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β-Blockers Reduce Mortality in Patients Undergoing High-Risk Non-Cardiac Surgery

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Abstract

Background: β-Adrenergic receptor antagonists (β-blockers) are frequently used with the aim of reducing perioperative myocardial ischemia and infarction. However, randomized clinical trials specifically designed to evaluate the effects of β-blockers on mortality in patients undergoing non-cardiac surgery have yielded conflicting results.

Objective: This study aimed to examine the effect of perioperative β-blockers on total and cardiovascular mortality in patients undergoing non-cardiac surgery.

Methods: We conducted a meta-analysis of randomized clinical trials that examined the effects of β-blockers versus placebo on cardiovascular and all-cause mortality in patients undergoing non-cardiac surgery. We extracted data from articles published before 30 November 2009 in peer-reviewed journals indexed in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE and CINAHL. Data extraction was carried out independently by two reviewers on the basis of an intent-to-treat approach, and inconsistencies were discussed and resolved in conference. The present meta-analysis was undertaken according to the Quality of Reporting of Meta-analyses (QUORUM) statement.

Results: A total of 2148 records were screened, from which we identified 74 randomized controlled trials for non-cardiac surgery. After excluding 49 studies that did not report the clinical outcome of interest or were subanalyses or presented duplicate data, the final search left 25 clinical trials. Treatment with β-blockers had no significant effect on all-cause mortality (odds ratio [OR] 1.15; 95% confidence interval [CI] 0.92, 1.43; p = 0.2717) or cardiovascular mortality (OR 1.13; 95% CI 0.85, 1.51; p = 0.5855). However, surgical risk category markedly differed across the studies. According to Joint American College of Cardiology and American Heart Association guidelines for perioperative assessment of patients having non-cardiac surgery, five trials evaluated the effect of β-blockers in patients treated with emergency and vascular surgery (high-risk category) whereas 15 and five trials evaluated the effect of β-blockers in intermediate low and intermediate high surgical risk categories, respectively. Subgroup analyses showed that the surgical risk category and dose titration of β-blockers to target heart rate affected the estimate of the effect of β-blockers for all-cause and cardiovascular mortality. β-Blockers reduced total mortality by 61% more in patients who underwent high-risk surgery than in those who underwent intermediate high- or intermediate low-risk surgery. When cardiovascular mortality was assessed, the benefit of β-blockers was 74% greater in trials that titrated β-blockers to heart rate than in trials that did not, although formal statistical significance was not achieved.

Conclusions: These data suggest that β-blockers may be useful for reducing mortality in patients who undergo high-risk non-cardiac surgery.

Introduction

The 2009 Joint American College of Cardiology (ACC) and American Heart Association (AHA) updated guidelines on perioperative cardiovascular (CV) evaluation and care for non-cardiac surgery[1-3] recently reviewed recommendations for therapy with β-adrenergic receptor antagonists (β-blockers). The recommendation to continue β-blockers in patients undergoing

surgery who are receiving this therapy to treat conditions such as angina, arrhythmias, hypertension, or other ACC/AHA class I guideline indications did not change in the 2009 update.[1,3] The recommendation to use β-blockers in patients undergoing vascular surgery who are at high cardiac risk (evidence of coronary artery disease, cardiac ischemia on preoperative testing) shifted from I to IIa class of evidence.[1,3]

Similarly, the recent guidelines of the European Society of Cardiology (ESC) for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery[4] recommend the perioperative use of β-blockers in patients with established coronary artery disease or myocardial ischemia diagnosed by preoperative stress testing, as well as in patients scheduled for high-risk surgery (class I, level of evidence B).

Although several small randomized controlled trials (RCTs) suggested an improved perioperative (30-day) and long-term (1- to 2-year) outcome in high-risk patients,[1-3] these new recommendations were based on additional information provided by the results of three recent meta-analyses[5-7] and of the POISE (Perioperative Ischemic Evaluation) trial.[8]

While β-blockers significantly reduced non-fatal myocardial infarction (MI),[8] the most worrisome aspect of the perioperative use of β-blockers in patients undergoing non-cardiac surgery is the negative prognostic impact on 30-day mortality observed in the POISE trial.[8] In this trial, a total of 8351 patients, most of them at intermediate medical risk, were randomized to receive extended-release metoprolol succinate or placebo; at 30 days the incidence of a composite endpoint of CV death, non-fatal MI and non-fatal cardiac arrest was lower in the metoprolol group than in the placebo group (5.8% vs 6.9%, hazard ratio [HR] 0.83; $p = 0.04$) but more patients randomized to receive metoprolol died of any cause (3.1% vs 2.3%; $p = 0.03$).[8]

On the other hand, perioperative treatment with β-blockers in high-risk surgery[9-11] was associated with a clear benefit in the reduction of fatal events compared with placebo,[9-11] suggesting that the risk of the surgical procedure may substantially influence the protective effect of β-blockers on mortality.

