

Inhibition of the Renin Angiotensin Aldosterone System: Focus on Aliskiren

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Abstract

The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a major endocrine/paracrine system that regulates blood pressure (BP) via angiotensin release and fluid and electrolyte homeostasis via aldosterone release. RAAS should be constantly suppressed and any degree of activity may lead to hypertension (HTN) and associated target organ damage. Activation of the RAAS in the pathogenesis of HTN, CVD and renal disease is well documented. Also benefits of inhibition of RAAS, as an effective way to intervene in pathogenesis HTN, CVD and CRF, has been well recognized. RAAS may be blocked by drugs at various points and is important target site for five distinctive classes of hypertensive drugs; beta blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone inhibitors. Inhibition of renin activity and the blocked of RAAS cascade at its primary steps, has long been proposed as the optimal means of RAAS Inhibition. Renin inhibitor provides more effective means of RAAS Inhibition. Aliskiren is the first in a new class of orally active, non-peptide, low molecular weight direct renin inhibitor (DRI) available for clinical use and potential new approach to the blockade of the RAAS. An average plasma half-life of 23.7 hours (range 20–45 hours) , makes drug suitable for once daily administration. BP-lowering affect of aliskiren is associated with a decreased, not increased, generation of Ang I, as it blocks generation of Ang I from angiotensinogen, by inhibiting the active enzymatic site of renin. Aliskiren has generally been well tolerated with adverse events and discontinuation rates similar to placebo in most clinical trials. Aliskiren has the potential to be useful in this wide spectrum of conditions and may provide organ protection independent of BP reductions.

Introduction

The renin-angiotensin system (RAS) or the renin-angiotensin-aldosterone system (RAAS) is a major endocrine/paracrine system that plays a pivotal role in blood pressure (BP) regulation and fluid and electrolyte homeostasis. The RAAS regulates BP via angiotensin release and body electrolyte content via aldosterone release. Renin, a circulating enzyme, with one known substrate angiotensinogenase, is a key regulator of the RAAS and is released from juxtaglomerular cells in kidneys, in response to fall in blood pressure level due to dietary sodium restriction. It establishes a short-term defense mechanism against hypovolemic hypotension. However, when dietary sodium is plentiful, RAAS should be constantly suppressed and any degree of activity may lead to hypertension (HTN) and associated target organ damage. Although renin was discovered more than a century ago, the significance of this system in the pathogenesis of cardiovascular and renal disorders has gained wide acceptance only during the past 3 decades.¹ This article will review role of RAAS in development of HTN & cardiovascular disease (CVD), with overview of present RAAS inhibitors and role of oral Direct Renin inhibitor.

RAAS & its Role in Cardiovascular Disease

Renin was first discovered, characterized and named in 1898 by Robert Tigerstedt. Half century later Braun-Menedez and colleagues and Page and Helmer independently showed that renin was a circulating aspartic proteinase that cleaves the peptide bond between leu10 and val11 in angiotensinogen,² to yield decapeptide angiotensin I (Ang I), in the rate limiting step of the cascade. The inactive Ang I is further converted into octapeptide angiotensin II (Ang II) [Ang-(1-8)] a biologically active potent constrictor, by angiotensin-converting enzyme (ACE), primarily within the capillaries of the lungs.

The Ang II a powerful vasoconstrictor thus formed acts on receptors of Ang II (AT-1 receptors), it acts on the musculature and thereby raises the resistance posed by these arteries to the heart. In order to overcome this increase in load, heart works more vigorously, triggering increase in BP. Ang II also acts on the adrenal glands and releases aldosterone, which stimulates the epithelial cells of the kidneys to increase re-absorption of salt and water, leading to increased blood volume and BP. The RAAS also acts on the CNS to increase water intake by stimulating thirst, as well as conserving blood volume, by reducing urinary loss through the secretion of Vasopressin from the posterior pituitary gland. This excessive activity of the renin system is associated with HTN and target organ damage, mediated largely through the actions of Ang II on the angiotensin AT1 receptor. Beside causing vasoconstriction and fluid retention, Ang II and aldosterone also exert other harmful effects on the CV system, including endothelial damage, sympathetic activation, collagen formation, myocardial fibrosis, and decreased nitric oxide

