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STATE-OF-THE-ART PAPER

## Renin Inhibition in Hypertension

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Fifty years ago, investigators identified renin inhibition as the preferred pharmacologic approach to blockade of the renin-angiotensin system. Renin is a monospecific enzyme that catalyzes the rate-limiting step in the synthesis of angiotensin II. Amplified enzymatic activity and additional physiological effects occur when renin and pro-renin bind to the (pro)renin receptor. Until very recently, development of clinically effective renin inhibitors remained elusive. Molecular modeling was used to develop aliskiren, a potent, low-molecular-weight, nonpeptide, direct renin inhibitor with sufficient bioavailability to produce sustained suppression of plasma renin activity after oral administration. In patients with hypertension, aliskiren produces dose-dependent blood pressure (BP) reduction and 24-h BP control up to a dose of approximately 300 mg once daily; at these doses, aliskiren shows placebo-like tolerability. Its antihypertensive potency is approximately equivalent to that of angiotensin receptor blockers, angiotensin-converting enzyme inhibitors, and diuretics. After abrupt withdrawal, persistent BP reduction and prolonged suppression of plasma renin activity is observed. When combined with diuretics, fully additive BP reduction is seen. When given with an angiotensin receptor blocker, aliskiren produces significant additional BP reduction indicative of complimentary pharmacology and more complete renin-angiotensin system blockade. Clinical trials are currently underway assessing the effects of aliskiren combined with an angiotensin receptor blocker on intermediate markers of end organ damage, and long-term end point trials are planned. The results of these studies will ultimately determine the place of renin inhibition and aliskiren in the treatment of hypertension and related cardiovascular disorders. The effect of aliskiren on receptor-bound renin and pro-renin is the subject of active investigation. (J Am Coll Cardiol 2008;51:519-28) © 2008 by the American College of Cardiology Foundation

In 1957, Skeggs et al. (1) with rather remarkable foresight postulated 3 possible approaches to pharmacologic inhibition of the renin-angiotensin system (RAS) (Fig. 1): 1) inhibition of angiotensin-converting enzyme (ACE); 2) direct interference with the action of angiotensin II (A II); and 3) inhibition of the circulating enzyme, renin. "Since renin is the initial and rate-limiting substance," these authors observed, "the last approach would be the most likely to succeed." In the intervening 50 years, ACE inhibition and angiotensin II receptor type 1 (AT<sub>1</sub>) blockade have indeed become integral components of cardiovascular pharmacotherapy, compiling an impressive track record in reducing blood pressure (BP) (2), changing the natural history of heart failure (3-6) and proteinuric renal disease (7-9), and conferring cardiovascular protection in a variety of clinical circumstances.

The development of clinically effective renin inhibitors has, however, remained elusive because of difficulties in identifying suitable agents with the required combination of high affinity for renin's active site and sufficient bioavailability to permit chronic oral administration (10). The recent

U.S. Food and Drug Administration approval of the first direct renin inhibitor, aliskiren, thus constitutes an important milestone in the history of RAS blockade (11), making it possible for the Skeggs et al. (1) theoretically preferred approach to receive widespread clinical application and testing.

The Skeggs et al. (1) preference for renin inhibition was based on the fact that the reaction catalyzed by renin is the first and rate-limiting step in the synthesis of A II, which was by then recognized as the primary effector hormone of the RAS. The discovery of the (pro)renin receptor constitutes an additional reason to focus attention on renin inhibition (12). When bound to the (pro)renin receptor, the enzymatic activity of renin is amplified and renin exerts physiological effects that are entirely independent of A II production. In addition, pro-renin, long thought to be merely an inactive precursor of renin, becomes biologically active when bound to this receptor. The expanding physiological role ascribed to renin and pro-renin and the possibility that renin inhibitors could interfere with both suggests that these agents could ultimately prove to have very different tissue effects compared with earlier RAS blockers.

In this review we will discuss the structure and function of renin and pro-renin, recent discoveries relevant to their

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**Abbreviations and Acronyms**

- A I/II** = angiotensin I/II
- ACE** = angiotensin-converting enzyme
- BP** = blood pressure
- Cmax** = maximum serum concentration
- dTGR** = double transgenic rats
- HCTZ** = hydrochlorothiazide
- LVH** = left ventricular hypertrophy
- PAI** = plasminogen activator inhibitor
- PRA** = plasma renin activity
- PRC** = plasma renin concentration
- RAS** = renin-angiotensin system
- TGF** = transforming growth factor

physiological actions, and available data regarding the effects of the renin inhibitor aliskiren in the treatment of hypertension and related cardiovascular disorders.

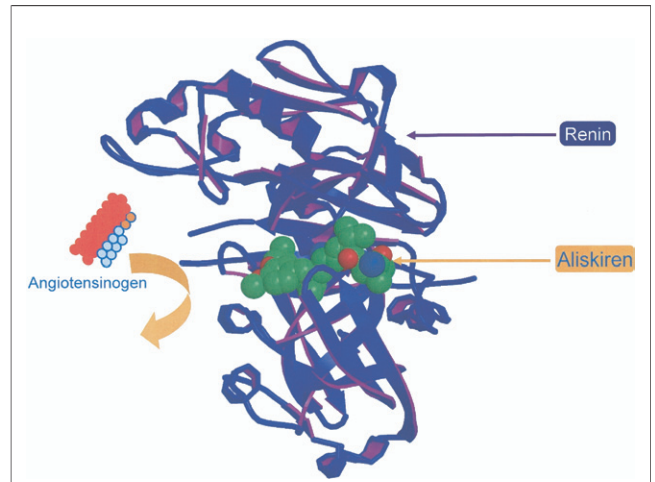
**The Structure and Function of Renin**

Renin belongs to a family of enzymes referred to as aspartic proteases, which also includes the enzymes pepsin, cathepsin, and chymosin (13). Renin is a monospecific enzyme that displays remarkable specificity for its only known substrate, angiotensinogen.

Renin consists of 2 homologous lobes, with the active site residing in the deep cleft located between them (14,15) (Fig. 2). The catalytic activity of the active site is due to 2 aspartic acid residues, 1 located in each lobe of the renin molecule. A key component of the active site is a

distinct subpocket (S3sp), which is specific to renin and unique among the aspartate proteases (15). The active site can accommodate 7 amino acid units of the substrate, angiotensinogen, and cleaves the Leu10-val11 peptide bond within angiotensinogen to generate angiotensin I (A I).

Classically, our understanding of the function and importance of renin relates entirely to its role in the generation of A II. The reaction catalyzed by renin is the rate-limiting step in A II formation. Neither A I nor A II can be synthesized at all in the absence of renin (or, as discussed below, nonproteolytically activated pro-renin). In addition, the conversion of

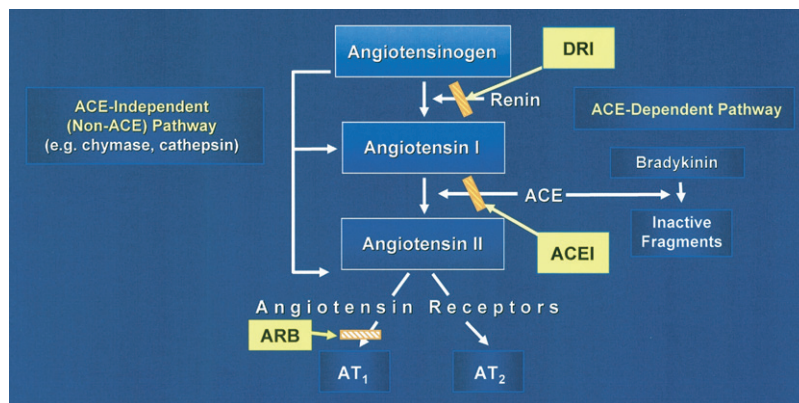


**Figure 2** X-Ray Crystallographic Representation of Aliskiren in the Binding Complex With Human Renin

Renin molecule consists of 2 homologous lobes with the active site located in the cleft between the 2 lobes. Aliskiren occupies a specific subpocket in the cleft and blocks the enzymatic function of renin.

angiotensinogen to A I is favored by a 5,000-fold concentration gradient, making it unlikely that substrate availability could limit A II production (10).