The aim of this systematic overview and meta-analysis was to examine the effect of β-adrenergic blockade on all-cause and CV deaths in perioperative medicine. We reviewed the evidence from RCTs for the use of β-blockers in non-cardiac surgery and we further tried to identify the ideal target population in which perioperative β-blocker therapy might be associated with a better outcome. In particular, we tested the hypothesis that differences in type of surgery may explain the different protective effects observed in clinical trials.

Methods

We reviewed RCTs that evaluated the effects of β-blockers on CV and all-cause death compared with placebo in patients undergoing non-cardiac surgery. We searched for eligible studies, using research methodology filters,[12] with the following terms: 'intraoperative care', 'perioperative care', 'preoperative care', 'surgical procedures, operative', 'surgery', 'labetalol', 'carvedilol', 'esmolol', 'atenolol', 'metoprolol', 'metoprolol succinate', 'propranolol', 'bisoprolol', 'oxprenolol', 'pindolol', 'penbutolol', 'acebutolol', 'nadolol', 'betaxolol', 'celiprolol', 'nebivolol', 'timolol', 'metipranolol', 'landiolol', 'carteolol', 'β-adrenergic blockers', 'adrenergic β-antagonist', 'β-blockers', and 'randomized controlled trial'.

We extracted data from articles published before 30 November 2009 in peer-reviewed journals indexed in MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and CINAHL. We checked the reference list of identified articles, previous systematic reviews and meta-analyses to find other potentially eligible studies. Data extraction was carried out independently by two reviewers (PV and FA) on the basis of an intent-to-treat approach, and inconsistencies were discussed and resolved in conference.

The present meta-analysis was undertaken according to the Quality of Reporting of Meta-analyses (QUORUM) statement.[13] We calculated odds ratios (ORs) and 95% confidence intervals (CIs) for all-cause and CV death for each trial separately and for the combination of studies according to a fixed-effect model.[14,15] The null hypothesis of homogeneity across individual trials was tested by using the Q-test. Pooled estimates were assessed for heterogeneity by using the I^2 and τ^2 statistics.[16] Publication bias was estimated visually by funnel plots or by use of regression tests for funnel plot asymmetry.[14] Since a large number of studies reported zero events in one or both arms we adopted an analysis strategy based on the treatment arm continuity correction as suggested by Sweeting et al.[17] Quality assessment was based on Cochrane Collaboration's tool for assessing risk of bias:[18] each trial was identified as low- or high-bias risk according to adequate generation of allocation sequence, adequate allocation concealment, adequate blinding of participants, personnel and outcome assessors, complete outcome data, selective outcome reporting, and other sources of bias.[18]

Heterogeneity was explored by conducting the analysis in the following pre-planned subgroups: (i) trial quality (low-bias vs high-bias); (ii) treatment duration (up to discharge, premedication only, 30 days); (iii) titration by protocol of β-blocker dosage for target heart rate (yes vs no); (iv) surgical risk (intermediate low, intermediate high, high).

Three different subgroups of surgical risk categories were defined according to the classification of surgical procedures as recommended by the ACC/AHA guidelines for perioperative assessment of patients having non-cardiac surgery.[1-3] Emergency and vascular surgery (aortic and other major vascular surgery including peripheral vascular surgery) was identified as a high-risk surgical category; intraperitoneal and intrathoracic surgery, carotid endarterectomy, head and neck surgery, orthopedic surgery, and prostate surgery were defined as an intermediate-risk category; cataract surgery, breast surgery, ambulatory surgery, and endoscopic or superficial procedures were defined as low risk.

The ACC/AHA guidelines on perioperative CV evaluation for non-cardiac surgery[1-3] suggest that three elements must be assessed to determine the risk of cardiac events: (i) patient-specific clinical variables; (ii) exercise capacity; and (iii) surgery-specific risk. For the unavailability of individual patient data from RCTs included in the analysis, patient-specific indices used to estimate the risk of cardiac complication during and after non-cardiac surgery were not analyzed as potential effect modifiers.

The potential effect modifiers, as identified from subgroup analysis, were further evaluated by multivariable random effect meta-regression.[19] To control for false-positive findings (type I error) when performing meta-regression with multiple covariates, we used the model F value and its statistical significance to assess whether there was evidence for an association of any of the covariates with the outcome.[19]

Analyses were done using Stata version 11 (StataCorp LP, College Station, TX, USA) and R version 2.9 (R Foundation for Statistical Computing, Vienna, Austria).

