Effects of antihypertensive-drug class on interindividual variation in blood pressure and risk of stroke: a systematic review and meta-analysis
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CRD summary
The authors concluded that drug-class effects on variation in blood pressure between individuals could account for differences in the effects of anti-hypertensive drugs on the risk of stroke independently of their effects on mean systolic blood pressure. Minimal trial details, unclear quality of the included trials, and concerns regarding the selection of articles, make the reliability of these conclusions uncertain.

Authors' objectives
To evaluate the differential effects of antihypertensive drugs on blood pressure variation and stroke prevention.

Searching
MEDLINE and the Cochrane Library were used to locate relevant reviews and meta-analyses, with search dates spanning 1950 to July 2009 and the search terms were reported. Reference lists of all identified articles were scanned, web tables were consulted, and handsearching of relevant journals was carried out. There were no language restrictions.

Study selection
Randomised controlled trials with more than two weeks of follow-up were eligible for inclusion if they compared groups that differed only by antihypertensive drug class, or compared drug against control. Trials had to report the number of patients and baseline and follow-up data for within-individual systolic or diastolic blood pressure. Excluded were trials of patients who had suffered an acute cardiovascular event within the last three months or who had active left ventricular failure at randomisation; portal hypertension; severe liver disease; pulmonary hypertension; dialysis dependent renal failure; life-limiting disease or disease resulting in significant functional impairment, excluding stroke more than three months before randomisation; or a hypertensive “crisis” at the start of treatment.

Included trials measured between-individual group variation in blood pressure, which was considered to be a surrogate for within-individual data. The included drug classes were dihydropyridine and non-dihydropyridine calcium-channel blockers; thiazide and thiazide-like diuretic drugs; angiotensin-converting enzyme inhibitors; β-blockers; angiotensin-2-receptor blockers; α-1 blockers; and placebo.

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

Assessment of study quality
Trial quality was assessed on the use of randomisation, blinding, and intention-to-treat analysis and details on washout of prior medications.

Two reviewers independently carried out the quality assessment.

Data extraction
The mean and standard deviation (SD) were extracted for systolic and diastolic blood pressure at baseline and follow-up, as were (where reported) average SDs of all blood pressure measurements across the follow-up period. Changes in inter-individual variance (SD²) were presented as the ratio of the variances and the percentage difference in the coefficient of variation. All analyses were based on the highest drug dose within each trial and the mean systolic blood pressure closest to one year of follow-up. To determine the risk of stroke, myocardial infarction, heart failure, and cardiovascular mortality the data were extracted, and odds ratios (ORs) calculated, from trials with more than 100 patients per treatment arm and at least one year of follow-up.

Two reviewers independently carried out the data extraction.
Methods of synthesis
Average treatment differences were pooled in a Mantel-Haenszel random-effects meta-analysis, using inverse variance weighting and 95% confidence intervals (CIs) were calculated. Across-trial analysis pooled the data for variation in blood pressure for each drug class (monotherapy or monotherapy-based regimens). Within-trial analysis assessed the group variation between drug classes. The comparison of changes in group variation was calculated as the follow-up versus baseline variance ratio (VR) and percentage difference in coefficient of variation. Pooled estimates were calculated for each drug class compared with all others; with each separate drug class; and with placebo. ORs were pooled to determine risk of cardiovascular events, as reported above. Heterogeneity was assessed using the X² test. Subgroup analyses reported parallel-group and crossover trial designs together and separately; and also explored the impact of trial size and dosing characteristics. Reporting bias was assessed using funnel plots, but these were not shown.

Results of the review
The review included 1,372 trials, of which 398 provided mean and SD data for systolic blood pressure (SBP) at follow-up. The results of the quality assessment were not reported. There was no evidence of reporting bias.

Variation in blood pressure: There were statistically significant reductions in variation of SBP resulting from the use of calcium-channel blockers (VR 0.81, 95% CI 0.76 to 0.86; 94 trials) and non-loop diuretic drugs (VR 0.87, 95% CI 0.79 to 0.96; 69 trials). Increased variation was reported following treatment with angiotensin-converting enzyme inhibitors (VR 1.08, 95% CI 1.02 to 1.15; 125 trials), angiotensin-receptor blockers (VR 1.16, 95% CI 1.07 to 1.25; 47 trials), and β-blockers (VR 1.17, 95% CI 1.07 to 1.28; 78 trials). Placebo comparison showed that calcium-channel blockers provided the greatest reduction in variation (VR 0.76, 95% CI 0.67 to 0.85; 34 trials).

Risk of events: Lower SD of SBP (VR ≤80) was associated with a significantly reduced risk of stroke (OR 0.79, 95% CI 0.71 to 0.87; 21 trials), despite only small reductions in mean SBP. There were no significant associations between VR and percentage difference in coefficient of variation for risk of myocardial infarction, heart failure, or cardiovascular mortality. Calcium-channel blockers showed a significantly reduced risk of stroke compared with all other drugs (OR 0.88, 95% CI 0.83 to 0.94; 19 trials). β-blockers showed an increased risk compared with all other drugs (OR 1.19, 95% CI 1.01 to 1.42; 10 trials).

Subgroup analyses: There was significant heterogeneity between trials in terms of VR (p<0.0001). Drug class contributed to a large proportion of the variation. Subgroup analysis showed similar results for crossover and parallel-group trials, and there was no significant difference in VR of SBP when the largest trial was removed from the analysis. Effects of VR on diastolic blood pressure showed a similar effect to those for the SD of SBP. Group variation was lower in trials of higher doses of calcium-channel blockers.

Authors’ conclusions
Drug-class effects on inter-individual variation in blood pressure can account for differences in effects of antihypertensive drugs on risk of stroke independently of effects on the mean systolic blood pressure.

CRD commentary
The review question was clear and the inclusion criteria were adequately stated for all aspects, except the patients of interest. The focus on between-group data conflicted with the inclusion criteria. This was noted by the authors to be an appropriate surrogate for within-individual data, but should be borne in mind when interpreting the review findings. The search strategy comprised two relevant databases, and attempts were made to minimise language bias. The authors acknowledged the potential for selection bias in the retrieval of systematic reviews and meta-analyses to locate the included trials. The review process was conducted with sufficient attempts to minimise errors and bias in the data extraction and quality assessment of trials, but the process of trial selection was not reported. Trial details, particularly patient and intervention characteristics, were not provided in detail, meaning that the generalisability of the findings was difficult to establish. Given the inability to assess the clinical variation, it was not clear whether the chosen method of synthesis was appropriate.

The authors’ conclusions reflected the evidence presented, but the extent to which these are reliable is unclear.
Implications of the review for practice and research

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

Research: The authors stated that future trials should pay particular attention to the detailed reporting of the blood pressure response to antihypertensive drug treatment.

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