REVIEW

Aliskiren and valsartan combination therapy for the management of hypertension

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Abstract: Combination therapy is necessary for most patients with hypertension, and agents that inhibit the renin-angiotensin-aldosterone system (RAAS) are mainstays in hypertension management, especially for patients at high cardiovascular and renal risk. Single blockade of the RAAS with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB) confers some cardiorenal protection; however, these agents do not extinguish the RAAS as evidenced by a reactive increase in plasma renin activity (PRA), a cardiovascular risk marker, and incomplete cardiorenal protection. Dual blockade with an ACE inhibitor and an ARB offers no additional benefit in patients with hypertension and normal renal and left ventricular function. Indeed, PRA increases synergistically with dual blockade. Aliskiren, the first direct renin inhibitor (DRI) to become available has provided an opportunity to study the merit of DRI/ARB combination treatment. By blocking the first and rate-limiting step in the RAAS, aliskiren reduces PRA by at least 70% and buffers the compensatory increase in PRA observed with ACE inhibitors and ARBs. The combination of a DRI and an ARB or an ACE inhibitor is an effective approach for lowering blood pressure; available data indicate that such combinations favorably affect proteinuria, left ventricular mass index, and brain natriuretic peptide in patients with albuminuria, left ventricular hypertrophy, and heart failure, respectively. Ongoing outcome studies will clarify the role of aliskiren and aliskiren-based combination RAAS blockade in patients with hypertension and those at high cardiorenal risk.

Keywords: aliskiren, valsartan, single-pill combination, hypertension, renin-angiotensin-aldosterone system, plasma renin activity

Hypertension is a progressive condition with significant health consequences.[1] Even slight elevations (ie, 2 mmHg) in blood pressure (BP) can substantially increase cardiovascular and cerebrovascular risk.[2,3] The ultimate goal of treating hypertension is to achieve and maintain a BP that will optimally reduce the risk for cardiovascular, cerebrovascular, and renal disease and death.[4,5] However, obtaining and maintaining adequate control of BP can be a challenge for many high-risk patients. According to the US National Health and Nutrition Examination Survey (NHANES), BP is effectively controlled in less than 40% of patients receiving antihypertensive therapy; patients with diabetes or cardiovascular, cerebrovascular, or renal disease fare even worse, exhibiting lower BP control rates than do patients without these comorbidities.[6,7] These observations suggest that more effective treatment strategies are needed for physicians to help patients achieve BP goals and, ultimately, to reduce hypertension-related disease and death.

Evidence continues to accumulate from landmark randomized trials showing the need for at least two antihypertensive agents to successfully treat hypertension in most

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patients. For example, in the ALLHAT trial, 63% of patients with hypertension and at least one additional cardiovascular risk factor required at least two antihypertensives to achieve a BP goal of <140/90 mmHg after 4.9 years of follow-up.[8] In the ASCOT-BPLA trial, which included more than 19,000 patients with hypertension and at least three additional cardiovascular risk factors, 78% of patients required treatment with at least two antihypertensive agents to maintain the target BP (<140/90 mmHg for patients without diabetes; <130/80 mmHg for patients with diabetes).[9] In AASK, an average of three agents were needed to achieve a mean arterial pressure goal of ≤92 mmHg.[10] Because combination treatment is eventually necessary, published guidelines recommend it as initial treatment for most patients, especially those with initial high BP and those with cardiovascular or renal risk.[4,5,11] This approach also allows patients to achieve the BP goal more quickly. In the ACCOMPLISH trial, in which 11,506 patients with high risk for hypertension were randomly assigned to receive combination therapy, 73% of patients were able to achieve BP control within 6 months.[12,13]

It is expected that prompt control of BP will discourage therapeutic inertia and might improve outcomes in patients with hypertension; however, few studies have been aimed at evaluating the relationship of attainment of early BP control with cardiovascular outcomes. The VALUE trial enrolled patients with hypertension and a history of cardiovascular disease, diabetes, or stroke. Attainment of BP control (systolic BP ≤140 mmHg) within 6 months was associated with a significant reduction in the risk for cardiovascular events and death, regardless of the type of drug used.[14] Furthermore, in the ASCOT trial, relative to those receiving an atenolol-based combination therapy regimen, hypertensive patients receiving an amlodipine-based regimen exhibited a significant reduction in the total number of coronary events associated with superior BP control, which was evident by 1 year of treatment.[9] Finally, the Syst-EUR trial found that, compared with delayed treatment and control, early treatment and control of BP in hypertensive adults 60 years or older resulted in a significant reduction in the frequency of, and risk (adjusted relative hazard) for, stroke and major cardiovascular events.[15] In this study, delayed onset of antihypertensive treatment also showed benefit in clinical outcomes by reduction of systolic BP in patients, albeit to a lesser extent than in the early-treatment group. The soon-to-be-released Joint Commission (JNC-8) recommendations are expected to further highlight the importance of the use of combination therapy early in the hypertension treatment algorithm.

