

Recent changes in the landscape of combination RAS blockade

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Benjamin J Epstein[†],
Steven M Smith and
Rushab Choksi

[†]Author for correspondence
101 S. Newell Drive, HPNP Bldg
212, Room 3316, University of
Florida, Gainesville,
FL 32610-0486, USA

The renin–angiotensin system (RAS) is a prime target for cardiovascular drug therapy. Inhibition of the RAS lowers blood pressure and confers protection against cardiovascular and renal events. These latter benefits cannot be entirely attributed to blood pressure lowering. Angiotensin-converting enzyme (ACE)-inhibitors and angiotensin receptor blockers (ARBs) have been studied extensively and, while there is irrefutable evidence that these agents mitigate the risk for cardiovascular and renal events, their protection is incomplete. In outcomes studies that have employed ACE-inhibitors or ARBs there has been a relatively high residual event rate in the treatment arm and this has been ascribed, by some, to the fact that neither ACE-inhibitors nor ARBs completely repress RAS. For this reason, combined RAS blockade with an ACE-inhibitor and ARB has emerged as a therapeutic option. In hypertension, combined RAS blockade elicits only a marginal incremental drop in blood pressure and it does not further lower the risk for cardiovascular events. In chronic heart failure and proteinuric renal disease, combining these agents in carefully selected patients is associated with a reduction in clinical events. Irrespective of the setting, dual RAS blockade is associated with an increase in the risk for adverse events, primarily hyperkalemia and worsening renal function. The emergence of the direct renin inhibitor, aliskiren, has afforded clinicians a new strategy for RAS blockade. Renin system blockade with aliskiren plus another RAS agent is the subject of ongoing large-scale clinical trials and early studies suggest promise for this strategy. Currently, combined RAS blockade with an ACE-inhibitor and an ARB should not be routinely employed for hypertension; however, the combination of an ACE-inhibitor or ARB with aliskiren might be considered in some patients given the more formidable blood pressure-lowering profile of this regimen. In carefully selected patients with heart failure or kidney disease, combination therapy with two RAS inhibitors should be considered.

KEYWORDS: angiotensin-converting enzyme inhibitor • angiotensin receptor blocker • blood pressure
• renin–angiotensin system

The renin–angiotensin system (RAS) is a central mediator in the pathophysiology of cardio-renal disease [1]. The major effector peptide, angiotensin (Ang) II, exerts an assortment of hemodynamic and nonhemodynamic effects that are capable of contributing to the progression of vascular disease. Of great importance is Ang II's predilection for promoting vasoconstriction, fibrosis, atherosclerosis, inflammation and endothelial dysfunction. Rightfully so, therapies aimed at interrupting this cascade, such as angiotensin-converting enzyme (ACE)-inhibitors, have been integrated quickly into clinical practice. There is now irrefutable evidence that these agents decrease the risk of cardiovascular events and slow the progression of renal disease in various patient groups [2–5].

Importantly, a portion of this benefit is not explained by changes in blood pressure alone; instead, it has been ascribed to pleiotropic actions characteristic of these agents [6].

The introduction of ACE-inhibitors into clinical practice represents an important step forward in the prevention and treatment of vascular disease; however, it was quickly recognized that ACE-inhibition might not be the ideal means for achieving RAS blockade [7]. In stepwise fashion, the angiotensin receptor blockers (ARBs) and direct renin inhibitors (DRIs) have emerged as new ways to block the RAS. Despite this evolution, none of the available therapeutic entities completely extinguish the harmful actions of the RAS. The ACE-inhibitors are susceptible to ACE escape, while ARBs block only a single Ang II

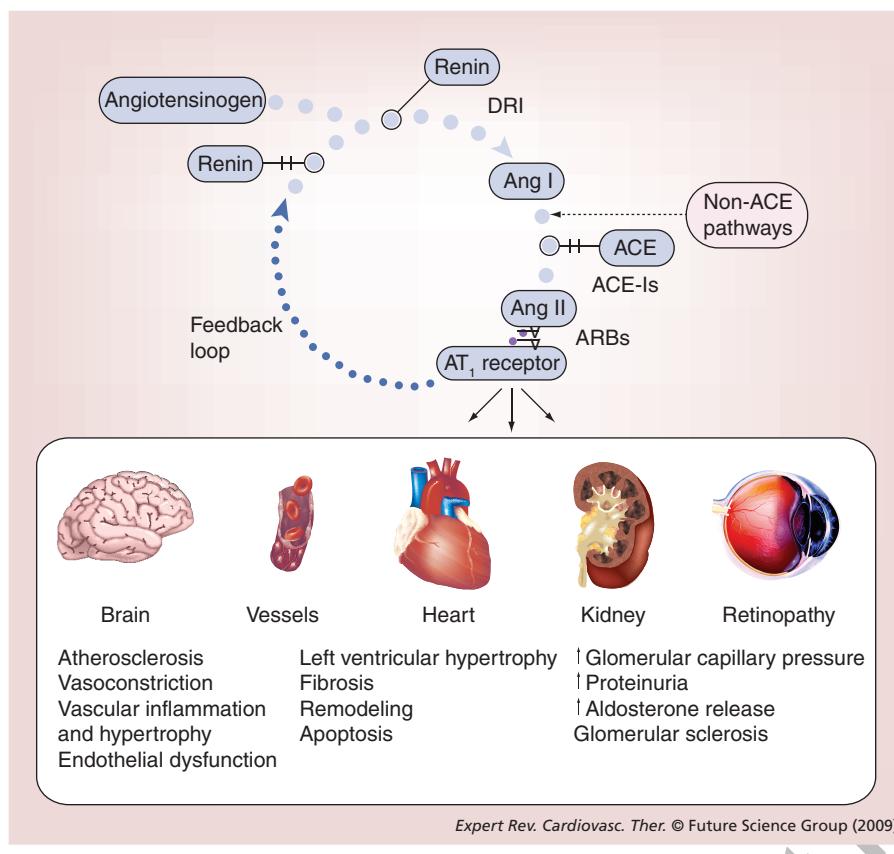


Figure 1. Effects of the renin–angiotensin system and mechanism of its inhibitors.

