Inhibiting the Renin-Angiotensin System to Prevent Cardiovascular Diseases: Do We Need a More Comprehensive Strategy?

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The renin-angiotensin system (RAS) plays a pivotal role in the progression of some forms of hypertension and cardiovascular disease. The development of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) has provided physicians with effective and well-tolerated inhibitors of the RAS. However, it remains open to question whether ACE inhibitors and ARBs have fully delivered the reductions in cardiovascular risk that we might have expected. There is little doubt that in conditions such as chronic and acute heart failure or diabetic nephropathy these drugs have provided significant protection. But, in patients with high-risk hypertension, for instance, the anticipated benefits of RAS blockade have been less obvious. This article provides a critical assessment of the results of clinical trials of ACE inhibitors and ARBs across a variety of clinical conditions and assesses the potential need for new methods for blocking the renin system, including the use of renin inhibitors.

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Key words: Angiotensin-converting enzyme inhibitors • Angiotensin receptor blockers • Hypertension • Renin • Renin inhibitors

The development of effective inhibitors of the renin-angiotensin system (RAS) has represented a major step forward in the treatment of hypertension and cardiovascular diseases. Based on experimental and clinical studies using angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), we now know that RAS activity may be a key factor in the pathophysiology and development of hypertension, renal disease, atherosclerosis, diabetes, and heart failure in a substantial number of patients.[1,2]

The role of the RAS in patients with primary hypertension is not known. However, in conditions such as diabetes mellitus and heart failure, dysregulation of the RAS is clear. It is now accepted that angiotensin II, the chief effector of this system, may play a role in cardiovascular remodeling, leading to structural and functional changes in the myocardium, kidneys, and vasculature.[2] Activity of the RAS in the pancreas and adipose tissue could play a big part in creating insulin resistance and diminishing beta cell responsiveness, thus making obese people more susceptible to diabetes.[3,4] The organ damage caused by the RAS may be independent of blood pressure (BP); increased plasma renin activity in patients with hypertension is associated with an increased risk of myocardial infarction (MI), even when BP levels are effectively controlled by antihypertensive therapy.[5]

Given the evidence for the importance of RAS activation in cardiovascular disease, it was widely anticipated that interrupting this system would represent a clear step forward in reducing cardiovascular morbidity and mortality. This article examines whether this outcome has actually occurred, and it looks forward to expected innovations in the area of RAS inhibition.

ACE Inhibitors and ARBs: Surveying the Evidence

ACE inhibitors and ARBs are very useful antihypertensive drug classes that have been proven to lower BP effectively and with good tolerability. The ARBs in particular have proven to be remarkably well tolerated—consistently demonstrating placebo-like tolerability—and have set a gold standard in safety for future antihypertensive therapies. But, the ultimate aim of drug treatment for hypertension is to reduce morbidity and mortality. Hence the key question in evaluating the success of ACE inhibitors and ARBs is: have these drugs delivered the improved cardiovascular outcomes that were anticipated?

In reality, the answer is not completely clear. ACE inhibitors and ARBs have not delivered the *major* reductions in cardiovascular outcomes that were predicted given the broad role of RAS activation in the pathophysiology of cardiovascular disease. This raises the issue of whether the RAS is as broadly dysregulated in hypertension as previously believed, or alternatively that our current strategies are not fully effective in blocking this system.

What is the evidence that ACE inhibitors and ARBs have not fully delivered the hoped-for reductions in cardiovascular outcomes? For instance, a recent meta-analysis of 27 randomized trials involving a total of 158,709 patients conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC) showed no significant advantage of ACE inhibitors or ARBs over other antihypertensive classes with regard to major clinical outcomes.[6] It might be more valuable, however, to discuss the results of individual clinical trials that have evaluated the effects of ACE inhibitors and ARBs in different clinical conditions, and to critically assess the evidence for benefits of these agents over other drug classes.

Landmark Outcome Trials in Patients at High Cardiovascular Risk

High-Risk Patients

ACE inhibitors in particular have improved outcomes in clinical trials of high-risk cardiovascular patients (in which some patients were not classified as hypertensive). The best known of these trials is the Heart Outcomes Prevention Evaluation (HOPE) study, in which the ACE inhibitor ramipril significantly reduced the incidence of MI, cardiovascular death, or stroke by 22% compared with placebo ($P < .001$) in high-risk patients (patients with a history of cardiovascular disease or with complicated diabetes).[7] Similarly, in the European Trial on Reduction of Cardiac Events with Perindopril in Patients with Stable Coronary Artery Disease (EUROPA) study, perindopril significantly reduced cardiovascular events by 20% compared with placebo ($P = .0003$).[8] Even so, since in both these studies BP was reduced by the ACE inhibitor treatment, it is likely that at least some of the cardiovascular benefits achieved by the ACE inhibitors were due to reductions in BP.

Interestingly, the benefits of ACE inhibitor therapy in HOPE and EUROPA have not been repeated in some other recent trials of high-risk patients. In the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial, adding an ACE inhibitor to conventional therapy did not provide additional cardiovascular benefits in patients with coronary artery disease (CAD). In particular, trandolapril did not reduce the incidence of the primary study endpoint of cardiovascular death, MI, or coronary revascularization compared with conventional therapy alone.[9] This study might have been confounded, however, by the beneficial effects of ongoing aggressive therapy with statins, antiplatelet drugs, and other risk-reducing therapies.