Results

A total of 2148 bibliographic records were screened. We initially identified 74 RCTs for non-cardiac surgery. We excluded 49 studies that did not report the clinical outcome of interest or were sub-analyses or duplicate data (see appendix). Hence, the remaining 25 clinical trials[8-10,20-41] were included in the analysis. Figure 1 shows the information flow diagram with details of included and excluded trials. We found no formal evidence for publication bias (p = 0.2998). Table I shows the main characteristics of included studies.[8-10,20-41] The 25 trials[8-10,20-41] were allocated to three different predefined subgroups of surgical risk categories: the intermediate low-risk category included 15 RCTs, the intermediate high-risk category included five RCTs, and five RCTs were included in high-risk surgery (table I).

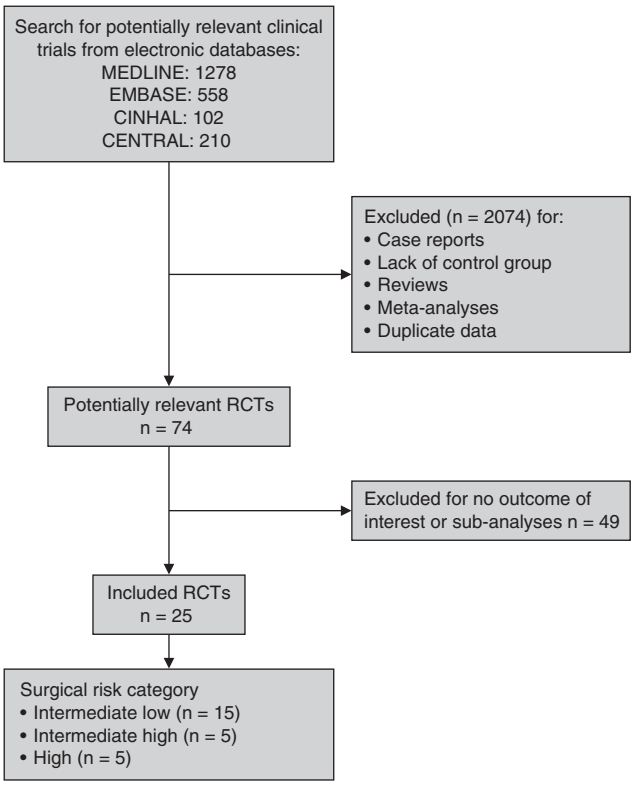

Fig. 1. Data sources and information flow of the systematic review. **RCT** = randomized controlled trial.

Of the 25 RCTs included in the analysis, 14 were identified as low-bias risk,[8,10,20,22-24,27,28,33-36,39,41] with the remaining RCTs classified as high-bias risk. Only six RCTS allowed for an increase by protocol of β-blockers to a target heart rate.[9,24,29,35,38,41] In ten RCTs, β-blockers were administered only as premedication,[22,23,26,27,30-33,36,37] in 12 RCTs the drug was given for 10 days or less,[10,20,21,25,28,29,34,35,38-41] while three trials involved use of the study drug for 30 days.[8,9,24]

All-Cause Death

Twenty-four studies reported all-cause death as a clinical outcome. Overall, 6623 patients were randomized to receive β-blockers and 6325 patients were assigned to the control groups (table I and figure 2); 175 and 155 died of any cause in the β-blocker and control groups, respectively. The ORs and 95% CIs for all-cause death for the combination of studies are shown in figure 2. Overall, treatment with β-blockers had no significant effect on all-cause death (figure 2, OR 1.15; 95% CI 0.92, 1.43; p = 0.2717).

As shown in figure 2, the pooled estimate was consistent across subgroups defined by trial quality and treatment duration.

Table I. Main characteristics of randomized clinical trials that evaluated the effects of β-adrenoceptor antagonists (β-blockers) on all-cause and cardiovascular death compared with placebo in patients undergoing non-cardiac surgery

