

# Aliskiren: first direct renin inhibitor for essential hypertension

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## KEY POINTS

- aliskiren is a selective inhibitor of renin licensed for the treatment of essential hypertension
- available as 150mg (28, £19.80) and 300mg (28, £23.80) tablets
- in short-term trials in patients with mild to moderate hypertension, monotherapy or combined therapy with aliskiren lowered blood pressure by as much as other commonly prescribed antihypertensive agents
- has also been shown to be effective in patients with diabetes, obese patients and in those with severe hypertension
- was well tolerated in clinical trials with treatment duration of up to one year; the commonest adverse event was diarrhoea
- the combination of aliskiren with an ACE inhibitor is associated with increased potassium levels; as monotherapy, the frequency of cough with aliskiren is less than with ACE inhibitors



**Aliskiren (Rasilez) is the first of a new class of anti-hypertensive agents, the direct renin inhibitors. Here, Steve Chaplin presents the clinical data relating to its efficacy and adverse effects, and Professor Sever comments on its potential place in the treatment of hypertension.**

The renin angiotensin system plays a complex role in blood pressure (BP) regulation (see Figure 1). In summary, renin, an enzyme synthesised by the kidney, is responsible for the conversion of angiotensinogen to angiotensin I. Angiotensin converting-enzyme (ACE) is responsible for the conversion of angiotensin I to angiotensin II. Angiotensin II promotes arterial tone, adrenal aldosterone secretion and renal sodium absorption and has additional effects on cell growth and sympathetic neurotransmission; it also inhibits renin release, providing a negative feedback mechanism.

Currently available antihypertensive agents affect different components of the renin system: beta-blockers reduce renin release from the juxtaglomerular apparatus, ACE inhibitors block the syn-

thesis of angiotensin II, and angiotensin-II receptor blockers (ARBs) block the final step in this pathway, the interaction of angiotensin II with its type I receptors. The use of ACE inhibitors and ARBs is associated with an increased concentration and plasma activity of renin due to the suppression of angiotensin II-dependent renin inhibition, and this increased plasma renin activity may be a risk factor for cardiovascular events.<sup>1</sup>

The National Institute for Health and Clinical Excellence (NICE) recommends a strategy of sequential drug treatment to reduce BP to a target of 140/90mmHg in patients without co-morbidity.<sup>2</sup> A lower target of 130/80mmHg is recommended for patients with established atherosclerotic cardiovascular dis-

ease, diabetes or chronic renal failure.<sup>3</sup> In many patients, these targets can only be achieved by combinations of antihypertensive drugs.

### Mode of action

Aliskiren (Rasilez) is licensed for the treatment of essential hypertension, either as monotherapy or in combination with other antihypertensives. A selective inhibitor of renin, aliskiren inhibits the renin-angiotensin system at the first step. It does not block the synthesis of angiotensin I in vascular walls and, unlike ACE inhibitors, it does not block the breakdown of bradykinin. Although plasma renin levels increase, plasma renin activity is reduced during treatment with aliskiren even in combination with another hypertensive.<sup>4</sup>

**Dosage**

The recommended dose is 150mg daily, increasing to 300mg daily if necessary. It should be taken with a light meal (bioavailability is reduced by 60-70 per cent by a high-fat meal), preferably at the same time each day.

No dose adjustment is recommended for mild to severe renal or hepatic impairment, or for older patients.<sup>4</sup>

