A systematic review and meta-analysis of aliskiren and angiotensin receptor blockers in the management of essential hypertension
Zheng Z, Shi H, Jia J, Li D, Lin S

CRD summary
This review concluded that aliskiren provided similar reductions in blood pressure to angiotensin receptor blockers (ARBs) in people with hypertension and no difference in adverse effects. Aliskiren combined with ARBs proved more effective in reducing blood pressure than either therapy alone. Data came from short-term studies that did not assess clinical outcomes, but the authors' conclusions appear reasonable.

Authors' objectives
To assess the antihypertensive effectiveness and safety of aliskiren compared with angiotensin receptor blockers (ARB) in people with mild to moderate hypertension.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL) (Issue 1, 2010), MEDLINE and Pre-MEDLINE (1966 to March 2010) and EMBASE (1980 to March 2010) were searched. Search terms were reported. Prospective trials registers, meeting abstracts and bibliographies of identified reports were checked. Statistical methods had to be described in English.

Study selection
Randomised controlled trials (RCTs) of at least four weeks duration that compared the effects of aliskiren with that of ARBs in adults with a clear diagnosis of primary hypertension were eligible for inclusion. Studies on people who had received any angiotensin converting enzyme inhibitors or ARBs or other antihypertensive agent within two weeks were excluded. The outcomes of interest were changes from baseline systolic and diastolic blood pressure, response rate based on achievement of target blood pressure and incidence of adverse effects.

Aliskiren doses in the included studies ranged from 37.5mg to 300mg. Comparators were losartan, irbesartan, amlodipine and valsartan. Some studies included hydrochlorothiazide in the control and comparator groups. Some studies used a fixed-dose regime and others up-titrated doses during the trial. Follow-up ranged from four to eight weeks.

Studies were assessed for inclusion by two reviewers independently. Disagreements were resolved by consensus or a third reviewer.

Assessment of study quality
Quality was assessed using the Cochrane quality checklist (generation of allocation sequence, allocation concealment, blinding, intention to treat and completeness of follow-up) and Jadad Score (maximum score of 5). Jadad scores of zero to 2 were taken to indicate low quality, 3 to 4 were moderate and 5 was high quality.

It was not clear how many reviewers assessed quality.

Data extraction
Data were extracted to calculate change from baseline seated systolic and diastolic blood pressure, blood pressure control rate and incidence of adverse events. Relative risk (RR) and 95% confidence intervals (CI) were calculated for dichotomous data and mean differences and 95% CI were calculated for continuous data. Dosage regimes were categorised as proportions of the manufacturer's maximum recommended daily dose.

It was not clear how many reviewers performed data extraction.

Methods of synthesis
Pooled relative risks and 95% CI and weighted mean differences (WMD) and 95% CI were calculated using a random-
effects or a fixed-effect model, depending on presence of heterogeneity. Heterogeneity was assessed using the Cochran Q test and $I^2$.

Funnel plots and Egger's test were used to assess publication bias.

**Results of the review**

Seven RCTs were included (5,488 participants in RCTs; it was unclear how many were included in analyses as those in the placebo groups were not included). Three studies scored 5 on the Jadad scale and four studies scored 3. Tests showed no evidence of publication bias.

Compared to ARBs, aliskiren showed no difference in the reduction in systolic or diastolic blood pressure or control rate of blood pressure at half maximum dose (three trials) or at maximum dose (five trials).

Aliskiren combined with ARBs was superior to aliskiren monotherapy at maximum dose for systolic blood pressure reduction (WMD -4.80, 95% CI -6.22 to -3.39, $I^2$=10.7%; 1,701 participants), diastolic blood pressure reduction (WMD -2.96, 95% CI -4.63 to -1.28, $I^2$=64%; 1,701 participants) and blood pressure control (RR 1.45, 95% CI 1.30 to 1.63, number of participants unclear). Aliskiren combined with ARBs was superior to ARB monotherapy at maximum dose for systolic blood pressure reduction (WMD -4.43, 95% CI -5.91 to -2.96, $I^2$=17.4%; 1,654 participants), diastolic blood pressure reduction (WMD -2.40, 95% CI -3.41 to -1.39, $I^2$=0%; 1,654 participants) and blood pressure control (RR 1.44, 95% CI 1.28 to 1.61).

Incidence of adverse effects was similar for aliskiren and ARBs (details reported).

**Authors’ conclusions**

Aliskiren provided similar reductions in blood pressure to ARBs in people with hypertension and no difference in adverse effects. Aliskiren combined with ARBs proved more effective in reducing blood pressure than either therapy alone.

**CRD commentary**

The aims of this review were clearly stated in terms of the inclusion criteria. The search covered several relevant sources. It seems that only studies published in English were eligible for inclusion, so language bias was possible. Tests for publication bias may have been unreliable due to the relatively small number of included studies. Methods of study selection were appropriate for reducing reviewer error or bias; methods for data extraction and quality assessment were unclear. Methods of quality assessment were appropriate, but the results (particularly for the Cochrane quality assessment methods) were neither reported clearly nor used to inform the analyses.

Methods of synthesis appeared appropriate. Differences between studies were investigated. Little information was presented about the included participants and this may have affected the generalisability of the results. The number of included participants was unclear as some studies appeared to have study groups that were not included in the analyses. Data were from short-term studies that did not appear to have assessed clinical outcomes. However, the authors conclusions appear reasonable.

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

**Practice:** The authors stated that until outcomes data become available there was no evidence base to justify replacing an angiotensin-converting enzyme (ACE) inhibitor or ARB with aliskiren for end-organ protection in patients. But Aliskiren represent an attractive new option as an add-on therapy for achieving blood pressure goals.

**Research:** The authors implied that further research was needed to compare the effects of aliskiren to ARBs on clinical outcomes.

**Funding**

None stated.

**Bibliographic details**

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.