The Angiotensin II Receptor Blockers: Opportunities Across the Spectrum of Cardiovascular Disease

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Angiotensin receptor blockers are a new class of agents that have made a major contribution to the treatment of hypertension. These agents effectively reduce blood pressure and are well tolerated. Other clinical trials have focused, however, on the much wider use of angiotensin receptor blockers in conditions such as congestive heart failure, postmyocardial infarction management, and diabetic nephropathy. Recent studies have provided evidence that these agents might confer target organ protection in hypertension that is equal to, and possibly better than, the benefits provided by conventional antihypertensive agents. Moreover, there is now little doubt that these drugs are effective alternatives to ACE inhibitors in heart failure and will become treatments of choice for patients with type 2 diabetes and nephropathy. Cardiovascular study outcomes have still not determined, however, whether high-risk patients would do better on angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors or a combination of both, except in cases of intolerance to ACE inhibitors.
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Angiotensin receptor blockers are a new class of agents that were initially introduced for the treatment of hypertension. Their appearance coincided, however, with a new focus in hypertension, specifically a strong interest in learning how differing classes of antihypertensive agents can affect cardiovascular prognosis. So, unlike early drug classes that were judged primarily by their ability to reduce blood pressure and be acceptably tolerated, the angiotensin receptor blockers have been—and continue to be—carefully scrutinized for their ability to prevent cardiac events, strokes, and loss of renal function.

Despite these important trends, there is also a growing recognition that tight control of blood pressure is a critical factor in optimizing treatment outcomes in hypertension. It has been recommended,[1] based on results of clinical outcomes trials,[2,3] that blood pressure be reduced below 140/90 mmHg when treating hypertensive patients in general and to even lower levels in patients with serious concomitant conditions like diabetes and nephropathy. It is known, though, that only one-quarter of hypertensive people in the United States have their blood pressures below the 140/90 mmHg target.[4] The angiotensin receptor blockers, which have powerful blood pressure-lowering effects as well as being exceptionally well tolerated, could provide at least part of the answer to this problem.

This interest in the angiotensin receptor blockers is not confined simply to patients whose primary cause for treatment is hypertension. Recently completed clinical trials, in addition to ongoing studies, have been focusing on outcomes in such conditions as congestive heart failure, postmyocardial infarction management, and diabetic nephropathy. It is widely believed that the renin-angiotensin system plays a major role in mediating the pathophysiology of these conditions and their clinical consequences, and the selectivity of the angiotensin receptor blockers in interrupting the potentially adverse actions of angiotensin II have made them logical agents for study. Indeed, this class appears to be more effective than even the angiotensin converting enzyme (ACE) inhibitors in blocking angiotensin II activity, although there are other pharmacologic differences (see below) that serve to even further differentiate these two types of drugs.

Table 1
The Principal Properties of the Available Angiotensin Receptor Blockers

Drug	Bioavailability (%)	Active metabolite	T (hr)	Peak effect (hr)	Usual dose range (mg)
Losartan	33	EXP3174*	2	1/3–4.0	50–100
Valsartan	25	No	6	2.0–4.0	80–320
Irbesartan	60–80	No	11–15	1.5–2.0	150–300
Eprosartan	13	No	5–9	1.0–3.0	400–800
Telmisartan	42	No	24	0.5–1.0	40–80
Candesartan	15	CV15959	9–13	3.0–4.0	8–32
Olmesartan medoxomil	26	Olmesartan	13	2.0	20–40

*Half-life=6–9 hours.

Basis for Angiotensin II Blockade

Hypertension provides the most direct rationale for using drugs that block the renin-angiotensin system, for there is abundant evidence that the vasoconstrictor effects of angiotensin II mediate at least part of the blood pressure excess in a large majority of patients. The rapidly seen effects on blood pressure of such agents as ACE inhibitors or angiotensin receptor blockers almost certainly reflect the direct hemodynamic responses to interrupting angiotensin mechanisms. The angiotensin receptor blockers appear to have the most straightforward effects because they directly block the vasoconstrictor actions of angiotensin II at its AT1 receptor. The ACE inhibitors work by reducing conversion of angiotensin I, which has no direct vascular effects of its own, into its active form, angiotensin II.