ACE-I: Angiotensin-converting enzyme inhibitor; Ang: Angiotensin; ARB: Angiotensin receptor blocker; AT₁: Angiotensin II receptor subtype 1; DRI: Direct renin inhibitor.

receptor subtype 1 (AT₁) and are unable to occupy all AT₁ receptors at any given moment. Likewise, aliskiren blocks the rate-limiting RAS step; however, its blockade is unlikely to be 100% [7–9].

In light of these limitations, combined RAS blockade with two agents has been used in clinical practice and evaluated in clinical trials [10–12]. ACE-inhibitors have been studied in combination with ARBs in patients with hypertension, diabetes, kidney disease, myocardial infarction and heart failure (HF) [13]. More recently, the DRI aliskiren has been combined with ACE-inhibitors or ARBs in patients with hypertension, left ventricular hypertrophy, HF and diabetic nephropathy [14]. While the rationale for combined RAS blockade is sound, the results of large-scale clinical trials have been mixed. Findings from these studies have reshaped the understanding of RAS blockade and should now serve to inform clinical practice. This article will review the rationale for combined RAS blockade and revisit clinical trials that have evaluated this strategy. Finally, we attempt to forecast the future role of combination RAS blockade in the treatment and prevention of cardiovascular disease.

Pharmacology of combined RAS blockade

The mechanism of action of ACE-inhibitors, ARBs and DRIs have been reviewed thoroughly in several recent manuscripts [15,16]. ACE-inhibitors block the conversion of Ang I to

Ang II by inhibiting the enzymatic activity of ACE (FIGURE 1). Additionally, since ACE is bioidentical to kininase, the enzyme that normally metabolizes bradykinin, ACE inhibition potentiates bradykinin levels. Cough and angioneurotic edema have been ascribed to this unanticipated effect of ACE inhibition on bradykinin [17]. While ACE-inhibitors have demonstrated long-term efficacy (probably due to their durable effects on bradykinin), their ability to suppress Ang II levels is short-lived [5]. Ang II can be formed independently of ACE; enzymes such as chymase, cathepsin G and chymostatin-sensitive angiotensin-generating enzyme (CAGE) are capable of releasing Ang II from Ang I. Also, since interruption of RAS at the level of ACE results in a compensatory rise in renin release and plasma renin activity (PRA), levels of Ang I surge during treatment (FIGURE 2) fueling non-ACE pathways and driving the production of Ang II [18]. The clinical implications of these escape phenomena are not well understood since the benefits of ACE-inhibitors are preserved in the long term [19,20].

The ARBs selectively interfere with Ang II binding at the AT₁. Since they block one of several Ang II receptors, ARBs, like ACE-inhibitors, do not completely suppress the RAS cascade. ARBs, like ACE-inhibitors, interrupt negative-feedback control of renin release and, therefore, increase PRA. Administration of irbesartan 150 mg resulted in a 205% increase in PRA (FIGURE 2) [21]. ACE-inhibitors, dihydropyridine calcium channel blockers and thiazide diuretics also potentiate increases in PRA [22–25]. The increase in Ang I during ARB therapy serves to increase Ang II levels. Theoretically, newly formed Ang II will interact with the unoccupied AT₂ receptor and have favorable biological effects, since the AT₂ receptor is believed to predominantly elicit effects that counterbalance the harmful actions of its counterpart, AT₁ [26]. While pharmacologically appealing, the clinical implications of unopposed AT₂ receptor activation are uncertain. The role of the AT₂ receptor in adults is debated; its greatest impact may be in the developing fetus [27]. In addition, there are other Ang II receptors with possible implications in cardiovascular and renal pathophysiology, so it is the net impact of the ARB on each of these receptors that determines the prevailing biological effect [28].

The uncertainties surrounding single-site RAS blockade with an ACE-inhibitor or ARB led to the supposition that combined blockade might confer more substantial benefit. By teaming an ACE-inhibitor with an ARB, combination therapy blocks the intermediate enzymatic step of Ang II formation and the final step of receptor activation and signaling. This is an attractive

concept because AT₁-mediated effects will be diminished irrespective of the source of Ang II (i.e., ACE or non-ACE) while allowing Ang II that does escape ACE inhibition to bind receptors other than AT₁. In fact this latter action, unopposed AT₂ activation, might be upregulated since combined blockade of ACE and AT₁ results in a synergistic rise in PRA and, therefore, Ang I [29]. For example, the combination of ramipril and valsartan increased PRA by 650% [29]. Whether this reflexive action is responsible for the smaller than expected fall in blood pressure with combination therapy or the lack of consistent benefit observed in large outcome studies is unknown.

The approval of aliskiren for the treatment of hypertension represents an important addition to the antihypertensive armamentarium. DRIs have long been revered for their potential therapeutic utility but difficulties in manufacturing potent, long-acting and orally bioavailable compounds hindered their development [16]. Aliskiren blocks the rate-limiting RAS step, conversion of angiotensinogen to Ang I, decreasing plasma PRA by 70% [30]. By catalyzing this transformation, renin is the ideal RAS pathway target for intervention. Indeed, aliskiren is the only RAS agent that decreases PRA. There is, however, a considerable rise in plasma renin concentration (PRC), although the implications have not been fully elucidated [31–33]. On one hand, in the face of aliskiren treatment, the newly released renin is enzymatically inert; aliskiren's high affinity for renin and substantial plasma and tissue concentrations render renin's ability to form Ang I essentially nonexistent [34]. On the other hand, renin and (pro)renin receptors have been recently identified and appear to mediate processes that might be detrimental to vascular and renal function [26]. Perhaps fortunately, these receptors are downregulated in the face of aliskiren treatment [35]. This downregulation may offset any possible deleterious effect of the rise in PRC with RAS agents.

The safety and incremental benefit of aliskiren in combination with an ACE-inhibitor or ARB have been investigated in several studies (see later). The addition of aliskiren to an ACE-inhibitor or ARB quenches the reactive rise in PRA that normally occurs during monotherapy with the latter agents [16]. When an ACE-inhibitor and aliskiren are given in tandem, sequential steps in the RAS cascade are blocked. Also, incorporation of the ACE-inhibitor preserves the bradykinin effect afforded by ACE inhibition. Conceptually, adding aliskiren to an ARB blocks the first and last steps of the RAS pathway. In both scenarios, aliskiren reduces the formation of Ang I, meaning that there is less substrate available to drive escape from the effects of the ACE-inhibitor or ARB. Whether one of these combinations is preferred over the other is unknown.

