Calcium channel blockers and cardiovascular outcomes: a meta-analysis of 175,634 patients


CRD summary
This review concluded that calcium channel blockers (CCBs) reduced risk of stroke and heart failure (compared to placebo) and dihydropyridine CCBs reduced risk of all-cause mortality (compared with active therapy) in high-risk cardiac patients. The reliability of these findings is unclear due to potential limitations in the data and methodology and the author's own reservations.

Authors' objectives
To evaluate the safety and effectiveness of calcium channel blockers compared to other drugs or placebo in reducing cardiovascular outcomes.

Searching
MEDLINE, The Cochrane Library and DARE, were searched up to May 2008 for publications in any language. Bibliographies of each retrieved article were handsearched. Some more recent publications were identified via colleagues. Search terms were reported.

Study selection
Randomised controlled trials (RCTs) that compared long-acting calcium channel blockers (CCB) with another hypertensive drug or placebo with assessment of cardiovascular events were eligible for inclusion. Trials that included patients selected on the basis of high blood pressure, diabetes mellitus, coronary heart disease, heart failure, peripheral vascular disease, cerebrovascular disease or renal disease were eligible for inclusion.

All included studies used more than one drug in each treatment group, but agents were generally applied in a stepped approach and the first-line agent was clearly identified. Studies that used inadequate doses of CCBs or short-acting calcium antagonists were excluded. CCBs used in the included trials were: dihydropyridine CCBs (amlodipine, felodipine, isradipine, lacidipine, nicardipine, nisoldipine, nifedipine GITS and retard, and nitrendipine); and non-dihydropyridine CCBs (verapamil and diltiazem). Non-CCBs used in the comparison groups included: angiotensin-converting enzyme inhibitors (ACEs); beta-blockers; angiotensin receptor blockers; and thiazide diuretics (full details of individual drugs were given). Most patients in the included studies either had hypertension or coronary heart disease. Mean age was 64 +/-5.8 years (range 54 to 76 years). Mean proportion of males was 63% (range 33 to 81%). The range of patients with diabetes was 11% to 100% and for smoking was 9% to 71%. Eligible outcomes included all-cause mortality, cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke and heart failure. Most of the included RCTs provided information on all outcomes.

Two independent reviewers performed the study selection. Any discrepancies were resolved by discussion and consensus.

Assessment of study quality
Methodological quality was assessed using the method of Detsky et al. 1992. Each study was awarded a quality score. Criteria included: randomisation; bias in treatment assignment; presence of criteria for outcome measurement; blinding; inclusion and exclusion criteria; loss to follow-up with relevant explanation; details of intervention and control regimes; appropriate statistical analysis; sample size justification before study commencement. Data on blinding were provided.

The authors did not state how many reviewers performed the validity assessment.

Data extraction
The number of events for each outcome was extracted and odds ratio (OR) and 95% confidence intervals (CIs) were calculated using intention-to-treat analyses. Major cardiovascular events were calculated by adding cardiovascular death, fatal or nonfatal myocardial infarction, fatal or nonfatal stroke and heart failure.
The authors did not state how many reviewers performed the extraction.

Methods of synthesis
Odds ratios were pooled using a fixed-effect model, a random-effects model or the Peto method, where appropriate. Where between-study heterogeneity was found using the Q statistic and I² test (p<0.10), a random-effects model was used and a sensitivity analysis was performed. Where event rates were less than 1%, an analysis was performed using the Peto method (applicable for every outcome) where pooled odds ratios were logarithmically transformed and weighted for the inverse of variance. The Bonferroni-Holm correction to control type 1 error rate was used to assess the effect of multiple comparisons on pooled estimates. A weighted random-effects meta-regression was used to identify 10 potential effect modifiers (details provided). The restricted maximum likelihood method was also used to estimate the additive component of variance (T²).

Publication bias was assessed using a modified Macaskill's test and the trim-and-fill method of Duvall and Tweedie. Other sensitivity analyses were performed.

