Expert Opinion

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Aliskiren: a renin inhibitor offering a new approach for the treatment of hypertension

Eoin O'Brien
The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland

In recent years, the renin–angiotensin–aldosterone system has been shown to be crucial not only in blood pressure haemostasis but also in the evolution of atherosclerosis, which ultimately determines morbidity and mortality. The angiotensin-converting enzyme inhibitors and, recently, the angiotensin receptor blockers (with their low adverse-effect profile) have added a new dimension to the drug treatment of hypertension. Just a decade after the introduction of angiotensin receptor blockers, physicians treating hypertension are now offered another exciting approach to achieving blockade of the renin–angiotensin–aldosterone system through the inhibition of renin. This review outlines the background evidence for aliskiren, the first orally active renin inhibitor.

Keywords: aliskiren, hypertension, RAAS, renin–angiotensin–aldosterone system, renin inhibition

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1. Introduction

The renin–angiotensin–aldosterone system (RAAS) plays a pivotal role in blood pressure regulation. Inhibition of the RAAS by angiotensin–converting enzyme inhibitors (ACEIs) or by angiotensin receptor blockers (ARBs) has been successfully used in the treatment of hypertension and heart failure [1-4]. There is now growing evidence that RAAS blockade may influence large vessel atherosclerosis and cardiovascular morbidity and mortality independently of blood pressure lowering [1,4]. As renin is the initial and rate-limiting step in the RAAS cascade that results in angiotensin II (Ang II) production and, as it is known that reduced activation of the Ang II receptor will counteract increased blood pressure and sympathetic tone as well as ameliorating harmful cardiovascular hypertrophy and renal lesions [3], it is logical to postulate that blocking renin would be more effective than downstream blockade with ACEIs or ARBs [4]. Moreover, pretreatment plasma renin activity (PRA) was shown to be a risk factor for myocardial infarction in hypertensive patients [5,6]; However, optimised RAAS suppression is difficult to achieve with currently available antihypertensive agents because ACEIs, ARBs and diuretics all activate compensatory feedback mechanisms that result in renin release and increased PRA [7,8] Pharmacological blockade of the Ang II receptors of the angiotensin (AT1)-subtype (although clinically as effective as the less specific ACE inhibition [9]) leaves the generation of Ang II unopposed with the potential for stimulation of other Ang II receptor subtypes [10]. In contrast to ACEIs, specific inhibitors of renin reduce Ang II generation but do not stimulate the production of other peptides (such as substance P or bradykinin) with the resultant absence of untoward drug effects (such as cough and angioedema) [3].

Although capable of reducing angiotensin levels and lowering blood pressure without any important adverse effects [11–14] early renin inhibitors administered intravenously had relatively low potency, poor oral bioavailability, short durations of action and high costs of synthesis, all of which mitigated against clinical use [15].

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Aliskiren, an octanamide, is the first known representative of a new class of completely nonpeptide, low molecular weight, orally active transition-state renin inhibitors [16]. Designed through the use of molecular modelling techniques, it is a potent and specific *in vitro* inhibitor of human renin, which has good water solubility and low lipophilicity and is resistant to biodegradation by peptidases in the intestine, blood circulation and the liver [16]. To quote a recent review [4], aliskiren has unambiguous clinical promise. This review examines the role of renin inhibition as a novel approach to the therapeutic management of hypertension.

2. Current status of antihypertensive drug therapy

Hypertension is the major risk factor for stroke, heart attack and heart failure. More than a quarter of the world's adult population – totaling nearly 1 billion – had hypertension in 2000, a figure that is anticipated to increase to 29% (1·56 billion) by 2025. This high prevalence of hypertension worldwide has contributed to the present pandemic of cardiovascular diseases, which are now responsible for 30% of all deaths worldwide [17]. It has been estimated, moreover, that about two-thirds of the global cerebrovascular disease burden and half the ischaemic heart disease burden are attributable to non-optimum blood pressure [18]. It is hardly surprising that the fiscal burden worldwide must rise to cope with the epidemic of hypertension. The global hypertension market in 2002 was worth ~ US$36 billion, and the top 4 blood pressure-lowering drugs alone accounted for yearly sales of US$8 billion [19].

The individual doctor faced with treating a hypertensive patient has an array of drugs from which to choose: diuretics, β-receptor blockers, α-receptor blockers, Ca^{2+} channel blockers, aldosterone antagonists, ACEIs and ARBs. In many patients a combination of these drugs will be required to achieve optimal control of blood pressure. The last addition to the antihypertensive armament was the introduction of the ARBs in 1995 [20]. One might well ask if another class of drug is needed, and yet the evidence is that the vast majority of patients at risk from the cardiovascular consequences of hypertension are not receiving optimal treatment [21]. Moreover, recent studies such as the Anglo-Scandinavian Cardiac Outcomes Trial have called into question the potential benefits with the newer (Ca^{2+} channel blockers and ACEIs) versus the potential hazards with older drugs (thiazide diuretics and β-blockers) [22].