Renin is produced through activation of its enzymatically inactive precursor, pro-renin. Pro-renin is synthesized as a prohormone, in that it contains a signal peptide that leads the inactive molecule to the exterior of the cell (16). Pro-renin concentration in human plasma is approximately 10-fold greater than the concentration of renin (17), and the proportion of circulating pro-renin is increased in patients with diabetes (18,19). The enzymatic inactivity of pro-renin is attributable to a 43-amino-acid N-terminal pro-peptide that covers the active site and blocks access to angiotensinogen.



**Figure 1** The Renin-Angiotensin Cascade and the 3 Available Approaches to Pharmacologic Inhibition of Production or Action of Angiotensin II

Direct renin inhibitors (DRI), angiotensin-converting enzyme inhibitors (ACEI), and angiotensin (AT) type 1 receptor blockers (ARB).

Pro-renin may be rendered enzymatically active in 2 ways, proteolytic and nonproteolytic activation. Proteolytic activation occurs via the actual removal of the pro-peptide chain. Most proteolytic activation of pro-renin occurs in the juxtaglomerular cells of the kidney leading to the production of active renin (20). Nonproteolytic activation is a 2-step process that allows pro-renin to acquire enzymatic activity without removal of the pro-segment. This process involves unfolding of the pro-peptide chain away from the enzymatic cleft followed by an additional conformational change (21). Nonproteolytic activation can be induced in vitro by exposure to cold and/or low pH (22,23) and, as discussed below, through binding to the (pro)renin receptor.

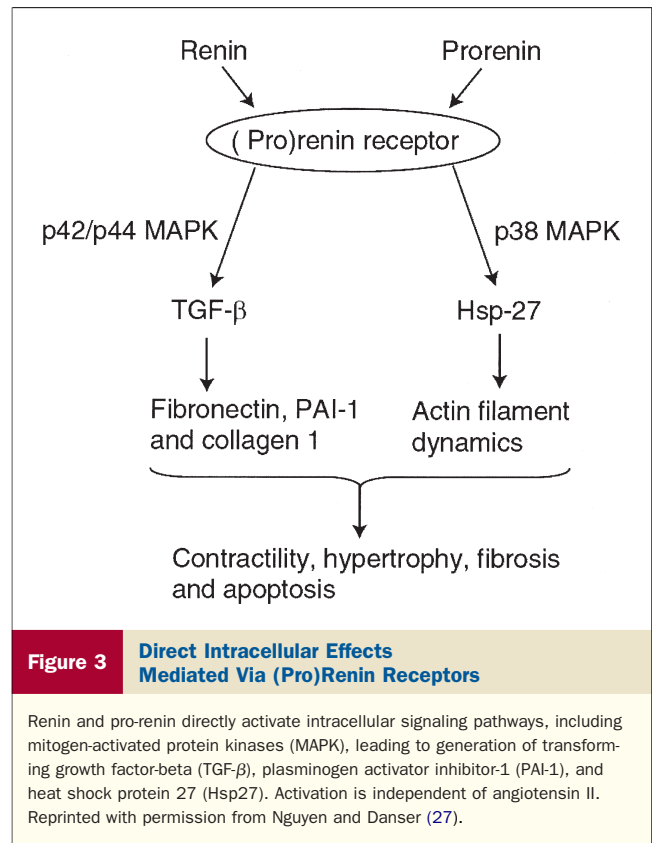
**The (pro)renin receptor.** In 2002, Nguyen et al. (12) discovered a high-affinity binding site for renin in cultured human mesangial cells. This site was subsequently cloned and is believed to represent the principal (pro)renin receptor. The term (pro)renin receptor is used to indicate that this receptor binds to both renin and pro-renin; in fact, binding to pro-renin occurs with somewhat greater affinity than to renin itself (24). The structure of the receptor consists of a 350-amino-acid protein with a single transmembrane domain. To date, (pro)renin receptors have been localized to vascular smooth muscle cells; to human heart, kidney, and brain; to mesangial cells; and to cells in the distal and collecting tubules of the renal parenchyma (12).

When renin binds to the (pro)renin receptor, its enzymatic activity is increased by 4- to 5-fold, accelerating the production of A I on the cell surface where it lies in close proximity both to tissue-bound ACE and to the AT<sub>1</sub> receptor. The binding of pro-renin results in nonproteolytic activation because of the conformational changes described above. This process allows pro-renin to assume full enzymatic activity and contribute to A I production. There is experimental evidence to suggest that the sequestration of circulating (pro)renin and its subsequent nonproteolytic activation may, in fact, be responsible for a large fraction of the A I production that occurs at the tissue level (12,25).

When bound to the (pro)renin receptor, both renin and pro-renin exert physiological effects which are entirely independent of A II (25–27). In various experimental models, renin and/or pro-renin have been shown to activate intracellular signaling pathways (p42/p44 and p38 MAP kinase), induce DNA synthesis, and stimulate the release of transforming growth factor (TGF)-β and plasminogen activator inhibitor (PAI)-1 (27–29) (Fig. 3). In one study, Huang et al. (29) showed that renin induced a dose-dependent increase in mesangial cell TGF-β despite the presence of a renin inhibitor (RO 42-5892), an angiotensin receptor blocker (losartan), or an ACE inhibitor (enalapril). Thus, this effect occurred without production of A II or stimulation of the AT<sub>1</sub> receptor.

### Development of Renin Inhibitors

The first-generation renin inhibitors were peptide analogues of the pro-segment of renin or substrate analogues of the



N-terminal amino-acid sequence of the renin substrate, angiotensinogen. Substitution of the dipeptide moiety at the cleavage site (the so-called scissile bond) resulted in selective renin inhibitors with an inhibitory potency in the micromolar range. Subsequently, compounds were developed in which the peptides at the scissile bond were replaced by noncleavable analogues with resultant potency in the nanomolar range (10,13,30,31,34).

Several of these peptide-like analogues were tested in animals and humans for their mechanistic and hemodynamic effects. In studies using sodium-depleted marmosets, the renin inhibitor, CGP 29 287, produced dose-dependent inhibition of plasma renin activity (PRA) and lowered BP during intravenous infusion (32). (PRA is determined using a radioimmunoassay that measures the capacity of plasma to generate A I, reflecting renin's enzymatic activity and not the mass of circulating renin. The latter is referred to as the plasma renin concentration [PRC].) Both remikiren and zankiren were shown to reduce PRA and increase PRC after oral administration indicating renin inhibition (30,33–35). When remikiren was administered to patients with hypertension, however, no statistically significant BP reduction was seen after 8 days of oral dosing (35,36).

