

Renin Inhibitors: Novel Agents for Renoprotection or a Better Angiotensin Receptor Blocker for Blood Pressure Lowering?

Eduardo Pimenta, MD^{a,*}, Suzanne Oparil, MD^b

KEYWORDS

- Hypertension • Renin inhibitors
- Renin-angiotensin-aldosterone system

The renin-angiotensin-aldosterone system (RAAS) is an important modulator of blood pressure (BP) and volume regulation in both normotensive and hypertensive persons.¹ The development of pharmacologic antagonists to its various components has proved useful in the treatment of hypertension and related target-organ damage. Renin, which is synthesized and released predominately from the juxtaglomerular granular epithelioid cells in the kidney, catalyzes the formation of angiotensin (Ang) I from angiotensinogen. Ang I, in turn, is processed by angiotensin-converting enzyme (ACE) and other proteases to form Ang II (Fig. 1). Renin is required for the production of Ang I and II.

Renin is synthesized as a preprohormone that contains a signal peptide that leads the inactive molecule to the exterior of the cell.² Prorenin is rendered enzymatically active by both proteolytic and nonproteolytic processes. Proteolytic

activation occurs via the actual removal of the pro-peptide chain. Most proteolytic activation of prorenin occurs within the juxtaglomerular cells.³ Nonproteolytic activation is a 2-step process that allows prorenin that has been secreted from the juxtaglomerular cells into the circulation to acquire enzymatic activity without removal of the pro-segment. While both prorenin and active renin are secreted from the juxtaglomerular cells into the circulation, prorenin is the predominant circulating form, accounting for approximately 90% of total renin in normal human plasma and for an even greater portion of the total in diabetic patients.⁴⁻⁶

The major physiologic and pathophysiologic effects of the RAAS are mediated by the octapeptide Ang II. Ang II has a variety of biological actions that lead to hypertension and related target organ damage. It is a potent vasoconstrictor and

Dr. Pimenta has no conflicts. Dr. Oparil has received grants-in-aid from Abbott Laboratories, Astra Zeneca, Boehringer Ingelheim, Bristol Myers-Squibb, Daiichi-Sankyo, Forest Laboratories, GlaxoSmithKline, Novartis, Merck & Co, Pfizer, Sankyo, Sanofi-Aventis, and Schering-Plough; and has served as a consultant for Bristol Myers-Squibb, Daiichi Sankyo, Merck & Co, Novartis, Pfizer, Sanofi Aventis, and The Salt Institute.

^a Department of Hypertension and Nephrology, Dante Pazzanese Institute of Cardiology, Av. Dr. Dante Pazzanese, 500, Sao Paulo, SP, Brazil, 04012-909.

^b Vascular Biology and Hypertension Program, University of Alabama at Birmingham, 703 19th Street South, ZRB 1034, Birmingham, AL 35294-2041, USA

* Corresponding author.

E-mail address: espimenta@hotmail.com (E. Pimenta).

Cardiol Clin 26 (2008) 527–535

doi:10.1016/j.ccl.2008.06.003

0733-8651/08/\$ – see front matter © 2008 Elsevier Inc. All rights reserved.

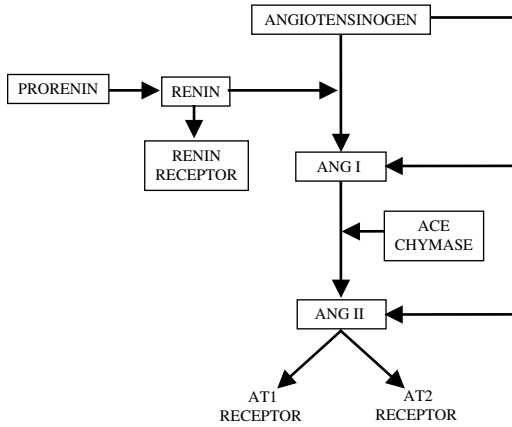


Fig. 1. Schematic representation of the renin-angiotensin-aldosterone system. ACE, angiotensin-converting enzyme; Ang, angiotensin; AT1, angiotensin II type 1 receptor; AT2, angiotensin II type 2 receptor.

stimulates sodium retention directly via renal vascular and tubular effects and indirectly by increasing aldosterone synthesis and release, thirst, and antidiuretic hormone release. Ang II also increases sympathetic outflow from the brain and norepinephrine release from peripheral sympathetic nerve terminals. In addition, Ang II is a potent growth hormone and mitogen, inducing both cell hyperplasia and hypertrophy. Importantly, Ang II inhibits renin release via a feedback mechanism that tends to stabilize BP in the normal range in normotensive individuals.

