

Renin Inhibition: What Are the Clinical Perspectives?

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Summary: Evidence that renin system blockade is useful in many patients with hypertension is overwhelming. Two recent lines of investigation have suggested that more complete blockade leads to improved clinical outcomes. One line of investigation involves the use of a combination of an angiotensin-converting enzyme inhibitor with an angiotensin-receptor blocker. The second line of investigation involves the use of very high dose angiotensin-receptor blocker. The interaction of renin with substrate is the rate-limiting step in the renin cascade; thus, the recent development of a powerful renin inhibitor also favors more complete blockade of the system. In many patients, this is likely to lead to improved treatment.

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The large number of recent reviews on renin inhibition suggests strongly that the equally recent development of powerful renin inhibitors is likely to have an important clinical impact.¹⁻⁸ The first mention of blockade of the renin system was made by Skeggs et al⁹ in their description of angiotensin-converting enzyme (ACE) in which they argued that, “as renin is the initial and rate-limiting substance in the renin-angiotensin-system (RAS), it would seem that renin inhibition would be the most likely to succeed.” In fact, the development of renin inhibitors lagged well behind blockade at the level of the ACE step or the angiotensin I (AT₁) receptor.

No pharmacologist would have chosen the ACE step as part of a planned approach to interrupting the renin system.² The development of ACE inhibitors was an unexpected by-product of snake venom toxicology. The development of AT₁-receptor blockers was more planned, but its inception was accidental—a product of high throughput screening that

identified AT₁-receptor blockade in an unlikely molecule, an imidazole derivative.

In the hierarchy of evidence that supports the interesting notion of evidence-based medicine, the large randomized controlled clinical trial stands at the top. These trials provide the most compelling evidence for similarity or difference in responses to drugs. The only comparative studies involving renin inhibition involve blood pressure response compared with an ACE or an angiotensin-receptor blocker (ARB) inhibitor (reviewed later). In the absence of information, the hierarchy turns to information from randomized controlled trials consideration of mechanism, the pharmacology of the drugs, the pathophysiology of the disease, epidemiology and genetics, and the tolerability of the agents available. These themes are developed in this article.

THE ANTIHYPERTENSIVE EFFECT

Similar to the ACE inhibitors and ARBs, renin inhibitors have been developed as antihypertensive agents. From the perspective of a company dealing with regulatory agencies, blood pressure reduction as a goal is very attractive. The reduction in blood pressure can be documented in months in studies involving hun-

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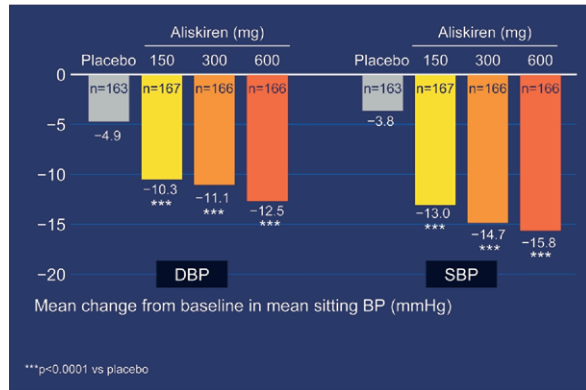


Figure 1. Blood pressure responses to graded doses of Aliskiren and to an ARB in patients with mild to moderate essential hypertension. The optimal Aliskiren dose was 300 mg/d. *** $P < .0001$ vs placebo. Reprinted with permission from Gradman et al.¹⁰

dreds of patients. Documenting change in natural history involves the assessment of thousands of patients in studies that extend over years.

The blood pressure effects of Aliskiren are compared with responses to an ARB in Figure 1. Aliskiren shows a dose-related blood pressure decrease that exceeds the response to placebo and matches the response to a full dose of the ARB.¹⁰ The optimal Aliskiren dose is 300 mg to induce a blood pressure decrease: increasing the dose does not add to the antihypertensive effect. Similar studies have been reported in comparison with graded dose of Aliskiren with losartan,¹¹ ramipril,¹² hydrochlorothiazide, alone and in combination,¹³ amlodipine,¹⁴ and lisinopril.¹⁵ In each case, Aliskiren matched but does not exceed the comparator, and in each case 300 mg proved to be the optimal Aliskiren dose.

If the blood pressure decrease associated with renin inhibition does not exceed that induced by ACE inhibitors or ARBs, which are very well studied and very well tolerated agents, and agents that either already are generic or soon will be, why should we be interested in renin inhibition? The answer lies not in the blood pressure effect, but in the potential for greater efficacy at the tissue level, and it is at the tissue level that tissue protection will occur.

