo (1.2 mm Hg,  $p < 0.001$ ). Candesartan 8 mg was associated with a greater reduction in DBP and SBP, relative to placebo, when compared with losartan 50 mg, during both daytime and night-time, and between 12 and 24 hours after dosing ( $p < 0.001$ ). Candesartan and losartan were well tolerated.

### ***candesartan (Atacand) in pediatrics***

Two randomized, double-blind multicenter, 4-week dose ranging studies were conducted to evaluate the effects of candesartan in pediatric patients.<sup>187</sup> In the first study, 193 patients 1 to < 6 years of age, 74% of whom had renal disease, were randomized to receive an oral candesartan 0.05, 0.2, or 0.4 mg/kg once daily. The primary analysis was slope of the change in SBP as a function of dose. Since there was no placebo group, the change from baseline likely overestimates the true magnitude of blood pressure effect. Nevertheless, SBP and DBP decreased 6/5.2 to 12/11.1 mm Hg from baseline across the 3 doses of candesartan.

In the second study, children 6 to < 17 years of age ( $n = 240$ ) were randomized to receive either placebo or low, medium, or high doses of candesartan. For children who weighed < 50 kg the doses of candesartan were 2, 8, or 16 mg once daily. For those > 50 kg, the candesartan doses were 4 mg, 16 mg, or 32 mg once daily. The placebo subtracted effect at trough for sitting SBP/sitting DBP for the different doses were from 4.9/3 to 7.5/7.2 mm Hg. Those enrolled were 47% African American. In children 6 to < 17 years, there was a trend for a lesser blood pressure effect for African Americans compared to other patients. There were too few individuals in the age group of 1 to < 6 years to determine whether African Americans respond differently than other patients to candesartan.

### ***eprosartan versus losartan (Cozaar)***

Eprosartan 600 mg once daily and losartan 50 mg once daily were compared in 60 patients with essential hypertension (baseline sitting DBP: 95 to 114 mm Hg) in a double-blind, randomized, 4-week study.<sup>188</sup> Blood pressure was reduced by -12.7/-12.4 mm Hg in the eprosartan group and -10.9/-9.6 mm Hg in the losartan group. A response was reported for 73% of eprosartan-treated patients and 53% of losartan-treated patients.

### ***irbesartan (Avapro) versus losartan (Cozaar)***

Following a placebo lead-in phase, a total of 567 patients were randomized in a double-blind manner to 1 of the 4 once-daily dosing treatment arms: placebo, losartan 100 mg, irbesartan 150 mg, or irbesartan 300 mg.<sup>189</sup> The duration of the study was 8 weeks, and baseline characteristics and demographics were comparable for the 4 groups. Results from the study were as follows: irbesartan 300 mg was statistically better than losartan 100 mg in reducing seated DBP (-11.7 and -8.7 mm Hg, respectively;  $p < 0.01$ ), and the antihypertensive effect of irbesartan 150 mg and losartan 100 mg did not differ significantly throughout the study. Conclusions from the study were that the administration of the maximally recommended doses irbesartan and losartan may result in significant differences in blood pressure reductions.

Designed to compare the effectiveness, safety, and tolerability of irbesartan and losartan, the study was a multicenter, randomized, double-masked, elective titration study for patients with mild to moderate hypertension.<sup>190</sup> After a 3-week placebo lead-in phase, 432 patients with a mean DBP of 95 to 115 mm Hg were randomly assigned to receive irbesartan 150 mg once daily or losartan 50 mg once

daily. When assessed at week 4, the daily dose of the medications was doubled (to irbesartan 300 mg or losartan 100 mg) if the DBP was greater than 90 mm Hg. At week 8, if the DBP remained greater than 90 mm Hg, HCTZ 12.5 mg once daily was added. In accordance with the prescribing information for losartan, the dose of losartan was decreased to 50 mg once daily when HCTZ was added. A total of 370 patients were evaluable for efficacy. The mean reduction in DBP at week 8 was significantly greater in patients receiving irbesartan monotherapy than in those receiving losartan monotherapy (-10.2 mm Hg versus -7.9 mm Hg, respectively). A greater proportion of irbesartan-treated patients responded to therapy compared to losartan-treated patients (78% versus 64%, respectively). Both regimens were well tolerated.

### ***losartan (Cozaar) in pediatrics***

In a double-blind, dose-response study, 175 hypertensive children were stratified by weight and randomized to losartan 2.5 mg to 5 mg (low dose group), 25 mg to 50 mg (middle), or 50 mg to 100 mg (high dose group) for 3 weeks.<sup>191</sup> Children were ages 6 to 16 years. In the first time period during active treatment, sitting trough DBP decreased in a dose-dependent manner (low dose, -6 mm Hg; middle dose, -11.7 mm Hg; high dose, -12.2 mm Hg;  $p < 0.0001$ ). In a second period of the study, patients were randomized to continue on losartan or to undergo a 2-week placebo wash-out period. In the second time period during placebo administration, DBP rose significantly in those patients receiving placebo who previously had been assigned to the middle and high doses of losartan ( $p = 0.003$ ). The manufacturer of losartan sponsored the study.

In 45 hypertensive children with chronic renal parenchymal disorders, the long-term efficacy and safety of losartan in treating hypertension and preserving renal function were evaluated.<sup>192</sup> Nearly all children had hypertension with half having concurrent hypertension and proteinuria. The mean age of the children was 12.85 years, and the mean follow-up was 2.42 years. Compared to baseline, losartan reduced SBP, DBP, and mean arterial blood pressure (MABP) by 9 to 12 mm Hg at the 3-month follow-up visit (all  $p < 0.01$ ). DBP and MABP remained significantly lower at all visits over 1 year ( $p < 0.005$  to  $0.0014$ ). By the last visit after 1 year of therapy, the percentage of normotensive patients increased significantly compared with baseline ( $p < 0.03$  for SBP,  $p < 0.0004$  for DBP). For patients with proteinuria, optimal reduction of proteinuria occurred over 3 to 12 months with reductions of 66 to 71% (all  $p < 0.01$ ). The mean glomerular filtration rate (GFR) reduction the year prior to losartan was 9.3 mL/min/1.73 m<sup>2</sup>, whereas the mean GFR on losartan saw a reduction of 1.4 mL/min/1.73 m<sup>2</sup> ( $p =$  not significant [NS]). No correlation existed between the blood pressure measurements and GFR or magnitude of blood pressure reductions and proteinuria. Eleven percent of patients experienced adverse effects that resulted in discontinuation of therapy.

A 12-week, double-blind, multinational study looked at the effects of losartan 0.7 to 1.4 mg/kg per day compared with placebo (normotensive stratum) or amlodipine 0.1 to 0.2 mg/kg per day up to 5 mg/day (hypertensive stratum) on proteinuria (morning-void urinary protein-creatinine ratio, baseline  $\geq 0.3$  g/g) in 306 children up to 17 years of age.<sup>193</sup> After 12 weeks of treatment with losartan, proteinuria was significantly reduced compared with amlodipine/placebo (-35.8% [95% CI, -27.6% to -43.1%] versus 1.4% [95% CI, -10.3% to 14.5%],  $p \leq 0.001$ ). Significance remained after adjustment for differences across treatment groups in change in BP (losartan produced incremental systolic and diastolic BP reductions versus amlodipine of 5.4 and 4.6 mm Hg, respectively; and versus placebo of 3.8 and 4 mm Hg, respectively). Proteinuria reduction was consistently observed in the normotensive (-34.4% losartan; 2.6% placebo) and hypertensive (-41.5% losartan; 2.4% amlodipine) strata, and in all

prespecified subgroups, including age, gender, race, Tanner stage, weight, prior therapy with angiotensin-converting enzyme (ACE) inhibitors or ARBs, as well as among the most common etiologies of proteinuria. Adverse event incidence was low and comparable in all groups.

