Review Paper

Direct Renin Inhibitors: A New Approach to Antihypertensive Drug Treatment

C. Venkata S. Ram, MD

Hypertension remains a leading cause of morbidity and mortality, affecting more than 60 million persons in the United States. Although the past 5 decades have witnessed advances in the therapeutic modalities available to treat hypertension and a dramatic decrease in morbidity and mortality related to hypertension, adequate blood pressure control has still not been achieved in a large number of patients. Therapeutic options to manage hypertension include agents that block the sympathetic nervous system, vasodilators, agents to control plasma volume, and drugs that act at various points in the renin-angiotensin system (RAS). Inadequate control of hypertension may be due in part to incomplete blockade of the RAS pathway in some patients; targeting a point earlier in this cascade might possibly improve control. Direct renin inhibitors, a new class of antihypertensive drugs, block the RAS pathway at the point of activation. Inhibition of renin prevents the downstream production of the potent vasoconstrictor angiotensin II, which is responsible for increasing blood pressure. Recent clinical data with aliskiren, a new direct renin inhibitor, suggest favorable results in patients with hypertension and a possible new treatment option. (J Clin Hypertens. 2007;9:615–621) ©2007 Le Jacq

From the Department of Internal Medicine, University of Texas Southwestern Medical Center, Dallas, TX
Address for correspondence:
C. Venkata S. Ram, MD, Medical Director, Texas Blood Pressure Institute, Director of Medical Education and Research, Dallas Nephrology Associates, Clinical Professor of Internal Medicine at the University of Texas Southwestern Medical Center, 13154 Coit Road, Suite 100, Dallas, TX 75240
E-mail: ramv@dneph.com
Manuscript received April 20, 2007;
revised June 7, 2007;
accepted June 13, 2007

www.lejacq.com **ID: 7125**

Hypertension affects approximately 60 million Americans and is a significant risk factor for premature cardiovascular disease.[1] Although its etiology is unknown, primary hypertension may be the consequence of both genetic factors and derangement of mechanisms that regulate cardiac output and arterial pressure.[2] In contrast, secondary hypertension is associated with an underlying cause (eg, chronic renal disease, obstructive sleep apnea, or adrenal disease).[2]

The renin-angiotensin system (RAS) plays a major role in the pathophysiology and development of hypertension, especially in patients with comorbidities such as diabetes or heart failure.[3] The RAS cascade regulates multiple pathways involved in blood pressure (BP) control (Figure 1). Renin, a protease produced by the juxtaglomerular cells of the kidney, is released in response to decreased circulating blood volume and BP. Renin cleaves angiotensinogen to angiotensin I (Ang I), which is then converted to angiotensin II (Ang II) by angiotensin-converting enzyme (ACE). The effects of Ang II include vasoconstriction, which can directly elevate BP, stimulation of both the adrenal cortex and the sympathetic nervous system, and augmentation of aldosterone release. Ang II can also be generated by local RAS in various tissue types and the regional vasculature.[4,5] In the heart, stimulation of the RAS leads to increased cardiac contraction and may lead to pathologic hypertrophy; in the brain, RAS enhances production of hypothalamic and pituitary hormones and increases sympathetic activity.[4,5] The RAS is also modulated by the activity of angiotensin peptides, which are produced in peripheral tissue and

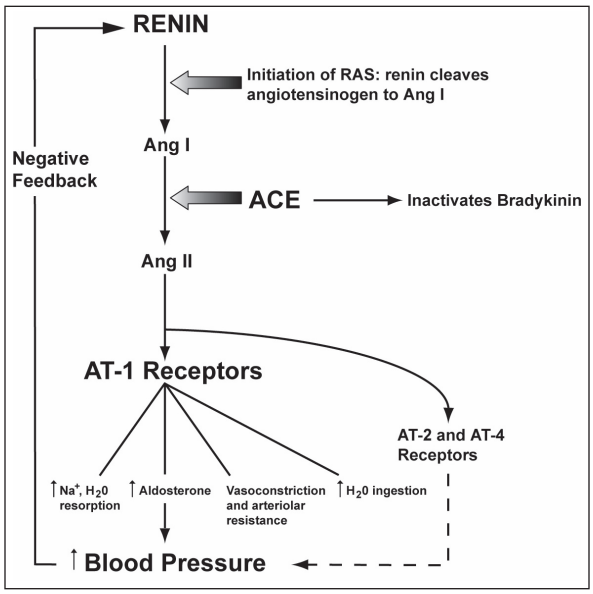

Figure 1. The renin-angiotensin system (RAS). ACE indicates angiotensin-converting enzyme; Ang, angiotensin; AT, angiotensin receptor.