Clearly, the benefits of blocking angiotensin II are not confined to hypertension but are important in all high-risk cardiovascular patients.

Another class of drugs that also have important effects on the renin-angiotensin system are the β-blockers, which have the property of inhibiting release of renin from the kidney.[5] A benefit of antagonizing this system is to prevent the effects of angiotensin II in vascular tissue that can result in endothelial damage, cell proliferation, oxidation, prothrombotic actions, and other outcomes that hasten development of atherosclerosis as well as play a role in precipitating acute vascular events. Clearly, the benefits of blocking angiotensin II are not confined to hypertension but are important in all high-risk cardiovascular patients.

Properties

The angiotensin receptor blockers differ from each other by whether they have competitive or insurmountable binding to the AT1 angiotensin II receptor, although so far it has not been possible to demonstrate any meaningful clinical differences that arise from this attribute. These agents also differ according to whether they work directly at the receptor or first

require conversion to an active metabolite. In the case of losartan, the parent compound as well as the metabolite is active at the receptor; and in the case of olmesartan medoxomil, the medoxomil moiety simply facilitates absorption from the bowel and then separates from the parent compound. Again, there appear to be no clinical differences that depend on whether a drug works directly or must first be derived from a prodrug. The angiotensin receptor blockers are all active when administered orally and generally have sufficiently long durations of hemodynamic action to be effective when taken once daily, although potentially there might be pharmacokinetic differences among the agents that could produce differences in their blood pressure effects during the later parts of the 24-hour treatment period. Some of the principal properties of these drugs are summarized in Table 1.

Table 2
Angiotensin II Receptors and Effects of Blockade

- Vascular AT1 receptors
  - Constantly expressed
  - Mediate vasoconstriction
  - Mediate angiotensin II arterial wall growth effects
- Vascular AT2 receptors
  - Expressed only after injury (sustained hypertension might provoke expression)
  - Mediate vasodilation
  - Mediate antiproliferative actions
  - Activate other factors, eg, nitric oxide, tissue kinins
- Potential double action of selective AT1 blockers
  - Directly block vasoconstrictor and growth actions of angiotensin II at AT1 receptors
  - Increase circulating angiotensin II levels
  - Unblocked AT2 receptors (if expressed), stimulated by increased angiotensin II activity, mediate vasodilation and growth inhibition
  - Net effect: AT1 blockade plus AT2 stimulation

The Receptor Hypothesis

Several receptors have been identified at which angiotensin II can bind, but so far only the AT1 and AT2 receptors have been defined in terms of physiologic function. The AT1 receptor mediates the best-known actions of angiotensin II, including its hemodynamic and trophic effects.

The AT2 receptor is particularly interesting, although its role in the adult is still far from clear. This receptor is found primarily during fetal development and is involved in mediating apoptosis, which is also known as programmed cell death. Expression of the AT2 receptor in normal adults requires a stimulus such as trauma or tissue injury. It is believed, however, that the pathologic consequences of hypertension and other cardiovascular risk factors can produce sufficient damage and disruption to the vascular wall to provoke expression of the AT2 receptor. When angiotensin II works at these receptors, it produces vasodilation and has inhibitory effects on cell growth. Activation of these receptors has been shown to induce nitric oxide production and may even increase generation of kinins at tissue sites. In a sense, the AT1 and AT2 receptors appear to have balanced and opposing effects when stimulated by angiotensin II, suggesting that unwanted actions mediated through the AT1 receptors can be offset by those at the AT2 receptors, provided that these latter receptors are expressed.

This concept may be critical in explaining potentially important benefits of the selective AT1 receptor blocking agents. During treatment with these drugs, there is a sharp increase in angiotensin II production. It is possible, therefore, that these drugs have a dual mechanism of action: on the one hand, direct blockade of the AT1 receptor, and on the other, stimulation of the AT2 receptor that is enhanced by the increased angiotensin II concentrations. The differential actions of these drugs could create important tissue-protective effects in settings where AT2 receptors might exist. In vitro studies have confirmed that AT1 blockade inhibits cell growth and that AT2 blockade (produced by nonclinical experimental agents) increases cell growth. It would be expected, then, that blockade of the AT1 receptor at the same time as stimulation of the AT2 receptor—which is the situation when the angiotensin receptor blockers are being administered—could produce a powerful antigrowth action. This hypothesis is summarized in Table 2.