Contemporary evidence from the studies noted herein will be incorporated into the updated guidelines as further evidence of the value of logical combination therapy for securing more effective and earlier BP control and improved outcomes. Combinations that include a renin-angiotensin-aldosterone system (RAAS) antagonist, such as an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), plus a calcium channel blocker or thiazide diuretic are the most effective, well-tolerated, and proven strategies.[11]

The role of the RAAS in hypertension management

The role of the RAAS in cardiovascular and renal homeostasis is well established, as is the role of an up-regulated RAAS in cardiovascular disease such as hypertension and ischemic heart disease.[16] Angiotensin II, the major effector peptide of the RAAS, contributes to the progression of target organ damage via a number of hemodynamic and cellular actions (Figure 1). By promoting vasoconstriction and aldosterone release and by increasing oxidative stress, as well as augmenting the production of cytokines, adhesion molecules, and growth factor in these target tissues, angiotensin II plays a pivotal role in cardiovascular and renal disease. Some of the other pathologic effects of angiotensin II include cardiac and vascular remodeling, inflammation, thrombosis, and even plaque rupture, the ultimate and lethal step in atherosclerosis.[17] With regard to renal disease, angiotensin II is partially responsible for promoting albuminuria and accelerating the decrease in the glomerular filtration rate associated with diabetic nephropathy, the leading cause of end-stage renal disease in the modern world.[18] Inhibitors of RAAS, such as ARBs, and, more recently, the direct renin inhibitor aliskiren, alone and in combination with an ARB, has been shown to slow the decrease in glomerular filtration rate and diminish albuminuria in patients with diabetic nephropathy.[19,20] In addition to angiotensin II, other RAAS components have been cited as biomarkers of cardiovascular risk. Elevated levels of plasma renin activity (PRA) have been shown to be independently associated with an increased risk for myocardial infarction (MI) in patients with hypertension.[21] More recently, in an analysis of 2913 patients with stable vascular disease or diabetes who were enrolled in the HOPE study, an elevated PRA was found to be associated with a 49% increase in the risk for major cardiovascular events.[22] In 1172 patients with severe coronary artery disease with no history of cardiac events, elevated PRA independently predicted a 40% increased risk for death and a twofold increased risk for hospitalization for congestive heart failure
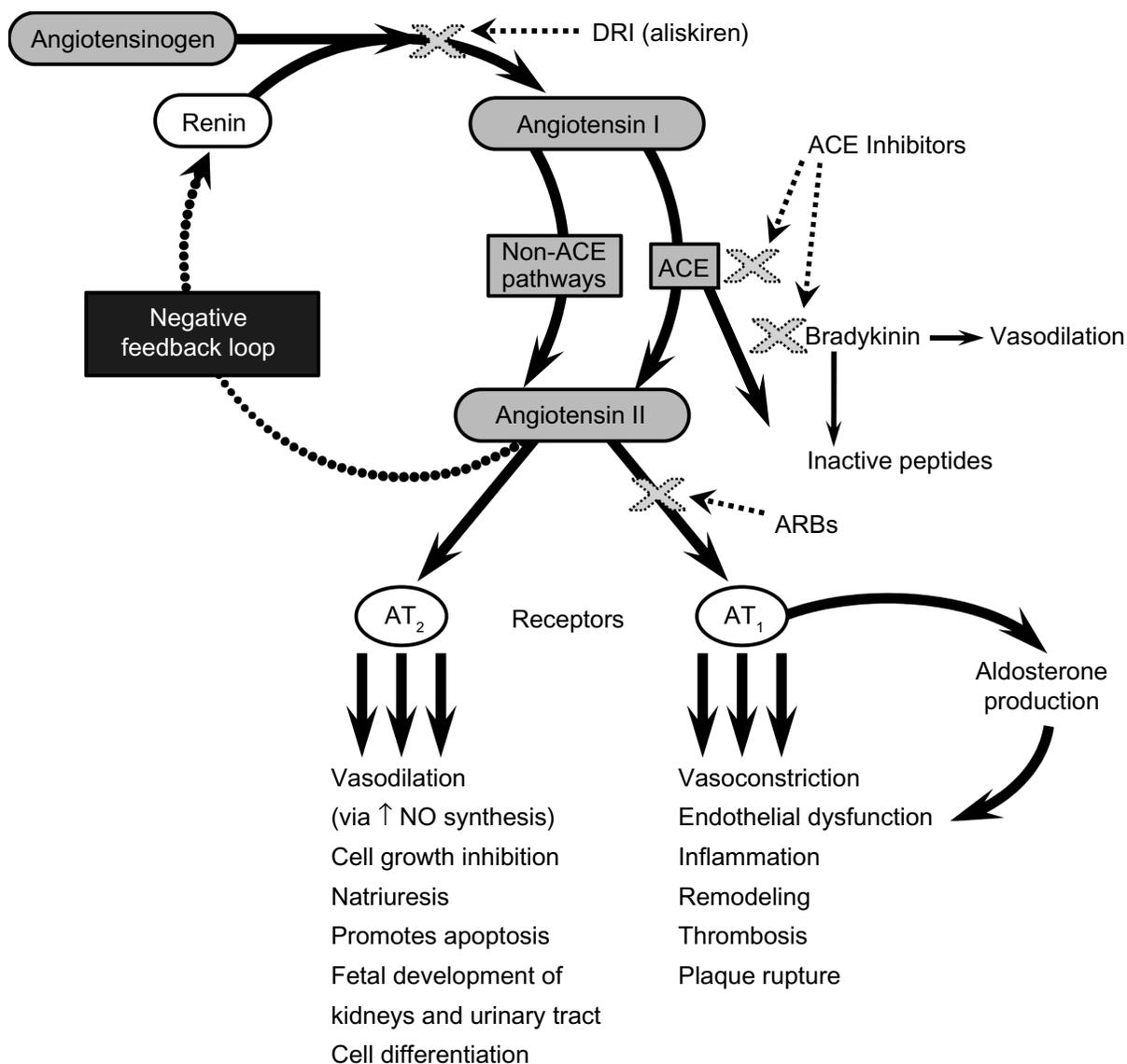
Figure 1 The renin-angiotensin-aldosterone system.
Abbreviations: DRI, direct renin inhibitor; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AT, angiotensin II receptor, type1/2; NO, nitric oxide.