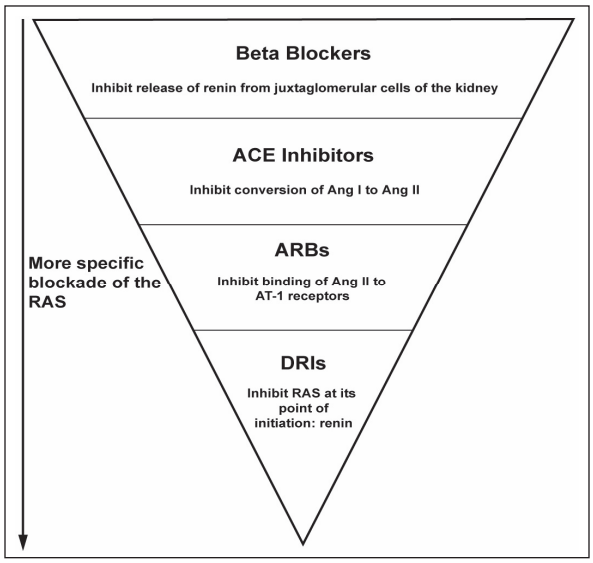

Figure 2. Renin-angiotensin system (RAS) inhibitors: evolution from indirect to direct blockade of RAS. ACE indicates angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT, angiotensin receptor; DRI, direct renin inhibitor.

regulate vascular resistance by stimulating smooth muscle growth and tissue metabolism.[4]

Because of the role of the RAS in the pathophysiology of hypertension and the correlation between aberrations in this system and comorbidities, blocking the RAS is one logical approach in treating hypertension. Clinical evidence has supported the importance of using medication to block the RAS alone or in combination with other antihypertensive agents to control hypertension and attenuate or prevent complications associated with hypertension, such as heart failure.[5,6]

The historical development of RAS inhibitors has moved from a broad, indirect approach to one that is targeted (Figure 2). β-Blockers were the earliest agents available, followed by the introduction of ACE inhibitors, angiotensin receptor blockers (ARBs) and, most recently, direct renin inhibitors (DRIs).

POSSIBLE LIMITATIONS OF β-BLOCKERS, ACE INHIBITORS, AND ARBS

Incomplete Inhibition of RAS

Commonly prescribed antihypertensive medications, including β-blockers, ACE inhibitors, and ARBs may not achieve complete inhibition of the RAS pathway due in part to the areas in the RAS that are affected.[7] β-Blockers act indirectly to reduce generation of renin, while ACE inhibitors and ARBs target downstream molecules in the pathway. Although ACE inhibitors are effective antihypertensive drugs, they do not block ACE-independent pathways that contribute to the generation of Ang II; about 40% of Ang I is converted to Ang II by pathways other than ACE.[8] Thus, ACE inhibition does not completely block Ang II production. Angiotensin escape may also be modulated by increased transcription of the ACE gene in cells exposed to ACE inhibitors.[9] It has been suggested that ACE escape may contribute to regeneration of angiotensin despite ACE inhibition, whereas this phenomenon is unlikely to occur with DRIs. Similarly, ARBs, which also reduce BP effectively in a large number of patients and block the effects of Ang II on the peripheral vasculature, may inhibit the negative feedback loop by which Ang II suppresses the release of renin from juxtaglomerular cells.[10] As a result, chronic use of ARBs can lead to an increase in plasma renin activity (PRA) via accumulation of Ang I and Ang II (Table).[7,10]

Lack of 24-Hour BP Control

Although many antihypertensive medications can be given once a day, drugs with a shorter half-life may require several daily doses to achieve 24-hour BP control. Studies of some agents such as losartan, an ARB, and ramipril, an ACE inhibitor, which are recommended to be administered once a day, have indicated that once-daily dosing may not offer persistent 24-hour BP control.[11,12] There are, however, many other available antihypertensive drugs that are effective when given once a day.

Failure to achieve complete 24-hour BP control may be associated with undesirable consequences.

Table. Effects of Antihypertensive Agents on Targets of the RAS Pathway

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

Abbreviation: RAS, renin-angiotensin system. ↓ decreased; ↑ increased. Adapted with permission from Brown.[7]

Chronic treatment with short-acting β-blockers, for example, leads to increased synthesis and hypersensitivity of β-adrenergic receptors. Under these conditions, sudden β-blocker withdrawal may induce unstable angina or myocardial infarction (MI) in individuals predisposed to myocardial events.[13] There are, of course, longer-acting formulations of β-blockers that achieve 24-hour BP control; shorter-acting agents are no longer widely used.

