Expanding the Opportunities for Blocking the Renin–Angiotensin System: Introduction to a Special Supplement

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The previous dogma that the renin–angiotensin system exerts its effects entirely through angiotensin II is now under challenge as scientists explore the properties of the prorenin/renin receptor and start to study local vascular actions of renin independent of its production of angiotensin in the plasma. The demonstrated blood pressure effects of the first clinically developed renin inhibitor, aliskiren, have confirmed the validity of this new class of drugs. Future research, exploring effects on the renin–angiotensin system that perhaps cannot be provided by the currently used blockers of this system, will test whether enhanced clinical benefits might result from this new pharmacologic strategy in patients at risk of cardiovascular events.
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During most of the last 3 decades, the renin–angiotensin–aldosterone system has been one of the primary targets for managing diseases of the cardiovascular system. Angiotensin-converting enzyme (ACE) inhibitors that oppose this system by preventing conversion of angiotensin I to angiotensin II, or angiotensin receptor blockers that oppose the system by antagonizing the effects of angiotensin II at its AT_1 receptor, are now indicated for such conditions as hypertension, diabetic nephropathy, and both chronic heart failure and the acute heart failure that can follow myocardial infarctions. In patients at high cardiovascular risk, these drugs also seem to be beneficial in preventing major fatal and nonfatal events, as well as the onset of type 2 diabetes and atrial fibrillation. The angiotensin receptor blockers perhaps are particularly useful in preventing stroke events in hypertension.

Despite these apparently impressive credentials, these drug classes may not have provided the full array of benefits that might be expected if the renin system were comprehensively blocked. In his carefully reasoned contribution to this supplement to *Reviews in Cardiovascular Medicine*, Dr. Thomas Giles reviews in detail the relevant clinical trials that have tested these therapies and explores how upgrading the efficacy of interventions on the renin–angiotensin system (RAS) could yet further improve clinical outcomes.[1]

Our Understanding of the RAS Continues to Grow

The enzyme renin was first discovered in the late 19th century, and we have continued to study and define what we now know to be a complex physiologic system. Dr. Norman Hollenberg's contribution to this supplement takes a broad look at the system as a whole.[2] He makes a compelling argument that we might be wise to shift our attention from the angiotensin end of the cascade where, owing to the development of the drug classes like ACE inhibitors and angiotensin receptor blockers, it has been focused during recent years. Instead, Hollenberg advises that there is still much to be learned about renin, and even its predecessor in the cascade, prorenin. Certainly, as he describes, some exciting recent research has created the possibility that these components of the system may have important physiologic and pathologic effects that are not accounted for in the conventional view of the RAS.

The history of our research into the RAS has been described in many places, but as Hollenberg points out, the 1950s was a period in which the main components of this system were finally defined and named. Hollenberg also makes the fascinating point—one that we typically overlook—that renin is the rate-limiting step of the entire system.

Major changes in our perception of the RAS came in the early 1970s, when two pivotal research reports, reflecting the work of Laragh and colleagues, had the effect of switching interest in this system from the domain of the hypertension expert into the mainstream of clinical medicine.[3,4] One of these articles, from 1972,[3] made the assertion that hypertensive patients with higher renin levels had a greater probability of major cardiovascular events than patients with normal or low renin levels. The second article, from the same year,[4] laid the groundwork for another bold hypothesis, namely that hypertension could be explained on the basis of a vasoconstriction/volume interaction in which vasoconstriction was directly related to the measurement of plasma renin activity, whereas the volume component that reflected excess sodium and water in the circulation was predicted by low renin activity.

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These concepts, particularly the one relating to prognosis, subsequently went beyond the bounds of hypertension and seemed to be applicable to the broader field of cardiovascular medicine. Almost certainly, these early clinical studies provided the stimulus for the subsequent dramatic exploration of the role of the RAS in vascular disease, and equally as important, for the development of drugs that work primarily by interrupting this system.

