REVIEW

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Angiotensin-receptor blockers: Benefits beyond lowering blood pressure

ABSTRACT

A number of controlled clinical trials provide evidence that angiotensin-receptor blockers improve the prognosis in a variety of conditions that place patients at high cardiovascular risk. The effect is more than one would expect from the effect of these agents on blood pressure alone. The results of some of these trials have expanded the indications for these drugs.

KEY POINTS

Losartan is now indicated for reducing the risk of stroke in patients with hypertension and left ventricular hypertrophy.

Irbesartan and losartan are indicated for treating diabetic nephropathy in patients with type 2 diabetes and hypertension.

Valsartan is indicated for treating heart failure (New York Heart Association class II–IV) in patients who cannot tolerate ACE inhibitors.

ALTHOUGH many studies have confirmed that angiotensin-receptor blockers (ARBs) lower blood pressure effectively, blood pressure reduction is only a surrogate end point. In recent years, clinical outcome trials have confirmed the value of these agents in protecting target organs, ie, the heart, brain, and kidneys.

This article focuses on the use of ARBs in the treatment of hypertension and reviews emerging evidence from clinical trials that ARBs offer target-organ protection.

THE ANGIOTENSIN-RECEPTOR BLOCKERS

Evidence that the renin-angiotensin-aldosterone system plays a role in initiating and maintaining hypertension prompted the development of drugs that block this system, ie, the angiotensin-converting enzyme (ACE) inhibitors and the ARBs.

Seven ARBs are available in the United States for treating hypertension:

- Candesartan (Atacand)[1]
- Eprosartan (Teveten)[2]
- Irbesartan (Avapro)[3]
- Losartan (Cozaar)[4]
- Olmesartan (Benicar)[5]
- Telmisartan (Micardis)[6]
- Valsartan (Diovan).[7]

In addition, in view of clinical trial results, (reviewed below), losartan is now indicated for reducing the risk of stroke in patients with hypertension and left ventricular hypertrophy; irbesartan and losartan are indicated for treating diabetic nephropathy in patients with type 2 diabetes and hypertension; and valsartan is indicated for treating heart failure (New York Heart Association

TABLE 1

Pharmacokinetic profiles of the angiotensin-receptor blockers

DRUG	BRAND NAME	DOSING RANGE*	BIOAVAILABILITY	HALF-LIFE (HOURS)
Candesartan	Atacand	4–32 mg	15%	9 (active metabolite)
Eprosartan	Teveten	400–800 mg	13%	5–9
Irbesartan	Avapro	75–300 mg	60%–80%	11–15
Losartan	Cozaar	25–100 mg	33%	2 (losartan) 6–9 (E 3174; active metabolite)
Olmesartan	Benicar	5–40 mg	26%	13
Telmisartan	Micardis	20–80 mg	42%–58%	24
Valsartan	Diovan	40–320 mg	25%	6

*All are given once daily

[NYHA] class II–IV) in patients who cannot tolerate ACE inhibitors.

All available ARBs are also available in fixed-dose combinations with the thiazide diuretic hydrochlorothiazide.

The ARBs are very well tolerated. The incidence of cough with ARBs is less than with ACE inhibitors.[8] Interestingly, one ARB has been shown to reduce the incidence of headache in patients with mild-to-moderate hypertension.[9]

The ARBs differ in their pharmacokinetic traits (TABLE 1). The duration of action (as based on the drug's half-life) is important to consider when choosing an antihypertensive agent. Long-acting drugs that provide 24-hour coverage are preferred over short-acting agents, for several reasons: patients are more likely to comply with once-daily dosing, therapy may be cheaper with fewer tablets taken per day, and blood pressure is more likely to be brought under control.

Nearly all the adverse effects of angiotensin II are mediated by the AT 1 receptor

MECHANISM OF ACTION

The ARBs act by selectively binding to and blocking the angiotensin II type 1 (AT 1) receptor.

