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Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Blessberger H, Kammler J, Domanovits H, Schlager O, Wildner B, Azar D, Schillinger M, Wiesbauer F, Steinwender C

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[Intervention Review]

Perioperative beta-blockers for preventing surgery-related mortality and morbidity

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ABSTRACT

Background

Randomized controlled trials have yielded conflicting results regarding the ability of beta-blockers to influence perioperative cardiovascular morbidity and mortality. Thus routine prescription of these drugs in unselected patients remains a controversial issue.

Objectives

The objective of this review was to systematically analyse the effects of perioperatively administered beta-blockers for prevention of surgery-related mortality and morbidity in patients undergoing any type of surgery while under general anaesthesia.

Search methods

We identified trials by searching the following databases from the date of their inception until June 2013: MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), Biosis Previews, CAB Abstracts, Cumulative Index to Nursing and Allied Health Literature (CINAHL), Derwent Drug File, Science Citation Index Expanded, Life Sciences Collection, Global Health and PASCAL. In addition, we searched online resources to identify grey literature.

Selection criteria

We included randomized controlled trials if participants were randomly assigned to a beta-blocker group or a control group (standard care or placebo). Surgery (any type) had to be performed with all or at least a significant proportion of participants under general anaesthesia.

Data collection and analysis

Two review authors independently extracted data from all studies. In cases of disagreement, we reassessed the respective studies to reach consensus. We computed summary estimates in the absence of significant clinical heterogeneity. Risk ratios (RRs) were used for dichotomous outcomes, and mean differences (MDs) were used for continuous outcomes. We performed subgroup analyses for various potential effect modifiers.

Main results

We included 88 randomized controlled trials with 19,161 participants. Six studies (7%) met the highest methodological quality criteria (studies with overall low risk of bias: adequate sequence generation, adequate allocation concealment, double/triple-blinded design with a placebo group, intention-to-treat analysis), whereas in the remaining trials, some form of bias was present or could not be definitively excluded (studies with overall unclear or high risk of bias). Outcomes were evaluated separately for cardiac and non-cardiac surgery.

CARDIAC SURGERY (53 trials)

We found **no clear evidence of an effect** of beta-blockers on the following outcomes.

- **All-cause mortality:** RR 0.73, 95% CI 0.35 to 1.52, 3783 participants, moderate quality evidence.
- **Acute myocardial infarction (AMI):** RR 1.04, 95% CI 0.71 to 1.51, 3553 participants, moderate quality evidence.
- **Myocardial ischaemia:** RR 0.51, 95% CI 0.25 to 1.05, 166 participants, low quality evidence.
- **Cerebrovascular events:** RR 1.52, 95% CI 0.58 to 4.02, 1400 participants, low quality evidence.
- **Hypotension:** RR 1.54, 95% CI 0.67 to 3.51, 558 participants, low quality evidence.
- **Bradycardia:** RR 1.61, 95% CI 0.97 to 2.66, 660 participants, low quality evidence.
- **Congestive heart failure:** RR 0.22, 95% CI 0.04 to 1.34, 311 participants, low quality evidence.

Beta-blockers significantly **reduced** the occurrence of the following endpoints.

- **Ventricular arrhythmias:** RR 0.37, 95% CI 0.24 to 0.58, number needed to treat for an additional beneficial outcome (NNTB) 29, 2292 participants, moderate quality evidence.
- **Supraventricular arrhythmias:** RR 0.44, 95% CI 0.36 to 0.53, NNTB five, 6420 participants, high quality evidence.
- On average, beta-blockers reduced **length of hospital stay** by 0.54 days (95% CI -0.90 to -0.19, 2450 participants, low quality evidence).

NON-CARDIAC SURGERY (35 trials)

Beta-blockers significantly **increased** the occurrence of the following adverse events.

- **All-cause mortality:** RR 1.25, 95% CI 1.00 to 1.57, 11,413 participants, low quality of evidence, number needed to treat for an additional harmful outcome (NNTH) 167.
- **Hypotension:** RR 1.50, 95% CI 1.38 to 1.64, NNTH 16, 10,947 participants, high quality evidence.
- **Bradycardia:** RR 2.23, 95% CI 1.48 to 3.36, NNTH 21, 11,033 participants, moderate quality evidence.

We found a **potential increase** in the occurrence of the following outcomes with the use of beta-blockers.

- **Cerebrovascular events:** RR 1.59, 95% CI 0.93 to 2.71, 9150 participants, low quality evidence.

Whereas no clear evidence of an effect was found when all studies were analysed, restricting the meta-analysis to low risk of bias studies revealed a significant increase in cerebrovascular events with the use of beta-blockers: RR 2.09, 95% CI 1.14 to 3.82, NNTH 265, 8648 participants.

Beta-blockers significantly **reduced** the occurrence of the following endpoints.

- **AMI:** RR 0.73, 95% CI 0.61 to 0.87, NNTB 76, 10,958 participants, high quality evidence.
- **Myocardial ischaemia:** RR 0.51, 95% CI 0.34 to 0.77, NNTB nine, 978 participants, moderate quality evidence.
- **Supraventricular arrhythmias:** RR 0.73, 95% CI 0.57 to 0.94, NNTB 112, 8744 participants, high quality evidence.

We found **no clear evidence of an effect** of beta-blockers on the following outcomes.

- **Ventricular arrhythmias:** RR 0.68, 95% CI 0.31 to 1.49, 476 participants, moderate quality evidence.
- **Congestive heart failure:** RR 1.18, 95% CI 0.94 to 1.48, 9173 participants, moderate quality evidence.
- **Length of hospital stay:** mean difference -0.45 days, 95% CI -1.75 to 0.84, 551 participants, low quality evidence.

Authors' conclusions

According to our findings, perioperative application of beta-blockers still plays a pivotal role in **cardiac surgery**, as they can substantially reduce the high burden of supraventricular and ventricular arrhythmias in the aftermath of surgery. Their influence on mortality, AMI, stroke, congestive heart failure, hypotension and bradycardia in this setting remains unclear.

In **non-cardiac surgery**, evidence shows an association of beta-blockers with increased all-cause mortality. Data from low risk of bias trials further suggests an increase in stroke rate with the use of beta-blockers. As the quality of evidence is still low to moderate, more evidence is needed before a definitive conclusion can be drawn. The substantial reduction in supraventricular arrhythmias and AMI in this setting seems to be offset by the potential increase in mortality and stroke.

PLAIN LANGUAGE SUMMARY

Influence of beta-blockers on perioperative adverse events

Any type of surgery is associated with an increased stress response, which can make the body vulnerable to untoward outcomes. These outcomes may range from death to a heart attack and rhythm disturbances to heart failure, stroke and the like. Beta-blockers are drugs that attenuate this stress response, which results in slowing down of heart rate and a fall in blood pressure. Whereas on the one hand, these effects are desirable to fight the stress response, the same effects—if pronounced—may cause very low blood pressure, a very low pulse and ultimately stroke or death.

In our analysis of current evidence (88 randomized controlled trials with 19,161 participants: heart surgery—53 trials, other types of surgery—35 trials), we showed that beta-blockers had a protective effect against rhythm disturbances after heart surgery. We found no evidence of an effect of beta-blockers on death; on the occurrence of heart attacks, strokes or heart failure; or on development of disproportionately low blood pressure or slow pulse during this type of surgery. Length of hospital stay after heart surgery was reduced by about 0.5 days in patients taking beta-blockers.

In non-cardiac surgery, beta-blockers increased the risk of death and stroke, the latter only when a representative group of high-quality trials was analysed. The protective effect against heart attacks and rhythm disturbances was counterbalanced by this increased risk of death and stroke. We could not identify evidence of an effect of beta-blockers on heart failure or length of stay in this group of patients.

In conclusion, perioperative use of beta-blockers seems beneficial overall in **cardiac surgery**, as they can substantially reduce the high burden of rhythm disturbances after cardiac surgery. Their influence on death, heart attacks, stroke, heart failure or development of disproportionately low blood pressure or slow pulse in this setting remains unclear.

In **non-cardiac surgery**, evidence shows an increase in death and a potential increase in stroke rate with the use of beta-blockers. The substantial reduction in rhythm disturbances and heart attacks in this setting seems to be offset by this potential increase in mortality and stroke. As the quality of evidence is still low to moderate, more evidence is needed before a definitive conclusion can be drawn.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Beta-blocker versus control—cardiac surgery

Beta-blocker versus control (placebo or standard care) for preventing surgery-related mortality and morbidity

Patient or population: patients with coronary heart disease and/or valvular heart disease

Settings: undergoing cardiac surgery

Intervention: beta-blocker versus control (placebo or standard care)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Beta-blocker versus control (placebo or standard care)				
All-cause mortality (30 days)—cardiac surgery Follow-up: up to 30 days	Study population		RR 0.73 (0.35 to 1.52)	3,783 (24 studies)	⊕⊕⊕⊖ moderate ^a	It was not possible to perform TSA because of the very small sample size.
	7 per 1000	5 per 1000 (2 to 11)				
	Moderate					
	7 per 1000	5 per 1000 (2 to 11)				
Acute myocardial infarction—cardiac surgery Follow-up: up to 30 days	Study population		RR 1.04 (0.71 to 1.51)	3,553 (22 studies)	⊕⊕⊕⊖ moderate ^{a,b}	TSA yielded an inconclusive result.
	28 per 1000	29 per 1000 (20 to 43)				
	Moderate					
	38 per 1000	40 per 1000 (27 to 57)				
Cerebrovascular events—cardiac surgery Follow-up: up to 30 days	Study population		RR 1.52 (0.58 to 4.02)	1,400 (4 studies)	⊕⊕⊕⊖ low ^c	It was not possible to perform TSA because of the very small sample size.
	7 per 1000	11 per 1000 (4 to 30)				

	Moderate					
	10 per 1000	15 per 1000 (6 to 40)				
Ventricular arrhythmias—cardiac surgery ECG Follow-up: up to 30 days	Study population		RR 0.37 (0.24 to 0.58)	2,292 (12 studies)	⊕⊕⊕⊖ moderate^d	TSA yielded an inconclusive result.
	54 per 1000	20 per 1000 (13 to 31)	NNTB: 29,			
	Moderate		95% CI: 24 to 44			
	66 per 1000	24 per 1000 (16 to 38)				
All supraventricular arrhythmias—cardiac surgery ECG Follow-up: up to 30 days	Study population		RR 0.44 (0.36 to 0.53)	6,420 (48 studies)	⊕⊕⊕⊕ high^b	TSA indicated a significant reduction in all supraventricular arrhythmias with the use of beta-blockers.
	345 per 1000	152 per 1000 (124 to 183)	NNTB: 5,			
	Moderate		95% CI: 5 to 6			Upon visual assessment of funnel plots and by applying Egger's test, a reporting bias was detected. However, correcting for the reporting bias did not change the effect estimate. In light of this, the quality of evidence was not downgraded for the presence of a reporting bias in this case.
	367 per 1000	161 per 1000 (132 to 195)				
Bradycardia—cardiac surgery ECG Follow-up: up to 30 days	Study population		RR 1.61 (0.97 to 2.66)	660 (8 studies)	⊕⊕⊕⊖ low^c	It was not possible to perform TSA because of the very small sample size.
	66 per 1000	106 per 1000 (64 to 174)				
	Moderate					
	14 per 1000	23 per 1000 (14 to 37)				
Hypotension—cardiac surgery Follow-up: up to 30 days	Study population		RR 1.54 (0.67 to 3.51)	558 (6 studies)	⊕⊕⊕⊖ low^c	It was not possible to perform TSA because of the very small sample size.
	27 per 1000	42 per 1000 (18 to 96)				

Moderate	
29 per 1000	45 per 1000 (19 to 102)

*The basis for the **assumed risk** is the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **ECG:** electrocardiogram; **NNTB:** number needed to treat for an additional beneficial outcome; **RR:** risk ratio; **TSA:** trial sequential analysis.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aSerious imprecision (-1) due to small sample compared with the calculated optimal information size and the wide confidence interval overlapping zones of no effect as well as potential harm and/or benefit.

^bReporting bias was detected upon visual assessment of the funnel plot and/or by applying Egger's test. Using the trim-and-fill method to adjust for this bias did not change the effect estimate. Thus the quality of evidence was not downgraded, as robustness of the effect estimate was not affected.

^cVery serious imprecision (-2) due to very small sample compared with the calculated optimal information size and the wide confidence interval overlapping zones of no effect as well as potential harm and/or benefit.

^dSerious imprecision (-1) due to small sample size.

Summary of findings 2. Beta-blocker versus control—non-cardiac surgery

Beta-blocker versus control (placebo or standard care) for conditions requiring non-cardiac surgery

Patient or population: patients with conditions requiring non-cardiac surgery

Settings: non-cardiac surgery in general anaesthesia

Intervention: beta-blocker versus control (placebo or standard care)

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Beta-blocker versus control (placebo or standard care)				
All-cause mortality (30 days)—non-cardiac surgery	Study population		RR 1.25 (1.00 to 1.57)	11,413 (13 studies)	⊕⊕⊕⊕ low ^{a,b}	It was not possible to perform TSA because of the small sample size compared with the optimal information size.
	24 per 1000	30 per 1000				

Follow-up: up to 30 days	(24 to 38)		NNTH: 167,			
	Moderate		95% CI: 73 to infinite			
	20 per 1000	26 per 1000 (20 to 31)				
Acute myocardial infarction—non-cardiac surgery Follow-up: up to 30 days	Study population		RR 0.73 (0.61 to 0.87)	10,958 (14 studies)	⊕⊕⊕⊕ high	TSA indicated a significant reduction in the incidence of acute myocardial infarction with the use of beta-blockers.
	49 per 1000	36 per 1000 (30 to 43)	NNTB: 76,			
	Moderate		95% CI: 52 to 157			
	36 per 1000	26 per 1000 (22 to 31)				
Cerebrovascular events—non-cardiac surgery Follow-up: up to 30 days	Study population		RR 1.59 (0.93 to 2.71)	9,150 (5 studies)	⊕⊕⊕⊖ low ^{c,d}	It was not possible to perform TSA because of the small sample size. Studies of poorer methodological quality were shown to introduce a source of bias. When meta-analysis was restricted to trials with an assumed lower risk of bias (placebo-controlled trials), beta-blockers statistically significantly increased the incidence of cerebrovascular events in non-cardiac surgery (RR 2.09, 95% CI 1.14 to 3.82, P value 0.02, NNH 265, 95% CI: 102 to 2058).
	5 per 1000	8 per 1000 (5 to 14)				
	Moderate					
	10 per 1000	16 per 1000 (9 to 27)				
Ventricular arrhythmias—non-cardiac surgery ECG Follow-up: up to 30 days	Study population		RR 0.68 (0.31 to 1.49)	476 (5 studies)	⊕⊕⊕⊖ moderate ^c	It was not possible to perform TSA because of the very small sample size.
	106 per 1000	72 per 1000 (33 to 158)				
	Moderate					
	159 per 1000	108 per 1000 (49 to 237)				
All supraventricular arrhythmias—non-cardiac surgery ECG	Study population		RR 0.73 (0.57 to 0.94)	8,744 (8 studies)	⊕⊕⊕⊕ high	TSA indicated a significant reduction in all supraventricular arrhythmias with the use of beta-blockers.
	33 per 1000	24 per 1000 (19 to 31)	NNTB: 112,			

Follow-up: up to 30 days	Moderate		95% CI: 70 to 505			
	124 per 1000	91 per 1000 (71 to 117)				
Bradycardia—non-cardiac surgery ECG Follow-up: up to 30 days	Study population		RR 2.23 (1.48 to 3.36)	11,033 (23 studies)	⊕⊕⊕⊖ moderate ^e	TSA indicated a significant increase in bradycardia with the use of beta-blockers.
	39 per 1000	87 per 1000 (58 to 131)	NNTH: 21,		95% CI: 11 to 53	
	Moderate					
	40 per 1000	89 per 1000 (59 to 134)				
Hypotension—non-cardiac surgery Follow-up: up to 30 days	Study population		RR 1.50 (1.38 to 1.64)	10,947 (22 studies)	⊕⊕⊕⊕ high	TSA indicated a significant increase in hypotensive episodes with the use of beta-blockers.
	126 per 1000	189 per 1000 (174 to 207)	NNTH: 16,		95% CI: 13 to 21	
	Moderate					
	65 per 1000	98 per 1000 (90 to 107)				

*The basis for the **assumed risk** was the median control group risk across studies. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **NNTB:** number needed to treat for an additional beneficial outcome; **NNTH:** number needed to treat for an additional harmful outcome; **RR:** risk ratio; **TSA:** trial sequential analysis.

GRADE Working Group grades of evidence.

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.

^aSerious imprecision (-1) due to small sample compared with the calculated optimal information size.

^bStudies with a poorer methodological quality introduced a significant source of bias (-1).

^cSerious imprecision (-1) due to small sample compared with the calculated optimal information size and the wide confidence interval overlapping zones of no effect as well as potential harm and/or benefit.

^dStudies with a poorer methodological quality introduced a significant source of bias (-1). Restricting the meta-analysis to studies of an assumed lower risk of bias significantly changed the effect estimate.

^eSerious inconsistency due to a high amount of unexplained heterogeneity (-1).

BACKGROUND

Cardiovascular mortality and morbidity are prevalent and costly in patients undergoing cardiac and non-cardiac surgery. Prevention of early postoperative complications remains a major issue in these interventions (Mangano 1990a; Mangano 1995). Surgery for acquired cardiac disease has a mortality rate of up to 3% (Kaplan 1993), a perioperative myocardial infarction rate up to 6% and overall complication rates of 15% to 24%, depending on the type of operation and patient co-morbidities (Hammermeister 1990). Even in non-cardiac surgery, an estimated 4% of patients will have a perioperative cardiac complication, and 0.5% will suffer a myocardial infarction (Fleisher 2001). Cardiac adverse events appear to be related to the persistently exaggerated sympathetic response that is associated with substantial increases in heart rate and myocardial oxygen consumption. Drugs that block beta-adrenergic receptors, and thus the sympathetic response are capable of preventing cardiac complications in patients with acute myocardial infarction (AMI), silent ischaemia and heart failure (Lancet 1986; Lancet 1999; Kjekshus 1987; Kjekshus 1991; Pepine 1994). Perioperative blockade of beta-adrenergic receptors therefore has been proposed to reduce the risk of perioperative complications in patients after cardiac and non-cardiac surgery (Mangano 1990b; Mangano 1996; Wallace 1998). Although several trials have provided encouraging findings demonstrating a reduced perioperative incidence of death from cardiac causes and non-fatal cardiovascular complications (Mangano 1990b; Mangano 1996; Wallace 1998), the routine administration of beta-blocking agents in unselected patients before major surgery is still discussed as a controversial topic, especially after the results of the POISE trial were published (POISE 2008), which demonstrated an increase of all-cause mortality and stroke with the use of beta-blockers. Until recently, recommendations were largely based on the results of four randomized trials (DECREASE-IV 2009; Mangano 1996; POISE 2008; Poldermans 1999). After the DECREASE (Dutch Echocardiographic Cardiac Risk Evaluation Applying Stress Echo) trial family—showing beneficial effects of beta-blockers on mortality and on prevention of myocardial infarction in the perioperative setting—was discredited in 2011 (Bouri 2013; Chopra 2012), perioperative use of beta-blockers became once again a matter of controversy. Therefore, it was our aim to summarize in a systematic way current knowledge on the issue of perioperative beta-blockade for prevention of the most relevant surgery-related adverse events.

OBJECTIVES

The objective of this review was to systematically analyse the effects of perioperatively administered beta-blockers for prevention of surgery-related mortality and morbidity in patients undergoing any type of surgery while under general anaesthesia.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs).

Types of participants

We included studies that looked at the effects of beta-blockers on adults 18 years of age or older undergoing any type of surgery while under general anaesthesia.

As opposed to these eligibility criteria as defined in the protocol (Wiesbauer 2007), we decided to consider trials in our meta-analysis that partially included patients not receiving general anaesthesia. Trials had to fulfil the following criteria to be eligible for inclusion: more than 100 randomly assigned participants operated on under general anaesthesia, or more than 70% of participants receiving general anaesthesia. We came to this conclusion, as we believed that a meta-analysis without data from the POISE (Perioperative Ischemia Evaluation Study), DIPOM (Diabetic Postoperative Mortality and Morbidity) or MaVS (Metoprolol After Vascular Surgery) trial would not find enough credibility within the clinical community.

We excluded trials investigating procedures that required local or regional anaesthesia only.

Types of interventions

Perioperative administration of beta-adrenoceptor-blockers via any route versus control (placebo or standard care). We defined the perioperative period as 30 days before to 30 days after surgery. Beta-blockers could be started before surgery, during surgery or at the latest by the end of the first day after surgery.

Types of outcome measures

We classified events as 'perioperative' if they occurred during or after surgery (from the time of induction of anaesthesia until 30 days after surgery).

Primary outcomes

- All-cause mortality, defined as death due to any cause occurring 30 days postoperatively or before hospital discharge (whichever occurs later).

Secondary outcomes

- Long-term all-cause mortality, defined as death due to any cause not qualifying as a primary endpoint.
- Death due to cardiac causes.
- Incidence of acute myocardial infarction (AMI) as defined by study authors (non-fatal if distinction was possible).
- Myocardial ischaemia as defined by study authors (minimal electrocardiographic (ECG) criteria: horizontal or descending ST depression of at least 1 mm).
- Cerebrovascular complications (transient ischaemic attack (TIA), prolonged reversible ischaemic neurological deficit (PRIND), stroke) as defined by study authors (non-fatal if distinction was possible).
- Ventricular arrhythmias (ventricular tachycardias and ventricular fibrillation).
- Supraventricular arrhythmias (atrial fibrillation, atrial flutter, other supraventricular arrhythmias, symptomatic supraventricular extrasystoles except sinus tachycardia).
- Bradycardia as defined by study authors (minimal criteria: below 60 beats per minute or requiring medical intervention).

- Hypotension as defined by study authors (minimal criteria: below 90 mmHg systolic blood pressure or requiring medical intervention).
- Ventricular extrasystoles.
- Congestive heart failure as defined by study authors.
- Bronchospasm.
- Length of hospital stay (LOS).
- Quality of life as defined by study authors.
- Cost of care.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2013 Issue 6), MEDLINE (Ovid SP, 1946 to June 2013), Embase (Ovid SP, 1974 to June 2013), Biosis Previews (1970 to June 2013), CAB Abstracts (1972 to June 2013), Global Health (1972 to June 2013), Life Sciences Collection (1982 to October 2010), Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCOhost, 1982 to June 2013), Derwent Drug File (1964 to June 2013), Science Citation Index Expanded (1900 to June 2013), International Pharmaceutical Abstracts (1970 to June 2013) and PASCAL (1977 to June 2013).

We used a highly sensitive search strategy (Higgins 2011) provided by The Cochrane Collaboration for identification of RCTs published in MEDLINE. We used Science Citation Index and its electronic counterpart Science Citation Index Expanded to identify studies referencing "key articles" in the field. In addition to applying these computer-enhanced search strategies, we surveyed the reference lists of relevant articles.

We designed our search strategy by defining an initial list of search terms. Using these terms, we performed a query of the latest publications in the field. We used the retrieved articles to modify the initial list of search terms. This was done to maximize sensitivity while trying not to decrease specificity. The final lists of terms and search strategies are provided in [Appendix 1](#) (MEDLINE), [Appendix 2](#) (EMBASE), [Appendix 3](#) (CENTRAL), [Appendix 4](#) (CINAHL) and [Appendix 5](#) (Biosis Previews, CAB Abstracts, Global Health, Life Sciences Collection, Derwent Drug File, Science Citation Index Expanded, International Pharmaceutical Abstracts, PASCAL, Conference Proceedings Citation Index–Science, System for Information on Grey Literature in Europe, British Library Inside Conferences, Conference Papers Index, Index to Scientific and Technical Proceedings and Books).

When multiple publications of a given data set were identified, we included the first published article in our analysis. We made an exception to this rule if a more recent publication corroborated the results of a larger cohort, longer follow-up, or both.

The first retrospective literature search was performed in July 2003. This literature search was updated in October 2010 and June 2013. Some databases could be searched only for a limited time interval (e.g. until 2003, until 2010).

Abstracts (and full-text articles, when information provided in the abstract was inconclusive) of retrieved publications were reviewed by two review authors independently to identify trials that met the preset inclusion criteria (FW and OS for trials published until 2003, HB and DA for trials published between 2003 and October 2010,

HB and JK for trials published after October 2010). We resolved differences of opinion by consultation with a third review author (CS or MS).

We imposed no language restrictions.

Searching other resources

For identification of so-called 'grey literature,' we surveyed databases that included conference proceedings, such as:

- Conference Proceedings Citation Index–Science (CPCI–Science) (1995 to June 2013);
- British Library Inside Conferences (1993 to 2003);
- System for Information on Grey Literature in Europe (SIGLE; 1976 to June 2013);
- Conference Papers Index (CONFSCI) (1973 to October 2010);
- Index to Scientific and Technical Proceedings and Books (ISTPB) (1978 to June 2013);
- Biosis Previews (1970 to June 2013); and
- CAB Abstracts (1972 to June 2013).

Furthermore, to identify studies that were not published because of negative results or for other reasons, we searched online trial registers.

- A registry of federally and privately supported clinical trials conducted in the United States and around the world: <http://clinicaltrials.gov>.
- The National Research Register, a public database of research projects funded by, or of interest to, the UK National Health Service (NHS): <http://www.nihr.ac.uk/Pages/NRRArchiveSearch.aspx>.
- Meta-register of controlled trials (International Standard Randomized Controlled Trial Number (ISRCTN) Register (international), Action Medical Research (UK), Medical Research Council (UK), The Wellcome Trust (UK), UK Trials (UK), National Institutes of Health (NIH) Clinical Trials Register (international), National Institute for Health Research (NIHR) Health Technology Assessment Programme (UK)): <http://www.controlled-trials.com/mrct>.

Data collection and analysis

Selection of studies

We included trials in which participants were randomly assigned to a beta-blocker group or a control group. Participants in the control group had to receive standard care or placebo. Trials had to investigate at least one of the outcomes listed above ([Primary outcomes](#); [Secondary outcomes](#)). Surgery had to be performed on study participants 18 years of age or older who were under general anaesthesia. We applied no restriction as to type of surgery.

As opposed to these eligibility criteria as defined in the protocol (Wiesbauer 2007), we decided to consider trials in our meta-analysis that partially included patients not receiving general anaesthesia. Trials had to fulfil the following criteria to be eligible for inclusion: more than 100 randomly assigned participants operated on while under general anaesthesia or more than 70% of participants receiving general anaesthesia. We came to this conclusion, as we believed that a meta-analysis without the POISE,

DIPOM or MaVS trial would not find enough credibility within the clinical community.

We excluded all procedures that required local or regional anaesthesia only.

Data extraction and management

Two review authors (HB and JK) independently extracted data from all studies. In cases of disagreement, we reassessed the respective studies to reach consensus. We used standardized forms for this purpose (see [Appendix 6](#)). We contacted the corresponding author (first author) if information was lacking that was deemed crucial for the decision whether to include the article in our meta-analysis. We considered study design (RCT, placebo or standard care group), type of intervention (beta-blocker vs control) and trial setting (hospital, type of surgery, general or regional/local anaesthesia) to be crucial information.

Assessment of risk of bias in included studies

To assess the quality of studies, we used type of control group (placebo or standard care, as assessed by the respective [Characteristics of included studies](#) tables), method and adequacy of randomization, allocation concealment, level of masking (blinding of study participants/personnel/outcome assessors), description of withdrawals, use of the intention-to-treat principle for data analysis (participants analysed as randomly assigned) and completeness of reported outcomes. We entered information on risk of bias of included trials into the respective risk of bias tables ([Characteristics of included studies](#)). We evaluated the following methodological qualities (low risk of bias, high risk of bias, unclear risk of bias).

Random sequence generation (selection bias)

- Low risk: adequate sequence generation reported using random number tables, computer random number generators, coin tossing or shuffling.
- High risk: randomization method that made allocation of participants predictable (quasi-randomization by date of birth or case record number, alteration).
- Unclear risk: Method of sequence generation not reported.

Allocation concealment (selection bias)

- Low risk: adequate measures to conceal allocations such as central randomization; serially numbered, opaque, sealed envelopes; or other convincing elements of concealment.
- High risk: inadequately concealed trials, using alteration methods, case record numbers or date of birth.
- Unclear risk: unclearly concealed trials, in which study authors did not report an allocation concealment approach at all, or reported an approach that did not fall into one of the categories mentioned above.

Blinding of participants, personnel and outcome assessors (detection bias)

- Low risk: single- (participant or doctor only), double- (participant and doctor) or triple (participant, doctor and outcome assessor)-blinded trials.
- High risk: open-label trials.
- Unclear risk: level of blinding not reported.

Incomplete outcome data (attrition bias)

- Low risk: trials that correctly used an intention-to-treat principle for data analysis (participants were analysed as randomly assigned) and with few losses to follow-up.
- High risk: trials that reported on excluded participants (participants were not analysed as randomly assigned) or major differences in dropouts between groups.
- Unclear risk: no reporting on exclusions.

Use of the intention-to-treat principle was assessed separately.

Selective reporting (reporting bias)

- Low risk: complete reporting of all outcomes previously defined in the methods section.
- High risk: selective underreporting of data (e.g. 'P < 0.05,' 'n.s.'), including only statistically significant results or only a subset of data.
- Unclear risk: no definitive judgement possible (e.g. abstract only).

Other bias

- Low risk: no other detectable sources of bias.
- High risk: certain study designs (e.g. cross-over RCT, cluster-RCT, more than two intervention groups, blocked randomization in an unblinded trial), deviation from the study protocol, fraud, early termination of a trial, different care programmes in different treatment arms.
- Unclear risk: no definitive judgement possible (e.g. abstract only).

We performed a sensitivity analysis using the first four quality criteria mentioned above. This was accomplished by performing meta-regression. Quality criteria were used as independent variables, and the point estimate was defined as the dependent variable. If one factor was associated with the point estimate in a statistically significant manner, results stratified according to the quality criteria were presented in the [Results](#) section. Among those stratified results, we attributed greater credibility to estimates coming from studies using higher quality standards. We avoided the use of so-called composite scales, as they were found to have low interscale reliability, and some failed to measure internal validity appropriately ([Juni 1999](#)).

Measures of treatment effect

- Dichotomous data: risk ratio (RR) with corresponding 95% confidence interval (CI).
- Continuous data: mean difference (MD) with corresponding 95% CI.

Unit of analysis issues

- Trials with multiple beta-blocker treatment groups: We included dichotomous outcomes of studies with one control group and added up the different beta-blocker arms to create a single beta-blocker group for generation of a single comparison. This was done to prevent a unit of analysis error. For continuous variables (i.e. length of stay and cost of care), we calculated combined mean and standard deviation values according to the formula provided in Chapter 7.7.3.8 of the *Cochrane Handbook for Systematic Reviews of Interventions* ([Higgins 2011](#)).

Dealing with missing data

- If information on both study group allocation and respective outcomes was available, we reincluded withdrawn participants in keeping with the intention-to-treat principle. If information was not available, we performed an available case analysis. We did not perform imputation techniques.
- We excluded continuous data assessing length of stay or cost of care if a range of dispersion (standard deviation or standard error) was not provided along with mean values. When both measures of spread (standard deviation and standard error) were presented, we used the standard deviation as the measure of choice. We did not apply imputation techniques.

Assessment of heterogeneity

We tested and evaluated heterogeneity using the so-called 'test of heterogeneity' at a significance level of P value < 0.1 , as well as the I^2 statistic, which describes the proportion of variability due to heterogeneity (Higgins 2002; Higgins 2003). As suggested by Higgins and colleagues, an I^2 value below 40% might not be important, whereas a value above 40% might represent moderate to severe heterogeneity. We explored heterogeneity using meta-regression, which assessed the influence that different study characteristics and participant characteristics had on the effect measure.

Assessment of reporting biases

We appraised reporting bias through visual assessment of funnel plots and Egger's regression model (regressing the magnitude of the point estimate vs precision) (Egger 1997).

In case of a suspected reporting bias, we used the 'trim-and-fill' method as a type of sensitivity analysis to correct for funnel asymmetry and to assess the impact of the potential bias on the robustness of the effect estimate (Duval 2000).

Data synthesis

We presented a statistical summary of treatment effects (RR) in the absence of significant clinical heterogeneity. We expressed dichotomous data as the risk ratio. We calculated the mean difference for length of stay. We calculated overall estimates using both fixed-effect and random-effects models for all outcomes. We presented results of the fixed-effect analysis if heterogeneity was judged to be low. If the results of fixed-effect and random-effects models differed substantially, or if the I^2 statistic was above 25% (both are signs of heterogeneity), we chose a random-effects model for presentation (DerSimonian 1986).

We used the software programmes RevMan 5.3 and STATA 12.0 to perform data analysis.

Subgroup analysis and investigation of heterogeneity

It is possible that treatment effects differed not because of statistical heterogeneity, but rather because of clinical heterogeneity (e.g. beta-blockers could be more useful in participants with good ventricular function as opposed to those with reduced ventricular function. The negative inotropic effect of these drugs might be desirable in the first group but harmful in the second). To evaluate this possibility, we assessed the most important clinical parameters (effect modifiers) that could have influenced the effects of beta-blockers on selected clinical outcomes.

We used meta-regression for subgroup analysis. If one of the factors influenced the effects of beta-blockers in a statistically significant way, we stratified for this factor in the Results section. We stratified for some factors a priori. They did not need to be associated with the point estimate in a regression analysis. This was done so that readers could get a feel for the data themselves. These stratifications include the following.

- Placebo versus standard care.
- Risk of surgery (non-cardiac surgery only: low- and medium-risk vs high-risk procedures).
- Start of beta-blocker therapy (before vs during vs after surgery).
- Type of beta-blocker.

Furthermore, we used meta-regression techniques to assess the following clinical factors for effect modification.

- Effect of age of study participants on overall effect.
- Effect of gender on overall effect.
- Types of surgery (high-risk vs low-risk operations).
- Factors that have the potential to increase perioperative risk (prevalence of coronary heart disease (CHD), previous myocardial infarction, prevalence of hypertension, reduced ejection fraction).
- Number of participants taking beta-blockers preoperatively.
- Whether invasive haemodynamic monitoring was used.
- Duration of beta-blocker treatment (up to 24 hours, two to seven days, eight to 14 days, nine to 21 days, exceeding 21 days).
- Whether beta-blockers were administered titrated by heart rate or in a fixed-dose regimen.

Sensitivity analysis

We used both fixed-effect and random-effects models for all outcomes and compared results. (If studies are homogeneous, results should be fairly similar. If outliers are present, results from fixed-effect and random-effects analyses should differ.) We used this measure to assess the robustness of estimates. Additionally, we explored interaction of methodological quality parameters and the effect estimate using meta-regression (type of hospital; type of control group; blinding status of participants, doctors and outcome assessors; use of intention-to-treat principle; specification of baseline characteristics; inclusion criteria; outcome variables and co-morbidities). If one of these factors was statistically significantly associated with the effect estimate, we carried out stratification for this parameter in the Results section and compared subgroup results of stratification with the overall effect estimate to assess its robustness.

Assessing the quality of evidence

We assessed quality of data by using the GRADE approach (Guyatt 2008). GRADE evaluates the body of evidence for an outcome according to different parameters.

- Risk of bias.
- Presence of a reporting bias.
- Inconsistency of data (heterogeneity): Is unexplained heterogeneity present in the data?
- Indirectness of data: Was the outcome of interest tested in a population of interest for the intervention of interest?

- Imprecision of data: Is the sample size smaller than the optimal size of information? Is the confidence interval wide, covering zones of no effect (RR 1.0), potential harm (RR 1.25) and potential benefit (RR 0.75)?

GRADE allows classification of the level of confidence regarding an estimate as very low, low, moderate or high.

Confidence levels can be interpreted as outlined below.

- **Very low:** We are very uncertain about the estimate.
- **Low:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
- **Moderate:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
- **High:** Further research is very unlikely to change our confidence in the estimate of effect.

Trial sequential analysis

Trial sequential analysis (TSA) is a type of statistical power analysis that can be used to further investigate the relevance of results ('strength of evidence') yielded by a meta-analysis (Wetterslev 2008). It is the counterpart of a sample size calculation as part of a conventional study design. TSA allows researchers to differentiate between 'spurious' significant findings caused by random error in a dataset with only small numbers of participants and trials and a 'truly' significant result with sufficient statistical power. Thereby, TSA also accounts for repeated significance testing.

Further details can be found in the 'User Manual for Trial Sequential Analysis (TSA),' provided by the Centre for Clinical Intervention Research of the Copenhagen Trial Unit (Thorlund 2011).

Basically, optimal information size and O'Brien-Fleming alpha-spending boundaries indicating the 'real' significance threshold are constructed by providing the numbers for alpha level, power, control group risk and interstudy heterogeneity. Furthermore, an 'inner wedge' marks the 'futility zone'—a non-superiority/inferiority area. Meta-analysis data are imported in a plot in which the x-axis represents the number of randomly assigned participants

and the y-axis represents the Z-score of the test statistics ($Z = 1.96$ with P value 0.05). The so-called Z-curve depicts the Z-score for any given number of randomly assigned participants. As more trials enter the meta-analysis, this curve extends farther to the right, indicating a larger cohort of randomly assigned participants. As the number of participants increases with every included trial, the Z-curve can now cross the upper or lower O'Brien-Fleming alpha-spending boundary, indicating a 'truly' significant effect, or can travel between the alpha-spending boundaries and the 'inner wedge,' which indicates an inconclusive result. If the Z-curve enters the 'inner wedge,' completion of further trials and randomization of participants are futile, as enough statistical power was accrued to show that there is no relevant difference between intervention and control groups.

TSA can be performed only if information size (number of participants) is large enough compared with optimal information size, and only if the outcome is dichotomous. We calculated TSA for every dichotomous outcome, if possible.

We downloaded the user manual and the software from www.ctu.dk/tsa.

RESULTS

Description of studies

Results of the search

Through the initial database search in July 2003 and updates in October 2010 and June 2013, we retrieved 10,175 titles and their respective abstracts (Appendix 7). All titles initially were independently screened by two review authors (FW and OS for trials published until December 2003, HB and DA for trials published until October 2010, HB and JK for trials after October 2010). Of all retrieved titles, we judged 9968 to be irrelevant for our review. We obtained and reviewed the full-text versions of the remaining 207 studies and excluded another 119 trials that did not match our inclusion criteria. Finally, we identified 88 trials relevant for our review (cardiac surgery: 53 trials; non-cardiac surgery: 35 trials; Figure 1). Data extraction for all included trials and assessment of risk of bias were independently performed by HB and JK from July until September 2013.

Figure 1. Flow chart of included trials. RCT = randomized controlled trial.

