

How strong is the evidence for the use of perioperative β blockers in non-cardiac surgery? Systematic review and meta-analysis of randomised controlled trials

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Abstract

Objective To determine the effect of perioperative β blocker treatment in patients having non-cardiac surgery.

Design Systematic review and meta-analysis.

Data sources Seven search strategies, including searching two bibliographic databases and hand searching seven medical journals.

Study selection and outcomes We included randomised controlled trials that evaluated β blocker treatment in patients having non-cardiac surgery. Perioperative outcomes within 30 days of surgery included total mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal cardiac arrest, non-fatal stroke, congestive heart failure, hypotension needing treatment, bradycardia needing treatment, and bronchospasm.

Results Twenty two trials that randomised a total of 2437 patients met the eligibility criteria. Perioperative β blockers did not show any statistically significant beneficial effects on any of the individual outcomes and the only nominally statistically significant beneficial relative risk was 0.44 (95% confidence interval 0.20 to 0.97, 99% confidence interval 0.16 to 1.24) for the composite outcome of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal cardiac arrest. Methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis showed that the evidence failed, by a considerable degree, to meet standards for forgoing additional studies. The individual safety outcomes in patients treated with perioperative β blockers showed a relative risk for bradycardia needing treatment of 2.27 (95% CI 1.53 to 3.36, 99% CI 1.36 to 3.80) and a nominally statistically significant relative risk for hypotension needing treatment of 1.27 (95% CI 1.04 to 1.56, 99% CI 0.97 to 1.66).

Conclusion The evidence that perioperative β blockers reduce major cardiovascular events is encouraging but too unreliable to allow definitive conclusions to be drawn.

Introduction

Several authors and guideline committees have advocated the use of β blockers for patients having non-cardiac surgery to prevent perioperative cardiovascular events.¹⁻⁴ Others have questioned the robustness of the evidence and have advocated the need for a large definitive randomised controlled trial.^{5 6}

Accurate understanding of the strength of the evidence for perioperative β blockers requires a systematic, comprehensive, and unbiased accumulation of the available evidence and methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis.⁷ We undertook a systematic review and meta-analysis to evaluate the effect of β blockers on cardiovascular events in patients having non-cardiac surgery.

Methods

Eligibility criteria—We included randomised controlled trials that evaluated the effect of β blocker treatment in patients having non-cardiac surgery. Randomised controlled trials were eligible regardless of their publication status, language, or primary objectives.

Study identification—Strategies to identify studies included an electronic search of two bibliographical databases (see appendix A on bmj.com); a hand search of seven anaesthesia journals (appendix A); consultation with experts; our own files; review of reference lists from eligible trials; use of the “see related articles” for publications in PubMed (April 2003); and search of SciSearch (April 2003) for publications that cited key publications.

Assessment of study eligibility—Two researchers independently evaluated study eligibility ($\kappa = 0.96$). Disagreements were resolved by consensus.

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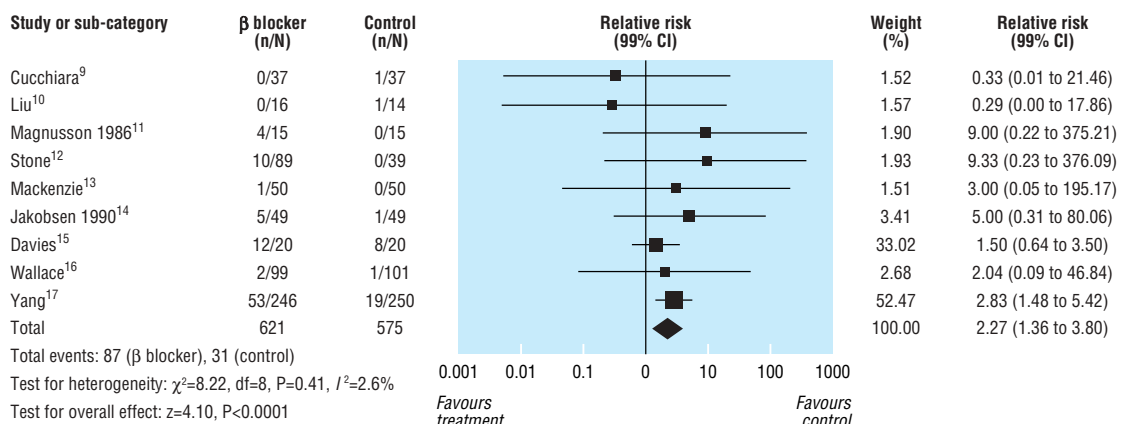


Fig 1 Relative risks for bradycardia needing treatment

Data collection and quality assessment—We abstracted descriptive data and markers of trial validity. We abstracted data on perioperative cardiovascular outcomes that occurred within 30 days of surgery (see bmj.com for details). Teams of two researchers independently abstracted data from all trials ($\kappa=0.69$ –1.0). Disagreements were resolved by consensus.

