A systematic review of selective and non-selective beta blockers for prevention of vascular events in patients with acute coronary syndrome or heart failure

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CRD summary
The review evaluated the influence of $\beta_2$-adrenergic receptor suppression in addition to $\beta_1$-receptor blockade in preventing vascular events in patients with acute coronary syndrome and heart failure. It concluded that additional $\beta_2$-receptor blockade was found to be more effective than $\beta_1$-receptor blockade alone. Despite variability among studies, the authors' conclusions reflected the evidence presented and are likely to be reliable.

Authors' objectives
To evaluate the influence of $\beta_2$-receptor suppression in addition to selective $\beta_1$-receptor blockade on the occurrence of vascular events and on all-cause mortality in patients with acute coronary syndrome or heart failure.

Searching
Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE and EMBASE were searched for relevant trials from 1981 to June 2009. Search terms were reported. No language restrictions were applied. Reference lists of retrieved papers were searched for additional trials.

Study selection
Randomised controlled (placebo or active) trials (RCTs) of $\beta$-adrenergic blockers ($\beta_1$ blockers and $\beta_1+2$ blockers) for secondary prevention of vascular events in patients with acute coronary syndrome or heart failure were eligible for inclusion. Outcomes of interest were all-cause mortality and vascular events (defined as fatal and non-fatal strokes and myocardial infarctions, fatal pulmonary embolisms and other venous thromboembolic events). To be eligible, only trials with treatments that lasted at least three months were considered. The $\beta$-blockers studied varied and included $\beta_1$ blockers (atenolol, betaxolol, bisoprolol, metoprolol and nebivolol) and $\beta_1+2$ blockers (bucindolol, carvedilol, propranolol and timolol). Follow-up ranged from three to 58 months, $\beta$-blocker doses and regimen varied across studies. Where reported, average age of patients ranged from 49 to 81 years. Most patients were male. Most studies were in patients with left ventricular ejection fraction (LVEF) less than 35% to 40% and New York Heart Association (NYHA) classification II to IV. Some patients received concomitant medication.

Two authors independently performed selection. Any disagreements were resolved by consensus and if necessary by arbitration by a third reviewer. Agreement between reviewers was tested by the Kappa (K) statistic and was found to be excellent (K=0.98)

Assessment of study quality
Validity was assessed using the Jadad scale. Domains assessed were adequacy of blinding and concealment, treatment allocation sequence and completeness of follow-up.

The authors did not state how validity assessment was performed

Data extraction
Data were extracted to calculate risk ratios (RR) and corresponding 95% confidence intervals (CI) for the outcomes of all-cause mortality and vascular events.

Two authors independently extracted data.

Methods of synthesis
Data were combined using the random-effects model of DerSimonian and Laird to obtain pooled risk ratios and
corresponding 95% CIs. Comparisons were made directly between β₁ and β₁+2 blockers (where available) or indirectly for comparisons of β₁ blockers versus placebo and β₁+2 blockers versus placebo.

Results were grouped according to diagnosis (acute coronary syndrome or heart failure) and outcome (all-cause mortality or vascular events). Statistical heterogeneity was assessed using X² (p<0.05) and I² tests. Influence of publication bias was assessed visually using a funnel plot.

A series of sensitivity analyses were performed: by including only high-quality trials (double-blind and loss to follow-up <20%) and analysing results by excluding one trial at a time; and analysing the effect of different β blockers. The influence of study follow-up was assessed by adjusting results for number of patient years.

Results of the review
A total of 33 RCTs was included (n=34,622, range 50 to 3,991 patients). Ten studies were rated high quality on the Jadad scale.

Acute coronary syndrome: β₁+2 blockers showed a statistically significant reduction over placebo with respect to all-cause mortality (RR 0.73, 95% CI 0.64 to 0.82; six studies) and vascular events (RR 0.71, 95% CI 0.59 to 0.84; six studies).

There were no statistically significant differences between β₁ blockers and placebo in all-cause mortality (five studies) and vascular events (three studies). There was no difference in all-cause mortality rates in direct comparisons between β₁ and β₁+2 blockers (one study).

Heart failure: β₁ blockers in comparison with placebo showed significant reduction in mortality (RR 0.76, 95% CI 0.68 to 0.87; seven studies) but not in vascular events (RR 1.33, 95% CI 0.86 to 2.04; three studies). β₁+2 blockers when compared with placebo reduced mortality rates significantly (RR 0.75, 95% CI 0.61 to 0.92; 10 studies) and vascular effects non-significantly (RR 0.80, 95% CI 0.64 to 1.00; six studies).

In direct comparison between β-blockers, all-cause mortality rates were significantly reduced with β₁+2 blockers (RR 0.86 95% CI 0.78 to 0.94; four studies) compared with β₁ blocking agents.

Statistical heterogeneity was not found to be present in all outcomes except for vascular events when comparing β₁+2 blockers with placebo in patients with heart failure (p=0.03, I²=50.1%).

There was funnel plot asymmetry for studies in heart failure, which indicated evidence for publication bias. There was no evidence for publication bias in studies with acute coronary syndrome (funnels plots not presented).

Inclusion of only high-quality trials, analysis of different β-blockers and removal of trials one by one did not seem to influence results. Adjusting for studies with longer follow-up (at least 12 months) did not seem to alter the results significantly.

Authors’ conclusions
Suppression of the β₂-adrenergic receptor in addition to the β₁-receptor may be more effective in preventing total mortality and vascular events in patients with acute coronary syndrome and heart failure. However, the literature is too heterogeneous to draw firm conclusions.

CRD commentary
The review question was clearly stated and supported by well-defined inclusion criteria. The search covered a number of different databases. No language restrictions were applied. There was little attempt to search for unpublished studies. Assessment of publication bias suggested that some studies in heart failure may have been missed. Assessment of study quality found only a small percentage of studies was rated high quality, but this did not appear to influence the results. The authors noted variability among studies in terms of study design, β blockers (types and dosages) and patients; formal assessment of statistical heterogeneity only indicated variability for one outcome. Subsequent sensitivity analyses failed to demonstrate any significant effects of variability of studies on the summary measures. Given the
variability found among studies, appropriate statistical methods were used to perform meta-analysis. As results were based on indirect comparisons between treatments, the review could have benefited from further analysis to provide a summary estimate for comparison between $\beta_1$ blockers and $\beta_{1+2}$ blockers. Overall, the review was well-conducted and the conclusions reflected the evidence presented. The authors’ conclusions are 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 additional studies to assess the beneficial effect of $\beta_{1+2}$ blockers in patients with acute coronary syndrome or heart failure were needed.

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