Results of the review
Twenty-seven relevant RCTs were identified (n=175,634). Detsky quality scores of RCTs ranged from 16 to 20. Sixteen RCTs were double-blind. Mean duration of follow-up was 3.4 years (range 0.3 to 5.5 years). A placebo was used in 10 RCTs.

Risk of all-cause death was reduced by dihydropyridine CCBs (OR 0.96, 95% CI 0.93 to 0.99). Although risk of all-cause death was significantly reduced by all CCBs, it was not significantly affected by non-dihydropyridine CCBs.

Risk of heart failure was increased by CCBs compared with active treatment (OR 1.17, 95% CI 1.11 to 1.24, p=0.0001 for heterogeneity) and decreased compared to placebo (OR 0.72, 95% CI 0.59 to 0.87) and in the subgroup of coronary heart disease patients (OR 0.76, 95% CI 0.61 to 0.95), but not in hypertensive patients (for these patients there was significant heterogeneity, p=0.001). ACEs decreased risk of heart failure compared to CCBs (OR 1.19, 95% CI 1.08 to 1.31).

CBCs did not increase the risk of: myocardial infarction (significant heterogeneity, p=0.004); cardiovascular death; and major cardiovascular events (significant heterogeneity, p=0.0001). Compared to placebo alone, CCBs significantly reduced risk of major cardiovascular events (OR 0.76, 95% CI 0.62 to 0.93, p=0.002 for heterogeneity).

CBCs decreased risk of fatal or nonfatal stroke (OR 0.86, 95% CI 0.82 to 0.90) and when compared to ACEs (OR 0.87, 95% CI 0.78 to 0.97). This result was only significant for dihydropyridine CCBs (OR 0.85, 95% CI 0.80 to 0.90) and not for non-dihydropyridine CCBs.

Additional sensitivity analysis: For all-cause death, the protective effect of CBCs was not present in trials with less than 20% of diabetic patients, more than 20% coronary heart disease patients, more than 10% heart failure patients and more than 10% previous myocardial infarction patients. Results of other sensitivity analyses were reported.

Meta-regression analysis for potential effect modifiers: A significant relationship was identified between blood pressure reduction and a favourable effect of CCBs on cardiovascular death, major cardiovascular events, heart failure and stroke. There was an association between major cardiovascular events and smoking or diabetes and an inverse relationship between baseline presence of heart failure and heart failure events.

Publication bias was identified only for myocardial infarction.

Authors' conclusions
Dihydropyridine CCBs reduced risk of all-cause mortality compared with active therapy. CCBs prevented heart failure compared to placebo, mostly driven by blood pressure reduction. CCBs reduced risk of stroke, and also when directly compared with ACEs. CCBs did not increase risk of cardiovascular death, myocardial infarction or major cardiovascular events.
CRD commentary
The review addressed a well-defined question in terms of participants, interventions, study design and relevant outcomes. Relevant databases were searched in any language. It appeared that unpublished studies were not considered. Risk of publication bias was assessed and generally found to be low except for the analysis of myocardial infarction. No start date for the search was given (earliest included study was in 1996). Study quality was assessed and quality scores were reported; although scores were reported, the significance of scores as to whether or not studies were of good, average or low quality was not given. Study selection was carried out with efforts to reduce error and bias; it was unclear whether this process was applied to other aspects of the review process. Relevant study details were reported, but with little information about placebos used; dosage regimes were not reported. The statistical method used for meta-analysis of RCTs seemed appropriate. Statistical heterogeneity was assessed; there was evidence for heterogeneity with some outcomes. Sensitivity analyses were carried out and potential effect modifiers were investigated. The authors suggested that several results should be interpreted with caution since they were either no longer significant after applying the Bonferroni-Holm correction or were affected by effect modifiers or showed evidence for heterogeneity or potential publication bias; therefore, the extent to which the authors' conclusions are reliable is unclear. However, the results for fatal and non fatal stroke seemed consistent.

Implications of the review for practice and research
Practice: The authors stated that CCBs can be safely used in high-risk cardiac patients.
Research: The authors did not state any implications for research.

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