Published in final edited form as:
Life Sci. 2010 February 27; 86(9-10): 289–299. doi:10.1016/j.lfs.2009.11.020.

Addressing the theoretical and clinical advantages of combination therapy with inhibitors of the renin-angiotensin-aldosterone system: antihypertensive effects and benefits beyond BP control

Carlos M. Ferrario, MD

Abstract

Aims—This article reviews the importance of the renin-angiotensin-aldosterone system (RAAS) in the cardiometabolic continuum; presents the pros and cons of dual RAAS blockade with angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs); and examines the theoretical and practical benefits supporting the use of direct renin inhibitors (DRIs) in combination with ACEIs or ARBs.

Main methods—The author reviewed the literature for key publications related to the biochemical physiology of the RAAS and the pharmacodynamic effects of ACEIs, ARBs, and DRIs, with a particular focus on dual RAAS blockade with these drug classes.

Key findings—Although ACEI/ARB combination therapy produces modest improvement in BP, it has not resulted in the major improvements predicted given the importance of the RAAS across the cardiorenal disease continuum. This may reflect the fact that RAAS blockade with ACEIs and/or ARBs leads to exacerbated renin release through loss of negative-feedback inhibition, as well as ACE/aldosterone escape through RAAS and non–RAAS-mediated mechanisms. Plasma renin activity (PRA) is an independent predictor of morbidity and mortality, even for patients receiving ACEIs and ARBs. When used alone or in combination with ACEIs and ARBs, the DRI aliskiren effectively reduces PRA. Reductions in BP are greater with these combinations, relative to the individual components alone.

Significance—It is possible that aliskiren plus either an ACEI or ARB may provide greater RAAS blockade than monotherapy with ACEIs or ARBs, and lead to additive improvement in BP and clinically important outcomes.

Keywords

hypertension; renin-angiotensin-aldosterone system (RAAS) inhibition; angiotensin II; angiotensin-(1–7); combination therapy; aliskiren; prorenin/renin receptor

Address for Correspondence: Carlos M. Ferrario, MD, Professor, Hypertension and Vascular Research Center, Wake Forest University School of Medicine, Medical Center Boulevard, Winston-Salem, NC 27157-1032, Phone: 336-716-9266, Fax: 336-716-6644, cferrari@wfubmc.edu.

Introduction

The renin-angiotensin-aldosterone system (RAAS) plays a key role in the pathophysiology and development of hypertension, atherosclerosis, congestive heart failure (CHF), type 2 diabetes mellitus (DM), and renal disease (Weir and Dzau 1999). Specifically, angiotensin II (Ang II) is a major effector of vasoconstriction, cell growth, sodium and water retention, and sympathetic activation; it appears to promote endothelial dysfunction, inflammation, oxidative stress, insulin resistance, and reduced β-cell responsiveness. The close relationship between the RAAS and hypertension has led to compelling indications to block the formation or activity of Ang II through use of angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) (Table 1) (Chobanian et al. 2003; Mancia et al. 2007).

Although ACEIs and ARBs are among the most effective and safe antihypertensives, when used as monotherapy they control blood pressure (BP) effectively (<140/90 mm Hg in uncomplicated patients, <130/80 mm Hg in diabetics/complicated patients) in only 40% to 60% of patients with mild-to-moderate hypertension (Ibrahim 2006). Furthermore, Weber and Giles (Weber and Giles 2006) noted that ACEIs and ARBs have not produced the major reductions in clinical outcomes that were predicted based on the centrality of the RAAS in the pathophysiology of cardiorenal disease. They speculate that additional novel methods of RAAS blockade may yield better control of hypertension and improved organ protection. One such approach explored combination therapy with ACEIs and ARBs. Although some studies have shown this combination to provide modest benefits beyond monotherapy with either class of agent, other studies, and particularly ONTARGET (Yusuf et al. 2008; Mann et al. 2008), have cast doubt on the long-term safety and effectiveness of this strategy.

Direct renin inhibitors (DRIs), when used in combination with ACEIs or ARBs, may provide more complete RAAS blockade, greater BP control, and better target-organ protection. This article reviews the importance of the RAAS in the cardiometabolic continuum, presents the pros and cons of dual RAAS blockade with ACEIs and ARBs, and examines the theoretical and practical benefits supporting the use of DRIs in combination with ACEIs or ARBs.

The Biochemical Physiology of the RAAS

Figure 1 illustrates the current biochemical pathways involved in the production of biologically active angiotensins. In the RAAS, enzymatically inactive prorenin, primarily synthesized in the kidney and accounting for 70% to 90% of the renin in the circulation, is proteolytically converted to enzymatically active renin in response to renal baroreceptor signaling, sodium concentration changes, sympathetic nerve stimulation, and negative feedback by Ang II on juxtaglomerular cells (Atlas 2007). Angiotensinogen, an α_2-globulin produced mainly in the liver, is cleaved by renin to generate angiotensin 1 (Ang I; Ang[1–10]). Plasma renin activity (PRA) clinically provides a measure of the endogenous rate of Ang I production. This assay appears to be an important predictor of adverse cardiovascular outcomes and death across the cardiovascular continuum. For example, untreated hypertensive patients with high PRA (vs low) had a 2.4-fold higher risk for cardiovascular disease (Alderman et al. 1997), and patients with severe coronary artery disease and high PRA (vs low) had a significantly greater risk for CHF hospitalization and all-cause death (Bair et al. 2009).

Ang I is then metabolized by membrane-bound angiotensin-converting enzyme (ACE), found in vascular endothelial, neuroepithelial, and renal proximal tubule cells to produce biologically active Ang II (Ang[1–8]). Although the ACE pathway is important for Ang II generation, Ang II can be formed by non-ACE pathways in various tissues via chymase, cathepsin G, and kallikrein-like enzymes. In a study of healthy volunteers, although virtually all Ang II produced in the kidneys was renin dependent, >40% of circulating Ang II was derived from non-ACE pathways (Hollenberg et al. 1998). Ihara and colleagues (Ihara et al. 1999) reported that >80%

of Ang II in normal and atherosclerotic aortas was derived from chymase-dependent pathways. This suggests that abnormal activation of local tissue RAAS through non-ACE pathways may have more of a role than originally thought and be clinically significant.

The pressor action of Ang II is chiefly the result of Ang II binding to the Ang II type 1 receptor (AT_1-R) in the heart, vasculature, kidneys, adrenal glands, brain, and adipocytes. Formation of the Ang II:AT_1-R complex results in the negative-feedback inhibition of renin release and the production and release of aldosterone from the adrenal cortex. The Ang II:AT_1-R complex also is responsible for receptor-mediated increases in contractile force, hypertrophy, and fibrosis in the heart; increases in vascular tone; constriction of renal arterioles; and increased reabsorption of sodium in the proximal segments of kidney nephrons. In contrast, the interaction of Ang II with the Ang II type 2 receptor (AT_2-R), which normally is present only in low levels in adults, has been hypothesized to provide some degree of cardiorenal protection through receptor-mediated vasodilatation, nitric-oxide (NO) release, kinin-mediated antiproliferative and pro-apoptotic effects in the heart and vasculature, and beneficial effects on sodium resorption by the proximal tubules in the kidney (Lifton et al. 2001). However, data from a meta-analysis have suggested that treatment with ARBs may significantly increase the risk for myocardial infarction (MI) by 8%, and that this “ARB-MI paradox” may be due in part to ARB-mediated upregulation and stimulation of the AT_2-R, resulting in growth promotion, fibrosis, hypertrophy, and atherogenic and proinflammatory effects (Strauss and Hall 2006). In contrast to AT_1-R blockade with ARBs, ACE inhibitors block the conversion of Ang I to Ang II. Because of this, ACE inhibitors are not associated with the increased levels of Ang II required for AT_2-R activation. However, due to the non-discriminating nature of ACE in terms of substrates, its inhibition increases the level of several ACE substrates, including bradykinin, substance P, and enkephalins. Of note, increases in bradykinin and substance P are thought to be responsible for ACE inhibitor-induced cough and angioedema (Dicpinigaitis 2006).