Nearly all the known adverse and toxic responses to angiotensin II are mediated through the AT 1 receptor, including vasoconstriction, aldosterone secretion, sympathetic activation, renal tubular sodium reabsorption, and decreased renal blood flow (TABLE 2).[10] Chronic AT 1 receptor stimulation also contributes independently to certain pathological processes such as vascular smooth muscle cell proliferation, left ventricular hypertrophy, glomerulosclerosis, vascular media hypertrophy, endothelial dysfunction, neointimal formation, atherosclerosis, stroke, and dementia.[10,11]

A second angiotensin II receptor (AT 2) has actions that tend to attenuate or offset those of AT 1 stimulation, with favorable effects on tissue growth and repair. It is involved in the control of cell proliferation, cell differentiation, angiogenesis, wound healing, tissue regeneration, and apoptosis (TABLE 2).

Rationale for ARBs

There are at least three pharmacologic rationales for interrupting the renin-angiotensin system with an ARB.

- Selective AT 1 blockade with an ARB should inhibit the negative cardiovascular consequences of excessive AT 1 receptor activation.
- Circulating angiotensin II (the levels of which undergo a compensatory rise during ARB treatment) will be able to act only at unopposed AT 2 receptors. This should preserve the favorable effects of angiotensin II, producing additional benefits beyond those related to blood pressure control.[10]
- Because they act at the final step of the renin-angiotensin system, ARBs should block

the effects of angiotensin II irrespective of whether it is generated systemically by ACE or within tissues by so-called ACE-independent pathways.

CAN ARBs REDUCE CARDIOVASCULAR RISK?

Almost 40% of people with hypertension have left ventricular hypertrophy, a strong predictor of congestive heart failure, stroke, and coronary heart disease. The risk of cardiovascular events rises incrementally with left ventricular mass, with no critical limit representing pathologic hypertrophy.

Aggressive blood pressure reduction causes regression of left ventricular hypertrophy. Once left ventricular hypertrophy regresses, the risk of cardiovascular and coronary heart disease mortality decreases substantially. Thus, left ventricular hypertrophy is not just an adaptive process to hypertension but is a clinical finding that should be corrected as soon as it is detected.

The LIFE study

Study name. Losartan Intervention For Endpoint Reduction in Hypertension (LIFE).[12]

Population. 9,193 patients, age 55 to 80 years, with hypertension and electrocardiographic evidence of left ventricular hypertrophy.

Treatment. Losartan 50 to 100 mg/day or atenolol (a beta-blocker) 50 to 100 mg/day; mean follow-up 4.8 years.

Results. Both drugs lowered blood pressure by a similar amount: losartan by 30.2/16.6 mm Hg and atenolol by 29.1/16.8 mm Hg. Yet the incidence of the primary end point (a composite of cardiovascular mortality, myocardial infarction, and stroke) was 13% lower with losartan compared with atenolol ($P = .021$). The difference was mainly due to a 25% lower risk of stroke with losartan ($P < .001$).

Antihypertensive therapy consisting of losartan and other medications resulted in greater regression of left ventricular hypertrophy than therapy consisting of atenolol and other medications. Regression was demonstrated even in patients older than 65 years, a finding of immense prognostic significance in this high-risk group. (In older patients, it is difficult to show regression.) Additionally, regression was more evident in women than in men,[13] and in whites than in blacks.[14]

New-onset diabetes was also significantly less frequent with losartan.

Comments. Although the LIFE study was not powered to detect a beneficial effect on cardiovascular outcomes, the findings suggest that losartan confers cardiovascular protection that is additional to its effect on blood pressure. LIFE further raises the possibility that beta-blockers should not be used as first-line monotherapy in patients with left ventricular hypertrophy.

The SILVHIA study

The Swedish Irbesartan Investigation Versus Atenolol (SILVHIA)[15] study also showed a greater reduction in left ventricular mass with an ARB than with a beta-blocker for an equivalent reduction in blood pressure.