As a group, the peptidomimetic renin inhibitors showed high in vitro and in vivo potency. However, their large molecular size and lipophilicity resulted in poor intestinal absorption and considerable first-pass hepatic metabolism, significantly limiting oral bioavailability (34). In



addition, all of these agents had short elimination half lives and high costs of synthesis and production. These factors precluded their successful development as antihypertensive agents (10).

### **Aliskiren**

The development of aliskiren was approached in a logical, analytical fashion and represents a significant breakthrough in medicinal chemistry. Renin is a protein that is soluble in water and amenable to X-ray crystallographic analysis (15). This provided the opportunity to analyze X-ray diffraction data for crystals of renin bound to renin inhibitors. Molecular modeling was then used to design a novel, low-molecular-weight, non-peptide renin inhibitor (37). The extended peptide-like backbone that characterized earlier peptidomimetic renin inhibitors was eliminated. The addition of various alkylether aromatic side chains promoted interaction with the S3sp subpocket of the active site and dramatically enhanced aliskiren's affinity for renin and its selectivity over other aspartic peptidases. Additional molecular remodeling, by replacement and substitution of side chains, resulted in a less lipophilic compound with a longer duration of action after oral dosing. Later, Drs. Alice Huxley (for whom aliskiren is named), Peter Herold, and others using retrosynthesis analysis were successful in simplifying the synthetic process and reducing the high cost of manufacture (38).

Aliskiren is an extremely potent competitive inhibitor of renin with an  $IC_{50}$  (concentration inhibiting 50% of activity) of 0.6 nmol/l (37). It has high specificity for primate renin, and shows a 10,000-fold lower affinity for related aspartic peptidases. This high specificity for renin makes it unlikely to produce adverse effects through interaction with other enzymes. In comparison with earlier renin inhibitors, aliskiren has favorable physiochemical properties with high aqueous solubility and lower lipophilicity, rendering it more resistant to degradation. This leads to improved bioavailability (approximately 2.6%) after oral administration.

**Preclinical studies: pharmacodynamic.** Species differences in the amino acid sequence of renin and angiotensinogen render human renin inhibitors weak as inhibitors of renin isoforms in nonprimate species (13,39). Thus, aliskiren inhibits human, marmoset, and rat plasma renin with  $IC_{50}$  values of 0.6, 2, and 80 nmol/l, and can be studied in marmosets (which are primates) but not in the commonly used rat models of hypertension. In marmosets that were sodium-depleted to activate the RAS, aliskiren at doses of 1 and 3 mg/kg produced complete inhibition of PRA for 6 and 24 h, respectively (40). Single oral doses lowered BP in a dose-dependent fashion. In the same animal model, aliskiren was more effective in reducing BP compared with the peptidomimetic renin inhibitors, remikiren and zankiren. Aliskiren was as effective in reducing BP as were comparable doses of valsartan and benazepril.

**Preclinical studies: end organ protection.** The specificity of aliskiren for primate renin precludes the use of most

animal models in which end organ effects of antihypertensive agents are commonly evaluated. The development of double transgenic rats (dTGR), which express the human genes for both renin and angiotensinogen, has provided a suitable animal model in which to investigate the tissue protective effects of renin inhibitors (41,42).

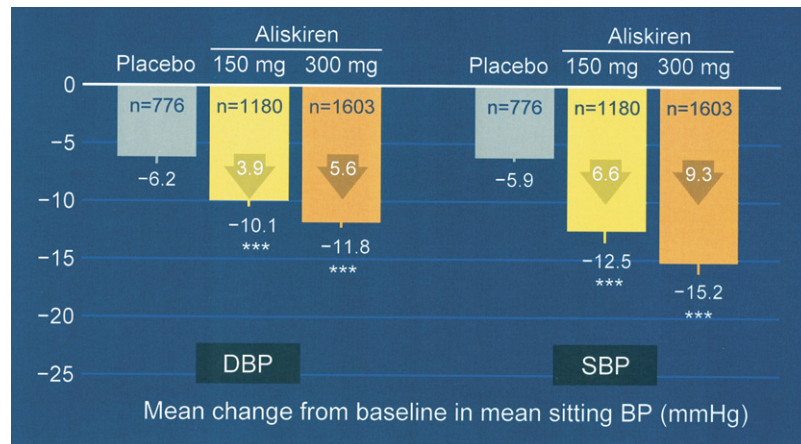
Pilz et al. (43) compared aliskiren and valsartan in preventing target organ damage in dTGR. Matched 6-week-old dTGR received either no treatment, low-dose or high-dose aliskiren, or low-dose or high-dose valsartan. Untreated dTGR showed severe hypertension, albuminuria, and increased serum creatinine by week 7, and 100% mortality rate by week 9. In contrast, high-dose valsartan and both doses of aliskiren lowered BP, reduced albuminuria and creatinine levels, and resulted in 100% survival at week 9. Treatment with aliskiren and high-dose valsartan also reduced left ventricular hypertrophy (LVH); the magnitude of this effect was somewhat greater with high-dose aliskiren.

In other renal protection studies using the double transgenic rat model, aliskiren reduced renal inflammation and fibrosis as well as albuminuria (44). In dTGR rats with diabetic nephropathy, aliskiren reduced albuminuria and other markers of renal damage, including gene expression of TGF- $\beta$  and collagens III and IV (45). When aliskiren was compared with ACE inhibitors or angiotensin receptor blockers (ARBs), the renal protective effects were approximately equal (43,45).

**Clinical pharmacology.** In healthy male subjects over a wide range of doses (40 to 1,800 mg), the plasma concentration of aliskiren peaks at 2 to 4 h after oral administration. The terminal half is 23 to 36 h, making the drug suitable for once-daily administration (46). The maximum serum concentration ( $C_{max}$ ),  $C_{max}$  at steady state, and area under the curve all increase proportionally after doses >80 mg. Administration of aliskiren with food results in lower mean  $C_{max}$  and area under the curve values than are obtained in the fasting state, although the drug was given without regard to meals in clinical trials. After a single intravenous infusion of 20 mg in healthy males, the plasma clearance of aliskiren was approximately 9 l/h, and the hepatic extraction ratio was approximately 10% with only minor involvement of the first-pass metabolism (46). The volume of distribution was approximately 135 l. In humans, aliskiren is 47% to 51% protein bound (47).

Aliskiren seems to have low potential for significant drug interactions. Co-administration of aliskiren did not significantly affect the pharmacokinetics of lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril, hydrochlorothiazide (HCTZ), or warfarin (48–51). When aliskiren was co-administered with furosemide, the area under the curve and  $C_{max}$  of furosemide were reduced by about 30% and 50%, respectively (52).

**Effects on the RAS.** In a crossover study in normotensive volunteers receiving a low-sodium diet, Nussberger et al. (53) evaluated the effects of 4 oral doses of aliskiren (40, 80,



**Figure 4** Antihypertensive Effects of Aliskiren Compared With Placebo

Results of the pooled analysis in 8,481 patients treated with aliskiren 150 and 300 mg compared with placebo. \*\*\* $p < 0.0001$  versus placebo. Values under the bars represent least-squares mean reduction  $\pm$  standard error of the mean; values in the arrows represent placebo-subtracted reductions. DBP = diastolic blood pressure; SBP = systolic blood pressure. Data from Dahlöf et al. (63).

