Renin-Angiotensin Aldosterone System and Hypertension: Current Approaches and Future Directions

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Epidemiology and Unmet Needs in Hypertension

John M. Flack, MD, MPH, FAHA

ABSTRACT

BACKGROUND: The persistent control of blood pressure (BP) to levels below current recommended levels is an important but often elusive goal for patients with hypertension.

OBJECTIVE: To provide an overview of unmet needs in contemporary hypertension treatment.

SUMMARY: The rationale for BP normalization is very persuasive. Incrementally higher BP levels predict higher rates of microvascular (e.g., retinopathy, stroke, nephropathy) and macrovascular disease (e.g., myocardial infarction), as well as organ (e.g., heart) failure. Accordingly, the pharmacologic reduction of BP levels with a broad range of mechanistically dissimilar agents reduces the risk of these BP-related complications. The primary prevention of BP-related complications has been closely linked to the magnitude of decreases in BP brought about pharmacologically, but some modest disease-specific differences have been noted between drug classes. However, pharmacologic blockade of the renin-angiotensin-aldosterone system in high-risk patients (e.g., patients with diabetic nephropathy) reduces the risk of BP-related renal end points more than treatment strategies that do not include these agents, even when BP levels are lowered to similar degrees.

CONCLUSION: Despite the large number of antihypertensive agents available, the majority of patients with hypertension who are treated with drugs do not attain goal BP levels. Though the reasons for this are complex and relate to various factors for patients, providers, and systems of medical care delivery, new pharmacologic treatments hold the potential to augment the reduction of BP levels while minimizing class-specific side effects.

KEYWORDS: Blood pressure, Vascular disease, Hypertensive agents, Hypertension

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such a level was both feasible and harmless. Given the current armamentarium of antihypertensive agents, this very low level will undoubtedly require a carefully assembled multidrug treatment strategy that will almost assuredly include a diuretic. The holy grail of antihypertensive treatment is to persistently reduce BP to below goal levels with drug regimens that maximize target-organ protection. Reducing cuff BP levels has typically served as a reliable proxy for the primary prevention of BP-related target-organ complications. Indeed, most of the risk reduction for BP-related complications, especially in nonhigh-risk hypertensive patients, can be statistically linked very closely, though not exclusively, to the magnitude of the reduction of the BP level with mechanistically dissimilar antihypertensive agents.

As White discusses in another article in this supplement, lowering BP throughout the entire 24-hour time interval is highly desirable. The most accurate way to determine that BP control truly occurs throughout the day and night is to use ambulatory BP monitoring. A less accurate way to assess 24-hour BP control is to determine BP levels just before morning dosing when the hypotensive effect of antihypertensive medication(s) is at its nadir.

In patients with hypertension who are at higher risk, such as those with diabetic nephropathy or at high cardiovascular risk, the superiority of suppressing the renin-angiotensin aldosterone system (RAAS) with angiotensin receptor blockers (ARBs) compared with other antihypertensive agents has been repeatedly demonstrated, most often in renoprotection and reduction of the renin-angiotensin aldosterone system (RAAS) with angiotensin receptor blockers (ARBs) compared with other antihypertensive agents, has been repeatedly demonstrated, most often in renoprotection and reduction of risk hypertensive patients will likely manifest residual risk for such criticism is that the benefits and safety of these targets have not been demonstrated explicitly in a randomized clinical trial in which a treatment arm goal was specified to be a BP of <130/80 mm Hg. However, though clinical trials provide a high level of evidence-based information, data from any trial must be both interpreted and considered in the context of all the available information, including previous clinical trials, rigorous observational studies, and physiologic and basic science observations.

If BP levels are to be persistently maintained below recommended goal levels, then practitioners must aim to drive BP levels well below these target BP levels. Thus, goal BP levels must be considered more like ceilings than floors. Even nonhigh-risk hypertensive patients will likely manifest residual risk for pressure-related CVD sequelae if BP levels are only lowered into the range of slightly below 140/90 mm Hg. Epidemiologic data document that the risk of CVD doubles for every 20/10 mm Hg increment above ~115/75 mm Hg. Currently recommended target-organ protection BP levels for nonhigh-risk patients with hypertension remain well above the upward inflection point for CVD risk (~115/75 mm Hg; Figure 1). Thus, given the extensive clinical database regarding the risks and benefits of pharmacologic treatment and the fact that virtually no unconfounded evidence exists that pharmacologic treatment is harmful in most patients with hypertension, striving to maintain BP levels as close to the upward inflection point (~115/75 mm Hg) for CVD risk with a combination of lifestyle modifications and drug therapies seems intuitively appealing. Nevertheless, attaining and maintaining such a BP level will be more difficult in high-risk patients with hypertension than in their nonhigh-risk counterparts. A qualified recommendation of this nature, however, does not obviate the necessity to prove its validity in clinical end point studies.

### Adequacy of Recommendations for Control of BP Levels

Current BP reduction targets for high-risk patients with hypertension—those with diabetes, vascular disease, previous CVD or coronary heart disease, and/or kidney disease—have received criticism for not being evidence-based. The likely reason for such criticism is that the benefits and safety of these targets have not been demonstrated explicitly in a randomized clinical trial in which a treatment arm goal was specified to be a BP of <130/80 mm Hg. However, though clinical trials provide a high level of evidence-based information, data from any trial must be both interpreted and considered in the context of all the available information, including previous clinical trials, rigorous observational studies, and physiologic and basic science observations.

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### Control of BP Levels

Thirty-one percent of white, 27% of black, and 41% of Mexican American people with hypertension are unaware of their
Seventy-five percent of people were unaware that they had hypertension, even though their BP was measured by a health professional within the previous year. Approximately 40% were taking a non-BP prescription medicine and the 75% of patients who were unaware that they had hypertension averaged at least 3 clinic visits to a physician's office a year. Accordingly, better identification of hypertension in our clinical practices seems warranted.

It is also important to identify all concurrent CVD risk factors and to undertake adequate risk stratification of patients before treatment. For example, application of the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) guidelines would require, at a minimum, that diabetes status be ascertained, that a spot urine albumin to creatinine ratio be obtained, and that serum creatinine be measured so that the glomerular filtration rate can be estimated.

Therapeutic Inertia

Therapeutic inertia is lack of practitioner action to intensify anti-hypertensive drug therapy or initiate new antihypertensive drugs for a patient with documented BP elevations. Therapeutic inertia occurs in the majority of hypertension visits that occur in the ambulatory outpatient setting among patients with documented BP elevations.20 Therapeutic inertia occurred at ~87% of clinic visits when BP was uncontrolled (> 140/90 mm Hg).21 It is important that higher therapeutic inertia scores were linked to significantly less longitudinal BP lowering. Accordingly, patients in the lowest therapeutic inertia quintile were ~33 times more likely than those in the highest quintile to attain BP control. The investigators further estimated that if therapeutic inertia could be avoided in ~30% of visits, BP control rates would increase from 45.1% to 65.9% in this hypertensive cohort.21

Therapeutic inertia is not solely the result of the practitioner, but likely represents a complex interaction between the patient and the practitioner. Patients are often reluctant to take either higher doses or additional antihypertensive medications, in part because they mistake BP-related side effects for drug-induced side effects. In clinical practice, patients’ belief that the long-term use of antihypertensive medication is potentially more harmful than persistent BP elevations with less-intense pharmacologic treatment is not uncommon. The practitioner often gets frustrated by seeing limited reductions in BP levels, which may be in part because of the use of suboptimal drug combinations, patient noncompliance, and patient reports of drug-induced side effects. Thus, the practitioner is susceptible to the incessant bargaining that occurs during office visits with patients promising to lose weight, begin exercising, reduce their salt intake, and so on—all so that no increases in antihypertensive drug therapy are prescribed. My impression is that this bargaining and practitioners’ susceptibility to such bargaining is particularly intense when the patient’s goal BP level is almost achieved but still above target.

Patient Noncompliance

Patient noncompliance with prescribed antihypertensive drug regimens is very common. High medication adherence (≥80%) compared with intermediate (50%-79%) and low (<50%) medication adherence to a single-pill antihypertensive drug regimen (as estimated by the medication possession ratio) was recently linked to greater BP control—43% for high, 34% for intermediate, and 33% for low medication adherence, respectively, over a 4-year period in 13 U.S. health plans. Furthermore, in this same study, there was a borderline significant inverse relationship between adherence and the number of unique nonantihypertensive drugs, and a strong direct relationship between the mean days of drug supply per pharmacy claim and adherence. The number of unique nonantihypertensive drugs taken per patient was inversely and strongly related to a lower BP control rate.

Patterns of antihypertensive medication nonadherence were reported across 21 studies of once-daily antihypertensive drug treatment using ambulatory electronic monitors. These authors found one half of patients with hypertension discontinued antihypertensive medications within one year, approximately 8% to 10% of scheduled drug doses were missed on any given day, weekend doses were more likely to be missed than weekday doses, and evening doses were more likely to be missed than morning doses. Intriguingly, the quality of execution of the daily drug dosing regimen in the early phase of treatment was a predictor of early discontinuation. There is a complex

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**FIGURE 1**

**Correlation Between Blood Pressure Targets and Risk of Cardiovascular Disease (CVD)**

*High-risk = diabetes mellitus and/or chronic kidney disease (eGFR<60 mL per minute per 1.73 m² or urine albumin creatinine ratio>200 mg per g).*
aggregate of reasons for patient noncompliance, which relate to patient, physician, and health care system factors. Nevertheless, these data provide some clues to potential strategies controlled by the practitioner that should minimize noncompliance. One easy-to-implement strategy that minimizes the loss of BP control during intermittent noncompliance is to use antihypertensive drugs with prolonged hypotensive effects (preferably effects that extend well beyond the 24-hour dosing interval). This approach should provide some coverage against loss of BP control during the vulnerable period between the missed dose and the next dose of medication taken (Figure 2).

### Optimizing Available Strategies

#### Lifestyle Modifications

Practitioners should always emphasize appropriate lifestyle changes that have shown benefit in lowering BP and/or increasing target-organ protection. The Table displays such lifestyle and behavioral changes. Many, though not all, hypertensive patients are overweight, and the implementation of the suggested lifestyle changes in many hypertensive patients will induce weight loss. At least a few of the recommendations are probably less familiar to the average patient. Calcium intake has been shown to reduce BP levels in persons with low daily intakes of calcium and/or hypovitaminosis D. Natural sources of calcium, such as low-fat dairy products, have been proven more effective than dietary supplements. Emerging data show that augmentation of dietary calcium intake promotes weight loss and lower body fat. A multifaceted approach such as that undertaken in the TOMHS study—weight loss, salt and alcohol restriction, and increased physical activity—should be considered. A diet similar or identical in composition to the Dietary Approaches to Stop Hypertension (DASH) diet is an excellent approach to making dietary changes that will reduce BP levels in many patients with hypertension. Dietary salt restriction not only lowers BP in the majority of hypertensive individuals but augments the BP-lowering effect of most antihypertensive drugs. Urinary protein excretion is also diminished by both salt restriction and weight loss.

#### Pharmacologic Strategies

A major step forward in pharmacologically treating hypertension is to minimize the reliance on monotherapy. In most trials in patients with hypertension, the average BP levels typically remain well above 140/90 mm Hg, even with combination therapy. It is a distinct minority of pharmacologically treated patients with hypertension who will attain their goal BP without the use of multiple antihypertensive drugs.

Combination drug therapy should be embraced with a vengeance. The JNC 7 guidelines and the International Society on Hypertension in Blacks (ISHIB) guidelines on hypertension both comment explicitly on the use of multidrug therapy.

When BP levels are > 20/10 mm Hg above normal (per JNC 7) or >15-20/10 mm Hg above normal (per ISHIB), practitioners should recommend the use of multiple antihypertensive drugs. Multiple antihypertensive drugs will be needed to attain and maintain goal BP levels in most hypertensive patients. Use of suboptimal antihypertensive drug regimens has been identified as a major cause of inadequate BP control in patients referred to specialty antihypertensive care settings. Pharmacologic antagonism of the RAAS, which is reviewed in this supplement by Atlas, has shown the most promise for conferring target-organ protection.

### Table: Lifestyle and Behavioral Changes to Lower Blood Pressure

<table>
<thead>
<tr>
<th>Changes</th>
<th>Intervention</th>
<th>Comment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical activity</td>
<td>Increase</td>
<td>Appropriate aerobic activity should be encouraged. Weight lifting (heavy) can raise blood pressure.</td>
</tr>
<tr>
<td>Diet</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sodium</td>
<td>Decrease</td>
<td>Approximately 2 g (87 mmol) of dietary sodium a day is a good target. Approximately 80% of dietary sodium comes from processed foods.</td>
</tr>
<tr>
<td>Potassium</td>
<td>Increase</td>
<td>Approximately 4.7 g (120 mmol) of dietary potassium a day is recommended by the Institute of Medicine. Fresh fruits and green leafy vegetables are good sources of dietary potassium.</td>
</tr>
<tr>
<td>Lifestyle</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alcohol</td>
<td>Limit</td>
<td>Fewer than 2 drinks (1 oz or 30 mL of ethanol) a day is recommended.</td>
</tr>
<tr>
<td>Smoking</td>
<td>Avoid or quit</td>
<td>Smoking acutely raises blood pressure.</td>
</tr>
</tbody>
</table>
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profession that can be statistically disentangled from reductions of BP levels. However, in free-living patients with hypertension who may consume ad libitum daily amounts of dietary sodium, the BP-lowering efficacy of RAAS blockers is attenuated more so than the BP-lowering efficacy of calcium antagonists (and probably diuretics), whereas RAAS blockers, during low dietary sodium intake, lower BP to a similar degree as calcium antagonists. This BP lowering was seen in an examination of the relationship of SBP and urinary sodium excretion, which confirmed that isradipine, a calcium antagonist, decreased BP responsiveness to sodium to a greater degree than either placebo or enalapril, an angiotensin-converting enzyme inhibitor (ACEI). However, it is fortuitous that diuretics and calcium antagonists both augment the reduction of BP levels of RAAS antagonists in high-sodium environments quite well.