### ***olmesartan (Benicar) versus losartan (Cozaar) versus valsartan (Diovan) versus irbesartan (Avapro)***

Losartan 50 mg, valsartan 80 mg, irbesartan 150 mg, and olmesartan 20 mg given once daily were compared for antihypertensive efficacy in 588 hypertensive patients with DBP of 100 to 115 mm Hg in a randomized, double-blind trial.<sup>194</sup> The majority of patients were male with a mean baseline BP of 157/104 mm Hg. After 8 weeks of therapy following randomization, olmesartan had significantly reduced sitting cuff DBP more than the other agents (olmesartan -11.5 mm Hg, losartan -8.2 mm Hg, valsartan -7.9 mm Hg, and irbesartan -9.9 mm Hg). SBP reductions were similar in all treatment groups. Patients were also evaluated on ambulatory blood pressure monitoring (ABPM).<sup>195</sup> More patients achieved blood pressure less than 140/80 mm Hg by ABPM in the olmesartan group (52.9%) versus losartan (40.3%;  $p=0.038$ ), valsartan (35.4%;  $p=0.004$ ), and irbesartan (47%;  $p=NS$ ).

### ***olmesartan (Benicar) in pediatrics***

The efficacy and safety of olmesartan in pediatric patients were evaluated in a randomized, double-blind study involving 302 hypertensive patients aged 6 to 16 years.<sup>196</sup> Hypertension was defined as SBP measured at or above the 95<sup>th</sup> percentile (90<sup>th</sup> percentile for patients with diabetes, glomerular kidney disease, or family history of hypertension) for age, gender, and height while off any antihypertensive medication was evaluated. The active treatment phase was conducted in 2 periods, with 2 cohorts in each period (cohort A, 62% Caucasian; cohort B, 100% African American). In period 1, patients were stratified by weight. Patients who weighed 20 to < 35 kg received 2.5 mg (low-dose) or 20 mg (high-dose) once daily and patients who weighed  $\geq$  35 kg were randomized to 5 mg (low-dose) or 40 mg (high-dose) olmesartan daily for 3 weeks. In period 2, patients maintained their olmesartan dose or were switched to placebo for an additional 2 weeks. Mean changes in seated trough SBP and DBP from the study baseline to the end of period 1 were -7.8/-5.5 mm Hg; -12.6/-9.5 mm Hg for low and high olmesartan doses, respectively, in cohort A, and -4.7/-3.5 mm Hg; -10.7/-7.6 mm Hg for low and high olmesartan doses, respectively, in cohort B. Mean blood pressure reductions were consistently smaller in cohort B than in cohort A. When analyzed by linear regression, a statistically significant olmesartan dose response was observed for seated trough SBP and DBP in cohort A ( $p=0.0008$  and  $p=0.0026$ , respectively), cohort B ( $p=0.0032$  and  $p=0.0125$ , respectively), and the combined cohorts A+B ( $p<0.0001$  for SBP and DBP). When adjusted for baseline body weight, a statically significant olmesartan dose response was observed in cohort A ( $p<0.0001$  for SBP and DBP), cohort B ( $p=0.0265$  and  $p=0.0084$  for SBP and DBP, respectively), and cohorts A+B ( $p<0.0001$  for both SBP and DBP). In period 2, blood pressure control decreased in those patients switching to placebo, whereas patients continuing to receive olmesartan therapy maintained consistent blood pressure reduction. The results from the analysis of covariance for the change in seated SBP for cohort A showed a difference between olmesartan and placebo of -3.6 mm Hg ( $p=0.0093$ ) in favor of olmesartan. This statistically significant effect was also observed for cohorts A+B (-3.16 mm Hg,  $p=0.0029$ ). Adverse events were generally mild and unrelated to study medication.

### ***telmisartan (Micardis) versus losartan (Cozaar)***

In a randomized, double-blind, placebo-controlled, 6-week trial, telmisartan 40 and 80 mg were compared to losartan 50 mg for efficacy and safety.<sup>197</sup> Following a 4-week placebo run-in phase, 223

patients with mild to moderate hypertension were randomized to 1 of the 4 groups. Ambulatory blood pressure monitoring was performed for 24 hours. All groups had significantly lower blood pressure compared to placebo. Telmisartan 40 mg and 80 mg lowered blood pressure significantly more than losartan or placebo at the time period of 18 to 24 hours after dosing ( $p < 0.05$ ). All therapies were well tolerated.

### ***telmisartan (Micardis) versus valsartan (Diovan)***

In a double-blind, randomized trial, telmisartan and valsartan were compared in 490 patients with hypertension.<sup>198</sup> Following a 2-week washout period, patients were randomized to telmisartan 40 mg to 80 mg daily or valsartan 80 mg to 160 mg daily with forced titration over 8 weeks. Early morning blood pressure was evaluated to determine the blood pressure reduction effects of each product during the last 6 hours of the dosing interval. Ambulatory blood pressure readings for the last 6 hours of the dosing interval were lower with telmisartan than valsartan (SBP:  $-11$  versus  $-8.7$  mm Hg, respectively;  $p = 0.02$ ; DBP:  $-7.6$  versus  $-5.8$  mm Hg, respectively,  $p = 0.01$ ). A second portion of the study included a placebo dose administered to mimic a missed dose. Both products reduced the blood pressure to a similar extent following the “missed dose” or after nearly 48 hours since the previous dose. Adverse events were similar between the 2 groups.

Similar findings were observed in 2 identically-designed randomized, double-blind, forced-titration studies with 887 hypertensive patients.<sup>199</sup> Telmisartan 40 to 80 mg daily and valsartan 80 mg to 160 mg daily were given for a total of 8 weeks. After 4 weeks on the higher dose, a dose of placebo was administered or active therapy. In another 2 weeks, crossover was performed to simulate a missed dose. Following active therapy, DBP was reduced by  $-7.6$  mm Hg and  $-5.8$  mm Hg with telmisartan and valsartan, respectively ( $p = 0.0044$ ). The last 6 hours mean SBP was reduced by  $-11.1$  mm Hg and  $-9.1$  mm Hg with telmisartan and valsartan, respectively ( $p = 0.0066$ ). After the missed dose, the 24-hour mean SBP/DBP was significantly reduced with telmisartan ( $-10.7/-7.2$  mm Hg) compared with valsartan ( $-8.7/-5.5$  mm Hg; for SBP,  $p = 0.0024$ ; for DBP,  $p = 0.0004$ ).

