Angiotensin Modulators: Angiotensin II Receptor Blockers Review

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FDA-approved Indications

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

Drug	Manufacturer	Indication(s)
candesartan (Atacand®)[1]	AstraZeneca	• Hypertension (including ages one to < 17 years) • Heart failure – (LVEF ≤40%, NYHA II-IV) to reduce risk of CV death and reduce hospitalizations for heart failure (in addition to ACE inhibitors or when ACE inhibitors are not tolerated)
eprosartan (Teveten®)[2]	Abbott	• Hypertension
irbesartan (Avapro®)[3]	Bristol-Myers Squibb	• Hypertension • Nephropathy in type 2 diabetic patients
losartan (Cozaar®)[4]	generic	• Hypertension (including ages 6-16 years) • Nephropathy in type 2 diabetic patients • Reduce the risk of stroke in hypertensive patients with LVH (not in Black patients)
olmesartan (Benicar®)[5]	Daiichi Sankyo	• Hypertension
telmisartan (Micardis®)[6]	Boehringer Ingelheim	• Hypertension • *80 mg tablets only:* Risk reduction of myocardial infarction (MI), stroke, or death from cardiovascular causes in patients 55 years of age or older at high risk of developing major cardiovascular events who are unable to take ACE inhibitors
valsartan (Diovan®)[7]	Novartis	• Hypertension (including ages 6-16 years) • Heart failure (NYHA II-IV) to reduce CHF hospitalizations • Reduction of cardiovascular mortality in clinically stable patients with left ventricular failure or left ventricular dysfunction following MI

FDA-approved Indications

LVH = left ventricular hypertrophy; HCTZ = hydrochlorothiazide

Drug	Manufacturer	Indication(s)
candesartan/HCTZ (Atacand HCT®)[8]	AstraZeneca	• Hypertension
eprosartan/HCTZ (Teveten HCT®)[9]	Abbott	• Hypertension
irbesartan/HCTZ (Avalide®)[10]	Bristol-Myers Squibb	• Hypertension (first line therapy in patients requiring multiple meds)
losartan/HCTZ (Hyzaar®)[11]	generic	• Hypertension (first line therapy in setting of prompt BP reduction) • Reduce the risk of stroke in hypertensive patients with LVH (not in Black patients)
olmesartan/HCTZ (Benicar HCT®)[12]	Daiichi Sankyo	• Hypertension
telmisartan/HCTZ (Micardis HCT®)[13]	Boehringer Ingelheim	• Hypertension
valsartan/HCTZ (Diovan HCT®)[14]	Novartis	• Hypertension (first line therapy in patients requiring multiple meds)

Overview

Approximately 76.4 million adults in the United States have hypertension.[15] Hypertension is an independent risk factor for cardiovascular disease, and antihypertensive treatment lowers the risk of cardiovascular disease. Angiotensin II receptor blockers (ARBs) are indicated for the treatment of hypertension either alone or in combination with other antihypertensive medications. The Seventh Report from the National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7) suggests that ARBs may be used as first-line therapy for patients with hypertension. ARBs may also be used in patients with compelling indications, such as heart failure (HF), chronic kidney disease, and diabetes mellitus.[16,17] ARBs are indicated for the treatment of hypertension either alone or in combination with other antihypertensive medications and offer an alternative in patients with heart failure and reduced left ventricular ejection fraction who are ACE inhibitor-intolerant.[18] Valsartan (Diovan) and candesartan (Atacand) are FDA-approved for the treatment of congestive heart failure (CHF). ACE inhibitors are still considered first-line therapy for the treatment of CHF; however, ARBs are considered an acceptable alternative.[19]

Diabetic nephropathy develops in 25 to 40 percent of patients over 20 to 25 years after diabetes onset. The prevalence of microalbuminuria ten years after diagnosis of diabetes is 25 percent.[20] Diabetic nephropathy is the most common cause of end-stage renal disease (ESRD) in the United States and accounts for 40 percent of all the patients with ESRD entering a dialysis program.[21] Type 1 and 2 diabetics are both at risk for the development of nephropathy and follow the same

progression to renal insufficiency and failure.

The first stage of the development of nephropathy is the presence of microalbuminuria. Microalbuminuria in type 2 diabetes mellitus is associated with increased risk of death and cardiovascular mortality.[22,23,24,25] Overt proteinuria and hypertension are associated with an even higher risk of cardiovascular events. Strategies for preventing the progression of renal failure in patients with diabetes mellitus include glycemic control and blood pressure control. Angiotensin-converting enzyme (ACE) inhibitors have been clearly shown to prevent early death in diabetic patients. Telmisartan (Micardis) and ramipril were similar in reducing 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.[26]

The 2010 American Diabetes Association (ADA),), the 2010 American Stroke Association, and the JNC-7 guidelines suggest that all patients with diabetes should receive ACE inhibitors or ARBs for the treatment of hypertension, to reduce the risk of stroke, and to delay the progression of diabetic nephropathy.[27,28,29] In patients with type 1 diabetes, hypertension, and any degree of albuminuria, ACE inhibitors have been shown to delay the progression of nephropathy. In patients with type 2 diabetes, hypertension, and microalbuminuria, both ACE inhibitors and ARBs have been shown to delay the progression to macroalbuminuria. In patients with type 2 diabetes, hypertension, macroalbuminuria, and renal insufficiency (serum creatinine > 1.5 mg/dL), ARBs have been shown to delay the progression of nephropathy. 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.