Figure 1. (Continued)

All-cause mortality	37 trials
Cardiac death	8 trials
Acute myocardial infarction	36 trials
Myocardial ischemia	18 trials
Ventricular tachycardia/fibrillation	17 trials
Ventricular extrasystoles	14 trials
Supraventricular arrhythmias	56 trials
Cerebrovascular events	9 trials
Congestive heart failure	8 trials
Bradycardia	31 trials
Hypotension	28 trials
Bronchospasm	11 trials
Length of stay	17 trials
Cost of care	3 trials

Included studies

We included 88 trials. We assessed the following types of surgery.

- Cardiac surgery (coronary artery bypass grafting and/or valve replacement): 53 trials.
- Other thoracic operations (lung resection, oesophagectomy, rigid bronchoscopy): four trials ([Bayliff 1999](#); [Jakobsen 1997](#); [Lai 2006](#); [Sandler 1990](#)).
- Vascular surgery: five trials ([Cucchiara 1986](#); [Miller 1990](#); [POBBLE 2005](#); [Raby 1999](#); [Yang 2006](#)).
- General (mostly abdominal) surgery: seven trials ([Coleman 1980](#); [Inada 1989](#); [Magnusson 1986](#); [Lee 2010](#); [Moon 2011](#); [Shukla 2010](#); [Stone 1988](#)).
- Maxillofacial surgery: two trials ([Apipan 2010](#); [Whitehead 1980](#)).
- Gynaecological surgery: four trials ([Burns 1988](#); [Jakobsen 1992](#); [Liu 1986](#); [Oxorn 1990](#)).
- Neurosurgery: three trials ([Gibson 1988](#); [Gupta 2011](#); [Kawaguchi 2010](#)).
- "Non-cardiac surgery" (not otherwise specified or different kinds of non-cardiac surgery): 10 trials ([DIPOM - Juul 2006](#); [Liu 2006](#); [Mangano 1996](#); [Marwick 2009](#); [Miller 1991](#); [Neary 2006](#); [POISE 2008](#); [Wallace 1998](#); [Yang 2008](#); [Zaugg 1999](#)).

All trials were published in English, except six (English abstracts were available for all trials).

- One German article ([Wenke 1999](#)).
- One Turkish article ([But 2006](#)).
- One Portuguese article (full-text English translation available) ([De Azevedo Lúcio 2003](#)).
- Three Chinese articles ([Lai 2006](#); [Liu 2006](#); [Yang 2008](#)).

We were all capable of reading English and German (as German is our native language). The Portuguese article was available in English (full translation), the Turkish article was translated by DA, who is bilingual (German and Turkish), and the Chinese articles were translated with the help of Dr. Y. Wang.

All trials included participants under general anaesthesia only, except the following four trials.

- [DIPOM - Juul 2006](#): 20% of participants received epidural anaesthesia only.
- [POISE 2008](#): 2482 participants (59.5%) in the metoprolol group and 2491 participants (59.6%) in the placebo group received general anaesthesia.
- [Raby 1999](#): General anaesthesia was provided in 73% of participants in the esmolol group and in 91% of participants in the placebo group.
- [Yang 2006](#) (MaVS): 12.7% of participants in the metoprolol group and 14.8% of those in the placebo group received regional anaesthesia only.

Individual data for the subgroup of participants who received general anaesthesia were not available for these trials.

We tried to establish contact with the following study authors to obtain additional information about trial design and outcomes under investigation.

- Prof Dr G Hamilton (University College London Medical School) was contacted by e-mail and kindly provided information about a trial listed on www.controlled-trials.com/mrct (ISRCTN13072628); this was the POBBLE (Perioperative Beta-Blockade) trial, which we had already included ([POBBLE 2005](#)).

- The corresponding authors of two trials were contacted by e-mail for more information about trial design (Chinese articles: [Lai 2006](#); [Liu 2006](#)), but no contact could be established.
- Dr P Rahimzadeh (Iran University of Medical Sciences) kindly provided information regarding the study 'Evaluation of the Metoprolol Effects in Controlled Hypotension and Reduction of Bleeding During Head and Neck Surgery' ([Rahimzadeh 2008](#)). Ultimately, this trial was not included because it assessed no outcome under investigation by this meta-analysis.
- Authors of identified abstracts were contacted for more information or for full-text publications ([Dy 1998](#); [Graham 1996](#); [Ogawa 2013](#)); contact was established only with Dr S. Ogawa, who kindly provided a full-text publication of his abstract, which was included in our meta-analysis ([Ogawa 2013](#)).
- The corresponding author of the POISE trial was contacted to provide data on measures of spread for the parameter length of stay and for the subset of participants receiving general anaesthesia ([POISE 2008](#)). Only a subgroup of participants were operated on while under general anaesthesia in POISE, and only median and interquartile range (IQR) values were provided for length of stay; this precluded inclusion in our meta-analysis, as these measures of spread were incompatible with our analysis. No contact could be established.

For further specification of trial characteristics, please refer to the [Characteristics of included studies](#) table and the flow chart of included and excluded studies ([Figure 1](#)).

Excluded studies

We excluded three studies during the review process: one because the study included a subset of participants from another trial published by the same group of authors ([Klötter-Weber 1998](#); see [Characteristics of excluded studies](#) table). This study provided the same participant data-set as was provided by [Pfisterer 1997](#). One trial was excluded because of allegations of fictitious data ([DECREASE-IV 2009](#)), and another trial by the same group of authors was excluded because credibility of data was uncertain ([Poldermans 1999](#)).

Following publication of the first version of this systematic review ([Blessberger 2014](#)), a previously included study was retracted ([Suttner 2009](#)). This trial has now been excluded and all relevant analyses and results have been amended accordingly.

Risk of bias in included studies

We found most studies to be of adequate methodological quality for inclusion in our analysis. Nevertheless, it should be mentioned that adherence to certain quality prerequisites, such as those published in the Consolidated Standards of Reporting Trials (CONSORT) statement on reporting of randomized controlled trials, was low, even for studies published after the year 2001 (the year the statement was published) ([Moher 2001](#)). For additional details, see the [Characteristics of included studies](#) table, as well as respective 'Risk of bias' tables, graph ([Figure 2](#)) and summary ([Figure 3](#)).

Figure 2. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants (performance bias)	Blinding of doctors/personnel (performance bias)	Blinding of outcome assessors (detection bias)	Incomplete outcome data (attrition bias)	Intention to treat analysis	Selective reporting (reporting bias)	Other bias
Abel 1983	+	+	+	+	+	+	+	+	+
Ali 1997	?	?	+	+	+	?	?	+	+
Apipan 2010	?	?	+	+	+	?	?	+	+
Auer 2004	+	+	+	+	?	+	+	+	+
Babin-Ebell 1996	?	?	+	+	+	+	+	+	+
Bayliff 1999	?	+	+	+	?	+	+	+	+
Bert 2001	+	?	+	+	+	+	+	+	+
Booth 2004	?	?	?	?	?	+	+	+	+
Burns 1988	?	?	+	+	+	?	?	+	+
But 2006	?	?	?	?	?	?	?	+	+
Coleman 1980	?	?	+	+	?	+	+	+	+
Connolly 2003	?	?	+	+	?	?	?	+	+
Cork 1995	?	?	+	+	?	?	?	+	+
Cucchiara 1986	?	?	+	+	?	+	+	+	+
Daudon 1986	?	?	+	+	+	?	?	+	+
De Azevedo Lúcio 2003	?	?	+	+	+	+	+	+	+
DIPOM - Juul 2006	+	+	+	+	+	+	+	+	+
Dy 1998	?	?	+	+	?	?	?	?	?
Evrard 2000	+	+	+	+	+	?	?	+	+
Forlani 2002	+	+	+	+	+	+	+	+	+
Gibson 1988	?	?	+	+	?	?	?	+	+
Games 1999	?	?	+	+	?	?	?	+	+

Figure 3. (Continued)

Grieson 1988	+	+	+	+	+	+	+	+	+
Gomes 1999	?	+	+	+	?	+	?	+	-
Graham 1996	?	?	?	?	?	?	?	-	+
Gupta 2011	+	+	+	+	+	+	-	+	+
Hammon 1984	+	?	+	+	?	?	?	+	+
Harrison 1987	?	?	+	+	+	?	?	+	+
Inada 1989	?	+	+	+	?	?	?	+	+
Ivey 1983	?	+	+	+	?	-	-	+	+
Jacquet 1994	?	?	-	-	-	-	-	+	-
Jakobsen 1992	?	?	+	+	?	?	?	+	+
Jakobsen 1997	?	?	+	+	?	+	-	+	+
Janssen 1986	?	+	-	-	-	-	-	-	+
Kawaguchi 2010	+	+	-	-	-	?	?	+	+
Khuri 1987	?	?	+	+	+	-	-	+	+
Kurian 2001	?	+	-	-	-	-	-	+	-
Lai 2006	?	?	-	-	-	-	-	+	+
Lamb 1988	?	?	-	-	-	?	?	+	+
Lee 2010	?	?	?	?	?	?	?	?	?
Liu 1986	?	?	+	+	?	?	?	+	+
Liu 2006	?	?	-	-	-	?	?	+	+
Magnusson 1986	?	?	+	+	?	-	-	+	+
Mangano 1996	+	+	+	+	+	+	?	+	+
Martinussen 1988	?	?	+	+	?	-	-	+	+
Marwick 2009	+	+	-	-	-	+	+	+	-
Matangi 1985	?	+	-	-	-	+	+	+	+
Matangi 1989	?	+	+	+	?	+	+	+	+
Materne 1985	?	?	-	-	-	?	?	+	+
Matsuura 2001	-	-	-	-	-	?	?	+	+
Miller 1990	+	+	+	+	?	?	?	+	+
Miller 1991	+	+	+	+	?	?	?	+	+
Mohr 1981	-	-	-	-	-	-	-	+	+
Moore 2011	?	+	+	+	+	?	?	+	+

Figure 3. (Continued)

Wong 1991	+	+	+	+	+	+	+	+	+
Moon 2011	?	+	+	+	+	?	?	+	+
Myhre 1984	?	?	-	-	-	-	-	+	+
Neary 2006	+	+	+	+	+	+	+	+	-
Neustein 1994	?	?	+	+	+	-	-	+	+
Nyström 1993	?	?	-	-	-	?	?	+	+
Ogawa 2013	+	+	-	-	-	+	?	?	?
Oka 1980	?	?	-	-	-	?	?	+	+
Ormerod 1984	?	?	-	-	-	-	-	+	+
Osada 2012	?	?	-	-	-	?	?	?	?
Oxorn 1990	?	?	+	+	+	?	?	+	+
Paull 1997	?	?	+	-	-	?	+	+	+
Pfisterer 1997	?	?	+	+	?	+	+	+	+
POBBLE 2005	+	+	+	-	+	+	+	+	+
POISE 2008	+	+	+	+	+	+	+	+	+
Raby 1999	+	+	+	-	+	+	?	+	+
Reves 1990	?	?	+	+	?	?	?	+	+
Rubin 1987	+	+	-	-	-	-	-	+	+
Sakaguchi 2012	-	-	-	-	-	?	?	+	+
Salazar 1979	?	?	-	-	-	?	?	+	+
Sandler 1990	+	?	+	+	?	?	?	+	+
Sezai 2011	+	+	+	+	?	-	-	+	+
Sezai 2012	+	+	-	+	?	-	-	+	-
Shukla 2010	?	?	+	+	?	?	?	?	?
Silverman 1982	-	-	-	-	-	?	?	+	+
Stephenson 1980	-	-	-	-	-	-	-	+	+
Stone 1988	?	?	-	-	-	?	?	+	+
Sun 2011	+	+	?	?	?	-	-	+	+
Suttorp 1991	?	?	+	+	?	-	-	+	+
Vecht 1986	?	?	+	+	?	?	?	+	+
Wallace 1998	+	+	+	+	+	?	+	+	+
Wong 1999	+	?	-	-	-	?	?	+	+

Figure 3. (Continued)

Variable 1990	?	+	+	+	+	+	+	+	+
Wenke 1999	+	?	-	-	-	?	?	+	+
White 1984	?	?	+	+	?	?	?	+	+
Whitehead 1980	?	+	+	+	+	?	?	+	+
Williams 1982	-	-	-	-	-	-	-	+	+
Yang 2006	+	+	+	+	?	+	+	+	+
Yang 2008	?	?	-	-	-	?	?	+	+
Zaugg 1999	?	?	-	-	-	-	-	+	+

Allocation

Only 24 of 88 studies (27%) reported that investigators applied a valid method of allocation sequence generation, such as coin tossing, centralized randomization via telephone or computer or use of a random number table. Eight trials (9%) used invalid methods of sequence generation (quasi-randomization by hospital record numbers, date of birth or alternate randomization) (Abel 1983; Evrard 2000; Matsuura 2001; Mohr 1981; Sakaguchi 2012; Silverman 1982; Stephenson 1980; Williams 1982). Most study authors did not specify the method of randomization used (56 trials; 64%). Thirty study authors (34%) reported that they used an appropriate method to maintain allocation concealment (preparation of the study drug by the hospital's pharmacy in identical outer packing, central randomization via telephone or computer or use of sealed, opaque, sequentially numbered envelopes), whereas 50 trials (57%) did not address this topic. In the eight trials (9%) mentioned above using quasi-randomization methods, allocation could be foreseen by date of birth, hospital record number or allocation of the participant recruited previously.

Blinding

We included 36 (41%) open-label studies, four (5%) single-blind studies, 32 (36%) double-blind trials and 11 (12.5%) triple-blind studies. We could not assess blinding status in five (5.5%) trials. Thus in about half of the included trials, doctors were not blinded to the study drug. However, we want to stress the fact that patients taking beta-blocker therapy are likely to be recognized by a skilled clinician because of the pharmacological properties of these drugs (which lead to lowering of blood pressure and slowing down of heart rate).

Incomplete outcome data

Handling of attrition remained unclear in most studies. Among all included studies, 20 (23%) reported incomplete outcome data and only 14 (16%) stated that investigators used an intention-to-treat analysis and actually analysed participants as randomly assigned (Bayliff 1999; Booth 2004; De Azevedo Lúcio 2003; DIPOM - Juul 2006; Marwick 2009; Matangi 1985; Matangi 1989; Neary 2006; Paull 1997; Pfisterer 1997; POBBLE 2005; POISE 2008; Wallace 1998; Yang 2006). In 29 trials (33%), data were analysed according to the per-protocol principle, whereas for 45 (51%) included studies, we could not make a final decision because incomplete outcome data were not reported.

Selective reporting

We judged selective reporting to be present in three trials. Two trials reported statistically significant results only (Graham 1996—conference abstract; Janssen 1986). In another trial (De Azevedo Lúcio 2003), study group allocation of participants with certain adverse events (AMI, stroke) remained unclear (selective underreporting).

Other potential sources of bias

Five (6%) of the included trials encompassed more than two intervention arms (Auer 2004; Bert 2001; Forlani 2002; Inada 1989; Stone 1988); four trials (4.5%) were terminated early (Jacquet 1994—high number of dropouts, Kurian 2001—high number of adverse events in beta-blocker group and recruiting problems, Neary 2006—recruiting problems, Sezai 2012—beta-blockers proved highly efficient in preventing atrial fibrillation in an interim analysis, and it was judged unethical to continue the trial); one trial used blocked randomization in an open-label setting, which might have made study group allocation predictable in some cases (Evrard 2000); one trial provided different care programmes for beta-blocker and control groups (Marwick 2009: heart rate-directed administration of beta-blocker exclusively in beta-blocker group (fixed-dose administration was used in the standard of care group), dobutamine stress echo for cardiovascular risk stratification exclusively in the standard of care group); and in one trial the number of patients taking beta-blockers before entry into the trial significantly differed between intervention and control groups (Gomes 1999).

Effects of interventions

See: [Summary of findings for the main comparison Beta-blocker versus control—cardiac surgery](#); [Summary of findings 2 Beta-blocker versus control—non-cardiac surgery](#)

In the following paragraphs, we present the results for cardiac and non-cardiac surgery derived from our analysis. Each outcome section is subdivided into five main subheadings: 'Overall effect,' 'Heterogeneity,' 'Reporting bias,' 'Sensitivity analysis' and 'Summary of confidence in estimates of effects using GRADE and TSA.'

Cardiac surgery

For a concise summary of the most important outcome variables see [Summary of findings for the main comparison](#).

All-cause mortality

Overall effect

We evaluated all-cause mortality with 24 trials that included 3783 participants. In 11 studies no deaths occurred in the beta-blocker group nor in the control group (Bert 2001; Connolly 2003; Forlani 2002; Hammon 1984; Ivey 1983; Janssen 1986; Martinussen 1988; Matsuura 2001; Nyström 1993; Paull 1997; Suttrop 1991). None of the remaining 13 trials found a statistically significant difference between beta-blocker and control groups at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on perioperative mortality, as evidenced by a fixed-effect risk ratio (RR) of 0.73 (95% confidence interval (CI) 0.35 to 1.52, P value 0.40; [Analysis 1.1](#)). Four studies allowed classification of cause of death as cardiac or non-cardiac (Gomes 1999; Oka 1980; Sezai 2011; White 1984). With respect to these trials, we found no clear evidence of an effect of beta-blockers on death from cardiac causes in the setting of cardiac surgery (RR 0.85, 95% CI 0.16 to 4.40, P value 0.84; [Analysis 1.4](#)). No studies investigated long-term mortality after the 30th postoperative day.

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.98). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker ([Analysis 3.1](#)) and type of beta-blocker ([Analysis 5.1](#)) did not detect sources of heterogeneity, and the effect estimate was consistently non-significant throughout all subgroups. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.94), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.75, 95% CI 0.34 to 1.66, P value 0.48) instead of a fixed-effect model (RR 0.73, 95% CI 0.35 to 1.52, P value 0.40). Restricting the meta-analysis to low risk of bias studies did not change estimates much (all studies: RR 0.73, 95% CI 0.35 to 1.52, P value 0.40; low risk of bias studies: RR 0.81, 95% CI 0.27 to 2.43, P value 0.70; [Analysis 2.1](#)). Meta-regression analysis of study parameters representing methodological quality identified no relevant interaction.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low and no evidence was found of a bias caused by studies of poorer methodological quality, overall information size was small (3783 participants; 5.1% compared with the optimal information size of 74,577 participants calculated to detect a 20% relative change in mortality, assuming a control group event rate of 0.96% (mean control group event rate) with a power of 80% at an alpha level of 0.05. It was not possible for

us to perform TSA analysis with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential harm or benefit (RR 1.25 and RR 0.75, respectively). We therefore classified the quality of evidence as moderate (severe imprecision due to wide CI and small sample size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Acute myocardial infarction

Overall effect

We evaluated the occurrence of AMI in 22 trials that included 3553 participants. In two studies no AMI occurred in the beta-blocker group nor in the control group (Evrard 2000; Forlani 2002). None of the remaining 20 trials found a statistically significant difference between beta-blocker and control groups at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on perioperative AMI in cardiac surgery, as evidenced by a fixed-effect RR of 1.04 (95% CI 0.71 to 1.51, P value 0.85; [Analysis 1.6](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.96). Thus we chose a fixed-effect model for presentation. We performed pre-specified subgroup analyses for start of beta-blocker and type of beta-blocker ([Analysis 3.6](#); [Analysis 5.6](#)). Results of all subgroups were consistently statistically non-significant. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.015), we found evidence of a reporting bias. Small studies tended to over-report a beneficial effect of beta-blockers in preventing perioperative AMI. Using the trim-and-fill method to correct for this bias did not change the point estimate nor the 95% CI (no study was simulated and added by this method to correct for the reporting bias).

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 1.08, 95% CI 0.73 to 1.61, P value 0.69) instead of a fixed-effect model (RR 1.04, 95% CI 0.71 to 1.51, P value 0.85). Restricting the meta-analysis to the seven placebo-controlled studies with an assumed lower risk of bias did not change estimates much (all studies: RR 1.04, 95% CI 0.71 to 1.51; low risk of bias studies: RR 1.38, 95% CI 0.71 to 2.69, P value 0.35; [Analysis 2.5](#)). Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low and we found no evidence of a bias caused by studies of poorer methodological quality, we detected a reporting bias (small-studies effect). The method that we used to correct for this bias did not change the effect estimate and 95% CI. Overall information size was small (3553 participants; 19.8% of optimal information size) compared with the optimal information size of 17,954 participants calculated to detect a 20% relative change in occurrence of AMI, assuming

a control group event rate of 3.8% (median control group event rate of included studies) with a power of 80% at an alpha level of 0.05. With the use of TSA, the O'Brien-Fleming alpha-spending boundaries were not crossed in either direction (Figure 4). The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential

harm or benefit (RR 1.25 and RR 0.75, respectively). We therefore classified the quality of evidence as moderate (serious imprecision due to wide CI and small sample size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Figure 4. TSA acute myocardial infarction—cardiac surgery.

Myocardial ischaemia

Overall effect

Four studies investigated myocardial ischaemia in cardiac surgery as defined by study authors (166 participants: Harrison 1987; Kurian 2001; Neustein 1994; Reves 1990). Most of the weight (58.1%) came from the trial conducted by Kurian and colleagues in 2001 (Kurian 2001), which was the only study to report a significant protective effect of beta-blockers (RR 0.30, 95% CI 0.09 to 0.96). None of the remaining three trials found a significant difference between beta-blocker and control groups at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on perioperative myocardial ischaemia in cardiac surgery,

as evidenced by a fixed-effect RR of 0.51 with a 95% CI of 0.25 to 1.05 (P value 0.07) (Analysis 1.8).

Heterogeneity

We found the amount of variance explained by between-study variation to be low ($I^2 = 18\%$, P value 0.30). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analysis for start of beta-blocker treatment (Analysis 3.8) led to isolation of the Kurian trial in the subgroup 'start after surgery,' which as a matter of fact yielded a statistically significant result, as the only trial included was one that detected a significant protective effect of beta-blocker treatment (for RR, see above 'Overall effect'). Stratification for type of beta-blocker was not possible, as all

studies used esmolol. Meta-regression analysis could not identify a clinical effect modifier.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate was virtually unchanged when we used a random-effects model (RR 0.55, 95% CI 0.23 to 1.32, P value 0.18) instead of a fixed-effect model (RR 0.51, 95% CI 0.25 to 1.05, P value 0.07). Restricting the meta-analysis to the three placebo-controlled studies with an assumed lower risk of bias did not change estimates much (all studies: RR 0.51, 95% CI 0.25 to 1.05, P value 0.07; low risk of bias studies: RR 0.80, 95% CI 0.31 to 2.10, P value 0.66; [Analysis 2.7](#)). Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low and we found no evidence was found of a bias caused by studies of poorer methodological quality, overall information size was very small (166 participants; 4.7% of optimal information size) compared with the optimal information size of 3538 participants calculated to detect a 20% relative change in incidence of myocardial ischaemia, assuming a control group event rate of 20.7% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential benefit (RR 0.75). We therefore classified the quality of evidence as low (very serious imprecision due to wide CI and very small sample size below 5% of optimal information size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Cerebrovascular events

Overall effect

Four studies evaluated cerebrovascular events in cardiac surgery (1400 participants). None of the four trials found a significant difference between beta-blocker and control groups at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on cerebrovascular events in cardiac surgery, as evidenced by a fixed-effect RR of 1.52 with a 95% CI of 0.58 to 4.02 (P value 0.40) ([Analysis 1.10](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.49). Thus we chose a fixed-effect model for presentation. We performed prespecified subgroup analyses for start of beta-blocker ([Analysis 3.10](#)) and type of beta-blocker ([Analysis 5.9](#)). Results of all subgroups were consistently statistically non-significant. When meta-regression analysis was applied, we detected no clinical effect modifiers.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates a potential reporting bias in this case.

Sensitivity analysis

The effect estimate was virtually unchanged when we used a random-effects model (RR 1.58, 95% CI 0.55 to 4.59, P value 0.40) instead of a fixed-effect model (RR 1.52, 95% CI 0.58 to 4.02, P value 0.40). All trials were placebo-controlled trials with blinding of participants and attending doctors. Meta-regression analysis of methodological quality parameters detected no relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low and we found no evidence of a bias caused by studies of poorer methodological quality, overall information size was very small (1400 participants; 2.0% of optimal information size) compared with the optimal information size of 70,005 participants calculated to detect a 20% relative change in the incidence of cerebrovascular events, assuming a control group event rate of 1.0% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0), and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as low (serious imprecision due to wide CI and very small sample size below 5% of optimal information size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Ventricular arrhythmias

Overall effect

Twelve studies evaluated the occurrence of ventricular arrhythmias in cardiac surgery (2292 participants). Two trials found a significant protective effect of beta-blockers compared with control at an alpha level of 0.05 ([Harrison 1987](#): RR 0.36, 95% CI 0.15 to 0.89; [Sun 2011](#): RR 0.10, 95% CI 0.01 to 0.77). In two trials ([Matangi 1989](#); [Nyström 1993](#)), no ventricular arrhythmias occurred in the beta-blocker group nor in the control group. Overall, beta-blockers statistically significantly reduced the incidence of ventricular arrhythmias in cardiac surgery by 63%, as evidenced by a fixed-effect RR of 0.37 with a 95% CI of 0.24 to 0.58 (P value < 0.0001) (absolute risk reduction 3.47%; number needed to treat for an additional beneficial outcome (NNTB) 29, 95% CI: 24 to 44; [Analysis 1.12](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.60). Thus we chose a fixed-effect model for presentation. We performed prespecified subgroup analyses for start of beta-blocker ([Analysis 3.11](#)), and type of beta-blocker ([Analysis 5.11](#)). Whereas a protective beta-blocker effect was evident when the drug was started during and after surgery

(RR 0.26, 95% CI 0.08 to 0.84, and RR 0.27, 95% CI 0.11 to 0.67, respectively), this effect was blunted when the drug was started before surgery (RR 0.62, 95% CI 0.31 to 1.26; [Analysis 3.11](#)). Indeed, meta-regression analysis identified start of beta-blocker treatment as an effect modifier (P value 0.03 before vs during surgery).

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.89), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate was virtually unchanged when we used a random-effects model (RR 0.40, 95% CI 0.25 to 0.63, P value < 0.0001) instead of a fixed-effect model (RR 0.37, 95% CI 0.24 to 0.58, P value < 0.0001), or when analysis was restricted to the seven placebo-controlled trials with an assumed low risk of bias (RR 0.41, 95% CI 0.25 to 0.68, P value 0.0006; [Analysis 2.10](#)). Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low and no evidence was found of a bias caused by studies of poorer methodological quality. Overall information size was small (2292 participants; 22.8% of optimal information size) compared with the optimal information size of 10,068 participants calculated to detect a 20% relative change in the incidence of ventricular arrhythmias, assuming a control group event rate of 6.6% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA was inconclusive, as the Z-curve did not cross either O'Brien-Fleming alpha-spending boundary ([Figure 5](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as moderate (serious imprecision due to small sample size compared with optimal information size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Figure 5. TSA ventricular arrhythmias—cardiac surgery.

Supraventricular arrhythmias

Overall effect

A total of 48 studies evaluated the occurrence of supraventricular arrhythmias in cardiac surgery (6420 participants). Thirty-two trials found a significant protective effect of beta-blockers compared with control at an alpha level of 0.05, whereas 16 trials did not show a significant effect compared with control. Overall, beta-blockers statistically significantly reduced the incidence of supraventricular arrhythmias in cardiac surgery by 56%, as evidenced by a random-effects RR of 0.44 with a 95% CI of 0.36 to 0.53 (P value < 0.00001) (absolute risk reduction 16.92%; NNTB 5, 95% CI: 5 to 6; [Analysis 1.16](#)).

Heterogeneity

We found the amount of variance explained by between-study variation was high ($I^2 = 77\%$, P value < 0.00001). Thus we chose a random-effects model for presentation. Stratification according to prespecified subgroup analyses (start of beta-blocker, type of beta-blocker) could not reduce statistical heterogeneity ([Analysis](#)

[3.15](#); [Analysis 5.15](#)). Beta-blockers showed a consistently significant protective effect in preventing supraventricular arrhythmias, irrespective of the start of the drug ([Analysis 3.15](#)). However, meta-regression found that duration of beta-blocker treatment was an effect modifier (P value 0.03 to 0.99, depending on exact duration of treatment). Stratification for this parameter could not explain statistical heterogeneity but revealed blunting of the protective effect when beta-blockers were administered only up to 24 hours ([Analysis 6.9](#)).

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.003), we found evidence of a reporting bias (small studies were likely to report pronounced protection of participants taking beta-blockers against supraventricular arrhythmias). Using the trim-and-fill method to adjust for this bias did not change the point estimate and the 95% CI (no study was imputed when this method was applied).

Sensitivity analysis

The effect estimate was not changed much when we used a fixed-effect model (RR 0.50, 95% CI 0.46 to 0.54, P value < 0.00001) instead of a random-effects model (RR 0.44, 95% CI 0.36 to 0.53, P value < 0.00001). Restricting the meta-analysis to the 20 placebo-controlled studies with an assumed lower risk of bias did not change the effect estimate much (all studies: RR 0.44, 95% CI 0.36 to 0.53, P value < 0.00001; low risk of bias studies: RR 0.60, 95% CI 0.48 to 0.76, P value < 0.0001; [Analysis 2.13](#)). Restricting supraventricular arrhythmias to atrial fibrillation or flutter did not change the effect estimate much (all supraventricular arrhythmias: RR 0.44, 95% CI 0.36 to 0.53, P value < 0.00001; atrial fibrillation and flutter only: RR 0.48, 95% CI 0.40 to 0.57, P value < 0.00001; [Analysis 1.14](#)). Meta-regression identified control group status (P value 0.01) as a methodological parameter influencing the effect estimate. Stratification for control group status was routinely performed ([Analysis 2.13](#)). Standard care controlled trials systematically overestimated the effect of beta-blocker in preventing supraventricular arrhythmias (RR 0.36, 95% CI 0.31 to 0.43, P value < 0.00001) but did not alter the effect estimate much.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was high and could not be sufficiently explained. We identified two sources of bias as caused by studies of poorer methodological quality (did not significantly change the effect estimate) and a reporting bias. In both cases, the protective effect of beta-blockers was overestimated. However, restricting the analysis to placebo-controlled trials and adjusting for reporting bias did not alter the effect estimate nor the 95% CI significantly. The overall information size was sufficient (6420 participants; 156.7% of optimal information size) compared with the optimal information size of 4097 participants calculated to detect a 20% relative change in the incidence of supraventricular arrhythmias when a control group event rate of 36.5% was assumed (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA showed a significant protective effect of beta-blockers as the Z-curve crossed the upper O'Brien-Fleming alpha-spending boundary ([Figure 6](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as high (no downgrading). Further research is very unlikely to change our confidence in the estimate of effect.

Figure 6. TSA supraventricular arrhythmias—cardiac surgery.

Bradycardia

Overall effect

Eight studies evaluated the occurrence of bradycardia in cardiac surgery (660 participants). One trial found a significant effect of beta-blockers causing bradycardia compared with control at an alpha level of 0.05 (Auer 2004: RR 4.68, 95% CI 1.12 to 19.55). In another trial (Cork 1995), no episodes of bradycardia occurred in the beta-blocker group nor in the control group. Six trials yielded non-significant results. Overall, we found no clear evidence of an effect of beta-blockers on the occurrence of episodes of bradycardia in cardiac surgery, as evidenced by a fixed-effect RR of 1.61 with a 95% CI of 0.97 to 2.66 (P value 0.06) (Analysis 1.20).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.50). Thus we chose a fixed-effect model for presentation. We performed prespecified subgroup analyses for start of beta-blocker (Analysis 3.19) and type of beta-blocker (Analysis 5.19) were performed. Except for one trial mentioned above that yielded a significant result using metoprolol and sotalol

(Auer 2004), subgroup stratification consistently provided non-significant results. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate was not changed much when we used a random-effects model (RR 1.39, 95% CI 0.84 to 2.31, P value 0.20) instead of a fixed-effect model (RR 1.61, 95% CI 0.97 to 2.66, P value 0.06). Restricting the meta-analysis to the six placebo-controlled studies with an assumed lower risk of bias led to a trend —albeit non-significant—towards a higher incidence of bradycardia with the use of beta-blockers (all studies: RR 1.61, 95% CI 0.97 to 2.66, P value 0.06; low risk of bias studies: RR 1.89, 95% CI 0.99 to 3.63, P value 0.05; Analysis 2.16). Meta-regression analysis

of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality or with a reporting bias, overall sample size was very small (660 participants; 1.4% of optimal information size) compared with the optimal information size of 47,355 participants calculated to detect a 20% relative change in the incidence of bradycardia, assuming a control group event rate of 1.43% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as low (very serious imprecision due to wide CI and very small sample size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Hypotension

Overall effect

Six studies evaluated the occurrence of hypotensive episodes in cardiac surgery (558 participants). None of the trials found a significant effect of beta-blockers causing hypotension compared with control at an alpha level of 0.05. All trials recorded episodes of hypotension in the beta-blocker group or in the control group. Overall, we found no clear evidence that beta-blockers induce hypotensive episodes in cardiac surgery, as evidenced by a fixed-effect RR of 1.54 with a 95% CI of 0.67 to 3.51 (P value 0.31) ([Analysis 1.22](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.60). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker ([Analysis 3.21](#)) and type of beta-blocker ([Analysis 5.21](#)), provided non-significant results throughout all subgroups. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. In this case, formal tests cannot distinguish between study variance of estimates and a potential reporting bias.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 1.48, 95% CI 0.60 to 3.69, P value 0.39) instead of a fixed-effect model (RR 1.54, 95% CI 0.67 to 3.51, P value 0.31). Restricting the meta-analysis to the five placebo-controlled studies with an assumed lower risk of bias also left the effect estimate unchanged (all studies: RR 1.54, 95% CI 0.67 to 3.51, P value 0.31; low risk of bias studies: RR 1.30, 95% CI 0.54 to 3.14, P value 0.56; [Analysis 2.18](#)). Meta-regression analysis

of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality nor a reporting bias, overall information size was very small (558 participants; 2.2% of optimal information size) compared with the optimal information size of 25,528 participants calculated to detect a 20% relative change in the incidence of hypotensive episodes, assuming a control group event rate of 2.7% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as low (serious imprecision due to wide CI and very small sample size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Ventricular extrasystoles

Overall effect

Five studies evaluated the incidence of ventricular extrasystoles in cardiac surgery (462 participants). None of the trials found a significant effect of beta-blockers preventing ventricular extrasystoles compared with control at an alpha level of 0.05. All trials recorded episodes of ventricular extrasystoles in the beta-blocker group or in the control group. Overall, we found no clear evidence of an effect of beta-blockers on the occurrence of ventricular extrasystoles in cardiac surgery, as evidenced by a fixed-effect RR of 0.58 with a 95% CI of 0.31 to 1.08 (P value 0.09) ([Analysis 1.18](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.40). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker ([Analysis 3.17](#)), and type of beta-blocker ([Analysis 5.17](#)), provided non-significant results throughout all subgroups. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.57, 95% CI 0.29 to 1.11, P value 0.10) instead of a fixed-effect model (RR 0.58, 95% CI 0.31 to 1.08, P value 0.09). Sensitivity analysis for type of control group was not possible, as all studies included a standard care control group. Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality nor a reporting bias. Overall information size was small (462 participants; 58.9% of optimal information size) compared with the optimal information size of 784 participants calculated to detect a 20% relative change in the incidence of ventricular extrasystoles, assuming a control group event rate of 5.0% (median control group event rate of included trials) with a power of 80% at an alpha level of

0.05. We performed TSA and it yielded an inconclusive result, with the Z-curve between the upper O'Brien-Fleming alpha-spending boundary and the zone of futility (inner wedge) (Figure 7). The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential benefit (RR 0.75). We therefore classified the quality of evidence as moderate (serious imprecision due to wide CI and small sample size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Figure 7. TSA ventricular extrasystoles—cardiac surgery.

Congestive heart failure

Overall effect

Three studies evaluated the incidence of congestive heart failure in cardiac surgery (311 participants). None of the trials found a significant effect of beta-blockers preventing or causing congestive heart failure compared with control at an alpha level of 0.05. All trials recorded occurrence of congestive heart failure in the beta-blocker group or in the control group. Overall, we found no clear evidence of an effect of beta-blockers on the occurrence of

congestive heart failure in cardiac surgery, as evidenced by a fixed-effect RR of 0.22 with a 95% CI of 0.04 to 1.34 (P value 0.10) (Analysis 1.24).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.95). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker (Analysis 3.23), and type of beta-blocker (Analysis 5.23),

provided non-significant results throughout all subgroups. When we applied meta-regression analysis no clinical effect modifiers were detected.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.22, 95% CI 0.04 to 1.36, P value 0.10) instead of a fixed-effect model (RR 0.22, 95% CI 0.04 to 1.34, P value 0.10). Sensitivity analysis for type of control group was not possible, as all studies had a placebo control group. Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality, overall information size was very small (311 participants; 1.28% of optimal information size) compared with the optimal information size of 24,242 participants calculated to detect a 20% relative change in the incidence of congestive heart failure, assuming a control group event rate of 2.86% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as low (very serious imprecision due to wide CI and very small sample size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Bronchospasm

Overall effect

Three studies evaluated the incidence of bronchospasm in cardiac surgery (196 participants). None of the trials found a significant effect of beta-blockers causing bronchospasm compared with control at an alpha level of 0.05. All trials recorded occurrence of bronchospasm in the beta-blocker group or in the control group. Overall, we found no clear evidence of an effect of beta-blockers on the occurrence of bronchospasm in cardiac surgery, as evidenced by a fixed-effect RR of 1.49 with a 95% CI of 0.31 to 7.14 (P value 0.62) ([Analysis 1.26](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.48). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analysis was performed for type of beta-blocker ([Analysis 5.25](#)). The effect of the exact type of beta-blocker on the development of bronchospasm remained non-significant in all subgroups. Stratification for start of beta-blocker was not possible, as all trials started beta-blocker treatment after

surgery. When we applied meta-regression analysis, no clinical effect modifiers were detected.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 1.53, 95% CI 0.25 to 9.51, P value 0.65) instead of a fixed-effect model (RR 1.49, 95% CI 0.31 to 7.14, P value 0.62). Restricting the meta-analysis to the two placebo-controlled studies with an assumed lower risk of bias did not change the estimate much (all studies: RR 1.49, 95% CI 0.31 to 7.14; low risk of bias studies: RR 0.98, 95% CI 0.14 to 6.67, P value 0.98; [Analysis 2.20](#)). Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality or a reporting bias, overall information size was very small (196 participants; 0.7% of optimal information size) compared with the optimal information size of 27,621 participants calculated to detect a 20% relative change in the incidence of bronchospasm, assuming a control group event rate of 2.5% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI was wide and overlapped the zone of no effect (RR 1.0) and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as low (very serious imprecision: wide confidence interval, very small sample size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Length of stay

Overall effect

Fourteen studies evaluated length of stay in cardiac surgery (2450 participants). Three trials reported a significant reduction in hospital stay among participants taking beta-blockers compared with control at an alpha level of 0.05 ([Booth 2004](#); [Sezai 2011](#); [Wenke 1999](#)), whereas 11 trials did not show a significant difference. Overall, we found that beta-blockers statistically significantly reduced length of hospital stay in cardiac surgery by 0.54 days, as evidenced by a random-effects mean difference of -0.54 with a 95% CI of -0.90 to -0.19 (P value 0.003) ([Analysis 1.28](#)).