The Comparison of Amlodipine Versus Enalapril to Limit Occurrences of Thrombosis (CAMELOT) study similarly failed to demonstrate improved outcomes with ACE inhibitor therapy in patients with angiographically documented stable CAD. CAMELOT compared the effects

of the ACE inhibitor enalapril or the calcium channel blocker amlodipine with placebo on cardiovascular events in patients with CAD. Although amlodipine significantly reduced the rate of cardiovascular events by 31% compared with placebo ($P = .003$), the effects of enalapril treatment—for the same degree of BP-lowering—were not significant (15% reduction; $P = .16$).[10] It is possible that this negative result reflected an inadequate dose of the ACE inhibitor, and, again, the study results could have been influenced by ongoing statin therapy.

Heart Failure Patients

Neurohormonal activation has been strongly implicated in the progression of heart failure, so RAS inhibitors and aldosterone might be expected to provide particular benefits in heart failure patients. Early trials such as the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS) supported this expectation by demonstrating that enalapril reduced mortality by 27% compared with placebo ($P = .003$) in patients with heart failure.[11]

Turning to ARBs, the Valsartan Heart Failure Trial (Val-HeFT) assessed the clinical outcome benefits of valsartan treatment in patients with chronic heart failure. In Val-HeFT, adding valsartan to existing therapies (including ACE inhibitors) led to a 13.2% reduction compared with placebo ($P = .009$) in the incidence of the primary study endpoint of mortality and cardiovascular morbidity, which was driven primarily by a reduction in hospitalizations due to heart failure.[12] However, in a small subset of patients not receiving ACE inhibitors, the ARB significantly reduced mortality and morbidity.

The Candesartan in Heart Failure Assessment of Reduction in Mortality and Morbidity (CHARM-Overall) trial showed that ARB treatment in chronic heart failure patients significantly reduced the hard endpoints of all-cause mortality by 10% ($P = .032$) and cardiovascular death by 13% ($P = .006$).[13] But, despite the interesting and important endpoint benefits observed with candesartan in the CHARM studies, residual mortality remained high (23% and 25% in the candesartan and placebo groups, respectively). The fact that nearly 1 in 4 patients died during the course of the trial despite treatment with an ARB (and, in some patients, an ACE inhibitor) shows that there might still be scope to improve clinical outcomes in the treatment of patients with heart failure. Among the strategies to be considered, alternative methods for inhibiting the RAS could be worth testing.

Post-Myocardial Infarction Patients

The benefits of ACE inhibitor treatment in patients with acute compromise of left ventricular systolic function following MI were demonstrated in the Survival and Ventricular Enlargement (SAVE) trial. SAVE showed that long-term treatment with the ACE inhibitor captopril significantly reduced mortality by 19% ($P = .019$) and also reduced cardiovascular morbidity compared with placebo.[14] The Valsartan in Acute Myocardial Infarction Trial (VALIANT) investigated whether the ARB valsartan alone or in combination with captopril would provide superior cardiovascular outcomes compared with captopril monotherapy in post-MI patients with impaired systolic function.[15] Results demonstrated that valsartan was equal to captopril monotherapy in its effects on major endpoints. The ACE inhibitor and ARB combination did not provide improved cardiovascular outcomes compared with the ACE inhibitor alone. The VALIANT data therefore suggest that further progress in this area, at least as far as the RAS is concerned, might require a different approach to inhibition.

Diabetic Nephropathy Patients

Diabetes mellitus is regarded as a compelling indication for the use of ACE inhibitors or ARBs in treating hypertension. Activation of the RAS is a key step in the progression of diabetic kidney disease, even when plasma levels of renin activity do not appear to be increased. ACE inhibitors and ARBs have demonstrated renoprotective benefits in patients with diabetic nephropathy in trials such as the Captopril Collaborative Study, the Reduction of Endpoints in NIDDM (non-insulin-dependent diabetes mellitus) with the Angiotensin II Antagonist Losartan (RENAAL), and the Irbesartan Diabetic Nephropathy Trial (IDNT).[16-18] Despite their very positive outcomes, inspection of the RENAAL and IDNT results reveals even further opportunities for improvement. Although ARB treatment in these trials significantly slowed the decline in renal function in patients with diabetic nephropathy, the absolute mean rate of decline in the glomerular filtration rate in both studies was still higher than the expected loss due to aging specified in guidelines from the National Kidney Foundation (Figure 1).[19] Progression of renal disease was delayed, but not halted. Likewise, proteinuria was significantly reduced, but overall it still remained clearly in the macroalbuminuria range.