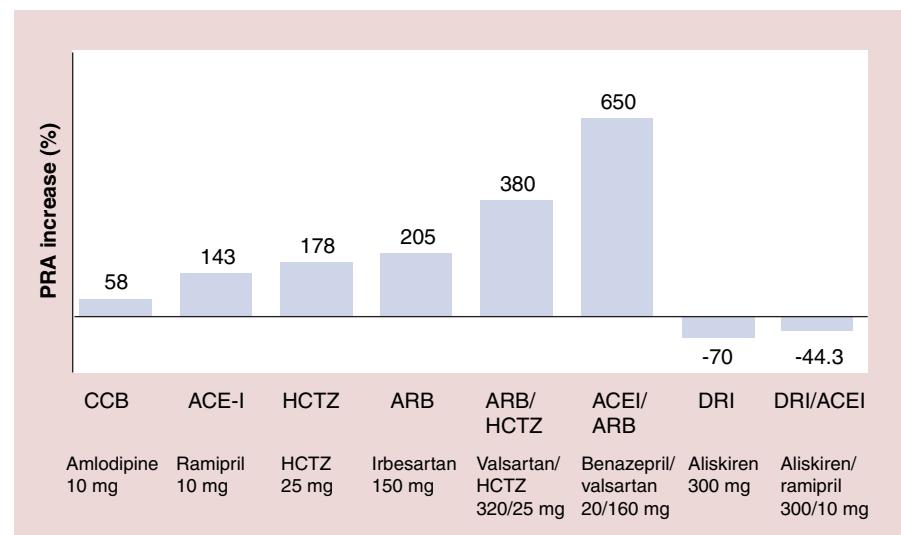


Figure 2. Change in plasma renin activity in patients treated with various antihypertensives and combination renin-angiotensin system blockade.

ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker; CCB: Calcium channel blocker; DRI: Direct renin inhibitor; HCTZ: Hydrochlorothiazide. Data from [21–25,29].

Recent clinical trials of combined RAS blockade

Hypertension

Early hypertension studies testing dual RAS blockade have revealed only modest incremental improvements in blood pressure despite more complete suppression of RAS (TABLE 1). In a meta-analysis of 14 blood pressure studies involving 434 study subjects, Doulton and colleagues compared the effects of combined RAS blockade (ACE-inhibitor/ARB) to either class alone on ambulatory and clinic blood pressure [36]. The authors observed an overall reduction in clinic and ambulatory blood pressure by approximately 4/3 mmHg with combination therapy compared with either class alone. Many of these trials dosed ACE-inhibitors only once daily, even though many ACE-inhibitors require twice-daily dosing to achieve adequate 24-h blood pressure control. By contrast, ARBs, with the exception of losartan, generally achieve effective 24-h blood pressure control with once-daily dosing. Consequently, it is unclear whether the small additional blood pressure-lowering effect of combination therapy truly represents more complete RAS blockade or is a manifestation of suboptimal ACE-inhibitor dosing. Regardless, the supplementary hypotensive action of adding a second RAS agent is less than expected when compared with other combinations.

In the largest combined RAS intervention study to date, the Ongoing Telmisartan Alone and in Combination with Ramipril Global End point (ONTARGET) trial (TABLE 2), dual therapy with an ACE-inhibitor (ramipril) and ARB (telmisartan) was compared with the respective monotherapies in 25,620 patients with vascular disease or high-risk diabetes, without evidence of HF [10]. Hypertension was prevalent, occurring in approximately 70% of study subjects at baseline. After a median follow-up of 56 months, the average additional systolic blood pressure-lowering effect of combination therapy compared with ramipril alone

Table 1. Mean change in clinic systolic blood pressure with combined angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy in hypertensives.

Study (year)	Patients on combination therapy	Change in blood pressure (mmHg [95% CI])	
		vs ACE-I monotherapy	vs ARB monotherapy
Azizi (2000)	60	-4.2 (-9.15, 0.75)	-2.5 (-7.73, 2.73)
Mogensen (2000)	69	-8.6 (-15.88, -1.32)	-11.2 (-18.41, -3.99)
Ferrari (2002)	10	-6.0 (-14.60, 2.60)	-5.0 (-11.13, 1.13)
Nakao (2003)	88	-0.1 (-0.50, 0.30)	-0.2 (-0.64, 0.24)
Morgan (2004)	23	-5.2 (-8.92, -1.48)	-3.7 (-8.21, 0.81)
Stergiou (2000)	20	-3.7 (-10.00, 2.60)	
Berger (2002)	12	-4.0 (-9.19, 1.19)	
Weir (2001)	25		-5.0 (-15.41, 5.41)
Overall effect		-3.8 (-6.74, -0.94)	-3.7 (-6.92, -0.39)

ACE-I: Angiotensin-converting enzyme inhibitor; ARB: Angiotensin receptor blocker.
Data adapted from [35].

was 2.4 mmHg. This is consistent with the aforementioned meta-analysis and more evidence to support the paltry antihypertensive action of ARBs when added to an ACE-inhibitor.

The incidence of the primary outcome (a composite of death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for HF) was not significantly different between combination therapy and ramipril alone (16.3 vs 16.5%, respectively). Likewise, no significant differences were observed among any of the individual components of the primary outcome, although all-cause death was numerically higher in the combination group (12.5 vs 11.8% of ramipril-treated subjects). These findings were unexpected; many believed that combining ramipril and telmisartan would afford more complete RAS blockade and significantly better blood pressure control that would translate into important reductions in clinical events. Even a reduction in systolic blood pressure of 2 mmHg in persons aged 60–69 years (median age in ONTARGET: ~66 years) would be expected to lower stroke mortality and mortality from ischemic heart disease or other vascular causes by as much as 10 and 7%, respectively [37]. The discordance between expected and actual outcomes is likely multifactorial. One contributing factor is the increased risk of adverse effects with combination therapy, especially renal events and hypotension. Subjects in the ramipril/telmisartan arm had an increased risk of developing major renal outcomes [38]. Whether the compensatory rise in PRA stimulated by combination therapy (which was presumably large but not reported) contributed to the lack of benefit has not been explored. The frequent use of antiplatelet agents (90%), statins (60%), other antihypertensive drugs (presumably most), and coronary intervention (50%) may have diluted the ability to detect a difference with combination therapy if one exists. Nevertheless, the event rate was still relatively high in all three arms and there was no trend signaling a possible benefit in favor

of combination therapy. One last, unrelated consideration which might explain the increased risk of mortality in the combination arm is the increased risk of cancer, especially cancers of the breast and lung, observed in this group.

