Hypertension Research (2012) 35, 17–19

www.nature.com/hr

COMMENTARY

Finding a place for aliskiren in the wide spectrum of blood pressure lowering agents

Fabio Angeli, Gianpaolo Reboldi and Paolo Verdecchia

Hypertension Research (2012) **35,** 17–19; doi:10.1038/hr.2011.159; published online 22 September 2011

The renin–angiotensin system (RAS) is a major regulator of blood pressure (BP) and cardiovascular (CV) homeostasis, in which the vasoactive peptide angiotensin (Ang) II has a central role.[1]

Several studies suggest that Ang II stimulates atherosclerosis by triggering basic reactions leading to growth, inflammation, instability and rupture of atherosclerotic plaques, facilitation of thrombosis, and ultimately increasing the risk of major vascular events.[1]

Inhibition of the RAS with angiotensin-converting enzyme inhibitors (ACE-Is) and angiotensin receptor blockers (ARBs) has been shown to lower BP effectively, and to attenuate the deleterious effects of Ang II. ACE-Is and ARBs improve CV outcomes over a wide range of conditions, including hypertension, heart failure (HF), post-myocardial infarction (MI), diabetes and nephropathies.[2]

Despite these improvements, numerous studies have shown a relatively high residual morbidity and mortality in patients receiving optimal treatment with ACE-Is and/or ARBs.[2,3] ACE-Is and ARBs block the generation and action, respectively, of Ang II. However, both classes stimulate renin release via a negative feedback mechanism, ultimately increasing plasma renin concentration and plasma renin activity (PRA).[4]

These findings have led to the suggestion that complete control of the RAS might be effective in reducing morbidity and mortality. Direct renin inhibitors (DRIs) offer the possibility for ample pharmacological manipulation of the RAS. DRIs target the RAS at its point of activation by preventing the formation of renin, the enzyme that catalyses the conversion of angiotensinogen to Ang I (Figure 1).

Renin is responsible for all 'downstream' events leading to production of Ang II and subsequent stimulation of its receptors.[4] Because renin is the only enzyme that promotes this conversion, it has been speculated that DRIs might provide a more effective means of blockade of the RAS than is possible with ACE-Is and/or ARBs (Figure 1).

ALISKIREN, THE FIRST RENIN INHIBITOR

Aliskiren is the first orally active DRI approved for the treatment of hypertension.

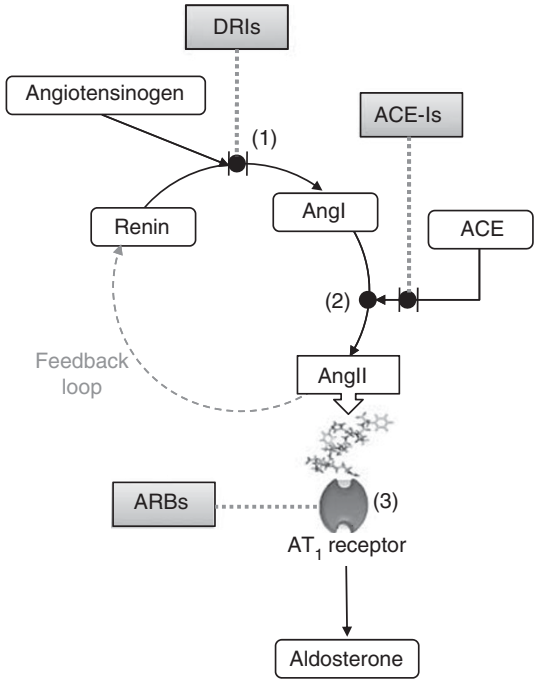

Figure 1 Different basic mechanisms for the pharmacological inhibition of the RAS: (1) inhibition of Ang I generation from angiotensinogen by DRIs; (2) inhibition of Ang II generation from Ang I achieved by ACE-Is and (3) inhibition of the action of Ang II at the level of its receptor(s) by ARBS. ACE-Is, angiotensin-converting enzyme inhibitors; Ang, angiotensin; ARBs, angiotensin receptor blockers; DRIs, direct renin inhibitors; RAS, renin–angiotensin system. A full color version of this figure is available at the *Hypertension Research* journal online.