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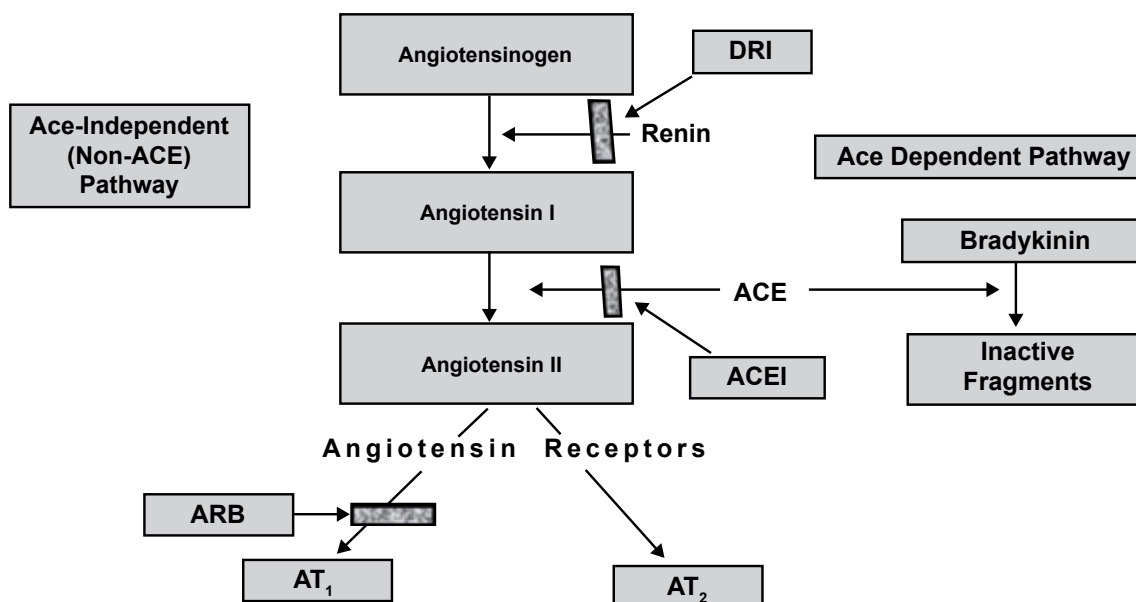


Fig. 1: The Renin–Angiotensin Cascade and the 3 Available Approaches to Pharmacologic Inhibition

production.^{3,4} Although activation neurohormonal pathways is vital for survival in scenario of hemodynamic instability, but in longer run these mechanisms are counterproductive and harmful and can lead to a progressive decline in cardiac function.

Activation of the RAAS in the pathogenesis of HTN, CVD and renal disease is well recognized. Studies have established close connection between HTN and development of CVD and renal disease. The CV events follow a liner relationship with BP, morality risk is doubled for every 20 mmHg and 10 mmHg rise in systolic & diastolic BP respectively, from the level of 115/75 mmHg⁵ and achieving BP reduction to the target levels (<140/90 mmHg for normal hypertensive or <130/80 mmHg for patients with diabetes and CRD), as defined by JNC 7 guidelines, greatly reduces the risk of CV events.⁶ The pharmacological interventions currently used for management of HTN include volume control with diuretics, suppression of central and peripheral sympathetic nervous system activity, vasodilatation with ion channel manipulation and blockade of RAAS.⁷

Inhibition of the RAAS

Advantage of inhibition of RAAS, as an effective way to intervene in pathogenesis HTN, CVD and CRF, has been well established.⁸⁻¹⁰ RAAS may be blocked by drugs at various points and is important target site for five distinctive classes of hypertensive drugs; beta blockers, renin inhibitors, angiotensin converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARBs) and aldosterone inhibitors. These drugs inhibit renin secretion, the enzymatic action of renin, the conversion of angiotensin I to angiotensin II, angiotensin II receptors or the effect of aldosterone, respectively¹¹ and have proven to be highly successful treatments for hypertension and related cardiovascular diseases.¹²