Effects on Blood Pressure

The angiotensin receptor blockers have an efficacy that is similar to the other well-established antihyper-

tensive drug classes. An interesting feature of these agents is their relatively shallow dose-response effects. In general, the difference in efficacy between the lowest and highest recommended doses of the angiotensin receptor blockers is in the range of 4–6 mmHg. For most of these drugs there is only a one-step titration process, a fact that adds to the convenience and simplicity of using them. The blood-pressure effects of this class have now been well described in the literature for losartan,[6] valsartan,[7] irbesartan,[8] telmisartan,[9] eprosartan,[10] and candesartan.[11] This last study was a meta-analysis of six randomized, double-blind, placebo-controlled, dose-response studies of candesartan. The drug with perhaps the simplest dosing regimen is losartan because there is relatively little increased efficacy when doses higher than the usual starting dose of 50 mg are used.[6] It is recommended that if additional antihypertensive efficacy is required, a transition to a fixed combination with a low dose of hydrochlorothiazide be used. This approach may be true for all the drugs in this class.

In the competitive environment of antihypertensive therapy, it has been inevitable that the manufacturers of the various agents in this class have done studies to show that their products are similar or possibly superior to others in the class. Some of these trials have already been published.[12–14] One study showed, for example that candesartan at maximal doses was superior to losartan at maximal doses.[12] Another study found that irbesartan at maximal doses was superior to maximal doses of losartan.[13] Such studies, although interesting, must be looked at with some caution. Differences in efficacy, for example, can be affected by the selection of doses or by other conditions of the trial. Conducting studies of the comparative efficacies of similar drugs can be a difficult and at times misleading venture; the issues involved in this type of research have been discussed in the literature.[15]

Adverse Effects

The angiotensin receptor blockers do not appear to produce meaningful symptomatic or metabolic side effects. Indeed, the side effects of these agents cannot be differentiated from placebo. Of interest, headache has been reported more commonly during placebo treatment of hypertension than during treatment with angiotensin receptor blockers, indicating not only the excellent profile of these agents, but that headache—contrary to our previously held beliefs about hypertension—might actually be a relatively common symptom of this condition. Cough is less frequent with these drugs than with the ACE inhibitors and appears to have an incidence similar to that of other antihypertensive drugs. However, like the ACE inhibitors, the angiotensin receptor blockers should not be administered during pregnancy or in patients with known or suspected renovascular disease.

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Comparisons with ACE Inhibitors

Because the angiotensin receptor blockers and the ACE inhibitors each interrupt the renin-angiotensin system, there has been a tendency to see the two classes as alternatives to each other. The ACE inhibitors, however, do not fully prevent conversion of angiotensin I to angiotensin II during chronic therapy, probably because enzymes other than the angiotensin converting enzyme—for example, chymase—may take a greater role in facilitating this conversion when ACE is blocked. It is believed that an important part of the hemodynamic and target organ-protective effects of the ACE inhibitors depends on such mechanisms as accumulation of kinins and the resulting enhancement of nitric oxide and prostaglandin mechanisms. On the other hand, the effects of the angiotensin receptor blockers appear to depend entirely on their actions at the AT1 receptor. In general, clinical trials comparing the antihypertensive efficacy of the two classes have shown comparable blood pressure-lowering effects. It is still too early to determine whether the two classes have similar effects when used for such indications as congestive heart failure or nephropathy.

