Beta-blockade after myocardial infarction: systematic review and meta regression analysis

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Authors' objectives
To assess the effectiveness of beta blockers in short-term treatment for acute myocardial infarction and in longer-term secondary prevention.

Searching

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) without crossover, with treatment lasting more than 1 day.

Specific interventions included in the review
Interventions (which were either short-term (up to 6 weeks after onset of pain) and/or long-term (6 to 48 months)) using beta blockers compared with a control. Long-term treatment regimens used acebutolol, alprenolol, atenolol, carvedilol, metoprolol, oxprenolol, pindolol, practolol, propranolol, sotalol, timolol, and xamoterol. Short-term treatment regimens used atenolol, labetalol, metoprolol, oxprenolol, pindolol, practolol, propranolol, timolol, acebutolol, sotalol, xamoterol, and betaxolol.

Participants included in the review
Patients with acute or past myocardial infarction.

Outcomes assessed in the review
All cause mortality and non-fatal re-infarction and withdrawal from treatment.

How were decisions on the relevance of primary studies made?
The authors do not state how the papers were selected for the review, or how many of the authors performed the selection.

Assessment of study quality
A formal assessment process is not reported however the authors state that data on loss to follow-up, level of blinding and concealment of allocation were extracted from the included studies. One reviewer performed the validity assessment which was checked by a second reviewer.

Data extraction
One reviewer performed the data extraction and data were checked by a second reviewer.

Data were extracted for the categories of: total number of patients randomised to active treatment or control, beta blocker, route and dose of drug, duration of treatment, loss to follow-up, level of blinding, concealment of allocation, specific study inclusion and exclusion criteria, duration of follow-up, deaths, re-infarctions and withdrawals.

Methods of synthesis
How were the studies combined?
Pooled odds ratios (ORs) with 95% confidence intervals (CIs) for short- and long-term treatments were calculated separately using the Mantel Haenszel fixed-effect model and also using a random-effects model (see Other Publications of Related Interest no.2).

Risk differences were calculated using a standard random-effects model and using the approach described by Ioannidis (see Other Publications of Related Interest no.1). For the long-term trials the authors also calculated pooled estimates of effect for each beta blocker using a fixed-effect model.

How were differences between studies investigated?
The authors tested for heterogeneity using the Q statistic. The authors also performed subgroup analyses on the effects of initial intravenous treatment in long-term trials, and the effect of additional treatment options through the proxy variable of publication date before or after the median year (1982). The authors also assessed convergence using the methods described by Geweke (see Spiegelhalter et al in Other Publications of Related Interest no.3) and visual inspection of convergence plots.

Results of the review
Eighty-two (82) RCTs with 54,234 participants. Fifty-one trials examined acute (short term) treatment with beta blockers (29,260 participants) and 31 trials examined long-term treatment with beta blockers (24,974 participants).

Overall, 10.1% randomised to beta blockers or control died.

In the short-term trials, the pooled random effects OR was 0.96 (95% CI: 0.85, 1.08), a small and statistically non-significant 4% reduction in the odds of death.

In the long-term trials, the pooled random effects OR was 0.77 (95% CI: 0.69, 0.85), a statistically significant 23% reduction in the odds of death.

Applying initial intravenous dose as a covariate term in the analysis suggested no additional benefit among patients treated in this manner (OR = 0.87, 95% CI: 0.61, 1.22).

Only 4 drugs individually reached statistical significance in the reduction in the odds of death in the long-term studies: propranolol (OR = 0.71, 95% CI: 0.59, 0.85); timolol (OR = 0.59, 95% CI: 0.46, 0.77); metoprolol (OR = 0.80, 95% CI: 0.66, 0.96); acebutolol (OR = 0.49, 95% CI: 0.25, 0.93). Meta regression in long-term trials did not identify a significant reduction in effectiveness in drugs with cardioselectivity but did identify a near significant trend towards decreased benefit in drugs with intrinsic sympathomimetic activity.

Most evidence is available for propranolol, timolol, and metoprolol. In long-term trials, the number needed to treat (NNT) for 2 years to avoid a death is 42, which compares favourably with other treatments for patients with acute or past myocardial infarction.

Withdrawal in trials from both treatment and control groups varied from 10% to 30% however different definitions and reporting made comparison of withdrawals problematic. Overall, 5,151 of 21,954 (23.5%) withdrew from treatment. No clinically important differences were observed between beta-blockers of differing cardioselectivity and intrinsic sympathomimeticity.

Authors' conclusions
The authors state that beta blockers are effective in long-term secondary prevention after myocardial infarction, but they are underused in such cases and lead to avoidable mortality and morbidity.

CRD commentary
The authors have clearly stated their research question and inclusion and exclusion criteria. The literature search appears thorough but the authors have not stated their search terms. Since there is no mention of language restrictions it is possible that additional relevant studies may have been missed. Although the authors also do not mention the
inclusion of unpublished data in the review, on-going trials are mentioned for possible inclusion in future reviews. Although data was extracted for validity assessment, the authors have not stated how the quality of the included studies was formally assessed. The authors have not reported on how the articles were selected. The authors have stated however how many of the reviewers were involved in the process of data extraction.

The data extraction is reported in tables and text. The statistical pooling was appropriate and the authors extracted data (where possible) to perform subgroup analyses. There were tests for heterogeneity but there was no discussion of the methodological and data limitations in the review.

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

**Implications of the review for practice and research**
The authors did not state any implications for further research and practice.

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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.