The renoprotective benefits of ACE inhibitors and ARBs in patients with diabetic renal disease were also evaluated in a recent meta-analysis of 127 randomized trials involving a total of 73,514 patients. This study confirmed that ACE inhibitor or ARB treatment provides renoprotective benefits, but indicated that these

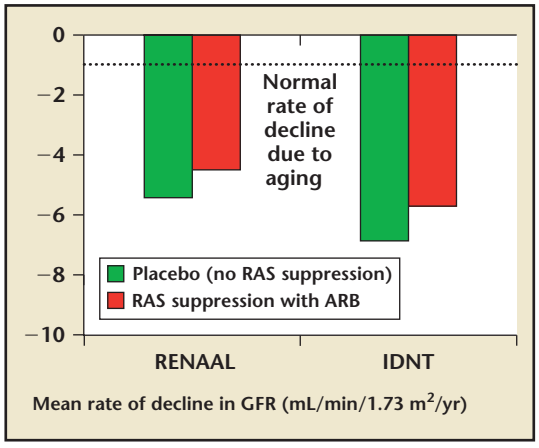

Figure 1. *Decline in renal function in patients with type 2 diabetic nephropathy in the Reduction of Endpoints in Non-Insulin Dependent Diabetes Mellitus with the Angiotensin II Antagonist Losartan (RENAAL) study and the Irbesartan in Diabetic Nephropathy Trial (IDNT). Figure indicates the annual rate of decline in the glomerular filtration rate (GFR) in patients receiving placebo or angiotensin receptor blocker (ARB) treatment with losartan (the RENAAL study) or irbesartan (the IDNT), as compared with the average loss due to aging specified by National Kidney Foundation guidelines.[19] RAS, renin-angiotensin system.*

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benefits are probably due to the BP-lowering effects of treatment.[20] The analysis also suggested that patients with diabetic nephropathy experienced no significant additional renoprotective benefits with ACE inhibitors or ARBs compared with other antihypertensive classes. As with other meta-analyses, however, this study could be faulted for pooling heterogeneous trial results and possibly obscuring important effects in key subgroups of patients. Still, it is reasonable to argue that further benefits might occur with more fully effective blockade of the RAS.

What about cardiovascular endpoints? Neither the RENAAL nor the IDNT results demonstrated a significant benefit of ARB treatment on cardiovascular morbidity and mortality,[17,18] although there were some interesting positive trends. As well, it could be argued that these studies were not adequately powered to examine such endpoints. The BPLTTC meta-analysis of subgroups of patients with diabetes in antihypertensive clinical trials indicated that ACE inhibitor or ARB treatment in these patients did not provide significantly greater benefits on cardiovascular events compared with other drug classes.[6] Again, however, caution should be exercised in interpreting subgroup data derived from meta-analyses.

Post-Stroke Patients

BP is recognized as an important determinant of the risk of stroke, and systematic reviews of randomized trials of antihypertensive agents have clearly shown that reductions in BP decrease the risk of stroke, with little or no difference observed among the effects of different drug classes.[21] The effects of ACE inhibitors in post-stroke patients were evaluated in the Perindopril Protection Against Recurrent Stroke Study (PROGRESS). This study examined the effects of perindopril, with the diuretic indapamide added at the discretion of the investigators, on the incidence of stroke in patients with a history of stroke or transient ischemic attack. Although perindopril therapy alone did not provide a significant benefit, perindopril combined with indapamide significantly reduced the risk of stroke by 43% ($P < .0001$) compared with placebo.[22] Given that the combination treatment also provided significantly greater BP reductions ($P < .001$) compared with perindopril alone, it is possible that the outcome benefits of therapy in PROGRESS were influenced by reductions in BP as well as by suppression of the RAS by perindopril.

It should be noted that results strongly in favor of specific benefits of RAS blockade in post-stroke patients were achieved in the Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention (MOSES) study. MOSES was the first trial to compare an ARB (eprosartan) with a calcium channel blocker (nitrendipine) in the secondary prevention of stroke in hypertensive patients. Results showed that with the same level of BP-reduction, an eprosartan-based treatment regimen significantly reduced the incidence of mortality and all cardiovascular and cerebrovascular events by 21% ($P = .014$) compared with a nitrendipine-based regimen.[23] These results indicate that ARB therapy may provide stroke protection beyond BP lowering in patients with hypertension, although MOSES remains the only major outcome study to demonstrate such a benefit. It is possible that the differential blocking effects of ARBs on angiotensin II type 1 and type 2 receptors (AT_1 and AT_2)—rather than overall inhibition of the RAS—could explain this benefit. Furthermore, it should be noted that the analyses were not performed on the time to first event, as is more conventional, but rather on all the events that occurred, so as to enhance the power of the study.

In a study of post-stroke patients, treatment with perindopril alone did not provide a significant benefit, but the combination of perindopril and indapamide significantly reduced the risk of stroke by 43%.

High-Risk Hypertension Patients

The Losartan Intervention For Endpoint Reduction in hypertension (LIFE) study is widely considered to be a landmark trial showing the outcome benefits of ARB treatment. In LIFE, losartan-based treatment significantly reduced the risk of the primary coronary and stroke composite endpoint by 13% ($P = .021$) compared with atenolol-based therapy, a result driven largely by the 25% reduction in the relative risk of stroke with losartan compared with atenolol.[24] It should be recalled, though, that ARB treatment in LIFE was originally expected to test whether the inability of older antihypertensive therapies to reduce the risk of coronary events reflected a need to more effectively block the RAS.[25] In fact, losartan did not significantly reduce the risk of cardiovascular mortality compared with atenolol in the overall cohort, whereas the rate of MI in the losartan group was definitely not lower than in patients receiving atenolol.[24]

The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) compared the effects on cardiovascular outcomes of treatment with amlodipine, the ACE inhibitor lisinopril, or the thiazide diuretic chlorthalidone in hypertensive patients aged 55 years or older with one or more risk factors for coronary heart disease. Although the stated conclusions of ALLHAT remain highly controversial, the study found that neither lisinopril nor amlodipine provided significantly greater cardiovascular benefits than the diuretic chlorthalidone.[26] Criticisms can be made that the problems inherent in the design of ALLHAT put the ACE inhibitor group at a clear BP disadvantage, but the fact remains that the expected superiority of the RAS inhibitor was not demonstrated.