Because these drugs have differing pharmacologic actions there has been interest in studying combination treatment with the ACE inhibitors and angiotensin receptor blockers. Early evidence suggests that this combination therapy may be more effective than either type of agent alone when used to treat proteinuria.[16] In congestive heart failure, the Valsartan in Heart Failure Trial (ValHeFT) showed that for certain end points—particularly hospitalization for heart failure—the combination may be more effective than the ACE inhibitor alone.[17] In hypertension, it has been difficult to establish real additivity, let alone synergy, when ACE inhibitors are combined with angiotensin receptor blockers,[18] although a recent trial indicated

Table 3
Major Clinical Trials with Angiotensin Receptor Blockers

Study name (population)	Treatment	End points	Outcome
ELITE (CHF patients)[26]	Losartan (n = 352) vs captopril (n = 370)	Primary = renal function; secondary = mortality	Primary = no significant difference; secondary = 46% lower risk of death in losartan group
ELITE II (CHF patients)[19]	Losartan (n = 1578) vs captopril (n = 1574)	Primary = mortality	Primary = no significant difference
IDNT (diabetic nephropathy with hypertension)[23]	Irbesartan vs amlodipine vs placebo (conventional antihypertensive treatment)	Time to progression of composite end point (doubling of baseline serum creatinine, end-stage renal failure, and all-cause mortality)	Primary = irbesartan significantly better in protecting renal function than amlodipine or conventional antihypertensive agents
IRMA 2 (type 2 diabetes with microalbuminuria)[25]	Irbesartan (150 mg) vs irbesartan (300 mg) vs placebo	Progression to nephropathy	Primary = significant production of nephropathy with 300-mg but not 150-mg dose
LIFE (hypertensive patients with ECG LVH)[20–22]	Losartan (n = 4605) vs atenolol (n = 4599)	Composite of fatal and nonfatal strokes and myocardial infarctions	Significant relative risk reductions favoring losartan of 13% in composite end point, 25% in stroke, and 25% in new-onset diabetes
RENAAL (diabetic nephropathy)[24]	Losartan vs placebo (conventional antihypertensive treatment)	Renal function (serum creatinine), terminal renal failure, mortality	Primary = significant renal protection by losartan compared with conventional antihypertensive agents
RESOLVD (CHF patients)[26]	Candesartan (n = 327) vs enalapril (n = 109) vs candesartan + enalapril (n =332)	Primary = changes in 6 min walking time, ejection fraction, and New York Heart Association class	Primary = no significant difference
ValHeFT (CHF patients)[17]	Valsartan (n = 2511) vs placebo (n = 2499	Primary = mortality, mortality + morbidity	Primary = mortality alone similar, but significant reductions in all-cause mortality and morbidity in the valsartan group, driven largely by reduction in number of hospitalizations

CHF, congestive heart failure; LVH, left ventricular hypertrophy; ELITE, Evaluation of Losartan in the Elderly; IDNT, Irbesartan Diabetic Nephropathy Trial; IRMA 2, Irbesartan Microalbuminuria Type 2; LIFE, Losartan Intervention for Endpoint Reduction in Hypertension; RENAAL, Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan; RESOLVD, Randomized Evaluation of Strategies for Left Ventricular Dysfunction; ValHeFT, Valsartan in Heart Failure Trial.

that whereas lisinopril and irbesartan had similar antihypertensive action when given as single agents, their combination was significantly more efficacious.[19]

Clinical Outcomes

Until now, eight major clinical trials based on angiotensin receptor blockers have reported the effects of these agents on clinical events. Of these trials, one has been based on hypertensive patients, three have been based on patients with diabetic nephropathy, and four on heart failure. These studies are summarized in Table 3.

The LIFE Study

The Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) clinical trial was not only the first important end point study in hypertension with an angiotensin receptor blocker,[20] but was also the first trial in which an antihypertensive agent of one class was significantly superior in reducing clinical outcomes compared to an agent from another class. The study, which was discussed in a previous issue of this publication,[21] was performed in hypertensive patients whose risk of cardiovascular events was increased by the presence of EKG evidence for left ventricular hypertrophy (LVH). The angiotensin receptor blocker losartan was compared with the β-blocker atenolol; the starting dose of each drug was 50 mg and could be increased to 100 mg if needed for control of blood pressure. Hydro-

Table 4
Selected End Points in the Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) Study: Adjusted Hazard Ratios (95% CI) for Losartan Relative to Atenolol

