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Alpha-2 adrenergic agonists for the prevention of cardiac complications among adults undergoing surgery (Review)

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[Intervention Review]

Alpha-2 adrenergic agonists for the prevention of cardiac complications among adults undergoing surgery

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ABSTRACT

Background

The surgical stress response plays an important role on the pathogenesis of perioperative cardiac complications. Alpha-2 adrenergic agonists attenuate this response and may help prevent postoperative cardiac complications.

Objectives

To determine the efficacy and safety of α-2 adrenergic agonists for reducing mortality and cardiac complications in adults undergoing cardiac surgery and non-cardiac surgery.

Search methods

We searched CENTRAL (2017, Issue 4), MEDLINE (1950 to April Week 4, 2017), Embase (1980 to May 2017), the Science Citation Index, clinical trial registries, and reference lists of included articles.

Selection criteria

We included randomized controlled trials that compared α-2 adrenergic agonists (i.e. clonidine, dexmedetomidine or mivazerol) against placebo or non-α-2 adrenergic agonists. Included trials had to evaluate the efficacy and safety of α-2 adrenergic agonists for preventing perioperative mortality or cardiac complications (or both), or measure one or more relevant outcomes (i.e. death, myocardial infarction, heart failure, acute stroke, supraventricular tachyarrhythmia and myocardial ischaemia).

Data collection and analysis

Two authors independently assessed trial quality, extracted data and independently performed computer entry of abstracted data. We contacted study authors for additional information. Adverse event data were gathered from the trials. We evaluated included studies using the Cochrane 'Risk of bias' tool, and the quality of the evidence underlying pooled treatment effects using GRADE methodology. Given the clinical heterogeneity between cardiac and non-cardiac surgery, we analysed these subgroups separately. We expressed treatment effects as pooled risk ratios (RR) with 95% confidence intervals (CI).

Main results

We included 47 trials with 17,039 participants. Of these studies, 24 trials only included participants undergoing cardiac surgery, 23 only included participants undergoing non-cardiac surgery and eight only included participants undergoing vascular surgery. The α-2 adrenergic agonist studied was clonidine in 21 trials, dexmedetomidine in 24 trials and mivazerol in two trials.

In non-cardiac surgery, there was high quality evidence that α-2 adrenergic agonists led to a similar risk of all-cause mortality compared with control groups (1.3% with α-2 adrenergic agonists versus 1.7% with control; RR 0.80, 95% CI 0.61 to 1.04; participants = 14,081; studies = 16). Additionally, the risk of cardiac mortality was similar between treatment groups (0.8% with α-2 adrenergic agonists versus 1.0% with control; RR 0.86, 95% CI 0.60 to 1.23; participants = 12,525; studies = 5, high quality evidence). The risk of myocardial infarction was probably similar between treatment groups (RR 0.94, 95% CI 0.69 to 1.27; participants = 13,907; studies = 12, moderate quality evidence). There was no associated effect on the risk of stroke (RR 0.93, 95% CI 0.55 to 1.56; participants = 11,542; studies = 7; high quality evidence). Conversely, α-2 adrenergic agonists probably increase the risks of clinically significant bradycardia (RR 1.59, 95% CI 1.18 to 2.13; participants = 14,035; studies = 16) and hypotension (RR 1.24, 95% CI 1.03 to 1.48; participants = 13,738; studies = 15), based on moderate quality evidence.

There was insufficient evidence to determine the effect of α-2 adrenergic agonists on all-cause mortality in cardiac surgery (RR 0.52, 95% CI 0.26 to 1.04; participants = 1947; studies = 16) and myocardial infarction (RR 1.01, 95% CI 0.43 to 2.40; participants = 782; studies = 8), based on moderate quality evidence. There was one cardiac death in the clonidine arm of a study of 22 participants. Based on very limited data, α-2 adrenergic agonists may have reduced the risk of stroke (RR 0.37, 95% CI 0.15 to 0.93; participants = 1175; studies = 7; outcome events = 18; low quality evidence). Conversely, α-2 adrenergic agonists increased the risk of bradycardia from 6.4% to 12.0% (RR 1.88, 95% CI 1.35 to 2.62; participants = 1477; studies = 10; moderate quality evidence), but their effect on hypotension was uncertain (RR 1.19, 95% CI 0.87 to 1.64; participants = 1413; studies = 9; low quality evidence).

These results were qualitatively unchanged in subgroup analyses and sensitivity analyses.

Authors' conclusions

Our review concludes that prophylactic α-2 adrenergic agonists generally do not prevent perioperative death or major cardiac complications. For non-cardiac surgery, there is moderate-to-high quality evidence that these agents do not prevent death, myocardial infarction or stroke. Conversely, there is moderate quality evidence that these agents have important adverse effects, namely increased risks of hypotension and bradycardia. For cardiac surgery, there is moderate quality evidence that α-2 adrenergic agonists have no effect on the risk of mortality or myocardial infarction, and that they increase the risk of bradycardia. The quality of evidence was inadequate to draw conclusions regarding the effects of alpha-2 agonists on stroke or hypotension during cardiac surgery.

PLAIN LANGUAGE SUMMARY

Using alpha-2 adrenergic agonists to prevent heart complications after major surgery

Review question

Do alpha-2 adrenergic agonists (clonidine, dexmedetomidine and mivazerol) reduce the number of deaths and heart complications when given around the time of surgery?

Background

Heart-related complications can lead to death and long hospital stays after surgery. Each year, about 300 million people undergo major surgery, of whom nine million experience serious heart complications. These complications may occur, in part, because surgery places a large stress on the heart. This stress can lead to high blood pressure and high heart rates during surgery, neither of which are good for the heart. Alpha-2 adrenergic agonists are a group of medicines that can prevent the blood pressure and heart rate from increasing during surgery. Thus, these medicines may also protect the heart from the stress of surgery. We wanted to find out if giving these medicines around the time of surgery could protect the heart from the stress of surgery and thus prevent major heart complications.

Study characteristics

We found 47 studies that were published up to May 2017. These studies involved 17,039 adults who had major surgery. Twenty-four studies involved 2672 adults having heart surgery. Twenty-three studies involved 14,367 adults undergoing major operations other than heart surgery. Forty studies compared alpha-2 adrenergic agonists to dummy treatment (placebo). The other seven studies compared them to other medicines. Twenty-one studies tested an alpha-2 adrenergic agonist medicine called clonidine, 24 studied another medicine called dexmedetomidine and two studied another medicine called mivazerol. The duration of alpha-2 adrenergic agonist medicine studied varied from one dose before surgery to three days of treatment. Most people who took part in these studies were men, and their average age was 60 to 70 years old. Fourteen studies reported receiving money from the company that manufactured the medicine being tested in the same study. Another 15 studies did not report where they received the money needed to fund the study. The number of people who took part in each study varied between 20 participants to as many as 10,000 participants. Nineteen studies included more than 100 participants.

Key results

We found that alpha-2 adrenergic agonists generally had no clear benefits for preventing death or major complications after surgery. For people having major operations other than heart surgery, alpha-2 adrenergic agonists did not lower their chances of dying, having a heart attack or having a stroke after surgery. We did not find sufficient evidence that, in people having heart surgery, alpha-2 adrenergic lowered the risk of dying or having a heart attack after surgery. There was some very limited evidence that these medicines might prevent strokes after heart surgery. Nonetheless, more research is needed before we can be certain that alpha-2 adrenergic agonists truly have this benefit.

These medicines also had some important side effects. People who received alpha-2 adrenergic agonists were much more likely to have low blood pressures or low heart rates during or after surgery.

Quality of evidence

We assessed the quality of all studies we identified using a specialized tool called the GRADE criteria. In general, we found that most of the evidence in these studies was moderate or high quality. Thus, based on our results, we can be reasonably certain that alpha-2 adrenergic agonists are not helpful for reducing the numbers of deaths or major heart complications that happen after surgery.

SUMMARY OF FINDINGS

Summary of findings for the main comparison. Alpha-2 adrenergic agonists compared to control in non-cardiac surgery

Alpha-2 adrenergic agonists compared to control in non-cardiac surgery

Patient or population: adults undergoing non-cardiac surgery
Setting: hospital inpatient care
Intervention: α-2 adrenergic agonist
Comparison: placebo or inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Risk ratio (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with α-2 adrenergic agonists				
All-cause mortality (within 30-days after surgery: any reported death)	Study population 17 per 1000	13 per 1000 (10 to 17)	**RR 0.80** (0.61 to 1.04)	14,081 (16 RCTs)	⊕⊕⊕⊕ **High**[1,2]	-
Cardiac mortality (within 30-days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause.)	Study population 10 per 1000	8 per 1000 (6 to 12)	**RR 0.86** (0.60 to 1.23)	12,525 (5 RCTs)	⊕⊕⊕⊕ **High**[1,2]	-
Myocardial infarction (within 30-days after surgery: as detected on an electrocardiogram or trans-oesophageal echocardiogram)	Study population 59 per 1000	55 per 1000 (41 to 75)	**RR 0.94** (0.69 to 1.27)	13,907 (12 RCTs)	⊕⊕⊕⊖ **Moderate**[1,2,3]	-
Acute stroke (within 30-days after surgery: new focal neurologic deficit with signs and symptoms lasting longer than 24 hours)	Study population 5 per 1000	4 per 1000 (3 to 8)	**RR 0.93** (0.55 to 1.56)	11,542 (7 RCTs)	⊕⊕⊕⊕ **High**[1]	-
Bradycardia (requiring pharmacological or pacemaker treatment during the period of study drug administration)	Study population 75 per 1000	119 per 1000 (89 to 160)	**RR 1.59** (1.18 to 2.13)	14,035 (16 RCTs)	⊕⊕⊕⊖ **Moderate**[1,2,4]	-

Hypotension (requiring treatment with inotropes or vasopressors during the period of study drug administration)	Study population 304 per 1000	377 per 1000 (313 to 450)	**RR 1.24** (1.03 to 1.48)	13,738 (15 RCTs)	⊕⊕⊕⊖ **Moderate**[1,2,4]	-

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[1]Risk of bias was not serious. Although multiple studies lacked proper allocation concealment and blinding, outcome unlikely to be influenced. Not downgraded.
[2]Indirectness not serious. Intervention (mivazerol) used in one large study not available for clinical use. Not downgraded.
[3]Evidence of publication bias in funnel plot of analysis. Downgraded by one level.
[4]Serious inconsistency between studies indicated by substantial heterogeneity. Downgraded by one level.

Summary of findings 2. Alpha-2 adrenergic agonists compared to control in cardiac surgery

Alpha-2 adrenergic agonists compared to control in cardiac surgery

Patient or population: adults undergoing cardiac surgery
Setting: hospital inpatient care
Intervention: α-2 adrenergic agonist
Comparison: placebo or inactive control

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Quality of the evidence (GRADE)	Comments
	Risk with control	Risk with α-2 adrenergic agonists				
All-cause mortality (within 30-days after surgery: any reported death)	Study population 21 per 1000	11 per 1000 (5 to 21)	**RR 0.52** (0.26 to 1.04)	1947 (16 RCTs)	⊕⊕⊕⊖ **Moderate**[1,2]	-

Cardiac mortality (within 30-days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause)	1 death from 12 participants in clonidine arm, and no deaths in 10 participants in control arm.		Not estimable	22 (1 RCT)	Not estimable	We did not GRADE evidence for this outcome as accurate estimation of RRs is not possible for such low event rates.
Myocardial infarction (within 30-days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause)	Study population		RR 1.01 (0.43 to 2.40)	782 (8 RCTs)	⊕⊕⊕⊖ **Moderate**[1,2]	-
	20 per 1000	21 per 1000 (9 to 49)				
Acute stroke (within 30-days after surgery: new focal neurologic deficit with signs and symptoms lasting longer than 24 hours)	Study population		RR 0.37 (0.15 to 0.93)	1175 (7 RCTs)	⊕⊕⊖⊖ **Low**[1,3]	Total of 18 acute stokes reported, with 14 in control group and 4 in treatment group.
	24 per 1000	9 per 1000 (4 to 22)				
Bradycardia (requiring pharmacological or pacemaker treatment during the period of study drug administration)	Study population		RR 1.88 (1.35 to 2.62)	1477 (10 RCTs)	⊕⊕⊕⊖ **Moderate**[1,4]	-
	64 per 1000	120 per 1000 (86 to 167)				
Hypotension (requiring treatment with inotropes or vasopressors during the period of study drug administration)	Study population		RR 1.19 (0.87 to 1.64)	1413 (9 RCTs)	⊕⊕⊖⊖ **Low**[1,2,5]	-
	332 per 1000	395 per 1000 (289 to 544)				

*__The risk in the intervention group__ (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; **RCT:** randomized controlled trial; **RR:** risk ratio.

GRADE Working Group grades of evidence
High quality: We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate quality: We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low quality: Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low quality: We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

[1]Risk of bias was not serious. Although multiple studies lack proper allocation concealment and blinding, outcome unlikely to be influenced. Not downgraded.

[2]Serious imprecision, because analysis was below optimal information size and confidence interval includes significant benefit and harm. Downgraded by one level.
[3]Very serious imprecision, because analysis is below optimal information size and number of events was very small. Downgraded by two levels.
[4]Serious imprecision, because analysis was below optimal information size. Downgraded by one level
[5]Serious inconsistency between studies indicated by substantial heterogeneity. Downgraded one level.

BACKGROUND

Description of the condition

Perioperative cardiac complications are a major health concern for the 312 million people who annually undergo major surgery worldwide (Meara 2015). For example, about 3% of people who undergo major non-cardiac surgery experience perioperative myocardial infarction (MI) (VISION 2014). Major cardiac complications, such as MI, lead to increased mortality, hospital stay and costs (Fleischmann 2003; Force 1990; VISION 2014). The surgical stress response may play an important role in the pathogenesis of these complications. Specifically, surgical stress stimulates the sympathetic nervous system, which in turns leads to increased plasma levels of norepinephrine and epinephrine (Halter 1997). These effects increase blood pressure and heart rate, which can predispose the myocardium to ischaemia, especially in people with decreased coronary blood flow reserve.

Description of the intervention

Alpha-2 (α-2) adrenergic agonists selectively bind to presynaptic α-2 adrenergic receptors to activate a negative feedback mechanism that inhibits central sympathetic outflow (Muzi 1992). These receptors are mainly located in the central nervous system, specifically in the brain stem and locus coeruleus. Activation of these receptors lead to hypotension, bradycardia, central sedation, anxiolysis and analgesia. Three specific α-2 adrenergic agonists that have been evaluated in people undergoing surgery, namely clonidine, dexmedetomidine and mivazerol. Clonidine and dexmedetomidine are available for clinical use, while the use of mivazerol has been restricted to clinical trials. Clonidine has a half-life of 12 to 18 hours with excellent bioavailability, lending to its suitability for once daily administration in oral tablet or transdermal patch forms. An intravenous (IV) formulation of clonidine is also available. Dexmedetomidine has a shorter half-life of only two hours and variable bioavailability, consequently making it more suited for administration as a continuous IV infusion (Flood 2015). Similarly, mivazerol is also administered as a continuous IV infusion (Oliver 1999).

How the intervention might work

As indicated above, α-2 adrenergic agonists inhibit central sympathetic outflow. Hence, they can attenuate perioperative haemodynamic abnormalities (Ellis 1994; McSPI-Europe 1997; Talke 1995), and perhaps also prevent cardiac complications. Furthermore, clonidine has the unique ability to reduce sympathetic activity without blunting the baroreflex, which is critical for responding to the fluctuations in circulating blood volume often encountered during surgery (Muzi 1992). Nonetheless, α-2 adrenergic agonists have important adverse effects, including hypotension and bradycardia (Biccard 2008). These haemodynamic effects may have clinically important consequences for people undergoing surgery. For example, in the Perioperative Ischemic Evaluation - 1 (POISE-1) randomized controlled trial (RCT), acute perioperative β-blockade increased risks of bradycardia, hypotension, acute stroke, and death (POISE 2008). Given that α-2 adrenergic agonists have both potential benefits and adverse effects, a quantitative systematic review may help determine their overall efficacy and safety.

Why it is important to do this review

Previous systematic reviews of perioperative α-2 adrenergic agonists have been published (Biccard 2008; Nishina 2002; Stevens 2003). However, two of them were restricted to individual α-2 adrenergic agonists, namely clonidine (Nishina 2002), and dexmedetomidine (Biccard 2008). The other review was restricted to studies published before 2002 (Stevens 2003). A systematic review according to the Cochrane methodology is therefore justified. The current review is an update to a previous Cochrane Review that included studies published before August 2008 (Wijeysundera 2009). This update was deemed necessary, in part, given the publication of the largest RCT to-date of perioperative α-2 adrenergic agonists, the Perioperative Ischemic Evaluation - 2 (POISE-2) trial (Devereaux 2014a).

OBJECTIVES

To determine the efficacy and safety of α-2 adrenergic agonists for reducing mortality and cardiac complications in adults undergoing cardiac surgery and non-cardiac surgery.

METHODS

Criteria for considering studies for this review

Types of studies

We included published RCTs.

Types of participants

We included adults (aged 18 years or older) undergoing surgery under general anaesthesia, neuraxial anaesthesia, or both. We excluded surgery performed under local anaesthesia or peripheral nerve blockade alone because such procedures are generally associated with a very low risk of mortality and morbidity. We also excluded surgery performed on pregnant women, organ transplant recipients, or people with substance withdrawal. Organ transplantation procedures may be associated with a high risk of mortality unrelated to cardiovascular causes, thereby masking any potential benefit from α-2 adrenergic agonists.

Types of interventions

The experimental intervention must have included clonidine, mivazerol or dexmedetomidine administration before surgery (within 24 hours), during surgery, or after surgery (within 48 hours). The medications must have been administered via IV, intramuscular, oral or transdermal routes. There were no restrictions on the dose, duration or frequency of the intervention.

We permitted active interventions in the comparator group only if the comparator was judged to have minimal to no effect on the primary or secondary outcomes. For example, in a trial where dexmedetomidine was being primarily evaluated for the role of providing postoperative sedation after major surgery, comparison to propofol was judged to be reasonable.

Types of outcome measures

Included trials had to evaluate the efficacy or safety of α-2 adrenergic agonists in reducing perioperative mortality or cardiac complications, or both. Studies were included if they measured one or more relevant outcomes, which included death, MI, heart failure (HF), acute stroke, supraventricular tachyarrhythmia (SVT) or

myocardial ischaemia. In addition, studies with similar objectives to our review were included, even if these same studies did not report any relevant outcome events (i.e. death, MI, HF, acute stroke, SVT, myocardial ischaemia).

Primary outcomes

1. All-cause mortality within 30 days after surgery: any reported death. The time period for outcome ascertainment in each trial was also documented.

Secondary outcomes

1. Cardiac mortality within 30 days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause. The time period for outcome ascertainment in each trial was also documented.
2. MI within 30 days after surgery: definition as per individual study (specific criteria employed were documented). The time period for outcome ascertainment in each trial was also documented.
3. Myocardial ischaemia within 30 days after surgery: as detected on an electrocardiogram (ECG) or trans-oesophageal echocardiogram (specific criteria employed were documented). The time period for outcome ascertainment in each trial was also documented.
4. SVT within 30 days after surgery: SVT, atrial fibrillation or atrial flutter. The time period for outcome ascertainment in each trial was also documented.
5. HF within 30 days after surgery: clinical diagnosis of HF or need for postoperative intra-aortic balloon pump support (applicable only for cardiac surgery). The time period for outcome ascertainment in each trial was also documented.

Adverse effects from treatment

1. Acute stroke within 30 days after surgery: new focal neurological deficit with signs and symptoms lasting longer than 24 hours. The time period for outcome ascertainment in each trial was also documented.

Physiological effects of treatment

1. Bradycardia requiring pharmacological or pacemaker treatment during the period of study drug administration.
2. Hypotension requiring treatment with inotropes or vasopressors during the period of study drug administration.

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (CENTRAL, 2017, Issue 4), MEDLINE (1950 to April week 4 2017), Embase (1980 to May 2017), the Science Citation Index and reference lists of articles. The Ovid platform was used for searching the electronic databases.

We searched MEDLINE using the search terms presented in Appendix 1. We then limited the studies to those identified simultaneously by a highly sensitive search strategy for identifying RCTs in MEDLINE (Dickersin 1994). Our search strategies for CENTRAL and Embase are presented in Appendix 1.

Searching other resources

We entered all trials selected for inclusion into the Science Citation Index to identify any additional relevant articles. The bibliographies of all included articles and published reviews were searched to identify any other potentially relevant studies for inclusion. Additionally, we searched clinical trial registries, namely ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP), for published studies meeting our inclusion criteria. These additional searches were completed in May 2017.

Data collection and analysis

Selection of studies

Two authors (DD, AS) independently performed literature searches for potentially relevant RCTs. All identified published full papers and abstracts were assessed independently for inclusion by the same two authors. We applied no language restrictions. We documented the reasons for exclusion for all excluded studies. We resolved all disagreements by consensus or involvement of a third author (DNW).

Data extraction and management

Two authors (DD, AS) independently extracted data from the included studies on a predesigned data abstraction form (Appendix 2). These same two authors independently entered all data into Review Manager 5 (RevMan 2014). We were not blinded to study authors, institution or journal when performing data abstraction. Where necessary, we contacted authors of published trials to provide any additional information required for the analyses (see Methods of the review).

Assessment of risk of bias in included studies

Two authors (DD, AS) independently evaluated the quality of all included trials using the criteria recommended by the Cochrane Anaesthesia, Critical and Emergency Care (ACE) Group. These criteria emphasize the adequacy of allocation concealment, randomization, blinding and intention-to-treat (ITT) analysis. Each included study was evaluated using the Cochrane 'Risk of bias' tool (Higgins 2011a). We were not blinded to study authors, institution or journal when performing quality assessment.

Measures of treatment effect

We performed all statistical analyses using Review Manager 5 (RevMan 2014). Given that all outcomes and adverse effects were dichotomous, all treatment effects were expressed as pooled risk ratios (RR) with 95% confidence intervals (CI).

Unit of analysis issues

We excluded cross-over trials and cluster randomized trials in this review. If a study had multiple treatment arms, comparisons were made between α-2 adrenergic agonist and placebo, or between α-2 adrenergic agonist and inactive control.

Dealing with missing data

If a study had missing relevant data in the published report, we attempted to contact the study authors up to three times to obtain these data. If data were missing due to participant attrition, and imputation methods were not used in the published report, we employed complete case analysis when importing the data.

Assessment of heterogeneity

We measured heterogeneity using the I^2 statistic: the proportion of total variation explained by between-study variation as opposed to chance (Higgins 2002; Higgins 2003). Higher I^2 statistics imply more heterogeneity between studies than would be expected by chance alone.

Assessment of reporting biases

We carried out funnel plot analyses to assess for publication bias (Egger 1997), with formal tests for asymmetry being performed only if meta-analyses pooled data from 10 or more studies (Higgins 2011b).

Data synthesis

Given the clinical heterogeneity between cardiac and non-cardiac surgery, we conducted analyses for these two subgroups separately. If an individual study included both cardiac and non-cardiac surgery procedures, we attempted to obtain subgroup-specific results from the authors. If such data were not available, and greater than 75% of participants underwent cardiac surgical procedures, the specific study was allocated to the cardiac surgery subgroup. Conversely, the study was allocated to the non-cardiac surgery subgroup if greater than 75% of participants underwent non-cardiac surgical procedures. In all other cases, the specific study was excluded from the review. In the presence of low heterogeneity (I^2 statistic 25% or less) (Higgins 2003), pooled RRs were calculated using the fixed-effect model. In the presence of moderate-to-significant heterogeneity (I^2 statistic greater than 25%) (Higgins 2003), we used the random-effects model and carried out post-hoc analyses to attempt to explain the heterogeneity.

Subgroup analysis and investigation of heterogeneity

A priori, we planned several subgroup analyses to determine the potential influence of the surgical procedure, the specific α-2 adrenergic agonist employed and coexistent therapies on the overall results. Subgroup-specific results were only calculated if there were two or more studies within the subgroup. These subgroup analyses were as follows.

1. Treatment effects of α-2 adrenergic agonists on mortality (all-cause and cardiac-cause), MI and ischaemia based on the type of non-cardiac surgical procedure, namely vascular versus non-vascular non-cardiac surgery. If a variety of surgical procedures were included in a study, we attempted to obtain subgroup-specific results from the authors. If such data were not available, and greater than 75% of participants underwent the same class of surgery, the specific study was allocated to that specific subgroup. Failing that, the specific study was excluded from the subgroup analysis based on procedure type. We used statistical tests of interaction to assess for the presence of any subgroup effects.
2. We calculated treatment effects for each of clonidine, mivazerol and dexmedetomidine on mortality (all-cause and cardiac-cause), and MI in non-cardiac surgery. Statistical tests of interaction were used to assess for the presence of any subgroup effects.

Sensitivity analysis

We planned several sensitivity analyses a priori to characterize the influence of study quality and outcome definitions on the overall results.

1. We restricted the meta-analyses to the subset of studies that clearly reported methods for blinding and allocation concealment.
2. We determined the effect of α-2 adrenergic agonists on MI in the subset of RCTs that strictly defined MI a priori as either significant new Q waves on an ECG or significant elevations in enzymatic markers of cardiac injury (MB isoenzyme of creatinine kinase, troponin-I, troponin-T).
3. We determined the effect of α-2 adrenergic agonists on myocardial ischaemia in the subset of RCTs that strictly defined ischaemia a priori as ST segment depression or elevation of 0.1 mV or greater for one minute or longer.

In addition, we performed four additional post-hoc analyses.

1. Significant statistical heterogeneity was identified when calculating the pooled effect of α-2 adrenergic agonists on hypotension during non-cardiac surgery. To explore potential explanations for this heterogeneity, we conducted subgroup analyses based on the specific agent (i.e. clonidine, mivazerol or dexmedetomidine) in the included trials. A statistical test of interaction was used to assess for the presence of a subgroup effect.
2. During the course of the review, we identified several very large included RCTs that might have highly influenced the overall pooled estimates. Therefore, we conducted a sensitivity analysis that excluded these very large RCTs.
3. Mivazerol is an experimental α-2 adrenergic agonist that was studied in several relatively large trials, but never proceeded through the approval process for clinical use. At the request of external peer reviewers of this review, we conducted a sensitivity analysis that excluded trials that evaluated mivazerol.
4. Several relevant studies were conducted prior to 1997, during a period when perioperative practice might not necessarily be generalizable to contemporary practice. At the request of external peer reviewers of this review, we conducted a sensitivity analysis that excluded trials where data were collected prior to 1997.

'Summary of findings' tables and GRADE

To characterize the confidence in the pooled estimated treatment effects better, we used GRADE methodology to assess the quality of evidence (Guyatt 2008). We generated 'Summary of findings' tables that separately presented pooled treatment effect estimates for the subgroups of participants who underwent non-cardiac surgery and cardiac surgery. To facilitate this process, data from the meta-analyses in Review Manager 5 (RevMan 2014), were initially exported into GRADEpro. The GRADE approach rates quality of evidence as high, moderate, low or very low (GRADE Handbook 2013). Since all data included in this review were from RCTs, the quality of evidence for each outcome of interest was initially rated as high level, and then potentially downgraded up to three levels based on any deficiencies in the quality of the underlying evidence. The quality of evidence underlying each pooled treatment effect estimate was assessed with respect to the risk of bias, inconsistency, indirectness,

imprecision and publication bias (Balshem 2011). The anticipated risk for comparison of each outcome was determined based on the event rate in the control group. Only outcomes judged as critically important, based on their impact on patient health or clinical decision-making, were chosen for presentation in the 'Summary of findings' tables. In this present review, we included the following outcomes in the 'Summary of findings' tables, provided that relevant estimated pooled treatment effects were present: all-cause mortality, cardiac mortality, MI, acute stroke, bradycardia and hypotension.

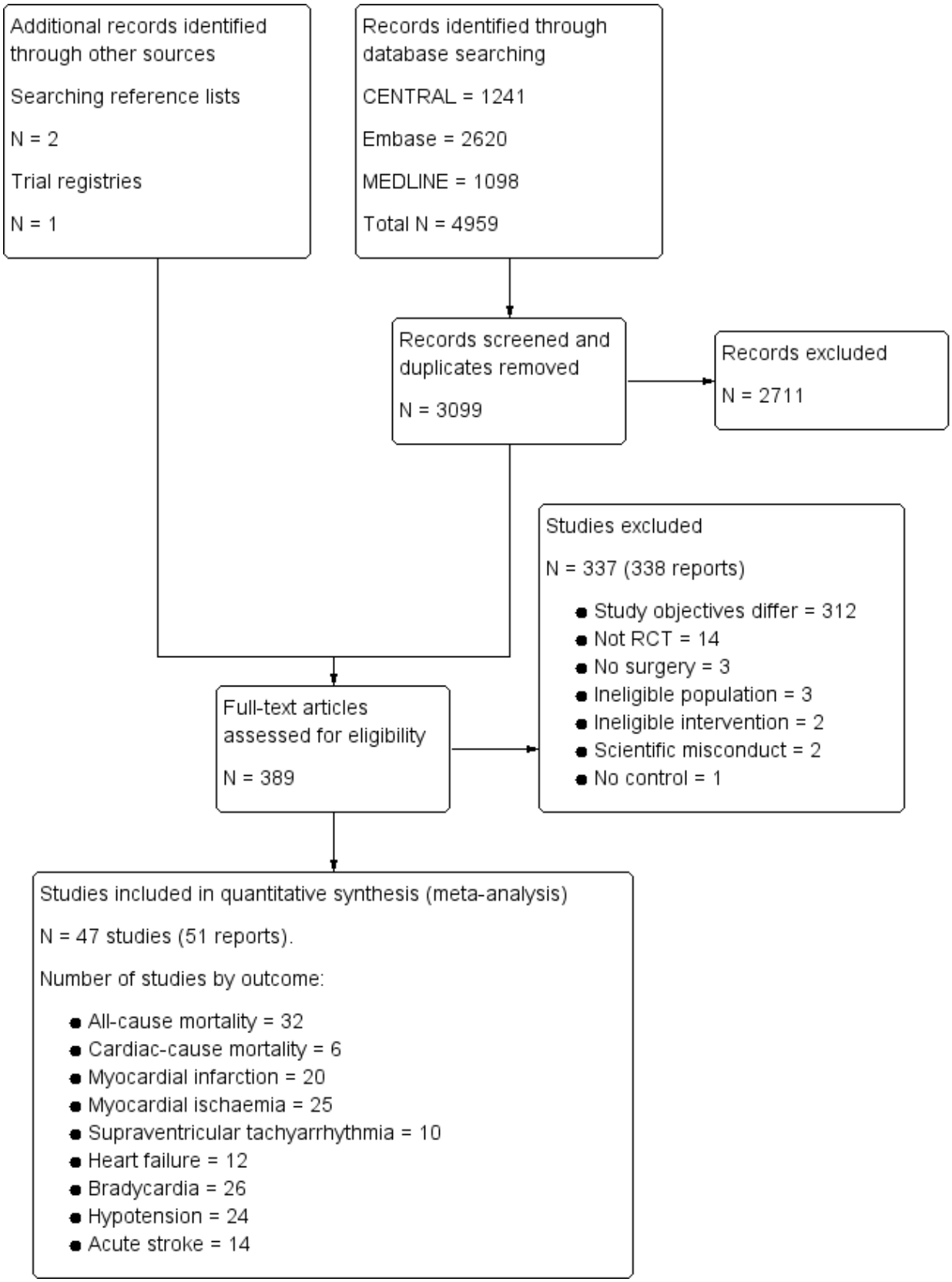
RESULTS

Description of studies

Results of the search

Our search results are presented in Figure 1. The authors identified 3099 separate papers in the literature search and three additional papers from other sources and in total read 389 papers in full.

Figure 1. Study flow diagram.



Included studies

We included 47 trials, which encompassed 17,039 participants (Abi-Jaoude 1993; Ammar 2016; Bergese 2010; Chi 2016; Cho 2016; Corbett 2005; Devereaux 2014a; Djaiani 2016; Dorman 1993; El-Kerdawy 2004; Ellis 1994; Ghignone 1986; Ghignone 1987; Helbo-Hansen 1986; Herr 2003; Jalonen 1997; Khalil 2013; Kim 2014a; Lee 2013a; Li 2017; Lipszyc 1991; Liu 2016; Loick 1999; Matot 2000; McSPI-Europe 1997; Myles 1999; Oliver 1999; Park 2014; Patel 2016; Pawlik 2005; Pluskwa 1991; Quintin 1993; Quintin 1996; Ren 2013; Shehabi 2009; Soliman 2016; Stuhmeier 1996; Su 2016; Talke 1995; Talke 2000; Venn 1999; Venn 2001; Viviano 2012; Wallace 2004; Wijeysundera 2014a; Xu 2014; Yin 2002). These studies are described in detail in the Characteristics of included studies tables.

Twenty four studies with 2672 participants involved cardiac surgery alone (Abi-Jaoude 1993; Ammar 2016; Chi 2016; Cho 2016; Corbett 2005; Djaiani 2016; Dorman 1993; El-Kerdawy 2004; Ghignone 1986; Helbo-Hansen 1986; Herr 2003; Jalonen 1997; Khalil 2013; Kim 2014a; Li 2017; Liu 2016; Loick 1999; Myles 1999; Park 2014; Patel 2016; Quintin 1993; Ren 2013; Shehabi 2009; Venn 1999). In all cases, the procedure involved was coronary artery bypass graft surgery or valve replacement surgery.

Of the 23 studies with 14,367 participants that involved non-cardiac surgery (Bergese 2010; Devereaux 2014a; Ellis 1994; Ghignone 1987; Lee 2013a; Lipszyc 1991; Matot 2000; McSPI-Europe 1997; Oliver 1999; Pawlik 2005; Pluskwa 1991; Quintin 1996; Soliman 2016; Stuhmeier 1996; Su 2016; Talke 1995; Talke 2000; Venn 2001; Viviano 2012; Wallace 2004; Wijeysundera 2014a; Xu 2014; Yin 2002), eight involved vascular procedures exclusively (Lipszyc 1991; McSPI-Europe 1997; Pluskwa 1991; Quintin 1996; Soliman 2016; Stuhmeier 1996; Talke 1995; Talke 2000), and seven involved non-vascular procedures exclusively (Ghignone 1987; Lee 2013a; Matot 2000; Pawlik 2005; Venn 2001; Viviano 2012; Xu 2014). One non-cardiac surgery study presented subgroup-specific results for both vascular and non-vascular procedures (Oliver 1999).

Sample size

The sample sizes of the included trials ranged from 20 participants to 10,010 participants. Fourteen studies had fewer than 50 participants (Abi-Jaoude 1993; Dorman 1993; Ghignone 1986; Ghignone 1987; Helbo-Hansen 1986; Lipszyc 1991; Matot 2000; Pawlik 2005; Pluskwa 1991; Quintin 1993; Quintin 1996; Talke 1995; Talke 2000; Venn 2001), 14 studies had 50 to 100 participants (Ammar 2016; Chi 2016; Corbett 2005; El-Kerdawy 2004; Ellis 1994; Jalonen 1997; Khalil 2013; Lee 2013a; Liu 2016; Loick 1999; Patel 2016; Viviano 2012; Xu 2014; Yin 2002), and 19 studies had greater than 100 participants (Bergese 2010; Cho 2016; Devereaux 2014a; Djaiani 2016; Herr 2003; Kim 2014a; Li 2017; McSPI-Europe 1997; Myles 1999; Oliver 1999; Park 2014; Ren 2013; Shehabi 2009; Soliman 2016; Stuhmeier 1996; Su 2016; Venn 1999; Wallace 2004; Wijeysundera 2014a).

Demographics of sample

The mean age of participants in most studies was 60 to 70 years. In addition, the ratio of men to women in the included studies was skewed, with trials generally recruiting disproportionally more men (Characteristics of included studies table).

Intervention and comparators

The number of studies that assessed dexmedetomidine was 24, clonidine was 21 and mivazerol was two. Treatment duration ranged from a single preoperative dose to a 72-hour course of treatment. With the exception of seven studies (Corbett 2005; Djaiani 2016; Herr 2003; Liu 2016; Park 2014; Shehabi 2009; Venn 2001), all trials compared α-2 adrenergic agonists against inactive control. Of the four studies with active controls, one compared dexmedetomidine to morphine (Shehabi 2009), whereas the remainder were comparisons of dexmedetomidine versus propofol.

All studies that evaluated dexmedetomidine employed the IV route of administration. Dexmedetomidine was administered intraoperatively in 15 studies, with administration being continued postoperatively in nine of them. The duration of postoperative administration varied across these nine studies, ranging from continuation until arrival to the critical care unit, to continuation for 48 hours. Nine additional studies investigated dexmedetomidine that was administered entirely after surgery in the critical care unit. Both studies of mivazerol administered the drug IV starting from the intraoperative period, with continuation until 72 hours after surgery.

There was considerable variation in the administration regimens used in trials that assessed clonidine. It was administered intraoperatively by the IV route in three studies, with one of these studies also administering an oral loading dose before surgery. A single study used IV clonidine that was administered only preoperatively (i.e. 30 minutes prior to surgery). Four studies employed clonidine administered using the combination of an oral preoperative loading dose, and subsequent maintenance via the transdermal route for 72 hours. Finally, 12 studies administered clonidine orally before surgery, with three of them administering an additional intraoperative dose via the nasogastric route.

Funding

Thirty-two studies reported their funding sources, whereas 15 did not (Abi-Jaoude 1993; Chi 2016; Cho 2016; El-Kerdawy 2004; Ghignone 1986; Ghignone 1987; Lipszyc 1991; Loick 1999; Myles 1999; Park 2014; Pluskwa 1991; Quintin 1993; Ren 2013; Stuhmeier 1996; Viviano 2012). Fourteen studies reported operational funding from pharmaceutical companies (Bergese 2010; Djaiani 2016; Helbo-Hansen 1986; Herr 2003; Jalonen 1997; Li 2017; McSPI-Europe 1997; Oliver 1999; Quintin 1996; Su 2016; Talke 1995; Talke 2000; Venn 1999; Venn 2001), and the remaining 18 studies reported that no pharmaceutical funds were used to complete the research (Ammar 2016; Corbett 2005; Devereaux 2014a; Dorman 1993; Ellis 1994; Khalil 2013; Kim 2014a; Lee 2013a; Liu 2016; Matot 2000; Patel 2016; Pawlik 2005; Shehabi 2009; Soliman 2016; Wallace 2004; Wijeysundera 2014a; Xu 2014; Yin 2002). Several studies in the latter group reported that a pharmaceutical company supplied the study drug as in-kind support, and explicitly stated no further funds were received from the company.

