How strong is the evidence for the use of perioperative beta blockers in non-cardiac surgery: systematic review and meta-analysis of randomised controlled trials


CRD summary
This review assessed the effectiveness of peri-operative beta-blocker treatment in patients undergoing noncardiac surgery. The authors concluded that the evidence for a reduction in cardiovascular events is encouraging but inconclusive. These conclusions are likely to be reliable, and are pending the results of further trials in this area.

Authors' objectives
To determine the effects of peri-operative beta-blocker treatment in patients undergoing noncardiac surgery.

Searching
MEDLINE (from 1966 to 2002) and EMBASE (from 1980 to 2002) were searched. In addition, the following journals were searched from 1985 to 2002: Acta Anaesthesiologica Scandinavica, Anaesthesia, Anesthesiology, Anesthesia and Analgesia, British Journal of Anaesthesia, Canadian Journal of Anesthesia, and Regional Anesthesia and Pain Medicine. Experts in the field were also contacted, and the references of eligible trials were checked. There were no restrictions on the language or publication status of the studies.

Study selection
Study designs of evaluations included in the review
Randomised controlled trials (RCTs) that compared beta-blocker treatment with either placebo or usual care were eligible for inclusion. The duration of follow-up ranged from the end of surgery to day 30 post-surgery across the trials.

Specific interventions included in the review
Studies that assessed beta-blockers compared with either placebo or standard care were eligible for inclusion. The treatment interventions varied across the studies, and ranged from brief intravenous beta-blockers administered just before surgery to 30-day post-operative beta-blocker use.

Participants included in the review
Studies that assessed patients undergoing noncardiac surgery were eligible for inclusion. The types of surgery the patients were undergoing was unrestricted in 8 studies, and included carotid endarterectomy, middle ear or nasal septum surgery, cholecystectomy or hernia repair, neurosurgery, gynaecological surgery or dental extractions, lower extremity orthopaedic surgery, thoracotomy for lung resection, thoracic surgery, abdominal aortic or arterial surgery, vascular surgery or knee arthroplasty in the remaining studies.

Outcomes assessed in the review
Studies that assessed the peri-operative outcomes of total mortality, cardiovascular mortality, nonfatal myocardial infarction (MI), nonfatal cardiac arrest, nonfatal stroke, congestive heart failure, hypotension warranting treatment, bradycardia needing treatment, bronchospasm, or a composite outcome measure of major peri-operative cardiovascular events (cardiovascular death, nonfatal MI, or nonfatal cardiac arrest), were eligible for inclusion. Peri-operative outcomes were defined as those that occurred within 30 days of surgery. Likewise, the events constituting cardiovascular death, and bradycardia and hypotension needing treatment, were also defined a priori.

How were decisions on the relevance of primary studies made?
Two reviewers independently assessed the relevance of primary studies. Any discrepancies were resolved through discussion and consensus.
Assessment of study quality
The validity of the primary studies appears to have been assessed according to: the methods of randomisation; whether the trial was stopped early; the blinding of patients, health care providers, data collectors and outcome assessors; and the completeness of follow-up. Two reviewers independently assessed study quality. Any disagreements were resolved through discussion and consensus.

Data extraction
Two reviewers independently extracted the data. Any disagreements were resolved through discussion and consensus. Data were abstracted on the relative risks (RRs) of the outcomes for patients receiving peri-operative beta-blocker treatment compared with those receiving placebo or standard care. The 95% and 99% confidence intervals (CIs) were then calculated for each RR. All data were extracted in an intention-to-treat format.

Methods of synthesis
How were the studies combined?
The studies were combined in a meta-analysis using the random-effects model of DerSimonian and Laird. Further statistical techniques were used to assess the sample size required for the meta-analysis to be both reliable and conclusive. Publication bias was not assessed.

How were differences between studies investigated?
Heterogeneity was assessed statistically using the I-squared test. I-squared was considered to be low if its value was less than 25%, and high if above 75%. The potential sources of heterogeneity that were explored included trial validity, treatment interventions and the duration of follow-up.

Results of the review
Twenty-two RCTs involving 2,437 participants were included.

A moderate number of major peri-operative cardiovascular events (18 cardiovascular deaths, 58 nonfatal MIs and 7 nonfatal cardiac arrests) were observed in the trials. Treatment with peri-operative beta-blockers was not associated with any significant treatment benefit on any of the individual outcomes of total mortality, cardiovascular mortality, nonfatal MI, nonfatal cardiac arrest, nonfatal stroke or congestive heart failure. For the composite outcome measure of major peri-operative cardiovascular event (cardiovascular death, nonfatal MI, or nonfatal cardiac arrest), a statistically significant treatment benefit in favour of treatment with beta-blockers was observed in comparison with placebo or usual care (RR 0.44, 95% CI: 0.20, 0.97). Moderate heterogeneity was observed across the trials, with I-squared equal to 42%. Treatment with beta-blockers was also associated with a significant increase in the risk of experiencing bradycardia needing treatment (RR 2.27, 95% CI: 1.53, 3.36) and hypotension needing treatment (RR 1.27, 95% CI: 1.04, 1.56). Both of these analyses were associated with low levels of heterogeneity: 3% and 6% for bradycardia needing treatment and hypotension needing treatment, respectively.

A Lan DeMets sequential monitoring boundary was conducted for the meta-analysis. The results indicated that the optimal information size needed to reliably detect a plausible treatment effect for the composite outcome of major peri-operative cardiovascular events was 6,124 participants, whereas the actual number of participants included in the meta-analysis was 1,152.

Authors’ conclusions
The evidence that peri-operative beta-blockers reduce major cardiovascular events is encouraging but too unreliable to allow definite conclusions to be drawn.

CRD commentary
The review question was clearly defined in terms of the interventions, participants, outcomes and study designs. Several sources were searched for relevant studies, and efforts were made to minimise both language and publication bias. Two
reviewers were involved in the study selection, validity assessment and data abstraction processes, therefore minimising the likelihood of reviewer bias and errors. The quality of the primary studies had been assessed, but it was unclear whether the methodological criteria reported in the paper were the full set of criteria that had been used in the review or just a subset.

Adequate details on the included trials were tabulated, thereby allowing the reader to assess whether the results of the meta-analysis were consistent with the primary evidence base reviewed. The use of a meta-analysis appears to have been appropriate, and efforts were made to explore differences between the trials. Overall, this was a well-conducted review in which the authors' conclusions were appropriately cautious. These 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 the findings of the review provide the rationale and impetus for a large adequately-powered RCT on peri-operative beta-blockers. They also stated that such a trial, the peri-operative ischaemic evaluation (POISE) trial has recently been initiated.

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**Other publications of related interest**

This additional published commentary may also be of interest. Kalra S, Kitchens J. Review: evidence of benefit for perioperative beta-blockers in noncardiac surgery is unreliable. ACP J Club 2006;144:17.

**Indexing Status**

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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.