Work from our laboratory first identified angiotensin-(1–7) (Ang[1–7]) as an active product of the RAAS and demonstrated that this peptide functions to oppose the endogenous action of tissue-borne Ang II (Ferrario et al. 1998; Ferrario et al. 1997; Ferrario et al. 2005b; Schiavone et al. 1988). In initial studies, the generation of Ang[1–7] was identified as a product of the metabolism of Ang I via the action of tissue endopeptidases, particularly vascular-endothelium–derived neprilysin (Santos et al. 1992; Welches et al. 1993; Yamamoto et al. 1992). Subsequently, Ang[1–7] is degraded to inactive fragments by ACE. Ang[1–7] provides cardiorenal protection (eg, vasodilation, antiproliferation, anti-fibrosis, and natriuresis) through binding to the Mas proto-oncogene receptor (Santos et al. 2003). Inhibition of the MAP kinase-phosphatase pathway via the Mas receptor appears to be the primary mechanism responsible for the inhibitory effects of Ang[1–7] on cardiac and vascular remodeling (Gallagher et al. 2008; Tallant et al. 2005).

The complexity of the biochemical cascade accounting for the biological actions of the RAAS in the control of cardiovascular function is underscored by additional sequential cleavage of Ang II into the equally potent aldosterone secretagogue angiotensin III (Ang III; Ang[2–8]) and to two other active angiotensins: angiotensin IV (Ang IV; Ang[3–8]) and Ang[1–7]. Although the production of Ang III and Ang IV is highest in the brain and kidney, their direct role in the maintenance of high BP in hypertension has not been demonstrated. In animal models, the Ang IV:Ang II type 4 receptor (AT_4-R) complex improved endothelial function and provided protection against acute cerebral ischemia (Faure et al. 2008; Vinh et al. 2008). On the other hand, recent research has buttressed the importance of the opposing role of Ang-(1–7) in physiology and pathology through the characterization of an ACE homologue (ACE2) that acts as a mono carboxypeptidase cleaving Ang II into Ang(1–7) (Vickers et al. 2002). In contrast to ACE, ACE2 is not inhibited by ACEIs such as captopril or lisinopril, nor does it share the same catalytic properties. ACE2 exhibits the highest efficiency (kcat/km) among Ang

(1–7)-forming enzymes and a 500-fold greater kcat/km for Ang II compared with Ang I. Similar to ACE, ACE2 exists in both soluble and membrane-associated forms with high expression in the kidney, heart, brain and testes. In this regard, ACE2 contains a single catalytic site that corresponds to the C-terminal domain of somatic ACE (Turner et al. 2002; Vickers et al. 2002). A critical step in the further understanding of ACE2 role in cardiovascular function was achieved by our demonstration that ACE2 maps to a defined quantitative trait locus (QTL) on the X chromosome in three different rat models of hypertension and that, in three salt-sensitive hypertensive rat strains, ACE2 messenger RNA and protein expression are markedly reduced (Crackower et al. 2002).

Although angiotensinogen has remained the undisputed substrate at which renin selectively cleaves the Leu^{10}-Leu^{11} bond of the glycoprotein to generate Ang I, recent studies revealed the existence of a peptide that derived fromangiotensinogen contains the first 12 amino acids within the N-terminus of the substrate. Nagata et al. (Nagata et al. 2006) showed the endogenous presence of the peptide, now termed angiotensin-(1–12) (Ang[1–12]), in a Japanese-derived strain of Wistar rats and its ability to serve as a substrate for the in vitro and in vivo generation of Ang II. The ability of Ang[1–12] to act as an endogenous substrate for the production of Ang II was documented by showing that the vasoconstrictor effects of Ang [1–12] in the isolated aorta and the systemic circulation were prevented by previous blockade with either captopril or the AT_1 receptor antagonist candesartan (Nagata et al. 2006). Moreover, studies from our laboratory showed increased content of Ang[1–12] in cardiac myocytes from spontaneously hypertensive rats (Jessup et al. 2008) and that generation of Ang II from Ang [1–12] is regulated by a non-renin enzyme (Ferrario et al. 2009; Trask et al. 2008). In a more recent study, Prosser et al. (Prosser et al. 2009) showed that cardiac chymase converted Ang [1–12] into Ang II. These findings may explain the observation that aliskiren does not produce complete suppression of plasma concentrations of Ang II and that the combination of aliskiren with losartan or valsartan induces greater blood-pressure responses and further target-organ protection (Chrysant et al. 2008; Dechend et al. 2007; Kamoi 2008; Legrand et al. 2008; Nussberger et al. 2002; Oparil et al. 2007a; Oparil et al. 2007b; Pool et al. 2007; Yarows et al. 2008). The enhanced antihypertensive response induced by the combination of aliskiren with an Ang II receptor antagonist suggests that Ang[1–12] may act as an alternate pathway for the generation of Ang I and Ang II during blockade of renin. Evidence of this possibility has been obtained from bilateral nephrectomized rats in which loss of renal renin was associated with increases in cardiac levels of Ang[1–12] and no changes in tissue levels of Ang II (Ferrario et al. 2009).

Although not confirmed in humans, additional studies in animals indicate that activation of the RAAS may occur via pathways that are Ang II–independent and therefore not subject to inhibition by ACEIs and ARBs. For example, two studies showed that there is a receptor in the heart, brain, kidney, and liver that binds both prorenin and renin, resulting in a 4-fold increase in the activity of renin as well as non-proteolytic activation of prorenin, presumably through unmasking of the catalytic site (Nguyen et al. 2002; Ichihara et al. 2004). In vitro, binding of renin to this receptor increased mitogen-activated protein (MAP) kinases, which were not suppressed by addition of an ACEI or ARB (Nguyen et al. 2002). MAP-kinase increases are implicated in the development of interstitial fibrosis and cardiac hypertrophy. These findings, and the extensive preclinical work on Ang[1–7], ACE2, and now Ang[1–12], present exciting possibilities for developing new therapeutic agents that block the RAAS (Trask and Ferrario 2007).

RAAS Blockade by ACEIs, ARBs, and DRIs

The direct inhibition of renin is a logical target for pharmacologic suppression of the RAAS, because renin-mediated cleavage of angiotensinogen to form Ang I is a rate-limiting first step

in the RAAS pathway. However, early attempts to develop DRIs met with little success, and research subsequently focused on developing ACEIs and ARBs, with approval of ACEIs throughout the 1980s and ARBs beginning in the mid 1990s. Table 2 summarizes the effects of DRIs, ACEIs, and ARBs on the RAAS.

As mentioned above, ACEIs, but not ARBs, lead to significant accumulation of bradykinin and substance P as ACE mediates the metabolism of these peptides. This potentially contributes to increased vasodilation and decreased thrombosis, atherogenesis, and tissue proliferation, but also is likely responsible for ACEI-related, dose-limiting side effects, such as angioedema and dry cough. Although acute administration of ACEIs effectively reduces Ang II levels, chronic administration can lead to “ACE escape” (Wong et al. 2004). In addition, the ability of glucocorticoids and estrogenic hormones to increase hepatic angiotensinogen production (Lalouel et al 2001) may lead to large increases in Ang I production and subsequent ACE escape.