Tolerability

The use of β-blockers, ACE inhibitors, and ARBs is influenced by their tolerability profiles. Although side effects of β-blockers vary among specific patient populations, these agents can reduce cardiac output by 20% to 25%, at least initially, and may induce weakness and fatigue.[14] Other adverse events of β-blockers include dizziness, headache, and insomnia.[15,16] β-Blockers can also mask the signs of hypoglycemia and exacerbate heart failure upon initiation of therapy, although these agents have been proven to be effective in the treatment of heart failure patients. Antagonism of bronchial β-receptors can lead to bronchospasm in patients with asthma or chronic obstructive pulmonary disease. β-Blockers, except for those with vasodilating effects, may negatively affect levels of serum lipids and may induce glucose intolerance.[17] In a few patients with diabetes, β-blockers increase levels of fasting glucose by up to 28 mg/dL and glycated hemoglobin A_{1c} (HbA_{1c}) by up to 1%.[18] Despite their potentially deleterious effects, the use of a β-blocker–based treatment regimen achieved a similar decrease in morbidity and mortality in diabetic patients when compared with an ACE inhibitor–based regimen.[19] There is some evidence to suggest that these diabetogenic effects are variable among β-blockers, with data suggesting that carvedilol, a β-blocker with α-blocking effects, has a less detrimental effect on HbA_{1c} than metoprolol.[18] Thus, there is growing recognition that the newer-generation β-blockers may have a better safety profile relative to the older β-blockers.

Drugs that target the RAS, such as ACE inhibitors and ARBs, may decrease insulin resistance and consequently limit the development of type 2 diabetes.[20] Some adverse effects of RAS inhibitors include cough, angioedema, and hyperkalemia, although in general they are only rarely observed in patients receiving ARB therapy.[10,21] Cough is the most common adverse effect of ACE inhibitors, experienced by up to 20% of patients; this is the primary reason for discontinuation of this drug class.[22] Less frequent adverse events of ACE inhibitors are transient and include skin rashes (10%) and a loss of taste (7%).[23] One potentially life-threatening safety concern with ACE inhibitors (occurring in 0.1% to 1% of patients) is angioedema, which may be alleviated by switching to another class of drugs.[24] In general, however, ACE inhibitors are well tolerated and have been shown to improve the quality of life of patients with hypertension.[10] As noted, ARBs rarely cause cough, angioedema, or hyperkalemia, and they are also safe and well tolerated; common adverse events reported in clinical trials include edema, dizziness, headache, and fatigue.[25–27] In the Valsartan Antihypertensive Long-Term Use Evaluation (VALUE) trial,[25] however, it was observed that the incidence of MI was greater with ARB-based therapy than with a calcium channel blocker–based regimen. The difference was probably due to better BP control with the calcium channel blocker and not from medication differences. No evidence of an increase in MI risk with ARBs has been demonstrated in well-controlled trials.

Direct Renin Inhibitors

The concept of renin inhibition for managing hypertension by blocking the RAS pathway at the point of activation has been hypothesized since the 1950s.[28] Renin inhibition blocks the RAS without increasing PRA and avoids angiotensin escape (or other pathways not blocked by β-blockers, ACE inhibitors, or ARBs) (Figure 2). The first generation of orally active renin inhibitors showed poor bioavailability and limited antihypertensive activity and were not considered suitable for clinical use.[28] Over the past decade, aliskiren, an orally active DRI, was developed and is now approved for the treatment of hypertension by the US Food and Drug Administration.[28] Although the bioavailability of aliskiren is only 2.5%, it has high specificity and