Heterogeneity

Between-study variance was large ($I^2 = 58\%$, P value 0.004). Thus we chose a random-effects model for presentation. Prespecified stratification for start of beta-blocker treatment led to a substantial reduction in statistical heterogeneity in the strata 'start before surgery' ($I^2 = 0\%$, P value 0.50; [Analysis 3.26](#)) and 'start during

surgery' ($I^2 = 0\%$, P value 0.44). Conversely, heterogeneity was still high in the group 'start after surgery' ($I^2 = 62\%$, P value 0.02). The effect estimate was influenced only mildly by start of beta-blocker treatment (before: mean difference -0.69, 95% CI -1.39 to 0.02; during: mean difference -0.71, 95% CI -0.83 to -0.59; after: mean difference -0.33, 95% CI -0.87 to 0.22). Much of the statistical heterogeneity was caused by substantial differences in the reported effect of metoprolol on length of hospital stay in metoprolol trials (Booth 2004: mean difference -0.70, 95% CI -0.82 to -0.58; Connolly 2003: mean difference 0.20, 95% CI -0.20 to 0.60; Wenke 1999: mean difference -1.41, 95% CI -2.20 to -0.62; Analysis 5.27).

Meta-regression found that the following clinical parameters were statistically significantly associated with the effect estimate: route of beta-blocker application (oral vs intravenous route: P value 0.004), percentage of included patients already taking beta-blockers before entry into the trial (P value 0.03) and gender (P value 0.003). Stratification for these three parameters did not reduce statistical heterogeneity (Analysis 6.13; Analysis 6.14; Analysis 6.15). We found that education in length of stay was more pronounced for parenteral administration (mean difference -0.84, 95% CI -1.42 to -0.25, P value 0.005 for subgroup overall effect) than for oral application (mean difference -0.56, 95% CI -1.14 to 0.02, P value 0.06 for overall subgroup effect; Analysis 6.13). Splitting the trials into two groups according to whether or not more than 43.3% (median of all studies) of included patients were taking beta-blockers before entry into the trial only mildly changed the effect estimate (below median: mean difference -0.69, 95% CI -1.21 to -0.16, P value 0.01 for overall subgroup effect; above median: mean difference -0.43, 95% CI -0.91 to 0.04, P value 0.08 for overall subgroup effect; Analysis 6.15). However, statistical significance was lost in the subgroup comprising trials with a higher than median percentage of patients who were taking beta-blockers before entry into the trial. When the effect of gender on the effect estimate was analysed (Analysis 6.14), a pronounced reduction in length of stay could be observed in trials with the percentage of female participants exceeding 20.8% (median of all trials, below median: mean difference -0.35, 95% CI -0.74 to 0.04, P value 0.08 for overall subgroup effect; above median: mean difference -0.67, 95% CI -1.21 to -0.13, P value 0.01).

Reporting bias

Visual assessment of the funnel plot indicated a reporting bias (small trials tended to report a pronounced reduction in length of stay), whereas formal assessment of funnel plot asymmetry could not confirm this finding (P value 0.892). In keeping with a conservative approach, we judged that a reporting bias was present. Using the trim-and-fill method to adjust for this bias did not change the point estimate and the 95% CI (no study was simulated and added by this method to correct for the reporting bias).

Sensitivity analysis

Prespecified stratification for type of control group could confirm a statistically significant reduction in length of stay in placebo-controlled trials, whereas this effect was blunted in standard care trials (placebo: mean difference -0.60, 95% CI -1.11 to -0.09, P value 0.02 for overall subgroup effect; standard care: mean difference -0.51, 95% CI -1.09 to 0.06, P value 0.08 for overall subgroup effect; Analysis 2.22). Meta-regression analysis identified blinding of participants and doctors (P value 0.001 and P value 0.002,

respectively), application of the intention-to-treat principle in data analysis (P value 0.005) and specification of co-morbidities (P value 0.002) as methodological factors statistically significantly influencing the effect estimate. Stratification of trials according to these parameters did not reduce statistical heterogeneity (Analysis 6.10; Analysis 6.11; Analysis 6.12; Analysis 6.16). Trials with blinding of participants and doctors, trials exactly specifying co-morbidities and trials applying the intention-to-treat principle in data analysis were thought to be of higher quality. Stratification, however, led to inconsistent results: Whereas reduction in length of stay was more pronounced in trials using the intention-to-treat principle (used: mean difference -0.57, 95% CI -0.85 to -0.30, P value < 0.0001 for overall subgroup effect; not used: mean difference -0.66, 95% CI -1.57 to 0.24, P value 0.15 for overall subgroup effect; Analysis 6.10) and specifying co-morbidities (specified: mean difference -0.69, 95% CI -0.80 to -0.57, P value < 0.00001 for overall subgroup effect; not specified: mean difference -0.44, 95% CI -1.10 to 0.21, P value 0.18 for overall subgroup effect; Analysis 6.16), reduction was blunted in trials using blinding of doctors and participants compared with unblinded trials (participants definitively blinded: mean difference -0.72, 95% CI -1.53 to 0.10, P value 0.09 for overall subgroup effect; participants not definitively blinded: mean difference -0.64, 95% CI -0.87 to -0.41, P value < 0.00001 for overall subgroup effect; Analysis 6.11; doctors definitively blinded: mean difference -0.69, 95% CI -1.45 to 0.07, P value 0.08 for overall subgroup effect; doctors not definitively blinded: mean difference -0.62, 95% CI -0.91 to -0.33, P value < 0.0001 for overall subgroup effect; Analysis 6.12).

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was high and could be explained only partially by stratification for start of beta-blocker treatment and type of beta-blocker (see above, 'Heterogeneity' and 'Sensitivity analysis'). We identified many sources of bias as caused by clinical parameters (route of beta-blocker application, percentage of participants pretreated with beta-blockers, gender) and by methodological quality criteria (blinding of participants and attending doctors, application of the intention-to-treat principle in data analysis, specification of co-morbidities in baseline characteristics). The impact of these factors on the effect estimate was only marginal, and we could not identify a clear pattern. Furthermore, we assumed the presence of a reporting bias upon visual inspection of the funnel plot. Adjusting for this bias did not change the effect estimate. Overall information size was sufficient (2450 participants; 213.97% of optimal information size) compared with the optimal information size of 1145 participants calculated to detect a mean difference of 0.5 days in length of stay, assuming a control group length of stay of 10.16 days with a standard deviation (SD) of 4.27 days (length of stay in control groups of included trials) with a power of 80% at an alpha level of 0.05. This estimate was calculated using a conventional sample size calculator (assuming between-study heterogeneity of 0%), as TSA currently is not available for continuous variables and therefore could not be performed. The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (mean difference 0) or significant prolongation of hospital stay (mean difference +0.5). We therefore classified the quality of evidence as low (multiple sources of bias: -1, serious inconsistency: -1). Further research is very likely to have an important impact on

our confidence in the estimate of effect and is likely to change the estimate.

Cost of care

Three trials reported on cost of care (Connolly 2003; Cork 1995; Sezai 2011). The respective numbers were too far apart (differed nearly 10-fold) to allow a meaningful analysis (Analysis 1.30). Connolly and colleagues reported that the total cost of care was USD 4586 in the beta-blocker group and USD 4414 in the control group (no SDs were provided by study authors), whereas in the studies by Cork and colleagues and Sezai and colleagues, on average USD 34,351 and USD 39,981 was spent for a participant in the beta-blocker group, and USD 31,551 and USD 35,679 was spent for a control participant, respectively. Thus all authors report higher costs of care for the intervention groups. This difference reached statistical significance only in the trial by Sezai and colleagues.

Quality of life

No trial reported on quality of life.

Non-cardiac surgery

For a concise summary of the most important outcome variables see [Summary of findings 2](#).

All-cause mortality

Overall effect

Thirteen trials reported on all-cause mortality (11,413 participants). The following types of surgery were evaluated: thoracic surgery (two trials), vascular surgery (three trials), neurosurgery (one trial) and 'non-cardiac' surgery (seven trials). In three trials, no deaths occurred in the beta-blocker group nor in the control group (Lai 2006; Miller 1990; Miller 1991). In the POISE trial (POISE 2008), a significant increase in mortality was observed, whereas in the remaining 13 trials, no significant difference was found between the beta-blocker group and the control group at an alpha level of 0.05. Overall, we found that beta-blockers increased perioperative mortality, as evidenced by a fixed-effect RR of 1.25 (95% CI 1.00 to 1.57, P value 0.05; absolute increase in risk: 0.50%, NNTH: 167, 95% CI: 73 to infinite, Analysis 1.2). Four studies allowed classification of cause of death as cardiac or non-cardiac (Mangano 1996; Marwick 2009; POISE 2008; Yang 2006). With respect to these trials, we found no clear evidence of an effect of beta-blockers on death from cardiac causes in the setting of non-cardiac surgery (RR 1.26, 95% CI 0.91 to 1.75, P value 0.17; Analysis 1.5). Four studies investigated long-term mortality after the 30th postoperative day (DIPOM - Juul 2006; Marwick 2009; Neary 2006; Wallace 1998). The effect estimate changed only slightly in number but lost its statistical significance, if the results of these long-term follow-ups were included in the analysis (RR 0.99, 95% CI 0.74 to 1.31, P value 0.92; Analysis 1.3). If adding long-term mortality data to surgical risk status, long-term all-cause mortality for participants who had undergone high risk surgery was statistically significantly decreased (RR 0.62, 95% CI 0.39 to 0.98, P value 0.04, Analysis 4.2).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.67). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker, type of beta-blocker and risk of surgery did not alter the results much, but the increase in mortality reached statistical

significance in the 'before surgery', 'metoprolol' and 'low and medium risk surgery' subgroups (start of beta-blocker: before: RR 1.30, 95% CI 1.03 to 1.63, P value 0.02 for overall subgroup effect; during: RR 0.54, 95% CI 0.18 to 1.62, P value 0.27 for overall subgroup effect; Analysis 3.2; risk of surgery: low and medium risk: RR 1.31, 95% CI 1.04 to 1.66, P value 0.02; high risk: RR 0.83, 95% CI 0.41 to 1.66, P value 0.59; Analysis 4.1). All these results were driven exclusively by one large trial, the POISE trial (POISE 2008), which represented 72.0% of the weight of the meta-analysis. Omitting this trial led to non-significant results in all three subgroups just mentioned. Meta-regression detected a statistically significant association between the surgical risk status (P value 0.04, Analysis 4.1, see before) and the effect estimate.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.20), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate was virtually unchanged when we used a random-effects model (RR 1.27, 95% CI 1.02 to 1.60, P value 0.03) instead of a fixed-effect model (RR 1.25, 95% CI 1.00 to 1.57, P value 0.05). Restricting the meta-analysis to low risk of bias studies also indicated increased mortality with the use of beta-blockers (all studies: RR 1.25, 95% CI 1.00 to 1.57, P value 0.05; low risk of bias studies: RR 1.29, 95% CI 1.02 to 1.62, P value 0.03 (Analysis 2.2)). This finding was blunted and lost its statistical significance when we analysed only trials with a poorer methodology (non-placebo controlled trials). Meta-regression analysis of methodological quality parameters revealed an association between type of hospital and the effect estimate (P value 0.02). Stratification for type of hospital showed a trend towards lower mortality at university hospitals than at other hospitals. We included multi-centre trials with more non-university hospitals than university hospitals in the 'non-university hospitals' subgroup. When the forest plot in Analysis 6.1 was inspected, we could identify a trend toward higher mortality in the 'non-university hospitals' group ('university hospitals' group: RR 0.58, 95% CI 0.15 to 2.14, P value 0.41 for overall subgroup effect, 'non-university hospitals' group: RR 1.27, 95% CI 1.02 to 1.60, P value 0.02 for overall subgroup effect). Again, these results were exclusively influenced by the POISE trial, and skipping this trial led to a non-significant result for both these groups.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low. However, we found evidence of a bias caused by over-reporting of positive study results by studies of poorer methodological quality. Overall information size was small (11,413 participants; 3.7% of optimal information size) compared with the optimal information size of 307,300 participants calculated to detect a 20% relative change in mortality, assuming a control group event rate of 2.0% (median control group event rate) with a power of 80% at an alpha level of 0.05. TSA was not possible, as no O'Brien-Fleming alpha-spending boundaries could be generated due to the small sample size in comparison with the optimal information size. The effect estimate of the meta-analysis was rather imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as low (serious imprecision due to small sample size and wide confidence interval: -1; bias caused

by studies of poorer methodological quality: -1). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Acute myocardial infarction

Overall effect

We evaluated the occurrence of AMI in 14 trials that included 10,958 participants. The following types of surgery were evaluated: 'non-cardiac' surgery: seven trials; thoracic surgery: two trials; vascular surgery: four trials; and general abdominal surgery: one trial. In three studies, no AMI occurred in the beta-blocker group nor in the control group (Lai 2006; Miller 1990; Stone 1988). Ten of the 11 remaining trials found no statistically significant difference between the beta-blocker group and the control group at an alpha level of 0.05. Only the large POISE trial (POISE 2008) could identify a protective effect of beta-blockers. This single trial had a weight of 80% in the meta-analysis. Overall, beta-blockers statistically significantly reduced perioperative AMI by 27% in non-cardiac surgery, as evidenced by a fixed-effect RR of 0.73 (95% CI 0.61 to 0.87, P value 0.0005) (absolute risk reduction 1.38%; NNTB 76, 95% CI: 52 to 157; Analysis 1.7).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.79). Thus we chose a fixed-effect model for presentation. We performed prespecified subgroup analyses for start of beta-blocker, type of beta-blocker and risk of surgery (Analysis 3.7; Analysis 4.4; Analysis 5.7). Subgroups comprising participants of the POISE trial ('before surgery,' 'metoprolol' and 'low and medium risk surgery') all indicated a significant protective beta-blocker effect that was lost when the POISE trial was excluded from the analysis. Meta-regression could not identify any clinical effect modifiers.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying the Egger's test (P value 0.30), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.73, 95% CI 0.61 to 0.88, P value 0.0007) instead of a fixed-effect model (RR 0.73, 95% CI 0.61 to 0.87, P value 0.0005). Skipping the largest trial, POISE (8351 participants), led to a non-significant result (RR 0.81, 95% CI 0.55 to 1.18, P value 0.27). Restricting the meta-analysis to the nine placebo-controlled studies with an assumed lower risk of bias again left the effect estimate virtually unchanged (all studies: RR 0.73, 95% CI 0.61 to 0.87, P value 0.0005; low risk of bias studies: RR 0.72, 95% CI 0.60 to 0.87, P value 0.0007; Analysis 2.6). Meta-regression analysis of methodological quality parameters did not detect relevant interactions.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality or a reporting bias. Overall information size was small (10,958 participants; 57.7% of optimal information size) compared with the optimal information size of 18,987 participants calculated to detect a 20% relative change in occurrence of AMI, assuming a control group event rate of 3.6% (median control group event rate of included studies) with a power of 80% at an alpha level of 0.05. However, when TSA was applied, the upper O'Brien-Fleming alpha-spending boundary was crossed, indicating a significant protective effect of beta-blockers in prevention of AMI in non-cardiac surgery (Figure 8). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as high (no downgrading). Further research is very unlikely to change our confidence in the estimate of effect.

Figure 8. TSA acute myocardial infarction—non-cardiac surgery.

Myocardial ischaemia

Overall effect

Fourteen studies investigated myocardial ischaemia in non-cardiac surgery as defined by study authors (978 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: three trials; neurosurgery: one trial; gynaecological surgery: two trials; vascular surgery: four trials; thoracic surgery: two trials; and general abdominal surgery: two trials. In four trials, no episodes of myocardial ischaemia occurred in the beta-blocker group nor in the control group. Two of the remaining 10 trials found a significant protective effect of beta-blockers at an alpha level of 0.05 (Stone 1988; Wallace 1998). Overall, beta-blockers statistically significantly reduced perioperative myocardial ischaemia in non-cardiac surgery by 49%, as evidenced by a random-effects RR of 0.51 with a 95% CI of 0.34 to 0.77 (P value 0.001; absolute risk reduction 11.90%; NNTB 9, 95% CI: 7 to 19; Analysis 1.9).

Heterogeneity

The amount of variance explained by between-study variation was moderate ($I^2 = 28\%$, P value 0.19). Thus we chose a random-effects

model for presentation. We performed prespecified subgroup analyses for start of beta-blocker treatment, type of beta-blocker and risk of surgery (Analysis 3.9; Analysis 4.5; Analysis 5.8). We could not fully explain statistical heterogeneity between trials by any of these stratifications. However, we found less heterogeneity for trials starting beta-blocker treatment during surgery (Analysis 3.9), and investigating high risk patients (Analysis 4.5). Furthermore, we noted a trend towards higher protection of beta-blockers against myocardial ischaemia in high-risk surgery (low and medium risk: RR 0.39, 95% CI 0.13 to 1.19, P value 0.10; high risk: RR 0.60, 95% CI 0.39 to 0.93, P value 0.02; Analysis 4.5). Meta-regression analysis of clinical quality parameters did not detect relevant interactions.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.28), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate was virtually unchanged when we used a fixed-effect model (RR 0.55, 95% CI 0.42 to 0.71, P value < 0.00001)

instead of a random-effects model (RR 0.51, 95% CI 0.34 to 0.77, P value 0.001). Restricting the meta-analysis to the nine placebo-controlled studies with an assumed lower risk of bias did not change the estimate much (all studies: RR 0.51, 95% CI 0.34 to 0.77, P value 0.001; low risk of bias studies: RR 0.65, 95% CI 0.49 to 0.86, P value 0.002; [Analysis 2.8](#)). Meta-regression analysis of methodological quality parameters detected control group status (P value 0.02), blinding status of participants (P value 0.02) and use of an intention-to-treat analysis (P value 0.02) as effect modifiers. When we performed stratification for these parameters was, it could be observed that higher study quality (presence of a placebo control group, blinding of participants and use of intention-to-treat analysis) resulted in attenuation of the protective beta-blocker effect versus the overall estimate (placebo: RR 0.65, 95% CI 0.49 to 0.86, P value 0.002; [Analysis 2.8](#); blinding of participants: RR 0.65, 95% CI 0.49 to 0.86, P value 0.002; [Analysis 6.3](#); use of intention-to-treat analysis: RR 0.68, 95% CI 0.50 to 0.91, P value 0.009; [Analysis 6.2](#); overall estimate: RR 0.51, 95% CI 0.34 to 0.77, P value 0.001; [Analysis 1.9](#)). However, the protective properties of beta-blockers remained statistically significant in all evaluated strata.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was moderate. We could not clearly identify the source of heterogeneity. We found evidence of a small bias caused by studies of poorer methodological quality that overestimated the protective effect of beta-blockers in prevention of myocardial ischaemia. This bias was shown not to significantly affect the effect estimate. We detected no reporting bias. Overall information size was small (978 participants; 3.9% of optimal information size) compared with the optimal information size of 24,924 participants calculated to detect a 20% relative change in incidence of myocardial ischaemia, assuming a control group event rate of 6.3% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA was inconclusive, as the Z-curve did not cross either O'Brien-Fleming alpha-spending boundary (figure not shown). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as moderate (serious imprecision due to small sample size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Cerebrovascular events

Overall effect

Five studies evaluated cerebrovascular events in non-cardiac surgery (9150 participants). The following types of surgery were evaluated: vascular surgery: one trial; 'non-cardiac' surgery: four trials. Only the largest of the five trials found a significant increase in cerebrovascular events in the beta-blocker group compared with the control group at an alpha level of 0.05 ([POISE 2008](#)). In contrast, the other four trials yielded non-significant results. Overall, we found no clear evidence of an effect of beta-blockers on cerebrovascular events in non-cardiac surgery, as evidenced by a fixed-effect RR of 1.59 with a 95% CI of 0.93 to 2.71 (P value 0.09) ([Analysis 1.11](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 15\%$, P value 0.32). Thus a fixed-effect model was chosen for presentation. We performed prespecified subgroup analyses (type of beta-blocker, risk of surgery; [Analysis 4.6](#); [Analysis 5.10](#)). Results of all subgroups were consistently statistically non-significant. Stratification for start of beta-blocker treatment was not possible, as all trials started beta-blocker treatment before surgery. Meta-regression analysis did not indicate an influence of clinical parameters on the effect estimate.

Reporting bias

No evidence was found of a reporting bias upon visual assessment of the funnel plot. Formal assessment of funnel plot asymmetry was not performed because fewer than 10 studies were combined. Formal tests cannot distinguish between-study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The overall effect estimate was driven mainly by the largest trial ([POISE 2008](#)), which was assigned 63.7% of the weight. Omitting this study shifted the point estimate towards no effect (RR 0.99, 95% CI 0.37 to 2.64, P value 0.99). The effect estimate was slightly changed when a random-effects model (RR 1.48, 95% CI 0.70 to 3.16, P value 0.31) was used instead of a fixed-effect model (RR 1.59, 95% CI 0.93 to 2.71, P value 0.09). Meta-regression analysis of methodological quality parameters detected a relevant influence of the control group (P value 0.05) and participants' blinding status (P value 0.05). Stratification for both of these parameters could completely eradicate statistical heterogeneity ([Analysis 2.9](#); [Analysis 6.4](#)). The effect estimate in the subgroups with an assumed lower risk of bias was shifted towards an increase in cerebrovascular events in the beta-blocker groups (RR 2.09, 95% CI 1.14 to 3.82, P value 0.02 for overall subgroup effect; absolute risk increase 0.39%; NNTH 265, 95% CI: 102 to 2058; [Analysis 2.9](#); RR 2.09, 95% CI 1.14 to 3.82, P value 0.02 for overall subgroup effect; absolute risk increase 0.39%; NNTH 255; [Analysis 6.4](#)). Again, these results were driven by the POISE trial. Omitting this trial from subgroup analyses blunted the negative effect of beta-blockers.

Summary of confidence in estimates of effects using GRADE and TSA

Statistical heterogeneity of the data was low and could be entirely eliminated by splitting the trials according to control group and blinding status. Studies of poorer methodological quality include a much smaller sample and tended to report a non-significant effect of beta-blockers on cerebrovascular events. No reporting bias was detected. Overall information size was small (9150 participants; 5.9% of optimal information size) compared with the optimal information size of 155,511 participants calculated to detect a 20% relative change in the incidence of cerebrovascular events, assuming a control group event rate of 1.0% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as low (presence of a bias introduced by studies of poorer methodological quality: -1; serious imprecision due to wide confidence interval and small sample size: -1).

-1). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Ventricular arrhythmias

Overall effect

Five studies evaluated the occurrence of ventricular arrhythmias in non-cardiac surgery (476 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: one trial; vascular surgery: one trial; and thoracic surgery: three trials. One trial found a significant protective effect of beta-blockers compared with control at an alpha level of 0.05 (Sandler 1990), whereas the other four yielded non-significant results. Overall, we found no clear evidence of an effect of beta-blockers on the incidence of ventricular arrhythmias in non-cardiac surgery, as evidenced by a random-effects RR of 0.68 with a 95% CI of 0.31 to 1.49 (P value 0.33) (Analysis 1.13).

Heterogeneity

The amount of variance explained by between-study variation was moderate to large ($I^2 = 45\%$, P value 0.12). Thus a random-effects model was chosen for presentation. Prespecified subgroup analyses (start of beta-blocker treatment, type of beta-blocker and risk of surgery) were able to eliminate statistical heterogeneity (Analysis 3.12; Analysis 4.7; Analysis 5.12). Meta-regression analysis identified start of beta-blocker treatment (P value 0.01), risk status of surgery (P value 0.01) and route of beta-blocker application (P value 0.01 for oral vs intravenous) as effect modifiers. Stratification for these parameters (Analysis 3.12; Analysis 4.7; Analysis 6.5) revealed a more pronounced, statistically significant protective effect of beta-blockers when given intravenously (only on trial Sandler 1990): RR 0.25, 95% CI 0.09 to 0.70, P value 0.008; Analysis 6.5) during surgery (only on trial (Sandler 1990): RR 0.25, 95% CI 0.09 to 0.70, P value 0.008; Analysis 3.12) in low- and medium-risk procedures (RR 0.34, 95% CI 0.14 to 0.82, P value 0.02; Analysis 4.7).

Reporting bias

No evidence of a reporting bias was found upon visual assessment of the funnel plot. Formal assessment of funnel plot asymmetry was not performed because fewer than 10 studies were combined. Formal tests cannot distinguish between-study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate was virtually unchanged when a fixed-effect model (RR 0.72, 95% CI 0.43 to 1.19, P value 0.20) was used instead of a random-effects model (RR 0.68, 95% CI 0.30 to 1.49, P value 0.33). Restriction of the analysis to low risk of bias trials was not possible, as all trials were placebo-controlled trials. Meta-regression analysis could not identify methodological parameters influencing the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

Statistical heterogeneity of the data was moderate to large and could be explained by stratification for clinical parameters (start of beta-blocker, route of application and risk of surgery). We did not detect a reporting bias. Overall information size was small (476 participants; 4.1% of optimal information size) compared with the optimal information size of 11,697 participants calculated to detect

a 20% relative change in the incidence of ventricular arrhythmias, assuming a control group event rate of 15.9% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible to perform TSA analysis with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI was large and overlapped the zone of no effect (RR 1.0) and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as moderate (serious imprecision due to wide confidence interval and small sample size: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Supraventricular arrhythmias

Overall effect

Eight studies evaluated the occurrence of supraventricular arrhythmias in non-cardiac surgery (8744 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: one trial; gynaecological surgery: two trials; thoracic surgery: four trials; and general abdominal surgery: one trial. Only the largest trials (POISE 2008) found a significant protective effect of beta-blockers compared with control at an alpha level of 0.05, whereas the other eight trials yielded non-significant results. Overall, beta-blockers statistically significantly reduced the incidence of supraventricular arrhythmias in non-cardiac surgery by 27%, as evidenced by a fixed-effect RR of 0.73 with a 95% CI of 0.57 to 0.94 (P value 0.01) (absolute risk reduction 0.84%; NNTB 112, 95% CI: 70 to 505; Analysis 1.17).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.53). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses showed that the protective effect of beta-blockers was blunted if the drug was not started until induction of anaesthesia (Analysis 3.16). The significant protective effect was only preserved in low- and medium-risk, but not in high risk surgery (Analysis 4.9). Metoprolol was the beta-blocker used for the greatest number of randomly assigned participants by far and proved to significantly reduce the incidence of all supraventricular arrhythmias (Analysis 5.16). The effect was blunted for other beta-blockers with only a very small number of randomly assigned participants. Looking only at studies investigating the incidence of atrial fibrillation and atrial flutter did not change the effect estimate (RR 0.73, 95% CI 0.56 to 0.95, P value 0.02; Analysis 1.15). Meta-regression analysis did not identify clinical effect modifiers.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between-study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

Much of the weight of the meta-analysis came from the large POISE trial (82.5%). Omitting this study from the analysis changed the effect estimate (RR 0.61, 95% CI 0.33 to 1.11, P value 0.10), and the result lost statistical significance. The effect estimate was virtually unchanged when we used a random-effects model (RR 0.74, 95%

CI 0.58 to 0.95, P value 0.02) instead of a fixed-effect model (RR 0.73, 95% CI 0.57 to 0.94, P value 0.01). Restriction of the analysis to placebo-controlled trials with an assumed low risk of bias again did not change the effect estimate (RR 0.75, 95% CI 0.59 to 0.96, P value 0.02; [Analysis 2.14](#)). Meta-regression analysis of methodological parameters did not detect an association between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

We found heterogeneity of the data was low, and that no reporting bias nor bias introduced by studies of poor methodological quality could be detected. Overall information size was fair (8744

participants; 85.4% of optimal information size) compared with the optimal information size of 10,243 participants calculated to detect a 20% relative change in the incidence of supraventricular arrhythmias, assuming a control group event rate of 12.4% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA showed a significant protective effect of beta-blockers as the Z-curve crossed the upper O'Brien-Fleming alpha-spending boundary ([Figure 9](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as high (no downgrading). Further research is very unlikely to change our confidence in the estimate of effect.

Figure 9. TSA supraventricular arrhythmias - non-cardiac surgery.

Bradycardia

Overall effect

Twenty-three studies evaluated the occurrence of bradycardia in non-cardiac surgery (11,033 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: five trials; gynaecological surgery: three trials; neurosurgery: three trials; thoracic surgery: two trials; vascular surgery: three trials; general abdominal surgery: five trials; and maxillofacial surgery: two trials. Three trials found no episodes of bradycardia in the beta-

blocker group nor in the control group. Of the remaining 20 trials, six found beta-blockers to significantly induce bradycardia, whereas 14 trials yielded non-significant results. Overall, we found that beta-blockers statistically significantly increased episodes of bradycardia by 123% in non-cardiac surgery, as evidenced by a random-effects RR of 2.23 with a 95% CI of 1.48 to 3.36 (P value < 0.0001) (absolute increase in risk 5.64%; NNTH 21, 95% CI: 11 to 53; [Analysis 1.21](#)).

Heterogeneity

The amount of variance explained by between-study variation was high ($I^2 = 76\%$, P value < 0.00001). Thus we chose a random-effects model for presentation. In the prespecified subgroup analyses for start of beta-blocker, type of beta-blocker and risk of surgery, only type of beta-blocker could reduce statistical heterogeneity ([Analysis 3.20](#); [Analysis 4.10](#); [Analysis 5.20](#)). The heart rate-slowing effect of beta-blockers was more pronounced when given before surgery than when given during surgery (before: RR 2.60, 95% CI 2.23 to 3.04, P value < 0.00001 ; during: RR 1.60, 95% CI 1.01 to 2.52, P value 0.04; [Analysis 3.20](#)) and in high-risk surgical procedures (high risk: RR 3.16, 95% CI 2.33 to 4.26, P value < 0.00001 ; low and medium risk: RR 1.88, 95% CI 1.04 to 3.40, P value 0.04; [Analysis 4.10](#)). Bradycardia was statistically significantly induced by all types of beta-blockers except esmolol, atenolol and nadolol ([Analysis 5.20](#)). However, the effects of nadolol were investigated by only a single trial with a small sample size. When we applied meta-regression analysis, prevalence of coronary heart disease (CHD) among study participants (P value 0.03) was associated with the effect estimate. Stratification for this clinical parameter found a stronger effect of beta-blockers causing bradycardia in trials with more participants diagnosed with CHD (CHD prevalence below median of 25%: RR 1.27, 95% CI 0.52 to 3.08, P value 0.60 for overall subgroup effect; CHD prevalence above median: RR 2.25, 95% CI 1.14 to 4.45, P value 0.02 for overall subgroup effect; [Analysis 6.8](#)). This stratification could not reduce statistical heterogeneity.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.93), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a fixed-effect model (RR 2.49, 95% CI 2.15 to 2.88, P value < 0.00001) instead of a random-effects model (RR 2.23, 95% CI 1.48 to 3.36, P value 0.0001), or when we restricted the meta-analysis to the 19 placebo-controlled studies with an assumed lower risk of bias (low

risk of bias studies: RR 2.13, 95% CI 1.31 to 3.46, P value 0.002; [Analysis 2.17](#)). Meta-regression identified the methodological parameters 'explicit specification of outcome parameters' and 'specification of baseline characteristics' to interact with the effect estimate. Studies of poorer methodological quality tended to significantly underestimate bradycardia (outcome variables explicitly specified: RR 2.65, 95% CI 2.11 to 3.32, P value < 0.00001 for overall subgroup effect; outcome variables not or vaguely specified: RR 0.93, 95% CI 0.72 to 1.20, P value 0.58 for overall subgroup effect; [Analysis 6.7](#); baseline characteristics specified: RR 2.70, 95% CI 2.13 to 3.44, P value < 0.00001 for overall subgroup effect; not specified: RR 1.09, 95% CI 0.63 to 1.87, P value 0.76 for overall subgroup effect; [Analysis 6.6](#)). Statistical heterogeneity could be reduced by stratification for these methodological parameters.

Summary of confidence in estimates of effects using GRADE and TSA

We found that heterogeneity of data was high and could be explained only partially by type of beta-blocker and methodological study quality parameters. We found Evidence of a bias caused by studies of poorer methodological quality. This bias, however, did not significantly influence the overall effect estimate. We did not judge reporting bias to be present. Overall information size was moderate (11,033 participants; 19.50% of optimal information size) compared with the optimal information size of 56,584 participants calculated to detect a 20% relative change in the incidence of bradycardia, assuming a control group event rate of 4.0% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA confirmed a significant effect of beta-blockers causing bradycardia, as the Z-curve crossed the lower O'Brien-Fleming alpha-spending boundary ([Figure 10](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential benefit (RR 0.75). We therefore classified the quality of evidence as moderate (serious inconsistency due to high heterogeneity of data that could be explained only partially: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Figure 10. TSA bradycardia - non-cardiac surgery.

Hypotension

Overall effect

Twenty-two studies evaluated the occurrence of hypotensive episodes in non-cardiac surgery (10,947 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: five trials; gynaecological surgery; one trial; neurosurgery; three trials; general abdominal surgery; five trials; vascular surgery; four trials; thoracic surgery; three trials; and maxillofacial surgery: one trial. In three trials, no hypotensive episodes occurred in the beta-blocker group nor the control group. Six of the remaining 19 trials found that beta-blockers significantly increased hypotensive episodes at an alpha level of 0.05, whereas 13 trials yielded non-significant results. Overall, we found that hypotensive episodes were statistically significantly increased by 50% in non-cardiac surgery if beta-blockers were administered, as evidenced by a fixed-effect RR of 1.50 with a 95% CI of 1.38 to 1.64 (P value < 0.00001) (absolute increase in risk 6.47%; NNT 16, 95% CI: 13 to 21; [Analysis 1.23](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 4\%$, P value 0.40). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start

of beta-blocker, type of beta-blocker and risk of surgery were performed ([Analysis 3.22](#); [Analysis 4.11](#); [Analysis 5.22](#)). The blood pressure-lowering effect of beta-blockers remained significant in all subgroup analyses investigating start of beta-blocker treatment and risk of surgery, as well as for all subgroups of types of beta-blocker that comprised more than one randomized trial. Stratification for risk of surgery could further reduce statistical heterogeneity to 0% in each subgroup ([Analysis 4.11](#)). Meta-regression analysis of clinical parameters did not detect any effect modifiers.

Reporting bias

Upon visual assessment of the funnel plot and formal assessment of funnel plot asymmetry while applying Egger's test (P value 0.44), we found no evidence of a reporting bias.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 1.40, 95% CI 1.29 to 1.53, P value < 0.00001) instead of a fixed-effect model (RR 1.50, 95% CI 1.38 to 1.64, P value < 0.00001). Restricting the meta-analysis to the 18 placebo-controlled studies with an assumed lower risk of bias also left the effect estimate unchanged (all studies: RR 1.50, 95% CI 1.38 to 1.64, P value < 0.00001; low risk of bias studies: RR 1.51, 95% CI 0.38

to 1.65, P value < 0.00001 ; [Analysis 2.19](#)). Meta-regression did not detect an interaction between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low, and we found no evidence of a bias introduced by studies of poorer methodological quality. We did not detect reporting bias. Overall information size was sufficient (10,947 participants; 107.0% of optimal information size) compared with the optimal information size of 10,232 participants calculated

to detect a 20% relative change in the incidence of hypotensive episodes, assuming a control group event rate of 6.5% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA showed a significant effect of beta-blockers causing hypotensive episodes as the Z-curve crossed the lower O'Brien-Fleming alpha-spending boundary ([Figure 11](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential benefit (RR 0.75). We therefore classified the quality of evidence as high (no downgrading). Further research is very unlikely to change our confidence in the estimate of effect.

Figure 11. TSA hypotension—non-cardiac surgery.

Ventricular extrasystoles

Overall effect

Nine studies evaluated the incidence of ventricular extrasystoles in non-cardiac surgery (492 participants). The following types of surgery were evaluated: general abdominal surgery: four trials; gynaecological surgery: three trials; vascular surgery: one trial; and maxillofacial surgery: one trial. Four trials found a significant effect of beta-blockers in preventing the occurrence of

ventricular extrasystoles at an alpha level of 0.05, whereas five trials yielded non-significant results. Overall, beta-blockers statistically significantly reduced the incidence of ventricular extrasystoles by 78% in non-cardiac surgery, as evidenced by a fixed-effect RR of 0.22 with a 95% CI of 0.13 to 0.37 (P value < 0.00001) (absolute risk reduction 24.51%; NNTB 4, 95% CI: 4 to 5; [Analysis 1.19](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.80). Thus we chose a fixed-effect model for presentation. We performed prespecified subgroup analyses for start of beta-blocker and type of beta-blocker ([Analysis 3.18](#); [Analysis 5.18](#)). Stratification for risk of surgery was not possible, as all studies were low- or medium-risk procedures. The protective effect of beta-blockers was consistent within all subgroups, reflecting different start points of beta-blocker treatment ([Analysis 3.18](#)). Meta-regression analysis found no association between clinical parameters and the effect estimate.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.27, 95% CI 0.16 to 0.44, P value < 0.00001) instead of a fixed-effect model (RR 0.22, 95% CI 0.13 to 0.37, P value < 0.00001). Restricting the meta-analysis to the eight

placebo-controlled studies with an assumed lower risk of bias also left the effect estimate unchanged (all studies: RR 0.22, 95% CI 0.13 to 0.37, P value < 0.00001; low risk of bias studies: RR 0.23, 95% CI 0.13 to 0.39, P value < 0.00001; [Analysis 2.15](#)). Meta-regression did not detect an interaction between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low, and we found no evidence of a bias introduced by trials of poorer methodological quality and no evidence of a reporting bias. Overall information size was small (492 participants; 26.8% of optimal information size) compared with the optimal information size of 1835 participants calculated to detect a 20% relative change in the incidence of ventricular extrasystoles, assuming a control group event rate of 28.6% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA showed a significant effect of beta-blockers protecting against ventricular extrasystoles, as the Z-curve crossed the upper O'Brien-Fleming alpha-spending boundary ([Figure 12](#)). The effect estimate of the meta-analysis was precise, as the 95% CI did not overlap the zone of no effect (RR 1.0) nor the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as high (no downgrading). Further research is very unlikely to change our confidence in the estimate of effect.

Figure 12. TSA ventricular extrasystoles—non-cardiac surgery.

