Perioperative β blockers in patients having non-cardiac surgery: a meta-analysis

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Summary

Background **American College of Cardiology and American Heart Association (ACC/AHA) guidelines on perioperative assessment recommend perioperative β blockers for non-cardiac surgery, although results of some clinical trials seem not to support this recommendation. We aimed to critically review the evidence to assess the use of perioperative β blockers in patients having non-cardiac surgery.**

Methods **We searched Pubmed and Embase for randomised controlled trials investigating the use of β blockers in non-cardiac surgery. We extracted data for 30-day all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, heart failure, and myocardial ischaemia, safety outcomes of perioperative bradycardia, hypotension, and bronchospasm.**

Findings **33 trials included 12 306 patients. β blockers were not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality, or heart failure, but were associated with a decrease (odds ratio [OR] 0·65, 95% CI 0·54–0·79) in non-fatal myocardial infarction (number needed to treat [NNT] 63) and decrease (OR 0·36, 0·26–0·50) in myocardial ischaemia (NNT 16) at the expense of an increase (OR 2·01, 1·27–3·68) in non-fatal strokes (number needed to harm [NNH] 293). The beneficial effects were driven mainly by trials with high risk of bias. For the safety outcomes, β blockers were associated with a high risk of perioperative bradycardia requiring treatment (NNH 22), and perioperative hypotension requiring treatment (NNH 17). We recorded no increased risk of bronchospasm.**

Interpretation **Evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. The ACC/AHA guidelines committee should soften their advocacy for this intervention until conclusive evidence is available.**

Funding **None.**

Introduction

The 2007 update on perioperative β blocker therapy in the American College of Cardiology and American Heart Association (ACC/AHA) guidelines for perioperative cardiovascular assessment for non-cardiac surgery recommends β blockers for patients already on therapy or who are having vascular surgery and have ischaemia on preoperative testing (class I) and for those having vascular surgery or intermediate or high-risk non-vascular surgery with high risk for coronary disease or those with established disease (class II).[1] Consequently, the Physicians Consortium for Performance Improvement and the Surgical Care Improvement Project both recommend perioperative β blockade.[2]

Some randomised trials do not support recommendations in the guidelines and have shown no beneficial effect of perioperative β blockade.[3–5] Despite these findings, the most recent ACC/AHA guideline update in 2007 states that "although many of the randomised controlled trials of β blocker therapy are small, the weight of evidence—especially in aggregate—suggests a benefit to perioperative β blockade during non-cardiac surgery in high-risk patients".[1] In the recently published, landmark POISE (perioperative ischaemic evaluation) trial,[6] perioperative metoprolol was associated with a 30% reduction in non-fatal myocardial infarction at the expense of 33% increased risk of all-cause mortality and a 117% increased risk of stroke.

We aimed to critically review the evidence for perioperative β blockers in patients undergoing non-cardiac surgery.

Methods

Search strategy and selection criteria

We searched Pubmed, Embase, and the Cochrane Library with the terms "β adrenergic blockers", "adrenergic βantagonist", "βblockers", "perioperative", "preoperative", and "intraoperative". We restricted our search to studies in human beings from January, 1966, to May, 2008. We checked the reference lists of identified articles, previous meta-analyses, and original studies identified by the electronic search to find other potentially eligible studies. There was no language restriction for the search. Authors of papers were contacted when results were unclear or when relevant data were not reported.

To be eligible, studies had to be randomised controlled trials with comparison of β blockers (intravenous or oral) with controls (other drugs, placebo, or no intervention) that started in the perioperative period in patients with or without cardiovascular comorbidities, that were of

non-cardiac surgery, and that assessed perioperative efficacy and safety outcomes within 30 days of surgery.

Three investigators (SB, SP, and SS) extracted data independently and in duplicate and assessed trial eligibility and quality (κ=0·96). Disagreements were resolved by consensus. The quality of trials was assessed with the methods recommended by the Cochrane Collaboration for assessing risk of bias.[7] The criteria used for quality assessment were sequence generation of allocation, allocation concealment, masking of participants, personnel, and outcome assessors, incomplete outcome data, selective outcome reporting, and other sources of bias. We classified studies with high or unclear risk for bias for any of the first three components as low quality.

Outcomes

The efficacy outcomes of interest were 30-day all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, and heart failure. The safety outcomes of interest were perioperative adverse events (bradycardia, hypotension, and bronchospasm).

Statistical analysis

The meta-analysis was done in line with recommendations from the Cochrane Collaboration and the Quality of Reporting of Meta-analyses guidelines[7,8] with standard software (Stata version 9.0).[9] Analyses were on an intention-to-treat basis. Heterogeneity was assessed with I^2 statistics.[10] I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance), we regarded I^2 of less than 25% as low and I^2 of more than 75% as high. We calculated the results with odds ratios (ORs) and 95% confidence intervals with the use of the Peto method.[11,12] The Peto OR is the best approach when there are few events in individual trials. We also present data analysed with other statistical techniques in our sensitivity analysis. Publication bias was estimated visually by funnel plots or by use of the Begg's test and the weighted regression test of Egger.[13] Numbers needed to treat or harm (NNT or NNH) were calculated from ORs.

Sensitivity analysis was done for nine sets of subgroups. Trials with low risk of bias were compared with those with high risk. We analysed subgroups of medical risk (the total percentage of patients with known coronary artery disease in each of the trials was used as a rough estimate of the medical risk grouping for each trial; trials with 25% or more patients with known coronary artery disease were regarded as having high medical risk groups, others were low medical risk trials). Surgical risk categories of trials were compared on the basis of classification of surgical procedures as recommended by the ACC/AHA guidelines for perioperative assessment of patients having non-cardiac surgery.[1] Other subgroup analyses were done for elderly patients (mean age ≥60 years) compared with young patients (others); duration of β blockade (premedication for ≤1 day *vs* >1 day); whether the protocol allowed for β-blocker up-titration for a heart-rate target or not; heart rate achieved in the β-blocker group (as an indicator of adequacy of β blockade); proportion of patients with perioperative bradycardia needing treatment (indicator of a possible excess β-blocker dose); and proportion of patients with perioperative hypotension needing treatment (indicator of a possible excess β-blocker dose). If any effects of treatment differed between subgroups ($p<0·05$), we estimated the difference according to tests of interaction.[14]

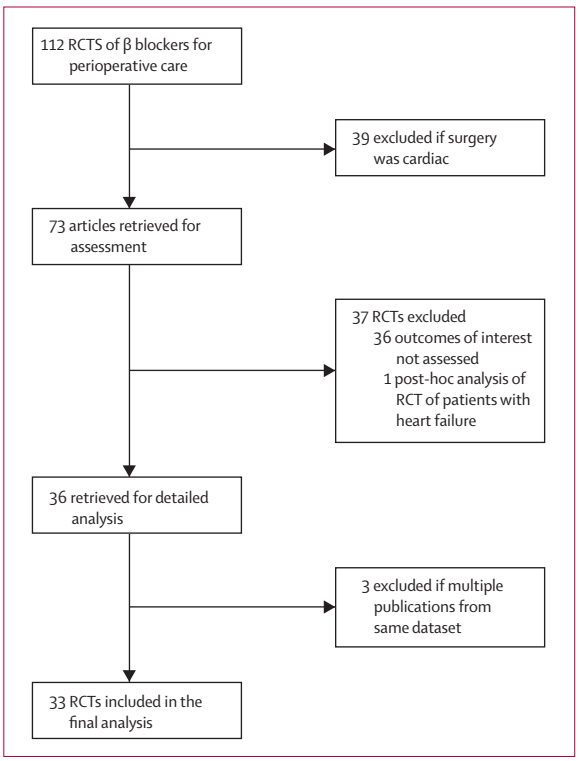

Figure 1: **Selection of studies**

Trial sequential analysis

In a single randomised trial, interim analyses increase the risk of type-1 error. To avoid an increase of overall type-1 error, monitoring boundaries can be used to decide whether a trial could be stopped early because of the p value being sufficiently small. Because no reason exists why the standards for a meta-analysis should be less rigorous than those for a single trial, analogous trial sequential monitoring boundaries can be used.[15,16] The underlying assumption for this analysis is that significance testing is done each time a new trial is published. Trial sequential analysis depends on the quantification of the required information size. In this context, the smaller the required information size, the more lenient the trial sequential analysis, thus the more lenient the criteria for statistical significance.[15,16] Cumulative meta-analyses of trials are at

risk of producing random errors from repetitive testing of accumulating data, and the information-size requirement, analogous to the sample size of a single clinical trial, might not be met.[15,16] The trial sequential analysis was done to maintain an overall 5% risk of type-1 error (the standard in most meta-analyses and systematic reviews) and we calculated the required information size (ie, the meta-analysis information size needed to detect or reject a certain intervention effect with a 20% risk of type-2 and power of 80%).[15,16] Information-size calculations were based on an assumption of plausible reductions in relative risk in the low-bias trials and on an a priori reduction of 15% for non-fatal myocardial infarction or 75% increase in relative risk for non-fatal stroke.[15,16]