The RAS as a Cause of Vascular Pathology

The link between plasma renin activity and myocardial infarction,[3] confirmed by a later, more robust study in 1991,[5] exposed a mechanism of disease that potentially could go well beyond hypertension. In fact, countless studies since that time have examined the vascular biology underlying the differing ways in which angiotensin II, the supposed effector hormone of the system, can accelerate arterial disease.[6] Mediators of disease like oxidative stress, proliferative changes, profibrotic and prothrombotic stimuli, and vasoconstriction can all be attributed to actions of angiotensin II in the vascular wall. On a more clinical scale, mechanisms underlying congestive heart failure, left ventricular hypertrophy, plaque rupture, and thrombotic events could be attributed to angiotensin II activity. Likewise, many of the connections between obesity and its cardiovascular, renal, and diabetic consequences could be attributed to the RAS.[7]

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So it is not surprising, as summarized previously,[8] that drugs like ACE inhibitors and angiotensin receptor blockers have improved survival and reduced major clinical events in several conditions of increased

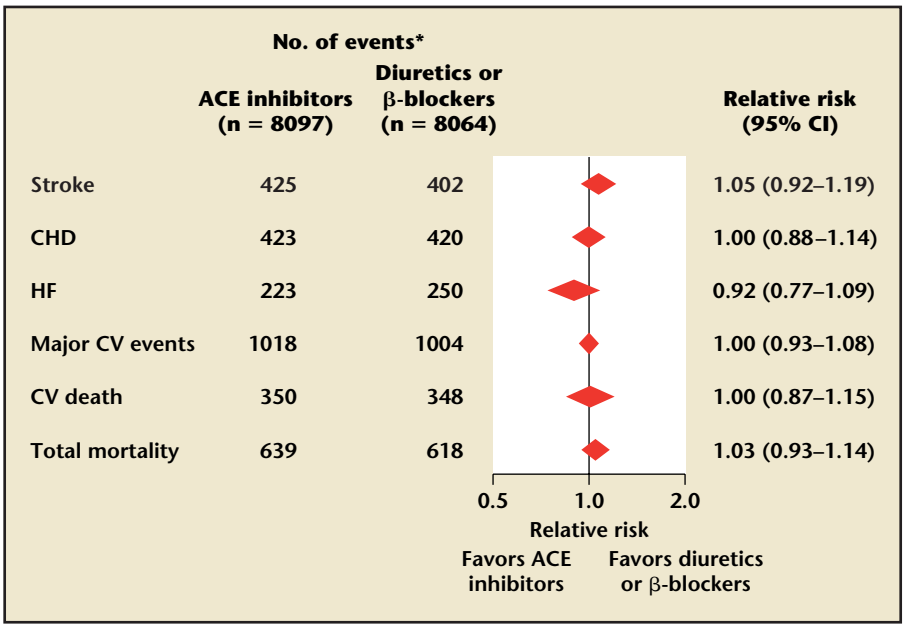


Figure 1. *Relative risk of cardiovascular (CV) events and mortality: angiotensin-converting enzyme (ACE) inhibitors vs diuretics or β-blockers. Diamonds represent the 95% confidence interval (CI) for pooled estimates of effect and are centered on pooled relative risk. CHD, congestive heart disease; HF, heart failure. *Includes the STOP-2, UKPDS-HDS, and CAPPP studies. Adapted with permission from Neal et al.*[9]

cardiovascular risk. But despite these important successes, the question remains whether these therapeutic strategies have fully provided the types of benefits that could be expected from effective blockade of the RAS.[8] Indeed, regarding clinical outcomes in the setting of hypertension, as shown in Figure 1, the blockers of the RAS have not been consistently more effective than other drug types in preventing key clinical endpoints like myocardial infarction or cardiovascular mortality.[9] Dr. Giles's article in this supplement examines these critical questions far more thoroughly.[1]

Still, it is appropriate to ask whether these useful but incomplete clinical benefits of angiotensin-blocking drugs bring into question the role of the RAS as a mediator of cardiovascular disease. Not necessarily. As Hollenberg points out,[2] the ACE inhibitors and angiotensin receptor blockers as single agents may not have the capacity to completely antagonize the RAS. And, as he also points out, newly available data show that renin and prorenin may exhibit vascular effects independent of the production and action of angiotensin in the circulation.

