Antihypertensive treatment and development of heart failure in hypertension: a Bayesian network meta-analysis of studies in patients with hypertension and high cardiovascular risk

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CRD summary
The authors concluded that evidence supported use of diuretics and angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) as first-line treatment for the prevention of heart failure in hypertensive patients. Given the potential for bias in the review, limitations with the included studies and uncertainties regarding multiple treatment comparisons, caution should be applied when interpreting the authors' conclusions.

Authors' objectives
To assess the effects of various different antihypertensive treatments in the prevention of heart failure in patients with hypertension or high cardiovascular risk.

Searching
PubMed and EMBASE were searched between 1997 and December 2009 for peer-reviewed publications. Search terms were reported. References of recently published meta-analyses were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared different antihypertensive strategies (as first-line treatment) in patients with hypertension or populations with high cardiovascular risk (>65% with hypertension) were eligible for inclusion. Eligible trials were required to include at least 200 patients and report the incidence of heart failure and other major cardiovascular events.

Included trials were mostly of patients with hypertension; some also had type 2 diabetes, additional risk factors (unspecified), nephropathy, left ventricular hypertrophy, vascular disease or coronary heart disease. Median patient age was 67 years. Most trials reported heart failure as a secondary endpoint; where reported, this was diagnosed using a validated end point. Heart failure was described as fatal or non-fatal. Patients were hospitalised or treated without hospitalisation. Antihypertensive drug treatments included calcium channel blockers, angiotensin-converting enzyme inhibitors, α-blockers, angiotensin II receptor blockers and diuretics; these were compared to placebo, β-blockers, conventional treatment or each other. Other outcomes reported were mean difference in blood pressure and all-cause and cardiovascular mortality.

Two reviewers independently screened trials for inclusion.

Assessment of study quality
The authors reported that all included trials met at least two quality criteria defined according to previously published criteria. No other details were provided.

The authors did not state how many reviewers assessed study quality.

Data extraction
The authors extracted outcome data into an excel spreadsheet; they did not state how many reviewers performed the data extraction.

Methods of synthesis
Summary odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using pairwise meta-analysis; a fixed-effect model was used unless there was evidence of statistical heterogeneity, in which case a random-effects model was used. Statistical heterogeneity was assessed using the X² test. Publication bias was assessed using Egger and Begg tests.
A Bayesian network analysis (mixed treatment comparison) was then performed using the SST-2-HOM model (random-effects baselines, homogeneous treatment variance) to calculate odds ratios and 95% credible intervals (CrIs). Subgroup analyses were undertaken for trials that enrolled a greater proportion of males or greater proportion of females and for trials with a mean age of patients younger or older than 67 years. Separate analysis was undertaken in trials that excluded patients with a history of heart failure.

Results of the review
Twenty-six RCTs (n=223,313) were included in the review. Follow-up ranged between two and 8.4 years. Overall incidence of heart failure was 8,554 (3.8%).

Pairwise meta-analysis:
The authors reported that angiotensin-converting enzyme inhibitors (OR 0.78, 95% CI 0.69 to 0.98; one RCT), angiotensin II receptor blockers (OR 0.85, 95% CI 0.55 to 1.31; two RCTs), calcium-channel blockers (OR 0.67, 95% CI 0.48 to 0.94; three RCTs) and diuretics (OR 0.37, 95% CI 0.23 to 0.61; one RCT) were more effective than placebo in preventing heart failure. However, the confidence intervals reported for angiotensin II receptor blockers suggested that there was no statistically significant difference between intervention and placebo.

Diuretics were statistically significantly more effective than α-blockers (OR 0.49, 95% CI 0.43 to 0.55; one RCT), angiotensin-converting enzyme inhibitors (OR 0.86, 95% CI 0.78 to 0.95; two RCTs) and calcium-channel blockers (OR 0.71, 95% CI 0.64 to 0.79; five RCTs) in preventing heart failure. The authors reported that conventional therapy (OR 0.84, CI 0.72 to 0.98; three RCTs), angiotensin-converting enzyme inhibitors (OR 0.84, 95% CI 0.76 to 0.93; three RCTs) and angiotensin II receptor blockers (OR 0.88, 95% CI 0.76 to 1.01; one RCT) were significantly more effective than calcium-channel blockers. However, the confidence intervals reported for angiotensin II receptor blockers suggested that there was no statistically significant difference between the two treatment groups. Angiotensin II receptor blockers were statistically more effective in preventing heart failure compared to conventional therapy (OR 0.67, 95% CI 0.47 to 0.95; two RCTs), but no other pairwise comparisons showed statistically significant differences. There was no evidence of statistical heterogeneity or publication bias.

Bayesian network meta-analysis:
All active treatments except α-blockers and β-blockers were statistically significantly more effective in preventing heart failure compared to placebo; the most effective active treatments were diuretics (OR 0.59, 95% CrI 0.47 to 0.72), angiotensin-converting enzyme inhibitors (OR 0.71, 95% CrI 0.58 to 0.84) and angiotensin II receptor blockers (OR 0.76, 95% CrI 0.62 to 0.90). Similar to pairwise comparisons, diuretics were significantly more effective than α-blockers, calcium-channel blockers and angiotensin-converting enzyme inhibitors and also conventional therapy, β-blockers and angiotensin II receptor blocker in preventing heart failure. All active treatments except β-blockers were significantly more effective than α-blockers. The authors suggested in the abstract that angiotensin II receptor blockers were more effective than calcium channel blockers: this was not supported by the credible intervals reported.

Subgroup analyses were reported in the review. Differences in blood pressure, all-cause mortality and cardiovascular mortality were reported for individual studies.

Authors’ conclusions
The evidence supported use of diuretics and angiotensin-converting enzyme inhibitors (or angiotensin receptor blockers) as first-line treatment for the prevention of heart failure in hypertensive patients. These treatments should be used in preference to calcium-channel blockers and β-blockers.

CRD commentary
The review question was clear and supported by appropriate inclusion criteria. The literature search was restricted to published trials and it was unclear whether there were any language restrictions. However, there was no evidence of publication bias. Study selection was undertaken in duplicate; it was unclear whether this was true for validity assessment and data extraction and so reviewer error and bias could not be ruled out. Few details on quality assessment were provided. Statistical analysis was substantial, although most pairwise comparisons included only one or two trials.
Uncertainties remained around the use of multiple treatment comparisons and this should be borne in mind when interpreting these findings. Details on patient characteristics and treatment regimens were lacking, but the authors reported that there was clinical and methodological heterogeneity among studies. There was no evidence of statistical heterogeneity for the pairwise comparisons. There was some discrepancy in the reporting of results, particularly for angiotensin II receptor blockers.

Given the potential for bias in the review, possible limitations with the included studies and uncertainties around the use of multiple treatment comparisons, caution should be applied when interpreting the authors' conclusions.

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

**Practice:** The authors stated that the findings from the review could not be generalised to the prevention of other cardiovascular outcomes.

**Research:** The authors stated that further research was needed to assess different combination treatments in patients at risk of heart failure and assess the efficacy of different antihypertensive treatments in patients with and without diabetes, nephropathy and a history of myocardial infarction.

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