**Beta-blocker benefit according to severity of heart failure**

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**CRD summary**

This review concluded that the degree of benefit from treatment with beta-blockers is similar regardless of the severity of heart failure (except for severe end-stage heart failure). The conclusions appear to follow from the evidence presented, but it is difficult to comment on the reliability of the conclusions because of lack of detail about the review methods and included studies.

**Authors' objectives**

To examine the relationship between the amplitude of benefit of beta-blockers and severity of disease in chronic heart failure.

**Searching**

MEDLINE was searched, but the dates of the searches and the search terms used were not provided. Trials from previous meta-analyses of beta-blockers for heart failure were also included. The authors of identified trials were contacted for further information. Some additional unpublished data were obtained from some trial investigators.

**Study selection**

**Study designs of evaluations included in the review**

Randomised controlled trials (RCTs) of parallel-group design only were eligible for inclusion.

**Specific interventions included in the review**

Studies comparing oral beta-blocker treatment with placebo were eligible for inclusion. The beta-blockers used in the included studies were metoprolol, carvedilol, bucindolol and bisoprolol.

**Participants included in the review**

Participants with heart failure were eligible for inclusion. No other inclusion or exclusion criteria were stated. No other details of the participants in the included studies were given.

**Outcomes assessed in the review**

The outcomes of interest were mortality from all causes and hospitalisation for worsening heart failure. Studies were only included if there were one or more deaths in each arm of the trial. The follow-up times were not stated. The outcomes were presented according to the class of drug (i.e. all beta-blockers) and by individual drugs, as well as according to severity of heart failure.

**How were decisions on the relevance of primary studies made?**

The authors did not state how the papers were selected for the review, or how many reviewers performed the selection.

**Assessment of study quality**

The authors did not state that they assessed validity.

**Data extraction**

The authors did not state how the data were extracted for the review, or how many reviewers performed the data extraction. Inversed variance weighted risk ratios (RRs) were calculated for the outcomes in the individual studies. The authors said that they used individual patient data (IPD) from one study for a separate analysis, but gave no details about how these data were collected. An overall prognostic score (based on a range of variables) was used to divide the participants into three groups according to severity of disease.
Methods of synthesis

How were the studies combined?
The studies were combined using a fixed-effect model. Pooled RRs were calculated, along with 95% confidence intervals (CIs). IPD from one study were also analysed separately according to severity of disease.

How were differences between studies investigated?
Statistical heterogeneity was explored using the chi-squared test, with the P-value for significance set at 0.05. To explore the source of heterogeneity, one or more studies appear to have been excluded from the analyses. Pre-specified subgroup analyses were carried out according to the pharmacological profile of the beta-blocker, and the severity of heart failure in terms of New York Heart Association (NYHA) classification and left ventricular ejection fraction (LVEF). Heterogeneity of the RR among subgroups was assessed using the Mantel-Haenszel test.

For the IPD, differences between the RRs for the different levels of severity were assessed using the Mantel-Haenszel test.

Results of the review
Sixteen RCTs (14,857 participants) were included. Seven studies tested the oral beta-blocker carvedilol (3,847 participants), 5 studies tested metoprolol (4,875 participants), and 2 studies each tested bisoprolol (3,288 participants) and bucindolol (2,847 participants).

Overall, compared with placebo, there was a 22% reduction in all-cause mortality (95% CI: 16, 28, P<0.001) with beta-blocker treatment and a 24% (95% CI: 20, 29, P<0.001) reduction in hospitalisations for heart failure. Significant heterogeneity was observed for all-cause mortality (P=0.035). This heterogeneity disappeared when one trial of bucindolol was excluded. This study and a further study of the same drug were then omitted from the subgroup analyses.

The benefit of beta-blocker treatment on mortality and hospitalisations for heart failure was similar for the drugs metoprolol, bisoprolol and carvedilol. Mortality was reduced by 31% (95% CI: 17, 42) with metoprolol, 29% (95% CI: 17, 40) with bisoprolol and 37% (95% CI: 24, 47) with carvedilol. Hospitalisations for heart failure were reduced by 28% (95% CI: 19, 36) with metoprolol, 32% (95% CI: 21, 42) with bisoprolol and 29% (95% CI: 18, 39) with carvedilol.

The effectiveness of beta-blockers in reducing mortality and hospitalisations for heart failure was similar for different grades of severity of heart failure, according to both the NYHA (4 studies) and LVEF (4 studies). Beta-blockers reduced mortality by 32% (95% CI: 21, 41) in NYHA class III disease, by 32% (95% CI: 19, 43) in NYHA class IV disease, by 34% (95% CI: 20, 45) in those with LVEF of 25% or greater, and by 29% (95% CI: 19, 38) in those with LVEF less than 25%.

When examining the IPD from one trial, similar results were found in that there were no significant differences in the number of deaths or hospitalisations between the different levels of heart failure severity (further details were provided in the paper).

Authors’ conclusions
The amplitude of benefit of the beta-blockers carvedilol, metoprolol and bisoprolol on mortality was similar, regardless of the different severities of heart failure.

CRD commentary
This review addressed a clear question. The search was limited to one database and no search terms were given. It is possible that studies were missed. There was little detail of the methods used, in particular how the study selection, data extraction and validity assessment processes were conducted, and by whom. With the exception of the type of beta-blocker used, no details of the individual studies (e.g. length of follow-up or the participants’ characteristics) were
given. Appropriate measures of effect were used, and the authors assessed and found the source of statistical heterogeneity.

The authors' conclusions appear to follow from the results presented, but it is difficult to verify the robustness of the results in this review given the lack of detail concerning the methodology and individual studies. The results were, however, confirmed in the analysis of IPD; this adds weight to the evidence presented, although again, few methodological details were reported to verify this. In terms of the generalisability of their findings, the authors commented that the results cannot be extrapolated to patients with more severe heart failure, such as very severe end stage NYHA class IV patients.

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

Research: The authors did not state any implications for further research. However, as the authors stated that there is no clear explanation of the lesser effect of bucindolol on mortality, this highlights an area for further research.

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