Renin–Angiotensin System Modulation for Treatment and Prevention of Cardiovascular Diseases: Toward an Optimal Therapeutic Strategy

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The unraveling of the role of the renin–angiotensin system (RAS) in health and disease is an example of how basic and applied scientists can decipher a complex biological system to better understand the pathophysiology of disease. Moreover, clinicians have been provided with drugs to modulate the RAS, including the angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs). ACE inhibitors and ARBs have revolutionized the way in which many diseases are treated, including hypertension, heart failure, diabetes mellitus, and kidney disease. Yet, despite the undoubted successes of these drugs, cardiovascular morbidity and mortality remain high. Clearly, lower blood pressure goals may be required. Because ACE inhibitors and ARBs target specific areas of the RAS, more impressive results might be obtained with a more global reduction in RAS activity. This article examines the results of clinical trials of ACE inhibitors and ARBs and assesses the potential for improving outcomes through a more global inhibition of the RAS with renin inhibitors.
[Rev Cardiovasc Med. *2007;8(suppl 2):S14-S21*]

Key words: Angiotensin receptor blocker • Angiotensin-converting enzyme inhibitor • Hypertension • Renin • Renin inhibitor

The proper functioning of the renin–angiotensin system (RAS) is, of course, necessary for good health. The RAS plays a major role in regulating sodium levels and intravascular volume and in modulating many local physiological processes. It is now recognized that dysregulation of the RAS may be a key factor in the pathophysiology and development of increased blood pressure (BP), renal disease, atherosclerosis, diabetes, and heart failure in a substantial number of patients.[1,2]

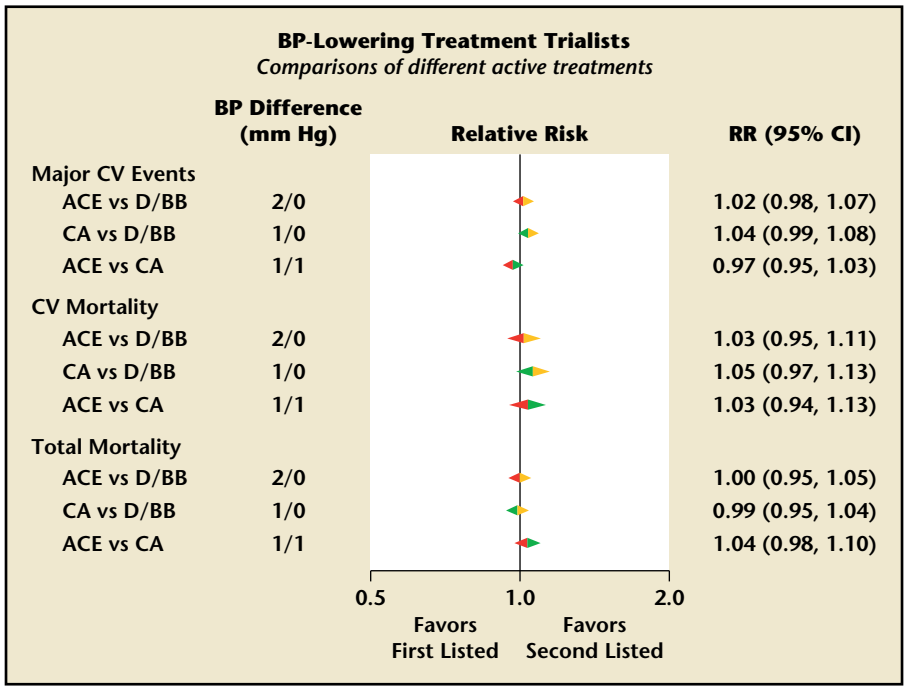

Figure 1. *A meta-analysis of antihypertensive clinical trials fails to show an advantage of angiotensin-converting enzyme (ACE) inhibitors over other classes of drugs. BP, blood pressure; RR, relative risk; CI, confidence interval; CV, cardiovascular; D/BB, diuretic/beta-blocker; CA, calcium antagonist. Adapted with permission from Blood Pressure Lowering Treatment Trialists' Collaboration.*[6]

The precise role of the RAS in increasing BP and producing target organ damage in patients with primary hypertension is not known. However, in conditions such as diabetes mellitus and heart failure, dysregulation of the RAS is apparent. And angiotensin II, the octapeptide that mediates the effects of the RAS, may play a role in cardiovascular pathological remodeling, leading to structural and functional changes in the myocardium, kidney, and vasculature.[2]

The RAS may also have an important role in the pathophysiology of the metabolic syndrome. Angiotensin II is produced by the visceral adipocytes and 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 angiotensin II may result from increased oxidative stress due to the action of this peptide on membrane NAD(P)H oxidase.

