Authors' objectives
To compare cardiovascular event rates in patients with mild or moderate hypertension who received nifedipine with active drug controls.

Searching
MEDLARS was searched from 1966 to August 1995 using the MeSH 'hypertension' and 'nifedipine' as a textword. Studies published in English, French, Italian, German or Spanish were included. Current Contents (CD-ROM), and the bibliographies of retrieved articles were also searched.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) were included if they had a minimum of 10 patients, were published in a peer-reviewed journal or supplement to such a journal, and reported adverse events by treatment group.

Specific interventions included in the review
Nifedipine, either as a monotherapy or in combination with other agents, was compared with a nondihydropyridine active drug or placebo. The nifedipine formulation was immediate-release, sustained-release or extended-release.

Participants included in the review
Patients with mild or moderate hypertension were included.

Outcomes assessed in the review
Definitive cardiovascular events and episodes of new-onset or increased angina were assessed. The cardiovascular events included death, nonfatal myocardial infarction, nonfatal stroke, and revascularisation procedure during the study period.

How were decisions on the relevance of primary studies made?
Papers were selected for inclusion by the consensus of two independent physician reviewers.

Assessment of study quality
The quality of the studies was assessed using the scoring systems of Chalmers et al. (see Other Publications of Related Interest no.1) and Jadad et al. (see Other Publications of Related Interest no.2). The selected studies were blinded as to the source, author(s), and treatment groups. Study quality was assessed by two reviewers, and any differences in opinion were resolved by consensus.

Data extraction
The selected studies were blinded as to the source, author(s) and treatment groups. The data were extracted by two reviewers independently, and any differences in opinion were resolved by consensus.

Methods of synthesis
How were the studies combined?
The within-study estimates of treatment effects could not be calculated because the majority of studies had no events in either the treatment or control arm. Placebo arms were excluded from the analysis due to small numbers. The incidence rates and odds ratio (OR) were calculated, along with the 95% confidence intervals (CIs), from the total number of events comparing nifedipine study arms with corresponding other active drug arms in the same studies. This unweighted
pooling was shown to give OR estimates that were equivalent to those obtained when using Peto's method (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
A statistical test of heterogeneity was not conducted because the majority of the studies had no events in both arms. Multiple logistic regression analyses were used to investigate whether the treatment effects were confounded with study-level covariates.

Results of the review
Ninety-eight RCTs (9,506 patients and 11,020 drug exposures) were included.

Nifedipine versus other active drugs: 14 events occurred during 5,198 exposures (0.27%) to nifedipine and 24 events occurred during 5,402 exposures (0.44%) to other active drug controls. The unadjusted ORs for nifedipine versus controls were 0.49 (95% CI: 0.22, 1.09) for definitive events and 0.61 (95% CI: 0.31, 1.17) for all events.

Nifedipine monotherapy versus combination therapy: the OR for nifedipine monotherapy was not significantly higher for definitive events (OR 1.40, 95% CI: 0.49, 4.03) or all events (OR 1.39, 95% CI: 0.59, 3.32). The OR for nifedipine in combination with another drug was significantly lower for definitive events (OR 0.09, 95% CI: 0.01, 0.66) and all events (OR 0.15, 95% CI: 0.03, 0.65). Differences in the ORs for nifedipine monotherapy and combined therapy were statistically significant (P<0.05) for definitive and all events.

Withdrawal rates due to adverse drug reaction were significantly higher for nifedipine therapy than controls, and were higher during nifedipine monotherapy than nifedipine combination therapy.

Authors’ conclusions
The results supported the safety of sustained- and extended-release nifedipine in the treatment of mild or moderate hypertension when it is used in combination with other drugs (diuretics or beta-blockers). Evidence from the controlled clinical trials that are in progress will be required to verify these conclusions.

CRD commentary
This review was methodologically rigorous with a thorough literature search, clear inclusion criteria, and an independent validity assessment.

However, its conclusions need to be interpreted cautiously. The possibility of publication bias cannot be ruled out. The authors discussed the following important limitations: the relatively small number of cardiovascular events on which the analyses were based; the relatively short duration of the studies; the inability to adjust per-person rates for the duration of drug treatment; the inability to explore dose relationships to adverse events; and the paucity of patient-level data to permit case-mix adjustment across studies.

The authors' conclusion follows from the results presented.

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Other publications of related interest


This additional published commentary may also be of interest. Rembold C. Review: nifedipine for hypertension may not increase the risk for cardiovascular events. ACP J Club 1998;128:2.

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Subject indexing assigned by NLM

MeSH
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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.