ACE Inhibitors block the formation of Ang II & have proved effective BP lowering agent. But they also cause a respective increase in the concentrations of Ang I that can subsequently be converted to Ang II by other pathways, such as the chymase system. ACE inhibitors are not specific for RAAS and can prevent ACE induced inactivation of bradykinin and substance P that are known

to be responsible for ACE Inhibitor related side effects such as cough and angioedema.¹³ Angiotensin-II receptor blockers (ARBs), inhibit RAAS by specifically blocking the AT₁ receptors. Leaving the other types of AT receptors such as AT₂R and AT₄R, unopposed to possible stimulation by Ang II, this stimulation of AT₂R can produce harmful agents like oxygen free radicals, pro-inflammatory cytokines and pro-fibrotic mediators and may promote left ventricular hypertrophy. Furthermore this partial suppression of RAAS, by both ACE inhibitors and ARB's, leads to considerable compensatory raise in the circulating active renin and Ang II, eventually leading to limit their therapeutic potential.¹⁴⁻¹⁶ This increase in levels of Ang II due to elevated plasma renin activity (PRA), is associated with CV events & end organ damage, in hypertensive patients. Moreover, PRA levels are associated with a higher incidence of myocardial infarction (MI) among hypertensive patients.¹⁷

Inhibition of renin activity and the blocked of RAAS cascade at its primary steps, has long been proposed as the optimal means of RAAS Inhibition. Renin inhibitor provides more effective means of RAAS Inhibition, than is possible with ACE inhibitors or ARBs,¹⁸⁻¹⁹ as it blocks formation of both Ang I and Ang II, with no activation of the AT receptors and no interference with bradykinin metabolism, thus enhancing its therapeutic potential. Effect of direct renin inhibitor (DRI), ACE inhibitors and ARBs on RAAS pathway, is depicted in table 1.

Attempts to block renin began in the 1950s, with the use of renin antibodies. The first synthetic renin inhibitor was pepstatin, which was followed by first-generation agents that were active but required parenteral administration. Oral agents that were subsequently developed, such as enalkiren, remikiren, and zankiren, had limited clinical use because they demonstrated poor bioavailability (< 2%), short half-lives, and weak antihypertensive activity.^{11, 20} Combination of molecular modeling and crystallographic structure analysis were later used to design renin inhibitors, lacking the extended peptide-like backbone of earlier inhibitors, for improved pharmacokinetic

Table 1 : Medication effect on RAAS pathway

	DRI	ACE-I	ARB
Ang ₁₋₇	↓	↑	↓
Ang I	↓	↑	↑
Ang II	↓	↓	↑
AT1 Receptors	Not Stimulated	Not Stimulated	Blocked
AT2 Receptors	Not Stimulated	Not Stimulated	Stimulated
Bradykinin	↔	↑	↔
PRA	↓	↑	↑
PRC	↑	↑	↑

(PK) properties.²¹ This led to discovery of Aliskiren, the first of new non-peptide direct renin inhibitor (DRI). Aliskiren was approved by the FDA & European regulatory bodies in 2007, for the treatment of hypertension. It is administered once daily, either as monotherapy or in combination with other antihypertensive agents.

Aliskiren

Aliskiren 2(S),4(S),5(S),7(S)-N-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-(4-methoxy-3-[3-methoxypropoxyl]-phenyl)-octanamide, is the first in a new class of orally active, non-peptide, low molecular weight (551.8 g/mol) renin inhibitor. The active substance of aliskiren is a hemifumarate salt. It is optically active with four chiral carbons, but exists as a single diastereoisomer.²¹ It is a highly potent inhibitor of renin ($IC_{50} = 0.6$ nM), with very high affinity and specificity for human renin. It binds to the S1/S3 pocket at the active site of renin molecule thus preventing the conversion of angiotensinogen to Ang I. Aliskiren, is first DRI with bioavailability of 2.5% and has shown to be generally well tolerated when given as single or multiple dose.⁷

The plasma concentration of aliskiren increased in a dose dependent manner, following oral administration in healthy volunteers, with peak concentrations reached after 3–6 hours. Oral bioavailability of aliskiren was about 5% (for 95% it is excreted unchanged in feces) and plasma steady-state levels were reached after 5–8 days of treatment. An average plasma half-life of 23.7 hours (range 20–45 hours),²² makes drug suitable for once daily administration. Aliskiren is not metabolized by cytochrome P450 system and has a low potential for drug interactions. It does not interact with warfarin and a number of other compounds including lovastatin, atorvastatin, digoxin, atenolol, celecoxib, metformin, ramipril, hydrochlorothiazide, and cimetidine.^{23, 24} Drug showed no clinically relevant interaction with PK of amlodipine, valsartan, HCTZ and ramipril, in healthy volunteers.²⁵

