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Epidural analgesia for adults undergoing cardiac surgery with or without cardiopulmonary bypass (Review)

Guay J, Kopp S

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[Intervention Review]

Epidural analgesia for adults undergoing cardiac surgery with or without cardiopulmonary bypass

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ABSTRACT

Background

General anaesthesia combined with epidural analgesia may have a beneficial effect on clinical outcomes. However, use of epidural analgesia for cardiac surgery is controversial due to a theoretical increased risk of epidural haematoma associated with systemic heparinization. This review was published in 2013, and it was updated in 2019.

Objectives

To determine the impact of perioperative epidural analgesia in adults undergoing cardiac surgery, with or without cardiopulmonary bypass, on perioperative mortality and cardiac, pulmonary, or neurological morbidity.

Search methods

We searched CENTRAL, MEDLINE, and Embase in November 2018, and two trial registers up to February 2019, together with references and relevant conference abstracts.

Selection criteria

We included all randomized controlled trials (RCTs) including adults undergoing any type of cardiac surgery under general anaesthesia and comparing epidural analgesia versus another modality of postoperative pain treatment. The primary outcome was mortality.

Data collection and analysis

We used standard methodological procedures as expected by Cochrane.

Main results

We included 69 trials with 4860 participants: 2404 given epidural analgesia and 2456 receiving comparators (systemic analgesia, peripheral nerve block, intrapleural analgesia, or wound infiltration). The mean (or median) age of participants varied between 43.5 years and 74.6 years. Surgeries performed were coronary artery bypass grafting or valvular procedures and surgeries for congenital heart disease. We judged that no trials were at low risk of bias for all domains, and that all trials were at unclear/high risk of bias for blinding of participants and personnel taking care of study participants.

Epidural analgesia versus systemic analgesia

Trials show there may be no difference in mortality at 0 to 30 days (risk difference (RD) 0.00, 95% confidence interval (CI) −0.01 to 0.01; 38 trials with 3418 participants; low-quality evidence), and there may be a reduction in myocardial infarction at 0 to 30 days (RD −0.01, 95% CI −0.02 to 0.00; 26 trials with 2713 participants; low-quality evidence). Epidural analgesia may reduce the risk of 0 to 30 days respiratory depression (RD −0.03, 95% CI −0.05 to −0.01; 21 trials with 1736 participants; low-quality evidence). There is probably little or no difference in risk of pneumonia at 0 to 30 days (RD −0.03, 95% CI −0.07 to 0.01; 10 trials with 1107 participants; moderate-quality evidence), and epidural analgesia probably reduces the risk of atrial fibrillation or atrial flutter at 0 to 2 weeks (RD −0.06, 95% CI −0.10 to −0.01; 18 trials with 2431 participants; moderate-quality evidence). There may be no difference in cerebrovascular accidents at 0 to 30 days (RD −0.00, 95% CI −0.01 to 0.01; 18 trials with 2232 participants; very low-quality evidence), and none of the included trials reported any epidural haematoma events at 0 to 30 days (53 trials with 3982 participants; low-quality evidence). Epidural analgesia probably reduces the duration of tracheal intubation by the equivalent of 2.4 hours (standardized mean difference (SMD) −0.78, 95% CI −1.01 to −0.55; 40 trials with 3353 participants; moderate-quality evidence). Epidural analgesia reduces pain at rest and on movement up to 72 hours after surgery. At six to eight hours, researchers noted a reduction in pain, equivalent to a reduction of 1 point on a 0 to 10 pain scale (SMD −1.35, 95% CI −1.98 to −0.72; 10 trials with 502 participants; moderate-quality evidence). Epidural analgesia may increase risk of hypotension (RD 0.21, 95% CI 0.09 to 0.33; 17 trials with 870 participants; low-quality evidence) but may make little or no difference in the need for infusion of inotropics or vasopressors (RD 0.00, 95% CI −0.06 to 0.07; 23 trials with 1821 participants; low-quality evidence).

Epidural analgesia versus other comparators

Fewer studies compared epidural analgesia versus peripheral nerve blocks (four studies), intrapleural analgesia (one study), and wound infiltration (one study). Investigators provided no data for pulmonary complications, atrial fibrillation or flutter, or for any of the comparisons. When reported, other outcomes for these comparisons (mortality, myocardial infarction, neurological complications, duration of tracheal intubation, pain, and haemodynamic support) were uncertain due to the small numbers of trials and participants.

Authors' conclusions

Compared with systemic analgesia, epidural analgesia may reduce the risk of myocardial infarction, respiratory depression, and atrial fibrillation/atrial flutter, as well as the duration of tracheal intubation and pain, in adults undergoing cardiac surgery. There may be little or no difference in mortality, pneumonia, and epidural haematoma, and effects on cerebrovascular accident are uncertain. Evidence is insufficient to show the effects of epidural analgesia compared with peripheral nerve blocks, intrapleural analgesia, or wound infiltration.

PLAIN LANGUAGE SUMMARY

Epidural analgesia for heart surgery with or without the heart lung machine in adults

Review question

We set out to determine from randomized controlled trials the effect of epidural pain relief on the number of deaths following surgery and risk of heart, lung, or nerve complications in adults undergoing heart surgery.

This review was first published in 2013, and it was updated in 2019.

Background

For epidural pain relief, a local anaesthetic, an opioid, or a mixture of both drugs is given through a catheter in the epidural space, which is the space immediately outside the membrane surrounding the cord. Epidural analgesia could reduce the risk of complications after surgery, such as lung infections including pneumonia, difficulty in breathing (respiratory failure), heart attack, and irregular heart rhythm caused by atrial fibrillation. A concern is that for cardiac surgery, the blood has to be thinned to reduce blood clotting, which may increase the chance of bleeding around the spinal cord. The collection of blood puts pressure on the spinal cord and can cause permanent nerve damage and disability.

Study characteristics

We included randomized controlled trials involving adults undergoing any type of cardiac surgery under general anaesthesia with or without cardiopulmonary bypass where researchers compared epidural pain relief around the time of surgery against other forms of pain relief. Surgeries performed were coronary artery bypass grafting or valvular procedures and surgeries for congenital heart disease. The average age of participants was between 43 and 75 years. Outcomes were measured up to one year after surgery.

We included 69 studies with 4860 participants. Where stated, the studies were funded by governmental resources (five studies), charity (eight), institutional resources (23), or in part by the industry (two). In all, 31 trials did not mention the source of funding. The evidence is current to November 2018.

Key results

When researchers compared epidural analgesia versus systemic pain relief (e.g. by an analgesic given directly into a vein), they could not detect any difference in the number of deaths in the first 30 days after surgery (38 studies, 3418 participants). There might be a difference in

the number of people experiencing heart attacks (26 studies, 2713 participants). These findings were supported by low-quality evidence. We found a small reduction in the risk of respiratory depression with epidural pain relief (21 studies, 1736 participants), but not in the risk of pneumonia (10 studies, 1107 participants) (low- or moderate-quality evidence). The reduced risk of respiratory depression was more obvious when cardiopulmonary bypass was needed for cardiac surgery. Epidural analgesia reduced the risk of atrial fibrillation or atrial flutter early in recovery at zero to two weeks (18 studies, 2431 participants; moderate-quality evidence). The number of cerebrovascular accidents was not clearly different (18 studies, 2232 participants), and no lasting neurological complications or epidural haematomas were reported (53 studies, 3982 participants; very low- or low-quality evidence). Although epidural analgesia may have reduced the duration of tracheal intubation, this was noted mainly in older studies, and clinical practices have changed since that time (40 trials, 3353 participants; moderate-quality evidence).

We found only six studies that compared epidural pain relief versus application of local anaesthetic on the body surface to produce peripheral nerve blocks directly into the space around the lungs (intrapleural analgesia) and onto the surgical wound (wound infiltration). These studies provided low- or very low-quality evidence and did not report on many of the outcomes for this review. Study authors reported no heart attacks and no epidural haematomas.

Quality of the evidence

We rated the quality of evidence as moderate, low, or very low. We included too few participants in our review to rule out any differences in the number of patient deaths between epidural analgesia and systemic analgesia, nor to see any increase in epidural haematomas.

Summary of findings for the main comparison. Epidural analgesia compared with systemic analgesia for cardiac surgery with or without cardiopulmonary bypass in adults

Epidural analgesia compared with systemic analgesia for cardiac surgery with or without cardiopulmonary bypass in adults

Patient or population: adults undergoing cardiac surgery with or without cardiopulmonary bypass
Settings: trials were conducted in university hospitals (n = 60) or at a tertiary care centre (n = 3). Trials were conducted in Australia (n = 3); Bangladesh (n = 1); Canada (n = 1); China (n = 2); Cuba (n = 1); Czech Republic (n = 2); Denmark (n = 5); Egypt (n = 1); Germany (n = 5); India (n = 6); Italy and UK (n = 1); Japan (n = 2); Korea (n = 1); Lithuania (n = 1); Macedonia (n = 1); Norway (n = 3); Poland (n = 1); Russia (n = 1); Serbia (n = 1); Spain (n = 1); Sweden (n = 3); Taiwan (n = 1); Turkey (n = 8); The Netherlands (n = 4); UK (n = 5); and USA (n = 3)
Intervention: epidural analgesia
Comparison: systemic analgesia

Outcomes	Illustrative comparative risks (95% CI)*		Risk difference or relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Systemic analgesia	Epidural analgesia				
Mortality (0 to 30 days)	**Study population**		**RD 0.00** (-0.01 to 0.01)	3418 (38 studies)	⊕⊕⊝⊝ **low**[a]	
	6 per 1000	**7 per 1000** (4 to 13)				
Myocardial infarction (0 to 30 days)	**Study population**		**RD -0.01** (-0.02 to 0.00)	2713 (26 studies)	⊕⊕⊝⊝ **low**[a]	
	40 per 1000	**28 per 1000** (21 to 39)				
Pulmonary complications (0 to 30 days)	**Respiratory depression**		**RD -0.03** (-0.05 to -0.01)	1736 (21 studies)	⊕⊕⊝⊝ **low**[b]	NNTB 32 (95% CI 22 to 102)
	Study population					
	70 per 1000	**42 per 1000** (30 to 57)				
	Pneumonia		**RD -0.03** (-0.07 to 0.01)	1107 (10 studies)	⊕⊕⊕⊝ **moderate**[c]	
	Study population					