Reactive increases in plasma renin concentration (PRC) and PRA during ACEI treatment may result in increased Ang II production via non-ACE pathways. Moreover, higher levels of Ang I may overcome the ability of ACEIs to effectively suppress ACE activity. ACE escape also may relate to the relatively low binding affinity of ACEIs for ACE and the relatively low levels of the dosing of ACEIs used in clinical practice to avoid drug-related adverse events. With ARBs, the reactive elevations in PRC and PRA lead to increases in Ang II levels (Schindler et al. 2007). This may result in greater competition and displacement of ARBs from AT_1-R sites and reduced antihypertensive efficacy (Burnier and Brunner 2000). Unlike ACEIs, ARBs block the effect of non–ACE-dependent Ang II on the AT_1-R and increase the interaction of Ang II with the AT_2-R, the benefits and risks of which are not completely understood.

As mentioned previously, in addition to other effects, AT_1-R activation results in the release of aldosterone from the adrenal cortex, which contributes to cardiorenal damage (Brown 2005; Remuzzi et al. 2008), and aldosterone antagonists provide benefits related to morbidity and mortality (Pitt et al. 1999; Pitt et al. 2003). Both ACEIs and ARBs inhibit aldosterone production. However, “aldosterone escape” is observed with both drug classes (Athyros et al. 2007), possibly owing to increased serum potassium levels (ACEIs or ARBs), ACE escape (ACEIs), or increased Ang II competing with the AT_1-R or binding to the AT_2-R (ARBs).

The discovery of novel, nonpeptide, renin antagonists in the early 1980s led to resurgent interest in the development of DRIs, culminating with the approval of aliskiren for the treatment of hypertension in 2007 (Jensen et al. 2008). DRIs provide more complete blockade of the RAAS (Fisher and Hollenberg 2005). Furthermore, although plasma prorenin and PRC increase due to interruption of the Ang II:AT_1-R–mediated negative-feedback inhibition of renin release, PRA remains reduced. It appears that DRIs are associated with a low incidence of hyperkalemia, similar to that observed in placebo recipients (Weir et al. 2007), and therefore may reduce the potential for aldosterone escape. Similar to ARBs (and unlike ACEIs), DRIs have no appreciable effect on bradykinin metabolism, and therefore may have better tolerability than ACEIs.

ACEIs and ARBs: Antihypertensive Effects and Clinical Benefits Beyond BP Control

Monotherapy with ACEIs and ARBs effectively controls BP in approximately 40% to 60% of patients with mild-to-moderate hypertension (Ibrahim 2006). Both drug classes reduce the risk of adverse cardiovascular outcomes and are considered suitable for the initiation and maintenance of antihypertensive treatment, either as monotherapy or in combination with other antihypertensives (Chobanian et al. 2003; Mancia et al. 2007).

A number of compelling indications exist for using ACEIs and ARBs, which extend beyond simple control of BP (Table 1) (Chobanian et al. 2003;Mancia et al. 2007). ACEIs and ARBs provide protective benefits in target organs, independent of their BP-lowering effects. Many of these benefits arise because the RAAS is abnormally activated in various forms of renal disease, as part of an adaptive response to loss of renal mass and subsequent changes in renal hemodynamics (Schiffrin et al. 2007). Patients who have renal disease, with or without concurrent DM, frequently experience hypertension, dyslipidemia, inflammation, atherosclerosis, vascular calcification, and/or acceleration in the development and progression of cardiovascular disease (Schiffrin et al. 2007). Because of this cardiorenal connection, ACEIs and ARBs are particularly useful for reducing proteinuria, preserving renal function, delaying renal disease, reducing left ventricular hypertrophy (LVH), and attenuating the fibrotic component of LVH (Mancia et al. 2007). As a result, guidelines from the National Kidney Foundation (National Kidney Foundation 2007) strongly recommend that patients with DM, chronic kidney disease (CKD), and hypertension be treated with ACEIs or ARBs, usually in combination with a diuretic, as a means for controlling BP, slowing the progression of CKD, and improving clinical outcomes. A meta-analysis of cardiovascular outcomes data from 25 trials involving nearly 46 000 patients with CKD and proteinuria showed that treatment with ACEIs or ARBs significantly reduced the risk for several cardiovascular outcomes (Figure 2) (Balamuthusamy et al. 2008). These agents also may reduce the incidence of new-onset DM (Andraws and Brown 2007).

Dual RAAS Blockade with ACEIs and ARBs

As reviewed above, the existence of multiple pathways for the generation of the biologically active angiotensin peptides posits the question as to how effective current approaches are to suppress the activity of Ang II. At each of the points within the cascade of the RAAS, alternate enzymatic pathways can bypass the blockade of the primary enzyme while it is also possible that intracellularly the formation of angiotensin peptides does not follow what has been characterized in the circulation or the extracellular compartment. Stimulation or repression of a physiological pathway brings about compensatory responses so that the all-or-nothing effect of a particular drug is rendered ineffective. As a response, the idea of combining drugs acting at different sites within the biochemical cascade of the RAAS gained acceptance and, among possible combinations the use of ACEI and ARB became a favorite.

Although the theoretical benefits of combined ACEI- and ARB-based therapy may enhance BP control and improve clinical outcomes in some subpopulations of patients, Weber and Giles (Weber and Giles 2006) observed that, for most patients, these RAAS-based therapies do not reduce the risk for major cardiovascular events (MCEs) to the extent expected based on the central role of the RAAS in the pathophysiology of hypertension and cardiorenal disease. They speculated that this may indicate that the RAAS is not as widely dysregulated in hypertension as previously thought, or that the current strategies and/or agents available for RAAS suppression are not as effective as they could or should be. With respect to the second argument, dual RAAS blockade at different sites in the RAAS pathway theoretically would have provided additive protective effects by further reducing systemic and local levels of some or all angiotensin peptides, which could further inhibit formation of the Ang II:AT_1-R effector complex and potentially avoid ACE and aldosterone escape mechanisms (van de Wal et al. 2005; Wolf and Ritz 2005; Unger and Stoppelhaar 2007; Cohn and Goldman 2008).

Although several studies have shown that ACEI/ARB combinations result in modest improvement in BP and proteinuria compared with treatment with only one of these drug classes (Ferrari et al. 2002; McMurray et al. 2003; Nakao et al. 2003; Krum et al. 2004; Kunz et al. 2008), others do not support this combination because of concerns about efficacy (modest improvement in BP with limited or no additional benefit on outcomes) and safety (Arici and

