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Direct renin inhibition with aliskiren – a new option in treating hypertension

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Editorial Office and Publishers
MediNews (Cardiology) Limited
9 Langton Street,
London, SW10 0JL
E-mail: production@bjcardio.co.uk
Website: www.bjcardio.co.uk

Design and Layout
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Instructions for authors
Can be obtained from the editorial office or from the website.

Advertising and sales enquiries:
Michael Young
42 Avondale Avenue,
Hinchley Wood, Esher,
Surrey, KT10 0DA.
Tel: +44 (0) 20 8339 0300
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E-mail: michael-young@btconnect.com

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Foreword

The advent of a new drug is always grounds for congratulations, given the enormous odds against any one molecule. The advent of a new class is welcome in any disease, and especially welcome when there has been a 12-year gap since the last innovation – angiotensin receptor blockers in 1994. Do we need new drugs for hypertension? Resoundingly, yes! Although a combination of clear guidelines, targets and incentives has revolutionised the treatment of hypertension in primary care, the majority of patients still fail to achieve the international target for systolic blood pressure of 140 mmHg in patients without diabetes, and still fewer achieve the target of 130 mmHg in patients with diabetes.

Do we need another blocker of the renin-angiotensin-aldosterone system (RAAS)? We are about to find out! On first principles, a drug which blocks the rate-limiting step in a pathway is more effective than drugs acting downstream. Of the previously available 'AB' drugs that block the RAAS, angiotensin-converting enzyme (ACE) inhibitors do not achieve 100% inhibition of angiotensin II (Ang II) production because of accumulation of angiotensin I substrate. Angiotensin receptor blockers (ARBs) do achieve marked right-shifts of the dose-response curve for angiotensin. But because ARBs also block the negative feedback of Ang II upon renin, there is a several-fold increase in Ang II levels, and some variation among ARBs in their ability to block access of these to the receptor. Beta-adrenergic blockers do block the rate limiting step of the RAAS. However, reduction in heart rate increases the arterial wave reflection from a stiffened aorta, and attenuates the efficacy of beta blockers in preventing strokes.

The direct renin inhibitor aliskiren arrives at a time of recognition that most patients need multiple drugs. Essential hypertension is a hugely complex disorder, at the molecular level. The change in thinking about hypertension pathogenesis and treatment has been reflected in the phase III programme of trials for aliskiren. As well as showing this to be as least as effective on its own as comparators, many studies looked at combinations – hitherto something of a black hole in the evidence base. The privilege of having a new drug brings also responsibility to use it wisely, and it is to be hoped that direct renin inhibitors will help answer many of the big questions which remain in hypertension management. To combat 'indolent hypertension' we need to create confidence among practitioners in combining more effective diuresis with more effective RAAS blockade – and provide the evidence base from which the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS) can achieve further dramatic improvements in the treatment of hypertension.

Morris Brown
Professor of Clinical Pharmacology
University of Cambridge, Addenbrooke's Centre for Clinical Investigation (ACCI) Level 6, Addenbrooke's Hospital, Box 110, Cambridge, CB2 2QQ.

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Direct renin inhibition with aliskiren – a new option in treating hypertension

Introduction

Worldwide prevalence figures for hypertension approach one billion affected individuals, and the condition is believed to cause at least seven million deaths per annum.[1] Hypertension (here defined as blood pressure [BP] ≥ 140/90 mmHg or treatment with antihypertensive medication) is common in Europe and North America.[2] Wolf-Maier's study, conducted in six European countries, Canada and the US, found that the average prevalence of hypertension in Europe was 44.2%, and 27.6% in North America.[2] Hypertension treatment in the European countries was on average less frequent than in North America.[2] Only 8% of hypertensive individuals in Europe had their hypertension controlled, compared with 23% in Canada and the US.[2] The authors found that the mean BP measurements and hypertension prevalence were strongly correlated with death rates from stroke, the cardiovascular condition with the highest relative risk from hypertension.[2]

Organs which are particularly susceptible to end-organ damage from hypertension include the kidney (proteinuria and renal failure), eyes (retinal disease) and heart (angina, myocardial infarction, heart failure and left ventricular hypertrophy).[3]