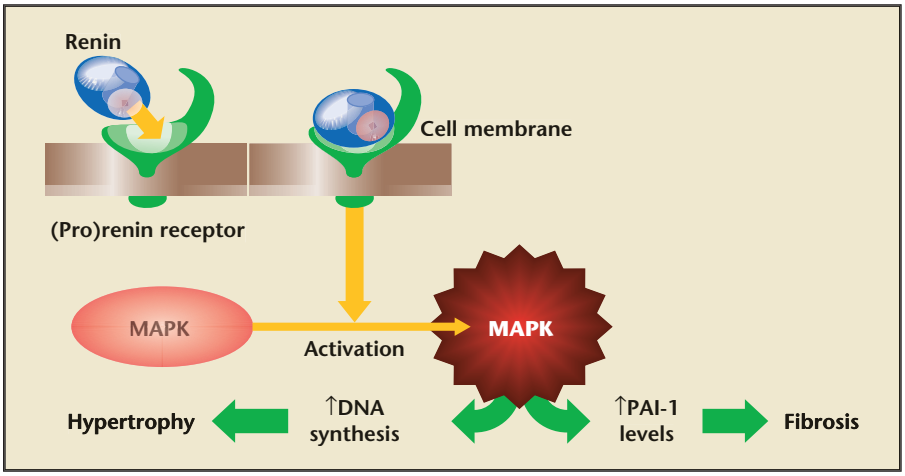
The cornerstone of this new concept is the recent discovery of the renin receptor. One of the important characteristics of this receptor is that it can be activated both by renin and prorenin. Because prorenin is abundantly available, probably several times more so than renin itself, this receptor may have a critical part to play.

Focus on Renin

There are 2 possible ways in which a renin receptor could channel important physiologic or pathophysiologic effects. One of these is linked to the ability of prorenin or renin to work on the substrate, angiotensinogen, while bound to the renin receptor within cell membranes. In turn, the angiotensin I thus produced is acted on by the ACE, also bound to the cell membrane, producing angiotensin II in immediate proximity to the AT_1 receptor at which it exerts its potentially harmful effects.

Studies in cell cultures indicate a second but equally interesting role for the renin/prorenin receptor. Figure 2 summarizes data indicating that activation of this receptor by prorenin or renin directly activates

Figure 2. *Activation of mitogen-activating protein kinase (MAPK) cell signaling pathways in cell culture by renin. Binding of renin to the (pro)renin receptor activates cell signaling pathways and may lead to increased tissue fibrosis and cellular hypertrophy. DNA, deoxyribonucleic acid; PAI-1, plasminogen activator inhibitor 1. Derived from data in Nguyen et al.*[10]



cell-signaling pathways by stimulating mitogen-activated protein (MAP) kinase. In turn, the MAP kinase promotes local mechanisms that can result in such potentially adverse effects as cellular hypertrophy, increased fibrosis, and possibly even enhanced production of thrombotic factors.[10]

The existence of these mechanisms, as discussed by both Giles and Hollenberg,[1,2] at least theoretically might explain how blockade of the RAS based on antagonizing angiotensin II may not fully block the RAS as a whole. Certainly, Hollenberg provides some fascinating data from his own research to illustrate the potential clinical importance of addressing renin (or prorenin) as well as angiotensin.

Indeed, this possibility exposes a fascinating twist in the story first proposed in 1972.[3] Back then, it was assumed that the measurements of plasma renin activity were simply surrogates for angiotensin II levels, which at that time could not readily be measured directly. It is now tantalizing to contemplate the possibility that the increased clinical events predicted by high plasma renin levels were, in fact, at least partly dependent on direct actions of renin itself.

Renin and Blood Pressure

Data put forward in 1973[11] led to a construct in which the measurement of plasma renin activity predicted the state of vasoconstriction or volume excess responsible for maintaining hypertension. In patients with inappropriately high levels of plasma renin activity, it was postulated that the RAS itself was responsible for causing vasoconstriction and raising blood pressure, whereas low plasma renin activity was indicative of hypertension being sustained by excess intravascular plasma volume. Hypertensive patients with so-called normal renin could be regarded as having components of both vasoconstriction and volume excess as the cause of their high blood pressure.