TABLE 2

Differential effects of AT 1 and AT 2 receptor stimulation by angiotensin II

AT 1 receptor stimulation
- Increased vasoconstriction
- Increased aldosterone synthesis and secretion
- Increased tubular sodium reabsorption
- Increased vasopressin secretion
- Increased cardiac hypertrophy
- Increased cardiac contractility
- Increased vascular smooth muscle proliferation
- Increased peripheral noradrenergic activity
- Increased extracellular matrix formation
- Decreased renal blood flow
- Decreased renal renin production
- Modulation of sympathetic nervous system activity
- Central osmoregulation

AT 2 receptor stimulation
- Regulation of:
  - Fetal tissue development
  - Cell growth and proliferation
  - Extracellular matrix composition
  - Cell differentiation
  - Apoptosis
  - Post-infarct left ventricular remodeling
- Increased neuronal regeneration
- Vasodilation (possibly)

SCOPE

The Study on Cognition and Prognosis in the Elderly (SCOPE)[16] evaluated the effects of candesartan on cerebrovascular function in elderly patients with hypertension. Candesartan therapy was associated with a tendency towards a reduction in cardiovascular and cerebrovascular events with no discernible consequence on cognitive function. The trial was not powered to show a benefit on cardiovascular outcomes.

The VALUE study

Study name. Valsartan Anti-hypertensive Long-term Use Evaluation (VALUE).[17,18]

Population. 15,245 patients, age 50 to 70 years, with hypertension plus other risk factors.

Treatment. Valsartan 60 to 160 mg/day vs amlodipine (a dihydropyridine calcium channel blocker) 5 to 10 mg/day; mean follow-up 4.2 years.

Results. Towards the end of the study, both the regimens lowered blood pressure by a similar amount; however, during the first few months of the trial, the reduction was more pronounced in the amlodipine group than in the valsartan group, and this difference was associated with a parallel difference in cardiovascular events. The outcomes did not differ between the groups beyond the first year of treatment. The rate of new-onset diabetes was significantly lower with valsartan.

Comment. The VALUE trial underscores the importance of early and sustained blood pressure control in hypertensive patients at high risk.

The lower incidence of diabetes in the valsartan group (and in the losartan group in the LIFE study[12]) is intriguing. Prospective studies such as the Nateglinide and Valsartan in Impaired Glucose Outcomes Research (NAVIGATOR) study[19] are designed to explore more objectively whether ARBs may offer an antidiabetic effect.

Left ventricular hypertrophy should be treated as soon as detected

ARBs REDUCE DIABETIC NEPHROPATHY

Diabetes remains the most frequent cause of end-stage renal disease in the United States. Hypertension, which is common among patients with type 2 diabetes, causes progression of renal disease.

Early and vigorous blood pressure control in patients with diabetes, preferentially using agents with proven renoprotective properties, is therefore required to minimize the loss of renal function. Current guidelines from the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7)[20] and the American Diabetes Association[21] recommend a blood pressure goal of less than 130/80 mm Hg in patients with diabetes.

Several controlled trials investigated the effects of ARBs in patients with type 2 diabetic nephropathy.

The IDNT study

Study name. Irbesartan Diabetic Nephropathy Trial (IDNT).[22]

Population. 1,715 patients, age 30 to 70, with type 2 diabetes, hypertension, proteinuria, and elevated serum creatinine.

Treatment. Irbesartan (titrated to 300 mg), amlodipine (titrated to 10 mg), or placebo; other antihypertensive agents (excluding ACE inhibitors, ARBs, or calcium channel blockers) could be added to achieve a target blood pressure of less than 135/85 mm Hg. Mean follow-up was 2.6 years.

Results. Irbesartan slowed the deterioration of renal function. The risk of the combined primary end point (doubling of baseline serum creatinine, development of end-stage renal disease, or death) was 20% lower with irbesartan than with placebo ($P = .02$) and 23% lower than with amlodipine ($P = .006$), and fewer patients receiving irbesartan had a doubling of their serum creatinine concentration than placebo-treated or amlodipine-treated patients.

These renal benefits of irbesartan over amlodipine were not explained by any differences in blood pressure achieved (140/77 mm Hg with irbesartan; 141/77 mm Hg with amlodipine).

The IRMA II study

Study name. Irbesartan in Patients With Type 2 Diabetes and Microalbuminuria (IRMA II).[23]

Population. 590 patients with type 2 diabetes and hypertension, but with less-advanced renal disease (persistent microalbuminuria) than those enrolled in IDNT.

Treatment. Irbesartan 150 mg, irbesartan 300 mg, or placebo for 2 years, plus additional antihypertensive therapy (except ACE inhibitors, ARBs, or dihydropyridine calcium channel blockers) to achieve a target blood pressure of less than 135/85 mm Hg at 3 months.