Has Interruption of the RAS by ACE Inhibitors and ARBs Achieved the Goal of Reducing Cardiovascular Morbidity and Mortality?

Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) have not delivered the *major* reductions in cardiovascular outcomes that were predicted on the basis of the belief that the RAS is broadly dysregulated in hypertension. For instance, a recent meta-analysis of 27 randomized trials involving 158,709 patients, conducted by the Blood Pressure Lowering Treatment Trialists' Collaboration (BPLTTC), showed no significant advantage of ACE inhibitors or ARBs over other classes of antihypertensives with regard to major clinical outcomes (Figures 1, 2).[5,6] An alternative hypothesis, of course, is that ACE inhibitors and ARBs are not fully effective in blocking this system.

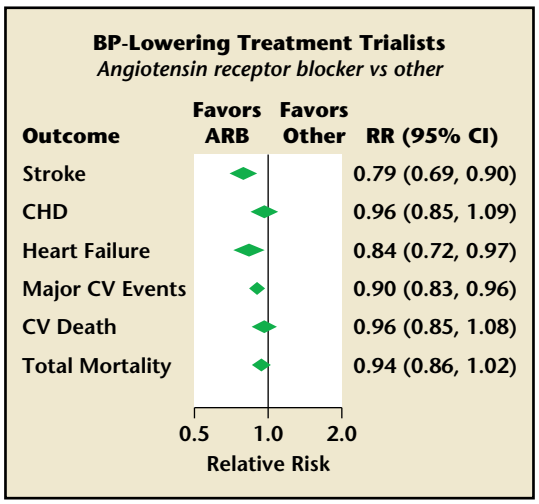

Figure 2. *A meta-analysis of antihypertensive clinical trials fails to show an advantage of the angiotensin receptor blockers (ARBs) over other classes of drugs. BP, blood pressure; RR, relative risk; CI, confidence interval; CHD, coronary heart disease; CV, cardiovascular. Adapted with permission from Blood Pressure Lowering Treatment Trialists' Collaboration.*[6]

Successes of ACE inhibitors and ARBs in Outcome Trials

The clinical benefits of ACE inhibitors and ARBs in certain subsets of patients, including patients at high risk and those with heart failure, post myocardial infarction (MI), and renal disease (Figure 3), cannot be denied. An examination of these subsets illustrates the benefits of modulating the RAS.

High-Risk Patients

In the Heart Outcomes Prevention Evaluation (HOPE) study, the ACE inhibitor ramipril significantly reduced the incidence of MI, cardiovascular death, or stroke by 22%