Excluded studies

After the full-text articles were reviewed, we excluded 337 studies. The reasons for these exclusions are presented in the Characteristics of excluded studies table, as well as the study flow diagram (Figure 1). The most common reason for exclusion was study objectives that differed from this present review (312

excluded studies). In these cases, the focus of these studies was to answer a question unrelated to the efficacy or safety of α-2 adrenergic agonists for reducing mortality or cardiac complications (e.g. assessing the efficacy of these drugs for providing analgesia). Of the remaining articles, 14 were excluded because the experimental design was not an RCT, three were excluded since participants did not undergoing surgery and three were excluded due to an ineligible population. Two studies could not be classified into either the cardiac or non-cardiac surgery subgroups, and were therefore excluded (Martin 2003; Triltsch 2002). A further two studies were excluded because the intervention was administered via an ineligible route (Nader 2009; Tzortzopoulou 2009), while one study was excluded due to lack of a control arm (Moghadam 2012). Three reports of two individual studies were excluded due to concerns about scientific misconduct (Boldt 1996; Wahlander 2005). In each of these cases, a lead author was found to have conducted scientific misconduct (Anon 2013; Rasmussen 2011; Wise 2013). Notably, both studies had been included in the previous 2009 version of this review (Wijeysundera 2009), at which point these issues with scientific misconduct had not yet been identified (Boldt 1996; Wahlander 2005).

Studies awaiting classification

No studies are currently awaiting classification.

Ongoing studies

We found no ongoing studies.

Risk of bias in included studies

The methodological quality of included studies is shown in the 'Risk of bias' figures (Figure 2; Figure 3). A visual summary of judgements about the quality and risk of bias for each trial is presented in Figure 3. Details explaining the judgements for each domain are presented in the 'Risk of bias' tables (Characteristics of included studies).

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

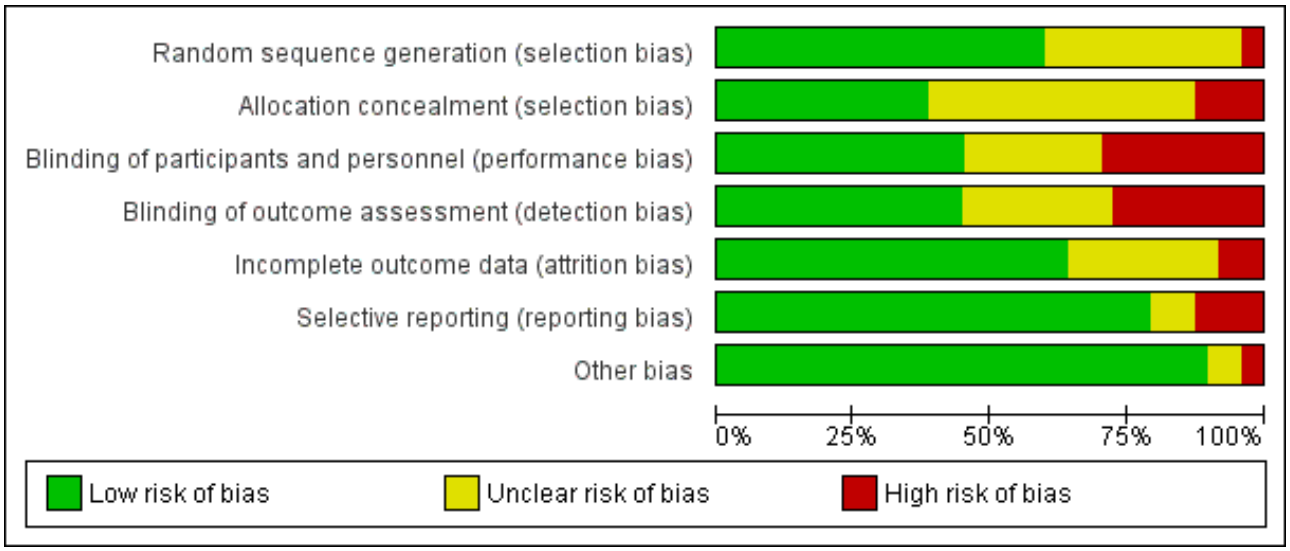


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

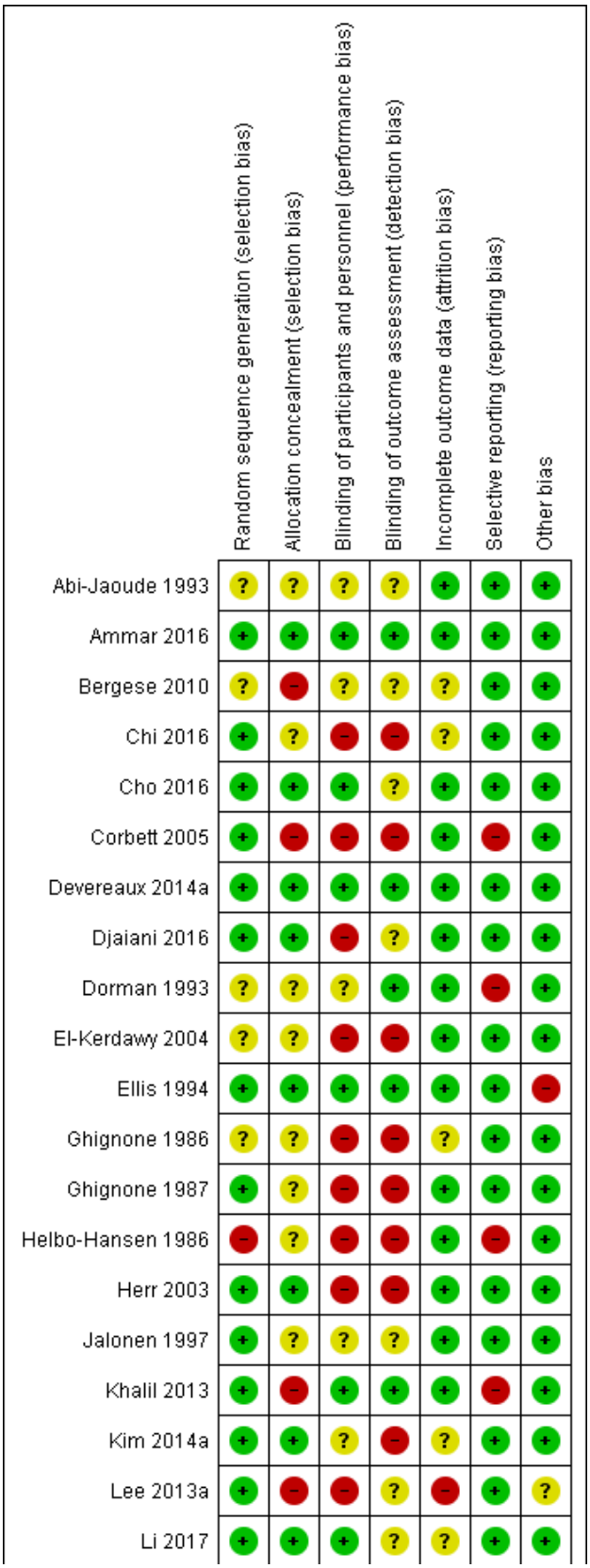
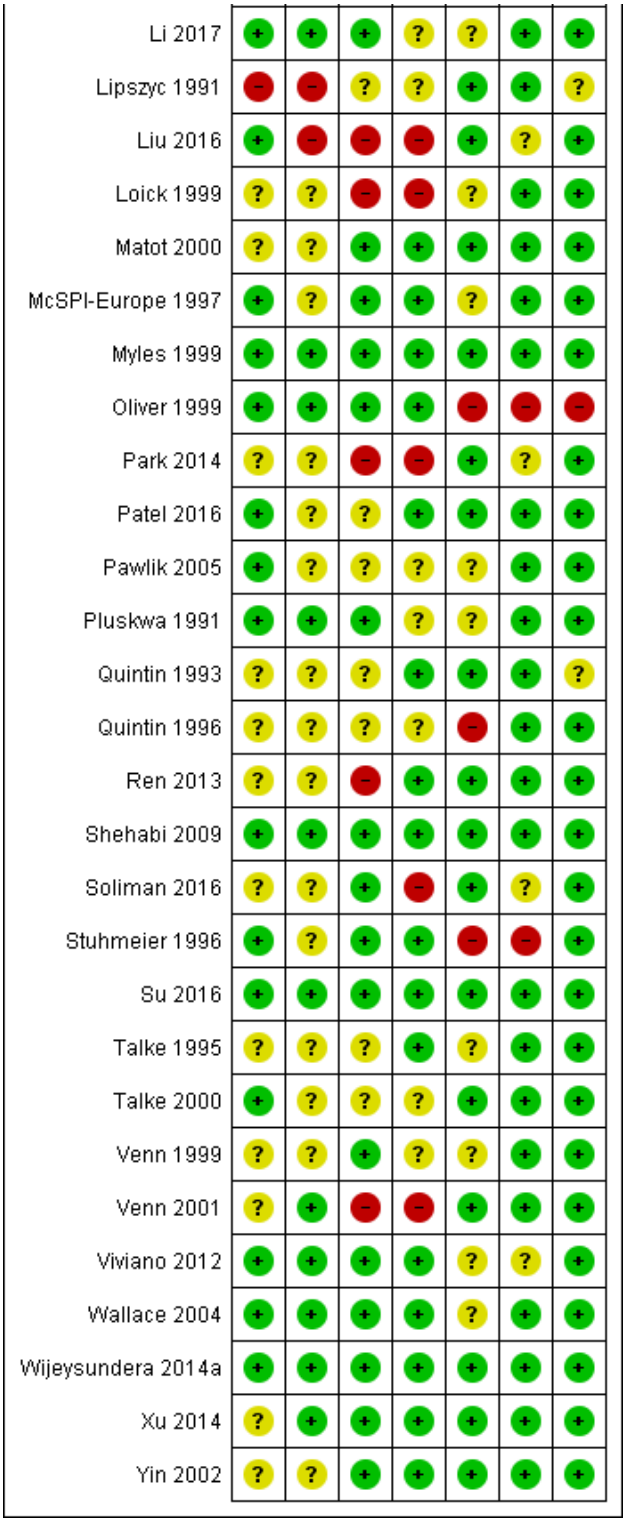


Figure 3. (Continued)



Allocation

Of the 47 included trials, only 28 were judged to have adequate methods of generating allocation sequences. Of the remaining 19 studies, two trials used methods likely to produces bias (Helbo-Hansen 1986; Lipszyc 1991), while the remaining trials were classified as having unclear risk of bias because the methods were not described in adequate detail. Concealment of allocation sequence was generally poor with only 18 studies reporting methods associated with low risk of bias, while six studies described methods associated with a high risk of bias (Bergese 2010; Corbett 2005; Khalil 2013; Lee 2013a; Lipszyc 1991; Liu 2016).

Only 16 studies reported adequate allocation sequence generation and allocation concealment.

Blinding

Although 31 studies described themselves as double-blind, only 21 clearly reported adequate methods for how blinding was achieved. Of the remaining 26 studies, 14 were open-label and therefore assessed to be high risk of bias, while the others were judged to have an unclear risk of bias. Outcome assessment was blinded in 21 trials, and therefore judged to be at low risk of bias. Only 16 trials demonstrated blinding of participants, personnel and outcome assessors.

Incomplete outcome data

Thirty trials reported no exclusions, exclusions deemed to be appropriate and ITT analysis. For four trials, exclusions (Lee 2013a; Oliver 1999; Quintin 1996; Stuhmeier 1996), were either not reported or judged as being excessive enough to likely cause bias. The remainder either failed to use ITT analysis or adequately account for exclusions. Only 11 studies reported a flow diagram of participants in the trial (Bergese 2010; Chi 2016; Devereaux 2014a; Kim 2014a; Lee 2013a; Li 2017; Liu 2016; Shehabi 2009; Su 2016; Viviano 2012; Wijeysundera 2014a), as is recommended in the CONSORT statement (Schulz 2010).

Selective reporting

Of the 47 trials, 37 demonstrated concordance between outcomes discussed in the methods or protocol and the outcomes reported. Four studies were judged to be of unclear risk of bias because they reported adverse events without discussing any surveillance methods (Liu 2016; Park 2014; Soliman 2016; Viviano 2012). The remaining six studies either failed to report major outcomes, or reported major outcomes not discussed in the relevant methods sections (Corbett 2005; Dorman 1993; Helbo-Hansen 1986; Khalil 2013; Oliver 1999; Stuhmeier 1996).

Other potential sources of bias

Five trials had other sources of bias classified as unclear risk or high risk. Two of the trials had high risk of bias due to significant changes in their methods during the trial recruitment phase. One trial terminated early (Ellis 1994), while the other changed its selection criteria (Oliver 1999). Three trials were classified as having unclear risk of bias, because two trials (Lipszyc 1991; Quintin 1993), were being published only in abstract form (therefore lacking complete peer-review), and another lacked reproducible selection criteria (Lee 2013a).

Effects of interventions

See: **Summary of findings for the main comparison** Alpha-2 adrenergic agonists compared to control in non-cardiac surgery; **Summary of findings 2** Alpha-2 adrenergic agonists compared to control in cardiac surgery

Non-cardiac surgery

Primary outcome

1. All-cause mortality within 30 days after surgery

Sixteen studies reported all-cause mortality, with 210 events (1.5%) among 14,081 participants. Alpha-2 adrenergic agonists had no statistically significant reduction in all-cause mortality (RR 0.80, 95% CI 0.61 to 1.04, P = 0.10), without any measurable heterogeneity (I^2 = 0%) (Analysis 1.1). The quality of this evidence was high (Summary of findings for the main comparison).

Secondary outcomes

1. Cardiac mortality within 30 days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause

Five studies reported cardiac-related deaths, with 114 events (0.9%) among 12,525 participants. Alpha-2 adrenergic agonists did not cause a statistically significant reduction in cardiac-related mortality (RR 0.86, 95% CI 0.60 to 1.23, P = 0.41) with low measurable heterogeneity (I^2 = 16%) (Analysis 1.2). The quality of evidence was high (Summary of findings for the main comparison).

2. Myocardial infarction within 30 days after surgery (definition as per individual study)

Twelve studies reported MIs, with 835 events (6.0%) among 13,907 participants. Alpha-2 adrenergic agonists were not associated with any statistically significant difference in the risk of MI (RR 0.94, 95% CI 0.69 to 1.27, P = 0.67) with moderate heterogeneity (I^2 = 37%) (Analysis 1.3). The quality of evidence was moderate (Summary of findings for the main comparison).

3. Myocardial ischaemia within 30 days after surgery: as detected on an electrocardiogram or transoesophageal echocardiogram (definition as per individual study)

Twelve studies reported myocardial ischaemia, with 291 events (21.1%) among 1379 participants. Alpha-2 adrenergic agonists did not significantly reduced the risk of ischaemia (RR 0.73, 95% CI 0.53 to 1.02, P = 0.06; I^2 = 45%) (Analysis 1.4).

4. Supraventricular tachycardia within 30 days after surgery: supraventricular tachycardia, atrial fibrillation or atrial flutter

Two studies reported SVTs, with one event (2.3%) among 44 participants. Both studies evaluated dexmedetomidine. Since there was no events reported in one of the studies (Venn 2001), pooled estimates were not calculated. The remaining trial showed no effect of α-2 adrenergic agonists on SVT (RR 1.11, 95% CI 0.05 to 24.07) (Analysis 1.5) (Talke 1995).

5. Heart failure within 30 days after surgery: clinical diagnosis of heart failure

Eight studies reported episodes of HF, with 107 events (1.0%) among 10,802 participants. There was no significant reduction in congestive heart failure (CHF) with perioperative α-2 adrenergic agonist use (RR 1.21, 95% CI 0.83 to 1.75, P = 0.32), with negligible heterogeneity (I^2 = 3%) (Analysis 1.6).

Adverse effects from treatment

1. Acute stroke within 30 days after surgery: new focal neurological deficit with signs and symptoms lasting longer than 24 hours

Seven studies reported acute strokes, with 56 strokes (0.5%) among 11,542 participants. Alpha-2 adrenergic agonists had no significant effect on acute stroke (RR 0.93, 95% CI 0.55 to 1.56 P = 0.79) with no measurable heterogeneity (I^2 = 0%) (Analysis 1.7). The quality of evidence for effects on acute stroke was high (Summary of findings for the main comparison).

Physiological effects of treatment

1. Bradycardia requiring pharmacological or pacemaker treatment

Sixteen studies reported bradycardia, with 1349 events (9.6%) in 14,035 participants. Within these 16 studies, α-2 adrenergic agonists significantly increased the risk of bradycardia (RR 1.59, 95% CI 1.18 to 2.13, P = 0.002), albeit with substantial heterogeneity (I^2 = 53%) (Analysis 1.8). The quality of evidence for treatment effects on bradycardia was moderate (Summary of findings for the main comparison).

2. Hypotension requiring treatment with inotropes or vasopressors

Fifteen studies reported hypotension, with 4766 events (34.7%) in 13,738 participants. Alpha-2 adrenergic agonists caused a significant increase in the risk of perioperative hypotension (RR 1.24, 95% CI 1.03 to 1.48, P = 0.02), albeit with substantial heterogeneity (I^2 = 54%) (Analysis 1.9). Based on a post-hoc subgroup analysis, the choice of drug may explain this heterogeneity (Analysis 4.4). Specifically, there was statistically significant evidence of subgroup effects based on whether the studies evaluated clonidine, dexmedetomidine or mivazerol (test of interaction P < 0.001). Clonidine significantly increased the risk of hypotension (RR 1.29, 95% CI 1.23 to 1.35, P < 0.001). Dexmedetomidine was also associated with an increased risk (RR 1.81, 95% CI 1.07 to 3.06, P = 0.03). Conversely, mivazerol did not increase the risk of hypotension (RR 0.95, 95% CI 0.82 to 1.10, P = 0.48). Clonidine and mivazerol subgroup analyses had no measurable heterogeneity (I^2 = 0%), whereas the dexmedetomidine subgroup analysis demonstrated significant heterogeneity (I^2 = 50%). The quality of evidence for treatment effects on hypotension was moderate (Summary of findings for the main comparison).

Cardiac surgery

Primary outcome

1. All-cause mortality within 30 days after surgery

Sixteen studies reported all-cause mortality, with 29 events (1.5%) among 1949 participants. Alpha-2 adrenergic agonists did not result in a statistically significant reduction in all-cause mortality (RR 0.52, 95% CI 0.26 to 1.04, P = 0.06), without any measurable heterogeneity (I^2 = 0%) (Analysis 2.1). The quality of this evidence was moderate (Summary of findings 2).

Secondary outcomes

1. Cardiac mortality within 30 days after surgery: sudden death or death resulting from a primarily identifiable cardiac cause

Only one study reported cardiac mortality, with 1 event among the 12 participants in the clonidine arm and no events among the 10 participants in the control arm (Loick 1999). Thus, no pooled analysis was performed.

2. Myocardial infarction within 30 days after surgery: definition as per individual study

Eight studies reported MIs, with 16 events (2.0%) among 782 participants. Alpha-2 adrenergic agonists were not associated with reduced risk of MI (RR 1.01, 95% CI 0.43 to 2.40, P = 0.98) in an analysis with no heterogeneity (I^2 = 0%) (Analysis 2.2). The quality of evidence was moderate (Summary of findings 2).

3. Myocardial ischaemia within 30 days after surgery: as detected on an electrocardiogram or transoesophageal echocardiogram (definition as per individual study)

Thirteen studies reported myocardial ischaemia, with 243 events (21.4%) among 1134 participants. Alpha-2 adrenergic agonists significantly reduced the risk of ischaemia (RR 0.69, 95% CI 0.56 to 0.86, P < 0.001) with no heterogeneity (I^2 = 0%) (Analysis 2.3).

4. Supraventricular tachycardia within 30 days after surgery: supraventricular tachycardia, atrial fibrillation or atrial flutter

Six studies reported SVTs, with 79 events (7.7%) among 1044 participants. Alpha-2 adrenergic agonists had no significant effect on the risk of SVT (RR 0.77, 95% CI 0.50 to 1.16, P = 0.21) with low measurable heterogeneity (I^2 = 24%) (Analysis 2.4).

5. Heart failure within 30 days after surgery: clinical diagnosis of heart failure or need for postoperative intra-aortic balloon pump support

Four studies reported 38 HF events (6.9%) among 549 participants. Alpha-2 adrenergic agonists had no statistically significant effect on the risk of HF (RR 0.90, 95% CI 0.49 to 1.63, P = 0.72) with no measurable heterogeneity (I^2 = 0%) (Analysis 2.5).

Adverse effects from treatment

1. Acute stroke within 30 days after surgery: new focal neurological deficit with signs and symptoms lasting longer than 24 hours

Seven studies reported acute stroke, with 18 events (1.5%) among 1175 participants. Alpha-2 adrenergic agonists significantly reduced the risk of acute stroke (RR 0.37, 95% CI 0.15 to 0.93, P = 0.03; I^2 = 0%) (Analysis 2.6). The quality of evidence was low (Summary of findings 2).

Physiological effects of treatment

1. Bradycardia requiring pharmacological or pacemaker treatment

Ten studies reported episodes of bradycardia, with 136 events (9.2%) among 1477 participants. Pooled analysis demonstrated that α-2 adrenergic agonists significantly increased the risk of bradycardia (RR 1.88, 95% CI 1.35 to 2.62, P = 0.0002) with no heterogeneity (I^2 = 0%) (Analysis 2.7). The quality of evidence was moderate (Summary of findings 2).

2. Hypotension requiring treatment with inotropes or vasopressors

Nine studies reported 494 episodes of hypotension (35%) among 1413 participants. Alpha-2 adrenergic agonists did not significantly increase the risk of hypotension (RR 1.19, 95% CI 0.87 to 1.64, P = 0.28) in an analysis with substantial heterogeneity (I^2 = 72%) (Analysis 2.8). The quality of evidence was low (Summary of findings 2).

Subgroup analyses

Vascular versus non-vascular non-cardiac surgery

There was no statistically significant evidence of subgroup effects based on procedure type (i.e. vascular versus non-vascular procedures) with respect to the outcomes of all-cause mortality (test of interaction P = 0.17; Analysis 3.1), cardiac mortality (test of interaction P = 0.13; Analysis 3.2), MI (test of interaction P = 0.13; Analysis 3.3), and myocardial ischaemia (test of interaction P = 0.17; Analysis 3.4).

Drug (i.e. clonidine, mivazerol or dexmedetomidine) evaluated in non-cardiac surgery

There was no statistically significant evidence of subgroup effects based on the specific α-2 adrenergic agonist evaluated with respect to the outcomes of all-cause mortality (test of interaction P = 0.50) (Analysis 4.1), and MI (test of interaction P = 0.48) (Analysis 4.3). Conversely, there was a statistically significant subgroup effect with respect to cardiac mortality (test of interaction P = 0.05) (Analysis 4.2). In these subgroup analyses, mivazerol significantly reduced cardiac mortality (RR 0.51, 95% CI 0.27 to 0.98, P = 0.04), whereas clonidine did not (RR 1.12, 95% CI 0.71 to 1.75, P = 0.63). There were insufficient studies that reported myocardial ischaemia as an outcome for dexmedetomidine or mivazerol to facilitate drug-specific subgroup analysis for the outcome.

Sensitivity analyses

Studies that clearly reported blinding and concealed allocation

The pooled effects of α-2 adrenergic agonists on all-cause mortality (RR 0.68, 95% CI 0.41 to 1.11, P = 0.12; participants = 13,066; studies = 7; Analysis 5.1), MI (RR 1.08, 95% CI 0.95 to 1.23, P = 0.26; participants = 13,026; studies = 6; Analysis 5.2), and myocardial ischaemia (RR 0.77, 95% CI 0.40 to 1.48, P = 0.43; participants = 412; studies = 3; Analysis 5.3) were qualitatively similar when analyses were restricted to trials that clearly reported methods for blinding and allocation concealment.

Strict definitions of myocardial infarction and ischaemia

When analyses were restricted to trials that strictly defined MI on ECG or enzymatic criteria, pooled treatment effects in non-cardiac surgery (RR 0.98, 95% CI 0.70 to 1.36, P = 0.90; participants = 13,003; studies = 8) and cardiac surgery (RR 0.76, 95% CI 0.19 to 2.98, P = 0.69; participants = 275; studies = 3) were qualitatively unchanged (Analysis 6.1). When analyses were restricted to studies that strictly defined events of myocardial ischaemia, the effects in non-cardiac surgery remained non-significant (RR 0.76, 95% CI 0.54 to 1.07, P = 0.12; participants = 1175; studies = 9). In cardiac surgery, the sensitivity analysis continued to demonstrate a reduction in the risk of ischaemia (RR 0.71, 95% CI 0.55 to 0.91, P = 0.007; participants = 820; studies = 8) (Analysis 6.2).

Influence of two large trials

The overall results of this review are likely highly influenced by two large RCTs in non-cardiac surgery, one of which assessed mivazerol (Oliver 1999), while the other assessed clonidine (Devereaux 2014a). Therefore, we performed a post-hoc sensitivity analysis that excluded these studies. After excluding these two trials, treatment effect on all-cause mortality became statistically significant (RR 0.45, 95% CI 0.22 to 0.93, P = 0.03; participants = 2174; studies = 14; Analysis 7.1). Conversely, the effect on cardiac mortality (RR 0.47, 95% CI 0.10 to 2.25, P = 0.35; participants = 618; studies = 3; Analysis 7.2), and MI (RR 0.56, 95% CI 0.25 to 1.25, P = 0.16; participants = 2000; studies = 10; Analysis 7.3) were statistically non-significant, albeit with more optimistic individual point estimates (i.e. pooled treatment effects shifted towards larger risk reductions).

Excluding drugs not introduced into clinical practice (i.e. mivazerol)

In post-hoc sensitivity analyses excluding the two trials that evaluated mivazerol (McSPI-Europe 1997; Oliver 1999), there was no change in pooled treatment effects pertaining to all-cause mortality, cardiac mortality, MI, SVT, HF, stroke, bradycardia, or hypotension (Analysis 8.1; Analysis 8.2; Analysis 8.3; Analysis 8.5; Analysis 8.6; Analysis 8.7; Analysis 8.8; Analysis 8.9). Conversely, the pooled treatment effect on ischaemia became statistically significant (RR 0.68, 95% CI 0.48 to 0.97, P = 0.03; participants = 1079; studies = 11; I^2 = 40%) (Analysis 8.4), albeit in an analysis with moderate heterogeneity and relatively few participants.

Restricting studies more representative of contemporary perioperative practice

When analyses pertaining to non-cardiac surgery were restricted to studies that collected data within the previous 20 years, there was no change in the pooled treatment effects pertaining to all-cause mortality, cardiac mortality, MI, HF or stroke (Analysis 9.1; Analysis 9.2; Analysis 9.3; Analysis 9.5; Analysis 9.6). Nonetheless, exclusion of older studies resulted in a significant reduction in the risk of myocardial ischaemia (RR 0.51, 95% CI 0.28 to 0.93, P = 0.03; participants = 634; studies = 6; I^2 = 48%) in an analysis with moderate heterogeneity (Analysis 9.4). In cardiac surgery, exclusion of older studies resulted in no substantive effect on the pooled treatment effects for MI, myocardial ischaemia, SVT, HF or stroke (Analysis 10.2; Analysis 10.3; Analysis 10.4; Analysis 10.5; Analysis 10.6). Conversely, the pooled treatment effect on all-cause mortality became statistically significant (RR 0.47, 95% CI 0.23 to 0.97; participants = 1782; studies = 13; I^2 = 0%) (Analysis 10.1).

Funnel plots

Funnel plots of included studies revealed no obvious publication bias with regard to the outcome of mortality (Figure 4), but some possible bias with regard to MI (Figure 5). Since this analysis pooled results from only nine studies, formal statistical testing for asymmetry was not conducted.

Figure 4. Funnel plot of comparison: 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, outcome: 1.1 All-cause mortality.

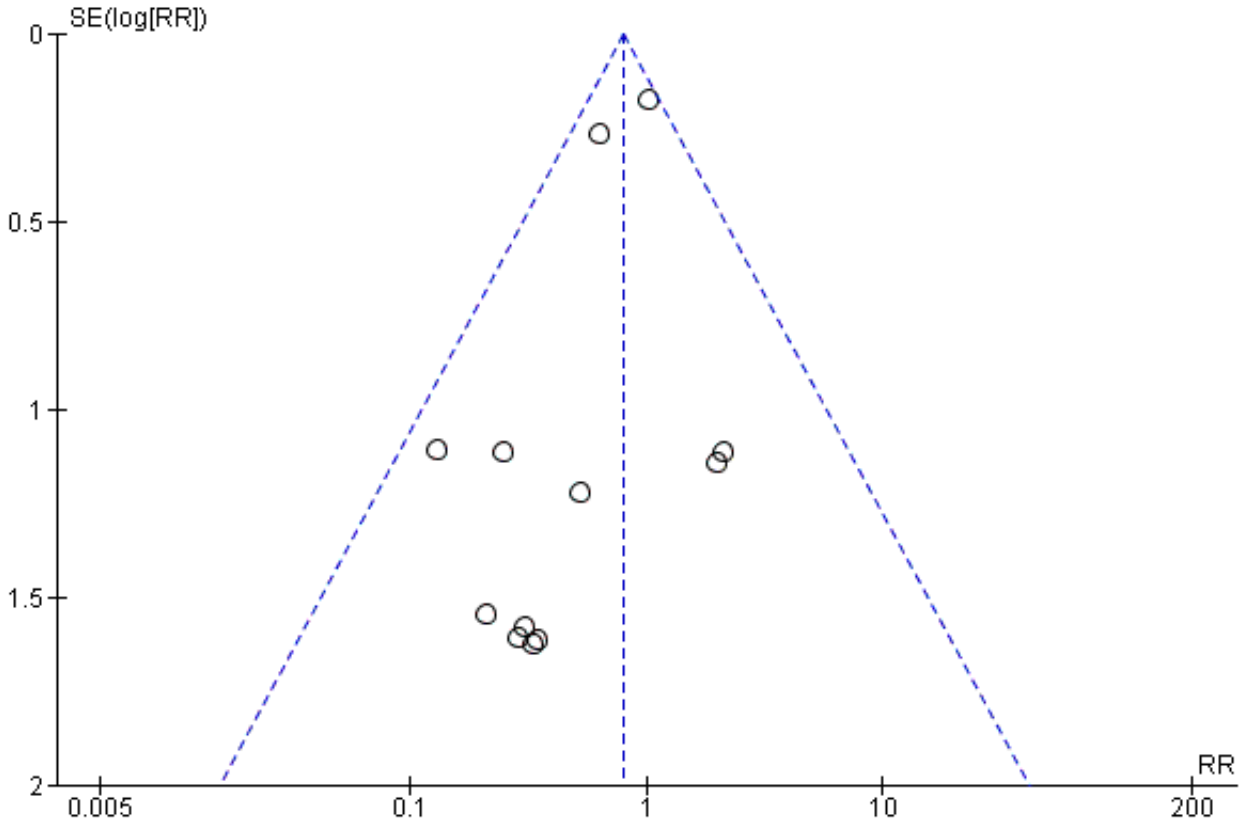
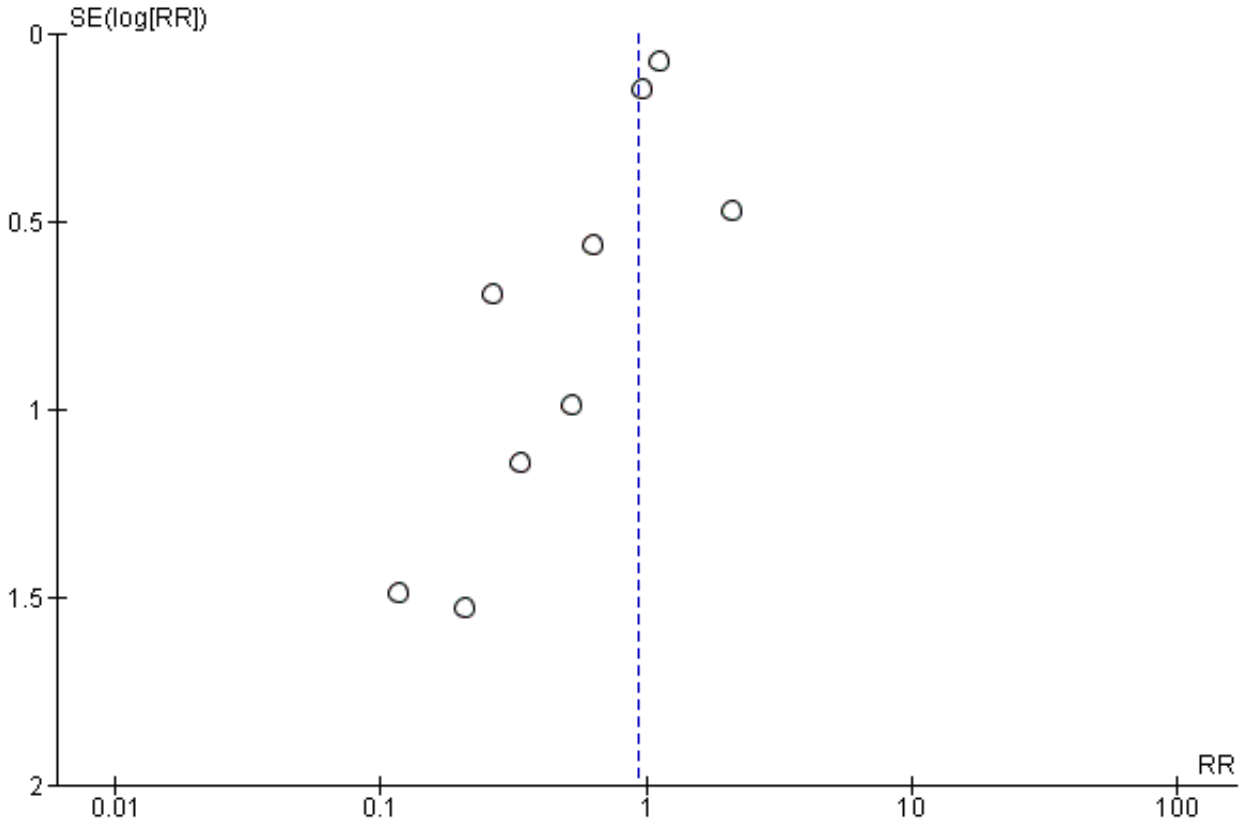


Figure 5. Funnel plot of comparison: 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, outcome: 1.3 Myocardial infarction.



DISCUSSION

Summary of main results

Our present review found high-quality evidence that perioperative α-2 adrenergic agonists did not reduce the risk of all-cause mortality, cardiac mortality or MI in people undergoing non-cardiac or cardiac surgery (Summary of findings for the main comparison; Summary of findings 2). These findings remained stable in sensitivity analyses restricted to studies that either demonstrated low risks of bias or employed strict definitions of MI. Aside from lacking any beneficial effect on these clinical outcomes, α-2 adrenergic agonists also conferred important risks, specifically increased rates of hypotension and bradycardia. While these haemodynamic effects were not associated with an increased risk of acute stroke, the 95% CIs for this pooled effect were wide (RR 0.93, 95% CI 0.55 to 1.56), thereby not excluding the possibility of a moderate increase in stroke risk with perioperative α-2 adrenergic agonists.

Overall completeness and applicability of evidence

The 47 RCTs included in this systematic review encompassed 17,039 participants, a wide range of relevant surgical procedures performed in several different countries internationally and clinically relevant dosing regimens of currently available α-2 adrenergic agonists (i.e. clonidine, dexmedetomidine). Furthermore, a significant number of participants from the included studies underwent surgery within the past decade. Thus, we are confident that the overall findings of our systematic review, namely that α-2 adrenergic agonists do not significantly reduce risks of cardiovascular complications or mortality when given prophylactically before major non-cardiac or cardiac surgery, can be reasonably extrapolated to contemporary perioperative practice.

Nonetheless, there were insufficient participants within specific subgroups to conclusively evaluate several potential benefits of α-2 adrenergic agonists, namely prevention of stroke, myocardial ischaemia and all-cause mortality after cardiac surgery. The subgroup analysis evaluating effects on stroke during cardiac surgery was small, with only seven included studies that encompassed 1175 participants (Analysis 2.6). The pooled estimate was based on low-quality data, calculated using very few outcome events (i.e. 18 strokes). Previous research has found that treatment effects are generally overestimated in meta-analyses that include relatively few outcome events (Thorlund 2011). Consistent with this possibility, the magnitude of the pooled estimate was somewhat implausible (RR 0.37, 95% CI 0.15 to 0.93), in that it suggested a 63% relative reduction in the risk of stroke from a single perioperative intervention. Therefore, further research is needed to determine whether α-2 adrenergic agonists can truly reduce the risk of acute stroke after cardiac surgery.

Similarly, the statistically significant pooled treatment effect on all-cause mortality was observed only in a post-hoc subset analysis restricted to cardiac surgery trials conducted after 1997 (Analysis

10.1). This subset was relatively small (13 studies encompassing 1782 participants), the pooled estimated was calculated using very few outcome events (i.e. 28 deaths) and the magnitude of the pooled estimate was somewhat implausible (RR 0.47, 95% CI 0.23 to 0.97) for a single intervention. More studies are needed to assess the effect of α-2 adrenergic agonists on all-cause mortality after cardiac surgery.

In a separate subgroup analysis in cardiac surgery, α-2 adrenergic agonists also caused a significant reduction in perioperative myocardial ischaemia (Analysis 2.3). Nonetheless, myocardial ischaemia is a surrogate outcome with important associated limitations (Svensson 2013). Especially in the absence of associated reductions in clinical important and patient-relevant outcomes such as mortality or MI, isolated reductions in perioperative myocardial ischaemia are not sufficient justifications for employing α-2 adrenergic agonists in clinical practice.

Quality of the evidence

This systematic review was supported by 47 RCTs that recruited 17,039 participants. The sample size of the included RCTs varied greatly, ranging from 20 to over 10,000 participants. Nineteen studies had over 100 participants, with only two studies involving over 1000 participants (Devereaux 2014a; Oliver 1999). The vast majority of these participants (14,367) were recruited into the 23 included trials in non-cardiac surgery. By comparison, the remaining 24 RCTs in cardiac surgery involved 2672 participants.

Only 16 studies reported adequate methods for random sequence generation and allocation concealment. Furthermore, although 31 studies described themselves as 'double-blinded,' only 21 studies reported appropriate methods to achieve blinding. Nonetheless, the majority of participants were from well-designed studies with adequate methods for allocation and blinding, thereby rendering them low risk to be influenced by selection bias, performance bias and detection bias.