ACE inhibition and diuretics were also compared in the Second Australian National Blood Pressure Study (ANBP2), which enrolled hypertensive patients ages 65 to 84 years.[27] In ANBP2, ACE-inhibitor therapy provided a modest 11% reduction ($P = .05$) in the risk of cardiovascular events or all-cause mortality compared with diuretic therapy, with the benefit being stronger in men than in women. ANBP2, therefore, showed benefits of RAS blockade, but failed to demonstrate a compelling advantage of treatment with an ACE inhibitor.

One study showed that a treatment regimen based on the calcium channel blocker amlodipine, with the addition of the ACE inhibitor perindopril, significantly reduced the incidence of stroke, total cardiovascular events, and all-cause mortality compared with an atenolol–diuretic regimen.

More recently, the BP-lowering arm of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) showed that a treatment regimen based on the calcium channel blocker amlodipine, with the addition of the ACE inhibitor perindopril, significantly reduced the incidence of stroke ($P = .0003$), total cardiovascular events ($P < .0001$), and all-cause mortality ($P = .025$) compared with an atenolol-diuretic regimen.[28] The primary coronary endpoint, however, failed to achieve statistical significance due to the early termination of the trial. Since this trial was essentially a comparison of combination therapies, it is unclear whether the superior outcomes in the amlodipine/perindopril group were due to the calcium channel blocker, the ACE inhibitor, or the combination of the 2.

The Valsartan Antihypertensive Long-term Use Evaluation (VALUE) trial was specifically designed to test in high-risk hypertensive patients whether the ARB valsartan would provide cardioprotective benefits beyond BP-lowering compared with amlodipine.[29] In the VALUE trial, the incidence of the primary composite cardiac endpoint was virtually identical in the valsartan and amlodipine groups. Amlodipine was associated with a lower incidence of MI compared with valsartan, although heart failure endpoints tended to be lower with valsartan.[29] The study authors noted that BP control in VALUE was better in the amlodipine arm, and the unequal BP reductions may have confounded the interpretation of the results. What is more, valsartan was not administered at its optimal RAS-blocking dose. Overall, however, VALUE does not appear to provide strong evidence for the cardiovascular superiority of an ARB over a calcium channel blocker.

ACE Inhibitors and ARBs: Can We Do Better?

Taken together, the picture that emerges from these outcome trials is far from clear. Although some studies of ACE inhibitors or ARBs have demonstrated outcome benefits over other antihypertensive drug classes, the results as a whole have been somewhat equivocal. If ACE inhibitors and ARBs have not provided the full measure of outcome benefits that we might expect from inhibitors of a system with such pathophysiological importance as the RAS, it is important that we understand why.

The RAS can be considered a classic feedback loop, because angiotensin II acts to inhibit the release of renin from the kidney.[30] RAS

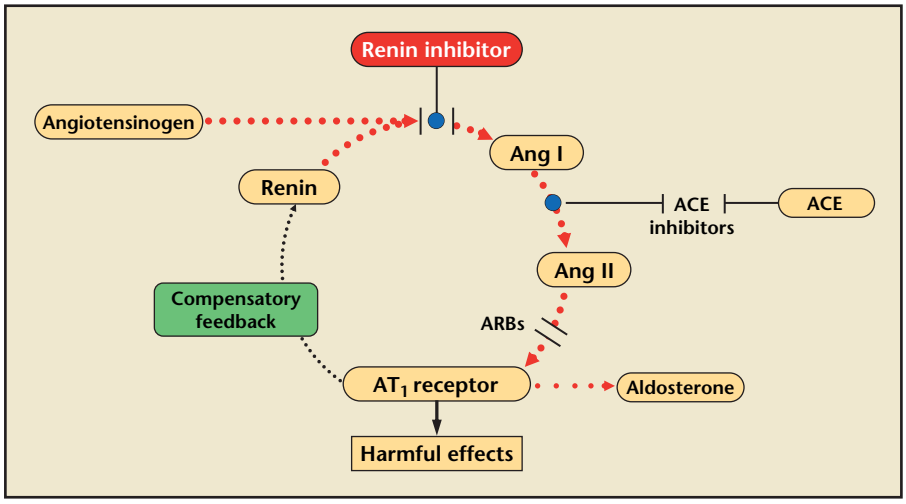

Figure 2. *Mechanisms by which the compensatory rise in renin stimulated by angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs), and diuretics leads to increased generation of angiotensin II. Figure shows that inhibition of the production or action of angiotensin II by ACE inhibitors or ARBs, respectively, prevents stimulation of the AT_1-receptor and disrupts the negative feedback loop through which angiotensin II normally inhibits renin release by the kidney. ACE inhibitors and ARBs thus stimulate a compensatory increase in renin release from the kidney, which ultimately leads to increased levels of angiotensin I and angiotensin II. A renin inhibitor would inhibit the reactive rise in renin activity that occurs with ACE inhibitors and ARBs and thus prevent increases in angiotensin I and angiotensin II levels. Ang, angiotensin; AT_1, angiotensin II type I.* www.medreviews.com

activity is governed by the rate-limiting step of the cycle, which is the action of renin on its substrate.[31] Inhibition of angiotensin II production (by ACE inhibitors) or action (by ARBs) disrupts the feedback loop by which angiotensin II normally inhibits renin release, so that these drugs actually stimulate the release of renin from the kidney and activate the RAS (Figure 2).[32]

prognosis.[34,35] The outcome benefits achieved with ARBs in patients with heart failure in Val-HeFT and CHARM required doses higher than those often used for BP-lowering effects (valsartan 160 mg bid and candesartan 32 mg qd, respectively), which might also reflect the need to counteract the compensatory increase in renin activity. Thus there may be scope for improved organ protection with new therapies that might provide more comprehensive inhibition of the RAS.