There is also growing evidence that the ACEIs and ARBs may have benefits that extend beyond blood pressure lowering. Blockade of the RAAS with ACEIs or ARBs apart from reducing blood pressure, also reduces left ventricular mass, and proteinuria, and they also decrease cardiovascular morbidity and mortality in patients with chronic heart failure and after myocardial infarction, and retard the progression of renal insufficiency in Type 1 and 2 diabetes mellitus and non-diabetic chronic renal disease [7]. However, optimised suppression of RAAS is difficult to achieve with ACEIs and ARBs because of compensatory feedback mechanisms that result in renin release and increased PRA [7].

The introduction, therefore, of a new class of antihypertensive medication, renin inhibitors, is welcome. Although a variety of potential renin inhibitors have been developed, their low potency and/or poor pharmacokinetic profiles prevented these compounds from being developed for clinical use [23,24] and 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-methoxypropoxy]phenyl)-octanamid hemifumarate, SPP100, Speedel/Novartis) is the most advanced of the new class of orally-active, nonpeptide, low-molecular weight renin inhibitors for the treatment of hypertension [25].

3. Pharmacology

3.1 Options for RAAS inhibition

Inhibition of RAAS results in a number of potential benefits, which include the haemodynamic consequences of Ang II neutralisation and suppression of the Ang II-dependent generation of growth-promoting pro-inflammatory cytokines, free oxygen radicals and fibrosis mediators in tissues [4]. The biochemical differences between RAAS inhibitors alone or in combination has been clearly summarised by Aziz *et al.* [4]. RAAS blockade has the potential to affect a number of circulating and tissue enzymes and substrates depending on primary target and distribution of the drug, and may affect non-ACE-dependent Ang II generation, bradykinin, Ang(1–7), NO release, prostacyclin, cGMP and chymotrypsin-like angiotensin–generating enzyme or chymase. ACE inhibition may result in continued Ang II generation in some organs (such as the kidneys, heart or blood vessels) and non-ACE pathways may be activated in some pathological situations resulting in the accumulation of vasodilator and natriuretic peptides (such as bradykinin and Ang[1–7]), and of the haematological peptide AcSDKP. In fact, the potential misunderstanding of basic terminology probably accounts for the considerable variability observed in the results of comparative studies. Indeed, the complexities of RAAS are such and the potential interactions of blockade and counter activation are so varied that little is known about the physiological consequences of activating the RAAS receptors. However, if such activation should prove to be deleterious, then renin inhibitors would clearly enjoy clinical advantages over alternative RAAS inhibitors [4].

3.2 Development of aliskiren

Renin is positioned as the first and rate-limiting enzymatic step in the RAAS cascade. Cleavage of the Leu10–Val11 peptide bond of angiotensinogen is the initiating step towards the generation of the potent vasoconstrictor Ang II. Renin has a remarkably high specificity for only one known substrate, angiotensinogen [4].

Sophisticated molecular modelling and the use of X-ray structure analysis have permitted significant improvement in the design of potent and selective inhibitors of renin. Analysis has shown that renin contains two β-sheet domains, with the active site residing in a cleft between these two domains. Each domain contributes one aspartic acid residue necessary for catalytic activity [4]. A key finding was the identification of a unique subpocket, denoted S3sp [26], which is specific to renin, thus providing a novel distinction among the class of aspartyl proteases (**Figure 1**) [27]. This observation led to the identification of aliskiren, an inhibitor with greatly enhanced binding affinity for renin and selectivity over that of other aspartyl proteases [4]. Aliskiren is a transition-state mimetic with increased hydrophilicity compared with previously described renin inhibitors [26] and is a potent and specific inhibitor of human renin *in vitro* with a median inhibitory concentration (IC_{50}) in the low nanomolar range [26,27]. Although aliskiren also displays high affinity for primate renin, it is notably less active against renin from the dog, rat, rabbit, pig and cat [26].

4. Animal studies

In Na^+-depleted conscious marmosets, mean arterial blood pressure was significantly reduced and the reduction persisted for > 24 h with heart rate being unchanged. Comparison of the blood pressure response with aliskiren was greater and of longer duration than with and ACEI or ARBs. A dose-dependent rise in plasma renin concentration and suppression of plasma renin activity following aliskiren administration confirmed substantial renin inhibition [28,29].