### ***valsartan (Diovan) versus losartan (Cozaar)***

Comparison of the antihypertensive efficacy of valsartan and losartan was the primary objective of an international, multicenter, double-blind, randomized, placebo-controlled, forced-titration study involving 1,369 patients with mild to moderate hypertension.<sup>200</sup> A secondary objective of the study was to compare the safety and tolerability of the 2 drugs. Initially, patients were randomized to receive valsartan 80 mg daily ( $n = 551$ ), losartan 50 mg daily ( $n = 545$ ), or placebo ( $n = 273$ ) for 4 weeks. The need for titration to higher doses of the medications was assessed at the end of the 4 weeks. Of the patients receiving valsartan, nearly 96% required an upward dosage titration to 160 mg, and 95.5% of patients receiving losartan required an upward dosage titration to 100 mg daily. A successful response to therapy was defined as a mean DBP of less than 90 mm Hg or a greater than  $-10$  mm Hg decrease in the mean DBP compared to baseline. All dosages of the medications studied were statistically significantly superior to placebo. Valsartan 80 mg and 160 mg daily were as effective as losartan 50 mg and 100 mg in the treatment of mild to moderate hypertension. In addition, the responder rates for patients receiving valsartan 160 mg were statistically superior ( $p = 0.021$ ) to losartan 100 mg daily. Both drugs were safe and well tolerated with an overall incidence of adverse events comparable to placebo.

Losartan and valsartan were compared in a 12-week study involving mild to moderate patients with hypertension.<sup>201</sup> Patients were randomized in a double-blind fashion to losartan 50 mg daily or

valsartan 80 mg daily for 6 weeks. After 6 weeks, if the DBP was greater than 90 mm Hg, the dose was doubled for the remainder of the study period. Patients (n=465) were evaluated at week 12 for the mean trough SBP. SBP reduction was similar between losartan (-9.9 mm Hg) and valsartan (-10.1 mm Hg). Patients achieving blood pressure reduction goals were 57% for losartan and 59% for valsartan. Both therapies were well tolerated.

### ***valsartan (Diovan) in pediatrics***

A study enrolled 261 hypertensive pediatric patients' ages 6 to 16 years. Patients who weighed < 35 kg received 10 mg, 40 mg, or 80 mg of valsartan daily (low, medium and high doses), and patients who weighed ≥ 35 kg received 20 mg, 80 mg, and 160 mg of valsartan daily (low, medium and high doses).<sup>202</sup> Renal and urinary disorders, and essential hypertension with or without obesity, were the most common underlying causes of hypertension in children enrolled in the study. At the end of 2 weeks, valsartan reduced both SBP and DBP in a dose-dependent manner. Overall, the 3 dose levels of valsartan (low, medium, and high) significantly reduced SBP by -8, -10, -12 mm Hg from the baseline, respectively. Patients were re-randomized to either continue receiving the same dose of valsartan or were switched to placebo. In patients who continued to receive the medium and high doses of valsartan, SBP at trough was -4 and -7 mm Hg lower than patients who received placebo treatment. In patients receiving low dose valsartan, SBP at trough was similar to that of patients who received placebo treatment. Overall, the dose-dependent antihypertensive effect of valsartan was consistent across all the demographic subgroups.

Efficacy and safety of valsartan were studied in 90 pediatric patients' ages 1 to 5 years (mean age of 3.2 years). The study population was 60% male, and 30% were African American.<sup>203</sup> Patients were randomly assigned to low-, medium-, or high-dose valsartan for 2 weeks (phase 1) and then randomly reassigned to placebo or remained on the same valsartan dose for 2 additional weeks (phase 2). Afterward, patients were enrolled into a 52-week, open-label phase where valsartan was dosed to achieve SBP less than 95th percentile. Statistically significant reductions in SBP and DBP of approximately 8.5 mm Hg and 5.7 mm Hg, respectively, were observed at the end of phase 1 in all of the valsartan dose groups. SBP and DBP were also significantly lower during phase 2 in valsartan patients versus placebo. SBP less than 95th percentile was achieved in 77.3% of patients during the open-label phase. Valsartan was well tolerated, and no effects on growth and development were observed. Adverse events occurred at similar frequencies in each of the 3 dose groups in phase 1 and at equal frequencies in the valsartan and placebo arms in phase 2. Serious adverse events and drug-related adverse events occurred infrequently during both the double-blind (2.2% and 5.6%, respectively) and open-label (14.8% and 6.8%, respectively) portions of the study. This was the first trial of an antihypertensive agent conducted in children < 6 years of age.

Three randomized, double-blind clinical trials assessed the antihypertensive effect of valsartan in children ages 1 to < 6 years of age (n=290).<sup>204</sup> All 3 studies demonstrated a reduction in blood pressure in those treated with valsartan, with 2 of the studies demonstrating a dose-dependent reduction in blood pressure.

### ***angiotensin II receptor blockers and the addition of hydrochlorothiazide or chlorthalidone***

The addition of hydrochlorothiazide (HCTZ) or chlorthalidone to an ARB has been shown to potentiate its antihypertensive effect as compared to the ARB alone.<sup>205,206,207,208,209,210,211,212,213,214,215,216,217,218,219,220,221,222,223,224,225</sup>

## Diabetic Nephropathy

### *candesartan (Atacand) versus placebo*

Three randomized trials of the DIRECT (Diabetic Retinopathy Candesartan Trials) Program were used to determine whether candesartan affects microalbuminuria incidence or rate of change in albuminuria in patients with type 1 and 2 diabetes.<sup>226</sup> Patients with type 1 (n=3,326) or type 2 (n=1,905) diabetes in 309 secondary care centers were randomized to candesartan 16 mg/day increasing to 32 mg/day versus placebo. Most patients were normotensive, and all had normoalbuminuria (median urinary albumin excretion rate, 5 mcg/min). Patients, caregivers, and researchers were blinded to treatment assignment, and patients were followed for a median duration of 4.7 years. Urinary albumin excretion rate was assessed annually by 2 overnight collections. If urinary albumin excretion rate was 20 mcg/min or greater, then 2 further urine collections were done. The primary endpoint was new microalbuminuria (3 or 4 collections of urinary albumin excretion rate  $\geq 20$  mcg/min). The secondary endpoint was rate of change in albuminuria. Individual and pooled results of the 3 trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95; 95% CI, 0.78 to 1.16; p=0.6). Pooled results showed that the annual rate of change in albuminuria was 5.53% lower (95% CI, 0.73% to 10.14%; p=0.024) with candesartan than with placebo.

### *irbesartan (Avapro) versus placebo*

Two large irbesartan trials in diabetic nephropathy are IDNT (versus amlodipine and placebo over 2.6 years) and IRMA-2 (versus placebo over 2 years). The renoprotective effect appears not to be directly related to blood pressure reduction alone.

