Effect of beta-blocker therapy on functional status in patients with heart failure: a meta-analysis

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CRD summary
This review examined the effectiveness of beta-blockers for improving New York Heart Association classification and exercise tolerance time in patients with chronic heart failure. The authors concluded that beta-blockers improved exercise tolerance time and dyspnoea, but not other related outcomes. The conclusions follow from the data presented and may be reliable.

Authors' objectives
To evaluate the effect of beta-blockers on New York Heart Association (NYHA) classification and exercise tolerance in patients with chronic heart failure.

Searching
MEDLINE, EMBASE, BIOSIS Previews, the Cochrane Library (Issue 3, 2004) and CINAHL were searched; the search terms were reported. The authors also stated that they searched Ovid, which is a database platform. With the exception of the Cochrane Library the search dates were not reported, although the authors stated that they focused on trials published after 1989. The citations of key articles from the Science Citation Index were screened, as were conference proceedings and meetings, while previous reviews and meta-analyses were handsearched and their references checked. Relevant pharmaceutical companies were also contacted.

Study selection
Randomised controlled trials (RCTs) with a parallel design that compared beta-blockers (selective and non-selective) with a placebo control added to background angiotensin-converting enzyme inhibitor treatment were eligible for inclusion. Studies that used additional physical training or drug therapy, or investigated drugs other than beta-blocker therapy, were excluded from the review. The beta-blockers used in the included studies were bucindolol, metoprolol, carvedilol, atenolol, bisoprolol, celebrolol and nebivolol; a range of doses were used. Trials that enrolled patients with an established diagnosis of symptomatic chronic heart failure were eligible for inclusion. Patients were required to have documented impairment of systolic function with a left ventricular ejection fraction of 45% or less, and to have been receiving treatment for a minimum of 12 weeks. Studies of patients with recent acute myocardial infarction, after heart transplantation, with predominant diastolic dysfunction, or with atrial fibrillation were excluded from the review. The great majority (98%) of patients in the included studies were NYHA classes II to IV. Patients with both ischaemic and non-ischaemic heart failure were included. The mean ages of the patients ranged from 48 to 64 years, while 79% of all patients were male. Eligible trials were required to report NYHA class and exercise tolerance, including peak oxygen uptake (PVO₂), exercise tolerance time and 6-minute walk distance. Mortality was also reported. The follow-up time ranged from 3 to 44 months.

Three reviewers assessed studies for inclusion in the review.

Assessment of study quality
Three authors assessed validity using the Jadad scale, which uses the criteria of randomisation, allocation concealment, blinding, and the treatment of withdrawals and drop-outs.

Data extraction
Where studies with multiple intervention arms used different doses of the same beta-blocker, only data on the highest dose were included in the review. Where two different beta-blockers were employed, the placebo arm was double-counted in the analysis. The numbers of patients who improved and did not improve (remained unchanged or deteriorated) relative to baseline were calculated for each outcome, as were the numbers who deteriorated or did not deteriorate (remained unchanged or improved). Where studies did not report the numbers of patients changing NYHA class, the numbers moving to class I or class IV were, respectively, considered to have improved or deteriorated.
insufficient data were available for baseline comparisons, differences between groups at the final assessment without adjustment for baseline were used in the meta-analysis. Standard errors were converted into standard deviations.

Three reviewers performed the data extraction.

Methods of synthesis
The study means and standard deviations were combined in meta-analyses for individual outcomes. Weighted mean differences (WMDs) were calculated for continuous data. Random-effects (DerSimonian and Laird) or fixed-effect (Peto) models were used, where deemed appropriate on the basis of heterogeneity. Statistical heterogeneity between the studies was assessed using the $\chi^2$ test. Where indicated, sensitivity analyses to examine the impact of a particular study were undertaken. Subgroup analyses based on relevant clinical factors, such as tests used and type of beta-blocker, were also undertaken in some instances. Publication bias was assessed using Begg's and Egger's tests.

Results of the review
Twenty-eight RCTs ($n=7,637$) were included in the review.

The studies were generally considered to be of a good quality, with a mean Jadad score of 3 out of a possible 5. All but two RCTs were double-blinded, and thirteen reported using an intention-to-treat or appropriate alternative analysis.

The pooled odds ratio (OR) for patients who improved in NYHA classification favoured beta-blockers (random-effects OR 1.5, 95% confidence interval, CI: 1.2, 1.9, $p=0.001$); there was statistically significant heterogeneity ($p=0.003$). The pooled OR for patients who deteriorated also favoured beta-blockers (fixed-effect OR 0.69, 95% CI: 0.54, 0.87, $p=0.002$); no statistically significant heterogeneity was detected ($p=0.145$). The total treatment effect also favoured beta-blockers (random-effects OR 1.80, 95% CI: 1.33, 2.43, $p<0.0001$), with some evidence of statistical heterogeneity ($p=0.081$).

Exercise tolerance time showed a significant effect of beta-blockers (random-effects WMD 33.24, 95% CI: 0.77, 65.71); the statistically significant heterogeneity appeared to stem from a single study ($p=0.020$). The results of subgroup analyses based on the maximal exercise test used were also reported. There were no significant differences between the groups for the outcomes of PVO$_2$ or 6-minute walk test.

The pooled OR for mortality favoured beta-blockers (fixed-effect OR 0.69, 95% CI: 0.59, 0.82, $p<0.0001$). No statistically significant heterogeneity was detected ($p=0.822$).

There was no evidence of publication bias (Begg's test, $p=0.138$; Egger's test, $p=0.469$).

Authors' conclusions
Chronic use of a beta-blocker in conjunction with an angiotensin-converting enzyme inhibitor improves dyspnoea and prolongs exercise tolerance time, but has no significant effect on the 6-minute walk distance or PVO$_2$.

CRD commentary
The review question and the inclusion criteria were extremely clear. The authors searched a number of relevant databases and other sources. They did not report the use of language restrictions and no evidence of publication bias was found, which reduces the probability that relevant studies were not included. The authors might have used measures designed to reduce error and bias in the study selection, validity assessment and data extraction processes. The validity assessment employed appropriate criteria. The decision to employ meta-analysis appears appropriate. While the double-counting of a placebo group in one multi-armed trial was inappropriate, this is unlikely to have unduly impacted on the results of the analysis. However, the use of separate analyses for patients who improved or did not improve was unhelpful. The authors' conclusions follow from the evidence presented and may be reliable.

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

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