Safety of nifedipine in angina pectoris: a meta-analysis

Authors' objectives
To compare cardiovascular event rates in patients with stable angina receiving nifedipine as monotherapy or combination therapy and in active drug controls.

Searching
MEDLARS (1966 to August 1995) was searched using the exploded MESH term "myocardial ischemia" and "nifedipine" as a textword. Studies published in English, French, Italian, German and Spanish languages were included. CD-ROM Current Contents and bibliographies of retrieved articles were also searched.

Study selection
Study designs of evaluations included in the review
Published randomised controlled trials (RCTs) that enrolled a minimum of 10 patients.

Specific interventions included in the review
Any nifedipine formulation, either as monotherapy or combination therapy, with a nondihydropyridine active drug or a placebo control were included. Nifedipine was used as monotherapy in the majority of nifedipine study arms and drug exposures. Most nifedipine combination therapy groups used beta-blockers. Nifedipine immediate-release formulations were used in 76.9% of nifedipine study arms. Starting doses of nifedipine were titrated upward to achieve the desired clinical responses to greater than or equal to 80 mg/d in some studies.

Participants included in the review
Patients with stable angina pectoris. The mean age of participants was 58.2 (range 49-63) years. 74.5% of included participants were male.

Outcomes assessed in the review
Outcome measures included: deaths, nonfatal myocardial infarction, nonfatal stroke, revascularisation procedures and episodes of increased angina. The definition of increased angina varied between studies.

How were decisions on the relevance of primary studies made?
Two physician reviewers assessed studies (with results sections blinded).

Assessment of study quality
Methodological criteria were assessed using the scoring system described by Chalmers et al and Jadad (see Other Publications of Related Interest). Selected studies were blinded as to source, author and treatment groups. Two reviewers assessed study quality. Differences in opinion were resolved by consensus.

Data extraction
Selected studies were blinded as to source, author and treatment groups. Two independent reviewers using a data extraction form extracted data. A third reviewer extracted details of treatment regimens from unblinded articles. Data extracted included: drug dosages, sample size, duration of treatment and study location. The extraction forms were subsequently compared and discrepancies resolved. Because the majority of studies had no events in either the treatment or control arm, within-study estimates of treatment effects could not be calculated.

Methods of synthesis
How were the studies combined?
Incidence rates and odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated from the total number of events comparing nifedipine study arms with corresponding other active drug arms in the same studies. Placebo arms were excluded from the analysis due to small numbers. Pooling was carried out using the Peto method and the unweighted method both gave similar results.

How were differences between studies investigated?

Heterogeneity statistics could not be calculated because the majority of studies had no events in both arms. Multiple logistic regression analyses were used to investigate whether treatment effects were confounded with study-level covariates (i.e. drug run-in, duration of treatment, parallel or crossover design, quality score, date of publication, and study location). Analyses of cardiovascular events were stratified by type of nifedipine formulation (IR (TID or QID dosing), SR (BID dosing), or ER (QD)) and by whether nifedipine was prescribed as monotherapy or combination therapy.

Results of the review

Sixty RCTs (3096 patients and 5571 treatment exposures 2635 nifedipine, 2655 other active drugs and 281 placebo).

Nifedipine versus other active drugs: 21/60 (35%) studies reported one or more cardiovascular events.

Overall unadjusted ORs for nifedipine versus other active drugs were not significant: major cardiovascular events OR = 1.40 95% CI: 0.56, 3.49, episodes of increased angina OR = 1.75 95% CI: 0.83, 3.67, or all events OR = 1.61 95% CI: 0.91, 2.87. ORs adjusted for type of drug regimen and other study level covariates increased but were not significant, major events OR = 1.45 95% CI: 0.58, 3.62 and for all events OR = 1.75 95% CI: 0.98, 3.13.

Nifedipine formulation:

The OR for immediate-release nifedipine was significantly higher than that for sustained or extended release nifedipine respectively for increased angina OR = 4.19 95% CI: 1.14, 12.49 versus OR = 0.30 95% CI: 0.06, 1.43 p=0.001 and all events OR = 3.09 95% CI: 1.39, 6.88 versus OR = 0.47 95% CI: 0.16, 1.36 p=0.006 but not the major event category OR = 1.96 95% CI: 0.59, 6.52 versus OR = 0.78 95% CI: 0.17, 3.49 p=0.36.

Nifedipine monotherapy versus combination therapy:

Differences in ORS were significant for episodes of increased angina 3.90 95% CI: 1.45, 10.45 versus N/A p=0.03, and all events combined 2.61 95% CI: 1.30, 5.26 versus 0.29 95% CI: 0.06, 1.37 p=0.01, but not for major events 1.53 95% CI: 0.54, 4.30 versus 1.22 95% CI: 0.17, 8.71 p=0.81.

Withdrawals:

Withdrawals were significantly higher on nifedipine monotherapy (all formulations) than active drug controls for both adverse drug reactions (OR=1.7 95% CI 1.3 to 2.2) and all causes (OR=1.5 95% CI 1.2 to 1.9).

Authors’ conclusions

Results suggest that adverse effects of nifedipine on cardiovascular events in patients with stable angina are due primarily to more frequent episodes of increased angina when monotherapy with immediate release formulation are used. Sustained-release formulations and concurrent use with beta-blockers do not appear to be associated with increased risk in the studies included in this data set. Long term RCTs remain the ‘gold’ standard to verify these conclusions.

CRD commentary

The review addressed a clear question and conducted a rigorous review of the evidence. Validity assessment was undertaken using a validated scoring system and details of the review process were comprehensive. Studies were combined appropriately given the limitations of available data. The authors stratified the analyses to reduce heterogeneity and considered confounding factors. Authors’ provided a good report of study limitations.
This review may, however, have missed information by only considering studies published in a limited number of languages and might be susceptible to publication bias. Although study validity was assessed the results of the validity assessment were not discussed in the context of the study results.

Data provided support the authors' conclusions.

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

Research: The authors suggest that more RCTs of longer duration with better reporting of duration of treatment, doses received and patient level data should be undertaken.

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