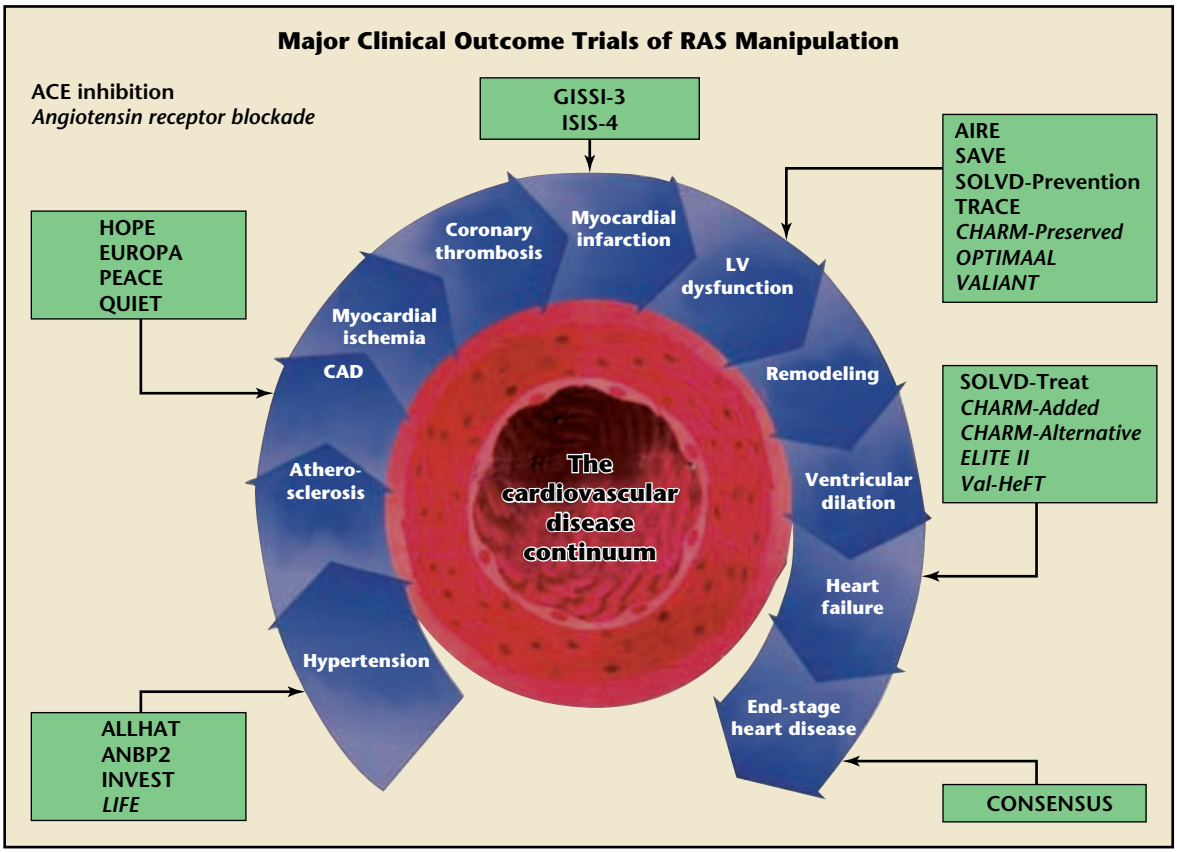

Figure 3. *Clinical trials of angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockade therapy in various subsets of cardiovascular disease have shown beneficial effects on outcomes of morbidity and mortality. RAS, renin–angiotensin–aldosterone system; CAD, coronary artery disease; LV, left ventricular.*

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 Stable Coronary Artery Disease (EUROPA) study, perindopril significantly reduced cardiovascular events by 20% compared with placebo ($P = .0003$).[8] However, at least some of the cardiovascular benefits achieved by ACE inhibitors could be attributed to reductions in BP.

The addition of an ACE inhibitor to conventional therapy did not provide additional cardiovascular benefits for patients with coronary artery disease (CAD) in the Prevention of Events with Angiotensin Converting Enzyme Inhibition (PEACE) trial.[9] Trandolapril did not reduce the incidence of the primary study endpoint of cardiovascular death, MI, or coronary revascularization compared with conventional therapy alone. However, the event rate was low, probably reflecting 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.[10] CAMELOT compared the effects of treatment with the ACE inhibitor enalapril or the calcium channel blocker (CCB) amlodipine with placebo on cardiovascular events in patients with CAD. Although amlodipine treatment 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; $P = .16$). Interestingly, in a cohort of patients who underwent serial intravascular ultrasound of the coronary arteries, a reduction in atherosclerotic plaque volume was related to the degree to which BP was lowered, regardless of the drug used.[11]

Heart Failure

Activation of the RAS, along with other neurohormonal systems such as the sympathetic nervous system,

is strongly linked to the progression of heart failure. The importance of interruption of the RAS in heart failure was demonstrated in the Cooperative North Scandinavian Enalapril Survival Study (CONSENSUS).[12] The ACE inhibitor enalapril reduced mortality by 27% compared with placebo ($P = .003$).