Patients with hypertension generate angiotensin II despite ACE inhibitor therapy. Studies have confirmed that this escape from ACE inhibition is associated with deteriorating control of blood pressure and poorer prognosis.

Does this stimulatory effect on the RAS matter? Clinical evidence suggests that it might. It was discovered more than 20 years ago that patients with hypertension generate angiotensin II despite ACE inhibitor therapy.[33] Subsequent studies have confirmed that this escape from ACE inhibition was associated with deteriorating control of BP and poorer

Does Increased RAS Suppression Improve Organ Protection?

Is there any evidence that we can obtain superior organ protection by increasing RAS suppression beyond what we can achieve with standard doses of ACE inhibitors or ARBs? For ARBs, recent evidence indicates that increasing the dosage beyond current recommended levels in patients with diabetes leads to modest but significantly greater renoprotective effects,[36] despite no further reduction in BP. These findings suggest that increased RAS suppression would be associated with improved organ protection independent of BP levels.

Another approach to enhancing RAS suppression is to combine ACE inhibitor therapy and ARB therapy. Some clinical evidence indicates that this approach shows promise. The combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial of 336 patients with non-diabetic renal disease demonstrated that combined treatment with trandolapril and losartan was significantly more effective at delaying the progression of kidney disease than was either drug alone (Figure 3).[37] Evidence from other large outcome trials is rather more equivocal. Significant additional outcome benefits were seen in chronic heart failure patients in the CHARM-Added trial,[38] but not in patients with acute heart failure following MI in VALIANT.[15] Unfortunately, where these studies were in agreement was that ACE inhibitor and ARB combination therapy lacked the excellent tolerability of the monotherapies, with hyperkalemia emerging as a particular problem in these complex patients with advanced disease.

In general, there is evidence that increasing RAS suppression beyond that achievable with currently approved doses of ACE inhibitor or ARB monotherapy can lead to improved clinical outcomes. But, although ACE inhibitors and ARBs

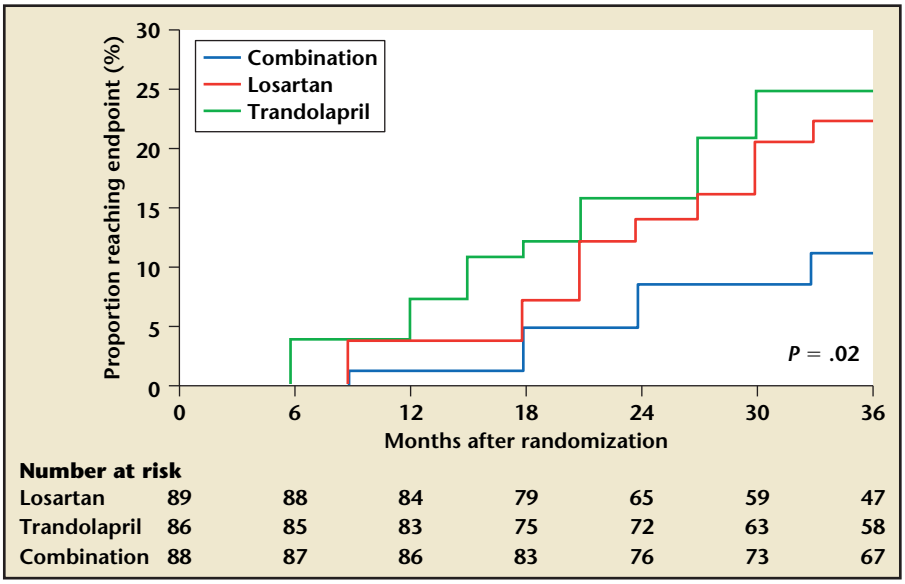

Figure 3. *Renoprotective benefits of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blocker (ARB) combination therapy in the combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE) trial. Figure indicates the percentage of patients in the COOPERATE trial reaching the primary study endpoint (time to doubling of serum creatinine concentration or end stage renal disease). Patients received treatment with either the ACE inhibitor trandolapril, the ARB losartan, or a combination of both drugs. Reprinted with permission from Elsevier.*[37] www.medreviews.com

have provided an excellent starting point for therapeutic inhibition of the RAS, we may need to look beyond these classes in order to optimize inhibition of this system.