The actions of Ang II can be antagonized by blocking Ang II at the AT1 receptor site or by reducing the generation of Ang II. β -blockers (BB) inhibit the β -adrenergic receptor-mediated release of renin from the kidney, thus reducing plasma renin activity (PRA).^{7,8} However, renin secretion from the juxtaglomerular cells is also regulated by chloride transport across the renal macula densa cells. Ang II receptor activity and renal perfusion pressure play important roles in renin release as well. β -adrenergic blockade alone

can therefore only partially decrease the secretion of renin and reduce the generation of Ang II.

ACE inhibitors and angiotensin receptor blockers (ARB) lower BP and prevent target organ damage and cardiovascular disease events by blocking the RAAS. ACE inhibitors were first developed as an unintended consequence of the search for an explanation for the drop in BP induced by the venom of a pit viper.⁹ The discovery in the venom of the snake *Bothrops jararaca* of a peptide that blocked kinase II led to the synthesis of the ACE inhibitors.^{10,11} ACE inhibitors are potent orally active inhibitors of the enzyme that converts the inactive decapeptide Ang I into the active octapeptide Ang II. Although ACE inhibitors decrease Ang II generation, they stimulate PRA by blocking feedback inhibition of renin release (Table 1). ARBs are selective antagonists of the AT1 receptor of Ang II that also stimulate PRA via blockade of Ang II-mediated feedback inhibition of renin release.

More recently, aliskiren, the first in a new class of orally effective direct renin inhibitors (DRIs) was approved for the treatment of hypertension. In this review, we discuss the history of the development of DRIs and available data regarding the effects of DRIs in the treatment of hypertension and related target organ damage.

HISTORY

Renin was discovered in 1898 by Tigerstedt and Bergman¹² with the observation that extracts of renal tissues increase BP. Since then numerous attempts have been made to inhibit renin and thus lower BP. The concept of renin inhibition for managing hypertension by blocking the RAAS pathway at its point of activation is very attractive since the renin-angiotensinogen reaction is the first and rate-limiting step in the synthesis of Ang II. It has been postulated that blocking the RAAS by inhibiting the catalytic action of renin directly would be potentially more efficacious in treating hypertension and associated with fewer adverse

Table 1
Effects of antihypertensive agents on targets of the renin-angiotensin-aldosterone system pathway

	Angiotensin I	Angiotensin II	Renin Concentration	Plasma Renin Activity
Direct renin inhibitors	↓	↓	↑	↓
Angiotensin receptor blockers	↑	↑	↑	↑
Angiotensin-converting enzyme inhibitors	↑	↓	↑	↑

↑ increased; ↓ decreased.

Data from Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449–56; with permission.

effects than blocking downstream components of the RAAS.¹³

While the concept of inhibiting renin directly is appealing, the development of effective orally active DRIs has been technically challenging. First, preclinical studies of DRIs designed for human use must be performed in primates, such as marmosets, or in transgenic models expressing both human renin and angiotensinogen genes, because of the species specificity of the renin-angiotensinogen reaction.¹⁴ The sequence of renin differs greatly among species, such that human renin will not cleave heterologous angiotensinogen and inhibitors designed for human renin will not inhibit the activity of heterologous renin. Second, the reagents used in the first attempts to inhibit human renin, renin antibodies, and synthetic analogs of the prosegment of prorenin, proved unsatisfactory for a variety of reasons.^{15,16} These proteins had short half lives when administered parenterally, were inactive when administered orally, and led to immunologic complications such as the development of autoantibodies. Accordingly, developmental efforts shifted toward a search for effective small molecule renin inhibitors.

The first successful small molecule inhibitor of renin was pepstatin, an aspartyl protease inhibitor.¹⁷ While pepstatin successfully inhibited renin *in vitro*, it had a variety of disadvantages, including lack of selectivity for renin and poor solubility in water. Structural derivatives of pepstatin increased its solubility and selectivity for renin, but none of these compounds was ever used clinically because of low efficacy *in vivo*, lack of oral bioavailability, and high cost of synthesis.^{18–20}

The first clinical experience with a selective renin inhibitor was obtained with the angiotensinogen analog renin inhibitor peptide (RIP).²¹ Although RIP effectively reduced BP during intravenous administration in humans, it was abandoned because of evidence of a direct cardiodepressant effect unrelated to the renin inhibition.