IDNT: Irbesartan 300 mg daily was compared to amlodipine 10 mg daily and placebo for the effect on progression of diabetic nephropathy in 1,715 type 2 diabetic hypertensive patients.<sup>227</sup> The target blood pressure was 135/85 mm Hg or less in all groups. In the double-blind, randomized trial, the primary endpoints were doubling of baseline serum creatinine concentration, development of ESRD, or death from any cause. The mean duration of follow-up was 2.6 years. Evaluating all the primary outcome measures as a group, irbesartan was associated with a 20% lower risk versus placebo (p=0.02) and 23% lower risk versus amlodipine (p=0.006). Each of the primary endpoints was evaluated separately to show similar findings. A slower increase in serum creatinine concentration in the irbesartan groups over the placebo and amlodipine groups was observed. The progression to ESRD trended lower in the irbesartan groups versus the other 2 groups (both p=0.07). Death was not statistically different among the groups. An evaluation of the CV outcomes was also performed on the study population.<sup>228</sup> Overall, the 3 groups were similar for the composite outcome of CV death, MI, CHF, stroke, and coronary revascularization. A trend in the reduction of the number of strokes was seen with amlodipine (p=0.18). Amlodipine patients had significantly fewer MI events (p=0.02). Irbesartan patients had significantly fewer CHF events compared to amlodipine (p=0.004) and placebo (p=0.048).

IRMA-2: In a randomized, double-blind, placebo-controlled trial, irbesartan 150 and 300 mg were evaluated for efficacy in 590 hypertensive type 2 diabetic patients with microalbuminuria for delaying the progression to diabetic nephropathy.<sup>229</sup> Diabetic nephropathy was defined as the persistence of albuminuria in overnight specimens with a urinary albumin excretion rate ( $>200$  mcg/min) and greater than 30% higher than baseline on 2 consecutive occasions. All 3 groups were comparable at baseline. Over the 2-year period, diabetic nephropathy was identified in 5.2% of the irbesartan 300 mg patients (p<0.001 versus placebo), 9.7% of the irbesartan 150 mg group (p=0.081 versus

placebo), and 14.9% of the placebo group. After adjusting for baseline level of microalbuminuria and blood pressure reduction achieved, the hazard ratio for diabetic nephropathy with irbesartan 150 mg was 0.56 ( $p=0.05$ ) and 0.32 with irbesartan 300 mg ( $p<0.001$ ). The decline in creatinine clearance did not differ among the groups during the study. Blood pressure, measured at trough, was significantly lower in the irbesartan 150 mg and 300 mg groups compared to placebo (143/83, 141/83, and 144/83 mm Hg, respectively;  $p=0.004$  for SBP for both irbesartan groups versus placebo). Irbesartan was associated with a reduction in the urinary excretion of albumin throughout the study with the greatest reduction seen with the 300 mg dose (38% reduction versus 24% reduction with 150 mg, 2% with placebo). Serious adverse events were reported more frequently with placebo ( $p=0.02$ ).

A substudy of the 133 patients from the IRMA-2 trial evaluated kidney function following the withdrawal of treatment with irbesartan.<sup>230</sup> At the end of the study, the mean arterial blood pressure (MABP) was similar in all groups – 105, 103, and 102 mm Hg for placebo, irbesartan 150 mg, and irbesartan 300 mg groups. Urinary albumin excretion rate was reduced by 8% ( $p=NS$  versus baseline), 34%, and 60%, respectively. One month after the withdrawal of all antihypertensives, MABP was unchanged in the placebo group and was significantly increased in both the irbesartan groups (109 and 108 mm Hg, respectively). Urinary albumin excretion rate was increased by 14% in the placebo group, 11% in the irbesartan 150 mg group, and was persistently reduced in the irbesartan 300 mg group (-47%,  $p<0.005$ ). Authors concluded that irbesartan 300 mg provides persistent renoprotective effects after discontinuation.

Another substudy ( $n=43$ ) of the IRMA-2 trial found that the effects of irbesartan on 24-hour ambulatory blood pressure monitoring and trough office blood pressure were similar.<sup>231</sup> The reduction in urinary albumin excretion at the end of the study was 0% (-86 to 42), 38% (-14 to 66), and 73% (59 to 82), respectively (overall,  $p<0.01$ ). Authors concluded that renoprotective effects of irbesartan are not purely dependent on blood pressure reductions.

A different substudy ( $n=269$ ) of the IRMA-2 trial analyzed the biomarkers of inflammatory activity at baseline and after 1 and 2 years. Irbesartan significantly decreased high-sensitivity C-reactive protein (hs-CRP) with a 5.4% decrease/year versus 10% increase/year with placebo ( $p<0.001$ ). Fibrinogen decreased 0.059 g/L/year in the irbesartan group versus 0.059 g/L/year increase for placebo ( $p=0.027$ ). Interleukin-6 (IL-6) showed a 1.8% increase/year with irbesartan versus 6.5% increase/year for placebo ( $p=0.005$ ). Changes in IL-6 were associated with changes in albumin excretion ( $p=0.04$ ). Irbesartan 300 mg once daily reduced low-grade inflammation in this population which could in turn reduce the risk of micro- and macrovascular disease.<sup>232</sup>

Another smaller randomized, double-blind trial with 124 hypertensive type 2 diabetic patients with microalbuminuria demonstrated that irbesartan 300 mg daily reduced urinary excretion of albumin and lowered SBP and DBP.<sup>233</sup> Normotensive patients had reduced urinary excretion of albumin.

### ***losartan (Cozaar) versus placebo***

Losartan has been studied in the RENAAL trial for 3.4 years demonstrating renoprotective effects compared to placebo. Numerous small trials have been performed with similar results.

RENAAL: Losartan was evaluated in 1,513 type 2 diabetic patients in addition to other antihypertensive treatment for the progression of doubling of serum creatinine concentration, ESRD, or death.<sup>234</sup> In the randomized, double-blind, placebo-controlled trial, patients were randomized to losartan 50 to 100 mg daily or placebo and followed for a mean of 3.4 years. Proteinuria was found to decline in the losartan

group but not in the placebo group ( $p < 0.001$ ). The losartan group had significantly less occurrence of doubling of the baseline serum creatinine concentration (25% risk reduction,  $p = 0.006$ ) and progression to end-stage renal disease (28% risk reduction,  $p = 0.002$ ). The incidence of death was similar in both groups. Losartan provides a 16% reduction in the composite endpoint of doubling of serum creatinine, progression to ESRD, or death compared to placebo ( $p = 0.022$ ). In another analysis of the data from RENAAL trial, higher baseline SBP (140 to 159 mm Hg) increased risk for ESRD or death by 38% ( $p = 0.05$ ) compared with those patients with baseline SBP below 130 mm Hg.<sup>235</sup>

A study with losartan demonstrated a significant reduction of 25% in the albumin excretion rate after 5 weeks of losartan therapy in 147 normotensive type 2 diabetic patients with microalbuminuria.<sup>236</sup> The trial was a multicenter, randomized, double-blind, placebo-controlled trial. Patients were randomized to losartan 50 mg or placebo daily for the first 5 weeks, and then losartan was increased to 100 mg daily. Losartan was associated with a 25% relative reduction in urinary albumin excretion after 5 weeks of 50 mg and 34% after 10 weeks. Creatinine clearance did not improve over the study period, and blood pressure was only slightly decreased in the normotensive population. Adverse effects were similar between the groups.

The effects of losartan on endothelial function were measured in 80 type 2 diabetics with microalbuminuria and 68 non-diabetic control patients.<sup>237</sup> Diabetic patients were randomized to losartan 50 mg daily or placebo for 6 months in the double-blind trial. Both endothelial dependent and independent vasodilation (both  $p < 0.001$ ) were significantly impaired in the diabetic patients with or without hypertension compared to the control patients. Blood pressure did not significantly change in either group in the study. Urinary mean albumin excretion rate decreased significantly in the losartan group ( $p < 0.001$ ) and increased significantly in the placebo group ( $p < 0.05$ ).