Trial	Year	Design	Setting	Experimental drug	Control	Surgical risk category
Bayliff et al.[20]	1999	Randomized, double-blind	Major thoracic surgery	Propranolol	Placebo	Intermediate low
BBSA[41]	2007	Randomized, double-blind	Surgery with spinal block	Bisoprolol	Placebo	Intermediate low
Cucchiara et al.[22]	1986	Randomized, double-blind	Carotid endarterectomy	Esmolol	Placebo	Intermediate low
Davies et al.[23]	1992	Randomized, double-blind	Carotid endarterectomy	Atenolol	Placebo	Intermediate low
DIPOM[28]	2006	Randomized, double-blind	Diabetic patients undergoing major non-cardiac surgery	Metoprolol	Placebo	Intermediate high
Jakobsen et al.[25]	1986	Randomized, double-blind	Middle ear or nasal septum surgery	Metoprolol	Placebo	Intermediate low
Dunkelgrun[24]	2009	Randomized, open-label 2×2 factorial design	Intermediate-risk patients undergoing non-cardiovascular surgery	Bisoprolol	Placebo	Intermediate low
Jakobsen et al.[26]	1997	Randomized, double-blind	Elective thoracotomy for lung resection	Metoprolol	Placebo	Intermediate low
Jakobsen et al.[27]	1990	Randomized, double-blind	Elective hysterectomy or orthopedic surgery	Metoprolol	Placebo	Intermediate low
Lai[29]	2006	Randomized, double-blind	Elective esophagectomy	Metoprolol	Placebo	Intermediate low
Magnusson et al.[30]	1986	Randomized, double-blind	Microlaryngoscopy	Metoprolol	Placebo	Intermediate low
Magnusson et al.[31]	1986	Randomized, double-blind	Cholecystectomy or hernia repair	Metoprolol	Placebo	Intermediate low
MaVS[10]	2006	Randomized, double-blind	Abdominal aortic surgery, infrainguinal or axillofemoral revascularizations	Metoprolol	Placebo	High
Miller et al.[32]	1991	Randomized, double-blind	Non-cardiovascular surgery	Esmolol	Placebo	Intermediate low
Miller et al.[33]	1990	Randomized, double-blind	Patients with CAD or at least two risk factors	Esmolol	Placebo	High
Neary et al.[34]	2006	Randomized, double-blind	High-risk patients undergoing emergency surgery	Atenolol	Placebo	High
POBBLE[21]	2005	Randomized, double-blind	Infrarenal vascular surgery	Metoprolol	Placebo	High
POISE[8]	2008	Randomized, double-blind	Patients with, or at risk of, atherosclerotic disease	Metoprolol CR	Placebo	Intermediate high
Poldermans et al.[9]	1999	Randomized, nonblinded	Major vascular surgery	Bisoprolol	Standard care	High
Raby et al.[35]	1999	Randomized, double-blind	High-risk vascular surgery	Esmolol	Placebo	Intermediate high
Rosenberg et al.[36]	1996	Randomized, double-blind	Endoscopic cholangiopancreatography	Metoprolol	Placebo	Intermediate low
Stone et al.[37]	1988	Randomized, nonblinded	Mildly hypertensive patients	Labetalol/atenolol/ oxprenolol	Untreated	Intermediate high
Urban et al.[38]	2000	Randomized, nonblinded	Elective total knee arthroplasty	Esmolol/metoprolol	Placebo	Intermediate low
Wallace et al.[39]	1998	Randomized, double-blind	Patients with, or at risk of, CAD	Atenolol	Placebo	Intermediate high
Zaugg et al.[40]	1999	Randomized, nonblinded	Elderly	Atenolol	Untreated	Intermediate low

BBSA = Beta Blocker in Spinal Anesthesia study; **CAD** = coronary artery disease; **CR** = controlled release; **DIPOM** = Diabetic Postoperative Mortality and Morbidity trial; **MaVS** = Metoprolol after Vascular Surgery trial; **POBBLE** = PeriOperative Beta-BLockadE trial; **POISE** = Perioperative Ischemic Evaluation trial.

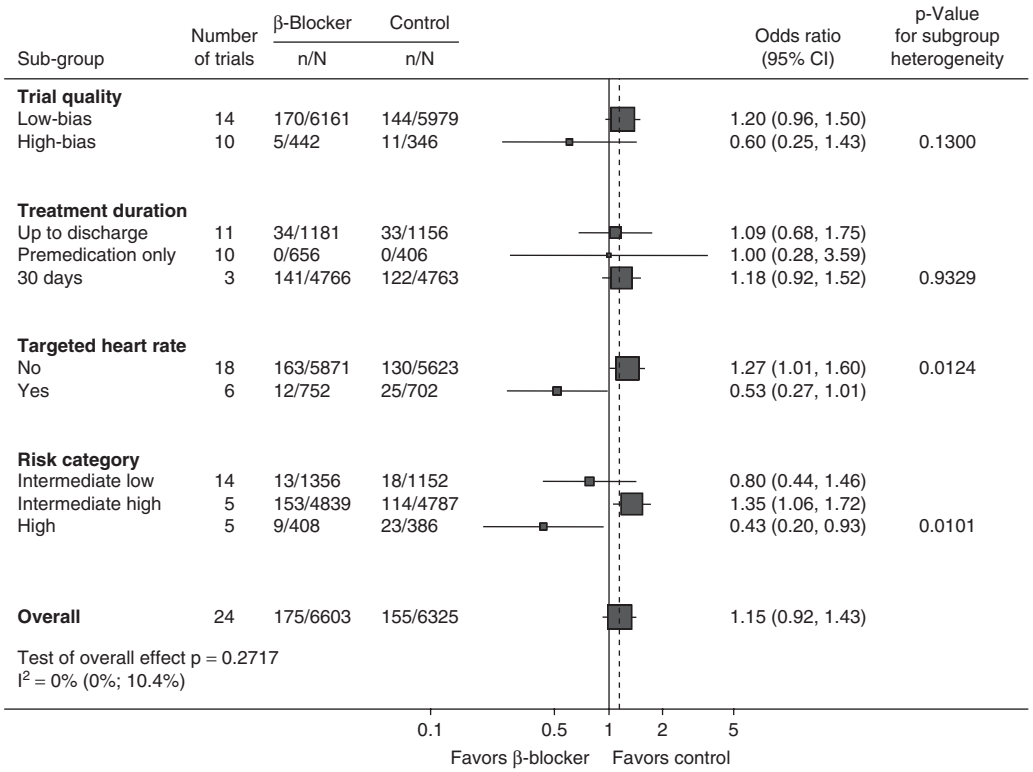

Fig. 2. Consistency of the pooled estimate for all-cause mortality associated with perioperative treatment with β-adrenergic receptor antagonists (β-blockers) across predefined subgroups (see text for details).