Subsequent efforts to develop small molecule renin inhibitors were directed toward synthesizing peptide analogs of the N-terminal amino acid sequence of angiotensinogen that contained amino acid substitutions at the renin cleavage site (scissile bond). These peptide inhibitors had limited potency (micromolar range) and were replaced with noncleavable analogs that had the advantages of greater potency (nanomolar range) and oral bioavailability.¹³ Some of those peptide-like analogs, eg, remikiren, enalkiren, and zankiren, reduced PRA and increased plasma renin concentration after oral administration in humans, indicating renin inhibition.^{22–25} However, these

drugs had a weak BP lowering effect when administered orally.^{25,26} Oral administration of remikiren and parenteral infusion of enalkiren in healthy salt-restricted volunteers did not lower BP or alter heart rate, but did evoke dose-dependent decreases in PRA, Ang I, and Ang II that were rapidly reversed after termination of the treatments.^{27,28} High-dose intravenous boluses of enalkiren did reduce BP in hypertensive patients when salt-depleted, while heart rate remained unchanged.²⁹ A comparison of placebo, enalaprilat (1.25 mg intravenously), and enalkiren (0.03 to 1.00 mg/kg intravenously) in hypertensive patients pretreated with hydrochlorothiazide (HCTZ) to activate the RAAS showed that enalkiren produced decreases in systolic BP (SBP) and diastolic BP (DBP) that were statistically significant compared with placebo but less robust than seen with enalaprilat.³⁰ Similarly, both orally and intravenously administered remikiren (Ro 42-5892) produced significant decreases in SBP, PRA, and circulating Ang II in hypertensive subjects.³¹ Oral administration of another compound, CGP-38560A, was compared with captopril, at what were considered to be maximal doses: 0.25 mg/kg of the renin inhibitor and 50 mg of captopril.³² BP decreased markedly after captopril (15.3 mm Hg), but not after renin inhibitor (6.4 mm Hg) administration.

The peptidomimetic renin inhibitors failed as antihypertensive medications because of their large molecular size and lipophilicity, which resulted in poor intestinal absorption and considerable first-pass hepatic metabolism, significantly limiting oral bioavailability.²³ In addition, their short duration of action and weak BP-lowering activity, as well as the successful marketing of ACE inhibitors and ARBs in the 1980s and 1990s contributed to the failure of the first-generation DRIs.³³

ALISKIREN

Aliskiren is a low molecular weight (MW 552, free base) nonpeptidic renin inhibitor that consists of a substituted octanamide (**Fig. 2**). 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 sub-pocket of the active site of renin and dramatically enhanced the affinity of aliskiren for renin and its selectivity over other aspartic peptidases. Retrosynthesis analysis was used to simplify the synthetic process and reduce the high cost of manufacture.¹³

Aliskiren, the only orally active renin inhibitor approved for the treatment of hypertension in humans, is a competitive transition state analog

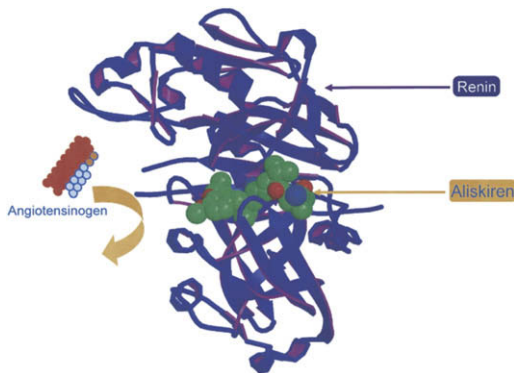


Fig. 2. Representation of the 3-dimensional structure of aliskiren. (From Gradman AH, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008; 51:519–28; with permission.)

and selective inhibitor of human renin. It has a therapeutic potential similar to that of other antagonists of the RAAS.³⁴ In humans, the plasma concentration of aliskiren increases dose-dependently after oral administration in doses of 40 to 640 mg/day, peaking after 3 to 6 hours.³⁵ The average plasma half-life is 23.7 hours, ranging from 20 to 45 hours, making aliskiren suitable for once-daily administration (**Table 2**). The oral bioavailability of aliskiren in humans is limited (2.7%).³⁵ Aliskiren is 47% to 51% protein bound and the steady-state plasma concentration is reached after 5 to 8 days of treatment. The main elimination route of aliskiren is via biliary excretion as unmetabolized drug.³⁵

Aliskiren is more potent and selective for human renin than the other orally active DRIs, ie, remikiren and enalkiren. Aliskiren is not metabolized by cytochrome P450, and thus has low potential for significant interactions with other drugs, eg, warfarin, lovastatin, digoxin, valsartan, amlodipine, metformin, celecoxib, atenolol, atorvastatin, ramipril, and HCTZ.^{36–39}

Aliskiren effectively blocks the RAAS. In a double-blind cross-over study in 18 healthy volunteers receiving a low-sodium diet, the effects of four oral doses of aliskiren (40, 80, 160, and 640 mg/day) compared with placebo and the ACE inhibitor enalapril (20 mg) on components of RAAS were evaluated.³⁵ Aliskiren reduced PRA in a dose-dependent manner after both a single oral dose and 8 days of repeated once-daily dosing. The highest doses of aliskiren reduced Ang II levels by a maximum of 89% and 75% on days 1 and 8, respectively, compared with placebo, and aliskiren \geq 80 mg/day decreased plasma and urinary aldosterone levels by 40% and 50%, respectively. Enalapril reduced Ang II levels similarly to aliskiren, but also increased PRA 15-fold.

