Clinical effects of beta-adrenergic blockade in chronic heart failure: a meta-analysis of double-blind, placebo-controlled, randomized trials

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Authors' objectives
To evaluate the overall results of beta-blockers in heart failure.

Searching
MEDLINE was searched extensively (search dates unclear). In addition, the references in the retrieved articles and conference abstracts were examined. Experts, investigators and sponsors in the pharmaceutical industry were also contacted.

Study selection
Study designs of evaluations included in the review
Double-blind, randomised, placebo-controlled, parallel-group trials were included.

Specific interventions included in the review
Beta-blockers. The beta1-selective drugs were metoprolol, bisoprolol and nebivolol; the non-selective drugs were carvedilol and bucindolol. Xamoterol was excluded as this compound has considerable agonist activity.

Participants included in the review
Patients with chronic heart failure were included. Patients with a recent myocardial infarction were excluded.

Outcomes assessed in the review
The outcomes assessed were:
- all-cause mortality;
- morbidity, defined as hospitalisation for worsening heart failure;
- the combined risk of all-cause mortality and hospitalisation for worsening heart failure (combined morbidity and mortality);
- changes in functional status, as assessed by the New York Heart Association (NYHA) classification; and
- changes in the left ventricular ejection fraction.

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
The quality of the studies was not formally assessed.

Data extraction
The authors do not state how the data were extracted for the review, or how many of the authors performed the data extraction. The results of most studies were obtained through direct communication with the investigators or sponsors.
Methods of synthesis

How were the studies combined?
The combined effect was estimated by weighting the result of each individual trial by the reciprocal of its variance. Fixed-effect or random-effects models were used, according to whether the test of heterogeneity was significant.

How were differences between studies investigated?
A chi-squared test was used to assess heterogeneity. Subgroup and sensitivity analyses were conducted. The robustness of the results of the meta-analysis was assessed by estimating how many trials with a neutral effect were required to produce a non-significant result.

Results of the review
Eighteen randomised controlled trials (1,305 patients in the placebo group and 1,718 patients treated with beta-blockers) were included.

All-cause mortality was lower in the beta-blocker group than in the placebo group: 7.5% versus 11.9 (pooled odds ratio 0.68, 95% confidence interval: 0.53, 0.88). However, this effect was moderately robust and varied according to the type of beta-blocker tested. The reduction of mortality risk was greater for nonselective beta-blockers than for beta1-selective agents. Beta-blockade increased the ejection fraction by 29% and reduced the combined risk of death or hospitalisation for heart failure by 37% (p<0.001). Both effects remained significant even if more than 90% of the trials were eliminated from the analysis, or if a large number of trials with a neutral result were added to the analysis. The effect of beta-blockade on NYHA functional class was of borderline significance (p=0.04) and disappeared with the addition or removal of only one moderate-size study.

Authors' conclusions
There was persuasive evidence supporting the idea that beta-blockade has a favourable effect on ejection fraction and the combined risk of death and hospitalisation for heart failure. In contrast, the effect of these drugs on other endpoints requires additional study.

CRD commentary
The inclusion criteria were clear and the details of the included studies were presented. Although study quality was not formally assessed, the validity of the included studies seemed high because only double-blind, placebo-controlled randomised studies were included. The description of the literature search lacked detail. The authors considered the potential problem of publication bias, and assessed the robustness of the meta-analysis based on the number of trials with neutral results that were required to overturn a significant result. The review's conclusions were appropriate in respect of the research evidence presented. The authors mentioned that several trials assessing the effect of beta-blockers on prolonging the life of patients with heart failure, were ongoing.

Implications of the review for practice and research
Further insights on the issue will be provided by the results of ongoing trials. However, given the persuasive evidence for a favourable effect of beta-blockade on the combined risk of morbidity and mortality, physicians would appear to have sufficient evidence to support the use of beta-blockers in heart failure, even before the completion of these large-scale studies.

Bibliographic details

PubMedID
9743509
Original Paper URL
http://circ.ahajournals.org/

Other publications of related interest

Indexing Status
Subject indexing assigned by NLM

MeSH
Adrenergic beta-Antagonists /therapeutic use; Chronic Disease; Double-Blind Method; Heart Failure /drug therapy /mortality; Humans; Randomized Controlled Trials as Topic

AccessionNumber
11998001637

Date bibliographic record published
30/11/1999

Date abstract record published
30/11/1999

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.