Use of ARBs to modulate the RAS in heart failure was examined in the Valsartan Heart Failure Trial (Val-HeFT).[13] Addition of 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, driven primarily by a reduction in hospitalizations for heart failure. 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 patients with chronic heart failure significantly reduced the hard endpoints of all-cause mortality by 10% ($P = .032$) and cardiovascular death by 13% ($P = .006$).[14]

Despite the positive effects of candesartan in the CHARM studies, residual mortality remained high (23% and 25% in the candesartan and placebo groups, respectively). That nearly 1 patient in 4 died during the course of the trial even with ARB (combined in some patients with ACE inhibitor) treatment suggests there is room for improvement with alternative strategies; among the strategies to be considered are alternative methods for inhibiting the RAS.

Post Myocardial Infarction

Following strong preclinical data, the benefits of ACE inhibitor treatment in patients with reduced left ventricular systolic function following MI were demonstrated in the Survival and Ventricular Enlargement (SAVE) trial.[15] 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. 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.[16] The study found that valsartan was equal to captopril monotherapy in its effects on major endpoints. The ACE inhibitor–ARB combination did not provide improved cardiovascular outcomes compared with the ACE inhibitor alone, although this finding might be explained by both drugs being administered at a time when patients were not hemodynamically stable. Nevertheless, the results of VALIANT suggest the need for alternative modulation of the RAS in post-MI patients.

Diabetic Nephropathy

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 are not increased. Both ACE inhibitors and ARBs have demonstrated renoprotective benefits in trials in patients with diabetic nephropathy, such as the Captopril Collaborative Study, the Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan (RENAAL) study, and the Irbesartan in Diabetic Nephropathy Trial (IDNT).[17-19] 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 glomerular filtration rate in both studies was still higher than the expected loss due to aging,[18,19] as specified in National Kidney Foundation guidelines.[20] Likewise, proteinuria was significantly reduced, but still remained in the macroalbuminuria range.

The benefits of ACE inhibitors and ARBs for patients with diabetic renal disease were evaluated in a recent meta-analysis of 127 randomized trials involving 73,514 patients.[21] This study confirmed that ACE inhibitor or ARB treatment provides renoprotective benefits, but indicated that these were probably due to the BP-lowering effects of treatment. The analysis also suggested that ACE inhibitor or ARB treatment of patients with diabetic nephropathy provided no significant additional renoprotective benefits compared with other antihypertensive classes. Perhaps further benefits might occur with more fully effective blockade of the RAS.

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Neither the RENAAL nor the IDNT studies demonstrated a significant beneficial effect of ARB treatment on cardiovascular morbidity and mortality.[18,19] Further, data from a meta-analysis of antihypertensive clinical trial results from the BPLTTC in the subgroups of patients with diabetes indicated that neither ACE inhibitor

nor ARB treatment provided significantly greater benefits for cardiovascular events than did other drug classes.[7]

Post Stroke

Blood pressure 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.[22] The Perindopril Protection Against Recurrent Stroke Study (PROGRESS) evaluated the effects of treatment with the ACE inhibitor perindopril (with addition of the diuretic indapamide at the discretion of the investigators) on the incidence of stroke in patients with a history of stroke or transient ischemic attack.[23] Although perindopril alone did not provide a significant benefit, the combination of perindopril and indapamide significantly reduced the risk of stroke by 43% ($P < .0001$) compared with placebo. Given that the combination treatment also provided significantly greater BP reductions ($P < .001$) than did 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.

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—the first trial to compare an ARB (eprosartan) with a CCB (nitrendipine) in the secondary prevention of stroke in hypertensive patients.[24] For 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. 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 should be noted that data analyses were not performed on the time to first event, as is more conventional, but rather, to enhance the power of the study, counted all the events that occurred.