(CHF) during long-term (>5 years) follow-up.[23] Evidence is also accumulating that the overproduction of aldosterone increases cardiovascular risk independent of its effects on BP, and, similar to angiotensin II, promotes inflammation, oxidative stress, and fibrosis.[24]

Although pharmacologic manipulation of the RAAS with ACE inhibitors and ARBs improves outcomes in hypertension and cardiovascular and renal disease, it provides only partial protection from disease progression (Table 1). This might be explained by the contributions of other mechanisms to disease or progression or by the inadequacy of ACE inhibitors and ARBs. Possible mechanisms for the inadequacies include interruption of negative feedback and a compensatory increase in renin and angiotensin

I levels, which can overcome ACE inhibition or result in the production of angiotensin II by non-ACE pathways (ie, ACE escape).[25] Further, the inability of ARBs to occupy all angiotensin II type (AT)₁ receptors at any given time[26] and aldosterone breakthrough[27,28] during ACE inhibition or ARB use are additional possible mechanisms for this lack of complete protection by ACE inhibition and angiotensin receptor blockade. For these reasons, inhibition of renin (the first and rate-limiting step in the RAAS; Figure 1) has long been a pharmacologic target for RAAS blockade; however, only recently has aliskiren emerged as the first direct renin inhibitor (DRI) available for clinical use.[29] By inhibiting the conversion of angiotensinogen to angiotensin I and by decreasing PRA, aliskiren may provide a more complete

Table 1 Outcomes in cardiovascular disease and renal disease with ACE inhibitors or ARBs

Cardiovascular disease

Study	Patients	Daily treatment regimen	Mean follow-up	Main outcome	Risk reduction versus comparator
HOPE[63]	9297 patients at high CV risk	Ramipril 10 mg daily versus placebo	5 years	Composite of MI, stroke, or death	↓22%
CONSENSUS[64]	235 patients with severe HF	Enalapril 2.5 to 4 mg versus placebo	188 days	Total mortality	↓27%
SOLVD[65]	1284 patients with chronic HF	Enalapril 2.5 to 20 mg	41.4 months	Total mortality	↓16%
Val-HeFT[66]	5010 patients with HF receiving standard HF therapy	Valsartan 160 mg versus placebo	23 months	Death and disease plus cardiac arrest, HF hospitalization, or need for IV vasodilators	No difference in mortality ↓13% in combined end point
LIFE[67]	9193 hypertensive patients with LVH	Losartan 50–100 mg versus atenolol 50–100 mg	4.8 years	Death, MI, stroke	↓13%
CHARM-alternative[68]	2028 patients with chronic HF intolerant of ACE inhibitors	Candesartan 32 mg versus placebo	33.7 months	CV death or HF hospitalization	↓23%

Renal disease

Study	Patients	Daily treatment regimen	Mean follow-up	Main outcome	Risk reduction versus comparator	Annual rate of renal function decline (mL/min/1.73 m²)
RENAAL[19]	1513 patients with type 2 diabetes and nephropathy	Losartan 50–100 mg versus placebo	3.4 years	Doubling of SCr, ESRD, or death	16%	Losartan: ↓4.4 Placebo: ↓5.2
IDNT[69]	1715 hypertensive patients with type 2 diabetes and nephropathy	Irbesartan 300 mg, amlodipine 10 mg, or placebo	2.6 years	Doubling of SCr, ESRD, or death	20% versus placebo 23% versus amlodipine	Irbesartan: ↓5.5 Amlodipine: ↓6.8 Placebo: ↓6.5

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; IV, intravenous; LVH, left ventricular hypertrophy; SCr, serum creatinine; ESRD, end-stage renal disease.

blockade of the RAAS and offers a new opportunity to explore multistep RAAS blockade.

The remainder of this article is directed at evaluating the experience accumulated with combination DRI/ACE or ARB, discussing the differences between dual RAAS blockade with ACE inhibitors/ARBs and DRI plus an ACE inhibitor or an ARB, and reviewing the role of combination aliskiren/valsartan in the treatment of hypertension.

Dual RAAS blockade
ACE inhibitor plus ARB

The success of single RAAS blockade with an ACE inhibitor or an ARB led researchers to theorize that dual RAAS blockade might confer an even greater benefit on BP lowering and cardiorenal outcomes. Unfortunately, this has not been consistently demonstrated. Combining an ACE inhibitor and an ARB produces only small, incremental reductions in BP. In a meta-analysis of randomized controlled trials in which ACE inhibitors and ARBs were administered in combination for the treatment of hypertension (defined as a sitting systolic BP [SBP] $\geq$140 mmHg and/or diastolic BP [DBP] $\geq$90 mmHg; mean ambulatory SBP or DBP of $\geq$130 mmHg or 85 mmHg, respectively; or use of anti-hypertensive agents), ambulatory SBP/DBP was reduced overall by 4.7/3.0 mmHg, compared with ACE inhibitor monotherapy, and by 3.8/2.9 mmHg, compared with ARB monotherapy.[30] Reductions in sitting SBP/DBP relative to ACE inhibitor or ARB monotherapy were 3.8/2.7 mmHg and 3.7/2.3 mmHg, respectively. Surrogate end point and outcome studies have not consistently shown clinical benefits of ACE inhibitor/ARB combination therapy compared with respective monotherapies (Table 2). Most recently, ONTARGET, the largest of these studies, determined that combining the ACE inhibitor ramipril with the ARB telmisartan did not provide high-risk patients who have hypertension with any additional cardiovascular protection than an ACE inhibitor or an ARB alone.[31,32] These results were unexpected and suggest that administration of an ACE inhibitor plus an ARB may not be optimal for blocking RAAS in patients with hypertension but without left ventricular dysfunction or kidney disease. Consequently, this approach should not be routinely prescribed for such patients.

