Aliskiren update

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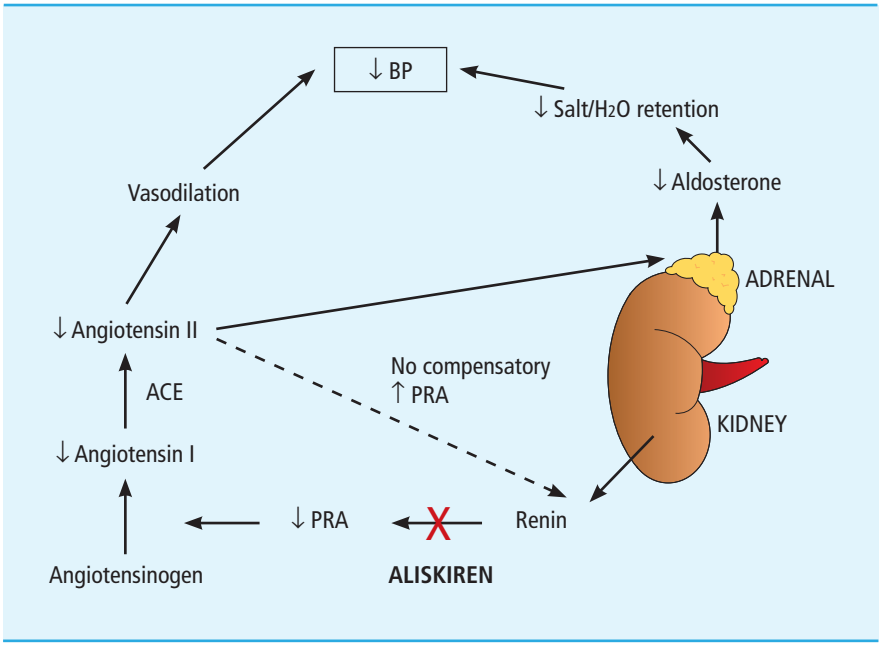

Figure 1. The pharmacological action of aliskiren, a direct renin inhibitor, which acts on the renin angiotensin aldosterone system to reduce plasma renin activity (PRA) and block the conversion of angiotensinogen to angiotensin I, the precursor of angiotensin II

Introduction

Aliskiren is a direct renin inhibitor and was originally approved in the European Union in 2007 for use as monotherapy or in combination with other antihypertensive drugs for the treatment of mild to moderate hypertension. Initially it was assessed in short-term trials, mainly focusing on its antihypertensive effect. Since the *Practical Diabetes* Drug Note on aliskiren was published in 2009,[1] new trials have been undertaken which have provided more information on its efficacy and safety.

These newer studies were designed to look at the effect of aliskiren treatment on longer-term cardiovascular outcomes in patients with heart failure and in people with diabetes.

Pharmacology

Aliskiren is a direct renin inhibitor, which acts on the renin angiotensin aldosterone system (RAAS) to reduce plasma renin activity and block the conversion of angiotensinogen to angiotensin I, the precursor of angiotensin II (Figure 1).

Evidence for use in diabetes

The first long-term safety trial was the Aliskiren Trial in Type 2 Diabetes Using Cardiorenal End-Points (ALTITUDE).[2] This double-blind, randomised control trial (n=8561), with a mean follow up of 33 months, examined the efficacy and safety of aliskiren compared to placebo, in reducing cardiovascular or renal events in patients with type 2 diabetes and evidence of microalbuminuria, macroalbuminuria or cardiovascular disease when added to an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker. Patients were randomised to aliskiren or placebo, and initial dosing was 150mg, increased to 300mg after four weeks if there were no safety concerns.

The trial was discontinued early by the independent data and safety monitoring committee in 2011 as they felt the excess risk of adverse events within the aliskiren group could not be offset by reduction in cardiovascular or renal events. At this stage of the trial, the primary endpoint (major cardiovascular or renal event) had occurred in 18.3%

in the aliskiren group, and in 17.1% in the placebo group. There was a higher incidence of hyperkalaemia, renal impairment and hypotension reported in the aliskiren group, and, at the time of the termination of the study drug, incidence of stroke was found to be higher in the aliskiren group vs placebo (25 vs 18; HR 1.34; p=0.044). By the end of study, however, the p-value for this increased risk was no longer statistically significant.

ALTITUDE showed no benefit from the addition of aliskiren to standard therapy in patients with type 2 diabetes in reducing cardiovascular and renal events, and was associated with more adverse events.

