Medicines Evidence Commentary

commentary on important new evidence from Medicines Awareness Weekly

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Cardiovascular disease: ALTITUDE study found no benefit with aliskiren and some evidence of harm

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The ALTITUDE study investigated the effect of aliskiren (a direct renin inhibitor) added to standard therapy with an ACE inhibitor or an angiotensin receptor blocker in people with type 2 diabetes who were at high risk of cardiovascular and renal events. The trial was terminated early due to a lack of benefit for aliskiren compared with placebo on cardiovascular and renal outcomes, and an increased risk of adverse events. Aliskiren is not included in the drugs recommended by NICE in the clinical guideline on hypertension or type 2 diabetes.

Overview and current advice

Aliskiren, a direct renin inhibitor is licensed for the treatment of essential hypertension in adults. The NICE clinical guideline on hypertension outlines a stepwise approach to drug treatment. In developing the NICE full guideline, the guideline development group concluded that there was insufficient evidence of aliskiren’s effectiveness to determine its suitability for use in resistant hypertension. Aliskiren is not included in the drugs recommended by NICE in the guideline.

The ALTITUDE study investigated aliskiren added to standard therapy in people with type 2 diabetes. The NICE clinical guideline on type 2 diabetes (which is currently being updated, publication date to be confirmed) recommends a once-daily, generic ACE inhibitor as the first-line blood pressure lowering treatment in most people with type 2 diabetes. For a person with continuing intolerance to an ACE inhibitor (other than renal deterioration or hyperkalaemia), an angiotensin receptor blocker (ARB) can be substituted. The use of aliskiren was not considered in this guideline, and blood pressure control (including target values and drug treatment) is outside the scope of the update.

Following the early termination of the ALTITUDE study, the Medicines and Healthcare Products Regulatory Agency (MHRA) issued a safety warning for aliskiren in March 2012, in light of European Medicines Agency (EMA) advice.
The MHRA stated that the combination of aliskiren with ACE inhibitors or ARBs has been associated with serious adverse cardiovascular and renal outcomes in a recent large clinical trial. This combination is now contraindicated in:

- people with type 1 or 2 diabetes
- people without diabetes with an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1.73 m².

In all other patient groups, aliskiren in combination with an ACE inhibitor or an ARB is not recommended. Any use of aliskiren (either as monotherapy or in combination with other medicines) is no longer recommended in any person with severe renal impairment (eGFR less than 30 mL/min per 1.73 m²).

This medicines evidence commentary discusses the findings from the ALTITUDE study, which resulted in its early termination.

See the NICE Evidence topic pages on hypertension and type 2 diabetes for a general overview of these conditions. The NICE pathways on hypertension and diabetes bring together all related NICE guidance and associated products on these conditions in a set of interactive topic-based diagrams. Renin-angiotensin system drugs is one of the therapeutic areas in the Key therapeutic topics - Medicines management options for local implementation document produced to support the QIPP medicines use and procurement work stream.

New evidence

The ALTITUDE study was a large, double-blind randomised controlled trial (RCT) including 8561 people aged 35 years or older (mean age 64.5 years) who had type 2 diabetes and evidence of microalbuminuria, macroalbuminuria or cardiovascular disease (Parving HH et al, 2012). Following a screening period, participants were randomised to aliskiren 150 to 300 mg daily (n=4274) or placebo (n=4287) in addition to standard therapy with an ACE inhibitor or ARB.

The primary outcome was a composite of the time to death from cardiovascular causes or the first occurrence of cardiac arrest with resuscitation; nonfatal myocardial infarction (MI); nonfatal stroke; unplanned hospitalisation for heart failure; end-stage renal disease, death attributable to kidney failure, or the need for renal replacement therapy with no dialysis or transplantation available or initiated; or a serum creatinine value that was at least double the baseline value. The secondary cardiovascular outcome was a composite of all 5 cardiovascular components of the primary endpoint. The secondary renal outcome was a composite of the renal components of the primary endpoint.

The trial was stopped prematurely in December 2011 after an interim analysis, on the basis that the increased risk of adverse events in the aliskiren group could not be offset against a reduction in major cardiovascular and renal events.