Pharmacology[30,31,32]

ACE inhibitors do not completely block the renin-angiotensin-aldosterone (RAA) system. 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 AT_1 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).

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. Consequently, there are increases in plasma renin activity and aldosterone secretion. Concurrent administration of an angiotensin II receptor antagonist and a thiazide diuretic may help to decrease potassium loss that occurs with thiazide diuretic therapy.[33]

Pharmacokinetics

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
candesartan (Atacand)[34]	Yes*	3-4	15	--	No effect	9	Yes ***	No
eprosartan (Teveten)[35]	No	1-2	13	--	<25%	20	Yes ***	Yes ***
irbesartan (Avapro)[36]	No	1.5-2	60-80	No effect	No effect	11-15	No	No
losartan (Cozaar)[37]	Yes**	1 / 3-4**	33	Decreased	↓ 10%	2 / 6-9**	No	Yes
olmesartan (Benicar)[38]	Yes	1-2	26	No effect	No effect	13	Yes ***	Yes ***
telmisartan (Micardis)[39]	No	0.5-1	42-58 dose dependent	--	↓ 6-20%	24	No	Yes
valsartan (Diovan)[40]	No	2-4	25	↓ 50%	↓ 40%	6	No	No
HCTZ[41]	No	1-5	65-75	↓ 20%	--	5-18	Yes	No

* candesartan cilexetil - active metabolite is candesartan

** losartan - active metabolite is EXP3174

*** dosage adjustments are not necessary

Contraindications/Warnings[42]

Hypersensitivity to any ARB is a contraindication. The HCTZ component in the combination agents is contraindicated in patients with anuria or a sulfa allergy.

ARBs should be used with caution in patients that are volume and salt depleted, have hyperkalemia, or have unilateral and bilateral renal artery stenosis.

Thiazide diuretics may also cause exacerbation or activation of systemic lupus erythematosus. The potential exists for electrolyte (e.g., hypercalcemia, hypochloremic alkalosis, hypokalemia, hypomagnesemia, hyponatremia, and hyperuricemia) or fluid imbalances; monitoring is recommended.

The FDA is evaluating data from two clinical trials in which patients with type 2 diabetes taking olmesartan (Benicar) had a higher rate of death from a cardiovascular cause compared to placebo.[43] 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 cardiovascular cause (MI, sudden death, or stroke) in the olmesartan-treated patients compared to placebo. The FDA's review is ongoing. It has not been concluded that olmesartan increases the risk of death. The FDA reminds practitioners that numerous clinical trials with olmesartan as well as trials with other ARBs have not suggested an increased risk of cardiovascular-related death. The FDA plans to review the primary data from the two trials as well as the total clinical-trial data on olmesartan. Currently, the FDA still believes that the benefits of olmesartan in patients with hypertension continue to outweigh the potential risks.

According to a July 2010 communication, the FDA is conducting a review of ARBs after a recently published study suggested that ARBs may be associated with a small increased risk of cancer.[44] The meta-analysis included data from over 60,000 patients in several long-term, randomized, controlled clinical trials evaluating ARBs for which adverse events related to cancer were captured during the study. These clinical trials were not designed to study the effects of ARBs on cancer risk. The mean duration of follow-up ranged from 1.7 to 4.8 years. New cancer occurrence was reported to be 7.2 percent for patients receiving ARBs compared to 6 percent for those not receiving ARBs (RR=1.08, 95% CI, 1.01-1.15). No statistically significant difference in cancer deaths was noted. The FDA has not concluded that ARBs increase the risk of cancer and will update the public when additional information is available. At this time, the FDA believes the benefits of ARBs continue to outweigh their potential risks.

Another meta-analysis assessed the association between antihypertensive drugs and cancer risk.[45] 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 (2·3%, 1·14, 95% CI, 1.02-1.28); however, this risk was not apparent in the random-effects model (odds ratio 1·15, 95% CI, 0.92-1.38).

Drug Interactions[46]

Significant drug interactions have not been reported with the ARBs. They can interact with potassium-sparing diuretics and potassium supplements. Candesartan (Atacand) and losartan (Cozaar) can increase lithium concentrations. Telmisartan (Micardis) can increase digoxin levels.

Diuretic agents 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 agent can reduce the diuretic, natriuretic, and antihypertensive effects of HCTZ. Cholestyramine and colestipol resins bind HCTZ and reduce its absorption from the gastrointestinal tract. Dosage adjustment of the antidiabetic drug may be required if given with HCTZ. Administration of carbamazepine and HCTZ may lead to symptomatic hyponatremia.[47]

Adverse Effects

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 ACE inhibitors, do not appear to occur as frequently with the ARBs. Angioedema has been reported with all ARBs, and the risk appears to be lower than with ACEIs.[48]

Drug	Dizziness	Edema	Back Pain	URI	Discontinuation Rate
candesartan (Atacand)[49] n=3,260 (n=1,106)	4	< 1	3 (2)	6 (4)	3.3 (3.5)
eprosartan (Teveten)[50]	≥ 1	< 1	< 1	8 (5)	4 (6.5)
irbesartan (Avapro)[51]	≥ 1	≥ 1	nr	nr	3.3 (4.5)
losartan (Cozaar)[52] n=1,075 (n=334)	3 (2)	≥ 1	2 (1)	8 (7)	2.3 (3.7)
olmesartan (Benicar)[53]	3 (1)	reported	> 1	nr	2.4 (2.7)
telmisartan (Micardis)[54] n=1,455 (n=380)	1	> 0.3	3 (1)	7 (6)	nr
valsartan (Diovan)[55] n=2,316 (n=888)	> 1	> 1	> 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

