Beta-blocker therapy for congestive heart failure: a systematic overview and critical appraisal of the published trials

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Authors' objectives
To evaluate the effect of beta-blockers on mortality and morbidity in the treatment of congestive heart failure (CHF).

Searching
MEDLINE was searched from period 1966 to March 1997 using the keywords 'beta adrenergic blocking agents' and 'heart failure'.

Study selection
Study designs of evaluations included in the review
Randomised clinical trials (RCTs) with at least 1 month of treatment were included.

Specific interventions included in the review
Beta-blockers. The following beta-blocker therapies were studied: acebutolol (400 mg), metoprolol (50, 61, 87, 92, 100 or 108 mg), bucindolol (12.5 to 200 mg, or 173, 184 or 200 mg), labetalol (275 mg), nebivolol (5 mg), bisoprolol (3.8 mg) or carvedilol (41 or 45 mg); placebo.

Concomitant medication included digitalis (15 trials), diuretics (15 trials), angiotensin-converting enzyme inhibitors (10 trials) and other vasodilators (7 trials).

Participants included in the review
Patients with CHF and reduced left ventricular ejection fraction were included.

Outcomes assessed in the review
The outcomes assessed were mortality, hospitalisation for CHF, actual heart transplantation, left ventricular ejection fraction and maximal exercise duration (exercise time by treadmill or bicycle).

How were decisions on the relevance of primary studies made?
Two authors independently selected the papers for the review and resolved any differences by consensus.

Assessment of study quality
The authors did not report the method used to assess validity, or how the validity assessment was performed. Predefined criteria for reviewing articles were RCTs, completeness of follow-up (95% or greater) and analysis by the 'intention-to-treat' principle.

Data extraction
The data were extracted independently by two authors with an agreement of 90%. The remaining disagreements were resolved in consultation with a third author.

Methods of synthesis
How were the studies combined?
The Mantel-Haenszel method for combining data, as described by Yusuf et al. (see Other Publications of Related Interest no.1) was used for combining information on discrete outcomes. Left ventricular ejection fraction and exercise tolerance were reported as the difference in change from baseline to follow-up between the treatments and control, and the pooled standard deviation of change score was imputed as described by Follmann et al (see Other Publications of
Related Interest no.2). A z-test was used to determine the significance of the difference between the two means. For discrete outcomes, the summary data were expressed as odds ratios (ORs) and their 99% confidence intervals (CIs).

The reliability of the available evidence from the meta-analyses for the efficacy of beta-blockers in CHF was assessed according to the method of Pogue and Yusuf (see Other Publications of Related Interest no.3).

How were differences between studies investigated?
The existence of between-trial heterogeneity of treatment effects was determined for each outcome, using the chi-squared test.

Results of the review
Eighteen published trials involving 2,986 patients were included (duration of treatment 1 to 23 months; weighted average 13 months). Complete data, by allocated treatment, were available for mortality (10 trials; 2,841 patients), for hospitalisation for heart failure (5 trials; 1,514 patients) and for heart transplantation (6 trials; 2,330 patients).

Data on left ventricular ejection fraction were available in 11 trials (941 patients) and complete data on exercise end points were available in 9 trials (855 patients). Metoprolol was evaluated in 7 trials (562 patients), bucindolol in 4 trials (209 patients), carvedilol in 2 trials (1,509 patients), nebivolol in 2 trials (36 patients), bisoprolol in 1 trial (641 patients), acebutolol in 1 trial (17 patients), and labetalol in 1 trial (12 patients).

There were 7 trials of patients with an idiopathic dilated etiology, 2 trials of those with an ischaemic etiology, 5 trials of those with a combination of idiopathic and ischaemic etiology, and 4 trials of those with a combination of idiopathic, ischaemic, hypertensive and valvular etiologies.

There was a lower rate of death in the active treatment group, 8.2% versus 12.6% in the control group (OR 0.72, 99% CI: 0.51, 1.00). In addition, there was a lower rate of hospitalisation for heart failure, 18.1% versus 28.8% (OR 0.54, 99% CI: 0.39, 0.74) and a trend towards a lower proportion of patients receiving heart transplantation, 1.1% versus 2.7% (OR 0.45, 99% CI: 0.20, 1.03). Overall, the absolute change in the left ventricular ejection fraction was 6.3% higher in the active treatment group (99% CI: 1.1, 11.54), and there was a non significant absolute decrease of 14.4 seconds in the exercise time for the treatment group, compared with the placebo (99% CI: -202.1, +175.2). There was no significant heterogeneity among the results of the trials investigating any of the outcomes.

Thirteen trials reported information on adverse effects (84% of all patients randomly assigned). There was an excess of the following in the treatment group when compared with the control group: dizziness, 16.2% versus 7.5% (OR 2.2, 95% CI: 1.7, 2.8); fatigue, 9.0% versus 2.6% (OR 1.10, 95% CI: 0.83, 1.46); bradycardia, 5.1% versus 0.6% (OR 4.29, 95% CI: 2.75, 6.70); and hypotension, 4.7% versus 1.7% (OR 2.21, 95% CI: 1.41, 3.46). In contrast, there was a significant reduction in the proportion of patients reporting worsening heart failure in the treatment group, 16.7% versus 25.1% in the control group (OR 0.59, 95% CI: 0.49, 0.71).

In evaluating the reliability of the available data, the optimal information size was calculated on the basis of a control mortality of 15%. These calculations indicated that 7,720 and 14,044 patients, based on a relative risk reduction of 20 and 15%, respectively, are the minimum sample sizes needed to reliably detect plausible treatment effects. The corresponding mortality end point indicated that the available evidence was not sufficiently convincing in the context of a cumulative meta-analysis.

Authors’ conclusions
While the available data on the use of beta-blockers in CHF appear to be promising, they are neither complete nor robust. The routine use of beta-blockers in patients with heart failure should await the results of ongoing studies.

CRD commentary
This was a thorough, well-conducted review that included clear objectives and used specific inclusion and exclusion criteria. However, only one database (MEDLINE) was searched, and no attempt was made to investigate unpublished data. [A: We wrote to a number of CHF investigators to inquire about unpublished studies but did not obtain any].
more extensive literature search may have uncovered further relevant studies. The authors’ conclusions seem to follow from the results presented.

**Implications of the review for practice and research**
The authors state that, although the effects on mortality were nominally statistically significant, the use of formal methods of interim monitoring adapted for meta-analyses suggests that substantially more patients still need to be studied in large scale trials, in order to provide reliable and conclusive evidence.

**Bibliographic details**

**PubMedID**
9738164

**Other publications of related interest**

This additional published commentary may also be of interest. Lader E. Review: beta-blockers reduce mortality and morbidity in congestive heart failure. ACP J Club 1999;130:7.

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