Beta-blockers reduce mortality in patients undergoing high-risk non-cardiac surgery

CRD summary
The authors concluded that perioperative use of β-blockers in non-cardiac surgery remained controversial, but the evidence suggested that β-blockers significantly reduced risks of mortality in patients who underwent high-risk non-cardiac surgery compared with patients in lower risk categories. Uncertainties surrounding the evidence and the potential for bias in the review mean that the authors' conclusions should be interpreted with caution.

Authors' objectives
To assess the effects of perioperative β-blockers on total and cardiovascular mortality in patients undergoing high-risk non-cardiac surgery.

Searching
MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL were searched up to November 2009. Search terms were reported. Reference lists of identified articles, relevant reviews and meta-analyses were searched.

Study selection
Randomised controlled trials (RCTs) that compared the effects of β-blockers versus a control on cardiovascular and all-cause mortality in patients who underwent non-cardiac surgery were eligible for inclusion.

Included trials were conducted between 1986 and 2009 in patients from a variety of settings. Some patients had diabetes or mild hypertension or were at risk of coronary artery disease. Emergency and vascular surgery (aortic and other major vascular surgery including peripheral vascular surgery) was defined as high-risk surgery. Intra-peritoneal and intra-thoracic surgery, carotid endarterectomy, head and neck, orthopaedic and prostate surgery were defined as intermediate-risk surgery. Cataract, breast and ambulatory surgery and endoscopic or superficial procedures were defined as low risk. β-blockers used were propranolol, bisoprolol, esmolol, atenolol, metoprolol, labetalol and oxprenolol. Control groups received placebo, standard care or no treatment. Ten trials administered β-blockers as premedication, 12 RCTs administered treatment for 10 days or less and three RCTs administered treatment for 30 days.

The authors did not state how many reviewers screened studies for inclusion.

Assessment of study quality
Trial quality was assessed in accordance with the Cochrane Collaboration's tool for assessing risk of bias with criteria on randomisation, allocation concealment, blinding, complete outcome data, selective outcome reporting and other sources of bias.

The authors did not state how many reviewers performed the quality assessment.

Data extraction
Two reviewers independently extracted mortality event data on an intention-to-treat basis to enable calculation of odds ratios (ORs) and 95% confidence intervals (CIs). Any discrepancies were resolved through discussion.

Methods of synthesis
Odds ratios and 95% CIs were combined using a fixed-effect model. Continuity correction analysis was applied where zero events occurred in one or both treatment arms.

Statistical heterogeneity was assessed using the Q-test, $I^2$ and $T^2$. Subgroup analyses were undertaken for trial quality, treatment duration (up to discharge, pre-medication only and up to 30 days), titration by protocol of β-blocker dosage for target heart rate (yes versus no) and surgical risk (intermediate low, intermediate high, high). Multivariable random-
effect meta-regression was used to assess the effects of potential modifiers (surgical risk category and β-blocker dosage to target heart rate) on the outcomes.

Publication bias was assessed using funnel plots.

**Results of the review**

Twenty-five RCTs were included in the review. Fifteen were categorised as intermediate low risk surgical categories, five as intermediate high risk and five as high risk. Fourteen RCTs were classed as being at low risk of bias and 11 RCTs were classed at high risk of bias.

**All-cause mortality:** 24 RCTs (6,623 participants received β-blockers and 6,325 control)

There was no statistically significant difference in all-cause mortality in patients who received β-blockers versus control. Subgroup analyses by trial quality and treatment duration did not significantly alter the findings. Subgroup analyses by surgical risk category showed statistically significant benefit with β-blockers in the high-risk group (OR 0.43, 95% CI 0.20 to 0.93; five RCTs) and trials that targeted heart rate (OR 0.53, 95% CI 0.27 to 1.01; six RCTs).

There was evidence of statistical heterogeneity for both comparisons. A forest plot indicated that there was a statistically significant benefit with controls in trials that did not target heart rate (OR 1.27, 95% CI 1.01 to 1.60; 18 RCTs) and in the intermediate high risk group (OR 1.35, 95% CI 1.06 to 1.72; five RCTs). Both comparisons had the greatest weighting in their subgroup analyses.

**Cardiovascular mortality:** 23 RCTs (7,471 participants received β-blockers and 7,222 control)

There was no statistically significant difference in cardiovascular mortality rates in patients who received β-blockers versus control. Subgroup analyses showed statistically significant benefit in favour of β-blockers in trials that targeted heart rate (OR 0.29, 95% CI 0.10 to 0.86; six RCTs). There was evidence of statistical heterogeneity. Subgroup analyses by trial quality, treatment duration and risk category did not alter the findings significantly.

Meta-regression findings were reported in the review. There was no evidence of publication bias.

**Authors' conclusions**

Perioperative use of β-blockers in non-cardiac surgery remains controversial, but the evidence suggests that β-blockers significantly reduce risk of mortality in patients undergoing high-risk non-cardiac surgery compared with patients in the lower risk categories. Dose titration of β-blockers targeted on heart rate may contribute to explaining the beneficial effect of these drugs.

**CRD commentary**

The review question and supporting inclusion criteria were clearly defined. Several electronic databases were searched to identify relevant articles. It was unclear whether language restrictions were applied and as no apparent attempts were made to locate unpublished data, potentially relevant data may have been missed. There was no evidence of publication bias. Study quality was assessed using previously published criteria; just under half of the studies were assessed as being at high risk of bias. The authors reported that data extraction was undertaken in duplicate; it was unclear whether this was true for study selection and quality assessment and so reviewer error and bias could not be ruled out. Few patient and study details were reported, which made it difficult to assess whether pooling of the trials was appropriate. There was some evidence of statistical heterogeneity and attempts were made to investigate this. Only a small proportion of trials were classed as undergoing high risk surgery and it was not clear how many patients were included in these trials. Significant subgroup findings were based on comparisons with the least weighting.

Uncertainties about the available evidence and the potential for bias in the review process mean that the authors' conclusions should be interpreted with caution.

**Implications of the review for practice and research**
Practice: The authors stated that the usefulness of β-blockers remained unproved in patients undergoing either intermediate-risk or low-risk procedures. Routine administration was not recommended.

Research: The authors stated that further clinical trials were needed to identify the most appropriate timing of starting treatment with β-blockers before surgery and the duration of treatment after surgery. Further research was needed to consider the synergistic effect of concomitant therapies (antiplatelet agents and statins).

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