Dual RAS blockade may also be achieved by combining a DRI with an ACE-inhibitor or ARB. In an 8-week trial, Uresin and colleagues randomized 837 diabetic patients with concomitant hypertension to treatment with once-daily aliskiren (150 mg titrated to 300 mg), ramipril (5 mg titrated to 10 mg) or a combination of both (150/5 mg titrated to 300/10 mg) [39]. At study end, combination therapy was associated with a significant 4.6/2.1 mmHg additional reduction in clinic blood pressure when compared with ramipril, but not aliskiren monotherapy. Adverse events were generally similar among treatment groups. The incidence of serum potassium (K^+) of over 5.5 mEq/l was higher in the

combination group (5.5%) than either monotherapy group (2.2 and 2.6% for aliskiren and ramipril, respectively); however, no differences existed for serum K^+ over 6.0 mEq/l. Interestingly, the incidence of cough was significantly lower in persons randomized to combination therapy (1.8%) versus ramipril alone (4.7%). This tantalizing finding needs to be replicated in larger studies that more accurately capture the incidence of cough before it is accepted as an attribute of the DRI class.

Oparil and colleagues randomized 1797 hypertensive subjects to once-daily aliskiren 150 mg, valsartan 160 mg, or a combination of the two [40]. Following 8 weeks of therapy, combination therapy reduced placebo-corrected blood pressure by 12.6/8.1 mmHg and provided additional reductions of 4.2/3.2 and 4.4/2.5 mmHg over aliskiren and valsartan monotherapy, respectively. Serum K^+ levels of 5.5 or higher occurred in 4% of patients receiving aliskiren/valsartan, 2% receiving valsartan, and 3% receiving placebo; the incidence of K^+ of over 6.0 mEq/l was low in all three treatment arms. Chrysant *et al.* confirmed the low risk of hyperkalemia (2%) with aliskiren/valsartan in a long-term study [41]. Most cases of hyperkalemia were transient and returned to normal without intervention by the end of follow-up.

Hypertensive patients with evidence of left ventricular hypertrophy (left ventricle wall thickness ≥ 13 mm) but without an ejection fraction of 40% or lower or BMI-defined obesity were enrolled in the Aliskiren in Left Ventricular Hypertrophy (ALLAY) trial [42]. A total of 456 subjects were randomized to aliskiren, losartan or the combination daily for 9 months. Treatment with nonstudy drug RAS inhibitors, including ACE-inhibitors, ARBs, β -blockers and aldosterone antagonists was prohibited for the study duration. Aliskiren tended to reduce left ventricular mass index (LVMI) more than losartan but the difference was not significant (5.8 vs 4.8 g/m²; $p = 0.52$). Similarly, the combination of losartan and

Table 2. Percentage of subjects experiencing adverse events with dual renin–angiotensin system blockade with an angiotensin-converting enzyme inhibitor and angiotensin receptor blocker.

Study (year)	Primary indication	Hyperkalemia (%)	Renal impairment* (%)	Ref.
CHARM-ADDED (2003)	Heart failure			[11]
Candesartan (n = 1276)		3 [‡]	NR	
Placebo (n = 1272)		1 [‡]	NR	
VALIANT (2003)	MI and heart failure			[46]
Valsartan (n = 4885)		1.3	4.9 [§]	
Captopril (n = 4879)		0.9	3.0	
Combination (n = 4862)		1.2	4.8 [§]	
Val-HeFT (2001)	Heart failure			[45]
Valsartan (n = 2511)		NR	1.1 [§]	
Placebo (n = 2499)		NR	0.2	
ONTARGET (2008)	High-risk vascular disease or DM			[10]
Ramipril (n = 8576)		NR	10.2	
Telmisartan (n = 8542)		NR	10.6	
Combination (n = 8502)		NR	13.5 [§]	

*Renal impairment was not defined in any trial.

[‡]Serum K⁺ ≥ 6.0 mEq/l at any time during the study.

[§]Statistically significant difference compared to angiotensin-converting enzyme inhibitor monotherapy (ONTARGET, VALIANT) or placebo (Val-HeFT).

CHARM-ADDED: Candesartan Cilexetil in Heart Failure Assessment of Reduction in Mortality and Morbidity; DM: Diabetes mellitus; MI: Myocardial infarction; NR: No data reported on this adverse event; ONTARGET: Effectiveness and Safety of Ramipril Alone Compared With Telmisartan Alone and in Combination With Ramipril in Patients at High Risk for Cardiovascular Events; Val-HeFT: Valsartan Heart Failure Trial; VALIANT: Valsartan in Acute Myocardial Infarction.

aliskiren reduced LVMI numerically more than losartan monotherapy. Systolic blood pressure reductions were similar across groups, ranging from 5.5 to 6.6 mmHg. Likewise, no differences in the incidence of adverse effects were observed among the three treatment arms. Reductions in LVH of the magnitude observed in this trial with aliskiren, losartan and the combination have been associated with reductions in cardiovascular events in other studies and thus suggest a possible role for the treatment of patients with longstanding hypertension and LVH [43].

