Beta-blockers to reduce mortality in patients with systolic dysfunction: a meta-analysis

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Authors' objectives
To assess whether therapy with adrenergic beta-antagonists (beta-blockers) reduces the risk of mortality in patients with systolic dysfunction.

Searching
MEDLINE was searched from 1966 to February 2000 using MeSH terms and keywords. The results were limited to English language articles and the publication type 'clinical trial'. Other databases searched included International Pharmaceutical Abstracts, IDIS, Current Contents and the Cochrane Library. References from published clinical trials and reviewed articles were also examined, and the manufacturers of the three drugs tested were contacted.

Study selection
Study designs of evaluations included in the review
Randomised double-blind controlled trials were eligible for inclusion. Studies were excluded if the study duration was less than three months or if publication occurred before 1975. All of the identified trials were placebo-controlled.

Specific interventions included in the review
Beta-blockers were eligible for inclusion. The studies of beta-blockers identified and included were of bisoprolol (5mg once daily and 10 mg once daily), carvedilol (25 mg twice daily and 25 to 50 mg twice daily) and metoprolol (10 to 150 mg once daily and 200 mg once daily). Each study was placebo-controlled.

Participants included in the review
Patients who had a diagnosis of systolic heart failure were eligible for inclusion. The mean age of the patients was 60 years and the average proportion of men across the included studies was 78%. All of the patients were receiving pharmacological treatment for heart failure before study enrolment. The average ejection fraction ranged from 22 to 29%. In all studies the majority of the patients had New York Heart Association (NYHA) class II or III heart failure. Heart failure aetiology varied between the trials: all of the included patients in the ANZ carvedilol study had ischaemic heart failure; all those in the MDC metoprolol study had non-ischaemic heart failure; two thirds of those in the MERIT-HP metoprolol trial had ischaemic heart failure; and the other studies included approximately equal numbers of patients with each type (ischaemic or non-ischaemic) of heart failure.

Outcomes assessed in the review
Mortality, as either a primary or secondary outcome, was the stated outcome. The other outcomes reported were sudden death and cardiovascular death.

How were decisions on the relevance of primary studies made?
Two reviewers searched MEDLINE independently. No further details about decisions on relevance were given.

Assessment of study quality
The included studies were evaluated using Jadad's quality scale, which rated the quality of each study from 0 (worst) to 5 (best). Trials were included if they met the inclusion criteria. Only the six trials meeting the criteria were assessed for quality. The authors do not state how many of the reviewers performed the quality assessment.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the reviewers performed the data extraction. However, it was stated that two independent reviewers calculated the relative risk, relative risk reduction (RRR), absolute risk reduction, and the number-needed-to-treat for the total mortality end point reported in each trial.
Information was also abstracted on the following: patient characteristics at baseline, flow of patients from enrolment to post randomisation, dosages of beta-blockers and outcomes, and concomitant anti-arrhythmic medication. The patient characteristics included age, gender, heart failure aetiology, resting heart-rate, and systolic and diastolic blood-pressure.

**Methods of synthesis**

How were the studies combined?

When the trials were considered homogeneous, a meta-analysis was performed to pool the trial results. Pooled odds ratios (ORs) with 95% confidence intervals (95% CIs) were calculated using the Mantel-Haenszel fixed-effect model for total mortality and mortality caused by sudden death. Relative risk, RRR, absolute risk reduction, and the number-needed-to-treat for total mortality were also calculated.

How were differences between studies investigated?

Homogeneity of effect was assessed using a Q statistic. A P-value of less than 0.05 was considered statistically significant. A narrative synthesis was undertaken for the subgroup analysis.

**Results of the review**

Six randomised controlled trials (N=9,171) were included. The number of patients in the studies ranged from 383 to 3,991. The two bisoprolol trials included 641 and 2,647 patients; the two carvedilol trials included 415 and 1,094 patients; and the two metoprolol trials included 383 and 3,991 patients.

