Nifedipine: dose-related increase in mortality in patients with coronary heart disease

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Authors' objectives
To assess the effect of nifedipine dose on mortality and to review the potential mechanisms of such an effect.

Searching
The authors do not provide details of the sources searched or the strategies used.

Study selection
Study designs of evaluations included in the review
All published randomised controlled trials (RCTs) of nifedipine in the secondary prevention of CHD for which mortality data were available, were included.

Specific interventions included in the review
Nifedipine at doses of 30, 40, 50, 60, 80 and 100 mg/day, to a maximum of 120 mg.

Participants included in the review
Patients with coronary heart disease (CHD). Of the 16 studies included, 12 included patients with myocardial infarction (MI), 3 included patients with unstable angina and 1 included patients with stable angina, with and without a history of prior infarction.

Total number of participants involved was 4,171 (control group, n=4,183).

Outcomes assessed in the review
Mortality was assessed.

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 authors performed the selection.

Assessment of study quality
The authors do not report the method used to assess quality, or how the quality assessment was performed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction.

Methods of synthesis
How were the studies combined?
A formal meta-analysis was carried out to combine the trials. This involved stratification by trial so that comparisons between intervention and placebo always involved patients in the same trial.

Maximum likelihood methods were used to calculate the relative risks (RR) for mortality, the confidence interval (CI) and to test for heterogeneity. Analysis of the dose-response relationship was carried out by using the natural logarithm of the RR as the dependent variable in a regression model, weighted by the inverse of the variance of the RR, and nifedipine dose as the independent variable.
How were differences between studies investigated?
Statistical tests of heterogeneity were carried out based on maximum likelihood methods.

Results of the review
Sixteen studies: 12 included MI patients, 3 included patients with unstable angina and 1 included patients with stable angina, with and without a history of prior infarction.

Overall, the use of nifedipine was associated with a significant increase in total mortality (RR 1.16; 95% CI: 1.01, 1.33). A dose-response relationship also appeared to exist: for daily doses of 30 to 50, 60 and 80 mg, the RR for total mortality were 1.06 (95% CI: 0.89, 1.27), 1.18 (95% CI: 0.93, 1.50) and 2.83 (95% CI: 1.35, 5.93), respectively. These high doses of nifedipine were significantly associated with increased mortality (P =0.01).

Authors' conclusions
In patients with CHD, the use of short-acting nifedipine in moderate-to-high doses causes an increase in total mortality.

CRD commentary
There was little quality assessment of the included trials. Given the fact that the lower bound of the CI for the main effect is close to 1.0, it would have been useful to have examined the size and direction of the effect in a subset of the higher quality trials. However, the small number of RCTs may have precluded such an analysis. In this context the search strategy is important: no information is given as to what databases were searched, and a wider search may have produced a larger number of trials for analysis.

Implications of the review for practice and research
The effects of nifedipine on morbidity and mortality remain untested in hypertensive patients. In addition, the effects of using a beta-blocker in combination with a calcium antagonist need to be tested in large scale clinical trials to determine whether this could reduce the risk of mortality.

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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.