This hypothesis seemed to be borne out by simple clinical experience. A tool that was vital in this work was the β-blocker, a type of drug that in most cases has an inhibitory effect on renin release from the kidney.[12] So, it was possible to demonstrate that an agent, for example propranolol, was more effective in reducing blood pressure in high renin patients than in normal or low renin patients.[13] On the other hand, a diuretic was shown to be most effective in reducing blood pressure in low renin patients and least effective in patients with high plasma renin activity.[14] It was also possible to demonstrate that the renin–angiotensin–aldosterone system could mediate the blood pressure response to therapy. For example, a diuretic could be shown to be most effective in reducing blood pressure in those patients whose reactive increases in renin and aldosterone were relatively suppressed.[15]

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The β-blockers were actually the first group of drugs demonstrated to have anti-renin effects and in that sense were the true forerunners of the ACE inhibitors and the angiotensin receptor blockers. Like the β-blockers, it was also possible with the newer drug classes to show, at least acutely during the several hours following the first dose, that blood pressure changes were related to baseline measurements of plasma renin activity.[16] During chronic therapy with the ACE inhibitors and angiotensin receptor blockers, it was less possible to link effects on the RAS to blood pressure changes, presumably because all of these drugs have additional properties that could separately contribute to their overall blood pressure actions.

Still, it is reasonable to claim that the original observations in the early 1970s were a major stimulus for developing drugs that could work selectively to block the RAS. Likewise, the vasoconstriction/volume hypothesis foreshadowed our contemporary use of antihypertensive agents—particularly the growing reliance on combinations of RAS blockers and diuretics—for the routine management of hypertension across a broad spectrum of patients.[17] The newest blockers of the system, the direct renin inhibitors, seem to be the appropriate successors to the original β-blockers, as well as drugs working beyond the point of activation of the RAS.

The Renin Inhibitors

Logically speaking, attempts to interrupt the RAS should have begun with drugs working on renin rather than on angiotensin II. But, as briefly discussed in this supplement by Drs. Alan Gradman and Darren Traub,[18] agents that directly inhibit the action of renin have been very difficult to produce. Most early attempts depended on dipeptide products that worked well when administered intravenously but were not effective when taken orally. Clearly, peptides do not readily survive in the bowel, and it proved too difficult and too expensive to produce products that could be absorbed in sufficient

quantities to exhibit meaningful clinical effects.

The recent availability of aliskiren marks a major breakthrough in medicinal chemistry. For the first time, it has been possible to synthesize a product that can be absorbed to an extent sufficient to provide therapeutic efficacy. Even though approximately 3% of this drug typically gets into the systemic circulation after oral dosing, clearly this amount is consistent enough to provide strong effects on renin activity and blood pressure.

Clinical trials have now established that aliskiren is a clinically efficacious antihypertensive drug. The contribution by Gradman and Traub to this supplement details the major studies that have now established the clinical value of this agent.[18] This work demonstrates that aliskiren has a clear dose–response effect and that it has antihypertensive efficacy comparable to that observed with other major drug classes. As might be expected, this agent also works well when combined with such drugs as diuretics or calcium channel blockers.

Important among the clinical data marshaled by Gradman and Traub are studies indicating that aliskiren produces significant additional blood pressure reductions when added to full doses of other blockers of the RAS. For instance, preliminary findings indicate that, when combined with a full dose of an ACE inhibitor, aliskiren provides a significant additional blood pressure–lowering effect. If this observation can be confirmed, it will underscore a critically important attribute of this new renin inhibitor. If we assume that full doses of drugs working to prevent the production or the hemodynamic effects of angiotensin II are already in place, then the additional effects of aliskiren would indicate that there could be physiologically important blood pressure properties of the RAS that cannot be entirely explained by the action of angiotensin II. In other words, it is possible to contemplate the possibility that renin activity is directly influencing blood pressure by pathways separate from our traditional view of the RAS. This concept clearly remains to be explored more thoroughly by future basic science and clinical studies.

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Conclusion

Our standard pathway to medical progress has depended on increasing our understanding of disease processes and then devising strategies to address them. But at the same time, the development of innovative drugs can provide the tools to better study basic mechanisms and so in turn broaden treatment opportunities. In fact, this sequence has been true for all the major drug types mentioned in this commentary: the β-blockers, ACE inhibitors, angiotensin receptor blockers, and even the direct renin inhibitors.

It is intriguing that coinciding with the feasibility of using renin inhibitors we have refocused attention on both the physiologic and also the potentially adverse direct effects of renin and prorenin. The previous dogma that the RAS exerts its effects entirely through angiotensin II is now under challenge as scientists explore the properties of the prorenin/renin receptor and start to study local vascular actions of renin independent of its production of angiotensin in the plasma.