	148 per 1000	**79 per 1000** (59 to 105)				
Atrial fibrillation or atrial flutter (0 to 2 weeks)	**Study population**		**RD -0.06** (-0.10 to -0.01)	2431 (18 studies)	⊕⊕⊕⊖ **moderate**[c]	NNTB 14 (95% CI 8 to 90)
	327 per 1000	**258 per 1000** (234 to 283)				
Risk of neurological complications (0 to 30 days)	**Cerebrovascular accident**		**RD -0.00** (-0.01 to 0.01)	2232 (18 studies)	⊕⊖⊖⊖ **very low**[d]	
	Study population					
	12 per 1000	**11 per 1000** (6 to 18)				
	Epidural haematoma		**RD 0.00** (-0.01 to 0.01)	3982 (53 studies)	⊕⊖⊖⊖ **low**[a]	
	Study population					
	0 per 1000	**0 per 1000** (0 to 2)				
Duration of tracheal intubation	Mean duration of tracheal intubation was **0.78 SMD lower** (-1.01 to -0.55)			3353 (40 studies)	⊕⊕⊕⊖ **moderate**[c]	The difference was equivalent to 2.4 hours[e] and was more evident in older trials (see text)
Pain at rest at 6 to 8 hours after surgery	Mean pain scores were **1.35 SMD lower** (-1.98 to -0.72)			502 (10 studies)	⊕⊕⊕⊖ **moderate**[f]	The difference was equivalent to 1 on a score from 0 to 10[e]
Haemodynamic support (in hospital)	**Hypotension or need for vasopressor boluses**		**RD 0.21** (0.09 to 0.33)	870 (17 studies)	⊕⊖⊖⊖ **low**[g]	The number needed to harm is 4 (95% CI 3 to 12)
	Study population					
	451 per 1000	**284 per 1000** (243 to 330)				

Inotropic or vasopressor infusions		**RD 0.00** (-0.06 to 0.07)	1821 (23 studies)	⊕⊖⊖⊖ **low**[h]	
Study population					
344 per 1000	**338 per 1000** (302 to 376)				

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Confidence intervals were calculated using VassarStats (http://www.vassarstats.net/).
CI: confidence interval; NNTB: number needed to treat for an additional beneficial outcome; RD: risk difference; SMD: standardized mean difference.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level for risk of bias and by one level for imprecision.
[b]Downgraded by one level for risk of bias and by one level for possibility of publication bias.
[c]Downgraded by one level for risk of bias.
[d]Downgraded by one level for risk of bias, by one level for imprecision, and by one level for publication bias.
[e]The equivalence was obtained by multiplying the SMD by a typical standard deviation of one of the included trials (Higgins 2011a).
[f]Downgraded by one level for heterogeneity.
[g]Downgraded by two levels for risk of bias.

Summary of findings 2. Epidural analgesia compared with peripheral nerve blocks for cardiac surgery in adult

Epidural analgesia compared with peripheral nerve blocks for cardiac surgery without cardiopulmonary bypass in adults

Patient or population: adults undergoing cardiac surgery without cardiopulmonary bypass

Settings: trials were conducted in university hospitals in Egypt (n = 1) or India (n = 3)

Intervention: epidural analgesia

Comparison: peripheral nerve blocks (erector spinae plane block (n = 1) or paravertebral blockade (n = 3))

Outcomes	**Illustrative comparative risks (95% CI)***		**Risk difference or relative effect (95% CI)**	**No. of participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Peripheral nerve block	**Epidural analgesia**				

Mortallity (0 to 30 days	**Study population**		RD -0.03 (-0.08 to 0.02)	145 (1 study)	⊕⊖⊖⊖ **very low**[a]
	43 per 1000	**13 per 1000** (2 to 72)			
Myocardial infarction (0 to 30 days)	**Study population**		RD 0.00 (-0.07 to 0.07)	76 (2 studies)	⊕⊖⊖⊖ **very low**[a]
	0 per 1000	**0 per 1000** (0 to 90)			
Pulmonary complications (0 to 30 days)	We found no data for this outcome (respiratory depression or pneumonia)				
Atrial fibrillation or atrial flutter (0 to 2 weeks)	We found no data for this outcome				
Risk of neurological complications (0 to 30 days)	**Cerebrovascular accident**				
	Study population		**RD 0.00** (-0.03 to 0.03)	145 (1 study)	⊕⊖⊖⊖ **very low**[a]
	0 per 1000	**0 per 1000** (0 to 49)			
	Epidural haematoma				
	Study population		**RD 0.00** (-0.03 to 0.03)	271 (4 studies)	⊕⊕⊖⊖ **low**[b]
	0 per 1000	**0 per 1000** (0 to 27)			
Duration of tracheal intubation	**Study population**		**MD -0.08 hour** (-0.54 to 0.38 hour)	271 (4 studies)	⊕⊖⊖⊖ **very low**[a]
	6.82 ± 2.14 hours (mean ± SD)	6.67 ± 2.31 hours (mean ± SD)			
Pain at rest at 6 to 8 hours after surgery (score from 0 to 10)	**Study population**		**MD 0.12** (-0.42 to 0.66)	90 (2 studies)	⊕⊖⊖⊖ **very low**[a]
	2.20 ± 0.79	1.80 ± 0.22			

	(mean ± SD)	(mean ± SD)			
Haemodynamic support (in hospital)	**Hypotension or need for vasopressor boluses**		**RD 0.05** (-0.08 to 0.18)	40 (1 study)	⊕⊕⊖⊖ **low**[b]
	Study population				
	50 per 1000	0 per 1000 (0 to 161)			
	Inotropic or vasopressor infusions				
	We found no data for this outcome				

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Confidence intervals were calculated using VassarStats (http://www.vassarstats.net/) with no continuity correction.
CI: confidence interval; MD: mean difference; RD: risk difference; SD: standard deviation.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one for risk of bias and by two levels for imprecision.
[b]Downgraded by two levels for imprecision.

Summary of findings 3. Epidural analgesia compared with intrapleural analgesia for cardiac surgery in adults

Epidural analgesia compared with intrapleural analgesia for cardiac surgery in adults

Patient or population: adults undergoing cardiac surgery without cardiopulmonary bypass

Settings: university hospital in India

Intervention: epidural analgesia

Comparison: intrapleural analgesia

Outcomes	Illustrative comparative risks* (95% CI)		Risk difference or relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				

	Intrapleural analgesia	Epidural analgesia				
Mortality (0 to 30 days)	We found no data for this outcome					
Myocardial infarction (0 to 30 days)	**Study population**		**RD 0.00** (-0.07 to 0.07)	50 (1 study)	⊕⊕⊝⊝ **low**[a]	
	0 per 1000	**0 per 1000** (0 to 71)				
Pulmonary complications (0 to 30 days)	We found no data for this outcome (respiratory depression or pneumonia)					
Atrial fibrillation or atrial flutter) (0 to 2 weeks)	We found no data for this outcome					
Risk of neurological complications (0 to 30 days)	**Cerebrovascular accident**					
	We found no data for this outcome					
	Epidural haematoma					
	Study population		**RD 0.00** (-0.07 to 0.07)	50 (1 study)	⊕⊕⊝⊝ **low**[a]	
	0 per 1000	**0 per 1000**				
Duration of tracheal intubation	**Study population**		**MD -0.30** (-1.20 to 0.60 hour)	15 (1 study)	⊕⊕⊝⊝ **very low**[b]	17 participants in the epidural analgesia group and 14 in the intrapleural analgesia group were extubated in the operating room Means and SDs given by study authors are those for the rest of the participants
	4.1 ± 0.59 hours (mean ± SD)	3.8 ± 1.13 hours (mean ± SD)				
Pain at rest at 6 to 8 hours (score from 0 to 10)	**Study population**		**MD 0.84** (0.31 to 1.37)	50 (1 study)	⊕⊕⊝⊝ **low**[a]	
	4.52 ± 1.08	3.68 ± 0.82				

Haemodynamic support (in hospital)	We found no data for this outcome

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI). Confidence intervals were calculated using VassarStats (http://www.vassarstats.net/).
CI: confidence interval; MD: mean difference; RD: risk difference; SD: standard deviation.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by two levels for imprecision.
[b]Downgraded by one level for risk of bias and by two levels for imprecision.

Summary of findings 4. Epidural analgesia compared with wound infiltration for cardiac surgery in adults

Epidural analgesia compared with wound infiltration for adults undergoing cardiac surgery without cardiopulmonary bypass

Patient or population: adults undergoing cardiac surgery without cardiopulmonary bypass

Settings: university hospital in Taiwan

Intervention: epidural analgesia

Comparison: wound infiltration

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No. of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Wound infiltration	Epidural analgesia				
Mortallity (0 to 30 days)	We found no data for this outcome					
Myocardial infarction (0 to 30 days)	We found no data for this outcome					
Pulmonary complications	We found no data for this outcome (respiratory depression or pneumonia)					

(0 to 30 days)	
Atrial fibrillation or atrial flutter (0 to 2 weeks)	We found no data for this outcome
Risk of neurological complications (0 to 30 days)	We found no data for this outcome (cerebrovascular accident or epidural haematoma)
Duration of tracheal intubation	One trial with 37 participants published as a conference abstract reported no difference in time to tracheal extubation between epidural analgesia and intravenous patient-controlled analgesia plus wound infusion (numbers and P value not provided) (very low quality)[a]
Pain at rest at 6 to 8 hours (score from 0 to 10)	One trial with 37 participants published as a conference abstract reported lower pain scores with epidural analgesia (numbers and P value not provided) (very low quality)[a]
Haemodynamic support (in hospital)	We found no data for this outcome

*The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: confidence interval.

