Are calcium antagonists beneficial in diabetic patients with hypertension?

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CRD summary
This review, which assessed the effects of calcium antagonists in hypertensive patients with diabetes mellitus, was poorly conducted and reported. The authors concluded that calcium antagonists are safe and effective in reducing most types of cardiovascular morbidity and mortality in diabetic hypertensive patients. However, given the many limitations of the review, these conclusions must be treated with caution.

Authors' objectives
To assess the effects of calcium antagonists in hypertensive patients with diabetes mellitus.

Searching
MEDLINE was searched and pertinent articles cited in the identified references were checked. The search terms were reported. Only English language articles published before April 2003 were included.

Study selection
Study designs of evaluations included in the review
Only prospective randomised controlled trials of at least 12 months’ duration were eligible for inclusion. Across the trials, the follow-up ranged from 2 to 8.4 years.

Specific interventions included in the review
Studies in which antihypertensive drugs were compared with placebo or with another antihypertensive agent were eligible for inclusion. The included studies were of the following calcium antagonists: nisoldipine, amlodipine, felodipine, nitrendipine, isradipine and nifedipine. Other antihypertensive agents were angiotension-converting enzyme (ACE) inhibitors (enalapril, fosinopril, captopril, lisinopril), beta-blockers, diuretics or angiotensin-receptor blockers (ARBs).

Participants included in the review
Studies of patients with diabetes and hypertension were included in the review. Not all of the included trials were specifically of patients with diabetes and hypertension, and it was unclear how the authors separated out the data relating to patients with diabetes from those without. The mean age of the patients included in the primary studies ranged from 55 to 76 years.

Outcomes assessed in the review
Inclusion criteria relating to the outcomes were broad, with studies reporting morbidity or mortality being eligible for inclusion. The outcomes reported in the review were decrease in blood-pressure, coronary heart disease (CHD), heart failure, myocardial infarction (MI), stroke and total mortality.

How were decisions on the relevance of primary studies made?
The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. The odds ratios (ORs) for CHD, heart failure, MI, stroke and total mortality, along with the 95% confidence
intervals (CIs), were extracted from each study.

**Methods of synthesis**

**How were the studies combined?**
The pooled OR and 95% CI were calculated for selected outcomes. Details were not reported although citations were given in the review.

**How were differences between studies investigated?**
Statistical heterogeneity was tested for. Details of the method used were not reported although citations were given in the review.

**Results of the review**
Fourteen studies (n=23,751) were included in the review, nine of which involved a calcium antagonist. Four studies were placebo-controlled (n=2,321), two of which were of calcium antagonists.

Compared with placebo, one trial of calcium antagonists generated a statistically significant reduction in the odds of any cardiovascular outcome (OR 0.37, 95% CI: 0.18, 0.93), stroke (OR 0.27, 95% CI: 0.12, 0.76) and total mortality (OR 0.45, 95% CI: 0.28, 0.91). However, the results from the other trial showed no statistically significant difference for any of these outcomes. The data were not pooled across these trials.

Trials that compared calcium antagonists with either beta-blockers or diuretics (4 trials, n=11,773) found that there was no statistically significant differences for pooled results for odds of CHD, stroke, heart failure or total mortality. The only statistically significant finding was that for CHD when amlodipine was compared with diuretics or beta-blockers (OR 0.58, 95% CI: 0.37, 0.92).

Trials that compared calcium antagonists with ACE inhibitors or ARBs (4 trials, n=2,462) found that there were no statistically significant differences for pooled results for odds of MI, stroke, heart failure or total mortality. Two trials found a statistically significant increased risk of MI with the calcium antagonist compared with an ACE inhibitor (nisoldipine versus enalapril OR 5.5, 95% CI: 2.10, 14.6; felodipine/isradipine versus enalapril/captopril OR 1.96, 95% CI: 1.09, 3.57).

**Authors’ conclusions**
Calcium antagonists are safe and effective in reducing most types of cardiovascular morbidity and mortality in diabetic hypertensive patients, although compared with other antihypertensives their use is associated with a lesser reduction in risk of heart failure.

**CRD commentary**
This was a poorly conducted and reported systematic review. The search was limited, and publication and language bias probable. The potential for publication bias was not investigated. Methods to minimise error and bias in the review were not reported. Although the authors’ objective was clear, the inclusion criteria were poorly framed and trials not involving calcium antagonists were included in the review. It seemed that only results for selected outcomes were reported, and these were not consistent across all the comparisons made. In addition, it was unclear how data specific to diabetic patients were derived from the individual studies, and the quality of the included studies was not assessed. Given the many limitations of this review, the authors’ conclusions need to be interpreted with caution. The authors’ claim that the review demonstrates the safety of calcium antagonists is not supported by the review findings.

**Implications of the review for practice and research**
Practice: The authors suggested that calcium antagonists are not necessarily less safe or effective than ACE inhibitors or ARBs in diabetic patients. However, this is not clearly supported by the review.
Research: The authors stated that the safety and efficacy of combination therapy (not defined) should be assessed in randomised controlled trials.

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