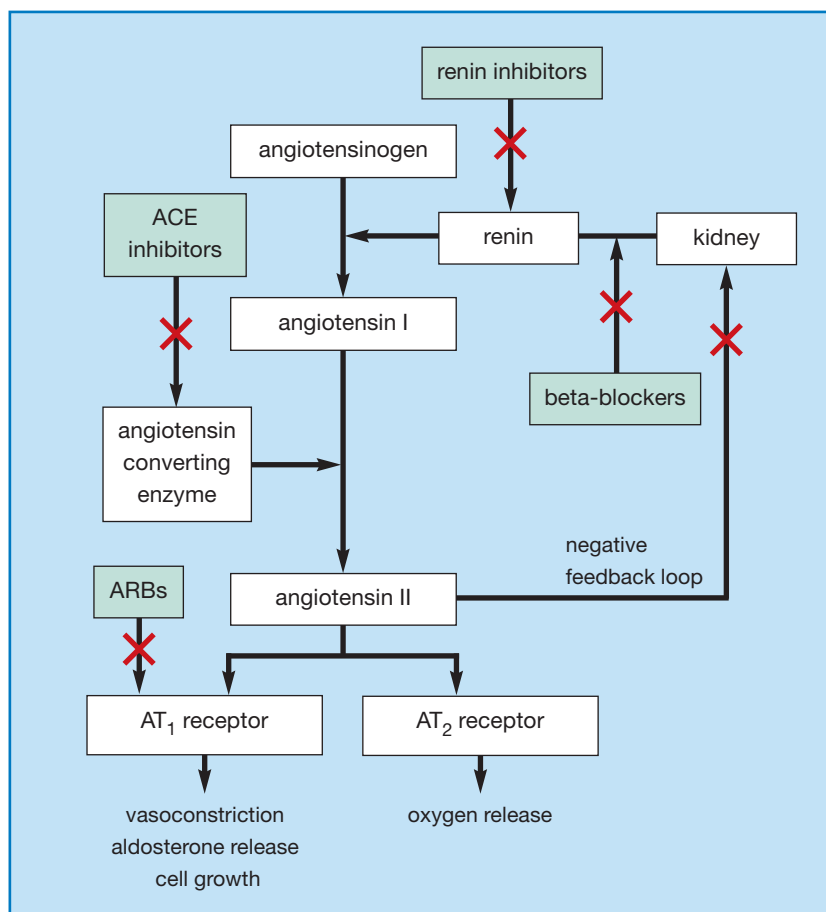
**Clinical trials**

Aliskiren has been evaluated in a large number of double-blind randomised trials, mostly in patients (mean age 55) with mild to moderate hypertension and lasting 4-26 weeks.<sup>5</sup> The primary end-points were the change in mean diastolic pressure or, in two trials conducted in older patients and those with severe hypertension, systolic pressure. The possible long-term effects of aliskiren on cardiovascular outcomes and target organ damage are unknown.

Pooled analysis of placebo-controlled trials showed that monotherapy with aliskiren reduced BP by a mean of approximately 11/9mmHg at a dose of 150mg daily (5/3mmHg after adjustment for placebo) and 15/11mmHg at 300mg daily (9/6mmHg, see Table 1).<sup>5</sup> There were too few data to provide conclusive evidence of differences in response between ethnic groups.

BP reductions with aliskiren alone were similar to those with monotherapy with ramipril (in patients with diabetes), hydrochlorothiazide, irbesartan (Aprovel) and lisinopril (in patients over 65).

Combinations of aliskiren with hydrochlorothiazide (including obese patients), amlodipine, valsartan (Diovan), atenolol and ramipril (in patients with diabetes) reduced BP by approximately 4-



**Figure 1.** The role of the renin angiotensin system in BP regulation and the sites of action of renin inhibitors and other antihypertensive agents

Treatment	Change from baseline			
	Mean	Placebo-subtracted		
Age group	<65	≥65	>65	≥65
<b>DBP</b>				
placebo	-5.8	-8.2		
aliskiren 150mg	-9.0	-11.4	-3.2	-3.2
aliskiren 300mg	-11.3	-11.2	-5.5	-3.0
<b>SBP</b>				
placebo	-6.0	-4.3		
aliskiren 150mg	-11.1	-13.1	-5.1	-8.8
aliskiren 300mg	-15.2	-13.5	-9.2	-9.2

**Table 1.** Change in mean diastolic and systolic pressure with 150mg and 300mg aliskiren

7/2-4mmHg more than monotherapy with the second drug. In combination with hydrochlorothiazide, aliskiren was as effective as hydrochlorothiazide plus ramipril, amlodipine, irbesartan (Co-

Aprovel) or, in patients with severe hypertension, lisinopril.