Blood pressure has a continuous impact on the risk of cardiovascular events.[4] The 'ideal' level is arbitrary but guidelines generally recommend drug therapy at systolic blood pressure (SBP) ≥ 140 mmHg and diastolic blood pressure (DBP) ≥ 90 mmHg.[4] Target blood pressures are below 140/90 mmHg for the general population, with lower targets (below 130/80 mmHg) for those with renal disease, established cardiovascular disease or diabetes.[4] The majority of adults do not have their blood pressure controlled to these targets, for reasons that include physician inertia, the need to combine drugs, poor patient compliance, side effects and poor communication of guidelines.[4]

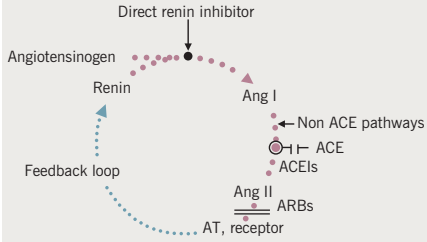
The recent A/CD algorithm from the National Institute for Health and Clinical Excellence (NICE) and the British Hypertension Society (BHS) allows for a sequence of up to six drug classes to control resistant hypertension.[5] But since patients may develop side effects to more than one agent, and since even in trials mean SBP is not always lowered to below 140 mmHg, the need for new, well tolerated agents and combinations remains.[4]

The advantages of direct renin inhibition

The hormone renin plays a central role in the regulation of blood pressure and in the regulation of extracellular fluid volume, sodium balance and cardiovascular function.[6] The most important tonic regulator of renin secretion is the negative feedback of angiotensin on renin synthesis.[6] Renin acts on the substrate angiotensinogen, forming angiotensin; this is broken down to angiotensin II, which constricts arteries and leads to the secretion of aldosterone. Increased angiotensin II has short-term haemodynamic effects (increased blood pressure) and long-term structural effects (end-organ damage).[6]

Antihypertensive agents that act on the renin-angiotensin-aldosterone system (RAAS) include the angiotensin-converting enzyme (ACE) inhibitors and the angiotensin II receptor blockers (ARBs). It remains open to question whether these agents have fully delivered the anticipated reductions in cardiovascular risk.[7] The explanation may lie in the fact that inhibition of angiotensin II production (by ACE inhibitors) or action (by ARBs) disrupts the feedback loop by which angiotensin II normally inhibits renin release.[7] Thus, these drugs actually stimulate the release of renin and activate the RAAS.[8] Combined blockade using both these drug classes has been used in an attempt to overcome the 'escape' observed with single-site RAAS blockers.[7] An interesting and logical alternative would be to inhibit renin itself, which is the first, highly regulated and rate-limiting step of the system (**figure 1**).

Figure 1. Site of action of the direct renin inhibitor, aliskiren



Adapted from Azizi M *et al. J Hypertens* 2006; **24**:243–560
Key: ACE=angiotensin-converting enzyme; ACEI=ACE inhibitors; ARBs=angiotensin receptor blockers

Development of aliskiren

Development of the first synthetic analogues capable of inhibiting renin revealed a number of technical problems. The initial agents were unsuitable for clinical development for reasons of specificity, potency and pharmacokinetic profile.[9] Wood and colleagues[9] employed a combination of molecular modelling and crystallographic structure analysis to design renin inhibitors that lacked the peptide-like backbone of earlier inhibitors, and this led to the discovery of aliskiren, a highly potent and selective inhibitor of human renin (**figure 2**). It binds to a pocket in the renin molecule, blocking initial cleavage of angiotensinogen to form angiotensin I.[9]

After once-daily oral dosing, it was found to lower BP effectively over 24 hours and to provide sustained lowering of plasma renin activity (PRA).[9] (Plasma renin activity

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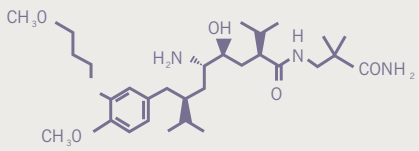
Figure 2. The molecular structure of aliskiren