Special Populations

Pediatrics

Losartan (Cozaar), Olmesartan (Benicar), and valsartan (Diovan) are indicated for the treatment of hypertension in children ages six to 16 years. Candesartan (Atacand) is indicated for the treatment of hypertension in children ages one to less than 17 years of age. Candesartan use in pediatric patients with a glomerular filtration rate less than 30 mL/min/1.73 m^2 have not been studied. Also candesartan doses above 0.4 mg/kg or 32 mg have not been studied in this

population. Safety and effectiveness in the pediatric population have not been established for the other ARBs.

Safety and efficacy of HCTZ have not been established in children.

losartan (Cozaar) in pediatrics

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.[56] 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 systolic blood pressure (SBP), diastolic blood pressure (DBP), and mean arterial blood pressure (MABP) by 9 to 12 mm Hg at the three-month follow-up visit (all $p<0.01$). DBP and MABP remained significantly lower at all visits over one year ($p<0.005$ to 0.0014). By the last visit after one 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 three to twelve months with reductions of 66 to 71 percent (all $p<0.01$). The mean glomerular filtration rate (GFR) reduction the year prior to losartan was 9.3 mL/min/1.73 m^2 whereas the mean GFR on losartan saw a reduction of 1.4 mL/min/1.73 m^2 (p=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.

In a double-blind, dose-response study, 175 hypertensive children were stratified by weight and randomized to losartan 2.5 to 5 mg (low dose group), 25 to 50 mg (middle) or 50 to 100 mg (high dose group) for three weeks.[57] Children were ages six 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 two-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.

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 ≥0.3 g/g) in 306 children up to 17 years of age.[58] After 12 weeks of treatment with losartan, proteinuria was significantly reduced compared with amlodipine/placebo (-35.8 percent [95% CI, -27.6 percent to -43.1 percent] versus 1.4 percent [95% CI, -10.3 percent to 14.5 percent], $p \leq 0.001$). 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 percent losartan; 2.6 percent placebo) and hypertensive (-41.5 percent losartan; 2.4 percent amlodipine) strata, and in all prespecified subgroups, including age, gender, race, Tanner stage, weight, prior therapy with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, as well as among the most common etiologies of proteinuria. Adverse event incidence was low and comparable in all groups.

valsartan (Diovan) in pediatrics

A study enrolled 261 hypertensive pediatric patients' ages six to 16 years. Patients who weighed < 35 kg received 10, 40 or 80 mg of valsartan daily (low, medium and high doses), and

patients who weighed ≥ 35 kg received 20, 80, and 160 mg of valsartan daily (low, medium and high doses).[59] 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 two weeks, valsartan reduced both SBP and DBP in a dose-dependent manner. Overall, the three 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 one to five years (mean age of 3.2 years). The study population was 60 percent male, and 30 percent were Black.[60] Patients were randomly assigned to low-, medium-, or high-dose valsartan for two weeks (phase 1) and then randomly reassigned to placebo or remained on the same valsartan dose for two 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 percent 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 three 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 percent and 5.6 percent, respectively) and open-label (14.8 percent and 6.8 percent, respectively) portions of the study. This was the first trial of an antihypertensive agent conducted in children less than six years of age.

candesartan (Atacand) in pediatrics

Two randomized, double-blind multicenter, four-week dose ranging studies were conducted to evaluate the effects of candesartan in pediatric patients.61 In the first study, 193 patients one to less than six years of age, 74 percent of whom had renal disease, were randomized to receive an oral candesartan 0.05, 0.20 or 0.40 mg/kg once daily. The primary analysis was slope of the change in systolic blood pressure (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 diastolic blood pressure (DBP) decreased 6.0/5.2 to 12.0/11.1 mm Hg from baseline across the three doses of candesartan.

In the second study children six 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, 16 or 32 mg once daily. The placebo subtracted effect at trough for sitting systolic blood pressure/sitting diastolic blood pressure for the different doses were from 4.9/3.0 to 7.5/7.2 mm Hg. Those enrolled were 47 percent Black. In children six to < 17 years there was a trend for a lesser blood pressure effect for Blacks compared to other patients. There were too few individuals in the age group of one to less than six years to determine whether Blacks respond differently than other patients to candesartan.

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 six to 16 years.[62] Hypertension was defined as systolic blood pressure measured at or above the 95th percentile [90th 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 two periods, with two cohorts in each period (cohort A, 62 percent white; cohort B, 100 percent black). 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≥ 35 kg were randomized to 5 mg (low -dose) or 40 mg (high-dose) olmesartan daily for three weeks. In period 2, patients maintained their olmesartan dose or were switched to placebo for an additional two weeks. Mean changes in seated trough systolic and diastolic blood pressure from the study baseline to the end of period 1 were -7.8/-5.5 mm Hg and -12.6/-9.5 mm Hg for low and high olmesartan doses, respectively, in cohort A, and -4.7/-3.5 mm Hg and -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 analyzes by linear regression, a statistically significant olmesartan dose response was observed for seated trough systolic and diastolic blood pressure 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 systolic and diastolic). When adjusted for baseline body weight, a statically significant olmesartan dose response was observed in cohort A (p<0.0001 for systolic and diastolic blood pressure), cohort B (p=0.0265 and p=0.0084, respectively), and cohorts A+B (p<0.0001 for systolic and diastolic blood pressure). 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 systolic blood pressure 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.