On the other hand, subgroup analysis showed a significantly favorable effect of β-blockers in high-risk surgery (p = 0.0101 for heterogeneity between subgroups) and in trials that titrated by protocol β-blocker dosage for target heart rate (p = 0.0124 for heterogeneity between subgroups). Remarkably, 57% and 47% risk reductions for all-cause death were noted in the high-risk surgery subgroup (figure 2, OR 0.43; 95% CI 0.20, 0.93) and in trials targeting heart rate (figure 2, OR 0.53; 95% CI 0.27, 1.01), respectively.

Cardiovascular Death

In 23 studies total cardiovascular deaths were reported as an outcome. Overall, 7471 and 7222 patients were assigned to β-blocker and control groups, respectively (table I); 93 CV deaths were observed in the β-blocker group and 85 CV deaths in the control group. Overall, patients randomized to β-blocker therapy showed no significant effect on the risk of CV death (figure 3, OR 1.13; 95% CI 0.85, 1.51; p = 0.5855). The prognostic effect of β-blockers did not differ across subgroups of trial quality and treatment duration.

The perioperative use of β-blockers in high-risk surgical procedures was associated with a lesser risk of CV death (figure 3, OR 0.45; 95% CI 0.15, 1.35) than in intermediate low-risk (figure 3, OR 0.96; 95% CI 0.38, 2.39) or intermediate high-risk (figure 3, OR 1.25; 95% CI 0.91, 1.71) subgroups, although the formal test for heterogeneity between subgroups was not statistically significant (p = 0.2027). On the other hand, the benefit of perioperative use of β-blockers was driven by trials in which the dose of β-blockers was titrated by protocol for target heart rate (p = 0.0109 for heterogeneity between subgroups).

Meta-Regression Analysis

Stratified analyses may be used to investigate the possibility that treatment effects vary between predefined subgroups. However, comparisons between subgroups can be more suitably performed by random effect meta-regression.[42] Therefore, we performed multivariable meta-regression analyses using the different surgical risk categories and the titration of β-blocker dosage to target heart rate as effect modifiers (see Methods section). For all-cause death (table II), meta-regression analysis showed that the surgical risk category markedly affected the estimate of the effect of β-blockers (model F = 3.70; p = 0.0287). The benefit of β-blockers in reducing all-cause mortality was 61% greater (OR = 0.390; 95% CI 0.164, 0.925; p = 0.033) in the