Adapted from Wood JM *et al.* [9]

describes and quantifies the enzyme's catalytic action.) By contrast, the angiotensin-converting enzyme (ACE) inhibitors and angiotensin II receptor blockers (ARBs) are associated with elevation of PRA in parallel with increased renin release.[8]

Pharmacokinetics

A linear relationship between drug dose and pharmacokinetic parameters (area under the curve [AUC] and maximum concentration [Cmax]) was shown in a four-treatment crossover study in 32 healthy subjects.[10] The volunteers were randomised into four dosing sequence groups, and each received one dose of 75, 150, 300 and 600 mg of aliskiren. Blood samples were taken over a 96-hour period from each dose of aliskiren. The pooled half-life was calculated as 40 hours, which supports once-daily dosing of the drug.[10]

Hypertensive patients often require drug therapy for co-morbid conditions, so potential pharmacokinetic interactions of new agents need to be assessed.[11] Dieterle[11] investigated interactions between single oral doses of aliskiren and lovastatin, atenolol, celecoxib and cimetidine in healthy male adults. There were no clinically important alterations in half-life, mean maximum concentration or systemic availability of aliskiren in the presence of these other agents.[11]

Patients with hypertension frequently require more than one antihypertensive agent to reach target.[4] Vaidyanathan[12] assessed interactions between aliskiren and the antihypertensive drugs amlodipine, valsartan, HCTZ and ramipril in healthy subjects. Some small changes in exposure were observed but none were considered clinically relevant.[12]

Pharmacokinetics and safety of a single dose of aliskiren were observed in patients with hepatic impairment.[13] No significant effects were observed, and dosage adjustment is unlikely to be needed in patients with liver disease.[13]

Aliskiren was investigated in healthy volunteers and in patients with type 2 diabetes (which can affect the absorption and disposition of drugs). Similar profiles were seen in both groups after a single oral dose, and there was no correlation between glycaemic control and pharmacokinetic measures.[14]

Ethnic groups differ in terms of drug metabolism. Properties of the drug are similar across different ethnic groups (Japanese and Caucasian), and it is well tolerated by both groups.[15]

In another study, aliskiren was given to elderly (≥ 65 years) and younger healthy subjects.[16] The findings indicated that no initial dose adjustment should be needed for elderly patients.[16] In conclusion, there are no clear contra-indications for use of this agent in patients with a wide variety of co-morbidities and who are taking a variety of commonly used drugs.[11-16]

Efficacy of aliskiren monotherapy

The efficacy of aliskiren 150, 300 and 600 mg has been evaluated in patients with mild-to-moderate hypertension (DBP 95–110 mmHg).[17] A total of 652 patients were randomised in this eight-week study to receive double-blind treatment with once-daily doses of aliskiren, irbesartan or placebo. Irbesartan was chosen since it is an ARB with an established efficacy and safety profile.

Each of the three doses of aliskiren significantly ($p<0.001$) decreased trough mean sitting DBP compared with placebo (–9.28 mmHg, 150 mmHg; –11.77 mmHg, 300 mg; –11.50 mmHg, 600 mg). All doses also significantly ($p<0.001$) decreased trough mean sitting SBP compared with placebo (–11.36 mmHg, 150 mg; –15.76 mmHg, 300 mg; –15.73 mmHg, 600 mg). Dose dependence was demonstrated for the 150 and 300 mg doses, with no further reduction with the 600 mg dose. Irbesartan 150 mg also significantly ($p<0.05$) reduced both mean sitting DBP and SBP compared to placebo (–8.88 and –12.50 mmHg, respectively).

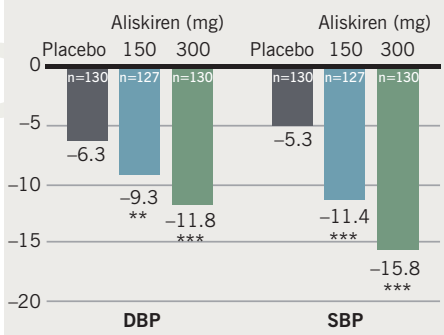
The antihypertensive effect of aliskiren 150 mg was comparable to that of irbesartan 150 mg; aliskiren 300 mg and 600 mg lowered DBP significantly ($p<0.05$) more than irbesartan (**figure 3**).[17]

