Effects of different blood-pressure-lowering regimens on major cardiovascular events: results of prospectively-designed overviews of randomised trials

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CRD summary
This was a well-conducted meta-analysis of individual patient level data that found that treatment with any commonly used antihypertensive regimen reduces the risk of total major cardiovascular events, while larger reductions in blood-pressure produce larger reductions in risk. The results also showed that regimens based on angiotensin-converting enzyme inhibitors, or diuretics or beta-blockers, are more effective at preventing heart failure than regimens based on calcium antagonists.

Authors' objectives
To estimate the effects of strategies based on different drug classes, or those targeting different blood-pressure (BP) goals, on the risks of major cardiovascular events and death.

Searching
A registry of ongoing and planned trials eligible for this review was established in 1998. Trials were identified by searching electronic databases and by checking reference lists, conference proceedings and review articles. Experts in the field and drug manufacturers were contacted. All trials identified subsequent to the setting up of the register were to be added to the register and their investigators invited to join the collaboration.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs) that had planned a minimum follow-up of 1,000 patient-years in each randomisation group were eligible for the review. The trials were not to have reported their main results prior to July 1995, and follow-up had to be complete and outcome data available by June 2003.

Specific interventions included in the review
Studies that compared a BP-lowering drug regimen with placebo, or compared two different classes of BP-lowering drug or the effects of regimens with different BP-lowering goals, were eligible for inclusion. The included studies compared different drug regimens with placebo: angiotensin-converting enzyme (ACE) inhibitor versus placebo, angiotensin-receptor blocker (ARB) versus placebo, or calcium antagonist versus placebo. They also compared different drug classes: ACE inhibitor versus a diuretic or beta-blocker, calcium antagonist versus a diuretic or beta-blocker, or ACE inhibitor versus a calcium antagonist. The remaining included studies compared regimens with different BP goals, e.g. the reduction of diastolic BP to below 85 mmHg rather than to 100 mmHg.

Participants included in the review
Studies of patients being treated because of high BP, diabetes, coronary heart disease (CHD), peripheral vascular disease cerebrovascular disease, or renal disease were eligible for inclusion. Studies of patients treated primarily because of acute myocardial infarction or heart failure were not eligible. In the included studies, the majority of patients were treated primarily because of high BP. The overall mean age of the patients was 65 years and 65% were male.

Outcomes assessed in the review
It was unclear what the inclusion criteria for studies were in terms of outcomes. However, there were six predefined outcomes for the review: stroke, CHD, heart failure, major cardiovascular event (stroke, CHD, heart failure or death), death from any cardiovascular cause and total mortality.

How were decisions on the relevance of primary studies made?
The authors contacted primary study investigators regarding potentially eligible studies.
Assessment of study quality
The individual patient data were checked for completeness and consistency: completeness of patient records, balance of randomisation, and other indicators of possible anomalies. Internal consistency of the data was confirmed by a direct comparison of the trial level analysis with the summary data provided from each trial. Results of these comparisons were discussed with the original investigators to ensure that the primary studies were correctly included in the review. The validity assessments were conducted as part of the data extraction and analysis for the review.

Data extraction
The data requested for each participant included baseline characteristics recorded at or immediately prior to random allocation to treatment, selected measurements taken during follow-up, and details of all predefined outcomes during the scheduled follow-up period (see Other Publications Of Related Interest). Relative risks (RRs) and 95% confidence intervals (CIs) were calculated separately for every outcome and every trial.

Methods of synthesis
How were the studies combined?
Pooled RRs and 95% CIs were calculated using a fixed-effect model.

How were differences between studies investigated?
Heterogeneity was tested using the chi-squared Q statistic. If heterogeneity was found (P<0.10) then further analyses using a random-effects model were performed. Associations between the size of the reduction in BP and the reduction in risk between randomised comparisons were estimated by plotting pooled RRs for every comparison and outcome against the corresponding mean BP difference, weighted by the number of individuals in each treatment group. No formal test of association was performed.

Results of the review
Twenty-nine trials (n=162,341) were included in the review.

Stroke.
Regimens based on ACE inhibitors, calcium antagonists or ARBs statistically significantly reduced the risk of stroke compared with placebo, as did more intensive BP-lowering regimens compared with less intensive ones. Differences between different active treatment regimens were not statistically significant and the RRs were all close to 1.

CHD.
Regimens based on ACE inhibitors or calcium antagonists had small and just statistically significant beneficial effects on the risk of CHD compared with placebo. However, the differences between ARB and placebo, and between more intensive and less intensive BP-lowering regimens, were not statistically significant. Differences between different active treatment regimens were not significant and the RRs were all close to 1.

Heart failure (that caused death or hospital admission).
Regimens based on ACE inhibitors or ARBs had statistically significantly beneficial effects on the risk of heart failure compared with placebo. However, the differences between calcium antagonists and placebo, and between more intensive and less intensive BP-lowering regimens, were not statistically significant; there was a tendency for calcium antagonists to increase the risk of heart failure. The difference between calcium antagonists and other active treatments was significantly in favour of ACE inhibitors and diuretics or beta-blockers.

Major cardiovascular events.
Regimens based on ACE inhibitors, calcium antagonists or ARBs statistically significantly reduced the risk of stroke compared with placebo, as did more intensive BP-lowering regimens compared with less intensive ones. Differences
between different active treatment regimens were not statistically significant and the RRs were all close to 1.

Cardiovascular death.

Regimens based on ACE inhibitors or calcium antagonists had small and just statistically significant beneficial effects on the risk of cardiovascular death compared with placebo. However, the differences between ARBs and placebo, and between more intensive and less intensive BP-lowering regimen, were not statistically significant. Differences between different active treatment regimens were not significant and the RRs were all close to 1.

Total mortality.

Regimens based on ACE inhibitors had a statistically significant beneficial effect on total mortality compared with placebo. However, differences between ARBs or calcium antagonists and placebo, and between more intensive and less intensive BP-lowering regimens, were not statistically significant. Differences between different active treatment regimens were not significant and the RRs were again all close to 1.

Effect of reductions in BP.

For all seven randomised comparisons, the weighted mean difference in BP was directly associated with differences in the risk of stroke, CHD, major cardiovascular events, cardiovascular death and total mortality, but not with the risk of heart failure.

Authors' conclusions
Treatment with any commonly used antihypertensive regimen reduced the risk of total major cardiovascular events, while larger reductions in BP produced larger reductions in risk. The results also showed that regimens based on ACE inhibitors, diuretics or beta-blockers were much more effective at preventing heart failure than regimens based on calcium antagonists.

CRD commentary
This was a well-conducted meta-analysis of individual patient level data. While details of the searches conducted to identify studies were not reported, it is unlikely that trials meeting the inclusion criteria for the review were missed, although the criteria for studies to start and complete within a certain timeframe might have excluded some relevant studies. The methods of the review were described well and it appears that every effort was made to check the reliability of the data and minimise bias in the review. However, the results from individual trials were not reported. The statistical methods used were appropriate and the results of the many meta-analyses were presented clearly in forest plots. The authors' conclusions appear reliable.

Implications of the review for practice and research
Practice: The results of the present review should enhance the ability of clinicians and health policy-makers to make evidence-based decisions about antihypertensive treatment.

Research: Further analyses of the data are required to address questions relating to the optimal regimens for people with diseases such as diabetes and nephropathy. The effects on other outcomes, such as new-onset diabetes or renal failure, also need investigation.

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