Amlodipine and angiotensin-converting enzyme inhibitor combination versus amlodipine monotherapy in hypertension: a meta-analysis of randomized controlled trials
Lv Y, Zou Z, Chen GM, Jia HX, Zhong J, Fang WW

CRD summary
The authors concluded that combination treatment with amlodipine and ACEIs was more effective than amlodipine monotherapy in blood pressure control and had fewer adverse events in patients with hypertension. This was a well-conducted review. The authors’ conclusion reflects the evidence presented, but reliability should be treated with caution due to the suboptimal quality of included studies.

Authors’ objectives
To evaluate the efficacy and tolerability of combination amlodipine and angiotensin-converting enzyme inhibitors (ACEIs) compared with amlodipine monotherapy in patients with hypertension.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and EMBASE were searched to June 2009 for published studies in English. Search terms were reported. Reference lists of relevant studies and meta-analyses were scanned.

Study selection
Randomised controlled trials (RCTs) that compared amlodipine and angiotensin-converting enzyme inhibitors (ACEIs) with amlodipine monotherapy in patients with hypertension were eligible for inclusion in the review. Trials had to report on at least one outcome from blood pressure, therapeutic blood pressure response, mortality, cerebrocardiovascular event rates, adverse events and withdrawal.

Included studies were of adult patients (mean age 55.5 years) with even numbers of men and women. Severity of hypertension ranged from stage I to III. Some participants had co-existing conditions such as type 2 diabetes and risk of endothelial function. Median body weight was 76.4kg (range 53.5kg to 92.1kg). Median body mass index was 29kg/m² (range 25.1kg/m² to 32.4kg/m²). Drug doses varied between studies. Amlodipine doses were not always the same across combination and monotherapy regimens. Trial duration varied from four to 48 weeks (median eight weeks). More than half of the studies were conducted in USA; there were three UK studies. The primary outcome was reduction of systolic and diastolic blood pressure.

Two reviewers independently selected trials for inclusion; this process was checked by a third reviewer.

Assessment of study quality
Trial quality was assessed in terms of adequacy of randomisation, allocation concealment, blinding (of patients, healthcare providers, data collectors and outcome assessors) and follow-up. The Cochrane risk of bias tool was used to indicate low, moderate or high risk of bias.

Two reviewers independently carried out the quality assessment.

Data extraction
Data were extracted to enable calculation of relative risk (RR), mean difference and 95% confidence intervals (CI).

Two reviewers independently extracted data. Differences were resolved by discussion and with the involvement of a third reviewer, where necessary.

Methods of synthesis
Relative risks and weighted mean differences (WMDs) were pooled in a random-effects meta-analysis (DerSimonian and Laird). Statistical heterogeneity was assessed using Cochran Q and the $I^2$. Study variation was explored in subgroup, sensitivity and meta-regression analyses. Publication bias was assessed using a funnel plot and with Begg's test. The trim-and-fill method was used to adjust for the effect of publication bias.

**Results of the review**

Seventeen RCTs ($n=3,291$ participants) were included in the meta-analysis. There were 12 parallel group and five crossover trials. Fourteen trials were considered to be at high risk of bias due to unclear allocation concealment and inadequate description of blinding. Withdrawal rates were less below 20% in most cases.

Combination treatment was associated with a statistically significant greater reduction in clinical systolic blood pressure (WMD 5.72, 95% CI 4.10 to 7.33; 11 trials) and clinical diastolic blood pressure (WMD 3.62, 95% CI 4.85 to 2.39; 11 trials). Subgroup and meta-regression analyses revealed no substantial influences on the primary outcome. Combination treatment showed greater reductions in mean ambulatory systolic blood pressure (WMD 4.24, 95% CI 6.82 to 1.67) and diastolic blood pressure (WMD 2.23, 95% CI 3.73 to 0.69) over a 24-hour period and a higher therapeutic rate (RR 1.36, 95% CI 1.07 to 1.73; five trials).

Overall adverse events (RR 0.86, 95% CI 0.75 to 0.99; eight trials) and oedema (RR 0.40, 95% CI 0.29 to 0.56; 11 trials) were significantly lower following combination treatment. Cough rate increased (RR 3.28, 95% CI 2.03 to 5.29; nine trials). There was no evidence of publication bias.

Sensitivity analysis demonstrated the robustness of the results.

**Authors' conclusions**

In hypertensive patients, combination treatment that involved amlodipine and ACEIs was more effective than amlodipine monotherapy in blood pressure control and had fewer adverse events.

**CRD commentary**

The review question was clear. Inclusion criteria were potentially reproducible. The search strategy included some relevant sources. The restriction to studies published in English meant that some studies may have been missed and associated biases could not be ruled out. Publication bias was assessed. Appropriate quality assessment criteria were applied and the results indicated that most of the included studies were methodologically flawed. The review process was well reported and included sufficient attempts to minimise error and bias. Study details were presented clearly. Statistical heterogeneity was taken into account in the chosen method of synthesis.

This was a well-conducted review. The authors' conclusion reflects the evidence presented, but reliability should be treated with caution due to the suboptimal quality of the included studies.

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

**Practice**: The authors did not state any implications for practice.

**Research**: The authors stated that well-designed long-duration RCTs were needed to evaluate the safety and efficacy of amlodipine/ACEI combination therapy in patients with hypertension. Study outcomes should include clinical and ambulatory blood pressure reduction, blood pressure control, blood pressure response, cerebrocardiovascular events, mortality and adverse events. Exploration of the mechanisms of ACEIs and how they impact on cardiovascular disease morbidity and mortality was recommended.

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