The analyses pertaining to the primary and secondary outcomes in people undergoing non-cardiac surgery were generally robust. These findings were judged as moderate to high quality by GRADE methodology (Summary of findings for the main comparison). Although many studies failed to report adequate methods to avoid risk of bias, the specific outcomes were unlikely to be influenced and thus no downgrading of quality was necessary. In addition, there was a potential threat of indirectness since the second largest RCT evaluated mivazerol (Oliver 1999), which is not available for clinical use. However, given the similarity of mivazerol to dexmedetomidine (which is available for clinical use), we reasoned that this risk was likely not serious. Conversely, funnel plots suggested that the pooled treatment effects on MI was affected by publication bias (Figure 5). The asymmetry in the funnel plots was produced by two small studies with seemingly unrealistic effect sizes (Ellis 1994; Stuhmeier 1996). While the combined weight of these studies was less than 3% of the pooled analysis, we downgraded the evidence by one level because of suspicion of publication bias for an outcome known to be influenced by performance bias (Analysis 1.3). Finally, the quality of evidence for the physiological effects of bradycardia and hypotension were both downgraded because of substantial heterogeneity (I^2 greater than 50%) in the analyses (Analysis 1.8; Analysis 1.9).

The quality of evidence for the effects of α-2 adrenergic agonists in cardiac surgery was generally lower, largely due to imprecision resulting from significantly fewer participants in the pooled analyses (Summary of findings 2). The quality of evidence for all outcomes was downgraded because the optimal information size of 2000 participants was not achieved, and the 95% CIs of the pooled estimates did not rule out clinically significant effects (GRADE Handbook 2013). Thus, the quality of evidence for the analyses pertaining to all-cause mortality and MI was moderate. As there were very few outcomes events in the analysis of acute stroke (i.e. 18 strokes), it was downgraded another level and judged as low quality. Finally, the presence of substantial imprecision in pooled analysis pertaining to hypotension led to the quality of this evidence being downgraded to low (I^2 = 72%; Analysis 2.8). Nonetheless, the magnitude of the association between α-2 adrenergic agonists and hypotension in cardiac surgery (RR 1.19, 95% CI 0.87 to 1.64) was qualitatively very similar to that observed in non-cardiac surgery (RR 1.24, 95% CI 1.03 to 1.48), where the quality of evidence was moderate.

Potential biases in the review process

There were several limitations to our review process. First, while our search was exhaustive in that it covered all major medical indexes and clinical trial registries, we might have missed some published trials only listed in other less commonly used indices. Nonetheless, we believe it unlikely that our search strategy missed any relevant studies of at least moderate size and quality. Second, we only included studies reporting subgroup-specific outcome data based on surgical procedure type (i.e. cardiac surgery versus non-cardiac surgery). Consequently, we excluded any study that did not predominantly include procedures (greater than 75%) from either of these surgical procedure subgroup, unless subgroup-specific outcome data could be obtained from the authors. Consequently, two otherwise eligible studies could not be included in this systematic review (Martin 2003; Triltsch 2002). In excluding these studies, we balanced the risk of biasing the analyses with the loss of additional data, and chose the latter to maintain the integrity of our analyses.

Agreements and disagreements with other studies or reviews

There are several potential reasons why the theoretically beneficial physiological effects of α-2 adrenergic agonists did not translate into reduced rates of major postoperative cardiac complications. First, α-2 adrenergic agonists might not have sufficiently reduced heart rates to mitigate the risks of perioperative MI, as has been previously proposed (Devereaux 2014a). This hypothesis is supported by the observation that, while perioperative β-blockers caused more significant bradycardia than α-2 adrenergic agonists, rates of perioperative MI were reduced with β-blockers but not α-2 adrenergic agonists (Wijeysundera 2014b). Second, the predominant mechanism underlying perioperative MI in many affected people might not be increases in blood pressure and heart rate induced by the surgical stress response. For example, almost 30% of people with postoperative MI do not have significant obstructive coronary artery disease (Sheth 2015). It is unlikely that limiting perioperative increases in heart rate would help prevent MI in such people. Third, at a population-level, the beneficial effects of heart rate reduction in some people undergoing surgery might have been offset by equal numbers of people who experienced deleterious effects from significant perioperative hypotension.

Notably, our overall findings with respect to the absence of major reductions in perioperative cardiovascular risk from α-2 adrenergic agonists was somewhat consistent with results seen with prophylactic therapy with other sympatholytic agents. Specifically, β-adrenergic blockers have been shown to cause a net harmful effect in non-cardiac surgery (Wijeysundera 2014b). It remains to be seen whether any strategy of prophylactically attenuating haemodynamic abnormalities with sympatholytic agents can safely reduce perioperative cardiac risk. Indeed, if future RCTs with either alternative regimens of previously evaluated sympatholytic agents (i.e. α-2 adrenergic agonists, β-adrenergic blockers) or alternative negative chronotropic agents (e.g. ivabradine) fail to show net overall benefit, the general strategy for perioperative cardiac risk reduction may have to shift from *prophylactic therapy* to *early treatment*. Specifically, as opposed to administering these medications to a broad group of people before surgery, clinicians might instead consider targeting treatment in high-risk people identified on the basis of ischaemic ECG changes or elevated cardiac troponin concentrations early after surgery.

Comparison of our present systematic review on perioperative α-2 adrenergic agonists with a prior systematic review of perioperative β-adrenergic blockers in non-cardiac surgery also provides some potential insights into the mechanisms underlying perioperative stroke (Wijeysundera 2014b). Specifically, α-2 adrenergic agonists (RR 1.24, 95% CI 1.03 to 1.48) and β-adrenergic blockers (RR 1.47, 95% CI 1.34 to 1.60) conferred approximately similar risks of perioperative hypotension. Despite this similarity in haemodynamic effects, β-blockers (RR 1.86, 95% CI 1.09 to 3.16) conferred significantly increased risks of perioperative acute stroke while α-2 adrenergic agonists did not (RR 0.93, 95% CI 0.55 to 1.56). These contrasting effects are also evident when comparing two large individual perioperative RCTs of these two different drug classes, namely the POISE-1 trial of metoprolol (POISE 2008) and the POISE-2 trial of clonidine (Devereaux 2014a). Specifically, while metoprolol (hazard ratio (HR) 1.55, 95% CI 1.38 to 1.74) and clonidine (HR 1.32, 95% CI 1.24 to 1.40) caused qualitatively similar increases in rates of hypotension, metoprolol significantly increased risks of stroke (HR 2.17, 95% CI 1.26 to 3.74) while clonidine did not (HR 1.06, 95% CI 0.54 to 2.05). These findings suggest that, despite the previously observed association between perioperative hypotension and stroke (POISE 2008), the mechanisms underlying perioperative acute stroke are likely more complex than simply a decrease in perfusion pressure. Further research is needed to better delineate these mechanisms, and thereby inform the development of strategies to help prevent this often devastating perioperative complication (POISE 2008).

Importantly, perioperative α-2 adrenergic agonists do have other potential benefits that may justify their selective use in some people undergoing surgery. Specifically, in a previous systematic review of 30 small RCTs encompassing 1792 participants, these agents decreased both postoperative pain intensity and morphine consumption (Blaudszun 2012). Our present study provided additional data supporting the safety of using α-2 adrenergic agonists as an adjunct therapy for managing postoperative acute pain, provided that there is adequate attention to the associated risks of hypotension and bradycardia.

Strengths

Our present review had several strengths. The literature search was extensive and encompassed all languages. In addition, our study utilized a substantially larger data set than previous reviews (Biccard 2008; Nishina 2002; Stevens 2003; Wijeysundera 2003; Wijeysundera 2009). Finally, we performed multiple sensitivity analyses to assess the potential influence of study quality, outcome definition and publication bias on our overall conclusions.

Limitations

Our review had several limitations that should be considered. First, the results were heavily influenced by two large trials of mivazerol (Oliver 1999) and clonidine (Devereaux 2014a) in non-cardiac surgery. While excluding these large trials from the meta-analysis resulted in somewhat more optimistic point estimates for individual pooled treatment effects, these pooled estimates remained statistically non-significant. Second, as with any systematic review, our results may have been affected by publication bias. Though funnel plots indicated no obvious bias in the reporting of death (all-cause and cardiac-cause), they did suggest reporting bias may be present for MI. Third, our present analysis pooled trials of α-2 adrenergic agonists with differing selectivity for their target receptors, namely α-2 adrenoceptors and non-adrenergic imidazoline receptors (Khan 1999). Specifically, both mivazerol and dexmedetomidine have considerably greater selectivity for these target receptors than clonidine. Furthermore, when comparing the two large individual trials that dominated this meta-analysis (Devereaux 2014a; Oliver 1999), clonidine had no effect on mortality and increased rates of significant perioperative hypotension, while mivazerol, a more selective α-2 adrenergic agonist that is not currently available for clinical use, was associated with trends towards reduced mortality and had no effect on rates of hypotension. Importantly, these contrasting findings might have also been due to the different time periods when the studies were conducted, differences in study design, differences in participant characteristics or chance. Nonetheless, the contrasting findings still suggest that any future RCT of α-2 adrenergic agonists for cardiac risk reduction in people undergoing surgery should focus on agents with higher selectivity for α-2 adrenoceptors, such as dexmedetomidine or mivazerol.

AUTHORS' CONCLUSIONS

Implications for practice

Our study found high-quality data to firmly conclude that there are no compelling reasons for employing perioperative α-2 adrenergic agonists to reduce the risks of perioperative death or major cardiac complications in people undergoing surgery. These agents do not reduce the risks of death, myocardial infarction (MI) or acute stroke after surgery. Furthermore, they are associated with important adverse effects, namely increased risks of hypotension and bradycardia.

Implications for research

First, randomized controlled trials (RCTs) of clonidine for reducing perioperative cardiovascular risk should not be performed in the future because the Perioperative Ischemic Evaluation - 2 (POISE-2) trial provides compelling evidence that this specific agent lacks benefit. Second, while it is presently unclear whether more selective α-2 adrenergic agonists, such as dexmedetomidine or mivazerol, have differing effects on clinical outcomes in comparison to clonidine, there are at least theoretical reasons to pursue this hypothesis in future trials. Thus, future RCTs of perioperative α-2 adrenergic agonists should focus on these more

selective agents. Any such future trial should also adhere to quality standards for RCTs including blinding (participants, caregivers, outcome adjudicators), allocation concealment and intention-to-treat analysis. Third, appropriately designed future RCTs are needed to determine whether more selective α-2 adrenergic agonists can help prevent perioperative stroke or all-cause death after cardiac surgery.

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Meara 2015

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Abi-Jaoude 1993

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	24 participants undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 59 (7.5); placebo group: 56 (12). **Sex:** 17 men, 7 women. **Exclusion criteria:** emergency surgical procedures, LVEF < 0.5, and chronic clonidine treatment.
Interventions	1. Clonidine 5 µg/kg orally 2 hr before surgery. 2. Placebo.
Outcomes	1. MI. 2. Myocardial ischaemia (ST depression > 0.1 mV for > 3 min before CPB). 3. Hypotension (requiring drug treatment). 4. Heart failure.
Notes	Funding: source not disclosed. Declarations of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm, and described that "management was double blind throughout the study period." No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.

Abi-Jaoude 1993 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Ammar 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	50 ASA class II or III people scheduled for cardiac surgery using CPB. **Age (yr):** mean (SD): dexmedetomidine group: 55 (7); placebo group: 59 (6). **Sex:** 38 men, 12 women. **Exclusion criteria:** aged > 75 yr, LVEF < 55%, pre-existing severe LV hypertrophy, cardiomyopathies, Grade II (pseudonormal filling) and Grade III (restrictive filling) diastolic dysfunction, preoperative AF, pericardial disease, drug dependence, cerebrovascular diseases, use of α-2 agonists, type I diabetes mellitus, renal disease, significant pulmonary disease and hepatic insufficiency.
Interventions	1. Dexmedetomidine initiated 5 min before CPB at 1 µg/kg IV over 15 min, followed by 0.5 µg/kg/hr until 6 hr after surgery. 2. Normal saline placebo using identical protocol.
Outcomes	1. All-cause mortality (30 days). 2. Ischaemia (acute coronary syndrome). 3. Acute stroke.
Notes	Funding: Minoufiya University. Declaration of interest: no conflict of interest. Recruitment dates: June 2012 to February 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization using random number table.
Allocation concealment (selection bias)	Low risk	Independent statistician assigned to perform central randomization to ensure proper concealment.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants and clinicians blinded to assignment throughout study period.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome assessment.

Ammar 2016 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Bergese 2010

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	124 people undergoing elective awake fibreoptic intubation for anticipated difficult airway. **Age (yr):** range 19-78. **Sex:** 69 men, 36 women. **Exclusion criteria:** pregnant or lactating women, use of α-2-adrenergic agonist or antagonist within 14 days, use of opioid administered orally or IV within 1 hr or intramuscularly within 4 hr, presence of increased intracranial pressure or cerebrospinal fluid leak, acute alcoholic intoxication, uncontrolled seizure disorder, history of acute unstable angina, laboratory-confirmed acute MI within past 6 weeks, HR < 50 bpm, SBP < 90 mmHg, complete heart block unless person had a pacemaker, or liver transaminase enzymes > 2 times upper normal limit.
Interventions	1. Dexmedetomidine 1 µg/kg loading dose IV followed by 0.7 µg/kg/hr infusion, 15 min prior to airway topicalization until completion of awake fibreoptic intubation. 2. Placebo (normal saline) given in identical manner.
Outcomes	1. All-cause mortality. 2. Hypotension (SBP < 80 mmHg or 30% below baseline, DBP < 50 mmHg). 3. Bradycardia (< 40 bpm or 30% below baseline).
Notes	Funding: Hospira, Inc. Declarations of interest: authors received personal fees from pharmaceutical company. Recruitment dates: 7 August 2006 to 26 January 2007 at 17 medical centres in US.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	1:1 randomization, stratified by Mallampati and ASA classification. No details on methods provided.
Allocation concealment (selection bias)	High risk	Authors stated randomization schedule used.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Not discussed.

Bergese 2010 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	9 participants in dexmedetomidine and 11 participants in placebo group did not receive study drug because surgery was cancelled.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Chi 2016

Methods	Randomized controlled trial comparing dexmedetomidine (high dose and low dose) versus placebo.
Participants	100 people undergoing OPCAB for 3-vessel disease. With 34 participants in high-dose, 33 in low-dose and 33 in placebo groups. **Age (yr):** mean (SD): high-dose: 56 (7); low-dose: 54 (7); placebo: 56 (8). **Sex:** 60 men, 40 women. **Exclusion criteria:** LVEF < 40%, LV aneurysm, acute MI in 2 weeks before OPCAB surgery, AF, need for cardiac valve replacement, associated vascular diseases, severe systemic diseases involving renal and hepatic systems, respiratory disease (forced vital capacity < 50% of predicted values) and preoperative left bundle-branch block.
Interventions	1. High dose: dexmedetomidine loading dose 1 µg/kg IV over 5 min prior to induction of anaesthesia, then maintenance dose 0.6 µg/kg/hr until end of procedure. 2. Low dose: dexmedetomidine loading dose 0.6 µg/kg IV over 5 min prior to induction of anaesthesia, then maintenance dose 0.3 µg/kg/hr until end of procedure. 3. Placebo (normal saline) delivered in same volume.
Outcomes	No outcomes reported (study not included in analyses).
Notes	Funding: not stated. Declarations of interest: not stated. Recruitment dates: June 2012 to December 2013.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomization sequence.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.

Chi 2016 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	105 participants enrolled and randomized; however, 5 excluded from analysis because of conversion to CPB (n = 3), reoperation for major bleeding within 4 hr (n = 1) and incomplete data acquisition (n = 1). While these were a relatively small number of participants, there was no indication that post-hoc exclusion was planned.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Cho 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	200 people scheduled for cardiac surgery with CPB. **Age (yr):** mean (SD): dexmedetomidine group: 64 (12); saline group: 62 (13). **Sex:** 96 men, 104 women. **Exclusion criteria:** left main coronary artery occlusion > 50%, haemodynamically significant arrhythmia, LVEF < 30%, intra-aortic balloon pump or ventricular assist device, estimated GFR < 15 mL/min/1.73 m^2, use of α-2 adrenergic agonist to treat hypertension, untreated hypertension, previous exposure to dexmedetomidine or history of severe allergy to drugs.
Interventions	1. Dexmedetomidine continuous infusion 0.4 µg/kg/hr IV starting immediately after anaesthetic induction and continuing for 24 hr after surgery. 2. Normal saline infused in identical manner.
Outcomes	1. All-cause mortality (in hospital). 2. Stroke (not defined).
Notes	Funding: not directly stated; however, they stated no commercial associations. Declarations of interest: no conflict of interest. Recruitment dates: June 2013 to January 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias)	Low risk	Matched placebo and intervention, prepared by independent member of staff. All staff involved in direct care were blinded to allocation arm.

Cho 2016 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Blinded outcome assessment not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Corbett 2005

Methods	Randomized controlled trial comparing dexmedetomidine versus propofol.
Participants	89 people undergoing non-emergent CABG surgery with an expected length of intubation < 24 hr. **Age (yr):** mean (SD): 63 (10.4). **Sex:** 73 men, 16 women **Exclusion criteria:** hypersensitivity to either drug or any component of drugs; severe hypotension immediately before initiation of study drug; HR 40 bpm immediately before initiation of study drug; renal insufficiency; hepatic dysfunction; requirement for continued neuromuscular blocking agents postoperatively; requirement for epidural or spinal anaesthesia; gross obesity; history of alcohol or drug abuse. Participants withdrawn from study if length of intubation exceeded 48 hr.
Interventions	1. Dexmedetomidine 1 µg/kg IV loading dose then 0.4 µg/kg/hr infusion, beginning immediately after surgery. 2. Propofol 0.2-0.7 µg/kg/hr IV infusion.
Outcomes	1. All-cause mortality. 2. Supraventricular tachyarrhythmia.
Notes	Funding: Society of Critical Care Medicine, Clinical Pharmacy and Pharmacology Section, Ortho-Biotech Fellowship Grant, and departmental funds. Declaration of interest: not stated. Recruitment dates: October 2002 to April 2004.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of random-number table.
Allocation concealment (selection bias)	High risk	Methods of concealment not discussed. Allocation took place in operating room at end of operation.

Corbett 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	High risk	Do not discuss length of intubation or ICU stay as outcomes in methods; however, they were reported.
Other bias	Low risk	None.

Devereaux 2014a

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	10,010 people undergoing elective non-cardiac surgery (38% orthopaedic, 27% general, 6% vascular). **Age (yr):** mean (SD): clonidine group: 68.5 (10.4); placebo group: 68.6 (10.3). **Sex:** 5283 men, 4727 women. **Exclusion criteria:** see extensive list in published protocol (Devereaux 2014b).
Interventions	1. Clonidine 0.2 mg oral dose 2-4 hr prior to surgery with placement of 0.2 mg/day transdermal patch placed at same time and removed 72 hr after surgery. 2. Placebo (matched pill and patch).
Outcomes	1. All-cause mortality. 2. Cardiac mortality. 3. MI (biochemical evidence of myocardial ischaemia and pathological changes on ECG or ECHO, or coronary intervention (PCI, CABG)). 4. Heart failure (clinical signs with radiographic evidence). 5. Hypotension (SBP < 90 mmHg requiring treatment), bradycardia (HR < 55 bpm requiring treatment). 6. Stroke (new focal neurological deficit lasting > 24 hr or leading to death).
Notes	Funding: grants from Canadian Institutes of Health Research, Commonwealth Government of Australia's National Health and Medical Research Council, Spanish Ministry of Health and Social Policy, and Boehringer Ingelheim. In this 2-by-2 factorial design trial, Bayer Pharma provided the aspirin study drug while Boehringer Ingelheim provided the clonidine study drug. Declarations of interest: several authors received personal fees from pharmaceutical companies but declared that these fees had no relation or influence on the study. Recruitment dates: July 2010 to December 2013. Although some participants underwent surgery with only a nerve block, this accounted for < 1% of total sample.
Risk of bias	

Devereaux 2014a *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated block randomization stratified by ASA stratum and centre.
Allocation concealment (selection bias)	Low risk	Central 24-hr randomization centre.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported, "Patients, health care providers, data collectors, and outcome adjudicators are blinded to treatment allocation." Matched placebo used in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome adjudicators blinded. Detailed definitions of outcomes provided.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analysis used and all missing data and participants accounted for.
Selective reporting (reporting bias)	Low risk	Outcomes determined a priori and reported in a separate publication.
Other bias	Low risk	None.

Djaiani 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus propofol.
Participants	185 participants aged > 60 yr undergoing elective complex cardiac surgery and aged > 70 yr undergoing either isolated coronary revascularization or single-valve surgery (repair or replacement) with use of CPB. **Age (yr):** mean (SD): dexmedetomidine group: 73 (6.4); propofol group: 72 (6.2). **Sex:** 138 men, 45 women. **Exclusion criteria:** serious mental illness, delirium, severe dementia or emergency procedures.
Interventions	1. Dexmedetomidine bolus 0.4 µg/kg IV (over 10-20 min) upon arrival on ICU, followed by 0.2-0.7 µg/kg/hr infusion for a maximum of 24 hr. 2. Propofol infusion 25-50 µg/kg/min until readiness for tracheal extubation.
Outcomes	1. All-cause mortality.
Notes	Funding: funded, in part, by Hospira Inc, and Department of Anesthesia and Pain Management, Toronto General Hospital, Toronto, Ontario, Canada. Declaration of interest: authors declared no potential conflicts. Recruitment dates: July 2011 to July 2014.

Risk of bias

Bias	Authors' judgement	Support for judgement

Djaiani 2016 *(Continued)*

Random sequence generation (selection bias)	Low risk	Computer-generated randomization in blocks of 4.
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes generated according to randomization schedule and opened by a study co-ordinator.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Only participants blinded.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Unblinded outcome assessment. Unclear if it would affect outcome of death.
Incomplete outcome data (attrition bias) All outcomes	Low risk	185 participants randomized and 183 analysed. 1 participant died in operating room, and 1 participant underwent off-pump coronary revascularization surgery based on intraoperative decision and was excluded from analysis.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Dorman 1993

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	43 people undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 65 (2); placebo group: 61 (2). **Sex:** 37 men, 6 women. **Exclusion criteria:** LVEF < 45%, LV end-diastolic pressure > 18 mmHg, or chronic clonidine exposure.
Interventions	1. Clonidine 5 µg/kg orally 90 min before surgery, then 5 µg/kg via nasogastric tube 10 min before initiation of CPB. 2. Placebo suspension administered in a similar protocol.
Outcomes	1. Myocardial ischaemia (use of nitrates for ischaemic ECG changes). 2. Bradycardia (requiring intraoperative pacing).
Notes	Funding: grant from Society of Cardiovascular Anesthesiologists. Declaration of interest: not discussed.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors described prospective randomization but did not describe methods.
Allocation concealment (selection bias)	Unclear risk	Not discussed.

Dorman 1993 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Reported use of placebo in control arm but did not describe details regarding blinding.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded investigator used to independently assess ST changes. Blinding for other outcomes not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	High risk	No prespecified outcomes discussed in methods.
Other bias	Low risk	None.

El-Kerdawy 2004

Methods	Randomized controlled trial comparing dexmedetomidine versus control.
Participants	50 people undergoing OPCAB graft surgery. **Age (yr):** mean (SD): dexmedetomidine group: 61 (8); control group: 62 (4). **Sex:** 30 men, 22 women (error in manuscript, 2 additional participants) **Exclusion criteria:** LVEF < 45%, LV end-diastolic pressure > 18 mmHg, cardiac valvular abnormality, atrioventricular block, chronic clonidine or methyldopa treatment, or SBP < 90 mmHg.
Interventions	1. Dexmedetomidine 1 µg/kg IV loading dose then 0.15 µg/kg/hr infusion, beginning 30 min before surgery. Infusion continued until 2 hr after extubation (maximum duration 24 hr). 2. Control group received no intervention.
Outcomes	1. Myocardial ischaemia (ST depression or elevation > 0.1 mV for > 1 min after surgery).
Notes	Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated participants randomly allocated but methods not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.

El-Kerdawy 2004 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Ellis 1994

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	61 people, with a diagnosis or risk factors of coronary artery disease, who were undergoing major non-cardiac surgery (82% vascular) **Age (yr):** median (IQR): clonidine group: 69 (61-74); placebo group: 68 (63-75). **Sex:** 29 men, 32 women. **Exclusion criteria:** chronic methyldopa or clonidine therapy, serum creatinine > 30 mg/dL, planned carotid endarterectomy surgery, planned thoracic aortic aneurysm surgery, pulse < 50 bpm, or PR interval > 0.24 sec.
Interventions	1. Clonidine transdermal patch 200 µg/day for 72 hr from night before surgery. In addition, clonidine 300 µg orally 60-90 min before surgery. 2. Placebo skin patches and tablets were administered in an identical protocol.
Outcomes	1. All-cause mortality (7 days). 2. MI (persistent new Q-wave on ECG, or CK-MB > 40 IU) (7 days). 3. Myocardial ischaemia (ST depression > 0.1 mV or elevation > 0.2 mV for > 1 min). 4. Heart failure.
Notes	Study was terminated early at 61 participants due to low incidence of ischaemia. It was originally designed to recruit 160 participants in 2 arms. Funding: Anesthesiology Young Investigator Award from the Foundation for Anesthesia Education and Research. Declaration of interest: not stated. Recruitment dates: November 1990 to May 1992.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors reported use of computer-generated random numbers.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.

Ellis 1994 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported that all participants and clinicians were blinded to treatment assignment throughout study.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment by an investigator not involved in care of participant, blinded to allocation.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	High risk	Study terminated early because of a lower than expected rate of myocardial ischaemia; unclear whether this unblinded interim analysis was prespecified.

Ghignone 1986

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	24 people with hypertension who were NYHA class 3-4 with LVEF > 0.5 and undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 60 (9); control group: 58 (5). **Sex:** 13 men, 11 women. **Exclusion criteria:** none.
Interventions	1. Clonidine 5 µg/kg orally 90 min before surgery. 2. Control group received standard treatment.
Outcomes	1. Myocardial ischaemia (assessed by changes in ST and T waves).
Notes	Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated participants were randomly assigned but did not describe methods.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias)	High risk	Criteria for outcome assessment not prespecified. Open-label.

Ghignone 1986 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Inconsistency in reporting number of participants in each arm (i.e. Figure 2).
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Ghignone 1987

Methods	Randomized controlled trial comparing clonidine versus placebo
Participants	30 people ASA II-III with hypertension undergoing non-cardiac surgery (abdominal, head and neck, orthopaedic). **Age (yr):** mean (SD): clonidine group: 49 (15); control group: 48 (13). **Sex:** 14 men, 16 women. **Exclusion criteria:** severe hypertension (DBP > 110 mmHg), heart failure, chronic airway obstruction, MI with 2 yr, active angina pectoris.
Interventions	1. Clonidine 5 µg/kg orally 90 min before surgery. 2. Control group received standard treatment.
Outcomes	1. Myocardial ischaemia (ST depression > 2 mm). 2. Hypotension (requiring drug treatment).
Notes	Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Described use of random-number table.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Criteria for outcome assessment not prespecified. Open-label.
Incomplete outcome data (attrition bias)	Low risk	All data reported.

Ghignone 1987 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Helbo-Hansen 1986

Methods	Randomized controlled trial comparing clonidine versus control.
Participants	40 people undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 52 (10); control group: 55 (7). **Sex:** 36 men, 4 women **Exclusion criteria:** concurrent valve replacement or aneurysmectomy planned, disseminated disease other than essential arterial hypertension or diabetes, preoperative medication included α-adrenergic receptor blockers, ganglion blockers, loop-diuretics, clonidine or methyldopa, LVEF < 40%, AF, atrioventricular block, SBP < 80 mmHg at time of study drug administration.
Interventions	1. Clonidine 4 µg/kg IV 10 min before skin incision, 2 µg/kg IV 30 min after CPB, and 1 µg/kg IV after skin suture. 2. Control group received isotonic saline at same time points.
Outcomes	1. All-cause mortality (1 month). 2. MI (not defined).
Notes	Funding: Boehringer Ingelheim International. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Authors described use of 'stratified randomisation.' Stratification abandoned for last few participants to even out groups.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo used in control arm; however, details of blinding not discussed.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not discussed,
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported,

Helbo-Hansen 1986 *(Continued)*

Selective reporting (reporting bias)	High risk	MI and mortality not prespecified as outcomes in methods,
Other bias	Low risk	None.

Herr 2003

Methods	Randomized controlled trial comparing dexmedetomidine versus propofol. Analyses performed on intention-to-treat basis.
Participants	295 people undergoing CABG surgery. **Age (yr):** mean (SD): dexmedetomidine group: 62 (10); propofol group: 62 (9). **Sex:** 265 men, 30 women. **Exclusion criteria:** pregnant women, neurological condition preventing evaluation, unstable or uncontrolled diabetes, grossly obese, ejection fraction < 30%, hospitalized for drug overdose. People who received neuromuscular block, epidural or spinal anaesthesia in postoperative period or any other factor that investigator determined would affect study data (i.e. haemodynamic instability) were discontinued from study.
Interventions	1. Dexmedetomidine 1 µg/kg IV bolus, then 0.4 µg/kg/hr infusion, beginning immediately after surgery. 2. Propofol based on institutional protocols.
Outcomes	1. MI (not defined). 2. Supraventricular tachyarrhythmia. 3. Heart failure. 4. Hypotension. 5. Bradycardia.
Notes	Funding: supported by Abbot Laboratories. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of blocked randomization.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias)	Low risk	All data reported.

Herr 2003 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Jalonen 1997

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	80 people undergoing CABG surgery. **Age (yr):** mean (SD): dexmedetomidine group: 55 (9), placebo group: 56 (8). **Sex:** 67 men, 13 women. **Exclusion criteria:** left main coronary artery stenosis > 50%, significant valvular dysfunction, severe concurrent systemic disorders, preoperative medication with clonidine or α-methyldopa, strong susceptibility to allergic reactions, and uninterpretable results of ECG (e.g. left bundle branch block).
Interventions	1. Dexmedetomidine 50 ng/kg/min IV before surgery for 30 min, followed by 7 ng/kg/min IV intraoperatively. 2. Saline placebo administered in identical protocol.
Outcomes	1. All-cause mortality (7 days). 2. MI (new persistent Q-waves on ECG and CK-MB > 70 U/L). 3. Myocardial ischaemia (ST depression > 0.1 mV or elevation > 0.2 mV for > 1 min). 4. Supraventricular tachyarrhythmia. 5. Heart failure. 6. Hypotension (SBP < 80 mmHg after surgery). 7. Bradycardia (HR < 50 bpm after surgery).
Notes	Funding: supported by Orion Corporation. Declaration of interest: not stated. Recruitment dates: June 1992 to March 1993.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of permuted block randomization.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias)	Unclear risk	Blinded ECG interpretation but no other outcomes discussed.

Jalonen 1997 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Khalil 2013

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	50 people undergoing OPCAB graft surgery. **Age (yr):** mean (SD): dexmedetomidine group: 58.1 (10): placebo group: 58.9 (10). **Sex:** 31 men, 19 women. **Exclusion criteria:** body mass index > 35 kg/m^2; left main coronary artery disease; left bundle branch block; severe combined renal, hepatic or respiratory disorders; or any contraindication to use of dexmedetomidine. Post-hoc exclusion of people who developed severe haemodynamic alterations or arrhythmias requiring CPB.
Interventions	1. Dexmedetomidine 1 µg/kg IV bolus over 10 min at induction, followed by a 0.5 µg/kg/hr IV infusion until end of surgery, then a 0.25 µg/kg/hr IV infusion until arrival in ICU. 2. Saline placebo administered in identical protocol.
Outcomes	1. All-cause mortality (until hospital discharge, mean 6 days).
Notes	Funding: reported no financial support received for research. Declaration of interest: stated no conflict of interest. Recruitment dates: January to September 2008.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors reported use of a 'random number table.'
Allocation concealment (selection bias)	High risk	Concealment not discussed. Use of random number table high risk.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as blinded. Intensivist and anaesthesiologist caring for participants were blinded. Described use of matched placebo in control arm. Separate members of staff responsible for managing the infusion, who were not involved in care of participant.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinding of outcome assessment not discussed. Outcome of all-cause mortality low risk to be influenced.

Khalil 2013 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	High risk	Adverse event data not reported (stated as not significant).
Other bias	Low risk	None.

Kim 2014a

Methods	Randomized controlled trial comparing dexmedetomidine versus lidocaine versus combination versus control.
Participants	153 people (40 dexmedetomidine, 36 lidocaine, 39 combined, and 38 control) under-going OPCAB. Only participants in dexmedetomidine and control group included in meta-analyses. **Age (yr):** median (IQR): dexmedetomidine group: 63 (56-68); control group: 65 (57-72). **Sex:** 60 men, 18 women. **Exclusion criteria:** planned CPB and people diagnosed with arrhythmia with medication or pacemaker. Post-hoc exclusion of cases with unexpected conversion to CPB during surgery.
Interventions	1. Dexmedetomidine 0.3 µg/kg/hr IV starting after induction of anaesthesia and titrated within 0.3-0.7 µg/kg/hr to maintain mean blood pressure within 20% of preoperative value. Infusion was continued until 24 hr postoperatively. 2. Lidocaine. 3. Dexmedetomidine + lidocaine. 4. Control group did not receive an infusion.
Outcomes	1. All-cause mortality (1 year). 2. Myocardial ischaemia (measured CK-MB and cTnI at 4 hr, day 1 and day 2 postoperatively; however, threshold to define outcome not stated).
Notes	Funding: no external funding. Declaration of interest: not stated. Recruitment dates: September 2012 to August 2013.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Internet-based computer-generated randomization sequence.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Anaesthesiologist not blinded to study drug. Participants and surgeon kept blinded; however, no placebo used in control group.

Kim 2014a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	High risk	Data analyst blinded. No discussion of blinding of outcome assessment. Outcomes definition for myocardial ischaemia not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	160 participants initially randomized, 4 participants excluded due to unexpected conversion to surgery with CPB. 3 participants further excluded from analysis because there was a missing laboratory value; however, groups they were allocated to not disclosed.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Lee 2013a

Methods	Randomized controlled trial comparing dexmedetomidine versus remifentanil versus placebo.
Participants	85 participants (28 dexmedetomidine, 28 low-dose remifentanil, 29 placebo) ASA physical status I-II and aged 20-65 yr, undergoing laparoscopic-assisted vaginal hysterectomy. Only dexmedetomidine and placebo group were included in meta-analyses. **Age (yr):** mean (SD): dexmedetomidine group: 49 (6); placebo group: 48 (5). **Sex:** women. **Exclusion criteria:** allergy to dexmedetomidine, clinically significant medical or psychiatric conditions, pregnancy, history of alcohol or drug abuse, or opioid-containing pain or sedative medications.
Interventions	1. Dexmedetomidine 1 µg/kg IV bolus over 10 min, 15 min prior to induction, followed by 0.7 µg/kg/hr IV infusion until surgical closure complete. 2. Remifentanil. 3. Saline placebo administered in identical protocol.
Outcomes	1. Mortality. 2. Hypotension (not defined). 3. Bradycardia (not defined).
Notes	Funding: study supported by Wonkwang University, Iksan, South Korea. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors reported use of a 'random number table.'
Allocation concealment (selection bias)	High risk	Concealment not discussed. Use of a random number table was high risk.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Reported use of placebo in control group. Blinding not discussed.

Lee 2013a *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed and outcomes not defined.
Incomplete outcome data (attrition bias) All outcomes	High risk	5 participants lost to follow-up for conversion to open surgery or re-exploration for postoperative bleeding. Not predefined in exclusion criteria or methods.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Unclear risk	Selection bias: exclusion criteria vague (i.e. "clinically significant medical or psychiatric condition").

Li 2017

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	285 elderly people (age ≥ 60 yr) undergoing elective CABG or valve replacement surgery, or both. **Age (yr):** mean (SD): dexmedetomidine group: 66.4 (5.4); placebo group: 67.5 (5.3). **Sex:** 197 men, 88 women. **Exclusion criteria:** history of schizophrenia, epilepsy, Parkinson's disease or severe dementia; inability to communicate because of severe visual/auditory dysfunction or language barrier; history of functional neurosurgery or brain injury; preoperative sick sinus syndrome, severe bradycardia (HR < 50 bpm), second-degree or above atrioventricular block without pacemaker; severe hepatic insufficiency (Child-Pugh grades C); severe renal insufficiency (requirement of renal replacement therapy); person refused to participate in study.
Interventions	1. Dexmedetomidine 0.6 µg/kg bolus IV over 10 min, follow by 0.4 µg/kg/hr infusion until end of operation, and then 0.1 µg/kg/hr until end of mechanical ventilation. 2. Normal saline placebo administered in identical protocol.
Outcomes	1. All-cause mortality (30-day). 2. Acute stroke (30-day). 3. Bradycardia (requiring treatment, intraoperative or postoperative). 4. Hypotension (requiring treatment, intraoperative or postoperative).
Notes	Funding: Scientific Research Fund (2015) from Peking University First Hospital. Study drugs manufactured and supplied by Jiangsu Hengrui Medicine Co, Ltd, Jiangsu, China. Declaration of interest: Dr DX Wang received lecture fees or travel expenses (or both) for lectures given at domestic academic meetings from Jiangsu Hengrui Medicine Co, Ltd, China. Prof D Ma was supported by BOC Chair grant, Royal College of Anaesthetists, and BJA Fellowship grant, London, UK. Other authors reported no conflict of interests. Recruitment: 1 December 2014 to 19 July 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Centre-stratified randomization with a block size of 4 using SAS statistical package by an independent biostatistician.

Li 2017 *(Continued)*

Allocation concealment (selection bias)	Low risk	Randomization results sealed in sequentially numbered letters and stored at site of investigation until end of study.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	All investigators, healthcare team members and participants blinded to treatment group assignment throughout study period. Study drugs prepared and coded by independent pharmacist.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not formally discussed but outcomes unlikely to be influenced.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	More participants in dexmedetomidine group (8) were lost to follow-up than in control group (3), which may influence results given low frequency of outcomes.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Lipszyc 1991

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	40 people undergoing vascular (carotid artery) surgery. **Age:** not reported. **Sex:** not reported. **Exclusion criteria:** not reported.
Interventions	1. Clonidine 4 µg/kg orally 90 min before surgery. 2. Placebo was given using matched oral tablets.
Outcomes	1. Myocardial ischaemia (ST depression > 0.1 mV for > 1 min).
Notes	Published as an abstract. Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Not described as randomized trial.
Allocation concealment (selection bias)	High risk	Not discussed.
Blinding of participants and personnel (performance bias)	Unclear risk	Authors described study as 'double-blind.' Reported use of placebo in control arm. No other details reported.