Statistical analysis—For each trial we calculated the relative risks of the outcomes for patients receiving perioperative β blocker treatment compared with patients receiving placebo or standard care. We did analyses on an intention to treat basis. We pooled relative risks by the random effects model. We calculated an I^2 value as a measure of heterogeneity for each outcome analysis. Because no reason exists why the standards for a meta-analysis should be less rigorous than those for a good single randomised controlled trial, we used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis to assess the reliability and conclusiveness of the available evidence on perioperative β blockers.⁸ We used this monitoring boundary as a way of determining whether the evidence in our meta-analysis was reliable and conclusive (see bmj.com).

Results

Included trials

We identified 22 randomised controlled trials published between 1980 and 2004 that fulfilled our eligibility criteria (see bmj.com). The 22 trials randomised a total of 2437 patients. The median sample size was 61 patients. The type of non-cardiac surgery was unrestricted in eight trials. Treatment interventions varied from brief intravenous β blocker just before surgery to 30 day postoperative β blocker use. The duration of follow-up was limited to the end of surgery in one trial and until discharge from the recovery room in five trials.

Quality assessment

Most randomised controlled trials fulfilled our quality measures (for example, all trials had complete patient follow-up) (see bmj.com).

Effect of perioperative β blockers

Overall only a moderate number of major perioperative cardiovascular events occurred (18 cardiovascular

deaths, 58 non-fatal myocardial infarctions, and 7 non-fatal cardiac arrests). Perioperative β blockers did not show any statistically significant beneficial effects on any of the individual outcomes. Patients in four trials had fatal events. Nine deaths (five cardiovascular) occurred among the 453 patients randomised to β blocker treatment, compared with 19 deaths (13 cardiovascular) among the 454 patients randomised to placebo or standard care (relative risk 0.56, 95% confidence interval 0.14 to 2.31, 99% confidence interval 0.09 to 3.60 for total mortality; 0.40, 0.14 to 1.15, 0.10 to 1.60 for cardiovascular mortality).

The individual safety outcomes in patients treated with perioperative β blockers showed a relative risk of 2.27 (1.53 to 3.36, 1.36 to 3.80) for bradycardia needing treatment (fig 1) and 1.27 (1.04 to 1.56, 0.97 to 1.66) for hypotension needing treatment. Both these analyses showed low heterogeneity (I^2 of 3% for bradycardia needing treatment and 6% for hypotension needing treatment).

Eight trials had patients who had a major perioperative cardiovascular event (cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest) (fig 2). Twenty eight major perioperative cardiovascular events occurred among the 589 patients randomised to β blocker treatment, compared with 55 among the 563 patients randomised to placebo or standard care (relative risk 0.44, 0.20 to 0.97, 0.16 to 1.24). Moderate heterogeneity existed across the trial results ($I^2=42\%$).

Exploring heterogeneity

Three trials did not fulfil all our quality measures. Their pooled relative risk for major perioperative cardiovascular events was 0.13 (0.04 to 0.38, 0.03 to 0.54) with $I^2=0\%$. The remaining five high quality trials had a pooled relative risk for major perioperative cardiovascular events of 0.82 (0.49 to 1.36, 0.42 to 1.59) with $I^2=0\%$.

Reliability and conclusiveness of composite outcome result

We calculated that the optimal information size needed to reliably detect a plausible treatment effect, for the composite outcome of major perioperative cardiovascular events, is 6124 patients. Currently, 1152 patients have been randomised in the β blocker randomised controlled trials with patients who have had a major perioperative cardiovascular event (fig 3). The sequen-

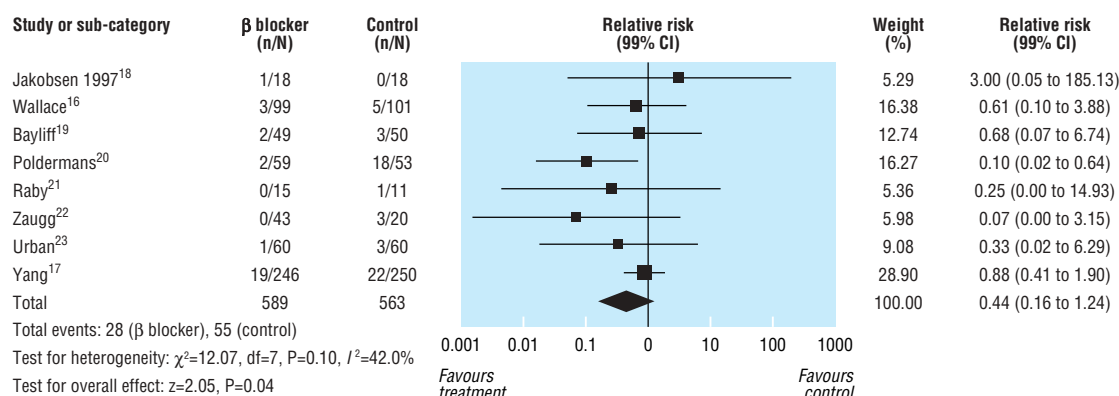


Fig 2 Relative risks for major perioperative cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest)

tial monitoring boundary has not been crossed, indicating that the cumulative evidence is unreliable and inconclusive.