GRADE Working Group grades of evidence.
High quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[a]Downgraded by one level for risk of bias and by two levels for imprecision.

BACKGROUND

Description of the condition

The addition of thoracic epidural analgesia to general anaesthesia has been suggested to benefit patients after cardiac surgery (Svircevic 2013). However, this regional anaesthetic technique is controversial because the insertion of an epidural catheter in patients requiring full heparinization for cardiopulmonary bypass may lead to an epidural haematoma. The benefits of practicing off-pump surgery instead of operating with the aid of cardiopulmonary bypass are not recognized by everyone, except perhaps for decreased risk of cerebrovascular accident and for high-risk patients (Kowalewski 2016). Some clinicians argue that cardiopulmonary bypass induces a more severe inflammatory response. Also, using cardiopulmonary bypass usually requires more complete heparinization than off-pump surgery. For this reason, we decided to evaluate all our outcomes while subgrouping the data by with or without cardiopulmonary bypass.

Description of the intervention

Epidural analgesia is a technique by which a local anaesthetic or an opioid or a mixture of both drugs is given in the epidural space (Guay 2016a; Guay 2016b; Salicath 2018). Epidural analgesia produces a superior quality of analgesia and may reduce the risk of postoperative complications such as pneumonia, respiratory failure, and myocardial infarction (Guay 2006; Guay 2014; Guay 2016a; Guay 2016b). Epidural analgesia may also shorten the duration of tracheal intubation as well as the time spent in an intensive care unit, which could have economic benefits (Guay 2016b).

How the intervention might work

High thoracic epidural analgesia may provide cardioprotective effects. High thoracic epidural analgesia increases myocardial oxygen availability, as reported in Lagunilla 2006, and reduces myocardial oxygen consumption (Hutchenson 2006). The latter is attributed to an attenuation of sympathetic response to the surgical stimuli (Kirno 1994). An influence on inflammatory response to the surgical stress and/or the cardiopulmonary bypass has also been reported (Volk 2003).

Why it is important to do this review

A possible complication of epidural analgesia includes spinal cord compression caused by a haematoma, which can result in paraplegia (Bos 2018). Systemic anticoagulation is needed for cardiac surgery and may increase the incidence of epidural haematoma related to the use of an epidural catheter (Horlocker 2018). While reviewing the literature, Landoni and colleagues found 25 cases of epidural haematoma out of 88,820 positioned epidurals in patients undergoing cardiac surgery, for an estimated risk of catheter-related epidural haematoma of 3 per 10,000 procedures (95% confidence interval (CI) 2 to 4 per 10,000 procedures) (Landoni 2015). For the general population, the incidence of haematoma related to an epidural would be 1 per 10,000 procedures (95% CI 0 to 6 per 10,000 procedures) (Moen 2004). Although the incidence found by Landoni and colleagues may seem relatively low, the consequences of this complication may sometimes be catastrophic. In their large trial, Moen and colleagues reported 33 spinal haematomas related to neuraxial blocks. Only 6 of 33 patients made a full recovery, and 27 suffered permanent neurological damage (Moen 2004). It is therefore mandatory to have a clear view of the real benefits of epidural analgesia in cardiac surgery patients, so that patients and clinicians can make an informed decision when choosing the mode of postoperative analgesia.

This is an update of a previously published Cochrane review (Svircevic 2013).

OBJECTIVES

To determine the impact of perioperative epidural analgesia in adults undergoing cardiac surgery, with or without cardiopulmonary bypass, on perioperative mortality and cardiac, pulmonary, or neurological morbidity.

METHODS

Criteria for considering studies for this review

Types of studies

We included randomized controlled trials (RCTs). We excluded observational studies, quasi-randomized trials, cross-over trials, and cluster-randomized trials. We did not exclude studies on the basis of language of publication or publication status.

Types of participants

We included adult participants undergoing general anaesthesia for all types of cardiac surgery with or without cardiopulmonary bypass.

Types of interventions

We included trials that compared cardiac surgery including one group of participants with and one group of participants without epidural analgesia (Table 1). We excluded studies that compared cardiac surgery with participants with and participants without spinal anaesthesia. We included studies in which investigators administered epidural analgesia as a single shot block or as a continuous infusion for any duration and containing a local anaesthetic alone (extended duration or not), or in combination with an opioid (extended duration or not), or an opioid alone. We did not exclude studies in which trialists added an adjuvant other than an opioid to the solution. We excluded trials comparing nerve blocks versus systemic analgesia. For the comparator, we included all other modes of analgesia and divided them into:

1. all forms of systemic analgesia (opioid-based regimen or other), regardless of the route of administration (intravenous (with or without a self-administered patient-controlled device), intramuscular, or oral analgesia);
2. peripheral nerve blocks;
3. intrapleural analgesia; and
4. wound infiltration.

Types of outcome measures

Primary outcomes

1. Risk of mortality (0 to 30 days, six months, and one year)

Secondary outcomes

1. Risk of myocardial infarction (0 to 30 days; study author's definitions (Table 2))
2. Risk of pulmonary complications
   a. Respiratory depression (0 to 30 days; study author's definitions (Table 3))
   b. Pneumonia (0 to 30 days; study author's definitions (Table 3))
3. Riisk of atrial fibrillation or atrial flutter during surgery and up to two weeks after surgery
4. Risk of neurological complications
   a. Cerebrovascular accident (0 to 30 days; study author's definitions (Table 4))
   b. Risk of serious neurological complications from epidural analgesia (lasting (> 3 months) sensory or motor deficit) or epidural haematoma (with or without epidural analgesia) (0 to 30 days)
5. Duration of tracheal intubation (Table 5)
6. Pain scores (rest and movement at 6 to 8, 24, 48, and 72 hours)
7. Haemodynamic support (in hospital)
   a. Hypotension or need for vasopressor boluses
   b. Inotropic or vasopressor infusions

Search methods for identification of studies

Electronic searches

We searched the Cochrane Central Register of Controlled Trials (2018, Issue 11), Ovid MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE (1946 to 19 November 2018), Embase (1974 to 19 November 2018), the Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO host), and Web of Science (Science Citation Index (SCI)/Social Sciences Citation Index (SSCI)) (19 November 2018). We applied no language or publication status restriction. The exact search strategies can be found in Appendix 1.

Searching other resources

We screened reference lists from retrieved randomized trials, reviews, meta-analyses, and systematic reviews (Appendix 2), to identify additional trials.

We searched for conference abstracts from 2012 to 2017: American Society of Regional Anesthesia spring meetings, and European Society of Anaesthesiology, European Society of Regional Anaesthesia, and American Society of Anesthesiologists (December 2017) meetings.

We searched the World Health Organization International Clinical Trials Registry Platform (www.who.int/trialsearch), as well as ClinicalTrials.gov (http://www.clinicaltrials.gov), to identify trials in progress (February 2019). For trials in progress, we did not retain trials past the date of completion and not updated within the last two years. We did this to avoid listing registered trials that are unlikely to ever be completed by study authors.

Data collection and analysis

Selection of studies

We independently screened the lists of all titles and abstracts identified by the search above. We retrieved and independently read articles of interest to determine their eligibility for inclusion. We resolved discrepancies by discussion. We examined for classification trials that might be included and that we found through sources other than electronic databases (included, excluded, or awaiting classification). We documented the selection process in sufficient detail to complete a PRISMA flow diagram (Moher 2009). We listed all reasons for exclusion in a Characteristics of excluded studies table.

Data extraction and management

We independently extracted data. For selected studies, we entered the following variables into our data extraction form: risk of bias as measured with the Cochrane tool; and outcomes and factors chosen a priori for assessment of heterogeneity (Higgins 2011a; Higgins 2011b). We extracted dichotomous data as the number of participants experiencing the event and the total number of participants in each treatment group. We extracted continuous data as means, standard deviations, and total numbers of participants. When data were not available in these formats, we extracted data as P values, numbers of participants, and direction of effect. We did not consider medians as equivalent to means, and we did not estimate standard deviations from quartiles or ranges. We entered first the site where the study was performed and the date of data collection (to facilitate exclusion of duplicate publications), then whether the study was included in the review or the reason for exclusion. After we reached agreement, one review author entered into the comprehensive meta-analysis the data and moderators for heterogeneity exploration (Comprehensive Meta-Analysis 2007). Also, after we reached agreement, we entered the risk of bias evaluation into Review Manager 5 (Review Manager 2014). We resolved disagreements by discussion. We contacted all study authors for additional information. We entered data for analysis into Review Manager in the format required to include the maximal number of studies (events and total numbers of participants for each group; means, standard deviations, and numbers of participants included in each group; or generic inverse variance, if necessary). When possible, we entered the data into an intention-to-treat analysis.

Assessment of risk of bias in included studies

We independently assessed the quality of included studies by using the Cochrane 'Risk of bias' tool found in RevMan 5 (Higgins 2011a), to examine random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, or other risks of bias. We resolved disagreements by discussion. We assessed risk of bias on the basis of information presented in the reports or according to additional information received from study authors, while making no assumptions. We judged trials without a published protocol to be at low risk of bias for selective reporting when researchers provided in the results section the results for all measurements prespecified in the methods section.

Measures of treatment effect

We planned to report results as risk ratios (RRs) and to provide 95% confidence intervals (95% CIs) for dichotomous data (McColl 1998). Due to the large number of trials with zero cells, we analysed dichotomous data as risk differences (RDs). We reported results for continuous data (time of tracheal intubation) as mean differences (MDs) with 95% CIs. For continuous data, because some data were extracted from different scales (days, hours, or minutes), and some data were available only as P values, we reported results as

standardised mean differences (SMDs) with 95% CIs. For results reported as SMDs, we gave equivalence on a clinical scale. For SMDs, we considered 0.2 a small effect, 0.5 a medium effect, and 0.8 a large effect (Pace 2011). When an effect was found, we calculated using the odds ratio the number to treat for an additional beneficial outcome (NNTB) or the number needed to treat for an additional harmful outcome (NNTH) (Cates 2016; Deeks 2002). When we were not able to demonstrate an effect, we calculated the number of participants required in a large trial to make sure that enough participants were included in the retained studies to justify a conclusion on the absence of effect (Brant 2017; Pogue 1998).