Congestive heart failure

Overall effect

Five studies evaluated the incidence of congestive heart failure in non-cardiac surgery (9173 participants). The following types of surgery were evaluated: 'non-cardiac' surgery two trials; thoracic surgery: one trial; vascular surgery: one trial; and abdominal surgery: one trial. None of the trials found a significant effect of beta-blockers preventing or causing congestive heart failure compared with control at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on congestive heart failure in non-cardiac surgery, as evidenced by a fixed-effect RR of 1.18 with a 95% CI of 0.94 to 1.48 (P value 0.16) ([Analysis 1.25](#)).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.77). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker, type of beta-blocker and risk of surgery consistently yielded non-significant results ([Analysis 3.24](#);

[Analysis 4.12](#); [Analysis 5.24](#)). Meta-regression analysis detected no association between clinical parameters and the effect estimate.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

If the largest trial, POISE (POISE 2008; 88.3% of weight), was skipped, we found that the effect estimate changed only slightly (RR 1.48, 95% CI 0.80 to 2.77, P value 0.21). Furthermore, the effect estimate remained unchanged when we used a random-effects model (RR 1.18, 95% CI 0.94 to 1.48, P value 0.16) instead of a fixed-effect model (RR 1.18, 95% CI 0.94 to 1.48, P value 0.16). All trials were placebo controlled, which precluded stratification for control group status. Meta-regression did not detect an interaction between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

Heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality nor of a reporting bias. Overall information size was sufficient (9173 participants; 95.5% of optimal information size) compared with the optimal information size of 9,602 participants calculated to detect a 20% relative change in the incidence of congestive heart failure, assuming a control group event rate of 6.9% (median control group

event rate of included trials) with a power of 80% at an alpha level of 0.05. TSA indicated futility, as the Z-curve crossed the lower boundary of the inner futility wedge (Figure 13). The effect estimate of the meta-analysis was imprecise, as the 95% CI overlapped the zone of no effect (RR 1.0) and the zone of potential harm (RR 1.25). We therefore classified the quality of evidence as moderate (serious imprecision due to wide confidence interval overlapping zones of no effect and potential harm: -1). Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Figure 13. TSA congestive heart failure - non-cardiac surgery.

Bronchospasm**Overall effect**

Eight studies evaluated the incidence of bronchospasm in non-cardiac surgery (1080 participants). The following types of surgery were evaluated: 'non-cardiac' surgery: two trials; gynaecological surgery: one trial; neurosurgery: one trial; thoracic surgery: one trial; vascular surgery: two trials; and general abdominal surgery: one trial. In one trial, no events occurred in the beta-blocker group nor in the control group. The remaining seven trials did not detect a statistically significant difference between beta-blocker and control groups at an alpha level of 0.05. Overall, we found no clear evidence of an effect of beta-blockers on the occurrence of bronchospasm in

non-cardiac surgery, as evidenced by a fixed-effect RR of 0.94 with a 95% CI of 0.55 to 1.59 (P value 0.81) (Analysis 1.27).

Heterogeneity

The amount of variance explained by between-study variation was low ($I^2 = 0\%$, P value 0.77). Thus we chose a fixed-effect model for presentation. Prespecified subgroup analyses for start of beta-blocker, type of beta-blocker and risk of surgery were performed (Analysis 3.25; Analysis 4.13; Analysis 5.26). The effect estimate was consistently non-significant in all subgroups. Meta-regression analysis detected no association between clinical parameters and the effect estimate.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

The effect estimate remained virtually unchanged when we used a random-effects model (RR 0.85, 95% CI 0.50 to 1.46, P value 0.56) instead of a fixed-effect model (RR 0.94, 95% CI 0.55 to 1.59, P value 0.81). Restricting the meta-analysis to the seven placebo-controlled studies with an assumed lower risk of bias again left the effect estimate virtually unchanged (all studies: RR 0.94, 95% CI 0.55 to 1.59, P value 0.81; low risk of bias studies: RR 0.98, 95% CI 0.57 to 1.67, P value 0.94 for overall subgroup effect; [Analysis 2.21](#)). Meta-regression did not detect an interaction between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

Whereas heterogeneity of the data was low, and we found no evidence of a bias caused by studies of poorer methodological quality nor of a reporting bias, overall information size was very small (1080 participants; 3.6% of optimal information size) compared with the optimal information size of 30,078 participants calculated to detect a 20% relative change in the incidence of bronchospasm, assuming a control group event rate of 2.3% (median control group event rate of included trials) with a power of 80% at an alpha level of 0.05. It was not possible for us to perform TSA with such a small information size. The effect estimate of the meta-analysis was imprecise, as the 95% CI was wide and overlapped the zone of no effect (RR 1.0) and the zones of potential benefit and harm (RR 0.75 and RR 1.25, respectively). We therefore classified the quality of evidence as low (very serious imprecision due to very small sample size and wide confidence interval: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Length of stay

Overall effect

Three studies evaluated length of stay in non-cardiac surgery (551 participants). The following types of surgery were evaluated: vascular surgery: one trial; 'non-cardiac' surgery: one trial; and general abdominal surgery: one trial. One trial reported a significant reduction in hospital stay among participants taking beta-blockers compared with control at an alpha level of 0.05, whereas two trials did not show a significant difference. Overall, we found no clear evidence of an effect of beta-blockers on length of hospital stay in non-cardiac surgery, as evidenced by a random-effects mean difference of -0.45 with a 95% CI of -1.75 to 0.84 (P value 0.49) ([Analysis 1.29](#)).

Heterogeneity

The amount of variance explained by between-study variation was moderate ($I^2 = 36\%$, P value 0.21). Thus we chose a random-effects model for presentation. Prespecified stratification for start of beta-blocker, type of beta-blocker and risk of surgery could

not significantly reduce statistical heterogeneity ([Analysis 3.27](#); [Analysis 4.14](#); [Analysis 5.28](#)). The reduction in length of stay reached statistical significance in the subgroups 'during surgery,' 'low and medium risk procedure' and 'esmolol' (only one trial [Lee 2010](#): mean difference -0.40, 95% CI -0.58 to -0.22, P value <0.0001 for subgroup effect; mean difference -0.40, 95% CI -0.58 to -0.22, P value < 0.0001 for subgroup effect; [only one trial [Lee 2010](#): mean difference -0.40, 95% CI -0.58 to -0.22, P value < 0.0001 for subgroup effect, respectively). These results were driven mainly by the trial by Lee and colleagues ([Lee 2010](#); 73.0% of the weight of the meta-analysis), which reported a significant reduction in hospital stay with the use of beta-blockers and was predominant in the above mentioned subgroups. Meta-regression analysis detected no association between clinical parameters and the effect estimate.

Reporting bias

We found no evidence of a reporting bias upon visual assessment of the funnel plot. We did not perform formal assessment of funnel plot asymmetry because fewer than 10 studies were combined. Formal tests cannot distinguish between study variance of estimates and a potential reporting bias in this case.

Sensitivity analysis

When we used a fixed-effect model instead of a random-effects model, the effect estimate changed only modestly in number but reached statistical significance (mean difference -0.40, 95% CI -0.58 to -0.22, P value <0.0001). Prespecified stratification for type of control group modestly altered the effect estimate which remained statistically not significant (placebo: mean difference -4.58, 95% CI -16.07 to 6.91, P value 0.43 for overall subgroup effect; [Analysis 2.23](#)). Meta-regression did not detect an interaction between methodological parameters and the effect estimate.

Summary of confidence in estimates of effects using GRADE and TSA

We noted a moderate amount of unexplained heterogeneity of the data. We could not identify a reporting bias or a bias introduced by studies of poorer methodological quality. Overall information size was very small (551 participants; 2.8% of optimal information size) compared with the optimal information size of 19,854 participants calculated to detect a mean difference of 0.5 days in length of stay, assuming a control group length of stay of 12.8 days with an SD of 17.8 days (mean length of stay in control groups of included trials) and a power of 80% at an alpha level of 0.05. We calculated this estimate using a conventional sample size calculator (assuming between-study heterogeneity of 0%), as the TSA software currently can be used only to calculate the optimal information size for dichotomous outcomes. The effect estimate of the meta-analysis was imprecise, as the 95% CI was wide and overlapped the zones of relevant prolongation and reduction of hospital stay (mean difference +0.5 and -0.5 days, respectively). We therefore classified the quality of evidence as low (very serious imprecision due to wide confidence interval and very small sample size: -2). Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Cost of care

No trial reported on cost of care.

Quality of life

No trial reported on quality of life.

DISCUSSION

We could identify 88 randomized controlled trials with a total of 19,161 randomly assigned study participants that met our inclusion criteria. Our study looked at 13 different outcomes, and overall effect estimates could be calculated for 11 of them. The most important outcomes are presented in the summary of findings tables, which are presented separately for cardiac and non-cardiac surgery ([Summary of findings for the main comparison](#); [Summary of findings 2](#)).

Summary of main results

All-cause mortality

Cardiac surgery

In our analysis of 24 trials comprising 3783 participants, we found no clear evidence of an effect of beta-blockers on all-cause mortality (RR 0.73, 95% CI 0.35 to 1.52, P value 0.40) nor death from cardiac causes (RR 0.85, 95% CI 0.16 to 4.40, P value 0.84) in heart surgery. As the number of randomly assigned participants was rather small and the confidence interval was wide, with overlapping zones of no effect and potential harm or benefit of therapy, no definitive conclusion can be drawn from our data.

Current guidelines on the use of beta-blockers in aortocoronary bypass surgery suggest that patients with an ejection fraction greater than 30% should receive beta-blockers preoperatively to reduce in-hospital mortality ([Hillis 2011](#)). This class IIa recommendation was based on smaller RCTs and observational studies indicating reduced mortality with the use of beta-blockers in bypass surgery. Besides, all patients undergoing aortocoronary bypass surgery are diagnosed with coronary heart disease and therefore should receive beta-blockers if not contraindicated for other reasons (class Ia recommendation; [Montalescot 2013](#)).

Non-cardiac surgery

In our analysis of 13 trials comprising 11,413 participants, we found beta-blockers to increase all-cause mortality (RR 1.25, 95% CI 1.00 to 1.57, P value 0.05). Statistical significance was lost, if only cardiac mortality (RR 1.26, 95% CI 0.91 to 1.75, P value 0.17) was analysed or data from long-term follow-ups were added (RR 0.99, 95% CI 0.74 to 1.31, P value 0.92). No publication bias was detected in our dataset. Restricting the meta-analysis to trials with an assumed lower risk of bias in our sensitivity analysis (i.e. placebo-controlled trials) revealed increased risk of death from any cause in the beta-blocker group too (RR 1.29, 95% CI 1.02 to 1.62, P value 0.03). Our results were driven mainly by the largest trial, POISE ([POISE 2008](#)), which dominated subgroup analyses. Mortality was increased if beta-blockers were administered before surgery or in low- and medium-risk procedures, and if the duration of treatment exceeded 21 days. All of these were features of the POISE trial, and if POISE was omitted from subgroup analyses, all of these parameters lost statistical significance. However, as POISE met the highest methodological standards and recruited more than 8000 participants, we feel confident about our pooled estimates. Interestingly, stratification of trials according to surgical risk revealed conflicting results, as long-term all-cause mortality for participants who had undergone high risk surgery (RR 0.62, 95% CI

0.39 to 0.98, P value 0.04) was statistically significantly decreased. As the number of randomly assigned participants was far lower than the optimal information size, further trials may change our confidence in the estimate of effect.

Previous European Society of Cardiology (ESC) guidelines for preoperative cardiac risk assessment and perioperative cardiac management in non-cardiac surgery recommended the use of beta-blockers if patients had been treated previously with beta-blockers (class Ic), were undergoing high-risk surgery (class Ib) or were diagnosed with ischaemic heart disease or exhibited myocardial ischaemia with stress testing (class Ib) ([Poldermans 2009](#)). In their recent 2014 guidelines on cardiovascular assessment and management in non-cardiac surgery ([Kristensen 2014](#)), the European Society of Cardiology (ESC) and European Society of Anaesthesiology (ESA) issued joint recommendations that took into account both the results of POISE ([POISE 2008](#)) and recent discussions concerning the credibility of the DECREASE trial family data ([Poldermans 1999](#), [DECREASE-IV 2009](#)). Beta-blockers should be continued if patients are on a beta-blocker long-term medication prior to planned surgery (class I, level of evidence A). Initiation of beta-blocker treatment may be considered in high risk individuals (more than two revised cardiac risk index clinical risk factors, proven ischaemic heart disease or myocardial ischaemia) undergoing intermediate or high risk surgery (class IIb, level of evidence B). If beta-blockers are started before surgery, atenolol or bisoprolol may be considered as first choice (class IIb, level of evidence B), as metoprolol serum levels vary to a greater extent due to a CYP2D6 dependent metabolism. Beta-blocker therapy should be commenced between 30 and 2 days prior to surgery, and titration of beta-blocker dose is mandatory (target resting heart rate 60-70 beats per minute, target systolic blood pressure >100 mmHg).

As opposed to previous guidelines ([Fleisher 2007](#)), current American College of Cardiology (ACC)/American Heart Association (AHA) guidelines are more reluctant in recommending perioperative use of beta-blockers, too, for the reasons outlined above ([Fleisher 2014](#)). Beta-blocker treatment should be continued in the perioperative setting if it is part of the patient's long-term medication (class I, level of evidence B). Start of beta-blockers may be considered only in intermediate or high risk individuals with proven myocardial ischaemia or in patients with at least three revised cardiac risk index clinical risk factors (class IIb, level of evidence C and B, respectively). Thereby, beta-blockers should not be started on the day of surgery (class III, level of evidence B). Guidance of beta-blocker dosage by clinical circumstances (such as bradycardia or hypotension) is reasonable (class IIa, level of evidence B).

POISE and the DECREASE trial family:

The PeriOperative ISchemic Evaluation (POISE) trial ([POISE 2008](#)) was published in 2008 and showed increased mortality in the beta-blocker group (odds ratio (OR) 1.33, 95% CI 1.03 to 1.74, P value 0.03, 8351 participants). This effect was explained by a higher incidence of stroke caused by hypotension (risk factor with the highest population attributable risk). However, these findings were not confirmed by the 2009 DECREASE-IV trial (1066 participants at intermediate cardiac risk randomly assigned to a beta-blocker group, a fluvastatin group, a beta-blocker and fluvastatin group and a double control group). The combined outcome parameter 'cardiovascular death or myocardial infarction' was lower in the

beta-blocker group than in the control group (HR 0.34, 95% CI 0.17 to 0.67, P value 0.002), whereas the incidence of stroke did not significantly differ between these groups (P value 0.68). The DECREASE family of studies was later discredited in 2011 because of allegations of fictitious data ([Chopra 2012](#), [Bouri 2013](#)). We therefore decided against the inclusion in our meta-analysis of both DECREASE trials meeting our eligibility criteria ([DECREASE-IV 2009](#); [Poldermans 1999](#)). Whereas allegations of fictitious data were raised for DECREASE-IV, the DECREASE-I trial ([Poldermans 1999](#)) did not undergo thorough investigation as it was more than 10 years old. The DECREASE-I trial ([Poldermans 1999](#)) examined the effect of bisoprolol in 112 high-risk individuals identified by stress echocardiography undergoing vascular surgery. The study authors found that all-cause mortality could be reduced by as much as 83% (OR 0.17, 95% CI 0.04 to 0.83). This trial was not placebo controlled and therefore was unblinded. Furthermore, the study authors were criticized for reporting above average event rates in their control group, which could also account for the unusually strong protective effect. Third, another point of criticism was based on the fact that this trial was stopped early because interim analysis had shown reduced event rates in the intervention group. Previous experience mandates though that skepticism should apply when unusually large treatment effects are reported by trials that have to be stopped early ([Devereaux 2004](#); [Wheatley 2003](#)). In the light of these facts, results of DECREASE-I have to be classified as insecure and therefore were not considered in our meta-analysis.

Researchers hypothesized that increased mortality and risk of stroke in the POISE trial may be caused by two factors: First, beta-blockers were started only two to four hours before surgery. Second, beta-blockers were not heart rate-titrated in the POISE trial. Participants in the POISE trial were confronted with the study drug immediately before surgery in a (rather high) fixed dose. This might have reduced the plaque-stabilizing effect, which requires prolonged drug action, and might have caused bradycardia or hypotension in participants just above the eligibility criterion for beta-blocker application of 50 beats per minute. Thus timing and mode of beta-blocker application (fixed goal vs heart rate-titrated) may play a role. We could identify the start time of beta-blocker treatment as effect modifier in our set of data (see above), whereas the mode of application was not shown to interact with the effect estimate.

In our meta-analysis, we found that data from the POISE trial seem to have counterbalanced neutral or positive results from other trials, ultimately leading to an increase in mortality. A recently published meta-analysis of 'secure' randomized controlled trials investigating the effect of perioperative beta-blockade in non-cardiac surgery ([Bouri 2013](#)) also found an increase in all-cause mortality with the use of beta-blockers (RR 1.27, 95% CI 1.01 to 1.60, P value 0.04).

Acute myocardial infarction

Cardiac surgery

In our analysis of 22 trials (3553 participants) investigating perioperative AMI in patients undergoing heart surgery, we found no clear evidence of an effect of beta-blockers on the occurrence of this outcome (RR 1.04, 95% CI 0.71 to 1.51, P value 0.85). A reporting bias was judged to be present. Smaller studies tended to overestimate the protective effect of beta-blockers. However, using the trim-and-fill method to adjust for the reporting bias did

not change the effect estimate. Restricting the meta-analysis to trials with an assumed lower risk of bias did not much change the effect estimate either (RR 1.38, 95% CI 0.71 to 2.69, P value 0.35). The trauma of the aortocoronary bypass operation itself (potential occlusion of coronary arteries caused by manipulation resulting in endothelial injury) may constitute a major determinant in developing AMI in these patients rather than the sympathetic stress response or increased oxygen demand, which can be influenced with the use of beta-blockers. As the number of randomly assigned participants was rather small and the confidence interval was wide, leading to overlapping zones of no effect and potential harm or benefit of therapy, no definitive conclusion can be drawn from our data (moderate quality of evidence).

Non-cardiac surgery

As was found previously by other investigators ([Bangalore 2008](#); [Bouri 2013](#); [Stevens 2003](#)), in our analysis of 14 trials with a total of 10,958 participants, current evidence supported a protective effect of beta-blockers against perioperative AMI. The overall RR from a fixed-effect model was 0.73 and reached statistical significance (95% CI 0.61 to 0.87, P value 0.0005). TSA could confirm the protective effect of beta-blockers. Additionally, the estimate was precise. We therefore classified the quality of evidence as high.

Results were again driven mainly by the POISE trial. In this trial, the decrease in AMI was not large enough to compensate for the increased cerebrovascular risk leading to elevated all-cause mortality in the beta-blocker group. Studies that found a reduction in mortality with the use of beta-blockers have attributed the decrease in perioperative mortality mainly to a reduction in (fatal) perioperative AMI (e.g. [Mangano 1996](#)). A recent meta-analysis of 'secure' randomized controlled trials in non-cardiac surgery also found AMI to be significantly reduced in the beta-blocker group (RR 0.73, 95% CI 0.61 to 0.88, P value 0.001; [Bouri 2013](#)).

In summary, we feel confident about our findings, as they are supported by both current literature and pathophysiology (see 'Myocardial ischaemia').

Myocardial ischaemia

Cardiac surgery

Only four trials (166 participants) investigated the occurrence of myocardial ischaemia in cardiac surgery. As outlined above, myocardial ischaemia may be a sequel of trauma of surgery more than of stress response and increased oxygen demand in this setting. When pooling the four trials (RR 0.51, 95% CI 0.25 to 1.05, P value 0.07), we found no clear evidence of an effect of beta-blockers on this outcome. Overall, the number of randomly assigned participants (information size) was very small, and thus the quality of evidence was rated low.

Non-cardiac surgery

Upon analysing 14 studies (978 participants), we found that beta-blockers could prevent perioperative myocardial ischaemia, as evidenced by an overall RR of 0.51 (95% CI 0.34 to 0.77, P value 0.001). We detected a bias introduced by studies of poorer methodological quality. Stratification for certain quality parameters attenuated the protective effect of beta-blockers versus the overall estimate, but it never lost statistical significance (see

Effects of interventions). As the number of participants was quite small, quality of evidence was classified as moderate.

The reduction in myocardial ischaemia caused by perioperative beta-blockers is consistent with the findings of Stevens and colleagues and Bangalore and colleagues (Bangalore 2008; Stevens 2003). Stevens and co-workers reported odds ratios of 0.32 and 0.47 for perioperative and postoperative ischaemia, respectively. The effect size was found to be within the same range by Bangalore (OR 0.36, 95% CI 0.26 to 0.50). One limitation of these findings is that in most trials, intraoperative ischaemia was studied, and therefore detection of ischaemia was based on ECG monitoring rather than on symptoms. The anti-ischaemic properties of beta-blockers are well known and can be explained by the negative inotropic and chronotropic effects that reduce myocardial oxygen consumption. As a consequence, the heart can cope with a decreased blood supply without experiencing ischaemia. Ischaemic episodes can trigger ventricular rhythm disturbances, and a reduction in ischaemia could account for the reduced rate of ventricular arrhythmias seen in patients taking perioperative beta-blockers (see below, 'Ventricular arrhythmias and extrasystoles').

Cerebrovascular events

Cardiac surgery

Only four trials (1400 participants) evaluated cerebrovascular events in the setting of cardiac surgery. Overall, we found no clear evidence of an effect of beta-blockers on stroke or TIA, according to our data (RR 1.52, 95% CI 0.58 to 4.02, P value 0.40). The information size was very low, and the 95% CI showed wide overlapping zones of no effect and potential harm or benefit. Thus quality of evidence was judged to be low, and no definitive conclusion can be drawn from our data.

Again, the technique of surgery causing macro-embolization and micro-embolization (use of extracorporeal cardiopulmonary bypass during surgery and manipulation of the aorta during surgery) may heavily influence the incidence of cerebrovascular events after heart surgery (Hillis 2011).

Non-cardiac surgery

Five trials comprising 9150 participants reported on the occurrence of cerebrovascular events in the setting of non-cardiac surgery. Overall, we found no clear evidence of an effect of beta-blockers on the incidence of perioperative cerebrovascular events (RR 1.59, 95% CI 0.93 to 2.71, P value 0.09). Meta-regression analysis, however, identified methodological quality parameters that could interact with the effect estimate (control group status and blinding status; see **Effects of interventions**). Stratification for these effect modifiers revealed a statistically significant increase in cerebrovascular events if only trials with an assumed lower risk of bias were analysed (placebo-controlled trials: RR 2.09, 95% CI 1.14 to 3.82, P value 0.02). This result was influenced mainly by the POISE trial, which was of highest methodological quality and observed an increase in stroke with the use of beta-blockers. This effect was explained by a higher incidence of stroke caused by hypotension (risk factor with the highest population attributable risk). In our opinion, higher credibility shall be given to trials with higher methodological quality. Thus in conclusion, a harmful effect of beta-blockers must be assumed. As the information size of participants was small compared with the optimal information size,

and given that evidence of bias was found, the quality of evidence was classified as low.

A higher incidence of stroke in participants taking beta-blockers who were undergoing non-cardiac surgery was confirmed by the findings of Bouri and colleagues in their recent meta-analysis of 'secure' trials (RR 1.73, 95% CI 1.00 to 2.99, P value 0.05; Bouri 2013).

Ventricular arrhythmias and extrasystoles

Cardiac surgery

Twelve trials comprising 2292 participants confirmed a protective effect of beta-blockers on the occurrence of ventricular tachycardias and fibrillation (RR 0.37, 95% CI 0.24 to 0.58, P value < 0.0001). Subgroup analysis found that start of beta-blocker therapy was an effect modifier. Thereby, beta-blockers lost their protective potential when started before surgery. This effect goes against all pathophysiological reasoning, as up-titration of beta-blockers well in advance of surgery should ensure their antiarrhythmic effect at the time of surgery. This phenomenon can be explained in two ways: As with all subgroup analyses, results may reflect a play of chance. Second, all three trials conducted with sotalol fell into the subgroup 'start before surgery.' Sotalol was the least potent beta-blocker to prevent ventricular arrhythmias, most likely because of its proarrhythmic properties (class III antiarrhythmic drug; see **Analysis 5.11**). Clustering of all sotalol trials within a single subgroup therefore blunted the protective effects of beta-blocker treatment. In our opinion the type of beta-blocker rather than the start of treatment influenced the effect estimate. As the information size was small, quality of evidence was classified as moderate.

In contrast to these findings, the five trials (462 participants) investigating the effect of beta-blockers on premature ventricular beats yielded a non-significant result (RR 0.58, 95% CI 0.31 to 1.08, P value 0.09). As sample size was small and the effect estimate was imprecise, with overlapping zones of no effect and potential benefit, overall quality of evidence was rated as moderate.

In conclusion, beta-blockers were not able to reduce the occurrence of ventricular extrasystoles in the setting of cardiac surgery, probably mainly because of the trauma of surgery and the stress response. However, data suggest that beta-blockers effectively prevented deterioration in ventricular tachycardias and fibrillation, as ventricular extra beats are known to spark off these tachyarrhythmias.

Non-cardiac surgery

Five studies with 476 accrued participants investigated the occurrence of ventricular arrhythmias in non-cardiac surgery. Incidence of ventricular arrhythmias was found to be higher for non-cardiac surgery than for cardiac surgery. This was presumably caused by a broader definition of 'ventricular tachycardia (VT),' including non-sustained VTs, and tighter ECG monitoring (every two minutes during bronchoscopy, Sandler 1990; Holter ECG monitoring for 72 hours, POBBLE 2005) in some non-cardiac surgery trials. When the data were pooled, we found no clear evidence of an effect of beta-blockers on the occurrence of VTs (RR 0.68, 95% CI 0.31 to 1.49, P value 0.33). Start of beta-blocker treatment, route of beta-blocker application and risk status of surgery were identified as effect modifiers. Stratification for these parameters revealed a protective, statistically significant effect of beta-blockers when administered intravenously during surgery in

low- or medium-risk procedures. These findings were influenced mainly by two metoprolol trials (Jakobsen 1997; POBBLE 2005). Both of these trials were high-risk surgery trials (lung resection and infrarenal aortic surgery, respectively). It is conceivable that in high-risk procedures, oral beta-blocker administration cannot be assured, and intravenous application is superior in this setting. This hypothesis is consistent with the fact that ventricular extra beats were significantly reduced in non-cardiac surgery with the use of beta-blockers (RR 0.22, 95% CI 0.13 to 0.37, P value < 0.00001). Stratification for risk of surgery was not possible, as all 492 participants in the nine trials reporting on this outcome underwent low- or medium-risk surgery procedures. Quality of evidence was judged to be moderate for ventricular arrhythmias (small sample size and wide confidence interval) and high for ventricular extrasystoles (no downgrading).

To summarize the evidence, the protective effect of beta-blockers against ventricular arrhythmias in non-cardiac surgery is not uniform. Our data indicate that patients undergoing high-risk procedures may benefit from intravenous drug application during the surgery. We could show that beta-blockers have the potential to prevent perioperative ventricular arrhythmias such as ventricular tachycardias, ventricular fibrillation and ventricular premature beats in certain subgroups of patients. This is important, as ventricular rhythm disturbances are potentially debilitating and life-threatening.

Similar numbers can be found in the setting of prevention of ventricular arrhythmias after AMI. In their trial, Ryden and colleagues found that administration of the beta-blocker metoprolol reduced the odds of development of ventricular fibrillation by as much as 65% in the postinfarction period (Ryden 1983). An elevated sympathetic stress response can be held accountable for many cases of ventricular arrhythmia in perioperative and postinfarction settings. Therefore it is not surprising that beta-blockers exert similar preventive effects in both circumstances. We could show that beta-blockers are capable of reducing ventricular arrhythmias, especially after cardiac surgery (see above, 'Cardiac surgery').

Supraventricular arrhythmias

Cardiac surgery

A large body of evidence investigating this outcome was available for meta-analysis. Forty-eight trials comprising 6420 participants found that beta-blockers significantly reduced the incidence of supraventricular arrhythmias in the aftermath of heart surgery (RR 0.44, 95% CI 0.36 to 0.53, P value < 0.00001). When scrutinizing the data, we detected a reporting bias and bias introduced by studies of poorer methodological quality. In both cases, the protective effect of beta-blockers was overestimated. Restricting the meta-analysis to the 20 placebo-controlled trials with an assumed lower risk of bias (RR 0.60, 95% CI 0.48 to 0.76, P value < 0.0001) and restricting the meta-analysis to atrial fibrillation and flutter only (RR 0.48, 95% CI 0.40 to 0.57, P value < 0.00001) did not alter the effect estimate much. The large amount of statistical between study heterogeneity could not be explained sufficiently by stratification for clinical or methodological parameters. TSA indicated a significant protective effect of beta-blockers, and the overall information size was adequate. Thus the quality of evidence was classified as high.

As many as 30% of patients develop postoperative atrial fibrillation in the aftermath of cardiac surgery (Lauer 1989). Therefore, in the past, much attention has been attributed to prevention of this disease entity. 2011 ACCF/AHA guidelines on coronary artery bypass surgery issued a class Ib recommendation to start beta-blocker treatment at least 24 hours before surgery to prevent postoperative atrial fibrillation and its sequelae (Hillis 2011). In the meta-analysis of 27 trials and 3840 participants performed by Crystal and colleagues on prevention of postoperative atrial fibrillation (AF) in cardiac surgery, beta-blockers reduced the odds of developing postoperative atrial fibrillation by 61% (OR 0.39, 95% CI 0.28 to 0.52) (Crystal 2002). The authors likewise detected a significant amount of between-trial heterogeneity in their data but could not identify its source. Our analysis of 48 trials including 6420 participants revealed similar overall findings (RR 0.44, 95% CI 0.36 to 0.53) in a likewise heterogenous set of data. We found that only a small amount of intertrial heterogeneity in our review depended on control group status (Analysis 2.13). In our analysis of 20 placebo-controlled trials, beta-blockers reduced the risk of developing supraventricular arrhythmias by 40% (RR 0.60, 95% CI 0.48 to 0.76, P value < 0.0001). In our opinion, this value appears to be physiologically more plausible than the 61% reduction reported in other reviews (Crystal 2002).

Non-cardiac surgery

Eight trials comprising 8744 randomly assigned participants investigated the effect of beta-blockers on the incidence of supraventricular arrhythmias in non-cardiac surgery. Meta-analysis found that beta-blockers significantly reduce the occurrence of supraventricular arrhythmias (RR 0.73, 95% CI 0.57 to 0.94, P value 0.01). The beneficial effect was blunted in high risk patients if the drug was not started until anaesthesia was induced. Restriction of the meta-analysis to only atrial fibrillation and flutter left the effect estimate virtually unchanged (RR 0.73, 95% CI 0.56 to 0.95, P value 0.02). Much of the weight of the pooled estimate came from the POISE trial. Without inclusion of POISE in the analysis, the statistically significance of the protective effect was lost (RR 0.61, 95% CI 0.33 to 1.11 P value 0.10). TSA confirmed the protective effect of beta-blockers. As information size was adequate, the quality of evidence was rated high.

The reduction in arrhythmias was more pronounced in cardiac surgery trials than in non-cardiac surgery trials. We observed this finding for ventricular arrhythmias as well. The stronger effect of beta-blockers in the cardiac surgery subgroup may be due to the higher burden of supraventricular and ventricular arrhythmias in the setting of this type of surgery.

Bradycardia

When evaluating trials investigating bradycardia, we noticed that bradycardia was defined very differently by study authors. Some classified a heart rate below 60 beats per minute as bradycardia, whereas others detected an episode of bradycardia only if heart rate fell below 40 beats per minute, or if bradycardia required treatment. These different thresholds for bradycardia are likely to have caused clinical and statistical heterogeneity (see 'Non-cardiac surgery' below).

Cardiac surgery

In our analysis of eight trials (660 participants), we found no clear evidence of an effect of beta-blockers on episodes of bradycardia in the setting of heart surgery (RR 1.61, 95% CI 0.97 to 2.66, P value 0.06). No effect modification was detected. As overall information size was very small, the quality of evidence was classified as low. As the confidence interval overlapped both the zone of no effect and the zone of potential harm (RR 1.25), no definitive conclusion can be drawn at the moment from our data.

On the one hand, slowing down heart rate is an intrinsic effect of beta-blockers, and one may argue that without detection of any episodes of bradycardia, the drug may be underdosed, whereas on the other hand, patients undergoing cardiac surgery are under tight haemodynamic control, and doctors probably are more determined than in non-cardiac surgery to keep these haemodynamic variables stable within a small range and to take action well in advance of a pulse below 40 or 50 beats per minute. Finally, because of the very small sample size, the true effect of beta-blockers may have gone undetected (imprecision).

Non-cardiac surgery

In our analysis of 23 trials comprising 11,033 participants, beta-blockers significantly induced episodes of bradycardia (RR 2.23, 95% CI 1.48 to 3.36, P value < 0.0001). All types of beta-blockers except esmolol (short half-life and thus good controllability), atenolol and nadolol (only very few randomly assigned participants in this subgroups) statistically significantly induced episodes of bradycardia (class effect). Statistical interstudy heterogeneity was high and could be explained in part by type of beta-blocker and methodological study quality parameters. Different definitions of bradycardia may have contributed to this effect. Subgroup analyses revealed that trials with a higher percentage of patients diagnosed with coronary heart disease and investigating a high-risk surgery setting were more prone to episodes of bradycardia. Furthermore, start of the beta-blocker before surgery was associated with a higher incidence of bradycardia. This effect may reflect a more pronounced impact of beta-blocker effect if up-titrated before surgery. Studies of poorer methodological quality systematically underestimated bradycardia induced by beta-blockers. Stratification for these parameters did not significantly change the effect estimate. As serious inconsistency of data was noted, the quality of evidence was rated moderate.

Bangalore and colleagues in their respective meta-analysis also found that beta-blockers significantly induce bradycardia (OR 2.74, 95% CI 2.29 to 3.29, P value < 0.0001; [Bangalore 2008](#)). Compared with our results, in this meta-analysis, only 'bradycardia requiring treatment' was evaluated.

Hypotension

Cardiac surgery

When pooling the six trials (558 participants) exploring the influence of beta-blockers on hypotension in cardiac surgery, we found no clear evidence of an effect of beta-blockers on episodes of hypotension, as evidenced by an RR of 1.54 with a confidence interval of 0.67 to 3.51 (P value 0.31). No source of bias and no effect modifier could be identified. As the confidence interval was wide with overlapping zones of no effect, potential harm or benefit, and given that information size was very small, we classified the quality of evidence as low.

As outline above (section 'Bradycardia') a reduction in heart rate and thereby a reduction in blood pressure are inherent properties of beta-blockers. Again, in our opinion, control of heart rate and blood pressure is much tighter in patients undergoing heart surgery than in those undergoing non-cardiac surgery (see below, 'Non-cardiac surgery'). Furthermore, information size was much less than in non-cardiac surgery (558 vs 10,947 participants), which makes a potential effect of beta-blockers harder to detect.

Non-cardiac surgery

As opposed to cardiac surgery, meta-analysis of 22 trials (10,947 participants) in non-cardiac surgery indicated that beta-blockers significantly increased hypotensive episodes (RR 1.50, 95% CI 1.38 to 1.64, P value < 0.00001). This effect remained unchanged and consistent throughout all subgroup analyses and was confirmed by TSA. As no source of bias was identified and information size was adequate, the quality of evidence was rated high.

Results from two other meta-analyses were within the same range compared with our estimate: Bangalore and colleagues found a 62% increase in hypotensive episodes (OR 1.62, 95% CI 1.44 to 1.82, P value < 0.0001; [Bangalore 2008](#)), and meta-analysis of 'secure' RCTs by Bouri and colleagues revealed a 51% rise in hypotension in the beta-blocker group (RR 1.51, 95% CI 1.37 to 1.67, P value < 0.00001; [Bouri 2013](#)). In the POISE trial, hypotension was the risk factor with the highest population attributable risk that caused stroke and ultimately increased mortality in patients taking beta-blockers ([POISE 2008](#)).

Congestive heart failure

Cardiac surgery

Three trials comprising 311 randomly assigned participants evaluated the occurrence of congestive heart failure in cardiac surgery. We found no clear evidence of an effect of beta-blockers on the incidence of this outcome (RR 0.22, 95% CI 0.04 to 1.34, P value 0.10). No effect modification was detected, especially for ejection fraction. The very small information size and the wide confidence interval covering zones of no effect and potential harm or benefit indicated low quality of evidence. More data are needed before definitive conclusions can be drawn.

Non-cardiac surgery

The available body of evidence was much larger in non-cardiac surgery. Five studies (9173 participants) evaluated congestive heart failure in the perioperative setting. We found no evidence of an effect of beta-blockers on the occurrence of congestive heart failure (RR 1.18, 95% CI 0.94 to 1.48, P value 0.16). The effect of beta-blocker treatment remained non-significant throughout all subgroup analyses. As no sources of bias were detected and information size was sufficient but the confidence interval was wide, the quality of evidence was classified as moderate. TSA indicated futility, which means that further studies investigating this outcome are very unlikely to add significant information, as the information size is already large enough to allow review authors to conclude that beta-blockers do not significantly influence the occurrence of congestive heart failure after non-cardiac surgery.

Our findings are consistent with results of the meta-analysis by Bangalore and colleagues ([Bangalore 2008](#)). Likewise, the review authors could not find an interaction between beta-blocker intake

and development of perioperative congestive heart failure (OR 1.20, 95% CI 0.95 to 1.52, P value 0.13).

Bronchospasm

Cardiac surgery

Three trials comprising only 196 participants evaluated bronchospasm in the setting of cardiac surgery. We found no clear evidence of an effect of beta-blockers on the occurrence of bronchospasm (RR 1.49, 95% CI 0.31 to 7.14, P value 0.62). Because of the very small information size and the wide confidence interval with overlapping zones of no effect, potential harm or benefit, we classified the quality of evidence as low. Evidence on this topic was very limited, and no definitive conclusion can be drawn from our data.

Non-cardiac surgery

Eight studies (1080 participants) reported on the occurrence of bronchospasm. We found no clear evidence of an effect of beta-blockers on this outcome (RR 0.94, 95% CI 0.55 to 1.59, P value 0.81). Because of the very small information size and the wide confidence interval with overlapping zones of no effect, potential harm or benefit, we classified the quality of evidence as low.

The incidence of bronchospasm was also investigated by the meta-analysis conducted by Bangalore and colleagues (Bangalore 2008). The authors of this meta-analysis likewise could not find a significant effect of beta-blockers on the development of bronchospasms (OR 0.98, 95% CI 0.56 to 1.72, P value 0.96).

Length of stay (LOS)

Cardiac surgery

Overall, beta-blockers reduced length of hospital stay by 0.54 days on average (95% CI -0.90 to -0.19 days, P value 0.003) when 14 trials (2450 participants) assessing this outcome were pooled. When scrutinizing these data, we identified many sources of bias and effect modifiers: gender, route of beta-blocker administration and percentage of participants receiving beta-blocker therapy before entry into the trial, as clinical parameters and blinding of participants and doctors and use of the intention-to-treat principle as methodological parameters significantly interacted with the effect estimate. Furthermore, a reporting bias was detected that did not alter the effect estimate after adjustment. No clear pattern of parameters affecting the effect size could be determined, except for the reporting bias (small studies tended to overestimate the effect of beta-blockers in reducing hospital stay). For the exact numbers, see [Effects of interventions](#). Although the information size was adequate, these multiple inconsistencies led to classification of the quality of evidence as low only.