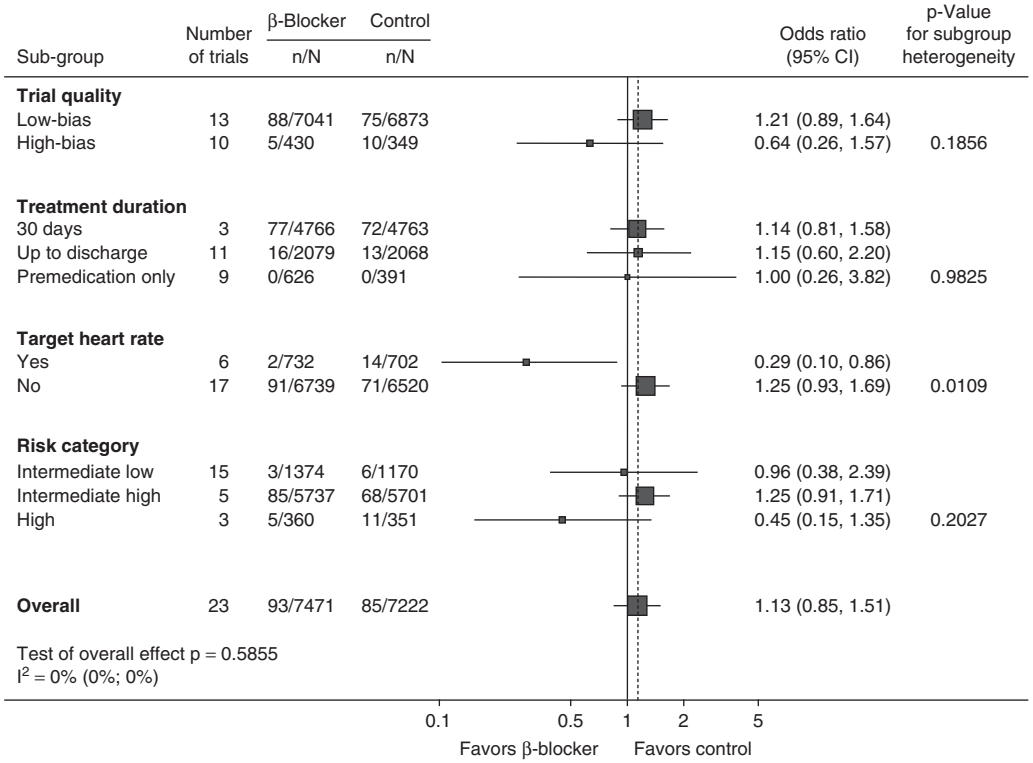

Fig. 3. Consistency of the pooled estimate for cardiovascular mortality associated with perioperative treatment with β-adrenergic receptor antagonists (β-blockers) across predefined subgroups (see text for details).

high-risk than in the intermediate high-risk category. No difference was observed between intermediate low- and intermediate high-risk categories (OR = 0.937; 95% CI 0.373, 2.355; p = 0.890). Multivariable random-effect analyses did not confirm target heart rate as a potential effect modifier (OR = 0.496; 95% CI 0.184, 1.338; p = 0.166).

When CV mortality was assessed (table III), none of the tested covariates achieved statistical significance. However, β-blockers reduced the risk by 74% at the point estimate in trials that up-titrated β-blockers for target heart rate (OR = 0.259; 95% CI 0.062, 1.076; p = 0.063), although statistical significance was not formally achieved.

Discussion

The perioperative use of β-blockers in patients is still controversial. In individual trials[8,20,24,28] and meta-analyses,[5-7] these drugs did not reduce all-cause and CV mortality in patients undergoing non-cardiac surgery, especially in intermediate- or low-risk surgical procedures.[20,24] In addition, previous systematic reviews and meta-analyses[5-7] did not formally investigate the effect of some trial-level covariates as potential effect modifiers on the overall estimate.

In our analysis, subgroup analysis and meta-regression techniques demonstrated that β-blockade was associated with a reduced risk of mortality in patients undergoing high-risk non-cardiac surgery. These patients showed a significant 61% reduction in the risk of total mortality with the use of β-blockers when compared with patients in the lower risk categories.

Moreover, dose titration of β-blockers targeted on heart rate contributed to the explanation of the beneficial effect of these

Table II. Risk of all-cause death in relation to Joint American College of Cardiology and American Heart Association (ACC/AHA) surgical risk categories and target heart rate (see text for details). Estimates obtained by multivariable meta-regression using a random effect model

Covariate	Odds ratio	Standard error	p-Value	95% CI
Target heart rate				
No	1			
Yes	0.496	0.251	0.166	0.184, 1.338
ACC/AHA risk category				
High	0.390	0.172	0.033	0.164, 0.925
Intermediate high[a]	1			
Intermediate low	0.937	0.441	0.890	0.373, 2.355

a Reference category.

Table III. Risk of cardiovascular death in relation to Joint American College of Cardiology and American Heart Association (ACC/AHA) surgical risk categories and target heart rate (see text for details). Estimates obtained by multivariable meta-regression using a random effect model

Covariate	Odds ratio	Standard error	p-Value	95% CI
Target heart rate				
No	1			
Yes	0.259	0.188	0.063	0.062, 1.076
ACC/AHA risk category				
High	0.782	0.557	0.730	0.193, 3.162
Intermediate high[a]	1			
Intermediate low	1.073	0.563	0.893	0.384, 3.000

a Reference category.

drugs, although the effect bordered on nominal significance after adjustment for surgical risk.

Supportive Data for β-Blocker Therapy in High-Risk Surgery

In the intermediate low surgical risk category, β-blockers seem to have weak protective effects against major CV complications. A small randomized, double-blind, placebo-controlled trial compared propranolol (administered every 6 hours for 5 days) with placebo in patients undergoing surgical procedures at intermediate risk.[20] The primary outcome was the reduction in arrhythmias requiring treatment. A non-significant, but clinically relevant, 70% relative risk reduction in the rate of treated arrhythmias was observed with propranolol ($p = 0.071$). However, a slight increase in all-cause death was documented in the propranolol group.[20]

Similarly, in the BBSA (Beta Blocker in Spinal Anesthesia) trial,[41] the effect of bisoprolol was compared with that of placebo on 1-year follow-up in patients undergoing surgery with spinal block at intermediate low risk. The mean duration of treatment was 4.9 days in the bisoprolol group and 5.1 days in the placebo group. The incidence of all-cause death was identical between treatment groups (OR 1.00; 95% CI 0.06, 16.09).