Race should be avoided as a criterion on which to base the selection of antihypertensive drug therapy. Diuretics and calcium blockers have been promulgated as meriting favor in blacks, while beta-blockers and RAAS antagonism have been advocated in whites. These recommendations appear to contradict physiologic data that suggest that blacks have greater activation of the RAAS than whites. Furthermore, increasing dietary sodium intake (which undermines BP reduction with RAAS antagonists) consequently suppresses renin but also turns on the synthesis of vascular angiotensin II while suppressing the production of nitric oxide. There is strong evidence that despite the greater BP responses of whites compared with those of blacks to monotherapy with a ACEI (for example, the BP response distributions are wide—much wider than the differences in the means of the race-specific response distributions—and these distributions overlap to a very large degree), the addition of either a calcium antagonist or a diuretic to RAAS blockers enhances the BP response and also eliminates racial differences in BP response. Thus, the vast majority of the BP response distribution to RAAS monotherapy is shared between races, rendering this factor a grossly inaccurate predictor of BP responses for individuals of either race targeted. Finally, the use of self-identified race as a criterion for drug selection will become increasingly inapplicable to an ever-enlarging sector of the U.S. population, given that this sector is phenotypically not black or white.

New Therapies

Because many patients still do not reach their target BP level, there remains an unmet need to find new antihypertensive therapies that are safe, reduce BP effectively, and provide target-organ protection. It appears unlikely that pharmacologic interruption of any physiologic system in isolation is going to reduce BP to a level that will allow most hypertensive patients to attain BP normalization on a single agent. Therefore, newer therapies need to combine well with older therapies, so that they may be effectively integrated into multidrug regimens.

Direct Renin Inhibitors

One pharmacologic approach has been targeted at the RAAS, but unlike ACEIs and ARBs, it has a novel mechanism of action. Direct renin inhibitors (DRIs) are the newest antihypertensive drug class on the market in the United States. Aliskiren, the first drug in this class to receive Food and Drug Administration (FDA) approval, is indicated for treatment of hypertension in doses of 150 mg and 300 mg once daily. Aliskiren has a long terminal half-life (24-40 hours) and, after abrupt withdrawal, BP rises very slowly over several weeks back to pretreatment levels. Despite providing blockade of the rate-limiting step in the synthesis of angiotensin II, the addition of an ARB to aliskiren provides incremental BP lowering. The drug is partially metabolized via the cytochrome 3A4 pathway, although approximately one quarter of the absorbed dose is excreted in the urine as the parent drug. There is no need, however, to alter aliskiren dosing in persons with either chronic kidney or liver disease. As with other RAAS blockers, combining aliskiren with diuretics produces a very significant incremental BP response with attenuation of the risk of diuretic-induced hypokalemia, and with a lower incidence of cough and angioedema compared with ACEIs. In an article in this supplement, Pool provides an in-depth review of aliskiren and the clinical utility of this agent.

Summary

Control of BP to levels persistently below target levels will require multiple antihypertensive agents in the majority of patients with hypertension. The use of thiazide diuretics and calcium antagonists with RAAS antagonists represents the logical combinations that reduce BP very effectively. Pharmacologic antagonism of the RAAS (ACEIs, ARBs, or DRIs) has shown the most promise for preventing target-organ injury or failure to a degree not solely explained by the reduction of BP levels. Practitioners should attempt to implement multidimensional lifestyle and behavioral changes that will also help reduce BP levels. Antihypertensive agents do not lower risk for all BP-related end points equivalently, even when cuff BP is lowered to a similar degree, but the need for multiple antihypertensive agents to control BP affords the practitioner the ability to use highly effective drug combinations that both reduce BP and protect target organs.

DISCLOSURES

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Epidemiology and Unmet Needs in Hypertension


The Renin-Angiotensin Aldosterone System: Pathophysiological Role and Pharmacologic Inhibition

Steven A. Atlas, MD

ABSTRACT

BACKGROUND: The renin-angiotensin aldosterone system (RAAS) is a hormonal cascade that functions in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. Dysregulation of the RAAS plays an important role in the pathogenesis of cardiovascular and renal disorders.

OBJECTIVES: To review the role of the RAAS in the development of hypertensive cardiovascular disease and related conditions and provide an overview of the classes of pharmacologic agents that inhibit this system.

RESULTS: The RAAS is initiated by the regulated secretion of renin, the rate-limiting enzyme that catalyzes the hydrolysis of angiotensin (Ang) I from the N-terminus of angiotensinogen. Ang I is in turn hydrolyzed by angiotensin-converting enzyme (ACE) to form Ang II, a potent vasoconstrictor and the primary active product of the RAAS. Recent evidence has suggested that other metabolites of Ang I and II may have biological activity, particularly in tissues. Development of agents that block the RAAS (e.g., beta blockers, ACE inhibitors [ACEIs], and angiotensin receptor blockers [ARBs]) began as a therapeutic strategy to treat hypertension. Preclinical and clinical studies have indicated important additional cardiovascular and renal therapeutic benefits of ACEIs and ARBs. However, blockade of the RAAS with these agents is incomplete.

CONCLUSION: Therapeutic approaches that target more complete inhibition of the RAAS may offer additional clinical benefits for patients with cardiovascular and renal disorders. These approaches may include dual blockade using ACEIs and ARBs in combination, or new therapeutic modalities such as direct renin inhibition with aliskiren, recently approved for the treatment of hypertension.

KEYWORDS: Renin-angiotensin aldosterone system; Hypertension; Angiotensin II, renin; ACE inhibitors; Angiotensin receptor blockers

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The renin-angiotensin aldosterone system (RAAS) plays an integral role in the homeostatic control of arterial pressure, tissue perfusion, and extracellular volume. It functions as an unusual endocrine axis in which the active hormone, angiotensin (Ang) II, is formed in the extracellular space by sequential proteolytic cleavage of its precursors. This pathway is initiated by the regulated secretion of renin, the rate-limiting processing enzyme. Although renin was discovered more than a century ago,1 the significance of this system in the pathogenesis of cardiovascular and renal disorders has gained wide acceptance only during the past 3 decades, in large part because of the availability of specific pharmacologic agents that can block the system.

In this article, I will review the evidence concerning the role of the RAAS in the development of hypertensive cardiovascular disease and related conditions and provide an overview of the agents that inhibit this system.

Historical Perspective

In 1898, Tigerstedt and Bergmann published an account of their research demonstrating the existence of a heat-labile substance in crude extracts of rabbit renal cortex that caused a sustained increase in arterial pressure.1 They proposed the term “renin” for a presumed humoral pressor agent secreted by the kidney, a concept that was widely disputed or ignored until the classical studies of Goldblatt and colleagues, published in 1934, that showed that renal ischemia induced by clamping of the renal artery could induce hypertension.1 Shortly thereafter it was shown that the ischemic kidney also released a heat-stable, short-lived pressor substance, in addition to renin. This finding eventually led to the recognition that renin’s pressor activity was indirect and resulted from its proteolytic action on a plasma substrate (eventually termed “angiotensinogen”) to liberate a direct-acting pressor peptide. This peptide was initially termed “angiotonin” or “hypertensin” by competing investigators in the United States (Page and colleagues) and in Argentina (Braun-Menendez and colleagues), who ultimately compromised on the term “angiotensin.”2 In the early 1950s, during attempts at purification, Skeggs and colleagues discovered that this peptide existed in 2 forms, eventually termed Ang I and II.2 In later work, they demonstrated that Ang I was cleaved by a contaminating plasma enzyme, termed “angiotensin-converting enzyme,” to generate the active pressor peptide Ang II.2 Soon after, the work of several investigators, including Laragh, Genest, Davis, Ganong, and their colleagues, culminated in the discovery that Ang II also stimulated the release of the adrenal cortical hormone aldosterone, a major

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vascular, adrenal gland, ovary, placenta, and adipose tissue. These landmark discoveries established the concept that a single system, the RAAS, was involved in the regulation of both blood pressure and fluid and electrolyte balance.

### Components of the RAAS

The renin-angiotensin aldosterone hormonal cascade begins with the biosynthesis of renin by the juxtaglomerular cells (JG) that line the afferent (and occasionally efferent) arteriole of the renal glomerulus. Renin is synthesized as a preprohormone, and mature (active) renin is formed by proteolytic removal of a 43-amino-acid prosegment peptide from the N-terminus of prorenin, the proenzyme or renin precursor. Mature renin is stored in granules of the JG cells and is released by an exocytotic process involving stimulus-secretion coupling into the renal and then the systemic circulation. In addition to this regulated pathway, it appears that the kidney also releases unprocessed prorenin via a constitutive pathway. In fact, prorenin accounts for about 70% to 90% of the immunoreactive renin in the human circulation. The potential biological significance of this finding is poorly understood at present.

Active renin secretion is regulated principally by 4 interdependent factors: (1) a renal baroreceptor mechanism in the afferent arteriole that senses changes in renal perfusion pressure, (2) changes in delivery of NaCl (sensed as changes in Cl− concentration) to the macula densa cells of the distal tubule (which lie close to the JG cells and, together, form the “JG apparatus”), (3) sympathetic nerve stimulation via beta-1 adrenergic receptors, and (4) negative feedback by a direct action of Ang II on the JG cells. Renin secretion is stimulated by a fall in perfusion pressure or in NaCl delivery and by an increase in sympathetic activity. Renin is also synthesized in other tissues, including brain, adrenal gland, ovary, and visceral adipose tissue, and perhaps heart and vascular tissue. The factors regulating synthesis and possible actions of renin in these other tissues are poorly understood.

Control of renin secretion is a key determinant of the activity of the RAAS. Renin regulates the initial, rate-limiting step of the RAAS by cleaving the N-terminal portion of a large molecular weight globulin, angiotensinogen, to form the biologically inert decapeptide Ang I or Ang-(1-10), as shown in the Figure. The primary source of systemic circulating angiotensinogen is the liver, but angiotensinogen mRNA expression has also been detected in many other tissues, including kidney, brain, heart, vascular, adrenal gland, ovary, placenta, and adipose tissue. Angiotensinogen is secreted constitutively by the liver, so plasma levels are generally stable and do not change acutely; however, both hepatic and extrahepatic synthesis have been shown to rise in response to glucocorticoids, estrogens and other sex steroids, thyroid hormone, inflammatory cytokines (e.g., interleukin-1 and tumor necrosis factor), and Ang II. Adrenal insufficiency, orchietomy, hypothyroidism, and insulin deficiency have been associated with a decline in plasma concentration and/or tissue mRNA expression of angiotensinogen. Long-term elevations in angiotensinogen concentration, which occur with pregnancy, Cushing’s syndrome, or glucocorticoid treatment, may be a risk factor for hypertension, although there is evidence that chronic stimulation of angiotensinogen may be partly compensated for by a reduction in renin secretion.

The inactive decapeptide Ang I is hydrolyzed by angiotensin-converting enzyme (ACE), which removes the C-terminal dipeptide to form the octapeptide Ang II [Ang-(1-8)], a biologically active, potent vasoconstrictor. ACE is a membrane-bound exopeptidase and is localized on the plasma membranes of various cell types, including vascular endothelial cells, microvillar brush border epithelial cells (e.g., renal proximal tubule cells), and neuroepithelial cells. It is this membrane-bound ACE that is thought to be physiologically important. ACE also exists in a soluble form in plasma, but this form may simply reflect turnover and clearance of membrane-bound ACE. ACE (also known as kininase II) metabolizes a number of other peptides, including the vasodilator peptides bradykinin and kallidin, to inactive metabolites. Thus, functionally, the enzymatic actions of ACE potentially result in increased vasoonstriction and decreased vasodilation.

Although Ang II is the primary active product of the RAAS, there is evidence that other metabolites of Ang I and II may have significant biological activity, particularly in tissues. Ang III and IV are formed by the sequential removal of amino acids from the N-terminus of Ang II by the action of aminopeptidases (Figure). They are most likely produced in tissue with high levels of aminopeptidases A and N, such as brain and kidney tissue. Ang III [Ang-(2-8)], a heptapeptide formed by removal of the first N-terminal amino acid, is present in the central nervous system (CNS), where it is thought to play an important role in tonic blood pressure maintenance and in hypertension. Ang IV [Ang-(3-8)] is a hexapeptide formed by further enzymatic degradation of Ang III. Preclinical studies have suggested a cooperative effect of Ang IV in Ang II signaling. For instance, it appears that in the brain, Ang IV increases blood pressure by cooperating with Ang II on angiotensin II type 1 (AT1) receptor signaling (see below), because its hemodynamic effects require the presence of both Ang II and functional AT1 receptors.

Peptides truncated at the C-terminus of Ang II may also have biological activity. For example, Ang-(1-7), a heptapeptide fragment of Ang II, can be formed from Ang I or Ang II by the actions of several endopeptidases or from Ang II by the action of carboxypeptidases, including one with significant structural homology to ACE (which has been termed “ACE 2”). Unlike ACE, this enzyme does not convert Ang I to Ang II and its activity is not affected by ACE inhibitors (ACEIs). Ang-(1-7), which appears to act via a unique receptor (see below), was first described to have vasodilatory effects and act as a natural ACEI. Cardioprotective effects have also been proposed to result from a direct effect of Ang-(1-7)
The classical RAAS pathway is highlighted in boldface type. Renin, normally secreted in response to underperfusion of the kidneys (not shown), cleaves the decapeptide Ang I from angiotensinogen, and Ang I is converted to Ang II by ACE. The dashed lines indicate feedback inhibition of renin secretion, which occurs both via a direct AT1 receptor-mediated action of Ang II (“short loop”) and via AT1-mediated restoration of blood pressure and volume (“long loop”). Other pathways that are speculative or of unproven physiological significance in vivo are depicted in light text. Ang II can also be cleaved by aminopeptidases to form Ang III and Ang IV. These peptides exert their biological effects by binding to various subtypes of angiotensin receptors. In addition, Ang-(1-7) can be formed directly from Ang I by the action of endopeptidases (not shown), and further metabolism of peptides to inactive fragments involves several amino-, carboxy-, and endopeptidases. A number of other proteolytic enzymes are shown that potentially can contribute to Ang I or Ang II synthesis. Lastly, both renin and prorenin may exert direct cellular actions by binding to a specific prorenin/rexin receptor. ACE=angiotensin-converting enzyme; Ang=angiotensin; AP/AAP-N=aminopeptidase A/aminopeptidase N; AT-R=angiotensin receptor subtype; CAGE=chymostatin-sensitive angiotensin II-generating enzyme; CP-P=carboxypeptidase P; MAP=mitogen-activated protein; Mas-R=Mas receptor; P/R=prorenin/rexin receptor; PAI-1=plasminogen activator inhibitor-1.

The Renin-Angiotensin Aldosterone System: Pathophysiological Role and Pharmacologic Inhibition

on heart cells or a generalized systemic effect,8 but evidence for such actions in human studies is lacking. ACE 2 can also cleave a single amino acid from the C-terminus of Ang I to form Ang-(1-9), a peptide with no known function at this time.