Aliskiren treatment was well tolerated. The incidence of adverse events during treatment was similar to results obtained in patients treated with either placebo or irbesartan. Results of this study indicate that aliskiren 300 mg could be used to obtain additional BP lowering in patients who do not achieve adequate BP control with aliskiren 150 mg.[17]

A dose-ranging study of aliskiren 150, 300 and 600 mg once-daily in patients with mild-to-moderate hypertension (mean sitting DBP 95–110 mmHg) was performed by Oh and colleagues.[18] The safety population consisted of 672 patients, recruited from 68 centres internationally. They were randomised in double-blind fashion to one of the three doses of aliskiren or placebo for eight weeks. A subgroup of 216 patients also underwent 24-hour ambulatory BP monitoring (ABPM).[18]

Aliskiren was significantly superior to placebo in lowering mean sitting DBP and SBP ($p<0.0001$). After eight weeks, aliskiren 150, 300 and 600 mg reduced mean sitting DBP by 10.3, 11.1 and 12.5 mmHg, respectively, compared with 4.9 mmHg with placebo. Corresponding values for mean

Figure 3. Chart showing the dose-dependent reductions in diastolic and systolic blood pressure with aliskiren monotherapy



Adapted from Gradman AH *et al.*[17]
Key: DBP = diastolic blood pressure; SBP = systolic blood pressure; BP = blood pressure; **p < 0.005 *vs.* placebo; ***p < 0.0005 *vs.* placebo

sitting SBP were 13.0, 14.7 and 15.8 mmHg, respectively, compared with 3.8 mmHg with placebo. Maximal or near maximal reductions were achieved by week 4 and were sustained to eight weeks.[18]

In the ABPM subgroup, aliskiren 150, 300 and 600 mg reduced mean 24-hour DBP relative to placebo by 8.16, 7.56 and 9.04 mmHg, respectively. Ambulatory BP reductions were observed during both daytime and night-time. Consistent with its long half-life, BP suppression with aliskiren administered at approximately 8 am was maintained for 24 hours, including the high-risk period of the early hours of the morning following the dose. Plasma renin activity was reduced from baseline by 79.5%, 81.1% and 75.0%, respectively, by aliskiren 150 mg, 300 and 600 mg. By contrast, PRA increased by 19.5% from baseline in the placebo group.[18]

A pooled analysis from five placebo-controlled trials and two active controlled trials involving 7,060 patients with mild-to-moderate hypertension[19] showed that aliskiren reduced SBP effectively in both elderly and younger patients. Aliskiren 150 mg reduced SBP by 11.1 mmHg in those aged <65 years and by 13.1 mmHg in those older than 65. The reductions observed with aliskiren 300 mg were 15.2 and 13.5 mmHg, respectively.[19]

Aliskiren combination therapy

Patients often require more than one antihypertensive agent in order to reach blood pressure targets.[20] What is the experimental evidence for the benefit of combination therapy using aliskiren? Diuretics such as thiazides are often used as first-line therapy but their efficacy may be limited by activation of the RAAS (to compensate for volume depletion). Thus, the combination of a thiazide plus a direct renin inhibitor could be a useful one.[20]

Villamil and colleagues[20] performed a study in 2,776 patients aged 18 years or older with mild-to-moderate hypertension. Patients were randomised to receive double-blind treatment with placebo, aliskiren monotherapy (75, 150 or 300 mg), hydrochlorothiazide (HCTZ) (6.25, 12.5 or 35 mg) or a combination of aliskiren and HCTZ for eight weeks.

