Mini-Review

Direct Renin Inhibition with Aliskiren in Hypertension and Target Organ Damage

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The Joint National Committee and the World Health Organization are in agreement that hypertension in most patients who are treated is controlled inadequately and that rates of cardiovascular morbidity remain high. Additional pharmacologic treatments could ameliorate this situation. The renin-angiotensin-aldosterone system has been a highly successful pharmacologic target, as the system is strongly implicated in the development of hypertension-related target organ damage. However, compensatory increases in plasma renin levels that lead to adjustments in angiotensin production and conversion present limitations for existing renin-angiotensin-aldosterone system inhibitors. A once-daily, orally effective, small-molecule renin inhibitor, aliskiren, is now available to address angiotensin production directly at its rate-limiting step. Studies in humans attest to an effective BP-lowering effect, a side effect profile no different from AT1 receptor blockers, and the option of combination therapies. A novel animal model of human renin hypertension in the rat attest to target organ protection. Because angiotensin receptor blockade, angiotensin-converting enzyme inhibition, calcium channel blockade, and diuretic therapy all lead to sharp increases in plasma renin activity, aliskiren offers a novel circumvention.


The National High Blood Pressure Education Program recently presented its seventh report prepared by the Joint National Committee (1). The report indicated that 50 million or more Americans have BP levels that warrant treatment. Worldwide prevalence estimates for hypertension approach 1 billion individuals, and approximately 7.1 million deaths per year are attributed to hypertension. The World Health Organization estimates that poor BP control is largely responsible for two thirds of strokes and half of ischemic heart disease. A recent European review of essential hypertension drew a similar picture (2). Effective medical treatment has been available to lower BP for almost 50 years. Indeed, treatment of hypertension has been credited with the decline in stroke and heart attack rates observed in North America and Europe over the past few decades. Awareness of hypertension has increased in the United States from approximately 50% of people who have hypertension to 70%. Similarly, the percentage of hypertensive people who are receiving treatment has increased from 31 to 59%. The European figures are similar in kind (2). Nevertheless, the control rates are unacceptable. Twenty years ago, the control rate in the United States was 29% of those who were receiving treatment. The current value is 34%. A recent epidemiologic investigation of six European countries, Canada, and the United States reported that across all age groups examined, BP levels were the lowest in the United States and the highest in Germany. Rates of hypertension treatment in the European countries were on average lower than in North America (3). For the European countries, on average only 8% of hypertensive individuals had their condition controlled.

These data do not inspire confidence. The rate of decline in hypertension-related morbidity has slowed in the past decade; however, the incidence of chronic heart failure and ESRD is now increasing (1). Various explanations have been suggested. Possibly, poor compliance on the part of the patients is responsible. Another possibility is that awareness of prevention strategies and their implementation by primary physicians may not always be optimal. Finally, some lay the blame at the feet of the health care system or third-party payers. Undoubtedly, all of these factors play a role. However, an additional explanation might be that we need better drugs for patients with essential hypertension. The current therapeutic strategy is aimed at volume regulation with diuretics, sympathetic nervous system activity suppression by means of peripheral adrenergic receptor blockers or centrally acting drugs, vascular smooth muscle cell tone reduction by means of ion channel manipulation, and inhibition of the renin-angiotensin-aldosterone system (RAAS). In any given patient, several concomitant pharmacologic targets must be addressed. Indeed, patients who require four or more classes of drugs to achieve the current treatment guidelines are no rarity.

Novel antihypertensive therapies that offer the potential for improved targeting of the mechanisms that underpin organ damage in hypertension and cardiovascular disease would be of great value. One potential target for which effective inhibitors have been sought for several decades is renin, the enzyme that catalyzes the rate-limiting step of the RAAS.
RAAS Inhibition to Approach Hypertension

RAAS activity is initiated by the cleavage of the peptide angiotensinogen to the decapeptide angiotensin I (Ang I) by the enzyme renin; the key product of the renin system is the octapeptide hormone angiotensin II (Ang II), which is formed from Ang I by the angiotensin-converting enzyme (ACE; Figure 1). RAAS plays a key role in volume regulation and the maintenance of BP. However, excessive activity of the renin system is associated with hypertension and target organ damage, mediated largely through the actions of Ang II on the angiotensin AT$_1$ receptor. The introduction of ACE inhibitors ushered in a new era of therapeutic possibilities for patients with hypertension, heart failure, and renal failure. However, physicians soon learned that in terms of lowering BP, ACE inhibitors were no more effective than existing antihypertensives as a monotherapy and, like existing drugs, still had to be combined with other treatments, particularly diuretics, to achieve BP control.