A multicenter, controlled trial followed 285 normotensive patients with type 1 diabetes and normoalbuminuria for 5 years.<sup>238</sup> Patients were randomly assigned to receive losartan 100 mg per day, enalapril (Vasotec®) 20 mg per day, or placebo. The primary endpoint was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy endpoint was a progression on a retinopathy severity scale of 2 steps or more. A total of 90 and 82% of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the 5-year period did not differ significantly between the placebo group (0.016 units) and the enalapril group (0.005 units,  $p = 0.38$ ) or the losartan group (0.026 units,  $p = 0.26$ ), nor were there significant treatment benefits for other biopsy-assessed renal structural variables. The 5-year cumulative incidence of microalbuminuria was 6% in the placebo group, 17% ( $p = 0.01$  by the log-rank test) in the losartan group, and 4% ( $p = 0.96$  by the log-rank test) in the enalapril group. The odds of retinopathy progression by 2 steps or more was reduced by 65% in the enalapril group (odds ratio, 0.35; 95% CI, 0.14 to 0.85) and by 70% in the losartan group (odds ratio, 0.3; 95% CI, 0.12 to 0.73) when compared to placebo, independently of changes in blood pressure.

### ***telmisartan (Micardis) versus ramipril (Altace)***

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;  $p = 0.037$ ).<sup>239</sup> Secondary outcomes of dialysis and doubling of creatinine had

similar results. Estimated glomerular filtration rate (eGFR) declined least with ramipril compared with telmisartan (–2.82 [SD 17.2] mL/min/1.73 m<sup>2</sup> 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. Combination therapy worsened renal outcomes and was associated with increased adverse events.

## Heart Failure

### ***candesartan (Atacand) versus placebo***

The CHARM trials evaluated the use of candesartan in patients with chronic heart failure.<sup>240</sup> In the randomized, double-blind, controlled set of clinical trials, candesartan and placebo were compared for effects on CV mortality and morbidity. Overall, nearly 7,600 patients with heart failure were enrolled. Candesartan (titrated to 32 mg daily) or placebo were given to patients with preserved left ventricular function (CHARM-Preserved), those patients with intolerance to angiotensin-converting enzyme (ACE) inhibitors (CHARM-Alternative), and in addition to ACE inhibitors (CHARM-Added). Overall, candesartan had a lower all-cause mortality rate than placebo over an approximate 3-year follow-up period (23 versus 25%, respectively; unadjusted hazard ratio 0.91; 95% CI, 0.83 to 1; p=0.055; covariate adjusted 0.9; 95% CI, 0.82 to 0.99; p=0.032).<sup>241</sup> Cardiovascular death or hospitalization related to CHF was significantly less in the overall candesartan group. In those patients with preserved left ventricular function (ejection fraction greater than 40%), candesartan reduced hospitalizations due to CHF (22 versus 24% over 3 years, respectively; unadjusted hazard ratio 0.89; 95% CI, 0.77 to 1.03; p=0.118; covariate adjusted 0.86; 95% CI, 0.74 to 1; p=0.051).<sup>242</sup> In patients who did not tolerate ACE inhibitors due to cough, renal dysfunction, or hypotension, candesartan or placebo were compared.<sup>243</sup> Lower rate of CV death and hospitalization related to CHF were reported with candesartan (33 versus 40%; unadjusted hazard ratio 0.77; 95% CI, 0.67 to 0.89; p=0.0004; covariate adjusted hazard ratio 0.7; 95% CI, 0.6 to 0.81; p<0.0001). For the ACE-intolerant population, the discontinuation rate was similar between candesartan (30%) and placebo (29%). The CHARM-Added trial evaluated the addition of candesartan to ACE inhibitors, beta-blockers, and other CHF treatments.<sup>244</sup> For those patients on candesartan after a median of 41 months, lower CV death and hospitalization for CHF were reported (38 versus 42%; unadjusted hazard ratio 0.85; 95% CI, 0.75 to 0.96; p=0.011; covariate adjusted, p=0.01). Functional NYHA classifications were improved with the use of candesartan.<sup>245</sup> Overall, discontinuations due to adverse effects were more common in the candesartan group.

### ***valsartan (Diovan) versus placebo***

The valsartan heart failure trial (Val-HeFT) was conducted in 5,010 subjects to assess the efficacy of adding valsartan (titrated to 160 mg twice daily) to an existing maximized regimen of diuretics, digoxin, beta-blockers, ACE inhibitors, or combinations of these medications.<sup>246</sup> The trial was a placebo-controlled, double-blind, randomized trial, and the major endpoints were mortality and all-cause morbidity and mortality. Other endpoints included hospitalization, ejection fraction, quality of life, symptoms, and NYHA classification. The valsartan group had a 13.2% lower incidence of all-cause morbidity and mortality (p=0.009) and a 27.5% lower hospitalization rate (p<0.001) as compared to placebo. Ejection fraction, symptoms, and NYHA classification, as well as quality of life, improved significantly in the valsartan group as compared to placebo. The greatest benefit was seen in patients

receiving valsartan who were not receiving an ACE inhibitor. Patients receiving an ACE inhibitor, valsartan, and a beta-blocker had a worse outcome for heart failure morbidity.

### ***sacubitril/valsartan (Entresto) versus enalapril in adults***

PARADIGM-HF: A randomized, double-blind, multinational, trial was conducted in patients with symptomatic CHF (NYHA class II–IV) and systolic dysfunction (LVEF  $\leq$  40%) comparing sacubitril/valsartan (n=4,187) and enalapril (n=4,212).<sup>247</sup> Patients had to have been on an ACE inhibitor or ARB for at least 4 weeks and on maximally-tolerated doses of beta-blockers. Patients with a SBP < 100 mmHg at screening were excluded. The primary objective was to determine whether sacubitril/valsartan was superior to enalapril alone in reducing the risk of the combined endpoint of CV death or hospitalization for HF. After discontinuing their existing ACE inhibitor or ARB therapy, patients entered sequential single-blind run-in periods during which they received enalapril 10 mg twice daily, followed by sacubitril/valsartan 100 mg twice daily, increasing to 200 mg twice daily. Patients who successfully completed the sequential run-in periods were randomized to receive either sacubitril/valsartan 200 mg twice daily or enalapril 10 mg twice daily in addition to recommended therapy. The primary endpoint was the first event in the composite endpoint of CV death or hospitalization for HF. The trial was stopped early, according to prespecified rules, after a median follow-up of 27 months, because the boundary for an overwhelming benefit with sacubitril/valsartan had been crossed. At the time of study closure, the primary outcome had occurred in 914 patients (21.8%) in the sacubitril/valsartan group and 1,117 patients (26.5%) in the enalapril group (HR in the sacubitril/valsartan group, 0.8; 95% CI, 0.73 to 0.87;  $p < 0.001$ ). Compared to enalapril, in patients with CHF (NYHA Class II-IV) and reduced ejection fraction, sacubitril/valsartan has been able to reduce CV death and first HF hospitalization by about a 20% relative risk reduction and decrease the relative risk of all-cause mortality by 16%. The sacubitril/valsartan group had higher proportions of patients with hypotension and angioedema but lower proportions with renal impairment, hyperkalemia, and cough than the enalapril group.