Erdem 2009). In a crossover study of 64 hypertensive patients not achieving BP control with full-dose valsartan, the addition of amlodipine reduced ambulatory 24-hour BP to a greater extent than the addition of benazepril (−15.2/−9.9 mm Hg vs −8.6/−6.3 mm Hg, respectively; $P<.05$) (Stergiou et al. 2005). Similarly, ACEI/ARB combination therapy was less effective for lowering BP than ARB/thiazide diuretic combination therapy in a study of 327 hypertensive patients uncontrolled by ARB monotherapy (Waeber et al. 2001) and in a study of 88 African Americans with hypertension (Weir et al. 2001). In the VALIANT study of 14 703 elderly patients with left ventricular systolic dysfunction, CHF, or both after MI, combination ACEI/ARB therapy was no more effective than monotherapy with either agent for reducing the risk for death and MCEs (White et al. 2005). Two meta-analyses of patients with CHF or left ventricular dystrophy (LVD; including CHARM-Added, Val-HeFT, and VALIANT) also showed that ACEI/ARB combination therapy significantly increases the risk for adverse events (eg, hypertension, worsening renal function, and hyperkalemia), necessitating treatment discontinuation (Phillips et al. 2007; Lakhdar et al. 2008). The largest study of an ACEI/ARB combination conducted to date is ONTARGET, in which >25 000 patients at high risk for MCEs (eg, vascular disease, high-risk DM without CHF) were randomized to receive the ACEI ramipril or the ARB telmisartan in monotherapy or ACEI/ARB combination therapy at maximum recommended doses. After the median follow-up period of 4.7 years, the rates for the primary composite outcome (cardiovascular-related death, MI, stroke, and hospitalization for CHF) were similar for the 3 treatment arms (16.3% to16.7%), but the risk for worsening renal function was higher in the combination arm, as was the rate of discontinuation due to hypotension, syncope, decreased kidney function, and hyperkalemia (Yusuf et al. 2008). In a subsequent analysis of renal outcomes, the risk for the primary composite outcome (dialysis, doubling of serum creatinine, and death) was 9% higher with combination therapy than monotherapy ($P=.038$), despite significant benefits of combination therapy on indices of proteinuria (Mann et al. 2008). However, these results have been questioned, given that ONTARGET was primarily a cardiovascular-outcomes study; renal outcomes were not rigorously or consistently defined, and few patients had microalbuminuria (13%) or macroalbuminuria (4%) (Sarafidis and Bakris 2008; Berns 2009). Nevertheless, ONTARGET has raised questions regarding the place in therapy for the ACEI/ARB combination (Messerli 2009), a finding that is in keeping with previous experimental studies from my laboratory. In these studies we found that the combination of lisinopril and losartan abrogated the upregulation of cardiac ACE2 mRNA that was observed when animals were administered the single treatments (Ferrario et al. 2005a).

There are several possible clinical and experimental reasons why dual RAAS blockade with ACEIs and ARBs has not resulted in the expected benefits. These include study-design issues as well as theoretical mechanistic considerations. As noted by Arici and Erdem (Arici and Erdem 2009), many clinical studies have been small and of short duration, and most used submaximal doses of ACEIs and ARBs both alone and in combination. Most combination studies were not designed to maximize BP control and, in fact, achieved only modest improvement in BP (~3 to 4 mm Hg) over monotherapy with an ACEI or ARB (Doulton et al. 2005). Additionally, many early studies used once-daily dosing with short-acting ACEIs. Therefore, it is possible that low ACEI concentrations at trough in combination studies using short-acting ACEIs could have increased the likelihood of both acute (method-related) and chronic (mechanistic-mediated) ACE escape. Administration of diuretics also has resulted in increases in PRA (Lijnen et al. 1981), and the use of diuretics as concurrent medications usually is permitted in ACEI and ARB studies.

Increases in both PRA and ACE escape have been associated with adverse clinical outcomes in patients on ACEI or ARB therapy. For example, in a study of 70 patients with CHF, elevated PRA despite 6 months of treatment with an ACEI was an independent predictor of elevated Ang II levels ($P=.0004$), and elevated plasma Ang II levels were an independent predictor of

death or worsening CHF (*P*=.002) (Roig et al. 2000). In another study, 699 patients with CHF underwent a complete clinical and biochemical workup at baseline and were monitored for a median of 23 months; 81% of them were receiving an ACEI or ARB (Vergaro et al. 2008). Elevated baseline PRA was an independent predictor of death or the need for cardioversion in patients with implantable cardioverter devices (*P*<.001), and PRA was higher in patients on RAAS inhibitors relative to those not receiving RAAS inhibitors (*P*=.017). In Val-HeFT, analysis of 4300 patients with CHF who had neurohormonal measurements showed that increased baseline PRA was an independent predictor of all-cause mortality (*P*=.011) and of combined mortality and morbidity (*P*=.0025) (Latini et al. 2004). This was observed despite the fact that the majority of patients were receiving treatment with an ACEI and approximately half were also receiving treatment with an ARB. A recent post hoc analysis of Val-HeFT data showed that PRA was 3.7 times higher in patients receiving ACEIs (vs those not receiving them), and that higher PRA at baseline was associated with greater mortality among patients receiving ACEIs (*P*=.0005) (Masson et al. 2009). Taken together, these findings strongly indicate that PRA is related to adverse clinical outcomes even for patients receiving treatment with ACEIs and/or ARBs, and further raises the possibility that DRIs may be useful alone or in combination with ACEIs or ARBs for reducing the risk for these outcomes.

Knowledge of the complexity of the biochemical pathways mediating the formation of angiotensin peptides suggests that combined ACEI/ARB therapy may induce greater synthesis of intracellular Ang II due to a direct effect of the increased plasma or tissue renin on the prorenin/renin receptor (Pro-RR). I advance this hypothesis from the lessons learned from previous experiments conducted in our laboratory (Ferrario et al. 2005b) and the emerging evidence that the binding of prorenin and renin to the Pro-RR (Nguyen and Contrepas 2008) can lead to stimulation of intracellular formation of Ang II or even activation of growth-promoting signaling pathways via a non-Ang II dependent pathway. By promoting the reversible activation of prorenin and enhancing the enzyme activity of mature renin the Pro-RR activates mitogen-activated protein kinase and hypertrophic, hyperplastic, profibrotic, and cyclooxygenase-2-signaling (Nguyen and Contrepas 2008).

DRIs: Suppression of PRA and Potential Role in Dual RAAS Blockade

As reviewed in the following sections, PRC increases in response to monotherapy with aliskiren, ACEIs, ARBs, amlodipine, aldosterone antagonists, or thiazide diuretics (or combination therapy with aliskiren plus any of these agents), whereas PRA decreases to below baseline when aliskiren is used alone or in combination with other antihypertensives (studies with thiazide diuretics are included because these agents increase PRA levels (Lijnen et al. 1981). Results are summarized below and in Table 2, and only the studies that assessed RAAS biomarkers are described below.

Studies in healthy volunteers

The effects of aliskiren in combination with an ARB on components of the RAAS were explored in a double-blind crossover study in 12 mildly sodium-depleted, healthy, normotensive volunteers who received aliskiren 300 mg, valsartan 160 mg, or aliskiren/valsartan 150/80 mg (Azizi et al. 2004). Twenty-four hours after dosing, PRC increased 14.1-fold and 5.7-fold in response to aliskiren and valsartan monotherapy, respectively, and PRA decreased by 39% with aliskiren but increased 3-fold with valsartan. Levels of Ang I and Ang II decreased by 26% and 36%, respectively, with aliskiren and increased 10-fold and 6-fold with valsartan. The combination of aliskiren and valsartan resulted in a 12-fold increase in PRC and attenuation of the valsartan-induced increases in PRA (1.4–2.1 ng/mL/h), Ang I (11–44 pg/mL), and Ang II (9–19 pg/mL). The rate of urinary aldosterone excretion was greater for subjects receiving valsartan 160 mg than those on either aliskiren 300 mg or aliskiren/valsartan 150/80 mg (18, 13, and 12 μg/24 h, respectively; both *P*<0.05).

In a pharmacodynamic study in 12 normotensive subjects on a high-sodium diet, levels of PRA, Ang I, and Ang II increased (vs baseline) 48 hours after administration of valsartan 320 mg, but decreased 48 hours after administration of aliskiren 300 mg (Azizi et al. 2007). Aliskiren 300 mg stimulated PRC to a greater extent than valsartan 320 mg, decreased urinary aldosterone excretion for a longer period, and resulted in similar improvements in BP. Compared with valsartan 320 mg, aliskiren/valsartan 150/160 mg resulted in higher PRC (4,080 vs 2201 pg/h/mL area under the curve over 48 h [$AUC_{0–48}$]; $P<0.05$), lower PRA (11 vs 49 ng/mL/h; $P<0.05$), lower Ang I (235 vs 643 pg/h/mL; $P<0.05$), lower Ang II (109 vs 255 pg/h/mL; $P<0.05$), and a lower rate of urinary aldosterone excretion (7.15 vs 9.91 μg/48 h; $P<0.05$).