The development of the double transgenic rat, harbouring both the human renin and human angiotensinogen genes, has provided an alternative to primate models for the evaluation of renin inhibitors. In these rats, which develop rapidly progressive hypertension with severe organ damage at a young age, aliskiren has been shown to dose-dependently lower blood pressure and be equipotent to enalaprilat and valsartan following intravenous administration, and be equi-effective to blockade with ACEIs and ARBs following oral administration. Further animal studies [4,29,30] suggest that aliskiren infusions prolong survival, reduce proteinuria and cardiac hypertrophy, and attenuate macrophage infiltration into the heart and kidney. Taken together, these animal studies show that aliskiren effectively lowers blood pressure without altering heart rate and that it may also provide target organ protection by inhibition of Ang II.

The potential for beneficial interaction between renin inhibition with Ang II receptor blockade either by ACE inhibition or ACE receptor blockade has also been studied in animal models and a consistent synergistic antihypertensive effect has been shown in the spontaneously hypertensive rat [31], and the addition of aliskiren results in greater than additive antihypertensive effects [23]. As Aziz *et al.* [4] point out, these animal studies assessed the effects of combining single-site RAAS inhibitors at submaximal doses, whereas future studies should focus on the outcome of adding a second single-site RAAS inhibitor on to a maximum dose of initial therapy to determine if there is target organ protection over and beyond blood pressure lowering.

5. Human pharmacokinetics

In 1996, a specific renin receptor was discovered on cultured mesangial cells and renin was found to bind to this receptor with high affinity [32]. The observation that the renin catalytic site is distinct from the receptor binding site (which is expressed in the glomerular mesangium and in the subendothelium of coronary and renal arteries) has led Aziz *et al.* [4] to speculate that this enhanced catalytic activity may provoke further end-organ damage and that a renin inhibitor might afford additional protection over that of other RAAS inhibitors. Additional speculation is afforded by the fact that the same receptor also binds prorenin, which has a renin–like action [33] and acts as a powerful predictor of microvascular complications in diabetes mellitus; if the action of prorenin on the renin receptor accounts for this relationship, the therapeutic potential of renin inhibition becomes even greater than the effects described so far.

The pharmokinetics of aliskiren in humans has been fully summarised by Aziz *et al.* [4]. The high potency of aliskiren against human renin compensates for its low absolute bioavailability. In healthy male subjects, plasma concentrations of aliskiren peak at 2 – 4 h after administration with a mean terminal half-life of 23 – 36 h after the administration of multiple doses of aliskiren over a dose range of 40 – 1800 mg; maximum serum concentration (C_{max}), C_{max} at steady state ($C_{max,ss}$), Area under the curve from 0 – 1 h $(AUC)_{0–1}$ and AUCt increase over proportionally with doses > 80 mg. Consistent with a half-life of ~ 30 h, aliskiren accumulates following multiple once-daily administrations as indicated by the accumulation ratios of between 1.4 and 3.9 with accumulation being more pronounced at higher doses. The intake of aliskiren 150 mg with food results in mean C_{max} and $AUC_{0–1}$ values that are 81 and 62% lower, respectively, than those obtained in the fasting state. After the administration of a single infusion of aliskiren 20 mg i.v. over 20 min in healthy male subjects, plasma clearance was found to be approximately 9 l/h, the hepatic extraction ratio was ~ 10% and distribution volume at steady state was ~ 135 l. The mean absolute bioavailability of the hard gelatin 75 mg capsule is 2.6%. Intersubject variability in the main pharmacokinetic parameters C_{max} and AUC is 32 – 70% on average for aliskiren 40 – 1800 mg/p.o. with only a minor contribution of the hepatic first-pass effect. Aliskiren binds moderately strongly to plasma proteins. In humans, mean protein-binding levels of 49.5% were recorded, with the binding concentration being independent over the range 10 – 500 ng/ml [4].