The hormonal effects of dual RAAS blockade with aliskiren and the ARB valsartan were evaluated in 12 mildly sodium-depleted normotensive individuals in a double-blind crossover-designed study.⁴⁰ Participants received aliskiren 300 mg, valsartan 160 mg, a combination of aliskiren 150 mg plus valsartan 80 mg, or placebo. Valsartan monotherapy increased PRA, Ang I, and Ang II, while PRA, Ang I, and Ang II levels with combination therapy were similar to placebo, indicating that the addition of aliskiren to valsartan eliminates the compensatory increase in PRA and Ang caused by ARBs.

RENOPROTECTIVE EFFECTS OF ALISKIREN

Renoprotective effects of aliskiren have been demonstrated in double transgenic rats (dTGR) that express genes for both human renin and angiotensinogen. Aliskiren has been compared with 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.¹⁴ Untreated dTGR showed severe hypertension, albuminuria, and increased serum creatinine by week 7, with a 100% mortality rate by week 9. In

Table 2
Pharmacokinetic properties of oral renin inhibitors

	Bioavailability, %	IC ₅₀ , nmol/L	Plasma Half Life, h (SD)
Aliskiren	2.7	0.6	23.7 (7.6)
CGP 38560	<1.0	0.7	1.1
Enalkiren	NA	14.0	1.6 (0.4)
Remilkiren	<1.0	0.8	9.4 (4.1)
Zankiren	NA	1.1	NA

IC₅₀ is the concentration needed for 50% inhibition of human renin. NA indicates data not available. Data from Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449–56; with permission.

contrast, both doses of aliskiren and high-dose valsartan 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), and the magnitude of the aliskiren effect was somewhat dose-dependent.

Other animal studies showed that aliskiren protects the kidney by reducing renal inflammation and albuminuria. Administration of aliskiren or losartan to dTGR and control Sprague-Dawley rats reduced albuminuria and complement activation.⁴¹ In another study performed in a rat model of advanced diabetic nephropathy, aliskiren reduced albuminuria and other markers of renal damage, including expression of transforming growth factor (TGF)- β and collagens III and IV.⁴² When aliskiren was compared with ACE inhibitors or ARBs in these models, the renal and cardiac protective effects were approximately equal.^{14,42}

Aliskiren also reduces albuminuria in humans. A study of 15 patients with type 2 diabetes and elevated urinary albumin/creatinine ratio (UACR > 30 mg g⁻¹) examined the effects on SBP and UACR of treatment with aliskiren 300 mg once daily and furosemide in a stable dose for 28 days, followed by a 4-week withdrawal period.⁴³ Both 24-hour SBP assessed by ambulatory BP monitoring and UACR decreased significantly with aliskiren. UACR decreased significantly (17%) in the first 2 to 4 days of treatment and reached a maximum reduction of 44% at the end of the treatment period (Fig. 3). UACR decreased progressively throughout the treatment period, whereas the 24-hour BP did not fall further after day 7. Five of the 15 patients had greater than 50% reduction in albuminuria at the end of treatment compared with baseline; 11 of the 15 had greater

than 25% reduction, and 13 had greater than 10% reduction. During posttreatment washout, UACR remained significantly below baseline for 12 days.

ALISKIREN IN THE TREATMENT OF HUMAN HYPERTENSION

Aliskiren, both as monotherapy and in combination with other agents, has been evaluated extensively in hypertensive patients. Aliskiren monotherapy has a dose-dependent antihypertensive effect that is significantly greater than placebo. In a randomized double-blind study, 652 patients with mild to moderate hypertension defined as DBP \geq 95 and <110 mm Hg, were assigned to receive placebo, irbesartan 150 mg, or once-daily doses of aliskiren (150, 300, or 600 mg) for 8 weeks after a 2-week placebo run-in period.⁴⁴ Once-daily oral treatment with each of the three doses of aliskiren significantly decreased mean sitting SBP and DBP compared with placebo (Fig. 4). No additional BP reduction was obtained with aliskiren 600 mg. After 8 weeks of treatment, 21% and 50% ($P < .05$) of patients assigned to placebo and aliskiren 300 mg, respectively, achieved BP control defined as BP lower than 140/90 mm Hg.