Unit of analysis issues

We included only parallel-group trials. If a study contained more than two groups, we fused two groups (by using the appropriate formula for adding standard deviations when required) when we thought they were equivalent (taking our factors for heterogeneity exploration into account), or we separated them and split the control group in half if we thought they were different.

Dealing with missing data

We contacted all study authors for additional information. We made no imputation.

Assessment of heterogeneity

We considered clinical heterogeneity before pooling results, and we examined statistical heterogeneity before carrying out any meta-analysis. We quantified statistical heterogeneity by using the I^2 statistic. We quantified the amount of heterogeneity as low (I^2 < 25%), moderate (I^2 = 25% to 74%), or high (I^2 = 75% or higher), depending on the value obtained for the I^2 statistic (Higgins 2003).

Assessment of reporting biases

We assessed publication bias by using a funnel plot, followed by Duval and Tweedie's trim and fill technique (Borenstein 2009; Duval 2000a; Duval 2000b). This technique not only assesses whether publication bias is likely, it also yields an estimate of effect size after correction for the possibility of publication bias when such bias is detected.

Data synthesis

We analysed data using Review Manager 5 and Comprehensive Meta-Analysis Version 2.2.044 with fixed-effect (I^2 < 25%) or random-effects models (I^2 ≥ 25%) (Comprehensive Meta-Analysis 2007; Review Manager 2014). For dichotomous data, we planned to provide results as RRs (values best understood by clinicians; McColl 1998), but due to the large number of trials with zero cells, we had to give results as RDs. For some continuous data, we had to enter data as P values, numbers of participants, and direction of effect using the RevMan 5 calculator (see Measures of treatment effect). In such cases, MDs cannot be obtained. We then presented our results as SMDs and gave clinical equivalents calculated as follows: SMD multiplied by a typical SD on a clinical scale of one of the included trials (Higgins 2011b). For results in which the intervention produced an effect, we calculated the NNTB or the NNTH by using the odds ratio (http://www.nntonline.net/visualrx/) (Cates 2016). If an effect could not be demonstrated, we also calculated the number of participants required in a large trial to ensure that enough participants were included in the retained studies to justify a conclusion based on absence of effect (Brant 2017; Pogue 1998).

Subgroup analysis and investigation of heterogeneity

We divided all our outcomes as cardiac surgery with cardiopulmonary bypass and as off-pump surgery (Kowalewski 2016). We looked at year of publication as a factor for heterogeneity so we could take into account changes in clinical practice and types of drugs used over time. We analysed subgroup differences using Review Manager (Chi^2), and we considered a P value < 0.05 as significant for subgroup differences. We evaluated the effect of time by examining meta-regressions between effect size and year of publication (pneumonia and duration of tracheal intubation), using Comprehensive Meta-Analysis 2007.

Sensitivity analysis

We performed a sensitivity analysis on risk of bias.

'Summary of findings' table and GRADE

We judged the quality of the body of evidence according to the GRADE system and presented this assessment in 'Summary of findings' tables for each comparison for all of our outcomes: mortality (0 to 30 days), myocardial infarction, respiratory complications (respiratory depression or pneumonia), atrial fibrillation or atrial flutter, neurological complications (cerebrovascular accident or epidural haematoma), duration of tracheal intubation, pain at six to eight hours, and haemodynamic support (GRADEpro GDT; Schünemann 2013). For risk of bias, we judged the quality of evidence as high when we derived most information from studies at low risk of bias, and we downgraded quality when we obtained most information from studies at high or unclear risk of bias (allocation concealment and blinding of outcome assessors). For inconsistency, we downgraded the quality of evidence when the I^2 statistic was 75% or higher without satisfactory explanation. We did not downgrade the quality of evidence for indirectness because outcomes were based on direct comparisons performed on the population of interest and were not surrogate markers. For imprecision, we downgraded the quality of evidence when the confidence interval around the effect size was large or overlapped an absence of effect and failed to exclude an important benefit or harm, or when the number of participants was less than the number required in a large trial. For publication bias, we downgraded the quality of evidence when correcting for the possibility of publication bias as assessed by Duval and Tweedie's fill and trim analysis changed the conclusion. It is noteworthy that although factors influencing the quality of evidence are additive – such that the reduction or increase in each individual factor is added together with the other factors to reduce or increase the quality of evidence for an outcome – grading the quality of evidence involves judgements that are not exclusive. Therefore, GRADE is not a quantitative system for grading the quality of evidence. Each factor for downgrading or upgrading reflects not discrete categories but a continuum within each category and among categories (Schünemann 2013). When the body of evidence is intermediate with respect to a particular factor, the decision about whether a study falls above or below the threshold for upgrading or downgrading the quality depends on judgment. Reviewers may decide not to downgrade, even if they have some uncertainty around a specific category, when they already downgraded for another factor and further lowering the quality of evidence for this outcome would seem inappropriate (Schünemann 2013).

When the quality of the body of evidence is high, further research is very unlikely to change our confidence in the estimate of effect.

When quality is moderate, further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. When quality is low, further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate. When the quality is very low, any estimate of effect is very uncertain. Studies with low quality and very low quality of evidence are considered equivalent to observational studies.

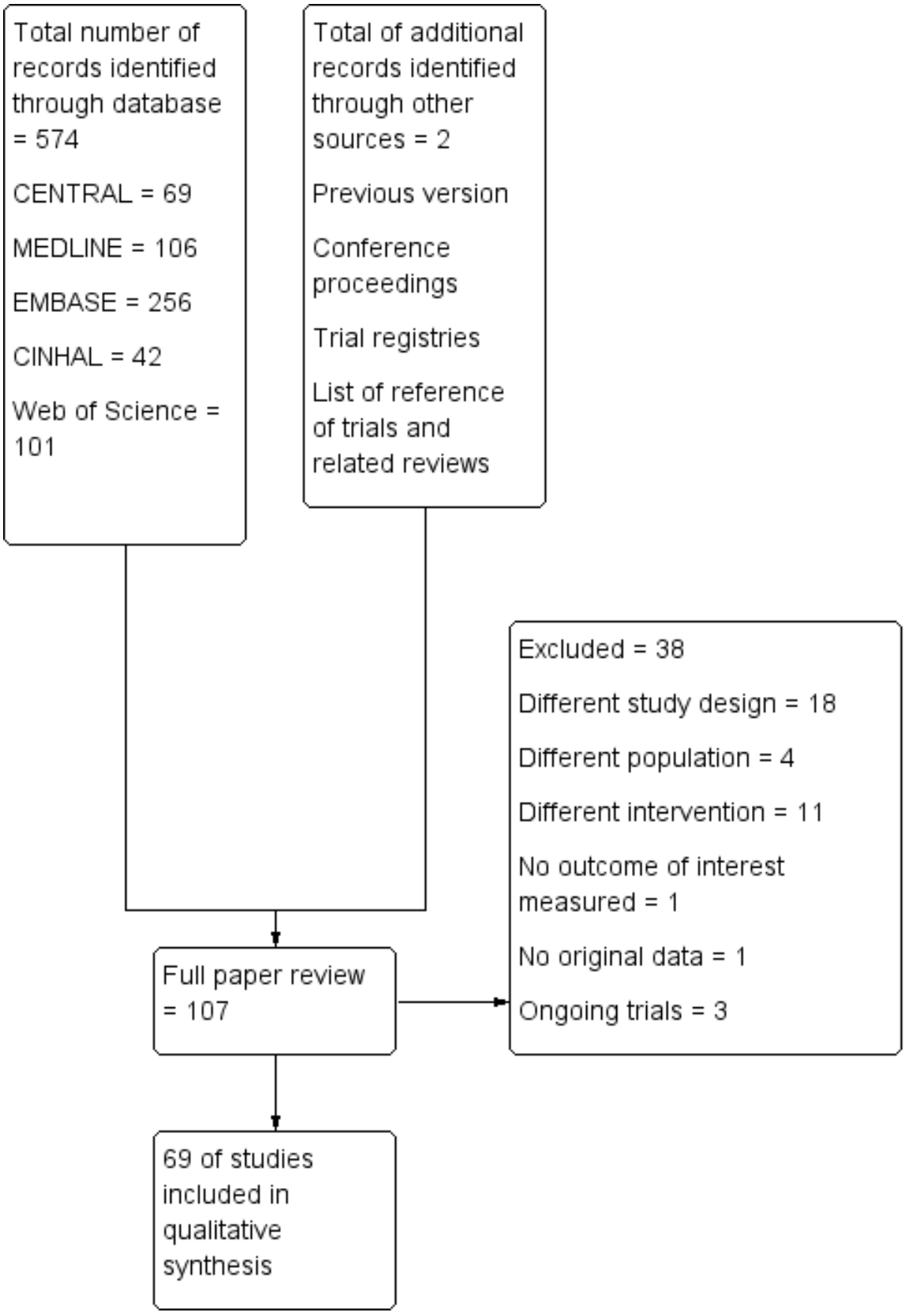
RESULTS

Description of studies

Results of the search

We identified 574 titles from the electronic search: 69 from CENTRAL, 106 from MEDLINE, 256 from EMBASE, 42 from CINHAL, and 101 from the Web of Science. We identified two additional trials from the other sources. We reviewed 107 trials for potential eligibility. Of these 107 trials, we excluded 38 for various reasons (see Figure 1 Excluded studies, Characteristics of excluded studies, and Characteristics of ongoing studies).

Figure 1. Study flow diagram for update in 2019.



Included studies

We included 69 trials with 4860 participants: 2404 given epidural analgesia and 2456 given comparators. Trials were published between 1988 and 2018.