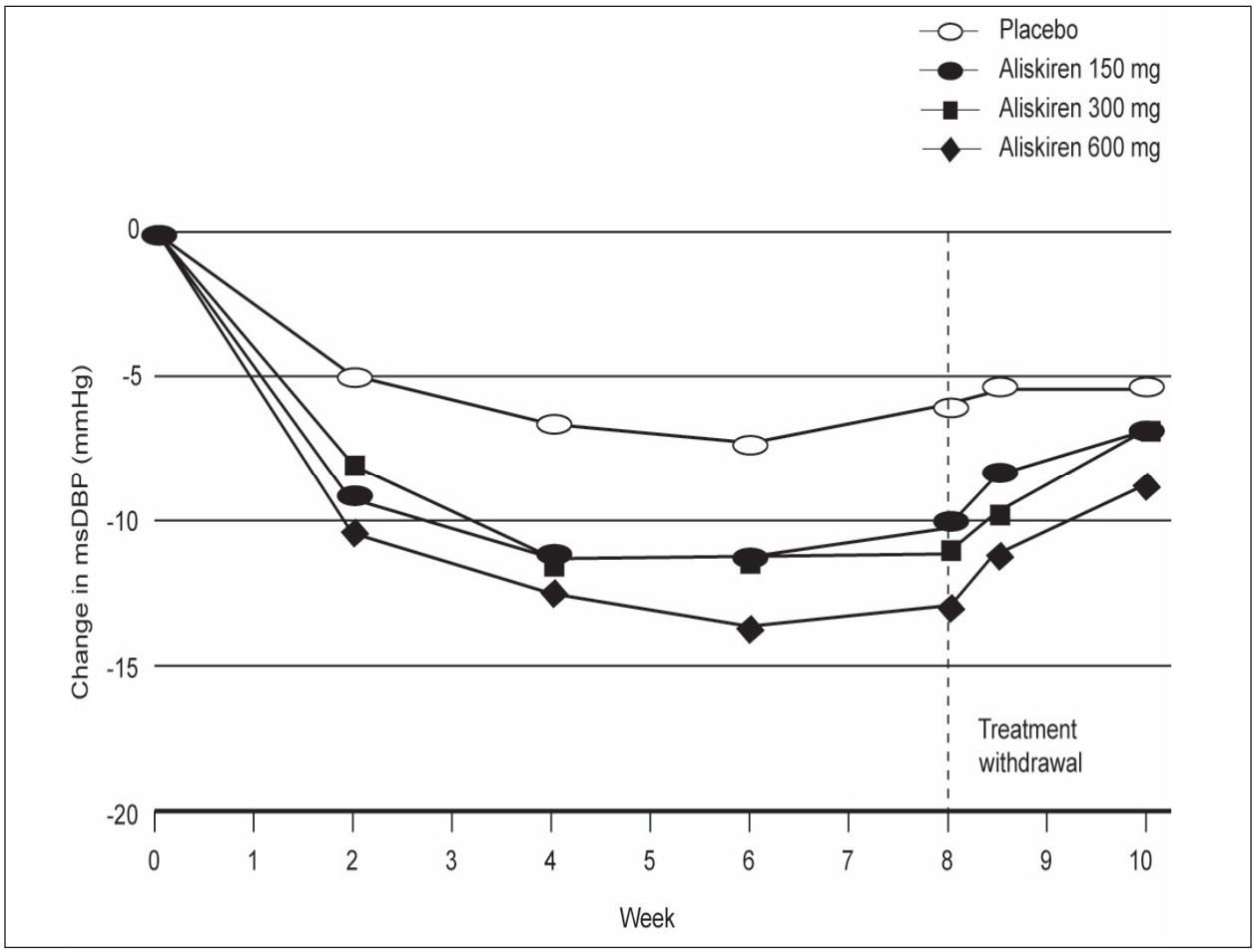

Figure 3. Effects of aliskiren 150 mg to 600 mg on blood pressure in patients with mild to moderate hypertension: changes in mean sitting diastolic blood pressure (msDBP) during double-blind treatment and withdrawal period. Reprinted with permission from Oh et al.[31]

affinity for human renin.[29] Unlike previous DRIs, which had to be administered intravenously, aliskiren is effective in lowering BP when administered orally. Studies in volunteers showed that aliskiren is minimally metabolized and also has little or no interaction with the cytochrome P450 enzyme system.[28] Peak plasma concentrations occur 1 to 3 hours after oral administration with a mean plasma elimination half-life of 40 hours.[30] Aliskiren has been approved for once-daily administration.

In a phase III study assessing the efficacy of aliskiren monotherapy on BP control (N=672), treatment with aliskiren at 150 mg, 300 mg, and 600 mg resulted in a dose-dependent reduction in BP over an 8-week treatment period, compared with patients receiving placebo.[31] After 8 weeks of treatment, mean sitting BP reductions were 13.0/10.3 mm Hg, 14.7/11.1 mm Hg, and 15.8/12.5 mm Hg in patients receiving aliskiren 150 mg, 300 mg, and 600 mg, respectively, compared with 3.8/4.9 mm Hg in patients given placebo (placebo-corrected decreases of 9.2/5.4, 10.9/6.2, and 12.0/7.6 mm Hg). Decreases in mean ambulatory BP demonstrated that the antihypertensive effect was sustainable throughout the 24-hour dosing period. When aliskiren was withdrawn, no rebound hypertension was observed, and reductions in BP persisted to some degree for up to 2 weeks. Although BP levels did rise over this 2-week withdrawal period, they did not reach levels observed in the placebo-treated group (Figure 3).[31] As with other RAS inhibitors, the magnitude of BP reduction in blacks was significantly less than that recorded in whites.[31]

A recent multicenter clinical trial conducted in 1123 patients with hypertension demonstrated that aliskiren monotherapy provided effective BP control (Figure 4), but with a greater antihypertensive effect when administered in combination with valsartan.[26] Aliskiren 150 mg monotherapy reduced BP by 12.1/10.3 mm Hg compared with 16.6/12.1 mm Hg following combination aliskiren 150 mg/valsartan 160 mg therapy.