Pregnancy

Valsartan (Diovan, Diovan HCT) is Pregnancy Category D. All other ARBs and their HCTZ combinations are Pregnancy Category C for the first trimester and Category D for the second and third trimesters. Drugs that act directly on the RAA system can cause injury and even death to the developing fetus; therefore, these agents should be discontinued as soon as possible once pregnancy is detected.

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 Black population.[63,64]

Renal Impairment

Thiazides should be used with caution in severe renal disease as they may precipitate azotemia. Cumulative effects of the drug may develop in patients with impaired renal function.

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

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
candesartan (Atacand)[65]	16 mg once daily; Pediatrics: 1 to <6 yrs: 0.2 mg/kg once daily; 6 to <17 yrs - <50 kg weight – 4 to 8 mg once daily; >50 kg weight: 8 to 16 mg once daily[f]	8 - 32 mg; Pediatrics: 1 to < 6 yrs: 0.05-0.4 mg/kg daily; 6 to <17 yrs: < 50 kg weight: 4 to 16 mg daily; > 50 kg weight: 4 to 32 mg daily May give doses divided once or twice daily	--	--	4 - 32 mg once daily	--	no dosage recommendation[a]	4, 8, 16, 32 mg tablets
eprosartan (Teveten)[66]	600 mg once daily	400 - 800 mg/day; divided doses once or twice daily	--	--	--	--	no dosage recommendation[b]	400, 600 mg tablets
irbesartan (Avapro)[67]	150 mg once daily	75 - 300 mg once daily	300 mg once daily	--	--	--	75 mg once daily	75, 150, 300 mg tablets
losartan (Cozaar)[68]	50 mg once daily Pediatrics (6-16 yrs): 0.7 mg/kg/day (or 50 mg daily)	25 - 100 mg/day; divided doses once or twice daily Pediatrics (6-16 yrs): 0.7 mg/kg/day (or 50 mg daily) to max of 1.4 mg/kg/day or 100 mg daily	50 - 100 mg once daily	Reduction of stroke risk with HTN and LVH: 50 - 100 mg daily	--	--	25 mg once daily	25, 50, 100 mg tablets
olmesartan (Benicar)[69]	20 mg once daily Pediatrics (6-16 yrs): <35 kg 10 mg once daily; ≥ 35 kg 20 mg once daily[f]	20 - 40 mg once daily Pediatrics (6-16 yrs): <35 kg 10-20 mg once daily; ≥ 35 kg 20-40 mg once daily[f]	--	--	--	--	no dosage recommendation[c]	5, 20, 40 mg tablets
telmisartan (Micardis)[70]	40 mg once daily	20 - 80 mg once daily	--	CV risk reduction: 80 mg once daily	--	--	no dosage recommendation[d]	20, 40, 80 mg tablets
valsartan (Diovan)[71]	80 mg – 160 mg once daily	80 - 320 mg once daily Pediatrics (6-16 yrs): 1.3 - 2.7 mg/kg once daily (40 – 160 mg)	--	--	40 - 160 mg twice daily	20 mg twice daily to 160 mg twice daily	no dosage recommendation[e]	40, 80, 160, 320 mg tablets

[a] Manufacturer recommends correcting condition prior to initiating treatment with candesartan, or therapy be initiated under close medical supervision with consideration given to administration of a lower dose of candesartan.
[b] Manufacturer recommends correcting condition prior to initiating treatment with eprosartan, or initiating therapy under close medical supervision.
[c] Manufacturer recommends therapy be initiated under close medical supervision with consideration given to administration of a lower starting dose of olmesartan.
[d] Manufacturer recommends correcting condition prior to initiating treatment with telmisartan, or initiating therapy under close supervision.
[e] Manufacturer recommends correcting condition prior to initiating treatment with valsartan or initiating therapy under close medical supervision.
[f] Pediatric suspension may be compounded for pediatric patients.

Dosages (continued)

Drug	Initial hypertension dosage when starting combination therapy	Hypertension dosage range	Availability
candesartan/HCTZ (Atacand HCT)[72]	16/12.5 mg once daily	16/12.5 mg to 32/25 mg per day	16/12.5, 32/12.5, 32/25 mg tablets
eprosartan/HCTZ (Teveten HCT)[73]	600/12.5 mg once daily	600/12.5 mg to 600/25 mg once daily; may add eprosartan 300 mg in the evening for maximal control	600/12.5, 600/25 mg tablets
irbesartan/HCTZ (Avalide)[74]	150/12.5 mg once daily	150/12.5 mg to 300/25 mg once daily	150/12.5, 300/12.5, 300/25 mg tablets
losartan/HCTZ (Hyzaar)[75]	50/12.5 mg once daily	50/12.5 mg once or twice daily or 100/25 mg once daily	50/12.5, 100/12.5, 100/25 mg tablets
olmesartan/HCTZ (Benicar HCT)[76]	20/12.5 mg once daily	20/12.5 mg to 40/25 mg once daily	20/12.5, 40/12.5, 40/25 mg tablets
telmisartan/HCTZ (Micardis HCT)[77]	40/12.5 mg once daily	40/12.5 mg to 160/25 mg once daily	40/12.5, 80/12.5, 80/25 mg tablets
valsartan/HCTZ (Diovan HCT)[78]	160/12.5 mg once daily	80/12.5 mg to 320/25 mg once daily	80/12.5, 160/12.5 160/25, 320/12.5, 320/25 mg tablets