As already noted, Ang II is the primary effector of a variety of RAAS-induced physiological and pathophysiological actions. At least 4 angiotensin receptor subtypes have been described.9 The type 1 (AT1) receptor mediates most of the established physiological and pathophysiological effects of Ang II (Figure). These include actions on the cardiovascular system (vasoconstriction, increased blood pressure, increased cardiac contractility, vascular and cardiac hypertrophy), kidney (renal tubular sodium reabsorption, inhibition of renin release), sympathetic nervous system, and adrenal cortex (stimulation of aldosterone synthesis).7

The AT1 receptor also mediates effects of Ang II on cell growth and proliferation, inflammatory responses, and oxidative stress.2 This receptor, which is typical of the G protein-coupled receptor superfamily containing 7 membrane-spanning sequences, is widely distributed on many cell types in Ang II target organs.

The type 2 (AT2) receptor is abundant during fetal life in the brain, kidney, and other sites, and its levels decrease markedly in the postnatal period. There is some evidence that, despite low levels of expression in the adult, the AT2 receptor might mediate vasodilation and antiproliferative and apoptotic effects.
in vascular smooth muscle and inhibit growth and remodeling in the heart.\textsuperscript{7,8} In the kidney, it has been proposed that activation of AT\textsubscript{2} receptors may influence proximal tubule sodium reabsorption and stimulate the conversion of renal prostaglandin E\textsubscript{2} to prostaglandin F\textsubscript{2α}.\textsuperscript{5,7} However, the importance of any of these AT\textsubscript{2}-mediated actions remains uncertain.

The type 4 (AT\textsubscript{4}) receptors are thought to mediate the release of plasminogen activator inhibitor 1 by Ang II and by the N-terminal truncated peptides (Ang III and Ang IV), but the function of the type 3 (AT\textsubscript{3}) receptors is unknown.\textsuperscript{9} Lastly, the putative effects attributed to the C-terminal truncated peptide Ang 1-7, including vasodilatation, natriuresis, antiproliferation, and cardiac protection, are presumed to be mediated by a unique receptor that does not bind Ang II, most likely a product of the Mas proto-oncogene known as the Mas receptor.\textsuperscript{3}

In addition to receptors for the angiotensin peptides, very recent evidence suggests the existence of high-affinity cell surface receptors that bind both renin and prorenin in several tissues, including heart, brain, placenta, and kidney, with localization to glomerular mesangium and subendothelial vascular smooth muscle.\textsuperscript{10} One receptor that has been carefully characterized has been reported to cause reversible activation of bound prorenin and to enhance the catalytic activity of bound renin, thus serving as a template for local Ang I generation. The receptor also has been reported to initiate intracellular signaling, independent of Ang peptide synthesis, leading to activation of mitogen-activated protein kinases ERK1 and ERK2 (Figure).\textsuperscript{10}

These findings raise the possibility of Ang II-independent effects on cellular growth responses by renin or prorenin. An intriguing series of studies raises the possibility that such putative receptor-mediated mechanisms may contribute to the development of experimental diabetic nephropathy.\textsuperscript{11} Research into this new aspect of RAAS biology is progressing at a rapid pace, although there is as yet no evidence for human counterparts to these novel mechanisms.

As already noted, Ang II, via the AT\textsubscript{1} receptor, also stimulates the production of aldosterone by the zona glomerulosa, the outermost zone of the adrenal cortex. Aldosterone is a major regulator of sodium and potassium balance and thus plays a major role in regulating extracellular volume. It enhances the reabsorption of sodium and water in the distal tubules and collecting ducts (as well as in the colon and salivary and sweat glands) and thereby promotes potassium (and hydrogen ion) excretion.\textsuperscript{12} Ang II, together with extracellular potassium levels, are the major regulators of aldosterone, but Ang II synthesis may also be stimulated by adrenocorticotropic hormone (ACTH; corticotropin), norepinephrine, endothelin, and serotonin and inhibited by atrial natriuretic peptide and nitric oxide (NO). It is also important to note that Ang II is a major trophic factor for the zona glomerulosa, which can atrophy (reversibly) in its absence.
generating systems have been postulated to exist in the heart, peripheral blood vessels, kidney, brain, adrenal glands, pituitary, adipose tissue, testes, ovaries, and skin.\textsuperscript{7,13} Serine proteases, including several kallikrein-like enzymes (tonins), cathepsin G, and chymase are thought to contribute to Ang II formation in the tissue RAAS.\textsuperscript{14} Studies have suggested that non-ACE pathways are, by inference, responsible for about 40% of Ang II generation in the intact human kidney\textsuperscript{15} and that chymase is the dominant Ang II-generating pathway in the human heart, coronary arteries, and atherosclerotic aorta in vitro.\textsuperscript{14,16} It has thus been proposed that abnormal activation of the tissue RAAS may contribute to the pathogenesis of cardiovascular disease even in the absence of derangements in the circulating system.\textsuperscript{16} It must be considered, however, that the bulk of the evidence favoring alternate enzymatic pathways in the synthesis of angiotensin peptides comes from in vitro or indirect observations, so that such concepts remain speculative at present.

Under physiological conditions, the apparent function of the cardiac RAAS is to maintain cellular balance of inhibiting and inducing cell growth, and proliferation and mediation of adaptive responses to myocardial stretch.\textsuperscript{19} The majority of Ang II in cardiac tissue appears to be produced by local synthesis of Ang I and subsequent local conversion to Ang II, rather than from uptake of peptides from the systemic circulation.\textsuperscript{7} Although it has been suggested that locally synthesized renin and/or additional proteolytic enzymes may be involved in this synthetic process, current evidence favors the concept that circulating renin and angiotensinogen, which are able to pass through the endothelial barrier, are taken up by cardiac tissue where they act locally.\textsuperscript{20} Ang II exerts an inotropic effect (at least in atrial preparations), mediates myocyte hypertrophy via the AT\textsubscript{1} receptor, and is involved in cardiac remodeling.\textsuperscript{19} Pathologic activation of cardiac RAAS, perhaps through local upregulation of ACE levels, has been proposed to contribute to the development and maintenance of left ventricular hypertrophy.\textsuperscript{18}

Vascular smooth muscle, endothelial, and endocardial cells generate Ang I and Ang II, again apparently via the uptake of circulating renin.\textsuperscript{7} It has been suggested that the vascular RAAS contributes to the maintenance of cardiovascular homeostasis through its effects on both AT\textsubscript{1} and AT\textsubscript{2} receptors and mediates long-term effects on vascular remodeling by stimulating proliferation of vascular smooth muscle cells and fibroblasts.\textsuperscript{19} Endothelial dysfunction is associated with upregulation of local tissue ACE, which might contribute to disrupting the balance of vasodilation and vasoconstriction. Activation of vascular ACE may also alter other functions, including vascular smooth muscle cell growth and the inflammatory and oxidative state of the vessel wall.\textsuperscript{18} In addition, the production of reactive oxidative species (superoxide and hydrogen peroxide), which is enhanced by Ang II, has been associated with inflammation, atherosclerosis, hypertrophy, remodeling, and angiogenesis.\textsuperscript{19}

The intrarenal RAAS may explain the primary role of Ang II as a paracrine substance in the control of renal function. The direct intrarenal actions of Ang II include renal vasoconstriction, tubular sodium reabsorption, sensitivity of tubuloglomerular feedback, modulation of pressure-natriuresis, and promotion of renal tissue growth.\textsuperscript{7,13} Under normal conditions, Ang II constrains both the afferent and efferent arterioles and stimulates mesangial cell contraction, which results in reduced renal blood flow, glomerular filtration rate (GFR), and filtered sodium load.\textsuperscript{7} On the one hand, overactivation of the intrarenal RAAS may thus contribute to the pathophysiology of sodium-retaining states, such as hypertension and congestive heart failure (CHF).\textsuperscript{7} On the other hand, in conditions characterized by severe impairment of renal perfusion, such as renal artery stenosis, the afferent circulation, which is dilated as a result of autoregulation, is relatively refractory to the constrictive actions of Ang II, and the predominant constriction of efferent arterioles by Ang II plays a major role in maintaining glomerular perfusion pressure and, thus, GFR.

Although systemic Ang II may affect CNS function at selected sites, the brain is largely isolated from the circulating RAAS by the blood-brain barrier. Therefore, local Ang II synthesis by a brain RAAS has been proposed to play a role in central blood pressure regulation.\textsuperscript{19} Increases in brain renin activity, renin and angiotensinogen mRNA, and detectable numbers of AT\textsubscript{1}- and AT\textsubscript{2}-receptor subtypes have been reported in hypertensive rats.\textsuperscript{19} Selective inhibition of brain AT\textsubscript{1}- and AT\textsubscript{2}-receptors has been shown to lower blood pressure in hypertensive rats.\textsuperscript{13} Furthermore, direct administration of Ang II into the brain has been shown to increase blood pressure\textsuperscript{13,19} as a result of the combined effects of vasopressin release, sympathetic nervous system activation, and inhibition of baroreflexes.\textsuperscript{13} Studies in transgenic rats with permanent inhibition of brain angiotensinogen synthesis have demonstrated significantly lower systolic blood pressure compared with controls.\textsuperscript{19}

All components of the RAAS are present in adrenal cortex and comprise the adrenal RAAS. Renin and angiotensinogen mRNA have been identified in the adrenal gland, and Ang II formation has been demonstrated in zona glomerulosa cells.\textsuperscript{7} Most (90%) adrenal renin activity has been localized to the zona glomerulosa,\textsuperscript{7} and more than 90% of adrenal Ang II originates at local tissue sites.\textsuperscript{21} In transgenic animal models it has been shown that sodium restriction can increase adrenal renin and aldosterone independently of plasma or kidney renin concentrations. Additionally, bilateral nephrectomy, which decreases cardiac and vascular renin, does not decrease adrenal renin in experimental animals.\textsuperscript{7,21} These findings support the concept of kidney-independent renin (and thus, Ang II) production in the adrenal glands. It is not known if the adrenal RAAS functions as a paracrine or autocrine system or if it has a pathophysiologic role, and the relative importance of systemic versus locally synthesized Ang II in the control of adrenal function is uncertain.
Generally speaking, it is thought that the physiologic role of tissue RAAS is complementary to the classical circulating RAAS and serves as a mechanism for longer-term maintenance of balance or homeostasis at the tissue level between opposing effects mediated by the system (e.g., growth promotion and inhibition in the heart and vasculature). Pathophysiologic processes might hypothetically occur when components of the RAAS are overexpressed or inhibited, thus disturbing the intricate balance of this regulatory system.

### Dysregulation of the RAAS in Cardiovascular Disorders

Dysregulation of the RAAS is involved in the pathogenesis of several hypertensive disorders (Table). It should be noted that RAAS dysregulation in clinical hypertensive disorders has been conceptualized at the level of the classical circulating RAAS, and the potential contributions of tissue RAAS dysregulation remain poorly defined.

In addition to RAAS involvement in secondary forms of hypertension, there is evidence that perturbations of the RAAS are involved in essential hypertension as well as in the responses of cardiovascular and renal tissue to hypertensive and nonhypertensive injury. It is established that plasma renin levels vary widely in patients with “essential” hypertension (Table).

- Approximately 15% of patients with essential hypertension have mild to moderate increases in plasma renin activity (PRA), with several postulated mechanisms, including increased sympathetic activity and mild volume depletion. Such high-renin essential hypertension is particularly prevalent among younger males. The majority (50% to 60%) of essential hypertensive patients have PRA within the “normal” range, although it has been argued that a normal renin level in the face of hypertension (which ought to suppress renin secretion) may be inappropriate.

Therapeutic responses to RAAS blocking agents indicate that maintenance of normal renin levels may indeed contribute to blood pressure elevation, suggesting that renin-dependent mechanisms may be involved in more than 70% of patients with essential hypertension. On the other hand, about 25% to 30% have evidence of low or suppressed renin levels, a finding that may be an expected response or that may, in some cases, reflect, by analogy to primary aldosteronism, sodium or volume excess (so-called “volume-dependent” hypertension). Low-renin hypertension is more common among older people with hypertension, women, African Americans, and patients with type 2 diabetes, as well as among patients with chronic renal parenchymal disease.

Although such patients often have lesser blood pressure-lowering benefit from RAAS blocking agents, there is evidence that the circulating levels of PRA might not necessarily reflect tissue activities of the system. This is particularly evident with regard to the kidney, with several lines of evidence pointing to substantial involvement of intrarenal Ang II in progression of renal damage (and substantial benefit of RAAS blockade), despite low circulating levels of renin and Ang II.

The RAAS also plays a pivotal role in several nonhypertensive conditions, and in particular in CHF and the other edematous disorders (cirrhosis with ascites and the nephrotic syndrome). In these conditions, all characterized by underperfusion of the kidneys due to reduced “effective arterial volume,” secondary hypersecretion of renin leads to secondary aldosteronism, which makes an important contribution to progressive edema. In addition, with regard to heart failure, the contribution of Ang II to increased peripheral vascular resistance (cardiac afterload) also plays a major role in progressive ventricular dysfunction.

Beyond progression of renal disease, there is additional clear evidence (again from responses to RAAS blockade) of involvement of Ang II in development of both vascular and cardiac hypertrophy and remodeling, as well as on mechanisms that contribute to vascular damage and atherosclerosis, effects that appear to have major impact on morbidity and mortality.

The RAAS also plays a “passive” role in such events—that is, that tissue injury can be accelerated even in the presence of “normal” Ang II levels.