Elevated PRA has been identified as an independent predictor of morbidity and mortality ($p=0.0025$) in a large-scale trial of 4,300 patients with congestive heart failure.²⁶ Aliskiren inhibits the renin by directly targeting the renin enzyme, at the point of activation and blocking the conversion of angiotensinogen to Ang I and decreasing levels of Ang I and Ang II. Aliskiren decreases PRA by approximately 50–80% and provides similar reductions when administered in combination with drugs known to increase PRA such as the ACE inhibitor ramipril, the ARB valsartan or the diuretic HCTZ.²⁷

Aliskiren decreased PRA, Ang I and Ang II levels in normotensive volunteers in a dose dependent manner, decrease in plasma and urine aldosterone levels were also noted with daily aliskiren doses of 80 mg and above. Aliskiren 160 mg and enalapril 20 mg doses were comparable in terms of their

inhibitory effects on Ang II levels. Neither BP nor heart rate was affected by aliskiren and enalapril in these normotensive subjects.²⁸ In a within-subject study, 12 sodium-depleted normotensive subjects were randomly given placebo, aliskiren 300 mg/day, valsartan 160 mg/day, and the combination of aliskiren and valsartan (150 mg/day +80 mg/day). As expected, aliskiren alone decreased PRA while valsartan alone increased PRA, Ang I and Ang II. The combination of aliskiren and valsartan completely eliminated the rise in PRA elicited by valsartan.²⁹

Direct Renin inhibition with aliskiren

Efficacy of once-daily administration of aliskiren has been established in different Phase II and III studies. Clinical trials have evaluated aliskiren in the treatment of patients with mild to moderate hypertension (diastolic blood pressure (DBP) ≥ 95 mm Hg and < 110 mm Hg, either as monotherapy or in combination with diuretics, calcium channel blockers [CCBs], ACEIs, or ARBs).

In a sub group analysis of 26-week randomised, double-blind trial, comparing effect aliskiren 150mg and ramipril 5mg on PRA, plasma renin concentration (PRC) and other biomarkers, 842 patients (mean sitting diastolic blood pressure (msDBP) 95-109 mmHg) were randomised to aliskiren 150 mg or ramipril 5 mg, after placebo run-in. BP reduction were greater with aliskiren than ramipril based therapy at Week 26 (17.9/13.3 vs. 15.2/12.0 mmHg, $p<0.05$) and persisted for longer after stopping aliskiren. Aliskiren based therapy produced sustained BP and PRA (-63%, $p<0.05$; $n=103$) reductions over 26 weeks, ramipril-based therapy lowered BP and increased PRA (+143%, $p<0.05$; $n=100$). PRA reductions persisted 4 weeks after stopping aliskiren, suggesting an inhibitory effect beyond the elimination half-life of the drug²⁷. A 12-month randomized study compared the antihypertensive efficacy of once-daily doses of aliskiren 300 mg and HCTZ 25 mg, in 1124 patients (msDBP 95-109 mmHg), Add on therapy with amlodipine 5 to 10 mg was used as needed to achieve a target BP of $< 140/90$ mmHg. BP reductions were significantly greater with aliskiren vs. HCTZ based therapy at week 26 (-20.3/-14.2 vs. -18.6/-13.0 mm Hg; $P<0.05$) and were also greater at week 52 (-22.1/-16.0 vs. -21.2/-15.0 mm Hg; $P<0.05$ for msDBP). At the end of the monotherapy period (week 12), aliskiren 300 mg was superior to HCTZ 25 mg in reducing BP (-17.4/-12.2 vs. -14.7/-10.3 mm H; $P<0.001$). Aliskiren both as monotherapy and with amlodipine provided significantly greater BP reductions than the respective HCTZ regimens.³⁰ In the post hoc analysis of 396 obese hypertensive patients (BMI ≥ 30 kg/m²) in this study, aliskiren monotherapy provided good tolerability and significantly greater BP reductions than HCTZ at week 12 (-16.7/-12.3 vs. -12.2/-9.1 mmHg, $p \leq 0.001$) and 52 endpoint (19.9/-15.5 vs. -17.5/-13.3 mmHg; $P=0.138$ for SBP and $P=0.007$ for DBP), in obese hypertensive patients. Mean BP reductions from baseline with aliskiren-based therapy were similar in obese and non-obese patients³¹.