Length of hospital stay is often seen as a proxy for economic burden. However, it has to be taken into account that length of hospital stay is probably heavily influenced by local policies and healthcare regulations, economic resources and current guidelines besides the patient's physical condition. Therefore, it is a very unreliable parameter, which in our opinion is reflected by the large unexplained intertrial heterogeneity of the data and the large number of significant interactions not following a clear pattern. Furthermore, as a reporting bias is present, the reduction in length of stay may be overestimated in our meta-analysis.

In their analysis of seven trials of 2008 participants, Crystal and colleagues found that sotalol could reduce LOS by as much as 0.4 days, and other beta-blockers reduced LOS by 0.66 days. Nevertheless, their findings did not reach statistical significance (Crystal 2002). We think that our analysis is in agreement with their results. The statistical significance in our review can be explained by a larger participant collective, and by the fact that we did not differentiate between sotalol and other beta-blockers.

Non-cardiac surgery

Three trials with 551 accrued randomized participants reported on length of stay in non-cardiac surgery. The intertrial heterogeneity was moderate and could not be sufficiently explained by subgroup analyses. As mentioned above, this may reflect the fact that factors other than adverse events after surgery heavily influenced length of hospital stay. Overall, we found no clear evidence of an effect of beta-blockers on length of stay (mean difference -0.45 days, 95% CI -1.75 to 0.84 days, P value 0.49). As information size was very small and the confidence interval was wide, the quality of evidence was judged to be low. Data from the largest trial, POISE, could not be included, as no measure of spread was provided in the publication nor in supplements on the world wide web (median values were the same for beta-blocker and control groups in POISE: eight days (POISE 2008).

Cost of care

Cardiac surgery

Three trials reported on cost of care. The respective numbers were too far apart (nearly 10-fold) and thus precluded meaningful statistical analysis. All study authors reported higher costs in the beta-blocker intervention group. The relevance of this finding is unclear, as calculating hospital costs is a sophisticated endeavour with many potential pitfalls and heavily depends on the economic environment and the national healthcare system. Therefore, numbers are unlikely to be comparable. The higher costs for patients receiving beta-blockers leaves room for speculation. However, more evidence is needed before making further inferences.

Non-cardiac surgery

No trial reported on cost of care.

Quality of life

No trial reported on quality of life.

Overall completeness and applicability of evidence

Our meta-analysis is based on large numbers of RCTs and participants. The quality of evidence was classified using TSA and GRADE in the Results section ([Effects of interventions](#), [Summary of findings for the main comparison](#); [Summary of findings 2](#)). Our findings are consistent with pathophysiological concepts as outlined above. Conversely, data on cost of care were assessed by only three trials, which precluded meaningful analysis, and trials investigating quality of life were not available.

Quality of the evidence

In general, trials that were not placebo-controlled reported larger effects than placebo-controlled trials. This was true for almost

all outcomes. Reasons for a larger effect in standard care trials include lack of blinding and lack of the so-called placebo effect in control groups. One should thus be cautious when presented with large effects stemming from trials that were not placebo controlled. Intertrial heterogeneity was often to some extent attributable to the control group status (placebo vs standard care). Separate examination of placebo-controlled trials and trials with standard care groups often resulted in significantly reduced heterogeneity. Whenever a factor of study quality affected between-trial heterogeneity in a statistically significant way, results from trials with higher quality standards should be regarded as more valid. Placebo-controlled trials are generally regarded as the gold standard of clinical trials. Therefore, results from these trials should more accurately reflect the true effect of beta-blockers.

To enhance the quality of meta-analysis data, we included only randomized controlled trials in our analysis. However, only six (7%) of 88 trials met (and reported) the highest quality criteria (adequate sequence generation, adequate allocation concealment, double- or triple-blinded design, intention-to-treat analysis and absence of other sources of bias): [DIPOM - Juul 2006](#); [Mangano 1996](#); [POBBLE 2005](#); [POISE 2008](#); [Wallace 1998](#); [Yang 2006](#). We applied meta-regression analysis to evaluate the impact that study quality parameters exhibited on effect estimates. In cases of cerebrovascular events in non-cardiac surgery, we could show that control group status (placebo vs standard of care) statistically significantly influenced the effect estimate (see [Effects of interventions](#)).

When grading the quality of evidence using GRADE and TSA, we classified the following outcomes as very low, low, moderate or high quality.

Very low

We are very uncertain about the estimate.

Cardiac surgery: cost of care.

Non-cardiac surgery: none.

Low

Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Cardiac surgery: myocardial ischaemia, cerebrovascular events, bradycardia, hypotension, congestive heart failure, bronchospasm, length of stay.

Non-cardiac surgery: all-cause mortality, cerebrovascular events, bronchospasm, length of stay.

Moderate

Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Cardiac surgery: all-cause mortality, AMI, ventricular arrhythmias, ventricular extrasystoles.

Non-cardiac surgery: myocardial ischaemia, ventricular arrhythmias, bradycardia, congestive heart failure.

High

Further research is very unlikely to change our confidence in the estimate of effect.

Cardiac surgery: supraventricular arrhythmias.

Non-cardiac surgery: AMI, supraventricular arrhythmias, hypotension, ventricular extrasystoles.

Potential biases in the review process

Despite efforts made by the review authors (FW, OS, HB, DA, JK) to identify as many RCTs as possible, we might have missed published trials not listed in the databases searched for this meta-analysis.

We included only trials that investigated at least one outcome specified in the Methods section. Because of the vast scope of the literature search and the large number of search results and included trials, this *modus operandi* seemed justified. This approach was used to focus on the main clinical outcomes and became inevitable for handling the vast quantity of data. However, it may have introduced a source of bias. We judged the impact of potentially missing studies as small only in number compared with the available set of data derived from a large number of trials.

Furthermore, we could not contact all study authors to gather further information about trial design or data analysis (e.g. performance of an intention-to-treat analysis) because of the large number of studies. However, it would be likely that study authors—if contacted—would over report trial design quality criteria. Further limitations inherent to this type of meta-analysis include different study designs of the included trials that are combined to calculate summary point estimates.

Results of outcomes calculated for non-cardiac surgery were heavily influenced by the POISE trial. We therefore performed sensitivity analyses in the Results section (Does omitting data from the POISE trial change the overall estimate?) if we believed that the effect estimate was driven mainly by this study. However, it has to be stated that the POISE trial met the highest quality standards and was very large. So we feel confident in including it in our overall estimates.

As opposed to the eligibility criteria defined in the protocol, we decided to consider trials in our meta-analysis that partially included participants not receiving general anaesthesia. Trials had to fulfil the following criteria to be eligible for inclusion: more than 100 randomly assigned participants operated on under general anaesthesia, or more than 70% of participants receiving general anaesthesia. We came to that conclusion, as we believed a meta-analysis without the POISE, DIPOM or MaVS trial would not find enough credibility within the clinical community. Excluding these trials would have meant losing hundreds of randomly assigned participants. However, we cannot exclude a potential bias introduced by participants who did not receive general anaesthesia in these trials (low-risk procedures). We tried without success to obtain information about the subsets of participants from these trials who were operated on while under general anaesthesia.

AUTHORS' CONCLUSIONS

Implications for practice

According to our findings, perioperative application of beta-blockers still plays a pivotal role in **cardiac surgery**, as they can substantially reduce the high burden of supraventricular and ventricular arrhythmias in the aftermath of surgery. Furthermore, beta-blockers are a mainstay of conservative coronary heart disease therapy (Fihn 2012). More evidence is needed to definitively assess the role of beta-blockers in influencing mortality, preventing AMI and causing stroke, hypotension and bradycardia in this setting. However, it is highly likely that surgical trauma rather than beta-blockers is an important co-factor causing AMI and cerebrovascular events, as well as hypotension (blood loss), in heart surgery.

In **non-cardiac surgery**, evidence indicates an increase in all-cause mortality and the incidence of stroke with the use of beta-blockers. As the quality of evidence is still low to moderate and mainly based on one single trial (POISE 2008), more trials investigating these outcomes are needed to come to a definitive conclusion. Beta-blockers substantially reduced supraventricular arrhythmias and AMIs in this setting. According to our data, these benefits are potentially counterbalanced by increased risks of stroke and death. After assessment of cardiovascular risk factors, the individual risk of stroke, hypotension and bradycardia should be weighed against potential benefits (prevention of acute myocardial infarction and arrhythmias) for every patient.

Implications for research

Further research is needed in the field of non-cardiac surgery so that firm conclusions can be drawn as to whether beta-blockers increase all-cause mortality and cerebrovascular events.

Furthermore, timing of beta-blocker application may have an important influence on their effect (plaque stabilization, haemodynamic adaptation). Larger trials investigating this topic are needed for a definitive conclusion.

Research is needed on the issue of quality of life, as virtually no data at all are available. From a patient perspective, this is probably one—if not the most important—outcome. It is fairly easy to evaluate quality of life through established questionnaires. We suggest that future trials should focus their attention on this endpoint as well.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Abel 1983

Methods	Quasi-randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 91 participants; beta-blocker: 41 participants; standard care: 50 participants (100% of participants were taking beta-blockers preoperatively) Mean age: 56.6 years Percentage of female participants: 17
Interventions	Participants received either propranolol or standard care; treatment was initiated during surgery and was continued until hospital discharge
Outcomes	Primary outcomes: supraventricular arrhythmias; secondary outcomes: ventricular arrhythmias, myocardial infarction, hospital mortality
Notes	Type of surgery: elective coronary artery bypass grafting (CABG)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization (last digit of hospital record number)
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial

Abel 1983 (Continued)

Incomplete outcome data (attrition bias) All outcomes	High risk	9 withdrawals in beta-blocker group due to bradycardia (2), severe hypotension (3), preoperative myocardial infarction (2), biventricular failure (1), and cardiac arrest (1)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Ali 1997

Methods	Randomized, open-label clinical trial; beta-blocker versus standard care	
Participants	Overall: 210 participants; each group consisting of 105 participants (all were taking beta-blockers pre-operatively) Mean age: 64.2 years Percentage of female participants: 31.9	
Interventions	All participants were taking beta-blockers before initiation of the study. The 105 participants who were randomly assigned to the 'standard-care group' did not receive beta-blockers perioperatively, whereas beta-blockers were continued in the intervention group. The following beta-blockers were used: atenolol, metoprolol and sotalol	
Outcomes	Primary outcomes: atrial fibrillation Secondary outcomes: mortality, myocardial infarction; time of observation, induction of surgery until discharge	
Notes	Type of surgery: elective CABG	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial

Ali 1997 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Apipan 2010

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 60 participants; propranolol: 30 participants; placebo: 30 participants Mean age: 25.5 years Percentage of female participants: 63.3
Interventions	Participants received 10 mg propranolol or placebo orally 30 minutes before induction of anaesthesia (single-drug application)
Outcomes	Primary outcome: heart rate during surgery Secondary outcomes: amount of sodium nitroprusside and blood loss during surgery
Notes	Type of surgery: orthognathic surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	'The anaesthesiologist and patients were kept unaware of which group the patient was in'
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessors (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported

Apipan 2010 (Continued)

Intention to treat analysis	Unclear risk	Not reported
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Auer 2004

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 253 participants; metoprolol: 62 participants; sotalol: 63 participants; metoprolol + amiodarone: 63 participants; placebo: 65 participants. Mean age: 65.6 years Percentage of female participants: 39.5
Interventions	Participants received treatment 24 to 48 hours before surgery until the eighth postoperative day. Participants were followed until hospital discharge
Outcomes	Primary outcome: postoperative atrial fibrillation Secondary outcomes: mortality, cerebrovascular events, hypotension, bradycardia, ventricular tachycardia, length of stay
Notes	Type of surgery: cardiac surgery (CABG and valvular surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization table was used for sequence generation
Allocation concealment (selection bias)	Low risk	Randomization schedule was sealed
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Three participants were excluded from analysis after randomization (1 participant refused surgery, 1 was refused to be operated on by the surgeon and 1 suffered from a stroke before the time of surgery—exact group allocation unclear). Participants were not analysed as randomly assigned (256 were randomly assigned)

Auer 2004 (Continued)

Intention to treat analysis	High risk	See above
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	More than 2 treatment groups, but results were presented identically for all groups

Babin-Ebell 1996

Methods	Open-label, randomized clinical trial; calcium antagonists versus blockers versus standard care
Participants	Overall: 103 participants; beta-blocker: 33 participants; calcium antagonist: 33 participants; control: 37 participants Mean age: 62.9 years Percentage of female participants: 20
Interventions	Participants were assigned to receive propranolol, diltiazem or no antiarrhythmic agent. Treatment was administered intraoperatively and up to 72 hours postoperatively
Outcomes	Primary outcomes: supraventricular tachyarrhythmias Secondary outcomes: acute myocardial infarction, bradycardia; outcomes were assessed up to 7 days following surgery
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Six participants were excluded from analysis of supraventricular arrhythmias (bradycardia, hypotension, perioperative myocardial infarction)
Intention to treat analysis	High risk	Not analysed as randomly assigned

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Babin-Ebell 1996 (Continued)

Selective reporting (re-reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Bayliff 1999

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 99 participants; beta-blocker: 49 participants; placebo: 50 participants Mean age: 62.4 years Percentage of female participants: 38.4
Interventions	Participants received propranolol or placebo; treatment was started preoperatively and was administered orally every 6 hours for 5 days
Outcomes	Primary outcomes: arrhythmias requiring treatment (until 3 days following surgery, detected by Holter ECG) Secondary outcomes: overall arrhythmia rate, myocardial ischaemia, mortality, bradycardia, hypotension, length of stay (no data for standard deviation of LOS provided)
Notes	Type of surgery: major thoracic operations (pneumectomy, lobectomy, oesophagectomy)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomization in blocks of four, exact method of sequence generation unclear
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below
Intention to treat analysis	Low risk	No withdrawals, participants analysed as randomly assigned
Selective reporting (re-reporting bias)	Low risk	Not detected

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Bayliff 1999 (Continued)

Other bias	Low risk	Not detected
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Bert 2001

Methods	Randomized, open-label, controlled trial comparing a beta-blocker ($\pm$ magnesium), digitalis ($\pm$ magnesium), magnesium and standard care
Participants	Overall: 387 participants Magnesium: 63 participants Digoxin: 62 participants Magnesium and digoxin: 62 participants Beta-blocker (propranolol): 71 participants Magnesium and beta-blocker: 69 participants Control: 60 participants Mean age: 63.7 years (average of propranolol and control groups) Percentage of female participants: 20.6 (average of propranolol and control groups)
Interventions	Participants were assigned to 1 of 6 groups (see Methods). The studied beta-blocker was propranolol. Treatment was started postoperatively, upon arrival at the ICU, and was continued for 4 days
Outcomes	Primary outcomes: atrial tachyarrhythmias; secondary outcomes: mortality, acute myocardial infarction, premature ventricular beats, ventricular arrhythmias and length of stay
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	No participants lost to follow-up. 3 participants who did not undergo surgery were excluded after enrolment
Intention to treat analysis	High risk	Not analysed as randomly assigned

Bert 2001 (Continued)

Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	More than 2 treatment groups, but outcomes were presented for all treatment groups identically

Booth 2004

Methods	Randomized, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 72 participants; beta-blocker: 33 participants; placebo: 39 participants Mean age: 61.3 years Percentage of female participants: 36.1
Interventions	Participants received a single dose of metoprolol 10 mg or placebo intravenously during CABG surgery
Outcomes	Primary outcomes: isoproterenol-stimulated adenylyl cyclase activity (beta-adrenoceptor signalling) and major clinical endpoints (supraventricular arrhythmias, inotropic support) Secondary outcome: length of stay
Notes	Type of surgery: CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Unclear risk	Not specified
Blinding of doctors/personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below
Intention to treat analysis	Low risk	Study authors stated they used the intention-to-treat principle for data analysis
Selective reporting (reporting bias)	Low risk	Not detected

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Booth 2004 (Continued)

Other bias	Low risk	Not detected
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Burns 1988

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 86 female participants; beta-blocker: 39 participants; placebo: 47 participants Mean age: 34.2 years Percentage of female participants: 100
Interventions	Participants received nadolol or placebo; treatment was given preoperatively as an oral single dose 12 hours before laparoscopy, and no further dose of the study medication was administered
Outcomes	Primary outcome: all types of arrhythmias (bradycardia, atrial and ventricular tachyarrhythmias, supraventricular premature beats, ventricular premature beats)
Notes	Type of surgery: laparoscopy (gynaecological surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	ECG tracings were interpreted by 2 observers blinded to study group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

But 2006

Methods	Randomized, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 45 participants; beta-blocker: 15 participants; placebo: 15 participants; magnesium sulfate: 15 participants Mean age: 57.5 years Percentage of female participants: 46.7
Interventions	Participants with diabetes mellitus type II received placebo (saline) or esmolol intravenously from induction of anaesthesia until 12 hours after surgery
Outcomes	Primary outcomes: amount of glucose-insulin-potassium infusion consumption, blood glucose levels Secondary outcomes: bradycardia, hypotension, length of stay, dysrhythmias, inotropic support
Notes	Type of surgery: CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Unclear risk	Not specified
Blinding of doctors/personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Coleman 1980

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 38 participants; beta-blocker: 24 participants; control: 14 participants

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Coleman 1980 (Continued)

Mean age: 40.8 years

Percentage of female participants: 57.1

Interventions	Participants were assigned to receive 2 mg metoprolol or 4 mg metoprolol or saline as placebo. Treatment was given before induction of anaesthesia
Outcomes	Primary outcomes: cardiovascular responses (haemodynamic responses, sinus arrhythmia, supraventricular ectopics, ventricular ectopics, ST-segment changes)
Notes	Type of surgery: elective general surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Participants were given 4 mL of solution intravenously, which consisted of saline as placebo or metoprolol. The assignment code was unknown to investigators until completion of the study
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 participants excluded because of unreadable ECG recordings (1 placebo group, 3 beta-blocker group)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Connolly 2003

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 1000 participants; beta-blocker: 500 participants; placebo: 500 participants Mean age: 62.5 years Percentage of female participants: 21

Connolly 2003 (Continued)

Interventions	Participants received metoprolol or placebo; treatment was started postoperatively and was administered until hospital discharge or 14 days after surgery (whichever occurred sooner)
Outcomes	Primary outcome: length of stay (LOS) Secondary outcomes: arrhythmias (supraventricular and ventricular arrhythmias), myocardial infarction, cost of care, stroke, death, haemodynamic parameters
Notes	Type of surgery: elective heart surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Cork 1995

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 30 participants; beta-blocker: 16 participants; placebo: 14 participants Mean age: 61.5 years Percentage of female participants: 36.7
Interventions	Participants received esmolol or placebo; treatment was administered only intraoperatively

Cork 1995 (Continued)

Outcomes	No clear primary outcome was specified; multiple haemodynamic and laboratory parameters were recorded in addition to death, dysrhythmias, LOS and cost of care
Notes	Type of surgery: elective heart surgery involving cardiopulmonary bypass and aortic cross-clamping

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Cucchiara 1986

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 62 participants; beta-blocker: 32 participants; placebo: 30 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	Participants received esmolol or placebo; treatment was administered intravenously during anaesthesia
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: myocardial ischaemia, bradycardia, hypotension, bronchospasm
Notes	Type of surgery: carotid endarterectomy

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Cucchiara 1986 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	12 participants were excluded from analysis because of protocol violations
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Daudon 1986

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 100 participants; beta-blocker: 50 participants; standard care: 50 participants Mean age: 53.5 years Percentage of female participants: 5
Interventions	Participants received acebutolol or standard care; treatment was initiated 36 hours postoperatively and was continued until discharge
Outcomes	Primary outcome: atrial fibrillation/flutter Secondary outcome: perioperative myocardial infarction
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
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Daudon 1986 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

De Azevedo Lúcio 2003

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 200 participants; beta-blocker: 100 participants; standard care: 100 participants Mean age: 60.5 years Percentage of female participants: 27
Interventions	Participants received metoprolol or standard care; treatment was started 12 hours postoperatively and was continued for 7 days or until hospital discharge, whichever occurred first
Outcomes	Primary outcome: atrial fibrillation/flutter Secondary outcomes: death, myocardial infarction (group affiliation not specified), stroke (group affiliation not specified)
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified

De Azevedo Lúcio 2003 (Continued)

Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below
Intention to treat analysis	Low risk	"Analysis was carried out based on the principle intention-to-treat"
Selective reporting (reporting bias)	High risk	8 study participants suffered from a myocardial infarction, and 5 suffered from a stroke. Study group allocation of these participants was not specified
Other bias	Low risk	Not detected

DIPOM - Juul 2006

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 921 diabetic participants naive to beta-blockers with diabetes mellitus older than 39 years; metoprolol: 462 participants; placebo: 459 participants Mean age: 64.9 years Percentage of female participants: 41.5
Interventions	Participants received metoprolol or placebo; treatment was started the evening before surgery and was continued until hospital discharge (maximum 8 postoperative days). Median follow-up was 18 months for primary outcome (6 to 30 months)
Outcomes	Primary composite outcome: all-cause mortality, myocardial infarction, unstable angina or new congestive heart failure Secondary outcomes: all-cause mortality, cardiac mortality, non-fatal cardiac morbidity
Notes	Type of surgery: orthopaedic, neurological, vascular, gynaecological, thoracic, intra-abdominal and other operations (major non-cardiac surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated allocation sequence

DIPOM - Juul 2006 (Continued)

Allocation concealment (selection bias)	Low risk	Participants were centrally randomly assigned
Blinding of participants (performance bias) All outcomes	Low risk	"The DIPOM trial is an investigator initiated and controlled, randomised placebo controlled, multicentre trial with central randomisation and blinding of all parties in all phases. The code was broken when analyses were completed and a conclusion formulated"
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessors (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below
Intention to treat analysis	Low risk	Study authors used intention-to-treat principle in their analysis
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Dy 1998

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus flecainide versus placebo
Participants	Overall: 201 participants; beta-blocker: 67 participants; flecainide: 68 participants; placebo: 66 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	Participants received metoprolol, flecainide or placebo; treatment was started after extubation and was continued until 24 hours before discharge
Outcomes	Primary outcome: atrial fibrillation, period of observation unclear
Notes	Type of surgery: elective CABG. Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified

Dy 1998 (Continued)

Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Conference abstract
Other bias	Unclear risk	Conference abstract

Evrard 2000

Methods	Randomized, open-label clinical trial; beta-blocker versus standard care
Participants	Overall: 206 participants; beta-blocker: 103 participants; control: 103 participants Mean age: 61 years Percentage of female participants: 11
Interventions	Participants received sotalol or no antiarrhythmic agent. Treatment was started on the first postoperative day, no time of discontinuation was specified
Outcomes	Primary outcomes: supraventricular and ventricular arrhythmias Secondary outcomes: LOS, mortality
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'Blocked randomization in a prospective open manner'
Allocation concealment (selection bias)	High risk	Blocked randomization in an unblinded trial
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial

Evrard 2000 (Continued)

Blinding of doctors/per- sonnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome as- sessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (re- porting bias)	Low risk	Not detected
Other bias	High risk	Blocked randomization in an open-label trial: Study allocation might have been predictable in some cases

Forlani 2002

Methods	Randomized, open-label clinical trial; beta-blocker versus standard care
Participants	Overall: 207 participants; beta-blocker (sotalol): 51 participants; control: 50 participants, beta-blocker + magnesium: 52 participants, magnesium: 54 participants Mean age: 64 years Percentage of female participants: 14.9
Interventions	Participants received sotalol, magnesium, sotalol and magnesium or no antiarrhythmic agent. Sotalol was started orally on the morning of the first postoperative day and then was continued for 4 weeks (dose reduction after 5 days of initial treatment)
Outcomes	Primary outcome: atrial fibrillation Secondary outcomes: postoperative hospital length of stay, myocardial infarction, all-cause mortality
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial

Forlani 2002 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants with an intraoperative myocardial infarction were excluded from analysis
Intention to treat analysis	High risk	Not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	More than 2 intervention groups

Gibson 1988

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 40 participants; beta-blocker: 21 participants; placebo: 19 participants Mean age: 51.4 years Percentage of female participants: 42.5
Interventions	Participants received esmolol or placebo; treatment was intravenously administered during anaesthesia
Outcomes	Primary outcome: control of perioperative hypertension Secondary outcomes: hypotension, bradycardia
Notes	Type of surgery: different neurosurgical interventions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial

Gibson 1988 (Continued)

Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Gomes 1999

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 85 participants; beta-blocker: 40 participants; placebo: 45 participants Mean age: 65.2 years Percentage of female participants: 35.3
Interventions	Participants received sotalol or placebo; treatment was started 24 to 48 hours preoperatively and was continued for 4 days postoperatively. Participants were followed until hospital discharge
Outcomes	Primary outcome: atrial fibrillation Secondary outcomes: mortality, adverse events
Notes	Type of surgery: elective CABG ± valve replacement

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Pharmacy at each institution dispensed medication and placebo pills for all participants
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified

Gomes 1999 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors reported incomplete outcome data
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Significantly more participants from the control group than from the treatment group were receiving long-term beta-blocker treatment before they entered the study

Graham 1996

Methods	Randomized, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 320 participants; beta-blocker: 213 participants (103 participants 25 mg metoprolol and 110 participants 50 mg metoprolol); placebo: 107 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	Participants received metoprolol (high or low dose) or placebo; treatment was started postoperatively; duration of administration was unclear
Outcomes	Primary outcome: atrial fibrillation
Notes	Type of surgery: elective CABG. Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Unclear risk	Not specified
Blinding of doctors/personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified

Graham 1996 (Continued)

Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	High risk	Conference abstract, thus authors likely reported on only a subset of data
Other bias	Low risk	Not detected

Gupta 2011

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 66 participants; atenolol: 22 participants; clonidine: 22 participants; placebo: 22 participants Mean age: not specified Percentage female participants: not specified
Interventions	Participants received a single oral dose of placebo, atenolol or clonidine 2 hours before surgery
Outcomes	Primary outcome: haemodynamic response to nasal speculum insertion (heart rate and blood pressure) Secondary outcomes: bradycardia, hypotension, consumption of fentanyl and propofol
Notes	Type of surgery: neurosurgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 3 study groups according to a computer-generated randomization schedule
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	'An independent anaesthesia registrar, blinded to study group allocation and not involved in anaesthesia management, observed changes in heart rate, mean arterial pressure, ... , and sedation'
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessors (detection bias) All outcomes	Low risk	See above
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not detected
Intention to treat analysis	High risk	2 participants in the atenolol group were excluded from analysis because of bradycardia. Participants were not analysed as randomly assigned by the study authors. However, these 2 participants were included in our analysis (outcome 'bradycardia')

Gupta 2011 (Continued)

Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	3 intervention groups—outcomes were presented identically for all groups

Hammon 1984

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 50 participants; beta-blocker: 24 participants; placebo: 26 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	Participants received propranolol or placebo. Treatment was started orally 24 to 48 hours preoperatively and was continued for 1 month
Outcomes	Primary outcomes: atrial and ventricular arrhythmias Secondary outcomes: death, myocardial infarction, bradycardia
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Harrison 1987

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 30 participants; beta-blocker: 15 participants; placebo: 15 participants Mean age: 56.4 years Percentage of female participants: 10
Interventions	Participants received esmolol or placebo; treatment was administered IV intraoperatively
Outcomes	Primary outcome: intraoperative myocardial ischaemia, intraoperative arrhythmias
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	'The ST trends and ECG strips were evaluated for myocardial ischaemia independently by a cardiologist who had no knowledge of the patient's treatment group'
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Inada 1989

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus lidocaine versus placebo
Participants	Overall: 40 participants; labetalol 5 mg: 10 participants; labetalol 10 mg: 10 participants; lidocaine: 10 participants; placebo: 10 participants

Inada 1989 (Continued)

Mean age: 51.3 years

Percentage of female participants: 53.3

Interventions	Participants received labetalol (5 or 10 mg), lidocaine or placebo; treatment was administered before induction and 2 minutes before the stimulus of intubation
Outcomes	Primary outcome: haemodynamic response Secondary outcome: dysrhythmias
Notes	Type of surgery not specified

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Participants received study drugs from "identical syringes" intravenously: content of syringes not predictable in advance
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	More than 2 intervention groups: 3 intervention groups

Ivey 1983

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 109 participants; beta-blocker: 53 participants; placebo: 56 participants. Only participants receiving 80 mg or more propranolol per day were eligible for this study Mean age: 56.8 years Percentage of female participants: data not provided

Ivey 1983 (Continued)

Interventions	Participants received propranolol or placebo beginning 24 hours postoperatively. The study was discontinued after the fifth postoperative day
Outcomes	Primary outcome: supraventricular tachycardia Secondary outcome: mortality
Notes	Type of surgery: CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	'Randomization was performed by the hospital pharmacy in a double-blind manner.' Control group participants 'received an exact propranolol placebo on an identical schedule'
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	Participants were excluded after randomization because of myocardial infarction or dysrhythmias
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Jacquet 1994

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 42 participants; beta-blocker: 25 participants; standard care: 17 participants Mean age: 60.3 years Percentage of female participants: 11.9
Interventions	Participants received sotalol or standard care; treatment was started 6 hours postoperatively (IV) and was continued orally for 3 months

Jacquet 1994 (Continued)

Outcomes	Primary outcome: supraventricular arrhythmias	
Notes	Type of surgery: elective CABG	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	6 participants were withdrawn from analysis (3 because of bradycardia, 3 as the result of hypotension)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned; 6 participants in the beta-blocker group had to be excluded from the study because of drug-related side effects
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Early stopping: 'Because of the large number of drop-outs with this treatment it was decided to end the study after 6 months even though there was a trend towards better results with sotalol than without'

Jakobsen 1992

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 40 participants; beta-blocker: 20 participants; placebo: 20 participants Mean age: 41 years Percentage of female participants: 100
Interventions	Participants received a single dose of metoprolol (100 mg orally) or matching placebo 1 to 2.5 hours before surgery
Outcomes	Primary outcomes: changes in catecholamine levels, heart rate, arrhythmias, blood pressure and peri-operative blood loss

Jakobsen 1992 (Continued)

Notes Type of surgery: hysterectomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Jakobsen 1997

Methods	Randomized, placebo-controlled, double-blind trial, beta-blocker versus placebo
Participants	Overall: 35 participants; beta-blocker: 18 participants; placebo: 17 participants (1 of 18 participants withdrawn) Mean age: 60.4 years Percentage of female participants: 34.3
Interventions	Participants received metoprolol or placebo orally 1.5 hours before surgery
Outcomes	Primary outcomes: perioperative haemodynamic effects, surgical stress response Secondary outcomes: dysrhythmias, myocardial infarction, bradycardia, hypotension
Notes	Type of surgery: elective thoracotomy for lung resection (general anaesthesia with thoracic epidural blockade)

Risk of bias
Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Jakobsen 1997 (Continued)

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was withdrawn from the placebo group because an epidural catheter could not be accomplished
Intention to treat analysis	High risk	Not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Janssen 1986

Methods	Randomized, open-label trial; 2 beta-blockers versus standard care
Participants	Overall: 130 participants; sotalol: 41 participants; metoprolol: 39 participants; standard care: 50 participants; here, only the metoprolol and standard care groups are considered Mean age: 58.5 years Percentage of female participants: 19.2
Interventions	Participants received sotalol, metoprolol or standard of care; treatment was started parenterally post-operatively, then 50 mg metoprolol 3 times a day orally until hospital discharge
Outcomes	Primary outcome: supraventricular tachycardias
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified

Janssen 1986 (Continued)

Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	21 participants excluded from analysis (2 myocardial infarction, 12 inotropic support after CABG, 1 death, 1 bradycardia, 5 inappropriate data)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	High risk	Only statistically significant results were reported
Other bias	Low risk	Not detected

Kawaguchi 2010

Methods	Randomized, open-label multi-centre trial; beta-blocker versus standard of care
Participants	Overall: 56 participants (patients with subarachnoid haemorrhage and a heart rate above 90/min undergoing intracranial aneurysm repair surgery); landiolol: 28 participants; standard care: 28 participants Mean age: 57.2 years Percentage of female participants: 67.9
Interventions	Participants received landiolol or standard of care during intracranial aneurysm repair surgery. Landiolol was administered intravenously during surgery. Participants were prospectively followed until hospital discharge
Outcomes	Primary outcomes: haemodynamic parameters, tissue injury markers Secondary outcomes: mortality, acute myocardial infarction, bradycardia, hypotension
Notes	Type of surgery: neurosurgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization list

Kawaguchi 2010 (Continued)

Allocation concealment (selection bias)	Low risk	Envelope method
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/per-sonnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome as-sessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (re- porting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Khuri 1987

Methods	Randomized, placebo-controlled, triple-blind trial; nadolol versus placebo
Participants	Overall: 141 participants; beta-blocker: 67 participants; placebo: 74 participants Mean age: 59.9 years Percentage of female participants: data not provided
Interventions	Participants received nadolol or placebo; treatment was started on the first postoperative day and was continued for 6 weeks
Outcomes	Primary outcome: postoperative arrhythmias Secondary outcomes: hypotension, myocardial infarction, mortality
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence genera- tion (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified

Khuri 1987 (Continued)

Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Outcome assessor blinded ('analysed by an independent observer')
Incomplete outcome data (attrition bias) All outcomes	High risk	7 participants were excluded from analysis because of "insufficient postoperative data"
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Kurian 2001

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 68 participants; beta-blocker: 31 participants; standard care: 37 participants Mean age: 60.7 years Percentage of female participants: 14.7
Interventions	Participants received esmolol or standard care; treatment was started 120 minutes before extubation and was continued until 180 minutes after extubation
Outcomes	Primary outcome: perioperative myocardial ischaemia (120 minutes before until 180 minutes after tracheal extubation)
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not further specified
Allocation concealment (selection bias)	Low risk	Numbered, sealed envelopes
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial

Kurian 2001 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants were withdrawn (2 because of hypotension in the esmolol group, 1 in the esmolol group and 1 in the control group because of insufficient monitoring)
Intention to treat analysis	High risk	Study authors stated they used the intention-to-treat principle for analysis but participant were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Early termination of trial due to many adverse events and problems in participant recruitment

Lai 2006

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 60 participants; beta-blocker: 30 participants; standard of care: 30 participants Median age: 66.5 years Percentage of female participants: 18.3
Interventions	Participants 65 years of age or older diagnosed with oesophageal cancer received metoprolol or standard care. Treatment was started at the induction of anaesthesia and was continued until 72 hours postoperatively
Outcomes	Primary outcomes: haemodynamic parameters Secondary outcomes: serum levels of troponin T, myocardial infarction, atrial fibrillation, mortality, myocardial ischaemia
Notes	Type of surgery: oesophagectomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial

Lai 2006 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants were withdrawn from the study after randomization. Exact point of time and study group allocation were unclear
Intention to treat analysis	High risk	Not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Lamb 1988

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 60 participants; beta-blocker: 30 participants; standard care: 30 participants Mean age: 54.9 years Percentage of female participants: 13.3
Interventions	Participants received atenolol or standard care; treatment was started 72 hours before surgery and was continued for 7 days
Outcomes	Primary outcome: supraventricular arrhythmias
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias)	High risk	Open-label trial

Lamb 1988 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Lee 2010

Methods	Randomized, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 60 participants; esmolol: 30 participants; placebo: 30 participants Mean age: 35.4 years Percentage female participants: 56.7
Interventions	Participants received esmolol or saline placebo during surgery intravenously with a bolus before intubation or extubation, respectively
Outcomes	Primary outcomes: postoperative nausea, vomiting and pain Secondary outcomes: haemodynamic variables, length of stay (surgery until discharge)
Notes	Type of surgery: laparoscopic appendectomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants 'were randomly placed into 2 groups'
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants (performance bias) All outcomes	Unclear risk	Not specified
Blinding of doctors/personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias)	Unclear risk	Not reported

Lee 2010 (Continued)

All outcomes

Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not detected
Other bias	Unclear risk	Not detected

Liu 1986

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 30 participants; beta-blocker: 16 participants; placebo: 14 participants Mean age: 45.3 years Percentage of female participants: 90
Interventions	Participants received esmolol or placebo; treatment was administered during anaesthesia intra-venously
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: dysrhythmias (bradycardia, ventricular ectopic beats) during surgery
Notes	Type of surgery: mainly gynaecological procedures

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified

Liu 1986 (Continued)

Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Liu 2006

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 30 participants; beta-blocker: 15 participants; standard of care: 15 participants Mean age: 69.5 years Percentage of female participants: 46.7
Interventions	Participants received metoprolol intravenously during surgery or standard care
Outcomes	Primary outcomes: haemodynamic parameters Secondary outcomes: myocardial ischaemia, troponin levels, hypotension, bradycardia
Notes	Type of surgery: non-cardiac surgery (lung resection, oesophagectomy, gastrectomy)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Magnusson 1986

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 27 participants with arterial hypertension; beta-blocker: 13 participants; placebo: 14 participants Mean age: 57.6 years Percentage of female participants: 63.0
Interventions	Participants received metoprolol or placebo tablets and saline; treatment was started 2 weeks before surgery until postoperative day 1
Outcomes	Outcomes: multiple haemodynamic parameters, heart failure, ventricular extrasystoles, bradycardia, hypotension
Notes	Type of surgery: cholecystectomy, herniorrhaphy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	"Two patients in the treatment group and one patient in the placebo group were subsequently excluded because of complications during treatment"
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Mangano 1996

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
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Mangano 1996 (Continued)

Participants	Overall: 200 participants; beta-blocker: 99 participants; placebo: 101 participants; participants were included if they had, or were at risk for, coronary artery disease; same population as Wallace 1998 Mean age: 67.5 years Percentage of female participants: data not provided
Interventions	Participants received atenolol or placebo; treatment was started preoperatively and was continued until hospital discharge
Outcomes	Primary outcome: mortality from all causes during the 2 years after discharge Secondary outcomes: myocardial infarction, unstable angina, congestive heart failure, myocardial revascularization, adverse events
Notes	Type of surgery: non-cardiac surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer generated, randomized list"
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors reported incomplete outcome data
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Martinussen 1988

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 75 participants; beta-blocker: 35 participants; placebo: 40 participants Mean age: 55.4 years

Perioperative beta-blockers for preventing surgery-related mortality and morbidity (Review)

Martinussen 1988 (Continued)

Percentage of female participants: 17.6

Interventions	Participants received propranolol or placebo; treatment was started on the evening of the day of surgery and was continued until the end of the fourth day after surgery
Outcomes	Primary outcome: supraventricular tachyarrhythmias Secondary outcome: myocardial infarction
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	33 participants already randomly assigned were excluded from analysis (in 14 participants, a nasogastric tube for drug administration could not be placed, 19 participants developed disorders as specified in the discontinuation criteria); originally 108 participants were randomly assigned
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Marwick 2009