PARAGON-HF: A multicenter, randomized, double-blind trial compared sacubitril/valsartan to valsartan in 4,822 patients with symptomatic heart failure (NYHA class II to IV), LVEF  $\geq$  45%, and structural heart disease (enlargement or hypertrophy) to determine if the combination reduced the rate of the composite endpoint of total HF hospitalizations and CV death compared to valsartan alone.<sup>248,249</sup> Patients were randomized to sacubitril/valsartan (target dose 97 mg/103 mg) or valsartan (target dose, 160 mg) twice daily. There were 894 and 1,009 primary events in the sacubitril/valsartan group and valsartan groups, respectively (rate ratio, 0.87; 95% CI, 0.75 to 1.01;  $p = 0.06$ ). The incidence of death due to CV causes was 8.5% in the combination group compared to 8.9% in the valsartan group (HR, 0.95; 95% CI, 0.79 to 1.16), and 690 and 797 hospitalizations for heart failure occurred in the sacubitril/valsartan and valsartan groups, respectively (rate ratio, 0.85; 95% CI, 0.72 to 1). A higher incidence of hypotension and angioedema occurred in the sacubitril/valsartan group than the valsartan group, while a higher incidence of hypokalemia occurred in the valsartan group. The researchers concluded that sacubitril/valsartan therapy did not result in a lower rate of the composite outcome in patients with preserved ejection fraction compared to valsartan alone.

### ***sacubitril/valsartan (Entresto) versus enalapril in pediatrics***

PANORAMA-HF: In a multinational, double-blind trial, 110 pediatric patients 1 to < 18 years old with heart failure (NYHA/Ross class II-IV) due to systemic left ventricular systolic dysfunction (LVEF  $\leq$  40%)

were randomized to sacubitril/valsartan (target maintenance dose of 31 mg/kg twice daily) or enalapril.<sup>250</sup> The trial excluded patients with systemic right ventricles and single ventricles. At 12 weeks, the endpoint of change in plasma NT-proBNP from baseline was not statistically significant between the groups (44% for sacubitril/valsartan and 33% for enalapril); however, the reductions for both groups were similar to or greater than reported in adults. Since sacubitril/valsartan improved outcomes and reduced NT-proBNP in the adult trial (PARADIGM-HF), it was considered reasonable to infer that the effect on NT-proBNP in PANORAMA-HF demonstrated improved cardiovascular outcomes in pediatric patients.

## Cardiovascular Morbidity and Mortality Reduction

### *losartan (Cozaar) versus atenolol (Tenormin®)*

A double-masked, randomized study of 9,193 patients (ages 55 to 80 years) with essential hypertension and left ventricular hypertrophy (LVH) was conducted to compare the effects of losartan and atenolol on the incidence of CV events including death, MI, or stroke over at least 4 years in the LIFE study.<sup>251</sup> Patients were included if the initial sitting blood pressure was at least 160 to 200/95 to 115 mm Hg with documented LVH. Both losartan and atenolol significantly reduced blood pressure with a mean reduction of -30/-17 mm Hg and -29/-17 mm Hg, respectively. Losartan reduced the overall risk for CV endpoints by 13% (p=0.021). Cardiovascular deaths did not differ between the groups. Fatal and non-fatal stroke risk reduction was 25% with losartan compared to atenolol (p=0.001), and new onset diabetes occurred less frequently in the losartan group. In a predetermined sub-analysis, diabetic patients (n=1,195) were evaluated separately in the LIFE study.<sup>252</sup> Both drugs significantly reduced blood pressure to a similar degree with 85% of the losartan group and 82% of the atenolol group in the diabetic population achieving a DBP less than 90 mm Hg. Losartan reduced the combined risk of CV death, MI, or stroke by 24% compared to atenolol (p=0.031). Losartan also reduced the risk of death from CV causes by 37% compared to atenolol; however, no significant differences in the risk of MI or stroke were found between the 2 groups. Patients with isolated systolic hypertension (n=1,326) also were observed to have a 25% risk reduction in the composite endpoint of CV death, MI, and stroke with losartan over atenolol despite both drugs reducing blood pressure to a similar degree.<sup>253</sup> Regression of LVH with losartan was greater than that observed with atenolol starting within 6 months after initiation of therapy.<sup>254</sup> New onset atrial fibrillation was lower in the losartan group compared with that of the atenolol group despite similar blood pressure reduction (6.8 versus 10.1 per 1,000 person-years; RR, 0.67; 95% CI, 0.55 to 0.83; p<0.001).<sup>255</sup> A post-hoc analysis of the LIFE study evaluated the effects of losartan in women.<sup>256</sup> Women in the losartan group had significant reductions in the primary composite endpoint (215 versus 261; HR, 0.82; 95% CI, 0.68 to 0.98; p=0.031), stroke (109 versus 154; HR, 0.71; 95% CI, 0.55 to 0.9; p=0.005), total mortality (HR, 0.77; 95% CI, 0.63 to 0.95; p=0.014), and new-onset diabetes (HR, 0.75; 95% CI, 0.59 to 0.94; p=0.015) versus the atenolol group, with no between-treatment difference for MI (HR, 1.02; 95% CI, 0.74 to 1.39; p=0.925), CV mortality (HR, 0.86; 95% CI, 0.64 to 1.14; p=0.282), or hospitalization for HF (HR, 0.94; 95% CI, 0.68 to 1.28; p=0.677). More women in the losartan group required hospitalization for angina (HR, 1.7; 95% CI, 1.16 to 2.51; p=0.007). Risk reductions for the primary composite endpoint, stroke, total mortality, and new-onset diabetes were significantly greater with losartan versus atenolol in women with hypertension and LVH in the LIFE study.

### ***telmisartan (Micardis) versus ramipril (Altace)***

ONTARGET was a randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes.<sup>257</sup> After a 3-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. 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 2 drugs was associated with more adverse events without an increase in benefit.

### ***telmisartan (Micardis) versus placebo***

A randomized, double-blind, placebo-controlled, multicenter, 2.5-year study of 20,332 patients with a recent ischemic stroke compared telmisartan 80 mg daily initiated soon after an ischemic stroke to placebo to evaluate the primary outcome of recurrent stroke.<sup>258</sup> Secondary outcomes included major CV events (CV death, recurrent stroke, MI, or new or worsening HF) and new-onset diabetes. The primary outcome of first recurrent stroke occurred in 8.7% in the telmisartan group, as compared with 9.2% in the placebo group (HR, 0.95; 95% CI, 0.86 to 1.04;  $p = 0.23$ ). This nonsignificant difference was consistent across various subtypes of stroke. The number of patients with a major CV event was 13.5% in the telmisartan group as compared with 14.4% in the placebo group (HR, 0.94; 95% CI, 0.87 to 1.01). In addition, telmisartan did not significantly reduce the risk of new onset diabetes (1.7% versus 2.1%; HR, 0.82; 95% CI, 0.65 to 1.04;  $p = 0.10$ , telmisartan versus placebo, respectively).