Although few direct comparisons exist, the additional blood pressure reduction achieved with dual RAS inhibition over monotherapy is likely inferior to that achieved with the addition of a calcium channel blocker or thiazide diuretic to RAS-inhibitor monotherapy. ACE-inhibitors combined with thiazides, β-blockers or calcium channel blockers lower systolic blood pressure by approximately 14 mmHg [44], far exceeding blood pressure reductions achieved in most dual RAS blockade trials to date. Moreover, most dual RAS inhibition trials have examined only surrogate end points (e.g., blood pressure or proteinuria) rather than hard clinical end points (e.g., mortality). The results of ONTARGET clearly demonstrate that enhanced RAS blockade and a small incremental reduction in blood pressure with ACE-inhibitor/ARB combination therapy does not necessarily translate into improved outcomes [32]. Thus, current evidence does not support dual RAS blockade for the routine treatment of hypertension. Future trials, including Efficacy and Safety of Aliskiren and Aliskiren/Enalapril Combination on Morbi-Mortality in Patients With Chronic Heart Failure (ATMOSPHERE) (Clinical Trials.gov number, NCT00853658), will more appropriately define the role of combined RAS blockade including DRIs in reducing meaningful clinical events.

Heart failure

Inappropriate neurohormonal activation, including the sympathetic nervous system and RAS, is fundamental in the development and progression of chronic HF (CHF). Consequently, RAS blockade is a cornerstone of HF therapy, both in those with established disease and those at risk of developing HF. However, since monotherapeutic regimens of both ACE-inhibitors and ARBs incompletely suppress the RAS, dual RAS inhibition has emerged as a pharmacologically attractive option in combating the high mortality associated with HF.

The Candesartan in Heart Failure – Assessment of Reduction in Mortality and Morbidity (CHARM-ADDED) program randomized 2548 subjects with HF (NYHA class II–IV and LV ejection fraction ≤ 40%) on stable ACE-inhibitor therapy to additional therapy with candesartan (target dose: 32 mg after a 6-week titration) or placebo (TABLE 2) [11]. The primary outcome was a composite of cardiovascular death or unplanned hospital admission for HF. The majority of patients were NYHA functional class II (24.5%) or III (73%) with a mean LV ejection fraction of 28% and mean baseline blood pressure of approximately 125/75 mmHg. At baseline, 96% of subjects were receiving ‘optimized’ ACE-inhibitor therapy, which consisted of any ACE-inhibitor judged to be appropriately dosed by the study physician. Additionally, 90% of subjects received concomitant diuretic therapy, whereas 55 and 17% received β-blockers and spironolactone, respectively. After a median duration of 41 months, treatment with candesartan significantly reduced the composite end point by 15% (HR: 0.85; 95% CI: 0.75–0.96; p = 0.01) and each component of the primary end point with the exception of all-cause mortality. Subgroup analyses observed the greatest benefit in those treated with β-blockers and those achieving the recommended dose of ACE-inhibitor. The addition of candesartan was associated with significantly more

Table 3. Adverse events in subjects on combined renin–angiotensin system blockade including a direct renin inhibitor and angiotensin-converting enzyme inhibitor or angiotensin receptor blocker.

Study (year)	Primary indication	$K^+ \geq 6.0 \text{ mEq/l}$	$\text{SCr} \geq 2.0 \text{ mg/dl}$	Ref.
AVOID (2008)	Diabetic nephropathy			[57]
Aliskiren (n = 301)		14 (4.7%)*	37 (12.4%)	
Placebo (n = 298)		5 (1.7%)	54 (18.2%)	
Oparil <i>et al.</i> (2007)	Hypertension			[40]
Placebo (n = 458)		6 (1%)	0	
Valsartan (n = 455)		5 (1%)	2 (0.4%)	
Aliskiren (n = 437)		4 (1%)	1 (0.2%)	
Combination (n = 446)		2 (0.5%)	4 (0.9%)	
ALLAY (2009)	Hypertension and LVH			[42]
Losartan (n = 129)		1 (0.7%)	1 (0.7%)	
Aliskiren (n = 154)		3 (2.0%)	0	
Combination (n = 154)		1 (0.7%)	1 (0.7%)	
ALOFT (2008)	Heart failure			[47]
Aliskiren		3 (1.9%)	11 (7.1%)	
Placebo		6 (4.2%)	8 (5.6%)	

*p = 0.06 for the comparison with placebo.

ALLAY: Aliskiren in Left Ventricular Hypertrophy; ALOFT: Aliskiren Observation of Heart Failure Treatment; AVOID: Aliskiren in The Evaluation of Proteinuria in Diabetes; LVH: Left ventricular hypertrophy; NR: No data reported on this adverse event.

adverse events, including increased creatinine and hyperkalemia (TABLE 2), and more candesartan-allocated subjects discontinued treatment due to adverse events compared with placebo.

The Valsartan Heart Failure Trial (Val-HeFT) (TABLE 2) included 5010 subjects with similar baseline characteristics to the aforementioned CHARM-ADDED trial; however, fewer subjects received concomitant ACE-inhibitor (93%), diuretic (85%) and β-blocker (35%) therapy [45]. Subjects were randomized to add-on therapy with valsartan or placebo with 84 and 93% achieving the target dose of 320 mg, respectively (mean valsartan dose achieved: 254 mg). Background ACE-inhibitor doses were less tightly controlled compared with the CHARM-ADDED study. Primary end points included all-cause mortality and a composite of mortality and morbidity, defined as the incidence of cardiac arrest with resuscitation, HF hospitalization, or receipt of intravenous inotropic or vasodilator therapy for 4 h or longer. Following a mean study duration of 23 months, no significant differences in all-cause mortality were observed. The composite end point of mortality and morbidity was significantly reduced by 13% in the valsartan group (28.8 vs 32.1% for valsartan and placebo, respectively; p = 0.009), owing primarily to a 4.5% absolute risk reduction in hospitalization for HF. Interestingly, a *post hoc* subgroup analysis revealed an approximately 40% higher risk of all-cause death (p = 0.009) and a nearly 20% higher risk of the composite end point (p = 0.10) in those randomized to valsartan who were on baseline ACE-inhibitor and β-blocker therapy. It has been suggested that this might reflect excessive neurohormonal attenuation with dual RAS and β-blockade, although this finding of harm with triple neurohormonal blockade has not been duplicated in other studies. Accordingly, it might have simply been chance due to the multiple comparisons made in the Val-HeFT study. Valsartan was associated with a greater discontinuation rate due to adverse events (9.9 vs 7.2% for placebo), including renal impairment (TABLE 2).