Lipszyc 1991 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Unclear risk	Study published as abstract and not formally peer reviewed.

Liu 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus propofol.
Participants	88 participants, aged ≥18 yr, undergoing elective cardiac surgery with CPB, admitted to ICU while intubated and ventilated, and lack of prior AF or flutter before receiving sedation in ICU. **Age (yr):** mean (IQR): dexmedetomidine group: 53 (46.0-63.0); propofol group: 57 (49.3-62.0). **Sex:** 35 men, 53 women. **Exclusion criteria:** HR < 50 bpm, atrioventricular conduction block grade II or III (unless a pacemaker had been installed), MAP < 55 mmHg (despite appropriate IV volume replacement and vasopressor treatment), acute severe neurological disorder, propofol or dexmedetomidine allergy or other contraindications. In addition, people who had received ≥ 2 sedatives within 24 hr postoperatively excluded.
Interventions	1. Dexmedetomidine ≤ 1.5 μg/kg/hr adjusted to maintain RASS at 0 to -3, from arrival in ICU until extubation. 2. Propofol ≤ 3 mg/kg/hr adjusted to maintain RASS at 0 to -3.
Outcomes	1. Mortality (in hospital). 2. AF (no consistent P waves before each QRS complex) (96 hr). 3. Bradycardia (HR < 60 bpm for > 5 min). 4. Hypotension (MAP < 65 mmHg for > 3 min).
Notes	Funding: authors stated, "not applicable." Declaration of interest: declared no conflict of interest. Recruitment dates: January 2015 to December 2015. First Affiliated Hospital of Zhejiang University.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Random number table used.

Liu 2016 *(Continued)*

Allocation concealment (selection bias)	High risk	Used random number table but no discussion of concealment.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Only 1 participants in each group excluded because they received sedatives.
Selective reporting (reporting bias)	Unclear risk	Mortality reported but not listed as outcome in methods.
Other bias	Low risk	None.

Loick 1999

Methods	Randomized controlled trial comparing clonidine versus thoracic epidural anaesthesia versus control.
Participants	70 people (24 clonidine, 25 epidural, 21 control) undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 62 (11); placebo group: 63 (7). **Sex:** 36 men, 9 women. **Exclusion criteria:** disorders of intestine and liver, gastritis, duodenal ulcer, autonomic neuropathy, diabetes mellitus.
Interventions	1. Clonidine 5 µg/kg orally 90 min before surgery, followed by 5 µg/kg via nasogastric tube 10 min before initiation of CPB. 2. Thoracic epidural anaesthesia. 3. Control group received standard care.
Outcomes	1. All-cause mortality (6 months). 2. MI (troponin T > 0.1 ng/mL). 3. Myocardial ischaemia (ST depression > 0.1 mV or ST elevation > 0.2 mV). 4. Bradycardia (requiring pacing).
Notes	Only participants in clonidine and control arms included in analyses. Data on ischaemia available for only 29 participants (clonidine group: 14; control group: 15). Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**

Loick 1999 *(Continued)*

Random sequence generation (selection bias)	Unclear risk	Authors stated participants randomly allocated but methods not described.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	2 participants in control arm excluded because of repeat thoracotomy for bleeding.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Matot 2000

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	36 people ASA I-III, aged ≥ 50 yr undergoing microlaryngoscopy and rigid bronchoscopy under general anaesthesia. **Age (yr):** mean (SD): clonidine group: 63 (9); placebo group: 61 (10). **Sex:** 26 men, 10 women. **Exclusion criteria:** preoperative use of clonidine, HR < 50 bpm, atrioventricular block, left bundle-branch block or gastrointestinal disturbance that would hinder absorption medication.
Interventions	1. Clonidine 300 µg orally 90 min prior to surgery. 2. Placebo.
Outcomes	1. Myocardial ischaemia (ST depression > 0.1 mV or elevation > 0.2 mV for > 1 min). 2. Hypotension (requiring drug treatment). 3. Heart failure.
Notes	Funding: institutional funding. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors stated participants randomly allocated but methods not described.

Matot 2000 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described use of coded oral preparations with placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinician who analysed ECGs was blinded to treatment assignment. Criteria were prespecified to define ischaemia, hypotension and bradycardia.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

McSPI-Europe 1997

Methods	Randomized controlled trial comparing mivazerol (high and low dose) versus placebo.
Participants	317 people (17 excluded) with coronary artery disease undergoing vascular surgery under general anaesthesia for > 1 hr. (high-dose group: 98; low-dose group: 99; placebo: 103). **Age (yr):** mean (SD): high-dose group: 67 (10); low-dose group: 65 (10); placebo group: 66 (8). **Sex:** 233 men, 67 women. **Exclusion criteria:** taking methyldopa, α-2 adrenergic agonists or tricyclic antidepressants; in cardiogenic shock and had clinical signs of heart failure or required chronic inotropic support for ventricular dysfunction; unstable angina or uncontrolled hypertension; conduction defects that precluded electrocardiographic analysis of ST segments; pregnant or ASA physical status V.
Interventions	1. High-dose mivazerol 4 µg/kg IV bolus 20 min prior to induction of anaesthesia and continued as a 1.5 µg/kg/hr infusion for 72 hr after surgery. 2. Low-dose mivazerol 2 µg/kg IV bolus and 0.75 µg/kg/hr infusion. 3. Placebo.
Outcomes	1. All-cause mortality. 2. Cardiac mortality. 3. MI (persistent new Q-wave or CK-MB > 100 ng/mL). 4. Myocardial ischaemia (ST depression > 0.1 mV or ST elevation > 0.2 mV for > 1 min during first 24 postoperative hr). 5. Heart failure. 6. Bradycardia (requiring drug treatment). 7. Hypotension (requiring drug treatment).
Notes	Mivazerol arms were combined in analyses. Funding: grants from UCB Pharma and the Ischemia Research and Education Foundation.

McSPI-Europe 1997 *(Continued)*

Declaration of interest: stated no conflict of interest.

Recruitment dates: March to December 1993.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of blocked stratified randomization.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported use of placebo in control arm. Reported that staff who undertook clinical care were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Authors reported that staff who interpreted ECG recordings, diagnosed MI by ECG criteria and performed statistical analyses were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Excluded 7 participants for 'technical reasons,' which is ambiguous. Table 2 only reported results for 98/103 participants in placebo group.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Myles 1999

Methods	Randomized controlled trial comparing clonidine versus placebo
Participants	156 people (6 excluded) undergoing CABG surgery. **Age (yr):** mean (SD): clonidine group: 65 (11); placebo group: 65 (9). **Sex:** 128 men, 28 women. **Exclusion criteria:** receiving clonidine or alpha-methyldopa, allergic to clonidine, considered very high risk (clinical severity score > 9), hypotensive (SBP < 120 mmHg), heart failure, ejection fraction < 25%, AF or atrioventricular block, left bundle branch block or had a pacemaker.
Interventions	1. Clonidine 5 µg/kg orally 90 min before surgery, followed by 5 µg/kg via nasogastric tube before CPB. 2. Placebo.
Outcomes	1. All-cause mortality (1 month). 2. MI (CK-MB fraction > 5%). 3. Myocardial ischaemia (intraoperative ST depression > 0.1 mV or ST elevation > 0.2 mV for > 2 min). 4. Bradycardia (HR < 50 bpm requiring drug therapy). 5. Hypotension (mean blood pressure < 65 mmHg requiring drug therapy).
Notes	Funding: not discussed.

Myles 1999 *(Continued)*

Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of stratified randomization.
Allocation concealment (selection bias)	Low risk	Independent randomization by research pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported use of a placebo in control arm. In addition, they described that "investigators and patients" were blinded to treatment assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Diagnosis of MI by ECG and biochemical criteria was made by a blinded clinician. Statistical analyses performed by staff blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Exclusions reported with valid explanations provided.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Oliver 1999

Methods	Randomized controlled trial comparing mivazerol versus placebo. Analyses performed on intention-to-treat basis.
Participants	2854 people with a diagnosis or risk factors for coronary artery disease who were undergoing vascular, abdominal, thoracic or orthopaedic surgery. Results only presented for 1897 with coronary artery disease. **Age (yr):** 48% aged 65-75. **Sex:** 1403 men, 494 women. **Exclusion criteria:** unstable angina, MI in past 14 days, uninterpretable ECG Q-waves, cardiogenic shock, prescribed alpha-methyldopa or clonidine, severe hepatic disorders, renal insufficiency, emergency surgery, pregnant or nursing women.
Interventions	1. Mivazerol 4 µg/kg IV bolus 20 min before induction of anaesthesia, and 72 hr IV infusion at 1.5 µg/kg/hr. 2. Placebo (normal saline).
Outcomes	1. All-cause mortality (30 day). 2. Cardiac cause mortality (30 days). 3. MI (persistent new Q-wave with clinical syndrome or troponin-T > 1 µg/L). 4. Hypotension (requiring drug treatment). 5. Bradycardia (requiring drug treatment).

Oliver 1999 *(Continued)*

Notes	2857 participants were recruited in total, but only results for 1897 participants with coronary artery disease were reported. Funding: UCB SA Pharma Sector. Declaration of interest: State steering committee not sponsored by UCB Pharma but further potential conflicts not stated. Recruitment dates: June 1994 to February 1997.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of a computer-generated randomization schedule with stratification by institution.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Authors reported that all outcomes were adjudicated by staff who were blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	High risk	Only presented data for 1897/2854 recruited participants.
Selective reporting (reporting bias)	High risk	Reported primary outcome on participants with known coronary heart disease and excluded 957/2854 participants who were at risk.
Other bias	High risk	Adaptive study design. Study inclusion criteria were modified after monitoring of blinded data (1304 participants recruited). Since event rates in participants with risk factors for coronary artery disease were lower than expected, trial protocol was amended to focus only on participants with pre-existing coronary artery disease.

Park 2014

Methods	Randomized controlled trial comparing dexmedetomidine versus remifentanil.
Participants	142 people undergoing open heart surgery with CPB. **Age (yr):** mean (SD): dexmedetomidine group: 51 (16); remifentanil group: 54 (13). **Sex:** 79 men, 63 women. **Exclusion criteria:** re-do and emergency surgery; severe pulmonary or systemic disease; LVEF < 40%; pre-existing renal dysfunction (serum creatinine level > 2.0 mg/dL); documented preoperative dementia, Parkinson's disease or recent stroke; and aged > 90 yr or < 17 yr. In addition, people who had psychotropic medications, evidence of progressed heart block and surgery requiring deep hypothermic circulatory arrest involving thoracic aorta were excluded.

Park 2014 *(Continued)*

Interventions	1. Dexmedetomidine loading dose 0.5 µg/kg, then maintenance dose 0.2-0.8 µg/kg/hr to maintain an RASS of 3 (before extubation) and 2 (after extubation), from arrival in ICU until extubation. 2. Remifentanil 1000-2500 µg/hr titrated to same sedation target.
Outcomes	1. AF. 2. Stroke. 3. Bradycardia (HR < 55 bpm). 4. Systolic hypotension (SBP < 90 mmHg).
Notes	Funding: not discussed. Declaration of interest: declared no conflict of interest. Recruitment dates: April 2012 to March 2013. Konkuk University Medical Center.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Stated participants randomly assigned, but no further description provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not discussed. Presumed to be open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not discussed. Presumed to be open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Unclear risk	Reported adverse events not discussed in methods.
Other bias	Low risk	None.

Patel 2016

Methods	Randomized controlled study comparing clonidine versus clonidine + ketamine versus placebo.
Participants	50 people undergoing OPCAB with stable angina and preserved myocardial function **Age (yr):** mean (SD): clonidine group: 58 (8); placebo group: 62 (6). **Sex:** 46 men, 4 women.

Patel 2016 *(Continued)*

	Exclusion criteria: diabetes mellitus, renal or liver disease, rhythm disorders, concomitant heart valve surgery, ejection fraction < 40%, and emergency surgery.
Interventions	1. Clonidine 1 mg/kg IV 30 min before going to operating room. 2. clonidine + ketamine. 3. Placebo saline IV 30 min before going to operating room.
Outcomes	1. All-cause mortality (30 day). 2. MI. 3. Hypotension (SBP < 60 mmHg). 4. Bradycardia (HR < 40 bpm).
Notes	Funding: stated no financial support for research. Declaration of interest: declared no conflict of interest. Recruitment dates: January 2015 to September 2015.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computerized randomization table.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Participants, data collector and data processor kept blinded. Clinicians blinding not discussed.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Participants, data collector and data processor were kept blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Pawlik 2005

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	30 people with a diagnosis of obstructive sleep apnoea who were undergoing head-and-neck surgery. **Age (yr):** mean (SD): clonidine group: 49 (5); placebo group: 54 (8). **Sex:** 28 men, 2 women.

Pawlik 2005 *(Continued)*

	Exclusion criteria: history of MI within 6 months, resting room air saturation < 90%, taking clonidine to treat hypertension preoperatively.
Interventions	1. Clonidine 2 µg/kg orally on night before surgery and on morning of surgery. 2. Matched placebo given at identical times.
Outcomes	1. Myocardial ischaemia (angina requiring treatment). 2. Bradycardia (HR < 40 bpm and requirement for atropine).
Notes	Funding: support from institutional departments. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of a computer program to perform randomization.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant excluded from haemodynamic analysis because of an angiotensin-converting enzyme inhibitor overdose on postoperative ward.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Pluskwa 1991

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	30 people (1 excluded) undergoing vascular (carotid artery) surgery. **Age (yr):** mean (SD): clonidine group: 67 (8); placebo group: 67 (10). **Sex:** 21 men, 8 women. **Exclusion criteria:** unstable angina pectoris or on long-term clonidine therapy.
Interventions	1. Clonidine 300 µg orally 90 min before surgery. 2. Placebo.
Outcomes	1. MI (not defined).

Pluskwa 1991 *(Continued)*

	2. Bradycardia (intraoperative HR < 45 bpm). 3. Hypotension (intraoperative SBP < 100 mmHg for > 3 min and requiring drug treatment).
Notes	Funding: not discussed. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of a random number table.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported study was double-blind and that matched placebo was used in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant excluded after randomization when a thrombosis in carotid artery was discovered intraoperatively. 1 participant had data partially excluded because they required reoperation.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Quintin 1993

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	26 people undergoing CABG surgery. **Age:** not reported. **Sex:** not reported. **Exclusion criteria:** not reported.
Interventions	1. Clonidine 2.5 µg/kg orally before induction of anaesthesia. 2. Placebo.
Outcomes	1. Myocardial ischaemia (ST deviation > 0.1 mV for > 5 min before CPB).
Notes	Results of a pilot study published as a letter to editor. Funding: not discussed. Declaration of interest: not stated.

Quintin 1993 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors reported allocating participants in a randomized manner but provided no further details.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ECG changes assessed by 2 independent observers blinded to treatment arm.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Unclear risk	Not formally peer reviewed.

Quintin 1996

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	24 people (3 excluded) with hypertension who were undergoing vascular (aortic) surgery. **Age (yr):** mean (SD): clonidine group: 64 (8); placebo group: 69 (5). **Sex:** 17 men, 4 women. **Exclusion criteria:** treatment with clonidine, gaunabenz, rilmelidine, methyldopa or reserpine.
Interventions	1. Clonidine 6 µg/kg orally 120 min before induction of anaesthesia, followed by 3 µg/kg IV infusion over 60 min after aortic declamping. 2. Placebo.
Outcomes	1. All-cause mortality. 2. Cardiac-cause mortality. 3. Bradycardia (intraoperative requiring drug treatment). 4. Hypotension (intraoperative).
Notes	Funding: national research foundations and Boehringer-Ingelheim. Declaration of interest: not stated.

Risk of bias

Quintin 1996 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors reported prospective randomization but provided no further details.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	High risk	3 participants excluded for surgical reasons (2) or inadequate data collection (1).
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Ren 2013

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	162 people undergoing off-pump CABG surgery. **Age:** mean (SD): dexmedetomidine group: 60 (4); placebo group: 58 (6). **Sex:** 53 men, 109 women. **Exclusion criteria:** aged > 75 yr, ejection fraction < 40% or bradycardia based on preoperative diagnosis (HR < 50 bpm), preoperative history of arrhythmia, preoperative SBP < 90 mmHg, obesity, type I or type II diabetes mellitus, drug dependence, and history of psychiatry and cerebrovascular diseases.
Interventions	1. Dexmedetomidine 0.2-0.5 µg/kg/hr IV infusion following first vascular anastomosis until stable in ICU for 12 hr. 2. Normal saline delivered at identical rate.
Outcomes	1. All-cause mortality (72 hr post-surgery). 2. Myocardial ischaemia (ST segment elevation of 2 mm or depression of 1 mm for > 60 seconds) (72 hr post-surgery). 3. Supraventricular tachyarrhythmia (72 hr post-surgery).
Notes	Funding: not discussed. Declaration of interest: not stated. Recruitment dates: January 2010 to January 2011.
Risk of bias	

Ren 2013 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors reported allocating participants in a randomized manner but provide no further details.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Blinding not discussed. Reported use of matched placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not done; however, outcomes unlikely to be affected given predefined criteria.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Shehabi 2009

Methods	Randomized controlled trial comparing dexmedetomidine versus morphine.
Participants	306 people aged ≥ 60 yr undergoing on-pump cardiac surgery (including CABG, valve replacement surgery, or both). **Age (yr):** median (IQR): dexmedetomidine group: 72 (66-76); morphine group: 71 (65-75). **Sex:** 225 men, 81 women. **Exclusion criteria:** allergic to any of study medications, receiving other α-2 adrenergic agonists such as clonidine or psychoactive agents other than night-time hypnotics, preoperative HR < 55 bpm or SBP < 90 mmHg (or both), bodyweight > 150 kg or a preoperative creatinine > 140 µmol/L (1.6 mg/dL) or creatinine clearance < 50 mL/min (calculated by Cockcroft Gault formula). In addition, people with documented preoperative dementia, Parkinson's disease, recent seizures and unable to understand English and thus unable to participate in delirium assessment were excluded.
Interventions	1. Dexmedetomidine 0.3 µg/kg/hr IV infusion started within 1 hr of ICU admission until removal of chest drains or until 48 hr of ventilation, and titrated to motor activity assessment scale of 2-4 (range of infusion 0.1-0.7 µg/kg/hr). 2. Morphine 30 µg/kg/hr IV infusion (range of infusion 10-70 µg/kg/hr).
Outcomes	1. All-cause mortality (in hospital). 2. Myocardial ischaemia (troponin rise > 3 ng/mL) (during ICU stay, mean 45 hr). 3. Supraventricular tachyarrhythmia (during ICU stay, mean 45 hr). 4. Hypotension (SBP < 90 mmHg or decrease of 20%) (during ICU stay, mean 45 hr). 5. Bradycardia (HR < 55 bpm) (during ICU stay, mean 45 hr). 6. Stroke (new persistent neurological impairment) (during ICU stay, mean 45 hr).

Shehabi 2009 *(Continued)*

Notes	Funding: support solely from institutional or departmental (or both) sources, though study drug provided by Hospira. Declaration of interest: authors declared no conflict of interest. Recruitment dates: August 2004 to December 2007.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of computer-generated randomization with blocks of 10.
Allocation concealment (selection bias)	Low risk	Centralized randomization with a research pharmacist who prepared study drugs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported study was double blinded and stated "surgeons, anaesthetists, and intensive care medical and nursing staff were blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not discussed but outcomes clearly defined and unlikely to be influenced.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Soliman 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	150 people undergoing elective aortic vascular surgery (aortic aneurysm or aortobifemoral anastomosis). **Age (yr):** mean (SD): dexmedetomidine group: 58 (7); placebo group: 58 (8). **Sex:** 75 men, 75 women. **Exclusion criteria:** acute MI, congestive heart failure, heart block, obese people or emergency.
Interventions	1. Dexmedetomidine 1 µg/kg IV over 15 min before induction, then an infusion of 0.3 µg/kg/hr to end of procedure. 2. Normal saline in identical protocol.
Outcomes	1. All-cause mortality. 2. MI (myocardial injury as a result of myocardial ischaemia and associated with ST-segment changes and elevated troponin level). 3. Myocardial ischaemia (ischaemia of myocardium associated with ST-segment changes without elevation in troponin level).

Soliman 2016 *(Continued)*

4. Stroke.
5. Hypotension.
6. Bradycardia.

Notes	Funding: authors stated no support. Declaration of interest: declare no conflict of interest. Recruitment dates: 2013-2015. Kasr El-Aini Hospital, Cairo University, Egypt.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"The patients classified randomly (by simple randomization)." Details not discussed.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The medication was prepared by the nursing staff and given to anaesthetist blindly."
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All date reported.
Selective reporting (reporting bias)	Unclear risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Stuhmeier 1996

Methods	Randomized controlled trial comparing clonidine versus placebo. Analyses were performed on intention-to-treat basis.
Participants	297 people undergoing vascular surgery. **Age (yr):** mean (range): overall: 64 (28-82). **Sex:** 206 men, 91 women. **Exclusion criteria:** chronic myocardial ischaemia, preoperative digitalis or chronic clonidine medication, AF, bundle branch block, second degree or greater atrioventricular-nodal block on preoperative ECG. Criteria for post hoc exclusion were transfer to another hospital within 4 days, redo surgery, another surgery within 1 week, missing data.
Interventions	1. Clonidine 2 µg/kg orally 90 min before induction of anaesthesia.

Stuhmeier 1996 *(Continued)*

	2. Placebo administered in identical protocol.
Outcomes	1. Cardiac mortality (death from dysrhythmia or heart failure). 2. MI (new persistent Q-waves on ECG, or CK-MB elevation > 40 U/L or 10%). 3. Myocardial ischaemia (intraoperative ST deviation > 0.1 mV for > 1 min). 4. Bradycardia (requiring drug treatment).
Notes	Funding: not discussed. Declaration of interest: not stated. Recruitment dates: June 1993 to December 1994.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of a random number table.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as 'double-blind.' Reported use of a matched placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Clinicians who evaluated all ECG recordings were blinded to treatment assignment. No other details on blinding provided.
Incomplete outcome data (attrition bias) All outcomes	High risk	47 participants excluded from outcome analysis (from 297 total) because of transfers to other hospitals (14) or departments (10) within 4 days after surgery, redo surgery required within 1 week (8), other surgery within 1 week (8) and missing outcome data (7).
Selective reporting (reporting bias)	High risk	Primary and secondary outcomes of interest were not prespecified in methods.
Other bias	Low risk	None.

Su 2016

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	700 people aged ≥ 65 yr undergoing elective non-cardiac surgery under general anaesthesia and were admitted to ICU after surgery. **Age (yr):** mean (SD): dexmedetomidine group: 74 (7); placebo: 74 (7). **Sex:** 432 men, 268 women. **Exclusion criteria:** preoperative history of schizophrenia, epilepsy, Parkinsonism or myasthenia gravis; inability to communicate in preoperative period (coma, profound dementia or language barrier); brain injury or neurosurgery; known preoperative LVEF < 30%, sick sinus syndrome, severe sinus bradycardia (< 50 bpm), or second-degree or greater atrioventricular block without pacemaker; serious hepatic dys-

Su 2016 *(Continued)*

	function (Child-Pugh class C); serious renal dysfunction (undergoing dialysis before surgery) or low likelihood of survival for > 24 hr.
Interventions	1. Dexmedetomidine 0.1 µg/kg/hr within 1 hr of arrival to ICU, until first postoperative day. 2. Normal saline administered in identical protocol.
Outcomes	1. All-cause mortality (30 days). 2. MI (increase of troponin T concentration above hospital laboratory's MI threshold and either new Q waves (duration ≥ 0.03 sec) or persistent changes (4 days) in ST-T segment) (30 days). 3. Stroke (persisted new focal neurological deficit and confirmed by neurological imaging) (30 days). 4. Bradycardia (HR < 55 bpm or a decrease > 20% from baseline). 5. Hypotension (SBP < 95 mmHg or a decrease > 20% from baseline).
Notes	Funding: Braun Anaesthesia Scientific Research Fund and Wu Jieping Medical Foundation. A Chinese pharmaceutical company provided drugs used in study. Declaration of interest: several authors, including first author, received funding from pharmaceutic companies. Recruitment dates: 17 August 2011 to 20 November 2013. Peking University First Hospital and Peking University Third Hospital in Beijing.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Biostatistician, who was independent of data management and statistical analyses, generated random numbers (in a 1:1 ratio)."
Allocation concealment (selection bias)	Low risk	"The results of randomisation were sealed in sequentially numbered envelopes and stored at the site of investigation until the end of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Clinicians, participants and study members blinded to treatment group assignment.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Outcome assessment blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Talke 1995

Methods	Randomized controlled trial comparing 3 dexmedetomidine arms (low, medium and high doses), and 1 placebo arm.

Talke 1995 *(Continued)*

Participants	25 participants, with a diagnosis or risk factors of coronary artery disease, undergoing vascular surgery. **Age (yr):** mean (SD): dexmedetomidine group (combined): 65 (9); placebo group: 66 (6). **Sex:** not reported. **Exclusion criteria:** unstable angina, uninterpretable ECG, taking clonidine or tricyclic antidepressant preoperatively or did not received study drug for first 24 hr postoperatively.
Interventions	1. Low-dose dexmedetomidine IV infusion intraoperatively until 48 hr after surgery with total dose 2.64 µg/kg. 2. Medium-dose dexmedetomidine IV infusion intraoperatively until 48 hr after surgery with total dose 5.31 µg/kg. 3. High-dose dexmedetomidine IV infusion intraoperatively until 48 hr after surgery with total dose 8.03 µg/kg. 4. Placebo.
Outcomes	1. All-cause mortality (period unspecified). 2. MI (elevated CK-MB levels or new Q-waves). 3. Myocardial ischaemia (S-T or T-wave changes on ECG). 4. Supraventricular tachyarrhythmia. 5. Bradycardia (requiring drug treatment). 6. Hypotension (requiring drug treatment). 7. Heart failure.
Notes	Dexmedetomidine arms were combined for purpose of analyses. Funding: support grant from Orion Corporation, a pharmaceutical company. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Described as randomized but details not provided.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	All staff who analysed ECG recordings were blinded to treatment assignment. No other details of blinding reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	1 participant in dexmedetomidine arm excluded because of emergent reoperation.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.

Talke 1995 *(Continued)*

Other bias	Low risk	None.

Talke 2000

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo. Analyses performed on intention-to-treat basis.
Participants	41 people undergoing vascular surgery. **Age (yr):** mean (SD): dexmedetomidine group: 66 (9); placebo group: 65 (9). **Sex:** 37 men, 4 women. **Exclusion criteria:** pregnant, taking clonidine or tricyclic antidepressants, or had second or third-degree heart block.
Interventions	1. Dexmedetomidine 1.2 µg/min IV for 20 min starting 20 min prior to surgery, then 0.8 µg/min IV for 40 min, 0.35 µg/min IV for 240 min and then 0.15 µg/min IV until 48 hr postoperatively. 2. Placebo (normal saline).
Outcomes	1. All-cause mortality (48 hr postoperatively).
Notes	Funding: grant from Orion Corporation, a pharmaceutical company. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of random permuted blocks with stratification by centre.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Authors described study as 'double-blind.' Reported use of placebo in control arm. No other details reported.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Venn 1999

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	105 people (7 excluded) who had undergone cardiac (83%) and non-cardiac (17%) surgery, and needed > 6 hr of mechanical ventilation and sedation after surgery. **Age (yr):** mean (SD): dexmedetomidine group: 63 (14); placebo group: 64 (12). **Sex:** 73 men, 25 women. **Exclusion criteria:** serious central nervous system trauma or undergoing neurosurgery; requirement for neuromuscular blocking agents, epidural or spinal anaesthesia; any contraindications or allergy to any of trial drugs; gross obesity (> 50% above ideal bodyweight); admission for a drug overdose, prior enrolment in a trial with any experimental drug in last 30 days; uncontrolled diabetes and excessive bleeding that would be likely to require reoperation.
Interventions	1. Dexmedetomidine within 1 hr of arrival in ICU as 1 µg/kg IV loading dose and a 0.2-0.7 µg/kg/hr infusion for 6-24 hr. 2. Placebo (normal saline) matched and administered using identical protocol.
Outcomes	1. All-cause mortality. 2. MI. 3. Myocardial ischaemia. 4. Supraventricular tachyarrhythmia. 5. Bradycardia (requiring drug treatment). 6. Hypotension (requiring drug treatment).
Notes	Excluded participants receiving epidural or spinal anaesthesia. Funding: Abbott Laboratories. Declaration of interest: 1 author performs consultancy work for Abbott Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors described study as randomized but no other details reported.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as 'double-blind.' Reported use of a matched placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not discussed.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	7 participants withdrawn from study because of reoperation for bleeding (3), bradycardia and hypotension (2), residual neuromuscular blockade (1) and surgeon's request (1). These participants were included in safety data.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.

Venn 1999 *(Continued)*

Other bias	Low risk	None.

Venn 2001

Methods	Randomized controlled trial comparing dexmedetomidine versus propofol.
Participants	20 people undergoing non-vascular non-cardiac surgery and required > 8 hr of mechanical ventilation after surgery. **Age (yr):** mean (range): dexmedetomidine group: 65 (60-77), propofol group: 67 (64-74). **Sex:** not reported. **Exclusion criteria:** none reported.
Interventions	1. Dexmedetomidine 2.5 µg/kg/hr IV loading dose upon arrival in ICU and 0.2-0.5 µg/kg/hr infusion. 2. Propofol 1 mg/kg IV loading dose upon arrival in ICU, and 1-3 mg/kg/hr infusion.
Outcomes	1. All-cause mortality (35 days). 2. Bradycardia (requiring drug treatment). 3. Hypotension (requiring drug treatment).
Notes	Funding: supported in part by Abbott Laboratories, a pharmaceutical company. Declaration of interest: 1 author performed consultancy work for Abbott Laboratories.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors described study as randomized but no other details reported.
Allocation concealment (selection bias)	Low risk	Sealed envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	Open-label.
Blinding of outcome assessment (detection bias) All outcomes	High risk	Open-label.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Viviano 2012

Methods	Randomized controlled trial comparing clonidine versus ropivacaine epidural versus placebo.
Participants	60 people undergoing elective lung resection. **Age (yr):** median (IQR): clonidine group: 67 (61-73); saline group: 67 (50-71). **Sex:** 24 men, 16 women. **Exclusion criteria:** aged < 18 yr; guardianship/conservatorship (people who were in a coma, had advanced Alzheimer's disease or had other serious illnesses or injuries); refusal to participate; pre-existing alterations of immune system or undergoing treatments or having disorders with direct influence on immune system; pregnancy; contraindications for epidural catheter insertion; contraindications for clonidine, ropivacaine or remifentanil treatment; previous treatment with trial drugs or drugs belonging to same pharmacological group; NYHA Functional Classification ≥ class III heart failure; and MI in 8 weeks before surgery.
Interventions	1. Clonidine 150 µg IV bolus following induction of anaesthesia followed by a 20-100 µg/hr IV infusion. 2. Ropivacaine epidural. 3. Normal saline administered in identical protocol.
Outcomes	1. All-cause mortality (during hospital admission).
Notes	Funding: not reported. Declaration of interest: declare no conflict of interest. Recruitment dates: January 2006 to May 2007.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization with block size of 6.
Allocation concealment (selection bias)	Low risk	Central randomization with an independent research pharmacist preparing all study drugs.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors reported "all personnel and participants were blinded to treatment assignment for the duration of the study." A research pharmacist supplied study drugs in coded syringes.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Not discussed; however, outcome unlikely to be influenced.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Authors stated that all randomized participants completed trial. 10/70 participants included were later excluded. Participants withdrawn during operation, and not included in randomization which was technically not possible. 1 participant removed as they experienced a cardiac arrest resulting in unbinding and excluded from final analysis.
Selective reporting (reporting bias)	Unclear risk	Adverse events not discussed in methods but reported.
Other bias	Low risk	None.

Wallace 2004

Methods	Randomized controlled trial comparing clonidine versus placebo. Analyses performed on intention-to-treat basis.
Participants	190 people with a diagnosis or risk factors of coronary artery disease, undergoing elective non-cardiac surgery (26% vascular, 18% abdominal, 5% thoracic). **Age (yr):** mean (SD): clonidine group: 68 (8); placebo group: 69 (9). **Sex:** not reported. **Exclusion criteria:** unstable angina in month prior to surgery; uninterpretable Holter ECG secondary to left bundle-branch block, cardiac pacemaker dependency or marked resting ST-segment and T-wave abnormalities that precluded ECG ST-segment interpretation; preoperative use of clonidine, methyldopa or tricyclic antidepressants; symptomatic aortic stenosis; SBP < 100 mmHg and refusal or inability to give informed consent.
Interventions	1. Clonidine 200 µg orally on night before surgery and on morning of surgery. 200 µg/day transdermal patch applied on night before surgery, and removed on postoperative day 4. 2. Placebo.
Outcomes	1. All-cause 30-day mortality. 2. MI (ECG changes and CK-MB elevation). 3. Myocardial ischaemia (ST deviation > 0.1 mV for > 1 min on Holter monitoring). 4. Heart failure. 5. Hypotension (SBP < 80 mmHg). 6. Bradycardia (HR < 40 bpm).
Notes	10.5% prevalence of epidural use. Funding: supported by a grant-in-aid from American Heart Association, Veterans Administration Merit Review Funding, Ischemia Research and Education Foundation, Northern California Institute for Research and Education. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Authors described use of a computer-generated randomization schedule.
Allocation concealment (selection bias)	Low risk	Allocation by an independent pharmacist.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as 'double-blind.' Reported use of a matched placebo in control arm.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	ECG and safety data analysed by independent clinicians blinded to treatment arm.
Incomplete outcome data (attrition bias)	Unclear risk	12 participants withdrawn from study for cancellation of procedure (10), hypotension (1) and chest pain (1).

Wallace 2004 *(Continued)*

All outcomes

Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Wijeysundera 2014a

Methods	Randomized controlled trial comparing clonidine versus placebo. Analyses performed on intention-to-treat basis.
Participants	168 people considered to be an intermediated to high risk of perioperative cardiac complications undergoing elective non-cardiac surgery (28% vascular) with an expected hospital length of stay ≥ 48 hr and receiving oral β-blocker therapy for ≥ 30 days prior to surgery. **Age (yr):** mean (SD): clonidine group: 70 (8); placebo group: 72 (8). **Sex:** 118 men, 50 women. **Exclusion criteria:** pre-existing use of α-2 adrenergic agonists, prior adverse reaction to α-2 adrenergic agonists, decompensated heart failure, LVEF < 40%, SBP < 90 mmHg, known clinically significant aortic stenosis and concomitant life-threatening disease likely to limit life expectancy to < 30 days.
Interventions	1. Clonidine 200 µg orally 1 hr prior to surgery and 200 µg/day transdermal patch applied which was removed on postoperative day 4 or hospital discharge (whichever occurred earlier). 2. Placebo administered in identical protocol.
Outcomes	1. All-cause mortality (30 days). 2. MI (myocardial injury with symptoms, ECG changes, PCI or new changes on ECHO). 3. Myocardial ischaemia (troponin I or T concentration exceeding threshold at which coefficient of variation for assay was 10%). 4. Hypotension (SBP < 90 mmHg necessitating study drug withdrawal or treatment). 5. Bradycardia (requiring treatment or withdrawal of study drug). 6. Heart failure. 7. Acute stroke.
Notes	Funding: Heart and Stroke Foundation of Ontario and Canadian Anesthesia Research Foundation. Declaration of interest: declared no conflicts of interest. The lead (DNW) and senior (WSB) authors of this study were authors on this present systematic review; however, neither author was involved in primary data abstraction or quality assessment process in this review. Recruitment dates: June 2006 to November 2007 (Toronto General Hospital), January 2008 to August 2009 (Vancouver General Hospital), September 2007 to November 2008 (Victoria Hospital).

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Authors reported use of computer-generated randomization schedule.
Allocation concealment (selection bias)	Low risk	Permuted blocks with varying size used and randomization lists only available to research pharmacists.

Wijeysundera 2014a *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors stated participants, clinicians and data collectors blinded to treatment assignment. Reported use of a matched placebo in control arm. Drugs were prepared by research pharmacists.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Authors stated data collectors and outcome adjudicators blinded to treatment assignment. Outcomes defined with explicit criteria.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All outcomes reported. Intention-to-treat analysis used with 7% dropout (6 clonidine and 4 placebo).
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Xu 2014

Methods	Randomized controlled trial comparing dexmedetomidine versus placebo.
Participants	80 participants aged 41-75 yr, ASA II-III and diagnosis of coronary heart disease undergoing elective hip surgery with an expected duration > 2 hr. **Age (yr):** mean (SD): dexmedetomidine group: 60 (5); placebo: 59 (6). **Sex:** 37 men, 43 women. **Exclusion criteria:** history of hypertension, hypotension, diabetes mellitus, arrhythmia, cerebrovascular disease, severe arrhythmia, heart failure or a combination; taking non-steroidal anti-inflammatory drugs and hormonal medications for underlying diseases; any known sensitivity to study medications or previous anaesthetic exposure within 1 year; abnormal preoperative liver and kidney function; abnormal levels of cTnI, GP-BB and myocardial enzymes; and LVEF < 40%.
Interventions	1. Dexmedetomidine 1 µg/kg IV bolus over 10 min followed by a maintenance infusion of 0.2 µg/kg/hr. 2. Normal saline placebo administered in identical protocol.
Outcomes	1. MI (change in ST segment > 0.1 mV, development of a new Q wave) (24 hr).
Notes	Funding: grants from National Natural Science Foundation of China, Science and Technology Agency, Bureau of Chinese Medicine, Project of Medical Technology, Clinical Scientific Research of Medical Association and clinical scientific research fund of Chinese Medical Association. Declaration of interest: declared no conflict of interest.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Quote: "This study was a prospective randomized double-blind trial." Random sequence generation not discussed.
Allocation concealment (selection bias)	Low risk	Sealed envelopes used. Opened by anaesthesiologist not involved in care of participant.

