The effect of combination treatment with aliskiren and blockers of the renin-angiotensin system on hyperkalaemia and acute kidney injury: systematic review and meta-analysis
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CRD summary
The review concluded that the use of aliskiren in combination with angiotensin converting enzyme inhibitors or angiotensin receptor blockers was associated with an increased risk of raised serum potassium levels (hyperkalaemia). The authors' conclusions are based on the presented results, so they should be considered reliable.

Authors' objectives
To assess the safety of using aliskiren combined with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers.

Searching
The following databases were searched: MEDLINE (1948 to May 2011); EMBASE (1980 to May 2011); and Cochrane Central Register of Controlled Trials (CENTRAL, 1993 to May 2011). The search strategy was available as a web appendix. Clinicaltrials.gov registry, the Novartis clinical trial results database, and abstracts from the past five years from conferences of American Society of Nephrology and European Renal Association were searched. No language restrictions were applied. Bibliographies of identified articles were scanned. Studies published only as abstracts were not considered for inclusion.

Study selection
Studies eligible for inclusion were randomised controlled trials that compared aliskiren in combination with either angiotensin-converting enzyme inhibitors or angiotensin receptor blockers versus monotherapy of aliskiren, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Eligible trials had to be of at least four weeks duration. Trials of patients receiving chronic dialysis were excluded. Relevant outcomes were pre-specified as the incidence of hyperkalaemia or acute kidney injury. No restrictions were placed on dosing regimes.

Included trials compared the interventions listed above in parallel group RCTs with from two to five treatment arms; some trials also used a placebo control. The dosages in the included trials varied, but nearly all were reported to have given up to the maximum recommended dosage. Trial duration ranged from eight to 36 weeks. The mean age of patients per trial arm ranged from 58 years to 68 years. Most patients were men. Only two trials reported predefined safety outcomes. All trial patients had relatively preserved kidney function.

Two reviewers independently reviewed papers for inclusion with all disagreements being resolved by consensus.

Assessment of study quality
The Cochrane Risk of Bias tool was used to assess the methodological quality of included trials based on criteria of sequence generation, allocation concealment, blinding, attrition, selection bias, and other biases. Trials which could not be assessed in any of these domains were excluded from the review.

Two reviewers independently reviewed papers for risk of bias with all disagreements being resolved by consensus or referral to a third reviewer.

Data extraction
Data were extracted using a custom form according to the results reported in each study. Authors were contacted for missing data where possible. Two reviewers independently extracted the data, with all disagreements being resolved by consensus.

Methods of synthesis
A random-effects model was used to account for expected variability within and between the studies. Risk ratios (RRs), risk differences (RDs) and numbers needed to harm (NNH) were calculated along with 95% confidence intervals (CIs) for incidence of hyperkalaemia and acute kidney injury. For the analyses, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers were considered together as one class of drug. Heterogeneity was assessed using the Cochran Q test and associated $I^2$ values.

Funnel plots were used to evaluate publication bias.

**Results of the review**

Ten RCTs (n=4,814 patients) were included in the review. One trial was excluded due to insufficient data (no reply from the authors). The risk of bias was judged to be low across the included trials (more details reported in paper). The lack of masking in some trials was felt to be less relevant given the laboratory-based safety outcomes being assessed. Withdrawal rates were less than 20% in all trials.

**Hyperkalaemia:** The risk of hyperkalaemia was significantly higher in patients given combined aliskiren and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy compared with patients given angiotensin-converting enzyme inhibitor/angiotensin receptor blocker as monotherapy (RR 1.58, 95% CI 1.24 to 2.02; NNH 43, 95% CI 28 to 90; 10 trials; n=4,814). The risk of hyperkalaemia was significantly higher in patients given combined aliskiren and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy compared with patients given aliskiren as monotherapy (RR 1.67, 95% CI 1.01 to 2.79; NNH 50, 95% CI 33 to 125; six trials; n=2,974).

**Acute kidney injury:** The risk of acute kidney failure was not significantly greater in patients given combined aliskiren and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy compared with patients given angiotensin-converting enzyme inhibitor/angiotensin receptor blocker as monotherapy (eight trials; n=4,345) or in patients who were given combined aliskiren and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker therapy compared with patients given aliskiren as monotherapy (five trials; n=3,063).

No significant heterogeneity was observed for any of the analyses.

Further analyses including comparisons of moderate and severe hyperkalaemia, and a retrospective sensitivity analysis were reported in the paper.

Publication bias was not observed.

**Authors’ conclusions**

The use of aliskiren in combination with angiotensin converting enzyme inhibitors or angiotensin receptor blockers was associated with an increased risk of hyperkalaemia. Careful monitoring of serum potassium levels was recommended.

**CRD commentary**

This review set out to evaluate a clear clinical question with appropriate inclusion criteria. A reasonable range of databases and sources were used to locate eligible papers with no language restrictions. Standard review practices of using two researchers to screen, quality assess and data extract were followed throughout, which reduced the likelihood of reviewer error or bias.

The quality assessment of included trials was clear and transparent. Trial quality was considered in relation to the outcomes and question of interest. Data synthesis appeared to be appropriate and was clearly reported. The authors noted that all the included trials were sponsored by Novartis Pharmaceuticals, the manufacturer of aliskiren.

The conclusions of the review are based on the presented results and considered potential limitations of the available evidence base, so they should be considered reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that patients who received combination treatment including aliskiren for renin-angiotensin
system blockade should be monitored carefully for serum potassium levels. The review included trials where the populations had relatively preserved kidney function; applying these findings to routine clinical practice should be done with caution.

**Research:** The authors stated that further research to clarify the role and safety of using aliskiren in combination therapy on key clinical outcomes is needed.

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