	Mean age (years)	AHA/ACC surgical procedure risk class	Cardiac inclusion criteria	β-blocker therapy (n)	Comparison (n)	Preoperative drug dose	Postoperative drug dose	Duration of treatment
Bayliff (1999)[22]	62·5	Intermediate	12% with CAD	Propranolol (49)	Placebo (50)	10 mg by mouth	10 mg four times daily by mouth	5 days
BBSA (2007)[31]	70	Intermediate	Known CAD or with at least two risk factors for CAD	Bisoprolol (112)	Placebo (112)	5–10 mg by mouth	5–10 mg by mouth daily	10 days or until discharge
Burns (1988)[41]	34·2	Intermediate	No known CAD	Nadolol (39)	Placebo (47)	20–40 mg 12 h presurgery	None	Premedication only
Coleman (1980)[42]	41·5	Intermediate	None described	Metoprolol (27)	Placebo (15)	2 mg or 4 mg intravenously	None	Premedication only
Cucchiara (1986)[23]	NR	Intermediate	Patients with MI in past 6 months and CHF were excluded	Esmolol (37)	Placebo (37)	500 μg/kg/min for 4 min; 300 μg/kg/min for 8 min	None	Premedication only
Davies (1992)[24]	68·5	Intermediate	27·5% with CAD	Atenolol (20)	Placebo (20)	50 mg by mouth, 2 h before surgery	None	Premedication only
DIPOM (2006)[4]	64·8	Intermediate–high	61·5% with CAD	Metoprolol (462)	Placebo (459)	100 mg by mouth, 2 h before induction, or 5 mg intravenously	100 mg daily to discharge or maximum 8 days	Hospital discharge
Gibson (1988)[43]	51·5	Intermediate	None described	Esmolol (21)	Placebo (19)	40 mg/min for 4 min before extubation and then 24 mg/min for 10 min	10 min after extubation	Discharge from recovery room
Inada (1989)[44]	NR	Intermediate	Patients with CHF, UA excluded	Labetalol (20)	Placebo (10)	5 mg or 10 mg 2 min before anaesthesia	None	Premedication only
Jakobsen (1986)[25]	32·9	Intermediate	No cardiovascular disease	Metoprolol (9)	Placebo (10)	50 mg 1 day before and 100 mg 1·5–3·0 h before anaesthesia	None	Premedication only
Jakobsen (1990)[46]	38·5	Intermediate	None described	Metoprolol (50)	Placebo (50)	100 mg by mouth, 1–3 h before surgery	None	Premedication only
Jakobsen (1992)[45]	41	Intermediate	No cardiac disease	Metoprolol (20)	Placebo (20)	100 mg by mouth 1–2·5 h before surgery	None	Premedication only
Jakobsen (1997)[34]	60·6	Intermediate	Patients without cardiovascular problems	Metoprolol (18)	Placebo (18)	100 mg by mouth 1·5 h before surgery	100 mg by mouth, daily	4–10 days
Lai (2006)[35]	66·5	Intermediate	No cardiac disease	Metoprolol (30)	Control (30)	0·02 mg/kg intravenously before and 5 min after intubation, same dose after skin incision with up-titration to maintain heart rate between 50–80 BPM	25 mg by mouth three times daily	3 days
Leslie (1989)[47]	NR	Intermediate	None described	Labetalol (40)	Placebo (20)	0·25, 0·5, 0·75 or 1 mg/kg just before surgery	None	Premedication only
Liu PL (1986)[48]	45·2	Intermediate	None described	Esmolol (16)	Placebo (14)	500 μg/kg/min for 4 min; 300 μg/kg/min for 8 min given 5 min before anaesthesia	None	Premedication only
Liu YH (2006)[36]	69·5	Intermediate	No cardiac disease	Metoprolol (15)	Placebo (15)	0·5 mg and 1·5 mg intravenously before anaesthesia and after tracheal intubation	None	Premedication only
Mackenzie (1989)[49]	NR	Intermediate	None described	Timolol (25)	Placebo (25)	10 mg 72 min before anaesthesia	None	Premedication only
Magnusson (1986)[50]	62	Intermediate	7·5% with previous MI	Metoprolol (19)	Placebo (21)	200 μg/kg intravenously 20 min before anaesthesia	None	Premedication only
Magnusson (1986)[37]	57·5	Intermediate	No previous MI or CHF	Metoprolol (15)	Placebo (15)	200 mg/day for 2 weeks before surgery, 15 mg intravenously 15 min before anesthesia	None	Premedication only
MaVS (2006)[5]	66·1	High	13·5% with CAD; no history of CHF	Metoprolol (246)	Placebo (250)	50–100 mg 2 h before surgery repeat 2 h later	50–100 mg twice daily	Day 5 or until discharge

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	Mean age (years)	AHA/ACC surgical procedure risk class	Cardiac inclusion criteria	β-blocker therapy (n)	Comparison (n)	Preoperative drug dose	Postoperative drug dose	Duration of treatment
(Continued from previous page)								
Miller (1991)[26]	56	Intermediate	10·4% with CAD; no MI or CHF within 6 min	Esmolol (368)	Placebo (180)	100 or 200 mg intravenously just before anaesthesia	None	Premedication only
Miller (1990)[40]	NR	High	With CAD or ≥2 risk factors but no CHF or MI within 6 months	Esmolol (30)	Placebo (15)	1·5 mg/kg or 3·0 mg/kg just before anaesthesia	None	Premedication only
Neary (2006)[27]	NR	High	High risk for cardiac complications	Atenolol (18)	Placebo (20)	1·25 mg atenolol intravenously before anaesthesia and every 30 min during surgery to a max of 5 mg	50 mg by mouth daily or 5 mg intravenously twice daily	7 days
POBBLE (2005)[3]	73·5	High	Previous MI excluded	Metoprolol (55)	Placebo (48)	50 mg twice daily up to surgery and then minimum 100 mg on morning of surgery, 2–4 mg intravenously over 5–10 min before intubation	50 mg twice daily	7 days
POISE (2007)[6]	69	Intermediate–high	With a history of CAD, peripheral artery disease, stroke, or CHF within the past 3 years or with three of seven risk factors*	Metoprolol CR (4174)	Placebo (4177)	100 mg in the 2–4 h before surgery, 100 mg in 6 h after, and 200 mg 12 h later	200 mg daily	30 days
Poldermans (1999)[32]	67·5	High	51·5% with CAD; abnormal dobutamine stress echocardiography	Bisoprolol (59)	Standardised care (53)	5–10 mg/day for 1 week before surgery	5–10 mg/day	30 days
Raby (1999)[28]	68	Intermediate–high	Preoperation ischaemia on holter monitor testing	Esmolol (15)	Placebo (11)	100 μg/kg/min immediately after surgery	100–300 μg/kg/min	2 days
Rosenberg (1996)[29]	56·5	Low	None described	Metoprolol (19)	Placebo (19)	100 mg by mouth 2 h before endoscopy	None	Premedication only
Stone (1988)[38]	65·2	Intermediate–high	9·4% with CAD	Labetalol, Atenolol, Oxprenolol (89)	Untreated (39)	Labetalol 100 mg, atenolol 50 mg, or oxprenolol 20 mg 2 h before induction	None	Premedication only
Urban (2000)[39]	69·5	Intermediate	16·8% patients with previous MI; 21·5% with angina; known or probable ischaemic heart disease	Esmolol/ Metoprolol (52)	Placebo (55)	250 mg/h intravenously within 1 h after surgery, oral thereafter	50 mg/day by mouth	2 days
Wallace (1998)[30]	67·5	Intermediate–high	44% with CAD known CAD	Atenolol (99)	Placebo (101)	5–10 mg intravenously 30 min before induction of anaesthesia	10–20 mg/day intravenously or 50–100 mg/day by mouth	7 days
Zaugg (1999)[33]	74·5	Intermediate	37% with previous MI; known CAD but without CHF	Atenolol (43)	Untreated (20)	5–10 mg intravenously 30 min before induction	10–20 mg intravenously	3 days

BBSA=Beta Blocker in Spinal Anesthesia study. BPM=beats per minute. CAD=coronary artery disease. DIPOM=Diabetic Postoperative Mortality and Morbidity trial. DM=diabetes mellitus. MaVs=Metoprolol After Vascular Surgery trial. MI=myocardial infarction. POBBLE=PeriOperative Beta–BLockadE trial. POISE=Perioperative Ischemic Evaluation trial. UA=unstable angina. *Risk factors: having high-risk surgery, history of chronic heart failure (CHF), diabetes mellitus (DM), renal insufficiency, ≥70 years of age, history of transient ischaemic attack, or undergoing urgent or emergent surgery.