In another randomized, double-blind, placebo-controlled trial, 672 hypertensive patients (mean sitting DBP 95 to 109 mm Hg) received placebo or aliskiren 150, 300, or 600 mg once daily.⁴⁵ After 8 weeks, aliskiren 150, 300, and 600 mg significantly reduced mean sitting BP (systolic/diastolic) by 13.0/10.3, 14.7/11.1, and 15.8/12.5 mm Hg from baseline, respectively, versus 3.8/4.9 mm Hg with placebo (all $P < .0001$ for SBP and DBP). Aliskiren significantly reduced mean 24-hour ambulatory BP and its BP-lowering effect persisted for up to 2 weeks after treatment withdrawal. Aliskiren 150, 300, and 600 mg reduced PRA (geometric

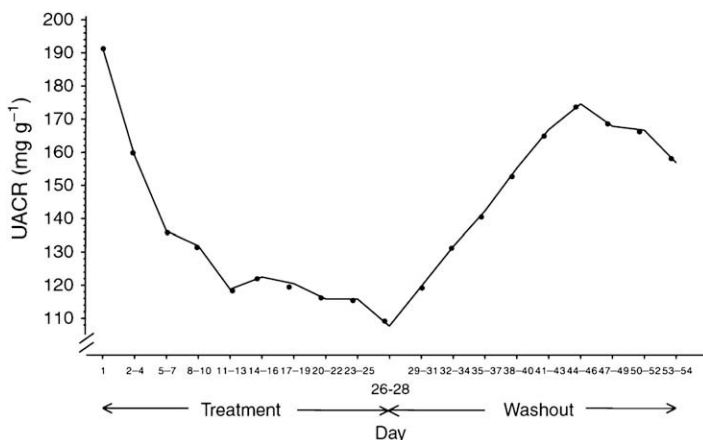


Fig. 3. Urinary albumin/creatinine ratio in diabetic patients with micro- or macroalbuminuria treated with aliskiren for 28 days followed by 28 days washout. (From Persson F, Rossing P, Schjoedt KJ, et al. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. *Kidney Int* 2008;73(12):1419–25; with permission).

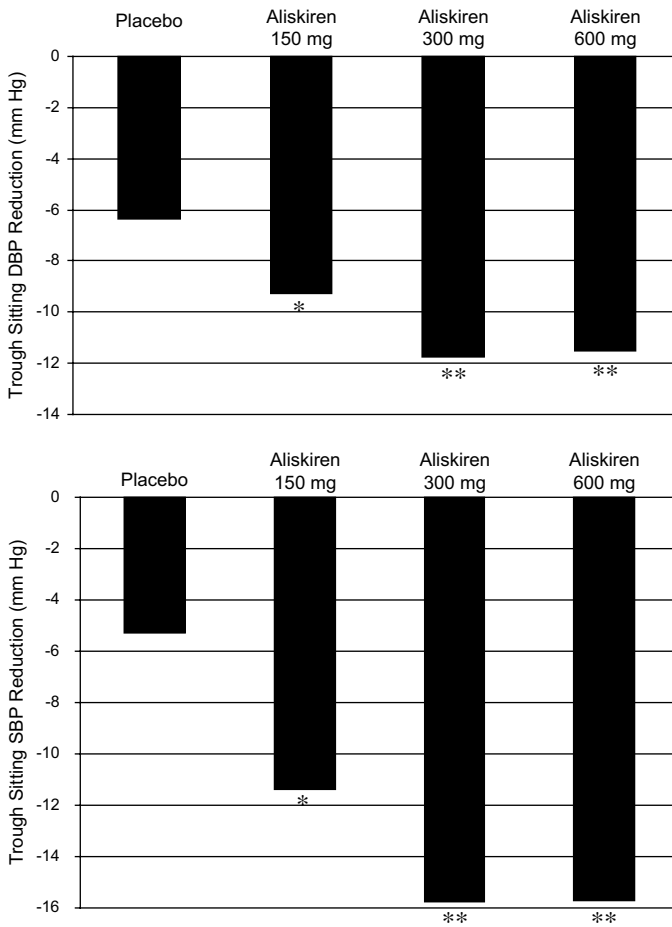


Fig. 4. Blood pressure reduction achieved with aliskiren compared with placebo. SBP, systolic blood pressure; DBP, diastolic blood pressure. * $P < .01$ compared with placebo; ** $P < .0001$ compared with placebo.

mean change from baseline) by 79.5%, 81.1%, and 75.0%, respectively, whereas PRA increased by 19.5% from baseline in the placebo group. Aliskiren treatment resulted in dose-dependent increases from baseline in renin concentration. Aliskiren was well tolerated; overall adverse event rates were 40.1%, 46.7%, and 52.4% with aliskiren 150, 300, and 600 mg, respectively, compared with 43.0% with placebo.

A pooled analysis that included 8481 patients who participated in double-blind trials and received aliskiren monotherapy or placebo for 8 to 12 weeks showed that once-daily aliskiren, 150 or 300 mg, produced reductions in mean trough sitting DBP of 10.1 and 11.8 mm Hg, respectively, compared with 6.2 mm Hg for placebo ($P < .0001$).⁴⁶ Trough SBP was lowered by 12.5 and 15.2 mm Hg, compared with 5.9 mm Hg for placebo ($P < .0001$). There were no statistically significant differences in the magnitude of BP reduction in men versus women or in patients younger versus older than 65 years.