## **Post Myocardial Infarction**

### ***valsartan (Diovan) versus captopril versus captopril and valsartan***

VALIANT: A double-blind, randomized clinical trial compared valsartan, captopril, and the combination in 14,703 patients with recent (0.5 to 10 days) MI complicated by left ventricular systolic dysfunction, heart failure, or both.<sup>259</sup> The primary outcome measure was death from any cause. Patients were randomized to valsartan ( $n = 4,909$ ) 20 mg twice daily titrated up to 160 mg twice daily, captopril ( $n = 4,909$ ) 6.25 mg 3 times daily titrated up to 50 mg 3 times daily, or the combination ( $n = 4,885$ ) of valsartan (20 mg twice daily titrated up to 80 mg twice daily) plus captopril (6.25 mg 3 times daily titrated up to 50 mg 3 times daily). The median follow up was 24.7 months. Death from any cause was similar among the 3 groups. The secondary endpoints of CV death, recurrent MI, or hospitalization for heart failure were also similar among the 3 groups. The combination arm had lower BP measurements and an increase in reported adverse effects and significantly higher discontinuation rate versus captopril ( $p < 0.05$ ). Valsartan was shown to be noninferior to captopril in the study.

## META-ANALYSES

A meta-analysis of 11 randomized controlled trials compared telmisartan with losartan in 1,832 patients with hypertension. The main efficacy measures were reduction in DBP and SBP, and therapeutic response of DBP and SBP.<sup>260</sup> Ten trials with 1,792 patients reported reduction in clinic BP; 6 trials with 1,163 patients reported ambulatory BP reduction; 7 trials with 1,675 patients reported therapeutic response of BP. Telmisartan resulted in a significant reduction in clinic DBP (weighted mean difference [MD], 1.52 mmHg; 95% CI, 0.85 to 2.19) and SBP (weighted MD, 2.77; 95% CI, 1.9 to 3.63) compared with losartan. There was also a significant reduction in 24-hour mean ambulatory DBP (weighted MD, 2.49; 0.56 to 4.42) and SBP (weighted MD, 2.47; 95% CI, 0.4 to 4.55) with telmisartan compared to losartan. There was also a significant increase in therapeutic response of DBP (relative risk [RR], 1.14; 95% CI, 1.04 to 1.23) and SBP response (RR, 1.1, 95% CI, 1.01 to 1.2) with telmisartan compared to losartan. Both treatments were well tolerated.

A meta-analysis of 9 studies with 11,007 participants compared the CV mortality of ARBs compared to ACE inhibitors.<sup>261</sup> Overall, there was no difference between groups in total mortality (risk ratio [RR], 0.98; 95% CI, 0.88 to 1.1), total CV events (RR, 1.07; 95% CI, 0.96 to 1.19), or CV mortality (RR, 0.98; 95% CI, 0.85 to 1.13). However, there was a slight advantage of ARBs compared to ACE inhibitors in withdrawals due to adverse effects (RR, 0.83; 95% CI, 0.74 to 0.93).

A meta-analysis of 9 trials evaluated the safety and tolerability of combination ACE inhibitor and ARB versus ACE inhibitor in patients with HF or left ventricular dysfunction (LVD).<sup>262</sup> A total of 9,199 patients received combination therapy, and 8,961 patients received an ACE inhibitor only. Patients receiving combination therapy had an increased risk of developing any adverse effect by 2.3% (RR, 1.27; 95% CI, 1.15 to 1.4;  $p < 0.00001$ , inter-study heterogeneity [ $I^2$ ] = 15.9%, number needed to harm [NNH]=42), hypotension by 1.1% (RR, 1.91; 95% CI, 1.37 to 2.66;  $p = 0.0002$ ;  $I^2 = 26.6%$ ; NNH=89), worsening renal function by 1% (RR, 2.12; 95% CI, 1.3 to 3.46;  $p = 0.003$ ;  $I^2 = 67.3%$ ; NNH=100), and hyperkalemia by 0.6% (RR, 4.17; 95% CI, 2.31 to 7.53;  $p < 0.00001$ ;  $I^2 = 0%$ ; NNH=149). There was no difference in angioedema (RR, 0.88; 95% CI, 0.43 to 1.8;  $p = 0.72$ ;  $I^2 = 0%$ ) or cough (RR, 0.84; 95% CI, 0.65 to 1.09;  $p = 0.19$ ,  $I^2 = 0%$ ). 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 6 randomized comparative trials including 49,924 patients showed no significant differences between ARB and ACE inhibitor on the risk of MI (OR, 1.01; 95% CI, 0.95 to 1.07;  $p = 0.75$ ), CV mortality (OR, 1; 95% CI, 0.98 to 1.08;  $p = 0.23$ ), and total mortality (OR, 1.03; 95% CI, 0.97 to 1.1;  $p = 0.2$ ).<sup>263</sup> Overall, the risk of stroke was slightly lower with ARBs than ACE inhibitor (OR, 0.92; 95% CI, 0.85 to 0.99;  $p = 0.037$ ), the direct ACE inhibitors 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 ( $p = 0.12$ ).

A meta-analysis of 4 randomized trials, comprising a total of 8,152 patients, investigated the effects of ACE inhibitors (1 trial), ARB (2 trials), or both treatments (1 trial) in patients with HF and preserved LVEF.<sup>264</sup> Risk ratios (RR) and 95% CI were calculated using a fixed-effect estimate method in the randomized trials. Compared with placebo or no treatment, treatment with ACE inhibition or ARB was associated with lower rates of hospitalization for HF (RR, 0.9; 95% CI, 0.81 to 0.99;  $p = 0.032$ ), though

not CV mortality (RR, 1.01; 95% CI, 0.9 to 1.13; p=0.85). In all 3 studies where these endpoints were combined, the one-year incidence of CV death or hospitalization for HF was lowered by ACE inhibition or ARB (RR, 0.74; 95% CI, 0.58-0.94; p=0.014). Compared with placebo, ACE inhibition or ARB significantly lowered risks of hospitalization for HF and the combined endpoint of CV mortality and hospitalization for HF at 1 year, in patients with HF and preserved LVEF. However, there was no significant effect on mortality during more prolonged follow-up; the width of the 95% confidence limits is compatible with a benefit as large as 10% or a hazard as large as 13%.

Another meta-analysis assessed the effect of ACE inhibitors and ARBs on CV events in patients with HF (n=47,662; 38 placebo-controlled or active drug trials).<sup>265</sup> The authors found that ACE inhibitors were superior to ARBs in the reduction of all-cause mortality (risk ratio, 0.89 [95% CI, 0.83 to 0.96; p=0.001] versus risk ratio, 1.03 [95% CI, 0.98 to 1.086; p=0.28], respectively) and CV mortality (risk ratio, 0.86 [95% CI, 0.78 to 0.94; p=0.001] versus risk ratio, 1.01 [95% CI, 0.92 to 1.12; p=0.78], respectively); however, no statistical superiority was demonstrated when evaluating only head-to-head trials of ACE inhibitors and ARBs.