Table 1: **Baseline characteristics of trials included**

Because of the low risk of the outcomes in our meta-analysis, several trials report zero events in both β blocker and control groups. Exclusion of these trials could inflate the size of pooled treatment effects.[17] To compensate for this we applied an empirical continuity correction of 0·01 in zero-event trials as a sensitivity analysis as suggested by Friedrich and colleagues.[17] We used the empirical continuity correction of 0·01 suggested by Sweeting and co-workers.[12]

Role of the funding source

There were no sponsors for this study. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We identified 112 randomised controlled trials, of which 73 were retrieved for detailed assessment (figure 1). We excluded 40 trials—36 of which did not evaluate outcomes of interest, one that was a small subgroup analysis from a larger non surgical cohort,[18] and three that were multiple publications from the same dataset[19–21]—leaving 33 trials that fulfilled our inclusion criteria.

Table 1 and the webtable summarise the baseline characteristics, and quality assessment, respectively. The

See Online for webtable

33 trials included 12 306 patients having non-cardiac surgery, 6311 (51%) patients randomly assigned to the β-blocker group, and 5995 (49%) to the control group. The β blocker used, dose given, timing of administration, and the duration of administration varied in the trials (table 1). The definitions used for efficacy and safety outcomes were heterogeneous (webtable).

Of 33 randomised controlled trials included in the analysis, 16 reported adequate generation of the allocation sequence and adequate allocation concealment, and 19 reported adequate masking of participants, personnel, and outcome assessors (webtable). On the basis of the quality assessment, 13 trials were deemed as low bias risk,[4–6,22–31] with the rest classed as high bias risk (webtable).

For the overall cohort, β blocker therapy was not associated with any significant reduction in the risk of all-cause mortality, cardiovascular mortality (figure 2), or heart failure (figure 3), but was associated with a 35% decreased risk of non-fatal myocardial infarction (NNT 63) and a 64% decreased risk of myocardial ischaemia (NNT 16) at the expense of a 116% increased risk of non-fatal strokes (NNH 275; figure 3).

The beneficial effect of β blockers for some outcomes was driven by trials with high bias risk. We recorded no increase in the risk of all-cause mortality, 81% decreased risk of non-fatal myocardial infarction (NNT 15), and 69% decreased risk of myocardial ischaemia (NNT 9) with no significant beneficial effect on the outcomes of cardiovascular mortality and heart failure (figures 2 and 3). However, analysis of low bias risk trials showed a 28% increased risk of all-cause mortality (NNH 164) and a 116% increased risk of non-fatal stroke (NNH 275), with only a 28% decreased risk of non-fatal myocardial infarction (NNT 80), 59% decreased risk of myocardial ischaemia (NNT 23), and no beneficial effect on the outcomes of cardiovascular mortality and heart failure (figures 2 and 3). A test for interaction showed significant effects of trial quality on all-cause mortality, cardiovascular mortality, and non-fatal myocardial infarction (figures 2 and 3).

Heterogeneity was small for all-cause mortality, cardiovascular mortality, non-fatal myocardial infarction, and myocardial ischaemia, mainly driven by trials with high bias risk. The tests for publication bias were negative (webfigure 1).

See Online for webfigures 1–4

The trial-sequential-monitoring boundary constructed for an intervention effect on 30-day mortality suggested by the low-bias trials with a required information size of 14183 participants is not crossed by the cumulative *Z* curve, which indicates that the crossing of the traditional boundary (p=0·05) might be a random error. The cumulative *Z* curve is, however, close to breaking through the trial sequential monitoring boundary (webfigure 2).

The cumulative *Z*-curve for trials with low bias risk does not cross any of the boundaries, neither the traditional (p=0·05) nor the trial sequential monitoring boundary constructed for a required information size of 34862 participants, which indicates lack of evidence for any effect of perioperative β blockade on cardiovascular mortality (webfigure 2).

The cumulative *Z*-curve crosses the traditional boundary (p=0·05) as well as the trial sequential monitoring boundary constructed for a required information size of 22579 supporting the evidence that perioperative β blockade reduces the occurence of non-fatal myocardial infarction among survivors by 15% (webfigure 2).

The trial sequential monitoring boundary constructed for a required information size of 12188 participants is crossed supporting an association between perioperative β blockade and increased occurrence of non-fatal stroke by at least 75% among survivors (webfigure 2).

Analysing all low bias risk trials for any of the above outcomes, including zero-event trials, did not noticeably change the results (results not shown).

For the entire cohort, β blockers were associated with a high risk of perioperative bradycardia (OR 3·13, 95% CI 2·51–3·92, p<0·0001; I^2=29·5; NNH 8; webfigure 3) perioperative bradycardia requiring treatment (NNH 22; figure 4), perioperative hypotension (1·69, 1·39–2·05, p<0·0001; I^2=3·4; NNH 11; webfigure 4) and perioperative hypotension requiring treatment (NNH 17; figure 5). However, we recorded no increased risk of bronchospasm (figure 6).

There was increased risk of perioperative adverse haemodynamic outcomes across the quality subgroups. However, there was a greater risk of perioperative hypotension (figure 5) requiring treatment in high-bias risk trials than in low-bias risk trials with a significant test for interaction (p=0·041).

There was modest heterogeneity for the outcome of perioperative bradycardia with no or low heterogeneity for other safety outcomes (figure 4).

The POISE trial carried the greatest weight for all of the above analyses. A sensitivity analysis with or without POISE showed that before POISE, there was a 53% reduction in the risk of non-fatal myocardial infarction and a 64% reduction in the risk of myocardial ischaemia, with no beneficial effect for other efficacy outcomes with β blockers compared with controls (tables 2 and 3). POISE showed a 31% reduction in the risk of non-fatal myocardial infarction at the expense of 34% increased risk of all-cause mortality and an 89% increased risk of non-fatal stroke. However the tests for interaction between these groups (before POISE and with POISE) were not significant for any of the outcomes (tables 2 and 3).

Of 33 trials, seven enrolled high medical-risk patients (≥25% of patients in the trial with known coronary artery disease).[4,6,24,28,30,32,33] The test for interaction did not show a significant effect of the medical risk category on any of the efficacy outcomes (tables 2 and 3).

17 trials enrolled elderly patients (mean age ≥60 years).[3–6,22,24,28,30–39] However, the test for interaction did