### RAAS Inhibition

**Early Preclinical Findings**

Because renin is the initial and rate-limiting step in the RAAS cascade, it has long been considered the logical therapeutic target for blocking the system. Preclinical studies with anti-renin antibodies and then with early synthetic renin inhibitors established the potential utility of RAAS inhibition. In these studies, renin inhibition induced decreases in plasma renin levels (generally measured in these early studies as plasma renin activity or PRA), Ang I, Ang II, and aldosterone, along with decreases in blood pressure. These studies also provided evidence that blood pressure-lowering activity was due to inhibition of PRA. However, pharmacologic activity of the early renin inhibitors could only be achieved with intravenous infusion, and the development of an orally active direct renin inhibitor was fraught with numerous difficulties arising from issues of potency, low bioavailability, duration of action, and costs of synthesis. As a result, further development of these agents was halted in the mid-1990s. Concurrently, other strategies for inhibiting the RAAS progressed to clinical use.
# Hypertensive Disorders Involving Dysregulation of the Renin-Angiotensin Aldosterone System

<table>
<thead>
<tr>
<th>Hypertensive Disorders</th>
<th>RAAS Dysregulation</th>
<th>Clinical Manifestations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renin-secreting neoplasms</td>
<td>Primary hypersecretion of renin by renal hemangioepicytomas (“JG cell tumors”), some Wilms’ tumors and renal and extrarenal carcinomas (ovary, pancreas, lung) Secondary aldosteronism</td>
<td>Severe renin-dependent hypertension (accelerating hypertension common) Hypokalemia; sodium retention limited by pressure natriuresis</td>
</tr>
<tr>
<td>Renovascular hypertension Atheromatous (main) Fibromuscular (main or branch) Renal emboli/segmental infarcts Renal artery aneurysms Renal artery dissection/injury Subcapsular hematoma</td>
<td>Hypersecretion of renin due to segmental, unilateral, or bilateral renal ischemia Secondary aldosteronism</td>
<td>Hypertension (usually renin-dependent, accelerating hypertension common); progressive renal dysfunction possible Sodium retention (depending on extent of renal compromise); hypokalemia may be masked by decreased distal delivery of sodium</td>
</tr>
<tr>
<td>Malignant hypertension and other renal small vessel disease (e.g., polyarteritis, scleroderma, hemolytic uremic syndrome, lupus)</td>
<td>Hypersecretion of renin due to generalized renal ischemia Secondary aldosteronism</td>
<td>Severe renin-dependent hypertension Renal dysfunction Microangiopathic hemolytic anemia Hypertensive encephalopathy Sodium retention and hypokalemia variable (as above)</td>
</tr>
<tr>
<td>Pheochromocytoma and other catecholamine-secreting tumors</td>
<td>Hypersecretion of renin due to catecholamine excess Renal ischemia due to extrinsic renal compression and/or neurofibromatosis involving the renal artery (occasionally) Secondary aldosteronism</td>
<td>Sustained or paroxysmal hypertension (accelerating hypertension common) Other typical manifestations of catecholamine excess Hypokalemia; sodium retention often limited by pressure natriuresis</td>
</tr>
<tr>
<td>Essential hypertension</td>
<td>HR (~15%)—PRA mildly elevated, cause uncertain (sympathetic drive?, hypovolemia?) NR (~60%)—PRA within “normal” range, but may be inappropriate in setting of hypertension LR (~25%)—PRA low due to several possible mechanisms (sodium/volume excess?, nephrosclerosis?, appropriate response?)</td>
<td>Hypertension usually responds well to RAAS blockade Increased susceptibility to heart attack or stroke? Hypertension often responds to RAAS blockade Hypertension responds best to diuretics, calcium channel- or alpha1-blockers Tissue RAAS may not be similarly suppressed (e.g., kidney)</td>
</tr>
<tr>
<td>Primary aldosteronism and other MC excess</td>
<td>Primary hypersecretion of aldosterone or other MC hormone (e.g., DOC) by adrenal neoplasms; or very rare genetic syndromes resulting in MC hormone dysregulation Secondary suppression of renin and Ang II</td>
<td>Hypertension (may be severe at times) Hypokalemia and hypomagnesemia Sodium and volume expansion, without edema (limited by “mineralocorticoid escape”) Reversible atrophy of contralateral adrenal cortex (due to suppressed Ang II)</td>
</tr>
</tbody>
</table>

Ang=angiotensin aldosterone system; DOC=deoxycorticosterone; HR=high renin; JG=juxtaglomerular; LR=low renin; MC=mineralocorticoid; NR=normal renin; PRA=plasma renin activity; RAAS=renin-angiotensin aldosterone system. A ? indicates that the true etiology is unknown.
Beta Blockers
In the 1970s, Laragh and colleagues showed that, in patients with various types of hypertension, beta-blocker therapy (propranolol) reduced plasma renin levels by blocking sympathetically (beta,)-mediated renin release by the kidney.26 They concluded that the reduction in plasma renin level (by about 75%) was closely correlated with reductions in blood pressure. They also showed that propranolol reduced aldosterone secretion. Their results demonstrated the viability of pharmacologic blockade of the RAAS as a therapeutic strategy.

A more recent study demonstrated parallel suppression of Ang II and PRA during beta-blocker therapy in hypertensive subjects.27 In addition to suppression of renin release, there is evidence that beta blockade may also inhibit intrarenal conversion of prorenin to renin.27,28 The blood pressure-lowering activity of beta blockers occurs via both renin-dependent and renin-independent mechanisms. Although many studies suggest a preferential effect among patients with high-renin forms of hypertension,25,26 there is evidence for benefit in low-renin hypertension as well, particularly with high-dose propranolol therapy (320 mg to 980 mg daily), independent of changes in PRA.29

Angiotensin-Converting Enzyme Inhibitors
Early studies performed in the 1960s showed that peptides from the venom of the Brazilian arrowhead viper (Bothrops jararaca) inhibited kinase II, an enzyme that facilitates degradation of bradykinin, and which was later shown to be identical to ACE.2 Synthetic analogues of the peptide fraction of snake venom, such as the nonapeptide teprotide, were shown to lower blood pressure in patients with hypertension and produce beneficial hemodynamic effects in patients with heart failure.2 These findings encouraged the search for orally active inhibitors of ACE, the first of these, captopril, was designed based on known inhibitors of another zinc-containing metalloprotease, carboxypeptidase A, and included a sulfhydryl-containing amino acid to serve as ligand for the zinc moiety. Because many of the unacceptable side effects of captopril, such as proteinuria, skin rashes, and altered taste, were attributed to the sulfhydryl group, subsequent work led to the development of ACEIs that replaced this group with a carbonyl group (e.g., lisinopril, benazepril, quinapril, ramipril, perindopril, cilazapril, trandolapril) or phosphoryl group (losinopril).30,31 The presence of the carbonyl group conferred greater lipophilicity, which actually improved binding to ACE, and improved tissue penetration.31

ACEIs competitively block the action of ACE and thus the conversion of Ang I to Ang II, thereby reducing circulating and local levels of Ang II. ACEIs also decrease aldosterone and vasopressin secretion and sympathetic nerve activity, but there is controversy regarding their efficacy in blocking other "tissue" actions of the RAAS.32 Short-term ACEI therapy is associated with a decrease in Ang II and aldosterone and an increase in renin release and Ang I. There is some evidence, however, that over the long term ACE inhibition may be associated with a return of Ang II and aldosterone toward baseline levels ("ACE escape")—perhaps, it is proposed, through activation of the so-called alternate pathways (Figure).32,33 Undoubtedly this phenomenon has been greatly exaggerated, particularly from early studies using faulty methodology that did not specifically measure Ang II, and the relevance of alternate pathways of Ang II synthesis in the intact human is unclear at present. On the other hand, because ACEIs are all competitive inhibitors of the enzyme, it is possible that increased levels of Ang I (provoked by the compensatory increase in PRA due to loss of negative feedback inhibition) can tend to partially overcome the blockade.34 This would be especially likely in high-renin or volume-depleted patients with a particularly robust reactive rise in PRA.

In general, short-term, pharmacodynamic responses to decreases in Ang II through inhibition of ACE include dose-dependent reductions in cardiac preload and afterload, with lowering of systolic and diastolic blood pressure, but, in normotensive and hypertensive patients without cardiac dysfunction, little or no change in cardiac output or capillary wedge pressure. Of note, unlike direct-acting arterial vasodilators, ACEI-induced reductions in total peripheral vascular resistance occur without a significant change in heart rate.32 ACEIs also decrease renal vascular resistance, increase renal blood flow, and promote sodium and water excretion. Mainly through cellular effects in the kidney and through alterations in glomerular hemodynamics, ACEIs also may prevent the progression of microalbuminuria to proteinuria, reduce proteinuria in patients with established glomerular disease, and prevent or delay the progression of renal insufficiency to end-stage renal disease. Efficacy in long-term trials has been demonstrated particularly in patients with nondiabetic nephropathies or in patients with insulin-dependent (type 1) diabetes.32,35,36

Because ACE is identical to kininase II, ACEIs may also lead to elevation of bradykinin levels in some tissues (but unlikely in the circulation); this effect is potentially associated with increased bradykinin-dependent release of NO and vasoactive prostaglandins, including prostacyclin and prostaglandin E2.32 These actions may potentially contribute to the vasodilatory, antithrombotic, antiatherogenic, and antiproliferative effects of ACEI, although the importance of this pathway is debated.32

In 40% to 60% of patients with mild-to-moderate hypertension, ACEI monotherapy produces a satisfactory reduction in blood pressure.37 In this population, ACEIs contribute to reversal of cardiac hypertrophy, and do so with significantly greater efficacy than beta blockers.38 In patients with CHF, ACEIs relieve pulmonary congestion by a balanced reduction in cardiac preload and afterload. They appear to induce venous vasodilation, which increases peripheral venous capacitance and reduces right atrial pressure, pulmonary arterial pressure, capillary wedge pressure,
and left ventricular filling volumes and pressures. ACEIs also induce arterial vasodilation, which reduces peripheral vascular resistance (afterload) and increases cardiac output in this patient population. ACEIs have also been shown to improve endothelial dysfunction in patients with heart failure, as well as in patients with coronary artery disease and type 2 diabetes.

In early landmark trials in patients with CHF (such as CONSENSUS, SOLVD, and V-HeFT-II), ACEIs were shown not only to markedly improve symptoms and functional status, but also to dramatically reduce mortality. In subsequent studies in patients who have suffered a myocardial infarction (MI), such as SAVE, AIRE, and TRACE, ACEI therapy has been shown to prevent or retard ventricular remodeling and progression to CHF, and thereby to reduce overall mortality and prolong survival. Furthermore, results of the HOPE trial and other smaller studies indicate broad cardiovascular benefits of ACEI therapy in “high-risk” patients (including both hypertensive and normotensive individuals), and it is possible that these benefits occur in part independently of their blood pressure-lowering effect.

Several large-scale studies of various ACEIs have shown a reduction in incidence of new-onset diabetes in association with ACEI therapy. For example, this has been shown with captopril in patients with hypertension (CAPP), with ramipril in patients at high risk for cardiovascular disease (HOPE), with enalapril in patients with left ventricular dysfunction (SOLVD), and with trandolapril in patients with stable coronary disease (PEACE). The mechanism of this benefit has not been determined.

ACEI therapy is generally well tolerated by most patients but is nonetheless associated with some significant side effects. Most frequent among these is a dry cough, which has been attributed to accumulation of substance P (which is normally degraded by kininase II). More serious side effects common to all ACEIs include angioedema (which is potentiated by decreased catabolism of kinins) and fetal abnormalities and mortality. Other “physiologic” consequences of ACE inhibition may include hypotension, deterioration of renal function, and hyperkalemia. Lastly, toxic effects, associated mainly with captopril, include abnormal (metallic or salty) taste, rash, neutropenia, hepatic toxicity, and proteinuria (membranous nephropathy).

**Angiotensin Receptor Blockers (ARBs)**

As mentioned earlier, the AT1 receptor mediates most of the known actions of Ang II that contribute to hypertension and volume dysregulation (vascular smooth muscle contraction, aldosterone secretion, dipsogenic responses, renal sodium reabsorption, and pressor and tachycardic responses) as well as to cardiovascular damage (cellular hypertrophy or proliferation, prothrombotic and proinflammatory effects, and superoxide formation). Thus, with the discovery of different receptor subtypes, specific antagonism of Ang II action at the AT1 receptor became a logical therapeutic target, one considered likely to be more specific than ACE inhibition. Development of orally active, nonpeptide, selective AT1 receptor blockers began in the 1990s with the synthesis of losartan. Since that time, several ARBs have been synthesized, including valsartan, irbesartan, candesartan, eprosartan, telmisartan, and olmesartan.

Because ARBs act by blocking Ang II action at the receptor level, rather than by inhibiting its synthesis, they ought to antagonize AT1-mediated effects of Ang II no matter how it is synthesized. In other words, if there were significant Ang II synthesis in tissues by alternate pathways, such as chymase in the heart, this would limit the efficacy of ACEIs (but not of ARBs) through a mechanism postulated to contribute to the “escape” phenomenon following long-term ACE inhibition.

In contrast to the ACEIs, ARB therapy actually results in an increase in Ang II levels. As with ACE inhibition, blockade of the AT1 receptor inhibits the negative feedback loop, leading to increased renin secretion and thus to increased synthesis of Ang I. In the case of ARBs, the increase in Ang I leads to a commensurate increase in Ang II, which is freely able to bind to AT1 or other receptor subtypes. Earlier preclinical studies have suggested that beyond AT1 receptor blockade, activation of the AT2 receptor might mediate additional beneficial actions on the vasculature, heart, and kidneys, in part via a bradykinin/NO/cGMP pathway, an effect that would further distinguish ARBs from ACEIs. But as attractive as this hypothesis is, there are no clinical data to indicate that this pathway is a major mechanism of ARB action in humans.

Like the ACEIs, ARBs reduce blood pressure by decreasing systemic vascular resistance; they do not affect heart rate and have minimal effect on cardiac output in the nonfailing heart. Reduced systemic vascular resistance results from a combination of inhibition of Ang II-mediated vasoconstriction, reduced sympathetic nervous system activity, and reduced extracellular volume (i.e., by direct inhibition of proximal sodium reabsorption and by inhibition of aldosterone release). ARB monotherapy produces a satisfactory reduction in blood pressure in 40% to 60% of patients with mild-to-moderate hypertension. ARB therapy has also been shown to reduce markers of inflammation in patients with atherosclerosis, suggesting an anti-inflammatory effect, and to reverse endothelial dysfunction in patients with hypertension, indicating the possibility of significant antiatherogenic effects. In patients with hypertension, ARB therapy has also been shown to improve arterial compliance independent of the blood pressure-lowering effect. This observation suggests that ARB therapy may contribute to reversal of vascular wall damage.

A number of recent large trials support the idea that the ARB class may confer benefits on target organ protection beyond the lowering of blood pressure per se. In patients with hypertension and left ventricular hypertrophy, ARB-based therapy, compared with beta-blocker (atenolol)-based therapy with identical blood pressure control, has been shown to significantly reduce the...
composite risk of cardiovascular death, stroke, and MI and to decrease the rate of new-onset diabetes (LIFE study). Similarly, ARB-based therapeutic regimens, compared with conventional therapy, have been shown to reduce the progression of nephropathy in patients with diabetic nephropathy (IDNT, RENAAL studies). In nonhypertensive conditions, ARBs have shown benefits comparable to those of ACEIs. In patients with chronic heart failure, addition of an ARB, compared with placebo, to conventional treatment has been shown to significantly reduce the risk of cardiovascular mortality and hospitalization (CHARM, Val-HeFT studies). In high-risk post-MI patients, ARB therapy has been shown to reduce the risks of all-cause mortality, recurrent MI, sudden cardiac death, revascularization, coronary artery bypass grafting, or all-cause hospital admission to a degree similar to that of ACEI therapy (OPTIMAAL study).