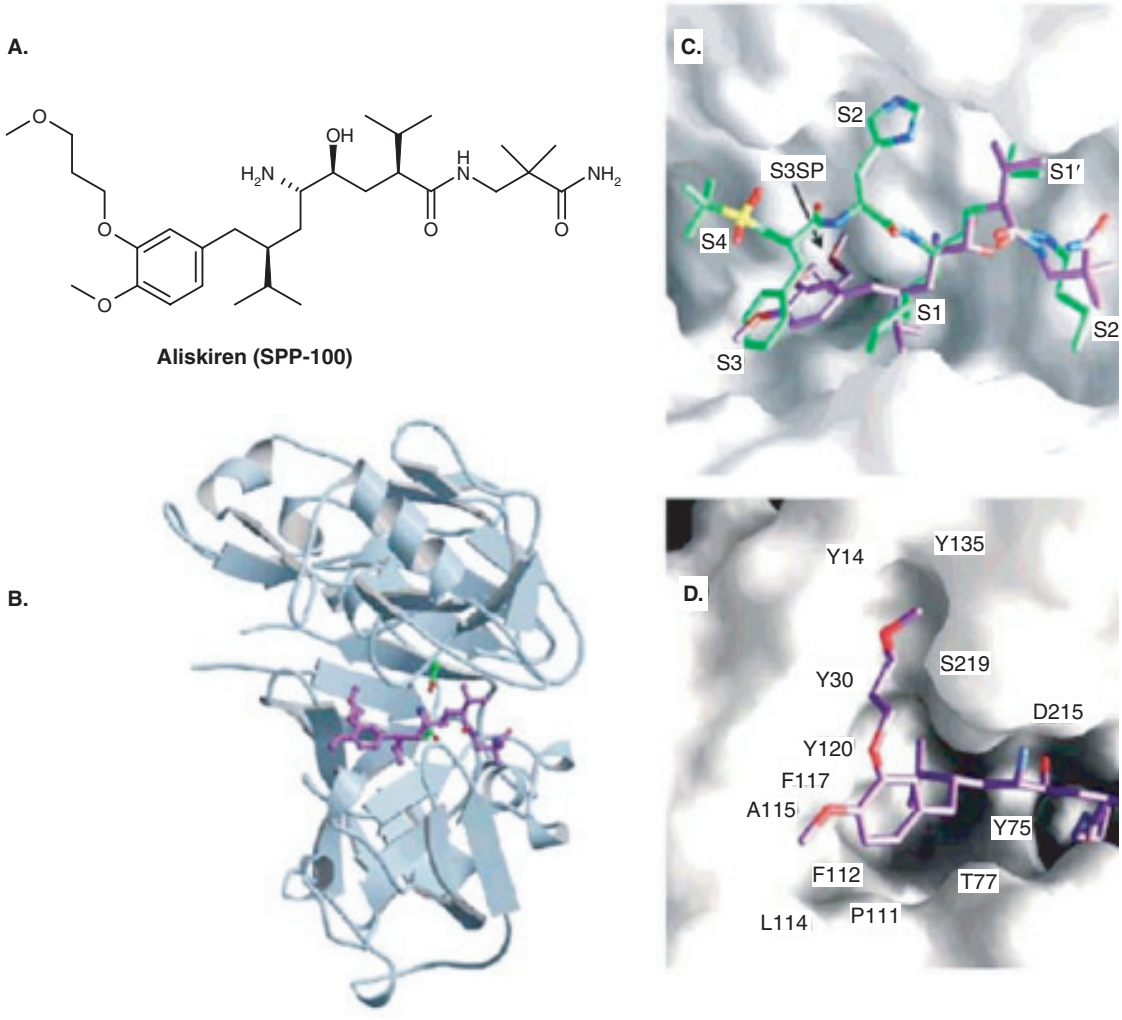

Figure 1. Aliskiren, a highly selective, tight-binding inhibitor of human renin. A. Chemical structure of aliskiren (SPP-100; IUPAC name: 2(*S*),4(*S*),5(*S*),7(*S*)-*N*-(2-carbamoyl-2-methylpropyl)-5-amino-4-hydroxy-2,7-diisopropyl-8-[4-methoxy-3-(3-methoxypropoxy-phenyl]-octanamide). **B. – D.** X-ray crystal structure representations of aliskiren co-crystallised with recombinant glycosylated human renin at 2.2 Å resolution. **B.** General view of aliskiren (ball and stick representation, with all bonds to carbon atoms shown in purple) in the binding complex with human renin; the enzyme β-strands are represented as arrows and α-helices as ribbons. Aliskiren can be seen to occupy the S3 to S2′ subsites, thereby blocking the catalytic function of the enzyme. **C.** Close-up view of aliskiren (purple) binding to the active site of human renin with the enzyme specificity pockets S4 to S2′ being indicated. Superposition with the peptidic inhibitor CGP 38560A (green) indicates the differences in binding interactions for aliskiren. **D.** Extended view of aliskiren binding to the large hydrophobic S1-S3 site, and the newly discovered non-substrate pocket $S3^{sp}$ of renin, accommodating the methoxyalkoxy sidechain of the inhibitor essential for strong binding. In this view, the active site is rotated by ~ 90° relative to the horizontal axis as compared with **A.** and **B.** Ser219 inducing a H-bond interaction via its sidechain OH group to the inhibitor is indicated. Note also the positioning of the polar OMe moiety filling the hydrophobic S3 pocket of the enzyme.