	All patients (losartan: n = 4605; atenolol: n = 4588)		Diabetic patients (losartan: n = 586; atenolol: n = 609)	
	Hazard ratio*	*P*-value	Hazard ratio*	*P*-value
Primary composite end point†	0.87 (0.77–0.98)	*P* = .021	0.76 (0.58–0.98)	*P* = .031
Cardiovascular mortality	0.89 (0.73–1.07)	*P* = .206	0.63 (0.41–0.95)	*P* = .028
Stroke	0.75 (0.63–0.88)	*P* = .001	0.79 (0.55–1.14)	*P* = .204
Myocardial infarction	1.07 (0.88–1.31)	*P* = .491	0.83 (0.55–1.25)	*P* = .373
New onset diabetes	0.75 (0.63–0.88)	*P* = .001	Not applicable	

*Adjusted for degree of left ventricular hypertrophy and Framingham risk score at baseline.
† Cardiovascular mortality, stroke, and myocardial infarction.

chlorothiazide and other agents were added if needed. The average age of patients was 67 years. In the losartan group, baseline blood pressure was 174/98 mmHg, and it fell by 30/17 mmHg by the end of the study; the baseline value in the atenolol group was 175/98 mmHg, and it fell by 29/17 mmHg.

Similarly, there was a 25% relative reduction in the incidence of new-onset diabetes mellitus in the losartan group.

The principal results of the study are summarized in Table 4. The primary end point was the composite of fatal and nonfatal heart attacks and strokes; this was reduced by 13% (*P* = .021) in the losartan group relative to the atenolol group. There was no difference between the two groups in the incidence of myocardial infarction, but stroke incidence was relatively lower by 25% in the losartan group. Similarly, there was a 25% relative reduction in the incidence of new-onset diabetes mellitus in the losartan group. As shown in Figure 1, the benefits of losartan were observed just as clearly in those patients in this trial who were diabetic at baseline.[22] Because β-blockers are already recommended by the Joint National Committee (JNC) VI[1] as preferred first-line treatment for hypertension, the apparent superiority of an angiotensin receptor blocker creates a situation in which this newer class could now be considered the routine approach for initiating antihypertensive treatment. Ongoing studies with other angiotensin receptor blockers might be helpful in confirming the validity of this change.

Diabetic Nephropathy

As summarized in Table 3, the Irbesartan Diabetic Nephropathy Trial (IDNT)[23] and the Reduction of Endpoints in NIDDM With the Angiotensin II Antagonist Losartan (RENAAL)[24] trial were each carried out in patients with type 2 diabetes and nephropathy (manifested by proteinuria). The two trials were similar in that treatment with an angiotensin receptor blocker (irbesartan in the IDNT trial, and losartan in the RENAAL trial) was compared primarily with conventional therapy (placebo plus hydrochlorothiazide and β-blockers, as needed, to provide targeted blood-pressure reduction). In each trial, despite virtually identical blood-pressure effects in the comparison groups, the angiotensin receptor blocker was significantly superior in reducing the primary composite end point (doubling of serum creatinine, development of end-stage renal failure, and all-cause mortality). In the IDNT trial, there was a separate calcium channel blocker-based arm, and again the angiotensin receptor blocker was more effective in preserving renal function.

Despite these impressive renal findings, there were no significant differences between the angiotensin receptor blockers and the conventional therapies in effects on other cardiovascular end points, although neither study was powered nor designed to explore such differences. A further trial exploring renal issues was the Irbesartan Microalbuminuria Type 2 (IRMA 2) study,[25] also summarized in Table 3, which was performed in patients with diabetes and microalbuminuria. This trial demonstrated that irbesartan, when compared with conventional anti-