Aliskiren monotherapy was significantly superior to placebo in reducing mean sitting DBP (p=0.0002, overall Dunnett's test), reducing this parameter in a dose-dependent manner. Reductions from baseline were 8.7, 8.9 and 10.3 mmHg at doses of 75, 150 and 300 mg, respectively.[20] The 150 mg and 300 mg doses were significantly superior to placebo whereas the 75 mg dose was not. HCTZ monotherapy also reduced mean sitting DBP from baseline, with reductions of 9.1, 10.1 and 9.4 mmHg at doses of 6.25, 12.5 and 25 mg, respectively (**figure 4**).[20]

All combinations were superior to placebo (p<0.0001). Almost all were also superior to both monotherapies. Reductions in mean sitting DBP from baseline with combination therapy ranged from 10.4 to 14.3 mmHg. Responder rates for all combinations of aliskiren with HCTZ 25 mg and for aliskiren 300 mg plus HCTZ 12.5 mg were superior to both monotherapies.[20] With all combinations, except the lowest dose of each drug, control rates were superior to placebo. Combinations utilising the higher doses of one or both drugs gave control rates that were statistically superior to each component monotherapy.[20]

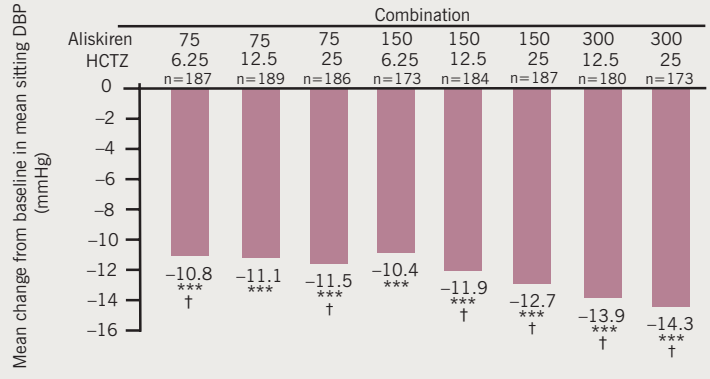
Aliskiren appeared to reduce the risk of developing hypokalaemia during treatment with HCTZ. Hypokalaemia (potassium < 3.5 mmol/L) occurred in 3.9% and 5.2% of patients treated with HCTZ 12.5 and 25 mg, respectively. When patients were given these doses of HCTZ in combination with aliskiren, the frequency of hypokalaemia fell to 0.7–2.0% for HCTZ 12.5 mg and 2.2–3.4% for HCTZ 25 mg.[20]

What of double inhibition of the RAAS? Anxieties about double inhibition have largely been laid to rest by results from trials such as CHARM-Added, and inhibition of renin could address the issue of angiotensin II 'escape'. The efficacy of aliskiren alone and in combination with the ACE inhibitor ramipril was investigated in a dose-escalation study involving 837 patients with hypertension and diabetes.[21] Patients were randomised to double-blind treatment with either aliskiren 150 mg once daily, ramipril 5 mg once daily or a combination of these same doses of both agents. After four weeks of treatment, patients were given aliskiren 300 mg once daily, ramipril 10 mg once daily or both agents at this higher dose for a further four weeks.[21]

At week 8, there was a significantly greater (p<0.05) reduction in mean sitting DBP with the combination (–12.7 mmHg) compared to either monotherapy (–11.3 mmHg for aliskiren; –10.7 mmHg for ramipril).[21] This reduction for aliskiren was shown to be statistically non-inferior compared to ramipril. The addition of aliskiren to ramipril provided an additional mean reduction in blood pressure of 4.6/2.0 mmHg.

The efficacy and safety of aliskiren given alone or in combination with the ARB valsartan were compared in a study of patients with hypertension (mean sitting

Figure 4. The combination of aliskiren and hydrochlorothiazide (HCTZ) provides double-digit lowering of mean sitting diastolic blood pressure



Adapted from: Vilamil A *et al.*[20]
Key: DBP = diastolic blood pressure. Pairwise comparisons: ***p<0.0001 *vs.* placebo; †p<0.05 *vs.* each component monotherapy

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DBP ≥ 95 mmHg and < 110 mmHg).[22] After washout and placebo run-in periods, patients were randomised to aliskiren 150 mg once daily, valsartan 160 mg once daily, the combination of aliskiren 150 mg and valsartan 160 mg once daily, or placebo once daily for four weeks. At that point, all patients were force-titrated to aliskiren 300 mg once daily, valsartan 320 mg once daily, the combination of aliskiren 300 mg and valsartan 320 mg once daily, or placebo once daily for another four weeks. The study randomised a total of 1,797 patients.[22]