160, and 640 mg) compared with placebo and the ACE inhibitor enalapril (20 mg) on components of the RAS. After single oral doses and 8 days of repeated once-daily dosing, aliskiren reduced PRA in a dose-dependent manner. Compared with placebo, the highest doses of aliskiren reduced A II levels by a maximum of 89% and 75% on days 1 and 8, respectively. At doses of aliskiren  $>80$  mg/day, there was a 40% to 50% decrease in both plasma and urinary aldosterone levels. Higher doses of aliskiren enhanced natriuresis. Although enalapril reduced A II levels acutely to a comparable degree as aliskiren, its administration was associated with a  $>15$ -fold increase in PRA. Both aliskiren and enalapril increased PRC.

Azizi et al. (54) examined the mechanistic aspects of dual RAS blockade after single oral doses of aliskiren and the AT<sub>1</sub> receptor blocker valsartan. In a crossover study, placebo, aliskiren (300 mg), valsartan (160 mg), and a low-dose combination of the 2 drugs (aliskiren 150 mg + valsartan 80 mg) were given to 12 sodium-depleted normotensive men. As monotherapy, aliskiren decreased PRA. Valsartan increased PRA as well as circulating levels of A I and A II. In the combination arm, PRA, A I, and A II levels were approximately equal to placebo. Thus, addition of aliskiren eliminated the compensatory increase in PRA and its downstream products that occurred after acute ARB administration.

### Aliskiren in Hypertension

Aliskiren has been extensively evaluated, as monotherapy and in combination with other agents, in clinical trials involving more than 11,000 adult patients with hypertension. In several trials PRA and PRC were measured, providing an opportunity to observe the effect of chronic oral dosing on components of the RAS.

**Comparison with placebo.** Eight placebo-controlled trials have assessed the antihypertensive effects of aliskiren monotherapy (55–62). Short-term treatment (4 to 8 weeks) with once-daily aliskiren at doses  $>75$  mg/day consistently produced significant BP reduction compared with placebo. A dose-response relationship was documented up to 300 mg/day; little or no additional BP reduction was observed with a higher dose (600 mg). When given for 8 weeks, three doses of aliskiren (150, 300, and 600 mg/day) reduced PRA by 70% to 73% from baseline without a measurable dose-dependent effect on this parameter. Increases in PRC were dose-related in patients receiving 150 mg (+128%), 300 mg (180%), and 600 mg (386%).

Most of the antihypertensive effects of aliskiren were achieved during the first 2 weeks, and near-maximum BP reduction occurred by week 4. As measured by 24-h ambulatory BP monitoring, aliskiren significantly reduced mean ambulatory systolic and diastolic BP over 24 h. The antihypertensive effect was sustained throughout the dosing interval with trough-to-peak ratios of 64% for the 150 mg dose and 98% for the 300 mg dose as reported in one study.

A pooled analysis reported by Dahlöf et al. (63) included 8,481 patients who participated in double-blind trials and received treatment with aliskiren monotherapy or placebo for 8 to 12 weeks (Fig. 4). Once-daily aliskiren, 150 and 300 mg, produced reductions in mean trough sitting diastolic BP of 10.1 and 11.8 mm Hg, respectively, compared with 6.2 mm Hg for placebo ( $p < 0.0001$ ). Trough systolic BP was lowered by 12.5 and 15.2 mm Hg, compared with 5.9 mm Hg for placebo ( $p < 0.0001$ ). There was no statistical difference in the magnitude of BP reduction in men and women or in patients younger or older than 65 years.

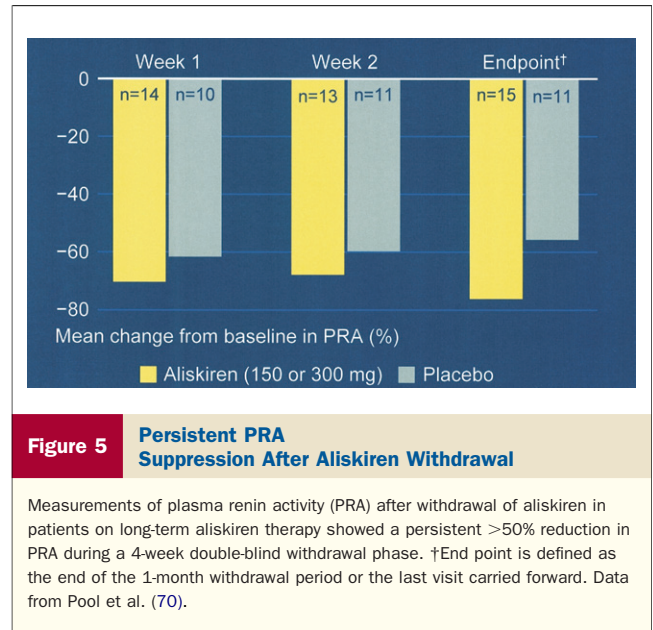
**Comparison with other antihypertensive agents.** Aliskiren has been compared with commonly used antihypertensive agents, including HCTZ, ramipril, and several angiotensin receptor blockers. In general, the efficacy of aliskiren was similar to other antihypertensive drugs. Eight weeks of treatment with aliskiren at doses of 150 and 300 mg/day resulted in BP reduction comparable to that of standard therapy with low-dose HCTZ (12.5 mg/day, 25 mg/day). Monotherapy with HCTZ activated the RAS. The PRA increased by 44.7% at a dose of 12.5 mg/day and 71.9% with 25 mg/day; corresponding increases in PRC were 26.1% and 108.4%, respectively (56).

Two trials have compared the BP-lowering effects of aliskiren with that of the ACE inhibitor ramipril. In hypertensive diabetic patients, aliskiren (300 mg) was equally effective in lowering mean sitting diastolic BP (the primary efficacy variable) compared with ramipril (10 mg) (64). A significantly greater reduction in sitting systolic BP was seen in aliskiren-treated patients. Similar results were obtained in a longer term (6 months) comparison of aliskiren and ramipril in nondiabetic hypertensive patients (65). Ramipril also produced RAS activation. In one study, ramipril 10 mg increased both PRA (+110.6%) and PRC (+67.9%).

Multiple studies have evaluated the efficacy and safety of aliskiren in comparison with various ARBs (losartan, irbesartan, valsartan). In a 4-week study that included ambulatory BP monitoring, there was no statistical difference between the change in daytime systolic BP with 100 mg/day losartan and 300 mg aliskiren (66). In another study, the antihypertensive efficacy of aliskiren 150 mg was found to be similar to that of irbesartan 150 mg/day, which at this dose increased both PRA (+116.3%) and PRC (+107.0%) (55). Aliskiren was compared directly with valsartan as part of an 8-week study in which both drugs were forced-titrated to their maximum U.S. Food and Drug Administration-approved dosage (aliskiren 300 mg, valsartan 320 mg); reductions in systolic BP and diastolic BP were almost identical (13.0/9.0 mm Hg, 12.8/9.7 mm Hg,  $p = \text{NS}$ ) (61).

**Safety.** In a pooled analysis of data including 2,316 patients who received aliskiren monotherapy, the tolerability profile of aliskiren was similar to that of placebo or ARBs at doses up to 300 mg daily (67). At the 600-mg dose, an increased incidence of diarrhea (9.5%) was observed in comparison with placebo (1.2%). The total number of reported adverse events and the rate of discontinuation because of adverse events were similar to those for placebo. Serious adverse events occurred in 11 patients (0.5%) who received aliskiren compared with 5 patients (0.6%) who received placebo.

