Systematic review of the impact of beta blockers on mortality and hospital admissions in heart failure

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Authors' objectives
To provide more reliable estimates of the impact of beta-blockers on mortality and hospital admissions in patients with heart failure.

Searching
MEDLINE was searched from January 1998 to January 2000 using the keywords 'beta blocker', 'clinical trials' and 'congestive heart failure'. In addition, the abstract reports from the main cardiology and heart failure meetings were handsearched from 1996 to 2000. The authors also checked that previously published meta-analyses had covered all randomised trials published between 1975 to 1997, by repeating the search from January 1970 to December 1999. The authors restricted the review to published papers or abstracts.

Study selection
Study designs of evaluations included in the review
The inclusion criteria specified placebo-controlled trials with random allocation or parallel-group design. Trials were excluded if they had a crossover design.

Specific interventions included in the review
Comparisons of oral beta-blockers and inactive controls. The included studies compared bisoprolol, bucindolol, carvedilol, metoprolol and nebivolol, in a wide range of doses, with placebo.

Participants included in the review
The inclusion criteria specified trials of participants with congestive heart failure. The average age and ejection fraction of the participants in the included studies were 61.6 years and 26%, respectively. Approximately 4% of the participants were female. The aetiologies of heart failure in the included patients were coronary artery disease (52%), non-ischaemic dilated cardiomyopathy (33%), idiopathic dilated cardiomyopathy (14%) and hypertrophic cardiomyopathy (0.3%). The proportion of patients with NYHA functional class I, II, III and IV were 1.4, 28.3, 68.3 and 7.2%, respectively. Diuretics were prescribed to 91% of the patients, angiotensin-converting enzyme inhibitors to 91%, digitalis to 62%, and vasodilators to 26%.

Outcomes assessed in the review
The primary outcome was mortality, but the authors also included information about hospital admission where available. Trials were excluded if mortality data were not available. The actual outcomes in the included studies were all cause-mortality, cardiovascular hospital admission, all-cause hospital admission, and the composite of mortality or hospital admission.

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 reviewers performed the selection.

Assessment of study quality
The authors do not state that they assessed validity. However, the degree of blinding was described.

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.
extraction. The data extracted included: patient characteristics such as age, gender, aetiology of heart failure, NYHA functional class, other treatments, and compliance to treatment; trial design; treatment and dosage; follow-up time; and outcomes, i.e. all-cause mortality, mortality and hospital admissions.

**Methods of synthesis**

How were the studies combined?
The data for mortality, hospital admission and the composite of mortality or hospital admission were pooled. The odds ratios (ORs) were calculated using fixed-effect (Mantel-Haenszel) and random-effects (DerSimonian and Laird) models. Trials that had no events reported in either treatment group were excluded from the analysis.

How were differences between studies investigated?
Heterogeneity was tested using the chi-squared statistic, with the level of significance set at 0.10.

**Results of the review**

Twenty-two randomised controlled trials (RCTs) were included; 20 of these were double-blind, one was single-blind and in one case the allocation concealment was not specified. A total of 10,480 patients were randomised, 5,507 to active treatment and 4,973 to control. The double-blind RCTs included 10,410 patients, the single-blind RCT 20 patients, and the unblinded RCT 50 patients.

For the effect of beta-blockade on all-cause mortality, the OR was 0.65 (95% confidence interval, CI: 0.57, 0.74, P<0.00001). Heterogeneity among these 14 trials was not significant (chi-squared 8.44 d.f.=13, P=0.81). For the effect of beta-blockade on hospitalisation, the OR was 0.63 (95% CI: 0.56, 0.71, P<0.00001). For these 13 trials, chi-squared was 5.00 (d.f.=12, P=0.95). For the effect of beta-blockade on the combined end point of all-cause mortality or hospital admission for heart failure, the OR was 0.68 (95% CI: 0.61, 0.65, P<0.00001). For these 9 trials, chi-squared was 5.22 (d.f.=8, P=0.73).

**Authors' conclusions**
The effects of beta-blockers in reducing mortality and the need for hospital admission due to heart failure in a broad range of patients were dramatic. These benefits should be implemented as a priority, since beta-blocker treatment is inexpensive and heart failure carries a high risk of death and disability.

**CRD commentary**
The review question was clear and details of the primary data, data pooling and tests of heterogeneity were well presented. The selection criteria for including studies were clearly stated for study design, outcomes and the intervention. The electronic literature search was limited to MEDLINE, which means that some relevant studies could have been missed. It is unclear why the review was restricted to data published in manuscript or abstract form. The inclusion of other sources of data (e.g. unpublished studies) may have helped reduce the possibility of publication bias. No attempt to assess publication bias was described. A validity assessment of the primary studies would have been useful. The methods used to determine whether the papers were suitable for inclusion were not described. More details would have been useful; for example, it was unclear how many reviewers were involved in this process, or whether they were blinded to the source of the papers.

This meta-analysis is consistent with previous reviews and, despite some limitations, it adds to the evidence base on the efficacy of beta-blockers for the treatment of heart failure.

**Implications of the review for practice and research**
Practice: The authors state that the effects of beta-blockers in reducing mortality and the need for hospital admission due to heart failure are dramatic. These benefits should be implemented as a priority, since this treatment is inexpensive and heart failure carries a high risk of death and disability.
Research: The authors state that further information on the effect of beta-blockers in elderly patients and women would be useful.

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