At week 8, the aliskiren/valsartan group had greater reductions in mean sitting DBP compared to baseline (-12.2 mmHg): these were greater than the reductions observed with aliskiren (-9.0 mmHg) and valsartan monotherapy (-9.7 mmHg). These differences were also observed in mean sitting SBP, which was reduced by -17.2 mmHg in the combination group *vs.* -12.8 mmHg with valsartan and -13.0 mmHg with aliskiren. The control rate was greater for combination treatment (49%) than for aliskiren alone (37%) or valsartan alone (34%). In a subgroup of patients who underwent 24-hour ambulatory blood pressure monitoring, combination therapy provided significantly greater reductions in 24-hour systolic and diastolic pressures compared with either monotherapy.[22]

The efficacy and tolerability of aliskiren as additional therapy to the calcium channel blocker (CCB) amlodipine were investigated in a double-blind randomised trial (n=545).[23] Patients whose blood pressure goals were not achieved after treatment with amlodipine 5 mg daily for four weeks were randomised to continue on the same dose, to amlodipine 10 mg daily or to the combination of amlodipine 5 mg and aliskiren 150 mg daily for six weeks.

Dose incrementation and drug combination strategies produced similar reductions in systolic and diastolic blood pressure, which were significantly greater than reductions seen with amlodipine 5 mg daily. The first two strategies also achieved a better responder rate (about 60%) compared to the lower dose of amlodipine (45%). Interestingly, the combination treatment was better tolerated than the higher dose of amlodipine, with a lower incidence of peripheral oedema.[23]

Safety data

Aliskiren has an overall safety profile comparable to placebo and similar to, or better than, other commonly used antihypertensive agents. Safety data have been collected from about 8,500 patients who have received the agent in clinical trials. These trials enrolled patients with mild-to-moderate hypertension (DBP 95–109 mmHg); most had co-morbid conditions and were using other medications.[19]

Adverse events reported with aliskiren treatment were similar in nature and frequency to those reported by patients taking placebo, except that diarrhoea was reported more often with aliskiren doses of 600 mg daily or more.[24] Usually, the diarrhoea did not lead to withdrawal from the study, and it did not increase in frequency with longer duration of treatment. The most common reported side effects were headache and nasopharyngitis; these were both reported more often in the placebo group than in the aliskiren group.[19] Side effects of antihypertensive treatment are relevant to patient adherence in what may be an asymptomatic condition[4]. The ARBs were the first class of antihypertensive agent to demonstrate an overall side effect profile similar to placebo,[4] and it appears that aliskiren may have a similar side-effect profile (**table 1**).[19]

Safety of aliskiren in combination with the antihypertensive classes of ARBs, thiazides, CCBs and ACE inhibitors has been evaluated.[19] The combination of aliskiren with other drugs that act on the RAAS was as safe as monotherapy, except that higher rates of increased serum potassium were observed with the combination of aliskiren and an ACE inhibitor in a diabetic population. Aliskiren does not exacerbate ACE-inhibitor-related cough and may even reduce it. There was also a trend towards a decrease in peripheral oedema with the combination of aliskiren and a CCB.

Small, dose-related decreases in red blood cell count, haemoglobin level and haematocrit have been observed with aliskiren (and with ACE inhibitors and ARBs).[24] With the exception of the subgroup described above, there is no apparent effect of aliskiren on serum potassium, blood urea nitrogen or creatinine.

No new or different safety findings were seen in the 12-month study included in the data set. This confirmed the safety and tolerability of aliskiren, alone or in combination with HCTZ, for at least one year.[25]

Looking ahead

Long-term morbidity and mortality studies form part of the ASPIRE HIGHER clinical trial programme. ALTITUDE (Aliskiren trial in type 2 diabetic nephropathy) will assess aliskiren

Table 1. Adverse events with aliskiren (pooled data from placebo-controlled trials)