The Antihypertensive and Lipid-Lowering Treatment to prevent Heart Attack (ALLHAT) investigators recently substantiated this fact (4). The poorer levels of BP control achieved in the ACE inhibitor arm of ALLHAT may reflect, at least in part, that ACE inhibitor/diuretic combinations were not allowed by the trial protocol (5). This design feature probably also resulted in the notably poorer BP control that was observed in the black patient subgroup of the trial.

Patients who receive ACE inhibitors initially have lower circulating Ang II levels; however, the levels commonly increase to earlier baseline concentrations (6,7). The same situation is also true for circulating aldosterone concentrations. The phenomenon has been termed “escape.” The introduction of the angiotensin receptor blockers (ARB), a drug class that can block the Ang II AT$_1$ receptor directly, was expected to settle the RAAS issue by inhibiting all of the negative effects of RAAS activation. After all, actions of Ang II such as salt retention, aldosterone release, vascular smooth muscle cell contraction, and growth factor activity all involve activation of the AT$_1$ receptor. However, the introduction of this drug class, although of undoubted clinical benefit, still may not block the RAAS satisfactorily (8).

ACE Inhibitors and ARB Provide Incomplete RAAS Suppression

Suppression of the RAAS after treatment with either ACE inhibitors or ARB remains incomplete (9). A key reason for this is that these therapies stimulate a reactive increase in renin activity (10), because they disrupt the short feedback loop (Figure 1) by which Ang II normally inhibits the release of renin from the kidney (11). Bernstein et al. (12) used mouse models to demonstrate the central role of renin in the control of BP. They showed that mice with gene disruptions involving angiotensinogen, renin, ACE, and the AT$_1$ receptor all display a similar phenotype, with a 35-mmHg reduction in BP. These experiments underscore that the RAAS is central to BP control. Importantly, whereas ACE $-/-$ mice had barely detectable Ang II levels, ACE $+/+$ mice had normal Ang II levels but showed higher Ang I levels so that their Ang II/Ang I ratio was approximately half normal. Thus, the compensatory mechanism in these mice was to increase Ang I levels so that Ang II levels were sustained. These data suggest that normal BP was maintained in these animals through the regulated production of renin. Indeed, mice with one, two, three, or four copies of the ACE gene exhibited BP levels that were indistinguishable from those of wild-type mice, showing that it was the activity of renin (not ACE) that was the key regulator of BP.

A second issue with ACE inhibitors and perhaps ARB is that they may not provide effective inhibition of tissue RAAS activity (13). Crowley et al. (14) recently demonstrated the importance of extrarenal AT$_1$ receptors. They performed difficult cross-transplantation experiments in AT$_1$ receptor $-/-$ and wild-type mice. The authors found that when the AT$_{1A}$ receptor was deleted in the recipient animal, even transplantation of a wild-type donor kidney that expressed the AT$_{1A}$ receptor did not restore normal BP; this discrepancy could not be explained by altered aldosterone generation. These data cast some doubt on the prevailing dogma of the kidney as the sole, final common pathway of BP regulation and suggest that AT$_1$ receptor actions in systemic tissues such as the vascular and/or the central nervous system make nonredundant contributions to BP regulation. It is interesting that the group further showed that interruption of the AT$_1$ receptor-mediated short feedback loop in the kidney was not sufficient to explain the marked stimulation of renin production induced by global AT$_1$ receptor deficiency or by receptor blockade. Nevertheless, this finding underscores the multiplicity of mechanisms that stimulate renin responses.