Dr F Angeli is at the Section of Cardiology, Hospital Media Valle del Tevere, Pantalla, Perugia, Italy.
and G Reboldi is at the Department of Internal Medicine, University of Perugia, Perugia, Italy and P Verdecchia is at the Department of Internal Medicine, Hospital of Assisi, Assisi, Italy.
E-mail: fangeli@cardionet.it

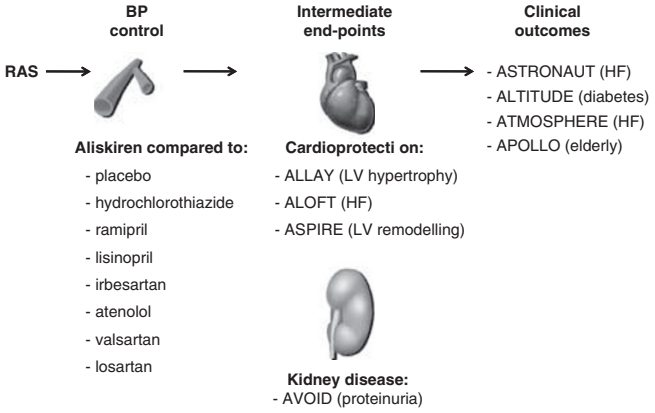

Figure 2 Main trials (most of them included in the ASPIRE HIGHER clinical program) investigating the clinical role of aliskiren in the manipulation of the renin–angiotensin system. ALLAY, Aliskiren in Left Ventricular Hypertrophy; ALOFT, Aliskiren Observation in Heart Failure Treatment; ALTITUDE, Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints; APOLLO, Aliskiren in Prevention of Later Life Outcomes; ASPIRE, Aliskiren Study in Post-MI Patients to Reduce Remodelling; ASTRONAUT, Aliskiren Trial on Acute Heart Failure Outcomes; ATMOSPHERE, Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure; AVOID, Aliskiren in the Evaluation of Proteinuria in Diabetes; BP, blood pressure; HF, heart failure; LV, left ventricular; RAS, renin–angiotensin system. A full color version of this figure is available at the *Hypertension Research* journal online.

Aliskiren is a low-molecular-weight hydrophilic nonpeptide, which exerts a potent and specific competitive inhibition on renin in primates.[5] The very high specificity for renin (10 000-fold higher affinity for renin than for other aspartic peptidases) makes aliskiren unlikely to cause adverse effects potentially related to inhibition of other peptidases. Aliskiren blocks the RAS at its rate-limiting step and induce a net reduction in Ang I, Ang II and aldosterone levels[5] (Figure 1). However, in contrast to ACE-Is and ARBs, aliskiren inhibits the activity of secreted renin and markedly lowers PRA.[4]

Although results from a wide clinical program is still expected to prove the efficacy of aliskiren in reducing major clinical events,[3] its potential clinical benefits have been indirectly tested investigating the effects on BP and intermediate outcome measures.

EFFECTS ON BP

In the last few years, the effects of aliskiren on BP were tested in several trials conducted in patients with hypertension (Figure 2). In placebo-controlled studies, aliskiren showed a dose-related systolic/diastolic BP lowering effect at doses between 75 and 300 mg per day.[6] When compared with active treatments, aliskiren was generally as effective as hydrochlorothiazide, ramipril, lisinopril, irbesartan, atenolol, valsartan and losartan in reducing BP in short-term studies.[3] In longer double-blind trials, aliskiren-based therapy was at least as effective as ramipril-based therapy and more effective than hydrochlorothiazide-based therapy.[3]