	Placebo n = 781	Aliskiren 75 mg n = 478	Aliskiren 150 mg n = 774	Aliskiren 300 mg n = 768	Aliskiren 600 mg n = 296	All aliskiren n = 2,316
Any SAE, n (%)	5 (0.6)	3 (0.6)	3 (0.4)	4 (0.5)	1 (0.3)	11 (0.5)
Any AE, n (%)	314 (40.2)	193 (40.4)	290 (37.5)	309 (40.2)	130 (43.9)	922 (39.8)
Discontinuations due to AE, n (%)	27 (3.5)	8 (1.7)	12 (1.6)	20 (2.6)	5 (1.7)	45 (1.9)
Adverse events, reported by >2% of patients for aliskiren monotherapy overall, n (%)						
Headache	68 (8.7)	31 (6.5)	42 (4.5)*	44 (5.7)*	15 (5.1)	132 (5.7)**
Nasopharyngitis	45 (5.8)	34 (7.1)	33 (4.3)	29 (3.8)	5 (1.7)**	101 (4.4)
Diarrhoea	9 (1.2)	6 (1.3)	9 (1.2)	18 (2.3)	28 (9.5)***	61 (2.6)*
Fatigue	12 (1.5)	11 (2.3)	5 (0.6)	13 (1.7)	7 (2.4)	36 (1.6)
Dizziness	17 (2.2)	6 (1.3)	9 (1.2)	19 (2.5)	8 (2.7)	42 (1.8)
Upper respiratory tract infection	12 (1.5)	4 (0.8)	7 (0.9)	13 (1.7)	7 (2.4)	31 (1.3)

Adapted from: Weir M *et al.*[19]
Key: AE=adverse event; SAE=serious adverse event; *p<0.05; **p<0.01; ***p<0.0001 *vs.* placebo

in secondary prevention of cardiovascular and renal events in patients with type 2 diabetes and high cardiovascular and/or renal risk. Aliskiren 300 mg daily will be compared with placebo against background ACE inhibitor or ARB therapy, and the primary end point is a composite of cardiovascular and renal events.

ASPIRE (Aliskiren study in post-MI patients to reduce remodelling) will assess aliskiren in high-risk post-MI patients with renal dysfunction.

Results from the ALOFT (ALiskiren Observation of heart Failure Treatment) study were presented at the European Society of Cardiology congress in Vienna in September 2007. The study enrolled 302 hypertensive patients with NYHA Class II–IV heart failure and B-type natriuretic peptide (BNP) > 100 pg/ml; they were followed up for three months. The primary end point was to evaluate safety and tolerability of aliskiren when added to standard therapy. Findings from the trial showed there was no significant excess of hypotension or renal dysfunction. Interestingly, compared to placebo, aliskiren reduced plasma N-terminal proBNP by 25% (p=0.01061), plasma BNP by 25% (p=0.0160) and urinary aldosterone by 21% (p=0.0150).[26]

Studies are also in progress to assess the effects of aliskiren on surrogate cardiovascular and renal markers that have been shown to predict events and outcome. It is hoped that these will provide useful indicators of the degree of end-organ protection afforded by direct renin inhibition. AVOID (Aliskiren in the evaluation of proteinuria in diabetes) is a six-month study of aliskiren 150 and 300 mg once daily added to losartan 100 mg once daily plus optimised hypertension treatment in 496 patients with controlled hypertension, type 2 diabetes and proteinuria. The primary end point is the urinary albumin/creatinine ratio, which is an indicator of albuminuria. It will be interesting to compare these results with those from trials using ARBs such as RENAAL (losartan)[27] and IDNT (irbesartan).[28] These trials showed that reduction in albuminuria was related to reduction in risk of end-stage renal disease during follow-up.[27,28]

ALLAY (Aliskiren left ventricular assessment of hypertrophy) will compare aliskiren with losartan and the combination of aliskiren and losartan in 480 overweight hypertensive patients treated for nine months. The objectives are to determine whether the combination achieves superior regression of left ventricular hypertrophy compared to monotherapy, and to compare the amount of regression achieved with each monotherapy. Left ventricular hypertrophy is correlated with the risk of cardiovascular events and increases the risk of stroke, coronary heart disease and heart failure.[29]

Summary

In conclusion, direct renin inhibition represents a new mechanism for addressing hypertension by blocking the rate-limiting step of activation of the RAAS. Studies conducted to date indicate that it is an effective and well-tolerated antihypertensive agent whether used as monotherapy or in combination with other agents, with the potential to modify end-organ damage.

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