6. Clinical studies

6.1 Comparison of the hormonal effects of aliskiren with the ACE inhibitor, enalapril, in normotensive subjects

Nussberger *et al.* [3] demonstrated that in normotensive healthy subjects with a sodium intake of 100 mM/day, aliskiren 40 – 640 mg in solution for 8 days inhibited PRA in a dose-dependent manner, suppressed the production of plasma Ang I and II, decreased plasma and urinary aldosterone concentrations and increased plasma immunoreactive active renin concentration in a double-blind, three-way crossover study. Plasma aliskiren concentrations increased overproportionally to the administered dose. The results

obtained suggested to the authors that the hormonal effects of aliskiren 160 mg were equivalent to those of a tablet of enalapril 20 mg. Blood pressure and heart rate were not significantly affected by either drug and aliskiren was well tolerated. Both drugs had a small acute natriuretic effect on the first day of treatment, with no significant decrease observed following repeated dosing. The authors concluded that aliskiren has the potential to become the first orally active renin inhibitor to provide a true alternative to ACEIs and ARBs in the treatment of hypertension and other cardiovascular and renal diseases [3].

6.2 Comparison of the hormonal effects of aliskiren and the ARB, valsartan, in normotensive subjects

In 2004, Aziz *et al.* [34] conducted a double-blind, placebo-controlled, randomised, 4-period cross-over single oral dose study in mildly Na^+-depleted normotensive subjects to investigate the hormonal and haemodynamic effects of a combination of a high dose (300 mg) of aliskiren with the standard antihypertensive dose (160 mg) of the ARB valsartan [34]. Subjects were mildly Na^+ depleted to increase plasma renin concentration, thereby amplifying the renin response to AT_1 receptor blockade and to enhance the renin dependence of blood pressure in normotensive subjects [35]. In this study, both drugs had a similar blood pressure-lowering effect and were well tolerated; however, aliskiren decreased plasma renin activity, and Ang I and II levels for 48 h, whereas valsartan increased these levels; plasma renin concentration was increased more and for longer and urinary aldosterone was decreased for longer with aliskiren than with valsartan. The authors concluded that the longer duration of RAAS inhibition by aliskiren suggests that Ang II was more efficiently blocked by the renin inhibitor than by the ARB in the kidneys and that the beneficial effect of aliskiren may be due to a combination of the long plasma half-life of this molecule and its high affinity for human renin. The clinical application of these findings might have particular relevance in circumstances in which Ang II generation within the kidney is activated by pathways dependent on or independent of ACE (such as in patients with diabetic nephropathy [36]) or in African-American hypertensives on a high-salt diet [37].

6.3 Comparison of the haemodynamic effects of aliskiren with the ARB, losartan, in hypertensive subjects

Stanton *et al.* [38] performed a randomised, double-blind, parallel group study in 226 patients aged 21 – 70 years with mild to moderate essential hypertension comparing the 4-week blood pressure-lowering effects and safety of aliskiren 37.5, 75, 150 and 300 mg/day with those of losartan 100 mg/day and showed dose-dependent decreases in daytime ambulatory systolic blood pressure and plasma renin activity in patients treated with aliskiren (**Figure 2**). There was no difference in blood pressure lowering of daytime ambulatory systolic blood pressure between aliskiren 75, 150 and 300 mg/day and losartan 100 mg/day. The authors concluded that aliskiren, through inhibition of renin, was an effective and safe orally active blood pressure-lowering drug [38].

6.4 Comparison of the haemodynamic effects of aliskiren with the ARB, irbesartan, in hypertensive subjects

Gradman *et al.* [39] performed a randomised, multi-centre, double-blind, placebo-controlled, active comparator, 8-week, parallel group trial in 652 patients with mild to moderate hypertension in which they compared the office, sitting diastolic blood pressure-lowering effects at trough of aliskiren 150, 300 or 600 mg/day and (the ARB) irbesartan 150 mg/day. Aliskiren significantly decreased trough diastolic blood pressure at 8 weeks in a dose-dependent manner but the dose–response curve was flat (**Figure 3**). Doses of aliskiren $\geq$ 300 mg/day had a significantly greater antihypertensive effect than irbesartan 150 mg, whereas aliskiren 150 mg had a similar effect to irbesartan 150 mg. The safety profile of aliskiren was similar to those of the placebo and irbesartan [39].