Studies in patients with hypertension, cardiovascular disease, or diabetes

Three clinical studies evaluated aliskiren alone or in combination with an ARB (valsartan), thiazide diuretic (hydrochlorothiazide [HCTZ]), or both on RAAS biomarkers in patients with mild-to-moderate hypertension (Oparil et al. 2007a; Villamil et al. 2007; Geiger et al. 2009). Another study evaluated aliskiren in combination with a calcium channel blocker (amlodipine) in patients with mild-to-moderate hypertension (Drummond et al. 2007), and a further trial evaluated aliskiren alone and in combination with an ACEI (ramipril) on RAAS biomarkers in patients with mild-to-moderate hypertension and DM (Table 3) (Uresin et al. 2007). In all of these studies, monotherapy with valsartan, amlodipine, or ramipril generally resulted in marked increases in PRC and PRA, whereas treatment with HCTZ either increased these parameters or, in patients who had already received 4 weeks of treatment, had little effect on these parameters. Aliskiren monotherapy (150 or 300 mg) yielded even greater increases in PRC, but in contrast, PRA decreased by ~70% relative to baseline. A reduction in PRA was observed when aliskiren was administered in combination with valsartan, amlodipine, ramipril, or HCTZ, whereas triple therapy with aliskiren/valsartan/HCTZ blunted the increase in PRA associated with valsartan/HCTZ. In all 5 studies, reductions in mean sitting (ms) systolic blood pressure (SBP) and diastolic blood pressure (DBP) were significantly greater for recipients of aliskiren combination therapy than for patients on aliskiren alone or the active comparator alone (Table 3). In the study by Oparil and colleagues of 1797 hypertensive patients (Oparil et al. 2007a), levels of plasma aldosterone increased slightly in placebo subjects (+7%). In contrast, these levels decreased significantly in patients on valsartan 320 mg (−25%; $P=0.0007$ vs placebo) and aliskiren/valsartan 300/320 mg (− 31%; $P<0.0001$), and remained relatively unchanged in those on aliskiren 300 mg (−6%; $P>0.05$). In the study by Uresin and coworkers (Uresin et al. 2007) (837 patients with hypertension and DM), levels of plasma aldosterone were lower than baseline after 8 weeks of aliskiren/ramipril 300/10 mg (−18%; $P=0.034$), but not after aliskiren 300 mg or ramipril 10 mg alone (−8% and −2%, respectively).

In all studies, the administration of aliskiren alone or in combination with other antihypertensive agents was well tolerated. The ASPIRE HIGHER clinical program will further define the role of aliskiren in the management of cardiovascular and renal diseases (Sever et al. 2009). Of particular interest are large-scale studies that will examine the benefits of aliskiren on morbidity and mortality, including its combination with ACEIs or ARBs. These include the ATMOSPHERE and ASTRONAUT studies in patients with CHF, the ALTITUDE trial in patients with DM, and the APOLLO study in elderly patients with or without previous cardiovascular events.

Benefits Beyond BP Control

The potential benefits of dual RAAS therapy with aliskiren appear to extend beyond simple control of BP. Aliskiren is a potent, long-acting, renal vasodilator with a pronounced natriuretic effect in normotensive healthy volunteers on a low-sodium diet; its renal vasodilator effects are approximately twice as large as those of ACEIs and 40% greater than those of ARBs (Fisher et al. 2008). This suggests that aliskiren may provide greater and more effective

blockade of the RAAS in the kidney. Evidence for renoprotective effects stem from the 6-month, double-blind, placebo-controlled AVOID study, which compared aliskiren 300 mg versus placebo when combined with losartan 100 mg and optimal antihypertensive therapy in 599 patients with type 2 DM, diabetic nephropathy, and relatively well-controlled msSBP/msDBP (~135/78 mm Hg at baseline) (Parving et al. 2008). Combination therapy reduced albuminuria (mean urinary albumin:creatinine ratio [UACR]) by 20% relative to losartan alone (P<0.001) despite the negligible differences in BP between the 2 arms (2/1 mm Hg; P>0.05). Additionally, the UACR was reduced by ≥50% in 24.7% of patients receiving combination therapy compared with 12.5% on losartan monotherapy (Pπ.001). These findings are similar to those of a 3-month, open-label study of aliskiren monotherapy in 15 patients with type 2 DM and albuminuria (Persson et al. 2008), in which aliskiren 300 mg resulted in a 44% reduction from baseline in the UACR (P<0.001). Persson and colleagues recently reported the results of a randomized, double-blind, crossover study in 26 hypertensive patients with type 2 DM and albuminuria (Persson et al. 2009). Two months of treatment with aliskiren 300 mg or irbesartan 300 mg similarly reduced albuminuria by 48% and 58%, respectively, compared with placebo (P<0.001). The combination of aliskiren/irbesartan reduced albuminuria by 71% compared with placebo (P<.001), an antiproteinuric effect that was significantly greater than that of either monotherapy (P<0.05).

Dual RAAS therapy with aliskiren may help slow or reverse cardiac end-organ damage. In the ALLAY study of 465 patients with hypertension and LVH, treatment with aliskiren 300 mg or losartan 100 mg for 9 months reduced left ventricular mass −4.9 and − 4.8 g/m^2, respectively (both P<0.0001 vs baseline; P<0.0001 for noninferiority) (Solomon et al. 2009). Combination aliskiren/losartan 300/100 mg resulted in modestly greater improvements in left ventricular mass (−5.8 g/m^2; P<0.0001 vs baseline; P=.52 vs losartan). In the ALOFT study mentioned previously, aliskiren 150 mg (plus ACEI or ARB) produced a greater reduction in plasma brain natriuretic peptide (BNP) compared with placebo (−61.0 vs −12.2 pg/mL; P=0.011) (McMurray et al. 2008). This may have clinical consequences for patients with CHF, because the Val-HeFT study suggests that there is a 1.2% increase in the risk of death and the risk for CHF-related hospitalization associated with each 10-pg/mL increment in BNP (Latini et al. 2004). The beneficial effect of aliskiren on BNP levels appeared independent of the changes from baseline in BP and heart rate, which were similar for the 2 study groups.

Summary

From a theoretical standpoint, direct inhibition of renin has long been recognized as a promising target for inhibiting the RAAS, because renin is the first rate-limiting enzymatic step in the RAAS pathway. From a practical standpoint, ACEIs and ARBs have not provided the major improvements in clinical outcomes that might be predicted based on the central role of the RAAS in the cardiorenal disease continuum. Moreover, the value of combination ACEI/ARB therapy has been called into question, particularly in light of the results from ONTARGET. Based on what is known to date, it may be suggested that DRIs in combination with ACEIs or ARBs may yield better clinical outcomes through more effective RAAS blockade at distinct and complementary sites. The ultimate role of aliskiren in combination therapies with ACEIs, ARBs, and other antihypertensives will be better defined through future studies, which are being conducted as part of the ASPIRE HIGHER clinical program.

Acknowledgments

Editorial support was provided by John Leinen, PhD, at Oxford PharmaGenesis Inc., Newtown, PA, and was funded by Novartis Pharmaceuticals Corporation, East Hanover, NJ. In addition to support provided by NHLBI grant PO1 HL051952, the author gratefully acknowledges grant support in part provided by Unifi, Inc., Greensboro, NC, and Farley-Hudson Foundation, Jacksonville, NC.

