Benefits of beta blockers in patients with heart failure and reduced ejection fraction: network meta-analysis


CRD summary
This well-conducted review concluded that beta-blockers (as a class) reduced mortality in patients with heart failure, but no obvious differences were found between individual beta-blockers; further head-to-head comparisons were needed. The authors’ conclusions appear to reflect the evidence presented and are likely to be reliable.

Authors’ objectives
To assess the comparative effectiveness of beta-blockers for patients with heart failure and reduced ejection fraction (lower volume of blood pumped from the heart).

Searching
PubMed, EMBASE, CINAHL, Cochrane Central Register of Controlled Trials, and Web of Science were searched for publications in English up to 2011; search terms were reported. References of included studies, recent meta-analyses, and conference abstracts (American College of Cardiology, American Heart Association, European Society of Cardiology) were handsearched.

Study selection
Randomised controlled trials (RCTs) that compared beta-blockers with another beta-blocker or comparator in patients with heart failure and reduced ejection fraction were eligible for inclusion. Trials had to report mortality data. Trials with less than 100 patients or a follow-up of less than three months were excluded.

The mean age of included patients ranged from 49 to 76 years; the proportion of men ranged from 54 to 90%. The proportion of patients with ischaemic heart failure ranged from 29% to 89% (where reported). Baseline left ventricular ejection fraction ranged from 17% to 36% (where reported). Patients received atenolol, bisoprolol, bucindolol, carvedilol, metoprolol, nebivolol, or placebo/standard treatment. Most individual beta-blockers were compared with placebo; two trials compared beta-blockers with an angiotensin-converting enzyme inhibitor; one trial directly compared two beta-blockers.

Two reviewers independently selected studies for inclusion with any differences resolved through discussion.

Assessment of study quality
The Cochrane risk-of-bias tool was used to assess trial quality. This included items such as blinding, allocation concealment, attrition, and selective reporting.

Two reviewers independently assessed trial quality with any differences resolved through discussion.

Data extraction
Outcomes (all-cause mortality, cardiovascular death, sudden death, drug discontinuation, and left ventricular ejection fraction from baseline) were extracted from each trial to calculate odds ratios (ORs) for dichotomous data and mean differences (MDs) for continuous data, with associated 95% confidence intervals (CIs). For trials with follow-up longer than 12 months, log hazards ratios (HRs) with 95% confidence intervals were calculated based on the number of events and mean duration of follow-up.

Two reviewers independently extracted data with any differences resolved through discussion.

Methods of synthesis
Data were pooled using conventional pair-wise random-effects meta-analysis that compared beta-blockers with comparators. Heterogeneity was assessed using $I^2$ and the Q statistic.

Bayesian network meta-analyses were conducted using a random-effects binomial model to examine the comparative
effectiveness of the individual beta-blockers. Model fit was assessed using deviance and deviance information criterion statistics.

Meta-regression analyses examined the impact of dosage (target and mean achieved dose) on treatment effect. Additional sensitivity analyses included using a random-effects Poisson model (which estimated hazard ratios).

Publication bias was assessed by visual inspection of funnel plots and using Harbord's modification of Egger's test. In addition, the trim-and-fill method was used to adjust for potential publication bias.

**Results of the review**

Twenty-one trials were included in the review (23,122 patients). Median follow-up was 12 months. All trials had a low risk of bias.

The conventional pair-wise meta-analysis that compared beta-blockers with all comparators showed reduced odds of mortality (OR 0.71, 95% CI 0.64 to 0.80; I²=33%; 21 studies). Similar evidence of benefit was found when examining only odds ratios from trials using shorter term follow-up and hazard ratios from trials using longer term follow-up. Bayesian network meta-analyses produced similar effect estimates.

Beta-blockers were associated with reducing the odds of cardiovascular death, reducing the odds of sudden death, and a change in left ventricular ejection fraction in conventional pair-wise and Bayesian network meta-analyses. Conventional pair-wise meta-analyses suggested that drug discontinuation was less likely for beta-blockers, but this was not confirmed in the Bayesian analyses.

In the Bayesian network meta-analyses, there was no evidence to indicate a substantial difference between individual beta-blockers for mortality or any other outcome. Exclusion of active controls did not change the conclusions of the analyses.

There was no evidence of substantial heterogeneity in most analyses. No evidence of publication bias was identified for any outcomes. The meta-regression suggested that dosage of beta-blockers did not impact on effect estimates.

Further information from additional analyses were reported in the paper.

**Authors' conclusions**

Beta-blockers provided mortality benefits in patients with heart failure and reduced ejection fraction. However, the benefits may be a class effect rather than the superiority of any single agent. Further head-to-head trials were needed to determine if there were differences in effectiveness between individual beta-blockers.

**CRD commentary**

The review question and inclusion criteria were clear. The search included good coverage of databases, but trial studies published in other languages than English may have been missed. Attempts were made to identify unpublished trials. No evidence of publication bias or small-study effect was detected. Appropriate methods were used to minimise error and bias in review processes.

Pooling data seemed appropriate; there did not appear to be substantial heterogeneity. It was questionable why a head-to-head trial of beta-blockers was included in the conventional pair-wise meta-analyses of beta-blockers versus comparators. However, limiting to placebo-controlled trials did not appear to affect the conclusions. The Bayesian network meta-analyses appeared appropriate, although further information on goodness-of-fit statistics and convergence could have been provided.

The review was well conducted. The authors' conclusions appear to reflect the evidence presented and are likely to be reliable.

**Implications of the review for practice and research**

**Practice:** The authors stated that beta-blockers should be used for all stable patients with current or previous symptoms of heart failure and reduced left ventricular ejection fraction (unless contraindicated).
Research: The authors stated that further head-to-head trials of beta-blockers were needed to examine whether they differed in effectiveness. Further research should examine the effect of geographical location on effectiveness of beta-blockers. They suggested that individual patient data meta-analyses may reduce the impact of inconsistent reporting of outcomes across trials.

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