Methods	Randomized, multi-centre, open-label, controlled trial; universal beta-blocker therapy versus standard of care
Participants	Overall 400 participants; beta-blocker: 197 participants; standard care: 203 participants Mean age: 72.5 years Percentage of female participants: 36

Marwick 2009 (Continued)

Interventions	Participants at intermediate cardiovascular risk were randomly assigned to universal beta-blocker therapy or usual care (beta-blockers were continued in participants already taking them and were newly prescribed in participants identified as at high risk based on evidence of ischaemia during dobutamine stress echocardiography). Beta-blockers were started at least 1 week before surgery and were continued until 30 days after surgery
Outcomes	Primary endpoint: major cardiovascular event (cardiac death or non-fatal myocardial infarction) Secondary outcomes: all-cause mortality, hypotension, bradycardia, length of stay, cerebrovascular events
Notes	Type of surgery: major, non-cardiac surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-based online data entry and treatment allocation
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 17 participants in the beta-blocker group and 17 in the control group did not fulfil the protocol. However, they were included in the analysis based on the intention-to-treat principle
Intention to treat analysis	Low risk	See above
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Differential care programmes for treatment groups: heart rate-directed administration of beta-blocker exclusively in beta-blocker group (fixed-dose administration in standard of care group), dobutamine stress echo for cardiovascular risk stratification exclusively in standard of care group

Matangi 1985

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 164 participants (all participants received beta-blockers preoperatively); beta-blocker: 82 participants; standard care: 82 participants

Matangi 1985 (Continued)

Mean age: 55.2 years

Percentage of female participants: 20.7

Interventions	Participants received propranolol or placebo; treatment was started postoperatively and was continued until the time of discharge
Outcomes	Primary outcomes: supraventricular arrhythmias, ventricular arrhythmias, ventricular premature beats Secondary outcome: acute myocardial infarction
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	In 4 participants, beta-blocker therapy was discontinued because of side effects (low cardiac output, bronchospasm, nightmares), but "all patients were analysed according to the intention-to-treat principle"
Intention to treat analysis	Low risk	See above
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Matangi 1989

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 70 participants; beta-blocker: 35 participants; placebo: 35 participants Mean age: 59.2 years Percentage of female participants: 21.4

Matangi 1989 (Continued)

Interventions	Participants received atenolol or placebo (at first intravenously, then orally); treatment was started postoperatively and was continued for 6 days
Outcomes	Primary outcome: supraventricular arrhythmias Secondary outcomes: acute myocardial infarction, adverse events
Notes	Type of surgery: CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Sealed envelopes were used in 1985 (see Matangi 1985)
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	4 withdrawals before random assignment (1 participant died during surgery, 2 suffered from an intraoperative myocardial infarction and required high-dose inotropic support, 1 had bronchospasms postoperatively)
Intention to treat analysis	Low risk	Study authors stated that they had applied the intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Materne 1985

Methods	Randomized, open-label trial, beta-blocker versus standard care
Participants	Overall: 71 participants; beta-blocker: 32 participants; standard care: 39 participants Mean age: 56.6 years Percentage of female participants: 15.5
Interventions	Participants received acebutolol or standard care; treatment was started 24 hours after initiation of surgery; no end of the treatment period was specified
Outcomes	Primary outcome: supraventricular and ventricular arrhythmias

Materne 1985 (Continued)

Secondary outcome: haemodynamic parameters

Notes	Type of surgery: elective CABG	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Matsuura 2001

Methods	Randomized, open-label trial, beta-blocker versus standard care
Participants	Overall: 80 participants; beta-blocker: 40 participants; standard care: 40 participants Mean age: 61 years Percentage of female participants: 19
Interventions	Participants received sotalol or standard care; treatment was started on the first postoperative day and was continued for 2 weeks
Outcomes	Primary outcome: atrial fibrillation Secondary outcome: length of stay
Notes	Type of surgery: elective CABG

Matsuura 2001 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization: "patients were randomized alternately"
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	3 participants were potentially withdrawn (unclear)
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Miller 1990

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 45 participants (those above 75 years of age with coronary artery disease or a minimum of 2 risk factors for coronary artery disease); beta-blocker: 30 participants; placebo: 15 participants Mean age: 59 years Percentage of female participants: 15.6
Interventions	Participants received a single IV bolus of esmolol or placebo at induction of anaesthesia
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: death, myocardial infarction, myocardial ischaemia, hypotension
Notes	Type of surgery: elective peripheral vascular surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
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Miller 1990 (Continued)

Random sequence generation (selection bias)	Low risk	Computer-generated randomization schedule
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Miller 1991

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 548 participants; beta-blocker: 368 participants; placebo: 180 participants Mean age: 55.7 years Percentage of female participants: 52.0
Interventions	Participants received a bolus of esmolol or placebo at induction of anaesthesia
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: bradycardia, hypotension, bronchospasm
Notes	Type of surgery: elective non-cardiac surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization in blocks of 45 for each centre," study author has stated that computer-generated randomization was used (Miller 1990)
Allocation concealment (selection bias)	Low risk	See above

Miller 1991 (Continued)

Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Mohr 1981

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 85 participants; beta-blocker: 37 participants; standard care: 48 participants Mean age: 56.6 years Percentage of female participants: 15.3
Interventions	All participants were receiving preoperative propranolol; in the standard care group, beta-blockers were withdrawn preoperatively, and in the intervention group, treatment was continued
Outcomes	Primary outcome: supraventricular arrhythmias Secondary outcomes: myocardial infarction, perioperative death
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization: "odd or even last numbers on medical records"
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial

Mohr 1981 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants who died were not included in the analysis
Intention to treat analysis	High risk	Not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Moon 2011

Methods	Randomized, triple-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 54 participants; esmolol: 27 participants; placebo: 27 participants Mean age: 39.4 years Percentage of female participants: 100
Interventions	Participants received esmolol or saline placebo intravenously (loading dose followed by maintenance dose). The exact duration of drug application was not explicitly specified, but it can be inferred unambiguously that treatment was given during general anaesthesia
Outcomes	Primary outcome: consumption of sevoflurane and fentanyl Secondary outcome: haemodynamic parameters (bradycardia, hypotension)
Notes	Type of surgery: laparoscopic gynaecological surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	'Anaesthesiologists not involved in the patients' anaesthetic management prepared the covered syringe pump for esmolol or placebo solutions and held the randomization codes until the end of the study'
Blinding of participants (performance bias) All outcomes	Low risk	See above
Blinding of doctors/personnel (performance bias)	Low risk	See above

Moon 2011 (Continued)

All outcomes

Blinding of outcome assessors (detection bias) All outcomes	Low risk	Intraoperative haemodynamic variables were assessed by an anaesthesiologist blinded to study allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Myhre 1984

Methods	Randomized, open-label trial, beta-blocker versus standard care	
Participants	Overall: 36 participants (all had stable angina pectoris and were taking beta-blockers preoperatively); beta-blocker: 16 participants; standard care: 20 participants Mean age: 56.0 years Percentage of female participants: 20.0	
Interventions	Participants received propranolol or standard care; treatment was restarted 2 hours postoperatively and was continued for 7 days (as all participants in the propranolol group were taking beta-blockers preoperatively)	
Outcomes	Primary outcome: supraventricular tachyarrhythmias Secondary outcome: acute myocardial infarction	
Notes	Type of surgery: elective CABG	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial

Myhre 1984 (Continued)

Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	1 participant died and was excluded from the analysis
Intention to treat analysis	High risk	Not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Neary 2006

Methods	Randomized, triple-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 38 participants; beta-blocker: 18 participants; placebo: 20 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	Cardiac high-risk participants naive to beta-blockers who underwent non-elective emergency surgery were randomly assigned to receive atenolol or placebo (from induction of anaesthesia until seventh postoperative day)
Outcomes	Primary outcome: mortality and non-fatal cardiac events until 30 days after surgery. A long-term follow-up was also performed (2 years)
Notes	Type of surgery: non-elective, non-cardiac emergency surgery (gastrointestinal resection surgery, major limb amputation, arterial reconstruction, orthopaedic procedures)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The study medication was provided in 1 box per participant containing placebo, as well the active drug, in similar looking batches. The anaesthesiologist randomly chose 1 pack at the induction of anaesthesia
Allocation concealment (selection bias)	Low risk	"The box also contained a sealed envelope with details of which packs contained the active drug in case of an emergency."
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias)	Low risk	ECGs and lab reports were evaluated by "blinded cardiology staff"

Neary 2006 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	"19 patients were withdrawn because relatives removed consent" before randomization
Intention to treat analysis	Low risk	Participants were analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	High risk	Early stopping: Of 400 patients planned to be included, only 38 were enrolled because of recruiting problems

Neustein 1994

Methods	Randomized, triple-blind, placebo-controlled trial; beta-blocker versus placebo	
Participants	Overall: 38 participants; beta-blocker: 16 participants; placebo: 22 participants Mean age: 64.0 years Percentage of female participants: 35.0	
Interventions	Participants received esmolol or placebo; treatment was administered intraoperatively	
Outcomes	Primary outcome: intraoperative myocardial ischaemia	
Notes	Type of surgery: elective CABG	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants were excluded from analysis (1 in the beta-blocker group because of bradycardia and hypotension and 1 in the control group as the result of a wide QRS complex that did not allow interpretation of intraoperative myocardial ischaemia); number of enrolled participants = 40

Neustein 1994 (Continued)

Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Nyström 1993

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 101 participants; beta-blocker: 50; standard care: 51 Mean age: 59.5 years Percentage of female participants: 12.9
Interventions	Participants received sotalol or standard care; treatment was started on the morning of the day of surgery; study ended on the sixth postoperative day
Outcomes	Primary outcome: atrial fibrillation Secondary outcomes: mortality, ventricular arrhythmias
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected

Nyström 1993 (Continued)

Other bias	Low risk	Not detected
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Ogawa 2013

Methods	Randomized, controlled, open-label trial; beta-blocker versus standard of care
Participants	Overall: 136 participants; landiolol: 68 participants; standard of care: 68 participants Mean age: 70.5 years Percentage of female participants: 22.8
Interventions	Participants received standard of care or landiolol. Landiolol was started after induction of anaesthesia and was continued for 48 hours (heart rate titrated)
Outcomes	Primary outcome: incidence of postoperative atrial fibrillation Secondary outcomes: laboratory markers of ischaemia and inflammation, heart rate
Notes	Type of surgery: off-pump CABG (16.9% emergency surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Treatment group allocation was performed using 'a random number program'
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	'None of the patients was withdrawn from the study'
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not detected
Other bias	Unclear risk	Not detected

Oka 1980

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 54 participants; beta-blocker: 19 participants; standard care: 35 participants Mean age: 54.7 years Percentage of female participants: 37
Interventions	All participants received preoperative beta-blockers; in the standard care group, beta-blockers were withdrawn preoperatively; in the beta-blocker group, they were continued, with observation until hospital discharge
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: supraventricular arrhythmias, mortality, acute myocardial infarction
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Ormerod 1984

Methods	Randomized, open-label trial; beta-blocker versus digoxin versus standard care
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Ormerod 1984 (Continued)

Participants	Overall: 90 participants; beta-blocker: 27 participants; digoxin: 30 participants; standard-care: 33 participants Mean age: 53.2 years Percentage of female participants: 11.7
Interventions	Participants received propranolol, digoxin or standard care; treatment was started on the morning after operation; no end of drug administration was specified
Outcomes	Primary outcome: atrial fibrillation Secondary outcome: ventricular extrasystoles
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	Randomization was performed 1 week before surgery. 4 participants were excluded after the surgery because oral drug administration was impossible (low cardiac output or assisted ventilation after operation)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	3 intervention arms; results were presented identically for all groups

Osada 2012

Methods	Conference abstract. Randomized, controlled, open-label trial; beta-blocker versus standard of care
Participants	Overall: 141 participants; landiolol: 73 participants; standard of care: 68 participants Mean age: data not provided

Osada 2012 (Continued)

Percentage of female participants: data not provided

Interventions	Participants received landiolol intravenously or standard of care. Landiolol was started upon arrival in the intensive care unit after surgery and was continued for 48 hours
Outcomes	Primary outcome: occurrence of postoperative atrial fibrillation
Notes	Type of surgery: open-heart surgery (CABG, valve surgery, thoracic aorta surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Unclear risk	Not detected (in abstract)
Other bias	Unclear risk	Not detected (in abstract)

Oxorn 1990

Methods	Randomized, triple-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 48 participants; 2 esmolol groups, each consisting of 16 participants; placebo: 16 participants Mean age: 42.6 years Percentage of female participants: 100
Interventions	Participants received esmolol or placebo as a single dose; treatment was administered intraoperatively
Outcomes	Primary outcomes: perioperative hypertension and tachycardia

Oxorn 1990 (Continued)

Secondary outcome: ventricular extrasystoles

Notes	Type of surgery: hysterectomy	
<i>Risk of bias</i>		
Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, triple-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Cardiologist assessing the ECG was blinded to study group allocation
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Paul 1997

Methods	Randomized, placebo-controlled, single-blind trial; beta-blocker versus placebo
Participants	Overall: 100 participants; beta-blocker: 50 participants; placebo: 50 participants Mean age: 63.4 years Percentage of female participants: 11
Interventions	Participants received metoprolol or placebo; treatment was started when postoperative oral feeding was possible (typically 24 hours after surgery); no end of drug administration was specified
Outcomes	Primary outcome: atrial fibrillation Secondary outcome: mortality
Notes	Type of surgery: elective CABG

Paull 1997 (Continued)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Single-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Single-blind trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Single-blind trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Low risk	Study authors stated they used the intention-to-treat principle for data analysis
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Pfisterer 1997

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 255 participants; beta-blocker: 126 participants; placebo: 129 participants Mean age: 60.6 years Percentage of female participants: 13.3
Interventions	Participants received sotalol or placebo; treatment was started 2 hours before induction of anaesthesia; treatment was given for a total of 3 months
Outcomes	Primary outcome: supraventricular tachyarrhythmias/atrial fibrillation Secondary outcomes: ventricular arrhythmias, bradycardia, hypotension
Notes	Type of surgery: elective CABG or aortic valve surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
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Pfisterer 1997 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Randomized, placebo-controlled, double-blind trial
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study authors reported incomplete outcome data
Intention to treat analysis	Low risk	Study authors stated they used the intention-to-treat principle for data analysis
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

POBBLE 2005

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 97 participants; beta-blocker: 53 participants; placebo: 44 participants Mean age: 73.5 years Percentage of female participants: 22.7
Interventions	Participants received oral metoprolol or placebo; treatment was started on the day before surgery and was continued until the seventh postoperative day
Outcomes	Primary outcomes: fatal and non-fatal cardiovascular events (myocardial infarction, unstable angina, ventricular tachycardia, or stroke) within 30 days of operation Secondary outcomes: length of hospital stay
Notes	Type of surgery: elective infrarenal vascular surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Central randomization via Web page

POBBLE 2005 (Continued)

Allocation concealment (selection bias)	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	'Anesthesiologists were unblinded to the drug allocation because those involved in the trial at participating centers would have immediately identified the active treatment and, for safety reasons, refused to collaborate in a blind-ed fashion'
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Holter-ECG results were coded centrally
Incomplete outcome data (attrition bias) All outcomes	Low risk	Incomplete outcome data were reported
Intention to treat analysis	Low risk	Study authors stated they used the intention-to-treat principle for data analysis
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

POISE 2008

Methods	Randomized, placebo-controlled, triple-blind multi-centre trial; beta-blocker versus placebo
Participants	Overall: 8351 participants with or at risk of atherosclerotic disease; metoprolol: 4174 participants; placebo: 4177 participants Mean age: 69 years Percentage of female participants: 36.6
Interventions	Participants received metoprolol succinate or placebo; treatment was started 2 to 4 hours before surgery and was continued for 30 days
Outcomes	Primary composite outcome: cardiovascular death, non-fatal myocardial infarction, non-fatal cardiac arrest Secondary outcomes: all-cause mortality, hypotension, bradycardia, stroke, congestive heart failure, new-onset atrial fibrillation
Notes	Type of surgery: non-cardiac surgery (vascular, intraperitoneal, orthopaedic and other)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization phone service

POISE 2008 (Continued)

Allocation concealment (selection bias)	Low risk	Randomized, placebo-controlled, triple-blind multi-centre trial
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind multi-centre trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind multi-centre trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Outcome adjudicators were masked to treatment allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below.
Intention to treat analysis	Low risk	Study authors stated they used the intention-to-treat principle for data analysis
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Raby 1999

Methods	Randomized, placebo-controlled, triple-blinded trial; beta-blocker versus placebo.
Participants	Overall: 26 participants; beta-blocker: 15 participants; placebo: 11 participants Mean age: 68.2 years Percentage of female participants: 53.8
Interventions	Participants received esmolol or placebo; treatment was administered intraoperatively
Outcomes	Primary outcome: perioperative myocardial ischaemia Secondary outcomes: myocardial infarction, unstable angina
Notes	Type of surgery: aortic aneurysm repair, infrainguinal arterial bypass, carotid endarterectomy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Coin flipping
Allocation concealment (selection bias)	Low risk	See above

Raby 1999 (Continued)

Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled triple-blinded trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Despite the double-blind study design, a "significantly higher use of alternative beta-blockers in the placebo group compared with the esmolol group" was noted. The study authors suggested that "managing clinicians recognized patients receiving the active drug or placebo despite blinding"
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Holter monitoring was interpreted "by a technician blinded to patient characteristics and randomization"
Incomplete outcome data (attrition bias) All outcomes	Low risk	"No patient in our study had beta-blocker therapy suspended because of unacceptable side effects"
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Reves 1990

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 30 participants; beta-blocker: 16 participants; placebo: 14 participants Mean age: 56.1 years Percentage of female participants: 10
Interventions	Participants received esmolol or placebo; treatment was administered intraoperatively
Outcomes	Primary outcome: resolution of tachycardia and hypertension Secondary outcome: myocardial ischaemia
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial

Reves 1990 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Rubin 1987

Methods	Randomized, open-label trial; beta-blocker versus digoxin versus standard care
Participants	Overall: 123 participants; beta-blocker: 37 participants; digoxin: 46 participants; standard care: 40 participants Mean age: 55.4 years Percentage of female participants: data not provided
Interventions	Participants received propranolol, digoxin or standard care; treatment was started on the first postoperative day and continued for 6 weeks
Outcomes	Primary outcome: atrial fibrillation
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were randomized by lot"
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial

Rubin 1987 (Continued)

Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	27 participants were excluded from analysis after randomization
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	3 intervention arms—outcomes were reported identically for all intervention groups

Sakaguchi 2012

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 60 participants; landiolol: 30 participants; standard care: 30 participants Mean age: 69.0 years Percentage of female participants: 46.7
Interventions	Participants received landiolol or standard of care. Landiolol was administered heart rate titrated; it was started upon admission to the intensive care unit after surgery and was continued until 72 hours after surgery
Outcomes	Primary outcome: occurrence of atrial fibrillation after surgery
Notes	Type of surgery: heart valve surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	'60 subjects were randomized into 2 groups by the coin toss method.' Coin tossing is a valid method used to generate a randomization sequence. In our opinion, however, it is highly unlikely that coin tossing would result in exactly 30 participants in each study group. With such a low number of participants, we would expect an unequal number of participants in each trial arm if the randomization sequence was generated with coin flipping
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial

Sakaguchi 2012 (Continued)

Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Salazar 1979

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 42 participants; beta-blocker: 20 participants; standard care 22 participants Mean age: data not provided Percentage of female participants: data not provided
Interventions	All participants received propranolol before surgery. Participants received propranolol or standard care; treatment was restarted immediately after surgery in the propranolol group; no end of therapy was specified
Outcomes	Primary outcomes: supraventricular arrhythmias, atrial fibrillation Secondary outcomes: hypotension
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial

Salazar 1979 (Continued)

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Sandler 1990

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 45 participants; beta-blocker: 30 participants; placebo: 15 participants Mean age: 60 years Percentage of female participants: 35.6
Interventions	Patients received esmolol (100 mg or 200 mg) or placebo; treatment was administered intraoperatively
Outcomes	Primary outcomes: increased heart rate, increased blood pressure Secondary outcome: ventricular arrhythmias
Notes	Type of intervention: rigid bronchoscopy

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified

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Sandler 1990 (Continued)

Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Sezai 2011

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus saline placebo
Participants	Overall: 140 participants; landiolol: 70 participants; placebo: 70 participants Mean age: 67.6 years Percentage female participants: 8.6
Interventions	Intravenous landiolol or saline placebo was started during surgery and was continued for 48 hours
Outcomes	Primary endpoint: occurrence of atrial fibrillation during 1 week after surgery Secondary endpoints: mortality, haemodynamic parameters, total cost of hospital treatment, multiple laboratory parameters indicating myocardial ischaemia or inflammation, length of stay, congestive heart failure, stroke
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants 'were randomized into two groups by the lottery method'
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	Double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants were withdrawn after randomization because of 'lack of sufficient data'
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected

Sezai 2011 (Continued)

Other bias	Low risk	Not detected
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Sezai 2012

Methods	Randomized, single-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 101 participants; landiolol: 34 participants; landiolol + oral bisoprolol: 33 participants; placebo: 34 participants Mean age: 68.2 years Percentage of female participants: 18.8
Interventions	Participants were randomly assigned to receive landiolol IV or saline placebo IV or to receive oral bisoprolol and IV landiolol. The trial was double-blinded for the application of IV drugs and was single-blinded for oral bisoprolol treatment. Both beta-blocker groups were combined as a single beta-blocker group versus saline placebo in our analysis. Study drugs were started during surgery and were continued for 3 days
Outcomes	Primary outcome: atrial fibrillation within first week after surgery Secondary outcomes: haemodynamic parameters, multiple lab parameters indicating myocardial ischaemia or inflammation, mortality, acute myocardial infarction, congestive heart failure, length of stay
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Patients were randomized into three groups by the lottery method'
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Participants were blinded for IV treatment but not for oral treatment
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Medical staff was blinded for IV and oral treatment
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	4 participants were excluded after randomization (off-pump CABG, other surgery done concomitantly)
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned

Sezai 2012 (Continued)

Selective reporting (re-reporting bias)	Low risk	Not detected
Other bias	High risk	The trial was stopped early after an interim analysis for ethical reasons (occurrence of atrial fibrillation was statistically significant less in the beta-blocker group than in the control group, but the incidences of adverse events were not different) The results for all 3 treatment groups were presented identically

Shukla 2010

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 60 participants; esmolol: 30 participants; saline placebo: 30 participants Mean age: 43.6 years Percentage of female participants: 50
Interventions	Participants received esmolol or saline placebo intravenously 15 minutes before induction of anaesthesia until the end of surgery
Outcomes	Outcome parameters: haemodynamic variables (heart rate, mean arterial pressure), intraoperative morphine consumption, sedation level, nausea, emesis, pruritus, respiratory depression, postoperative pain and morphine consumption
Notes	Type of surgery: major lower abdominal surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants 'were randomly divided—Not specified
Allocation concealment (selection bias)	Unclear risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	'Randomized, double-blind study'
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	See above
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not reported
Intention to treat analysis	Unclear risk	Not specified

Shukla 2010 (Continued)

Selective reporting (reporting bias)	Unclear risk	Not detected
Other bias	Unclear risk	Not detected

Silverman 1982

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 100 participants; beta-blocker: 50 participants; standard care: 50 participants Mean age: 56.7 years Percentage of female participants: 7
Interventions	Participants received propranolol or standard care; treatment was initiated after surgery and was continued until discharge
Outcomes	Primary outcome: supraventricular arrhythmias Secondary outcome: perioperative myocardial infarction
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization: "randomization was by birthdate"
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Stephenson 1980

Methods	Quasi-randomized (according to date of birth), open-label trial; beta-blocker versus standard care
Participants	Overall: 223 participants; beta-blocker 87 participants; standard care: 136 participants Mean age: 55.2 years Percentage of female participants: 9.0%
Interventions	Participants received propranolol or standard care; treatment was started at the time of discharge from the intensive care unit after surgery; no end of drug administration was specified
Outcomes	Primary outcome: postoperative cardiac arrhythmias (supraventricular and ventricular)
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Randomization by date of birth
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	2 participants who received the study drug and developed bradycardia were excluded from the analysis
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Stone 1988

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 128 participants; beta-blocker (3 different beta-blocker groups; see below 'Other bias'): 89 participants; standard care: 39 participants

Stone 1988 (Continued)

Mean age: 65.4 years

Percentage of female participants: 29.7

Interventions	Participants (with untreated hypertension) received atenolol, labetalol, oxprenolol or standard care; treatment was administered as a single oral tablet before induction of anaesthesia
Outcomes	Primary outcome: myocardial ischaemia Secondary outcomes: acute myocardial infarction, bradycardia, hypotension, ventricular extrasystoles
Notes	Type of surgery: abdominal, peripheral, and vascular surgery (no further specification)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	More than 2 intervention groups (3 beta-blocker groups: atenolol, labetalol, oxprenolol; control)

Sun 2011

Methods	Randomized, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 58 participants; esmolol: 30 participants; placebo: 28 participants Mean age: data not provided Percentage female participants: data not provided

Sun 2011 (Continued)

Interventions	Participants received an IV single shot of esmolol or saline placebo during surgery before removal of the aortic clamp
Outcomes	Primary outcome: cardiac recovery after cardiopulmonary bypass as assessed by occurrence of arrhythmias, haemodynamic parameters and vasoactive drug use
Notes	Type of surgery: elective single mitral valve replacement in participants with rheumatic heart disease

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	'Patients were randomly assigned to two groups by a computer program'
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Unclear risk	Not specified
Blinding of doctors/personnel (performance bias) All outcomes	Unclear risk	Not specified
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	2 control group participants were excluded from the study as the result of pericarditis after randomization
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Suttorp 1991

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 300 participants; beta-blocker: 150 participants; placebo: 150 participants Mean age: 62 years Percentage of female participants: 22
Interventions	Participants received sotalol or placebo; treatment was started 4 to 6 hours postoperatively and was continued until the sixth day after surgery
Outcomes	Primary outcome: supraventricular tachyarrhythmias

Suttorp 1991 (Continued)

Notes Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants were excluded from analysis because of protocol violations (per-protocol analysis); 303 participants enrolled
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Vecht 1986

Methods	Randomized, double-blind, placebo-controlled trial; beta-blocker versus placebo
Participants	Overall: 132 participants; beta-blocker: 66 participants; placebo: 66 participants Mean age: 54.1 years Percentage of female participants: 8.3
Interventions	Participants received timolol or placebo; treatment was started postoperatively, and no end of administration was specified
Outcomes	Primary outcome: supraventricular tachyarrhythmias
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
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Vecht 1986 (Continued)

Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, double-blind, placebo-controlled trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Wallace 1998

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 200 participants; beta-blocker: 99 participants; placebo: 101 participants; same population as in Mangano 1996 Mean age: 67.5 years Percentage of female participants: data not provided
Interventions	Participants received atenolol or placebo; treatment was started preoperatively and was continued until hospital discharge
Outcomes	Primary outcome: mortality from all causes during the 2 years after discharge Secondary outcomes: myocardial infarction, unstable angina, congestive heart failure, myocardial revascularization, adverse events
Notes	Type of surgery: non-cardiac surgery

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Computer-generated, randomized list retained by the hospital pharmacy"

Wallace 1998 (Continued)

Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, triple-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Low risk	Outcome assessors were blinded
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Low risk	Study authors stated that they used the intention-to-treat principle
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Wenke 1999

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 200 participants; beta-blocker: 100 participants; standard care: 100 participants Mean age: 63.6 years Percentage of female participants: 23
Interventions	Participants received metoprolol or standard care; treatment was initiated postoperatively, and the observation period ended on the tenth postoperative day
Outcomes	Primary outcome: supraventricular arrhythmias Secondary outcomes: acute myocardial infarction, length of stay
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not specified

Wenke 1999 (Continued)

Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

White 1984

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 41 participants; beta-blocker: 21 participants; placebo: 20 participants Mean age: 55.5 years Percentage of female participants: 17.1
Interventions	Participants received timolol or placebo; treatment was started 3 to 7 hours postoperatively and was continued for 7 days
Outcomes	Primary outcome: supraventricular tachyarrhythmias Secondary outcomes: mortality, death due to cardiac causes, myocardial ischaemia
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial

White 1984 (Continued)

Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Whitehead 1980

Methods	Randomized, placebo-controlled, triple-blind trial; beta-blocker versus placebo
Participants	Overall: 60 participants; beta-blocker: 30 participants; placebo: 30 participants Mean age: 24.5 years Percentage of female participants: data not provided
Interventions	Participants received metoprolol or placebo; treatment was administered as an IV single shot before induction of anaesthesia
Outcomes	Primary outcome: cardiac arrhythmias (supraventricular and ventricular)
Notes	Type of surgery: removal of wisdom teeth

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Low risk	Application of equal looking ampoules
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias)	Low risk	Anaesthesiologist evaluating ECG and haemodynamic parameters was blinded to study group allocation

Whitehead 1980 (Continued)

All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Williams 1982

Methods	Quasi-randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 60 participants; beta-blocker: 28 participants; standard care: 32 participants Mean age: 55.3 years Percentage of female participants: 18.3
Interventions	Participants received propranolol or standard care; treatment was started at noon of the participant's first postoperative day; no clear end of drug administration was specified
Outcomes	Primary outcome: postoperative arrhythmias (supraventricular and ventricular)
Notes	Type of surgery: elective CABG

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomization: "patients were randomized by odd or even birthdate"
Allocation concealment (selection bias)	High risk	See above
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	5 participants were excluded from analysis because of postoperative heart failure requiring IABP perioperatively (65 participants randomly assigned)

Williams 1982 (Continued)

Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Yang 2006

Methods	Randomized, placebo-controlled, double-blind trial; beta-blocker versus placebo
Participants	Overall: 496 participants; beta-blocker: 246 participants; placebo: 250 participants Mean age: 66.1 years Percentage of female participants: 28.0
Interventions	Participants received metoprolol or placebo; treatment was started 2 hours before surgery and was continued until hospital discharge or for a maximum duration of 5 days
Outcomes	Primary composite outcome (30 days): myocardial infarction, unstable angina, new CHF, atrial and ventricular arrhythmias, all-cause mortality Secondary outcomes: hypotension, bradycardia
Notes	Type of surgery: abdominal aortic surgery, infrainguinal or extra-anatomical revascularization

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was constructed in blocks of four by the study statistician and study medication preparations by the pharmacists"
Allocation concealment (selection bias)	Low risk	See above
Blinding of participants (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of doctors/personnel (performance bias) All outcomes	Low risk	Randomized, placebo-controlled, double-blind trial
Blinding of outcome assessors (detection bias) All outcomes	Unclear risk	Not specified
Incomplete outcome data (attrition bias) All outcomes	Low risk	See below
Intention to treat analysis	Low risk	Study authors stated that they used the intention-to-treat principle for data analysis

Yang 2006 (Continued)

Selective reporting (reporting bias)	Low risk	Not detected
Other bias	Low risk	Not detected

Yang 2008

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 102 participants; beta-blocker: 51 participants; standard of care: 51 participants Mean age: 71.0 years Percentage of female participants: 58.8
Interventions	Participants received standard care or metoprolol (orally or intravenously, blood pressure and heart rate titrated); treatment was started 2 hours before surgery and was continued until 30 days after surgery
Outcomes	Primary outcomes: changes in heart rate, levels of creatine kinase (CK-MB), mortality, acute myocardial infarction, stroke
Notes	Type of surgery: non-cardiac surgery (major abdominal)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Not specified
Intention to treat analysis	Unclear risk	Not specified
Selective reporting (reporting bias)	Low risk	Not detected

Yang 2008 (Continued)

Other bias	Low risk	Not detected
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Zaugg 1999

Methods	Randomized, open-label trial; beta-blocker versus standard care
Participants	Overall: 59 participants; beta-blocker: 40 participants; standard care: 19 participants Mean age: 74.7 years Percentage of female participants: 58.7
Interventions	Participants (65 years of age or older) were divided into 3 groups: <ul style="list-style-type: none"> Group 1: standard care Group 2: Preoperative and postoperative administration of atenolol (up until 72 hours postoperatively) Group 3: Intraoperative administration of atenolol
Outcomes	Primary outcome: haemodynamic variables Secondary outcomes: myocardial infarction and ischaemia, stress hormone levels
Notes	Type of surgery: non-cardiac surgery (major abdominal surgery, hip replacement, intrathoracic surgery)

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not specified
Allocation concealment (selection bias)	Unclear risk	Not specified
Blinding of participants (performance bias) All outcomes	High risk	Open-label trial
Blinding of doctors/personnel (performance bias) All outcomes	High risk	Open-label trial
Blinding of outcome assessors (detection bias) All outcomes	High risk	Open-label trial
Incomplete outcome data (attrition bias) All outcomes	High risk	4 dropouts: 1 control participant who received beta-blockers and 3 participants in the treatment group (massive surgical bleeding, false anaesthetic agent, participant with pacemaker)—63 participants randomly assigned
Intention to treat analysis	High risk	Participants were not analysed as randomly assigned
Selective reporting (reporting bias)	Low risk	Not detected

Zaugg 1999 (Continued)

Other bias	Low risk	Not detected
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Abbreviations:

CABG: Coronary artery bypass graft.

CHF: Congestive heart failure.

CK-MB: Creatine kinase (MB isoenzyme).

DIPOM: Diabetic Postoperative Mortality and Morbidity.

ECG: Electrocardiogram.

IABP: Intra-aortic balloon pump.

ICU: Intensive care unit.

LOS: Length of stay

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
DECREASE-IV 2009	Allegations of fictitious data.
Klöter-Weber 1998	Subpopulation of Pfisterer 1997 .
Poldermans 1999	Credibility of data is uncertain.
Suttner 2009	Manuscript was retracted.

DATA AND ANALYSES
Comparison 1. Beta-blocker versus control (placebo or standard care)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—cardiac surgery	24	3783	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.52]
2 All-cause mortality (30 days)—non-cardiac surgery	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.57]
3 Long-term mortality—non-cardiac surgery	13	11413	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.31]
4 Death due to cardiac causes—cardiac surgery	4	320	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.40]
5 Death due to cardiac causes—non-cardiac surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
6 Acute myocardial infarction—cardiac surgery	22	3553	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.51]
7 Acute myocardial infarction—non-cardiac surgery	14	10958	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Myocardial ischaemia—cardiac surgery	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.05]
9 Myocardial ischaemia—non-cardiac surgery	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
10 Cerebrovascular events—cardiac surgery	4	1400	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.58, 4.02]
11 Cerebrovascular events—non-cardiac surgery	5	9150	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.71]
12 Ventricular arrhythmias—cardiac surgery	12	2292	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.24, 0.58]
13 Ventricular arrhythmias—non-cardiac surgery	5	476	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.31, 1.49]
14 Atrial fibrillation and flutter—cardiac surgery	36	5372	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.40, 0.57]
15 Atrial fibrillation and flutter—non-cardiac surgery	3	8510	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
16 All supraventricular arrhythmias—cardiac surgery	48	6420	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.36, 0.53]
17 All supraventricular arrhythmias—non-cardiac surgery	8	8744	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
18 Ventricular extrasystoles—cardiac surgery	5	462	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.08]
19 Ventricular extrasystoles—non-cardiac surgery	9	492	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.13, 0.37]
20 Bradycardia—cardiac surgery	8	660	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.97, 2.66]
21 Bradycardia—non-cardiac surgery	23	11033	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.48, 3.36]
22 Hypotension—cardiac surgery	6	558	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.67, 3.51]
23 Hypotension—non-cardiac surgery	22	10947	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.38, 1.64]
24 Congestive heart failure—cardiac surgery	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.34]
25 Congestive heart failure—non-cardiac surgery	5	9173	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26 Bronchospasm—cardiac surgery	3	196	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.31, 7.14]
27 Bronchospasm—non-cardiac surgery	8	1080	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.59]
28 Length of stay—cardiac surgery	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
29 Length of stay—non-cardiac surgery	3	551	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.75, 0.84]
30 Cost of care—cardiac surgery	3	1170	Mean Difference (IV, Random, 95% CI)	3968.25 [908.08, 7028.43]

Analysis 1.1. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 1 All-cause mortality (30 days)—cardiac surgery.

Analysis 1.2. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 2 All-cause mortality (30 days)—non-cardiac surgery.

Analysis 1.3. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 3 Long-term mortality—non-cardiac surgery.

Analysis 1.4. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 4 Death due to cardiac causes—cardiac surgery.

Analysis 1.5. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 5 Death due to cardiac causes—non-cardiac surgery.

Analysis 1.6. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 6 Acute myocardial infarction—cardiac surgery.

Analysis 1.7. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 7 Acute myocardial infarction—non-cardiac surgery.

Analysis 1.8. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 8 Myocardial ischaemia—cardiac surgery.

Analysis 1.9. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 9 Myocardial ischaemia—non-cardiac surgery.

Analysis 1.10. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 10 Cerebrovascular events—cardiac surgery.

Analysis 1.11. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 11 Cerebrovascular events—non-cardiac surgery.

Analysis 1.12. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 12 Ventricular arrhythmias—cardiac surgery.

Analysis 1.13. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 13 Ventricular arrhythmias—non-cardiac surgery.

Analysis 1.14. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 14 Atrial fibrillation and flutter—cardiac surgery.

Analysis 1.15. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 15 Atrial fibrillation and flutter—non-cardiac surgery.

Analysis 1.16. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 16 All supraventricular arrhythmias—cardiac surgery.

Analysis 1.17. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 17 All supraventricular arrhythmias—non-cardiac surgery.

Analysis 1.18. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 18 Ventricular extrasystoles—cardiac surgery.

Analysis 1.19. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 19 Ventricular extrasystoles—non-cardiac surgery.

Analysis 1.20. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 20 Bradycardia—cardiac surgery.

Analysis 1.21. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 21 Bradycardia—non-cardiac surgery.

Analysis 1.22. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 22 Hypotension—cardiac surgery.

Analysis 1.23. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 23 Hypotension—non-cardiac surgery.

Analysis 1.24. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 24 Congestive heart failure—cardiac surgery.

Analysis 1.25. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 25 Congestive heart failure—non-cardiac surgery.

Analysis 1.26. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 26 Bronchospasm—cardiac surgery.

Analysis 1.27. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 27 Bronchospasm—non-cardiac surgery.