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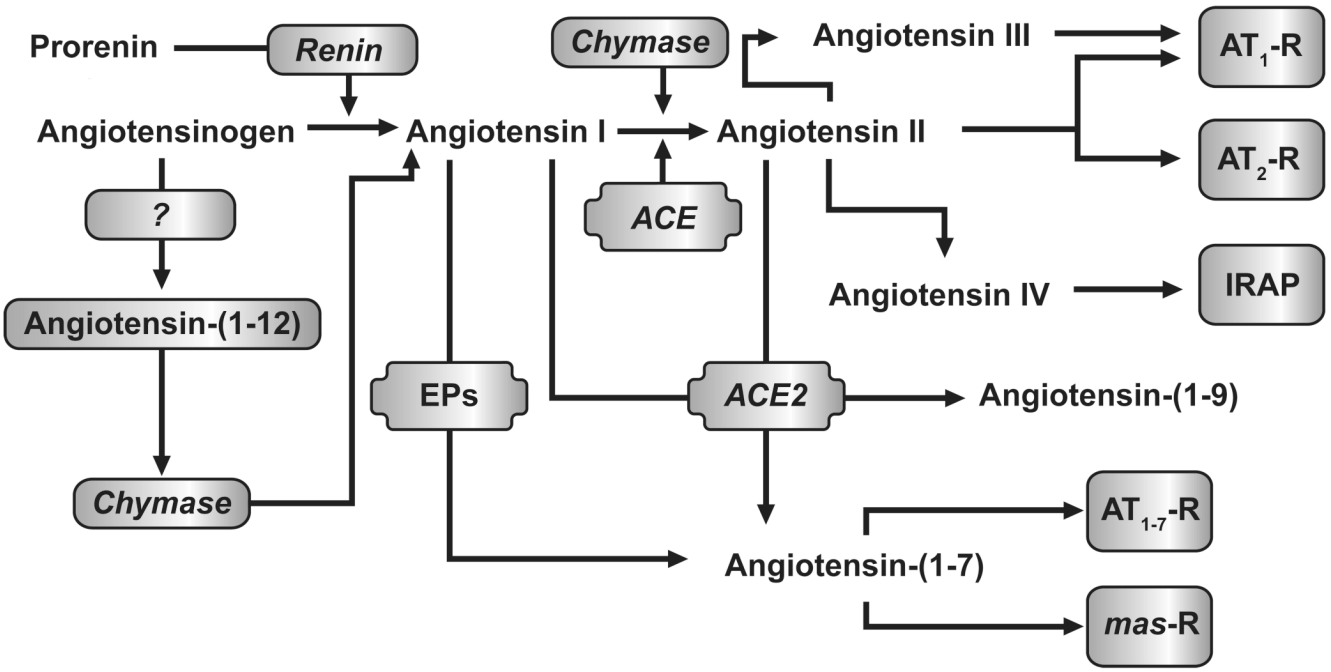

Figure 1.

Biochemical pathways denoting the enzymes and intermediate peptides involved in the formation of active angiotensin peptides. ACE = angiotensin-converting enzyme; AT_1-R = angiotensin type 1 receptor; AT_2-R = angiotensin type 2 receptor; IRAP = insulin-regulated aminopeptidase; mas-R = Mas receptor.

[Note: for black & white reproduction/printing only]