It may be concluded from these studies in hypertensive subjects that aliskiren once daily is as effective and possibly more effective than ARBs in lowering blood pressure.

6.5 Synergistic effect of aliskiren in combination with a thiazide diuretic, an ACE inhibitor and an ARB in hypertensive subjects

Thiazide diuretics, ACEIs and ARBs all cause reactive rises in plasma renin activity and it is tempting to hypothesise that renin inhibition with aliskiren would prevent this reactive rise in PRA, and be accompanied by enhanced blood pressure lowering. In three open-label studies in patients with mild-to-moderate hypertension in whom aliskiren in combination with hydrochlorothiazide (n = 23), ramipril (n = 21) or irbesartan (n = 23) was administered [40], the diuretic combination significantly lowered daytime ambulatory pressures compared with aliskiren monotherapy; the ACEI combination significantly lowered both day- and night-time ambulatory pressures compared with ramipril monotherapy and the ARB combination significantly lowered night-time pressures compared with irbesartan monotherapy. Aliskiren alone significantly ($p < 0.0001$) inhibited PRA by 65%, whereas monotherapy with an ACEI and ARB caused 90 and 175% increases in PRA, respectively; however, PRA levels were similar to baseline untreated levels when aliskiren was co-administered with hydrochlorothiazide, ramipril or irbesartan. These results suggest that renin inhibition with aliskiren in combination with a thiazide diuretic, an ACEI or ARB might provide increased renin–angiotensin system suppression and improved 24-h blood pressure control, which might be expected to provide better target organ protection in patients with hypertension.

