An evaluation of beta-blockers, calcium antagonists, nitrates, and alternative therapies for stable angina

Heidenreich P A, McDonald K M, Hastie T, Fadel B, Hagan V, Lee B K, Hlatky M A

Authors' objectives
To compare: (1) the relative efficacy and tolerability of treatment with beta-blockers, calcium antagonists, and long-acting nitrates for patients who have stable angina; and (2) the efficacy of alternative therapies in patients who have stable angina.

Searching
MEDLINE (from 1966 to 1997) and EMBASE (from 1974 to 1997) were searched for publications in the English language using the following search criteria: MeSH term 'angina pectoris' or the textword 'angina', and publication type 'randomized controlled trial' or textword containing a form of the word 'random'. The authors also performed searches using publication type 'controlled clinical trial' or the textword 'double-blind'. The bibliographies of identified articles were examined for additional relevant studies.

For the search on alternative therapies, the following keywords were also used: 'meditation', 'prayer', 'naturopathy', 'chiropractic', 'osteopathic', 'holistic', 'natural medicine', 'homeopathy', 'mind-body', 'unorthodox', 'integrative ayurvedic', 'acupuncture', 'herbal', 'relaxation' and 'chelation'.

Study selection
Study designs of evaluations included in the review
For traditional drugs, the inclusion criteria for study design specified randomised parallel design or blinded crossover studies, which lasted at least one week. Trials that used a study medication during the run-in period prior to randomisation were excluded.

For alternative therapies, randomised controlled trials (RCTs) were required, but those of less than one week in duration were not excluded.

Specific interventions included in the review
For traditional therapies, direct comparisons of two or three of the major anti-anginal drug classes: long-acting nitrates, beta-blockers and calcium antagonists. The specific interventions were:

- long-acting nitrates, i.e. isosorbide mononitrate, isosorbide dinitrate, pentonitrol, aprenolol, LB46 and bisoprolol;
- beta-blockers, i.e. propranolol (initial mean dosage 183 mg/day), atenolol (initial mean dosage 95 mg/day), metoprolol (initial mean dosage 177 mg/day), nadolol (initial mean dosage 107 mg/day), bisoprolol (initial mean dosage 10 mg/day), carvedilol (initial mean dosage 50 mg/day), epanolol (initial mean dosage 200 mg/day), bopindolol (initial mean dosage 1 mg/day), labetolol (initial mean dosage 400 mg/day), penbutolol (initial mean dosage 40 mg/day) and pindolol (initial mean dosage 60 mg/day); and
- calcium antagonists, i.e nifedipine (initial mean dosage 41 mg/day), verapamil (initial mean dosage 313 mg/day), diltiazem (initial mean dosage 222 mg/day), bepridil (initial mean dosage 200 mg/day), nicardipine (initial mean dosage 78 mg/day), amlodipine (initial mean dosage 3 mg/day) and felodipine (initial mean dosage 10 mg/day). In the traditional therapy comparisons, studies of one drug versus placebo, dose comparisons of one drug, and one drug versus a two-drug combination were excluded.

For alternative therapies, comparisons of alternative therapies with placebo, nitrates, calcium antagonists or beta-blockers. Any alternative therapies were to have been included (meditation, prayer, naturopathy, chiropractic, osteopathic, holistic, natural medicine, homeopathy, mind-body, unorthodox, integrative ayurvedic, acupuncture, herbal, relaxation and chelation), but only studies of herbal remedies or acupuncture were found.
Participants included in the review
The inclusion criteria for the participants specified participants with a history of stable angina. In beta-blockers versus calcium antagonists, the mean age of the participants was 57 years and 84% were male. In nitrates versus calcium antagonists, the mean age of the participants was 62 years and 77% were male. In beta-blockers versus nitrates, the mean age of the participants was 57 years and 80% were male.

Outcomes assessed in the review
The inclusion criteria for the outcomes specified the number of angina episodes per week (patient recorded), the number of nitroglycerin uses per week (patient recorded), the total exercise time, and the time to 1-mm ST depression on a treadmill or exercise bicycle. The tolerability measure was the rate of participant withdrawal from the study as a result of adverse events (cardiac and noncardiac symptoms and death), exclusive of protocol violations or loss to follow-up. All side-effects from the following classes were recorded: worsening angina, headache, other central nervous system disturbance, gastrointestinal disturbance, and peripheral oedema. The review also recorded the end point of cardiac death or nonfatal myocardial infarction for studies in which either was reported.

How were decisions on the relevance of primary studies made?
Two independent reviewers selected the studies.

Assessment of study quality
No formal assessment of quality was undertaken.

Data extraction
Two independent reviewers extracted data from selected articles, and any differences were resolved by consensus. The outcome data were extracted a third time by the project director or another cardiologist.

Studies of calcium antagonists were grouped by duration and type of drug (e.g. nifedipine versus non-nifedipine). A random group of 16 studies were checked to look for errors in abstraction or database entry. All the studies were rechecked for the end points of mortality, angina episodes, nitroglycerin use, exercise time and adverse events.