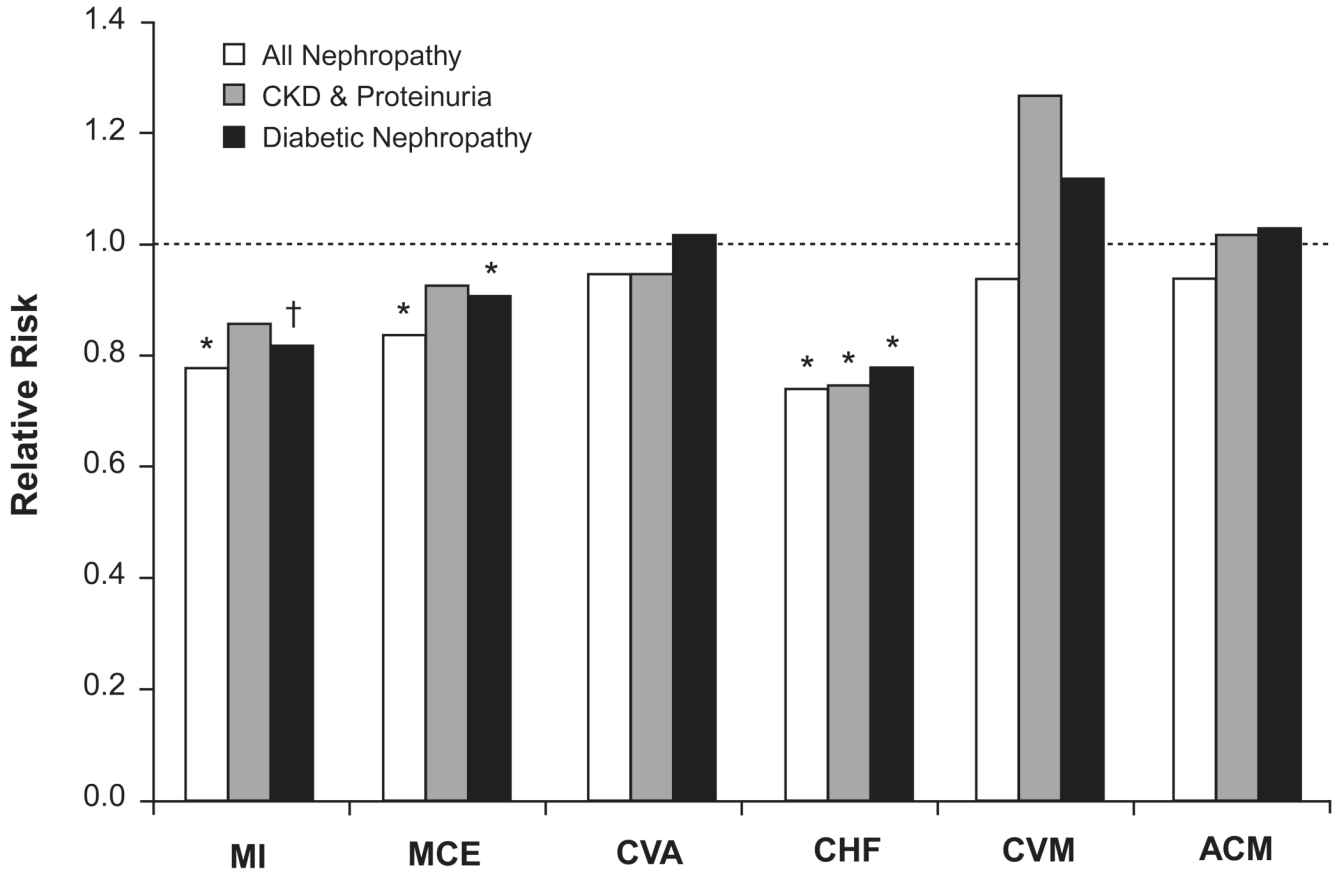

Fig. 2a

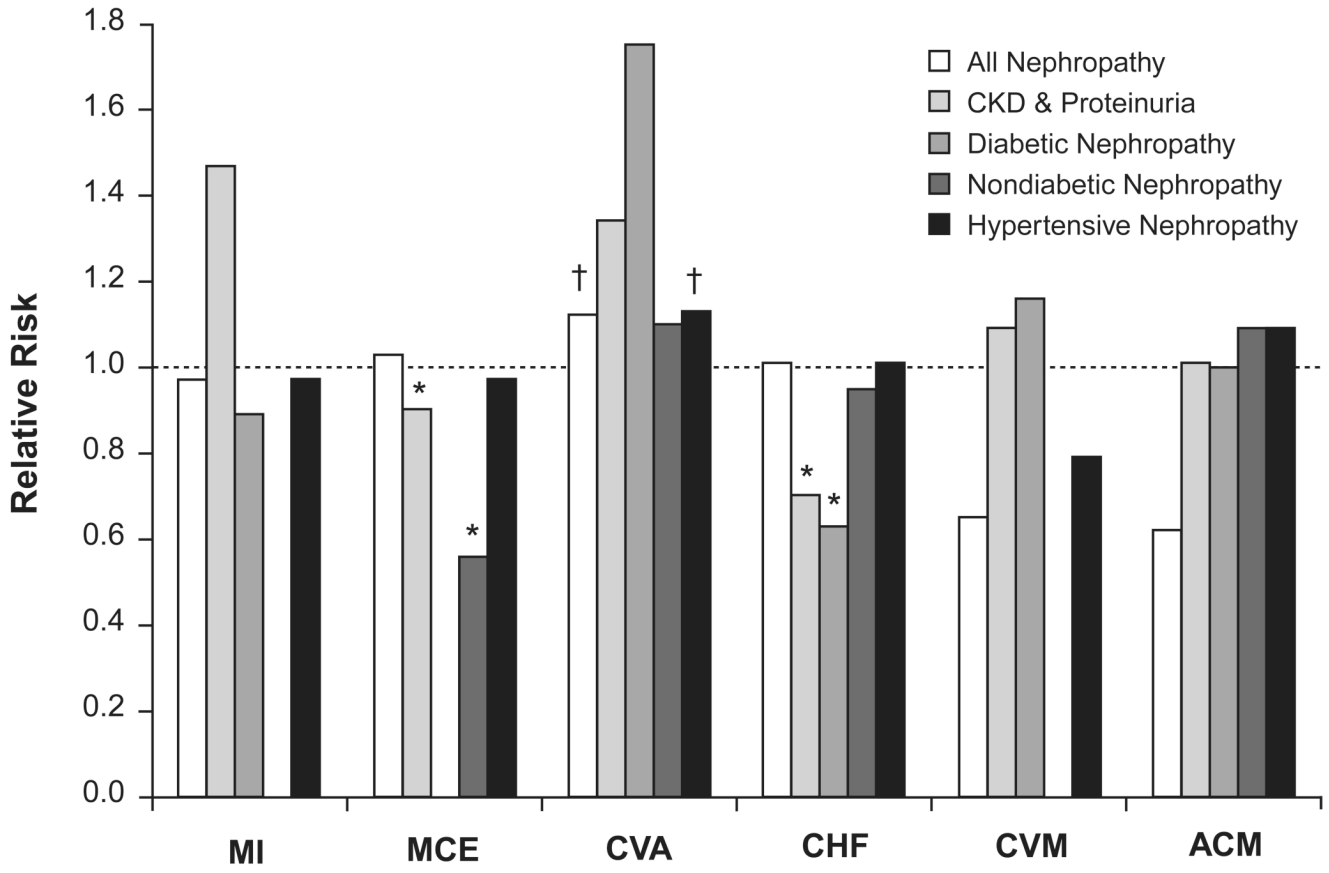

Fig. 2b

Figure 2.

Relative risk for cardiovascular outcomes in patients with chronic kidney disease. (A) ACEIs or ARBs Versus Placebo; (B) ACEIs or ARBs Versus Non-RAAS Antihypertensives. **P*<0.05, †*P*=0.05. ACEI = angiotensin-converting enzyme inhibitor; ACM = all-cause mortality; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; CVA = cerebrovascular accident; CVM = cardiovascular mortality; MCE = major cardiovascular event (eg, MI, CVA, coronary revascularization, unstable angina); MI = myocardial infarction; RAAS = renin-angiotensin-aldosterone system. Adapted from Balamuthusamy et al. (Balamuthusamy et al. 2008)

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Table 1

Indications and contraindications for the use of ACEIs and ARBs (Chobanian et al. 2003; Mancia et al. 2007)

	ACEIs		ARBS	
Guideline	**2007 ESH/ESC**	**JNC 7**	**2007 ESH/ESC**	**JNC 7**
Indications	CHF	CHF	CHF	CHF
	Diabetes/DN	Diabetes	Diabetes/DN	Diabetes
	CKD	CKD	CKD	CKD
	Post-MI	Post-MI	Post-MI	
	Proteinuria/MA	Prevention of recurrent stroke	Proteinuria/MA	
	LVH	High risk of coronary disease	LVH	
	Recurrent AF		Recurrent AF	
	Metabolic syndrome		Metabolic syndrome	
	Prevention of recurrent stroke		Prevention of recurrent stroke	
	Carotid atherosclerosis		ACEI-induced cough	
	LVD			
	Nondiabetic nephropathy			
Contraindications	Pregnancy		Pregnancy	
	Hyperkalemia		Hyperkalemia	
	Bilateral renal artery stenosis		Bilateral renal artery stenosis	
	Angioneurotic edema			

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; AF = atrial fibrillation; ARB = angiotensin receptor blocker; CHF = congestive heart failure; CKD = chronic kidney disease; DN = diabetic nephropathy; ESC = European Society of Cardiology; ESH = European Society of Hypertension; JNC 7 = Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure; LVD = left ventricular dysfunction; LVH = left ventricular hypertrophy; MA = microalbuminuria; MI = myocardial infarction.

Table 2

Biochemical differences in the various methods used to inhibit the the renin-angiotensin-aldosterone system (RAAS). Note the additive effects (⬆ + ⬆ [increases] or ⇩+⇩ [decreases]) of dual RAAS blockade. Adapted from Azizi et al (Azizi et al. 2006)

	Single-site RAAS blockade			Dual RAAS blockade		
Component	**ACEI**	**ARB**	**DRI**	**ACEI + ARB**	**DRI + ARB**	**DRI + ACEI***
Enzymes						
Plasma renin activity	⬆	⬆	⇩	⬆+⬆	⇩	⇩
Plasma renin concentration	⬆	⬆	⬆	⬆+⬆	⬆+⬆	⬆+⬆
Renal immunoreactivity	⬆	⬆	⬆	⬆+⬆	⬆+⬆	⬆+⬆
Plasma prorenin	⬆	⬆	⬆	⬆+⬆	⬆+⬆	⬆+⬆
Plasma ACE	⇩	↔	↔	⇩	↔	⇩
Tissue ACE	⇩	↔	↔	⇩	↔	⇩
Substrate concentrations						
Angiotensinogen	⇩	⇩	↔	⇩+⇩	↔	↔
Angiotensin I	⬆	⬆	⇩	⬆+⬆	⇩ or ↔	⇩ or ↔
Bradykinin	⬆	↔	↔	⬆	↔	⬆
AcSDKP	⬆	↔	↔	⬆	↔	⬆
Receptors						
Angiotensin type 1 receptor	↔	⊠	↔	↔ and ⊠	↔ and ⊠	↔
Angiotensin type 2 receptor	↔	⬆	↔	⬆	↔	↔
Bradykinin B_2	⬆	⬆	↔	⬆+⬆	↔	⬆
End products						
Angiotensin II	⇩	⬆	⇩	⇩ or ↔	⇩ or ↔	⇩+⇩
Non–ACE dependent angiotensin II	**(A)**	⊠	⊠	⊠	⊠	
Angiotensin III	⇩	⬆	⇩	⇩ or ↔	⇩ or ↔	⇩+⇩
Angiotensin IV	⇩	⬆	⇩	⇩ or ↔	⇩ or ↔	⇩+⇩
Angiotensin[1–7]	⬆	⬆	⬆	⬆+⬆	⬆ or ↔	⬆
Aldosterone	⇩	⇩	⇩	**(B)**	⇩+⇩	⇩+⇩
Miscellaneous						
Tissue RAAS	⇩	⊠	⇩	⇩ and ⊠	⇩ and ⊠	⇩+⇩

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[*] Based on theoretical considerations.