In the Valsartan in Acute Myocardial Infarction (VALIANT) trial, 14,808 subjects with HF and a recent history of myocardial infarction were randomized to captopril, valsartan, or both and followed for a median of 24.7 months [46]. No significant differences were observed among the three groups for the primary end point, all-cause mortality (TABLE 2). Likewise, combination therapy was associated with no improvement in secondary outcomes in the overall population or any subgroup. Furthermore, combined RAS blockade was associated with the greatest frequency of drug-related adverse events and discontinuations due to adverse events. The lack of benefit in this setting as opposed to in CHF might be due to the time course and intensity of RAS activity in the ACS setting versus CHF. In CHF, RAS activity is chronically activated and may escape single-site blockade whereas in ACS the RAS may be activated in more of a burst fashion with less need for dual-site blockade.

Recently, direct renin inhibition with aliskiren has been studied in the setting of CHF in patients already being treated with an ACE-inhibitor or ARB. The Aliskiren Observation of Heart Failure Treatment (ALOFT) trial randomized 302 subjects with stable NYHA class II–IV HF, hypertension and brain natriuretic peptide (BNP) levels above 100 pg/ml to aliskiren 150 mg or placebo in addition to conventional HF therapy, including an ACE-inhibitor (83 and 84%, respectively) or an ARB (16 and 14%, respectively) [47]. Almost all patients received concomitant β-blocker therapy. Aliskiren 150 mg was well tolerated in this population and none of the prespecified safety end points, which included renal dysfunction, symptomatic hypertension and hyperkalemia, occurred more frequently with aliskiren compared with placebo (TABLE 3). This was true despite the use of an ACE-inhibitor or ARB in combination with a β-blocker (~95% of subjects) and spironolactone (~33% of subjects). Following 12 weeks of therapy, mean BNP levels decreased by

12 pg/ml in placebo-treated patients compared with a 61 pg/ml reduction in aliskiren-treated subjects ($p = 0.016$ for the comparison), suggesting beneficial neurohormonal effects associated with the addition of aliskiren therapy. The magnitude of change in BNP with aliskiren is nearly double that obtained with the addition of valsartan, isosorbide dinitrate/hydralazine, or spironolactone to optimal background therapy [44,48,49]. N-terminal proBNP and urinary aldosterone were also reduced. No significant differences were observed in the development of signs/symptoms of HF or echocardiographic changes between groups during the short follow-up. Collectively, these findings suggest that aliskiren might be associated with improved morbidity and mortality in HF. However, the favorable hemodynamic and neurohormonal effects from early studies will need to be confirmed in larger studies powered to evaluate important clinical outcomes.

The overall mixed results of dual RAS blockade for HF subjects suggests that such therapy may be beneficial in carefully selected patients; however, routine use of combined therapy is not recommended, consistent with the most recent focused update of the American College of Cardiology/American Heart Association HF guidelines [50]. Moreover, such therapy is likely associated with a greater incidence of adverse effects and subsequent discontinuation (TABLES 2 & 3) [51]. Patients receiving dual RAS blockade must be closely monitored to attenuate the impact of these effects.

Renal disease

Numerous large-scale clinical trials have demonstrated the antiproteinuric effects associated with ACE-inhibitors [52,53] and ARBs [54,55]. However, large-scale trials of combination therapy have not consistently reproduced these findings and several important limitations hinder a complete understanding of the role of dual RAS blockade in this population. A recent systematic review and meta-analysis reviewed 49 trials involving 6181 subjects that assessed the effects of RAS monotherapy and combination therapy on proteinuria levels [56]. Not surprisingly, most studies favored treatment with ARBs over placebo and calcium channel blockers in reducing proteinuria at 1–4 and 5–12 months of follow-up. Outcomes among ARB-treated patients were no different than those treated with ACE-inhibitor therapy, suggesting similar efficacy among and within these classes. Combined ACE-inhibitor/ARB therapy was associated with a greater overall reduction in proteinuria levels for both follow-up periods when compared with ACE-inhibitor or ARB therapy alone; however, most trials were small (mean total sample size: 35 for ARB vs combination therapy; 40 for ACE-inhibitor vs combination therapy) and the majority of individual trials observed nonsignificant reductions in proteinuria. Furthermore, combination therapy afforded significantly greater reductions in proteinuria than ARB monotherapy for both follow-up periods, whereas when compared with ACE-inhibitor monotherapy, combination therapy was only more effective in trials assessing 1–4 months of follow-up. Several design limitations are noteworthy. Blood pressure was

often better controlled in the combination arm and the dose of background ACE-inhibitor therapy was often not the maximal antiproteinuric dosage, making interpretation of the findings difficult. Both of these shortcomings cloud the study interpretation because it is unclear whether the benefit was entirely related to more complete RAS blockade. Instead, these findings may reflect greater blood pressure lowering or converting low dose, suboptimal ACE inhibition to adequate blockade.

The Irbesartan in the Management of Proteinuric Patients at High Risk for Vascular Events (IMPROVE) avoided many of the shortcomings noted earlier. Subjects were randomized to an appropriate antiproteinuric dose of ramipril (10 mg) with the addition of irbesartan (300 mg) or placebo [12]. Following 20 weeks of treatment, combination therapy was no more effective than ramipril monotherapy in reducing albumin excretion rates in hypertensives with concomitant microalbuminuria and high cardiovascular risk. The absence of any significant benefit persisted despite additional, albeit minor, blood pressure reductions afforded by combination therapy (2.9/1.8 mmHg).

The well-conducted and recently completed Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID) trial has contributed to the understanding of dual RAS blockade in patients with proteinuria. AVOID allocated 599 Type 2 diabetic subjects with concomitant nephropathy treated with losartan 100 mg to 6 months of treatment with aliskiren (150 and 300 mg for 3 months each) or placebo in a double-blind fashion [57]. The primary efficacy outcome was a reduction in the urinary albumin:creatinine ratio at 6 months. In subjects treated with aliskiren, the albumin:creatinine (UACR) ratio fell by 20% compared with those receiving placebo ($p < 0.001$ for the comparison), which remained significant after adjustment for a small, nonsignificant blood pressure reduction (2/1 mmHg) in the aliskiren group. Aliskiren treatment resulted in a twofold increase in the number of patients who achieved a reduction in UACR of 50% or greater (24.7 vs 12.5%; $p < 0.0005$). Reductions in proteinuria have been correlated with reductions in the risk for progression of renal disease and cardiovascular events [43,58,59]. Elevations in serum potassium of over 5.5 mEq/l occurred in 13.7 vs 10.8% of patients treated with aliskiren/losartan and losartan, respectively. More patients in the aliskiren/losartan arm experienced increases in potassium to over 6.0 mEq/l (4.7 vs 1.7%); however, this should be tempered with the observation that there were numerically fewer cases of hypokalemia in the combination treatment group.