Maximal clinical effects of combination therapy are seen two to four 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 percent of participants entering the investigation. Despite some inherent bias found in all studies including those sponsored and/or funded by pharmaceutical manufacturers, the studies in this therapeutic class review were determined to have results or conclusions that do not suggest systematic error in their experimental study design. While the potential influence of manufacturer sponsorship/funding must be considered, the studies in this review have also been evaluated for validity and importance.

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

candesartan (Atacand) and 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.[79] A placebo run-in period was completed for the first four weeks of the study. If the patients' sitting 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 eight 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 more than 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 to 32 mg daily) and losartan (50 to 100 mg daily) were compared in 332 patients.[80] In an eight-week, randomized, double-blind, parallel group study, patients had a mean trough DBP of 90 mm Hg or greater following at least four 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 percent 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 percent for candesartan versus 6.5 percent for losartan).

Another US-based, double-blind, randomized, forced-titration study compared candesartan and losartan in 611 patients with essential hypertension.[81] 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 two weeks, doses were doubled. Candesartan reduced blood pressure (BP) at trough (24 hours post dosing), six 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 two treatments (58.8 percent for candesartan and 52.1 percent for losartan). Adverse events were similar between the groups.

A similarly designed study also evaluated candesartan and losartan in 654 hypertensive patients.[82] 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 percent 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 six weeks in 256 patients with mild to moderate hypertension.[83] 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 h after dosing (p<0.001). Candesartan and losartan were well tolerated.

eprosartan (Teveten) and 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, four-week study.[84] 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 percent of eprosartan-treated patients and 53 percent of losartan-treated patients.

irbesartan (Avapro) and losartan (Cozaar)

Following a placebo lead-in phase, a total of 567 patients were randomized in a double-blind manner to one of four once daily dosing treatment arms: placebo, losartan 100 mg, irbesartan 150 mg, or irbesartan 300 mg.[85] The duration of the study was eight weeks, and baseline characteristics and demographics were comparable for the four 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.[86] After a three-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 four, 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 eight, 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 eight 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 percent versus 64 percent, respectively). Both regimens were well tolerated.

olmesartan (Benicar) versus losartan (Cozaar), valsartan (Diovan), and 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.[87] The majority of patients were male with a mean baseline BP of 157/104 mm Hg. After eight 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).[88] More patients achieved BP less than 140 /80 mm Hg by ABPM in the olmesartan group (52.9 percent) versus losartan (40.3 percent; p=0.038), valsartan (35.4 percent; p=0.004), and irbesartan (47 percent; p=NS).

telmisartan (Micardis) and losartan (Cozaar)

In a randomized, double-blind, placebo-controlled, six-week trial, telmisartan 40 and 80 mg were compared to losartan 50 mg for efficacy and safety.[89] Following a four week placebo run-in phase, 223 patients with mild to moderate hypertension were randomized to one of the four groups. Ambulatory blood pressure monitoring was performed for 24 hours. All groups had significantly lower blood pressure compared to placebo. Telmisartan 40 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) and valsartan (Diovan)

In a double-blind, randomized trial, telmisartan and valsartan were compared in 490 patients with hypertension.[90] Following a two-week washout period, patients were randomized to telmisartan 40 to 80 mg daily or valsartan 80 to 160 mg daily with forced titration over eight weeks. Early morning blood pressure was evaluated to determine the blood pressure reduction effects of each product during the last six hours of the dosing interval. Ambulatory blood pressure readings for the last six 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 two groups.

Similar findings were observed in two identically designed randomized, double-blind, forced-titration studies with 887 hypertensive patients.[91] Telmisartan 40 to 80 mg daily and valsartan 80 to 160 mg daily were given for a total of eight weeks. After four weeks on the higher dose, a dose of placebo was administered or active therapy. In another two 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 six 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) and losartan (Cozaar)

Comparison of the antihypertensive efficacy of valsartan and Iosartan 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.[92] A secondary objective of

the study was to compare the safety and tolerability of the two drugs. Initially, patients were randomized to receive valsartan 80 mg daily (n=551), losartan 50 mg daily (n=545), or placebo (n=273) for four weeks. The need for titration to higher doses of the medications was assessed at the end of the four weeks. Of the patients receiving valsartan, nearly 96 percent required an upward dosage titration to 160 mg, and 95.5 percent 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 and 160 mg daily were as effective as losartan 50 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.[93] Patients were randomized in a double-blind fashion to losartan 50 mg daily or valsartan 80 mg daily for six weeks. After six 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 percent for losartan and 59 percent for valsartan. Both therapies were well tolerated.

angiotensin II receptor blockers and the addition of hydrochlorothiazide

The addition of hydrochlorothiazide (HCTZ) to an ARB has been shown to potentiate its antihypertensive effect as compared to the ARB alone.[94,95,96,97,98,99,100,101,102,103,104,105,106,107,108,109,110,111,112,113]