It is not clear why combination RAAS blockade was unsuccessful in ONTARGET; however, several mechanisms are worthy of consideration. Perhaps single-step RAAS blockade sufficiently diminishes the deleterious effects of RAAS so that further blockade does not provide a measurable clinical benefit in this population. This does not seem likely because ACE inhibitors and ARBs do not fully extinguish overactive RAAS activity in high-risk patients and because higher doses of ACE inhibitors and ARBs have been shown to improve outcomes.[33,34] It could also be that the population enrolled in ONTARGET was well treated at baseline, resulting in a low event rate, which would require longer follow-up or a higher risk population for the benefit to be detected. The findings might also be inherent to the combination of an ACE inhibitor and an ARB. The combination did not markedly lower BP, compared with the single RAAS agent regimens. Additionally, combination ACE inhibitor/ARB treatment potentiates an exponential increase in PRA, which could further drive ACE and aldosterone escape pathways (Figure 1).

Although the combination of an ACE inhibitor and an ARB interrupts two important steps in the RAAS pathway, it does not interfere with the rate-limiting step in the pathway: the conversion of angiotensinogen to angiotensin I by renin. Several studies have underscored the importance of this step, measured as PRA, in predicting the risk for cardiovascular events. In the SAVE trial, in patients with acute MI, two neurohormones (PRA and atrial natriuretic peptide) were independently predictive of future cardiovascular disease (assessed by multivariate analysis).[35] Elevated PRA at the time of hospital discharge for acute MI was associated with a 60% increased risk for total cardiovascular disease and a 100% increased risk for severe heart failure. In the Val-HeFT study, higher baseline PRA was associated with increased rates of morbidity and mortality in patients with stable moderate to severe heart failure.[36] Whether the introduction of an RAAS antagonist, such as aliskiren, that reduces PRA levels is capable of offering greater cardioprotection is a question that has only recently been entertained.

Aliskiren plus ACE inhibitor or ARB

Researchers have shown that additional reductions in BP can be achieved when aliskiren is combined with an ACE inhibitor or an ARB.[37,38] In pilot studies, the addition of aliskiren 150 mg once daily to ramipril 5 mg once daily for 3 weeks lowered ambulatory daytime and nighttime SBP an additional 7 to 8 mmHg; when added to once-daily irbesartan 150 mg, aliskiren reduced daytime SBP an additional 1.9 mmHg and nighttime SBP an additional 4.2 mmHg.[37] In another study, oncedaily aliskiren 150 mg/ramipril once-daily 10 mg for 8 weeks reduced mean sitting SBP/DBP by an additional 4.6/2.1 mmHg, compared with ramipril

Table 2 Outcome studies that included combination treatment with ACE inhibitors and ARBs

Cardiovascular disease

Study	Patients	Daily treatment regimen	Mean follow-up	Main outcome	Main findings with combination therapy
VALIANT[70]	4909 4909 4885 Acute MI patients with HF/LVD	Valsartan Captopril Both	24.7 months	Death	Combination did not improve survival relative to either monotherapy (19%–20% in each group died) or other key secondary outcomes despite additional BP lowering. The combination group experienced more AEs than either monotherapy group
CHARM-added[71]	2548 patients with HF and LVD receiving ACE inhibitor	Candesartan or placebo	41 months	CV death or HF hospitalization	Outcomes experienced by 42% of patients in placebo group and 38% in candesartan group ($P = 0.011$). Combination produced larger BP reductions but caused more patients to discontinue treatment for AEs (24% versus 18%; $P = 0.0003$)
Val-HeFT[66]	5010 patients with HF	Valsartan 160 mg vs placebo	23 months	Death and death plus cardiac arrest, HF hospitalization, or need for vasodilators	Among the 366 patients who were receiving an ACE inhibitor plus a β-blocker, valsartan adversely affected total risk of death; among the 366 patients not receiving an ACE inhibitor, valsartan ↓ risk for death 33% and composite end point 44% (versus 0% and ↓13% for combined valsartan/ACE inhibitor)
ONTARGET[31]	8576 8542 8502 Patients with vascular disease or high-risk diabetes without HF	Ramipril 10 mg Telmisartan 80 mg Both	56 months	Composite of CV death, MI, stroke, or HF hospitalization	Primary outcome occurred to a similar degree in each group (16.3%–16.7% patients) Compared with ramipril, greater rates of hypotensive symptoms with combination (4.8%) (1.7%; $P < 0.001$) and renal dysfunction (13.5% versus 10.2%; $P < 0.001$)