Aliskiren has shown at least equivalent activity when compared with both ACE inhibitors and

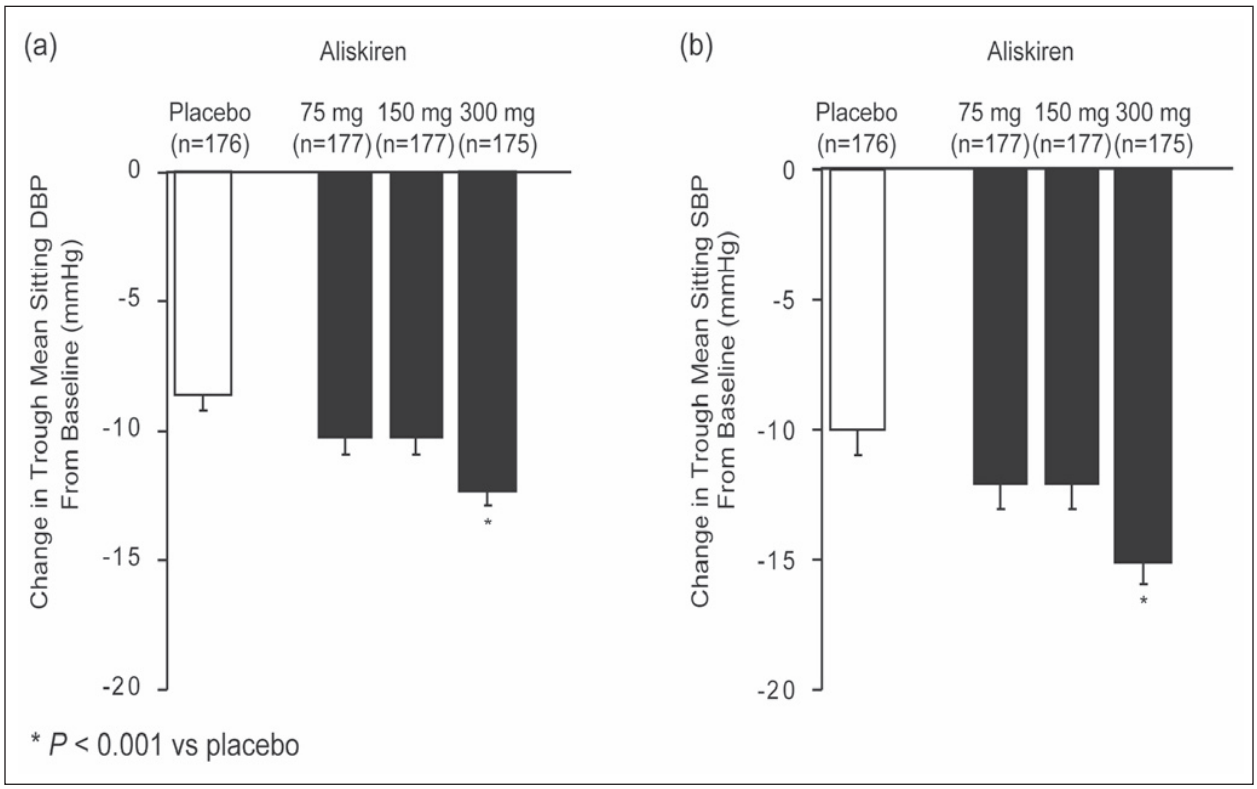

Figure 4. Changes from baseline in (a) trough mean sitting diastolic blood pressure (DBP) and (b) trough mean sitting systolic blood pressure (SBP) at end point after treatment with aliskiren monotherapy. Graph shows least-squares mean changes from baseline in patients receiving treatment with placebo (open bars) or monotherapy with aliskiren 75, 150, or 300 mg once daily (filled bars). Data are presented as the least-squares mean ± standard error of the mean. Reprinted with permission from Pool et al.[26]

ARBs. Once-daily dosing of aliskiren reduced PRA and plasma concentrations of Ang I in normal participants compared with an expected >15-fold increase in these levels with the ACE inhibitor enalapril (since an ACE inhibitor blocks the conversion of Ang I to Ang II).[32] Reductions in Ang II were similar for both drugs. The effects of aliskiren were dose-dependent, with an 80% reduction in Ang II concentrations observed at high doses. Similarly, the combination of low-dose aliskiren plus low-dose valsartan resulted in a synergistic inhibition of the RAS hormones that was comparable to administration of a higher dose of aliskiren alone.[33] Recently, in a pooled analysis of 1093 patients with hypertension, Taylor and colleagues[34] demonstrated that unlike ramipril and hydrochlorothiazide, aliskiren monotherapy significantly reduced PRA from baseline ($P<.0001$), despite a dose-dependent increase in renin concentration. As expected, when aliskiren 300 mg was combined with either ramipril or hydrochlorothiazide, PRA was significantly suppressed ($P<.0001$).[34]