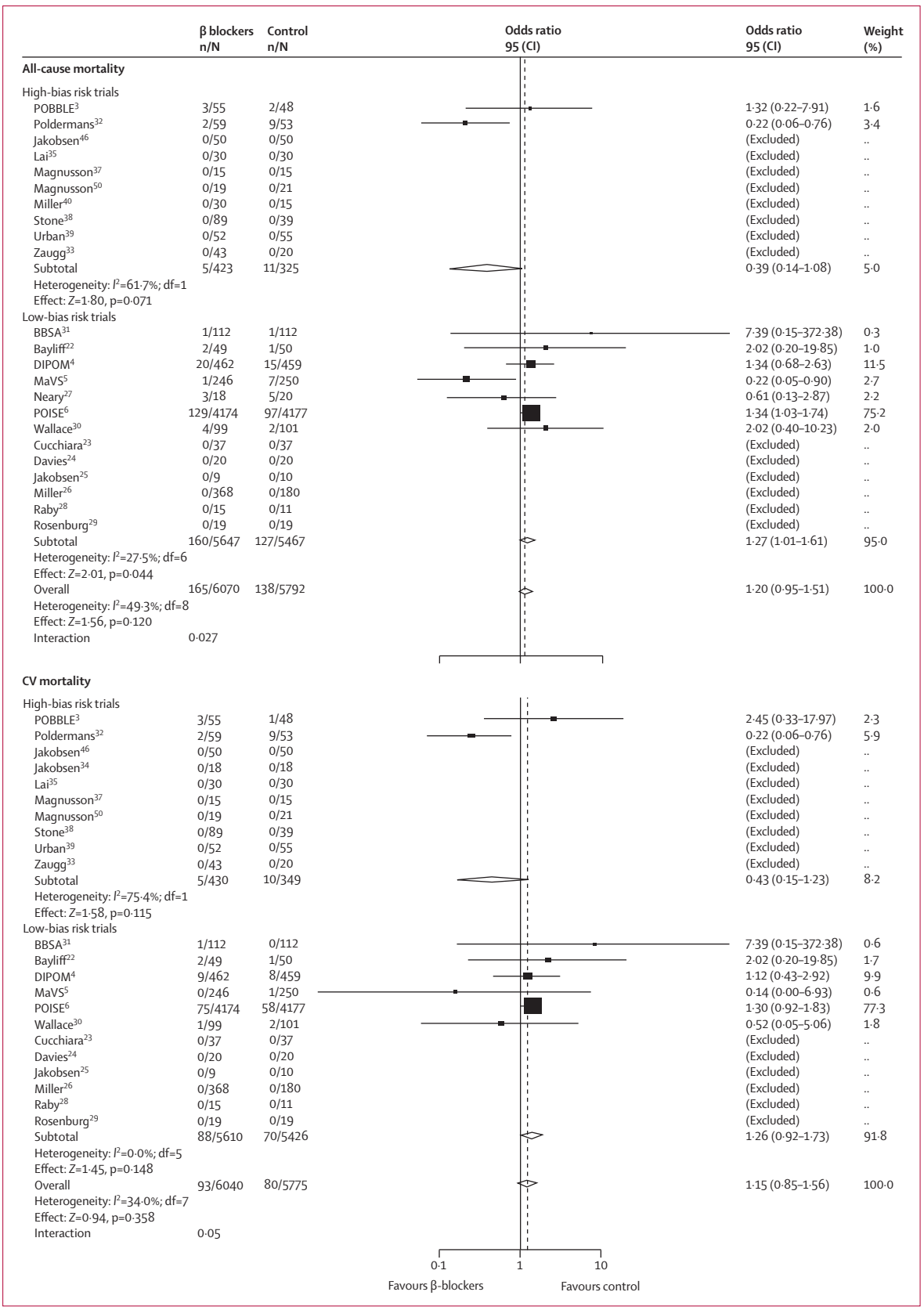


Figure 2: **Odds ratios for mortality outcomes associated with perioperative treatment with β blockers**

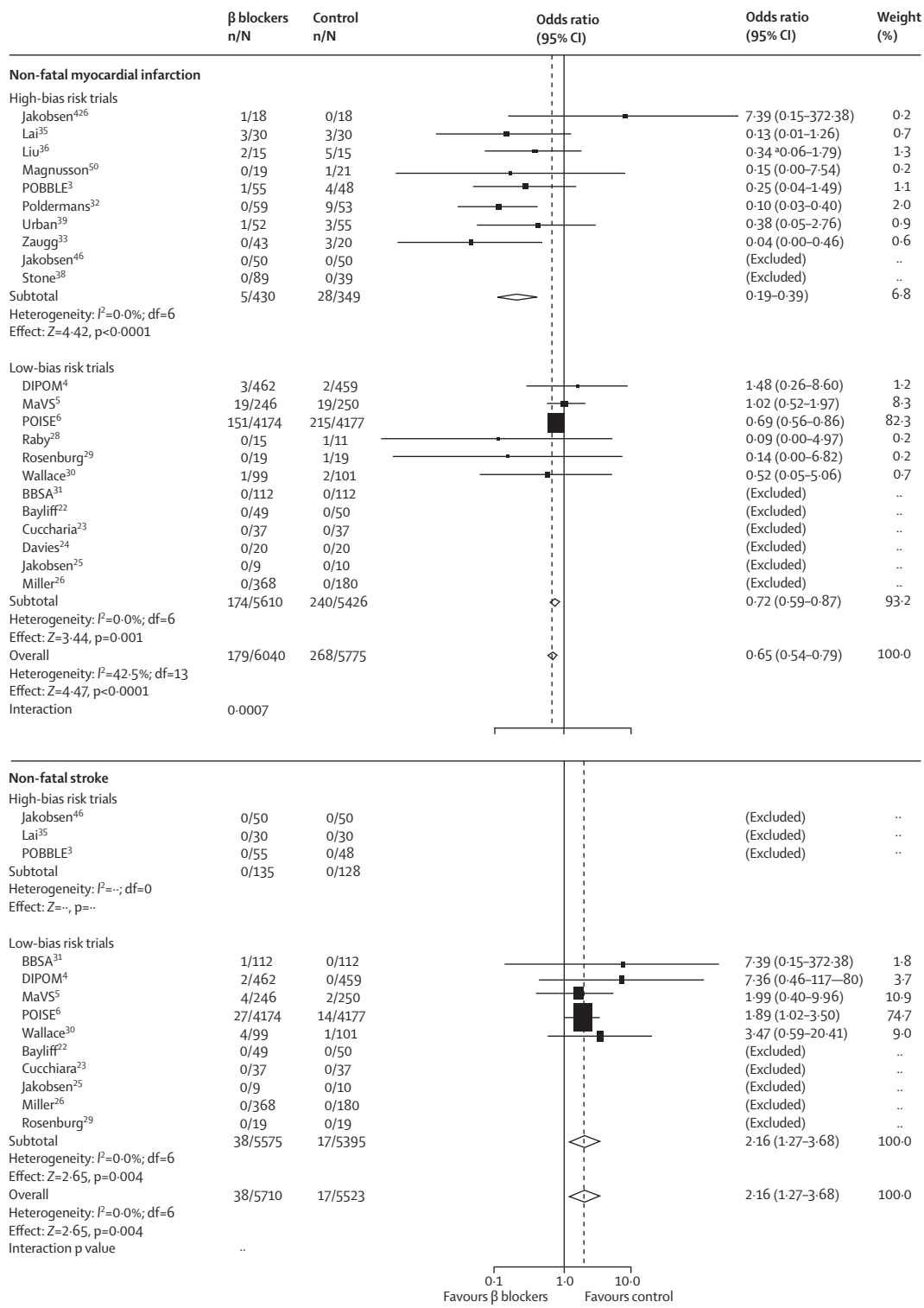
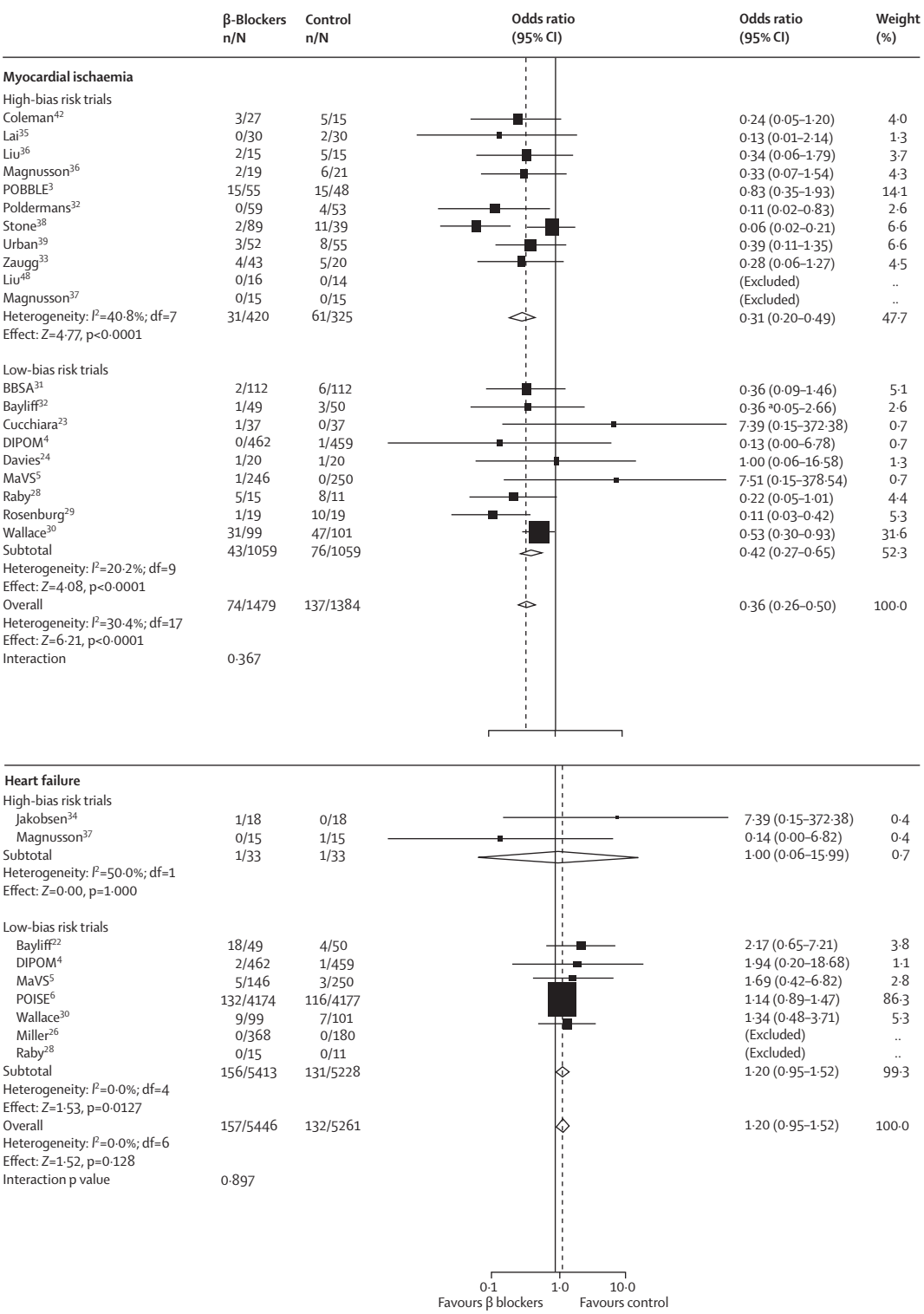