Source of funding

Of the 66 included studies:

1. five were funded by governmental resources;
2. eight by charity;
3. 23 by departmental/institutional resources; and
4. two in part by the industry; and
5. 31 trials did not specify their sources of funding.

Setting

The trials were conducted at university hospitals (n = 66) or in tertiary care centre hospitals (n = 3).

The trials were conducted in Australia (n = 3); Bangladesh (n = 1); Canada (n = 1); China (n = 2); Cuba (n = 1); Czech Republic (n = 2); Denmark (n = 5); Egypt (n = 2); Germany (n = 5); India (n = 9); Italy and UK (n = 1); Japan (n = 2); Korea (n = 1); Lithuania (n = 1); Macedonia (n = 1); Norway (n = 3); Poland (n = 1); Russia (n = 1); Serbia (n = 1); Spain (n = 1); Sweden (n = 3); Taiwan (n = 2); Turkey (n = 8); The Netherlands (n = 4); UK (n = 5); and USA (n = 3).

Participants

The mean (or median) age of participants varied between 43.5 years and 74.6 years (Characteristics of included studies).

The types of surgeries performed were:

1. coronary artery bypass grafting (CABG) (n = 62);
2. mainly CABG (n = 1);
3. CABG or valve procedures (n = 4);
4. heart surgery for participants older than 15 years of age with congenital disease (n = 1); and
5. various cardiac procedures (n = 1).

The surgeries were performed:

1. with cardiopulmonary bypass (n = 50);
2. with off-pump surgery (n = 15); and
3. on some participants with and some participants without cardiopulmonary bypass (n = 4).

Interventions

See Table 1.

Investigators administered epidural analgesia as a single injection block (n = 3); or as a continuous epidural analgesia with patient-controlled analgesia (n = 7) or without patient-controlled analgesia (n = 51); or as repeated injections through a catheter (n = 6).

The solution contained a local anaesthetic alone (n = 23); an opioid alone (n = 3); or a mixture of a local anaesthetic and an opioid (n = 41).

Two studies added clonidine and one added ketamine. A majority of studies added no other adjuvant to the solution (n = 64).

Local anaesthetics used were bupivacaine (n = 55); bupivacaine and ropivacaine (n = 1); ropivacaine (n = 7); levobupivacaine (n = 3); or mepivacaine (n = 1).

Opioids used were fentanyl (n = 24); morphine (n = 10); morphine or butorphanol (n = 1); sufentanil (n = 9); or hydromorphone (n = 1).

Mishra 2004 and Petrovski 2006 provided no details.

Comparators

See Table 1.

Researchers compared epidural analgesia versus systemic analgesia alone (n = 63), paravertebral blockade (n = 3), erector spinae plane block (n = 1), intrapleural analgesia (n = 1), or wound local anaesthetic infusion (n = 1).

Systemic analgesia consisted of morphine (intravenous (IV) patient-controlled analgesia (PCA) (n = 7), IV infusion (n = 4), or on request (n = 9)); morphine or alfentanil (n = 2); fentanyl (IV PCA (n = 1) or infusion (n = 3)); nicomorphine (n = 1); piritramide (n = 5); tramadol (n = 4); meperidine (n = 3); meperidine and tramadol (n = 1); fentanyl and tramadol (n = 1); ketobemidone (n = 1); papaveretum (n = 1); diclofenac (n = 1); or various opioids (n = 4). The other trials did not provide details on systemic analgesia.

Study authors performed paravertebral blockade with bupivacaine infusion (n = 3).

Others performed erector spinae plane block with bupivacaine infusion (n = 1).

Some researchers provided intrapleural analgesia with repeated injections of bupivacaine (n = 1).

Others provided wound infusion with 0.15% bupivacaine (n = 1).

Excluded studies

We excluded 35 trials for the following reasons: different study design (n = 18), different study population (n = 4), different intervention (n = 11), or lack of original data in the publication (n = 1).

See Characteristics of excluded studies.

Studies awaiting classification

We have no studies awaiting classification.

Ongoing trials

We identified three ongoing trials (CTRI/2012/04/002608; CTRI/2018/05/013902; NCT03719248).

See Characteristics of ongoing studies.

Risk of bias in included studies

See Figure 2 and Figure 3.

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

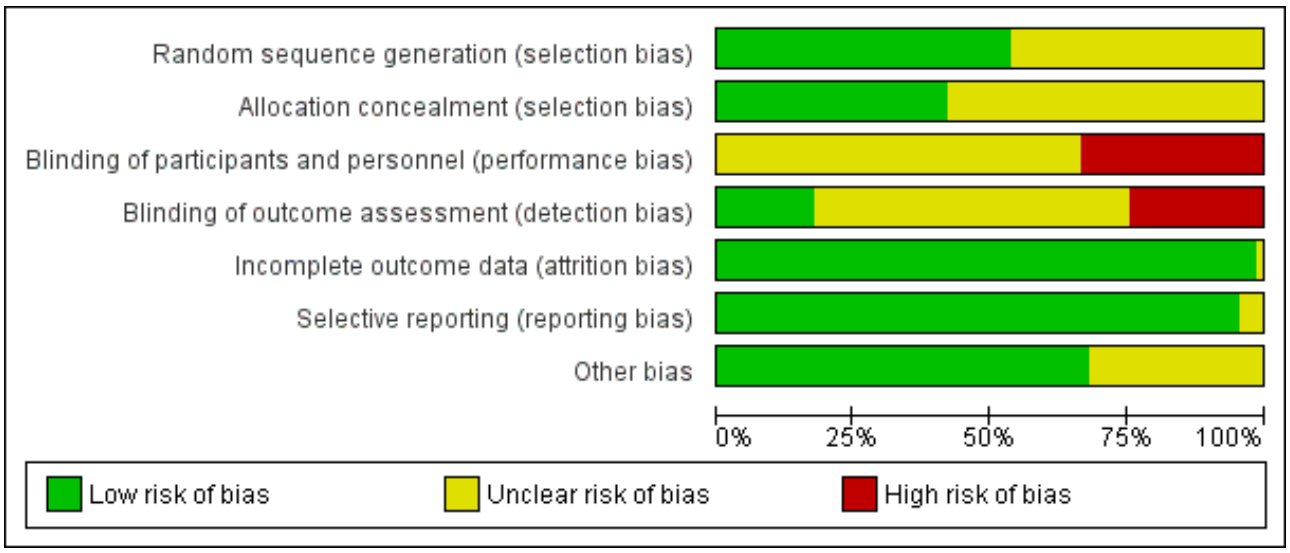


Figure 3. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

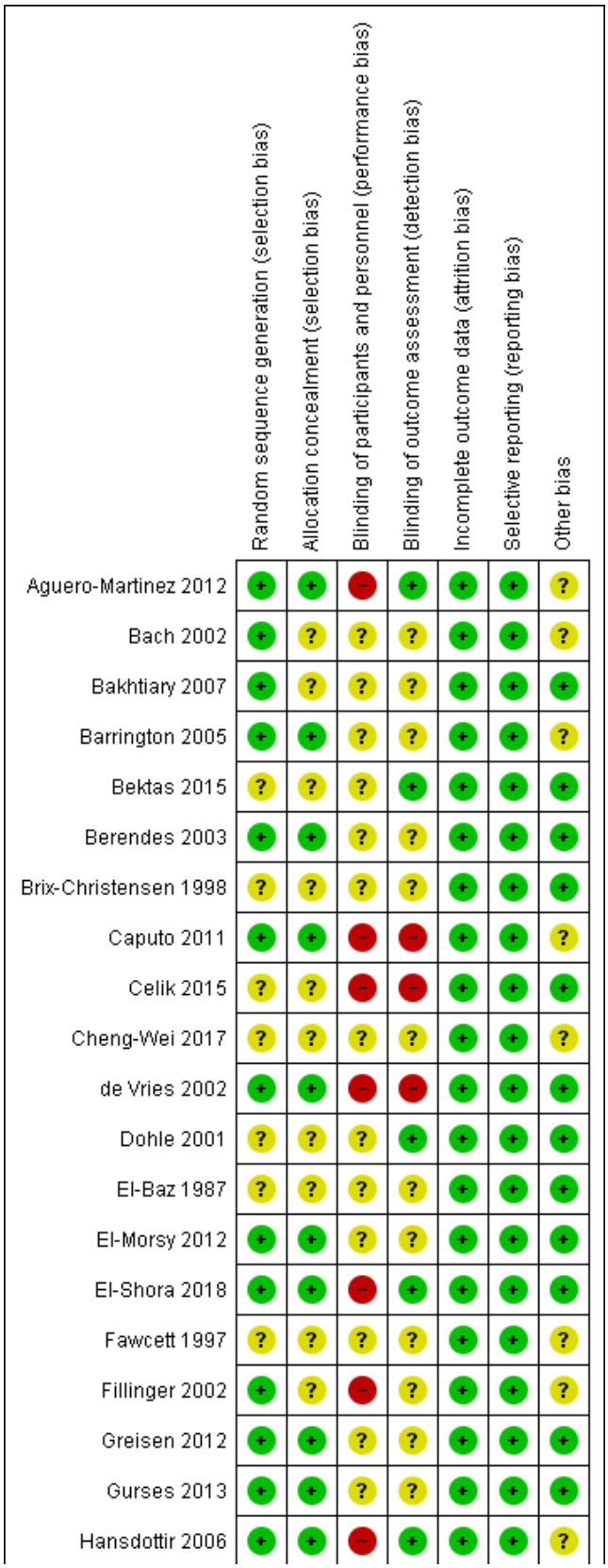


Figure 3. (Continued)