After a median follow up of 32.9 months, the primary outcome occurred in 783 people (18.3%) in the aliskiren group compared with 732 (17.1%) in the placebo group (hazard ratio [HR] 1.08, 95% confidence interval [CI] 0.98 to 1.20, p=0.12). The secondary cardiovascular outcome occurred in 590 people (13.8%) in the aliskiren group compared with 539 (12.6%) in the placebo group (HR 1.11, 95% CI 0.99 to 1.25, p=0.09). All components of the cardiovascular outcome, with the exception of unplanned hospitalisation for heart failure, occurred more frequently in the aliskiren group. For cardiac arrest with resuscitation this difference was statistically significant (19% with aliskiren compared with 8% with placebo, p=0.04), but for the other cardiovascular outcomes there was no statistically significant difference. The secondary renal outcome occurred in 257 people (6.0%) in the aliskiren group compared with 251 (5.9%) in the placebo group (HR 1.03, 95% CI 0.87 to 1.23, p=0.74).
During the trial 563 people (13.2%) in the aliskiren group and 437 people (10.2%) in the placebo group discontinued study medication because of an adverse event (p<0.001). Hyperkalaemia, renal impairment and hypotension were the most common reasons for discontinuing study medication and occurred more frequently in the aliskiren group. Discontinuation due to hyperkalaemia was 4.8% with aliskiren compared with 2.6% with placebo, p<0.001; for renal impairment it was 1.5% compared with 1.3%, p=0.30; and for hypotension 0.7% compared with 0.3%, p=0.02.

At the interim analysis there was a higher risk of stroke in the aliskiren group compared with the placebo group (HR 1.34, 95% CI 1.01 to 1.77, p=0.044). However, at study close out there was no longer a statistically significant difference between groups (3.4% with aliskiren compared with 2.8%)

**Commentary**

**Commentary provided by the NICE Medicines and Prescribing Centre**

The findings of the ALTITUDE study highlight the importance of trials which assess patient orientated outcomes rather than disease orientated outcomes. A previous study had shown that dual therapy with aliskiren and an ARB reduced albuminuria (a disease orientated renal outcome) in people with type 2 diabetes, renal disease and hypertension compared with an ARB alone. However, in the ALTITUDE study, patient orientated renal outcomes, such as end-stage renal disease or kidney failure, were not reduced with aliskiren added to an ACE inhibitor or an ARB; and neither was doubling of baseline serum creatinine.

Dual therapy with aliskiren and an ACE inhibitor or an ARB actually had harmful renal and cardiovascular effects, with an increased risk of hyperkalaemia and hypotension compared with an ACE inhibitor or ARB alone. This increased risk of hyperkalaemia with dual therapy was also seen in a systematic review and meta-analysis of 10 RCTs (n=4,814) of aliskiren added to an ACE inhibitor or an ARB. The ALTITUDE study also found no reduction in patient-orientated cardiovascular outcomes with dual therapy, and for one endpoint (cardiac arrest with resuscitation), dual therapy increased the risk.

Results from the ALTITUDE study add to the concerns about dual renin angiotensin system blockade. As is discussed in the renin-angiotensin system drugs key therapeutic topic, dual therapy with an ACE inhibitor plus an ARB already has only a limited place in treatment – for example, in a small minority of people with heart failure.

Prescribing data show that the number of prescriptions dispensed for aliskiren has decreased by more than a third in the financial year 2012/13 compared with 2011/12, most likely in response to the MHRA warnings in March 2012. Despite this, there were still nearly 53,000 items of aliskiren dispensed in primary care in England in 2012/13, at a cost of approximately £1.5 million.

Prescribers should continue to follow the recommendations given in the NICE clinical guideline on hypertension and type 2 diabetes, neither of which include aliskiren. In light of prescribing data demonstrating that a significant amount of aliskiren is still being prescribed, localities may wish to examine prescribing patterns for aliskiren.

**Study sponsorship**

This randomised controlled trial was funded by Novartis.

**References**

1. Novartis (2013) Rasilez (aliskiren) summary of product characteristics
6. NHS Business Services Authority: personal communication, June 2013

About this Medicines Evidence Commentary

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