Aliskiren monotherapy has been compared with representatives of several different classes of antihypertensive medications and has been shown to produce comparable or greater reductions in BP. For example, in a double-blind study, 842 patients with hypertension (mean sitting DBP 95 to 109 mm Hg) were randomized to aliskiren 150 mg or the ACE inhibitor ramipril 5 mg.⁴⁷ Dose titration (to aliskiren 300 mg/ramipril 10 mg) and subsequent addition of hydrochlorothiazide (12.5 mg, titrated to 25 mg if required) were permitted at weeks 6, 12, 18, and 21 for inadequate BP control. The active treatment period was completed by 81.6% of patients. At week 26, aliskiren-based therapy produced greater mean reductions in SBP (17.9 versus 15.2 mm Hg, $P = .0036$) and DBP (13.2 versus 12.0 mm Hg, $P = .025$) and higher rates of SBP control (<140 mmHg; 72.5% versus 64.1%, $P = .0075$) compared with ramipril-based therapy. During withdrawal, BP increased more rapidly after stopping ramipril-based than aliskiren-based therapy.

When used in combination with a thiazide diuretic, aliskiren is more effective than either monotherapy in reducing BP. In an 8-week, double-blind, placebo-controlled trial, 2776 patients with mean sitting DBP 95 to 109 mm Hg were randomized to receive once-daily treatment with aliskiren (75, 150, or 300 mg), hydrochlorothiazide (HCTZ) (6.25, 12.5, or 25 mg), the combination of aliskiren and HCTZ, or placebo, in a factorial design.⁴⁸ Combination treatment was superior to both component monotherapies in reducing BP (maximum SBP/DBP reduction of 21.2/14.3 mm Hg from baseline with aliskiren/HCTZ 300/25 mg), and resulted in a higher responder rate (patients with DBP < 90 mm Hg and/or ≥ 10 mm Hg reduction) and a better control rate (patients achieving SBP/DBP < 140/90 mm Hg) than either monotherapy. Aliskiren monotherapy reduced PRA by up to 65% from baseline and when HCTZ was combined with aliskiren, decreases in PRA of 46.1% to 63.5% were observed.

Dual RAAS inhibition with maximum recommended doses of the DRI aliskiren and the ARB valsartan has shown greater antihypertensive efficacy than monotherapy with either agent. In a double-blind study, 1797 patients with hypertension (mean sitting DBP 95 to 109 mm Hg and 8-hour daytime ambulatory DBP ≥ 90 mm Hg) were randomly assigned to receive once-daily aliskiren 150 mg, valsartan 160 mg, a combination of aliskiren 150 mg and valsartan 160 mg, or placebo for 4 weeks, followed by forced titration to maximum recommended doses for another 4 weeks.⁴⁹ At week 8, the mean sitting SBP was lowered from baseline by 17.2, 12.8, 13.0, and 4.6 mm Hg, respectively, and mean sitting DBP was lowered from baseline by 12.2, 9.7, 9.0, and 4.1 mm Hg, respectively, with the combination of aliskiren

300 mg and valsartan 320 mg, valsartan 320 mg monotherapy, aliskiren 300 mg monotherapy, and placebo ($P < .0001$ combination compared with placebo or either monotherapy) (Fig. 5). The proportion of patients achieving a successful response to treatment at week 8 was significantly higher with the combination of aliskiren and valsartan (66%) than with aliskiren alone (53%; $P = .0003$) or valsartan alone (55%; $P = .001$). Valsartan monotherapy produced significantly greater increases in PRA from baseline than did placebo (160% versus 18%; $P = .0003$). By contrast, aliskiren alone significantly reduced PRA by 73% ($P < .0001$ versus placebo), while the combination of aliskiren and valsartan led to a 44% reduction in PRA ($P < .0001$ versus placebo). The combination of aliskiren and valsartan provided significantly greater reductions in plasma aldosterone concentration from baseline at week 8 than did placebo (-31% versus $+7\%$; $P < .0001$). Valsartan alone also reduced aldosterone concentration (-25% ; $P = .0007$ versus placebo), while aliskiren monotherapy had no significant effect on aldosterone concentration. The rates of adverse events and laboratory abnormalities were similar in all groups.

Some have hypothesized that reactive renin secretion may limit the effectiveness of DRIs.⁵⁰ Although aliskiren suppresses PRA, it causes major reactive increases in plasma renin concentration. If the system is at all leaky, allowing even a small percentage of the excess prorenin generated during DRI treatment to be activated, the antihypertensive effect of the DRI may be offset, limiting its utility as an antihypertensive agent. Further study and additional clinical experience with aliskiren and other DRIs, as they become available, are needed to validate or refute this hypothesis.