In the POISE trial,[8] 2425 patients (58.1%) in the metoprolol group and 2461 patients (58.9%) in the control group underwent intermediate low-risk surgical procedures. Overall, patients treated with metoprolol showed an increased risk of all-cause death compared with the control group. However, the major contributor to the higher mortality rate in the metoprolol group was sepsis. The mechanisms through which β-blockers may predispose to sepsis are unclear. The authors of the study hypothesized that the slower heart rate and the reduction in contraction induced by β-blockers could mask normal responses to systemic infection, which in turn could delay recognition and treatment or impede the normal immune response. Other explanations have also been offered to explain the increased risk of death with metoprolol. An aggressive protocol of β-blockade such as the one used in POISE[8] may have contributed to hemodynamic instability and resulted in adverse CV events leading to death. Metoprolol succinate 100 mg or placebo was administered 2–4 hours before surgery. Another dose of metoprolol 100 mg or placebo was given 6 hours after surgery (or even sooner if the heart rate was 80 beats/min or more and systolic blood pressure was ≥100 mmHg). Finally, metoprolol 200 mg or placebo was given 12 hours after the second dose and every 24 hours thereafter for 30 days. Such a protocol may have been too aggressive for patients exposed to the stress of non-cardiac surgery, particularly if they were β-blocker naïve.

In contrast to trials performed in intermediate low-risk surgical procedures, a quite clear benefit of perioperative β-blockers in patients having high-risk surgery was observed in other studies. The greatest protective effect of perioperative β-blockers on all-cause death was observed in patients undergoing vascular surgery.[9] Bisoprolol, when started at least 1 week before vascular surgery and continued for another 30 days after surgical procedures, showed a significant 78% risk reduction of all-cause death compared with placebo.

Similar results were obtained in the MaVS (Metoprolol after Vascular Surgery) trial.[10] Patients undergoing abdominal aortic surgery and infrainguinal or axillofemoral revascularizations were randomized to receive metoprolol ($n = 246$) or placebo ($n = 250$). During a 30-day follow-up, the incidence of all-cause death was remarkably lower in the metoprolol group (0.4%) compared with the placebo group (2.8%).

Rationale for Perioperative β-Blockade

MI is the most frequent cause of death during and after surgery. A recent overview[6] of prospective cohort studies, gathering a sample of more than 300 patients, estimated that 3.9% (95% CI 3.3, 4.6) of patients experience a major perioperative cardiac event including cardiac death, MI, and cardiac arrest after non-cardiac surgery. The cause of cardiac death was attributable to MI in about 66% of the cases and to arrhythmia or heart failure in 34%. Notably, in-hospital mortality may range from 15% to 25% in patients with MI during or immediately after non-cardiac surgery.[43-46] Moreover, non-fatal perioperative MI is an independent risk factor for CV death and new non-fatal MI during the 6 months following surgery.[47]

Several basic mechanisms may contribute to explain the benefit of perioperative β-blockers. These drugs are expected to

consistently reduce myocardial oxygen supply and demand.[48] As left ventricular coronary perfusion occurs predominantly during diastole, coronary blood flow decreases particularly distal to coronary stenoses and in the metabolically active subendocardium. Reducing the heart rate directly decreases oxygen demand via reversal of the Bowditch-Treppe effect (proportional change in contractility with heart rate).[48]

In addition, the complex inter-relationships between the sympathetic nervous system, the heart, and the innate inflammatory immune response may provide other explanations for the benefit of perioperative β-blockade. β-Blockers may limit activation of inflammatory responses including leukocyte recruitment, metalloproteinase activity, monocyte activation, growth factor release, and inflammatory cytokine responses.[49,50] Selective blockade of β1-receptors inhibits leukocyte chemotaxis, free radical production, and monocyte activation. These mechanisms decrease the levels of inflammatory cytokines in the myocardium[51] and systemic circulation.[52]

Other potential effects of perioperative β-blockade have been suggested including antiarrhythmic and antirenin effects and augmentation of natriuretic peptide release.[53] In particular, β-blockers have antiarrhythmic effects, especially in the setting of acute ischemia: they reduce circulating free fatty acids via inhibition of lipolysis, protecting against ventricular fibrillation and sudden cardiac death.[48] Finally, β-blockers have demonstrated prophylactic properties mediated by an enhanced rate control in perioperative atrial dysrhythmias.[48]

Future Directions of Clinical Research

Some aspects of perioperative β-blocker use remain unaddressed, as suggested by the recent updates of ESC and ACC/AHA guidelines.[48]

It is unclear whether the potential benefit of β-blockers in patients undergoing non-cardiac surgery is a class effect that is equally valid for all agents. Studies that documented a clear protective effect of perioperative β-blockade in non-cardiac surgery used β1-receptor-selective agents with a long duration of action. A recent population-based, retrospective cohort analysis[54] included 37 151 elderly consecutive patients admitted for elective surgery and receiving atenolol or metoprolol. Of these, 1038 patients experienced an MI or died, and the rate of this composite endpoint was significantly lower for patients receiving atenolol than for those receiving metoprolol (2.5% vs 3.2%, $p < 0.001$). Moreover, the lower risk observed in the atenolol group remained significant after adjustment for measured demographic, medical, and surgical factors.[54]