The reactive plasma renin stimulation by ACE inhibitors or ARB gives rise to numerous explanations for why current RAAS inhibitors are sometimes suboptimal or not effective. A
problem with ACE inhibitors is that the reactive increase in plasma renin activity may ultimately lead to increased Ang II generation by ACE-independent pathways such as dipeptidases, which are found in several tissues, including the kidney (15). The gradual Ang II level increase in the face of ACE inhibitor therapy has been termed “ACE escape” (9). Clinical studies have confirmed that this phenomenon is associated with deteriorating control of BP in patients with hypertension (6) and with poorer prognosis in patients with heart failure (7). The evidence that the reactive rise in renin activity may limit the therapeutic benefits ofARB treatment is less clear-cut. However, recent clinical trials in patients with heart failure have indicated that twice-daily treatment with an ARB may be necessary to provide effective blockade of the effects of Ang II (16,17), a possible indication that the renin increase may be clinically relevant in patients with considerable neurohormonal activation. Indeed, increased plasma renin activity could result in actions independent of the AT1 receptor. ARB therapy leaves the AT2 receptor open for occupancy in the face of increased Ang II levels. This state of affairs is viewed as salubrious by some but by no means all investigators. Thus, whereas some preclinical studies have shown that AT2 receptor activation may be associated with beneficial effects, such as vasodilation and inhibition of renin release (18), other studies have suggested that AT2 receptor-mediated signaling pathways could lead to harmful effects such as vascular cell proliferation (19,20). Furthermore, in the face of ARB therapy, various Ang fragments, such as Ang I-7, Ang III, and Ang IV, may appear in greater concentrations. Preclinical studies have shown that Ang IV may upregulate the prothrombotic plasminogen activator inhibitor-1 and thereby lead to prothrombotic, vasoconstrictor, or undesired trophic effects. The fragments are an area of intense study; however, there is some doubt as to the clinical importance of these fragments (21).

High plasma renin activity per se may represent a cardiovascular risk factor. A study of 2902 hypertensive patients showed that pretreatment plasma renin activity was independently and directly associated with the risk for myocardial infarction, even though the patients subsequently achieved BP control with antihypertensive therapy (22). It should be noted, however, that this study did not investigate whether the effects of plasma renin activity were independent of Ang II. Nevertheless, elevated plasma renin activity has also been associated with the presence of target organ damage, including renal dysfunction (23) and left ventricular hypertrophy (24). Alderman et al. (25) recently reported that although black individuals, the elderly, individuals with diabetes, and women are said to exhibit more commonly low-renin hypertension, this was by no means the case. These findings indicate that the use of a renin inhibitor to suppress the reactive rise in renin activity, alone or in combination with ACE inhibitors or ARB, may have considerable potential for the prevention of end organ damage in hypertension.

Properties of Renin

Renin is an aspartic protease that has two homologous lobes (26). The cleft between the lobes contains the active site with two catalytic aspartic residues. Unlike other aspartic proteases, renin has only one known substrate, angiotensinogen, which it cleaves to form Ang I. An inactive form of renin exists; the biosynthetic precursor of renin is termed prorenin and is 5 kD larger, with a 43-amino acid N-terminus that covers the enzymatic cleft and obstructs access to the active site. Prorenin circulates in plasma at 100-fold higher concentrations than renin and can be activated by proteolytic activity or by low pH and low temperatures. In the body, proteolytic activation occurs almost exclusively in the kidney by various processing enzymes.

Several renin receptors have been identified. These receptors also recognize prorenin and should probably be designated as (pro)renin receptors. The mannose-6-phosphate receptor, identical to the IGF II, binds and internalizes prorenin and renin and may serve a clearance function. Nguyen et al. (27) and Sealey et al. (28) demonstrated renin receptors in human mesangial cells and in membranes prepared from rat tissues, respectively. The receptor described by Nguyen et al., which was cloned from a human kidney library, is a 350-amino acid protein that has a single transmembrane domain and no homology with any known protein. Binding is specific for renin and prorenin; as a matter of fact, the receptor acts as a (pro)renin co-factor on the cell surface by enhancing renin catalytic activity and unmask receptor-bound prorenin catalytic activity. This activity would allow local, circulation-independent Ang II production. Also important is the finding that the binding of (pro)renin to the receptor triggers intracellular signaling; in vitro studies on cultured mesangial cells indicate that binding of renin to the receptor may stimulate activation of the intracellular mitogen-activated protein kinase pathway (27), suggesting that such binding may have profibrotic consequences. Although research into this area is at a very early stage, this signaling was the first demonstration of Ang II–independent renin-related effects and underscores the potential for increased renin levels to exert important effects on tissues that would not be inhibited by ACE inhibitor or ARB treatment.

