Long-term beta blockers for stable angina: systematic review and meta-analysis
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CRD summary
This review found that beta-blockers could reduce mortality and the rate of unstable angina, in patients with stable angina, compared with no treatment, but they were no more effective than other anti-angina agents. The lack of high-quality trials and limited reporting of the outcomes in each trial, mean that these results may not be reliable.

Authors' objectives
To assess the effects of long-term beta-blockers for patients with stable angina.

Searching
MEDLINE, EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and three Chinese databases were searched for articles from their inception to June 2010.

Study selection
Only randomised controlled trials of at least four weeks duration were eligible. Participants had to have stable chest pain syndrome with either diagnosed or suspected ischaemic heart disease. Trials had to compare beta-blockers with other anti-angina drugs, placebo or no treatment. The primary outcomes were all-cause mortality and fatal or non-fatal acute myocardial infarction. Secondary outcomes included coronary revascularisation, unstable angina, frequency of angina symptoms and adverse events.

In most of the included trials, the average age was over 50 years. Overall, 21% of patients were female, 42% had previous myocardial infarction, 13% had heart failure, 24% had hypertension, 10% had diabetes and 10% had previous heart surgery. Nine beta-blockers were considered and the most common were atenolol (seven trials) and metoprolol (six trials). Calcium-channel blockers were the most common comparator (14 trials); no intervention, placebo and other drugs were also used.

Two reviewers independently performed the study selection.

Assessment of study quality
The risk of bias for each trial was classified as high, moderate or low according to guidelines created by the Cochrane Collaboration, based on randomisation, allocation concealment, blinding, loss to follow-up and the use of an intention-to-treat analysis. The number of reviewers who performed the assessment was not stated.

Data extraction
Data on the numbers of events, for each outcome, were extracted to calculate odds ratios, with 95% confidence intervals. For the frequency of angina symptoms, the number of attacks per week was extracted to calculate weighted mean differences, with 95% confidence intervals. Two reviewers independently extracted the data.

Methods of synthesis
Pooled odds ratios were calculated, using a random-effects or fixed-effect Mantel-Haenszel meta-analysis. Pooled mean differences were calculated, using a random-effects inverse-variance meta-analysis. Heterogeneity was assessed using I². Sensitivity and subgroup analyses were performed, but the details of these were not reported. A funnel plot was used to assess publication bias.

Results of the review
There were 26 included trials, with 6,108 enrolled patients (range 19 to 1,460), of whom 5,340 completed the follow-up. Follow-up times ranged from four weeks to 84 months. Trials were generally considered to be at a moderate risk of bias, but there was a high risk in the Chinese trials.

Beta-blockers led to a statistically significant reduction in all-cause mortality, compared with no treatment (OR 0.40, 95% CI 0.20 to 0.79), but not compared with placebo (OR 0.92, 95% CI 0.62 to 1.38) nor calcium-channel blockers.
Beta-blockers did not reduce the incidence of acute myocardial infarction, compared with placebo (OR 0.84, 95% CI 0.49 to 1.44; three trials; $I^2=0$) nor calcium-channel blockers (OR 1.08, 95% CI 0.71 to 1.66; six trials; $I^2=0$).

There was no evidence of differences between beta-blockers and calcium-channel blockers for coronary revascularisation (OR 1.36, 95% CI 0.92 to 2.01; two trials; $I^2=0$) and none for unstable angina (OR 1.18, 95% CI 0.54 to 2.61; three trials; $I^2=69$%). Beta-blockers reduced the frequency of angina attacks (MD -1.05, 95% CI -2.13 to 0.02; four trials; $I^2=88$%), but this was not quite statistically significant. Publication bias was judged to be unclear.

**Authors' conclusions**

Beta-blockers could reduce mortality and the rate of unstable angina, in patients with stable angina, compared with no treatment, but they were no more effective than other anti-angina agents.

**CRD commentary**

This review addressed a relevant research question, using appropriate inclusion criteria. Six databases were searched, but unpublished material was not sought, so relevant trials may have been missed. The search terms were not reported, so the search may not be replicable. Action was taken to reduce reviewer bias and error at most stages of the review process, and risk of bias in the included trials was assessed. The authors noted that the quality of trials was generally moderate to poor, leaving the potential for bias, particularly in those trials that had no treatment as a comparator. The review overall included a large number of trials and patients, but each outcome was reported in very few trials, with the potential for outcome reporting bias due to limited reporting of the results in these trials.

For these reasons the results and conclusions should be treated with caution, and may not be reliable.

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

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

**Research**: The authors suggested that trials of beta-blockers were required, with a follow-up of at least five years, to assess their effect on outcomes, adverse events and cost-effectiveness.

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