Results. Irbesartan reduced albumin excretion significantly from baseline levels (–24% with 150 mg; –38% with 300 mg), whereas albumin excretion increased by 2% in the control group ($P < .001$). Irbesartan 300 mg also decreased the risk of progression to overt proteinuria by 70% compared with placebo ($P < .001$), and it restored normal urinary albumin excretion in more patients than placebo did (34% vs 21%; $P = .006$).

As in the IDNT, the renal benefits of irbesartan were independent of blood pressure-lowering.

The RENAAL study

Study name. Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL).[24]

Population. 1,513 patients, age 31 to 70 years, with type 2 diabetes and nephropathy.

Treatment. Losartan 50 to 100 mg or placebo, added to other antihypertensive drugs; mean follow-up 3.4 years.

Results. Losartan reduced the primary end point (doubling of baseline serum creatinine, end-stage renal disease, or death) by 16% and the individual incidences of a doubling of serum creatinine by 25% and end-stage renal disease by 28% vs placebo, but it did not decrease the death rate. The beneficial effects on kidney function exceeded those attributable to changes in systemic blood pressure.

Comments. In view of the results of IDNT and RENAAL, the JNC 7 report listed chronic renal disease as a compelling indication for ARBs when selecting drugs for treating hypertension.[20]

The MARVAL study

Study name. Microalbuminuria Reduction With Valsartan (MARVAL).[25]

Patient population. 332 patients, age 35 to 75, with type 2 diabetes and microalbuminuria.

Treatment. Valsartan 80 to 160 mg/day vs amlodipine 5 to 10 mg/day; follow-up for 24 weeks.

Results. The urinary albumin excretion rate decreased more among patients receiving valsartan than with amlodipine ($P < .001$). Normal albumin excretion was also restored in more patients with valsartan than with amlodipine ($P = .001$). These antiproteinuric effects of valsartan were evident despite similar blood pressure levels in both treatment groups.

NONDIABETIC NEPHROPATHY

The COOPERATE study

Study name. Combination Treatment of Angiotensin-II Receptor Blocker and Angiotensin-Converting-Enzyme Inhibitor in Non-diabetic Renal Disease (COOPERATE).[26]

Population. 263 patients with nondiabetic chronic renal disease.

Treatment. Losartan 100 mg daily vs trandolapril (an ACE inhibitor) 3 mg daily vs both drugs at the same doses; median follow-up 2.9 years.

Results. After 3 years of treatment, only 11% of the patients in the combination treatment group had reached the primary end point (doubling of the serum creatinine concentration or the onset of end-stage renal disease) compared with 23% of the patients receiving either losartan or trandolapril alone ($P < .02$).

Conclusions. The ARB and the ACE inhibitor were equally effective in retarding progression of renal disease; combination therapy may give an additional benefit.

Chronic renal disease is a compelling indication for an ARB when treating hypertension

ACUTE MI: ARBs ARE COMPARABLE TO ACEs

ACE inhibitors have been shown to reduce the risk of death and major nonfatal cardiovascular events after myocardial infarction (MI). Two studies have assessed whether ARBs offer benefits equivalent or superior to those of ACE inhibitors in this situation.

The OPTIMAAL trial

Study name. Optimal Therapy in Myocardial Infarction With the Angiotensin

II Antagonist Losartan (OPTIMAAL).[27]

Population. 5,477 patients, age 50 or older, with acute MI complicated by heart failure.

Treatment. Losartan 50 mg once daily or captopril 50 mg three times daily (plus conventional concomitant therapy). Treatment was started within 10 days of symptom onset and was continued for at least 6 months. Median follow-up was 2.7 years.

Results. No statistically significant differences were seen between the losartan and captopril groups in all-cause mortality, sudden cardiac death, resuscitated cardiac death, or fatal or nonfatal reinfarction. There was, however, a trend in event rates in favor of captopril, and significantly fewer cardiovascular deaths occurred with captopril (13.3% vs 15.3%; $P = .03$).

Comment. The researchers concluded that ACE inhibitors should remain the first-choice treatment after complicated acute MI. However, the dose of losartan used in this study was suboptimal and probably not therapeutically equivalent to that of captopril.

