Adverse effects of beta-blocker therapy for patients with heart failure: a quantitative overview of randomized trials


CRD summary
This review compared adverse events in beta-blocker- and placebo-treated patients. The authors concluded that the absolute increase in risk of adverse events associated with beta-blockers is small. The evidence presented supports the authors' conclusions, but the conclusions should be treated cautiously because of methodological and reporting limitations in the review.

Authors' objectives
To review randomised trials of beta-blockers in patients with heart failure to quantify the risks of adverse events.

Searching
MEDLINE was searched (from 1966 to 2002) using the terms 'adrenergic beta-antagonist' 'heart failure' and 'trial'. Only English language papers were sought. The reference lists of previous trials and reviews were checked. In addition, the US Food and Drug Administration website and Physicians' Desk Reference (PDR.net) were checked for reports of adverse events in trials of beta-blockers.

Study selection
Study designs of evaluations included in the review
Only randomised controlled trials (RCTs), with at least 100 people in each treatment group, were sought.

Specific interventions included in the review
The inclusion criteria specified beta-blockers compared with placebo. The drugs used in the included studies were metoprolol, bisoprolol, carvedilol and bucindolol. The mean duration of treatment ranged from 6 to 24 months.

Participants included in the review
Studies of people with heart failure with left ventricular dysfunction were sought. In the included studies, the mean age of the patients ranged from 49 to 63 years. The majority of the participants were men, ranging from 72 to 83% in the individual studies.

Outcomes assessed in the review
The main outcomes of interest were adverse events: heart failure deterioration (defined as hospitalisation, 'worsening' or causing withdrawal of therapy), hypotension, dizziness, bradycardia, fatigue and withdrawal of treatment, both overall and for individual adverse reactions. Definitions for these terms were taken as those in the individual studies. For bradycardia, this varied between heart rate less than 40 beats per minute, bradycardia causing hospital admission and 'symptomatic bradycardia'. Only studies with at least 6 months' follow-up were sought. Overall mortality was also reported.

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

Database of Abstracts of Reviews of Effects (DARE)
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The data were extracted by one reviewer and checked by two others. The extracted data included information on the frequency of adverse effects and associated withdrawals from treatment during the trials. Rates of withdrawal due to adverse events during the initial run-in period were also extracted. The relative risk (RR) and annual absolute risk increases per 1,000 people, together with 95% confidence intervals (CIs) and numbers-needed-to-treat (NNT), were calculated for outcomes in the individual studies.

**Methods of synthesis**

**How were the studies combined?**

The data were combined using fixed-effect and random-effects models. The results of the random-effects model were reported. The combined RR was estimated together with 95% CIs. To take into account differing follow-up periods, pooled incidence risk differences and NNT per year were also calculated to estimate the absolute risk.

**How were differences between studies investigated?**

Heterogeneity was examined using the chi-squared test. Subgroup analyses were performed to test whether studies with and without run-in periods had different results for withdrawals and mortality (i.e. in some studies all participants were treated with placebo or all were treated with a beta-blocker for a period before randomisation).

**Results of the review**

Nine RCTs (14,594 participants) were included.

When counting all people in all studies, 16% taking beta-blockers and 18% taking placebo stopped taking treatment before the end of the study. Beta-blockers were associated with a statistically significant reduction in all-cause withdrawal from study medication: the RR was 0.89 (95% CI: 0.81, 0.98) and the annual absolute risk reduction for withdrawal was 14 per 1,000 people (95% CI: -2, 29).

Beta-blocker therapy was associated with a significant reduction in all-cause mortality: the RR was 0.73 (95% CI: 0.62, 0.85) and the NNT for one year to prevent one death was 29.

Reductions in withdrawals and mortality occurred regardless of whether there was a run-in period before randomisation (P=0.74 and P=0.44, respectively, for withdrawal and mortality).

Beta-blocker therapy was associated with a significant reduction in hospitalisations for heart failure (8 studies; RR 0.72, 95% CI: 0.66, 0.83). The NNT to prevent one hospitalisation for heart failure was 25.

Beta-blockers were associated with a significant reduction in worsening of heart failure (4 studies; RR 0.83, 95% CI: 0.71, 0.98), and of withdrawal of therapy because of worsening heart failure (5 studies; RR 0.72, 95% CI: 0.54, 0.96).

Beta-blockers were associated with an increase in hypotension (7 studies; RR 1.41, 95% CI: 0.96, 2.06), and a significant increase in dizziness (4 studies; RR 1.37, 95% CI: 1.09, 1.71) and in bradycardia (7 studies; RR 3.62, 95% CI: 2.48, 5.28).

There was no clear association reported between beta-blockers and fatigue (3 studies; RR 1.04, 95% CI: 0.97, 1.11).

The risk of adverse effects associated with beta-blocker therapy did not differ significantly between those studies that did or did not have a pre-randomisation run-in treatment period, or in the study that included people with severe heart failure compared with the other studies.

**Authors' conclusions**

Beta-blocker therapy is generally well tolerated and associated with fewer overall withdrawals and less heart failure deterioration than placebo. Although beta-blocker treatment is associated with hypotension, dizziness and bradycardia, the absolute increases in risk were small and, overall, fewer people were withdrawn from beta-blocker therapy than from placebo.
CRD commentary
This review had clear aims with well-described inclusion criteria. The database search was limited to MEDLINE and to English language papers. There was no mention of attempts to find unpublished studies or those reported in other languages. It is possible that studies were missed, thus leading to bias in the results. The study selection process was not described and neither was the quality assessment. It is possible that selection bias at these stages could affect the results of a review. There was limited detail about the participants in the included studies. However, the authors did comment that it may not be appropriate to generalise from these studies since the study populations were generally healthier, younger and studied fewer women or elderly people, compared with the general population of people with heart failure. The authors' conclusions are supported by the results presented.

Implications of the review for practice and research
Practice: The authors stated that this review should alleviate concerns of physicians who are reluctant to prescribe beta-blockers to people with heart failure.

Research: The authors did not state any implications for further research.

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**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.