The interaction of renin with its substrate is rate-limiting, which interested Skeggs et al.⁹

What does the term *rate-limiting* actually mean?

THE RATE-LIMITING STEP

There are 3 locations in the renin-angiotensin cascade that are available for blockade. First, there is the interaction of renin with its substrate, angiotensinogen (Figure 2). Next is the ACE step, responsible for conversion of angiotensin (Ang) I to Ang II. Finally, there is the AT₁ receptor. Some would add the reduction in renin release induced by β -adrenergic blocking agents to the list.

An enzyme cascade consists of several component steps, which may limit the rate of overall reaction to a different extent. Each step is characterized by a rate constant, and the lowest rate constant is rate limiting, as the determinant of the rate of overall reaction in most, but not all, circumstances.² For example, a change in conditions may influence the specific activity of different enzymatic reactions differently. It has been argued as an alternative that the rate-limiting step is actually the most sensitive step, the step that can cause the largest change in overall velocity if perturbed. Unfortunately, most of us cannot translate a rate constant into a physically

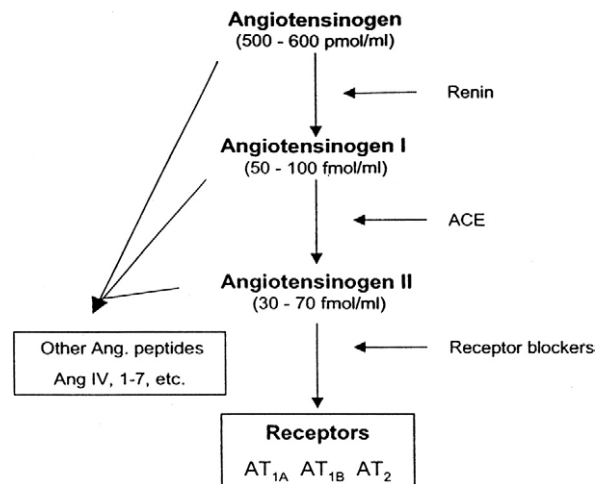


Figure 2. The renin cascade and the rate-limiting step. The concentrations of angiotensinogen, Ang I, and Ang II are shown in the boxes. Note that the concentration of Ang I exceeds that of Ang II by about 2-fold. The concentration of angiotensinogen, the renin substrate, exceeds the concentration of Ang I by 5,000-fold. That is the rate-limiting step. Reprinted with permission from Navar et al.¹⁶

meaningful model. As an alternative approach, Navar et al¹⁶ included in their description of the renin cascade not only the steps, but also the concentration of the various substrates and products along the way (Figure 2). Although the data in the figure represent findings in the rat, the findings in human beings are very similar. The concentration of Ang II, the powerful vasoconstrictor and stimulus to aldosterone release, was in the range of 30 to 70 fmol/mL. The concentration of Ang I, the substrate for ACE and the precursor to Ang II, was about double the concentration of Ang II, at 50 to 100 fmol/mL. The concentration of the substrate angiotensinogen was in the neighborhood of 500 to 600 pmol/mL. Thus, the renin-catalyzed step from substrate to Ang I is favored by a 5,000-fold concentration gradient. Clearly, if you want to block the system, the renin step should be the prime target.

MODELS

It is reasonable to ask what the expected responses are to blocking at each of the steps in the cascade. To a major degree the expectations are determined by the model that one uses for understanding the system and the pathways and metabolic products represented in that model.

For example, if one accepts the classic view of the renin-angiotensin system as a system defined by concentrations of the relevant mediators in the circulation, as still is believed by some, then blockade at the renin step, the ACE step, and the AT₁ receptor should induce an equivalent response. Indeed, that is the finding when arterial blood pressure is used as the marker. It would be reasonable to argue in this regard that perhaps this classic view provides an adequate description of the relation between blood pressure and the renin system. Although there is substantial debate about whether or not different classes of antihypertensives influence natural history differently, no one seems to debate the efficacy of these various classes of drug on blood pressure because they are very similar.^{17,18} Thus, if there is to be a difference, it is going to be at the tissue level, at which more effective blockade can

have an influence on natural history of disease that goes beyond blood pressure.

There are a number of models that differ from the classic model. As one example, there have been arguments made for significant non-ACE pathways in the generation of Ang II.¹⁹ Should non-ACE pathways be important, then blockade induced by an AT₁-receptor blocker or renin inhibitor might induce a response substantially larger than that induced by an ACE inhibitor. That possibility is reviewed later for the kidney. Others have argued for a wide range of products of Ang I metabolism, each with a distinctive pharmacology.²⁰ This fascinating area remains controversial, with little evidence as yet for an important role in human beings. Another potentially important model involves prorenin. Indeed, as evidence for an important role in pathology for prorenin accumulates, and because of its implications for renin blockade, the prorenin story merits special review.

