Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies


CRD summary
This review concluded that, with few exceptions, all classes of blood pressure lowering drug have similar effects in reducing coronary events and stroke for a given reduction in blood pressure. Despite some concerns over the review methods and quality of included trials, the meta-analyses included a large number of studies and the conclusions reflected the evidence presented.

Authors' objectives
To evaluate the efficacy of blood pressure lowering drugs in preventing coronary heart disease and stroke.

Searching
MEDLINE, the Cochrane Library and Web of Science were searched without language restrictions from inception to December 2007. Search terms were reported. Bibliographies of included studies and previous meta-analyses were also scanned.

Study selection
Randomised controlled trials (RCTs) of blood pressure lowering drugs, where any concomitant medication was also administered to control groups, that recorded at least five incidences of cardiac events or strokes, were eligible for inclusion. Studies of patients with chronic renal failure were excluded.

The main drug groups assessed were thiazides, beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and calcium channel blockers. Where reported, the mean age of participants ranged from 38 to 84 years, the mean baseline systolic blood pressure ranged from 112 to 186mmHg, the mean baseline diastolic blood pressure ranged from 70 to 119mmHg and study duration was from six months to 8.4 years.

The authors did not state how many reviewers performed the study selection.

Assessment of study quality
The authors did not state that they formally assessed validity. Blinding and loss to follow-up were reported in appendix tables available on-line.

Data extraction
The incidence of cardiac events, stroke and new diagnosis or exacerbation of heart failure were extracted on an intention-to-treat basis by two independent reviewers. Differences were resolved by consensus. Relative risks (RR) and 95% confidence intervals (CI) were calculated for cardiac events and stroke for each study. The mean difference in blood pressure was calculated for each trial.

Methods of synthesis
Studies were grouped according to patient history of cardiac disease and stroke and whether the trial had a placebo/no treatment control or an active comparator. Summary RR and 95% CI were calculated using a random-effects model. The summary RRs derived from placebo/no treatment controlled trials were standardised to account for between trial differences in blood pressure reduction. Heterogeneity was assessed using the \( \chi^2 \) statistic. Subgroup analyses were undertaken to investigate: differences in baseline systolic and diastolic blood pressure; history of vascular disease, coronary heart disease, myocardial infarction, or stroke; and class of blood pressure lowering drug.

Results of the review
One hundred and forty seven trials met the inclusion criteria (n=464,164): 92 were placebo controlled; 16 had no
Nearly a third of included trials were either single-blind or unblinded. Drop-out rates ranged from 0 to 20%.

Beta-blockers significantly reduced the risk of coronary events in patients with a history of coronary heart disease (RR 0.71, 95% CI: 0.66, 0.78, 37 trials) and after an acute myocardial infarction (RR 0.69, 95% CI: 0.62, 0.76, 27 trials), but not in patients with a long-term (11 trials) or no history (six trials) of coronary heart disease. All non-beta-blocker drugs combined showed a significant reduction in the risk of coronary events in patients with a history of coronary heart disease (RR 0.85, 95% CI: 0.81, 0.89, 64 trials).

With a reduction of 10mmHg in systolic, or 5mmHg in diastolic blood pressure, drugs significantly reduced the risk of coronary events (RR 0.78, 95% CI: 0.73, 0.83, 71 RCTs) and strokes (RR 0.59, 95% CI: 0.52, 0.67, 45 RCTs) compared to placebo. Results were reported separately for: patients with no history of vascular disease, or a history of coronary heart disease or stroke; different classes of drug; different baseline systolic and diastolic blood pressure.

Trials with active comparators showed no benefit of any one drug over another in the prevention of coronary events. For the prevention of stroke, calcium channel blockers had a greater preventative effect than other drugs (RR 0.91, 95% CI: 0.84, 0.98, 25 RCTs), and beta-blockers a less protective effect (RR 1.18, 95% CI: 1.03, 1.36, 13 RCTs).

Results of meta-analyses of cohort studies were presented alongside those from the current meta-analysis for comparison (see Other Publications of Related Interest).

Authors' conclusions
With the exception of the extra protective effect of beta-blockers after an acute myocardial infarction and calcium channel blockers in preventing stroke, all classes of drug have similar effect in reducing coronary events and stroke for a given reduction in blood pressure.

CRD commentary
The authors addressed a clear review question supported by appropriate inclusion criteria. Several relevant sources were searched but some large databases (such as EMBASE) were omitted. There was no specific search for unpublished data. However, the impact of publication bias may have been reduced as language restrictions were not applied and the meta-analysis included a very large number of trials. Though data extraction was conducted in duplicate, it was unclear whether attempts were made to reduce error and bias during the selection of studies. The authors did not state that they assessed study quality but some aspects were reported in tables available on-line. A large number of subgroup analyses were conducted but it was unclear whether these were planned a priori. The authors stated that further forest plots were available on-line giving the results of individual studies but these could not be located. There seemed to be some discrepancies between data presented in the body of the paper and the supplementary on-line tables. Despite the concerns highlighted, the meta-analyses did include a large number of trials, the pooled results seemed to be consistent across drug groups and populations and meta-analyses of observational studies, and the conclusions reflected the evidence presented.

Implications of the review for practice and research
Practice: The authors stated that guidelines on the use of blood pressure lowering drugs can be simplified so that drugs are offered to people with all levels of blood pressure. The authors stated that consideration should be given to replacing current policies that focus on routine measuring of blood pressure with policies that focus on routinely lowering blood pressure.

Research: The authors did not state implications for research.

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