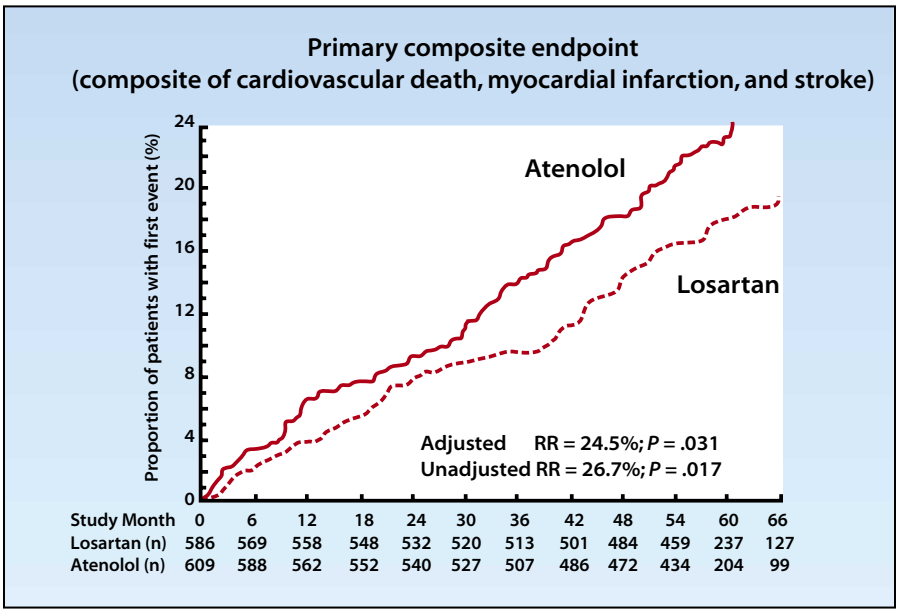

Figure 1. *Comparison of atenolol and losartan on end points in diabetic patients with hypertension and left ventricular hypertrophy. Data from Lindholm et al.*[22]

hypertensive therapy, significantly prevented progression to clinical nephropathy. It was noteworthy that a higher dose of this agent was more effective than a lower dose (300 mg versus 150 mg) in achieving renal protection, despite similar blood-pressure effects.

This might be an important observation, for it suggests that dose-response relationships for angiotensin receptor blockers and target organ effects may be different from those observed for hemodynamic effects. Certainly, there will be a great deal of interest in future trials in exploring higher-than-usual doses of these agents for preventing clinical end points.

Heart Failure

The two Evaluation of Losartan in the Elderly (ELITE) studies in heart failure are shown in Table 3. The first of these trials compared losartan 50 mg with the ACE inhibitor captopril 50 mg three times daily in patients with heart failure during short-term therapy and appeared to show a significant reduction in mortality for patients on the angiotensin receptor blocker.[26] But the later ELITE II study failed to confirm the findings of the first trial; in fact, there was no significant difference in major clinical end points between the two treatments, although losartan was better tolerated.[19] It is quite possible that losartan 50 mg once daily is not an adequate dose. Previous trials in heart failure have shown that, for ACE inhibitors at least, higher doses may be more protective than lower doses. The Randomized Evaluation of Strategies for Left Ventricular Dysfunction (RESOLVD) study (see Table 3) similarly showed no significant difference between an ACE inhibitor and an angiotensin receptor blocker.

More recently, the ValHeFT study[17] explored the addition of the angiotensin receptor blocker valsartan, given in a full dose of 160 mg twice daily, to ongoing conventional therapy with an ACE inhibitor (93% of patients) and other appropriate agents (including β-blockers in 35% of patients). There was no mortality benefit by adding the angiotensin receptor blocker (compared with adding placebo), but there was a clear reduction in adjudicated hospital admissions for heart failure in patients on valsartan. In the small subgroup of patients not receiving an ACE inhibitor, valsartan was sharply superior to placebo in reducing the composite end point of mortality and morbidity, thus indicating that the angiotensin receptor blockers might be highly acceptable alternatives to ACE inhibitors in those patients who cannot tolerate ACE inhibitors. Interestingly, the addition of the angiotensin receptor blocker was of greater value in those patients who were taking an ACE inhibitor but not a β-blocker, suggesting that all three drugs in combination (ACE inhibitors, angiotensin receptor blockers, and β-blockers) — bearing in mind that each of these drugs has clear neurohormonal effects—may be excessive, and that treatment should normally encompass only two such drug classes. Recently the U.S. Food and Drug Administration approved valsartan for the treatment of heart failure in patients who cannot tolerate ACE inhibitors.