Xu 2014 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	Drug prepared by separate anaesthesiologist uninvolved in participant care or study. Equal volume of normal saline used in control, and likely it was matched.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Blinded outcome adjudicator.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

Yin 2002

Methods	Randomized controlled trial comparing clonidine versus placebo.
Participants	60 people with coronary artery disease undergoing non-cardiac surgery (10% vascular, 50% intraperitoneal, 27% orthopaedic). **Age (yr):** mean (SD): clonidine group: 63 (5); placebo group: 60 (6). **Sex:** 49 men, 11 women. **Exclusion criteria:** physical status other than ASA III, systemic hypotension (SBP < 90 mmHg), severe atrioventricular conduction block including second-degree Mobitz type II and third-degree AV block, left bundle branch block, implantation of cardiac pacemaker or chronic clonidine exposure.
Interventions	1. Clonidine 3 µg/kg orally 90 min before surgery. 2. Placebo.
Outcomes	1. Myocardial ischaemia (ST deviation > 0.1 mV for > 3 min during first 24 postoperative hr).
Notes	Funding: grant of National Science Council, Taiwan. Declaration of interest: not stated.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Authors described participants being prospectively randomized but provided no other details.
Allocation concealment (selection bias)	Unclear risk	Not discussed.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Authors described study as 'double-blind.' Reported use of a placebo in control arm. Authors described that "anaesthesia providers in the study were blind to all research information."

Yin 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Interpretation of all ECGs was performed by staff blinded to treatment assignment.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All data reported.
Selective reporting (reporting bias)	Low risk	Outcomes reported were concordant with methods.
Other bias	Low risk	None.

AF: atrial fibrillation; ASA: American Society of Anesthesiologists; bpm: beats per minute; CABG: coronary artery bypass graft; CK-MB: creatinine kinase - MB; CPB: cardiopulmonary bypass; cTnI: cardiac troponin I; DBP: diastolic blood pressure; ECG: electrocardiogram; ECHO: echocardiogram; GP-BB: glycogen phosphorylase BB; GFR: glomerular filtration rate; HR: heart rate; hr: hours; ICU: intensive care unit; IQR: interquartile range; IU: international units; IV: intravenous; LV: left ventricular; LVEF: left ventricular ejection fraction; MAP: mean arterial pressure; MI: myocardial infarction; min: minute; n: number; NYHA: New York Heart Association; OPCAB: off-pump coronary artery bypass; PCI: percutaneous coronary intervention; RASS: Richmond Agitation-Sedation Scale; SD: standard deviation; SBP: systolic blood pressure; sec: second; yr: year.

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abd Aziz 2011	Study objectives differed.
Abdalla 2003	Study objectives differed.
Abdel-Meguid 2013	Study objectives differed.
Abdelmageed 2011	Study objectives differed.
Aho 1991a	Study objectives differed.
Aho 1991b	Study objectives differed.
Aho 1992	Study objectives differed.
Akin 2008	Quasi-randomized trial design (participants divided into 2 groups based on order in which they were admitted to the intensive care unit).
Akkaya 2014	Study objectives differed.
Aldehayat 2011	Study objectives differed.
Aliyeva 2009	Study objectives differed.
Altan 2005	Study objectives differed.
Altindis 2008	Study objectives differed.
Amminikutty 2015	Study objectives differed.
Anvaroglu 2008	Study objectives differed.

Study	Reason for exclusion
Apitzsch 2000	Study objectives differed.
Arain 2002	Study objectives differed.
Arain 2004	Study objectives differed.
Arora 2015	Not randomized design.
Ayoglu 2007	Study objectives differed.
Ayoglu 2008	Study objectives differed.
Babu 2013	Study objectives differed.
Bajwa 2011	Study objectives differed.
Bajwa 2012	Study objectives differed.
Bakan 2015	Study objectives differed.
Bakhamees 2007	Study objectives differed.
Bakri 2015	Study objectives differed.
Balaraju 2013	Study objectives differed.
Basar 2008	Study objectives differed.
Batista 2015	Study objectives differed.
Bayram 2011	Study objectives differed.
Bayram 2012	Study objectives differed.
Beg 2001	Study objectives differed.
Beigh 2003	Study objectives differed.
Bekker 2008	Study objectives differed.
Bekker 2013	Study objectives differed.
Benhamou 1994	Study objectives differed.
Bernard 1991a	Study objectives differed.
Bernard 1991b	Study objectives differed.
Bernard 1993	Study objectives differed.
Bernard 1994	Study objectives differed.
Bhanderi 2014	Study objectives differed.
Bharti 2010	Study objectives differed.

Study	Reason for exclusion
Bharti 2013	Study objectives differed.
Bhattacharjee 2010	Study objectives differed.
Bicer 2006	Study objectives differed.
Bindu 2013	Study objectives differed.
Boldt 1996	Scientific misconduct (Rasmussen 2011; Wise 2013).
Bouslama 2013	Study objectives differed.
Bozgeyik 2014	Study objectives differed.
Buggy 1997	Study objectives differed.
Bulow 2007	Study objectives differed.
Bulow 2016	Study objectives differed.
But 2006	Study objectives differed.
Campagni 1999	Study objectives differed.
Carabine 1991a	Study objectives differed.
Carabine 1991b	Study objectives differed.
Carabine 1992	Study objectives differed.
Caumo 2009	Study objectives differed.
Ceballos 2011	Study objectives differed.
Celebi 2013	Study objectives differed.
Chadha 1992	Study objectives differed.
Chaoba 2011	Study objectives differed.
Chaturvedi 2014	Not randomized design.
Chen 2013	Study objectives differed.
Chen 2014	Study objectives differed.
Chen 2014a	Study objectives differed.
Cheung 2011	Study objectives differed.
Cheung 2014	Study objectives differed.
Cho 2015	Study objectives differed.
Chua 2010	Study objectives differed.

Study	Reason for exclusion
Cindea 2012	Study objectives differed.
Curtis 2002	Study objectives differed.
De Deyne 2000	Study objectives differed.
De Kock 1992	Study objectives differed.
De Kock 1994	Study objectives differed.
De Kock 1995	Study objectives differed.
De la Mora-Gonzalez 2012	Not randomized design.
Delaunay 1991	Study objectives differed.
Demirhan 2011	Study objectives differed.
Dhorigol 2010	Study objectives differed.
Dimou 2003	Study objectives differed.
Doak 1993	Study objectives differed.
Dobrydniov 1999	Study objectives differed.
Dobrydnjov 2002	Study objectives differed.
Dogan 2008	Study objectives differed.
Dorman 1997	Study objectives differed.
Durmus 2007	Study objectives differed.
Eberhart 2000	Study objectives differed.
El 2012	Not randomized design.
Elkassem 2008	Study objectives differed.
Elliott 1997	Study objectives differed.
Ellis 1998	Study objectives differed.
ElSheikh 2010	Study objectives differed.
Elvan 2008	Study objectives differed.
Engelman 1989	Study objectives differed.
Eremenko 2014a	Study objectives differed.
Eremenko 2014b	Not randomized design.
Erkola 1994	Study objectives differed.

Study	Reason for exclusion
Ezri 1998	Study objectives differed.
Favre 1995	Study objectives differed.
Fehr 2001	Study objectives differed.
Feld 2003	Study objectives differed.
Feld 2006	Study objectives differed.
Feld 2007	Study objectives differed.
Flacke 1987	Study objectives differed.
Frank 1999	Study objectives differed.
Frank 2000a	Study objectives differed.
Frank 2000b	Study objectives differed.
Frank 2002	Study objectives differed.
Galindo 2008	Study objectives differed.
Gandhi 2017	Study objectives differed.
Ganter 2005	Study objectives differed.
Gao 2012	Study objectives differed.
Garcia-Guiral 1994	Study objectives differed.
Ghatak 2010	Study objectives differed.
Ghosh 2008	Study objectives differed.
Gomez-Vazquez 2007	Study objectives differed.
Goyagi 1996	Study objectives differed.
Grottke 2003	Study objectives differed.
Grundmann 1997	Study objectives differed.
Guglielminotti 1998	Study objectives differed.
Gupta 2011a	Study objectives differed.
Gupta 2011b	Study objectives differed.
Gupta 2011c	Study objectives differed.
Gupta 2012	Study objectives differed.
Guven 2011	Study objectives differed.

Study	Reason for exclusion
Hahm 2002	Study objectives differed.
Hall 2006	Participants did not undergo surgery.
Handa 2000	Study objectives differed.
Harsoor 2013	Study objectives differed.
Harsoor 2014	Study objectives differed.
Hashemian 2017	Study objectives differed.
Hazra 2014	Study objectives differed.
Hidalgo 2005	Study objectives differed.
Higuchi 2002	Study objectives differed.
Honarmand 2007	Study objectives differed.
Horn 1997	Study objectives differed.
Horng 2007	Study objectives differed.
Hwang 2015	Study objectives differed.
Ishiyama 2006	Study objectives differed.
Jaakola 1994	Study objectives differed.
Jabalameli 2005	Study objectives differed.
Javaherfroosh 2009	Study objectives differed.
Jeffs 2002	Study objectives differed.
Jellish 2001	Study objectives differed.
Ji 2013	Not randomized design.
Joao 2014	Study objectives differed.
Joris 1993	Study objectives differed.
Joris 1998	Study objectives differed.
Joshi 2012	Study objectives differed.
Juarez-Pichardo 2009	Study objectives differed.
Kajiyama 2009	Not randomized design.
Kalajdzija 2011	Study objectives differed.
Kang 2012	Study objectives differed.

Study	Reason for exclusion
Kang 2013	Study objectives differed.
Kang 2015	Study objectives differed.
Karaman 2013	Study objectives differed.
Karaman 2015	Study objectives differed.
Kawasaki 2014	Not randomized design.
Kaya 2010	Study objectives differed.
Kaymak 2008	Study objectives differed.
Ke 2013	Study objectives differed.
Keniya 2011	Study objectives differed.
Khafagy 2012	Study objectives differed.
Kim 2012	Study objectives differed.
Kim 2013a	Study objectives differed.
Kim 2013b	Study objectives differed.
Kim 2013c	Study objectives differed.
Kim 2014b	Not randomized design.
Korkmaz 2013	Study objectives differed.
Koyuncu 2009	Study objectives differed.
Kulka 1996	Study objectives differed.
Kumari 2012	Study objectives differed.
Lang 2011	Study objectives differed.
Lattermann 2001	Study objectives differed.
Launo 1991	Study objectives differed.
Laurito 1991	Study objectives differed.
Laurito 1993	Study objectives differed.
Lawrence 1997	Study objectives differed.
Le Guen 2014	Study objectives differed.
Lee 2012	Study objectives differed.
Lee 2013b	Study objectives differed.

Study	Reason for exclusion
Leino 2011	Study objectives differed.
Levanen 1995	Study objectives differed.
Li 2010	Study objectives differed.
Li 2013	Study objectives differed.
Liu 2013	Study objectives differed.
Lu 2013	Study objectives differed.
Lyons 1997	Study objectives differed.
Ma 2013	Study objectives differed.
Mahendru 2013	Study objectives differed.
Maldonado 2009	Study objectives differed.
Malek 2009	Study objectives differed.
Malek 2010a	Not randomized design.
Malek 2010b	Study objectives differed.
Manne 2014	Study objectives differed.
Mannion 2005	Study objectives differed.
Marangoni 2005	Study objectives differed.
Marchal 2001	Study objectives differed.
Mariappan 2014	Study objectives differed.
Marinangeli 2002	Study objectives differed.
Martin 2003	Half the participants underwent cardiac surgery and half underwent non-cardiac surgery; therefore, it did not meet inclusion criteria for either subgroup (cardiac surgery versus non-cardiac surgery subgroups).
Massad 2009	Study objectives differed.
Mishra 2012	Study objectives differed.
Mizrak 2010	Study objectives differed.
Mizrak 2012	Study objectives differed.
Mizrak 2013	Study objectives differed.
Moghadam 2012	Participants were known substance abusers.
Mohamed 2012	Study objectives differed.

Study	Reason for exclusion
Mohamed 2013	Control group did not meet inclusion criteria.
Mohammadi 2007	Study objectives differed.
Mohammadi 2008	Study objectives differed.
Mousa 2013	Study objectives differed.
Muhammad 2012	Study objectives differed.
Murari Sudre 2004	Study objectives differed.
Myatra 2010	Participants did not undergo surgery.
Nader 2001	Study objectives differed.
Nader 2009	Treatment given by alternative route.
Nakagawa 2001	Study objectives differed.
Nitta 2013	Study objectives differed.
Nour El-Din 2004	Study objectives differed.
Nunez-Bacarreza 2006	Study objectives differed.
Oddby-Muhrbeck 2002	Study objectives differed.
Ohata 1999	Study objectives differed.
Ohtani 2008	Study objectives differed.
Ohtani 2011	Study objectives differed.
Okuyama 2005	Study objectives differed.
Omote 1995	Study objectives differed.
Onodera 2011	Study objectives differed.
Owen 1997	Study objectives differed.
Ozbakis 2008	Study objectives differed.
Ozkose 2006	Study objectives differed.
Panda 2012a	Study objectives differed.
Panda 2012b	Study objectives differed.
Pandazi 2011	Study objectives differed.
Pant 2012	Study objectives differed.
Parameswara 2012	Study objectives differed.

Study	Reason for exclusion
Paris 2009	Study objectives differed.
Park 1996	Study objectives differed.
Park 2012	Study objectives differed.
Parlow 1999	Study objectives differed.
Patel 2012	Study objectives differed.
Patil 2012	Participants did not undergo surgery.
Pestilci 2015	Study objectives differed.
Piper 1999	Study objectives differed.
Piper 2004	Study objectives differed.
Porkkala 1998	Study objectives differed.
Pouttu 1987	Study objectives differed.
Procaccini 1993	Study objectives differed.
Quintin 1990	Study objectives differed.
Quintin 1991a	Study objectives differed.
Quintin 1991b	Study objectives differed.
Raouf 2004	Study objectives differed.
Ray 2010	Study objectives differed.
Reddy 2013	Study objectives differed.
Richa 2008	Study objectives differed.
Rohrbach 1999	Study objectives differed.
Rosenfeld 1993	Study objectives differed.
Ruan 2011	Study objectives differed.
Rubino 2010	Study objectives differed.
Salgado 2008	Study objectives differed.
Salgado Filho 2013	Study objectives differed.
Samantaray 2012	Study objectives differed.
Sassi 2013	Study objectives differed.
Scheinin 1992	Study objectives differed.

Study	Reason for exclusion
Schlimp 2011	Study objectives differed.
Schreiberova 2008	Study objectives differed.
Segal 1991	Study objectives differed.
Selina 2011	Not randomized design.
Senses 2013	Study objectives differed.
Shams 2013	Study objectives differed.
Shin 2012	Study objectives differed.
Shin 2013	Study objectives differed.
Shrestha 2012	Study objectives differed.
Shukla 2011	Study objectives differed.
Si 2011	Study objectives differed.
Simoni 2009	Study objectives differed.
Singh 2011	Study objectives differed.
Singh 2013	Study objectives differed.
Singh Bajwa 2012	Study objectives differed.
Sitilci 2010	Study objectives differed.
Solanki 2013	Study objectives differed.
Soliman 2011	Study objectives differed.
Stapelfeldt 2005	Study objectives differed.
Stocche 2004	Study objectives differed.
Striebel 1993	Study objectives differed.
Sudar 2013	Study objectives differed.
Sulemanji 2007	Study objectives differed.
Sun 2013	Study objectives differed.
Sung 2000	Study objectives differed.
Taheri 2010	Study objectives differed.
Taittonen 1997a	Study objectives differed.
Taittonen 1997b	Study objectives differed.

Study	Reason for exclusion
Taittonen 1998	Study objectives differed.
Talke 1997	Study objectives differed.
Tanskanen 2006	Study objectives differed.
Techanivate 2012	Study objectives differed.
Tekin 2007	Study objectives differed.
Thomson 1998	Study objectives differed.
Toz 2010	Study objectives differed.
Traill 1993	Study objectives differed.
Triltsch 2002	Half the participants underwent cardiac surgery and half underwent non-cardiac surgery; therefore, it did not meet inclusion criteria for either subgroup (cardiac surgery versus non-cardiac surgery subgroups).
Tufanogullari 2008	Study objectives differed.
Turgut 2009	Study objectives differed.
Tzortzopoulou 2009	Treatment given by alternative route.
Unlugenc 2005	Study objectives differed.
Usta 2011	Study objectives differed.
Uyar 2008	Study objectives differed.
Vanderstappen 1996	Study objectives differed.
von Dossow 2006	Study objectives differed.
Vukovic 2012	Study objectives differed.
Wahlander 2005	Scientific misconduct (Anon 2013).
Wallenborn 2008	Not randomized design.
Wan 2011	Study objectives differed.
Wang 2012	Study objectives differed.
Wawrzyniak 2013	Study objectives differed.
Weilbach 2009	Study objectives differed.
Wright 1990	Study objectives differed.
Xu 2010	Study objectives differed.
Xue 2014	Not randomized design.

Study	Reason for exclusion
Yacout 2012	Study objectives differed.
Yadav 2013	Study objectives differed.
Yang 2013	Study objectives differed.
Yektaz 2011a	Study objectives differed.
Yektaz 2011b	Study objectives differed.
Yldrm 2012	Study objectives differed.
Yoganarasimha 2012	Study objectives differed.
Yotsui 2001	Study objectives differed.
Yu 2003	Study objectives differed.
Zalunardo 2000	Study objectives differed.
Zalunardo 2002	Study objectives differed.
Zalunardo 2010	Study objectives differed.
Zhang 2013a	Study objectives differed.
Zhang 2013b	Study objectives differed.
Zhou 2011	Study objectives differed.

DATA AND ANALYSES

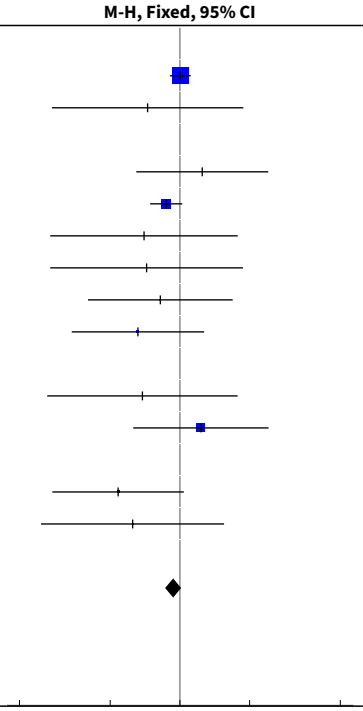
Comparison 1. Alpha-2 adrenergic agonists versus control in non-cardiac surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	16	14081	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.61, 1.04]
2 Cardiac mortality	5	12525	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.23]
3 Myocardial infarction	12	13907	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
4 Myocardial ischaemia	12	1379	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.53, 1.02]
5 Supraventricular tachyarrhythmia	2	44	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.05, 24.07]
6 Heart failure	8	10802	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.83, 1.75]
7 Acute stroke	7	11542	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.55, 1.56]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8 Bradycardia	16	14035	Risk Ratio (M-H, Random, 95% CI)	1.59 [1.18, 2.13]
9 Hypotension	15	13738	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.03, 1.48]

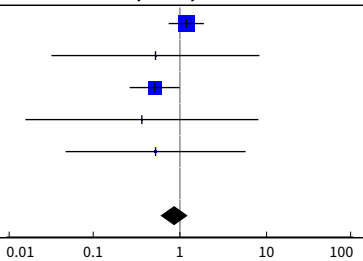
Analysis 1.1. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 1 All-cause mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bergese 2010	0/55	0/50			Not estimable
Devereaux 2014a	64/5009	63/5001		52.79%	1.01[0.72,1.43]
Ellis 1994	0/30	1/31		1.24%	0.34[0.01,8.13]
Lee 2013a	0/28	0/29			Not estimable
McSPI-Europe 1997	4/197	1/103		1.1%	2.09[0.24,18.47]
Oliver 1999	22/956	34/941		28.69%	0.64[0.38,1.08]
Quintin 1996	0/11	1/10		1.31%	0.31[0.01,6.74]
Soliman 2016	0/75	1/75		1.26%	0.33[0.01,8.05]
Stuhmeier 1996	1/145	2/152		1.64%	0.52[0.05,5.72]
Su 2016	1/350	4/350		3.35%	0.25[0.03,2.23]
Talke 1995	0/18	0/6			Not estimable
Talke 2000	0/22	1/19		1.34%	0.29[0.01,6.72]
Venn 2001	2/10	1/10		0.84%	2[0.21,18.69]
Viviano 2012	0/20	0/20			Not estimable
Wallace 2004	1/125	4/65		4.41%	0.13[0.01,1.14]
Wijeysundera 2014a	0/82	2/86		2.04%	0.21[0.01,4.3]
Total (95% CI)	**7133**	**6948**		**100%**	**0.8[0.61,1.04]**
Total events: 95 (Alpha-2 adrenergic agonists), 115 (Control)					
Heterogeneity: Tau^2=0; Chi^2=9.9, df=11(P=0.54); I^2=0%					
Test for overall effect: Z=1.64(P=0.1)					

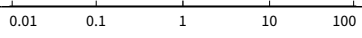


Analysis 1.2. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 2 Cardiac mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	38/5009	32/5001		51.72%	1.19[0.74,1.89]
McSPI-Europe 1997	1/197	1/103		2.12%	0.52[0.03,8.27]
Oliver 1999	13/956	25/941		40.69%	0.51[0.26,0.99]
Quintin 1996	0/10	1/11		2.32%	0.36[0.02,8.03]
Stuhmeier 1996	1/145	2/152		3.15%	0.52[0.05,5.72]
Total (95% CI)	**6317**	**6208**		**100%**	**0.86[0.6,1.23]**



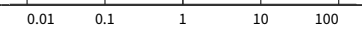
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Total events: 53 (Alpha-2 adrenergic agonists), 61 (Control)					
Heterogeneity: Tau²=0; Chi²=4.74, df=4(P=0.32); I²=15.56%					
Test for overall effect: Z=0.83(P=0.41)					



Favours treatment Favours control

Analysis 1.3. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 3 Myocardial infarction.

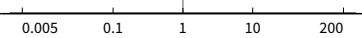
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Devereaux 2014a	329/5009	295/5001		41.71%	1.11[0.96,1.3]
Ellis 1994	0/30	2/31		1.02%	0.21[0.01,4.13]
McSPI-Europe 1997	3/197	6/103		4.54%	0.26[0.07,1.02]
Oliver 1999	78/956	79/941		32.17%	0.97[0.72,1.31]
Pluskwa 1991	0/15	0/15			Not estimable
Soliman 2016	1/75	3/75		1.79%	0.33[0.04,3.13]
Stuhmeier 1996	0/145	4/152		1.08%	0.12[0.01,2.14]
Su 2016	5/350	8/350		6.56%	0.63[0.21,1.89]
Talke 1995	0/18	0/6			Not estimable
Wallace 2004	2/125	2/65		2.37%	0.52[0.07,3.61]
Wijeysundera 2014a	12/82	6/86		8.75%	2.1[0.83,5.33]
Xu 2014	0/40	0/40			Not estimable
Total (95% CI)	**7042**	**6865**		**100%**	**0.94[0.69,1.27]**
Total events: 430 (Treatment), 405 (Control)					
Heterogeneity: Tau²=0.05; Chi²=12.61, df=8(P=0.13); I²=36.57%					
Test for overall effect: Z=0.42(P=0.67)					



Favours treatment Favours control

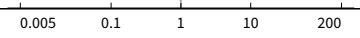
Analysis 1.4. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 4 Myocardial ischaemia.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ellis 1994	7/28	8/26		8.89%	0.81[0.34,1.92]
Ghignone 1987	0/15	2/15		1.18%	0.2[0.01,3.85]
Lipszyc 1991	8/20	5/20		8.1%	1.6[0.63,4.05]
Matot 2000	0/18	2/18		1.17%	0.2[0.01,3.89]
McSPI-Europe 1997	35/197	16/103		14.06%	1.14[0.67,1.97]
Pawlik 2005	0/15	1/15		1.06%	0.33[0.01,7.58]
Soliman 2016	3/75	14/75		5.64%	0.21[0.06,0.72]
Stuhmeier 1996	35/145	59/152		18.01%	0.62[0.44,0.88]
Talke 1995	11/18	3/6		8.66%	1.22[0.51,2.95]
Wallace 2004	18/125	20/65		13.66%	0.47[0.27,0.82]
Wijeysundera 2014a	15/82	12/86		11.27%	1.31[0.65,2.63]



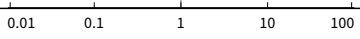
Favours treatment Favours control

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Yin 2002	5/30	12/30		8.29%	0.42[0.17,1.04]
Total (95% CI)	**768**	**611**		**100%**	**0.73[0.53,1.02]**
Total events: 137 (Alpha-2 adrenergic agonists), 154 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=19.9, df=11(P=0.05); I^2=44.72%					
Test for overall effect: Z=1.85(P=0.06)					



Analysis 1.5. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 5 Supraventricular tachyarrhythmia.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Talke 1995	1/18	0/6		100%	1.11[0.05,24.07]
Venn 2001	0/10	0/10			Not estimable
Total (95% CI)	**28**	**16**		**100%**	**1.11[0.05,24.07]**
Total events: 1 (Alpha-2 adrenergic agonists), 0 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.06(P=0.95)					



Analysis 1.6. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 6 Heart failure.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	48/5009	34/5001		69.57%	1.41[0.91,2.18]
Ellis 1994	4/28	5/26		10.6%	0.74[0.22,2.47]
Matot 2000	0/18	0/18			Not estimable
McSPI-Europe 1997	4/197	3/103		8.06%	0.7[0.16,3.06]
Talke 1995	2/18	1/6		3.07%	0.67[0.07,6.11]
Venn 2001	0/10	0/10			Not estimable
Wallace 2004	0/125	2/65		6.71%	0.1[0.01,2.15]
Wijeysundera 2014a	3/82	1/86		2%	3.15[0.33,29.64]
Total (95% CI)	**5487**	**5315**		**100%**	**1.21[0.83,1.75]**
Total events: 61 (Alpha-2 adrenergic agonists), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.13, df=5(P=0.4); I^2=2.53%					
Test for overall effect: Z=0.99(P=0.32)					

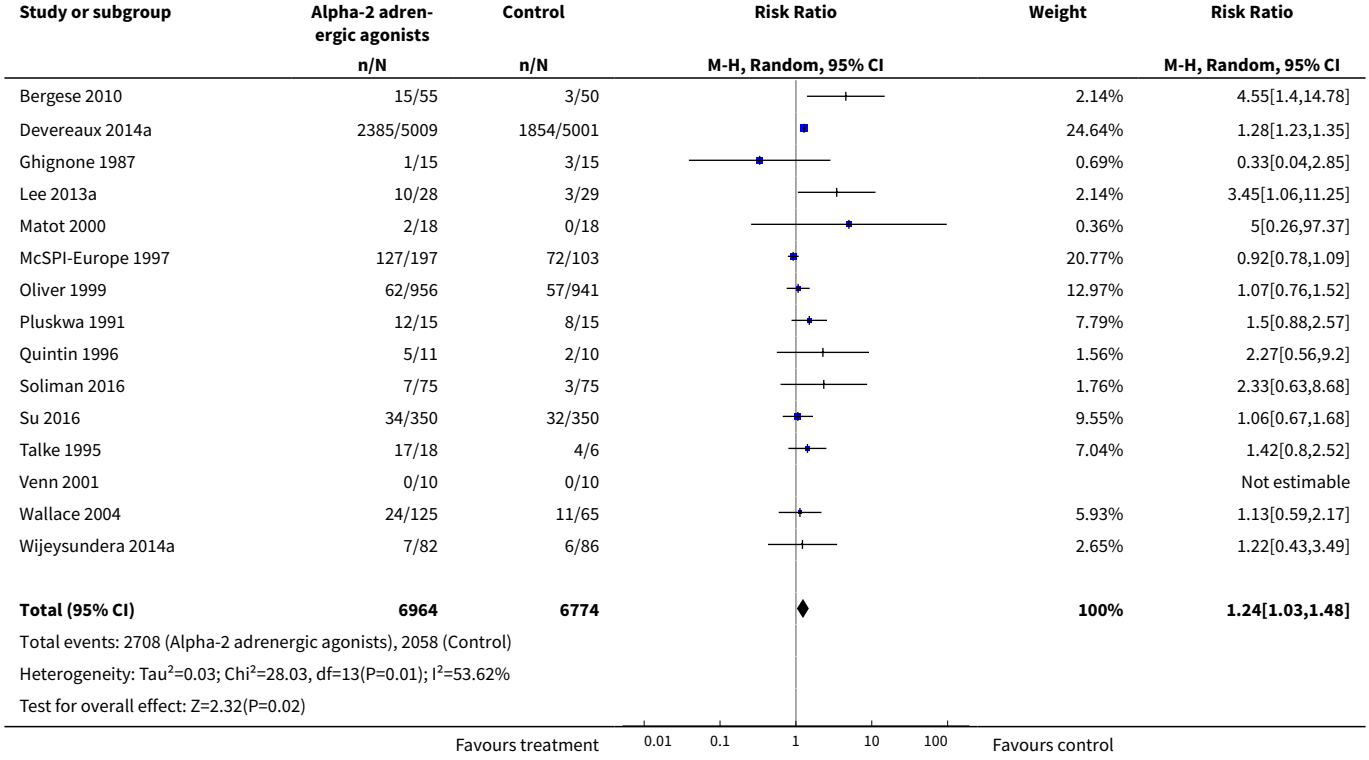
Analysis 1.7. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 7 Acute stroke.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	18/5009	17/5001		58.53%	1.06[0.55,2.05]
McSPI-Europe 1997	10/197	5/103		22.59%	1.05[0.37,2.98]
Soliman 2016	0/75	0/75			Not estimable
Su 2016	0/350	3/350		12.04%	0.14[0.01,2.76]
Talke 1995	1/16	1/8		4.59%	0.5[0.04,7]
Wallace 2004	1/125	0/65		2.26%	1.57[0.06,38.04]
Wijeysundera 2014a	0/82	0/86			Not estimable
Total (95% CI)	**5854**	**5688**		**100%**	**0.93[0.55,1.56]**
Total events: 30 (Alpha-2 adrenergic agonists), 26 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.05, df=4(P=0.73); I^2=0%					
Test for overall effect: Z=0.27(P=0.79)					

Analysis 1.8. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 8 Bradycardia.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bergese 2010	4/55	0/50		0.99%	8.2[0.45,148.52]
Devereaux 2014a	600/5009	403/5001		22.94%	1.49[1.32,1.68]
Lee 2013a	11/28	4/29		6.18%	2.85[1.03,7.9]
Matot 2000	0/18	0/18			Not estimable
McSPI-Europe 1997	64/197	36/103		18.31%	0.93[0.67,1.29]
Oliver 1999	81/956	36/941		17.01%	2.21[1.51,3.25]
Pawlik 2005	2/15	0/15		0.95%	5[0.26,96.13]
Pluskwa 1991	7/15	4/15		6.37%	1.75[0.64,4.75]
Quintin 1996	2/11	2/10		2.5%	0.91[0.16,5.3]
Soliman 2016	9/75	2/75		3.32%	4.5[1.01,20.13]
Stuhmeier 1996	23/145	30/152		14.29%	0.8[0.49,1.32]
Su 2016	5/350	1/350		1.75%	5[0.59,42.58]
Talke 1995	8/18	0/6		1.12%	6.26[0.41,94.82]
Venn 2001	0/10	0/10			Not estimable
Wallace 2004	12/125	2/65		3.45%	3.12[0.72,13.52]
Wijeysundera 2014a	1/82	0/86		0.82%	3.14[0.13,76.11]
Total (95% CI)	**7109**	**6926**		**100%**	**1.59[1.18,2.13]**
Total events: 829 (Alpha-2 adrenergic agonists), 520 (Control)					
Heterogeneity: Tau^2=0.09; Chi^2=27.59, df=13(P=0.01); I^2=52.88%					
Test for overall effect: Z=3.08(P=0)					

Analysis 1.9. Comparison 1 Alpha-2 adrenergic agonists versus control in non-cardiac surgery, Outcome 9 Hypotension.



Comparison 2. Alpha-2 adrenergic agonists versus control in cardiac surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	16	1947	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.26, 1.04]
2 Myocardial infarction	8	782	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.43, 2.40]
3 Myocardial ischaemia	13	1134	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.56, 0.86]
4 Supraventricular tachyarrhythmia	6	1044	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.50, 1.16]
5 Heart failure	4	549	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.63]
6 Acute stroke	7	1175	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.15, 0.93]
7 Bradycardia	10	1477	Risk Ratio (M-H, Fixed, 95% CI)	1.88 [1.35, 2.62]
8 Hypotension	9	1413	Risk Ratio (M-H, Random, 95% CI)	1.19 [0.87, 1.64]

Analysis 2.1. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 1 All-cause mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ammar 2016	0/25	0/25			Not estimable
Cho 2016	1/100	5/100		21.73%	0.2[0.02,1.68]
Corbett 2005	1/43	0/46		2.1%	3.2[0.13,76.6]
Djaiani 2016	1/91	0/92		2.16%	3.03[0.13,73.48]
Helbo-Hansen 1986	0/20	0/20			Not estimable
Jalonen 1997	0/40	0/40			Not estimable
Khalil 2013	0/25	0/25			Not estimable
Kim 2014a	0/40	1/38		6.68%	0.32[0.01,7.55]
Li 2017	2/142	4/143		17.32%	0.5[0.09,2.71]
Liu 2016	0/44	1/44		6.52%	0.33[0.01,7.97]
Loick 1999	1/24	0/21		2.31%	2.64[0.11,61.54]
Myles 1999	0/76	2/74		11.01%	0.19[0.01,3.99]
Patel 2016	0/25	0/25			Not estimable
Ren 2013	0/81	0/81			Not estimable
Shehabi 2009	2/152	4/147		17.67%	0.48[0.09,2.6]
Venn 1999	1/47	3/51		12.5%	0.36[0.04,3.36]
Total (95% CI)	**975**	**972**		**100%**	**0.52[0.26,1.04]**
Total events: 9 (Alpha-2 adrenergic agonists), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=4.92, df=9(P=0.84); I^2=0%					
Test for overall effect: Z=1.85(P=0.06)					

Analysis 2.2. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 2 Myocardial infarction.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abi-Jaoude 1993	1/11	0/13		4.65%	3.5[0.16,78.19]
Helbo-Hansen 1986	1/20	1/20		10.08%	1[0.07,14.9]
Herr 2003	3/148	1/147		10.12%	2.98[0.31,28.32]
Jalonen 1997	2/40	3/40		30.25%	0.67[0.12,3.78]
Loick 1999	1/24	0/21		5.36%	2.64[0.11,61.54]
Myles 1999	0/76	1/74		15.33%	0.32[0.01,7.84]
Patel 2016	0/25	0/25			Not estimable
Venn 1999	0/47	2/51		24.2%	0.22[0.01,4.4]
Total (95% CI)	**391**	**391**		**100%**	**1.01[0.43,2.4]**
Total events: 8 (Alpha-2 adrenergic agonists), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.57, df=6(P=0.73); I^2=0%					
Test for overall effect: Z=0.02(P=0.98)					

Analysis 2.3. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 3 Myocardial ischaemia.

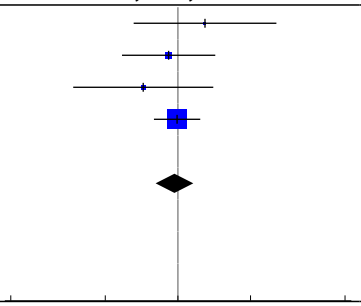
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abi-Jaoude 1993	2/11	3/13		1.91%	0.79[0.16,3.9]
Ammar 2016	1/25	1/25		0.69%	1[0.07,15.12]
Dorman 1993	8/22	13/21		9.23%	0.59[0.31,1.12]
El-Kerdawy 2004	0/25	7/25		5.21%	0.07[0,1.11]
Ghignone 1986	0/12	0/12			Not estimable
Jalonen 1997	14/40	19/40		13.19%	0.74[0.43,1.26]
Kim 2014a	1/40	1/38		0.71%	0.95[0.06,14.65]
Loick 1999	6/14	11/15		7.37%	0.58[0.3,1.15]
Myles 1999	15/76	22/74		15.47%	0.66[0.37,1.18]
Quintin 1993	3/13	6/13		4.16%	0.5[0.16,1.58]
Ren 2013	6/81	15/81		10.41%	0.4[0.16,0.98]
Shehabi 2009	35/152	35/147		24.7%	0.97[0.64,1.46]
Venn 1999	10/66	9/53		6.93%	0.89[0.39,2.04]
Total (95% CI)	**577**	**557**		**100%**	**0.69[0.56,0.86]**
Total events: 101 (Alpha-2 adrenergic agonists), 142 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.03, df=11(P=0.71); I^2=0%					
Test for overall effect: Z=3.31(P=0)					

Analysis 2.4. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 4 Supraventricular tachyarrhythmia.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Corbett 2005	1/43	0/46		1.07%	3.2[0.13,76.6]
Herr 2003	12/148	12/147		26.67%	0.99[0.46,2.14]
Jalonen 1997	9/40	10/40		22.15%	0.9[0.41,1.98]
Ren 2013	2/81	12/81		26.58%	0.17[0.04,0.72]
Shehabi 2009	3/152	5/147		11.26%	0.58[0.14,2.38]
Venn 1999	8/66	5/53		12.28%	1.28[0.45,3.7]
Total (95% CI)	**530**	**514**		**100%**	**0.77[0.5,1.16]**
Total events: 35 (Alpha-2 adrenergic agonists), 44 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.62, df=5(P=0.25); I^2=24.42%					
Test for overall effect: Z=1.25(P=0.21)					

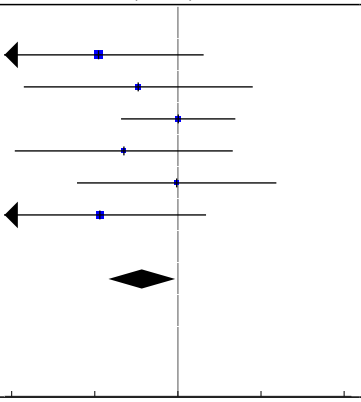
Analysis 2.5. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 5 Heart failure.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Abi-Jaoude 1993	2/11	1/13		4.56%	2.36[0.25,22.7]
Herr 2003	3/148	4/147		19.98%	0.74[0.17,3.27]
Jalonen 1997	1/40	3/40		14.93%	0.33[0.04,3.07]
Myles 1999	12/76	12/74		60.53%	0.97[0.47,2.03]
Total (95% CI)	**275**	**274**		**100%**	**0.9[0.49,1.63]**
Total events: 18 (Alpha-2 adrenergic agonists), 20 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.58, df=3(P=0.66); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					



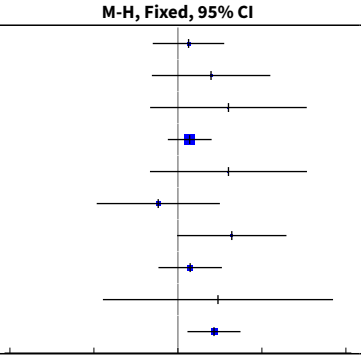
Analysis 2.6. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 6 Acute stroke.