Although prorenin and renin generally are closely correlated, there are states when prorenin levels far exceed those of renin; a physiologic example is pregnancy. A pathologic example is diabetes, in which active renin is suppressed. The existence of receptors for renin and prorenin may provide an explanation for the long-standing observation that renin and prorenin levels are markers of microvascular complications in patients with diabetes, particularly those involving the eye (29). Indeed, increases in prorenin are associated with the development of retinopathy (29,30) and may also predict the onset of microalbuminuria in patients with diabetes (31). Although at present there is no clinical evidence that prorenin levels per se represent anything more than a marker, Veniant et al. (32) generated a transgenic rat that expresses prorenin in the liver and reported that these animals developed cardiomyocyte hypertrophy and renal lesions, despite normal BP values. The clinical significance of these observations is currently uncertain; with regard to the potential effects of renin inhibitors, prorenin
and renin binding to the (pro)renin receptor is independent of the cleavage site, and signaling seems to occur even if the renin receptor is occupied by the renin inhibitor remikiren (Müller et al., unpublished observations).

**Direct Renin Inhibition**

Renin is the rate-limiting step in Ang II production and thus represents the most logical target for inhibition of the renin system. Whereas angiotensinogen is present at plasma concentrations of approximately 500 to 600 pmol, Ang I is present in the 50- to 100-fmol range and Ang II at approximately half that. From a pharmacologist’s perspective, the renin step would be the one earning the target focus, as it is the step with the largest step down in concentration. Work by Smithies et al. (33) using gene-dosing strategies showed that increased copies of the angiotensinogen gene increase BP, whereas increased copies of the ACE gene do not. Thus, blocking the conversion of angiotensinogen to Ang I has a particular rationale.

Potent renin inhibitors are not new. The early compounds were peptide inhibitors, such as isovaleryl-His-Pro-Phe-His-Sta-Leu-Phe-NH2 (SCRIP), that contained the amino acid statine (34). SCRIP was as effective as the ACE inhibitor enalaprilat in alleviating acute left ventricular failure (35). Similarly, Neisius et al. (36) studied a synthetic peptide renin inhibitor, an antirenin antibody, and enalaprilat in the marmoset. All three compounds increased renal blood flow to a similar degree. The synthesis of peptide analogs of the angiotensinogen N-terminal amino acid sequence produced competitive renin inhibitors, including several compounds that were effective in the nanomolar range. The best of these agents, remikiren and enalakiren, were very potent but had an oral bioavailability only of the order of 1 to 2%. Nevertheless, remikiren was shown effectively to reduce plasma renin activity and Ang I and Ang II levels in a dose-dependent manner when given orally to healthy humans (37).

Hollenberg et al. (8) performed studies of considerable physiologic interest with these early renin inhibitors. They measured changes in renal plasma flow in healthy volunteers who were given a 10-mmol/d sodium diet after ACE inhibition and renin inhibition. The three ACE inhibitors tested all increased renal blood flow by approximately 90 ml/min per 1.73 m². By contrast, the renin inhibitors enalakiren and zankiren increased renal blood flow to a significantly greater degree, namely 150 ml/min per 1.73 m². El-Amrani et al. (38) confirmed these findings in the guinea pig, an animal with renin that is susceptible to human renin inhibitors. The greater increase in renal blood flow stimulated by renin inhibitors is the result of greater suppression of intrarenal RAAS activity and reflects the inability of ACE inhibitors to block ACE-independent pathways for the generation of Ang II.