**Adverse effects**

Based on an analysis of all 5734 participants treated with aliskiren

75-600mg daily in the clinical trials programme (1270 for 12 months), as monotherapy or in combination with other agents, the overall rate of adverse events – 38 per cent – was similar to that associated with placebo – 40 per cent.<sup>5</sup>

The most common adverse event was dose-related diarrhoea (2.4 *vs* 1.2 per cent with placebo). Cough was less frequent with aliskiren than with ACE inhibitors (1 *vs* 3.8 per cent), and peripheral oedema was less common than with amlodipine (0.9 *vs* 7.3 per cent).<sup>5</sup> Fatigue, rash and influenza were also more frequent than with placebo.

In patients with diabetes taking aliskiren plus an ACE inhibitor, the

incidence of increased serum potassium was 5.5 per cent compared with 0.9 per cent with aliskiren alone and 0.6 per cent with placebo.

Clinically significant drug interactions with aliskiren have not been identified.<sup>4</sup>

### References

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*By Steve Chaplin, a pharmacist who specialises in writing on therapeutics*

## Place in therapy

About every 10 years, a new class of antihypertensive drug is launched and the recent release of aliskiren, the first direct inhibitor of renin, raises interesting questions and challenges about their potential role amongst our current strategies for treating hypertension.

NICE and the British Hypertension Society advocate drug treatment for uncomplicated hypertension based upon the A, C, D algorithm. It is recommended that an A drug, an ACE inhibitor or an ARB, is initial therapy for younger (<55 years) patients, and either a C, calcium channel blocker, or D, diuretic, drug is selected in older ( $\geq$ 55 years) patients.

The rationale for this selection of drug based on age is that the activity of the renin angiotensin-aldosterone system (RAAS) declines with age and clinical studies have shown that younger patients respond better to RAAS inhibitors, whereas in older sub-

jects who, in general, have a suppressed renin system, calcium channel blockers or diuretics are more effective.

At first glance, therefore, a renin inhibitor might be an alternative to an ACE inhibitor or an ARB when either of these classes is poorly tolerated. However, the clearest advantage of the ARBs over the ACE inhibitors, is better tolerability and, although the tolerability profile of aliskiren seems similar to that of an ARB, this drug is at best an alternative to an ARB when an ACE inhibitor causes side-effects. In contrast to ARBs, there are at present no outcome data in support of the long-term efficacy and safety of direct renin inhibitors.

The ACD algorithm advocates A drugs as add-on to C or D drugs in older patients who require additional therapy when treatment with a first-line drug fails to achieve treatment goals. Aliskiren could be an alternative to the ARB in this scenario but, again, without outcome data this drug would at present be second choice.

Clinical trials, to date, confirm an additive BP-lowering effect when aliskiren is used in combination with many other classes of drugs. In the ultimately treatment-resistant patient, another class of drug is a useful addition to current choices.

Due to the focus of interest on target organ damage in the hypertensive population, with particular regard to potential heart and kidney benefits through RAAS blockade that may go beyond BP lowering, studies with aliskiren have been and will be looked at closely. Preliminary results suggest additional reductions in proteinuria when aliskiren is combined with either an ACE inhibitor or an ARB, and further studies indicate more complete blockade of the RAAS in the kidney with aliskiren than with either ACE inhibitors or ARBs.

Ongoing studies in patients with left ventricular dysfunction may confirm additional advantages in combination with either an ACE inhibitor or an ARB in this high-risk population.

Economic factors will, in the short term, dictate the role of aliskiren in current practice, particularly as the first ARB, losartan, (Cozaar) loses its patent in 2009, meaning that all classes of antihypertensive drugs, with the exception of renin inhibitors, will be available in generic formulation.

The future role for aliskiren will therefore depend on the results of surrogate end-point studies and morbidity/mortality outcome studies, without which the preferential selection of a drug in today's climate of evidence-based medicine will be difficult.

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