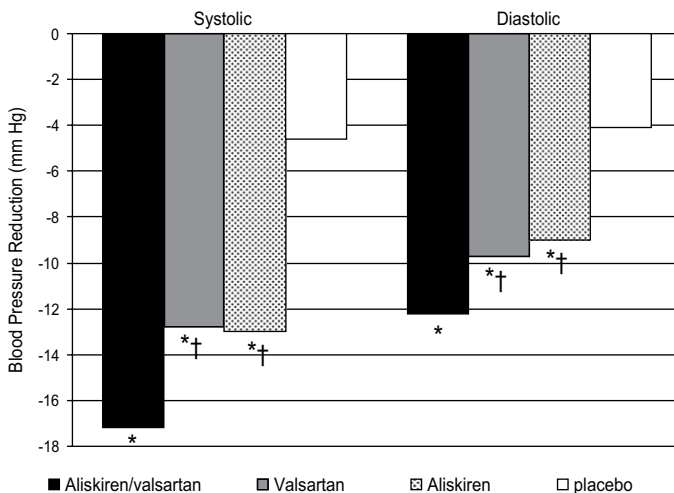


Fig. 5. Effect of study treatments on mean systolic and diastolic blood pressure. * $P < .0001$ compared with placebo; † $P < .0001$ compared with aliskiren/valsartan combination.

SUMMARY

Introduction of the DRI aliskiren has opened doors for newer possibilities in antihypertensive therapy. Aliskiren has antihypertensive efficacy comparable to other classes of antihypertensive medications, including diuretics, ACEinhibitors, ARBs, and calcium channel blockers and with a tolerability and safety profile similar to placebo. It also has additive antihypertensive effects when combined with these other drug classes. Preliminary studies of the effects of aliskiren on target organ damage demonstrate comparable or greater efficacy compared with other RAAS antagonists. Results of clinical outcome trials are needed to establish the role of this novel class of antihypertensive medication in the therapeutic armamentarium.

REFERENCES

- Pimenta E, Oparil S. Etiology and pathogenesis of systemic hypertension. In: Crawford MH, DiMarco JP, Paulus WJ, editors. *Cardiology*, 3rd edition. London: Mosby, in press.
- Danser AH, Denium J. Renin, pro-renin and putative (Pro)renin receptor. *Hypertension* 2005;46:1069–76.
- Reudelhuber TL, Ramla D, Chiu L, et al. Proteolytic processing of human pro-renin in renal and non-renal tissues. *Kidney Int* 1994;46:1522–4.
- Danser AH, Derx FH, Schalekamp MA, et al. 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.
- Luetscher JA, Kraemer FB, Wilson DM, et al. Increased plasma inactive renin in diabetes mellitus. A marker of microvascular complication. *N Engl J Med* 1985;312:1412–7.
- 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.
- Bühler FR, Laragh JH, Vaughan ED, et al. Antihypertensive action of propranolol: specific anti-renin responses in high and normal renin forms of essential, renal, renovascular and malignant hypertension. *Am J Cardiol* 1973;32:511–22.
- Michelakis AM, McAllister RG. The effect of chronic adrenergic receptor blockade on plasma renin activity in man. *J Clin Endocrinol Metab* 1972;34:386–94.
- Ondetti MA. Design of specific inhibitors of angiotensin-converting enzyme: new class of orally active antihypertensive agents. *Science* 1977;196:441–4.
- Ferreira SH. A bradykinin-potentiating factor present in the venom of *Bothrops jararaca*. *Br J Pharmacol* 1965;24:163–9.
- Ferreira SH, Greene X. Isolation of bradykinin-potentiating peptides from *Bothrops jararaca* venom. *Biochemistry* 1970;9:2583–93.
- Tigerstedt R, Bergman PG. Niere und Kreislauf. *Skand Arch Physiol* 1898;8:223–71.
- Gradman AH, Kad R. Renin inhibition in hypertension. *J Am Coll Cardiol* 2008;51:519–28.
- Pils 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.
- 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.
- Michel JB, Galen FX, Guettier C, et al. Immunological approach to blockade of the renin-substrate reaction. *J Hypertens* 1989;7:S63–70.
- Gross F, Lazar J, Orth H. Inhibition of the renin-angiotensinogen reaction by pepstatin. *Science* 1972;175:656.
- Evin G, Gardes J, Kreft C, et al. Soluble pepstatins: a new approach to blockade in vivo of the renin angiotensin system. *Clin Sci* 1978;55:167s–71s.
- Eid M, Evin G, Castro B, et al. New renin inhibitors homologous with pepstatin. *Biochem J* 1981;197:465–71.
- Boger J, Lohr NS, Ulm EH, et al. Novel renin inhibitors containing the amino acid statine. *Nature* 1983;303:81–4.
- Zusman RM, Burton J, Christensen D, et al. Hemodynamic effects of a competitive renin inhibitory peptide in humans. Evidence for multiple mechanisms of action. *Trans Assoc Am Physicians* 1983;96:365–74.
- Macfayden RJ, Jones CR, Doig JK, et al. Responses to an orally active renin inhibitor, remikiren (Ro 42-5892), after controlled salt depletion in humans. *J Cardiovasc Pharmacol* 1995;25:347–53.
- Rongen GA, Lenders JW, Smits P, et al. Clinical pharmacokinetics and efficacy of renin inhibitors. *Clin Pharmacokinet* 1995;29:6–14.
- Himmelman A, Bergbrant A, Svensson A, et al. 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.
- Ménard J, Boger RS, Moyse DM, et al. Dose-dependent effects of the renin inhibitor zankiren HCl after a single oral dose in mildly sodium-depleted normotensive subjects. *Circulation* 1995;91:330–8.
- Rongen GA, Lenders JW, 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.
- Camenzind E, Nussberger J, Juillerat L, et al. Effect of the renin response during renin inhibition: oral Ro 42-5892 in normal humans. *J Cardiovasc Pharmacol* 1991;18:299–307.