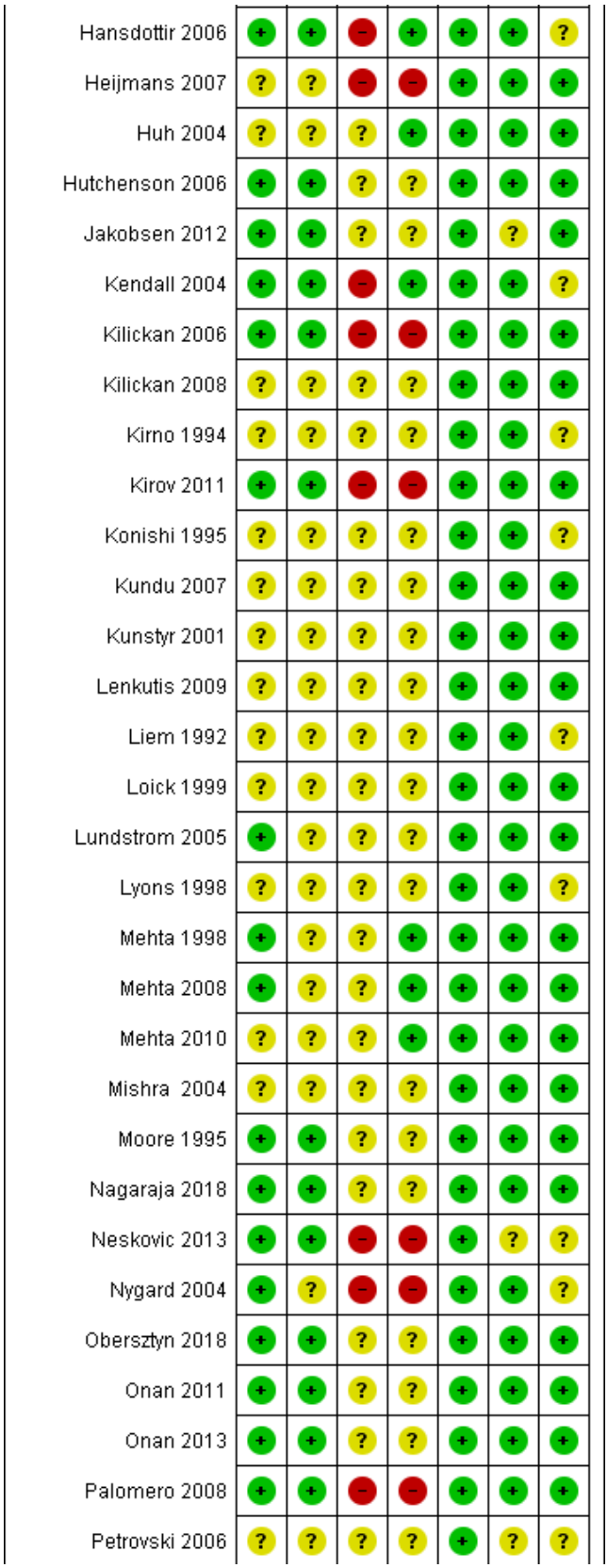
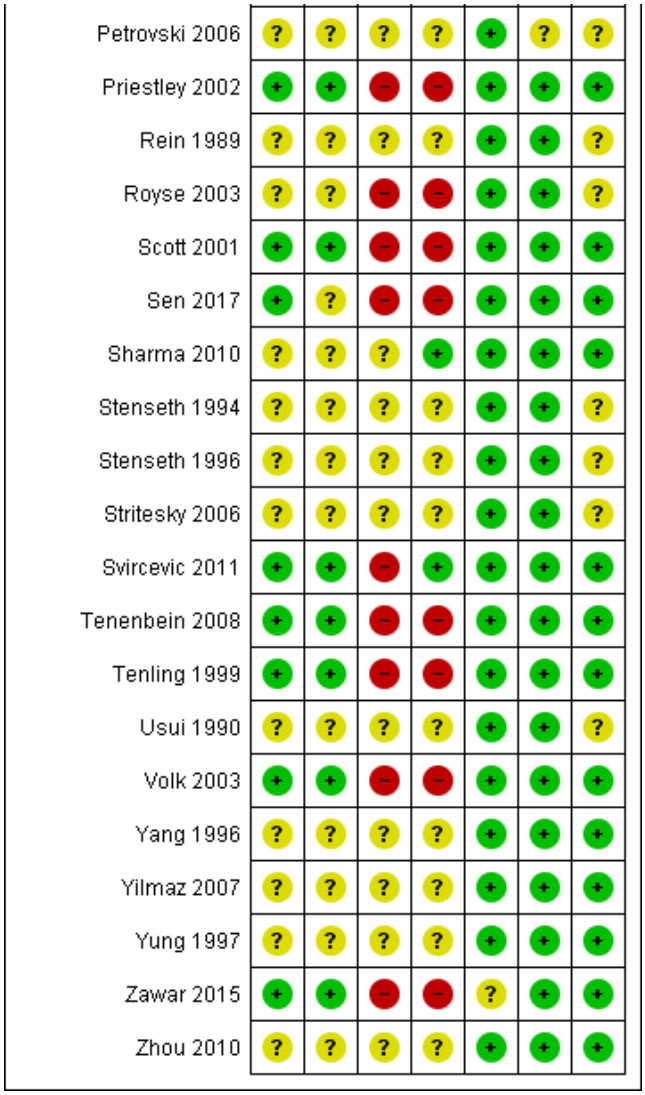


Figure 3. (Continued)



We judged that no trials were at low risk of bias for all domains. Overall, we judged that the following percentages of included trials were at low risk of bias: 54% for random sequence generation, 42% for allocation concealment, 0% for blinding of participants and of personnel taking care of study participants, 17% for blinding of outcome assessment, 99% for attrition bias, 96% for selective reporting bias, and 68% for other risks of bias (Figure 2).

We judged random sequence generation as causing low risk of bias for 37 trials and unclear/high risk of bias for the other 32 trials.

Allocation

We judged 29 trials as having low risk and 40 trials as having unclear/high risk of bias for allocation concealment.

Blinding

We judged all 69 trials as having unclear/high risk of bias for blinding of study participants and personnel taking care of participants.

We judged 12 trials as having low risk of bias and the other 57 trials as having unclear/high risk of bias for blinding of outcome assessment.

Incomplete outcome data

We judged one trial as having high/unclear risk and the other 68 trials as having low risk of attrition bias.

Selective reporting

None of the trials published a protocol; therefore we judged this domain using the methods section of trial reports. We judged three trials as having unclear/high risk and the other 66 trials as having low risk of reporting bias.

Other potential sources of bias

We judged 47 trials to have low risk and 22 trials to have unclear/high risk of other bias.

We judged five trials as having low risk of bias for random sequence generation, allocation concealment, and blinding of outcome

assessment (Aguero-Martinez 2012; El-Shora 2018; Hansdottir 2006; Kendall 2004; Svircevic 2011).

Risk of bias for each study

Aguero-Martinez 2012

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel and for other risks of bias (the group given systemic analgesia contained more aged participants).

Bach 2002

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (control group consisted of 27 participants, 13 of whom received a dopexamine infusion; supported in part by the industry).

Bakhtiary 2007

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Barrington 2005

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (prevalence of cerebrovascular and peripheral vascular disease was more frequent in the epidural group).

Bektas 2015

We judged this trial to have low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk for random sequence generation, allocation concealment, and blinding of participants and personnel.

Berendes 2003

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk for blinding of participants and personnel and blinding of outcome assessment.

Brix-Christensen 1998

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Caputo 2011

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (groups had similar demographic characteristics except for lung disease/chronic obstructive airways disease, which was more common in the epidural group, i.e. 23% vs 12%).

Celik 2015

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Cheng-Wei 2017

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (conference abstract with limited information).

de Vries 2002

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Dohle 2001

We judged this trial to have low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel.

El-Baz 1987

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

El-Morsy 2012

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

El-Shora 2018

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel.

Fawcett 1997

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (groups well balanced except for cardiopulmonary bypass time: 107 minutes for the epidural analgesia group vs 78 minutes for the no epidural group).

Fillinger 2002

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (groups had similar demographic data, except for the fact that 11 participants in the epidural group had a history of a myocardial infarction within the three months immediately preceding surgery compared with two participants in the systemic analgesia group ($P < 0.005$)).

Greisen 2012

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Gurses 2013

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel.

Hansdottir 2006

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel and other risks of bias (groups had similar demographic data, except for a higher incidence of off-pump coronary artery bypass grafting in the epidural group and longer cardiopulmonary bypass time in the systemic analgesia group).

Heijmans 2007

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Huh 2004

We judged this trial to have low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, and blinding of participants.

Hutchenson 2006

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Jakobsen 2012

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel, blinding of outcome assessment, and selective reporting.

Kendall 2004

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, and selective reporting; and unclear/high risk of bias for blinding of participants and personnel and other risks of bias (not in intention-to-treat analysis).

Kilickan 2006

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Kilickan 2008

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Kirno 1994

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation. allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (no details on preoperative demographic data of groups).

Kirov 2011

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Konishi 1995

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (some participants had laparotomy to take the gastroepiploic artery used for coronary grafting).

Kundu 2007

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Kunstyr 2001

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Lenkutis 2009

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Liem 1992

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis; groups differed for time of surgery and number of mammary artery bypasses).

Loick 1999

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Lundstrom 2005

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Lyons 1998

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (conference abstract with limited information).

Mehta 1998

We judged this trial to have low risk of bias for random sequence generation, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for allocation concealment and blinding of participants and personnel.

Mehta 2008

We judged this trial to have low risk of bias for random sequence generation, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for allocation concealment and blinding of participants and personnel.

Mehta 2010

We judged this trial to have low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel.

Mishra 2004

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Moore 1995

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Nagaraja 2018

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Neskovic 2013

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, and incomplete outcome data; and unclear/high risk of bias for blinding of participants and personnel, blinding of outcome assessment, selective reporting, and other risks of bias (not in intention-to-treat analysis).

Nygard 2004

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, and selective reporting; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis).

Obersztyn 2018

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Onan 2011

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Onan 2013

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Palomero 2008

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Petrovski 2006

We judged this trial to have low risk of bias for incomplete outcome data; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, selective reporting, and other risks of bias (conference abstract with limited information).

Priestley 2002

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Rein 1989

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis).