**Persistence of effect after discontinuation.** The effects occurring after abrupt withdrawal of aliskiren have been investigated in several controlled studies. Rebound hypertension has not been reported. On the contrary, persistence of BP-lowering effects has been consistently documented



(68–70). In one study, patients who had received 11 months of aliskiren monotherapy were randomized to continued aliskiren or placebo during a 4-week double-blind withdrawal phase. Patients receiving placebo had a gradual increase in BP during the withdrawal period. The BP in the placebo group did not return to pre-treatment values, however, and PRA remained >50% below baseline levels, indicating that the renin inhibition provided by aliskiren extends well beyond the plasma half-life of the drug (70) (Fig. 5). This prolonged suppression of PRA might be explained by animal studies showing the localization and retention of aliskiren in the kidneys of dTGR for up to 3 weeks after its discontinuation (71).

**Combination therapy.** Most patients with hypertension require multiple drugs, and the safety and efficacy of aliskiren has been studied in combination with thiazide diuretics, calcium channel blockers, ACE inhibitors, and ARBs (56,60,61,64,72). For reasons discussed later, considerable emphasis has been placed on the evaluation of aliskiren in combination with other blockers of the RAS.

Because of their complimentary pharmacologic actions, diuretics are natural combination partners with drugs such as aliskiren that block the RAS. In a large factorial design study, 2776 patients with stage I and II hypertension received placebo, aliskiren (75, 150, or 300 mg), HCTZ (6.25, 12.5, or 25 mg), or various combinations of aliskiren + HCTZ over an 8-week period (56). The BP reduction with combinations of aliskiren and HCTZ seemed to be fully additive (i.e., the BP-reducing effect observed with combinations was approximately equal to the sum of BP reduction obtained with each component) less the placebo response. At the highest combination dose (aliskiren 300 mg + HCTZ 25 mg), an average BP reduction of 21.2/14.3 mm Hg was seen. In obese hypertensive subjects, aliskiren 300 mg/HCTZ 25 mg was equipotent compared with



irbesartan 300 mg/HCTZ 25 mg indicating that the combination of a renin inhibitor and a diuretic is as effective as commonly used diuretic/ARB combinations (60). Combination with aliskiren blocked the increases in PRA seen with HCTZ monotherapy while PRC levels increased markedly. Administration of aliskiren/HCTZ 150/12.5 mg reduced PRA (−49.6%) and increased PRC (+305%).

One study has assessed the efficacy and tolerability of aliskiren combined with a calcium channel blocker (72). Patients showing an inadequate response to amlodipine 5 mg/day were randomized to either continued therapy with amlodipine 5 mg, up-titration to amlodipine 10 mg, or the addition of aliskiren 150 mg to amlodipine 5 mg. Up-titration of amlodipine or addition of aliskiren resulted in significantly greater BP reduction than continuation of amlodipine 5 mg/day, with no difference between the low-dose combination and high-dose amlodipine. The 10-mg amlodipine dose was associated with a higher incidence of treatment-related peripheral edema (a dose-dependent side effect of calcium channel blockers) compared with the low-dose combination (11.2% vs. 2.1%). Important unanswered questions include the potency of higher dose combinations and whether aliskiren, like ACE inhibitors, will be found to decrease the rate of treatment-emergent edema seen with high doses of amlodipine and other calcium channel blockers.

**Dual RAS blockade.** The effects of dual RAS blockade with aliskiren and the ACE inhibitor ramipril were studied in 837 patients with diabetes and hypertension (64). The doses used in this study were the most commonly used dose of ramipril (10 mg), the maximum recommended dose of aliskiren (300 mg), and the combination of these doses (aliskiren/ramipril 300/10 mg). The BP was reduced by 16.6/12.8 mm Hg with combination therapy, which was statistically greater than the BP reduction seen with aliskiren (14.7/11.3 mm Hg) or ramipril (12.0/10.7 mm Hg) alone. Combination with the renin inhibitor blocked the increases in PRA seen with ACE inhibitor monotherapy while PRC levels increased significantly.

The clinical effectiveness and safety of a high-dose combination of aliskiren and the ARB valsartan was tested in 1,797 patients with a mean baseline BP 154/100 mm Hg (61). Patients were randomly assigned to receive placebo, aliskiren, valsartan, or the combination of aliskiren/valsartan. Dosage in the active treatment arms was titrated to the maximum recommended doses of each agent (aliskiren 300 mg, valsartan 320 mg); the combination dose was aliskiren/valsartan 300/320 mg.

The high-dose combination reduced BP by a mean of 17.2/12.2 mm Hg, significantly greater than was observed with either component (aliskiren 13.0/9.0 mm Hg, valsartan 12.8/9.7 mm Hg). The PRA increased with valsartan (+160%), decreased with aliskiren (−73%), and was also suppressed by the combination (−44%). The PRC increased with all active treatments; the increase in the combination therapy arm (+912%) was statistically greater

than that seen with aliskiren (+468%) or valsartan (+138%) alone.

The high-dose combination of aliskiren and valsartan was well tolerated. There was an increased incidence of hyperkalemia ( $K^+ >5.5$  mmol/l) in patients receiving the combination compared with those receiving monotherapy. In 13 of 18 patients with this finding, potassium returned to the normal range at study end without dosage adjustment (61).

### Renin Inhibition: Perspective

Renin inhibitors are a new class of agents, and there are as yet no clinical data regarding the ability of aliskiren to prevent clinical end points or reduce end organ damage over and above the presumed effects of BP reduction per se. Although there are supportive data from animal studies, it is also unknown whether aliskiren will prove to be superior, equal, or inferior to ACE inhibitors or ARBs in terms of end organ protection. These are the key outstanding questions, the answers to which will ultimately determine the place of renin inhibition and aliskiren in the treatment of hypertension and related cardiovascular disorders.

There are reasons to speculate that renin inhibition might prove to be a superior strategy for blocking the RAS compared with existing drugs. These relate to effects on A II generation, as well as to possible influences on the activities of renin and pro-renin when bound to (pro)renin receptors. Aliskiren is a potent inhibitor of renin, and its bioavailability is sufficient to produce sustained suppression of PRA and BP reduction after chronic oral dosing. This suppression is present whether the drug is given alone or in combination and persists after drug discontinuation. It is logical to assume that PRA suppression also leads to downstream suppression of A II formation.

The long-term effects of aliskiren on circulating A II levels have, however, not been reported. In a recent article, Sealey and Laragh (73) raised the question of whether the marked increases in PRC levels seen with aliskiren might be sufficient to overwhelm the renin inhibition produced by the drug. These investigators hypothesize that the inability of aliskiren to reduce BP by more than is achieved with ACE inhibitors and ARBs suggests that an ACE-escape-like phenomenon may be operative. The observation that the percentage inhibition of PRA remains relatively constant despite escalating aliskiren doses also suggests that significant A II generation may continue despite renin inhibition. Data regarding circulating A II levels in hypertensive patients receiving aliskiren would be useful in quantifying the degree of RAS suppression actually achieved with chronic dosing.

The discovery of the (pro)renin receptor and ongoing elucidation of its functions are rapidly changing our conceptual understanding of the RAS. Available data point to an expanded role for renin and a pathogenetic role for pro-renin in the genesis of human disease. The observation that pro-renin becomes biologically active when bound to



the (pro)renin receptor is of particular interest in view of data linking pro-renin with the development of microvascular disease in diabetic patients (18,19). If renin inhibitors block these newly recognized actions of renin and pro-renin, this might well constitute a therapeutic advantage over ACE inhibitors and ARBs.