The mean follow-up of the studies ranged from 0.54 years (median) to 1.9 years. Two of the trials scored the highest quality rating (5), while the other four trials all scored 4. Compared with placebo, the use of beta-blockers significantly reduced total mortality when all six trials were combined (OR 0.66, 95% CI: 0.58, 0.75). For this outcome Q was 9.3, indicating homogeneity of the six trials. The five trials that reported sudden death (MERIT-HF, CIBIS-II, MDC, CBIS, US Carvedilol) were assessed to be homogeneous (Q=7.0). Compared with placebo, sudden death was significantly reduced (OR 0.61, 95% CI: 0.5, 0.75). All of the trials evaluated cardiovascular death, but since they were considered to be heterogeneous with respect to this outcome (Q=12.7), a summary statistic was not reported.

A subgroup analysis in two of the studies (MERIT-HF and CIBIS-II) indicated that patients with NYHA class III heart failure had a greater but non significant RRR in mortality than did those of NYHA class IV and II heart failure. There was no difference in mortality benefit between the three groups, based on exercise test performance in the US Carvedilol study.

A decrease in mortality was seen in patients with both ischaemic and non-ischaemic heart failure in CIBIS-II, MERIT-HF, and US Carvedilol studies. All three studies noted a significantly reduced mortality in patients with ischaemic heart failure. The US Carvedilol trial demonstrated a statistically-significant decrease in mortality in patients with non-ischaemic heart failure receiving beta-blocker therapy, while MERIT-II and CIBIS-II did not.

None of the trials showed a clinically significant decrease in systolic or diastolic blood-pressure, but a decrease in heart rate of approximately 10 to 15 beats per minute was seen. In the US Carvedilol study, increased dizziness in the carvedilol-treated patients was noted compared with placebo, particularly after a dosage increase. This dissipated with use.

**Authors' conclusions**

All patients with NYHA class II and III heart failure should receive beta-blocker therapy with bisoprolol, carvedilol or metoprolol. Therapy should be initiated only in stable patients using a low dose of a beta-blocker. This dose may be subsequently gradually titrated upward by doubling the current dose every 1 to 2 weeks on the basis of clinical response and patient tolerability.

**CRD commentary**
The review was a useful summary of the effects of three beta-blockers. However, relevant trials may have been missed since the search was limited to articles published in English. No procedures were reported for the selection of the trials. Only Q statistics were given for the tests of heterogeneity and it was stated that a P-value of less than 0.05 was considered significant, rather than the more usual 0.1. It is therefore possible that the trial heterogeneity recorded for cardiovascular mortality was a false positive. Furthermore, there was no attempt to combine the trials for this outcome using a random-effects model, which allows for heterogeneity. While there was insufficient detail to assess the appropriateness of using such a model, the authors did in fact note that a summary outcome would be misleading for this outcome.

The results for sudden death were pooled, but a narrative synthesis was also given; this was difficult to understand since the relevant row in Table 2 was mis-printed and did not match the text in the 'Results' section. The authors correctly drew attention to potentially invalid results based on subgroup analyses, due to variations in study designs. They also offered a useful explanation, in terms of study design, for why the RRR (mortality) for carvedilol was nearly twice that of bisoprolol and extended-release metoprolol, despite the absolute risk reductions being similar. In general, however, the authors' conclusions seem to be valid for this patient population.

Implications of the review for practice and research
Practice: The authors state that currently published trials have not included sufficiently large numbers of elderly patients and, therefore, the extrapolation of the data to this patient population should be done with caution. Also, the effects of race and ethnicity have yet to be systematically addressed.

Research: The authors state that studies designed to assess the impact of beta blockade in patients with heart failure depending on the aetiology of their disease would allow for further maximisation of benefit. Clinical trials are needed to determine the optimal dosing regimes of beta-blockers. In addition, comparative clinical trials with a mortality end point have not been conducted. Efficacy comparisons between selective and nonselective beta-blockers are necessary to quantify the survival benefits.

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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.