Analysis 1.28. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 28 Length of stay—cardiac surgery. **Analysis 1.29. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 29 Length of stay—non-cardiac surgery.** **Analysis 1.30. Comparison 1 Beta-blocker versus control (placebo or standard care), Outcome 30 Cost of care—cardiac surgery.**

Comparison 2. Stratification placebo versus standard care

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—cardiac	24	3783	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.52]
1.1 Placebo	12	2221	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.27, 2.43]
1.2 Standard care	12	1562	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.26, 1.80]
2 All-cause mortality (30 days)—non-cardiac	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.57]
2.1 Placebo	9	10795	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [1.02, 1.62]
2.2 Standard care	4	618	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.31, 2.06]
3 Death due to cardiac causes—cardiac surgery	4	320	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.40]
3.1 Placebo	3	266	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.86]
3.2 Standard care	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.03, 14.05]
4 Death due to cardiac causes—non-cardiac surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
4.1 Placebo	3	9047	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.89, 1.74]
4.2 Standard care	1	400	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 75.42]
5 Acute myocardial infarction—cardiac surgery	22	3553	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.51]
5.1 Placebo	7	1737	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.71, 2.69]
5.2 Standard care	15	1816	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.57, 1.43]
6 Acute myocardial infarction—non-cardiac surgery	14	10958	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
6.1 Placebo	9	10209	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.60, 0.87]
6.2 Standard care	5	749	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.15, 2.60]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7 Myocardial ischaemia—cardiac surgery	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.05]
7.1 Placebo	3	98	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.31, 2.10]
7.2 Standard care	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.09, 0.96]
8 Myocardial ischaemia—non-cardiac surgery	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
8.1 Placebo	9	645	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.86]
8.2 Standard care	5	333	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.07, 0.48]
9 Cerebrovascular events—non-cardiac surgery	5	9150	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.71]
9.1 Placebo	3	8648	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.14, 3.82]
9.2 Standard care	2	502	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.09, 1.67]
10 Ventricular arrhythmias—cardiac surgery	12	2292	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.24, 0.58]
10.1 Placebo	7	1653	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.25, 0.68]
10.2 Standard care	5	639	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.12, 0.75]
11 Atrial fibrillation—cardiac surgery	36	5372	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.40, 0.57]
11.1 Placebo	15	2959	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.51, 0.76]
11.2 Standard care	21	2413	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.32, 0.46]
12 Atrial fibrillation—non-cardiac surgery	3	8510	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
12.1 Placebo	2	8450	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.58, 0.98]
12.2 Standard care	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.98]
13 All supraventricular arrhythmias—cardiac surgery	48	6420	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.36, 0.53]
13.1 Placebo	20	3401	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.48, 0.76]
13.2 Standard care	28	3019	Risk Ratio (M-H, Random, 95% CI)	0.36 [0.31, 0.43]
14 All supraventricular arrhythmias—non-cardiac surgery	8	8744	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
14.1 Placebo	7	8684	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.59, 0.96]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.2 Standard care	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.98]
15 Ventricular extrasystoles—non-cardiac surgery	9	492	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.13, 0.37]
15.1 Placebo	8	364	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.13, 0.39]
15.2 Standard care	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.05, 0.69]
16 Bradycardia—cardiac surgery	8	660	Risk Ratio (M-H, Fixed, 95% CI)	1.61 [0.97, 2.66]
16.1 Placebo	6	454	Risk Ratio (M-H, Fixed, 95% CI)	1.89 [0.99, 3.63]
16.2 Standard care	2	206	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.55, 2.72]
17 Bradycardia—non-cardiac surgery	23	11033	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.48, 3.36]
17.1 Placebo	19	10419	Risk Ratio (M-H, Random, 95% CI)	2.13 [1.31, 3.46]
17.2 Standard care	4	614	Risk Ratio (M-H, Random, 95% CI)	2.45 [1.34, 4.48]
18 Hypotension—cardiac surgery	6	558	Risk Ratio (M-H, Fixed, 95% CI)	1.54 [0.67, 3.51]
18.1 Placebo	5	516	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [0.54, 3.14]
18.2 Standard care	1	42	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [0.28, 107.62]
19 Hypotension—non-cardiac surgery	22	10947	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.38, 1.64]
19.1 Placebo	18	10333	Risk Ratio (M-H, Fixed, 95% CI)	1.51 [1.38, 1.65]
19.2 Standard care	4	614	Risk Ratio (M-H, Fixed, 95% CI)	1.44 [1.11, 1.88]
20 Bronchospasm—cardiac surgery	3	196	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.31, 7.14]
20.1 Placebo	2	111	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.14, 6.67]
20.2 Standard care	1	85	Risk Ratio (M-H, Fixed, 95% CI)	3.87 [0.16, 92.32]
21 Bronchospasm—non-cardiac surgery	8	1080	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.59]
21.1 Placebo	7	1024	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.57, 1.67]
21.2 Standard care	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.85]
22 Length of stay—cardiac surgery	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
22.1 Placebo	9	1902	Mean Difference (IV, Random, 95% CI)	-0.60 [-1.11, -0.09]
22.2 Standard care	5	548	Mean Difference (IV, Random, 95% CI)	-0.51 [-1.09, 0.06]
23 Length of stay—non-cardiac surgery	3	551	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.75, 0.84]
23.1 Placebo	2	151	Mean Difference (IV, Random, 95% CI)	-4.58 [-16.07, 6.91]
23.2 Standard care	1	400	Mean Difference (IV, Random, 95% CI)	-0.20 [-2.23, 1.83]

Analysis 2.1. Comparison 2 Stratification placebo versus standard care, Outcome 1 All-cause mortality (30 days)—cardiac.

Analysis 2.2. Comparison 2 Stratification placebo versus standard care, Outcome 2 All-cause mortality (30 days)—non-cardiac.

Analysis 2.3. Comparison 2 Stratification placebo versus standard care, Outcome 3 Death due to cardiac causes—cardiac surgery.

Analysis 2.4. Comparison 2 Stratification placebo versus standard care, Outcome 4 Death due to cardiac causes—non-cardiac surgery.

Analysis 2.5. Comparison 2 Stratification placebo versus standard care, Outcome 5 Acute myocardial infarction—cardiac surgery.

Analysis 2.6. Comparison 2 Stratification placebo versus standard care, Outcome 6 Acute myocardial infarction—non-cardiac surgery. **Analysis 2.7. Comparison 2 Stratification placebo versus standard care, Outcome 7 Myocardial ischaemia—cardiac surgery.**

Analysis 2.8. Comparison 2 Stratification placebo versus standard care, Outcome 8 Myocardial ischaemia—non-cardiac surgery.

Analysis 2.9. Comparison 2 Stratification placebo versus standard care, Outcome 9 Cerebrovascular events—non-cardiac surgery.

Analysis 2.10. Comparison 2 Stratification placebo versus standard care, Outcome 10 Ventricular arrhythmias—cardiac surgery.

Analysis 2.11. Comparison 2 Stratification placebo versus standard care, Outcome 11 Atrial fibrillation—cardiac surgery.

Analysis 2.12. Comparison 2 Stratification placebo versus standard care, Outcome 12 Atrial fibrillation—non-cardiac surgery.

Analysis 2.13. Comparison 2 Stratification placebo versus standard care, Outcome 13 All supraventricular arrhythmias—cardiac surgery.

Analysis 2.14. Comparison 2 Stratification placebo versus standard care, Outcome 14 All supraventricular arrhythmias—non-cardiac surgery.

Analysis 2.15. Comparison 2 Stratification placebo versus standard care, Outcome 15 Ventricular extrasystoles—non-cardiac surgery.

Analysis 2.16. Comparison 2 Stratification placebo versus standard care, Outcome 16 Bradycardia—cardiac surgery.

Analysis 2.17. Comparison 2 Stratification placebo versus standard care, Outcome 17 Bradycardia—non-cardiac surgery.

Analysis 2.18. Comparison 2 Stratification placebo versus standard care, Outcome 18 Hypotension—cardiac surgery.

Analysis 2.19. Comparison 2 Stratification placebo versus standard care, Outcome 19 Hypotension—non-cardiac surgery.

Analysis 2.20. Comparison 2 Stratification placebo versus standard care, Outcome 20 Bronchospasm—cardiac surgery.

Analysis 2.21. Comparison 2 Stratification placebo versus standard care, Outcome 21 Bronchospasm—non-cardiac surgery.

Analysis 2.22. Comparison 2 Stratification placebo versus standard care, Outcome 22 Length of stay—cardiac surgery.

Analysis 2.23. Comparison 2 Stratification placebo versus standard care, Outcome 23 Length of stay—non-cardiac surgery.

Comparison 3. Stratification for start of beta-blocker therapy

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—cardiac surgery	24	3783	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.35, 1.52]
1.1 Before surgery	7	790	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.14, 1.68]
1.2 During surgery	3	271	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.13, 2.66]
1.3 After surgery	14	2722	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.38, 4.12]
2 All-cause mortality (30 days)—non-cardiac surgery	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.57]
2.1 Before surgery	8	10666	Risk Ratio (M-H, Fixed, 95% CI)	1.30 [1.03, 1.63]
2.2 During surgery	5	747	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.18, 1.62]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3 Death due to cardiac causes—cardiac surgery	4	320	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.40]
3.1 Before surgery	2	139	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.03, 14.05]
3.2 During surgery	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
3.3 After surgery	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.44]
4 Death due to cardiac causes—non-cardiac surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
4.1 Before surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
4.2 During surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Long-term mortality—non-cardiac surgery	13	11413	Risk Ratio (M-H, Random, 95% CI)	0.99 [0.74, 1.31]
5.1 Before surgery	8	10666	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.76, 1.40]
5.2 During surgery	5	747	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.27, 1.45]
5.3 After surgery	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Acute myocardial infarction—cardiac surgery	22	3553	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.71, 1.51]
6.1 Before surgery	5	450	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.34, 1.91]
6.2 During surgery	2	171	Risk Ratio (M-H, Fixed, 95% CI)	1.72 [0.23, 12.65]
6.3 After surgery	15	2932	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.70, 1.66]
7 Acute myocardial infarction—non-cardiac surgery	14	10958	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.61, 0.88]
7.1 Before surgery	9	10730	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.62, 0.89]
7.2 During surgery	4	202	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.04, 1.99]
7.3 After surgery	1	26	Risk Ratio (M-H, Random, 95% CI)	0.25 [0.01, 5.62]
8 Myocardial ischaemia—cardiac surgery	4	166	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.25, 1.05]
8.1 Before surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.2 During surgery	3	98	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.31, 2.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.3 After surgery	1	68	Risk Ratio (M-H, Fixed, 95% CI)	0.30 [0.09, 0.96]
9 Myocardial ischaemia—non-cardiac surgery	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
9.1 Before surgery	4	524	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.23, 1.01]
9.2 During surgery	9	428	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.17, 0.95]
9.3 After surgery	1	26	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.21, 1.02]
10 Cerebrovascular events—cardiac surgery	4	1400	Risk Ratio (M-H, Fixed, 95% CI)	1.52 [0.58, 4.02]
10.1 Before surgery	1	190	Risk Ratio (M-H, Fixed, 95% CI)	0.17 [0.01, 4.23]
10.2 During surgery	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.67]
10.3 After surgery	2	1070	Risk Ratio (M-H, Fixed, 95% CI)	2.43 [0.70, 8.38]
11 Ventricular arrhythmias—cardiac surgery	12	2292	Risk Ratio (M-H, Random, 95% CI)	0.40 [0.25, 0.63]
11.1 Before surgery	5	687	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.31, 1.26]
11.2 During surgery	2	88	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.84]
11.3 After surgery	5	1517	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.11, 0.67]
12 Ventricular arrhythmias—non-cardiac surgery	5	476	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.19]
12.1 Before surgery	4	431	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.55, 1.86]
12.2 During surgery	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.09, 0.70]
12.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Atrial fibrillation—cardiac surgery	36	5372	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.40, 0.57]
13.1 Before surgery	7	992	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.39, 0.65]
13.2 During surgery	5	464	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.31, 0.78]
13.3 After surgery	24	3916	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.37, 0.59]
14 Atrial fibrillation and flutter—non-cardiac surgery	3	8510	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
14.1 Before surgery	2	8450	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.58, 0.98]
14.2 During surgery	1	60	Risk Ratio (M-H, Fixed, 95% CI)	0.11 [0.01, 1.98]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
14.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15 All supraventricular arrhythmias—cardiac surgery	48	6420	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.36, 0.53]
15.1 Before surgery	10	1132	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.39, 0.61]
15.2 During surgery	7	600	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.32, 0.82]
15.3 After surgery	31	4688	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.55]
16 All supraventricular arrhythmias—non-cardiac surgery	8	8744	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
16.1 Before surgery	4	8571	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.94]
16.2 During surgery	4	173	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.32, 2.17]
16.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Ventricular extrasystoles—cardiac surgery	5	462	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.08]
17.1 Before surgery	1	36	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.02, 9.48]
17.2 During surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17.3 After surgery	4	426	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.12]
18 Ventricular extrasystoles—non-cardiac surgery	9	492	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.13, 0.37]
18.1 Before surgery	3	241	Risk Ratio (M-H, Fixed, 95% CI)	0.12 [0.04, 0.32]
18.2 During surgery	6	251	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.18, 0.59]
18.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
19 Bradycardia—cardiac surgery	8	660	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.84, 2.31]
19.1 Before surgery	3	325	Risk Ratio (M-H, Random, 95% CI)	2.06 [0.63, 6.77]
19.2 During surgery	4	265	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.58, 2.77]
19.3 After surgery	1	70	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.91]
20 Bradycardia—non-cardiac surgery	23	11033	Risk Ratio (M-H, Fixed, 95% CI)	2.49 [2.15, 2.88]
20.1 Before surgery	13	10063	Risk Ratio (M-H, Fixed, 95% CI)	2.60 [2.23, 3.04]
20.2 During surgery	10	970	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [1.01, 2.52]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
21 Hypotension—cardiac surgery	6	558	Risk Ratio (M-H, Random, 95% CI)	1.48 [0.60, 3.69]
21.1 Before surgery	2	275	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.06, 8.97]
21.2 During surgery	1	30	Risk Ratio (M-H, Random, 95% CI)	3.0 [0.35, 25.68]
21.3 After surgery	3	253	Risk Ratio (M-H, Random, 95% CI)	1.65 [0.50, 5.38]
22 Hypotension—non-cardiac surgery	22	10947	Risk Ratio (M-H, Random, 95% CI)	1.40 [1.29, 1.53]
22.1 Before surgery	11	9917	Risk Ratio (M-H, Random, 95% CI)	1.41 [1.26, 1.58]
22.2 During surgery	11	1030	Risk Ratio (M-H, Random, 95% CI)	1.38 [1.04, 1.83]
22.3 After surgery	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
23 Congestive heart failure—cardiac surgery	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.34]
23.1 Before surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
23.2 During surgery	2	241	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.69]
23.3 After surgery	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.91]
24 Congestive heart failure—non-cardiac surgery	5	9173	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]
24.1 Before surgery	5	9173	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]
24.2 During surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Bronchospasm—non-cardiac surgery	8	1080	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.59]
25.1 Before surgery	3	339	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.53, 1.73]
25.2 During surgery	5	741	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.28, 2.73]
25.3 After surgery	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
26 Length of stay—cardiac surgery	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
26.1 Before surgery	3	530	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.39, 0.02]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
26.2 During surgery	5	372	Mean Difference (IV, Random, 95% CI)	-0.71 [-0.83, -0.59]
26.3 After surgery	6	1548	Mean Difference (IV, Random, 95% CI)	-0.33 [-0.87, 0.22]
27 Length of stay—non-cardiac surgery	3	551	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.75, 0.84]
27.1 Before surgery	2	491	Mean Difference (IV, Random, 95% CI)	-4.56 [-16.30, 7.19]
27.2 During surgery	1	60	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.58, -0.22]
27.3 After surgery	0	0	Mean Difference (IV, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 3.1. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 1 All-cause mortality (30 days)—cardiac surgery.

Analysis 3.2. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 2 All-cause mortality (30 days)—non-cardiac surgery.

Analysis 3.3. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 3 Death due to cardiac causes—cardiac surgery.

Analysis 3.4. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 4 Death due to cardiac causes—non-cardiac surgery.

Analysis 3.5. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 5 Long-term mortality—non-cardiac surgery.

Analysis 3.6. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 6 Acute myocardial infarction—cardiac surgery.

Analysis 3.7. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 7 Acute myocardial infarction—non-cardiac surgery.

Analysis 3.8. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 8 Myocardial ischaemia—cardiac surgery.

Analysis 3.9. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 9 Myocardial ischaemia—non-cardiac surgery.

Analysis 3.10. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 10 Cerebrovascular events—cardiac surgery.

Analysis 3.11. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 11 Ventricular arrhythmias—cardiac surgery.

Analysis 3.12. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 12 Ventricular arrhythmias—non-cardiac surgery.

Analysis 3.13. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 13 Atrial fibrillation—cardiac surgery.

Analysis 3.14. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 14 Atrial fibrillation and flutter—non-cardiac surgery.

Analysis 3.15. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 15 All supraventricular arrhythmias—cardiac surgery.

Analysis 3.16. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 16 All supraventricular arrhythmias—non-cardiac surgery.

Analysis 3.17. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 17 Ventricular extrasystoles—cardiac surgery.

Analysis 3.18. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 18 Ventricular extrasystoles—non-cardiac surgery.

Analysis 3.19. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 19 Bradycardia—cardiac surgery.

Analysis 3.20. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 20 Bradycardia—non-cardiac surgery.

Analysis 3.21. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 21 Hypotension—cardiac surgery.

Analysis 3.22. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 22 Hypotension—non-cardiac surgery.

Analysis 3.23. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 23 Congestive heart failure—cardiac surgery.

Analysis 3.24. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 24 Congestive heart failure—non-cardiac surgery.

Analysis 3.25. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 25 Bronchospasm—non-cardiac surgery.

Analysis 3.26. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 26 Length of stay—cardiac surgery. **Analysis 3.27. Comparison 3 Stratification for start of beta-blocker therapy, Outcome 27 Length of stay—non-cardiac surgery.**

Comparison 4. Stratification for risk status of non-cardiac surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—non-cardiac	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.57]
1.1 Low and medium risk	6	10367	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.04, 1.66]
1.2 High risk	7	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.41, 1.66]
2 Long-term mortality—non-cardiac surgery	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.30]
2.1 Low and medium risk	6	10367	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.98, 1.45]
2.2 High risk	7	1046	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.39, 0.98]
3 Death due to cardiac causes—non-cardiac surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
3.1 Low and medium risk	2	8751	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.93, 1.84]
3.2 High risk	2	696	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.07, 2.93]
4 Acute myocardial infarction—non-cardiac surgery	14	10958	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
4.1 Low and medium risk	8	10206	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.59, 0.87]
4.2 High risk	6	752	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.49, 1.31]
5 Myocardial ischaemia—non-cardiac surgery	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 Low and medium risk	8	610	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.13, 1.19]
5.2 High risk	6	368	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.39, 0.93]
6 Cerebrovascular events—non-cardiac surgery	5	9150	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.71]
6.1 Low and medium risk	4	9053	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.91, 2.69]
6.2 High risk	1	97	Risk Ratio (M-H, Fixed, 95% CI)	2.5 [0.10, 59.88]
7 Ventricular arrhythmias—non-cardiac surgery	5	476	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.19]
7.1 Low and medium risk	2	245	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.14, 0.82]
7.2 High risk	3	231	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.56, 2.07]
8 Atrial fibrillation—non-cardiac surgery	3	8510	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.56, 0.95]
8.1 Low and medium risk	1	8351	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.58, 0.99]
8.2 High risk	2	159	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.11, 1.23]
9 All supraventricular arrhythmias—non-cardiac surgery	8	8744	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.57, 0.94]
9.1 Low and medium risk	5	8550	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.59, 0.99]
9.2 High risk	3	194	Risk Ratio (M-H, Fixed, 95% CI)	0.48 [0.21, 1.07]
10 Bradycardia—non-cardiac surgery	23	11033	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.48, 3.36]
10.1 Low and medium risk	14	9936	Risk Ratio (M-H, Random, 95% CI)	1.88 [1.04, 3.40]
10.2 High risk	9	1097	Risk Ratio (M-H, Random, 95% CI)	3.16 [2.33, 4.26]
11 Hypotension—non-cardiac surgery	22	10947	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.38, 1.64]
11.1 Low and medium risk	13	9850	Risk Ratio (M-H, Fixed, 95% CI)	1.58 [1.42, 1.76]
11.2 High risk	9	1097	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [1.15, 1.49]
12 Congestive heart failure—non-cardiac surgery	5	9173	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]
12.1 Low and medium risk	2	8378	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.88, 1.44]
12.2 High risk	3	795	Risk Ratio (M-H, Fixed, 95% CI)	1.60 [0.84, 3.05]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13 Bronchospasm—non-cardiac surgery	8	1080	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.59]
13.1 Low and medium risk	5	725	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.33, 3.24]
13.2 High risk	3	355	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.50, 1.64]
14 Length of stay—non-cardiac surgery	3	551	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.75, 0.84]
14.1 Low and medium risk	2	460	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.58, -0.22]
14.2 High risk	1	91	Mean Difference (IV, Random, 95% CI)	-12.8 [-26.67, 1.07]

Analysis 4.1. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 1 All-cause mortality (30 days)—non-cardiac.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: $Z=2(P=0.05)$					
Test for subgroup differences: $\text{Chi}^2=1.52, \text{df}=1 (P=0.22), I^2=34.05\%$					
Favours beta-blocker 0.01 0.1 1 10 100 Favours control					

Analysis 4.2. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 2 Long-term mortality—non-cardiac surgery.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 Low and medium risk					
Miller 1990	0/30	0/15			Not estimable
Miller 1991	0/368	0/180			Not estimable
DIPOM - Juul 2006	74/462	72/459		33.52%	1.02[0.76,1.38]
POISE 2008	129/4174	97/4177		44.99%	1.33[1.03,1.73]
Yang 2008	0/51	1/51		0.7%	0.33[0.01,8]
Marwick 2009	6/197	5/203		2.29%	1.24[0.38,3.99]
Subtotal (95% CI)	5282	5085		81.49%	1.19[0.98,1.45]
Total events: 209 (Experimental), 175 (Control)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=2.35, \text{df}=3(P=0.5); I^2=0\%$					
Test for overall effect: $Z=1.79(P=0.07)$					
4.2.2 High risk					
Wallace 1998	13/99	23/101		10.57%	0.58[0.31,1.07]
Bayliff 1999	2/49	1/50		0.46%	2.04[0.19,21.79]
POBBLE 2005	3/53	1/44		0.51%	2.49[0.27,23.11]
Yang 2006	0/246	4/250		2.07%	0.11[0.01,2.09]
Neary 2006	5/18	8/20		3.52%	0.69[0.28,1.74]
Lai 2006	0/30	0/30			Not estimable
Kawaguchi 2010	1/28	3/28		1.39%	0.33[0.04,3.01]
Subtotal (95% CI)	523	523		18.51%	0.62[0.39,0.98]
Total events: 24 (Experimental), 40 (Control)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=4.2, \text{df}=5(P=0.52); I^2=0\%$					
Test for overall effect: $Z=2.05(P=0.04)$					
Total (95% CI)	5805	5608		100%	1.09[0.91,1.3]
Total events: 233 (Experimental), 215 (Control)					
Heterogeneity: $\text{Tau}^2=0; \text{Chi}^2=12.22, \text{df}=9(P=0.2); I^2=26.36\%$					
Test for overall effect: $Z=0.91(P=0.36)$					
Test for subgroup differences: $\text{Chi}^2=6.67, \text{df}=1 (P=0.01), I^2=85\%$					
Favours beta-blocker 0.01 0.1 1 10 100 Favours control					

Analysis 4.3. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 3 Death due to cardiac causes—non-cardiac surgery.

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.3.1 Low and medium risk					
Favours beta-blocker 0.01 0.1 1 10 100 Favours control

Analysis 4.4. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 4 Acute myocardial infarction—non-cardiac surgery.

Analysis 4.5. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 5 Myocardial ischaemia—non-cardiac surgery.

Analysis 4.6. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 6 Cerebrovascular events—non-cardiac surgery.

Analysis 4.7. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 7 Ventricular arrhythmias—non-cardiac surgery.

Analysis 4.8. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 8 Atrial fibrillation—non-cardiac surgery.

Analysis 4.9. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 9 All supraventricular arrhythmias—non-cardiac surgery.

Analysis 4.10. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 10 Bradycardia—non-cardiac surgery.

Analysis 4.11. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 11 Hypotension—non-cardiac surgery.

Analysis 4.12. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 12 Congestive heart failure—non-cardiac surgery.

Analysis 4.13. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 13 Bronchospasm—non-cardiac surgery. **Analysis 4.14. Comparison 4 Stratification for risk status of non-cardiac surgery, Outcome 14 Length of stay—non-cardiac surgery.**

Comparison 5. Stratification for type of beta-blocker

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—cardiac	23	3655	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.40, 1.80]
1.1 Metoprolol	5	1516	Risk Ratio (M-H, Fixed, 95% CI)	2.38 [0.36, 15.85]
1.2 Propranolol	8	768	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.13, 1.92]
1.3 Sotalol	8	1092	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.08, 4.80]
1.4 Esmolol	1	30	Risk Ratio (M-H, Fixed, 95% CI)	2.65 [0.12, 60.21]
1.5 Timolol	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.44]
1.6 Landiolol	2	208	Risk Ratio (M-H, Fixed, 95% CI)	0.43 [0.06, 2.85]
2 All-cause mortality (30 days)—non-cardiac	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.00, 1.57]
2.1 Metoprolol	6	10027	Risk Ratio (M-H, Fixed, 95% CI)	1.28 [1.01, 1.62]
2.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.19, 21.79]
2.3 Atenolol	2	238	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.40, 2.87]
2.4 Esmolol	2	593	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2.5 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.38, 3.99]
2.6 Landiolol	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.01]
3 Long-term mortality—non-cardiac surgery	13	11413	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.91, 1.30]
3.1 Metoprolol	6	10027	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.97, 1.42]
3.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.19, 21.79]
3.3 Atenolol	2	238	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.36, 1.02]
3.4 Esmolol	2	593	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.5 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.38, 3.99]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.6 Landiolol	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.04, 3.01]
4 Death due to cardiac causes—cardiac surgery	4	320	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.16, 4.40]
4.1 Propranolol	1	54	Risk Ratio (M-H, Fixed, 95% CI)	0.6 [0.03, 14.05]
4.2 Sotalol	1	85	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 Timolol	1	41	Risk Ratio (M-H, Fixed, 95% CI)	2.86 [0.12, 66.44]
4.4 Landiolol	1	140	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 8.04]
5 Death due to cardiac causes—non-cardiac surgery	4	9447	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.91, 1.75]
5.1 Metoprolol	2	8847	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.91, 1.78]
5.2 Atenolol	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.05, 5.54]
5.3 Esmolol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.4 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	3.09 [0.13, 75.42]
6 Acute myocardial infarction—cardiac surgery	21	3310	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.67, 1.48]
6.1 Metoprolol	2	1200	Risk Ratio (M-H, Fixed, 95% CI)	2.0 [0.91, 4.40]
6.2 Propranolol	11	1088	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.41, 1.21]
6.3 Sotalol	4	643	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.08, 4.16]
6.4 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.32, 5.53]
6.5 Acebutolol	1	100	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.55]
6.6 Nadolol	1	141	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.02, 8.87]
6.7 Landiolol	1	68	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.15]
7 Acute myocardial infarction—non-cardiac surgery	13	10830	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.87]
7.1 Metoprolol	7	10062	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.61, 0.88]
7.2 Atenolol	3	297	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.11, 0.99]
7.3 Esmolol	2	71	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.01, 5.62]
7.4 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.47, 2.24]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Myocardial ischaemia—non-cardiac surgery	13	850	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.48, 0.83]
8.1 Metoprolol	4	225	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.39, 1.06]
8.2 Propranolol	1	99	Risk Ratio (M-H, Random, 95% CI)	0.34 [0.04, 3.16]
8.3 Atenolol	2	259	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.47, 0.96]
8.4 Esmolol	5	211	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.16, 2.42]
8.5 Landiolol	1	56	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.01, 7.85]
9 Cerebrovascular events—cardiac surgery	4	1465	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.56, 3.60]
9.1 Metoprolol	2	1127	Risk Ratio (M-H, Fixed, 95% CI)	1.68 [0.52, 5.40]
9.2 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.22]
9.3 Landiolol	1	140	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.06, 15.67]
9.4 Sotalol	1	128	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.01, 8.28]
10 Cerebrovascular events—non-cardiac surgery	5	9150	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.71]
10.1 Metoprolol	3	8550	Risk Ratio (M-H, Fixed, 95% CI)	1.69 [0.93, 3.08]
10.2 Atenolol	1	200	Risk Ratio (M-H, Fixed, 95% CI)	4.08 [0.46, 35.87]
10.3 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.10, 2.78]
11 Ventricular arrhythmias—cardiac surgery	12	2357	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.65]
11.1 Metoprolol	2	1127	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.07, 1.07]
11.2 Propranolol	5	588	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.22, 0.79]
11.3 Sotalol	3	484	Risk Ratio (M-H, Random, 95% CI)	2.09 [0.46, 9.55]
11.4 Atenolol	1	70	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
11.5 Esmolol	2	88	Risk Ratio (M-H, Random, 95% CI)	0.26 [0.08, 0.84]
12 Ventricular arrhythmias—non-cardiac surgery	5	476	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.19]
12.1 Metoprolol	2	132	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.64, 2.50]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.20 [0.01, 4.14]
12.3 Atenolol	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.98]
12.4 Esmolol	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.09, 0.70]
13 Atrial fibrillation—cardiac surgery	35	5244	Risk Ratio (M-H, Random, 95% CI)	0.49 [0.41, 0.58]
13.1 Metoprolol	7	1969	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.56, 0.83]
13.2 Propranolol	9	892	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.34, 0.82]
13.3 Sotalol	9	1347	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.57]
13.4 Atenolol	1	60	Risk Ratio (M-H, Random, 95% CI)	0.10 [0.01, 0.73]
13.5 Esmolol	2	87	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.46, 1.75]
13.6 Acebutolol	2	171	Risk Ratio (M-H, Random, 95% CI)	0.09 [0.01, 0.66]
13.7 Landiolol	5	545	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.27, 0.54]
13.8 Timolol	2	173	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.25, 1.25]
14 Atrial fibrillation and flutter—non-cardiac surgery	3	8510	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.96]
14.1 Metoprolol	2	8411	Risk Ratio (M-H, Random, 95% CI)	0.50 [0.11, 2.37]
14.2 Propranolol	1	99	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.15, 2.42]
14.3 Esmolol	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
15 All supraventricular arrhythmias—cardiac surgery	47	6292	Risk Ratio (M-H, Random, 95% CI)	0.44 [0.37, 0.54]
15.1 Metoprolol	9	2241	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.43, 0.80]
15.2 Propranolol	16	1421	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.34, 0.61]
15.3 Sotalol	10	1383	Risk Ratio (M-H, Random, 95% CI)	0.46 [0.37, 0.56]
15.4 Atenolol	2	130	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.07, 0.76]
15.5 Timolol	2	173	Risk Ratio (M-H, Random, 95% CI)	0.64 [0.08, 5.08]
15.6 Esmolol	2	87	Risk Ratio (M-H, Random, 95% CI)	0.90 [0.46, 1.75]
15.7 Nadolol	1	141	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.09, 0.42]
15.8 Landiolol	5	545	Risk Ratio (M-H, Random, 95% CI)	0.38 [0.27, 0.54]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
15.9 Acebutolol	2	171	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.01, 2.39]
16 All supraventricular arrhythmias—non-cardiac surgery	8	8744	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.58, 0.95]
16.1 Metoprolol	4	8484	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.57, 0.96]
16.2 Propranolol	1	99	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.14, 1.93]
16.3 Esmolol	2	75	Risk Ratio (M-H, Random, 95% CI)	2.89 [0.53, 15.81]
16.4 Nadolol	1	86	Risk Ratio (M-H, Random, 95% CI)	0.20 [0.03, 1.60]
17 Ventricular extrasystoles—cardiac surgery	5	462	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.31, 1.08]
17.1 Propranolol	4	391	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.27, 1.87]
17.2 Acebutolol	1	71	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.21, 1.11]
18 Ventricular extrasystoles—non-cardiac surgery	8	364	Risk Ratio (M-H, Fixed, 95% CI)	0.23 [0.13, 0.39]
18.1 Metoprolol	3	125	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.14, 0.80]
18.2 Esmolol	3	123	Risk Ratio (M-H, Fixed, 95% CI)	0.31 [0.14, 0.69]
18.3 Labetalol	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.03, 2.44]
18.4 Nadolol	1	86	Risk Ratio (M-H, Fixed, 95% CI)	0.05 [0.01, 0.39]
19 Bradycardia—cardiac surgery	8	725	Risk Ratio (M-H, Fixed, 95% CI)	1.78 [1.11, 2.83]
19.1 Propranolol	2	120	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.56, 2.65]
19.2 Sotalol	2	213	Risk Ratio (M-H, Fixed, 95% CI)	3.98 [1.02, 15.55]
19.3 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.91]
19.4 Esmolol	2	59	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 68.26]
19.5 Landiolol	1	136	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.48, 2.56]
19.6 Metoprolol	1	127	Risk Ratio (M-H, Fixed, 95% CI)	5.24 [1.20, 22.98]
20 Bradycardia—non-cardiac surgery	22	10905	Risk Ratio (M-H, Random, 95% CI)	2.14 [1.42, 3.22]
20.1 Metoprolol	8	9136	Risk Ratio (M-H, Random, 95% CI)	2.88 [2.40, 3.45]
20.2 Propranolol	2	159	Risk Ratio (M-H, Random, 95% CI)	5.89 [1.60, 21.64]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
20.3 Atenolol	2	244	Risk Ratio (M-H, Random, 95% CI)	1.47 [0.50, 4.31]
20.4 Esmolol	6	794	Risk Ratio (M-H, Random, 95% CI)	0.74 [0.30, 1.82]
20.5 Labetalol	1	30	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
20.6 Landiolol	1	56	Risk Ratio (M-H, Random, 95% CI)	3.2 [1.36, 7.54]
20.7 Bisoprolol	1	400	Risk Ratio (M-H, Random, 95% CI)	1.90 [1.00, 3.63]
20.8 Nadolol	1	86	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.73, 1.21]
21 Hypotension—cardiac surgery	6	623	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.62, 2.97]
21.1 Propranolol	1	42	Risk Ratio (M-H, Fixed, 95% CI)	5.48 [0.28, 107.62]
21.2 Sotalol	2	213	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.19, 5.96]
21.3 Esmolol	1	30	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.35, 25.68]
21.4 Nadolol	1	141	Risk Ratio (M-H, Fixed, 95% CI)	1.66 [0.29, 9.61]
21.5 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.15, 6.71]
21.6 Metoprolol	1	127	Risk Ratio (M-H, Fixed, 95% CI)	0.21 [0.01, 4.28]
22 Hypotension—non-cardiac surgery	21	10819	Risk Ratio (M-H, Fixed, 95% CI)	1.50 [1.38, 1.63]
22.1 Metoprolol	8	9136	Risk Ratio (M-H, Fixed, 95% CI)	1.48 [1.34, 1.63]
22.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.09, 3.26]
22.3 Atenolol	2	244	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.58, 2.44]
22.4 Esmolol	7	854	Risk Ratio (M-H, Fixed, 95% CI)	1.83 [1.29, 2.58]
22.5 Labetalol	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
22.6 Bisoprolol	1	400	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.05, 2.31]
22.7 Landiolol	1	56	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.88, 1.49]
23 Congestive heart failure—cardiac surgery	3	311	Risk Ratio (M-H, Fixed, 95% CI)	0.22 [0.04, 1.34]
23.1 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.91]
23.2 Landiolol	2	241	Risk Ratio (M-H, Fixed, 95% CI)	0.19 [0.02, 1.69]
24 Congestive heart failure—non-cardiac surgery	5	9173	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.94, 1.48]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
24.1 Metoprolol	3	8874	Risk Ratio (M-H, Fixed, 95% CI)	1.14 [0.90, 1.45]
24.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	2.04 [0.66, 6.34]
24.3 Atenolol	1	200	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.51, 3.38]
24.4 Esmolol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
24.5 Bisoprolol	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
25 Bronchospasm—cardiac surgery	3	196	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.31, 7.14]
25.1 Propranolol	1	85	Risk Ratio (M-H, Fixed, 95% CI)	3.87 [0.16, 92.32]
25.2 Atenolol	1	70	Risk Ratio (M-H, Fixed, 95% CI)	3.0 [0.13, 71.22]
25.3 Timolol	1	41	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.38]
26 Bronchospasm—non-cardiac surgery	8	1080	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.59]
26.1 Metoprolol	1	40	Risk Ratio (M-H, Fixed, 95% CI)	1.0 [0.07, 14.90]
26.2 Propranolol	1	99	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.41, 1.45]
26.3 Atenolol	1	200	Risk Ratio (M-H, Fixed, 95% CI)	7.14 [0.37, 136.46]
26.4 Esmolol	3	655	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.30, 5.45]
26.5 Labetalol	1	30	Risk Ratio (M-H, Fixed, 95% CI)	0.5 [0.03, 7.19]
26.6 Landiolol	1	56	Risk Ratio (M-H, Fixed, 95% CI)	0.33 [0.01, 7.85]
27 Length of stay—cardiac surgery	12	2159	Mean Difference (IV, Random, 95% CI)	-0.52 [-0.89, -0.16]
27.1 Propranolol	1	131	Mean Difference (IV, Random, 95% CI)	0.0 [-0.91, 0.91]
27.2 Metoprolol	3	1272	Mean Difference (IV, Random, 95% CI)	-0.58 [-1.30, 0.15]
27.3 Sotalol	5	557	Mean Difference (IV, Random, 95% CI)	-0.39 [-0.81, 0.04]
27.4 Esmolol	2	59	Mean Difference (IV, Random, 95% CI)	-0.65 [-1.88, 0.58]
27.5 Landiolol	1	140	Mean Difference (IV, Random, 95% CI)	-2.80 [-4.92, -0.68]
28 Length of stay—non-cardiac surgery	3	551	Mean Difference (IV, Random, 95% CI)	-0.45 [-1.75, 0.84]
28.1 Bisoprolol	1	400	Mean Difference (IV, Random, 95% CI)	-0.20 [-2.23, 1.83]
28.2 Metoprolol	1	91	Mean Difference (IV, Random, 95% CI)	-12.8 [-26.67, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
28.3 Esmolol	1	60	Mean Difference (IV, Random, 95% CI)	-0.40 [-0.58, -0.22]

Analysis 5.1. Comparison 5 Stratification for type of beta-blocker, Outcome 1 All-cause mortality (30 days)—cardiac.

Analysis 5.2. Comparison 5 Stratification for type of beta-blocker, Outcome 2 All-cause mortality (30 days)—non-cardiac.

Analysis 5.3. Comparison 5 Stratification for type of beta-blocker, Outcome 3 Long-term mortality—non-cardiac surgery.

Analysis 5.4. Comparison 5 Stratification for type of beta-blocker, Outcome 4 Death due to cardiac causes—cardiac surgery.

Analysis 5.5. Comparison 5 Stratification for type of beta-blocker, Outcome 5 Death due to cardiac causes—non-cardiac surgery.