In a 4-week study, aliskiren 37.5 mg, 75 mg, 150 mg, or 300 mg once daily was compared with losartan 100 mg once a day. Dose-dependent reductions from baseline in daytime ambulatory SBP (ASBP) were obtained with all doses of aliskiren ($P=0.0002$ vs. baseline for all doses). The changes in daytime ASBP with the 3 highest doses of aliskiren were similar to those obtained with losartan 100 mg, and the heart rate remained unaltered. All doses of aliskiren also led to significant dose-dependent decreases of PRA between -55% and -83% ($P=0.0008$ vs. baseline), whereas PRA increased by 110% with losartan.³² In 8-week

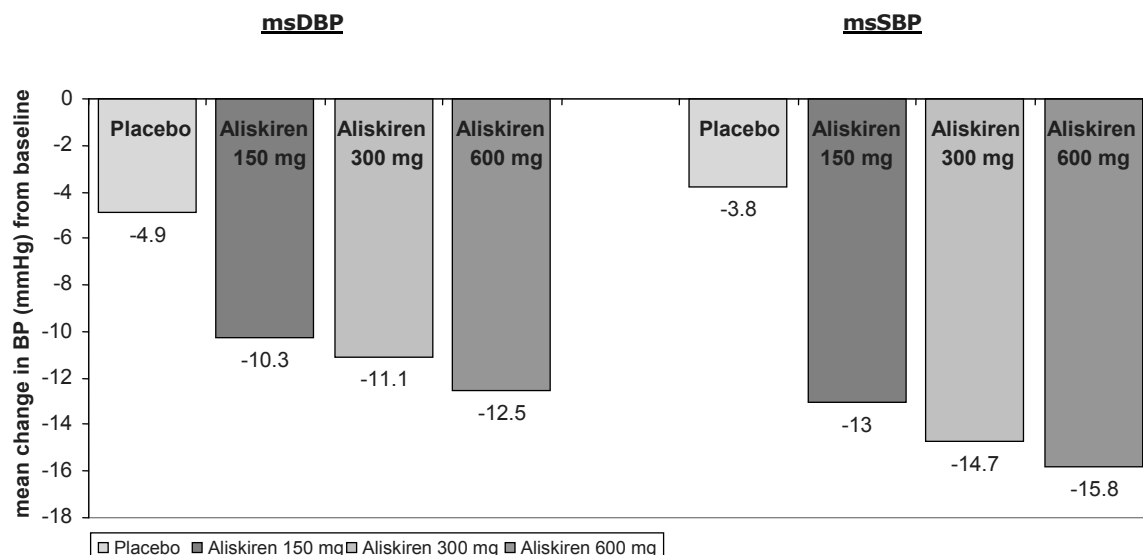


Fig. 2 : Effect of aliskiren monotherapy vs. placebo on BP in patients with mild to moderate hypertension

