Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis


CRD summary
This review combined direct within-trial between-drug comparisons of first-line antihypertensive agents with indirect evidence derived from trials that had one treatment in common. Low-dose diuretics were found to be the most effective first-line treatment for preventing cardiovascular disease mortality and morbidity. Although the results are supported by the evidence presented, indirect comparisons are not as reliable as direct comparisons.

Authors' objectives
To summarise evidence concerning the safety and efficacy of various antihypertensive therapies used as first-line agents, and to evaluate these in terms of major cardiovascular events and all-cause mortality. The primary aim was to compare low-dose diuretics with each of the other first-line therapies.

Searching
MEDLINE was searched from 1995 to 2002 and references were obtained from previous meta-analyses and journal reviews. The search terms were given in the paper. No language restrictions were applied.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials that evaluated major CVD end points in hypertensive patients and lasted at least one year were sought. Studies published since 1995 had to have a minimum of 400 person-years observation. Open-label studies that used an untreated control group were included.

Specific interventions included in the review
The inclusion criteria stated first-line pharmacological antihypertensive therapies, limited to the six most commonly used classes of drugs (diuretics, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin-receptor blockers, calcium-channel blockers and alpha blockers. In the included studies, the diuretics were considered as either low-dose or high-dose, based on equivalent doses of chlorthalidone or hydrochlorothiazide. Comparisons were made versus no treatment (defined as either placebo, untreated or usual care), or between drugs.

Studies that included other treatments, such as smoking cessation or lipid lowering, that would confound the results were excluded. Studies on drugs other than the six main antihypertensive agents were excluded.

Participants included in the review
The participants were those being treated for hypertension. People with congestive heart failure (CHF) or myocardial infarction (MI) were excluded.

Outcomes assessed in the review
The primary outcomes of interest were cardiovascular mortality and morbidity. In the included studies, the outcomes were: coronary heart disease (CHD), defined as MI or CHD death; stroke; CHF; major cardiovascular disease (CVD) events, defined as CHD, stroke, CHF and other CVD mortality; and total mortality.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
The authors do not state that they assessed validity.

**Data extraction**
Two authors independently extracted the data and any differences were resolved by consensus. The relative risk (RR) and standard error were calculated for each trial.

**Methods of synthesis**
How were the studies combined?
Data for any drug treatment versus no treatment were combined using a standard meta-analysis. RRs and 95% confidence intervals (CIs) were calculated.

The main analysis consisted of a network meta-analysis. This used information from direct (within-trial) and indirect (between-trial) comparisons to indirectly compare different drug treatments. RRs and 95% CIs were calculated.

How were differences between studies investigated?
The authors do not state how differences between the studies were investigated. However, they do report on heterogeneity between the studies within the standard meta-analysis.

For the network meta-analysis, the authors looked at the variances of differences between comparisons for the same treatments to estimate the degree of incoherence. Incoherence can be used either to adjust for estimated treatment differences or, if the incoherence is large, to show that combining trials may be inappropriate.

**Results of the review**
Forty-two studies were included (192,478 participants). For standard meta-analyses, the number of trials which reported on each end point was 24 for CHD, 23 for stroke, 7 for CHF, 28 for major CVD events, 23 for CVD mortality and 25 for total mortality.

For network meta-analyses, the number of trials which were used in indirect comparisons was 25 for CHD, 25 for stroke, 15 for CHF, 29 for major CVD events, 26 for CVD mortality and 23 for total mortality. The numbers of patients for each meta-analysis were not reported.

Compared with no treatment, any active treatment was associated with important reductions in the risks of all major outcomes. However there was significant heterogeneity for stroke and major CVD events. Using the network meta-analysis, the low-dose diuretics were superior to placebo for all outcomes: the RR was 0.79 (95% CI: 0.69,0.92) for CHD, 0.51 (95% CI: 0.42, 0.62) for CHF, 0.71 (95% CI: 0.63, 0.81) for stroke, 0.76 (95% CI: 0.69, 0.83) for CVD events, 0.81 (95% CI: 0.73, 0.92) for CVD mortality and 0.90 (95% CI: 0.84, 0.96) for total mortality.

The network meta-analysis showed that none of the other first-line treatments (beta-blockers, angiotensin-converting enzyme inhibitors, calcium-channel blockers, alpha blockers or angiotensin-receptor blockers) were significantly better than low-dose diuretics for any outcome.

Incoherence for each meta-analysis was small.

**Authors’ conclusions**
Low-dose diuretics are the most effective first-line treatment for preventing cardiovascular disease mortality and morbidity.

**CRD commentary**
This was a clearly written paper which updates an earlier review (see Other Publications of Related Interest). The database search was somewhat limited, although the authors did use information from previous reviews to supplement it; it is possible that some studies may have been missed. The information on the included studies was rather limited.
Novel statistical methods were used to make indirect comparisons between different drug classes. The methods were well described and the authors appear to have considered some of the problems related to this form of comparison. However, it is generally accepted that whilst indirect comparisons can add to knowledge about the effects of treatment, these are not as reliable as direct comparisons.

Implications of the review for practice and research
Practice: The authors state that clinical practice and treatment guidelines should reflect the evidence that low-dose diuretics are the most effective.

Research: The authors state that future trials should use low-dose diuretics as the standard for clinically useful comparisons.

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Other publications of related interest

This additional published commentary may also be of interest. Davidson RA. Review: low-dose diuretics are the best first-line antihypertensive therapy. ACP J Club 2004;140:3.

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