**Aliskiren, First in a New Class of Oral Renin Inhibitors**

Rahuel et al. (39) used crystal structure analysis of renin-inhibitor complexes combined with computational methods to design inhibitors that bound as predicted to the renin S1/S3 pocket. However, the new inhibitors also interacted with a hitherto unrecognized large, distinct, subpocket of the enzyme that extends from the S3-binding site toward the hydrophobic core of the enzyme. Binding to this S3(sp) subpocket was essential for high binding affinity. This unprecedented binding mode guided the drug-design process in which the mostly hydrophobic interactions within subsite S3(sp) were optimized. The investigators’ design approach led to compounds with high in vitro affinity and specificity for renin, favorable bioavailability, and excellent oral efficacy in lowering BP in primates. One of these compounds was aliskiren (Figure 2). Wood et al. (40) expanded these investigations on aliskiren further in the marmoset and in humans. They found that aliskiren decreased BP in sodium-depleted marmosets and increased plasma immunoreactive renin levels, whereas plasma renin activity was reduced through inhibition. Initial ambulatory BP monitoring studies in eight hypertensive patients, who ingested 75 or 150 mg of the compound, showed daytime and nighttime BP-lowering effects. Higher doses, up to 640 mg, caused more complete renin inhibition but no side effects.

Nussberger et al. (41) tested aliskiren in normal volunteers and found that the drug produced dose-dependent and long-lasting decreases in aldosterone levels and Ang II concentrations; the 160 mg dose of aliskiren provided similar effects to the ACE inhibitor enalapril at a dose of 20 mg. Natriuresis was enhanced by aliskiren, whereas potassium excretion was not influenced. Stanton et al. (42) tested four doses of aliskiren up to 300 mg/d in patients with mild to moderate hypertension. BP

![Figure 2. General view of aliskiren (ball-and-stick representation, with all bonds to carbon atoms shown in purple) in the binding complex with human renin; the enzyme β strands are represented as arrows and α helices as ribbons. Inset shows the chemical structure of aliskiren.](image-url)
and plasma renin activity were reduced satisfactorily. The BP responses were similar to those observed with a 100 mg/d dose of the ARB losartan (the current maximum approved daily dose for the treatment of hypertension). Recently, Gradman et al. (43) reported the results of a multicenter study involving 652 patients. The patients were randomly assigned to receive double-blind treatment with once-daily oral aliskiren (150, 300, and 600 mg), the ARB irbesartan 150 mg, or placebo. Aliskiren treatment reduced systolic BP by 11.4, 15.8, and 15.7 mmHg (at doses of 150, 300, and 600 mg, respectively), whereas diastolic BP fell by 9.3, 11.8, and 11.5 mmHg, respectively, compared with a reduction of 5.3/6.3 mmHg (systolic/diastolic BP) for placebo and 12.5/8.9 mmHg for irbesartan 150 mg. Thus, once-daily oral treatment with aliskiren lowered BP effectively (Figure 3), with a safety and tolerability profile comparable to that of irbesartan and placebo, in patients with mild to moderate hypertension. Aliskiren 150 mg was as effective as irbesartan 150 mg (the recommended starting dose of irbesartan for the treatment of hypertension) in lowering BP.

Because a key theoretical advantage of renin inhibitors is their ability to suppress the reactive rise in renin activity stimulated by other RAAS blockers, Azizi et al. (44) investigated the possibility that aliskiren might find utility when combined with an ARB. Twelve mildly depleted normotensive individuals were studied in this double-blind, placebo-controlled, randomized, four-period, crossover study. Aliskiren 300 mg decreased plasma renin activity and Ang I and Ang II levels for 48 h. Importantly and in contrast to valsartan 160 mg treatment, an aliskiren 150 mg + valsartan 80 mg combination did not increase plasma renin activity or plasma angiotensin levels, even though the plasma concentrations of renin were increased. The investigators noted that a renin inhibitor and ARB combination could provide synergistic effects on RAAS hormone levels, and it is also important to note that the presence of a renin inhibitor effectively suppressed the rise in renin activity that would normally be stimulated by an ARB.