Other Studies

Several clinical trials with angiotensin receptor blockers in heart failure and hypertension patients, and in patients immediately following myocardial infarction with reduced left ventricular ejection fractions, have just been completed or should be completed in the next 12–24 months. The Optimal Trial in Myocardial Infarction with the Angiotensin II Antagonist Losartan (OPTIMAAL) has now been completed. The results, which are somewhat disappointing, were reported orally at the 2002 Meetings of the European

Society of Cardiology and have been published.[27] In 5477 patients with reduced left ventricular systolic function following myocardial infarction, the primary end point of all-cause mortality tended to be greater in those patients randomized to treatment with losartan than in those who received the ACE inhibitor captopril during an average follow-up period of 2 to 7 years. Among the other end points captopril actually was significantly superior to losartan in preventing cardiovascular death. As with the ELITE II study, these results may reflect inadequate dosing: captopril was given as 50 mg three times daily, whereas the losartan dose was only 50 mg once daily. Fortunately, the Valsartan in Acute Myocardial Infarction Trial (VALIANT), in the same type of patient, has been using what appears to be appropriate doses of the angiotensin receptor blocker valsartan and so should provide a more definitive assessment of the relative benefits of ACE inhibitors and angiotensin receptor blockers, as well as of the combination of the two, in patients with impaired left ventricular function.

The Study on Cognition and Prognosis in the Elderly (SCOPE) and Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trials in hypertension are also well advanced, and their results may be helpful in allowing further interpretation of the exciting results from the LIFE study. Although not yet published, the preliminary results of SCOPE were recently presented at the 2002 Meetings of the European Society of Hypertension. They appear to support the results of the LIFE study, which showed that, compared with conventional treatment, an angiotensin receptor blocker (candesartan) can reduce the incidence of stroke in hypertensive patients. Moreover, in older patients with evidence of early cognitive impairment, the angiotensin receptor blocker appeared to be more effective than conventional drugs in slowing down further intellectual deterioration.

The evidence in congestive heart failure is also of interest, and it appears that the angiotensin receptor blockers can be regarded as legitimate alternatives to ACE inhibitors.

Conclusions

The angiotensin receptor blockers clearly have made a major contribution to the treatment of hypertension. They effectively reduce blood pressure and are well tolerated. Moreover, there is already compelling evidence that these agents might provide target organ protection that is at least as good as—and possibly superior to—the benefits provided by conventional antihypertensive agents. There is also now little doubt that these drugs will be treatments of choice for patients with type 2 diabetes and nephropathy. Because the prevalence of type 2 diabetes has been growing so dramatically, this indication could be of great importance. The evidence in congestive heart failure is also of interest, and it appears that the angiotensin receptor blockers can be regarded as legitimate alternatives to ACE inhibitors. Similarly, depending on the outcomes of clinical trials now under way, the angiotensin receptor blockers may also find an important role in the management of postmyocardial infarction patients. It is still not possible for any of these indications to determine—except in those instances of intolerance to ACE inhibitors—whether certain patients would do better to receive either an ACE

Main Points

- Angiotensin receptor blockers are a new class of agents that have made a major contribution to the treatment of hypertension; they effectively reduce blood pressure and are well tolerated.
- Recent clinical trials have focused on the wider use of angiotensin receptor blockers in conditions such as congestive heart failure, postmyocardial infarction management, and diabetic nephropathy.
- There is compelling evidence that these agents might provide target organ protection that might be superior to the benefits provided by conventional antihypertensive agents.
- Angiotensin receptor blockers will also become treatments of choice for patients with type 2 diabetes and nephropathy.
- To date, cardiovascular studies based on these agents have not yet established whether certain patients would have better results on angiotensin receptor blockers or angiotensin converting enzyme (ACE) inhibitors or a combination of both, except in cases where patients are intolerant of ACE inhibitors.

inhibitor or an angiotensin receptor blocker. Although there still may be some opportunities to test whether the combination of these two drug classes might be of value in certain settings, for the moment it still remains difficult to discriminate between them in terms of their beneficial effects on major cardiovascular end points. ■

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