PRORENIN

By the mid 1990s it had become clear that prorenin was associated, very powerfully, with the genesis of microvascular disease (nephropathy and retinopathy) in patients with diabetes mellitus.²¹ Prorenin is present in the circulation in human beings in very high concentrations, about 10 times greater than the concentration of renin. Because prorenin seemed to have no action on blood pressure, blood vessels, or aldosterone release, it was thought to be metabolic waste. For that reason, it was considered to be a marker of disease, rather than being involved in a mechanistic fashion. On the other hand, the concordance between plasma prorenin concentration and microvascular disease was so very powerful that it was difficult to avoid thinking about a mechanistic relationship, but the responsible pathway had not been identified.

In 2002, that situation changed dramatically with the identification of a receptor, isolated from cultured human mesangial cells, that binds renin very avidly.²² This receptor not only binds renin, it binds prorenin equally well. Surprisingly, binding to the receptor increases the catalytic activity of renin 5-fold and provides

prorenin with complete catalytic activity. Perhaps even more surprising is accumulating evidence that activation of this receptor, now called the *prorenin receptor*, not only is capable of generating Ang I and Ang II, but also is capable of activating potentially important intracellular pathways without an intervening involvement of Ang I or Ang II.²²⁻²⁴ Because these pathways lead to the release of agents that are important in the development of tissue fibrosis, an obvious link to disease pathogenesis now exists.^{23,24}

Recently, Huang et al²⁴ confirmed and extended this line of investigation by testing the hypothesis that renin, independent of its enzymatic action to enhance angiotensin synthesis, would lead to the release of important mediators of fibrosis. Renin in vitro in relatively low concentrations induced unambiguous increases in transforming growth factor- β 1 that were both dose- and time-dependent. The responses were not altered by adding the Ang II receptor antagonist losartan or by adding the ACE inhibitor enalapril in high concentration, nor were they influenced by a direct renin inhibitor. Renin in vitro also led to an increase in Pai-1 and collagen-1 messenger RNA, a response partially blocked by neutralizing antibodies to transforming growth factor- β . Tissue Ang I and Ang II levels were extremely low. Perhaps most importantly, they used RNA interference to decrease expression of the renin receptor and showed blockade of the induction of transforming growth factor- β in vitro. Although studies performed in vitro are a long way from the situation of patients in the clinic, it is difficult to ignore this emerging story. It also is difficult to ignore their overall conclusion, "Thus, renin may contribute to renal fibrotic disease, particularly when therapeutic Ang II blockade elevates plasma renin."²⁴

Treatment of patients with ACE inhibitors and ARBs, probably via the short feedback loop, leads to a sharp increase in renin release and plasma renin concentration. The only blocker of the system that can render it quiescent is renin inhibition. Whether this also will render quiescent actions via the prorenin receptor is the important next question.

RESPONSES AT THE TISSUE LEVEL

Multiple observations in multiple tissues and models have provided compelling evidence that when agents that block the renin-angiotensin system are effective in changing the natural history of disease, their action occurs primarily at the tissue level.¹ Species differences in the pathways for Ang II generation made it crucial that studies be performed in human beings. The logic used for studying the human kidney was straightforward: if all of the Ang II acting on the renal circulation was formed through the classic pathway with Ang I conversion to Ang II occurring only in the transit of blood through the lung, one would anticipate that ACE inhibition, renin inhibition, and Ang II antagonists would induce an identical renal response measured as an increase in renal plasma flow.²⁵ We chose renin inhibition as the initial pathway for exploring the control mechanism for several reasons. The remarkable substrate specificity of the renin reaction made mechanistic specificity of the renin inhibitor very likely. Moreover, because both ACE and renin inhibition would lead to a decrease in plasma Ang II concentration this would facilitate comparison of the degree of blockade achieved. Our anticipated result was that the renal hemodynamic response to ACE inhibition in healthy volunteers on a low-salt diet would reflect not only a decrease in local Ang II formation, but also reduced kinin degradation. The result would be an accumulation of vasodilator products including bradykinin, kinin-dependent prostaglandin formation, and activation of endothelial nitric oxide release. To our surprise, the renal vasodilator response to the renin inhibitor available at that time, Enalkiren, exceeded the response to the ACE inhibitor, captopril. Because of our surprise, we performed a more elaborate study, double-blind, in which volunteers were studied 3 times. On one day they received placebo, on another day Enalkiren, and captopril on the third day—in random order. The placebo in this study did nothing. Captopril increased renal plasma flow by 90 to 100 mL/min/1.73 m², which essentially was identical to the earlier study (Figure 3). The renin inhibitor produced a 50% larger response of around 140 to 150 mL/min/1.73 m². Although renin is a fastidious en-