RAS Suppression by Inhibiting Renin

Given that overall RAS activity is regulated by the activity of renin, and that the effects of ACE inhibitors and ARBs are potentially attenuated by the increased release of renin, inhibiting the action of renin stands out as a logical approach to improving the completeness of RAS suppression. Indeed, inhibition of renin was identified as the optimum means of inhibiting the RAS as long ago as 1957.[31] Efforts to develop a clinically effective renin inhibitor have been ongoing for longer than 30 years, but until recently they have been thwarted by problems with poor pharmacokinetics, low efficacy, and complexity of synthesis.[39]

Renin inhibition prevents the formation of angiotensin I and angiotensin II (whether generated by ACE-dependent or ACE-independent pathways), as well as all the angiotensin peptides that are subsequently derived from angiotensin I and angiotensin II.[39] The addition of a renin inhibitor to ACE inhibitor or ARB therapy would neutralize the compensatory rise in plasma renin activity that these agents induce (Figure 2), potentially enhancing suppression of the RAS. Moreover, because the renin enzyme is so specific—angiotensinogen is its only known natural substrate—renin inhibition would be expected to provide these additional benefits without additional side effects.[40] As yet, however, the clinical effects of this type of dual RAS blockade have not been tested, although the results of a study measuring the combined effects of an ACE inhibitor (ramipril) and a renin inhibitor (aliskiren) on components of the RAS are expected to be reported soon.

Because attempts to develop an effective oral renin inhibitor have long met with failure, many experts doubted that an agent such as a cardiovascular drug could be created. However, interest in renin as a target for antihypertensive therapy has recently been resurrected by the development of aliskiren, the first in a new class of orally effective renin inhibitors.[41] Studies in healthy volunteers showed that treatment with aliskiren caused dose-dependent reductions in plasma renin activity and angiotensin II levels.[42] Early clinical trials in patients with hypertension showed that this drug provided antihypertensive efficacy comparable to that of the ARBs losartan and irbesartan,[43,44] with placebo-like tolerability.[44,45] Moreover, a pilot study in healthy volunteers showed that aliskiren in combination with valsartan neutralized the compensatory rise in plasma renin activity and angiotensin II that is normally stimulated by the ARB,[46] suggesting that a renin inhibitor might be able to expand the reach of existing RAS inhibitors. The results of further studies investigating the organ-protective and outcome benefits of aliskiren are awaited.

The Importance of Target Organ Damage: The Hypertension Writing Group New Definition of Hypertension

The discovery that RAS activation is a contributor to the development of target organ damage in some patients with hypertension, independent of the effects of BP, has led to a growing realization that BP values alone represent an incomplete indicator of the presence of target organ damage and overall cardiovascular risk. Indeed, trials such as HOPE and

Table 1
Hypertension Writing Group Definition and Classification of Hypertension

Classification	Normal	Stage 1 Hypertension	Stage 2 Hypertension	Stage 3 Hypertension
Descriptive Category (BP Pattern and CVD Status)	Normal BP or rare BP elevations AND no identifiable CVD*	Occasional or intermittent BP elevations OR risk factors or markers suggesting early CVD*	Sustained BP elevations OR evidence of progressive CVD*	Marked and sustained BP elevations OR evidence of advanced CVD*
CVD Risk Factors†	None	≥ 1 risk factor present	Multiple risk factors present	Multiple risk factors present
Early Disease Markers‡	None	0-1	≥ 2	≥ 2 present with evidence of CVD
Target Organ Disease§	None	None	Early signs present	Overtly present with or without CVD events

*BP elevations refer to levels > 140/90 mm Hg. CVD designation is determined by the constellation of risk factors, early disease markers, and target organ disease.
†Cardiovascular risk factors include increased age, elevated BP (> 140/90 mm Hg), overweight/obesity (body mass index ≥ 24 kg/m^2), abdominal obesity, dyslipidemia, elevated fasting blood glucose (or insulin resistance or diabetes), smoking, family history of premature CVD, sedentary lifestyle, and elevated high-sensitivity C-reactive protein.
‡Early disease markers defined according to system, eg, blood pressure (includes loss of nocturnal BP dipping, widened pulse pressure), cardiac (includes mild left ventricular hypertrophy, increased atrial filling pressure), vascular (includes increased central arterial stiffness, increased carotid intima-media thickness, endothelial dysfunction), renal (includes microalbuminuria, elevated serum creatinine), and retinal (hypertensive retinal changes).
§Target organ damage and overt CVD defined according to system, eg, cardiac (includes moderate to severe left ventricular hypertrophy, symptomatic heart failure, myocardial infarction, angina pectoris, ischemic heart disease), vascular (includes peripheral arterial disease, carotid arterial disease, aortic aneurysm), renal (albuminuria, chronic kidney disease or end-stage renal disease), and cerebrovascular (stroke, transient ischemic attack).
BP, blood pressure; CVD, cardiovascular disease.

EUROPA showed that RAS inhibitor treatment can provide outcome benefits even in patients who have BP levels below the threshold for diagnosis of hypertension.[7,8]

The Hypertension Writing Group has responded to this realization by proposing a new definition of hypertension in which BP values are considered alongside indicators of target organ damage and cardiovascular risk[47]:

> Hypertension is a progressive cardiovascular syndrome arising from complex and interrelated etiologies. Early markers of the syndrome are often present before blood pressure elevation is observed; therefore, hypertension cannot be classified solely by discrete blood pressure thresholds. Progression is strongly associated with functional and structural cardiac and vascular abnormalities that damage the heart, kidneys, brain, vasculature and other organs, and lead to premature morbidity and death.

The proposed Hypertension Writing Group definition and classification of hypertension is presented (Table 1).