**Preclinical Target Organ Protection Studies with Renin Inhibitors**

The species specificity of renin is such that human renin inhibitors can be tested practicably only in the marmoset and the guinea pig. The former is a primitive primate, and the latter has no tail, and neither is ideal for hypertension-related studies. To get around this problem, Ganten, Mullins, Murakami, and others (45) generated two transgenic rat strains. One strain harbors the human renin gene with its own promoter; the second harbors the human angiotensinogen gene with an albumin promoter. Rat renin will not cleave human angiotensinogen, and human renin will not cleave rat angiotensinogen. Thus, the double-transgenic (dTGR) offspring are under the influence of two transgenes that generate large quantities of Ang II in the circulation, the vasculature, the heart, and the kidneys. Untreated dTGR die of cardiac cachexia, while in renal failure, at age 8 wk. The model is ideal to test human renin inhibitors, particularly in terms of elucidating mechanisms of target organ damage and subsequent repair.

In our first study, 6-week-old dTGR were matched by albuminuria (2 mg/d) and divided into five groups (46). Untreated dTGR were compared with aliskiren-treated (3 and 0.3 mg/kg per day) and valsartan-treated (10 and 1 mg/kg per day) rats. The purpose of the low-dose valsartan group was to prolong survival sufficiently to permit the animals to be studied after 7 wk. Treatment was from week 6 through week 9. At week 6, all groups had elevated systolic BP. Untreated dTGR showed increased BP (202 ± 4 mmHg), serum creatinine, and albuminuria (34 ± 5.7 mg/d) at week 7. By week 9, both doses of aliskiren lowered BP (115 ± 6 and 139 ± 5 mmHg) and albuminuria (0.4 ± 0.1 and 1.6 ± 0.6 mg/d) and normalized serum creatinine. Mortality was 100% in untreated dTGR and 26% in low-dose valsartan–treated (1 mg/kg per day) rats, whereas in all other groups, survival was 100%; BP levels were similar to those expected for a normal nontransgenic rat. dTGR that were treated with low-dose valsartan had cardiac hypertrophy (4.4 ± 0.1 mg/g), increased left ventricular wall thickness, and diastolic dysfunction. We concluded that in dTGR, equieffective antihypertensive doses of valsartan or aliskiren attenuated end-organ damage. Thus, renin inhibition compares favorably to angiotensin receptor blockade in reversing organ damage in dTGR.

In our second study that included aliskiren, we assessed complement expression, as well as C-reactive protein (CRP) production, in this dTGR model (47). We found that CRP elevation, macrophages, T cells, TNF-α, C1q, C3, C3c, and C5b-9 expression all preceded albuminuria in untreated dTGR. C1q, C3, C3c, and C5b-9 were observed in the dTGR vessel media. C5b-9 co-localized with IL-6. Aliskiren and the ARB losartan reduced albuminuria, TNF-α, CRP, and complement C1q, C3, C3c, and C5b-9 expression to control levels. The effect of aliskiren on C3c and C5b-9 is shown in Figure 4. Our data showed that in this Ang II–induced model, complement acti-
The human renin inhibitor aliskiren reduces complement C3c and C5b-9 in Ang II–induced renal damage.

Perspectives
Hypertension-induced cardiovascular diseases are the most common cause of death worldwide. BP control is still woefully inadequate in all countries. The RAAS has been a superb target. However, adequate RAAS blockade cannot be achieved with ACE inhibitors or ARB because of counter-regulatory mechanisms. The primary rate-limiting step in the RAAS now can be pharmacologically inhibited directly. Renin inhibition may offer protection of target organs such as the kidney and the eye beyond what can be achieved with current antihypertensive therapies, thereby addressing the most common causes of organ damage, such as ESRD and blindness. Renin inhibition could be combined with ACE inhibition or AT₁ receptor blockade to inhibit both Ang II and aldosterone generation. Clinical studies investigating benefits of renin inhibition are in progress, but the promising results obtained with renin inhibitors in animal models of end-organ damage suggest that this drug class may have great potential.

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renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 111: 1012–1018, 2005


While pharmacological renin inhibition is an exciting approach to reducing target organ damage and progression of chronic kidney disease, Heinze *et al.* in this month’s *JASN* (889–899) have shown that conventional blockade of the renin-angiotensin system with ACE inhibitors or AT1 receptor blockers enhances renal allograft patient and graft survival, emphasizing the importance of the renin-angiotensin system in renal disease progression.