Renal outcomes

Study	Patients	Daily treatment regimen	Mean follow-up	Main outcome	Main findings with combination therapy
CALM[72]	199 patients with hypertension, type 2 diabetes, and MAU	Candesartan or lisinopril, followed by candesartan, lisinopril, or the combination	12 weeks	Change in UACR and BP	UACR reduced 50% with combination, 24% with candesartan, and 39% with lisinopril ($P = 0.04$ for combination vs candesartan and >0.20 versus lisinopril BP reduced 25.3/16.3, 14.1/10.4, and 16.7/10.7 mmHg with combination, candesartan and lisinopril ($P \leq 0.005$ for either monotherapy versus combination)
IMPROVE[73]	405 hypertensive, high risk CV patients with MAU	Ramipril plus irbesartan Ramipril plus placebo	20 weeks	Change in UAER	UAER reduced 46% with combination versus 42% with ramipril/placebo; $P = 0.540$ AEs similar between groups
ONTARGET[32]	8576 8542 8502	Ramipril 10 mg Telmisartan 80 mg Both	56 months	Composite renal outcome of doubling of SCr, ESRD, or death	Main outcome occurred most frequently with combination (14.5%; $P = 0.037$) versus 13.4% with telmisartan and 13.5% with ramipril eGFR decrease (mL/min/1.73m^2): ramipril, −2.82; telmisartan, −4.12; combination, −6.11; ($P < 0.001$ comparisons with ramipril) Worse outcomes despite reduced proteinuria with combination therapy Combination had no clear benefit in overt diabetic nephropathy

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MI, myocardial infarction; HF, heart failure; LVD, left ventricular dysfunction; BP, blood pressure; AE, adverse event; MAU, microalbuminuria; UACR, urinary albumin/creatinine ratio; CV, cardiovascular; UAER, urinary albumin excretion rate; AEs, adverse events; SCr, serum creatinine; ESRD, end stage renal disease; eGFR, estimated glomerular filtration rate.

monotherapy in patients with diabetes ($P \leq 0.01$).[38] In healthy volunteers, therapeutic doses of aliskiren produced long-lasting increases in renal plasma flow, the magnitude of which far exceeded that of either the use of an ACE inhibitor or an ARB. Accompanying the increased renal plasma flow was a significant increase in natriuresis, indicating more effective RAAS blockade.[39] In addition, results of two recent studies show the enhanced renoprotective effects of aliskiren when combined with maximal ARB treatment in type 2 diabetes, independent of any additional BP-lowering effects.[20,40] When aliskiren (150 mg daily for 3 months, then 300 mg daily for 3 months) was added to once-daily losartan 100 mg in 599 patients in the AVOID study, the mean urinary/albumin creatinine ratio was reduced by an additional 20% relative to losartan-only (placebo group) treatment ($P < 0.001$), with only a small difference in BP-lowering (an additional 2/1 mmHg lower).[20] Adverse event profiles were similar between aliskiren/losartan and losartan alone. In the second study, placebo, aliskiren 300 mg once daily, irbesartan 300 mg once daily, or the combination of aliskiren/irbesartan were directly compared for 2-month treatment periods in a 4×4 crossover design in 26 patients.[40] Compared with the rates for placebo, albuminuria and albumin fractional clearance rates were reduced 58% and 46% with irbesartan, 48% and 56% with aliskiren, and 71% and 67% with the combination ($P \leq 0.028$ and $P = 0.001$ versus either monotherapy), respectively.

The effects of aliskiren on surrogate markers of cardiovascular disease when combined with ACE inhibitors or ARBs have been examined in at least two studies.[41,42] The ALOFT study enrolled 302 patients with heart failure and hypertension who were already receiving stable doses of ACE inhibitors or ARBs and β-blockers. Patients were treated with aliskiren 150 mg or placebo daily for 3 months.[41] The primary efficacy end point in the study was the between-treatment levels of plasma N-terminal-pro-brain natriuretic peptide (NT-proBNP), a neurohormone biomarker that forecasts an increased risk for events in heart failure (HF) patients.[36] At the end of the study period, mean plasma NT-proBNP levels were elevated by 762 pg/mL with placebo but decreased significantly by 244 pg/mL with aliskiren ($P = 0.0106$). Urinary aldosterone (aldosterone is a downstream component of the RAAS cascade and urinary excretion is therefore a measure of the neurohormonal effect of aliskiren) decreased 9.24 nmol/d with aliskiren and 6.96 nmol/d with placebo ($P = 0.0150$), with no difference in plasma aldosterone or BP between groups. In the second study, the ALLAY trial,[42] 465 hypertensive patients with left ventricular hypertrophy (LVH; left ven-

tricular wall thickness ≥ 13 mm) and a body mass index >25 kg/m^2 were recruited. Patients were randomly assigned to receive 9 months of treatment with once-daily aliskiren 300 mg, losartan 100 mg, or a combination of both doses. If a study patient was receiving an ACE inhibitor or an ARB, they underwent a 3-month washout period prior to treatment. Left ventricular mass index was significantly reduced from baseline with losartan (4.8 g/m^2; 4.7%), aliskiren (4.9 g/m^2; 5.4%), and the combination (5.8 g/m^2; 6.4%; $P < 0.0001$ for each treatment group); differences between the combination and losartan monotherapy were not significant ($P = 0.52$). Blood pressure reductions were similar between groups. None of these studies showed any safety concerns with the combination of aliskiren plus an ACE inhibitor or an ARB, compared with monotherapy. Specifically, there were no differences in adverse events, including renal dysfunction, hyperkalemia, and discontinuation due to adverse events, including patients at risk for renal events (ie, with renal impairment and diabetes). Frequency of cough was less with the combination of aliskiren/ramipril (1.8%) than with ramipril monotherapy (4.7%) in the 8-week hypertension study,[38] though this difference was not significant ($P = 0.08$).