Notably, the ongoing Trial of Preventing Hypertension (TROPHY) study is investigating whether early RAS inhibitor treatment with an ARB in patients with prehypertension might prevent or delay the development of clinical hypertension.[48] Baseline cardiovascular risk profiles of the 809 subjects enrolled in TROPHY showed that 96% of subjects had at least one additional cardiovascular risk factor, 81% had 2 or more, and 13% had 5 or more additional risk factors.[49] These findings illustrate that in many patients, the risk of cardiovascular disease may begin to rise—due to risks such as early target damage—before BP reaches the current threshold for the diagnosis of hypertension. The potential benefits of early ARB treatment in protecting against RAS-induced organ damage in these patients will be of interest, although it is possible that the optimal time for intervention in the natural history of hypertension might be earlier than at the average age of 50 years studied in TROPHY.

Conclusions

The development of effective inhibitors of the RAS has led to a major step forward in our understanding of

the pathophysiology of cardiovascular disease. Indeed, the importance of target organ damage, such as that caused by RAS activation, has been recognized in the new definition of hypertension proposed by the Hypertension Writing Group. Although ACE inhibitors and ARBs have provided an excellent starting point for therapies targeting the RAS, clinical trial evidence indicates that there remains significant scope for testing whether increased and more comprehensive RAS suppression could produce additional clinical benefits. Aliskiren, the first in a new class of orally effective renin inhibitors, quite apart from its benefits as a single agent offers the potential to enhance the organ protection and outcome benefits of existing RAS inhibitors. Further trials investigating the effects of aliskiren and future renin inhibitors on cardiovascular and renal outcomes are getting underway. Renin inhibition may offer an important opportunity to examine whether the cardiovascular benefits of inhibiting the RAS can be fully realized. ■

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References

1. Volpe M, Savoia C, De Paolis P, et al. The renin-angiotensin system as a risk factor and therapeutic target for cardiovascular and renal disease. *J Am Soc Nephrol*. 2002;13(suppl 3): S173-S178.
2. Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens*. 1999; 12:205S-213S.
3. Hanes DS, Nahar A, Weir MR. The tissue renin-angiotensin-aldosterone system in diabetes mellitus. *Curr Hypertens Rep*. 2004;6:98-105.
4. Engeli S, Schling P, Gorzelniak K, et al. The adipose-tissue renin-angiotensin-aldosterone system: role in the metabolic syndrome? *Int J Biochem Cell Biol*. 2003;35:807-825.
5. Alderman MH, Ooi WL, Cohen H, et al. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens*. 1997;10:1-8.
6. Turnbull F, Neal B, Algert C, et al. Effects of different blood pressure-lowering regimens on major cardiovascular events in individuals with and without diabetes mellitus: results of prospectively designed overviews of randomized trials. *Arch Intern Med*. 2005;165:1410-1419.
7. Yusuf S, Sleight P, Pogue J, et al. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The Heart Outcomes Prevention Evaluation Study Investigators. *N Engl J Med*. 2000;342:145-153.
8. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). *Lancet*. 2003;362:782-788.
9. Braunwald E, Domanski MJ, Fowler SE, et al. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med*. 2004;351:2058-2068.
10. Nissen SE, Tuzcu EM, Libby P, et al. Effect of antihypertensive agents on cardiovascular events in patients with coronary disease and normal blood pressure: the CAMELOT study: a randomized controlled trial. *JAMA*. 2004;292: 2217-2225.
11. The CONSENSUS Trial Study Group. Effects of enalapril on mortality in severe congestive heart failure. Results of the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS). The CONSENSUS Trial Study Group. *N Engl J Med*. 1987;316:1429-1435.
12. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med*. 2001;345: 1667-1675.
13. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet*. 2003;362: 759-766.
14. Pfeffer MA, Braunwald E, Moye LA, et al. Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction. Results of the survival and ventricular enlargement trial. The SAVE Investigators. *N Engl J Med*. 1992;327:669-677.
15. Pfeffer MA, McMurray JJ, Velazquez EJ, et al. Valsartan, captopril, or both in myocardial infarction complicated by heart failure, left ventricular dysfunction, or both. *N Engl J Med*. 2003;349:1893-1906.
16. Lewis EJ, Hunsicker LG, Bain RP, Rohde RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. The Collaborative Study Group. *N Engl J Med*. 1993;329:1456-1462.
17. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med*. 2001;345:851-860.
18. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med*. 2001;345:861-869.
19. National Kidney Foundation. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification and stratification. *Am J Kidney Dis*. 2002;39(2 suppl 1):S1-S266.

Main Points

- Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have not delivered the *major* reductions in cardiovascular outcomes that were predicted given the broad role of renin-angiotensin system (RAS) activation in the pathophysiology of cardiovascular disease.
- Increased RAS suppression may improve organ protection. Increasing the dosage of ARBs beyond current recommended levels in patients with diabetes can lead to modest but significantly greater renoprotective effects, despite no further reduction in blood pressure. Another approach to enhancing RAS suppression is to combine ACE inhibitor therapy and ARB therapy.
- ACE inhibitor and ARB combination therapy lacks the excellent tolerability of the monotherapies, with hyperkalemia emerging as a particular problem in patients with advanced disease.
- Inhibiting the action of renin stands out as a logical approach to improving the completeness of RAS suppression.
- Blood pressure values alone represent an incomplete indicator of the presence of target organ damage and overall cardiovascular risk.