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High-Risk Hypertension

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.[25] Losartan-based treatment significantly reduced the risk of the primary coronary and stroke composite endpoint of the study by 13% ($P = .021$) compared with the atenolol-based therapy, a result driven largely by the 25% relative reduction in the risk of stroke with losartan compared with atenolol. It should be kept in mind, however, 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.[26] In fact, losartan did not significantly reduce the risk of cardiovascular mortality compared with atenolol in the overall cohort, and the rate of MI in the losartan group was no lower than in patients receiving atenolol.[25] The primary endpoint was driven by the reduction in stroke that may have resulted from a more pronounced reduction in central aortic pressure with losartan as compared with atenolol. This latter concept is supported by the Conduit Artery Function Evaluation (CAFÉ) substudy of the Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) study, as discussed below.

ACE inhibition and diuretics were also compared in the Second Australian National Blood Pressure Study (ANBP2), which enrolled hypertensive patients aged 65 to 84 years.[27] In this study, 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. Thus ANBP2, while showing benefits of RAS blockade, failed to demonstrate a compelling advantage of treatment with an ACE inhibitor.

More recently, the BP-lowering arm of ASCOT showed that a treatment regimen based on the CCB amlodipine, with 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, although the primary coronary endpoint failed to achieve statistical significance, given the early termination of the trial.[28] Because this was essentially a comparison of combination therapies, it is unclear whether the superior outcomes in the amlodipine/perindopril group were due to the CCB, the ACE inhibitor, or the combination of the two. As mentioned above, there was

less reduction in central aortic pressure with the atenolol-based regimen than the ACE inhibitor regimen.[29]

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 treatment.[30] In this trial, the incidence of the primary composite cardiac endpoint was virtually identical in the amlodipine and valsartan groups. However, amlodipine was associated with a lower incidence of MI compared with valsartan, though heart failure endpoints tended to be lower with valsartan. Because of the study design, there was an inequality in BP control in the early phase of the trial, and thus the unequal BP reductions may have confounded the interpretation of the results.

Addition of a renin inhibitor to an ACE inhibitor or ARB therapy would neutralize the compensatory rise in plasma renin activity induced by these agents, potentially enhancing suppression of the RAS.

Will Suppression of the RAS by Inhibition of Renin Produce the Cardiovascular Benefits Not Found With ACE Inhibitors and ARBs?

Overall activity of the RAS is regulated by the activity of renin. Because of the negative feedback loop stimulated by angiotensin II on the AT_1 receptor, the effects of ACE inhibitors and ARBs are potentially attenuated by the increased release of renin. Thus, inhibiting the action of renin seems a logical approach to improving the completeness of RAS suppression.

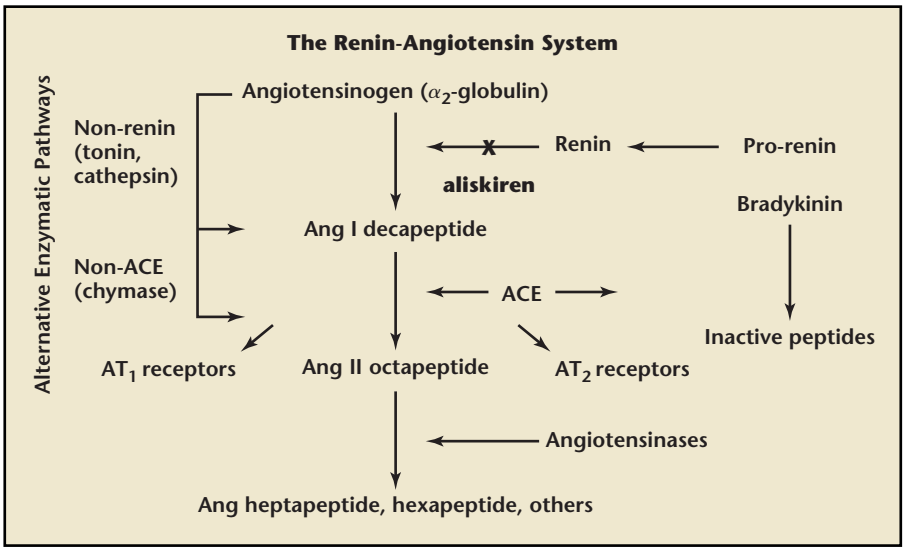
Renin inhibition prevents the formation of angiotensin I, angiotensin II (whether generated by ACE-dependent or -independent pathways), and all angiotensin peptides subsequently derived from angiotensin I and II (Figure 4).[31] Addition of a renin inhibitor to an ACE inhibitor or ARB therapy would neutralize the compensatory rise in plasma renin activity induced by these agents, 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. 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.