The effects of aliskiren on events occurring at the (pro)renin receptor remain largely unknown, however. In a recent article, Nguyen (74) succinctly summarized the important outstanding issues (Fig. 6). The first question is whether or not aliskiren inhibits the enzymatic activity of renin and pro-renin when they are bound to the (pro)renin receptor. The answer to this question will be particularly important in understanding aliskiren's mechanism of action.

Another fundamental question is whether renin inhibitors alter the non-A II-mediated activation of intracellular signaling pathways produced by receptor-bound renin and pro-renin. The direct receptor-mediated effects described to date are similar to classic tissue responses to AT<sub>1</sub> receptor stimulation, and are known to contribute to the development of cellular hypertrophy and fibrosis. Available evidence suggests that aliskiren does not inhibit these actions (75), but further investigation is clearly needed to clarify this important issue. In addition, because some renin inhibitors are known to drastically modify the structure of renin, future renin inhibitors may have different effects than aliskiren on the binding of renin to its receptor.

The ability of renin and pro-renin to produce potentially adverse effects independent of A II has raised concern that increases in PRC seen after aliskiren administration could have undesirable consequences. This seems unlikely because most available antihypertensive agents, including diuretics, calcium channel blockers, ACE inhibitors, and ARBs, also increase circulating renin levels. If increased renin levels

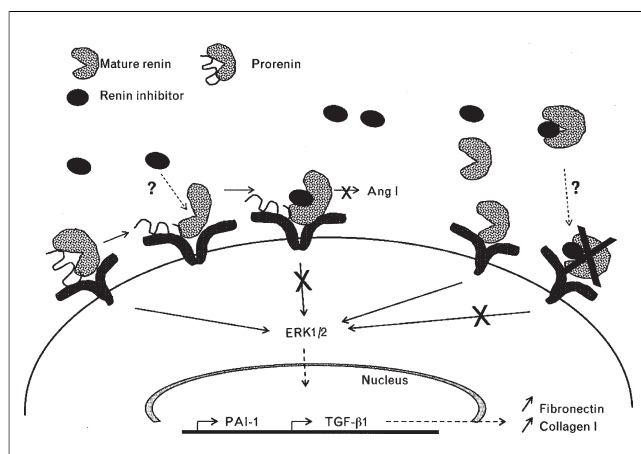
were deleterious, it is doubtful that these drugs would be as effective as they are in reducing long-term cardiovascular end points. Nevertheless, the PRC levels reported after administration of aliskiren—particularly when combined with other drugs—are significantly higher than have been seen with other antihypertensive regimens, and negative consequences cannot be categorically excluded.

In this context, it should be noted that there are methodological problems regarding the accuracy of PRC measurements made in the presence of renin inhibitors, including aliskiren. Renin levels are measured by direct immunoassay using a radiolabeled antibody specific for renin. In some circumstances, renin inhibitors are known to be capable of nonproteolytically activating pro-renin via conformational changes described earlier. Depending on the incubating conditions, this activated pro-renin can be detected by direct immunoassays as renin, leading to overestimation of renin concentration (76). Therefore, the magnitude of PRC increases reported in recent trials with aliskiren requires verification.

The results of the aliskiren/valsartan combination on BP support the concept that renin inhibitors and ARBs work by pharmacologic mechanisms that are distinct and complimentary. Like many hormonal systems, the RAS is self-regulating and controlled by negative feedback inhibition. Stimulation of the AT<sub>1</sub> receptor by A II suppresses renin release. By blocking the interaction of A II with its receptor, ARBs interfere with this negative feedback loop and stimulate renin production. When valsartan is given as monotherapy, PRA increases, whereas when it is combined with aliskiren, PRA is reduced (61). If compensatory RAS activation truly limits the effectiveness of AT<sub>1</sub> receptor blockade, it is a reasonable hypothesis that simultaneous administration of a renin inhibitor will produce more complete RAS suppression and better end organ protection compared with an ARB alone.

A combination strategy is being utilized in studies examining the effects of aliskiren on intermediate markers of end organ damage. In the recently presented ALOFT (ALiskiren Observation of Heart Failure Treatment) study, the addition of aliskiren, 150 mg/day, to standard therapy for heart failure (which included either an ACE inhibitor or ARB, if tolerated) resulted in significant reductions in the BNP levels in patients receiving aliskiren compared with standard therapy alone (77). In the ongoing AVOID (Aliskiren in eValuation of prOteinuria in Diabetes) study, aliskiren 300 mg/day or placebo is being added to background therapy with losartan 100 mg/day in hypertensive diabetic patients with proteinuria. The purpose of the study is to determine whether combination treatment reduces albuminuria more effectively than losartan given at doses that have been shown to be renal protective.

In the ALLAY (Aliskiren in Left Ventricular Assessment of Hypertrophy) trial, overweight patients with hypertension and LVH are receiving blinded treatment with aliskiren (300 mg), losartan (100 mg), or the combination



**Figure 6** Possible Effects of Renin Inhibitors on Receptor-Bound Renin and Pro-Renin

Potential sites of inhibition of the enzymatic activity and direct intracellular effects of receptor-bound renin and pro-renin. ERK1/2 = extracellular signal-regulated kinase 1/2; PAI-1 = plasminogen activator inhibitor-1; TGF-β = transforming growth factor-beta. Reprinted with permission from Nguyen (74).

(aliskiren/losartan 300/100 mg). The primary end point is left ventricular mass assessed by magnetic resonance imaging to determine whether the addition of a renin inhibitor increases the magnitude of LVH regression compared with that achievable with an ARB alone. Data from this study also should be helpful in excluding a negative effect related to excessive stimulation of (pro)renin receptors by elevated PRC levels because the intracellular changes initiated by (pro)renin receptor stimulation promote hypertrophy and fibrosis, which are central to LVH development.

In summary, 50 years after it was postulated to be the preferred approach to RAS blockade, an orally effective renin inhibitor has been introduced into clinical medicine. Many of the basic questions that must be answered when evaluating any new antihypertensive agent have been addressed. Aliskiren produces dose-dependent BP reduction and placebo-like tolerability up to the plateau in the dose-response curve that occurs at approximately 300 mg/day. Its antihypertensive potency is equivalent to those of ARBs, ACE inhibitors, and diuretics. Critical questions regarding the effectiveness of aliskiren in blocking the effects of renin/pro-renin at the site of the (pro)renin receptor remain to be answered. Clinical trials planned or in progress will address issues related to end organ protection and reduction in long-term cardiovascular end points.