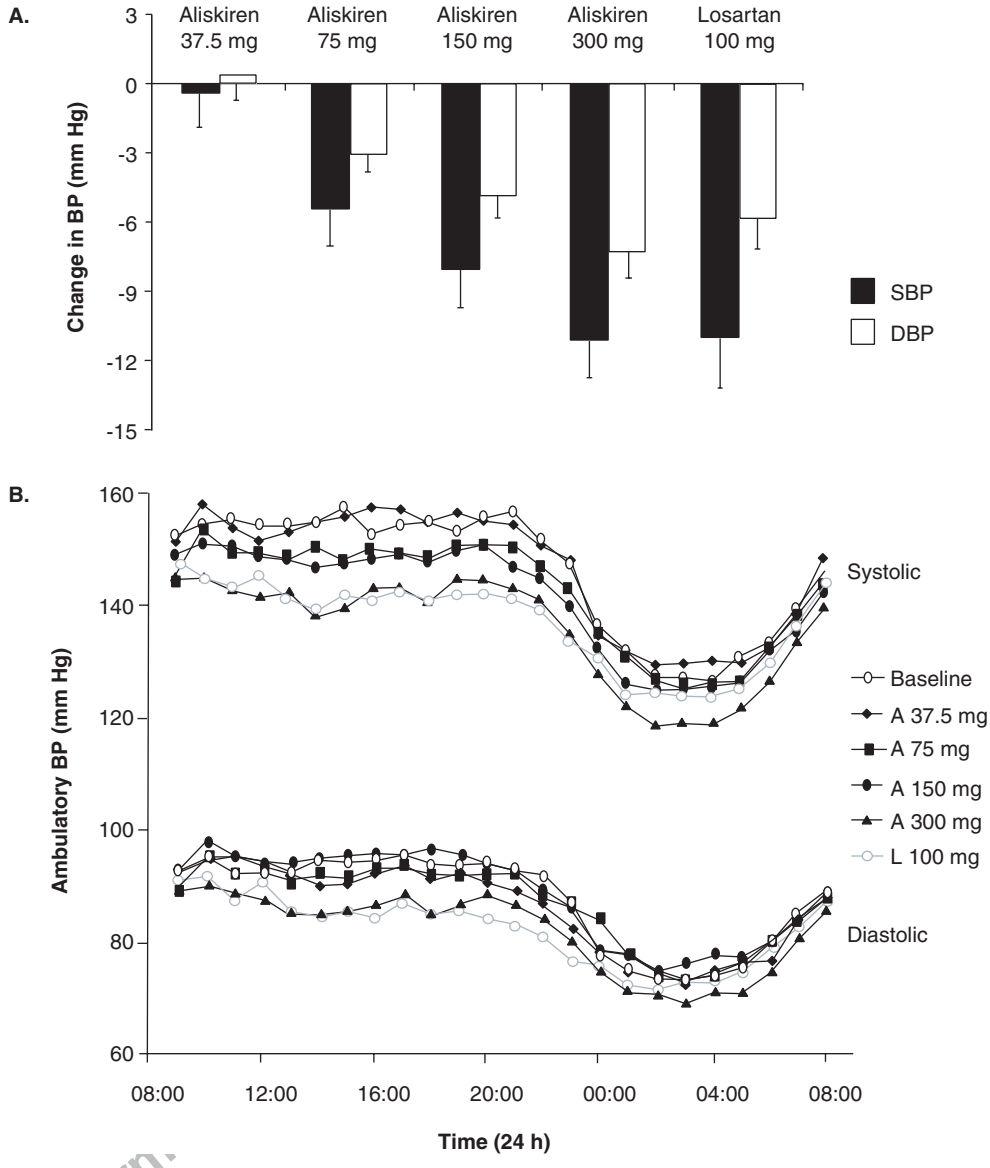

Figure 2. A. Mean (SEM) change in daytime ambulatory SBP and DBP after 4 weeks of treatment with A 37.5, 75, 150 and 300 mg and with L 100 mg. B. 24-h ambulatory blood pressure profiles at baseline and after 4 weeks of A 37.5, 75, 150 and 300 mg and L 100 mg.

Reproduced with permission from STANTON A, JENSEN C, NUSSBERGER J, O'BRIEN E: Blood pressure lowering in essential hypertension with an oral renin inhibitor, aliskiren. *Hypertension*. (2003) **42**:1137-1143 [38]. © 2006 Lippincott Williams & Wilkins.

A: Aliskiren; DBP: Diastolic blood pressure; L: Losartan; SBP: Systolic blood pressure.

7. Drug interactions

7.1 Interactions with common cardiovascular drugs

As patients with hypertension often require concomitant drug therapy for associated comorbidities, Dieterle *et al.* [40] investigated the pharmacokinetic interaction profile between single oral doses of aliskiren and lovastatin, atenolol, celecoxib and cimetidine in healthy male volunteers aged 18 – 45 years, according to a 2-period cross-over design. Overall, single doses of aliskiren showed no evidence of clinically important pharmacokinetic interactions with lovastatin, atenolol, celecoxib or cimetidine [41].

7.2 Interaction with warfarin

Dieterle *et al.* investigated the effects of aliskiren on the pharmacokinetics and pharmacodynamics of warfarin in a single-blind, placebo-controlled, randomised, 2-period cross-over study in 15 healthy male and female subjects each of whom received a single oral dose of 25 mg warfarin twice, once in the morning of the eighth day of treatment

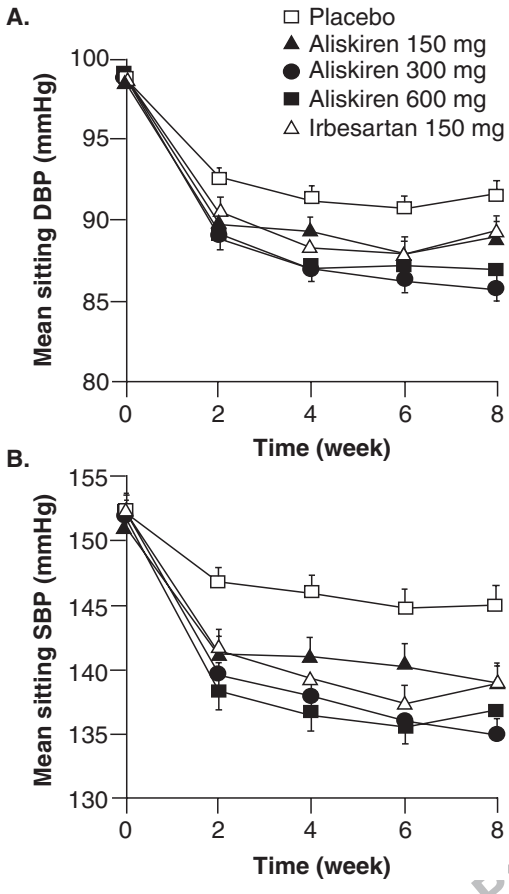

Figure 3. Effect of study treatment on trough mean sitting DBP and SBP throughout active treatment phase in patients with mild to moderate hypertension. Data represent absolute mean values of (**A.**) trough sitting DBP and (**B.**) SBP at 2-week intervals after treatment with placebo, aliskiren 150, 300 or 600 mg or irbesartan 150 mg. Data are presented as mean plus SEM.
Reproduced with permission from GRADMAN AH, SCHMIEDER RE, LINS RL, NUSSBERGER J, CHIANG Y, BEDIGIAN MP: Aliskiren, a novel, orally-effective renin inhibitor, provides antihypertensive efficacy and placebo-like tolerability similar to an AT_1-receptor blocker in hypertensive patients. *Circulation* (2005) **111**:1012-1018. © 2006 Lippincott Williams & Wilkins.
DBP: Diastolic blood pressure; SBP: Systolic blood pressure.

with 150 mg aliskiren and once at the same time point during treatment with placebo. Multiple doses of aliskiren had no detectable effect on the pharmacokinetics or pharmacodynamics of a single dose of warfarin in healthy subjects [42].

