Antihypertensive treatment and secondary prevention of cardiovascular disease events among persons without hypertension: a meta-analysis

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CRD summary
The authors concluded that antihypertensives reduced the risk of stroke, congenital heart failure, cardiovascular disease and mortality in individuals with history of cardiovascular disease, but without hypertension. This was a generally well conducted review, but variability between trials suggests that the authors’ conclusions should be interpreted with some caution.

Authors’ objectives
To assess the effects of antihypertensive treatment on secondary prevention of cardiovascular disease events and all-cause mortality among individuals without clinically defined hypertension.

Searching
MEDLINE (1950 to January 2011), EMBASE and Cochrane Central Register of Controlled Trials (CENTRAL) were searched without language restrictions. Search terms were reported. Reference lists of retrieved articles were searched manually.

Study selection
Randomised controlled trials (RCTs) that compared antihypertensive treatment versus control for the prevention of cardiovascular events (fatal or nonfatal stroke, fatal or nonfatal myocardial infarction, congestive heart failure and mortality) in adults (aged >18 years) with blood pressure less than 140mmHg systolic or less than 90mmHg diastolic were eligible for inclusion. Eligible studies were required to include patients with pre-existing cardiovascular disease or cardiovascular disease equivalents (such as diabetes) and report either measures of variance or sufficient data for these to be calculated.

The included studies were of patients with a mean age range 54.8 to 68 years. The proportion of men was 76%. Clinical history of patients at baseline varied between trials. Blood pressure was measured using various assessment tools. Definitions of participants without hypertension varied among trials. Antihypertensive drugs included different types and doses of beta-blocker, angiotensin receptor blocker (ARB), calcium channel blocker, angiotensin-converting enzyme inhibitor (ACEI) and diuretics. Mean trial duration ranged between 1.5 and 63 months.

Three reviewers independently screened studies for inclusion. Discrepancies were resolved through consensus with two other reviewers.

Assessment of study quality
Two reviewers independently assessed study quality according to criteria of randomisation, allocation concealment, similarity of groups at baseline, eligibility criteria, blinding, point estimates and intention-to-treat analysis. Trials received a score out of nine. Discrepancies were resolved through discussion and consensus.

Data extraction
Three reviewers independently extracted or calculated relative risks (RRs) or hazard ratios, and 95% confidence intervals (CIs). Absolute risk reductions were calculated. Where necessary, primary authors were contacted for additional information. Discrepancies were resolved through discussion with two other reviewers.

Methods of synthesis
Relative risks and 95% CIs were combined using fixed-effect or random-effects models, weighted by the inverse of the variance. Absolute risk reductions and 95% CIs were combined using a random-effects model. The Q test and I^2 statistic were used to assess statistical heterogeneity.

Subgroup analyses were conducted to assess the influence of the presence or absence of comorbidities at baseline and
type of antihypertensive treatment. Sensitivity analyses were performed by removal of one trial at a time and by restricting the analyses according to antihypertensive drug at baseline, definition of individuals without hypertension, trial size, follow-up duration and year of publication.

Publication bias was assessed using funnel plots and Begg and Eggers tests.

**Results of the review**

Twenty-five RCTs (n=64,162) were included in the review. Quality scores ranged between 7 and 9 (high quality).

Antihypertensive treatment statistically significantly reduced the risk of stroke (RR 0.77, 95% CI 0.61 to 0.98; seven RCTs, $I^2$=61.9%), myocardial infarction (RR 0.80, 95% CI 0.69 to 0.93; six RCTs, $I^2$=26.5%), congestive heart failure (RR 0.71, 95% CI 0.65 to 0.77; eight RCTs, $I^2$=0.0%), cardiovascular disease events (RR 0.85, 95% CI 0.80 to 0.90; 13 RCTs, $I^2$=35.4%), cardiovascular disease mortality (RR 0.83, 95% CI 0.69 to 0.99; six RCTs, $I^2$=43.6%) and all-cause mortality (RR 0.87, 95% CI 0.80 to 0.95; 15 RCTs, $I^2$=46.1%). Absolute risk reductions were reported.

Sensitivity analysis that removed one trial at a time resulted in non-significant findings for stroke, myocardial infarction and cardiovascular-related mortality. Other sensitivity analyses were reported in the review. Subgroup analysis showed non-significant findings using antihypertensive treatment for prevention of cardiovascular disease and all-cause mortality in patients with diabetes. Trial quality did not influence the findings on cardiovascular disease outcome or all-cause mortality.

There was no evidence of publication bias using Begg test. There was evidence of bias for stroke using Eggers test, but the trim and fill adjustment method showed no change on the overall effect estimate.

**Authors’ conclusions**

Antihypertensive treatment reduced the risk of stroke, congenital heart failure, cardiovascular disease events and all-cause mortality in individuals with clinical history of cardiovascular disease, but without hypertension. Additional RCTs are needed to assess these outcomes in patients without cardiovascular disease clinical recommendations.

**CRD commentary**

The review question and supporting inclusion criteria were clearly stated. The literature search was adequate. There were no language restrictions. There was no obvious attempt to identify unpublished data and so potentially relevant data may have been missed. Publication bias was assessed formally and did not appear to be significant enough to alter the findings. Trial quality was assessed using appropriate criteria. The authors reported that quality was high; no individual results were presented. Each stage of the review was undertaken in duplicate or triplicate, which reduced risks of reviewer error and bias. Given the variation in patient and treatment details, it was unclear whether pooling of the trials was appropriate. The authors went some way to identify sources of heterogeneity. Only a small number of trials reported on the outcomes of interest; the authors acknowledged this and the impact this had on the robustness of the findings.

This was a generally well conducted review. Heterogeneity among trials suggests that the authors’ conclusions should be interpreted with some caution.

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

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

**Research:** The authors stated a need for further studies to examine the baseline blood pressure levels at which antihypertensive treatment should be started in individuals with cardiovascular disease or equivalents, such as diabetes. Additional RCTs were needed to assess outcomes (stroke, congenital heart failure, cardiovascular disease events and all-cause mortality) in patients without cardiovascular disease clinical recommendations. Use of individual patient data would be most useful to eliminate some of the limitations associated with this review.

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