To date, most dual RAS blockade studies are limited by examining only surrogate markers such as proteinuria. Although proteinuria is correlated with an elevated propensity for progression of chronic kidney disease and development of renal failure, it is unknown whether the suggested benefits of combined RAS therapy impart sustained reductions in the risk of renal failure and mortality [60,61]. In the COOPERATE trial, combination ACE-inhibitor/ARB therapy purportedly reduced the primary composite end point of time to doubling of serum creatinine or end-stage renal disease by 62% (95% CI: 0.18–0.63) compared with trandolapril alone. However, this study was plagued by serious

methodological flaws that undermine its validity. A recent re-analysis of the data revealed much wider confidence intervals (95% CI: 0.19–2.68; $p = 0.31$) than originally reported, suggesting no beneficial effect of dual RAS blockade [62]. In ONTARGET, the largest study to date to assess renal outcome with combination therapy, ramipril and telmisartan were equivalent with respect to their effects on proteinuria and major renal outcomes [32]. Similar to the aforementioned meta-analysis, combined ramipril/telmisartan therapy was associated with greater reductions in proteinuria than either agent alone; yet, despite this beneficial effect on surrogate outcomes, treatment with combination therapy resulted in a significantly higher frequency of the composite primary end point of dialysis, doubling of serum creatinine, and all-cause death (14.5 [combination] vs 13.4 [telmisartan] and 13.5% [ramipril]; $p = 0.037$ for the comparison with ramipril) [32]. It is important to point out that in ONTARGET, patients had intact renal function at baseline; the impact of dual RAS blockade in patients with established kidney disease may be different. Likewise, the collection of renal events in ONTARGET has been criticized [63]. Aggressive RAS blockade can cause a small, transient increase in serum creatinine, which is hemodynamic in nature and does not reflect kidney damage. This may have been misclassified in the ONTARGET trial.

Expert commentary

RAS blockade is etched into the treatment algorithms for the management of hypertension, diabetes, and heart and renal disease and, in each case, it improves outcomes. However, it would be hasty to declare victory against these maladies. For example, in clinical trials that tested RAS blockade with either an ACE-inhibitor or ARB, the residual risk of death in treated patients ranged from 11% in patients with hypertension and LVH to 35% in patients with HF and a reduced ejection fraction [2,11,64,65]. Likewise, in persons with diabetic nephropathy, treatment with an ARB decelerated the annual loss of renal function from around 6.8 ml/min/year (normalized for body surface area) to 5.5 ml/min/year (normalized for body surface area), which is still markedly steeper than the 1 ml/min/year (normalized for body surface area) in nondiabetic persons [48]. This residual risk has compelled some to administer ACE-inhibitors with ARBs in clinical practice and has encouraged the design and execution of multiple clinical trials testing the utility of dual RAS blockade.

Pharmacologically, dual RAS blockade can be rationalized. Administering an ACE-inhibitor with an ARB further decreases AT₁-mediated processes and preserves the ACE-inhibitor's effect on bradykinin. However, both agents signal a complementary rise in PRA, which may ultimately overcome dual blockade or have other consequences. Recent studies indicate that adding an ARB to an ACE-inhibitor in patients with hypertension only minimally lowers blood pressure and does not improve outcomes. On the other hand, combining these agents in HF or kidney disease where local tissue RAS pathways may be activated does confer a small incremental reduction in events/disease progression. Combined RAS blockade comes at an increased risk for adverse events, especially renal dysfunction,

hyperkalemia, and orthostasis. Thus, the risk–benefit profile does not lend itself to use in hypertension, but does support use of this combination in thoughtfully selected patients with HF or proteinuria. Guidelines from Canada have already strongly advised clinicians to avoid combining ACE-inhibitors with ARBs in patients with hypertension and we suspect that this sentiment will be echoed in the JNC-8 guidelines [66].

The addition of aliskiren to an ACE-inhibitor or ARB is the most appealing pharmacological strategy for combination RAS blockade. Aliskiren reduces the typical rise in PRA that occurs with ACE-inhibitor or ARB monotherapy. It is the most complete RAS antagonist, decreasing PRA by at least 70%. When administered with an ACE-inhibitor, sequential steps in the formation of the system's effector peptide, Ang II, are blocked. Aliskiren may also lower the risk of cough by tempering the ACE-inhibitor-induced increase in bradykinin. We suspect that as aliskiren reduces levels of Ang I, unengaged circulating ACE scavenges for additional substrates such as bradykinin. Consequently, aliskiren treatment may buffer the rise in bradykinin and mitigate the risk of cough in patients given an ACE-inhibitor. The risk of cough was significantly lower with ramipril when it was given with aliskiren versus when it was given unopposed. This combination also effectively lowers blood pressure, though not as profoundly as combinations of a RAS agent with calcium channel blocker or diuretic, and was well tolerated. In ALOFT, nearly 85% of patients were on an ACE-inhibitor at baseline. In this safety trial, the addition of aliskiren was well tolerated in a vulnerable HF population, and there were favorable changes in a variety of surrogate markers, including BNP and cardiac function.

Concomitant use of an ARB and aliskiren blocks the final and rate-limiting step of RAS, respectively. These agents are less susceptible to escape phenomena compared with ACE-inhibitors and such a strategy may be envisioned to be more complete. However, this strategy is not expected to influence bradykinin levels, which might be perceived as an attribute and limitation; an attribute because the risk of cough and angioedema is negligible compared with placebo but a limitation because bradykinin is responsible for a variety of beneficial activities. In patients with hypertension, pairing an ARB with aliskiren significantly lowers blood pressure. The combination reduces proteinuria in patients with diabetic nephropathy and also tends to reverse LVH to a greater extent than ARB monotherapy. The combination has been well tolerated in clinical trials with a small increase in the risk of hyperkalemia emerging as the only important concern. Importantly, in the AVOID trial the increased risk of hyperkalemia was partially offset by a lower risk of hypokalemia and in ALOFT the risk of clinically significant hyperkalemia was low despite use of ACE-inhibitors and spironolactone in many patients.