The comparison of aliskiren with ramipril is of particular interest. It has been argued that ramipril is an appropriate benchmark to test the potential clinical benefits of aliskiren. The antihypertensive efficacy of ramipril has been confirmed in large-scale noncomparative studies conducted in general practice as well as in more rigorously controlled clinical trials.[7] In addition, in the Heart Outcomes Prevention Evaluation (HOPE) trial, ramipril significantly reduced CV morbidity and mortality in patients at high risk for CV events.[8] A recent meta-analysis by our group[9] showed that aliskiren monotherapy is slightly more effective than ramipril monotherapy in lowering BP. Overall, systolic BP was lower with aliskiren than with ramipril (weighted mean difference between the treatments 1.84 mm Hg ($P<0.0001$) and 1.87 mm Hg ($P=0.0055$) for fixed and random effect models, respectively); the standardized mean difference between the treatments was 2.58 (fixed effect model; $P<0.0001$) and 2.92 (random effect model; $P=0.0017$) in favour of aliskiren.[9]

In this context, the randomized, double-blind, parallel-group study of Zhu *et al.*[10] in the current issue of the Journal provides some additional data on the comparison of aliskiren with ramipril. Eligible patients enrolled across multiple centers in China, Thailand and India were randomly allocated to a once-daily treatment with one of the following regimens: aliskiren 300 mg, 150 mg, 75 mg or ramipril 5 mg.

Essentially, the study clearly showed that aliskiren, at the daily dose of 300 mg, provided a greater BP reduction than ramipril in patients with mild to moderate hypertension (defined as mean sitting diastolic BP $\geqslant 95$ and <110 mm Hg). In addition, the proportion of patients who reached the BP target ($<140/90$ mm Hg) was higher in all three aliskiren dose groups (300 mg: 52.29%; 150 mg: 48.11%; 75 mg: 45.68%) compared with ramipril 5 mg (43.65%) with the difference between aliskiren 300 mg and ramipril 5 mg being statistically significant ($P=0.0177$).[10]

Although the number of randomized patients ($n=1160$) was superior to previous studies that compared aliskiren with ramipril and the efficacy variables (changes in systolic and diastolic BP, pulse pressure and mean arterial pressure) were appropriately analyzed, some aspects of this study deserve specific comment.

Three different regimens of aliskiren (75, 150 and 300 mg per day) were compared with ramipril monotherapy at a fixed dose of 5 mg per day. Although the authors stated that 'the ramipril dose (5 mg) used in this study is the commonly prescribed dose in Chinese patients', it may be considered suboptimal for a comparative analysis. A thorough scrutiny of the literature reveals three previous controlled trials of parallel design, which analyzed the comparison between aliskiren and ramipril.[9] Notably, ramipril was usually up-titrated to 10 mg. Specifically, in two trials patients were randomized to aliskiren 150 mg once daily titrated to 300 mg or ramipril 5 mg titrated to 10 mg/day.[9] In another trial conducted in elderly subjects, patients were randomized either to aliskiren 150 mg per day or to ramipril 5 mg per day.[9] If systolic BP was not a goal after 4 weeks, study medication doses were doubled to aliskiren 300 mg per day or ramipril 10 mg per day.

EFFECTS ON INTERMEDIATE END POINTS

The effects of aliskiren on target-organ damage markers (for example, microalbuminuria, left ventricular (LV) hypertrophy, neurohumoral profile in HF) were recently investigated. Some clinical trials (Figure 2) tested the renoprotective and cardioprotective effects of aliskiren in hypertensive, diabetic subjects with nephropathy (Aliskiren in the Evaluation of Proteinuria in Diabetes (AVOID)), LV hypertrophy (Aliskiren in Left Ventricular Hypertrophy (ALLAY)), symptomatic HF (Aliskiren Observation in Heart Failure Treatment (ALOFT)), acute coronary symptoms and post-MI with low ejection fraction (Aliskiren Study in Post-MI Patients to Reduce Remodelling (ASPIRE)).[3]

Briefly, aliskiren demonstrated positive effects on the markers of CV and renal damage in (i) hypertensive patients with type 2 diabetes and nephropathy, by reducing proteinuria independently of BP control; (ii) in patients with hypertension, reducing LV hypertrophy and (iii) in patients with symptomatic HF, reducing plasma N-terminal probrain natriuretic peptide. However, aliskiren therapy did not have a beneficial effect on LV remodelling after MI.[3]

CLINICAL IMPLICATIONS

Aliskiren has the potential to become the first orally active renin inhibitor providing a true alternative to ACE-Is and ARBs. Aliskiren, at once-daily doses of 150 and 300 mg, demonstrates effective BP control, both alone and in combination with other antihypertensive agents, and an acceptable safety and tolerability profile in patients with hypertension. It reduces LV hypertrophy as effectively as an ARB, shows an antiproteinuric effect when added to an ARB and improves the neurohormonal profile of patients with HF.

