Meta-analysis: beta-blocker dose, heart rate reduction, and death in patients with heart failure

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CRD summary
This review concluded that the magnitude of heart rate reduction was statistically significantly associated with the survival benefit of beta-blockers in heart failure, but the dose of beta-blocker was not. The majority of the review process and the synthesis were well conducted. Despite the absence of a validity assessment, the conclusions appear likely to be reliable.

Authors' objectives
To determine whether the survival benefits of beta-blockers in patients with heart failure are associated with the magnitude of heart rate reduction or the dose of beta-blockers.

Searching
The following databases were searched without language restriction from 1966 to 2008: MEDLINE, EMBASE, CINAHL, SIGLE, Web of Science and the Cochrane Central Register of Controlled Trials. Search terms were reported. References of identified studies, recent meta-analyses and heart failure guidelines were also checked. Only studies published in full were eligible for inclusion.

Study selection
Placebo-controlled randomised controlled trials (RCTs) of beta-blockers in patients with heart failure which reported all-cause mortality were eligible for inclusion. Studies were required to use beta-blockers for at least one month and to enrol at least 50 patients.

Included studies assessed metoprolol, carvedilol, bisoprolol, bucindolol, nebivolol and atenolol. Titration schedules varied with the mean daily dose of beta-blocker ranging from 3.6 mg to 192 mg. Treatment durations ranged from three to 24 months. Mean ages of patients ranged from 49 to 76 years and the proportion of males ranged from 58% to 96%. The great majority of included studies only included patients with systolic dysfunction while ischaemic heart disease was present in between 28% and 90% of participants in most trials. The great majority of trials used a placebo in addition to standard anti-heart failure therapy except beta-blockers for their control groups; in the others the control group patients just received an angiotensin-converting enzyme inhibitor but no beta-blocker. The great majority of patients (median 93%) received an angiotensin-converting enzyme inhibitor while most also received digoxin (median 75%).

Two reviewers independently selected the studies for inclusion, with disagreements resolved through discussion.

Assessment of study quality
The authors did not state that they assessed validity.

Data extraction
Data were extracted on an intention-to-treat basis. The magnitude of heart rate reduction was calculated for each trial by comparing heart rate at the end of the dose titration period with baseline values and subtracting placebo group change from intervention group change. Risk ratios (RR) with 95% confidence intervals (CI) were calculated.

Two reviewers independently performed the data extraction and disagreements were resolved through discussion.

Methods of synthesis
Pooled RRs with 95% CIs were calculated using a DerSimonian and Laird random-effects meta-analysis. Statistical heterogeneity between studies was assessed using the Q statistic and the $I^2$ statistic. Meta-regression analyses were used.
to explore the following potential explanations for statistical heterogeneity: sex, age, ischaemic cause, left ventricular ejection fraction (LVEF), New York Heart Association (NYHA) class, atrial fibrillation, use of digoxin, baseline heart rate, magnitude of heart rate reduction with treatment, dose of beta-blocker, baseline systolic blood pressure, magnitude of reduction in systolic blood pressure with treatment, and specific beta-blocking agent. Continuous variables were explored both linearly and categorically using tertiles. The Wald test was used to assess significance. A sensitivity analysis was conducted using a Monte Carlo simulation to explore the effect of sampling variability around estimates of heart rate reduction in each trial. A number of subgroup analyses were also conducted.

**Results of the review**

Twenty-three RCTs (n=19,209) were included in the review, reporting a total of 2,720 deaths. There was some discrepancy in patient numbers between the tables and the text. Sample sizes ranged from 50 to 3,047.

There was statistically significantly lower mortality in the groups treated with beta-blockers than in the control groups (relative risk 0.76, 95% CI: 0.68, 0.84) with evidence of moderate heterogeneity ($I^2 = 30\%$, $p = 0.09$).

The magnitude of the survival benefit was significantly affected by the choice of beta-blocker. Metoprolol (relative risk 0.70, 95% CI: 0.58, 0.83), carvedilol (relative risk 0.66, 95% CI: 0.51, 0.87) and bisoprolol (relative risk 0.71, 95% CI: 0.61, 0.83) showed statistically significantly reduced death rates compared to placebo, but the comparisons were statistically non-significant for bucindolol, nebivolol and atenolol. The survival benefit for bucindolol was significantly lower (36% lower survival, 95% CI: 9%, 69%) than that for carvedilol. Results for other comparisons were also reported.

There was a statistically significant relationship between heart rate reduction and beta-blocker survival benefit ($p = 0.01$), with trials in the tertile with the greatest reductions in heart rate (median 15 beats/minute) showing greater survival benefits with beta-blockade (relative risk 0.64, 95% CI: 0.48, 0.86) than those in the tertile with the least reductions in heart rate (median eight beats/minute) (relative risk 0.91, 95% CI: 0.83, 0.99). Inclusion of heart rate reduction as a variable reduced heterogeneity to an $I^2$ value of 0%. Meta-regression showed that for every five beats/minute reduction in heart rate with beta-blocker treatment the relative risk for death was reduced by 18% (95% CI: 6%, 29%). A Monte Carlo sensitivity analysis produced an even greater estimate of the impact of heart rate reduction. No evidence of confounding by other variables was found in the meta-regression.

There was no statistically significant effect of beta-blocker dosing on mortality. The relative risk for death in the 15 trials where patients received high doses of beta-blockers was 0.74 (95% CI: 0.64, 0.86) compared with 0.78 (95% CI: 0.63, 0.96) in those where they received low doses of beta-blockers.

**Authors’ conclusions**

The magnitude of heart rate reduction was statistically significantly associated with the survival benefit of beta-blockers in heart failure, but the dose of beta-blocker was not.

**CRD commentary**

The review question was clear and was supported by specific inclusion criteria. The authors searched several relevant databases and included attempts to locate unpublished studies in their strategy. This, together with the lack of language restrictions reduced the chances of relevant studies being omitted and of language or publication bias. The authors used methods designed to reduce bias and error in the selection of studies and the extraction of data. No assessment of study validity was reported, which made it difficult to assess the reliability of the evidence on which the conclusions were based. The decision to employ meta-analysis and meta-regression appeared appropriate for the synthesis of data and the exploration of heterogeneity. The authors’ conclusions accurately reflected the results of this review, which included a very large number of patients and reported a substantial number of deaths. Despite the absence of a validity assessment, the conclusions appear likely to be reliable.

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

Practice: The authors did not state any implications for practice.

Research: The authors stated that the pooling of individual patient data by investigators of beta-blocker therapy in heart
failure patients is to be encouraged in order to further investigate whether up-titration of beta-blocker dose to trial doses is beneficial if substantial heart rate reduction has already been achieved with a lower dose, and whether increases above trial doses is beneficial if heart rate reduction is minimal. They also stated that research to assess the modulating effect of cardiac resynchronisation therapy or implantable cardio-defibrillators in patients receiving beta-blocker is warranted.

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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.