Do calcium channel blockers increase the diagnosis of heart failure in patients with hypertension?

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CRD summary
The review concluded that the results suggested patients with hypertension treated with calcium channel blockers had an increased incidence of heart failure, but that this effect should be researched further. Despite some potential limitations with the review process, and uncertain definitions of heart failure in the included trials (noted by the authors), the authors’ cautious conclusions reflect the evidence presented.

Authors’ objectives
To evaluate whether the use of calcium channel blockers increase the risk of heart failure in patients with hypertension.

Searching
PubMed (from 1950), EMBASE (from 1988), International Pharmaceutical Abstracts (IPA from 1970), Web of Science, BIOSIS Previews, Scopus and the Cochrane Library were searched up to 2009; search terms were reported. Bibliographies of each retrieved article were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared calcium channel blockers with active controls (other drugs) in patients with hypertension were eligible for inclusion. Trials had to recruit over 200 patients, have at least six months follow-up, and provide data on the incidence of heart failure. RCTs with the main eligibility criterion was heart failure, placebo-controlled trials, trials of renal transplantation patients and trials using two calcium channel blockers were excluded. Articles which were subgroup analyses of previously published major trials were also excluded.

The main type of calcium channel blockers used in included trials were dihydropyridines; most trials used amlodipine (2.5 to 10mg/day, some with adjunct perindopril or benazepril); other trials used nifedipine (10 to 60mg/day), felodipine, isradipine, lacidipine, nicardipine or nitrendipine. Other types of calcium channel blockers used were phenylalkylamines (diltiazem, 180-360mg/day) and benzothiazepines (verapamil, 180 to 240mg/day). The intervention in one trial was amlodipine with an angiotensin-converting enzyme inhibitor. Comparators used in included trials were angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and beta-blockers.

At trial entry, included patients had mean systolic blood pressure that ranged from 145 to 194mmHg and a mean diastolic blood pressure that ranged from 80 to 105mmHg. The mean age of patients ranged from 54 to 76 years; the proportion of men ranged from 33 to 78%. All patients had hypertension. Some trials included patients with other risk factors; those reported were coronary artery disease, diabetes mellitus, stroke and nephropathy. Most of the definitions of heart failure were based on systolic heart failure and clinical features, but only one in five trials used clear predefined criteria. The secondary outcome reported was myocardial infarction.

Two independent reviewers performed the selection, with disagreements resolved by consensus.

Assessment of study quality
Methodological quality was assessed using the Jadad score. Five criteria were used (with a maximum score of 5 points) including: randomisation present; randomisation method; double-blinding; method of blinding described and appropriate; and withdrawals and drop-outs described.

Although not explicitly stated, it appeared that two reviewers assessed validity independently, with disagreements resolved by consensus.
Data extraction
The number of events for each outcome were extracted to calculate odds ratios (OR) and 95% confidence intervals (CI). For continuous data, means plus or minus standard deviation (SD) or medians were extracted; these were used to calculate mean differences (MD) with 95% confidence intervals. Authors were contacted for information regarding their definition of heart failure.

The authors did not report how many reviewers performed the extraction.

Methods of synthesis
Odds ratios or weighted mean differences (WMDs) were pooled using a fixed-effect model (Mantel-Haenszel) if there was no significant heterogeneity and a random-effects model (DerSimonian-Laird) if there was significant heterogeneity. Between-trial heterogeneity was determined using $I^2$. Optimal sample size was calculated using Pahor-Furberg’s meta-analysis.

Cohen’s $K$ statistic was used to evaluate the concordance between the abstractors for study selection and also the concordance for Jadad scores.

Subanalyses were performed that compared calcium channel blockers with the different types of other active controls and patients with other risk factors.

Publication bias was assessed visually using funnel plots.

Results of the review
Nineteen RCTs were included in the review (n=158,023 patients, range 429 to 33,357, taken from Table 1). Cohen’s $K$ statistic for inter-reviewer agreement was 0.99 for study selection and 0.84 for quality evaluation using the Jadad score. The mean Jadad score was 3.4 points. Fifteen trials reported that heart failure assessment was blinded. Follow-up ranged from two to five years.

Heart failure: There were significantly higher numbers of patients with heart failure for the calcium channel blocker group compared with the active control group (OR 1.18, 95% CI 1.07 to 1.31; $I^2$=38%; 19 RCTs). There was a higher risk of heart failure for calcium channel blockers than for angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (OR 1.21, 95% CI 1.10 to 1.32; $I^2$=9%; nine RCTs); the risk was a little higher for calcium channel blockers than diuretics (OR 1.32, 95% CI 1.04 to 1.66; $I^2$=35%; seven RCTs). However, there was no significant difference in risk of heart failure for calcium channel blockers than beta-blockers ($I^2$=50%; three RCTs). Results were not changed for the type of calcium channel blocker, dihydropyridines (15 RCTs) or non-dihydropyridines (four RCTs). Subgroup analyses for patients with other risk factors showed a significantly increased risk of heart failure with calcium channel blockers for patients with diabetes (OR 1.71, 95% CI 1.21 to 2.41; $I^2$=0%; two RCTs) and for patients with isolated systolic hypertension (OR 1.18, 95% CI 1.01 to 1.39; $I^2$=0%; five RCTs), but not for patients with coronary artery disease ($I^2$=94%; two RCTs).

Blood pressure (15 RCTs): The reduction in diastolic blood pressure was significantly lower for calcium channel blockers versus other drugs (WMD -0.65mmHg, 95% CI -0.18 to -1.18; $I^2$=94%), but this was not clinically important. There was no significant difference in the reduction in systolic blood pressure between calcium channel blockers and control drugs ($I^2$=94%).

Myocardial infarction (16 RCTs): There was no significant difference in risk of myocardial infarction for calcium channel blockers versus active controls ($I^2$=40%; 16 studies).

All the reported results used a random-effects model.

A funnel plot showed no evidence of publication bias.

Authors' conclusions
The results suggested that patients with hypertension treated with calcium channel blockers had an increased incidence of heart failure, but this effect should be evaluated in future research.

**CRD commentary**
The review addressed a well-defined question for participants, interventions, study design and relevant outcomes. Relevant databases were searched, but it was not clear if any language restrictions were applied or whether unpublished studies were considered, so some studies could have been missed. No evidence of publication bias was identified. Efforts were made to reduce reviewer error and bias in study selection and probably in quality assessment, but it was not reported whether this applied to data extraction.

Trial quality was assessed using appropriate criteria; although the authors stated that trials were considered to be of acceptable quality, individual results were not reported. Relevant study details were reported, but there were some errors in the text. No details of loss to follow-up were given. Statistical heterogeneity was assessed and there was evidence for heterogeneity with some outcomes. The statistical method used for the meta-analysis of the RCTs seemed appropriate; suitable sub-group analyses were performed.

Despite some potential limitations arising from the review process, and the uncertain definition of heart failure in the included trials (noted by the authors), the authors’ cautious conclusions reflect the evidence presented.

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

**Practice:** The authors did not make any implications for practice.

**Research:** The authors suggested that future studies should investigate the mechanism by which calcium channel blockers increase heart failure. Future research should be performed to confirm these results, with a more stringent definition of heart failure and a careful evaluation of ventricular function at baseline.

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