Figure 3: **Odds ratios for 30-day non-fatal safety outcomes associated with perioperative treatment with β blockers**


β-Blockers n/N
Control n/N
Odds ratio (95% CI)
Odds ratio (95% CI)
Weight (%)
Myocardial ischaemia
High-bias risk trials
Coleman[42] 3/27 5/15 0·24 (0·05–1·20) 4·0
Lai[35] 0/30 2/30 0·13 (0·01–2·14) 1·3
Liu[36] 2/15 5/15 0·34 (0·06–1·79) 3·7
Magnusson[36] 2/19 6/21 0·33 (0·07–1·54) 4·3
POBBLE[3] 15/55 15/48 0·83 (0·35–1·93) 14·1
Poldermans[32] 0/59 4/53 0·11 (0·02–0·83) 2·6
Stone[38] 2/89 11/39 0·06 (0·02–0·21) 6·6
Urban[39] 3/52 8/55 0·39 (0·11–1·35) 6·6
Zaugg[33] 4/43 5/20 0·28 (0·06–1·27) 4·5
Liu[48] 0/16 0/14 (Excluded) ..
Magnusson[37] 0/15 0/15 (Excluded) ..
Heterogeneity: I^2=40·8%; df=7 31/420 61/325 0·31 (0·20–0·49) 47·7
Effect: Z=4·77, p<0·0001
Low-bias risk trials
BBSA[31] 2/112 6/112 0·36 (0·09–1·46) 5·1
Bayliff[32] 1/49 3/50 0·36 [a]0·05–2·66) 2·6
Cucchiara[23] 1/37 0/37 7·39 (0·15–372·38) 0·7
DIPOM[4] 0/462 1/459 0·13 (0·00–6·78) 0·7
Davies[24] 1/20 1/20 1·00 (0·06–16·58) 1·3
MaVS[5] 1/246 0/250 7·51 (0·15–378·54) 0·7
Raby[28] 5/15 8/11 0·22 (0·05–1·01) 4·4
Rosenburg[29] 1/19 10/19 0·11 (0·03–0·42) 5·3
Wallace[30] 31/99 47/101 0·53 (0·30–0·93) 31·6
Subtotal 43/1059 76/1059 0·42 (0·27–0·65) 52·3
Heterogeneity: I^2=20·2%; df=9
Effect: Z=4·08, p<0·0001
Overall 74/1479 137/1384 0·36 (0·26–0·50) 100·0
Heterogeneity: I^2=30·4%; df=17
Effect: Z=6·21, p<0·0001
Interaction 0·367
Heart failure
High-bias risk trials
Jakobsen[34] 1/18 0/18 7·39 (0·15–372·38) 0·4
Magnusson[37] 0/15 1/15 0·14 (0·00–6·82) 0·4
Subtotal 1/33 1/33 1·00 (0·06–15·99) 0·7
Heterogeneity: I^2=50·0%; df=1
Effect: Z=0·00, p=1·000
Low-bias risk trials
Bayliff[22] 18/49 4/50 2·17 (0·65–7·21) 3·8
DIPOM[4] 2/462 1/459 1·94 (0·20–18·68) 1·1
MaVS[5] 5/146 3/250 1·69 (0·42–6·82) 2·8
POISE[6] 132/4174 116/4177 1·14 (0·89–1·47) 86·3
Wallace[30] 9/99 7/101 1·34 (0·48–3·71) 5·3
Miller[26] 0/368 0/180 (Excluded) ..
Raby[28] 0/15 0/11 (Excluded) ..
Subtotal 156/5413 131/5228 1·20 (0·95–1·52) 99·3
Heterogeneity: I^2=0·0%; df=4
Effect: Z=1·53, p=0·0127
Overall 157/5446 132/5261 1·20 (0·95–1·52) 100·0
Heterogeneity: I^2=0·0%; df=6
Effect: Z=1·52, p=0·128
Interaction p value 0·897
0·1
1·0
10·0
Favours β blockers
Favours control

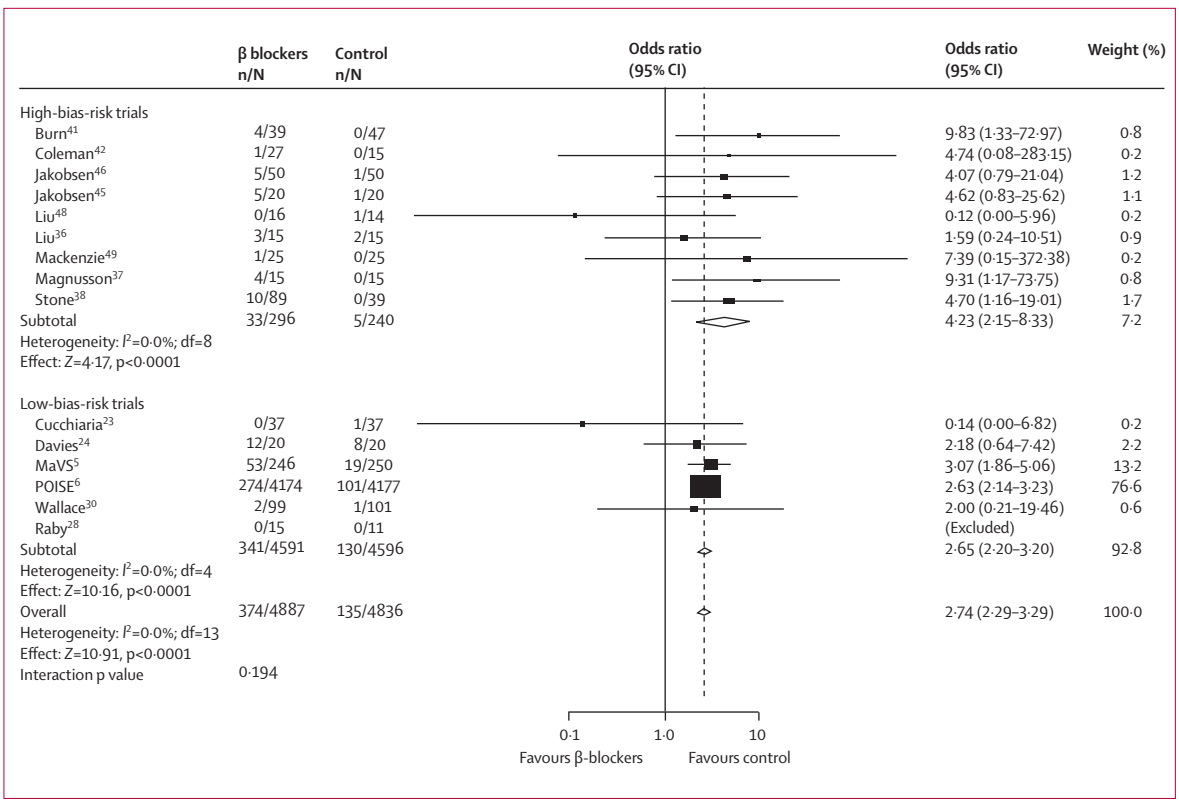


Figure 4: **Odds ratios for perioperative bradycardia requiring treatment associated with treatment with β blockers**

