The effects of calcium channel blockers on cardiovascular outcomes: a review of randomised controlled trials
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Authors' objectives
To review studies that have evaluated the effects of calcium-channel blockers (CCBs) on cardiovascular (CV) morbidity and mortality in hypertensive patients.

Searching
MEDLINE (via PubMed) was searched using the search terms 'calcium channel blockers', 'calcium antagonists', 'hypertension', 'randomised', 'morbidity' and 'mortality'. The Cochrane Library was also searched. The searches were conducted up to September 2001, but no start date was given. The authors also searched the reference lists of retrieved articles. Studies were also identified from the authors' personal knowledge of the literature and from the authors' colleagues.

Study selection
Study designs of evaluations included in the review
To be included, the studies had to be randomised controlled trials with a follow-up of at least 2 years and a sample size of at least 200. Two studies were excluded because alternate allocation was used to assign the treatment to recruited patients.

Specific interventions included in the review
To be included, the studies had to compare CCBs with placebo or another hypertensive. The drugs included in the review were: atenolol, amiloride, amlopidine, clonidine, chlorthalidone, diltiazem, enalapril, felodipine, fosinopril, hydrochlorothiazide, isradipine, lisinopril, metoprolol, nicardipine, nifedipine, nisoldipine, nitrendipine, pindolol, trichlormethiazide, and verapamil.

Participants included in the review
Patients with hypertension were eligible for inclusion. The presence or absence of co-morbidities was not specified in the inclusion criteria. Hypertension was defined differently in each of the 10 studies, with the diastolic blood-pressure ranging from greater than 90 mmHg to at least 105 mmHg, and/or a systolic blood-pressure ranging from greater than 140 mmHg to greater than 160 mmHg. Two studies were of patients with diabetes mellitus. One study was of high-risk patients with hypertension and one other CV risk factor (e.g. diabetes, hypercholesterolaemia or coronary heart disease). The studies were of patients in the USA, Europe, Israel and Japan. No age limit was specified in the inclusion criteria, but the patients were aged 40 years or above; no upper age limit was specified.

Outcomes assessed in the review
To be included in the review, the studies had to include CV events as a primary or secondary end point. The primary end points of the included studies were: blood-pressure; mortality; progression of carotid artery intimal-medial thickness; CV complications; 24-hour creatinine clearance; total serum cholesterol and blood sugar control; total stroke; CV mortality; composite end point of fatal and nonfatal stroke, fatal and nonfatal myocardial infarction, and other CV death; composite end point of death from any CV or cerebrovascular cause, nonfatal stroke, myocardial infarction, and heart failure.

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

Assessment of study quality
Only trials that were randomised were included. The authors used predefined adequate sample size to differentiate
Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction.

Methods of synthesis
How were the studies combined?
The results of the studies were described separately; there was no quantitative synthesis of the results.

How were differences between studies investigated?
Within the narrative summary, the studies were grouped according to their size (i.e. fewer than 1,500 participants and greater than 4,500 participants) and their end points; the results for patients with diabetes were discussed separately.

Results of the review
Ten randomised controlled trials were included in the review. These included a total of 32,742 patients.

The smaller studies produced mixed findings, particularly trials where the CCBs were compared with diuretics. The results from the larger studies were more consistent. Long-acting CCBs such as nifedipine, administered in a gastrointestinal-transport-system (GITS) formulation, nitrendipine and diltiazem, reduced CV morbidity and mortality in hypertensive patients. In the one study of high-risk hypertensive patients, nifedipine GITS was as effective as diuretic therapy in reducing CV events. Subgroup analysis in all four larger studies showed that the benefits of these CCBs apply to hypertensive patients with diabetes.

Authors' conclusions
This review supports the use of long-acting CCBs to reduce the risk of CV morbidity and mortality in patients with hypertension.

CRD commentary
The review question, search strategy and details of the primary data were clearly presented. It was unclear whether the authors had attempted to search for unpublished material, although they did mention an ongoing trial. The authors appear to have assessed the validity of the included trials to some extent (two were excluded because the method of randomisation was inadequate). The narrative synthesis was well presented and the studies were grouped according to study size; the authors placed greater emphasis on the larger randomised controlled trials. No information was provided on the review process, e.g. how many of the reviewers were involved and how decisions about study inclusion were made. Both authors had affiliations to trials included in the review. Two of the included trials (Syst-Eur and INSIGHT) were funded by Bayer AG.

Implications of the review for practice and research
Practice: The authors state that, wherever possible, the choice of antihypertensive treatment should be evidence-based. They also state that their review of published studies supports the use of long-acting CCBs to reduce the risk of CV morbidity and mortality in patients with hypertension. Research: The authors state that large, well-designed meta-analyses are probably the best method of establishing whether there are real differences in cause-specific end points between different classes of antihypertensives. They also suggest that large, well-designed, randomised controlled trials, which are well conducted and reported, would be an important source of information for influencing clinical practice.

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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.