Trials of safety and efficacy

The Aliskiren Trial on Acute Heart Failure Outcomes (ASTRONAUT) was designed to assess whether aliskiren would improve post discharge outcomes in patients who had been hospitalised with heart failure with reduced ejection fraction.[3] Of the patients enrolled in the study (n=1615), 662 patients (41%) had diabetes. The primary endpoint was cardiovascular death or re-hospitalisation with heart failure within six months. There were multiple secondary endpoints, including cardiovascular death or re-hospitalisation within 12 months. Overall, the study appeared to give a neutral result; however, a pre-specified subgroup analysis showed significant differences in outcomes between patients with diabetes and those without. Within six months, there was no significant difference between these patient groups in the primary endpoint. The rates of hyperkalaemia, hypotension and renal impairment were higher in the aliskiren group compared with placebo.

In study participants with diabetes there was a statistically significant adverse effect of aliskiren on 12-month cardiovascular death or re-hospitalisation (p=0.03), first cardiovascular event (p=0.02), and all-cause mortality (p<0.01). Additionally, all-cause mortality at six months was borderline for statistical significance (p=0.05) in the patients with diabetes mellitus, when compared with placebo. There was also a trend towards more hyperkalaemia (HR 2.39; p=0.07). In contrast, those without diabetes appeared to have more favourable outcomes, with those on aliskiren treatment significantly less likely to experience cardiovascular death, re-hospitalisation, first cardiovascular event and all-cause mortality than with placebo.

More recently, the Aliskiren Trial to Minimize Outcomes in Patients with Heart Failure (ATMOSPHERE), published earlier this year, compared aliskiren with enalapril and with the combination of aliskiren and enalapril in 7016 patients with heart failure.[4]

The aim of this trial was to determine if aliskiren was non-inferior to enalapril, and to test if the combination was superior to enalapril. The primary outcome was cardiovascular death or hospitalisation for heart failure. There was a single-blind, run-in period followed by randomisation to one of three groups, in a double-blind fashion. In light of the results of the ALTITUDE and ASTRONAUT trials, the clinical trials regulator mandated that people with diabetes should discontinue the treatment and be switched to conventional therapy, and no further patients with diabetes should be enrolled.

The primary outcome occurred in 32.9% (n=770) in the combined group, 34.6% (n=808) in the enalapril group, and 33.8% (n=791) in the aliskiren group. However, the pre-specified test for non-inferiority was not met. The addition of aliskiren to enalapril led to more adverse events without an increase in benefit. Overall, there was a median follow up of 37 months. On subsequent analysis, there was no evidence of a differential effect of aliskiren or of combination therapy in patients with diabetes, who were followed for a median of 24 months, as compared to those without diabetes.

Discussion

Increased plasma renin activity has previously been linked with adverse cardiovascular outcomes. Theoretically, a renin inhibitor such as aliskiren might help in reducing cardiovascular events, as well as aiding in the blocking of the RAAS cascade.

Since the previous note[1] on this drug, there is now clear evidence showing that aliskiren does not demonstrate any benefit in patients with diabetes in either reducing their cardiovascular risk, or indeed improving their outcomes in heart failure, either in addition to, or in place of, current standard therapy.

There is also a suggestion that it may in fact be harmful to patients with diabetes. The early termination of the ALTITUDE trial, and the results of the ASTRONAUT trial, would suggest that aliskiren should be avoided in patients with diabetes.

The results of the ATMOSPHERE trial would further suggest that, even in patients without diabetes, aliskiren alone is not superior to current therapy in heart failure, and appears to be inferior. Combination therapy does not improve cardiovascular outcomes, and appears to be associated with a higher incidence of adverse events.

Key points

- Aliskiren is a direct renin inhibitor approved for the treatment of mild to moderate hypertension
- Aliskiren has not been shown to improve cardiovascular outcomes in patients with diabetes or heart failure, and increases side effects of hyperkalaemia, hypotension and renal impairment
- Aliskiren may be used to treat hypertension in people with diabetes but does not have a wider role in reducing cardiovascular risk

Declaration of interests

There are no conflicts of interest declared.

References

1. Semple Y, Rankine L. Aliskiren. *Pract Diab Int* 2009;26;34–5.
2. Parving HH, *et al.* Cardiorenal end points in a trial of aliskiren for type 2 diabetes. *N Engl J Med* 2012;367:2204–13.
3. Maggioni AP, *et al.* Effect of aliskiren on post-discharge outcomes among diabetic and non-diabetic patients hospitalized for heart failure. *Eur Heart J* 2013;34:3117–27.
4. McMurray JJV, *et al.* Aliskiren, enalapril, or aliskiren and enalapril in heart failure. *N Engl J Med* 2016;374:1521–32.