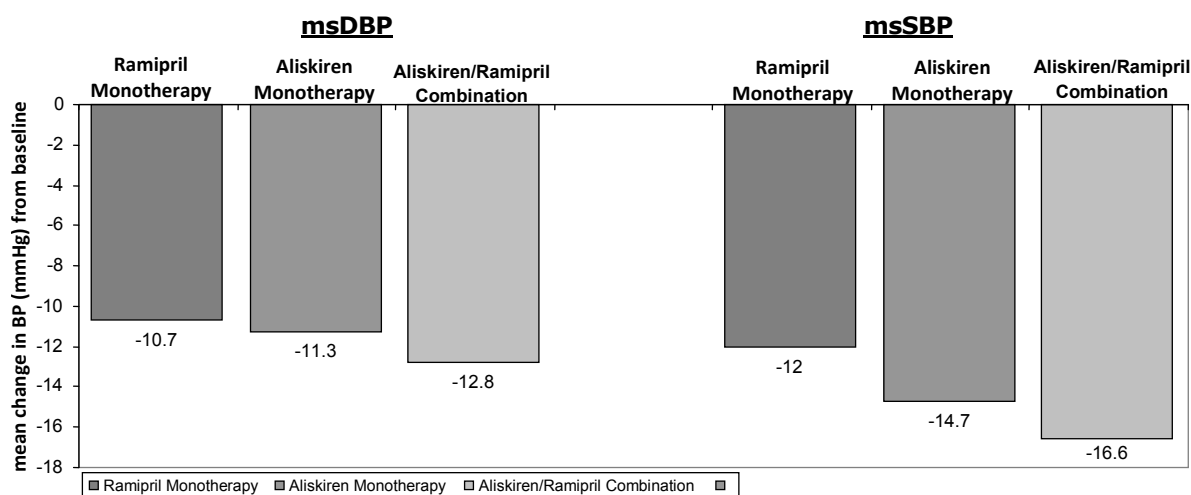


Fig. 3 : Effect of aliskiren or ramipril monotherapy vs. combination therapy at 8 weeks in diabetic patients with mild to moderate hypertension.³⁷

placebo controlled trials of once-daily aliskiren 150/300/600 mg or placebo³³ or irbesartan 150 mg.³⁴ All doses of aliskiren produced significant reduction in msDBP & msSBP than placebo ($P < 0.0001$, fig. 2). The antihypertensive effect persisted for 2 weeks after drug withdrawal, with BP levels lower in the aliskiren groups than in the placebo group.³³ Antihypertensive efficacy and control rates were comparable in the aliskiren 150 mg and irbesartan 150 mg arms but higher in the aliskiren 300 mg and aliskiren 600 mg arms.³⁴

Even though BP controlled can be achieved in some patients with aliskiren monotherapy, dual blockade of the RAAS by exploiting combination of aliskiren with other RAAS inhibitors, will play a important role in over all BP control, in future.

In a double-blind, multicenter trial, 694 hypertensive patients (msDBP ≥ 95 and < 110 mmHg), were randomised to once-daily aliskiren 150 mg (n=231), atenolol 50 mg (n=231) or the combination (150/50 mg; n=232) for six weeks. At Week 12, aliskiren, atenolol and aliskiren/atenolol lowered SBP and DBP from baseline by 14.3/11.3, 14.3/13.7 and 17.3/14.1 mmHg, respectively. SBP reductions with aliskiren/atenolol were significantly greater than those with aliskiren ($p=0.039$) or atenolol ($p=0.034$) alone, and DBP reductions were greater

than with aliskiren alone ($p < 0.001$). PRA was reduced to low levels (< 0.65 ng/ml/hour) at Week 12 endpoint in a greater proportion of patients receiving aliskiren (11/15 patients, 73.3%) or aliskiren/atenolol (18/23, 78.3%) than with atenolol (10/21, 47.6%). Study showed that aliskiren represents an attractive option for dual therapy with atenolol to improve SBP and may be an appropriate substitute for beta-blocker treatment in patients with uncomplicated hypertension.³⁵

The additional antihypertensive effects of adding 6 weeks of aliskiren therapy (75 mg in the first 3 weeks and 150 mg in the last 3 weeks) in patients with mild to moderate hypertension on monotherapy with ramipril (n=21) or irbesartan (n=23) was assessed in an open-label design using ambulatory blood pressure monitoring (ABPM). The addition of aliskiren to 5 mg of ramipril further lowered both day time and night time BP compared to ramipril monotherapy while the addition of aliskiren to 150 mg of irbesartan resulted in significant reduction in night time BP.³⁶ A double-blind multi-center trial, randomized 837 diabetic hypertensive patients (msDBP 96–109 mmHg) to once daily aliskiren (150 mg, titrated to 300 mg after 4 weeks; n=282), ramipril (5 mg titrated to 10 mg; n=278) or the combination for 8 weeks. When compared to ramipril or aliskiren