DIABETIC NEPHROPATHY

candesartan (Atacand) in diabetic nephropathy

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.[114] 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 two overnight collections. If urinary albumin excretion rate was 20 mcg/min or greater, then two further urine collections were done. The primary end point was new microalbuminuria (three or four collections of urinary albumin excretion rate ≥20 mcg/min). The secondary end point was rate of change in albuminuria. Individual and pooled results of the three trials showed that candesartan had little effect on risk for microalbuminuria (pooled hazard ratio, 0.95 [95% CI, 0.78 to 1.16]; p=0.60). Pooled results showed that the annual rate of change in albuminuria was 5.53 percent lower (95% CI, 0.73% to 10.14%; p=0.024) with candesartan than with placebo.

irbesartan (Avapro) in diabetic nephropathy

Two large irbesartan trials in diabetic nephropathy are IDNT (versus amlodipine and placebo over 2.6 years) and IRMA-2 (versus placebo over two 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.[115] 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 percent lower risk versus placebo (p=0.02) and 23 percent 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 two groups (both p=0.07). Death was not statistically different among the groups. An evaluation of the cardiovascular outcomes was also performed on the study population.[116] Overall, the three groups were similar for the composite outcome of cardiovascular 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.[117] 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 percent higher than baseline on two consecutive occasions. All three groups were comparable at baseline. Over the two-year period, diabetic nephropathy was identified in 5.2 percent of the irbesartan 300 mg patients (p<0.001 versus placebo), 9.7 percent of the irbesartan 150 mg group (p=0.081 versus placebo), and 14.9 percent 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 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 percent reduction versus 24 percent reduction with 150 mg, two percent 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 was evaluated for kidney function following the withdrawal of treatment with irbesartan.[118] 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 eight percent (p=NS versus baseline), 34 percent, and 60 percent, 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 percent in the placebo group, 11 percent in the irbesartan 150 mg group, and was persistently reduced in the irbesartan 300 mg group (-47 percent, 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.[119] The

reduction in urinary albumin excretion at the end of the study was zero percent (-86 to 42), 38 percent (-14 to 66), and 73 percent (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 one and two years. Irbesartan significantly decreased high-sensitivity C-reactive protein (hs-CRP) with a 5.4 percent decrease/year versus 10 percent 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 percent increase/year with irbesartan versus 6.5 percent 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.[120]

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.[121] Normotensive patients had reduced urinary excretion of albumin.

losartan (Cozaar) in diabetic nephropathy

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.[122] 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 percent risk reduction, p=0.006) and progression to end-stage renal disease (28 percent risk reduction, p=0.002). The incidence of death was similar in both groups. Losartan provides a 16 percent 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 percent (p=0.05) compared with those patients with baseline SBP below 130 mm Hg.[123]

A study with losartan demonstrated a significant reduction of 25 percent in the albumin excretion rate after five weeks of losartan therapy in 147 normotensive type 2 diabetic patients with microalbuminuria.[124] The trial was a multicenter, randomized, double-blind, placebo-controlled trial. Patients were randomized to losartan 50 mg or placebo daily for the first five weeks, then losartan was increased to 100 mg daily. Losartan was associated with a 25 percent relative reduction in urinary albumin excretion after five weeks of 50 mg and 34 percent 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.[125] Diabetic patients were randomized to losartan 50 mg daily or placebo for six 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 five years.[126] Patients were randomly assigned to receive losartan 100 mg per day, enalapril 20 mg per day, or placebo. The primary end point was a change in the fraction of glomerular volume occupied by mesangium in kidney-biopsy specimens. The retinopathy end point was a progression on a retinopathy severity scale of two steps or more. A total of 90 and 82 percent of patients had complete renal-biopsy and retinopathy data, respectively. Change in mesangial fractional volume per glomerulus over the five-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 five-year cumulative incidence of microalbuminuria was six percent in the placebo group, 17 percent (p=0.01 by the log-rank test) in the losartan group and four percent (p=0.96 by the log-rank test) in the enalapril group. The odds of retinopathy progression by two steps or more was reduced by 65 percent in the enalapril group (odds ratio, 0.35; 95% CI, 0.14 to 0.85) and by 70 percent in the losartan group (odds ratio, 0.30; 95% CI, 0.12 to 0.73) when compared to placebo, independently of changes in blood pressure.

telmisartan (Micardis) and ramipril

A pre-specified analysis of renal outcomes of the ONTARGET study, a 56-month, randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes showed that a composite primary renal end point of dialysis, doubling of serum creatinine, and death was similar for telmisartan 80 mg versus ramipril 10 mg, 13.4 percent versus 13.5, respectively (HR 1.00, 95% CI, 0.92 to 1.09) but was increased with combination therapy 14.5 percent (HR 1.09, 95% CI, 1.01 to 1.18, p=0.037).[127] 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^2 versus −4·12 [SD 17·4], p<0·0001) or combination therapy (−6·11 [SD 17·9], p<0·0001). Compared with ramipril, the increase in urinary albumin excretion was less with telmisartan (p=0.004) or with combination therapy (p=0.001). In the study of patients with high vascular risk, telmisartan was similar to ramipril in reducing renal outcomes. Combination therapy worsened renal outcomes and was associated with increased adverse events.