Uniqueness of DRI-based combinations

When an ACE inhibitor and an ARB are combined, each signals a large reactive increase in PRA. Conversely, a DRI-based combination therapy buffers the ACE inhibitor or ARB-induced increases in PRA such that the net effect on PRA is an approximate 50% reduction[43] (Figures 2
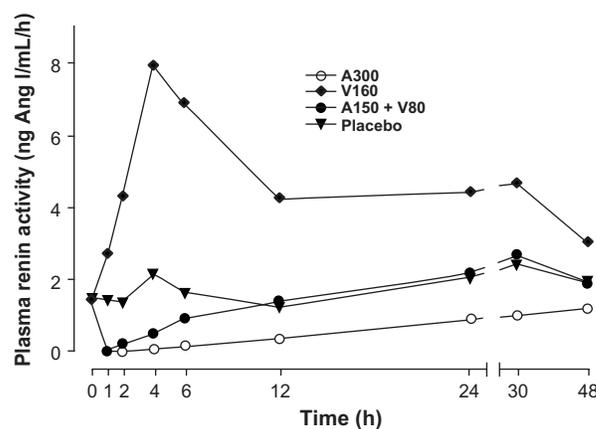

Figure 2 Time course of plasma renin activity in normotensive volunteers after administration of aliskiren 300 mg (open circles), valsartan 160 mg (diamonds), aliskiren 150 mg plus valsartan 80 mg (closed circles), and placebo (triangles). Reprinted with permission from Azizi M, Ménard J, Bissery A, et al. Pharmacologic demonstration of the synergistic effects of a combination of the renin inhibitor aliskiren and the AT1 receptor antagonist valsartan on the angiotensin II-renin feedback interruption. *J Am Soc Nephrol.* 2004;15(12):3126–3133.[44] Copyright © 2004 American Society of Nephrology.
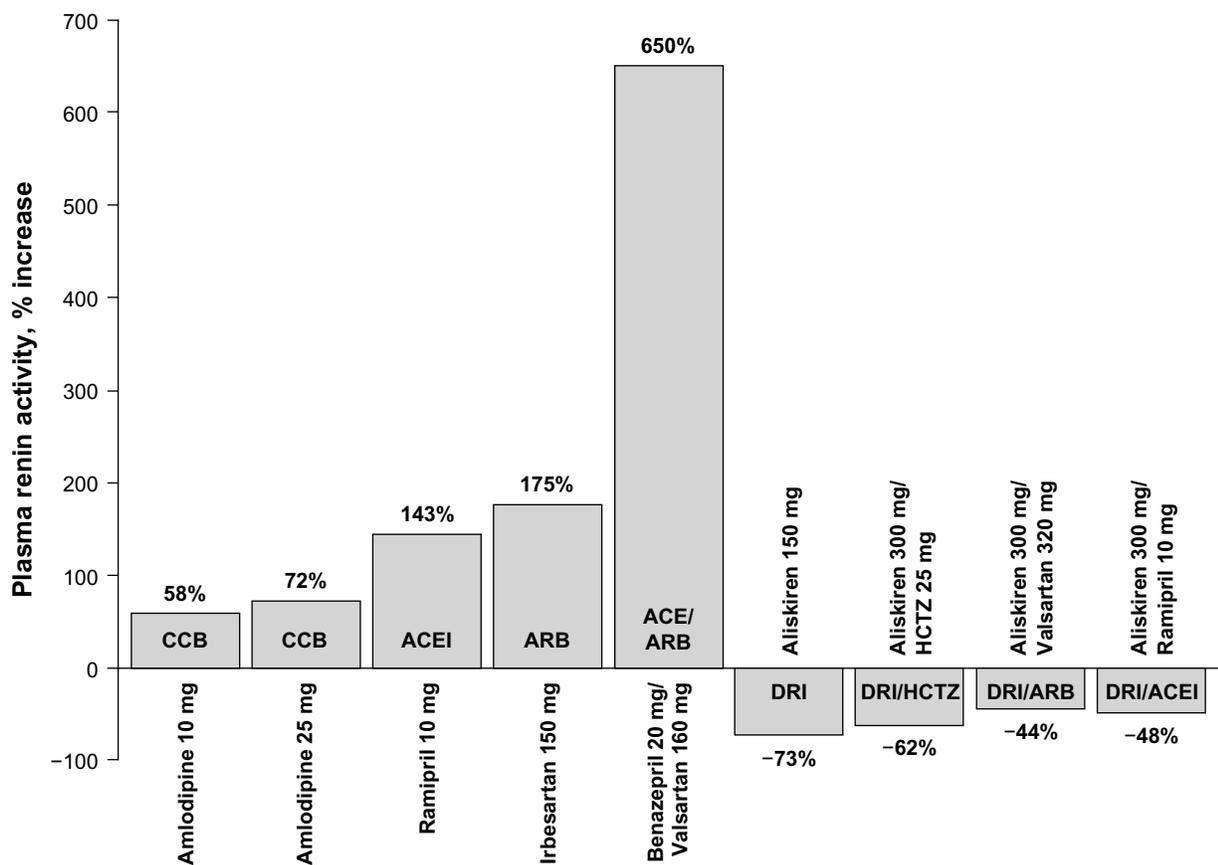**Notes:** A, aliskiren; V, valsartan.