Analysis 5.6. Comparison 5 Stratification for type of beta-blocker, Outcome 6 Acute myocardial infarction—cardiac surgery.

Analysis 5.7. Comparison 5 Stratification for type of beta-blocker, Outcome 7 Acute myocardial infarction—non-cardiac surgery.

Analysis 5.8. Comparison 5 Stratification for type of beta-blocker, Outcome 8 Myocardial ischaemia—non-cardiac surgery.

Analysis 5.9. Comparison 5 Stratification for type of beta-blocker, Outcome 9 Cerebrovascular events—cardiac surgery.

Analysis 5.10. Comparison 5 Stratification for type of beta-blocker, Outcome 10 Cerebrovascular events—non-cardiac surgery.

Analysis 5.11. Comparison 5 Stratification for type of beta-blocker, Outcome 11 Ventricular arrhythmias—cardiac surgery.

Analysis 5.12. Comparison 5 Stratification for type of beta-blocker, Outcome 12 Ventricular arrhythmias—non-cardiac surgery.

Analysis 5.13. Comparison 5 Stratification for type of beta-blocker, Outcome 13 Atrial fibrillation—cardiac surgery.

Analysis 5.14. Comparison 5 Stratification for type of beta-blocker, Outcome 14 Atrial fibrillation and flutter—non-cardiac surgery.

Study or subgroup	Beta-blocker n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Test for subgroup differences: $\chi^2=0.03$, $df=1$ ($P=0.85$), $I^2=0\%$					
Favours beta-blocker 0.01 0.1 1 10 100 Favours control					

Analysis 5.15. Comparison 5 Stratification for type of beta-blocker, Outcome 15 All supraventricular arrhythmias—cardiac surgery.

Study or subgroup	Beta-blocker n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.15.1 Metoprolol					
Janssen 1986	6/39	18/50		2.18%	0.43[0.19,0.97]
Graham 1996	38/213	30/107		3.08%	0.64[0.42,0.97]
Paull 1997	12/50	13/50		2.49%	0.92[0.47,1.82]
Dy 1998	10/67	24/66		2.55%	0.41[0.21,0.79]
Wenke 1999	4/100	37/100		1.85%	0.11[0.04,0.29]
De Azevedo Lúcio 2003	11/100	24/100		2.54%	0.46[0.24,0.88]
Connolly 2003	156/500	195/500		3.5%	0.8[0.67,0.95]
Booth 2004	5/33	4/39		1.47%	1.48[0.43,5.06]
Auer 2004	25/62	35/65		3.16%	0.75[0.51,1.09]
Subtotal (95% CI)	1164	1077		22.81%	0.59[0.43,0.8]
Total events: 267 (Beta-blocker), 380 (Control)					
Heterogeneity: $\tau^2=0.13$; $\chi^2=24.86$, $df=8$ ($P=0$); $I^2=67.81\%$					
Test for overall effect: $Z=3.37$ ($P=0$)					
5.15.2 Propranolol					
Salazar 1979	3/20	5/22		1.38%	0.66[0.18,2.41]
Oka 1980	2/19	16/35		1.3%	0.23[0.06,0.9]
Stephenson 1980	7/87	24/136		2.23%	0.46[0.21,1.01]
Mohr 1981	2/37	19/48		1.26%	0.14[0.03,0.55]
Silverman 1982	3/50	14/50		1.53%	0.21[0.07,0.7]
Williams 1982	1/28	6/32		0.71%	0.19[0.02,1.49]
Ivey 1983	7/53	9/56		2%	0.82[0.33,2.05]
Abel 1983	7/41	19/50		2.31%	0.45[0.21,0.96]
Hammon 1984	5/24	12/26		2.06%	0.45[0.19,1.09]
Ormerod 1984	4/27	9/33		1.73%	0.54[0.19,1.57]
Myhre 1984	2/16	9/20		1.27%	0.28[0.07,1.11]
Matangi 1985	8/82	19/82		2.3%	0.42[0.2,0.91]
Rubin 1987	6/37	15/40		2.16%	0.43[0.19,1]
Martinussen 1988	11/35	7/40		2.16%	1.8[0.78,4.13]
Babin-Ebell 1996	2/27	14/37		1.25%	0.2[0.05,0.79]
Bert 2001	13/71	23/60		2.7%	0.48[0.27,0.86]
Subtotal (95% CI)	654	767		28.33%	0.45[0.34,0.61]
Total events: 83 (Beta-blocker), 220 (Control)					
Heterogeneity: $\tau^2=0.09$; $\chi^2=20.87$, $df=15$ ($P=0.14$); $I^2=28.12\%$					
Test for overall effect: $Z=5.32$ ($P<0.0001$)					
5.15.3 Sotalol					
Janssen 1986	1/41	18/50		0.76%	0.07[0.01,0.49]
Suttrop 1991	24/150	46/150		3.03%	0.52[0.34,0.81]
Nyström 1993	5/50	15/51		1.96%	0.34[0.13,0.87]
Favours beta-blocker 0.01 0.1 1 10 100 Favours control

Analysis 5.16. Comparison 5 Stratification for type of beta-blocker, Outcome 16 All supraventricular arrhythmias—non-cardiac surgery.

Analysis 5.17. Comparison 5 Stratification for type of beta-blocker, Outcome 17 Ventricular extrasystoles—cardiac surgery.

Analysis 5.18. Comparison 5 Stratification for type of beta-blocker, Outcome 18 Ventricular extrasystoles—non-cardiac surgery.

Analysis 5.19. Comparison 5 Stratification for type of beta-blocker, Outcome 19 Bradycardia—cardiac surgery.

Analysis 5.20. Comparison 5 Stratification for type of beta-blocker, Outcome 20 Bradycardia—non-cardiac surgery.

Analysis 5.21. Comparison 5 Stratification for type of beta-blocker, Outcome 21 Hypotension—cardiac surgery.

Analysis 5.22. Comparison 5 Stratification for type of beta-blocker, Outcome 22 Hypotension—non-cardiac surgery.

Analysis 5.23. Comparison 5 Stratification for type of beta-blocker, Outcome 23 Congestive heart failure—cardiac surgery.

Analysis 5.24. Comparison 5 Stratification for type of beta-blocker, Outcome 24 Congestive heart failure—non-cardiac surgery.

Analysis 5.25. Comparison 5 Stratification for type of beta-blocker, Outcome 25 Bronchospasm—cardiac surgery.

Analysis 5.26. Comparison 5 Stratification for type of beta-blocker, Outcome 26 Bronchospasm—non-cardiac surgery.

Analysis 5.27. Comparison 5 Stratification for type of beta-blocker, Outcome 27 Length of stay—cardiac surgery.

Analysis 5.28. Comparison 5 Stratification for type of beta-blocker, Outcome 28 Length of stay—non-cardiac surgery.

Comparison 6. Stratification according to results of meta-regression analysis

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality (30 days)—non-cardiac surgery: hospital status	13	11413	Risk Ratio (M-H, Random, 95% CI)	1.27 [1.02, 1.60]
1.1 University hospital or predominantly university hospitals in multi-centre trials	7	1507	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.15, 2.14]
1.2 Other hospital or predominantly non-university hospitals in multi-centre trials	6	9906	Risk Ratio (M-H, Random, 95% CI)	1.31 [1.04, 1.65]
2 Myocardial ischaemia—non-cardiac surgery: use of intention-to-treat analysis	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
2.1 Intention-to-treat analysis definitely used	7	615	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.50, 0.91]
2.2 Intention-to-treat analysis not used or unclear	7	363	Risk Ratio (M-H, Random, 95% CI)	0.28 [0.11, 0.70]
3 Myocardial ischaemia—non-cardiac surgery: blinding status of participants	14	978	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.34, 0.77]
3.1 Participants were definitively blinded	9	645	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.49, 0.86]
3.2 Participants were not blinded or blinding status was unclear	5	333	Risk Ratio (M-H, Random, 95% CI)	0.19 [0.07, 0.48]
4 Cerebrovascular events—non-cardiac surgery: blinding status of participants	5	9150	Risk Ratio (M-H, Fixed, 95% CI)	1.59 [0.93, 2.71]
4.1 Participants were definitively blinded	3	8648	Risk Ratio (M-H, Fixed, 95% CI)	2.09 [1.14, 3.82]
4.2 Participants were not blinded or blinding status was unclear	2	502	Risk Ratio (M-H, Fixed, 95% CI)	0.39 [0.09, 1.67]
5 Ventricular arrhythmias—non-cardiac surgery: route of application	5	476	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.43, 1.19]
5.1 Oral application only	3	231	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.56, 2.07]
5.2 Parenteral application only	1	45	Risk Ratio (M-H, Fixed, 95% CI)	0.25 [0.09, 0.70]
5.3 Both parenteral and oral application	1	200	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.12, 3.98]
6 Bradycardia—non-cardiac surgery: specification of baseline characteristics	23	11033	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.48, 3.36]
6.1 Baseline characteristics specified	20	10825	Risk Ratio (M-H, Random, 95% CI)	2.70 [2.13, 3.44]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 Baseline characteristics not specified	3	208	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.63, 1.87]
7 Bradycardia—non-cardiac surgery: specification of outcome parameters	23	11033	Risk Ratio (M-H, Random, 95% CI)	2.23 [1.48, 3.36]
7.1 Outcome parameters explicitly defined	21	10885	Risk Ratio (M-H, Random, 95% CI)	2.65 [2.11, 3.32]
7.2 Outcome parameters vaguely or not defined	2	148	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.72, 1.20]
8 Bradycardia—non-cardiac surgery: influence of coronary heart disease	5	9241	Risk Ratio (M-H, Random, 95% CI)	1.53 [0.71, 3.27]
8.1 Percentage of participants diagnosed with coronary heart disease below median (25%)	3	690	Risk Ratio (M-H, Random, 95% CI)	1.27 [0.52, 3.08]
8.2 Percentage of participants diagnosed with coronary heart disease above median (25%)	2	8551	Risk Ratio (M-H, Random, 95% CI)	2.25 [1.14, 4.45]
9 All supraventricular arrhythmias—cardiac surgery: duration of beta-blocker therapy	35	4758	Risk Ratio (M-H, Random, 95% CI)	0.45 [0.36, 0.57]
9.1 Up to 24 hours	3	159	Risk Ratio (M-H, Random, 95% CI)	1.00 [0.56, 1.81]
9.2 2-7 days	19	2035	Risk Ratio (M-H, Random, 95% CI)	0.41 [0.26, 0.65]
9.3 8-14 days	6	1694	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.26, 0.70]
9.4 15-21 days	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9.5 More than 21 days	7	870	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.33, 0.57]
10 Length of stay—cardiac surgery: use of intention-to-treat analysis	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
10.1 Intention-to-treat analysis was applied	9	1055	Mean Difference (IV, Random, 95% CI)	-0.57 [-0.85, -0.30]
10.2 Intention-to-treat analysis was not applied or was unclear	5	1395	Mean Difference (IV, Random, 95% CI)	-0.66 [-1.57, 0.24]
11 Length of stay—cardiac surgery: blinding status of participants	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 Participants were definitively blinded	6	1699	Mean Difference (IV, Random, 95% CI)	-0.72 [-1.53, 0.10]
11.2 Participants were not blinded or blinding status was unclear	8	751	Mean Difference (IV, Random, 95% CI)	-0.64 [-0.87, -0.41]
12 Length of stay—cardiac surgery: blinding status of doctors	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
12.1 Doctors were definitively blinded	7	1800	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.45, 0.07]
12.2 Doctors were not blinded or blinding status was unclear	7	650	Mean Difference (IV, Random, 95% CI)	-0.62 [-0.91, -0.33]
13 Length of stay—cardiac surgery: route of beta-blocker application	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
13.1 Oral application only	7	1911	Mean Difference (IV, Random, 95% CI)	-0.56 [-1.14, 0.02]
13.2 Parenteral application only	4	271	Mean Difference (IV, Random, 95% CI)	-0.84 [-1.42, -0.25]
13.3 Both oral and parenteral	3	268	Mean Difference (IV, Random, 95% CI)	-0.11 [-0.78, 0.56]
14 Length of stay—cardiac surgery: influence of gender	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
14.1 Percentage of females below median (20.8%)	7	844	Mean Difference (IV, Random, 95% CI)	-0.35 [-0.74, 0.04]
14.2 Percentage of females above median (20.8%)	7	1606	Mean Difference (IV, Random, 95% CI)	-0.67 [-1.21, -0.13]
15 Length of stay—cardiac surgery: influence of beta-blocker premedication	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
15.1 Percentage of participants with prior beta-blocker therapy below median (43.3%)	7	676	Mean Difference (IV, Random, 95% CI)	-0.69 [-1.21, -0.16]
15.2 Percentage of participants with prior beta-blocker therapy above median (43.3%)	7	1774	Mean Difference (IV, Random, 95% CI)	-0.43 [-0.91, 0.04]
16 Length of stay—cardiac surgery: specification of co-morbidities	14	2450	Mean Difference (IV, Random, 95% CI)	-0.54 [-0.90, -0.19]
16.1 Co-morbidities not specified	6	1481	Mean Difference (IV, Random, 95% CI)	-0.44 [-1.10, 0.21]
16.2 Co-morbidities specified	8	969	Mean Difference (IV, Random, 95% CI)	-0.69 [-0.80, -0.57]

Analysis 6.1. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 1 All-cause mortality (30 days)—non-cardiac surgery: hospital status.

Analysis 6.2. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 2 Myocardial ischaemia—non-cardiac surgery: use of intention-to-treat analysis.

Analysis 6.3. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 3 Myocardial ischaemia—non-cardiac surgery: blinding status of participants.

Analysis 6.4. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 4 Cerebrovascular events—non-cardiac surgery: blinding status of participants.

Analysis 6.5. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 5 Ventricular arrhythmias—non-cardiac surgery: route of application.

Analysis 6.6. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 6 Bradycardia—non-cardiac surgery: specification of baseline characteristics.

Analysis 6.7. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 7 Bradycardia—non-cardiac surgery: specification of outcome parameters.

Analysis 6.8. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 8 Bradycardia—non-cardiac surgery: influence of coronary heart disease.

Analysis 6.9. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 9 All supraventricular arrhythmias—cardiac surgery: duration of beta-blocker therapy.

Analysis 6.10. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 10 Length of stay—cardiac surgery: use of intention-to-treat analysis.

Analysis 6.11. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 11 Length of stay—cardiac surgery: blinding status of participants.

Analysis 6.12. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 12 Length of stay—cardiac surgery: blinding status of doctors.

Analysis 6.13. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 13 Length of stay—cardiac surgery: route of beta-blocker application. **Analysis 6.14. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 14 Length of stay—cardiac surgery: influence of gender.**

Analysis 6.15. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 15 Length of stay—cardiac surgery: influence of beta-blocker premedication.

Analysis 6.16. Comparison 6 Stratification according to results of meta-regression analysis, Outcome 16 Length of stay—cardiac surgery: specification of co-morbidities.

APPENDICES

Appendix 1. Search filter for MEDLINE (Ovid SP)

1. exp Adrenergic beta-Antagonists/ or exp Bendroflumethiazide/ or (acebutolol* or adimolol* or afurolool* or alpha hydroxymetoprolol* or alprenolol* or amosulalol* or arotinolol* or atenolol* or befunolol* or bendroflumethiazide* or betaxolol* or bevantolol* or bfe 55 or bisoprolol* or bopindolol* or bornaprolol* or brefonalol* or bromoacetylalprenololmenthane* or bucindolol* or bucumolol* or bufetolol* or bufuralol* or bunitrolol* or bunolol* or bupranolol* or butofilolol* or butoxamine* or carazolol* or carteolol* or carvedilol* or celiprolol* or cetamolol* or cloranolol* or cyanoiodopindolol* or cyanopindolol* or deacetylmetipranolol* or diacetolol* or dihydroalprenolol* or dilevalol* or epanolol* or esmolol* or exaprolol* or falintolol* or flestolol* or flusoxolol* or hydroxybenzylpindolol* or indenolol* or iodocyanopindolol* or iodopindolol* or iprocrolol* or isamoltane* or isoxaprolol* or labetalol* or landiolol* or levobunolol* or levomoprolol* or medroxalol* or mepindolol* or mercuderamide* or metipranolol* or metoprolol* or moprolol* or nadolol* or nebivolol* or nifenalol* or nipradilol* or oxprenolol* or pafenolol* or pamatolol* or penbutolol* or pindolol* or practolol* or primidolol* or prizidilol* or pronetalol* or propranolol* or proxodolol* or ridazolol* or salcardolol* or sandoz 204545 or soquinolol* or sotalol* or spirendolol* or talinolol* or tertatolol* or tienoxolol* or tilisolol* or timolol* or tolamolol* or toliprolol* or trasitensin* or trepress* or tribendilol* or viskaldix* or xibenolol* or zolertine or (beta* adj3 (adrenergic* or blocker*))).ti,ab.
2. exp Premedication/ or Intraoperative Period/ or Intraoperative Complications/ or Perioperative Period/ or Postoperative Complications/ or Postoperative Period/ or Preoperative Period/ or (intraoperat* or perioperat* or peroperat* or postoperat* or preoperat* or premedicat*).ti,ab.
3. exp Specialties, Surgical/ or General Surgery/ or su.xs. or (surg* or operat*).ti,ab.
4. 1 and 2 and 3
5. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or clinical trials as topic.sh. or randomly.ab. or trial.ti.) not (animals not (humans and animals)).sh.
6. 4 and 5

Appendix 2. Search filter for Embase (Ovid SP)

1. beta adrenergic receptor blocking agent/ or bendroflumethiazide/ or (acebutolol* or adimolol* or afurolool* or alpha hydroxymetoprolol* or alprenolol* or amosulalol* or arotinolol* or atenolol* or befunolol* or bendroflumethiazide* or betaxolol* or bevantolol* or bfe 55 or bisoprolol* or bopindolol* or bornaprolol* or brefonalol* or bromoacetylalprenololmenthane* or bucindolol* or bucumolol* or bufetolol* or bufuralol* or bunitrolol* or bunolol* or bupranolol* or butofilolol* or butoxamine* or carazolol* or carteolol* or carvedilol* or celiprolol* or cetamolol* or cloranolol* or cyanoiodopindolol* or cyanopindolol* or deacetylmetipranolol* or diacetolol* or dihydroalprenolol* or dilevalol* or epanolol* or esmolol* or exaprolol* or falintolol* or flestolol* or flusoxolol* or hydroxybenzylpindolol* or indenolol* or iodocyanopindolol* or iodopindolol* or iprocrolol* or isamoltane* or isoxaprolol* or labetalol* or landiolol* or levobunolol* or levomoprolol* or medroxalol* or mepindolol* or mercuderamide* or metipranolol* or metoprolol* or moprolol* or nadolol* or nebivolol* or nifenalol* or nipradilol* or oxprenolol* or pafenolol* or pamatolol* or penbutolol* or pindolol* or practolol* or primidolol* or prizidilol* or pronetalol* or propranolol* or proxodolol* or ridazolol* or salcardolol* or sandoz 204545 or soquinolol* or sotalol* or spirendolol* or talinolol* or tertatolol* or tienoxolol* or tilisolol* or timolol* or tolamolol* or toliprolol* or trasitensin* or trepress* or tribendilol* or viskaldix* or xibenolol* or zolertine or (beta* adj3 (adrenergic* or blocker*))).ti,ab.
2. premedication/ or intraoperative period/ or peroperative complication/ or perioperative period/ or postoperative complication/ or postoperative period/ or preoperative period/ or (intraoperat* or perioperat* or peroperat* or postoperat* or preoperat* or premedicat*).ti,ab.
3. surgery/ or (surg* or operat*).ti,ab.
4. 1 and 2 and 3
5. (placebo.sh. or controlled study.ab. or random*.ti,ab. or trial*.ti,ab. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*))).ti,ab.) not (animals not (humans and animals)).sh.
6. 4 and 5

Appendix 3. Search filter for CENTRAL (The Cochrane Library)

- #1 MeSH descriptor Adrenergic beta-Antagonists explode all trees
- #2 MeSH descriptor Bendroflumethiazide explode all trees
- #3 (acebutolol* or adimolol* or afurolool* or alpha hydroxymetoprolol* or alprenolol* or amosulalol* or arotinolol* or atenolol* or befunolol* or bendroflumethiazide* or betaxolol* or bevantolol* or bfe 55 or bisoprolol* or bopindolol* or bornaprolol* or brefonalol* or bromoacetylalprenololmenthane* or bucindolol* or bucumolol* or bufetolol* or bufuralol* or bunitrolol* or bunolol* or bupranolol* or butofilolol* or butoxamine* or carazolol* or carteolol* or carvedilol* or celiprolol* or cetamolol* or cloranolol* or cyanoiodopindolol* or cyanopindolol* or deacetylmetipranolol* or diacetolol* or dihydroalprenolol* or dilevalol* or epanolol* or esmolol* or exaprolol* or falintolol* or flestolol* or flusoxolol* or hydroxybenzylpindolol* or indenolol* or iodocyanopindolol* or iodopindolol* or iprocrolol* or isamoltane* or isoxaprolol* or labetalol* or landiolol* or levobunolol* or levomoprolol* or medroxalol* or mepindolol* or mercuderamide* or metipranolol* or metoprolol* or moprolol* or nadolol* or nebivolol* or nifenalol* or nipradilol* or oxprenolol* or pafenolol* or pamatolol* or penbutolol* or pindolol* or practolol* or primidolol* or prizidilol* or pronetalol* or propranolol* or proxodolol* or ridazolol* or salcardolol* or sandoz 204545 or soquinolol* or sotalol* or spirendolol* or talinolol* or tertatolol* or tienoxolol* or tilisolol* or timolol* or tolamolol* or toliprolol* or trasitensin* or trepress* or tribendilol* or viskaldix* or xibenolol* or zolertine).ti,ab

#4 (beta* near (adrenergic* or blocker*)):ti,ab
 #5 (#1 OR #2 OR #3 OR #4)
 #6 MeSH descriptor Premedication explode all trees
 #7 MeSH descriptor Intraoperative Period explode all trees
 #8 MeSH descriptor Intraoperative Complications explode all trees
 #9 MeSH descriptor Perioperative Period explode all trees
 #10 MeSH descriptor Postoperative Complications explode all trees
 #11 MeSH descriptor Postoperative Period explode all trees
 #12 MeSH descriptor Preoperative Period explode all trees
 #13 (intraoperat* or perioperat* or peroperat* or postoperat* or preoperat* or premedicat*):ti,ab
 #14 (#6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
 #15 MeSH descriptor Specialties, Surgical explode all trees
 #16 (surg* or operat*):ti,ab
 #17 (#15 OR #16)
 #18 (#5 AND #14 AND #17)

Appendix 4. Search filter for CINAHL (EBSCO host)

S1. (MM "Adrenergic Beta-Antagonists") OR AB (acebutolol* or adimolol* or afurolol* or alpha hydroxymetoprolol* or alprenolol* or amosulalol* or arotinolol* or atenolol* or befunolol* or bendroflumethiazide* or betaxolol* or bevantolol* or bfe 55 or bisoprolol* or bopindolol* or bornaprolol* or brefonalol* or bromoacetylalprenololmenthane* or bucindolol* or bucumolol* or bufetolol* or bufuralol* or bunitrolol* or bunolol* or bupranolol* or butofilolol* or butoxamine* or carazolol* or carteolol* or carvedilol* or celiprolol* or cetamolol* or cloranolol* or cyanoiodopindolol* or cyanopindolol* or deacetylmetipranolol* or diacetolol* or dihydroalprenolol* or dilevalol* or epanolol* or esmolol* or exaprolol* or falintolol* or flestolol* or flusoxolol* or hydroxybenzylpindolol* or indenolol* or iodocyanopindolol* or iodopindolol* or iprocrolol* or isamoltane* or isoxaprolol* or labetalol* or landiolol* or levobunolol* or levomoprolol* or medroxalol* or mepindolol* or mercuderamide* or metipranolol* or metoprolol* or moprolol* or nadolol* or nebivolol* or nifenalol* or nipradilol* or oxprenolol* or pafenolol* or pamatolol* or penbutolol* or pindolol* or practolol* or primidolol* or prizidilol* or pronetalol* or propranolol* or proxodolol* or ridazolol* or salcardolol* or sandoz 204545 or soquinolol* or sotalol* or spirendolol* or talinolol* or tertatolol* or tienoxolol* or tilisolol* or timolol* or tolamolol* or toliprolol* or trasitensin* or trepress* or tribendilol* or viskaldix* or xibenolol* or zolertine) OR AB ((beta* and (adrenergic* or blocker*)))
 S2. ((MH "Premedication") OR (MH "Intraoperative Period") OR (MH "Postoperative Period") OR (MH "Intraoperative Complications") OR (MH "Preoperative Period") OR (MH "Postoperative Complications")) OR AB (intraoperat* or perioperat* or peroperat* or postoperat* or preoperat* or premedicat*)
 S3. (MH "Specialties, Surgical+") OR AB (surg* or operat*)
 S4. S1 and S2 and S3

Appendix 5. Search filter for Biosis Previews, CAB Abstracts, Global Health, Life Sciences Collection, Derwent Drug File, Science Citation Index Expanded, International Pharmaceutical Abstracts, PASCAL, Conference Proceedings Citation Index–Science, System for Information on Grey Literature in Europe, British Library Inside Conferences, Conference Papers Index, Index to Scientific and Technical Proceedings and Books

A, B, C, D combined with AND

A: beta-blocker (to be combined with OR)

Free Text:
 acebutolol*
 adimolol*
 afurolol*
 alpha hydroxymetoprolol*
 alprenolol*
 amosulalol*
 arotinolol*
 atenolol*
 befunolol*
 bendroflumethiazide*
 (beta* adj3 adrenergic*)
 beta blocker*
 betaxolol*
 bevantolol*
 bfe 55
 bisoprolol*
 bopindolol*

bornaprolol*
brefonalol*
bromoacetylalprenololmenthane*
bucindolol*
bucumolol*
bufetolol*
bufuralol*
bunitrolol*
bunolol*
bupranolol*
butofilolol*
butoxamine*
carazolol*
carteolol*
carvedilol*
celiprolol*
cetamolol*
cloranolol*
cyanoiodopindolol*
cyanopindolol*
deacetylmetipranolol*
diacetolol*
dihydroalprenolol*
dilevalol*
epanolol*
esmolol*
exaprolol*
falintolol*
flestolol*
flusoxolol*
hydroxybenzylpindolol*
indenolol*
iodocyanopindolol*
iodopindolol*
iprocrolol*
isamoltane*
isoxaprolol*
labetalol*
landiolol*
levobunolol*
levomoprolol*
medroxalol*
mepindolol*
mercuderamide*
metipranolol*
metoprolol*
moprolol*
nadolol*
nebivolol*
nifenalol*
nipradilol*
oxprenolol*
pafenolol*
pamatolol*
penbutolol*
pindolol*
practolol*
primidolol*
prizidilol*
pronetalol*
propranolol*
proxodolol*

ridazolol*
salcardolol*
sandoz 204545
soquinolol*
sotalol*
spirendolol*
talinolol*
tertatolol*
tienoxolol*
tilisolol*
timolol*
tolamolol*
toliprolol*
trasitensin*
trepress*
tribendilol*
viskaldix*
xibenolol*
zolertine*

B: perioperative (to be combined with OR)

Free Text:
intraoperat*
perioperat*
peroperat*
postoperat*
preoperat*
premedicat*

C: surgery (to be combined with OR)

Free Text:
surg*
operat*

D: RCT - Filter (to be combined with OR)

Free Text:
placebo*
random*
control*
prospectiv*
volunteer*
(clin* adj3 trial*)
(compar* adj3 stud*)
(singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)

Appendix 6. Trial data extraction form

1. Study ID

First author year / ID / Reviewer ID.

2. Citation

Journal.

Year.

Volume.

First page.

3. Title

4. Language

English, other (specify).

5. Study type

RCT, cross-over RCT, other (specify).

6. Centres

Single-centre, multi-centre, unclear.

7. Hospital

University hospital, other, unclear.

8. Allocation

Allocation was not concealed (e.g. quasi-randomized).

Allocation concealment was unclear.

Allocation was concealed (e.g. numbered sealed opaque envelopes).

9. Inclusion + exclusion criteria

Inclusion and exclusion criteria were not clearly defined in the text.

Inclusion and exclusion criteria were implicitly defined in the text.

Inclusion and exclusion criteria were explicitly defined in the text.

10. Intention-to-treat

Outcomes of patients who withdrew or were excluded after allocation were neither detailed separately nor included in an intention-to-treat.

Outcomes of patients who withdrew or were excluded after allocation were either detailed separately or included in an intention-to-treat or the text stated there were no withdrawals.

Unclear.

11. Baseline data

Treatment and control groups were not adequately described at entry.

Treatment and control groups were adequately described at entry (e.g. age, sex, weight, diseases, type of surgery, any scores).

Unclear.

12. Care programme

The text stated that the care programmes other than the trial options were not identical.

The text stated that the care programmes other than the trial options were identical.

Unclear.

13. Definition of outcome measures

Outcome measures were not clearly defined in the text.

Outcome measures were implicitly defined in the text.

Outcome measures were explicitly defined in the text.

14. Blinding

Subject was blinded (YES, NO, unclear).

Physician was blinded (YES, NO, unclear).

Outcome assessor was blinded (YES, NO, unclear).

15. Participants

Number of eligible participants

(leave blank if unclear / not stated).

Number of enrolled participants.

16. Withdrawals

Number of withdrawals (intervention group).

Number of withdrawals (control group).

17. Type of surgery

18. Risk of surgery

High risk:

any cardiac, high risk vascular (aortic dissection/aortic abdominal aneurysm repair), extensive abdominal (any hepatic/pancreatic/TU surgery), any organ transplantation, brain neurosurgery.

Intermediate risk:

lower abdominal, peripheral vascular (including carotid), any orthopaedic surgery on large joints (hip, knee, shoulder, including vertebral), mamma.

Low risk:

everything else: dermatologic interventions, ENT (=HNO), peripheral neuro, peripheral orthopaedic surgery.

19. Number of treatment groups (including control group)

Two, three, more (specify), cross-over design.

20. Drugs:

Control group, drug group 1, drug group 2-

Drug (specify).

Route.

Indicate if fixed dose (F) (e.g. 5 µg/kg/min) or goal-directed (D).

Dose.

Duration.

Time treatment was started (before, during, or after surgery).

21. Comments on treatment

22. Type of patients

Adult, paediatric, unclear.

22. Number of patients in the control group and intervention group

Overall number of patients, deaths, other outcomes.

24. Co-morbidity

Other diseases specified.

Other diseases not specified.

Unclear.

if other specified - which?

23. Data and characteristics of control group, drug group 1 and drug group 2

Age [mean] [median] or [SD] [SE] [IQR] [range] [individual patient data].

Sex: M / F [number] [%] [individual patient data].

Ethnic group (specify).

Weight [mean] [median] or [SD] [SE] [IQR] [range] [individual patient data].

ASA-score1 [mean] [median] or [SD] [SE] [IQR] [range] [individual patient data].

CARE-scale2 [mean] [median] or [SD] [SE] [IQR] [range] [individual patient data].

Other score (specify) [mean] [median] or [SD] [SE] [IQR] [range] [individual patient data].

25. Outcome measures

Is any of the following outcome-measures stated:

All-cause mortality (deaths due to any cause occurring 30 days postoperatively or before hospital discharge – whichever occurs later).

Long-term all-cause mortality (deaths due to any cause not qualifying as all-cause mortality listed above).

Deaths due to cardiac causes (until 30 days postoperatively, or until discharge).

Incidence of myocardial infarction.

Myocardial ischaemia (criteria of ischaemia met: yes/no).

Dysrhythmias.

Cerebrovascular complications.

Heart failure (occurring 30 days postoperatively, or until discharge)

Length of stay (in ICU or hospital).

Quality of life.

26. Additional comments on this study

27. Contact

Is it necessary to contact the author(s) (YES, NO, if YES: name and address of corresponding author).

Appendix 7. Search results

Database	Period of enquiry/last visit of website	Number of records
Biosis Previews	1970 to 6/2013	678
BLIC (British Library Inside Conferences)	1993 to 6/2003	35
CAB Abstracts	1972 to 6/2013	5
CENTRAL	May 2013	313
CINAHL	1982 to 6/2013	338
ClinicalTrials.gov	6/2013	95
CONFSCI	1973 to 10/2010	16
CPCI-Science	1995 to 6/2013	75
Derwent Drug File	1964 to 6/2013	557
Embase	1974 to 6/2013	5484
Global Health	1972 to 6/2013	13
IPA	1970 to 6/2013	63
ISTBP, ISTP/ISSHP	1978 to 6/2013	66
Life Sciences Collection	1982 to 10/2010	10
MEDLINE	1946 to 6/2013	964
mRCT	6/2013	214
National Research Register	6/2013	72
PASCAL	1977 to 6/2013	262
SCI-EXPANDED	1974 to 6/2013	914
SIGLE	1976 to 2013	1
Sum		10,175

Footnotes

Records retrieved from each database with respective period of enquiry.

WHAT'S NEW

Date	Event	Description
22 February 2018	New citation required and conclusions have changed	Removal of retracted study (Suttner 2009)
22 February 2018	Amended	Following publication of the first version of this systematic review, a previously included study was retracted (Suttner 2009). This trial has now been excluded and all relevant analyses and results have been amended accordingly. All NNTB/Hs were re-calculated according to the formula in the <i>Cochrane Handbook for Systematic Reviews of Interventions</i> (Higgins 2011) . Guideline recommendations were updated in the <i>Discussion</i> section.

CONTRIBUTIONS OF AUTHORS

Hermann Blessberger (HB), Juergen Kammler (JK), Hans Domanovits (HD), Oliver Schlager (OS), Brigitte Wildner (BW), Danyel Azar (DA), Martin Schillinger (MS)

Franz Wiesbauer (FW), Clemens Steinwender (CS).

Conceiving of the review: FW.

Co-ordinating the review: HB, JK, FW.

Undertaking manual searches: BW.

Screening search results: FW, OS, HB, DA, JK.

Organizing retrieval of papers: BW.

Screening retrieved papers against inclusion criteria: FW, OS, HB, DA, JK.

Appraising quality of papers: FW, OS, HB, DA, JK.

Abstracting data from papers: FW, OS, HB, DA, JK.

Writing to authors of papers for additional information: FW, HB.

Providing additional data about papers: not applicable.

Obtaining and screening data on unpublished studies: BW.

Managing data for the review: HB, JK, FW, BW.

Entering data into Review Manager ([RevMan 5.3](#)): HB, JK, FW.

Analysing RevMan statistical data: HB, FW.

Performing other statistical analysis not using RevMan: FW, HB.

Performing double entry of data: (data entered by person one: HB; data entered by person two: JK).

Interpreting data: HB, JK, CS, FW, HD, OS, BW, DA, MS.

Making statistical inferences: HB, FW.

Writing the review: HB, FW, BW, JK, CS.

Securing funding for the review: not applicable (no funding).

Performing previous work that was the foundation of the present study: E. Villanueva, R. Johnston and A. Rauli (preparation of first protocol draft).

Serving as guarantor for the review (one author): HB.

Taking responsibility for reading and checking the review before submission: HB.

DECLARATIONS OF INTEREST

H. Blessberger: received consultancy honoraria from Ever Neuro Pharma in 2012.

J. Kammler: none known.

H. Domanovits: received honoraria from MSD, Sanofi-Aventis, Boehringer-Ingelheim and Amomed Pharma for giving lectures and consulting.

O. Schlager: none known.

B. Wildner: none known.

D. Azar: none known.

M. Schillinger: none known.

F. Wiesbauer: received payments from Medtronic for lectures on cardiac resynchronization therapy and received travel grants to attend the EuroEcho meeting from GE and Medtronic. Dr. Wiesbauer was part-time employee of Ever Neuro Pharma between September 2010 and September 2011 and is currently managing director of Medmastery - a company producing online training materials for doctors. All these activities were unrelated to this review.

C. Steinwender: received honoraria from MSD, Sanofi-Aventis, Boehringer-Ingelheim, Bayer Austria, Medtronic, Biotronik, Abbott Vascular, St.Jude Medical and Boston Scientific for giving lectures.

Ever Neuro Pharma, Medmastery, Sanofi-Aventis, Boehringer-Ingelheim Europe, Medtronic, Biotronik, GE, Bayer Austria, Abbott Vascular, St. Jude Medical and Boston Scientific do not produce, market or distribute any of the studied drug entities.

MSD (timolol) and Amomed Pharma (esmolol) both have a beta-blocker in their portfolio.

SOURCES OF SUPPORT

Internal sources

- None, Other.

External sources

- None, Other.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

As opposed to the eligibility criteria defined in the protocol, we decided to consider trials in our meta-analysis that partially included participants not receiving general anaesthesia. Trials had to fulfil the following criteria to be eligible for inclusion: more than 100 randomly assigned participants operated on under general anaesthesia, or more than 70% of participants receiving general anaesthesia. We came to this conclusion, as we believed a meta-analysis without the POISE, DIPOM or MaVS trial would not find enough credibility within the clinical community.

The incidence of bronchospasm and the cost of care were added as secondary outcomes.

In addition to the subgroup analyses specified in the protocol, the following effect modifiers were analysed: gender, percentage of participants taking beta-blockers when entering the study, ejection fraction of participants, heart rate versus fixed-dose application of beta-blockers, type of hospital (university vs non-university), methodological parameters (control group status; blinding status of participants, doctors and outcome assessors; use of the intention-to-treat principle for data analysis; specification of baseline characteristics; inclusion and exclusion criteria).

Trial sequential meta-analysis (TSA) was introduced as a type of statistical power analysis that allows better appreciation of the validity of results yielded by the meta-analysis.

During the review process, we decided to use the risk ratio instead of the odds ratio, as recommended by the reviewers. The RR 'is a metric that is better comprehended and avoids over-estimation of the relative risk which is an inherent problem of the OR.'

Furthermore, outcomes were presented separately for cardiac and non-cardiac surgery, in accordance with the reviewers' recommendations. Pooling data from both of these types of surgery was considered to constitute a major source of clinical heterogeneity and thus would substantially limit validity. Therefore, pooled overall effect estimates were omitted.

NOTES

None.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic beta-Antagonists [adverse effects] [*therapeutic use]; Anesthesia, General; Arrhythmias, Cardiac [mortality] [prevention & control]; Bradycardia [chemically induced]; Cardiovascular Diseases [chemically induced] [mortality] [*prevention & control]; Cardiovascular Surgical Procedures [adverse effects] [mortality]; Cause of Death; Cerebrovascular Disorders [mortality] [prevention & control]; Hypotension [chemically induced] [mortality] [prevention & control]; Myocardial Infarction [mortality] [prevention & control]; Myocardial Ischemia [mortality] [prevention & control]; Postoperative Complications [mortality] [*prevention & control]; Randomized Controlled Trials as Topic; Surgical Procedures, Operative [*adverse effects] [mortality]

MeSH check words

Humans