CONGESTIVE HEART FAILURE

candesartan (Atacand)

The CHARM trials evaluated the use of candesartan in patients with chronic heart failure.[128] In the randomized, double-blind, controlled set of clinical trials, candesartan and placebo were compared for effects on cardiovascular 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 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 three-year follow-up period [23 versus 25 percent, respectively, unadjusted hazard ratio 0.91 (95% CI, 0.83-1.00), p=0.055; covariate adjusted 0.90 (0.82-0.99), p=0.032].[129] Cardiovascular death or hospitalization related to CHF were significantly less in the overall candesartan group. In those patients with preserved left ventricular function (ejection fraction greater than 40 percent), candesartan reduced hospitalizations due to CHF [22 versus 24 percent over three years, respectively; unadjusted hazard ratio 0.89; (95% CI, 0.77-1.03), p=0.118; covariate adjusted 0.86, (95% CI, 0.74-1.0), p=0.051].[130] In patients who did not

tolerate ACE inhibitors due to cough, renal dysfunction, or hypotension, candesartan or placebo were compared.[131] Lower rate of cardiovascular death and hospitalization related to CHF were reported with candesartan [33 versus 40 percent, unadjusted hazard ratio 0.77; (95% CI, 0.67-0.89); p=0.0004; covariate adjusted hazard ratio 0.70; (95% CI, 0.60-.81); p<0.0001]. For the ACE-intolerant population, the discontinuation rate was similar between candesartan (30 percent) and placebo (29 percent). The CHARM-Added trial evaluated the addition of candesartan to ACE inhibitors, beta-blockers, and other CHF treatments.[132] For those patients on candesartan after a median of 41 months, lower cardiovascular death and hospitalization for CHF were reported [38 versus 42 percent; unadjusted hazard ratio 0.85; (95% CI, 0.75 – 0.96); p=0.011; covariate adjusted, p=0.010]. Functional NYHA classifications were improved with the use of candesartan.[133] Overall, discontinuations due to adverse effects were more common in the candesartan group.

valsartan (Diovan)

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.[134] 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 percent lower incidence of all-cause morbidity and mortality (p=0.009) and a 27.5 percent 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.

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 cardiovascular events including death, MI, or stroke over at least four years in the LIFE study.[135] 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 cardiovascular endpoints by 13 percent (p=0.021). Cardiovascular deaths did not differ between the groups. Fatal and non-fatal stroke risk reduction was 25 percent 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.[136] Both drugs significantly reduced blood pressure to a similar degree with 85 percent of the losartan group and 82 percent of the atenolol group in the diabetic population achieving a DBP less than 90 mm Hg. Losartan reduced the combined risk of cardiovascular death, MI, or stroke by 24 percent compared to atenolol (p=0.031). Losartan also reduced the risk of death from cardiovascular causes by 37 percent compared to atenolol; however, no significant differences in the risk of MI or stroke were found between the two groups. Patients with isolated systolic hypertension (n=1,326) also were observed to have a 25 percent risk reduction in the composite endpoint of cardiovascular death, MI, and stroke with losartan over atenolol despite both drugs reducing blood pressure to a similar degree.[137] Regression of LVH with losartan was greater

than that observed with atenolol starting with six months after initiation of therapy.[138] 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].[139] A post-hoc analysis of the LIFE study evaluated the effects of losartan in women.[140] Women in the losartan group had significant reductions in the primary composite end point [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 0.90); 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: 1.70 (95% CI, 1.16 to 2.51); p=0.007]. Risk reductions for the primary composite end point, 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

ONTARGET was a randomized, double-blind, multicenter study of 25,620 patients with controlled hypertension with vascular disease or high-risk diabetes.[141] After a three week single-blind run-in period, patients were randomized to ramipril 10 mg daily, telmisartan 80 mg daily, or a combination of ramipril 10 mg and telmisartan 80 mg daily. The primary composite endpoint of the 56-month study was death from CV causes, MI, stroke, or hospitalization for HF. The primary outcome occurred in 1,412 patients versus 1,423 patients (16.5 percent versus 16.7 percent, RR, 1.01, 95% CI, 0.94 to 1.09), in the ramipril versus telmisartan groups, respectively. Telmisartan group had lower rates of cough (1.1 percent versus 4.2 percent, p<0.001) and angioedema (0.1 percent versus 0.3 percent, p=0.01), and a higher rate of hypotensive symptoms (2.6 percent versus 1.7 percent, p<0.001) compared to ramipril. The rate of syncope was the same in both groups (0.2 percent). In the combination group, the primary outcome occurred in 1,386 patients (16.3 percent, RR 0.99, 95% CI, 0.92 to 1.07), and there was an increased risk of hypotensive symptoms (4.8 percent versus 1.7 percent, p<0.001), syncope (0.3 percent versus 0.2 percent, p=0.03), and renal dysfunction (13.5 percent versus 10.2 percent, p<0.001) compared to the ramipril group. Telmisartan was equivalent to ramipril in patients with vascular disease or high-risk diabetes and was associated with less adverse events. The combination of the two drugs was associated with more adverse events without an increase in benefit.

telmisartan (Micardis)

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.[142] 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 percent in the telmisartan group, as compared with 9.2 percent 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 percent in the telmisartan group as compared with 14.4 percent 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 percent versus 2.1 percent, HR 0.82, 95% CI, 0.65 to 1.04, p=0.10, telmisartan versus placebo, respectively).