The VALIANT study

Study name. Valsartan in Acute Myocardial Infarction Trial (VALIANT).[28]

Population. 14,703 patients, age 18 or older, with acute MI complicated by left ventricular systolic dysfunction or heart failure.

Treatment. Valsartan 160 mg twice daily, captopril 50 mg three times daily, or a combination of valsartan 80 mg twice daily plus captopril 50 mg three times daily, beginning 0.5 to 10 days after an MI. Median follow-up was 2.1 years.

Results. Rates of all-cause mortality and the composite end point of cardiovascular death, MI, or hospitalization for heart failure were comparable with all three treatment regimens. The rate of adverse events was higher with combination treatment.

The OPTIMAAL investigators concluded that ACEs should remain the first choice in acute MI

ARBs ARE BENEFICIAL IN HEART FAILURE

Preliminary trials of ARBs in patients with heart failure—ie, the Evaluation of Losartan in the elderly [ELITE[29]] and ELITE II[30] trials; (see below)—were inconclusive. However, subsequent trials—ie, the Valsartan in Heart Failure Trial (Val-HeFT[31]) and the Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM[32]) program—demonstrated favorable outcomes, including a reduction in new-onset diabetes in CHARM.

The ELITE study

Study name. Evaluation of Losartan in the Elderly (ELITE).[29]

Population. 722 patients, age 65 years or older, with New York Heart Association (NYHA) class II to IV heart failure.

Treatment. Losartan 50 mg once daily vs captopril 50 mg three times daily; follow-up for 48 weeks.

Results. Losartan and captopril had similar effects on renal dysfunction (the primary end point). The all-cause mortality rate was significantly lower with losartan than with captopril.

The ELITE II study

Population. 3,152 patients, age 60 years or older with NYHA class II to IV heart failure.[30]

Treatment. Losartan 50 mg once daily vs captopril 50 mg three times a day; median follow-up 79.3 weeks.

Results. The captopril group had lower rates of all-cause mortality, sudden death, resuscitated cardiac arrest, and the composite of all-cause mortality or hospitalization, but the differences were not statistically significant.

Comments. The results of ELITE suggested that losartan might offer outcomes at least as good as ACE inhibitors do in patients with heart failure. However, ELITE II, which was better powered than ELITE for mortality, showed a trend in favor of captopril. As in OPTIMAAL, a better outcome with losartan might have been observed if a higher dose had been used.

Val-HeFT

Study name. Valsartan in Heart Failure Trial (ValHeFT).[31]

Population. 5,010 patients, age 18 years or older, with NYHA class II to IV heart failure.

Treatment. Valsartan 160 mg twice a day or placebo, added to a regimen that could include ACE inhibitors, diuretics, beta-blockers, and digoxin. Mean follow-up was 23 months.

Results. Valsartan significantly reduced the mortality and morbidity rates and improved clinical signs and symptoms when added to prescribed therapy. However, more mortality and morbidity were observed in the subgroup receiving valsartan, an ACE inhibitor, and a beta-blocker.

Comment. Based on Val-HeFT, valsartan is approved for the treatment of heart failure in patients who cannot tolerate ACE inhibitors. The JNC 7 report also recognized congestive heart failure as a compelling indication for ARBs in patients with hypertension.[20]

The finding of increased morbidity and mortality with the combination of an ACE inhibitor, a beta-blocker, and valsartan was unexpected and raised concern about excessive neurohormonal activation when drugs of these classes are used together.

The CHARM study

Study name. The Candesartan in Heart Failure: Assessment of Reduction in Morbidity and Mortality (CHARM) program.[32,33]

Population. 7,601 patients, age older than 18 years, with heart failure.

Treatment. Candesartan 32 mg daily vs placebo.

Results. Candesartan significantly reduced cardiovascular deaths and hospital admissions for heart failure.

Comments. CHARM has allayed concerns and fears about excessive neurohormonal inhibition and increased harm with combination therapy, as it showed no harmful effects of triple therapy with ACE inhibitor, an ARB, and a beta-blocker.

The CHARM study has allayed fears about combined ACE, ARB, and beta-blocker therapy in heart failure

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