Methods of synthesis
How were the studies combined?
The results of individual studies were combined using odds ratios (ORs) for discrete data (adverse events, cardiac death and myocardial infarction), mean differences for continuous data (number of angina episodes and number of nitroglycerin tablets used per week), and a standardised mean difference for exercise time. The 95% confidence intervals (CIs) were also calculated for each outcome. Fixed-effect calculations were made using the Peto method for ORs (see Other Publications of Related Interest no.1), while random-effects calculations were made using the DerSimonian and Laird method for mean differences (see Other Publications of Related Interest no.2).

How were differences between studies investigated?
Heterogeneity was tested using the Q statistic. The authors also examined differences between study subgroups of trials using analysis of variance.

Results of the review
Ninety RCTs were included in the review.

There was no statistical evidence of heterogeneity (p>0.20). The random-effects and fixed-effect methods of pooling gave similar estimates for all comparisons. The effects of excluding non-English publications were investigated; no significant differences were found for any of the outcome measures in this review.

A. Beta-blockers versus calcium antagonists (61 studies).

In the pooling of both long- and short-term studies, the rates of cardiac death and myocardial infarction were not
significantly different for treatment with beta-blockers versus calcium antagonists (OR 0.97, 95% CI: 0.67, 1.38, p=0.9). There were 0.31 (95% CI: 0.00, 0.62, p=0.05) fewer episodes of angina per week with beta-blockers than with calcium antagonists. When the comparison was restricted to trials comparing beta-blockers with nifedipine, there were 0.63 (95% CI: 0.21, 1.0) fewer angina events per week with beta-blockers.

Nitroglycerin tablet use per week was not significantly different between patients treated with beta-blockers and patients treated with calcium antagonists. There was a non significant reduction of 0.14 (95% CI: -0.19, 0.46) fewer nitroglycerin tablets per week with beta-blockers in those studies that compared beta-blockers with nifedipine.

There was a slightly greater total exercise time with calcium antagonists compared with beta-blockers. There was no significant difference in time to 1-mm ST depression (ischaemia) between calcium antagonists and beta-blockers. Similarly, there was no difference in exercise time to ischaemia when only trials comparing beta-blockers with nifedipine were evaluated. No differences were noted when short- and long-acting preparations of calcium antagonists were evaluated separately.

Beta-blockers were discontinued less often because of adverse events than calcium antagonists (OR 0.72, 95% CI: 0.60, 0.86, p<0.001). The absolute difference in the adverse event rate was 2.0 (95% CI: 0.5, 3.4) fewer events with beta-blockers, compared with calcium antagonists, for every 100 patients treated. The differences in adverse events between beta-blockers and calcium antagonists were most striking for nifedipine (OR for adverse events with beta-blockers versus nifedipine = 0.60, 95% CI: 0.47, 0.77).

B. Long-acting nitrates versus calcium antagonists (12 studies).

There were no significant differences in outcomes between these classes of medications. However, a trend (p=0.1) was noted for a greater number of angina episodes per week in patients who were taking long-acting nitrates.

C. Long-acting nitrates versus beta-blockers (6 studies).

There were no significant differences between beta-blockers and long-acting nitrates in any of the outcomes measured. A trend (p=0.8) towards increased nitroglycerin use per week was noted for patients who were taking long-acting nitrates.

The results for traditional therapies are also presented in a journal publication (see Other Publications of Related Interest no.3).

D. Alternative medicine for stable angina (12 studies).

Data from these studies were not pooled. For acupuncture (n=4), no significant differences were noted in angina episodes or nitroglycerin use. For herbal remedies (n=8), significant improvements in angina and exercise endurance and ST depression were noted in the herbal group one of the studies; the other results were mixed.

Authors’ conclusions

Calcium antagonists were associated with a greater number of angina episodes and adverse events, compared with beta-blockers, in trials of patients who have stable angina. Beta-blockers and non-nifedipine calcium antagonists had similar effects on adverse events, symptoms and exercise tolerance. The rates and frequency of angina between beta-blockers and calcium antagonists are accounted for in large part by nifedipine, which was associated with a higher rate of adverse events and angina symptoms. The duration of the trials was too short to determine differences in long-term rates of survival or myocardial infarction between calcium antagonists and beta-blockers.

The investigation of alternative therapies gave no clear indication of the benefit or harm from these therapies for patients who have stable angina.

CRD commentary

This was a well-conducted review. The authors stated the research question and reported, in detail, all categories of
inclusion and exclusion criteria. The literature search was fairly thorough and attempted to find unpublished or grey literature. While the searches were limited to English language publications, the reviewers performed further analyses to check if these exclusions would have altered the results (they did not). It is not stated whether there were tests for publication bias. One drawback was that the quality of the included studies was not formally assessed, and while the authors have reported how the articles were selected, they have not stated who performed the data extraction.

The data extraction was reported in tables in the appendices of the review, and was briefly summarised in the text of the review. The presentation of the primary studies is difficult to follow. The studies were statistically combined and tests to investigate possible heterogeneity were conducted, although the results were not reported very clearly. The authors' conclusions appear to follow from the results, and the suggestion that further research should be conducted is appropriate.

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

**Practice:** The authors did not state any implications for practice.

**Research:** The authors state that more long-term comparative trials are required to determine whether the different therapies confer a significant mortality difference in patients who have stable angina. Further studies could also examine the effects of treatments for stable angina in patients with co-morbidity such as heart failure or chronic obstructive pulmonary disease. Additional RCTs of alternative therapies in this patient population are necessary to reach conclusions about the efficacy and safety of alternative therapies.

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