On the basis of these considerations, hypertension, HF and proteinuric kidney disease are the conditions in which the effects of aliskiren can be exploited most. However, the potential effects on CV morbidity and mortality are yet to be determined in large clinical trials (Figure 2). In this context, some trials are ongoing to evaluate the effects of aliskiren on different clinical outcomes including reduction of CV death and rehospitalization in patients with congestive HF (Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT)), morbidity and mortality in patients with type 2 diabetes and pre-existing CV disease and/or kidney disease (Aliskiren Trial in Type 2 Diabetes Using Cardio-Renal Disease Endpoints (ALTITUDE)), morbidity and mortality in patients with chronic HF (Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE)) and major CV end points in elderly subjects with normal BP (Aliskiren in Prevention of Later Life Outcomes (APOLLO)).[3,4]

In the absence of prognostic data, aliskiren should be used as an alternative when other drugs are ineffective or poorly tolerated, or as an effective and well-tolerated add-on therapy to reach BP target.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

1 Jacoby DS, Rader DJ. Renin-angiotensin system and atherothrombotic disease: From genes to treatment. *Arch Intern Med* 2003; **163**: 1155–1164.

2 Angeli F, Reboldi G, Verdecchia P. Modern treatment of patients at risk: still a hope for ace inhibitors? *Expert Opin Pharmacother* 2011; **12**: 839–843.

3 Reboldi G, Gentile G, Angeli F, Verdecchia P. Pharmacokinetic, pharmacodynamic and clinical evaluation of aliskiren for hypertension treatment. *Expert Opin Drug Metab Toxicol* 2011; **7**: 115–128.

4 Verdecchia P, Angeli F, Mazzotta G, Gentile G, Reboldi G. The renin angiotensin system in the development of cardiovascular disease: Role of aliskiren in risk reduction. *Vasc Health Risk Manag* 2008; **4**: 971–981.

5 Wood JM, Maibaum J, Rahuel J, Grutter MG, Cohen NC, Rasetti V, Ruger H, Goschke R, Stutz S, Fuhrer W, Schilling W, Rigollier P, Yamaguchi Y, Cumin F, Baum HP, Schnell CR, Herold P, Mah R, Jensen C, O'Brien E, Stanton A, Bedigian MP. Structure-based design of aliskiren, a novel orally effective renin inhibitor. *Biochem Biophys Res Commun* 2003; **308**: 698–705.

6 Musini VM, Fortin PM, Bassett K, Wright JM. Blood pressure lowering efficacy of renin inhibitors for primary hypertension: A cochrane systematic review. *J Hum Hypertens* 2009; **23**: 495–502.

7 Anderson VR, Perry CM, Robinson DM. Ramipril: a review of its use in preventing cardiovascular outcomes in high-risk patients. *Am J Cardiovasc Drugs* 2006; **6**: 417–432.

8 Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The heart outcomes prevention evaluation study investigators. *N Engl J Med* 2000; **342**: 145–153.

9 Verdecchia P, Angeli F, Mazzotta G, Martire P, Garofoli M, Gentile G, Reboldi G. Aliskiren versus ramipril in hypertension. *Ther Adv Cardiovasc Dis* 2010; **4**: 193–200.

10 Zhu J-R, Sun N-L, Yang K, Hu J, Xu G, Hong H, Wang R, Tu Y-M, Ritter S, Keefe D, on behalf of the trial investigators. Efficacy and safety of aliskiren, a direct renin inhibitor, compared with ramipril in Asian patients with mild to moderate hypertension. *Hypertens Res* 2012; **35**: 28–33.