Like ACEIs, use of ARBs is contraindicated in pregnant women because of the association of RAAS blockade with increased fetal morbidity and mortality, particularly with exposure during the second and third trimester. ARB therapy is otherwise generally well tolerated, even in many patients who discontinue ACEI therapy because of side effects. Although rare reports of angioedema and cough have emerged from the early premarketing clinical trials with ARBs, it is currently debated whether these are truly associated with the class as they are with ACEIs. Most adverse events reported with ARB therapy are related to expected potential effects of RAAS blockade—for example, hypotension, hyperkalemia, and worsening renal function—and are similar to those encountered in patients taking ACEIs.

### Direct Renin Inhibitors

The most recent class of agents that block the RAAS to be introduced are the direct renin inhibitors represented by aliskiren, which was recently approved for treatment of hypertension. This compound differs from the ACEIs and ARBs in that, by blocking the catalytic activity of renin at the point of activation of the RAAS, it blocks the synthesis of all angiotensin peptides and prevents the compensatory increase in renin activity. This topic is dealt with in detail in another article in this series (see article titled “Direct Renin Inhibition: Focus on Aliskiren” by Pool).

### Future Directions

ACEIs and ARBs are currently indicated for the treatment of hypertension, diabetic nephropathy, post-MI left ventricular dysfunction, and chronic heart failure, and their use has been associated with improved survival and considerable cardiovascular and renal benefits in high-risk patients. These remarkable benefits have been obtained even though blockade of the RAAS with currently available agents may be incomplete, raising the possibility that additional therapeutic modalities for RAAS blockade might help to further slow progression of cardiovascular and renal disease.

First, blockade of the RAAS by ACEIs and ARBs is incomplete because their therapeutic response can be limited by the reactive rise in PRA. This is particularly so with the ACEIs, because a marked rise in Ang I may compete with the relatively low-affinity inhibition of ACE that they afford. Second, although the notion that selective blockade of AT1 receptors may be a preferred approach over ACE inhibition is based on attractive hypotheses (i.e., the potential benefits of AT1 receptor agonism and/or the ability to counteract the effects of ACE-independent pathways of Ang II synthesis), these hypotheses are largely unproven in humans. Moreover, there have been no large-scale clinical trials over the past 15 years that demonstrate a clear superiority of ARBs over ACEIs. Third, although our focus has been on Ang II as the only villain of the RAAS, the possibility that other angiotensin peptides might also contribute to cardiovascular pathology has never been adequately tested. Fourth, questions of mechanism aside, it is likely that differences in drug distribution and/or tissue penetration between or within the classes may limit the benefits of any single agent. Thus, it is reasonable at this point to ask whether more-complete blockade of the system will offer even more clinical benefits.

The clinical potential of simultaneous intervention at multiple sites of the RAAS is compelling. As has already been demonstrated in small clinical trials, dual RAAS blockade using an ACEI and ARB in combination may have potential clinical value in symptomatic patients with CHF or left ventricular systolic dysfunction and in patients with chronic proteinuric renal disease. With the recent availability of aliskiren, the first direct renin inhibitor approved for the treatment of hypertension, the opportunity is at hand to test new therapeutic approaches involving monotherapy with this agent or its use in combination with an ACEI or ARB for more complete blockade of the RAAS. Results obtained with this approach may direct investigators to explore additional therapeutic targets in the future, such as other angiotensin receptor subtypes, other relatively specific metabolic pathways (e.g., “ACE 2”), or other angiotensin peptides (e.g., Ang III, Ang IV, and Ang-(1-7)). Lastly, the possibility of molecular approaches such as antisense gene therapy, targeting, for instance, renin, angiotensinogen, the AT1 receptor, or ACE, will also likely be explored in the not-too-distant future.

### DISCLOSURES

The author discloses no potential bias or conflict of interest relating to this article.

### REFERENCES


Direct Renin Inhibition: Focus on Aliskiren

James L. Pool, MD

ABSTRACT

BACKGROUND: Despite the availability of many effective, well-tolerated drugs, a significant proportion of treated hypertensive patients still have uncontrolled high blood pressure (BP) and thus face serious morbidity and mortality. The renin-angiotensin aldosterone system (RAAS) is a key target for BP control and for cardiovascular and renal protection. Renin controls the rate-limiting step in the RAAS cascade and hence is the optimal target for RAAS suppression. Aliskiren is the first direct renin inhibitor (DRI) to be approved by the U.S. Food and Drug Administration and the European Medicines Agency for treating hypertension.

OBJECTIVE: To provide an overview of the pharmacology, pharmacokinetics, preclinical, and clinical efficacy and safety data on the DRI aliskiren.

RESULTS: Approximately 70% of essential hypertension is associated with elevated renin levels. Aliskiren is a potent and highly specific inhibitor of renin, with oral bioavailability of 2.6% and an elimination half-life of 40 hours, making it suitable for once-daily oral administration. Aliskiren dose-dependently reduced BP, inhibited plasma renin activity (PRA), attenuated renal damage in animal models, and showed efficient and longer-lasting blockade of the RAAS in normotensive human subjects compared with other RAAS inhibitors. The clinical efficacy and safety of aliskiren have been evaluated both as monotherapy and in combination with other antihypertensive agents in phase II and phase III trials of patients with mild to severe hypertension. When used as monotherapy, aliskiren led to significant dose-dependent reductions in BP from baseline that were greater than those obtained with placebo and comparable with those achieved with an angiotensin II receptor blocker (ARB). The combination of aliskiren with a diuretic, a calcium channel blocker (CCB), an angiotensin-converting enzyme inhibitor (ACEI), or an ARB generally had greater and longer-lasting BP-lowering efficacy than did single agents alone. Aliskiren also countered the reactive increase in PRA caused by diuretic, CCB, ACEI, and ARB therapy. Once-daily treatment with aliskiren was well tolerated.

CONCLUSIONS: As a DRI, aliskiren blocks the RAAS more completely than do other current downstream RAAS inhibitors. When used once daily, aliskiren is a safe and effective antihypertensive agent that can be used as monotherapy or in combination with other agents to provide additional options to improve BP control.

KEYWORDS: Aliskiren, Antihypertensives, Renin

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Inhibition of RAAS activity with ACE inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) has proven effective for not only controlling hypertension but also delaying the onset of diabetes mellitus, slowing renal damage in patients with hypertension, and reversing left ventricular hypertrophy. However, these agents are no more effective than other antihypertensive agents in reducing major cardiovascular events, which suggests an incomplete blockade of the RAAS. Inhibition of Ang II formation or action via ACEIs or ARBs does not provide optimal suppression of RAAS activity, because a compensatory increase in renin concentrations again increases Ang I and Ang II levels. Ang II can also be formed using pathways that do not involve ACE. Therefore inhibitors of ACE are no more effective than other antihypertensive agents in reducing major cardiovascular events, which suggests an incomplete blockade of the RAAS. Inhibition of Ang II formation or action via ACEIs or ARBs does not provide optimal suppression of RAAS activity, because a compensatory increase in renin concentrations again increases Ang I and Ang II levels. Ang II can also be formed using pathways that do not involve ACE.

Because it causes the conversion of angiotensinogen to Ang I, which is the rate-limiting step in the RAAS cascade, renin is the main determinant of RAAS activity and has been considered for at least 50 years the optimal target for RAAS suppression. Circulating renin can be taken up by cardiac and coronary tissues, leading to the long-lasting generation of Ang II via ACE and non-ACE activity that is only partially suppressed by an ACEI. Inhibition of renin would favor more complete blockade of the system. The successful production of a highly potent, selective, clinically effective oral renin inhibitor is a major development in the area of RAAS inhibition. This article provides an overview of direct renin inhibition (DRI) and reviews the pharmacologic and clinical profile of aliskiren, the first antihypertensive agent in a new class of drugs approved by the U.S. Food and Drug Administration (FDA) in more than 10 years. Aliskiren also received approval from the European Medicines Agency (EMEA).
Renin

Overactivity of the RAAS with high renin, Ang, and aldosterone levels causes fatal malignant hypertension and renovascular hypertension, whereas overactivity of the RAAS with milder elevations of renin levels has been associated with up to 70% of cases of essential hypertension. Patients with plasma renin activity (PRA) levels exceeding 0.65 ng/mL/h have renin-mediated hypertension, and those with lower PRA levels have salt hypertension, which accounts for the remaining 30% of essential hypertension.2

Renin is an aspartyl protease that is synthesized as prorenin, a proenzyme that is transformed into renin by cleavage of a 43-amino-acid segment from the N-terminal end (Figure 1). This activation process, which occurs exclusively in the juxtaglomerular cells of the kidney, is followed by the release of renin into the circulation system.9 Although it is synthesized in only a few tissues (eyes, adrenal glands, testes, ovaries, and brain), prorenin represents between 70% and 90% of the total plasma renin in individuals without diabetes and as much as 95% of the total plasma renin in individuals with diabetes.10 The local actions of renin are thus mediated by kidney-derived renin that is released into the circulation system and taken up by tissues. For example, cardiac Ang production depends on the conversion of angiotensinogen in extracellular fluid by plasma-derived renin.11

Renin receptors have been localized to glomerular mesangium and vascular smooth muscle cells within the subendothelium of glomerular and coronary arteries.9 The receptor colocalizes with renin. Cells transfected with receptor cDNA result in the expression of a membrane protein that specifically binds renin and prorenin with high affinity.9 Labeling studies have demonstrated high-affinity binding (Ki = 0.4 nM) of renin to receptors on cultured human mesangial cells.12

The binding of renin to its receptor with a single transmembrane domain has multiple and far-reaching consequences. Receptor binding induces a 4-fold increase in the catalytic activity of renin, remikiren, and zankiren, had limited clinical use because they lacked the extended peptide-like backbone of previous inhibitors and had improved pharmacokinetic properties.16 Aliskiren is the first of these new nonpeptide DRIs to be approved by the FDA for the treatment of hypertension. It is administered once daily, either as monotherapy or in combination with other antihypertensive agents. In Europe, aliskiren received approval from the EMEA for the treatment of hypertension.

Aliskiren

Aliskiren is a transition-state mimic agent with high hydrophilicity, which improves its oral bioavailability.18 It is a highly potent inhibitor of renin (IC50 = 0.6 nM) with a high affinity for renin and a high species specificity for primate renin. Aliskiren inhibits human, marmoset, and rat plasma renin with IC50 values of 0.6 nmol per L, 2.0 nmol per L, and 80 nmol per L, respectively. Therefore, preclinical testing has been performed in sodium-depleted marmosets and in spontaneously hypertensive rats.

In sodium-depleted marmosets, doses of aliskiren ranging from 0.3 mg per kg to 10 mg per kg caused a dose-dependent reduction in mean arterial BP.10 All doses of aliskiren completely inhibited PRA within 1.5 hours of administration, and this inhibition was sustained for more than 24 hours with the 3 mg per kg and 10 mg per kg doses.10 When the 3 mg per kg dose was
FIGURE 1 Pro(renin) Receptor Binding Initiates Intracellular Signaling; 1 of 3 Mechanisms to Activate Prorenin to Renin

AGT=angiotensinogen; ANG I=angiotensin I; MAP=mitogen-activated protein; PAI=plasminogen activator inhibitor; PRS=prorenin segment; TGF=transforming growth factor.
administered, BP was reduced by a maximum of 30 mm Hg without any effect on heart rate. The 10 mg per kg dose of aliskiren was more effective than similar doses of either benazepril or valsartan in reducing mean arterial pressure.19

Pilz and colleagues compared the effects of subcutaneous aliskiren 0.3 mg per kg per day, 3 mg per kg per day with valsartan 1 mg per kg per day, and 10 mg per kg per day with no treatment on the development of end-organ damage in hypertension in double-transgenic rats with high levels of serum creatinine and albuminuria.20 Both doses of aliskiren and the higher dose of valsartan reduced renal Ang I and Ang II content, maintained creatinine at normal levels, decreased albuminuria, prevented renal infiltration with inflammatory cells, reduced cardiac hypertrophy, and prolonged survival.20 However, aliskiren 3 mg per kg per day was significantly more effective than valsartan 10 mg per kg per day in reducing systolic BP (SBP), cardiac hypertrophy, and left ventricular wall thickness (P<0.05 for all endpoints).20 In this model, renin inhibition compared favorably with AT1 receptor blockade in reversing renal damage.

Subsequent studies in normotensive human subjects demonstrated efficient blockade of the RAAS with aliskiren. In 18 normotensive men with a sodium intake of 100 mmol/day, treatment with aliskiren (40 mg per day to 640 mg per day) for 8 days significantly and in a dose-dependent manner suppressed PRA and plasma concentrations of Ang I and Ang II.21 Maximal reduction of Ang II occurred within 1 hour of the administration of aliskiren, compared with 6 hours with a 20 mg dose of enalapril. The level of inhibition of Ang II by enalapril (57%) was similar to that with a 160 mg dose of aliskiren (56%).21 A dose of aliskiren ≥80 mg reduced plasma aldosterone levels within 3 hours of administration and, at the highest dose, these levels remained suppressed for up to 24 hours.21 In response to the reduction in Ang II level, plasma renin concentrations increased similarly with aliskiren 160 mg and enalapril 20 mg.21

A double-blind, placebo-controlled, randomized, 4-period crossover study in 12 normotensive men who were mildly sodium depleted compared a single high dose of aliskiren (300 mg), a standard dose of valsartan (160 mg), and their combination at half doses (aliskiren 150 mg plus valsartan 80 mg).22 In contrast to valsartan, aliskiren decreased PRA and Ang I and Ang II levels for 48 hours, inhibited urinary aldosterone secretion for a longer period, and resulted in greater and longer-lasting increases in plasma renin levels.22 In general, the effects of the low-dose combination were similar to those of aliskiren 300 mg than to those of valsartan 160 mg. The combination blunted the valsartan-induced increase in PRA and Ang I and Ang II concentrations, led to greater and longer suppression of urinary aldosterone excretion compared with valsartan alone, and was as effective as either monotherapy in reducing BP.22 The longer duration of RAAS inhibition by aliskiren compared with valsartan suggested that the effects of Ang II may be reduced more effectively by direct renin inhibition than by Ang receptor blockade.