Clinical studies are also needed to determine (i) the most appropriate timing of starting treatment with β-blockers before surgery, and (ii) the duration of therapy after the surgical procedure. Experimental models would support starting β-blockers as soon as possible before surgery. β-Blockers seem to have a direct effect on the modulation of intracellular signaling processes, including those involved in apoptosis. Importantly, decreased apoptosis has been reported only in carvedilol- and propranolol-pretreated rabbit hearts subjected to ischemia-reperfusion injury.[55] However, an early preoperative assessment and therapy with β-blockers started at least 7 days before vascular surgery demonstrated a significant prognostic impact.[9]

The relationship between duration of β-blocker therapy after surgery and the risk of major CV events is also unclear. In a prospective, observational clinical study, 323 patients aged 50 years or older with ischemic heart disease and admitted to hospital for elective non-cardiac surgery were studied[45] to determine the incidence of periprocedural MI. Overall, 50% of all MIs were observed within the first 48 hours after the day of surgery and the peak incidence occurred during the first postoperative night. The time distribution of periprocedural CV events after surgery probably supports the use of β-blockers for at least 2 days after surgery.

Another aspect that should be considered is the synergistic effect of concomitant therapies (i.e. antiplatelet agents, statins). The DECREASE-IV trial[24] properly assessed this topic. In this trial,[24] patients were randomized to receive combination treatment with bisoprolol and fluvastatin, or combination placebo control. Patients who received bisoprolol with or without fluvastatin had a significant reduction in the 30-day incidence of cardiac death and non-fatal MI compared with those who did not receive bisoprolol. Fluvastatin was associated with a favorable trend on this outcome, but failed to reach statistical significance.[24]

Limitations

A meta-analysis based on individual patient data, as opposed to aggregate data, can facilitate subgroup analyses and provide a more balanced interpretation and wider endorsement of the results.[56] Individual patient data were unavailable from RCTs included in our systematic review and the effects of β-blockers on different patient-specific risk classes (identified by the combinations of clinical information and laboratory tests) could not be performed.

Multivariable analyses[57-60] identified several combinations of clinical predictors, generally including ECG findings, history, and general medical status of patients, that could be used to estimate the risk of cardiac complications in individual

patients. However, these indices may not have sufficient discrimination to predict cardiac risk in patients with vascular disease,[61] and very little is known about the calibration of these prognostic models.[62] Conversely, high-risk type of surgery is identified as an independent predictor of major CV complications in all the multivariable analyses used to develop different risk indices, including the Revised Cardiac Risk Index (RCRI).[63] In addition, a recent systematic review[64] showed that the RCRI discriminated moderately well between patients at low versus high risk for cardiac events after mixed non-cardiac surgery, but it did not perform well at predicting cardiac events after vascular non-cardiac surgery or at predicting death.

Implications for Clinical Practice

The protective role and safety of extensive use of β-blockers in patients undergoing non-cardiac surgery is still under discussion. According to current guidelines,[1,3] patients on long-term β-blocker therapy should not discontinue treatment perioperatively. For patients not already on β-blocker therapy, initiation of therapy should be considered prior to high-risk surgery. Such therapy should be tailored to achieve hemodynamic stability (titrated to heart rate and blood pressure) and to avoid inappropriate acute administration of high doses. A treatment protocol such as that adopted in the POISE trial[8] might have been too aggressive, especially for older patients who had never received a β-blocker in the past. Presumably, it could promote hemodynamic instability and hypotension, especially in patients with left ventricular dysfunction.[8]

The most appropriate timing of starting treatment with β-blockers before surgery and the duration of therapy after undergoing a surgical procedure is not well established. Current guidelines[1,3] recommend starting treatment with β-blockers between 30 days and 1 week before surgery with a target resting heart rate of 60–70 beats/min and systolic blood pressure of >100 mmHg. Moreover, postoperative tachycardia requires, first of all, diagnosis and management of potential underlying causes (i.e. hypovolemia, hemorrhage, infection) before considering up-titration of the β-blocker dosage.

The usefulness of β-blockers remains unproven in patients who are undergoing either intermediate- or low-risk procedures and their routine administration is not recommended.

Conclusions

Although the perioperative use of β-blockers in non-cardiac surgery is still controversial, our analysis showed that β-blockade was associated with a significant reduced risk of mortality (61%) in patients undergoing high-risk non-cardiac surgery compared with patients in the lower risk categories.

In addition, dose titration of β-blockers targeted on heart rate may contribute to explaining the beneficial effect of these drugs.

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Appendix

List of excluded trials (n = 49)

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