Aliskiren (soon to be made available), the first in a new class of orally effective renin inhibitors, has increased interest in renin as a target for antihypertensive therapy.[32] Studies in healthy volunteers showed that aliskiren caused dose-dependent reductions in plasma renin activity and angiotensin II levels,[33] and early clinical trials in patients with hypertension showed that this drug had antihypertensive efficacy comparable to that of the ARBs losartan and irbesartan,[34,35] with placebo-like tolerability.[35,36] Moreover—and with possible relevance to the ability of a renin inhibitor to expand the reach of existing RAS inhibitors—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.[36] The results of further studies investigating the organ-protective and outcome benefits of aliskiren are awaited.

RAS Modulation in the Context of a New Definition of Hypertension

The discovery that RAS activation is a contributor to the development of

Figure 4. *A new approach to modulation of the renin–angiotensin system by blocking renin, the rate-limiting enzyme. This may provide a strategy to provide a more recognizable beneficial influence on target organ damage beyond blood pressure lowering than has been seen with angiotensin-converting enzyme (ACE) inhibitor and angiotensin receptor blockade therapy. Ang, angiotensin.*



target organ damage in some patients with hypertension, independent of the effects of BP, has led to a growing realization that BP values alone are an incomplete indicator of the presence of target organ damage and overall cardiovascular risk. Indeed, trials such as HOPE and EUROPA showed that RAS inhibitor treatment can provide outcome benefits even in patients with BP levels below the threshold for diagnosis of hypertension.[7,8]

The Hypertension Writing Group has responded to this by developing a proposed new definition of hypertension in which BP values are considered alongside indicators of target organ damage and cardiovascular risk: "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."[37] The group presents a definition and classification of hypertension.

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.[38-40] Baseline cardiovascular risk profiles of the 809 subjects enrolled in TROPHY showed that 96% of participants had at least 1 additional cardiovascular risk factor, 81% had 2 or more, and 13% had 5 or more.[39] These findings illustrate that in many patients, the risk of cardiovascular disease may begin to rise before BP reaches the current threshold for the diagnosis of hypertension, due to other co-occurring risks such as early target organ damage, in addition to rising BP. The potential benefits of early ARB treatment in protecting against RAS-induced organ damage in these patients will be of interest, though the optimal time for intervention in the natural history of hypertension might prove to be earlier than the average age of 50 years studied in TROPHY.

These findings illustrate that in many patients, the risk of cardiovascular disease may begin to rise before BP reaches the current threshold for the diagnosis of hypertension, due to other co-occurring risks such as early target organ damage, in addition to rising BP.

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. But 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, more comprehensive RAS suppression could produce additional clinical benefits. The development of aliskiren, the first in a new class of orally effective renin inhibitors, offers, quite apart from its benefits as a single agent, 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 beginning. 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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Main Points

- Dysregulation of the renin–angiotensin system (RAS) is a key factor in the pathophysiology and development of increased blood pressure (BP), renal disease, atherosclerosis, diabetes, and heart failure in some patients.
- The clinical benefits of angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) in patients at high risk and in cases of heart failure, post myocardial infarction (MI), diabetic nephropathy, post stroke, and high-risk hypertension have been demonstrated in many outcome trials.
- However, ACE inhibitors and ARBs have not delivered the major reductions in cardiovascular outcomes that were predicted on the basis of the belief that the RAS is broadly dysregulated in hypertension.
- Addition of a renin inhibitor to an ACE inhibitor or ARB therapy would potentially enhance suppression of the RAS.
- Aliskiren is the first in a new class of orally effective renin inhibitors; studies on the organ-protective and outcome benefits of aliskiren are under way.
- RAS activation is a contributor to the development of target organ damage in some patients with hypertension, independent of the effects of BP.
- The Hypertension Writing Group has proposed a new definition of hypertension in which BP values are considered alongside indicators of target organ damage and cardiovascular risk.