**Aliskiren Pharmacokinetics**

The pharmacokinetics of aliskiren deviate from dose linearity, with an overproportional increase in area under the curve (AUC) and Cmax with respect to the administered dose.22 The mean terminal half-life is approximately 40 hours after multiple administrations of a single dose, and repeated once-daily administration leads to drug accumulation.23 The mean absolute bioavailability is 2.6%.24 Administration with a high-fat meal reduces AUC and Cmax values by 71% and 85%, respectively, of those in the fasting state, so patients should be advised to take aliskiren in the same manner each day with respect to meal times.25 Peak plasma concentrations are reached 1 to 2 hours after dosing,23,24 and steady state is reached after 5 to 8 days of once-daily administration.21

The main pathway of elimination for aliskiren is via biliary excretion as unmetabolized drug. Less than 1% of an orally administered dose is excreted in urine.21 Aliskiren is not metabolized by, and does not induce or inhibit, cytochrome P450 enzymes and shows no clinically relevant pharmacokinetic interactions with warfarin,17 lovastatin,26 atenolol,26 celecoxib,26 cimetidine,26 amlopidine,27 valsartan,27 hydrochlorothiazide (HCTZ),27 or ramipril.27 Coadministration of aliskiren with furosemide, a commonly used loop diuretic, reduced the AUC of furosemide by 28% and Cmax by 49%, but the clinical significance of this remains uncertain.28 The pharmacokinetics of aliskiren remain unaffected by ethnicity,24 age,29 gender,30 hepatic impairment,30 renal impairment,31 and diabetes.23

**Studies in Patients With Hypertension**

Phase II and III clinical trials have demonstrated the efficacy of once-daily administration of aliskiren in the treatment of patients with mild to moderate hypertension (diastolic blood pressure [DBP] ≥95 mm Hg and <110 mm Hg, either as monotherapy or in combination with diuretics, calcium channel blockers [CCBs], ACEIs, or ARBs), or as monotherapy in the treatment of severe hypertension (DBP ≥105 mm Hg and <120 mm Hg). Two trials that evaluated both monotherapy and combination therapy with aliskiren are discussed below in Combination Therapy.32,33 Table 1 provides details of the study design and the main findings of all the trials that are discussed.

**Monotherapy**

In a 4-week study, aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg once daily was compared with losartan 100 mg once a day.34 Dose-dependent reductions from baseline in daytime ambulatory SBP (ASBP) were obtained with all doses of aliskiren (P=0.0002 vs. baseline for all doses).34 The changes in daytime ASBP with the 3 highest doses of aliskiren were similar to those obtained with losartan 100 mg34 and the heart rate remained unaltered. All doses of aliskiren also led to significant dose-dependent decreases of PRA between -55% and -83% (P<0.0008 vs. baseline), whereas PRA increased by 110% with losartan.35
### TABLE 1

**Phase II and III Double-Blind Clinical Trials of Once-Daily Aliskiren Treatment in Patients With Mild to Moderate Hypertension**

<table>
<thead>
<tr>
<th>Study</th>
<th>Study Design (Number of Patients Randomized; Mean Age)</th>
<th>Treatments/ Duration*</th>
<th>Effects of Aliskiren on Primary Efficacy Variable (Statistical Significance)</th>
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<tr>
<td><strong>Monotherapy</strong></td>
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<tr>
<td>Stanton et al.34 (2003)</td>
<td>r, db, ac (226; 52 years)</td>
<td>Aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg Losartan 100 mg 4 weeks</td>
<td>Lower daytime ASBP ($P=0.0002$ vs. baseline; all doses) No significant difference between aliskiren 75 mg, 150 mg, and 300 mg and losartan 100 mg in mean change in daytime ASBP (all doses: $P=NS$) Reductions from baseline in: MSSBP/MSDBP (mm Hg) A37.5 mg: -4.3/-1.9 A75 mg: -4.1/-0.2 A150 mg: -10.0/-2.2 A300 mg: -11.8/-5.7 L100 mg: -11.4/-5.5</td>
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<td>Gradman et al.35 (2005)</td>
<td>r, db, pc, ac (652; 56 years)</td>
<td>Aliskiren 150 mg, 300 mg, or 600 mg Irbesartan 150 mg Placebo 8 weeks</td>
<td>Lower trough MSDBP ($P&lt;0.001$ vs. placebo, all doses) Aliskiren 150 mg=irbesartan 150 mg Reductions from baseline in: MSSBP/MSDBP (mm Hg) CR A150 mg: -11.6/-9.8 38% A300 mg: -15.8/-11.8 50% A600 mg: -15.7/-11.5 46% Ir150 mg: -12.5/-8.9 34% Placebo: -5.3/-6.3 21%</td>
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<tr>
<td>Oh et al.36 (2007)</td>
<td>r, db, pc, (672; 53 years)</td>
<td>Aliskiren 150 mg, 300 mg, or 600 mg Placebo 8 weeks</td>
<td>Lower MSDBP and MSSBP (all doses; $P&lt;0.0001$ vs. placebo) Reductions from baseline in MSSBP/MSDBP levels at 8 weeks, and in RR and CR at 2 weeks postwithdrawal: MSSBP/MSDBP (mm Hg) RR CR A150 mg: -13.0/-10.3 59% 36% A300 mg: -14.7/-11.1 63% 42% A600 mg: -15.8/-12.5 69% 46% Placebo: -3.8/-4.9 36% 20%</td>
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<tr>
<td>Strasser et al.37 (2007)</td>
<td>mc, r, db (183; 55.4 years)</td>
<td>Aliskiren 150 mg/300 mg Lisinopril 20 mg/40 mg (option to add HCTZ) 8 weeks</td>
<td>Mean reductions from baseline in: MSSBP/MSDBP (mm Hg) RR A300 mg: -20.0/-18.5 81.5% L40 mg: -22.3/-20.1 87.9%</td>
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In an 8-week placebo-controlled study, Gradman and colleagues randomized patients to once-daily aliskiren 150 mg, 300 mg, or 600 mg; irbesartan 150 mg; or placebo.35 All doses of aliskiren reduced mean sitting DBP (MSDBP) and mean sitting SBP (MSSBP, $P<0.001$ vs. placebo for both variables).35 Antihypertensive efficacy and control rates were comparable in the aliskiren 150 mg and irbesartan 150 mg arms but higher in the aliskiren 300 mg and aliskiren 600 mg arms.35

In another placebo-controlled study, Oh and colleagues evaluated the effects of treatment withdrawal after 8 weeks of monotherapy with aliskiren (150 mg, 300 mg, or 600 mg).36 All doses of aliskiren produced greater reductions in MSDBP and mean MSSBP than did placebo ($P<0.0001$, Figure 2).36 as well as daytime and nighttime mean ambulatory DBP (ADBp) and ASBP.36 The antihypertensive effect persisted for 2 weeks after drug withdrawal, with BP levels lower in the aliskiren groups than in the placebo group.36

In an 8-week, active-controlled, parallel-group study, Strasser and colleagues compared the tolerability (primary endpoint) and efficacy of aliskiren 150 mg once daily with lisinopril 20 mg once
**Table 1 (continued)—Phase II and III Double-Blind Clinical Trials of Once-Daily Aliskiren Treatment in Patients With Mild to Moderate Hypertension**

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<td>Combination Therapy</td>
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<td>Villamil et al. 32 (2007)†</td>
<td>r, db, pc (2,776; 55 years)</td>
<td>Aliskiren 75 mg, 150 mg, or 300 mg HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 75 mg + HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 150 mg + HCTZ 6.25 mg, 12.5 mg, or 25 mg Aliskiren 300 mg + HCTZ 12.5 mg or 25 mg Placebo 8 weeks</td>
<td>Lowers MSDBP (P=0.0002 vs. placebo, overall Dunnett’s test; all doses) Lowers MSDBP (all combinations, P&lt;0.0001 vs. placebo; most combinations, P&lt;0.05 vs. monotherapy with either component) Reductions from baseline in: MSSBP/MSDBP (mm Hg)</td>
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<tr>
<td>Jordan et al. 38 (2007)</td>
<td>r, db (560; 54.1 years)</td>
<td>HCTZ 25 mg 4 weeks Then, for nonresponders to HCTZ: Aliskiren 150 mg, irbesartan 150 mg, amlodipine 5 mg, or placebo, each plus HCTZ 25 mg 4 weeks Aliskiren 300 mg, irbesartan 300 mg, amlodipine 10 mg, or placebo, each plus HCTZ 25 mg 8 weeks</td>
<td>Aliskiren/HCTZ: Lowers MSDBP (P&lt;0.0001 vs. placebo/HCTZ); treatment difference of -4.0 mm Hg for MSDBP and -7.2 mm Hg for MSSBP Aliskiren/HCTZ=irbesartan/HCTZ=amlodipine/HCTZ (P=NS for group difference)</td>
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<tr>
<td>Drummond et al. 39 2007</td>
<td>r, sb then db, parallel-group</td>
<td>Amlodipine 5 mg (db, 4 weeks) Amlodipine 5 mg, amlodipine 10 mg, or aliskiren 150 mg plus amlodipine 5 mg (db, 6 weeks)</td>
<td>Reductions from baseline in: MSSBP/MSDBP (mm Hg)</td>
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<td>Reductions from baseline in:</td>
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<td>MSSBP/MSDBP (mm Hg)</td>
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<td>Uresin et al.</td>
<td>r, db (837; 59.8 years) Patients with type 1 or type 2 diabetes</td>
<td>Aliskiren 300 mg</td>
<td>A300 mg: -14.7/-11.3</td>
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<td>Ramipril 10 mg</td>
<td>R10 mg: -12.0/-10.7</td>
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<td>Aliskiren/ramipril 300/10 mg</td>
<td>A300 mg/R10 mg: -16.6/-12.8</td>
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<td>Pool et al.</td>
<td>r, db, pc (1,123; 56 years)</td>
<td>Aliskiren 75 mg, 150 mg, 300 mg</td>
<td>Aliskiren 300 mg; P&lt;0.001 vs. placebo</td>
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<td>Valsartan 80 mg, 160 mg, or 320 mg</td>
<td>Aliskiren = valsartan</td>
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<td>Aliskiren (150 mg, 300 mg, or 600 mg)</td>
<td>Lowers MSDBP (aliskiren 300 mg; P&lt;0.05 vs. placebo), aliskiren/valsartan = valsartan/HCTZ (P=NS for group difference)</td>
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<td>Aliskiren/valsartan 75 mg/80 mg, 150 mg/160 mg, 300mg/320 mg</td>
<td>reductions from baseline in:</td>
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<td>Valsartan/HCTZ 160 mg/12.5 mg</td>
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<tr>
<td>Oparil et al.</td>
<td>r, db, pc (1,797; 52.3 years)</td>
<td>Aliskiren 300 mg</td>
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<td>Valsartan 320 mg</td>
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<td>Aliskiren/valsartan 300 mg/320 mg</td>
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*All treatments were administered once daily.

†This trial evaluated the efficacy of aliskiren as monotherapy and in combination with HCTZ. A total of 2,776 patients were randomized to placebo (n=195); aliskiren 75 mg, 150 mg, 300 mg monotherapy (n=184, 185, 183); HCTZ 6.25 mg, 12.5 mg, 25 mg monotherapy (n=194, 188, 176); or combination aliskiren/HCTZ therapy (75 mg/6.25 mg, n=188; 75 mg/12.5 mg, n=193; 75 mg/25 mg, n=186; 150 mg/6.25 mg, n=176; 150 mg/12.5 mg, n=186; 150 mg/25 mg, n=188; 300 mg/12.5 mg, n=181; 300 mg/25 mg, n=173). The total number of patients given in the table includes the placebo group.

‡This trial evaluated the efficacy of aliskiren as monotherapy (primary objective) and in combination with valsartan (secondary objective). A total of 1,123 patients were randomized to placebo (n=177); aliskiren 75 mg, 150 mg, 300 mg monotherapy (n=179, 178, 175); valsartan 80 mg, 160 mg, 320 mg monotherapy (n=58, 59, 60); combination aliskiren/valsartan (75 mg/80 mg, n=80; 150 mg/160 mg, n=60; 300 mg/320 mg, n=58); or combination valsartan/HCTZ 160 mg/12.5 mg (active control; n=50). The total number of patients given in the table includes the placebo group.

A = aliskiren; ac = active controlled/active comparator; ASBP = ambulatory systolic blood pressure; CR = control rate; db = double blind; HCTZ = hydrochlorothiazide; Ir = irbesartan; L = losartan; MADBP = mean ambulatory diastolic pressure; MASBP = mean ambulatory systolic pressure; MMSBP = mean sitting systolic blood pressure; NS = not significant; pc = placebo controlled; R = ramipril; r = randomized; RR = responder rate; sb = single blind; SBP = systolic blood pressure; V = valsartan.
daily in the treatment of uncomplicated severe hypertension (MSDBP $\geq 105$ mm Hg and $< 120$ mm Hg). If additional BP control was required, the dose of aliskiren or lisinopril could be doubled, with the option of adding HCTZ 25 mg once daily to the regimen. Titration to the higher dose of the antihypertensive occurred in 74% and 66% of the aliskiren and lisinopril groups, respectively. Rates of add-on therapy with HCTZ were similar between groups (aliskiren 54%, lisinopril 45%). Similar reductions in MSDBP were observed in the aliskiren and lisinopril groups.

**Combination Therapy**

Although BP may be controlled in some patients with aliskiren monotherapy, there is greater likelihood that combination therapy will be required to control BP in the majority of patients.

Two trials have evaluated the antihypertensive efficacy of aliskiren in combination with HCTZ, and 4 trials have studied the efficacy of dual RAAS inhibition with aliskiren and a CCB, an ACEI, or an ARB.

Villamil and colleagues evaluated treatment with once-daily aliskiren 75 mg, 150 mg, or 300 mg; HCTZ 6.25 mg, 12.5 mg, or 25 mg; or their combinations (aliskiren/HCTZ: 75 mg/6.25 mg, 75 mg/12.5 mg, 75 mg/25 mg, 150 mg/6.25 mg, 150 mg/12.5 mg, 150 mg/25 mg, 300 mg/12.5 mg, and 300 mg/25 mg) in an 8-week placebo-controlled study. Aliskiren 150 mg and 300 mg, all doses of HCTZ, and all combinations were superior to placebo in reducing MSDBP levels ($P<0.0001$). All combinations, with the exception of aliskiren/HCTZ 150 mg/6.25 mg and 75 mg/12.5 mg, were also more effective than either monotherapy in reducing MSDBP and MSSBP levels ($P<0.05$). Responder rates (the proportion of patients with MSDBP $<90$ mm Hg or $\geq 10$ mm Hg decrease from baseline) were significantly higher with aliskiren 300 mg ($P=0.0005$), HCTZ 12.5 mg and 25 mg ($P<0.02$), and with all combinations ($P<0.05$) than with placebo. Responder rates for all combinations of aliskiren with HCTZ 25 mg and aliskiren/HCTZ 300 mg/12.5 mg were significantly higher than for their respective monotherapies ($P<0.05$). A higher proportion of subjects achieved BP control (MSSBP/MSDBP $<140/90$ mm Hg) with combination therapy than with aliskiren or HCTZ monotherapy. Combinations containing higher doses of 1 or both drugs (aliskiren 150 mg or 300 mg or HCTZ 25 mg) yielded significantly higher control rates compared with monotherapy.