28. Delabays A, Nussberger J, Porchet M, et al. Hemodynamic and humoral effects of the new renin inhibitor enalkiren in normal humans. *Hypertension* 1989; 13:941–7.
29. Weber MA, Neutel JM, Essinger I, et al. Assessment of renin dependency of hypertension with a dipeptide renin inhibitor. *Circulation* 1990;81:1768–74.
30. Neutel JM, Luther RR, Boger RS, et al. Immediate blood pressure effects of the renin inhibitor enalkiren and the ACE inhibitor enalaprilat. *Am Heart J* 1991; 122:1094–100.
31. Van den Meiracker AH, Admiraal PJ, Man in't Veld AJ, et al. Prolonged blood pressure reduction by orally active renin inhibitor RO-42-5892 in essential hypertension. *Br Med J* 1990;301:205–10.
32. Jeunemaitre X, Menard J, Nussberger J, et al. Plasma angiotensin, renin and blood pressure during acute renin inhibition by GCP 38 560A in hypertensive patients. *Am J Hypertens* 1989;2: 819–27.
33. Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet* 2006;368:1449–56.
34. Nussberger J. Renin inhibitors. In: Oparil S, Weber MA, editors. *Hypertension: a companion to Brenner and Rector's the kidney*, 2nd edition. Philadelphia: Elsevier; 2005. p. 754–64.
35. Nussberger J, Wuerzner J, Jensen C, et al. Angiotensin II suppression in humans by the orally active renin inhibitor aliskiren (SPP100). Comparison with enalapril. *Hypertension* 2002;39:e1–e8.
36. Dieterle W, Corynen S, Vaidyanathan S, et al. 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.
37. Dieterle W, Corynen S, Vaidyanathan S, et al. Pharmacokinetic interactions of the oral renin inhibitor aliskiren with lovastatin, atenolol, celecoxib and cimetidine. *Int J Clin Pharmacol Ther* 2005;43:527–35.
38. Dieterich H, Kemp C, Vaidyanathan S, et al. Pharmacokinetic interaction of the oral renin inhibitor aliskiren with hydrochlorothiazide in healthy volunteers. *Clin Pharmacol Ther* 2006;79:P12 [abstract].
39. Dieterich H, Kemp C, Vaidyanathan S, et al. Aliskiren, the first in a new class of orally effective renin inhibitors, has no clinically significant drug interactions with digoxin in healthy volunteers. *Clin Pharmacol Ther* 2006;79:P64 [abstract].
40. Azizi M, Ménard 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.
41. Shagdarsuren E, Wellner M, Braesen JH, et al. Complement activation in angiotensin II-induced organ damage. *Circ Res* 2005;97:716–24.
42. Kelly DJ, Zhang Y, Moe G, et al. Aliskiren, a novel renin inhibitor, is renoprotective in a model of advanced diabetic nephropathy in rats. *Diabetologia* 2007;50:2398–404.
43. Persson F, Rossing P, Schjoedt KJ, et al. Time course of the antiproteinuric and antihypertensive effects of direct renin inhibition in type 2 diabetes. *Kidney Int* 2008;73(12):1419–25.
44. 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.
45. 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.
46. 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. *J Clin Hypertens* 2007;9:A157 [abstract].
47. Andersen K, Weinberger MH, Egan B, et al. Comparative efficacy and safety of aliskiren, an oral direct renin inhibitor, and ramipril in hypertension: a 6-month, randomized, double-blind trial. *J Hypertens* 2008;26:589–99.
48. Villamil A, Chysant 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.
49. 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.
50. 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.