20. Casas JP, Chua W, Loukogeorgakis S, et al. Effect of inhibitors of the renin-angiotensin system and other antihypertensive drugs on renal outcomes: systematic review and meta-analysis. *Lancet*. 2005;366:2026-2033.
21. Collins R, MacMahon S. Blood pressure, antihypertensive drug treatment and the risks of stroke and of coronary heart disease. *Br Med Bull*. 1994;50:272-298.
22. PROGRESS Investigators. Randomised trial of a perindopril-based blood-pressure-lowering regimen among 6,105 individuals with previous stroke or transient ischaemic attack. *Lancet*. 2001;358:1033-1041.
23. Schrader J, Luders S, Kulschewski A, et al. Morbidity and Mortality After Stroke, Eprosartan Compared with Nitrendipine for Secondary Prevention: principal results of a prospective randomized controlled study (MOSES). *Stroke*. 2005;36:1218-1226.
24. Dahlof B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359:995-1003.
25. Dahlof B, Devereux R, de Faire U, et al. The Losartan Intervention For Endpoint reduction (LIFE) in Hypertension study: rationale, design, and methods. The LIFE Study Group. *Am J Hypertens*. 1997;10:705-713.
26. ALLHAT Investigators. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-2997.
27. Wing LM, Reid CM, Ryan P, et al. A comparison of outcomes with angiotensin-converting–-enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med*. 2003;348:583-592.
28. Dahlof B, Sever PS, Poulter NR, et al. Prevention of cardiovascular events with an antihypertensive regimen of amlodipine adding perindopril as required versus atenolol adding bendroflumethiazide as required, in the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA): a multicentre randomised controlled trial. *Lancet*. 2005;366:895-906.
29. Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet*. 2004;363:2022-2031.
30. Vander AJ, Greelhoed GW. Inhibition of renin secretion by Ang II. *Proc Soc Exp Biol Med*. 1965;120:339-403.
31. Skeggs LT, Kahn JR, Lentz KE, Shumway NP. Preparation, purification and amino acid sequence of a polypeptide renin substrate. *J Exp Med*. 1957;106:439-453.
32. Azizi M, Menard J. Combined blockade of the renin-angiotensin system with angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor antagonists. *Circulation*. 2004;109:2492-2499.
33. Biollaz J, Brunner HR, Gavras I, et al. Antihypertensive therapy with MK 421: angiotensin II–renin relationships to evaluate efficacy of converting enzyme blockade. *J Cardiovasc Pharmacol*. 1982;4:966-972.
34. van den Meiracker AH, Man in 't Veld AJ, Admiraal PJ, et al. Partial escape of angiotensin converting enzyme (ACE) inhibition during prolonged ACE inhibitor treatment: does it exist and does it affect the antihypertensive response? *J Hypertens*. 1992;10:803-812.
35. Roig E, Perez-Villa F, Morales M, et al. Clinical implications of increased plasma angiotensin II despite ACE inhibitor therapy in patients with congestive heart failure. *Eur Heart J*. 2000;21:53-57.
36. Rossing K, Schjoedt KJ, Jensen BR, et al. Enhanced renoprotective effects of ultrahigh doses of irbesartan in patients with type 2 diabetes and microalbuminuria. *Kidney Int*. 2005;68:1190-1198.
37. Nakao N, Yoshimura A, Morita H, et al. Combination treatment of angiotensin-II receptor blocker and angiotensin-converting-enzyme inhibitor in non-diabetic renal disease (COOPERATE): a randomised controlled trial. *Lancet*. 2003;361:117-124.
38. McMurray JJ, Ostergren J, Swedberg K, et al. Effects of candesartan in patients with chronic heart failure and reduced left-ventricular systolic function taking angiotensin-converting-enzyme inhibitors: the CHARM-Added trial. *Lancet*. 2003;362:767-771.
39. Fisher ND, Hollenberg NK. Renin inhibition: what are the therapeutic opportunities? *J Am Soc Nephrol*. 2005;16:592-599.
40. Wood JM, Cumin F, Maibaum J. Pharmacology of renin inhibitors and their application to the treatment of hypertension. *Pharmacol Ther*. 1994;61:325-344.
41. Wood JM, Maibaum J, Rahuel J, et al. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun*. 2003;308:698-705.
42. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor Aliskiren (SPP100): comparison with enalapril. *Hypertension*. 2002;39:E1-E8.
43. Stanton A, Jensen C, Nussberger J, O'Brien E. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension*. 2003;42:1137-1143.
44. Gradman AH, Schmieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation*. 2005;111:1012-1018.
45. Oh B-H, Chung J, Khan M, et al. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in patients with hypertension. *J Am Coll Cardiol*. 2006;47(4 suppl A):1027.
46. Azizi M, Menard J, Bissery A, et al. Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol*. 2004;15:3126-3133.
47. Giles TD, Berk BC, Black HR, et al. Expanding the definition and classification of hypertension. *J Clin Hypertens*. 2005;7:505-512.
48. Julius S, Nesbitt S, Egan B, et al. Trial of preventing hypertension: design and 2-year progress report. *Hypertension*. 2004;44:146-151.
49. Nesbitt SD, Julius S, Leonard D, et al. Is low-risk hypertension fact or fiction? cardiovascular risk profile in the TROPHY study. *Am J Hypertens*. 2005;18:980-985.