A meta-analysis of 10 randomized controlled studies evaluated the effects of ARBs and ACE inhibitors on CV risk in hypertensive type 2 diabetes patients (n=21,871).<sup>266</sup> Specifically, the meta-analysis investigated the incidence of MI, stroke, CV events, and all-cause mortality. ARB/ACE inhibitor therapy did not have a significant reduction in all-cause mortality (HR, 0.91; 95% CI, 0.83 to 1; p=0.062; measure of heterogeneity= $I^2=21%$ ) but did result in a significant reduction in CV mortality (HR, 0.83; 95% CI, 0.72 to 0.96; p=0.012;  $I^2=0.9%$ ). Similarly, there was no reduction in MI (HR, 0.85; 95% CI, 0.53 to 1.37; p=0.511;  $I^2=66.5%$ ) or stroke (HR, 0.99; 95% CI, 0.85 to 1.15; p=0.855;  $I^2=0%$ ), but there was a reduction in overall CV events (HR, 0.9; 95% CI, 0.82 to 0.98; p=0.019;  $I^2=19.5%$ ). A meta-analysis aimed at evaluating the blood pressure lowering effects and incidences of heart attack, stroke, and death in patients taking hydrochlorothiazide (HCTZ) has been published.<sup>267</sup> Based on 14 studies, including 1,234 patients taking HCTZ, blood pressure lowering with HCTZ was inferior to all other classes, such as ACE inhibitors, ARBs, 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. A subsequent meta-analysis of 13 trials comparing ACE inhibitors and ARBs also analyzed CV outcomes in hypertensive patients with type 2 diabetes mellitus.<sup>268</sup> In total, 5 ACE inhibitor trials (24,976 patients) and 8 ARB trials (22,032 patients) were included and analyzed for the primary endpoints of all-cause mortality and CV mortality. Treatment with an ACE inhibitor was associated with significant reduction in all-cause mortality (OR, 0.87; 95% CI, 0.8 to 0.94; p=0.0008;  $I^2=50%$ ) and CV death (OR, 0.81; 95% CI, 0.68 to 0.98, p=0.03) compared with control group. Regarding effects of ARBs on all-cause mortality and CV mortality, there was no significant decrease in the occurrence of all-cause mortality (OR, 1.06; 95% CI, 0.97 to 1.15) and CV death (OR, 1.02; 95% CI, 0.78 to 1.33;  $I^2=54%$ ) compared with control therapy. ACE inhibitors significantly reduced the occurrence of MI (OR, 0.77; 95% CI, 0.66 to 0.9), HF (OR, 0.65; 95% CI, 0.47 to 0.9), stroke (OR, 0.88; 95% CI, 0.78 to 0.99), and other CV events (OR, 0.83; 95% CI, 0.73 to 0.95). However, the ARBs trials included did not show significant reduction in the occurrence of MI (OR, 0.88; 95% CI, 0.77 to 1.01), stroke (OR, 0.96; 95% CI, 0.84 to 1.09), HF (OR, 0.81; 95% CI, 0.61 to 1.07), and CV events (OR, 0.94; 95% CI, 0.88 to 1.01). It should be noted that significant heterogeneity was reported in several of the ACE inhibitor trials when all 5 trials were analyzed together for several of primary and secondary endpoints; however, the researchers were able to exclude 1 or more outlier trials to reduce heterogeneity. The study concluded that ACE inhibitor are

better than ARBs at providing CV protection from all-cause mortality, CV death, and major CV events in diabetic type-2 patients with hypertension.

## COMPARATIVE EFFICACY<sup>269,270,271,272,273,274,275,276,277,278,279,280,281,282,283,284</sup>

Drug	Dose	SBP Reduction (mm Hg)	DBP Reduction (mm Hg)
azilsartan (Edarbi™)	20 – 80 mg daily	12.1 – 15.5	6.2 – 9.4
candesartan (Atacand)	8 – 32 mg daily	8 – 12	4 – 8
candesartan/ HCTZ (Atacand HCT)	16/12.5 – 32/25 mg daily	14 – 19	8 – 11
eprosartan	200 – 400 mg twice daily	7 – 10	4 – 6
irbesartan (Avapro)	150 – 300 mg daily	8 – 12	5 – 8
irbesartan/HCTZ (Avalide)	150/12.5 – 300/25 mg daily	13 – 21	7 – 12
losartan (Cozaar)	50 – 150 mg daily	5.5 – 10.5	3.5 – 7.5
losartan/HCTZ (Hyzaar)	50/12.5 – 100/25 mg daily	9 – 15.5	5.5 – 9
olmesartan (Benicar)	20 – 40 mg daily	12 – 13	5 – 7
azilsartan/chlorthalidone (Edarbyclor)	40/12.5 – 40/25 mg daily	23 – 43	13 – 20
olmesartan/HCTZ (Benicar HCT)	20/12.5 – 40/25 mg daily	17 – 24	8 – 14
telmisartan (Micardis)	40 – 160 mg daily	9 – 13	6 – 8
telmisartan/HCTZ (Micardis HCT)	40/12.5 – 80/12.5 mg daily	16 – 21	9 – 11
valsartan (Diovan)	80 – 320 mg daily	6 – 9	3 – 6
valsartan/HCTZ (Diovan HCT)	80/12.5 – 320/25 mg daily	14 – 21	8 – 11

**Note:** Blood pressure reduction data are obtained from prescribing information and, therefore, should not be considered comparative or all inclusive.

## SUMMARY

Comparative trials have been conducted between angiotensin receptor blockers (ARBs) for the management of hypertension. According to prescribing information, all ARBs lower blood pressure to a similar degree. Limited data suggest that candesartan (Atacand), valsartan (Diovan), and irbesartan (Avapro) at higher dosages offer greater decreases in blood pressure than losartan (Cozaar). Initial trials indicate that azilsartan (Edarbi) may produce a greater systolic blood pressure lowering effect than some other agents; however, there are no long-term outcomes studies for this agent. ARBs are generally well tolerated.

ARBs have extensive data showing renal protective benefits in hypertensive diabetic patients with microalbuminuria. The benefits are over and above that of blood pressure reduction alone and extend to normotensive diabetic patients as well. Delay in progression of diabetic nephropathy by ARBs is likely a class effect, although more data are needed. Losartan (Cozaar) and irbesartan (Avapro) are

both FDA-approved for the treatment of diabetic nephropathy with an elevated serum creatinine and proteinuria in patients with type 2 diabetes and a history of hypertension.

Valsartan (Diovan) has been approved for use in heart failure (HF) and for use in post-myocardial infarction patients with left ventricular dysfunction, HF, or both. Candesartan (Atacand) is approved for patients with HF to reduce the risk of cardiovascular (CV) death and to reduce hospitalizations related to HF. Current guidelines recommend ACE inhibitors as the treatment of choice for HF. ARBs are recommended in patients unable to tolerate ACE inhibitors.

Sacubitril/valsartan (Entresto) is a combination product of a neprilysin inhibitor and an ARB for the use in patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction (HFrEF). In the PARADIGM-HF trial, sacubitril/valsartan was more effective in reducing death from CV causes or first-time HF hospitalization in patients with reduced ejection fraction than the currently recommended standard HF therapy, an ACE inhibitor. Clinical guidelines recommended that patients with chronic symptomatic HFrEF 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. Sacubitril/valsartan is administered in combination with other standard HF therapies, in place of an ACE inhibitor or other an ARB.

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