The demonstrated blood pressure effects of the first clinically developed renin inhibitor, aliskiren, have confirmed the validity of this new class of drugs. Future research, exploring effects on the RAS that perhaps cannot be provided by the

Main Points

- Newly available data show that renin and prorenin may exhibit vascular effects independent of the production and action of angiotensin in the circulation.
- Despite their apparently impressive credentials, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers may not have provided the full array of benefits that might be expected if the renin system were comprehensively blocked.
- The newest blockers of the renin–angiotensin system, the direct renin inhibitors, seem to be the appropriate successors to the drugs working on angiotensin.
- The demonstrated blood pressure effects of the first clinically developed renin inhibitor, aliskiren, have confirmed the validity of this new class of drugs.

currently used blockers of this system, will test whether enhanced clinical benefits might result from this new pharmacologic strategy in patients at risk of cardiovascular events. ■

References

1. Giles TD. Renin-angiotensin system modulation for treatment and prevention of cardiovascular diseases: toward an optimal therapeutic strategy. *Rev Cardiovasc Med*. 2007;8(suppl 2): S14-S21.
2. Hollenberg NK. The renin system: is direct renin inhibition different from blockade at the AT1 receptor or the angiotensin-converting enzyme step? *Rev Cardiovasc Med*. 2007;8(suppl 2): S7-S13.
3. Brunner HR, Laragh JH, Baer L, et al. Essential hypertension: renin and aldosterone, heart attack and stroke. *New Engl J Med*. 1972;286: 441-449.
4. Buhler FR, Laragh JH, Bear L, et al. Propranolol inhibition of renin secretion. A specific approach to diagnosis and treatment of renin-dependent hypertensive diseases. *N Engl J Med*. 1972;287:1209-1214.
5. Alderman MH, Madhavan S, Ooi WL, et al. Association of the renin-sodium profile with the risk of myocardial infarction in patients with hypertension. *N Engl J Med*. 1991;324:1098-1104.
6. Dzau V, Braunwald E. Resolved and unresolved issues in the prevention and treatment of coronary artery disease: a workshop consensus statement. *Am Heart J*. 1991;121:1244-1263.
7. Weber MA. The metabolic syndrome. In: Antman E, ed. *Cardiovascular Therapeutics*. Philadelphia: Elsevier; 2007.
8. Weber MA, Giles TD. Inhibiting the renin-angiotensin system to prevent cardiovascular diseases: do we need a more comprehensive strategy? *Rev Cardiov Med*. 2006;7:45-54.
9. Neal B, MacMahon S, Chapman N; Blood Pressure Lowering Treatment Trialists' Collaboration. Effects of ACE inhibitors, calcium antagonists and other blood pressure lowering drugs: results of prospectively designed overviews of randomized trials. *Lancet*. 2000;355:1955-1964.
10. Nguyen G, Burckle C, Sraer JD. The renin receptor: the facts, the promise and the hope. *Curr Opin Nephrol Hypertens*. 2003;12:51-55.
11. Laragh JH. Vasoconstriction-volume analysis for understanding and treating hypertension: the use of renin and aldosterone profiles. *Am J Med*. 1973;55:261-274.
12. Weber MA, Stokes GS, Gain JM. Comparison of the effects on renin release of beta-adrenergic antagonists with differing properties. *J Clin Invest*. 1974;54:1413-1419.
13. Drayer JI, Weber MA, Longworth DL, et al. The possible importance of aldosterone as well as renin in the long-term antihypertensive action of propranolol. *Am J Med*. 1978;64:187-192.
14. Weber MA, Drayer JI, Rev A, et al. Disparate patterns of aldosterone response during diuretic treatment of hypertension. *Ann Intern Med*. 1977;87:558-563.
15. Weber MA, Lopez-Ovejero JA, Drayer JI, et al. Renin reactivity as a determinant of responsiveness to antihypertensive treatment. *Arch Intern Med*. 1977;137:284-289.
16. Case DB, Wallace JIM, Keim HJ, et al. Possible role of renin in hypertension as suggested by renin-sodium profiling and converting enzyme inhibition. *N Engl J Med*. 1977;296:641-646.
17. White WB, Giles TD, Bakris GL, et al. Measuring the efficacy of antihypertensive therapy by ambulatory blood pressure monitoring in the primary care setting. *Am Heart J*. 2006;151:176-184.
18. Gradman AH, Traub D. The efficacy of aliskiren, a direct renin inhibitor, in the treatment of hypertension. *Rev Cardiovasc Med*. 2007;8(suppl 2):S22-S30.