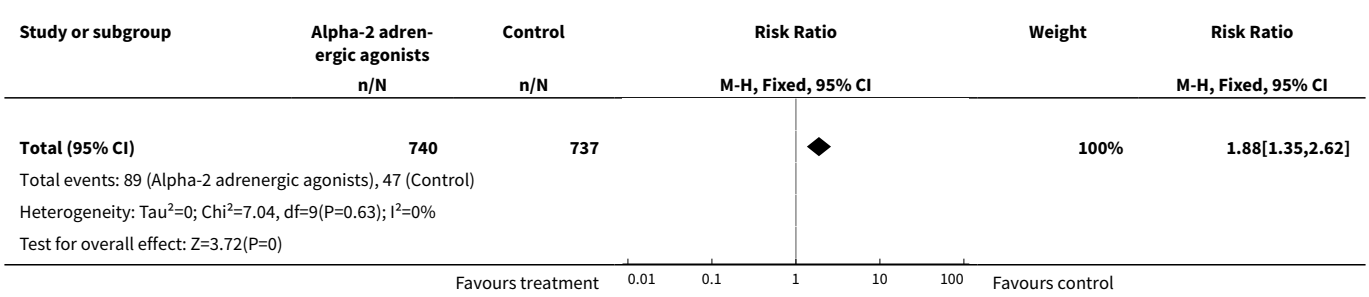
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ammar 2016	0/25	0/25			Not estimable
Cho 2016	0/100	4/100		27.7%	0.11[0.01,2.04]
Jalonen 1997	0/40	1/40		9.23%	0.33[0.01,7.95]
Li 2017	3/142	3/143		18.4%	1.01[0.21,4.91]
Park 2014	0/67	2/75		14.54%	0.22[0.01,4.57]
Shehabi 2009	1/152	1/147		6.26%	0.97[0.06,15.32]
Venn 1999	0/66	3/53		23.86%	0.12[0.01,2.18]
Total (95% CI)	**592**	**583**		**100%**	**0.37[0.15,0.93]**
Total events: 4 (Alpha-2 adrenergic agonists), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.38, df=5(P=0.64); I^2=0%					
Test for overall effect: Z=2.12(P=0.03)					



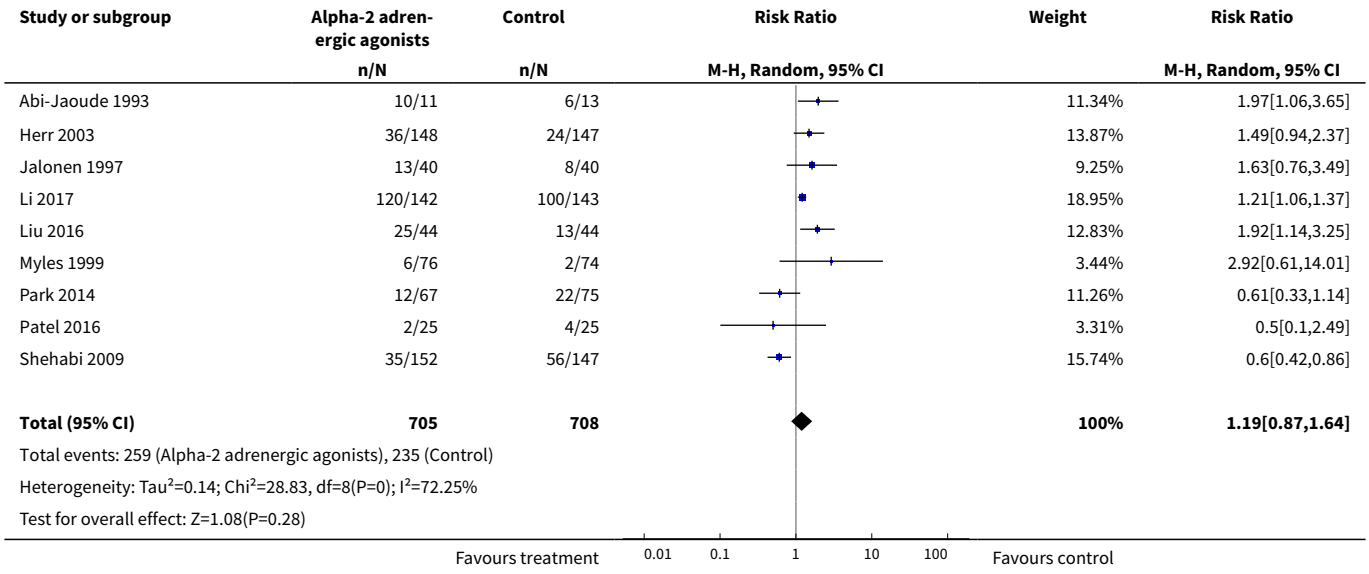
Analysis 2.7. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 7 Bradycardia.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Dorman 1993	7/22	5/21		10.77%	1.34[0.5,3.56]
Herr 2003	5/148	2/147		4.23%	2.48[0.49,12.6]
Jalonen 1997	4/40	1/40		2.11%	4[0.47,34.24]
Li 2017	22/142	16/143		33.57%	1.38[0.76,2.52]
Liu 2016	4/44	1/44		2.11%	4[0.47,34.38]
Loick 1999	2/24	3/21		6.74%	0.58[0.11,3.16]
Myles 1999	9/76	2/74		4.27%	4.38[0.98,19.6]
Park 2014	10/67	8/75		15.9%	1.4[0.59,3.34]
Patel 2016	1/25	0/25		1.05%	3[0.13,70.3]
Shehabi 2009	25/152	9/147		19.27%	2.69[1.3,5.56]





Analysis 2.8. Comparison 2 Alpha-2 adrenergic agonists versus control in cardiac surgery, Outcome 8 Hypotension.



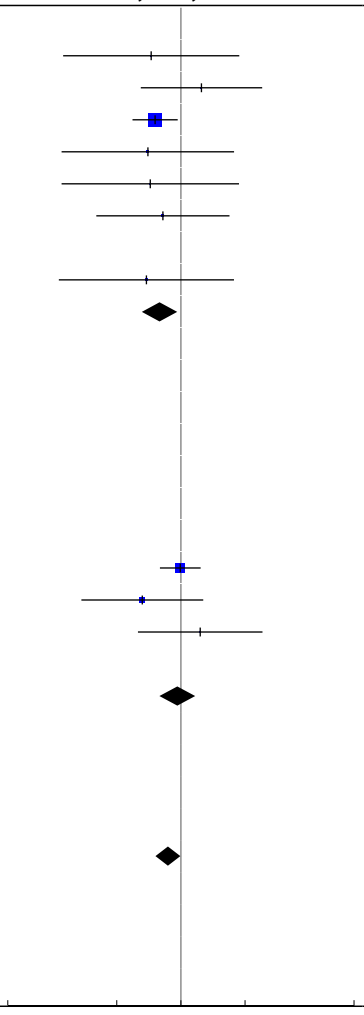
Comparison 3. Alpha-2 adrenergic agonists versus control in non-cardiac surgery - stratified by vascular versus non-vascular surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	13	3713	Risk Ratio (M-H, Fixed, 95% CI)	0.63 [0.40, 0.98]
1.1 Vascular surgery	8	1798	Risk Ratio (M-H, Fixed, 95% CI)	0.46 [0.25, 0.88]
1.2 Non-vascular surgery	6	1915	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.46, 1.67]
2 Cardiac mortality	4	2515	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 0.93]
2.1 Vascular surgery	4	1522	Risk Ratio (M-H, Fixed, 95% CI)	0.36 [0.16, 0.79]
2.2 Non-vascular surgery	1	993	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.35, 2.77]
3 Myocardial infarction	9	3539	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.17]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 Vascular surgery	7	1766	Risk Ratio (M-H, Random, 95% CI)	0.52 [0.27, 1.00]
3.2 Non-vascular surgery	3	1773	Risk Ratio (M-H, Random, 95% CI)	1.09 [0.55, 2.15]
4 Myocardial ischaemia	9	961	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.52, 1.17]
4.1 Vascular surgery	6	865	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.29]
4.2 Non-vascular surgery	3	96	Risk Ratio (M-H, Random, 95% CI)	0.23 [0.04, 1.34]

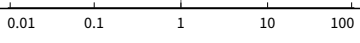
Analysis 3.1. Comparison 3 Alpha-2 adrenergic agonists versus control in non-cardiac surgery - stratified by vascular versus non-vascular surgery, Outcome 1 All-cause mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.1.1 Vascular surgery					
Ellis 1994	0/30	1/31		3.03%	0.34[0.01,8.13]
McSPI-Europe 1997	4/197	1/103		2.7%	2.09[0.24,18.47]
Oliver 1999	8/454	20/450		41.29%	0.4[0.18,0.89]
Quintin 1996	0/11	1/10		3.22%	0.31[0.01,6.74]
Soliman 2016	0/75	1/75		3.08%	0.33[0.01,8.05]
Stuhmeier 1996	1/145	2/152		4.01%	0.52[0.05,5.72]
Talke 1995	0/18	0/6			Not estimable
Talke 2000	0/22	1/19		3.3%	0.29[0.01,6.72]
Subtotal (95% CI)	**952**	**846**		**60.63%**	**0.46[0.25,0.88]**
Total events: 13 (Alpha-2 adrenergic agonists), 27 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.22, df=6(P=0.9); I^2=0%					
Test for overall effect: Z=2.37(P=0.02)					
3.1.2 Non-vascular surgery					
Bergese 2010	0/55	0/50			Not estimable
Lee 2013a	0/28	0/29			Not estimable
Oliver 1999	14/502	14/491		29.09%	0.98[0.47,2.03]
Su 2016	1/350	4/350		8.22%	0.25[0.03,2.23]
Venn 2001	2/10	1/10		2.06%	2[0.21,18.69]
Viviano 2012	0/20	0/20			Not estimable
Subtotal (95% CI)	**965**	**950**		**39.37%**	**0.88[0.46,1.67]**
Total events: 17 (Alpha-2 adrenergic agonists), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.87, df=2(P=0.39); I^2=0%					
Test for overall effect: Z=0.39(P=0.7)					
Total (95% CI)	**1917**	**1796**		**100%**	**0.63[0.4,0.98]**
Total events: 30 (Alpha-2 adrenergic agonists), 46 (Control)					
Heterogeneity: Tau^2=0; Chi^2=6.29, df=9(P=0.71); I^2=0%					
Test for overall effect: Z=2.04(P=0.04)					
Test for subgroup differences: Chi^2=1.92, df=1 (P=0.17), I^2=47.94%					



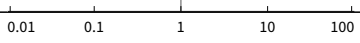
Analysis 3.2. Comparison 3 Alpha-2 adrenergic agonists versus control in non-cardiac surgery - stratified by vascular versus non-vascular surgery, Outcome 2 Cardiac mortality.

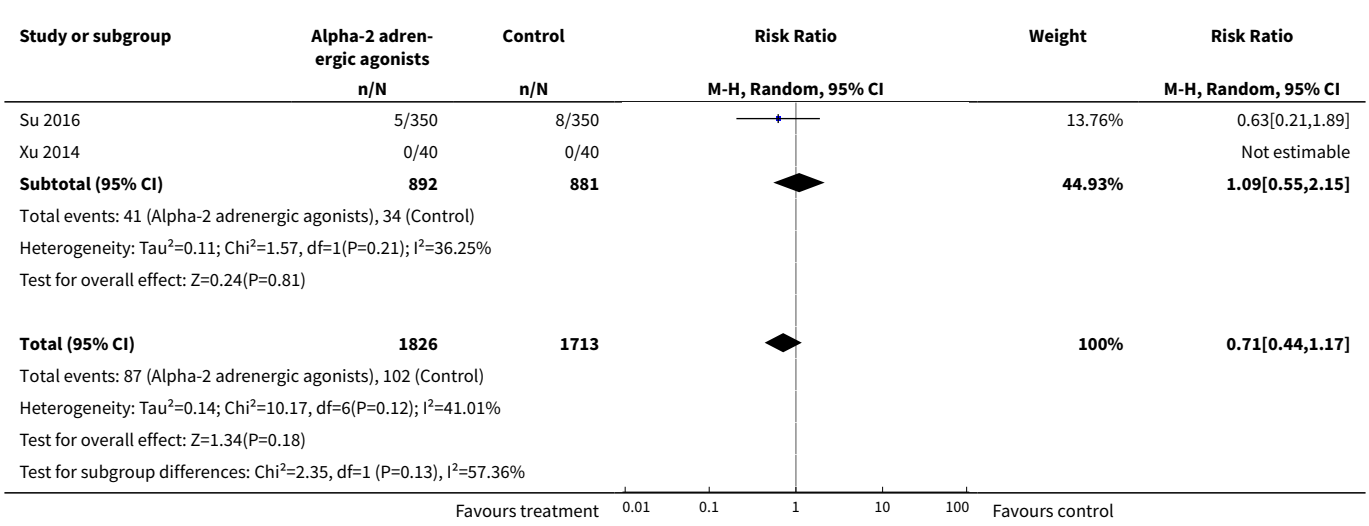
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
3.2.1 Vascular surgery					
McSPI-Europe 1997	1/197	1/103		4.4%	0.52[0.03,8.27]
Oliver 1999	6/454	18/450		60.55%	0.33[0.13,0.82]
Quintin 1996	0/10	1/11		4.81%	0.36[0.02,8.03]
Stuhmeier 1996	1/145	2/152		6.54%	0.52[0.05,5.72]
Subtotal (95% CI)	**806**	**716**		**76.3%**	**0.36[0.16,0.79]**
Total events: 8 (Alpha-2 adrenergic agonists), 22 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.2, df=3(P=0.98); I^2=0%					
Test for overall effect: Z=2.54(P=0.01)					
3.2.2 Non-vascular surgery					
Oliver 1999	7/502	7/491		23.7%	0.98[0.35,2.77]
Subtotal (95% CI)	**502**	**491**		**23.7%**	**0.98[0.35,2.77]**
Total events: 7 (Alpha-2 adrenergic agonists), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					
Total (95% CI)	**1308**	**1207**		**100%**	**0.51[0.27,0.93]**
Total events: 15 (Alpha-2 adrenergic agonists), 29 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.42, df=4(P=0.66); I^2=0%					
Test for overall effect: Z=2.18(P=0.03)					
Test for subgroup differences: Chi^2=2.25, df=1 (P=0.13), I^2=55.61%					



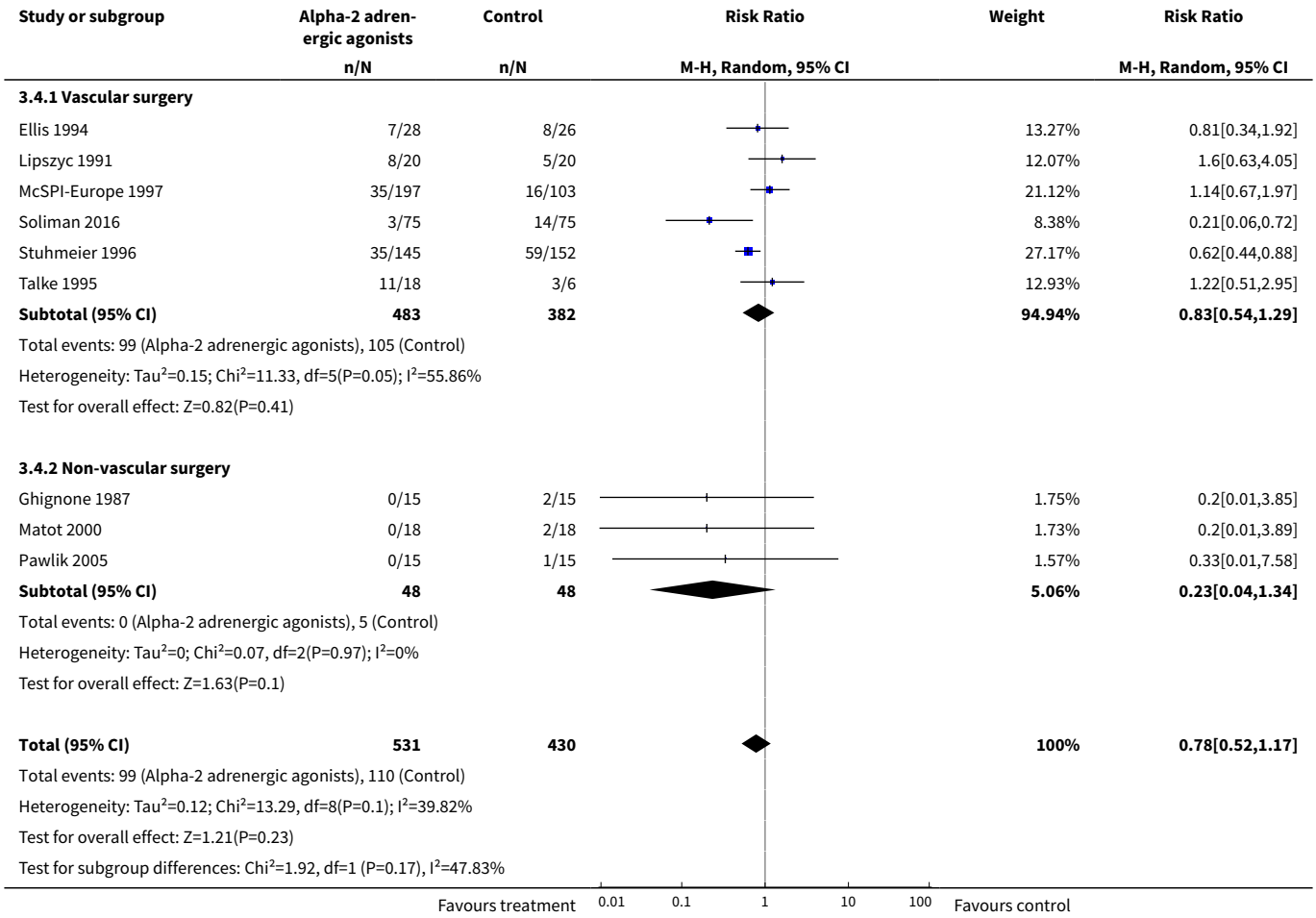
Analysis 3.3. Comparison 3 Alpha-2 adrenergic agonists versus control in non-cardiac surgery - stratified by vascular versus non-vascular surgery, Outcome 3 Myocardial infarction.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.3.1 Vascular surgery					
Ellis 1994	0/30	2/31		2.56%	0.21[0.01,4.13]
McSPI-Europe 1997	3/197	6/103		10.12%	0.26[0.07,1.02]
Oliver 1999	42/454	53/450		35.32%	0.79[0.54,1.15]
Pluskwa 1991	0/15	0/15			Not estimable
Soliman 2016	1/75	3/75		4.38%	0.33[0.04,3.13]
Stuhmeier 1996	0/145	4/152		2.7%	0.12[0.01,2.14]
Talke 1995	0/18	0/6			Not estimable
Subtotal (95% CI)	**934**	**832**		**55.07%**	**0.52[0.27,1]**
Total events: 46 (Alpha-2 adrenergic agonists), 68 (Control)					
Heterogeneity: Tau^2=0.13; Chi^2=4.9, df=4(P=0.3); I^2=18.43%					
Test for overall effect: Z=1.97(P=0.05)					
3.3.2 Non-vascular surgery					
Oliver 1999	36/502	26/491		31.16%	1.35[0.83,2.21]





Analysis 3.4. Comparison 3 Alpha-2 adrenergic agonists versus control in non-cardiac surgery - stratified by vascular versus non-vascular surgery, Outcome 4 Myocardial ischaemia.

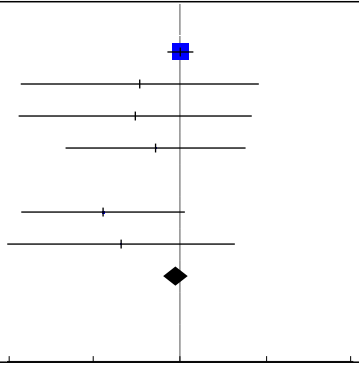


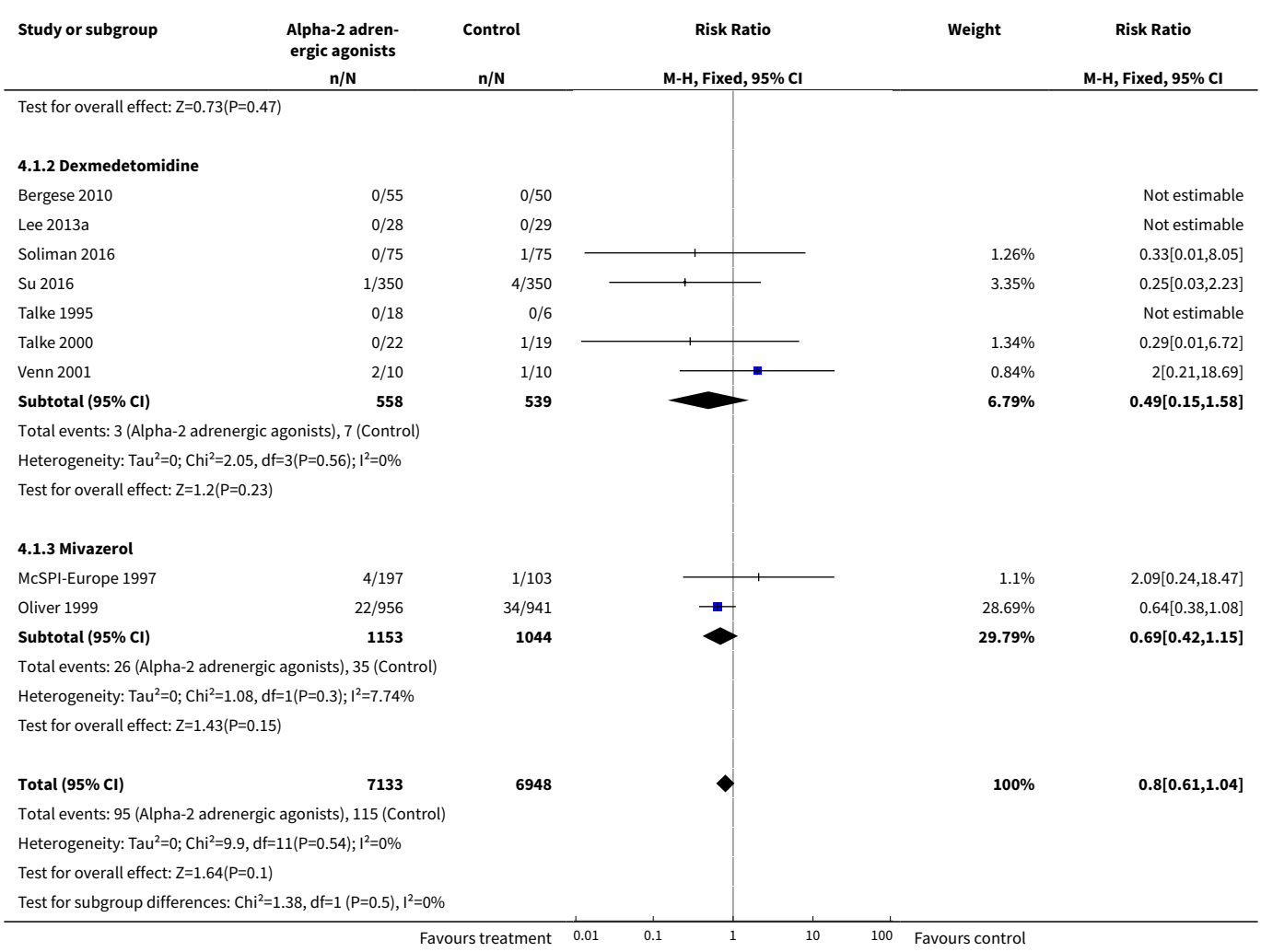
Comparison 4. Alpha-2 adrenergic agonists (stratified by drug) versus control in non-cardiac surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	16	14081	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.61, 1.04]
1.1 Clonidine	7	10787	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.64, 1.23]
1.2 Dexmedetomidine	7	1097	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.15, 1.58]
1.3 Mivazerol	2	2197	Risk Ratio (M-H, Fixed, 95% CI)	0.69 [0.42, 1.15]
2 Cardiac mortality	5	12525	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.60, 1.23]
2.1 Clonidine	3	10328	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.71, 1.75]
2.2 Mivazerol	2	2197	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.27, 0.98]
3 Myocardial infarction	12	13907	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.69, 1.27]
3.1 Clonidine	6	10756	Risk Ratio (M-H, Random, 95% CI)	1.05 [0.57, 1.92]
3.2 Dexmedetomidine	4	954	Risk Ratio (M-H, Random, 95% CI)	0.55 [0.20, 1.49]
3.3 Mivazerol	2	2197	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.17, 2.08]
4 Hypotension	15	13738	Risk Ratio (M-H, Random, 95% CI)	1.24 [1.03, 1.48]
4.1 Clonidine	7	10485	Risk Ratio (M-H, Random, 95% CI)	1.29 [1.23, 1.35]
4.2 Dexmedetomidine	6	1056	Risk Ratio (M-H, Random, 95% CI)	1.81 [1.07, 3.06]
4.3 Mivazerol	2	2197	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.82, 1.10]

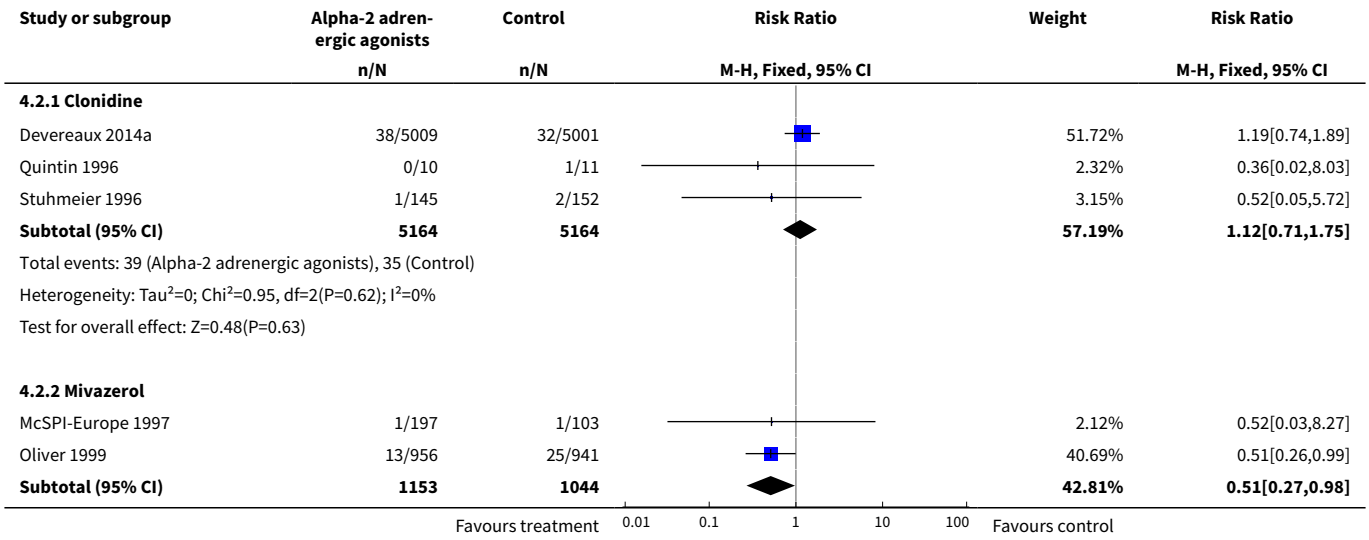
Analysis 4.1. Comparison 4 Alpha-2 adrenergic agonists (stratified by drug) versus control in non-cardiac surgery, Outcome 1 All-cause mortality.

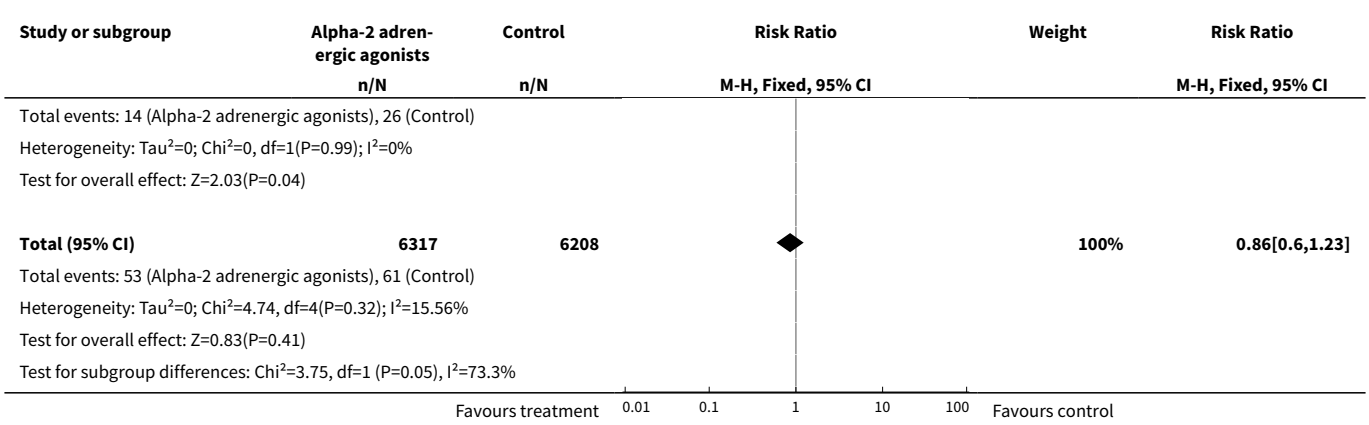
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 Clonidine					
Devereaux 2014a	64/5009	63/5001		52.79%	1.01[0.72,1.43]
Ellis 1994	0/30	1/31		1.24%	0.34[0.01,8.13]
Quintin 1996	0/11	1/10		1.31%	0.31[0.01,6.74]
Stuhmeier 1996	1/145	2/152		1.64%	0.52[0.05,5.72]
Viviano 2012	0/20	0/20			Not estimable
Wallace 2004	1/125	4/65		4.41%	0.13[0.01,1.14]
Wijeysundera 2014a	0/82	2/86		2.04%	0.21[0.01,4.3]
Subtotal (95% CI)	**5422**	**5365**		**63.42%**	**0.89[0.64,1.23]**
Total events: 66 (Alpha-2 adrenergic agonists), 73 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.45, df=5(P=0.36); I^2=8.21%					



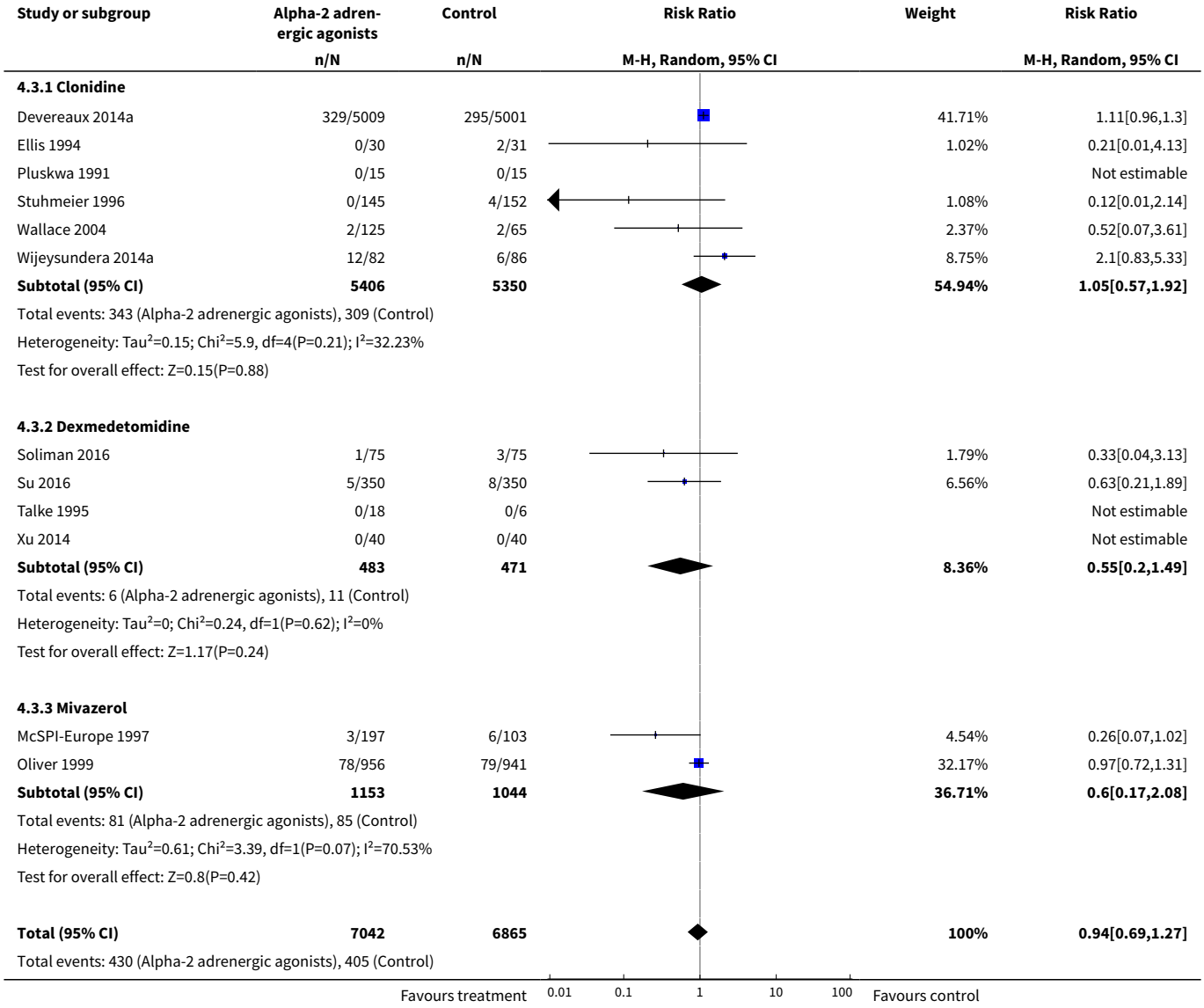


Analysis 4.2. Comparison 4 Alpha-2 adrenergic agonists (stratified by drug) versus control in non-cardiac surgery, Outcome 2 Cardiac mortality.





Analysis 4.3. Comparison 4 Alpha-2 adrenergic agonists (stratified by drug) versus control in non-cardiac surgery, Outcome 3 Myocardial infarction.



Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Heterogeneity: Tau²=0.05; Chi²=12.61, df=8(P=0.13); I²=36.57%					
Test for overall effect: Z=0.42(P=0.67)					
Test for subgroup differences: Chi²=1.48, df=1 (P=0.48), I²=0%					

Analysis 4.4. Comparison 4 Alpha-2 adrenergic agonists (stratified by drug) versus control in non-cardiac surgery, Outcome 4 Hypotension.

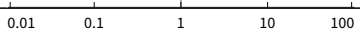
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
4.4.1 Clonidine					
Devereaux 2014a	2385/5009	1854/5001		24.64%	1.28[1.23,1.35]
Ghignone 1987	1/15	3/15		0.69%	0.33[0.04,2.85]
Matot 2000	2/18	0/18		0.36%	5[0.26,97.37]
Pluskwa 1991	12/15	8/15		7.79%	1.5[0.88,2.57]
Quintin 1996	5/11	2/10		1.56%	2.27[0.56,9.2]
Wallace 2004	24/125	11/65		5.93%	1.13[0.59,2.17]
Wijeysundera 2014a	7/82	6/86		2.65%	1.22[0.43,3.49]
Subtotal (95% CI)	**5275**	**5210**		**43.63%**	**1.29[1.23,1.35]**
Total events: 2436 (Alpha-2 adrenergic agonists), 1884 (Control)					
Heterogeneity: Tau²=0; Chi²=3.43, df=6(P=0.75); I²=0%					
Test for overall effect: Z=10.7(P<0.0001)					
4.4.2 Dexmedetomidine					
Bergese 2010	15/55	3/50		2.14%	4.55[1.4,14.78]
Lee 2013a	10/28	3/29		2.14%	3.45[1.06,11.25]
Soliman 2016	7/75	3/75		1.76%	2.33[0.63,8.68]
Su 2016	34/350	32/350		9.55%	1.06[0.67,1.68]
Talke 1995	17/18	4/6		7.04%	1.42[0.8,2.52]
Venn 2001	0/10	0/10			Not estimable
Subtotal (95% CI)	**536**	**520**		**22.63%**	**1.81[1.07,3.06]**
Total events: 83 (Alpha-2 adrenergic agonists), 45 (Control)					
Heterogeneity: Tau²=0.17; Chi²=8.08, df=4(P=0.09); I²=50.5%					
Test for overall effect: Z=2.21(P=0.03)					
4.4.3 Mivazerol					
McSPI-Europe 1997	127/197	72/103		20.77%	0.92[0.78,1.09]
Oliver 1999	62/956	57/941		12.97%	1.07[0.76,1.52]
Subtotal (95% CI)	**1153**	**1044**		**33.73%**	**0.95[0.82,1.1]**
Total events: 189 (Alpha-2 adrenergic agonists), 129 (Control)					
Heterogeneity: Tau²=0; Chi²=0.76, df=1(P=0.38); I²=0%					
Test for overall effect: Z=0.71(P=0.48)					
Total (95% CI)	**6964**	**6774**		**100%**	**1.24[1.03,1.48]**
Total events: 2708 (Alpha-2 adrenergic agonists), 2058 (Control)					
Heterogeneity: Tau²=0.03; Chi²=28.03, df=13(P=0.01); I²=53.62%					
Test for overall effect: Z=2.32(P=0.02)					
Test for subgroup differences: Chi²=16.72, df=1 (P=0), I²=88.04%					

Comparison 5. Alpha-2 adrenergic agonists versus control in non-cardiac surgery studies with blinding and concealed allocation

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	7	13066	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.41, 1.11]
2 Myocardial infarction	6	13026	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.95, 1.23]
3 Myocardial ischaemia	3	412	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.40, 1.48]

Analysis 5.1. Comparison 5 Alpha-2 adrenergic agonists versus control in non-cardiac surgery studies with blinding and concealed allocation, Outcome 1 All-cause mortality.