In another study, patients receiving aliskiren 150 mg/d exhibited comparable efficacy to that of irbesartan 150 mg/d in lowering BP (11.4/9.3 mm Hg and 12.5/8.9 mm Hg, respectively).[27] Patients receiving aliskiren 300 mg/d and 600 mg/d had significantly lower mean sitting diastolic BP than those receiving irbesartan 150 mg/d ($P<.05$).

Four open-label studies have reported that aliskiren did not change the pharmacokinetic effects of amlodipine, valsartan, hydrochlorothiazide, or ramipril and was well tolerated when administered in combination with these drugs.[35] Combination therapy of aliskiren and hydrochlorothiazide significantly decreased BP by 15.8/11.9 mm Hg compared with combination placebo/hydrochlorothiazide treatment (8.6/7.9 mm Hg) in obese patients with arterial hypertension in a recent randomized, double-blind, multicenter trial ($P<.0001$).[36] The reported decrease in BP in patients treated with aliskiren plus hydrochlorothiazide was similar to, but not better than, that observed in patients receiving hydrochlorothiazide in combination with either irbesartan (15.4/11.3 mm Hg) or amlodipine (13.6/10.3 mm Hg).[36] Aliskiren monotherapy or in combination with hydrochlorothiazide has demonstrated similar tolerability and antihypertensive efficacy compared with lisinopril monotherapy or in combination with hydrochlorothiazide.[37]

Aliskiren and lisinopril monotherapy reduced BP by 20.0/18.5 mm Hg and 22.3/20.1 mm Hg, respectively. Aliskiren has been shown to potentiate the therapeutic effects of diuretic, ACE inhibitor, and ARB treatments. Hydrochlorothiazide added to aliskiren monotherapy resulted in an additive effect on reducing daytime (P=.0007) and nighttime (P=.06) systolic BP; daytime (P=.0006) and nighttime (P=.09) diastolic BP were also lowered with combination therapy.[38] In this study, aliskiren attenuated the reactive increase in PRA caused by ACE inhibitors and ARBs. In contrast with other drugs, the use of aliskiren resulted in an inhibition of PRA. These observations confirm, in a clinical setting, the direct antirenin effect of aliskiren.

Available clinical data also suggest that aliskiren is well tolerated. Adverse effects reported by patients receiving aliskiren were similar to those reported by patients receiving placebo; for example, the frequency of diarrhea in patients given either placebo or aliskiren 150 mg was 1.2% and the rate remained similar in patients given aliskiren 300 mg (1.8%). Although a significantly increased incidence of diarrhea was seen with aliskiren 600 mg (11.4%; P=.0001), it should be noted that this is twice the highest marketed dose.[31] Although rare, angioedema was reported in 4 of 6460 patients (2 cases of angioedema with respiratory symptoms and 2 possible cases with periorbital edema without respiratory symptoms) who were evaluated for safety (incidence of 0.06%).[29] Similar data on tolerability also have been reported with many of the ARBs.

Preclinical studies performed in marmosets[39] and double-transgenic rats that express the human renin and human angiotensinogen genes[40] have demonstrated that aliskiren lowers BP in addition to attenuating end-organ damage.[40] In double-transgenic rats, aliskiren reversed albuminuria, reduced mortality, attenuated cardiac hypertrophy, and improved diastolic dysfunction.[40] The effects of aliskiren on end-organ damage in humans are currently being assessed in several ongoing and planned trials.

Use of DRIs: Possible Implications

Compared with conventional RAS inhibitors, DRIs may have the potential to induce a more complete blockade of the RAS due to its effects on lowering Ang I, Ang II, and PRA levels (Table). This may be clinically relevant, as a direct and independent association between PRA level and MI has been demonstrated.[41,42] In a study of 2902 hypertensive patients with a mean follow-up of 3.6 years, the incidence of MI was increased by 25% for every 2-unit increase in PRA.[41] Another study of patients who came to the emergency department with chest pain showed similar results with the median PRA level 2.7-fold higher in those with acute MI compared with patients who did not have a diagnosis of acute MI (P<.0001).[42] Although neither study reported the percentage of patients receiving either an ACE inhibitor or an ARB, in the multivariate analyses, drug class did not influence the association between the level of PRA and occurrence of MI. By inhibiting renin directly, it is not clear whether lack of reactive increase in PRA could bestow additional therapeutic benefit with regard to cardiovascular or target organ protection.