Treatment with aliskiren resulted in a reduction of PRA of up to 65% from baseline. An increase in PRA of up to 72% with HCTZ was averted with the aliskiren/HCTZ combination. Plasma renin concentrations increased with aliskiren, with HCTZ 25 mg, and with all combinations of aliskiren with HCTZ. An additional effect of combination therapy was a reduction in the incidence of hypokalemia compared with the patients receiving HCTZ monotherapy.

The effects of adding aliskiren 150 mg once daily to amlodipine 5 mg once daily in patients whose hypertension was not fully controlled with CCB monotherapy was compared with continuing treatment with amlodipine 5 mg or 10 mg once daily alone. At 6 weeks, patients who were treated with aliskiren 150 mg plus amlodipine 5 mg had significant additional reductions in MSDBP and MSSBP compared with patients who were treated with amlodipine 5 mg alone (mean change, in mm Hg, -8.5 and -4.8 for MSDBP, respectively, and -11.0 and -5.0 for MSSBP, respectively; $P<0.0001$). The proportion of patients who achieved a MSSBP of $<90$ mm Hg and/or at least a 10 mm Hg reduction from baseline was significantly greater for those treated with aliskiren 150 mg plus amlodipine 5 mg compared with amlodipine 5 mg alone (64.2% and 45.2%, respectively, $P=0.0005$). In addition, a significantly greater proportion of patients who were treated with aliskiren 150 mg plus amlodipine 5 mg achieved BP levels of $<140$ mm Hg/90 mm Hg compared with amlodipine 5 mg alone (42.8% and 22.6%, respectively, $P<0.0001$). The additional efficacy resulting from adding aliskiren to amlodipine therapy was comparable with that achieved by doubling the dose of amlodipine to 10 mg, but combination therapy was not associated with the increased incidence of edema that was reported with high-dose amlodipine treatment.

The effect of 12 weeks of add-on therapy with once-daily aliskiren 300 mg, irbesartan 300 mg, or amlodipine 10 mg, or placebo was studied in hypertensive obese patients who were unresponsive to 4 weeks of initial treatment with HCTZ 25 mg. At 8 weeks, the aliskiren/HCTZ combination reduced MSDBP and MSSBP significantly more than did HCTZ (mean
treatment difference, -4.0 mm Hg and -7.2 mm Hg, respectively; 
P < 0.0001).38 Reductions in BP with the combination regimen of aliskiren and HCTZ were comparable with reductions with irbesartan and HCTZ or with amlodipine and HCTZ.38 Responder rates and BP control rates were higher in patients who were switched to the aliskiren/HCTZ combination than in those continuing on HCTZ alone (week 12 responder rate of 76% vs. 58% [P = 0.004] and control rate of 58% vs. 33% [P = 0.0001]).38

A phase III study evaluated the use of aliskiren alone or in combination with the ACEI ramipril for managing hypertension in patients with type 1 or 2 diabetes mellitus.39 Patients were randomized and forced-titrated to receive once-daily aliskiren 300 mg, ramipril 10 mg, or aliskiren/ramipril in combination 300 mg/10 mg for 8 weeks. Reductions in MSSBP and MSDBP with aliskiren, ramipril, and aliskiren/ramipril were 14.7 mm Hg/11.3 mm Hg, 12.0 mm Hg/10.7 mm Hg, and 16.6 mm Hg/12.8 mm Hg, respectively (Figure 3a). A reactive increase in PRA of 111% after ramipril treatment was countered by aliskiren in patients receiving combination therapy, leading to an overall 44% reduction in PRA. These findings suggest that aliskiren, by enhancing RAAS blockade when added to an ACEI, provides additional antihypertensive efficacy in patients with diabetes and hypertension.

Pool and colleagues33 studied the first-ever combination of a DRI and an ARB. In a primary safety and tolerability study, the once-daily antihypertensive efficacy of aliskiren alone (75 mg, 150 mg, and 300 mg), valsartan alone (80 mg, 160 mg, and 320 mg), aliskiren/valsartan combinations (75 mg/80 mg, 150 mg/160 mg, and 300 mg/320 mg), and valsartan/HCTZ (160 mg/12.5 mg) was evaluated.33 Aliskiren 300 mg once daily significantly reduced MSDBP and MSSBP levels compared with placebo (P < 0.0001). The magnitude of BP reduction was similar for aliskiren and valsartan across all dose ranges.33 Reductions in MSDBP and MSSBP levels were comparable for the aliskiren/valsartan combinations and their respective component monotherapies.33 Responder rates with aliskiren monotherapy (P < 0.05, aliskiren 75 mg and 150 mg; P < 0.001, aliskiren 300 mg) and for all aliskiren/valsartan combinations (P < 0.05, aliskiren 150 mg/valsartan 160 mg; P < 0.001, aliskiren 300 mg/valsartan 320 mg) were significantly greater than with placebo. Responder rates for most combinations did not differ from those for their respective monotherapies.33 The reduction in BP and the responder rates with the 2 highest dose combinations were similar to those with the valsartan/HCTZ combination. Rates of BP control did not differ between the aliskiren/valsartan combinations and their component monotherapies.33

A phase III study was conducted in 1,797 patients with mild to moderate hypertension who were randomized to once-daily aliskiren 150 mg, valsartan 160 mg, aliskiren/valsartan 150 mg/160 mg, or placebo for 4 weeks; followed by forced titration to double the dose for another 4 weeks.41 At both 4 and 8 weeks, reductions in MSDBP and MSSBP were significantly greater with all active treatments than with placebo (P < 0.0001) (Figure 3b). The aliskiren/valsartan combination was significantly more effective than either component alone in reducing MSDBP and MSSBP (P < 0.0001), 24-hour mean ADBP and

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**FIGURE 3a** Efficacy of Ramipril or Aliskiren Monotherapy, or Combination Therapy, at 8 Weeks in Patients with Mild to Moderate Hypertension

**FIGURE 3b** Efficacy of Valsartan or Aliskiren Monotherapy, or Combination Therapy, at 8 Weeks in Patients with Mild to Moderate Hypertension

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*P < 0.05 for superiority versus ramipril monotherapy.
*P < 0.05 for superiority versus aliskiren monotherapy.
*P < 0.05 for non-inferiority for aliskiren monotherapy versus ramipril monotherapy.
MSSBP = mean sitting systolic blood pressure, MSDBP = mean sitting diastolic blood pressure.
ASBP (P<0.0001), and daytime and nighttime mean ADBP. The aliskiren/valsartan combination provided significantly smoother BP control for a 24-hour period (smoothness index 1.2 vs. 0.9 with either aliskiren or valsartan alone; P<0.05), with a trough to peak ratio of 0.79. The combination thus provided additional BP reductions that were maintained for 24 hours.

**Safety and Tolerability**

A pooled safety analysis has been conducted on data from 7 randomized double-blind multicenter studies in 4,704 patients with mild to moderate hypertension (monotherapy, 2,598; combination therapy, 2,106) treated with aliskiren (75 mg to 600 mg) for 6 to 8 weeks. In 5 placebo-controlled trials, the overall incidence of adverse events after 52 to 55 days of treatment was similar for aliskiren monotherapy and placebo (39.8% vs. 40.2%, respectively). Rates of discontinuation due to adverse events were low and were reported as between 1.7% and 2.6% with aliskiren 75 mg to 600 mg, respectively, and 3.5% with placebo. Overall, the most frequently reported adverse events with aliskiren and placebo were headache (5.7% vs. 8.7%; P<0.01 vs. placebo), nasopharyngitis (4.4% vs. 5.8%; P=NS), diarrhea (2.6% vs. 1.2%; P<0.05 vs. placebo), dizziness (1.8% vs. 2.2%; P=NS), and fatigue (1.6% vs. 1.5%; P=NS). Increased rates of diarrhea were reported mainly for the 600 mg dose of aliskiren (9.5% vs. 1.2; P<0.0001) and not at lower doses. Consequently, the highest recommended dose for aliskiren is 300 mg once daily because of a relatively flat BP response and increased incidence of adverse events with doses higher than 300 mg a day.

In the treatment of patients with severe hypertension, both aliskiren and lisinopril were well tolerated and no differences were noted between groups in the proportion of patients who reported an adverse event, the type of adverse event, or the rate of discontinuation due to an adverse event.

The addition of aliskiren 150 mg or 300 mg to valsartan, amlopidine, HCTZ, or ramipril therapy did not alter the frequency or type of adverse events compared with their respective monotherapies. In fact, some adverse effects may be avoided with aliskiren therapy when used in combination with other antihypertensive agents. The addition of aliskiren to ramipril therapy reduced the rate of cough (1.8%) compared with ramipril alone (4.7%); in patients receiving aliskiren 150 mg as add-on therapy to amlodipine 5 mg, the rate of edema was reduced to 2.1% compared with a rate of 11.2% with amlodipine 10 mg.

**Place in Therapy of Pharmacologic Direct Renin Inhibition**

Control of hypertension to below-target BP levels is crucial for reducing rates of adverse cardiovascular events. The National Health and Nutrition Examination Survey (1999–2004) showed an overall prevalence of hypertension (BP ≥140/90 mm Hg or use of antihypertensive medication) between 2003 and 2004 of 29.3%. For the same period, rates of BP control were 33%, 64%, and 33%, respectively, for all patients with hypertension, treated patients, and treated patients with diabetes, indicating that the treatment of hypertension remains suboptimal.

Aliskiren administered once daily provides another effective and safe option for the treatment of hypertension as monotherapy. However, approximately 70% of patients with hypertension, particularly high-risk patients with lower BP goals and patients whose BP exceeds SBP or DBP target values by ≥20 mm Hg or ≥10 mm Hg, respectively, will require combination therapy to achieve BP control. Aliskiren, which acts at the rate-limiting step in the RAAS pathway, is a logical component of combination therapy, because it enhances RAAS suppression and attenuates the reactive increase in PRA when added to other classes of antihypertensive agents. Combining agents (such as diuretics, ACEIs, and ARBs) that increase PRA with an agent (such as aliskiren) that neutralizes this activity appears to be a rational approach for optimizing BP control. Combined RAAS inhibition may allow the use of lower doses of each component to achieve more effective and durable RAAS suppression with potentially fewer adverse effects. Patients with severe hypertension, especially those with renal failure, may theoretically benefit from even more intensive RAAS inhibition through the blockade of additional steps of the pathway, but this approach needs further exploration.

Clinical studies have provided convincing evidence that aliskiren controls RAAS activity, reduces BP significantly, and displays good tolerability. Additionally, as with other RAAS inhibitors, RAAS blockade via direct renin inhibition has the potential to provide organ protection independent of BP reductions. A robust clinical development program is ongoing to evaluate the renoprotective and cardioprotective effects of aliskiren in which surrogate markers and major clinical outcomes will be analyzed as primary endpoints (Table 3). What may be on the horizon is the use of dual RAAS blockade, which includes

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>Potential Therapeutic Role of Direct Renin Inhibitors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monotherapy for hypertension</td>
<td></td>
</tr>
<tr>
<td>Component of combination therapy for hypertension, with a diuretic, a CCB, an ACEI, and/or an ARB</td>
<td></td>
</tr>
<tr>
<td>Alternative to ACEIs in patients with diabetic nephropathy or cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Alternative to ACEIs in patients with diabetic nephropathy or cardiovascular disease</td>
<td></td>
</tr>
<tr>
<td>Use in patients with diabetic nephropathy or in African American hypertensive patients, in whom intrarenal angiotensin II formation occurs via ACE or non–ACE-dependent pathways</td>
<td></td>
</tr>
</tbody>
</table>

ACE = angiotensin-converting enzyme; ACEI = ACE inhibitor; ARB = angiotensin receptor blocker; CCB = calcium channel blocker.
a DRI, as several trials will investigate whether combination therapy provides enhanced protection and improved outcomes over monotherapy.

**Summary and Conclusions**

The DRI aliskiren is a new orally available, highly specific, and effective inhibitor of RAAS activity. Both as monotherapy and in combination with a thiazide diuretic, a CCB, an ACEI, or an ARB, aliskiren reduces BP in patients with mild to moderate hypertension. Aliskiren has antihypertensive efficacy comparable with that of these other classes of antihypertensive agents, and counters the reactive increase in PRA when used in combination with these agents. In the treatment of patients with severe hypertension, aliskiren is comparable with lisinopril. Aliskiren has a tolerability profile similar to that of placebo and ARBs and is well tolerated when used in combination with other agents. Further studies will explore its potential as monotherapy or in combination with other antihypertensives, and for uses beyond BP reduction, such as renoprotection and cardioprotection.

**REFERENCES**


**TABLE 3** Aliskiren Clinical Development Program: Evaluating Surrogate Markers and Clinical Outcomes

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>N</th>
<th>Objective of Trial</th>
<th>Length of Trial</th>
<th>Primary Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>AGELESS</td>
<td>912</td>
<td>Compare the efficacy of aliskiren versus ramipril in lowering SBP in patients ≥65 years of age with systolic hypertension</td>
<td>36 weeks</td>
<td>Reduction from baseline in MSSBP</td>
</tr>
<tr>
<td>AVOID*</td>
<td>754</td>
<td>Determine the effect of adding aliskiren or placebo to background losartan treatment on proteinuria in diabetic patients</td>
<td>24 weeks</td>
<td>Percent reduction in UACR</td>
</tr>
<tr>
<td>ALLAY</td>
<td>480</td>
<td>Determine the effect of aliskiren alone or in combination with losartan on the regression of left ventricular mass in overweight hypertensive patients</td>
<td>34 weeks</td>
<td>Change in left ventricular mass</td>
</tr>
<tr>
<td>AVANT GARDE (TIMI 43)</td>
<td>1,152</td>
<td>Determine whether aliskiren, valsartan, or combination therapy will improve ventricular remodeling in high-risk patients who have been stabilized following ACS</td>
<td>9 weeks</td>
<td>Reduction of NT-proBNP from baseline</td>
</tr>
<tr>
<td>ASPIRE</td>
<td>860</td>
<td>Determine whether aliskiren attenuates pathological left ventricular remodeling in high-risk post-MI patients when added to standard therapy</td>
<td>36 weeks</td>
<td>Change in LVESV by echo</td>
</tr>
<tr>
<td>ALOFT*</td>
<td>320</td>
<td>Determine the safety and tolerability of adding aliskiren or placebo to standard heart failure treatment in patients with chronic heart failure</td>
<td>12 weeks</td>
<td>Tolerability and safety of aliskiren, change in BNP</td>
</tr>
<tr>
<td>ALTITUDE</td>
<td>8,400</td>
<td>Determine whether aliskiren with conventional treatment reduces cardiovascular and renal morbidity and mortality in high-risk patients with type 2 diabetes</td>
<td>4 years</td>
<td>Time to diabetic complications (secondary prevention trial)</td>
</tr>
</tbody>
</table>

*Study completed, results pending.
ACS = acute coronary syndrome; BNP = B-type natriuretic peptide; BP = blood pressure; echo = echocardiography; LVESV = left ventricular end systolic volume; MI = myocardial infarction; MSSBP = mean sitting systolic blood pressure; NT-proBNP = N-terminal proB-type natriuretic peptide; SBP = systolic blood pressure; UACR = urinary albumin/creatinine ratio.