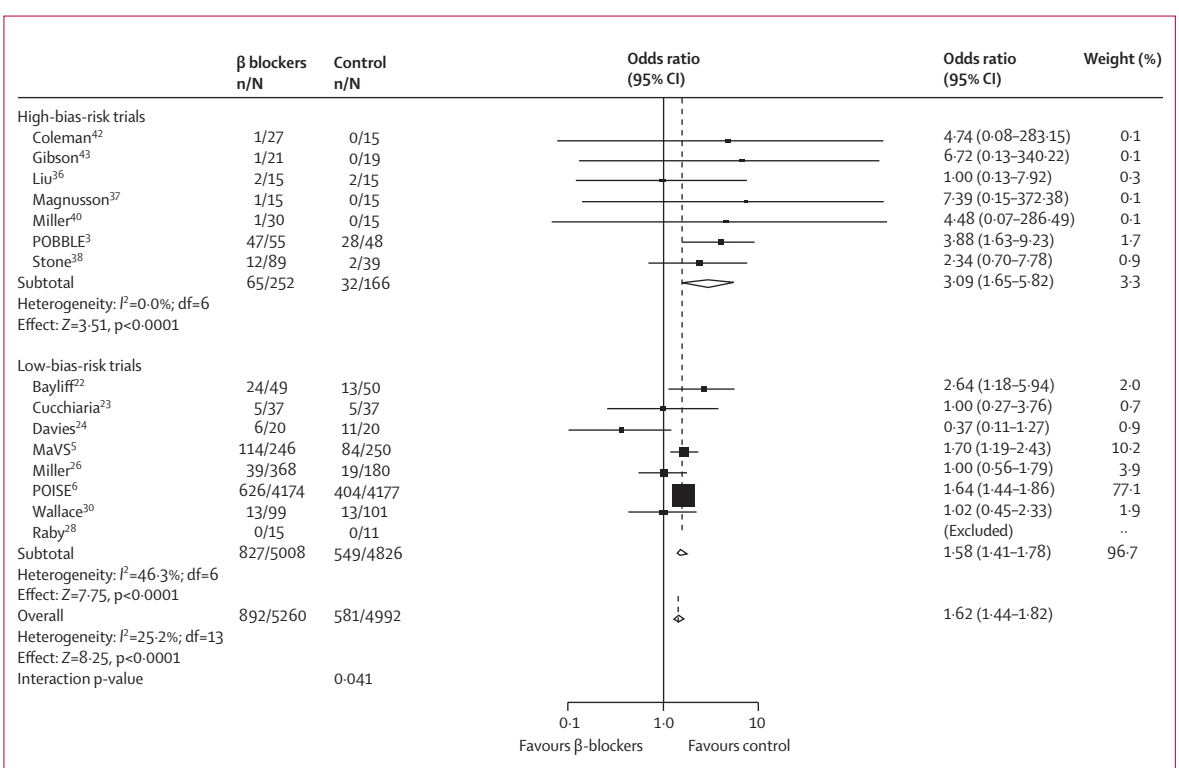


Figure 5: **Odds ratios for perioperative hypotension requiring treatment associated with treatment with β blockers**

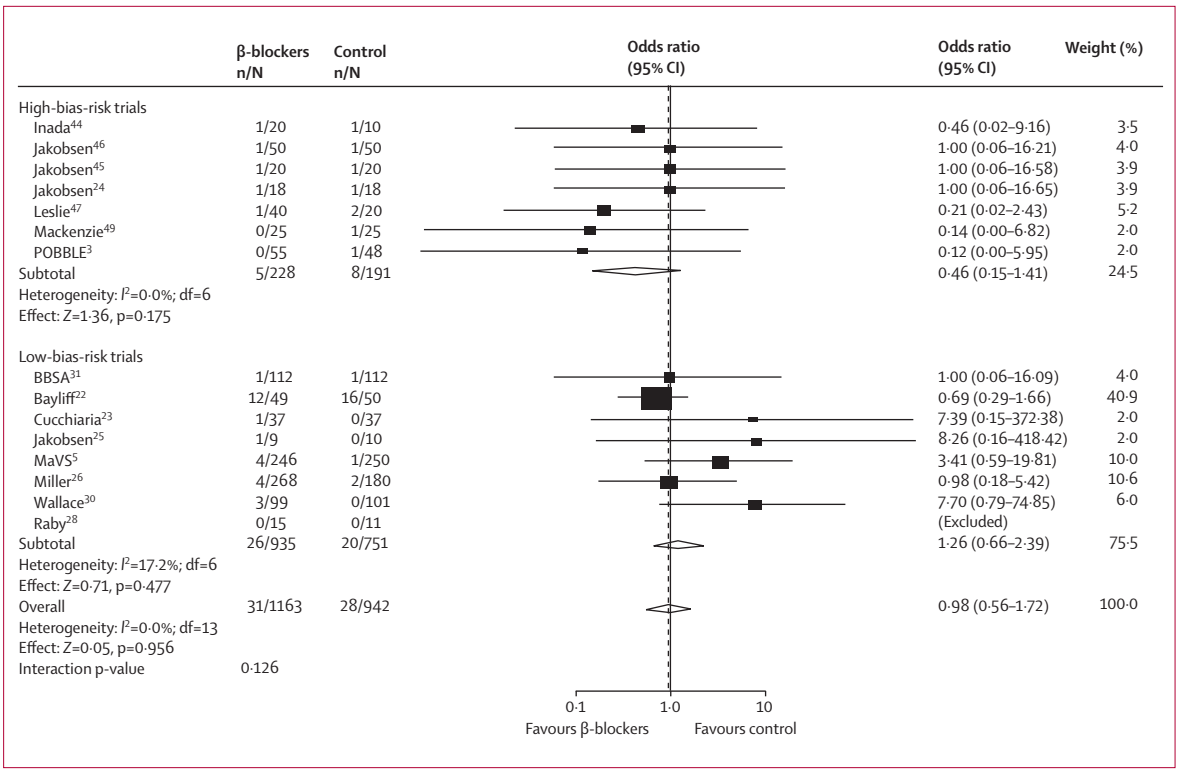


Figure 6: **Odds ratios for perioperative bronchospasm requiring treatment associated with treatment with β blockers**

not show a significant effect of age category on any of the efficacy outcomes.

Five trials enrolled high surgical-risk patients (emergency surgery, vascular surgery),[3,5,27,32,40] five enrolled intermediate-risk or high surgical-risk patients,[4,6,28,30,38] 22 enrolled intermediate surgical-risk patients (intrathoracic, intraperitoneal, carotid endarterectomy, head and neck, orthopedic, or prostate surgery),[22–26,31,33–37,39,41–50] and one enrolled low surgical-risk patients.[29] A sensitivity analysis on the basis of surgical risk categories showed a 63% decreased risk of all-cause mortality and a 44% decreased risk of non-fatal myocardial infarction in trials with high surgical risk (tables 2 and 3); this finding was driven largely by the trial by Poldermans and colleagues.[32] However, in the intermediate–high surgical risk trials, there was a 30% reduction in the risk of non-fatal myocardial infarction, 66% reduction in the risk of myocardial ischaemia, at the expense of a 35% increased risk of all-cause mortality and a 113% increased risk of non-fatal stroke (tables 2 and 3), which was driven mainly by the POISE trial.[6]

In 14 trials, the study drug was given for more than 1 day,[3–6,22,27,28,30–35,39] whereas the rest of the trials used the study drugs for 1 day or less. A test for interaction suggested a role of duration of β blockade for the outcome of myocardial ischaemia such that patients who received β blockade for 1 day or less had a greater decrease in the risk of myocardial ischaemia than did those who received the treatment for longer (84% *vs* 55% decrease; tables 2 and 3).

Only six trials[28,31–33,35,39] allowed for an increase of study drugs to a target heart rate in their protocol. The effect of drug increase was significant for the outcomes of all-cause mortality, cardiovascular mortality, and non-fatal myocardial infarction, such that there was a significant decrease in the risk of these outcomes with β blockade in the trials which allowed for an increase compared with those that did not (tables 2 and 3).

15 trials achieved a mean heart rate of 75 beats per min or less at study end in the β-blocker group,[3–6,25,28,31,32,34,36,37,43,45,46,50] whereas in nine trials the mean heart rate was greater than 75 beats per min.[23,26,29,30,33,35,38,39,48] Heart rate achieved was not significant for any of the efficacy outcomes apart from non-fatal myocardial infarction—trials that achieved heart rate of 75 beats per min or less reported a lower reduction in risk than did the other group (tables 2 and 3).

In the studies that reported proportion of patients with bradycardia requiring treatment, eight trials[5,24,36–38,41,45,46] reported 10% or greater incidence of bradycardia in the β-blocker group, whereas four[6,30,42,49] reported less than 10% incidence. Test for interaction suggested a significant effect for the outcome of all-cause mortality, such that trials with 10% or greater incidence of bradycardia showed greater beneficial effect of β blockers than did other trials (tables 2 and 3).

However, the test for interaction based on proportion of patients with hypotension requiring treatment in the β-blocker group suggested no interaction effect for any of the efficacy outcomes.

Discussion

Our meta-analysis of randomised controlled trials in patients having non-cardiac surgery showed no clear benefit of perioperative β blockers compared with control for the prevention of cardiovascular outcomes. For the overall cohort, we estimate that treatment of 1000 patients with β blockers results in 16 fewer non-fatal myocardial infarctions in survivors but at the expense of three disabling strokes, 45 patients with clinically significant perioperative bradycardia, 59 with hypotension, and potentially increased mortality.