Greater inhibition of the RAS with the use of DRIs could theoretically translate into greater reductions in BP and more patients reaching target BP levels. Experience gained thus far suggests, however, that while aliskiren is effective both as monotherapy and in combination with other drugs, BP-lowering effects do not appear to be greater than with other antihypertensive agents. It would appear that this new DRI will be most effective in combination with hydrochlorothiazide or another agent that blocks the RAS.

The favorable tolerability profile of aliskiren may also be a factor in increasing compliance with medication. Compliance is influenced by a number of factors affecting the patient and the physician, but complex dosing regimens and adverse safety profiles of some drugs can contribute to inconsistent utilization.

It is envisioned that DRIs will have some place in the management of hypertension. Additional studies are necessary to determine the exact role that medications such as aliskiren will play in hypertension management and whether outcomes will be improved with their use when compared with the use of other antihypertensive medications.

Acknowledgment: The author acknowledges the scientific and editorial assistance of ***Drs Denise Balog*** *and* ***Meera Nathan*** *in the preparation of this manuscript.*

References

1 Rosamond W, Flegal K, Friday G, et al. Heart disease and stroke statistics–2007 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2007;115:e69–e171.

2 Rudd P, Hagar RW. Hypertension mechanisms, diagnosis, and therapy. In: Topol EJ, ed. *Textbook of Cardiovascular Medicine*. Philadelphia, PA: Lippincott-Raven Publishers; 1998:109–143.

3 Weber MA, Giles TD. Inhibiting the renin-angiotensin system to prevent cardiovascular diseases: do we need a more comprehensive strategy? *Rev Cardiovasc Med*. 2006;7:45–54.