**DISCLOSURES**

The author discloses no potential bias or conflict of interest relating to this article.
Direct Renin Inhibition: Focus on Aliskiren


importance of blood pressure control over a 24-hour period

William B. White, MD

ABSTRACT
BACKGROUND: The circadian rhythm of blood pressure (BP) is associated with a high span during the awake period and a low span during the sleep period. Of interest is that cardiovascular (CV) events occur more frequently in the early morning period, the time when BP and heart rate rise steeply.

OBJECTIVE: To provide an overview of circadian BP and its correlation with adverse clinical outcomes and to discuss strategies for optimizing BP control over 24 hours.

SUMMARY: Patients who have an excessive morning surge in BP and those who lack the normal nocturnal BP fall (nondippers) have been shown to have an excessive incidence of strokes, heart failure, and other CV events. While there are numerous pathophysiologic mechanisms underlying abnormalities in the 24-hour BP profile, including abnormalities in sympathetic nervous system activity, salt and volume balance, and activation of the renin-angiotensin aldosterone system, for many patients the mechanisms remain unclear. Nevertheless, several of these known abnormalities can be modified by clinical interventions, including proper timing of antihypertensive drug therapy and use of classes of antihypertensives for which a substrate exists to induce a pharmacologic effect. It is particularly important to use therapies that will provide control throughout a 24-hour dosing interval.

CONCLUSION: While interventional strategies have not yet been shown to alter clinical outcomes, it is important to be cognizant of their physiologic basis and take them into consideration when making decisions regarding appropriate antihypertensive therapy.

KEYWORDS: Antihypertensive agents; Blood pressure monitoring, ambulatory; Circadian rhythm; Hypertension

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Arterial blood pressure (BP) has a daily variation characterized by substantial reductions during sleep, a rapid rise upon awakening, and increased variability during the awake period in ambulant normal subjects and hypertensive patients. The patterns of the circadian variation of BP were first established by Millar-Craig et al. using continuous intra-arterial monitoring.1 This novel study showed that BP was highest in early to mid-morning and then fell progressively throughout the day. In addition, the study showed that BP was lowest at night (nocturnal dip) but rose before awakening (morning surge).1 These findings demonstrated the potential importance of the circadian rhythm of BP in the management of hypertension, a factor that has been acknowledged since the mid-1960s2 but did not become part of the clinical hypertension domain until the 21st century.

Following the descriptive findings related to BP variability, researchers began to evaluate the physiologic characteristics that produce the BP rise during the early morning and the substantial BP reductions during sleep. The timing and amplitude of the natural rhythm of BP is influenced by intrinsic factors, such as neurohormonal regulation, but the effects of extrinsic factors, such as physical activity and dietary sodium, may be of greater significance. Additionally, behavioral influences, such as mental activity and emotional state,3 and lifestyle factors, such as smoking cigarettes and drinking alcohol, can also affect the natural rhythm of BP.4

Excessive BP levels during the course of a 24-hour period plausibly contribute to adverse cardiac outcomes, especially when the relationship between the early morning peak in cardiovascular (CV) events with the postawakening morning surge in BP is considered. Increases in the incidence of sudden death, nonfatal myocardial infarction (MI), unstable angina, and stroke in the morning indicate that a patient's physiologic status may play an important role in the onset of CV events.5 Intuitively, it appears that 24-hour control of BP should have an important clinical impact on the early morning increases in CV events.

Early Morning BP Surge

Blood pressure rises sharply in the morning in response to the activation of the sympathetic nervous system when one arises.6-10 This early morning surge is associated with other important hemodynamic and neurohormonal changes, including increases in heart rate, vascular tone and blood viscosity, and decreases in vagal activity.6,11-13 The activity of the sympathetic nervous system is quiescent during sleep, whereas awakening selectively increases epinephrine levels.8 Subsequent increases in BP and
heart rate are controlled by direct sympathetic neural input into the heart and vasculature in response to increases in activity and upright posture, rather than by an endogenous surge of plasma catecholamines.9

Nondippers—The Loss of the Nocturnal Decline in BP

The normal circadian rhythm of BP has a nocturnal decrease of 15% to 25% in BP compared with awake values. However, in 25% to 40% of patients with hypertension, a “nondipper” pattern is present. Since the 1980s, the nondipping pattern has been arbitrarily defined as when the BP reduction during sleep is less than 10% compared with BP while awake. Blunting of the nocturnal decrease in BP in patients with hypertension occurs for a variety of reasons, both in patients with essential hypertension and with secondary forms of hypertension. Clinical studies in patients with hypertension have found that a blunted nocturnal BP decrease occurs when there is an increase in adrenergic activity and a decrease in vagal activity during sleep.14-16 In some patients, there is even a significant increase in BP during sleep (and in the supine position), which leads to a “reverse dippers” or “riser” pattern—a finding that is associated with substantial cardiac morbidity.17 Japanese investigators also reported that a profile in which the nocturnal BP is > 20% less than the awake BP has been associated with increased white matter ischemic lesions in the brain.17 Thus, knowledge of the circadian profile of an individual patient (through 24-hour ambulatory BP monitoring) with hypertension may aid in identifying increased risk.

Clinical Implications of the Circadian Variability of BP

As stated above, the early morning BP surge is associated with an increase in the incidence of CV events, including stroke and MI.18-20 Pooled analyses of event data indicate that there is a 40% higher relative risk of acute MI, a 29% increased risk of sudden cardiac death, and a 49% higher relative risk of stroke between 6 a.m. and noon than during the rest of the day.19,20 In actual terms, this corresponds to approximately 1 in 11 MIs, 1 in 15 sudden deaths, and 1 in 8 strokes occurring in the early morning period when BP, heart rate, and the rate-pressure product increases most steeply.19,20

For many years, epidemiologic studies have shown that the timing of onset of CV events strongly parallels the circadian rhythm of BP. In an interesting analysis in Japan, Kario et al.21 demonstrated a 2.7-fold increase in the risk of a future stroke in older patients with hypertension who were in the top decile of the morning BP surge (> 34 mm Hg; Table). For each 10 mm Hg increase in the morning BP surge, there was a 24% increase in stroke risk (P=0.004). While it would be of great interest to perform a clinical trial devised to address the relationship between a reduction in the early morning BP and a possible reduction in CV events, this is unlikely to occur because of the enormous sample size required and the long period of follow-up that would be necessary.22

Loss of the nocturnal decline in BP has been associated with increased risk of cardiac, kidney, and vascular target-organ injury compared with patients whose decline in BP at night is normal.23 and can be independent of the clinic and 24-hour mean BP values.24,25 Additionally, patients with hypertension who exhibit a nocturnal BP increase compared with daytime BP (risers) have the worst prognosis for stroke and cardiac events.26-28 However, there is also some evidence that patients with marked nocturnal BP declines (extreme dippers) are at risk of lacunar strokes and silent myocardial ischemia.26

Clinical Factors That Affect the Circadian Rhythm of BP

Physical activity is the major determinant of BP rise during the day.25,27 As mentioned earlier, the influence of sleep and wakefulness on BP is mediated through cyclic variations of the autonomic nervous system. In the early morning, BP naturally rises sharply in response to activation of the sympathetic nervous system upon arousal.6,8 Sleep deprivation increases sympathetic activity and may disrupt circadian rhythmicity. The circadian BP rhythm—in particular, the nocturnal decline in BP—can be affected by sodium intake in patients with hypertension.28 In fact, Uzu et al.29 showed that a nondipper nocturnal BP pattern can be converted to a dipper pattern in response to salt restriction in salt-sensitive patients with hypertension.

The renin-angiotensin aldosterone system (RAAS), mainly via production of angiotensin II (Ang II), is a key regulator of BP. Renin secretion is activated in the early morning before arousal as a result of sympathetic neuronal activation.30,31 In addition, both renin and aldosterone demonstrate significant circadian patterns in both normotensive and hypertensive individuals.31 with peak values detected early morning, then falling to their lowest point in late evening (Figure 1).32,33 A similar pattern has been observed for Ang II.30

### TABLE  Correlation Between Morning Blood Pressure Surge and Cardiovascular Events

<table>
<thead>
<tr>
<th></th>
<th>AM Surge (n = 53)</th>
<th>Non-Surge (n = 466)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Silent ischemic infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>70†</td>
<td>48</td>
</tr>
<tr>
<td>Average number</td>
<td>2.3 ± 2.6</td>
<td>13 ± 2.6</td>
</tr>
<tr>
<td>Multiple ischemic infarcts</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prevalence (%)</td>
<td>57†</td>
<td>33</td>
</tr>
<tr>
<td>Ischemic strokes (%)</td>
<td>19.0†</td>
<td>7.3</td>
</tr>
</tbody>
</table>

*P<0.001
†P<0.01.
Importance of Blood Pressure Control Over a 24-Hour Period

The morning surge in hypertension, which is associated with increases in stroke events in older patients with hypertension, is mediated in part by the sympathetic nervous system and through the RAAS. A loss of decline in nocturnal BP is probably mediated through both RAAS activation and volume excess. These findings have led to the evaluation of the potential for blockade of the systems that lead to these abnormal profiles in circadian BP. Notwithstanding, the pharmacodynamics of antihypertensive drugs must play a role here, since control of nocturnal BP and BP during the early morning period will require that agents either have a reasonably long half-life or else be administered twice daily.

Modification of the timing of drug administration can alter the circadian BP profile. In fact, modification of the time of drug administration for many of the antihypertensive agents may affect the extent of 24-hour BP control and modify the circadian rhythm, including the conversion from a nondipper to a dipper profile.34,35 These effects are most uniform with blockers of the RAAS, which typically will have a substantial effect on nocturnal BP when they are administered at night while also maintaining adequate control during the daytime.35

Drugs with long duration of action may be particularly useful for blunting the early morning surge in BP. White et al.36 evaluated the effects of telmisartan alone and in combination with hydrochlorothiazide (HCTZ) on 24-hour BP, including the early morning period (Figure 2). Patients with hypertension received telmisartan 40 mg per day. If BP remained uncontrolled after 2 weeks, the dose was increased to 80 mg per day; if BP was still uncontrolled after another 4 weeks, HCTZ 12.5 mg was added and continued for a final 4-week period. Twenty-four-hour ambulatory BP monitoring was performed at baseline and at the end of the treatment period in 1,628 patients. Telmisartan alone and in combination with HCTZ produced significant reductions in both daytime and nighttime mean BP. The effect was more dramatic in patients with early morning surges, as shown in Figure 2.

Since most analyses have shown that renin activity begins to rise during the night and peaks in the morning period (Figure 1), another pharmacologic approach to consider in the treatment of nocturnal and early morning hypertension would be a long-acting direct renin inhibitor (DRI). Stanton et al.37 have provided data supporting the concept that aliskiren, a DRI with a plasma half-life of approximately 25-30 hours, might provide efficacy in patients with abnormal circadian BP variability, particularly in the high-risk populations discussed here (Figure 3). In this early trial of the agent, intermediate and higher doses (150 mg and 300 mg) were assessed in a trial compared with high-dose losartan (100 mg daily) and placebo.
As noted, the reductions in nocturnal BP were substantial with aliskiren 300 mg daily (Figure 3) and occurred when renin secretion begins to peak. Oh et al. also reported the results of a trial in 216 patients with hypertension who were randomized to 8 weeks’ treatment with aliskiren 150 mg, 300 mg, or 600 mg once daily or with placebo. Aliskiren significantly reduced mean 24-hour ambulatory BP compared with placebo at all dosages. Consistent with its long pharmacologic half-life, aliskiren effectively lowered BP throughout the 24-hour dosing period, persisting overnight and throughout the high-risk period in the early hours of the morning. Furthermore, no rebound effect was seen in this study after withdrawal of aliskiren.

Perhaps the most important clinical benefit of ambulatory BP monitoring in patients with hypertension and comorbid illnesses is to confirm that these patients have adequate control over a 24-hour period (Figure 4). Additionally, while there are potential benefits of conversion of a nondipping pattern to a dipping pattern, the possibility remains that excessive BP reduction at night might be associated with orthostatic hypotension or excessive hypotension during sleep in certain individuals, particularly the elderly. Ideally, changes in drug administration time could be followed by repeat ambulatory BP monitoring to assess the effects of therapy and rule out an excessive BP fall during the night. However, this practice is not likely to be covered by most third-party insurance payers. An alternative is to perform 1 ambulatory BP study that is paired with frequent self- or home BP measurement in order to obtain a frame of reference for future patient assessment using home BP measurements.

Conclusions

The importance of adequate BP control over the entire 24-hour period, particularly the early morning hours, cannot be overemphasized. Several of the pathophysiologic systems responsible for the circadian BP variability, especially salt balance and the RAAS, can be modulated by appropriate, long-acting therapy, and such interventions may result in improved clinical outcomes.

The confirmation that correcting 24-hour BP profiles results in clinical outcomes benefit will require clinical trials that specifically test this hypothesis. One example would be studies in which patients are randomized to different drug-dosing schedules with efficacy confirmed by sequential ambulatory BP monitoring versus standard office measurements. These outcomes could be initially composed of surrogate measures, such as changes in left ventricular hypertrophy, vascular structure and function, ischemic brain lesions, or proteinuria. If they suggest benefits, then large-scale studies with conventional CV endpoints would be justified and helpful for determining precisely when to use ambulatory BP monitoring in the clinical management of patients with hypertension.

DISCLOSURES

The author has served as a consultant to Boehringer and Novartis.

REFERENCES

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