Abbreviations: (A) = present; (B) = no major additive effect; ⇩ = decreased or inhibited; ⬆ = increased or stimulated; + = additive effect; ↔ = normal, no change, or not inhibited or stimulated; ⊠ = blocked; ACE = angiotensin converting enzyme; ACEI = angiotensin-converting enzyme inhibitor; AcSDKP = acetyl-Ser-Asp-Lys-Pro tetrapeptide; ARB = angiotensin receptor blocker; DRI = direct renin inhibitor; RAAS = renin-angiotensin-aldosterone system.

Table 3

Effects of treatment with aliskiren and amlodipine on PRC, PRA, and BP in randomized, double-blind studies in patients with hypertension, cardiovascular disease, or diabetes

			Geometric mean % change from baseline [n]				Mean sitting SBP/DBP (mm Hg)	
Study	**Drug**	**N**	**PRC**		**PRA**		**Baseline**	**Change from baseline**
Nussberger 2007 (adults with mild-to-moderate hypertension) (Nussberger et al. 2007)								
Week 8	Placebo	111	−9		−11		152/NA	−5/NA
	ALI 150 mg	112	+157		−69*		151/NA	−9/NA
	ALI 300 mg	115	+246*		−71*		152/NA	−15/NA
	ALI 600 mg	113	+497*		−75*		153/NA	−16/NA
	Irbesartan 150 mg	118	+105		+109		153/NA	−13/NA
Duprez 2009 (elderly patients with systolic hypertension) (Duprez et al. 2009)								
Week 12	ALI 150–300 mg	451	+246‡	[59]	−79‡	[59]	NA	−14.0*/−5.1†
	RAM 5–10 mg	439	+100	[62]	+147	[62]	NA	−11.6/−3.6
Week 36 (±HCTZ±AMLO)	ALI 150–300 mg	451	+469‡	[65]	−70‡	[65]	NA	NA
	RAM 5–10 mg	439	+173	[66]	+244	[66]	NA	NA
Andersen 2008, Andersen in press (adults with mild-to-moderate hypertension) (Andersen et al. 2008Andersen et al. 2009)								
Week 12	ALI 150–300 mg	420	ND		ND		151.3/98.8	−14.0†/−11.3†
	RAM 5–10 mg	422	ND		ND		151.5/98.9	−11.3/−9.7
Week 26 (±HCTZ)	ALI 150–300 mg	420	+224	[39]	−63	[103]	151.3/98.8	−17.9†/−13.2*
	RAM 5–10 mg	422	+145	[33]	+143	[100]	151.5/98.9	−15.2/−12.0
Oparil 2007 (adults with mild-to-moderate hypertension) (Oparil et al. 2007a)								
Week 8	Placebo	459	+19	[51]	+18	[51]	154.2/100.5	−4.6/−4.1
	ALI 150 mg	437	+468	[51]	−73	[51]	154.0/100.3	−13.0/−9.0
	VAL 160 mg	455	+138	[59]	+160	[59]	154.2/100.4	−12.8/−9.7
	ALI 150 mg + VAL 160 mg	446	+912†	[60]	−44‡	[60]	152.7/100.1	−17.2‡/−12.2‡
Villamil 2007 (adults with mild-to-moderate hypertension) (Villamil et al. 2007)								

Study	Drug	N	Geometric mean % change from baseline [n] PRC		PRA		Mean sitting SBP/DBP (mm Hg) Baseline	Change from baseline
Week 8	Placebo	195	+30		+1		152.7/99.3	−7.5/−6.9
	ALI 75 mg	184	+164		−54		153.2/99.4	−9.4/−8.7
	ALI 150 mg	185	+192		−65		153.4/98.8	−12.2/−8.9
	ALI 300 mg	183	+348		−58		154.4/99.3	−15.7/−10.3
	HCTZ 6.25 mg	194	+10		+4		153.4/99.3	−11.0/−9.1
	HCTZ 12.5 mg	188	+26		+45		153.4/99.1	−13.9/−10.1
	HCTZ 25 mg	176	+108		+72		154.5/99.1	−14.3/−9.4
	ALI 75 mg + HCTZ 6.25 mg	188	NA		−55		154.5/98.9	−14.3*/−10.8*
	ALI 150 mg + HCTZ 12.5 mg	186	NA		−50		154.1/99.1	−17.6*/−11.9*
	ALI 300 mg + HCTZ 25 mg	173	+1211		−62		154.6/99.3	−21.2*/−14.3*
Geiger 2009 (adults with mild-to-moderate hypertension unresponsive to HCTZ monotherapy) (Geiger et al. 2009)								
Week 8	HCTZ 25 mg	152	−29	[43]	−13	[43]	154.1/99.9	−6/−6
	ALI 150–300 mg + HCTZ 25 mg	166	+490	[47]	−41	[47]	153.3/99.3	−15‡/−11‡
	VAL 160–320 mg + HCTZ 25 mg	155	+561	[42]	+509	[42]	156.7/99.9	−18‡/−14‡
	ALI 150–300 mg + VAL 160–320 mg + HCTZ 25 mg	168	+1760	[52]	+39	[52]	152.7/99.2	−22‡§/−16‡§
Drummond 2007 (mild-to-moderate hypertension in amlodipine non-responding adults) (Drummond et al. 2007)								
Week 6	ALI 150 mg + AMLO 5 mg	187	NA		−74.4	[55]	150.5/95.7	−11.0/−8.5
	AMLO 5 mg	180	NA		−9.9	[48]	150.5/96.2	−5.0/−4.8
	AMLO 10 mg	178	NA		+58.0	[48]	150.8/96.5	−9.6/−8.0
Uresin 2007 (adults with mild-to-moderate hypertension + diabetes mellitus) (Uresin et al. 2007)								
Week 8	ALI 300 mg	282	+139	[84]	−66	[84]	157.4/98.4	−14.7/−11.3
	RAM 10 mg	278	+72	[72]	+106	[72]	155.9/98.2	−12.0/−10.7
	ALI 300 mg + RAM 10 mg	277	+331*	[77]	−48*	[77]	156.5/98.4	−16.6¶/−12.8*

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Study	Drug	N	Geometric mean % change from baseline [n]		Mean sitting SBP/DBP (mm Hg)	
			PRC	PRA	Baseline	Change from baseline
McMurray 2008 (adults with NYHA class II to class IV CHF receiving a BB + an ACEI or ARB) (McMurray et al. 2008)						
Month 3	Placebo	146	−10	−9	128/76	−1.3/−0.2
	ALI 150 mg	156	+142	−77	130/78	−4.1/−2.9

Studies are sorted by order of appearance in text.

[*] $P<.05$ vs active monotherapy comparator(s);

[†] $P<.01$ vs active monotherapy comparator(s);

[‡] $P<.001$ vs active monotherapy comparator(s);

[§] $P<.01$ vs either dual therapy;

[¶] $P<.001$ vs ramipril monotherapy.

Abbreviations: ACEI = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ALI = aliskiren; AMLO = amlodipine; BB = beta-blocker; BP = blood pressure; CHF = congestive heart failure; DBP = diastolic blood pressure; HCTZ = hydrochlorothiazide; NA = not available; ND = not done; NYHA = New York Heart Association; PRA = plasma renin activity; PRC = plasma renin concentration; RAM = ramipril; SBP = systolic blood pressure; VAL = valsartan.