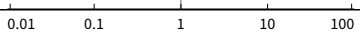
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Devereaux 2014a	64/5009	63/5001		48.51%	1.01[0.72,1.43]
Ellis 1994	0/30	1/31		2.38%	0.34[0.01,8.13]
Oliver 1999	22/956	34/941		36.91%	0.64[0.38,1.08]
Su 2016	1/350	4/350		4.78%	0.25[0.03,2.23]
Viviano 2012	0/20	0/20			Not estimable
Wallace 2004	1/125	4/65		4.84%	0.13[0.01,1.14]
Wijeysundera 2014a	0/82	2/86		2.59%	0.21[0.01,4.3]
Total (95% CI)	**6572**	**6494**		**100%**	**0.68[0.41,1.11]**
Total events: 88 (Alpha-2 adrenergic agonists), 108 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=7.33, df=5(P=0.2); I^2=31.79%					
Test for overall effect: Z=1.54(P=0.12)					



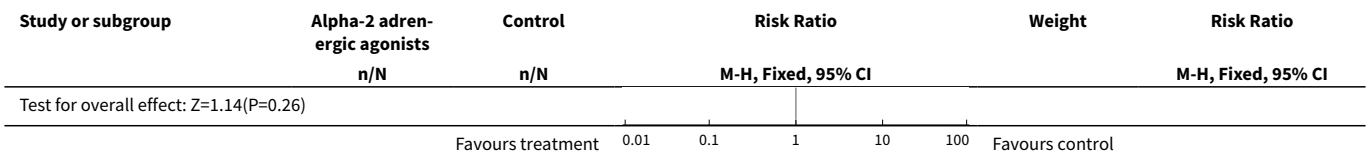
Favours treatment — Favours control

Analysis 5.2. Comparison 5 Alpha-2 adrenergic agonists versus control in non-cardiac surgery studies with blinding and concealed allocation, Outcome 2 Myocardial infarction.

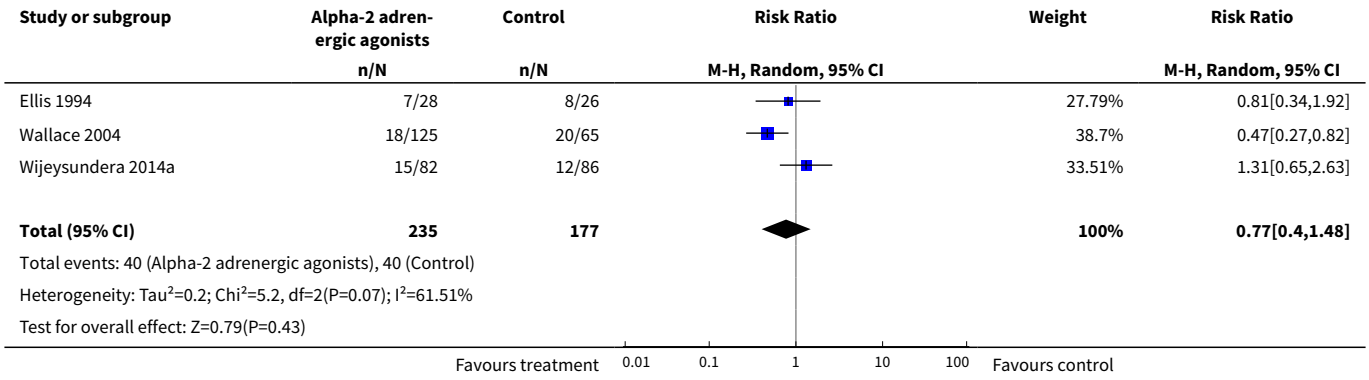
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	329/5009	295/5001		74.97%	1.11[0.96,1.3]
Ellis 1994	0/30	2/31		0.62%	0.21[0.01,4.13]
Oliver 1999	78/956	79/941		20.22%	0.97[0.72,1.31]
Su 2016	5/350	8/350		2.03%	0.63[0.21,1.89]
Wallace 2004	2/125	2/65		0.67%	0.52[0.07,3.61]
Wijeysundera 2014a	12/82	6/86		1.49%	2.1[0.83,5.33]
Total (95% CI)	**6552**	**6474**		**100%**	**1.08[0.95,1.23]**
Total events: 426 (Alpha-2 adrenergic agonists), 392 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.23, df=5(P=0.39); I^2=4.49%					



Favours treatment — Favours control



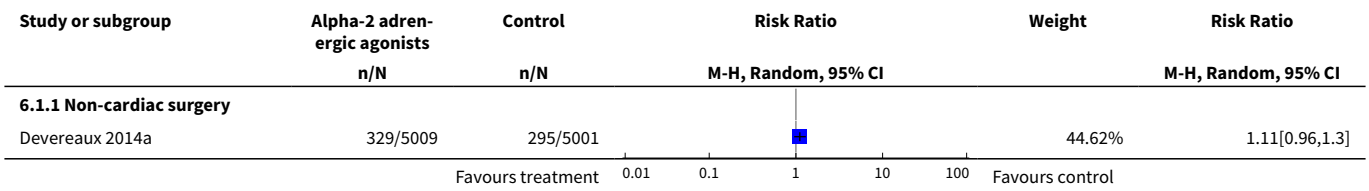
Analysis 5.3. Comparison 5 Alpha-2 adrenergic agonists versus control in non-cardiac surgery studies with blinding and concealed allocation, Outcome 3 Myocardial ischaemia.

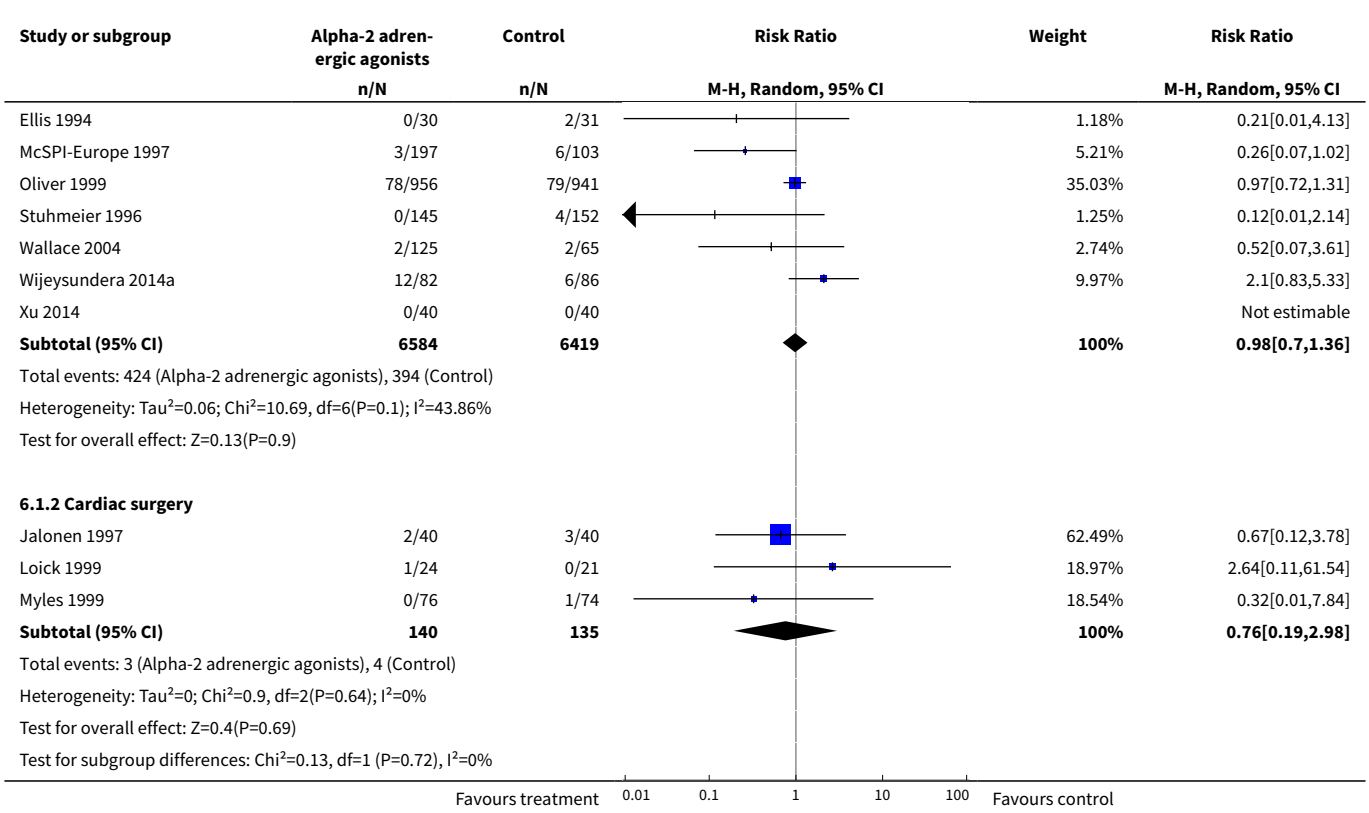


Comparison 6. Alpha-2 adrenergic agonists versus control in studies that used strict definitions of myocardial infarction or ischaemia

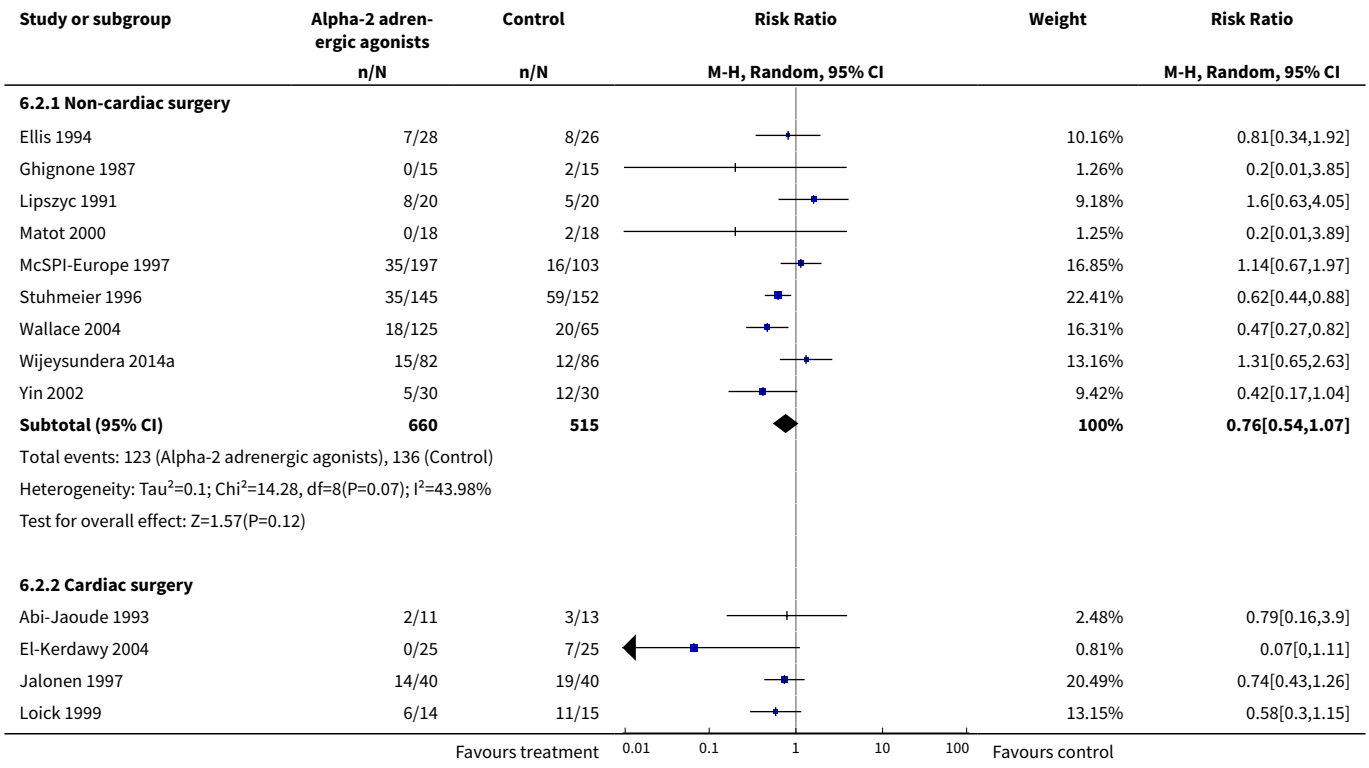
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction	11		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 Non-cardiac surgery	8	13003	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.70, 1.36]
1.2 Cardiac surgery	3	275	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.19, 2.98]
2 Myocardial ischaemia	17		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 Non-cardiac surgery	9	1175	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.54, 1.07]
2.2 Cardiac surgery	8	820	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.55, 0.91]

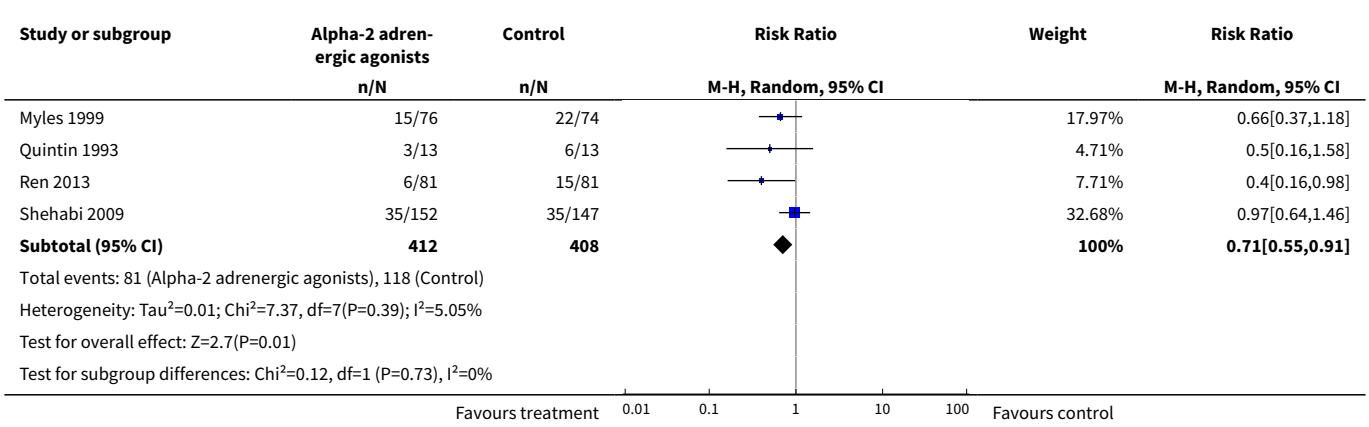
Analysis 6.1. Comparison 6 Alpha-2 adrenergic agonists versus control in studies that used strict definitions of myocardial infarction or ischaemia, Outcome 1 Myocardial infarction.





Analysis 6.2. Comparison 6 Alpha-2 adrenergic agonists versus control in studies that used strict definitions of myocardial infarction or ischaemia, Outcome 2 Myocardial ischaemia.

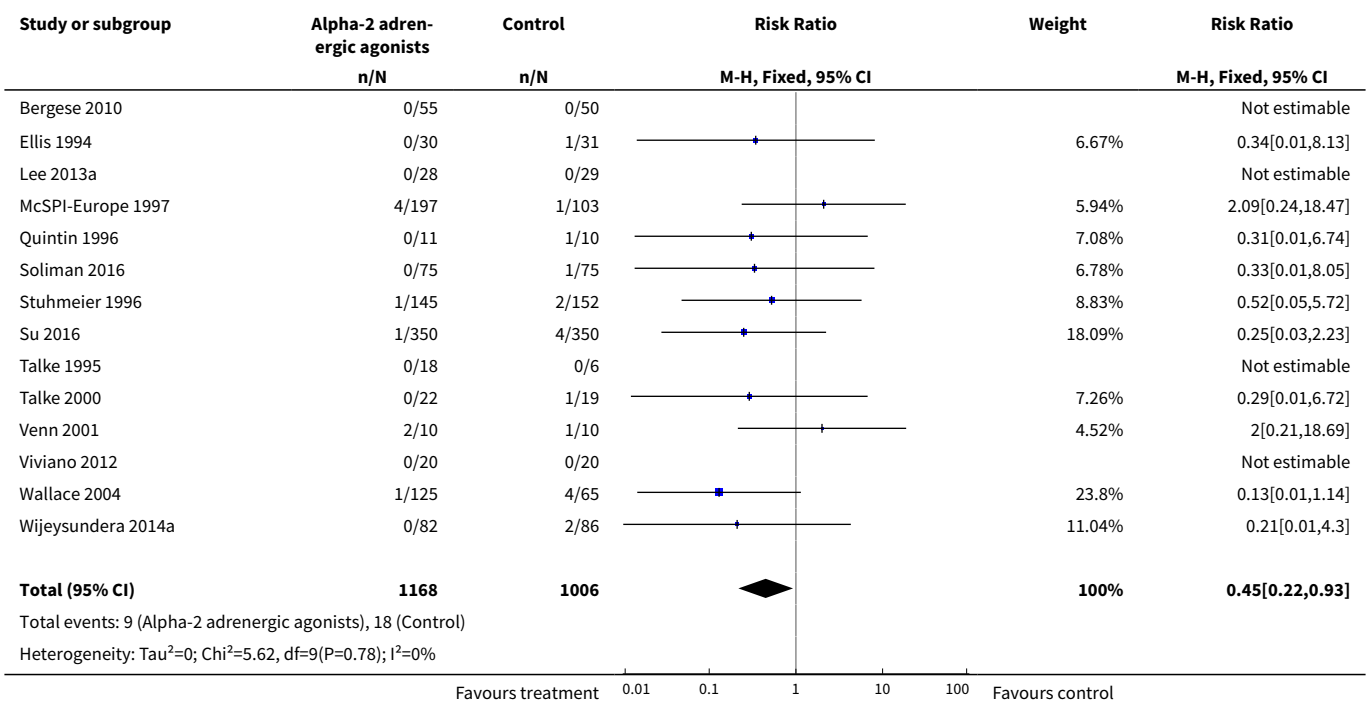




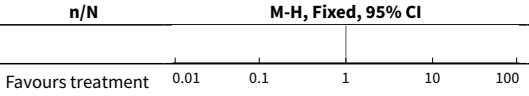
Comparison 7. Alpha-2 adrenergic agonists versus control in non-cardiac surgery (excluding Oliver 1999 and Devereaux 2014)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	14	2174	Risk Ratio (M-H, Fixed, 95% CI)	0.45 [0.22, 0.93]
2 Cardiac mortality	3	618	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.10, 2.25]
3 Myocardial infarction	10	2000	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.25, 1.25]

Analysis 7.1. Comparison 7 Alpha-2 adrenergic agonists versus control in non-cardiac surgery (excluding Oliver 1999 and Devereaux 2014), Outcome 1 All-cause mortality.

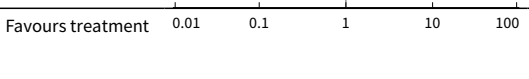


Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Test for overall effect: Z=2.16(P=0.03)					



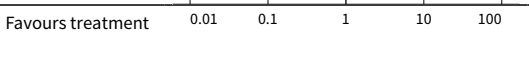
Analysis 7.2. Comparison 7 Alpha-2 adrenergic agonists versus control in non-cardiac surgery (excluding Oliver 1999 and Devereaux 2014), Outcome 2 Cardiac mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
McSPI-Europe 1997	1/197	1/103		27.94%	0.52[0.03,8.27]
Quintin 1996	0/10	1/11		30.52%	0.36[0.02,8.03]
Stuhmeier 1996	1/145	2/152		41.54%	0.52[0.05,5.72]
Total (95% CI)	**352**	**266**		**100%**	**0.47[0.1,2.25]**
Total events: 2 (Alpha-2 adrenergic agonists), 4 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=2(P=0.98); I^2=0%					
Test for overall effect: Z=0.94(P=0.35)					



Analysis 7.3. Comparison 7 Alpha-2 adrenergic agonists versus control in non-cardiac surgery (excluding Oliver 1999 and Devereaux 2014), Outcome 3 Myocardial infarction.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ellis 1994	0/30	2/31		6.04%	0.21[0.01,4.13]
McSPI-Europe 1997	3/197	6/103		18.28%	0.26[0.07,1.02]
Pluskwa 1991	0/15	0/15			Not estimable
Soliman 2016	1/75	3/75		9.63%	0.33[0.04,3.13]
Stuhmeier 1996	0/145	4/152		6.34%	0.12[0.01,2.14]
Su 2016	5/350	8/350		22.33%	0.63[0.21,1.89]
Talke 1995	0/18	0/6			Not estimable
Wallace 2004	2/125	2/65		11.89%	0.52[0.07,3.61]
Wijeysundera 2014a	12/82	6/86		25.5%	2.1[0.83,5.33]
Xu 2014	0/40	0/40			Not estimable
Total (95% CI)	**1077**	**923**		**100%**	**0.56[0.25,1.25]**
Total events: 23 (Alpha-2 adrenergic agonists), 31 (Control)					
Heterogeneity: Tau^2=0.43; Chi^2=10.03, df=6(P=0.12); I^2=40.19%					
Test for overall effect: Z=1.41(P=0.16)					

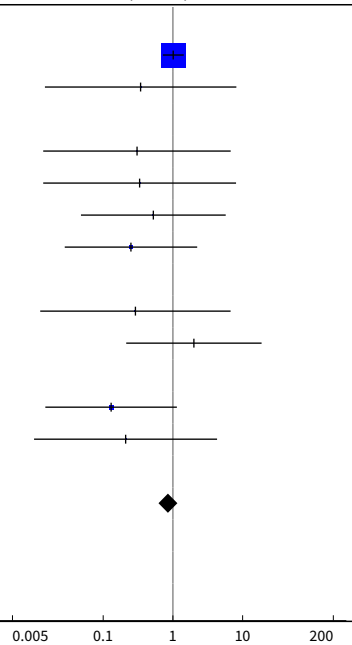


Comparison 8. Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	14	11884	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.62, 1.16]
2 Cardiac mortality	3	10328	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.71, 1.75]
3 Myocardial infarction	10	11710	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.59, 1.53]
4 Myocardial ischaemia	11	1079	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.97]
5 Supraventricular tachyarrhythmia	2	44	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.05, 24.07]
6 Heart failure	7	10502	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [0.85, 1.84]
7 Acute stroke	6	11242	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.49, 1.63]
8 Bradycardia	14	11838	Risk Ratio (M-H, Random, 95% CI)	1.66 [1.17, 2.36]
9 Hypotension	13	11541	Risk Ratio (M-H, Random, 95% CI)	1.33 [1.15, 1.55]

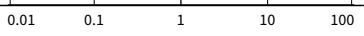
Analysis 8.1. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 1 All-cause mortality.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bergese 2010	0/55	0/50			Not estimable
Devereaux 2014a	64/5009	63/5001		75.19%	1.01[0.72,1.43]
Ellis 1994	0/30	1/31		1.76%	0.34[0.01,8.13]
Lee 2013a	0/28	0/29			Not estimable
Quintin 1996	0/11	1/10		1.87%	0.31[0.01,6.74]
Soliman 2016	0/75	1/75		1.79%	0.33[0.01,8.05]
Stuhmeier 1996	1/145	2/152		2.33%	0.52[0.05,5.72]
Su 2016	1/350	4/350		4.77%	0.25[0.03,2.23]
Talke 1995	0/18	0/6			Not estimable
Talke 2000	0/22	1/19		1.91%	0.29[0.01,6.72]
Venn 2001	2/10	1/10		1.19%	2[0.21,18.69]
Viviano 2012	0/20	0/20			Not estimable
Wallace 2004	1/125	4/65		6.28%	0.13[0.01,1.14]
Wijeysundera 2014a	0/82	2/86		2.91%	0.21[0.01,4.3]
Total (95% CI)	**5980**	**5904**		**100%**	**0.85[0.62,1.16]**
Total events: 69 (Alpha-2 adrenergic agonists), 80 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.15, df=9(P=0.52); I^2=0%					
Test for overall effect: Z=1.03(P=0.3)					



Analysis 8.2. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 2 Cardiac mortality.

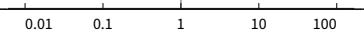
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	38/5009	32/5001		90.43%	1.19[0.74,1.89]
Quintin 1996	0/10	1/11		4.05%	0.36[0.02,8.03]
Stuhmeier 1996	1/145	2/152		5.51%	0.52[0.05,5.72]
Total (95% CI)	**5164**	**5164**		**100%**	**1.12[0.71,1.75]**
Total events: 39 (Alpha-2 adrenergic agonists), 35 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.95, df=2(P=0.62); I^2=0%					
Test for overall effect: Z=0.48(P=0.63)					



Favours treatment — Favours control

Analysis 8.3. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 3 Myocardial infarction.

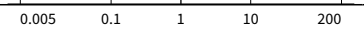
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Devereaux 2014a	329/5009	295/5001		53.71%	1.11[0.96,1.3]
Ellis 1994	0/30	2/31		2.41%	0.21[0.01,4.13]
Pluskwa 1991	0/15	0/15			Not estimable
Soliman 2016	1/75	3/75		4.17%	0.33[0.04,3.13]
Stuhmeier 1996	0/145	4/152		2.54%	0.12[0.01,2.14]
Su 2016	5/350	8/350		13.9%	0.63[0.21,1.89]
Talke 1995	0/18	0/6			Not estimable
Wallace 2004	2/125	2/65		5.44%	0.52[0.07,3.61]
Wijeysundera 2014a	12/82	6/86		17.83%	2.1[0.83,5.33]
Xu 2014	0/40	0/40			Not estimable
Total (95% CI)	**5889**	**5821**		**100%**	**0.95[0.59,1.53]**
Total events: 349 (Alpha-2 adrenergic agonists), 320 (Control)					
Heterogeneity: Tau^2=0.1; Chi^2=8.03, df=6(P=0.24); I^2=25.31%					
Test for overall effect: Z=0.2(P=0.84)					



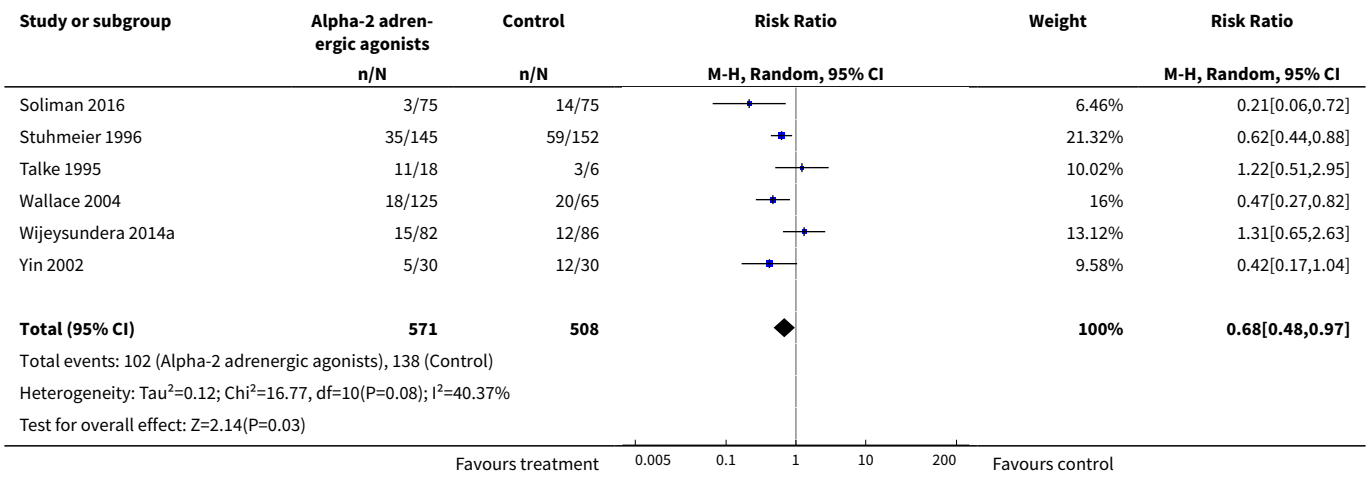
Favours treatment — Favours control

Analysis 8.4. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 4 Myocardial ischaemia.

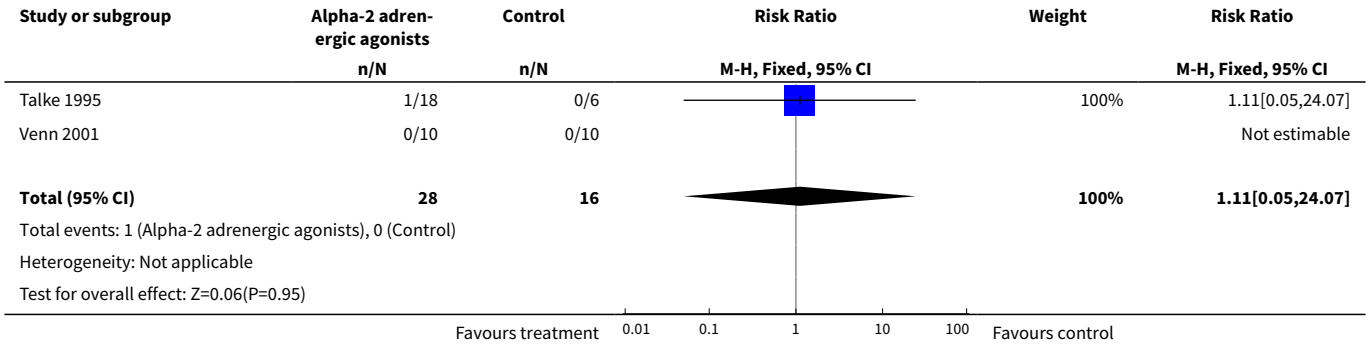
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Ellis 1994	7/28	8/26		10.28%	0.81[0.34,1.92]
Ghignone 1987	0/15	2/15		1.34%	0.2[0.01,3.85]
Lipszyc 1991	8/20	5/20		9.35%	1.6[0.63,4.05]
Matot 2000	0/18	2/18		1.33%	0.2[0.01,3.89]
Pawlik 2005	0/15	1/15		1.21%	0.33[0.01,7.58]



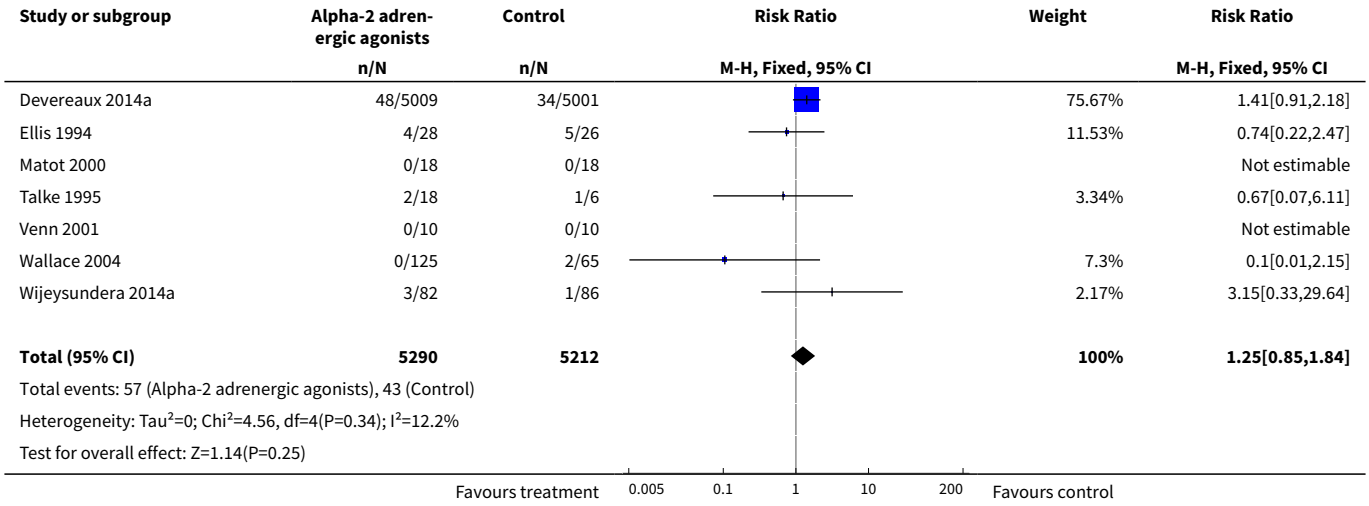
Favours treatment — Favours control



Analysis 8.5. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 5 Supraventricular tachyarrhythmia.



Analysis 8.6. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 6 Heart failure.



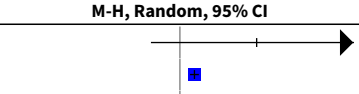
Analysis 8.7. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 7 Acute stroke.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Devereaux 2014a	18/5009	17/5001		75.61%	1.06[0.55,2.05]
Soliman 2016	0/75	0/75			Not estimable
Su 2016	0/350	3/350		15.55%	0.14[0.01,2.76]
Talke 1995	1/16	1/8		5.93%	0.5[0.04,7]
Wallace 2004	1/125	0/65		2.92%	1.57[0.06,38.04]
Wijeysundera 2014a	0/82	0/86			Not estimable
Total (95% CI)	**5657**	**5585**		**100%**	**0.9[0.49,1.63]**
Total events: 20 (Alpha-2 adrenergic agonists), 21 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.02, df=3(P=0.57); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					

Favours treatment — Favours control

Analysis 8.8. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 8 Bradycardia.

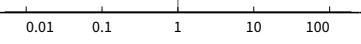
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bergese 2010	4/55	0/50		1.41%	8.2[0.45,148.52]
Devereaux 2014a	600/5009	403/5001		37.99%	1.49[1.32,1.68]
Lee 2013a	11/28	4/29		9.08%	2.85[1.03,7.9]
Matot 2000	0/18	0/18			Not estimable
Pawlik 2005	2/15	0/15		1.35%	5[0.26,96.13]
Pluskwa 1991	7/15	4/15		9.37%	1.75[0.64,4.75]
Quintin 1996	2/11	2/10		3.58%	0.91[0.16,5.3]
Soliman 2016	9/75	2/75		4.79%	4.5[1.01,20.13]
Stuhmeier 1996	23/145	30/152		22.2%	0.8[0.49,1.32]
Su 2016	5/350	1/350		2.5%	5[0.59,42.58]
Talke 1995	8/18	0/6		1.59%	6.26[0.41,94.82]
Venn 2001	0/10	0/10			Not estimable
Wallace 2004	12/125	2/65		4.97%	3.12[0.72,13.52]
Wijeysundera 2014a	1/82	0/86		1.17%	3.14[0.13,76.11]
Total (95% CI)	**5956**	**5882**		**100%**	**1.66[1.17,2.36]**
Total events: 684 (Alpha-2 adrenergic agonists), 448 (Control)					
Heterogeneity: Tau^2=0.08; Chi^2=15.58, df=11(P=0.16); I^2=29.41%					
Test for overall effect: Z=2.85(P=0)					



Favours treatment — Favours control

Analysis 8.9. Comparison 8 Alpha-2 adrenergic agonists (excluding mivazerol) versus control in non-cardiac surgery, Outcome 9 Hypotension.

Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
Bergese 2010	15/55	3/50		1.55%	4.55[1.4,14.78]
Devereaux 2014a	2385/5009	1854/5001		64.96%	1.28[1.23,1.35]
Ghignone 1987	1/15	3/15		0.48%	0.33[0.04,2.85]
Lee 2013a	10/28	3/29		1.55%	3.45[1.06,11.25]
Matot 2000	2/18	0/18		0.25%	5[0.26,97.37]
Pluskwa 1991	12/15	8/15		6.89%	1.5[0.88,2.57]
Quintin 1996	5/11	2/10		1.11%	2.27[0.56,9.2]
Soliman 2016	7/75	3/75		1.25%	2.33[0.63,8.68]
Su 2016	34/350	32/350		9.08%	1.06[0.67,1.68]
Talke 1995	17/18	4/6		6.05%	1.42[0.8,2.52]
Venn 2001	0/10	0/10			Not estimable
Wallace 2004	24/125	11/65		4.89%	1.13[0.59,2.17]
Wijeysundera 2014a	7/82	6/86		1.95%	1.22[0.43,3.49]
Total (95% CI)	**5811**	**5730**		**100%**	**1.33[1.15,1.55]**
Total events: 2519 (Alpha-2 adrenergic agonists), 1929 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=12.08, df=11(P=0.36); I^2=8.95%					
Test for overall effect: Z=3.81(P=0)					



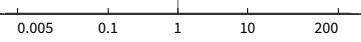
Favours treatment — Favours control

Comparison 9. Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years

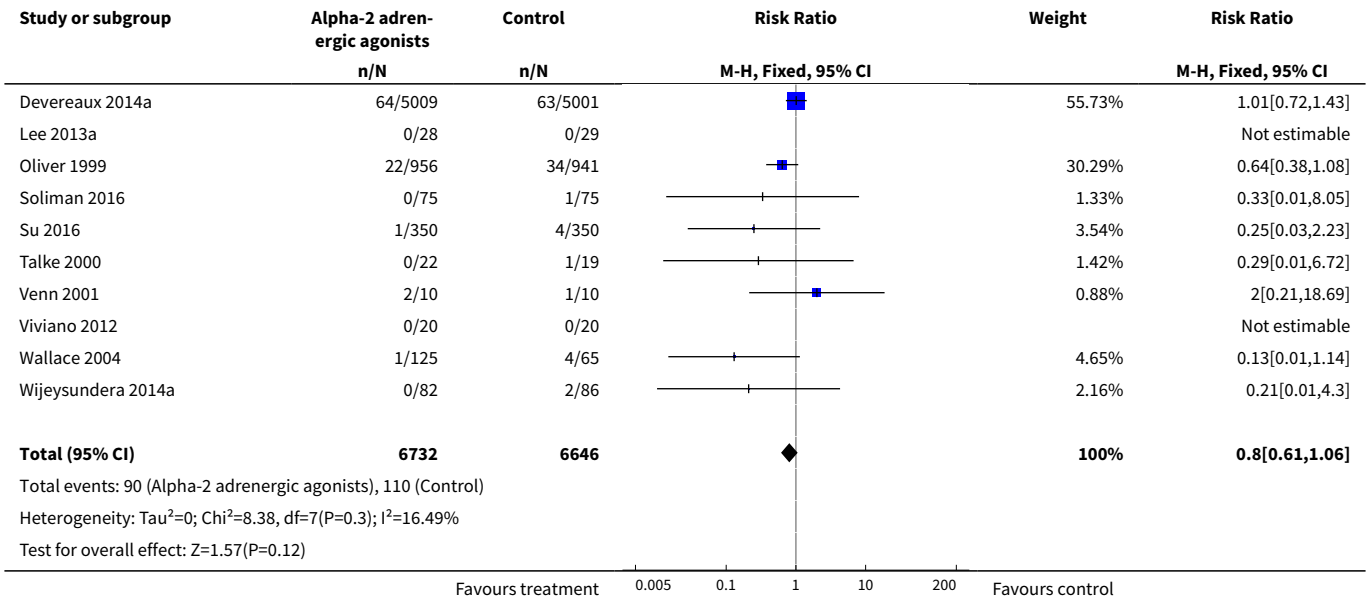
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	11	13378	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.61, 1.06]
2 Cardiac mortality	2	11907	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.29]
3 Myocardial infarction	7	13195	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.93, 1.24]
4 Myocardial ischaemia	6	634	Risk Ratio (M-H, Random, 95% CI)	0.51 [0.28, 0.93]
5 Heart failure	5	10424	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.89, 2.03]
6 Acute stroke	5	11218	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.50, 1.70]

Analysis 9.1. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 1 All-cause mortality.