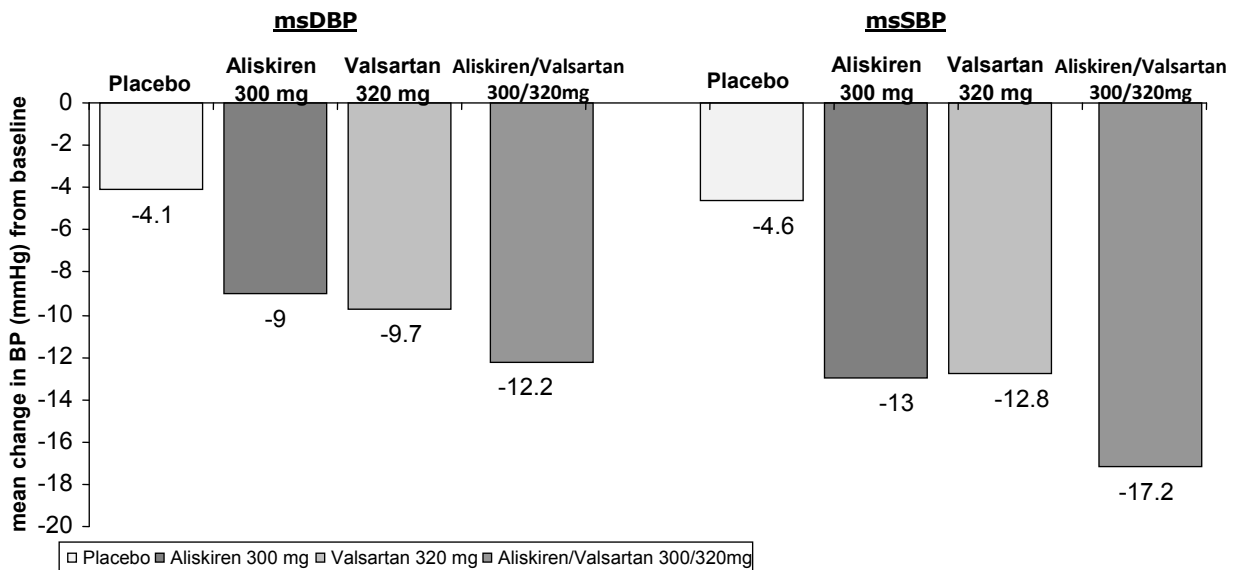


Fig. 4: Effect of aliskiren or valsartan monotherapy vs. combination therapy at 8 weeks in patients with mild to moderate hypertension.³⁸

monotherapy, aliskiren/ramipril combination provided superior reductions in msDBP ($p=0.004$ and 0.043 respectively). Reductions in msSBP and msDBP with aliskiren, ramipril, and aliskiren/ramipril were 14.7 mm Hg/ 11.3 mm Hg, 12.0 mm Hg/ 10.7 mm Hg, and 16.6 mm Hg/ 12.8 mm Hg, respectively (figure 3). An additional reduction in mean BP of $4.6/2.1$ mmHg was achieved by the addition of aliskiren to ramipril.³⁷

In a phase III study 1,797 patients with mild to moderate hypertension, were randomized to once-daily aliskiren 150 mg, valsartan 160 mg, aliskiren/valsartan 150 mg/ 160 mg, or placebo for 4 weeks; followed by forced titration to double the dose for another 4 weeks. At week 4 and 8, reductions in msDBP and msSBP were significantly greater with all active treatments than with placebo ($P<0.0001$, Figure 4). The aliskiren/valsartan combination was significantly more effective than either component alone in reducing msDBP and msSBP ($P<0.0001$), 24-hour mean ADBP and ASBP ($P<0.0001$), and daytime and nighttime mean ADBP. The aliskiren/valsartan combination provided significant additional BP reductions that were maintained for 24 hours.³⁸

Antihypertensive efficacy of aliskiren has been studied both in comparison to and in combination with HCTZ. In an 8-week double-blind, placebo-controlled trial in 2776 hypertensive patients with msDBP of 95 to 109 mmHg, aliskiren (75,150, 300 mg once daily) was compared with HCTZ (6.25, 12.5, and 25 mg once daily), and with the combination of the two agents. The results showed that aliskiren+HCTZ combination treatment was superior to both component monotherapies in reducing BP (maximum msSBP/msDBP reduction of $21.2/14.3$ mmHg from baseline with aliskiren/HCTZ 300/25 mg), and resulted in more responders (patients with msDBP <90 mmHg and/or ≥ 10 mmHg reduction) and better control rates (patients achieving msSBP/msDBP $<140/90$ mmHg) than either monotherapy.³⁹