POST MYOCARDIAL INFARCTION

valsartan (Diovan)

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.[143] 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 three times daily titrated up to 50 mg three 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 three times daily titrated up to 50 mg three times daily). The median follow up was 24.7 months. Death from any cause was similar among the three groups. The secondary endpoints of cardiovascular death, recurrent MI, or hospitalization for heart failure were also similar among the three 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.[144] Ten trials with 1,792 patients reported reduction in clinic BP; six trials with 1,163 patients reported ambulatory BP reduction; seven trials with 1,675 patients reported therapeutic response of BP. Telmisartan resulted in a significant reduction in clinic DBP (weighted mean difference 1.52 mmHg, 95% CI, 0.85 to 2.19) and SBP (2.77, 1.90 to 3.63) compared with losartan. There was also a significant reduction in 24-hour mean ambulatory DBP (2.49, 0.56 to 4.42) and SBP (2.47, 0.40 to 4.55) with telmisartan compared to losartan. There was also a significant increase in therapeutic response of DBP (relative risk (RR) 1.14, 1.04 to 1.23) and SBP response (1.10, 1.01 to 1.20) with telmisartan compared to losartan. Both treatments were well tolerated.

A meta-analysis of nine trials evaluated the safety and tolerability of combination ACEI and ARB versus ACEI in patients with HF or LVD.[145] A total of 9,199 patients received combination therapy, and 8,961 patients received an ACEI only. Patients receiving combination therapy had an increased risk of developing any adverse effect by 2.3 percent (RR 1.27, 95% CI, 1.15 to 1.40, $p<0.00001$, inter-study heterogeneity or I^2 15.9 percent, number needed to harm [NNH]=42), hypotension by 1.1 percent (RR 1.91, 95% CI, 1.37 to 2.66, $p=0.0002$, I^2 26.6 percent, NNH=89), worsening renal function by one percent (RR 2.12, 95% CI, 1.30 to 3.46, $p=0.003$, I^2 67.3 percent, NNH=100), and hyperkalemia by 0.6 percent (RR 4.17, 95% CI, 2.31 to 7.53, $p<0.00001$, I^2 0 percent, NNH=149). There was no difference in angioedema (RR 0.88, 95% CI, 0.43 to 1.80, $p=0.72$, I^2 0 percent) or cough (RR 0.84, 95% CI, 0.65 to 1.09, $p=0.19$, I^2 = 0 percent). This meta-analysis found the combination of ACEI and ARB combination therapy to be associated with increased adverse events in patients with LVD compared to ACEI therapy.

A meta-analysis of six randomized comparative trials including 49,924 patients showed no significant differences between ARB and ACEI on the risk of MI (OR 1.01, 95% CI, 0.95 to 1.07, $p=0.75$), CV mortality (OR 1.0, 95% CI, 0.98 to 1.08, $p=0.23$), and total mortality (OR 1.03, 95% CI, 0.97 to 1.10, $p=0.20$).[146] Overall, the risk of stroke was slightly lower with ARBs than ACEI (OR 0.92, 95% CI, 0.85 to 0.99; $p=0.037$), the direct ACEIs and ARBs comparison showing a non-significant trend in a similar direction. Statistical heterogeneity among trials was not

significant, with a low to null inconsistency statistic, for stroke (p=0.67), MI (p=0.86), CV mortality (p=0.14), and total mortality (p=0.12).

Comparative Efficacy

Drug	Dose	SBP reduction (mm Hg)	DBP reduction (mm Hg)
candesartan (Atacand)[147]	8 - 32 mg daily	8 – 12	4 - 8
candesartan/ HCTZ (Atacand HCT)[148]	16/12.5 - 32/25 mg daily	14 - 19	8 - 11
eprosartan (Teveten)[149]	200 - 400 mg twice daily	7 – 10	4 - 6
eprosartan/HCTZ (Teveten HCT)[150]	600/12.5 mg daily	10	5
irbesartan (Avapro)[151]	150 - 300 mg daily	8 – 12	5 - 8
irbesartan/HCTZ (Avalide)[152]	150/12.5 - 300/25 mg daily	13 - 21	7 - 12
losartan (Cozaar)[153]	50 - 150 mg daily	5.5 – 10.5	3.5 - 7.5
losartan/HCTZ (Hyzaar)[154]	50/12.5 - 100/25 mg daily	9 - 15.5	5.5 - 9
olmesartan (Benicar)[155]	20 - 40 mg daily	12-13	5 - 7
olmesartan/HCTZ (Benicar HCT)[156]	20/12.5 - 40/25 mg daily	17 - 24	8 - 14
telmisartan (Micardis)[157]	40 - 160 mg daily	9 - 13	6 - 8
telmisartan/HCTZ (Micardis HCT)[158]	40/12.5 - 80/12.5 mg daily	16 - 21	9 - 11
valsartan (Diovan)[159]	80 - 320 mg daily	6 - 9	3 - 6
valsartan/HCTZ (Diovan HCT)[160]	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 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). 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.

ACE inhibitors remain the treatment of choice for heart failure. Valsartan (Diovan) has been approved for use in heart failure and for use in the post-MI patient with left ventricular dysfunction, heart failure, or both. Candesartan (Atacand) is approved for heart failure patients to reduce the risk of cardiovascular death and to reduce hospitalizations related to heart failure.

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