In patients having non-cardiac surgery, myocardial infarction is the most common fatal complication

	All-cause mortality		Cardiovascular mortality		Non-fatal myocardial infarction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Statistical method						
Fixed-effect OR (CC)	B 165/6070; C 138/5792	1·20 (0·95 to 1·51)	B 93/6040; C 80/5775	1·15 (0·85 to 1·56)	B 179/6040; C 268/5775	0·65 (0·54 to 0·79)
Fixed-effect RR (CC)	B 165/6070; C 138/5792	1·19 (0·95 to 1·49)	B 93/6040; C 80/5775	1·15 (0·86 to 1·54)	B 179/6040; C 268/5775	0·66 (0·55 to 0·79)
Fixed-effect RD (CC)	B 165/6070; C 138/5792	0·005 (–0·001 to 0·010)	B 93/6040; C 80/5775	0·002 (–0·002 to 0·007)	B 179/6040; C 268/5775	–0·016 (–0·023 to –0·009)
Effect of POISE						
Pre-POISE	B 36/1896; C 41/1615	0·86 (0·54 to 1·36)	B 18/1866; C 22/1598	0·78 (0·41 to 1·46)	B 28/1866; C 53/1598	0·47 (0·30 to 0·74)
POISE	B 129/4174; C 97/4177	1·34 (1·03 to 1·74)	B 75/4174; C 58/4177	1·30 (0·92 to 1·83)	B 151/4174; C 215/4177	0·69 (0·56 to 0·86)
Interaction p value	..	0·102	..	0·166	..	0·132
Medical risk categories						
High	B 155/4891; C 123/4862	1·26 (0·99 to 1·60)	B 87/4891; C 77/4862	1·12 (0·82 to 1·53)	B 155/4891; C 233/4862	0·65 (0·53 to 0·80)
Low	B 7/1025; C 10/789	0·68 (0·26 to 1·77)	B 6/1043; C 3/807	1·87 (0·50 to 7·03)	B 24/1043; C 34/807	0·65 (0·38 to 1·10)
Interaction p value	..	0·209	..	0·459	..	0·872
Age						
Elderly (≥60 years)	B 162/5524; C 133/5446	1·22 (0·97 to 1·54)	B 93/5542; C 80/5464	1·15 (0·85 to 1·56)	B 179/5557; C 267/5479	0·65 (0·54 to 0·79)
Young (<60 years)	..	..	..	..	B 0/446; C 1/259	0·13 (0·003 to 6·82)
Interaction p value	..	..	..	..	..	0·415
Surgical risk categories						
Intermediate	B 3/804; C 1/600	2·80 (0·39 to 20·21)	B 3/622; C 1/618	2·80 (0·39 to 20·21)	B 4/822; C 15/618	0·24 (0·09 to 0·63)
Intermediate–high	B 153/4839; C 114/4787	1·35 (1·06 to 1·72)	B 85/4839; C 69/4787	1·25 (0·91 to 1·73)	B 155/4839; C 220/4787	0·70 (0·57 to 0·86)
High	B 9/408; C 23/386	0·37 (0·18 to 0·77)	B 5/360; C 11/351	0·40 (0·14 to 1·10)	B 20/360; C 32/351	0·56 (0·32 to 0·97)
Duration of β blockade						
≤1 day	B 0/637; C 0/385	..	B 0/607; C 0/370	..	B 2/607; C 6/370	0·29 (0·06 to 1·36)
>1 day	B 165/5433; C 138/5407	1·20 (0·95 to 1·51)	B 93/5433; C 80/5405	1·15 (0·85 to 1·56)	B 177/5433; C 262/5405	0·66 (0·54 to 0·79)
Interaction p value	..	..	..	..	..	0·305
Up-titration of β blockers for a target heart rate						
No	B 162/5759; C 129/5511	1·27 (1·00 to 1·60)	B 90/5729; C 71/5494	1·27 (0·93 to 1·73)	B 178/5729; C 249/5494	0·70 (0·58 to 0·85)
Yes	B 3/311; C 9/281	0·30 (0·09 to 0·98)	B 3/311; C 9/281	0·30 (0·09 to 0·98)	B 1/311; C 19/281	0·12 (0·05 to 0·30)
Interaction p value	..	0·019	..	0·024	..	0·0002
Heart rate achieved on β blockade						
≤75 BPM	B 156/5216; C 130/5206	1·20 (0·95 to 1·52)	B 90/5234; C 77/5224	1·16 (0·85 to 1·58)	B 177/5234; C 256/5224	0·67 (0·56 to 0·82)
>75 BPM	B 4/737; C 2/481	2·02 (0·40 to 10·23)	B 1/737; C 2/481	0·52 (0·05 to 5·06)	B 2/737; C 12/481	0·19 (0·06 to 0·56)
Interaction p value	..	0·540	..	0·509	..	0·029
Percentage of patients with bradycardia						
<10%	B 133/5273; C 99/4278	1·35 (1·04 to 1·76)	B 76/4273; C 60/4278	1·27 (0·91 to 1·78)	B 152/4273; C 217/4278	0·69 (0·56 to 0·85)
≥10%	B 1/420; C 7/374	0·22 (0·05 to 0·90)	B 0/420; C 1/374	0·14 (0·00 to 6·93)	B 21/420; C 24/374	0·80 (0·44 to 1·46)
Interaction p value	..	0·015	..	0·266	..	0·648
Percentage of patients with hypotension						
<15%	B 4/638; C 2/387	2·02 (0·40 to 10·23)	B 1/608; C 2/372	0·52 (0·05 to 5·06)	B 3/608; C 7/372	0·39 (0·10 to 1·51)
≥15%	B 135/4544; C 107/4545	1·27 (0·98 to 1·63)	B 80/4544; C 61/4545	1·31 (0·94 to 1·83)	B 171/4544; C 238/4545	0·70 (0·58 to 0·86)
Interaction p value	..	0·579	..	0·437	..	0·403

B=β-blocker group. BPM=beats per minute. C=control group.

Table 2: **Sensitivity analyses**

accounting for 10–40% of postoperative fatalities.[51] Despite recent advances in risk stratification and treatment of these patients, the 30-day mortality remains high (3–5%).[52] By extrapolation of the cardioprotective properties from patients with established coronary artery disease, β blockers have been promoted as potentially improving cardiovascular outcomes perioperatively.

Our meta-analysis of 33 trials and 12 306 patients provides an updated systematic review that is strengthened by the inclusion of POISE. Although β blockers were associated with a decreased risk of non-fatal myocardial infarction and myocardial ischaemia, they were associated with an increased risk of non-fatal stroke, and possibly with increased mortality. The apparent beneficial effect of β blockers was largely driven by high bias risk trials, whereas subgroup analyses of more reliable trials with low bias risk showed increased risk for all-cause mortality and non-fatal strokes. The excess stroke risk is consistent