Royse 2003

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis; epidural group had longer bypass time; supported in part by industry).

Scott 2001

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Sen 2017

We judged this trial to have low risk of bias for random sequence generation, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Sharma 2010

We judged this trial to have low risk of bias for blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, and blinding of participants and personnel.

Stenseth 1994

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis).

Stenseth 1996

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (not in intention-to-treat analysis).

Stritesky 2006

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (groups had similar demographic data, except for pulmonary disease).

Svircevic 2011

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, blinding of outcome assessment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel.

Tenenbein 2008

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Tenling 1999

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Usui 1990

We judged this trial to have low risk of bias for incomplete outcome data and selective reporting; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, and other risks of bias (additional co-analgesia for the group given systemic analgesia only).

Volk 2003

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel and blinding of outcome assessment.

Yang 1996

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Yilmaz 2007

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Yung 1997

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Zawar 2015

We judged this trial to have low risk of bias for random sequence generation, allocation concealment, selective reporting, and other risks of bias; and unclear/high risk of bias for blinding of participants and personnel, blinding of outcome assessment, and incomplete outcome data.

Zhou 2010

We judged this trial to have low risk of bias for incomplete outcome data, selective reporting, and other risks of bias; and unclear/high risk of bias for random sequence generation, allocation concealment, blinding of participants and personnel, and blinding of outcome assessment.

Effects of interventions

See: **Summary of findings for the main comparison** Epidural analgesia compared with systemic analgesia for cardiac surgery with or without cardiopulmonary bypass in adults; **Summary of findings 2** Epidural analgesia compared with peripheral nerve blocks for cardiac surgery in adult; **Summary of findings 3** Epidural analgesia compared with intrapleural analgesia for cardiac surgery in adults; **Summary of findings 4** Epidural analgesia compared with wound infiltration for cardiac surgery in adults

Comparison 1: epidural analgesia compared with systemic analgesia

Primary outcomes

1. Risk of mortality

1a. Mortality at 0 to 30 days

Thirty-eight trials with 3418 participants reported on mortality from 0 to 30 days after surgery: in hospital, at two weeks, or at 28 to 30 days. We obtained data from published reports or from study authors (n = 3; Bektas 2015; Celik 2015; Tenenbein 2008).

We did not find a difference in mortality at 0 to 30 days (risk difference (RD) 0.00, 95% confidence interval (CI) −0.01 to 0.01; Analysis 1.1; Summary of findings for the main comparison). There was no evidence of a small-study effect. With correction for the impact of asymmetry in the funnel plot, the RD would be 0.00 (95% CI −0.002 to 0.01). For trials judged as having low risk of bias for blinding of outcome assessment, the RD would be 0.00 (95% CI −0.01 to 0.01). Based on an incidence of death at one month of 1%, 34,318 participants (17,159 per group) would be required in a large trial to eliminate a 25% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality of evidence by one level for risk of bias, and by one level for imprecision, and we rated evidence as low quality.

1b. Mortality at six months

Seven trials with 407 participants gave results for mortality at six months (RD −0.00, 95% CI −0.03 to 0.03; Analysis 1.2). We obtained data from published reports or from study authors (n = 3; Bektas 2015; Celik 2015; Tenenbein 2008). We found no evidence of a small-study effect. Correction for asymmetry of the funnel plot leads to an estimated RD of −0.02 (95% CI −0.04 to 0.01). For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be 0.00 (95% CI −0.11 to 0.11). We downgraded the quality of evidence by one level for risk of bias and by two levels for imprecision, and we rated evidence as very low quality.

1c. Mortality at one year

Five trials with 849 participants reported on mortality at one year after surgery (RD −0.01, 95% CI −0.03 to 0.00; Analysis 1.3). We obtained data from published reports or from study authors (n = 3; Bektas 2015; Celik 2015; Tenenbein 2008). We found no evidence of a small-study effect. Correction for publication bias does not change the estimate. For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be −0.01 (95% CI −0.03 to 0.01). Based on a 3% mortality rate, 2416 participants (1208 per group) would be required to eliminate a 50% difference in a large trial (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality of evidence by one level for risk of bias and by two levels for imprecision, and we rated evidence as very low quality for absence of effect.

Secondary outcomes

1. Risk of myocardial infarction (0 to 30 days)

Twenty-six trials with 2713 participants gave results for myocardial infarction from 0 to 30 days: in hospital, at 30 days, or at an unspecified time point. The definition used by the study authors can be found in Table 2. We obtained data from published reports or from study authors (n = 3; Bektas 2015; Celik 2015; Neskovic 2013). Epidural analgesia may reduce myocardial infarction at 0 to 30 days

(RD −0.01, 95% CI −0.02 to 0.00; Analysis 1.4; Summary of findings for the main comparison). We found no statistically significant evidence of a small-study effect. The impact of asymmetry in the funnel plot leads to a trim and fill analysis estimate of RD −0.01 (95% CI −0.02 to 0.00) (fixed-effect model). For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be −0.00 (95% CI −0.03 to 0.02). Based on a 4% rate of myocardial infarction, 5640 participants (2820 per group) would be required in a large trial to eliminate a 30% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality of evidence by one for risk of bias and by one for imprecision, and we rated evidence as low quality.

2. Risk of pulmonary complications

2a. Respiratory depression (0 to 30 days)

Twenty-one trials with 1736 participants gave results for respiratory depression. Definitions used by study authors can be seen in Table 3. We obtained data from published reports or from study authors (n = 4; Bektas 2015; Celik 2015; Neskovic 2013; Tenenbein 2008). Results show that epidural analgesia decreases the risk of respiratory depression after cardiac surgery (RD −0.03, 95% CI −0.05 to −0.01; Analysis 1.5; Summary of findings for the main comparison). Egger's regression intercept indicates that a small-study effect might be present (P = 0.01; two-tailed). The asymmetry of the funnel plot leads to a trim and fill estimate of RD −0.01 (95% CI −0.03 to 0.00). For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be 0.01 (95% CI −0.05 to 0.06). A decreased risk of respiratory depression may apply only for cardiac surgery with cardiopulmonary bypass (RD −0.04, 95% CI −0.07 to −0.01) - not for off-pump surgery (RD −0.01, 95% CI −0.05 to 0.02). The NNTB is 32 (95% CI 22 to 102) (Appendix 3). Based on a 7.5% incidence, 932 participants (466 per group) would be required in a large trial to eliminate a 50% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality by one level for risk of bias and by one level for the possibility of publication bias that would change the conclusion, and we rated the quality of evidence as low.

2b. Pneumonia (0 to 30 days)

Ten trials with 1107 participants gave results for pneumonia. The definition used by study authors can be found in Table 3. We obtained data from published reports or from study authors (n = 4; Celik 2015; de Vries 2002; Neskovic 2013; Tenenbein 2008). There might be no difference in the risk of pneumonia (RD −0.03, 95% CI −0.07 to 0.01; Analysis 1.6; Summary of findings for the main comparison). We found no evidence of a small-study effect. The asymmetry of the funnel plot leads to a trim and fill estimate of RD −0.04 (95% CI −0.06 to −0.01). For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be −0.05 (95% CI −0.12 to 0.01). Heterogeneity (I^2) was 57% with no differences between subgroups. Trials were published between 2001 and 2015. The P value for effect size versus year of publication was 0.12 (residual P value 0.40). Based on a 16% incidence, 406 participants (203 per group) would be required in a large trial to eliminate a 50% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality by one level for risk of bias, and we rated the quality of evidence as moderate.

3. Risk of atrial fibrillation or atrial flutter during surgery and within two weeks after surgery

Eighteen trials with 2431 participants reported on atrial fibrillation or atrial flutter. Epidural analgesia reduces the risk of atrial fibrillation or atrial flutter (RD −0.06, 95% CI −0.10 to −0.01; Analysis 1.7; Summary of findings for the main comparison). We obtained data from published reports or from study authors (n = 2; Bektas 2015; Neskovic 2013). We found no evidence of a small-study effect. The asymmetry of the funnel plot leads to a trim and fill estimate of RD −0.07 (95% CI −0.12 to −0.02). The NNTB is 14 (95% CI 8 to 90) (Appendix 3). For trials judged as at low risk of bias for blinding of outcome assessment, the RD would be −0.09 (95% CI −0.17 to −0.01). Based on an incidence of 34%, 714 participants (357 per group) would be required in a large trial to eliminate a 25% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the evidence by one level for risk of bias, and we rated the quality of evidence as moderate.

4. Risk of neurological complications

4a. Cerebrovascular accident (0 to 30 days)

Eighteen trials with 2232 participants reported on the risk of cerebrovascular accident. Study authors' definitions can be found in Table 4. We obtained data from published reports or from study authors (n = 4; Bektas 2015; Celik 2015; Neskovic 2013; Tenenbein 2008). The effect of epidural analgesia on cerebrovascular accident was uncertain (RD −0.00, 95% CI −0.01 to 0.01; Analysis 1.8; Summary of findings for the main comparison). We found no evidence of a small-study effect. The asymmetry of the funnel plot leads to an estimated RD of −0.01 (95% CI −0.02 to −0.01). For trials judged as at low risk of bias for blinding of outcome assessment, the RD is −0.00 (95% CI −0.01 to 0.02). Based on an incidence of 1.5%, 22,778 participants (11,389 per group) would be required in a large trial to eliminate a 25% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the level of quality by one for risk of bias, by two levels for imprecision, and by one level to correct for the possibility that publication bias would change the conclusion, and we rated the quality of evidence as very low.

4b. Risk of serious neurological complications from epidural analgesia or epidural haematoma (0 to 30 days)

One trial reported one transient quadriparesis appearing on emergence of general anaesthesia for the epidural group (Tenenbein 2008). The participant awoke with quadriparesis (unable to move hands or legs). Computerized tomography (CT scan) showed that the tip of the epidural catheter had gone cephalad and was located at the cervical level (C_{3-4}), where the participant had a large osteophyte and cervical stenosis. By the time the CT scan was done, neurological function was returning, and the participant made a complete recovery. Study authors attributed this occurrence to local anaesthetic effect, which has been concentrated at the cervical level because of spinal stenosis.

