Long-acting calcium antagonists in patients with coronary artery disease: a meta-analysis
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CRD summary
The authors found that long-acting calcium channel blockers were associated with a reduced risk of stroke, angina pectoris and heart failure, and with a similar risk of other cardiovascular events, when compared to other antihypertensives or placebo. The review was generally well conducted, but a degree of caution may be advisable in interpreting the findings, due to some unexplained heterogeneity.

Authors' objectives
To evaluate the use of long-acting calcium channel blockers (CCBs) in patients with known coronary artery disease.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL) and EMBASE were searched from 1966 to August 2008. Search terms were reported. Reference lists of reviews, meta-analyses and studies retrieved were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared long-acting calcium channel blockers with other agents or placebo among participants with coronary artery disease (as defined by the primary studies) were eligible for inclusion. Eligible studies needed to report cardiovascular outcomes and have follow-up of at least one year. Outcomes of interest were all-cause and cardiovascular mortality, non-fatal myocardial infarction, stroke, angina pectoris and heart failure.

The included studies were designed to treat patients with angina pectoris, heart failure (predominantly ischaemic), hypertension and/or coronary heart disease, post myocardial infarction and post percutaneous coronary intervention. Mean or median age of participants ranged from 55 to 67 years. From 53% to 100% of participants were men. Baseline blood pressure ranged from 118 to 151mmHg systolic and from 71 to 86mmHg diastolic (where stated). Most studies excluded participants with moderate to severe heart failure. Included studies used varying diagnostic criteria and definitions of coronary heart disease. They compared a variety of dihydropyridine and non-dihydropyridine first-, second- and third-generation calcium channel blockers versus other antihypertensives (including angiotensin-converting enzyme inhibitors and beta-blockers) or placebo. The review included one study in which two thirds of participants had ischaemic myopathy. For other studies, study arms and participant groups that were not relevant to the review were excluded from analysis. Duration of follow-up ranged from one year to 4.9 years.

The authors stated neither how papers were selected for the review nor how many reviewers performed the selection.

Assessment of study quality
Study quality was evaluated using the Jadad scale of adequacy of randomisation, double blinding and reporting of withdrawals. Each study was awarded points out of a maximum of 5. Studies that scored 3 points or more deemed to be high quality.

The assessment was conducted independently by two reviewers. Disagreements were resolved by consensus.

Data extraction
Risk ratios (RRs) were calculated from the numbers of events in the control and intervention groups of each study, with 95% confidence intervals (CIs).

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Methods of synthesis
Studies were grouped by outcome and were combined to calculate pooled risk ratios and 95% CIs. Heterogeneity was assessed using funnel plots, $X^2$ test and the $I^2$ statistic. A fixed-effect model was used if studies were homogenous ($X^2$ p>0.05); otherwise, the DerSimonian and Laird random-effects model was used. Egger’s regression test was used to assess publication bias. Results were subgrouped by the type of calcium channel blocker (dihydropyridine/non-dihydropyridine). Sensitivity analyses were used to examine the impact of the indication for treatment and the generation of calcium channel blocker used in the individual studies.

**Results of the review**

Fifteen RCTs (17 arms) were included (n=47,694, range 248 to 22,576). A total of 23,451 participants were on calcium channel blockers, 16,251 on other antihypertensives and 7,992 on placebo. All RCTs were deemed high quality (Jadad score 3 to 5 points).

**Calcium channel blockers versus controls (other antihypertensives or placebo):** There was no statistically significant difference between the calcium channel blocker group and controls in all-cause mortality (15 comparisons), cardiovascular mortality (14 comparisons), non-fatal myocardial infarction (15 comparisons) and heart failure (11 comparisons); there was significant statistical heterogeneity for the outcome of heart failure ($I^2$=69.2%). There was a significantly reduced risk in the calcium channel blocker group compared to controls of stroke (RR 0.79, 95% CI 0.70 to 0.89; 11 comparisons, $I^2$=0%) and angina pectoris (RR 0.82, 95% CI 0.72 to 0.94, $I^2$=78.7%, random effects). Results were similar for dihydropyridines and non-dihydropyridines.

When compared with placebo alone, risk of heart failure was reduced in the calcium channel blocker group by 28% (p<0.0001). The results of other comparisons of calcium channel blockers versus placebo alone and calcium channel blockers versus other antihypertensives alone were reported in the review, as were the results of sensitivity analyses.

There was no evidence of significant publication bias.

**Authors’ conclusions**

Long-acting calcium channel blockers were associated with a reduced risk of stroke, angina pectoris and heart failure, and with a similar risk of other cardiovascular events, when compared with other antihypertensives or placebo.

**CRD commentary**

The objectives and inclusion criteria of the review were clear. Relevant sources were searched for studies. The restriction to published studies meant that the review was subject to potential publication bias, although formal testing did not indicate such bias. It was unclear whether the search was limited by language. Steps were taken to reduce the risk of reviewer bias or error by having more than one reviewer independently assess study validity and extract data; it was unclear whether such measures also applied to the study selection process. Some suitable criteria were used to assess study validity, although other important components of quality (such as allocation concealment and rate of withdrawals) were not reported. Appropriate methods were used to combine the studies, assess for heterogeneity and publication bias and to explore potential differences between the studies. However, where significant heterogeneity was detected it was addressed only by using a random-effects model, without discussion of any potential explanations. Some potential limitations of the review, such as differing clinical criteria used in the primary studies, were addressed in the text. The review was generally well conducted, but a degree of caution may be advisable in interpreting the findings, due to some unexplained heterogeneity.

**Implications of the review for practice and research**

**Practice:** The authors stated that long-acting calcium channel blockers were safe to use for treating patients with coronary artery disease.

**Research:** None stated.

**Funding**

No external funding.
Bibliographic details

PubMedID
19332231

DOI
10.1016/j.amjmed.2008.09.043

Original Paper URL
http://www.amjmed.com/article/S0002-9343(08)01104-2/abstract

Indexing Status
Subject indexing assigned by NLM

MeSH
Aged; Calcium Channel Blockers /adverse effects /pharmacokinetics /therapeutic use; Coronary Artery Disease /drug therapy /metabolism; Female; Humans; Male; Middle Aged; Randomized Controlled Trials as Topic; Risk Factors

AccessionNumber
12009104365

Date bibliographic record published
17/06/2009

Date abstract record published
03/02/2010

Record Status
This is a critical abstract of a systematic review that meets the criteria for inclusion on DARE. Each critical abstract contains a brief summary of the review methods, results and conclusions followed by a detailed critical assessment on the reliability of the review and the conclusions drawn.