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## REFERENCES

1. Skeggs LT, Kahn JR, Lentz KE, Shumway NP. Preparation, purification, and amino acid sequence of a polypeptide renin substrate. *J Exp Med* 1957;106:439–53.
2. Neal B, MacMahon S, Chapman N. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomized trials: Blood Pressure Lowering Treatment Trialists' Collaboration. *Lancet* 2000;356:1955–64.
3. Flather MD, Yusuf S, Kober L, et al. Long-term ACE-inhibitor therapy in patients with heart failure or left-ventricular dysfunction: a systematic overview of data from individual patients: ACE-Inhibitor Myocardial Infarction Collaborative Group. *Lancet* 2000;355:1575–81.
4. Cohn JN, Tognoni G. A randomized trial of the angiotensin-receptor blocker valsartan in chronic heart failure. *N Engl J Med* 2001;345:1667–75.
5. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet* 2003;362:759–66.
6. The SOLVD Investigators. Effect of enalapril on mortality and the development of heart failure in asymptomatic patients with reduced left ventricular ejection fractions. *N Engl J Med* 1992;327:685–91.
7. Lewis EJ, Hunsicker LG, Bain RP, et al. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy: The Collaborative Study Group. *N Engl J Med* 1993;329:1456–62.
8. Lewis EJ, Hunsicker LG, Clarke WR, et al. Renoprotective effect of the angiotensin-receptor antagonist irbesartan in patients with nephropathy due to type 2 diabetes. *N Engl J Med* 2001;345:851–60.
9. Brenner BM, Cooper ME, de Zeeuw D, et al. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. *N Engl J Med* 2001;345:861–9.
10. Fisher ND, Hollenberg NK. Is there a future for renin inhibitors? *Expert Opin Investig Drugs* 2001;10:417–26.
11. FDA Approves New Drug Treatment for High Blood Pressure. Available at: [www.fda.gov/bbs/topics/NEWS/2007/NEW01580.html](http://www.fda.gov/bbs/topics/NEWS/2007/NEW01580.html). Accessed October 2, 2007.
12. Nguyen G, Delarue F, Burcklé C, Bouzahir L, Giller T, Sraer J-D. Pivotal role of the renin/pro-renin receptor in angiotensin II production and cellular responses to renin. *J Clin Invest* 2002;109:1417–27.
13. Wood JM, Stanton JL, Hofbauer KG. Inhibitors of renin as potential therapeutic agents. *J Enzyme Inhib* 1987;1:169–85.
14. Sielecki AR, Hayakawa K, Fujinaga M, et al. Structure of recombinant human renin, a target for cardiovascular-active drugs, at 2.5 Å resolution. *Science* 1989;243:1346–51.
15. J. Rahuel V, Rasetti J, Maibaum H, et al. Structure-based drug design: the discovery of novel nonpeptide orally active inhibitors of human renin. *Chem Biol* 2000;7:493–504.
16. Danser AHJ, Denium J. Renin, pro-renin and putative (Pro)renin receptor. *Hypertension* 2005;46:1069–76.
17. Danser AHJ, Derckx FHM, Schalekamp MADH, Hense HW, Riegger GAJ, Schunkert H. Determinants of interindividual variation of renin and pro-renin concentrations: evidence for a sexual dimorphism of (pro)renin levels in humans. *J Hypertens* 1998;16:853–62.
18. Luetscher JA, Kraemer FB, Wilson DM, et al. Increased plasma inactive renin in diabetes mellitus a marker of microvascular complications. *N Engl J Med* 1985;312:1412–7.
19. Price DA, Porter LE, Gordon M, et al. The paradox of the low-renin state in diabetic nephropathy. *J Am Soc Nephrol* 1999;10:2382–91.
20. Reudelhuber TL, Ramla D, Chiu L, Mercure C, Seidah NG. Proteolytic processing of human pro-renin in renal and non-renal tissues. *Kidney Int* 1994;46:1522–4.
21. Derckx FHM, Deinum J, Lipovski M, Verhaar M, Fischli W, Schalekamp MADH. Nonproteolytic “activation” of pro-renin by active site-directed renin inhibitors as demonstrated by renin-specific monoclonal antibody. *J Biol Chem* 1992;267:22837–42.
22. Pitarresi TM, Rubattu S, Heinrikson R, Sealey JE. Reversible cryo-activation of recombinant human pro-renin. *J Biol Chem* 1992;267:11753–9.
23. Suzuki F, Hayakawa M, Nakagawa T, et al. Human pro-renin has “gate and handle” regions for its non-proteolytic activation. *J Biol Chem* 2003;278:22217–22.
24. Nabi AHMN, Kageshima A, Uddin MN, et al. Binding properties of rat pro-renin and renin to the recombinant rat renin/pro-renin receptor prepared by a baculovirus expression system. *Int J Mol Med* 2006;18:483–88.
25. Oliver JA. Receptor mediated actions of renin and pro-renin. *Kidney Int* 2006;69:13–5.
26. Nguyen G. Renin/pro-renin receptors. *Kidney Int* 2006;69:1503–6.
27. Nguyen G, Danser AHJ. The (pro)renin receptor: therapeutic consequences. *Expert Opin Investig Drugs* 2006;15:1131–5.
28. Ichihara A, Suzuki F, Nakagawa T, et al. Pro-renin receptor blockade inhibits development of glomerulosclerosis in diabetic angiotensin II type 1a receptor-deficient mice. *J Am Soc Nephrol* 2006;17:1950–61.
29. Huang Y, Wongamorntham S, Kasting J, et al. Renin increases mesangial cell transforming growth factor-beta1 and matrix proteins through receptor-mediated, angiotensin II-independent mechanisms. *Kidney Int* 2006;69:105–13.
30. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449–56.
31. Li YC. Inhibition of renin: an updated review of the development of renin inhibitors. *Curr Opin Investig Drugs* 2007;8:750–7.
32. Wood JM, Gulati N, Forgiarini P, Fuhrer W, Hofbauer KG. Effects of a specific and long-acting renin inhibitor in the marmoset. *Hypertension* 1985;7:797–803.
33. Macfayden RJ, Jones CR, Doig JK, Birnbock H, Reid JL. Responses to an orally active renin inhibitor, remikiren (Ro 42-5892), after controlled salt depletion in humans. *J Cardiovasc Pharmacol* 1995;25:347–53.
34. Rongen GA, Lenders JWM, Smits P, Thien T. Clinical pharmacokinetics and efficacy of renin inhibitors. *Clin Pharmacokinet* 1995;29:6–14.
35. Himmelmann A, Bergbrant A, Svensson A, Hansson L, Aurell M. Remikiren (Ro 42-5892)—an orally active renin inhibitor in essential