Figure 3 Effects of antihypertensive agents on plasma renin activity in patients with hypertension. [37,38,45,60–62]
Notes: CCB, calcium channel blocker; HCTZ, hydrochlorothiazide; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; DRI direct renin inhibitor.

and 3).[37,43–45] Reductions in PRA with aliskiren are sustained over 26 weeks of treatment and persist 4 weeks after discontinuation.[45] Suppression of PRA with aliskiren monotherapy and diminution of ACE inhibitor-induced and ARB-induced increases in PRA distinguishes DRI's mechanism of action from other RAAS inhibitors. Teaming aliskiren with an ARB functionally blocks the RAAS at the first and rate-limiting step and final receptor; this complementary mechanism provides significant reductions in PRA, angiotensin I, angiotensin II, and aldosterone.[46] Theoretically, any angiotensin I that is formed despite aliskiren treatment will be converted to angiotensin II and then bind at the unoccupied AT_2 receptor, eliciting favorable effects.

Combining a DRI with an ACE inhibitor blocks sequential steps in the RAAS cascade. Angiotensin I that is formed despite aliskiren treatment will be inhibited from conversion to angiotensin II by the ACE inhibitor. Angiotensin II that might be formed despite this dual blockade would bind and activate either AT receptor. Bradykinin potentiation will occur because of ACE inhibition. With either DRI combina-

tion, PRA is suppressed and formation of angiotensin I is greatly reduced, thus providing less substrate to drive escape pathways.

Aliskiren plus valsartan

The combination of aliskiren and the ARB valsartan was recently approved as a single-pill combination (SPC). Results of several studies support the BP-lowering effectiveness of combination therapy with these agents. In a study involving 1797 patients with mean sitting DBP between 95 and 109 mmHg and 8-hour daytime ambulatory DBP ≥90 mmHg, sitting SBP/DBP was reduced by 17.2/12.2 mmHg with once-daily aliskiren 300 mg/valsartan 320 mg, by 13.0/9.0 mmHg with aliskiren 300 mg, by 12.8/9.7 mmHg with valsartan 320 mg, and by 4.6/4.1 mmHg with placebo after 8 weeks of treatment ($P < 0.0001$ for combination versus monotherapy or placebo).[47] In a subset of 581 patients with stage 2 hypertension (SBP ≥160 mmHg) from this study, BP reductions were even more pronounced, in favor of the combination treatment, with mean reductions in

SBP/DBP of 22.5/11.4 mmHg with the combination compared with 17.3/8.9 mmHg with aliskiren, 15.3/8.3 mmHg with valsartan, and 7.9/3.7 mmHg with placebo ($P \leq 0.05$ for comparisons with monotherapy or placebo).[48] In a 6-month open-label study of 601 patients with hypertension (defined as having a mean sitting DBP between 90 and 109 mmHg), BP reductions were sustained with continued treatment. Mean SBP/DBP was reduced from baseline by 22.3/14.4 mmHg with once-daily aliskiren 300 mg/valsartan 320 mg.[49]

The combination of maximal dose (300 mg/320 mg) aliskiren/valsartan exhibited a safety and tolerability profile similar to that of monotherapy with either agent. In the 8-week study involving 1797 hypertensive patients,[47] adverse events and laboratory abnormalities occurred to a similar degree among all treatment groups. Headache was the main adverse event reported with the combination (reported in 4% of patients), which was less than with valsartan (5%) and placebo (9%). The proportion of patients experiencing increases in clinically relevant laboratory values is shown in Table 3. Overall, few patients experienced increases in serum potassium, creatinine, and blood urea nitrogen levels during treatment. In addition, in patients with elevated serum potassium levels >5.5 mmol/L at any time after baseline, serum potassium values returned to normal in 13 of 18 patients (72%), without necessitating treatment discontinuation. During the 6-month open-label study,[49] postbaseline serum potassium values >5.5 mmol/L were infrequent and tended to be transient. Only two patients in this 6-month study (0.3%) who received aliskiren/valsartan plus hydrochlorothiazide (HCTZ) were discontinued from treatment as a result of hyperkalemia.

Role of aliskiren/valsartan in the hypertension therapeutic armamentarium

Based on the established efficacy and safety profile of aliskiren/valsartan, this SPC is attractive for first-line use in the treatment of hypertension for those patients who have diabetes or who are at high risk for cardiovascular disease and are not likely to achieve BP goals with monotherapy, or as a second-line treatment for patients who have not achieved BP control with either an ACE inhibitor or ARB alone. In an 8-week comparative trial,[50] once-daily aliskiren 300 mg/valsartan 320 mg provided comparable reductions to once-daily valsartan 160 mg/HCTZ 12.5 mg, another SPC that can be used for initial and second-line treatment for hypertension. SPCs provide an attractive treatment choice because they can improve patient adherence to hypertension treatment, compared with administration of two separate agents.[51,52]

The effects of aliskiren combined with another RAAS agent on various surrogate end points in the AVOID, ALOFT, and ALLAY studies (proteinuria, NT–proBNP, LVH) suggest that aliskiren-based combinations may confer incremental vasculoprotective effects that are not accounted for by BP reductions alone and, therefore, may be particularly appealing for treatment of hypertension in patients with diabetes, kidney disease, or the metabolic syndrome.[26,41,42,53] More long-term data are needed to confirm its efficacy and safety in these patient populations. Moreover, the importance of neurohormonal activation in cardiovascular disease, and more specifically, the prognostic role of increased PRA with cardiovascular disease, signal a potential role for aliskiren in this regard and support the evaluation of aliskiren/ARB combinations in