8. Safety and tolerability

In clinical studies, the incidence of adverse events and the number of study discontinuations as a result of adverse effects during aliskiren treatment have been relatively low and were similar to results obtained in patients treated with either placebo or ARBS [38,39]. The most common adverse effects reported were fatigue, headache, dizziness and diarrhoea [38,39]. Moreover, there was no increase in the number of adverse events when increasing the dose of aliskiren and no significant clinical laboratory abnormalities have been recorded [38]. In contrast to ACEIs (which produce increased levels of bradykinin and substance P that may cause cough and angioedema), the selectivity of aliskiren for renin avoids these adverse reactions resulting in a side-effect profile similar to that of placebo.

Although aliskiren appears to be safe, future studies will need to assess the effects of aliskiren on renal function and biochemistry, especially serum K^+ levels in patients with renal impairment, heart failure and diabetes mellitus. Moreover, the additive or synergistic effects of combinations will have to be assessed in relation to the optimal doses and the tolerability of such combinations. The potential hazards of a complete RAAS inhibition require careful evaluation, especially in situations in which blood pressure and renal function are renin dependent (such as in elderly or salt-depleted patients), in patients receiving COX inhibitors, patients with renal artery stenosis and patients placed under anaesthesia [4].

9. Conclusion

Aliskiren, an octanamide, is the first known representative of a new class of completely nonpeptide, low molecular weight, orally active transition-state renin inhibitors. In clinical studies, it has been shown to be hormonally and haemodynamically equivalent or possibly superior to ACEIs and ARBs in reducing blood pressure and to have a side-effect profile similar to ARBs and placebo. It possesses synergistic potential when combined with a thiazide diuretic, an ACEI and an ARB. Aliskiren offers a new approach to the blockade of the RAAS.

10. Expert opinion

A new class of medication with the potential to improve the control of high blood pressure (the main risk for cardiovascular outcome in the growing epidemic of cardiovascular disease) must in itself generate interest but what makes the introduction of a renin inhibitor exciting and promising is the growing evidence that inhibition of the RAAS (quite apart from lowering blood pressure effectively with minimal adverse effects) may also reduce morbidity and mortality by preventing target organ involvement. So far, clinical evidence suggests that aliskiren is at least as effective, and probably more effective than ACEIs and ARBs in reducing blood pressure. The next step must involve studies to elucidate how inhibition of the RAAS can be maximised safely. ACEI–ARB combinations have proved to be promising but this strategy is limited by the adverse effects of ACEIs. Although effective, the combination of aliskiren with ACEIs may likewise be limited by the side effects of ACEIs, whereas the potential synergistic effects of aliskiren and ARBs would appear to offer the potential of effective blood pressure lowering without adverse

effects and with the additional benefits of target organ protection. The possibility that nocturnal blood pressure may be effectively reduced with a combination of aliskiren and an ARB offers promise for the treatment of nocturnal hypertension, which has been shown to be a potent risk for stroke and heart attack [43].

In view of preliminary data suggesting that the addition of an aldosterone antagonist to an ACEI or ARB may improve left ventricular function and reduce proteinuria more than an ACEI or ARB alone [44], it is tempting to postulate that a combination of aliskiren and an aldosterone antagonist might offer exciting possibilities provided the problem of hyperkalaemia did not prove to be insurmountable.

The blood pressure-lowering effect that can be achieved through blockade of the RAAS varies considerably from one hypertensive patient to another, with the possible range of decrease being very narrow in patients with low-renin profiles and much wider in high-renin patients [4]. This occurrence raises the possibility of being able to improve selection for treatment on the basis of the renin status of hypertensive patients. Clearly, the next decade will see much research into how blockade of the RAAS can be optimised, but (whatever the outcome) the introduction of renin inhibition with aliskiren clearly offers improved treatment for large numbers of patients with hypertension.

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Affiliation

Eoin O'Brien MD, FRCP (Lond), FRCP (Irel), FRCP (Edin), FACCP, Professor of Molecular Pharmacology
The Conway Institute of Biomolecular and Biomedical Research, University College Dublin, Belfield, Dublin 4, Ireland
Tel: +3 531 280 3865; Fax: +3 531 280 3688;
E-mail: eobrien@iol.ie