	Non-fatal stroke		Heart failure		Myocardial ischaemia	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Statistical method						
Fixed-effect OR (CC)	B 38/5710; C 17/5523	2·02 (1·18 to 3·46)	B 157/5446; C 132/5261	1·20 (0·95 to 1·52)	B 74/1479; C 137/1384	0·37 (0·27 to 0·52)
Fixed-effect RR (CC)	B 38/5710; C 17/5523	2·01 (1·18 to 3·43)	B 157/5446; C 132/5261	1·19 (0·95 to 1·49)	B 74/1479; C 137/1384	0·48 (0·38 to 0·62)
Fixed-effect RD (CC)	B 38/5710; C 17/5523	0·004 (0·001 to 0·006)	B 157/5446; C 132/5261	0·005 (0·001 to 0·011)	B 74/1479; C 137/1384	–0·054 (-0·071 to -0·036)
Effect of POISE						
Pre-POISE	B 11/1536; C 3/1346	2·34 (0·90 to 6·09)	B 25/1272; C 16/1084	1·63 (0·86 to 3·07)	B 74/1479; C 137/1384	0·36 (0·26 to 0·50)
POISE	B 27/4174; C 14/4177	1·89 (1·02 to 3·50)	B 132/4174; C 116/4177	1·14 (0·89 to 1·47)	NR	NR
Interaction p value	..	0·713	..	0·305	..	..
Medical risk categories						
High	B 33/4735; C 15/4737	2·13 (1·21 to 3·76)	B 143/4750; C 124/4748	1·16 (0·91 to 1·48)	B 43/717; C 72/685	0·41 (0·26 to 0·64)
Low	B 5/869; C 2/680	1·52 (0·44 to 5·31)	B 14/696; C 8/513	1·83 (0·77 to 4·34)	B 26/663; C 50/614	0·37 (0·22 to 0·61)
Interaction p value	..	0·629	..	0·292	..	0·767
Age						
Elderly (≥60 years)	B 38/5227; C 17/5227	2·01 (1·20 to 3·37)	B 157/5063; C 131/5066	1·21 (0·96 to 1·53)	B 69/1365; C 122/1284	0·39 (0·28 to 0·54)
Young (<60 years)	..	..	B 0/383; C 1/195	0·13 (0·003 to 6·82)	B 4/77; C 15/63	0·15 (0·05 to 0·43)
Interaction p value	..	..	..	0·259	..	0·096
Surgical risk categories						
Intermediate	B 1/655; C 0/469	7·39 (0·15 to 372·38)	B 9/450; C 5/263	1·92 (0·64 to 5·77)	B 19/435; C 41/404	0·35 (0·20 to 0·61)
Intermediate–high	B 33/4735; C 15/4737	2·13 (1·21 to 3·76)	B 143/4750; C 124/4748	1·16 (0·91 to 1·48)	B 38/665; C 67/610	0·34 (0·21 to 0·55)
High	B 4/301; C 2/298	1·27 (0·34 to 4·76)	B 5/246; C 3/250	1·69 (0·42 to 6·82)	B 16/360; C 19/351	0·67 (0·31 to 1·44)
Duration of β blockade						
≤1 day	B 0/483; C 0/296	..	B 0/383; C 1/195	0·13 (0·00 to 6·82)	B 10/238; C 32/174	0·16 (0·08 to 0·33)
>1 day	B 38/5227; C 13/4737	2·01 (1·20 to 3·37)	B 157/5063; C 131/5066	1·21 (0·96 to 1·53)	B 64/1241; C 105/1210	0·45 (0·32 to 0·65)
Interaction p value	..	..	..	0·259	..	0·01
Up-titration of β blockers for a target heart rate						
No	B 37/5568; C 17/5381	1·97 (1·17 to 3·31)	B 157/5431; C 132/5250	1·20 (0·95 to 1·52)	B 60/1168; C 104/1103	0·40 (0·28 to 0·58)
Yes	B 1/142; C 0/142	7·39 (0·15 to 372·38)	B 0/15; C 0/11	..	B 14/311; C 33/281	0·27 (0·14 to 0·51)
Interaction p value	..	0·517	..	..	..	0·299
Heart rate achieved on β blockade						
≤75 BPM	B 34/5108; C 16/5106	1·91 (1·11 to 3·28)	B 140/4930; C 121/4930	1·16 (0·91 to 1·49)	B 27/998; C 45/984	0·44 (0·26 to 0·76)
>75 BPM	B 4/553; C 1/367	3·47 (0·59 to 20·41)	B 9/467; C 7/281	1·34 (0·48 to 3·71)	B 42/385; C 83/385	0·32 (0·21 to 0·49)
Interaction p value	..	0·545	..	0·750	..	0·361
Percentage of patients with bradycardia						
<10%	B 31/4273; C 15/4278	2·02 (1·13 to 3·61)	B 141/4273; C 123/4278	1·15 (0·90 to 1·47)	B 34/126; C 52/116	0·48 (0·28 to 0·83)
≥10%	B 4/296; C 2/300	1·27 (0·34 to 4·76)	B 5/261; C 4/265	1·27 (0·34 to 4·73)	B 6/385; C 17/339	0·18 (0·07 to 0·44)
Interaction p value	..	0·528	..	0·884	..	0·07
Percentage of patients with hypotension						
<15%	B 4/504; C 1/318	3·47 (0·59 to 20·41)	B 9/482; C 8/296	1·16 (0·43 to 3·11)	B 39/282; C 68/222	0·36 (0·23 to 0·83)
≥15%	B 31/4524; C 16/4525	1·76 (1·01 to 3·08)	B 145/4469; C 123/4477	1·19 (0·93 to 1·51)	B 18/370; C 19/368	0·81 (0·39 to 1·69
Interaction p value	..	0·474	..	0·961	..	0·103

B=β blocker group. BPM=beats per minute. C=control group.

Table 3: **Sensitivity analyses**

with data on increased stroke risk with β blockers seen in patients with hypertension.[63] The analysis based on trials with high bias risk was dominated by Polderman and colleagues' trial,[32] in which 52% of patients had had previous myocardial infarction and all patients had a positive stress test. These patients might have needed to be on a β blocker for secondary prevention irrespective of the need to undergo surgery.

Our results also emphasise the need to closely monitor patients for bradycardia and hypotension. For the overall cohort, β-blocker intervention was associated with a significantly increased risk of perioperative bradycardia (overall), bradycardia requiring treatment, hypotension, and hypotension requiring treatment. In the POISE trial,[6] perioperative hypotension (hazard ratio 4·32, 95% CI 3·22–5·80) and bradycardia (1·99, 1·35–2·92) were independent predictors of all-cause mortality and, hence, these safety outcomes are not benign. However, the dose of metoprolol XL used in POISE was equivalent to eight times the dose of bisoprolol used in Poldermans and colleagues' trial. In view of the weight of this trial on the final analyses, whether high dose of the β blocker resulted in excess events in the POISE trial is unclear. In POISE, 15% of patients on β blockers developed clinically significant hypotension. However, the proportion of patients who developed hypotension was higher in other trials (Davies and colleagues 30%, MaVs 46%, Bayliff and co-workers 49%, POBBLE 85%) in the β-blocker arm, and a sensitivity analysis based on percentage of patients who developed clinically significant hypotension found no interaction effect (tables 2 and 3).

Our sensitivity analysis showed that for the high surgical risk group β blockers were associated with a decreased risk of all-cause mortality and non-fatal myocardial infarction, which was driven mainly by Poldermans and colleagues' trial. The preliminary results of the POISE trial seem to suggest the beneficial effects of β blockers in the vascular-surgery subgroup. Because there were only five strokes in the β-blocker group and four in the control group, the safety or lack thereof of β blockers for the endpoint of stroke in patients having high-risk vascular surgery cannot be attested with confidence. Our sensitivity analysis also indicated the beneficial effect of β blockers in the subgroup of trials which allowed for increase of these drugs to a target heart rate. In the six trials that allowed for an increase of β-blocker dose, three were unblinded,[32,33,39] in one the blinding was ineffective,[28] and one other trial did not report blinding.[35] Moreover, none of these trials reported incidences of clinically significant hypotension or bradycardia. Although in this analysis we noted no interaction effect of the heart rate achieved, a recent meta-analysis of ten trials found that more rigorous heart rate control (maximum perioperative heart rate 99 beats per minute) was associated with decreased risk of perioperative myocardial infarction but at the expense of increased risk of heart failure and bradycardia.[64] However, this analysis assessed myocardial infarction only, and four of the ten trials in these analyses were unblinded.

Finally, trial sequential analysis showed that β blockers might decrease the risk of non-fatal myocardial infarction by 15% and increase the risk of non-fatal strokes by 75%. For the outcome of all-cause mortality, the sequential monitoring boundaries are close to being crossed, suggesting harm.

As in other meta-analyses, because of the lack of data in each trial, we did not adjust our analyses for doses of drugs used nor for compliance to assigned therapy. We were not able to adjust our analyses for the type of β blocker used, the duration, and the protocol followed, which differed among the trials. Although detailed sensitivity analyses on most of these variables were done, given heterogeneity in the protocol, clinically relevant differences could have been missed in these analyses and are best assessed in meta-analyses of data for individual patients. There was heterogeneity in the definition of some outcomes (especially myocardial ischaemia) in the trials. None of the trials reported all the efficacy and safety outcomes. The sample size is too small to derive any definitive conclusions about the role of β blockers in high-risk surgery. We assessed short-term clinical benefit only and, hence, these results cannot be extrapolated into long-term clinical effects. The various subgroup analyses could be affected by multiple testing and hence the results from the subgroup analyses are, at best, hypothesis generating.

Evidence does not support the use of β-blocker therapy for the prevention of perioperative clinical outcomes in patients having non-cardiac surgery. β blockers seem to increase the risk of stroke and possibly all-cause mortality but decrease the risk of non-fatal myocardial infarction. In view of the increased risk of stroke, bradycardia, and hypotension (which were independent predictors of death in the POISE trial), β blockers should not be routinely used for perioperative treatment of patients undergoing non-cardiac surgery unless patients are already taking them for clinically indicated reasons (heart failure, coronary artery disease, previous myocardial infarction). The ACC/AHA guideline committee should soften their stance on perioperative β blockade until definitive evidence shows clear benefit. Use of perioperative β blockade as a performance measure, when there is no robust evidence for improved outcome, is inappropriate.

Contributors

SB and FHM came up with the concept and design, SB, SP, and SS gathered the data, SB, JW, CG, and FHM analysed and interpreted the data and drafted and critically revised the paper, SB, JW, and CG did the statistical analysis, FHM supervised the study.

Conflict of interest statement

SB, JW, SP, SS, and CG declare that they have no conflict of interest. FHM has received speakers fees from Abbott, GlaxoSmithKline, Novartis, Pfizer, AstraZeneca, Bayer, Boehringer Ingelheim, BMS, Forest, Sankyo, and Sanofi and research grants from GlaxoSmithKline, Pfizer, Novartis, and CardioVascular Therapeutics. None of the authors received any compensation for their work on this manuscript.

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