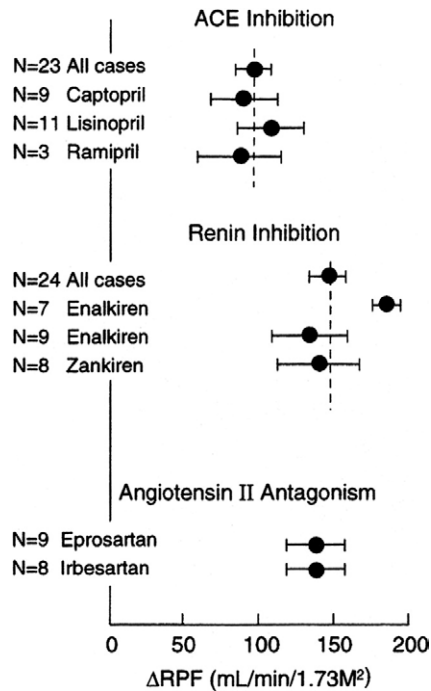


Figure 3. Meta-analysis of renovascular response to pharmacologic interruption of the renin system in healthy young men who are in balance on a 10-mEq sodium intake. Each agent was studied at the top of its dose–renal vascular relationship. From the ratio of flow increase induced by ACE inhibition, approximately two thirds of Ang II formation under these conditions is ACE dependent, and one third is generated by alternative, non-ACE pathways. There is no evidence for non–renin-dependent generation of angiotensin. Reprinted with permission from Hollenberg et al.¹⁹

zyme with great substrate specificity, one possible interpretation of these findings was that renin inhibitors acted via a mechanism unrelated to renin. Against this possibility is our finding that a high-salt diet blunted the renal response to renin inhibition. In that context, the development of the Ang II antagonist class created the possibility of a tie breaker. If the renin inhibitor acted via an alternative non-angiotensin-dependent mechanism, one would anticipate that Ang II antagonists would provide a different renovascular response under the conditions of our study. Conversely, if the renin inhibitor acted only through blockade of renin-dependent Ang II formation, one would anticipate an identical response. We went on to study several angiotensin antagonists: at the top of the dose-response relationship, the Ang II antagonist induced a response similar to or

slightly less than the response to the renin inhibitor.

In that study, we probably underestimated the response to renin inhibition because we reported findings only during the first several hours of administration. In a follow-up study we learned that a response to the renin inhibitor showed a continued increase over several hours, and so we probably underestimated the peak.²⁶

COMBINATION THERAPY

For a number of reasons, after the introduction of ARBs there has been an outpouring of reports on the influence on the kidney of ACE: ARB combinations. A recent review described 10 studies on combination therapy in patients with diabetic nephropathy and an additional 8 studies in patients with nephropathy unrelated to diabetes.²⁷ This outpouring of reports reflected a number of factors. First, although ACE inhibitors unambiguously are effective, very often in individual patients their effect was less than satisfactory. Second, there was a major ethical problem in dealing with 2 closely related drug classes. In view of the unambiguous efficacy of ACE inhibition, how could we justify withholding ACE inhibitors as part of a therapeutic trial? Industry made their contribution, enthusiastically endorsing the notion of combination treatment. One need not be cynical to realize that this maneuver increases market size.

All of the studies reported were deeply flawed because insufficient attention had been given to the issue of drug dose. In a proper study, at least 1 of the 2 agents used in combination should be administered in a dose documented to achieve a maximal response. Otherwise, the studies are not interpretable.

Is there a rationale for combination treatment if both involved the same final pathway—blockade of angiotensin production or its action? The answer is a somewhat tentative “yes.” The sigmoid shape of dose-response relationships is actually the integral of a normal distribution.²⁸ One of the features of that distribution is a predictable relation between dose and magnitude of response: the response will increase linearly over the range 16% of maximum to 84%

of maximum. The inflection point in dose-response relationships occurs at these 2 points. To move from the 84% to near the 100% of maximum response requires a very large increase in dose. Thus, one could argue that parsimony dictates that the 2 agents be administered at the dose required to achieve a response 84% of maximum. This will reduce the drug load and presumably the cost. Unfortunately, for none of the drugs involved do we have any idea of the maximum response and the dose to reach 84% of maximum.