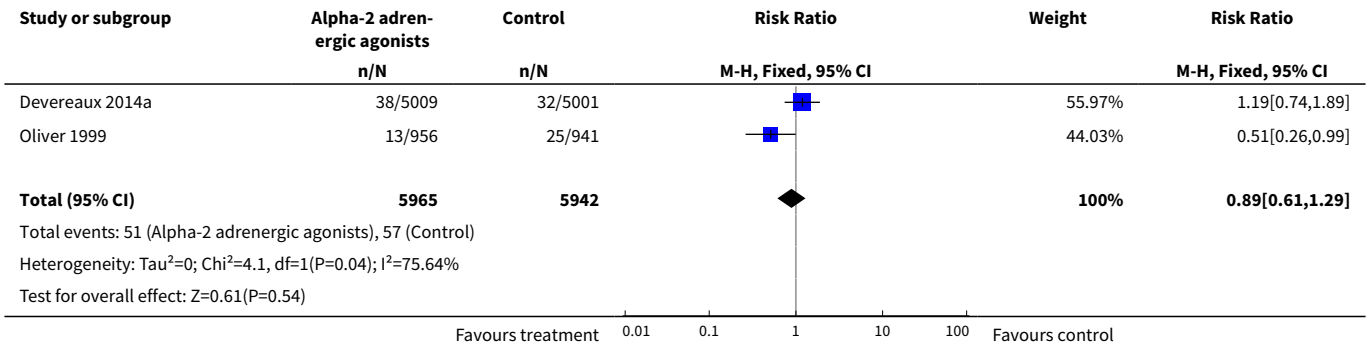
Study or subgroup	Alpha-2 adrenergic agonists n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bergese 2010	0/55	0/50			Not estimable



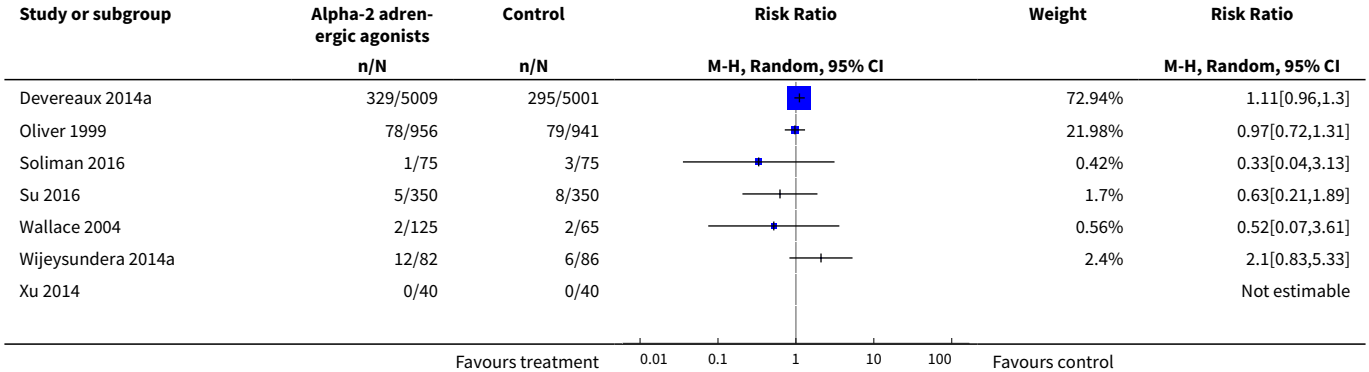
Favours treatment — Favours control

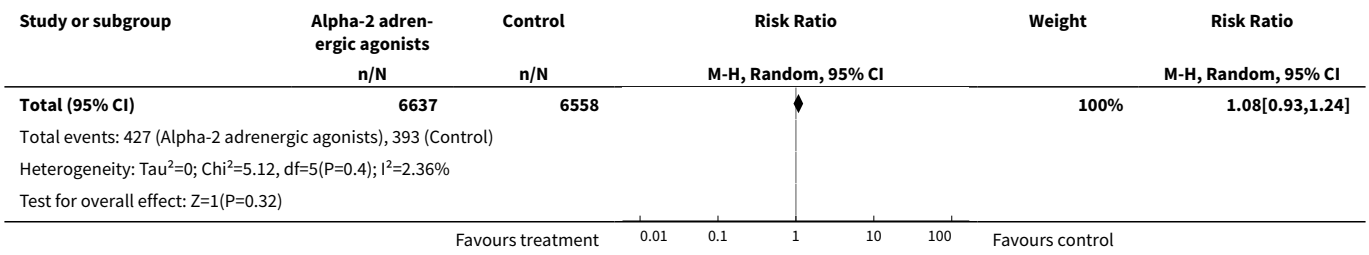


Analysis 9.2. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 2 Cardiac mortality.

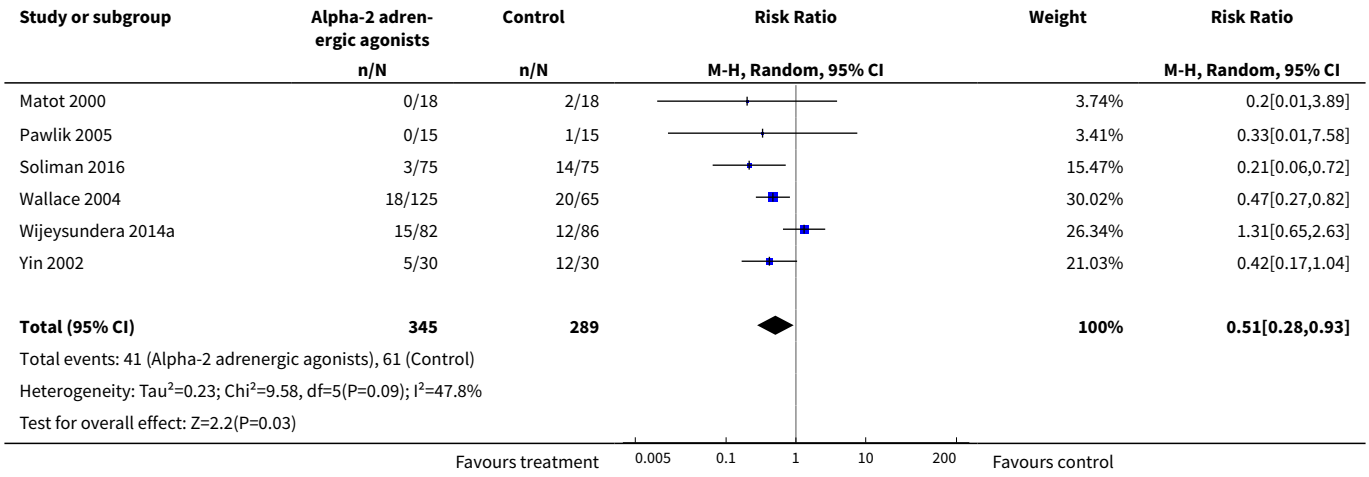


Analysis 9.3. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 3 Myocardial infarction.

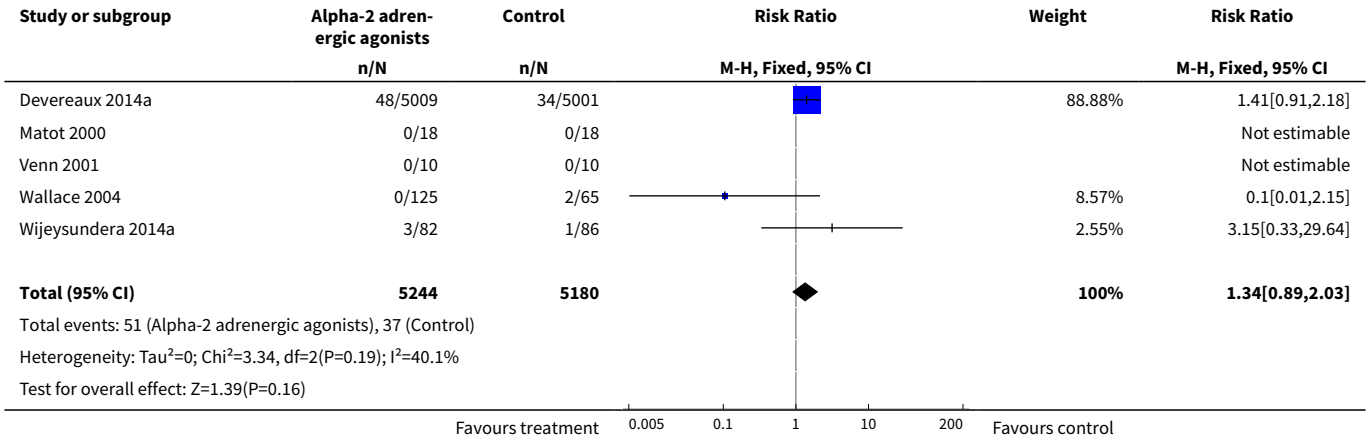




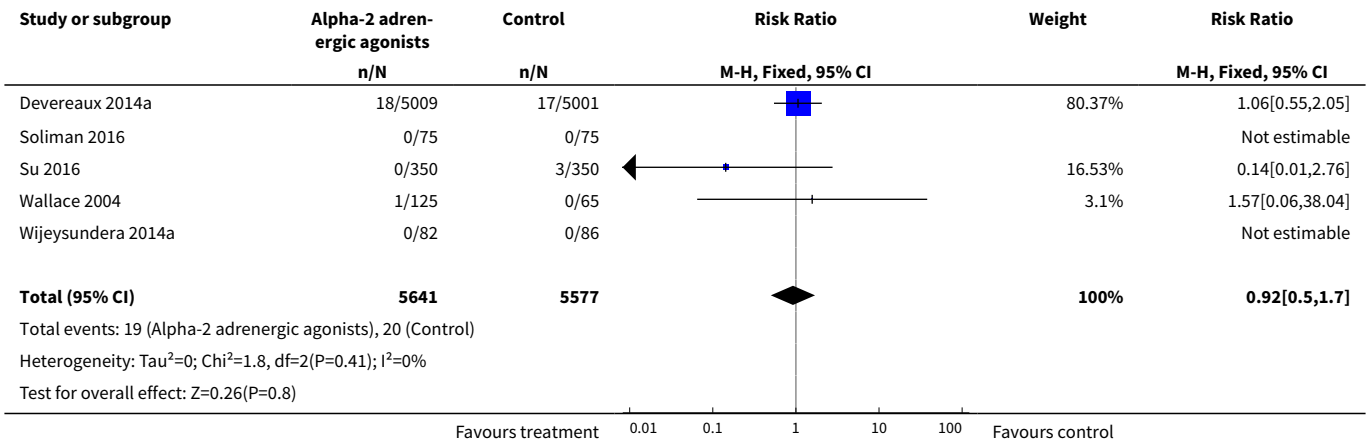
Analysis 9.4. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 4 Myocardial ischaemia.



Analysis 9.5. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 5 Heart failure.



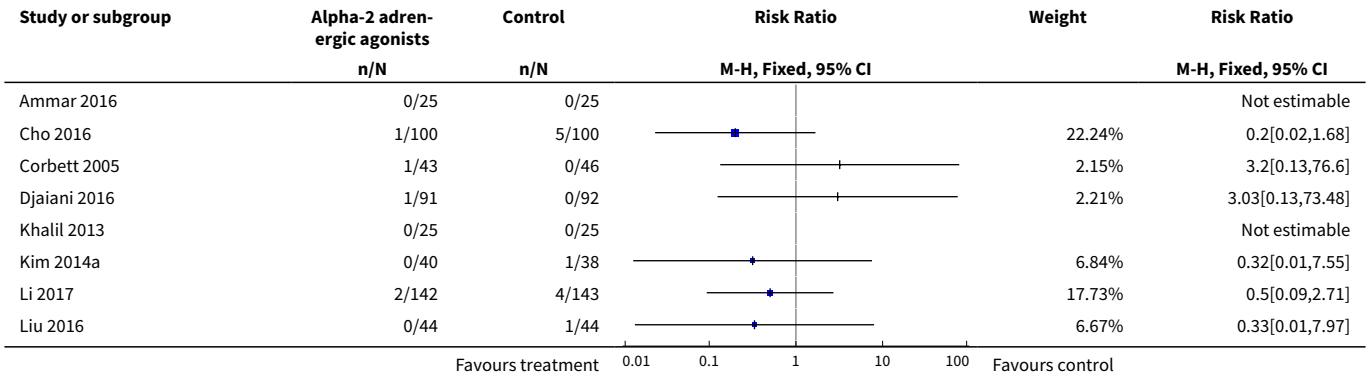
Analysis 9.6. Comparison 9 Alpha-2 adrenergic agonists versus control in non-cardiac surgery within past 20 years, Outcome 6 Acute stroke.

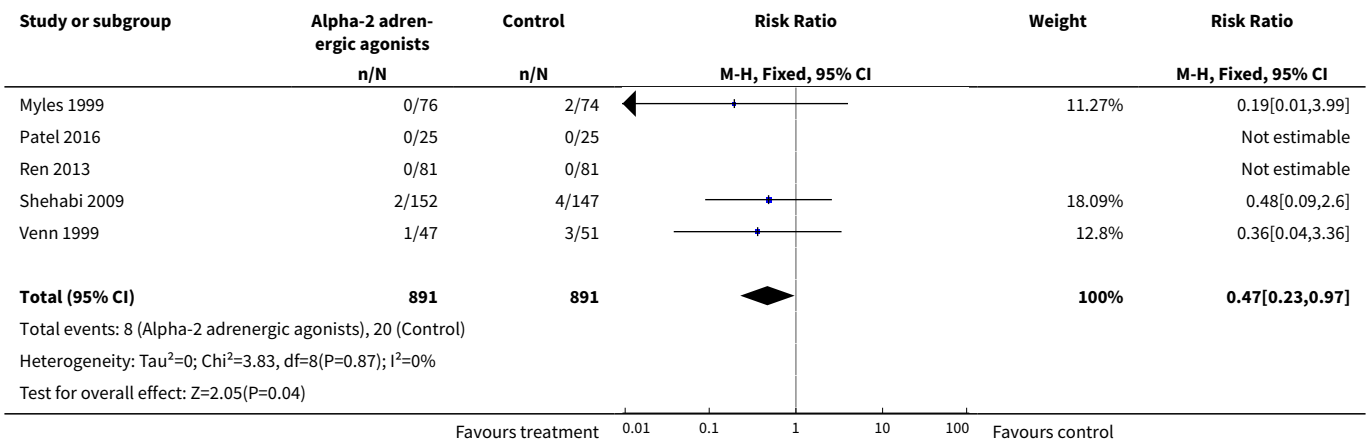


Comparison 10. Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years

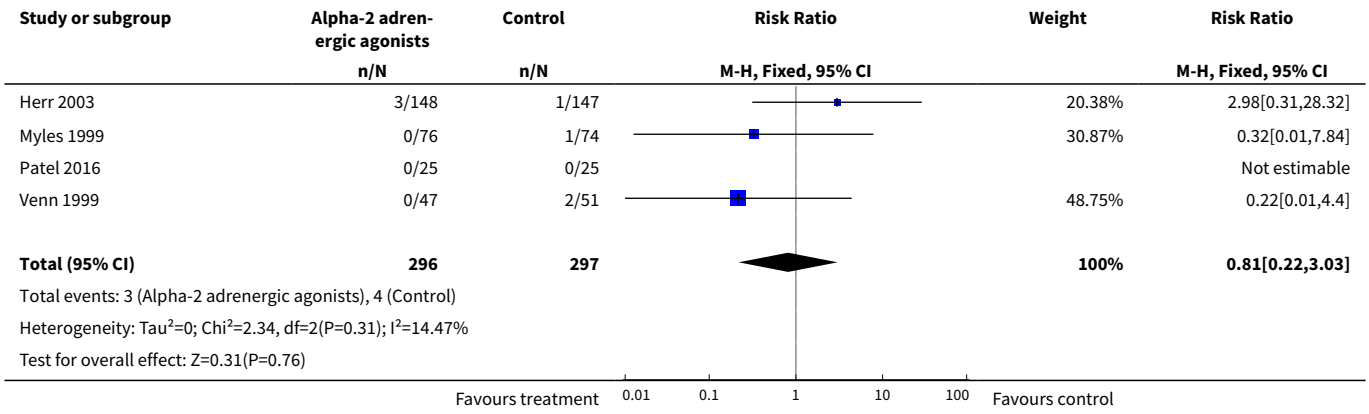
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 All-cause mortality	13	1782	Risk Ratio (M-H, Fixed, 95% CI)	0.47 [0.23, 0.97]
2 Myocardial infarction	4	593	Risk Ratio (M-H, Fixed, 95% CI)	0.81 [0.22, 3.03]
3 Myocardial ischaemia	7	908	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.54, 0.96]
4 Supraventricular tachyarrhythmia	5	964	Risk Ratio (M-H, Fixed, 95% CI)	0.73 [0.44, 1.19]
5 Heart failure	2	445	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.48, 1.77]
6 Acute stroke	6	1095	Risk Ratio (M-H, Fixed, 95% CI)	0.37 [0.14, 0.98]

Analysis 10.1. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 1 All-cause mortality.

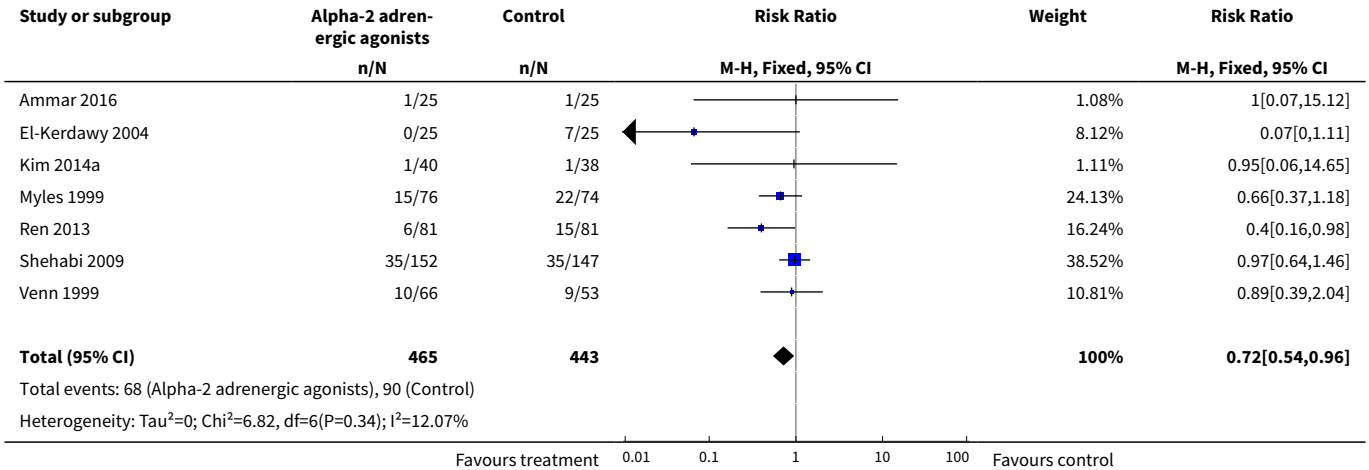


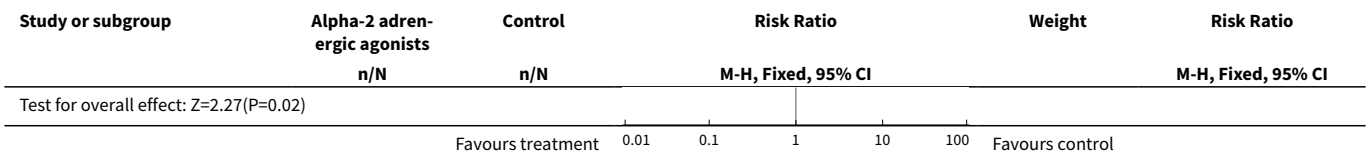


Analysis 10.2. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 2 Myocardial infarction.

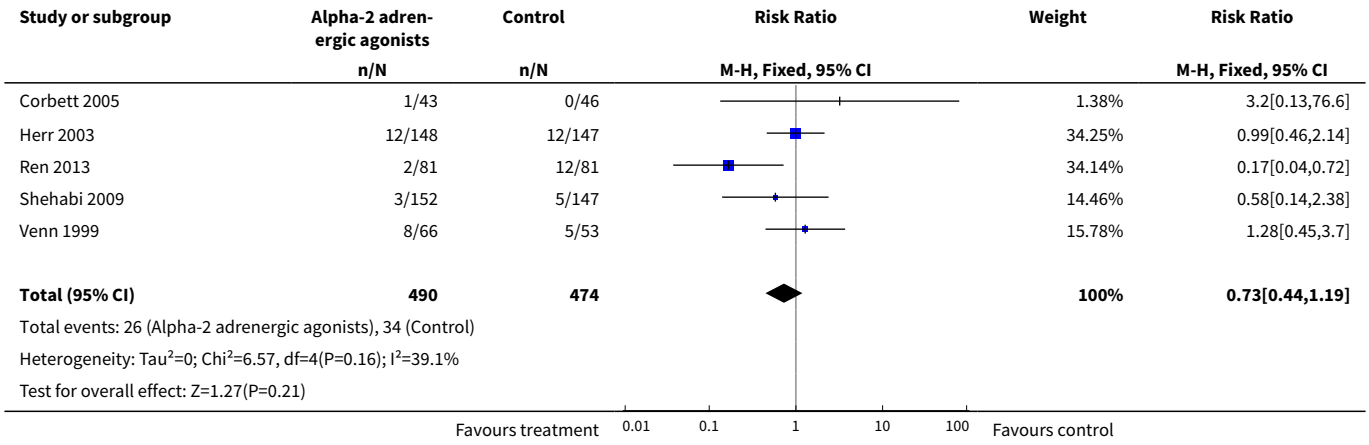


Analysis 10.3. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 3 Myocardial ischaemia.

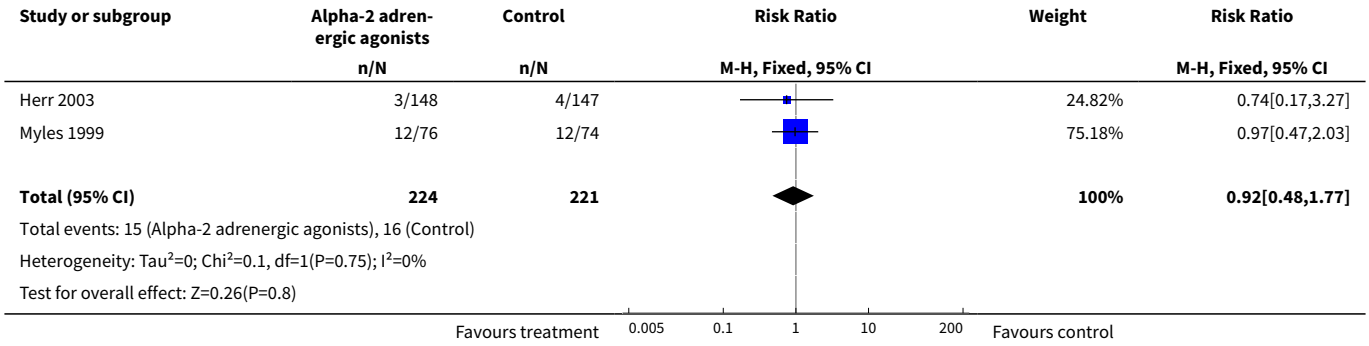




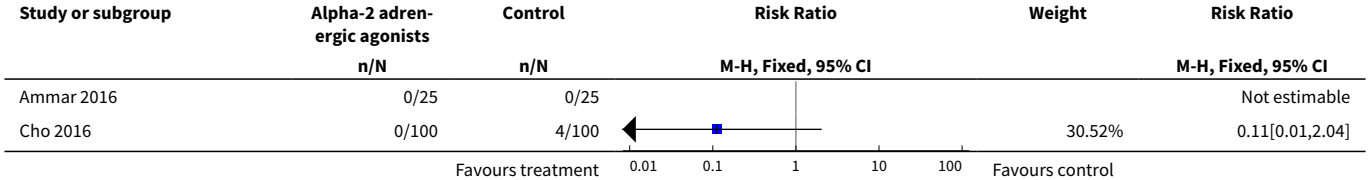
Analysis 10.4. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 4 Supraventricular tachyarrhythmia.

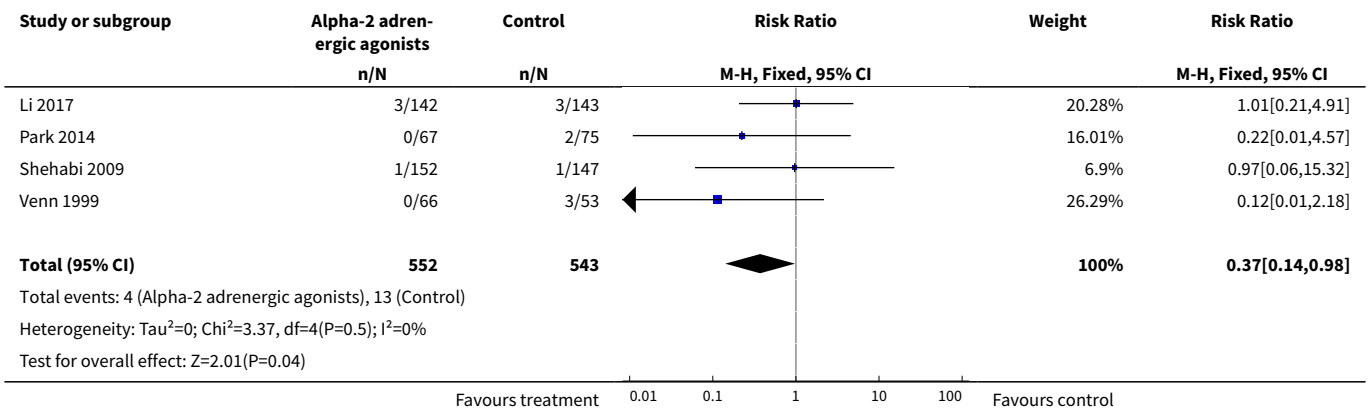


Analysis 10.5. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 5 Heart failure.



Analysis 10.6. Comparison 10 Alpha-2 adrenergic agonists versus control in cardiac surgery within past 20 years, Outcome 6 Acute stroke.





APPENDICES

Appendix 1. Search terms for electronic databases

MEDLINE (OvidSP) search terms:

1. postoperative complications/ or perioperative care/ or intraoperative complications/ or (intraoperative or perioperative or postoperative).mp.

2. exp clonidine/ or exp dexmedetomidine/ or mivazerol.mp.

3. ((randomized controlled trial or controlled clinical trial).pt. or randomized.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (animals not (humans and animals)).sh.

4. 1 and 2 and 3

Embase (OvidSP) search terms

1. postoperative complication/ or postoperative period/ or perioperative period/ or intraoperative period/ or peroperative care/ or peroperative complication/ or (perioperative or intraoperative or postoperative).ti,ab.

2. clonidine/ or dexmedetomidine/ or mivazerol.ti,ab.

3. (randomized-controlled-trial/ or randomization/ or controlled-study/ or multicenter-study/ or phase-3-clinical-trial/ or phase-4-clinical-trial/ or double-blind-procedure/ or single-blind-procedure/ or (random* or cross?over* or multicenter* or factorial* or placebo* or volunteer*).mp. or ((singl* or doubl* or trebl* or tripl*) adj3 (blind* or mask*)).ti,ab. or (latin adj square).mp.) not (animals not (humans and animals)).sh.

4. 1 and 2 and 3

CENTRAL search terms

#1 clonidine OR dexmedetomidine OR mivazerol
#2 perioperative OR preoperative OR postoperative
#3 #1 AND #2

Appendix 2. Data abstraction form

Study ID:

Reviewer:

Title:

Authors:

Journal:

Year: Volume:

Issue: Pages

Study quality

Randomized?

Allocation concealed?

How?

Blinded?

Intention-to-treat?

Drop-outs accounted?

Include?

Overall features

Surgical population (inclusion/exclusion):

Anesthesia type:

Alpha-2 agonist regimen(s) (dose, frequency)

Control arm regimens

Follow-up duration

Main outcome data

Dose & regimen:

Patients (n):

All-cause mortality:

Cardiac death:

Myocardial infarction:

Myocardial ischaemia:

Heart failure:

Supraventricular tachyarrhythmia:

Definition of myocardial infarction:

Definition of myocardial ischaemia:

Side effects data

Hypotension:

Bradycardia:

Acute stroke:

Other (specify):

Comments:

Subgroup results

Subgroup type:

Patients (n):

All-cause mortality:

Cardiac death:

Myocardial infarction:

Myocardial ischaemia:

Heart failure:

Supraventricular tachyarrhythmia:

Hypotension:

Bradycardia:

Acute stroke:

Other (specify):

Add further pages for any other relevant subgroups.

F E E D B A C K

Why pool results, 1 April 2018

Summary

I am troubled by the summary statements, because analysing the three drugs together is problematic.

Why mix dexmedetomidine studies with clonidine studies and present their pooled results? They have vastly different specificities for the alpha-2 receptor.

Why not include three subgroups, analysing studies of each of the drugs individually?

Meta-analysis of these drugs when used only in the postoperative setting would have been especially useful to Intensivists, especially dexmedetomidine alone.

In this study, page 17, especially reading from “The influence of two large studies” on, seems to show BENEFITS of alpha -2 blockers when two large studies (which did NOT include dexmedetomidine) were removed. Additional “subgroup” analyses after this section make for interesting reading which is not really reflected in the summary statements.

The summary of papers does not include results - so a super-quick meta-analysis of the dexmedetomidine - only studies is made more difficult.

In summary: this paper, Prima facie, debunks the use of these drugs perioperatively, but the details show that dexmedetomidine may well be very useful.

Reply

The author has raised several important issues, especially methodological concerns pertaining to subgroup analyses.

The effects of clonidine, dexmedetomidine, and mivazerol may indeed plausibly differ based on their different selectivity for alpha-2 adrenoceptors and non-adrenergic imidazoline receptors. Consequently, we specifically conducted formal statistical testing for such subgroup differences. This testing revealed no significant between-drug differences with respect to effects on death (P = 0.50) and myocardial infarction (P = 0.48), and borderline differences with respect to effects on cardiac death (P = 0.05). Consequently, our primary approach to present pooled treatment effects for all three drugs is consistent with existing published study data. Similarly, we advocate

against over interpreting the sensitivity analyses that excluded that two large studies, especially since there was only one resulting statistically significant pooled treatment effect, which was itself based on 27 outcome events.

Conversely, we do agree that dexmedetomidine holds some promise as a beneficial perioperative intervention, especially when reviewing more recent studies and studies restricted to cardiac surgery. Nonetheless, the findings of these subset analyses in our review may not be robust, especially due to the risk of inflated Type 1 error (i.e., false positive findings) from repeated statistical testing. Thus, we chose against including these potential benefits (e.g., significant reduction in mortality in contemporary cardiac surgery trials) in the summary statement that represents the strength of current evidence. Instead, these potential benefits warrant rigorous assessment in future research involving larger trials of specific drugs (i.e., dexmedetomidine) in targeted subgroups (i.e., cardiac surgery).

Contributors

Summary

David Collins. Intensivist / Anaesthetist. I do not have any affiliation with or involvement in any organisation with a financial interest in the subject matter of my comment.

Reply

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WHAT'S NEW

Date	Event	Description
12 September 2018	Feedback has been incorporated	Reply to feedback summary incorporated (Feedback 1)

HISTORY

Protocol first published: Issue 2, 2003
Review first published: Issue 4, 2009

Date	Event	Description
13 August 2018	Feedback has been incorporated	Feedback summary incorporated (Feedback 1).
13 March 2018	Amended	Typo corrected in Acknowledgements
4 May 2017	New citation required and conclusions have changed	No benefit of α-2 adrenergic agonists was identified with respect to the prevention of cardiac complications or death after surgery. The study methods were updated to include summary of findings tables, using GRADE methodology. The main analyses were subdivided into cardiac and non-cardiac studies. The inclusion criteria were broadened to include studies that only reported on acute stroke and heart failure outcomes. All studies excluded in the prior review were re-evaluated using the new criteria. The former author JS Bender has left the team and two new authors have joined, namely D Duncan and A Sankar.
4 May 2017	New search has been performed	1721 abstracts were screened, 199 full-texts were assessed for eligibility and 19 additional studies were included. A search of clinical trial registries identified one additional published study that was included. Three previously included reports of two studies

Date	Event	Description
		(Boldt 1996; Wahlander 2005) are now excluded because of reported scientific misconduct by lead authors. Two other previously included studies (Martin 2003; Triltsch 2002) are now excluded because the 2017 review conducted separate analyses for cardiac and non-cardiac surgical procedures, and these two studies could not be classified into either subgroup. Sensitivity analyses were added to assess for the influence of (i) studies that evaluated mivazerol and (ii) studies with data collection occurring more than 20 years previously.
1 August 2016	Amended	This review has two included studies that have been retracted (Boldt 1996; Wahlander 2005). The Cochrane authors are in the process of updating this review.
22 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Conceiving the review: DNW, WSB.

Coordinating the review: DNW.

Undertaking manual searches: DD, AS.

Screening search results: DD, AS.

Organizing retrieval of papers: DD, AS.

Screening retrieved papers against inclusion criteria: DD, AS.

Appraising quality of papers: DD, AS.

Abstracting data from papers: DD, AS.

Writing to authors of papers for additional information: DD, AS.

Data management for the review: DD.

Entering data into Review Manager 5 (RevMan 2014): DD, AS.

RevMan statistical data: DD.

Interpretation of data: DD, AS, WSB, DNW.

Statistical inferences: DD, AS, WSB, DNW.

Writing the review: DD, AS, WSB, DNW.

Performing previous work that was the foundation of the present study: DNW, WSB.

Guarantor for the review (one author): DNW.

Person responsible for reading and checking review before submission: DNW.

DECLARATIONS OF INTEREST

DD: no conflict of interest.

AS: no conflicts of interest.

WSB: the senior author of one included study (Wijeysundera 2014a); however, he had no involvement in either the data abstraction or quality assessment process. This author had no other relevant conflicts of interest.

DNW: the lead author of one included study (Wijeysundera 2014a); however, he had no involvement in either the primary data abstraction or quality assessment process. This author had no other relevant conflicts of interest.

SOURCES OF SUPPORT

Internal sources

- Department of Anesthesia, University of Toronto, Canada.

External sources

- Canadian Institutes of Health Research, Canada.

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Several changes have been made since the publication of the original protocol (Wijeysundera 2003).

Changes for the 2018 review.

1. The target population of 'all major surgery' was divided into the subgroups of cardiac and non-cardiac surgical procedures for all analyses. This alteration was in response to comments from an editorial board member, who raised concerns about the significant clinical heterogeneity between cardiac versus non-cardiac surgical procedures.
2. We did not include a planned subgroup analysis comparing α-2 adrenergic agonists to control in people receiving epidural or spinal anaesthesia as there was only one trial (Oliver 1999).
3. The inclusion criteria were broadened to include studies that only reported the outcomes of acute stroke and HF, based on comments from an editorial board member.
4. Given the large influence of two large RCTs (Devereaux 2014a; Oliver 1999), we performed a post-hoc sensitivity analysis that excluded these specific studies.
5. Based on based on comments received during the peer-review process, we performed post-hoc sensitivity analyses that excluded the two RCTs of mivazerol (McSPI-Europe 1997; Oliver 1999) since it is not available for clinical use.
6. Based on comments received during the peer-review process, we performed post-hoc sensitivity analyses that excluded studies where data collection or enrolment occurred more than 20 years ago, specifically to assess for the potential influence of temporal advances in perioperative on pooled treatment effects.
7. The quality of evidence underlying the main estimated pooled treatment effects was assessed based on the GRADE methodology and presented in 'Summary of findings' tables.

Changes for 2009 review (Wijeysundera 2009):

1. Based on comments from a peer reviewer (Peter Alston), the title was changed from 'Alpha-2 adrenergic agonists for the prevention of cardiovascular complications among patients undergoing cardiac or non-cardiac surgery' to 'Alpha-2 adrenergic agonists for the prevention of cardiac complications among patients undergoing surgery.'
2. We performed several post-hoc analyses that were not specified in the original protocol.
   a. A subgroup analysis was performed based on drug type to explain the moderate heterogeneity for the pooled effect of α-2 adrenergic agonists on perioperative hypotension.
   b. We performed a post-hoc subgroup analysis based on surgical procedure to explain the significant heterogeneity for the pooled effect of α-2 adrenergic agonists on perioperative bradycardia.
3. We have added acute stroke as a secondary outcome (side-effect from treatment) based on comments from a peer-reviewer (Helen Higham), and the results of the POISE-1 trial (POISE 2008). Specifically, the POISE-1 trial found that perioperative beta-blockers caused a significantly increased risk of perioperative acute stroke.

NOTES

August 2016

Two studies (Boldt 1996; Wahlander 2005), which were included in the previous 2009 version of this review (Wijeysundera 2009), were removed from the 2016 version of the review due to concerns about scientific conduct.

INDEX TERMS

Medical Subject Headings (MeSH)

Adrenergic alpha-Agonists [adverse effects] [*therapeutic use]; Clonidine [therapeutic use]; Dexmedetomidine [therapeutic use]; Heart Diseases [mortality] [*prevention & control]; Imidazoles [therapeutic use]; Intraoperative Complications [mortality] [prevention & control]; Myocardial Infarction [mortality] [prevention & control]; Postoperative Complications [mortality] [*prevention & control]; Randomized Controlled Trials as Topic; Stress, Physiological [drug effects]; Stroke [mortality]; Surgical Procedures, Operative [*adverse effects] [mortality]

MeSH check words

Humans