Two double-blind studies evaluating efficacy, safety and tolerability of a single-pill combination (SPC) of the aliskiren and HCTZ, in patients with poor response to aliskiren or HCTZ monotherapy (msDBP ≥ 90 and <110 mmHg). Patients were randomised to receive SPC of aliskiren/HCTZ (300/25 or 300/12.5 or 150/25 mg) or aliskiren 300 mg or HCTZ 25 mg monotherapy. Aliskiren/HCTZ SPC therapy provided significantly greater msSBP/DBP reductions ($p <0.001$) from

baseline, when compared to aliskiren 300 mg or HCTZ 25 mg alone.^{40, 41} In a diuretic combination study, the addition of 25 mg of HCTZ ($n=23$) to 150 mg of aliskiren daily for 3 weeks significantly lowered daytime pressure, compared with aliskiren monotherapy (systolic/diastolic mean change from baseline: daytime: -18.4 [2.1]/ -10.6 [1.7] versus -10.4 [1.8]/ -5.8 [1.4]; nighttime: -15.6 [2.7]/ -8.1 [1.8] versus -8.8 [2.9]/ -5.0 [2.2]).³⁶

Prospect on Direct Renin Inhibition with Aliskiren

Control of HTN to below-target BP levels is critical for reducing rates of associated Comorbidities. With number of hypertensive patients expected to go up from 972 million in year 2000 to 1.56 billion in year 2025,⁴² clinician's worldwide are confronted with challenge to ward off the dire complications of disease. Even the modest BP reduction can have a significant effect on cardiovascular morbidity and mortality risk. In middle-aged patients, lowering SBP by 10 mmHg (or DBP by 5 mmHg) reduces the risk of stroke death by 40% and death resulting from coronary artery disease (or other vascular disease) by approximately 30%.⁴³

Aliskiren is the first orally active DRI to provide more complete and effective blockade of RAAS, which plays a crucial role in chronic HTN and end-organ damage. BP-lowering affect of aliskiren is associated with a decreased, not increased, generation of Ang I, as it blocks generation of Ang I from angiotensinogen, by inhibiting the active enzymatic site of renin. Once daily administration of aliskiren both as mono & combination therapy provides effective and safe option for the treatment of HTN. However, a majority of patients with HTN remain poorly controlled with monotherapy and require two or more agents to achieve their target BP levels. Aliskiren whose antihypertensive efficacy is enhanced by drugs that trigger a reactive increase in the PRA such as diuretics, ACE inhibitors and ARB's, is a logical component of combination therapy as it neutralizes this activity and appears to be a rational approach for optimizing BP control. Also elevated levels of PRA has direct association

with cardiovascular risk in hypertensive patients, since aliskiren consistently reduce PRA, it can be an important therapeutic option in a wide number of clinical conditions like stable CAD, cerebrovascular disease, diabetes, and peripheral arterial disease, where the inhibition of the RAAS has shown to be beneficial. Additionally using two or more drugs, each at lower doses, provides more effective RAAS inhibition and is associated with lesser number of adverse event, than higher doses of a single drug.

Aliskiren has generally been well tolerated with adverse events and discontinuation rates similar to placebo in most clinical trials. The most common adverse effects reported with aliskiren were fatigue, headache, dizziness and diarrhea. Unlike ACE inhibitors, aliskiren does not affect the metabolism of bradykinin and substance P. Hence cough and angioedema are extremely rare with its use. Drug is also well tolerated in patients with hepatic impairment. Hypertensive Patients with renal failure, may theoretically benefit from even more intensive RAAS inhibition through the blockade of additional steps of the pathway.

Based on existing clinical data aliskiren appears to be effective and safe anti-hypertensive agent. It controls RAAS activity, reduces BP significantly, demonstrates good tolerability and has the potential to provide organ protection independent of BP reductions.

Summary and Conclusions

Aliskiren is the first representative of a new class of non-peptide, low molecular weight, and orally active transition state renin inhibitors. Its High aqueous solubility and affinity for renin, compensates for the low absolute bioavailability and long half-life makes it suitable for once daily administration. Aliskiren both as mono and combination therapy is effective in reducing BP with placebo like tolerability. Aliskiren has the potential to be useful in this wide spectrum of conditions, number of Clinical trials⁴⁴ are currently in progress to explore potential of aliskiren as monotherapy or in combination with other antihypertensive in prevention or regression of various forms of target organ damage in humans. The results of these trials will further define its place / role in treatment of HTN & associated Comorbidities.

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