Table 3 Laboratory abnormalities occurring during treatment with placebo, aliskiren 300 mg daily, valsartan 320 mg daily, or the combination of aliskiren 300 mg/valsartan 320 mg: results from an 8-week randomized, double-bind, placebo-controlled study and a 6-month, open-label study in patients with hypertension[47,49]

Laboratory abnormality	Number (%) of patients					
	8-week study[47]				6-month, open-label study[49]	
	Placebo n = 458	Aliskiren n = 437	Valsartan n = 455	Aliskiren/valsartan n = 446	Aliskiren/valsartan n = 396	Aliskiren/valsartan/HCTZ n = 588
Potassium						
<3.5 mmol/L	17 (4)	11 (3)	20 (4)	12 (3)	6 (1.5)	13 (6.8)
>5.5 mmol/L	12 (3)	7 (2)	7 (2)	18 (4)	10 (2.5)	2 (1.0)
≥6.5 mmol/L	6 (1)	4 (1)	5 (1)	2 (0.5)	1 (0.3)	0
Creatinine >176.8 µmol/L	0	1 (0.2)	2 (0.4)	4 (0.9)	1 (0.3)	1 (0.5)
Blood urea nitrogen >14.3 mmol/L	0	1 (0.2)	1 (0.2)	0	1 (0.3)	2 (1.0)

Abbreviation: HCTZ, hydrochlorothiazide (up to 25 mg daily).

Table 4 Cardiovascular morbidity and mortality outcome studies with aliskiren in the ASPIRE HIGHER program

Study	Patients	n	Intervention	Primary outcome	Planned follow-up
ALTITUDE	Type 2 diabetes and at high risk for fatal and nonfatal cardiorenal events	8600	Aliskiren 300 mg or placebo on top of conventional treatment (ACE inhibitor or ARB plus others)	Time to first event of CV death, resuscitated sudden death, MI, stroke, unplanned HF hospitalization, ESRD, renal death, doubling of SCr sustained for ≥ 1 month	4 years
ATMOSPHERE	Chronic HF	7041	Aliskiren 300 mg, enalapril 10 mg, or a combination	Time to first event of CV death or HF hospitalization	4 years
ASTRONAUT	Hospitalized for worsening HF	1782	Aliskiren 300 mg or placebo on top of standard therapy	Time to first occurrence of CV death or HF rehospitalization within 6 months	6 months
APOLLO	Elderly patients with normal to high BP and high CV risk		*Study in development*		

Abbreviations: ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; CV, cardiovascular; MI, myocardial infarction; HF, heart failure; ESRD, end stage renal disease; SCr, serum creatinine; BP, blood pressure.

outcomes studies. In addition, aliskiren either by itself or in combination with the ARB valsartan has been shown to have a potential benefit on reducing urinary aldosterone levels.[47] This mineralocorticoid hormone, aldosterone, is associated with the development of not only hypertension, but of cardiovascular and renal diseases as well.[54,55] In addition to having a hemodynamic effect, aldosterone is associated with inflammation, platelet aggregation, hypertrophy, and fibrosis.[56,57] Drugs such as eplerenone (a spironolactone derivative) that attenuate the activity of aldosterone have been shown to reduce the morbidity and mortality associated with heart failure and post-MI.[54] Therefore, an incremental reduction in aldosterone, by combining a DRI with an ACE-inhibitor or ARB, is expected to translate into organ protection and might explain the benefits observed to date in heart failure, diabetes mellitus associated nephropathy as well as LVH.[22,47,58] The ASPIRE HIGHER program was undertaken to evaluate potential cardiorenal effects of aliskiren over a spectrum of conditions in 14 different studies involving more than 35,000 patients.[59] To date, this is the largest and most comprehensive cardiorenal program undertaken to evaluate a particular pharmacologic intervention. Three of the studies evaluating surrogate end points have been discussed herein (AVOID, ALLAY, and ALOFT) and favorable effects of adding aliskiren to standard treatment have been found. The ASPIRE HIGHER program also includes four morbidity and mortality trials (Table 4), which were designed with the aim of improving the standard of care by adding a DRI to current best practice and also to elucidate the role of DRI therapy in situations in which there is no established effective standard of care. Results from the first of these trials (ALTITUDE) are expected in 2012.[58]

Conclusion

ACE inhibitors and ARBs have been valuable in improving outcomes in cardiovascular and renal diseases; however, there remains significant residual risk of cardiovascular events even when these agents are used, which could be attributable to incomplete blockade of the RAAS. In fact, ACE inhibitors and ARBs silence negative feedback control of RAAS and accelerate the production of angiotensin I. For this reason, direct renin inhibition has long been considered a possible therapeutic mechanism for hypertension and cardiovascular disease. The availability of aliskiren for the treatment of hypertension signals the beginning of a new era in RAAS blockade. Aliskiren's unique mechanism of action and ability to buffer PRA justifies its availability as an SPC with valsartan. Initial studies in patients with diabetic nephropathy, LVH, and HF have shown promising effects on surrogate markers and long-term outcome studies are under way; results are eagerly awaited. In the meantime, the combination of aliskiren plus valsartan affords clinicians an SPC agent with demonstrated superior RAAS protection and safe and effective BP lowering, making the combination an important addition to the antihypertensive repertoire.

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