Meta-analysis of trials comparing beta-blockers, calcium antagonists, and nitrates for stable angina

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Authors' objectives
To compare the relative efficacy and tolerability of treatment with beta-blockers, calcium antagonists, and long-acting nitrates for patients who have stable angina.

Searching
The authors searched for English language publications using the MEDLINE (1966-1997) and EMBASE (1974 to 1997) electronic databases using the search criteria of 'angina pectoris' or the textword 'angina' and the publication type 'randomized controlled trial' or text word containing a form of the word 'random'. The authors also performed searches using the criterion of 'controlled clinical trial' or text word 'double-blind'. The authors also searched the bibliographies of identified articles for additional relevant studies.

Study selection
Study designs of evaluations included in the review
Randomised parallel design or crossover studies comparing anti-anginal drugs from 2 or 3 different classes which lasted at least 1 week. Trials which used a run-in period prior to randomisation were excluded.

Specific interventions included in the review
Beta-blockers (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 (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)).

Participants included in the review
Patients diagnosed with a history of stable angina. In beta-blockers versus calcium antagonists the mean age of participants was 57 years of age and 84% were male. In nitrates versus calcium antagonists the mean age of participants was 62 years of age and 77% were male. In beta-blockers versus nitrates the mean age of participants was 57 years of age and 80% were male.

Outcomes assessed in the review
Cardiac death, myocardial infarction, study withdrawal due to adverse events, angina frequency (patient recorded), nitroglycerin use (patient recorded), and exercise duration (time to 1-mm ST depression on a treadmill or exercise bicycle).

How were decisions on the relevance of primary studies made?
Two independent reviewers performed the study selection.

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

Data extraction
Two independent reviewers extracted data from selected articles, and differences were resolved by consensus. Outcome data were extracted a third time by 1 of the investigators.

Studies of calcium antagonists were grouped by duration and type of drug (nifedipine versus non-nifedipine).

Methods of synthesis

How were the studies combined?

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. For each outcome, 95% confidence intervals (CIs) were also calculated. Fixed-effect calculations were made using the Peto method for ORs (see Petitti, Other Publications of Related Interest), while random-effects calculations were made using the DerSimonian and Laird method for mean differences (see Other Publications of Related Interest).

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).

Random-effects and fixed-effect methods of pooling gave similar estimates for all comparisons.

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 = 0.79).

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.

Beta-blockers were discontinued because of adverse events less often than were calcium antagonists (OR = 0.72, 95% CI: 0.60, 0.86; p < 0.001).

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).

For exercise time there were no statistically significant differences in time to ischemia (1-mm ST depression) between calcium antagonists and beta-blockers. Similarly, no difference in exercise time to ischemia was observed 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.

Too few trials compared nitrates with calcium antagonists or beta-blockers to draw firm conclusions about relative efficacy.

Authors' conclusions

Beta-blockers provide similar clinical outcomes and are associated with fewer adverse events than calcium antagonists in randomised trials of patients who have stable angina. The differences in adverse event 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.
CRD commentary
The authors have clearly stated their research question and some inclusion and exclusion criteria. The literature search appears thorough but the authors may have missed additional relevant studies by restricting the searches to English language publications. However, the authors have reported on how the articles were selected, and how many of the reviewers were involved in the data selection and extraction. The quality of the included studies was not formally assessed which is a drawback of the review especially since the individual studies are not listed in the article for review by the reader.

The data extraction is summarised by outcomes of interest in tables and text but details from individual studies are not given. The statistical pooling was appropriate and there were tests for heterogeneity, however the authors reported results for ORs using one method (fixed-effect) but changed to reporting results of mean differences from a random-effects model.

The authors discussed the methodological and data limitations in the review. The authors conclusions appear to follow from the results but should be viewed with caution because of the stated methodological limitations of the review.

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.

Bibliographic details

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Other publications of related interest

This additional published commentary may also be of interest. Gazewood JD. Medical therapy for stable angina. J Fam Pract 1999;48;660-1.

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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.