4 Phillips MI. Tissue renin-angiotensin systems. In: Izzo JL, Black HR, eds. *Hypertension Primer: The Essentials of High Blood Pressure*. 2nd ed. Baltimore, MD: Lippincott William & Wilkins; 1999:23–24.
5 Zaman MA, Oparil S, Calhoun DA. Drugs targeting the renin-angiotensin-aldosterone system. *Nat Rev Drug Discov.* 2002;1:621–636.
6 Weir MR, Dzau VJ. The renin-angiotensin-aldosterone system: a specific target for hypertension management. *Am J Hypertens.* 1999;12(pt 3):205S–213S.
7 Brown MJ. Direct renin inhibition–a new way of targeting the renin system. *J Renin Angiotensin Aldosterone Syst.* 2006;7(suppl 2):S7–S11.
8 Hollenberg NK, Fisher NDL, Price DA. Pathways for angiotensin II generation in intact human tissue: evidence from comparative pharmacological interruption of the renin system. *Hypertension.* 1998;32:387–392.
9 King SJ, Oparil S. Converting-enzyme inhibitors increase converting-enzyme mRNA and activity in endothelial cells. *Am J Physiol.* 1992;263:C743–C749.
10 Izzo JL, Moser M. Clinical impact of renin-angiotensin system blockade: angiotensin-converting enzyme inhibitors vs. angiotensin receptor antagonists. *J Clin Hypertens (Greenwich).* 2002;4(suppl 2):11–19.
11 Poirier L, de Champlain J, Larochelle P, et al. A comparison of the efficacy and duration of action of telmisartan, amlodipine and ramipril in patients with confirmed ambulatory hypertension. *Blood Press Monit.* 2004;9:231–236.
12 Nishimura T, Hashimoto J, Ohkubo T, et al. Efficacy and duration of action of the four selective angiotensin II subtype 1 receptor blockers, losartan, candesartan, valsartan and telmisartan, in patients with essential hypertension determined by home blood pressure measurements. *Clin Exp Hypertens.* 2005;27:477–489.
13 Leenen FH. Intermittent blood pressure control: potential consequences for outcome. *Can J Cardiol.* 1999;15(suppl C):13C–18C.
14 Flack JM. Therapy of hypertension. In: Greenberg A, ed. *Primer on Kidney Diseases*. 2nd ed. San Diego, CA: Academic Press; 1998:506–516.
15 Goldberg AI, Dunlay MC, Sweet CS. Safety and tolerability of losartan potassium, an angiotensin II receptor antagonist, compared with hydrochlorothiazide, atenolol, felodipine ER, and angiotensin-converting enzyme inhibitors for the treatment of systemic hypertension. *Am J Cardiol.* 1995;75:793–795.
16 Lindholm LH, Carlberg B, Samuelsson O. Should beta blockers remain first choice in the treatment of primary hypertension? A meta-analysis. *Lancet.* 2005;366:1545–1553.
17 Toda N. Vasodilating β-adrenoceptor blockers as cardiovascular therapeutics. *Pharmacol Ther.* 2003;100:215–234.
18 Bakris GL, Fonseca V, Katholi RE, et al. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. *JAMA.* 2004;292:2227–2236.
19 UK Prospective Diabetes Study Group. Efficacy of atenolol and captopril in reducing risk of macrovascular and microvascular complications in type 2 diabetes: UKPDS 39. *BMJ.* 1998;317:713–720.
20 Mason JM, Dickinson HO, Nicolson DJ, et al. The diabetogenic potential of thiazide-type diuretic and beta-blocker combinations in patients with hypertension. *J Hypertens.* 2005;23:1777–1781.
21 Chiu AG, Krowiak EJ, Deeb ZE. Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology. *Laryngoscope.* 2001;111:1729–1731.
22 Simon SR, Black HR, Moser M, et al. Cough and ACE inhibitors. *Arch Intern Med.* 1992;152:1698–1700.
23 Weinberger MH. Angiotensin converting enzyme inhibitors in the treatment of hypertension: efficacy, metabolic effects and side effects. *Cardiovasc Drugs Ther.* 1987;1:9–13.
24 Cicardi M, Zingale LC, Bergamaschini L, et al. Angioedema associated with angiotensin-converting enzyme inhibitor use: outcome after switching to a different treatment. *Arch Intern Med.* 2004;164:910–913.
25 Julius S, Kjeldsen SE, Weber M, et al. Outcomes in hypertensive patients at high cardiovascular risk treated with regimens based on valsartan or amlodipine: the VALUE randomised trial. *Lancet.* 2004;363:2022–2031.
26 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.
27 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;111:1012–1018.
28 Staessen JA, Li Y, Richart T. Oral renin inhibitors. *Lancet.* 2006;368:1449–1456.
29 Tekturna (aliskiren) [prescribing information]. East Hanover, NJ: Novartis Pharmaceuticals Corporation; March 2007.
30 Zhao C, Vaidyanathan S, Yeh C-M, et al. Aliskiren exhibits similar pharmacokinetics in healthy volunteers and patients with type 2 diabetes mellitus. *Clin Pharmacokinet.* 2006;45:1125–1134.
31 Oh BH, Mitchell J, Herron JR, et al. Aliskiren, an oral renin inhibitor, provides dose-dependent efficacy and sustained 24-hour blood pressure control in patients with hypertension. *J Am Coll Cardiol.* 2007;49:1157–1163.
32 Nussberger J, Wuerzner G, 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.
33 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;15:3126–3133.
34 Taylor AA, Anderson DR, Arora V, et al. Renin system suppression with the oral direct renin inhibitor aliskiren administered alone or in combination: a pooled analysis of 1093 patients with hypertension. Poster presented at: 56th Annual Scientific Session of the American College of Cardiology; March 24–27, 2007; New Orleans, LA.
35 Vaidyanathan S, Valencia J, Kemp C, et al. Lack of pharmacokinetic interactions of aliskiren, a novel direct renin inhibitor for the treatment of hypertension, with the antihypertensives amlodipine, valsartan, hydrochlorothiazide (HCTZ) and ramipril in healthy volunteers. *Int J Clin Pract.* 2006;60:1343–1356.
36 Jordan J, Engeli S, Boye SW, et al. Direct renin inhibition with aliskiren in obese patients with arterial hypertension. *Hypertension.* 2007;49:1047–1055. E-pub March 12, 2007.
37 Strasser RH, Puig JG, Farsang C, et al. The direct renin inhibitor aliskiren demonstrates comparable safety and efficacy to lisinopril in patients with severe hypertension. *J Hum Hypertens.* 2007 May 31; [Epub ahead of print].
38 O'Brien E, Barton J, Nussberger J, et al. Aliskiren reduces blood pressure and suppresses plasma renin activity in combination with a thiazide diuretic, an angiotensin-converting enzyme inhibitor, or an angiotensin receptor blocker. *Hypertension.* 2007;49:276–284.
39 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;23:417–426.
40 Pilz B, Shagdarsuren E, Wellner M, et al. Aliskiren, a human renin inhibitor, ameliorates cardiac and renal damage in double-transgenic rats. *Hypertension.* 2005;46:569–576.
41 Alderman MH, Ooi WL, Cohen H, et al. Plasma renin activity: a risk factor for myocardial infarction in hypertensive patients. *Am J Hypertens.* 1997;10:1–8.
42 Blumenfeld JD, Sealey JE, Alderman MH, et al. Plasma renin activity in the emergency department and its independent association with acute myocardial infarction. *Am J Hypertens.* 2000;13:855–863.