- hypertension. Effects on blood pressure and the renin-angiotensin-aldosterone system. *Am J Hypertens* 1996;9:517–22.
36. Roengen GA, Lenders JWM, Kleinbloesem CH, et al. Efficacy and tolerability of the renin inhibitor Ro 42-5892 in patients with hypertension. *Clin Pharmacol Ther* 1993;54:567–77.
  37. Wood JM, Maibaum J, Rahuel J, et al. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun* 2003;308:698–705.
  38. Whalen J. Small firms seek to profit from drug giants' castoffs. *The Wall Street Journal*. February 7, 2007.
  39. Corvol P, Menard J. Renin inhibition: immunological procedures and renin inhibitor peptides. *Fundam Clin Pharmacol* 1989;3:347–62.
  40. Wood JM, Schnell CR, Cumin F, et al. Aliskiren, a novel, orally effective renin inhibitor, lowers blood pressure in marmosets and spontaneously hypertensive rats. *J Hypertens* 2005;23:417–26.
  41. Ganten D, Wagner J, Zeh K, et al. Species specificity of renin kinetics in transgenic rats harboring the human renin and angiotensinogen genes. *Proc Natl Acad Sci U S A* 1992;89:7806–10.
  42. Fukamizu A, Sugimura K, Takimoto E, et al. Chimeric renin-angiotensin system demonstrates sustained increase in blood pressure of transgenic mice carrying both human renin and human angiotensinogen genes. *J Biol Chem* 1993;268:11617–21.
  43. Pilz B, Shagdarsuren E, Wellner M, et al. Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension* 2005;46:569–76.
  44. Shagdarsuren E, Wellner M, Braesen JH, et al. Complement activation in angiotensin II-induced organ damage. *Circ Res* 2005;97:716–24.
  45. Kelly DJ, Zhang Y, Moe G, Naik G, Gilbert RE. Aliskiren, a novel renin inhibitor, is renoprotective in a model of advanced diabetic nephropathy in rats. *Diabetologia* 2007;50:2398–404.
  46. Azizi M, Webb R, Nussberger J, et al. Renin inhibition with aliskiren: where are we now and where are we going? *J Hypertens* 2006;24:243–56.
  47. Vaidyanathan S, Valencia J, Kemp C, et al. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of HTN, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract* 2006;60:1343–56.
  48. Dieterle W, Corynen S, Vaidyanathan S, Mann J. Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* 2005;43:527–35.
  49. Dieterich H, Kemp C, Vaidyanathan S, Yeh C. Pharmacokinetic interaction of the oral renin inhibitor aliskiren with hydrochlorothiazide in healthy volunteers (abstr). *Clin Pharmacol Ther* 2006;79 Suppl:P12.
  50. Dieterich H, Kemp C, Vaidyanathan S, Yeh C. Aliskiren, the first in a new class of orally effective renin inhibitors, has no clinically significant drug interactions with digoxin in healthy volunteers (abstr). *Clin Pharmacol Ther* 2006;79 Suppl:P64.
  51. Dieterle W, Corynen S, Mann J. Effect of the oral renin inhibitor aliskiren on the pharmacokinetics and pharmacodynamics of a single dose of warfarin in healthy subjects. *Br J Clin Pharmacol* 2004;58:433–6.
  52. Tekturna (package insert). East Hanover, NJ: Novartis Pharmaceuticals Corporation, 2007.
  53. Nussberger J, Wuerzner G, Jensen C, Brunner HR. Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100): comparison with enalapril. *Hypertension* 2002;39:e1–8.
  54. Azizi M, Menard J, Bissery A, et al. Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II–renin feedback interruption. *J Am Soc Nephrol* 2004;15:3126–33.
  55. Gradman AH, Schmieder RE, Lins RL, et al. Aliskiren, a novel orally effective renin inhibitor, provides dose-dependent antihypertensive efficacy and placebo-like tolerability in hypertensive patients. *Circulation* 2005;111:1012–8.
  56. Villamil A, Chrysant SG, Calhoun D, et al. Renin inhibition with aliskiren provides additive antihypertensive efficacy when used in combination with hydrochlorothiazide. *J Hypertens* 2007;25:217–26.
  57. Oh BH, Mitchell J, Herron JR, et al. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-h blood pressure control in patients with hypertension. *J Am Coll Cardiol* 2007;49:1157–63.
  58. Kushihiro T, Itakura H, Abo Y, et al. Aliskiren, a novel oral renin inhibitor, provides dose-dependent efficacy and placebo-like tolerability in Japanese patients with hypertension. *Hypertens Res* 2006;29:997–1005.
  59. Pool JL, Schmieder RE, Azizi M, et al. Aliskiren, an orally effective renin inhibitor, provides antihypertensive efficacy alone and in combination with valsartan. *Am J Hypertens* 2007;20:11–20.
  60. Jordan J, Engeli S, Boye SW, et al. Direct renin inhibition with aliskiren in obese patients with arterial hypertension. *Hypertension* 2007;49:1047–55.
  61. Oparil S, Yarows SA, Patel S, et al. Efficacy and safety of combined use of aliskiren and valsartan in patients with hypertension: a randomized double-blind trial. *Lancet* 2007;370:221–9.
  62. Mitchell J, Oh B, Herron J, et al. Once-daily aliskiren provides effective, smooth 24-h blood pressure control in patients with hypertension (abstr). *J Clin Hypertens* 2006;8 Suppl A:A93.
  63. Dahlöf B, Anderson DR, Arora V, et al. Aliskiren, a direct renin inhibitor, provides antihypertensive efficacy and excellent tolerability independent of age or gender in patients with hypertension (abstr). *J Clin Hypertens* 2007;9 Suppl A:A157.
  64. Uresin Y, Taylor A, Kilo C, et al. Aliskiren, a novel renin inhibitor, has greater BP lowering than ramipril and additional BP lowering when combined with ramipril in patients with diabetes and hypertension (abstr). *J Hypertens* 2006;24 Suppl 4:82.
  65. Andersen K, Weinberger MH, Egan B, et al. Aliskiren-based therapy lowers blood pressure more effectively than ramipril-based therapy in patients with hypertension: a 6-month, randomized, double blind trial (abstr). *J Am Coll Cardiol* 2007;49 Suppl A:A371.
  66. Stanton A, Jensen C, Nussberger J, et al. Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension* 2003;42:1137–43.
  67. Weir MR, Bush C, Zhang J, et al. Antihypertensive efficacy and safety of the oral renin inhibitor aliskiren in patients with hypertension: a pooled analysis (abstr). *Eur Heart J* 2006;27 Suppl:299.
  68. Sica D, Gradman A, Lederballe O, et al. Aliskiren, a novel renin inhibitor, is well tolerated and has sustained BP-lowering effects alone or in combination with HCTZ during long-term (52 weeks) treatment of hypertension (abstr). *Eur Heart J* 2006;27 Suppl:121.
  69. Keefe DL, Andersen K, Weinberger MH, et al. Blood pressure lowering effects persist following the last dose of long-term therapy with aliskiren, an oral direct renin inhibitor (abstr). *J Am Coll Cardiol* 2007;49 Suppl A:372.
  70. Pool J, Gradman A, Kolloch R, et al. Aliskiren, a novel renin inhibitor, provides long-term suppression of the renin system, when used alone or in combination with hydrochlorothiazide in the treatment of hypertension (abstr). *Eur Heart J* 2006;27 Suppl:119.
  71. Feldman DL, Persohn E, Schutz H, et al. Renal localization of the renin inhibitor aliskiren (abstr). *J Clin Hypertens* 2006;8 Suppl A:80.
  72. Munger MA, Drummond W, Essop MR, et al. Aliskiren as add-on to amlodipine provides significant additional blood pressure lowering without increased oedema associated with doubling the amlodipine dose (abstr). *Eur Heart J* 2006;27 Suppl:117.
  73. Sealey JE, Laragh JH. Aliskiren, the first renin inhibitor for treating hypertension: reactive renin secretion may limit its effectiveness. *Am J Hypertens* 2007;20:587–97.
  74. Nguyen G. The (pro)renin receptor: patho physiological roles in cardiovascular and renal pathology. *Curr Opin Nephrol Hypertens* 2007;16:129–33.
  75. Saris JJ, 't Hoen PAC, Garrelds IM, et al. Pro-renin induces intracellular signalling in cardiomyocytes independently of angiotensin II. *Hypertension* 2006;48:564–71.
  76. Menard J, Guyene TT, Peyrard S, Azizi M. Conformational changes in pro-renin during renin inhibition in vitro and in vivo. *J Hypertens* 2006;24:529–34.
  77. McMurray J, Pitt B, Latini R, et al. ALOFT—a 12 week safety evaluation of aliskiren 150 mg vs. placebo when added to standard therapy for stable heart failure. Paper presented at: European Society of Cardiology Congress; September 2, 2007; Vienna, Austria.



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