Discussion

Perioperative β blockers may decrease the risk of major perioperative cardiovascular events but increase the risk of bradycardia and hypotension needing treatment. These results are based on only a moderate number of major perioperative cardiovascular events and patients with bradycardia needing treatment. A total of 1152 patients were randomised in the eight trials that had patients who had a major perioperative cardiovascular event. This number of patients randomised is much smaller than our calculated optimal information size. Our use of methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis showed that the current

evidence for perioperative β blocker is insufficient and inconclusive.

Strengths and weaknesses

We did a comprehensive search using seven strategies to identify randomised controlled trials, conducted eligibility decisions and data abstraction in duplicate and showed a high degree of agreement, obtained data from or confirmed them with all trialists, and evaluated the reliability and conclusiveness of the available evidence on perioperative β blockers through a method adapted from formal interim monitoring boundaries applied to cumulative meta-analysis.

Our systematic review focuses only on short term outcomes. Only one randomised controlled trial evaluated the effect of perioperative β blocker treatment on long term outcomes.²⁴ This trial is the long term follow-up component of a trial included in our review. The authors reported a greater than 50% reduction in the relative risk of death among patients who received atenolol during the two year follow-up. However, when deaths that occurred during the period when patients were receiving the study drug are included in the intention to treat analysis the reduction in the risk of death with atenolol is no longer statistically significant.⁶

Relation to other systematic reviews

Two other systematic reviews have evaluated the effects of perioperative β blockers.^{25 26} We included a lot more trials and used methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis to determine if the current evidence is reliable and conclusive.

Implications

Our systematic review provides encouraging evidence that perioperative β blockers may reduce the risk of major perioperative cardiovascular events but increase the risk of bradycardia and hypotension needing treatment in patients having non-cardiac surgery. Recommendations from authors and guideline committees for perioperative β blocker treatment for varying groups of patients having non-cardiac surgery warrant cautious interpretation.

Firstly, only a moderate number of events occurred in the perioperative β blocker trials. Secondly, the evidence from our meta-analyses suggests a large treatment effect, which is inconsistent with the results of the

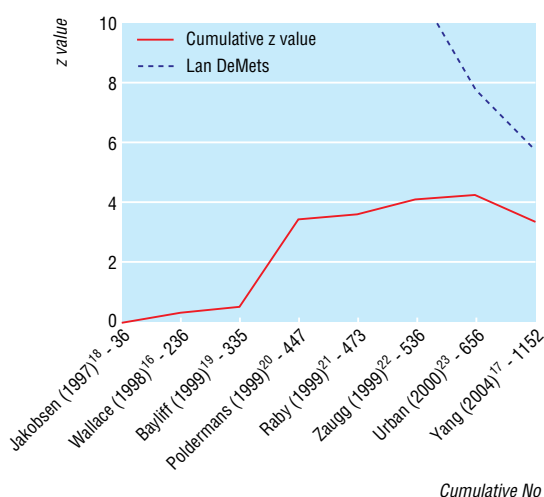


Fig 3 Cumulative meta-analysis assessing the effect of perioperative β blockers on the 30 day risk of major perioperative cardiovascular events (cardiovascular death, non-fatal myocardial infarction, or non-fatal cardiac arrest) in patients having non-cardiac surgery. The Lan-DeMets sequential monitoring boundary, which assumes a 10% control event rate and a 25% relative risk reduction with 80% power and a two sided $\alpha=0.01$, has not been crossed, indicating that the cumulative evidence is inconclusive

What is already known on this topic

Several authors and guidelines committees have advocated the use of β blockers in patients having non-cardiac surgery

The robustness of the evidence for this intervention has been questioned

What this study adds

Perioperative β blockers may decrease the risk of major perioperative cardiovascular events but increase the risk of bradycardia and hypotension needing treatment

The beneficial results, however, are based on only a moderate number of major events, and the findings depend on methodologically weak trials

Methods adapted from formal interim monitoring boundaries applied to cumulative meta-analysis show that the evidence for perioperative β blockers is insufficient and inconclusive

β blocker trials in myocardial infarction and congestive heart failure that have randomised more than 50 000 patients, and shown moderate treatment effects.^{27–31} Large treatment effects are unlikely, because a substantial number of perioperative cardiovascular pathogenic mechanisms that β blockers do not affect remain.

Thirdly, we found moderate heterogeneity ($I^2 = 42\%$), which weakens the reliability of the finding that major perioperative cardiovascular events are decreased. This finding is in contrast to the outcomes of bradycardia and hypotension needing treatment, which showed low heterogeneity. Fourthly, the question of whether a meta-analysis is definitive can be considered by using the logic of early stopping for a randomised controlled trial. Using this method we have shown that the cumulative evidence is inconclusive and further research is needed.

Our systematic review identifies the need for a large adequately powered randomised controlled trial on perioperative β blockers. Such a trial, the perioperative ischemic evaluation (POISE) trial, which plans to recruit 10 000 patients, was recently initiated and has recruited more than 4000 patients in 18 countries to date.

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