Based on these data, dual RAS blockade with an ACE-inhibitor and ARB should be used judiciously and only in select patients with HF or marked proteinuria. This modality should not be used for hypertension or in unselected patients with HF or proteinuria. Aliskiren has been studied in combination with

an ACE-inhibitor and ARB and may be a better option for use as part of dual RAS blockade in hypertension given that it extinguishes the compensatory PRA rise, significantly lowers blood pressure, and causes few adverse events. Outcomes data are needed to firmly secure aliskiren's role alongside ACE-inhibitors and ARBs and clinicians will need to consider the efficacy of aliskiren in the face of its increased acquisition cost versus other agents. The role of direct renin inhibition in HF, kidney disease and diabetes is still being elucidated, but initial studies have shown favorable changes in surrogate markers and reassuring safety data.

Five-year view

By 2014, several elements will impact the landscape of combined RAS blockade: the current literature will be enriched with additional studies evaluating combination ACE-inhibitor/ARB therapy; a series of clinical trials will report on the safety and efficacy of aliskiren with an ACE-inhibitor or ARB; and several novel antihypertensive agents that affect RAS will emerge.

The Combination Angiotensin Receptor Blocker and Angiotensin Converting Enzyme Inhibitor for Treatment of Diabetic Nephropathy VA (NEPHRON-D) study, which is comparing losartan to losartan plus lisinopril on the progression of kidney disease in 1850 patients with diabetes and overt proteinuria, will shed light on the utility of combination therapy in patients with renal disease. It is unlikely that this study or others will redefine the current view on dual RAS blockade with an ACE-inhibitor and ARB for the treatment of hypertension. Instead these studies will solidify the current position outlined earlier.

On the other hand, there is hope that direct renin inhibition, owing to its targeting of the rate limiting RAS step, suppression of the compensatory PRA rise, and downregulation of (pro)renin receptors, might demonstrate benefit in outcome studies where it is added to ACE-inhibitors or ARBs. A very large clinical trial program, Effectiveness Study of Single Photon Emission Computed Tomography (SPECT) Versus Positron Emission Tomography (PET) Myocardial Perfusion Imaging (ASPIRE HIGHER), is evaluating the safety and efficacy of aliskiren in 35,000 patients in 14 different studies enrolling diverse patient types (including those already treated with an ACE-inhibitor or ARB). The Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease End Points (ALTITUDE) trial will report whether the addition

of aliskiren to an ACE-inhibitor or ARB in patients with Type 2 diabetes decreases cardiovascular and renal events in 8600 high-risk patients. The ATMOSPHERE and Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) studies will evaluate the role of direct renin inhibition in chronic and acute HF, respectively. Aliskiren and Valsartan to Reduce NT-proBNP via Renin-Angiotensin–Aldosterone System Blockade (AVANT-GARDE) and Aliskiren Study in Post-MI Patients to Reduce Remodeling (ASPIRE) will determine whether the combination of aliskiren and another RAS agent improves ventricular hemodynamics in patients with a recent acute coronary syndrome and normal or reduced left ventricular function, respectively. In patients with diabetes and/or microalbuminuria the antihypertensive effect of the combination of aliskiren and valsartan will be examined in the TARGET HIGHER study. This program will be instrumental in defining the role of DRIs as part of combination RAS blockade.

It is plausible that new classes of antihypertensive agents will become available that show promise in combination with conventional RAS agents. These classes include the endothelin receptor antagonists, dual-acting angiotensin and endothelin receptor antagonists, and ARB-neutral endopeptidase inhibitors. These agents are currently being studied in a variety of different settings, including in combination with RAS agents. Such studies will help to determine the role for these novel agents. It is difficult to forecast how these evolving agents will affect clinical practice. It is likely that endothelin receptor antagonists will have the greatest utility when administered with a RAS agent in persons with salt-sensitive resistant hypertension. The dual acting agents, dual-acting angiotensin and endothelin receptor antagonists and ARB-neutral endopeptidase inhibitors, may be significantly more effective than monotherapy with a RAS blocker. If this is the case, then it will be important to determine the cost-effectiveness of using these newer agents instead of older, cheaper agents like ACE-inhibitors.

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Key issues

- The renin–angiotensin system (RAS) plays an important role in the pathobiology of cardiovascular and renal disease, but the optimal method for interrupting its end-organ effects is still under investigation.
- Angiotensin-converting enzyme (ACE)-inhibitors, angiotensin receptor blockers (ARBs) and direct renin inhibitors do not completely silence RAS and this may prevent the full potential of RAS blockade from being realized.
- Combining an ACE-inhibitor and ARB precipitates a large compensatory rise in plasma renin activity, only marginally lowers blood pressure, and is not associated with improved outcomes in hypertension.
- In congenital heart failure and proteinuria, combining an ACE-inhibitor and ARB impedes disease progression in carefully selected patients.
- Combining aliskiren with an ACE-inhibitor or ARB reduces blood pressure, improves surrogate end points like proteinuria, brain natriuretic peptide and left ventricular hypertrophy, and does not signal a reactive rise in plasma renin activity.
- Combining RAS agents increases the risk for hyperkalemia and may increase the risk of renal dysfunction in vulnerable patients.

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Affiliations

- Benjamin J Epstein, PharmD, BCPS Assistant Professor of Pharmacy and Medicine, Departments of Pharmacotherapy and Translational Research and Medicine, University of Florida, FL, USA and President, East Coast Institute for Research, Jacksonville, FL, USA
- Steven M Smith, PharmD Postdoctoral Fellow, Departments of Pharmacotherapy and Translational Research and Community Health and Family Medicine, University of Florida, FL, USA
- Rushab Choksi, PharmD Medical Science Liaison, Otsuka America Pharmaceutical, Inc., USA