In this area, the combination of a renin inhibitor with either an ACE or an ARB is more attractive than ACE:ARB combinations because of the short feedback loop and the reactive renin response to ACE inhibition and ARBs cited earlier. There is a reasonable chance that the renin response to blockade contributes to disease pathogenesis, especially in the case of the kidney.²⁴ Only renin inhibition renders the system quiescent.

TOLERABILITY

Another important issue involves tolerability. Indeed, it has been an important theme in the evolution of renin system blockade. When the ACE inhibitors came along, it was clear that they were better tolerated than the agents available up to that time: β -blockers, methyldopa, and diuretics. Within a few years, studies on quality-of-life measures made it clear that the ACE inhibitors were much better tolerated than the agents available hitherto. The earlier agents were responsible for a great deal of fatigue, substantial depression, and a very striking frequency of sexual difficulties. The quality-of-life measures focused on these areas and showed that the ACE inhibitors were much better tolerated. Not that the ACE inhibitors were free of adverse effects. Cough was frequent and very annoying. A rash was almost as frequent. Perhaps most importantly, the sporadic appearance of angioneurotic edema was potentially devastating.

When the ARBs came along, it was their tolerability that made them such an attractive advance. Their use in patients was free of cough, free of rash, and free of angioneurotic edema. Given the fact that these agents are

imidazole derivatives and given the rather dramatic pharmacology of this chemical class, one would have anticipated a rather substantial frequency of adverse effects. In fact, there have been none. Probably this factor alone accounts for the remarkable growth in their use, which antedated substantially the appearance of data on natural history.

Given the remarkable specificity of renin, which has only a single substrate and a single product, one would anticipate that the adverse effects associated with renin inhibition would be minimal. To date, they have been and they appear to be similar to the ARBs in this regard.

UNANSWERED QUESTIONS

We already know that Aliskiren—the first orally effective renin inhibitor—is well tolerated from a series of clinical trials.^{1-8,10-15} We also know from those studies in patients with uncomplicated mild to moderate essential hypertension that the blood pressure response to Aliskiren does not differ from the response induced by ARBs and ACE inhibitors. We do not yet know the response to this agent in patients who are likely to be especially responsive, including subclasses of patients with hypertension who are difficult to treat, or associated with diabetes mellitus, or obesity, or advanced atherosclerosis.

The early evolution of the role of captopril provides an excellent example. The first human exposure to captopril occurred late in 1976. Full-scale clinical investigation began in 1977. The drug was approved for the management of difficult hypertension in 1981, the shortest time for any agent in the antihypertensive area. Why? Captopril was found to be remarkably effective in patients with difficult hypertension who had responded poorly to standard triple therapy: a combination of a diuretic, a β -blocker, and a vasodilator. With clear evidence that captopril met a hitherto unmet need, it was easy for the regulatory agency to provide an accelerated review and early acceptance.

Tissue protection is crucial. It is easy to forget that we treat high blood pressure not to reduce the blood pressure number but rather to change the natural history of disease. There are compelling reasons, reviewed previously, to hope that renin inhibition—providing a degree

of blockade of the system not achieved easily with alternative agents—will result in improved tissue protection. The obvious candidate is renal injury, but ultimately the logic extends to vascular injury, myocardial infarction, heart failure, and stroke.

A role for interference with the renin receptor and in that way the contribution of prorenin represents an equally attractive target.

Although we do not yet have the answers, the studies required to address these issues already are under way. What shall we do in the interim until the relevant data become available? Most of us are likely to do what we have done in the past. There are patients for whom the construct developed in this article is especially attractive, in particular if they are doing poorly on current therapy. We do not have the option of telling patients who are currently in need to come back in 3 years when we have the data required for a definitive decision. In our clinical practice we have to act now to deal with problems now, and very often we have to do our best with the best available information. The introduction of renin inhibition is no exception. In the patient with type 1 diabetes mellitus and proteinuria, for example, in whom there is an inadequate response to an ACE inhibitor, it is entirely reasonable to try renin inhibition, monitoring the influence on proteinuria. It probably is equally appropriate to add the renin inhibitor to the ACE inhibitor. Based on identical logic, captopril was used widely for the patient with proteinuria well before the appearance of the compelling evidence required for regulatory approval.²⁹

Fortunately, based on the earlier experience of success with ACE inhibition and AT₁-receptor blockade, we will have the information required on the influence of the renin inhibitor much earlier in its development.

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