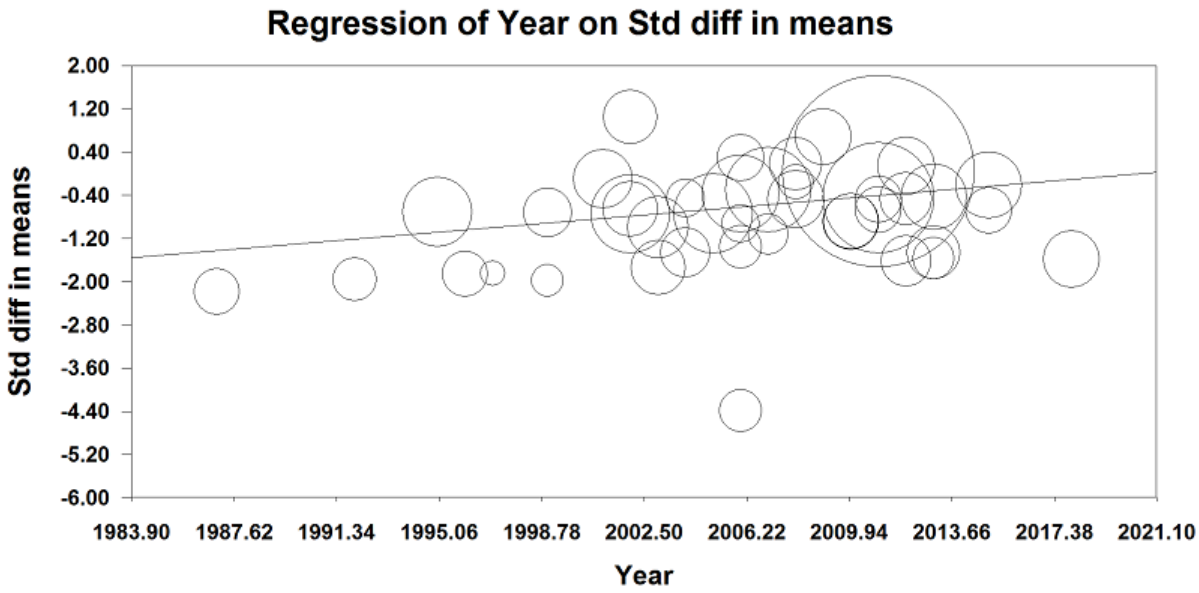
Study authors reported no episodes of epidural haematoma in any of the included studies. Researchers clearly reported the information for 53 trials with 3982 participants (RD 0.00, 95% CI −0.01 to 0.01; Analysis 1.9; Summary of findings for the main comparison). We obtained information from published reports or from study authors (n = 3; Celik 2015; de Vries 2002; Neskovic 2013). For trials judged as at low risk of bias for outcome assessment, the RD is unchanged. We downgraded the quality by one for risk of bias and by one for imprecision, and we rated the quality of evidence as low.

5. Duration of tracheal intubation

Forty trials with 3353 participants gave results for time to tracheal extubation. We obtained data from reports (n = 36) or from study

authors (n = 2; Celik 2015; Neskovic 2013). For seven trials, results were not available because means and standard deviations (SDs) had to be extracted as P values (Barrington 2005; Caputo 2011; Jakobsen 2012; Kirov 2011; Priestley 2002; Stritesky 2006; Svircevic 2011). Epidural analgesia reduces the time of tracheal intubation (standardised mean difference (SMD) −0.78, 95% CI −1.01 to −0.55; Analysis 1.10; Summary of findings for the main comparison). A small-study effect might be present (P = 0.0003; two-sided test; Egger's regression intercept). The asymmetry of the funnel plot leads to a corrected estimate (SMD −0.29, 95% CI −0.56 to −0.03). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD would be −0.75 (95% CI −1.25 to −0.25). We noted no difference between surgeries performed with or without cardiopulmonary bypass (P = 0.15 for heterogeneity between the first two subgroups). The effect was more evident in older trials: the P value for the meta-regression effect size versus the year of publication was less than 0.0001 (Figure 4). With inclusion of Kendall 2004 (SD in the control group 3.1 hours), the difference would be equivalent to 2.4 hours. Considering only the trials for which means and SDs were available would lead to an estimate of mean difference (MD) of −2.91 hours (95% CI −3.61 to −2.21; 33 studies with 2062 participants; Analysis 1.11). For these trials, the mean duration of tracheal intubation was 6.1 hours for epidural analgesia and 9.1 hours for systemic analgesia (Appendix 4). We downgraded the quality of evidence by one level for risk of bias, and we judged the quality of evidence as moderate.

Figure 4. Meta-regression. Effect of epidural analgesia on tracheal extubation versus year of publication. The effect was more evident in older trials: P value for the meta-regression effect size versus year of publication was < 0.0001.



6. Pain

6a. Pain at six to eight hours

Pain at rest at six to eight hours

From 10 trials with 502 participants, epidural analgesia may reduce pain at rest at six to eight hours (SMD −1.35, 95% CI −1.98 to −0.72; Analysis 1.12). For five trials, data were available as means and SDs (MD −2.26, 95% CI −4.84 to 0.32; Analysis 1.13). For trials judged as having low risk of bias for blinding of outcome assessment, SMD is −2.35 (95% CI −4.04 to −0.66), Egger's regression intercept showed the possibility of a small-study effect (P = 0.001; two-tailed). Duval and Tweedie's trim and fill analysis showed no evidence of publication bias. Based on data from Mehta 2010 (SD 0.7), the difference would be equivalent to 1 on a score from 0 to 10. In trials for which data were available as means and SDs, mean pain scores were 1.9 for epidural analgesia and 4.2 for systemic analgesia (Appendix 5). We downgraded the quality of evidence by one level for heterogeneity and rated it as moderate.

Pain on movement or coughing at six to eight hours

From five trials with 342 participants, epidural analgesia may reduce pain on movement at six to eight hours (SMD −1.39, 95% CI −2.16 to −0.62; Analysis 1.14). We found no statistically significant evidence of small-study effect. Correcting the asymmetry of the funnel plot gives an estimated SMD of −0.97 (95% CI −1.86 to −0.08). For trials with data available as means and SDs, the MD is −2.46 (95% CI −4.37 to −0.54; Analysis 1.15). For trials judged as at low risk of bias for blinding of outcome assessment (available only for off-pump surgery), the SMD is −1.01 (95% CI −1.24 to −0.78).

6b. Pain at 24 hours

Pain at rest at 24 hours

From 22 trials with 2033 participants, epidural analgesia may reduce pain at rest at 24 hours (SMD −0.93, 95% CI −1.22 to −0.65; Analysis 1.16). The difference was higher for off-pump surgery (P < 0.00001 for heterogeneity between subgroups; Analysis 1.16). Egger's regression intercept showed the possibility of a small-study effect (P = 0.001; two-tailed). Correcting the asymmetry of the funnel plot gives an estimated SMD of −0.43 (95% CI −0.74 to −0.13). For trials with data available as means and SDs, the MD is −1.53 (95% CI −2.51 to −0.55; Analysis 1.17). For trials judged as at low risk

of bias for blinding of outcome assessment, the SMD is −1.37 (95% CI −2.19 to −0.54).

Pain on movement or coughing at 24 hours

From 12 trials with 842 participants, epidural analgesia may reduce pain on movement at 24 hours (SMD −0.83, 95% CI −1.18 to −0.49; Analysis 1.18). Egger's regression intercept showed the possibility of a small-study effect (P = 0.02; two-tailed). We found no evidence of publication bias. For trials with data available as means and SDs, the MD is −1.74 (95% CI −2.63 to −0.86; Analysis 1.19). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD is −0.59 (95% CI −1.28 to 0.11).

6c. Pain at 48 hours

Pain at rest at 48 hours

From 15 trials with 1649 participants, epidural analgesia may reduce pain at rest at 48 hours (SMD −1.01, 95% CI −1.37 to −0.64; Analysis 1.20). Egger's regression intercept showed the possibility of a small-study effect (P = 0.01; two-tailed). Correcting the asymmetry of the funnel plot gives an estimated SMD of −0.38 (95% CI −0.78 to 0.02). For trials with data available as means and SDs, the MD is −1.31 (95% CI −1.99 to −0.64; Analysis 1.21). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD is −1.34 (95% CI −2.16 to −0.53).

Pain on movement or coughing at 48 hours

From 10 trials with 700 participants, epidural analgesia may reduce pain on movement at 48 hours (SMD −0.83, 95% CI −1.31 to −0.35; Analysis 1.22). Egger's regression intercept showed the possibility of a small-study effect (P = 0.04; two-tailed). Correcting the asymmetry of the funnel plot gives an estimated SMD of −1.06 (95% CI −1.49 to −0.64). For trials with data available as means and SDs, the MD is −1.30 (95% CI −2.00 to −0.60; Analysis 1.23). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD is −0.71 (95% CI −1.76 to 0.34).

6d. Pain at 72 hours

Pain at rest at 72 hours

From 12 trials with 897 participants, epidural analgesia may reduce pain at rest at 72 hours (SMD −1.09, 95% CI −1.57 to −0.62; Analysis 1.24). We found no statistically significant evidence of a small-study effect. Correcting the asymmetry of the funnel plot gives an estimated SMD of −1.20 (95% CI −1.71 to −0.69). For trials with data available as means and SDs, the MD is −1.02 (95% CI −1.41 to −0.63; Analysis 1.25). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD is −1.10 (95% CI −1.96 to −0.24).

Pain on movement or coughing at 72 hours

From nine trials with 654 participants, epidural analgesia may reduce pain on movement at 72 hours (SMD −0.62, 95% CI −1.13 to −0.11; Analysis 1.26). We found no statistically significant evidence of small-study effect. Correcting the asymmetry of the funnel plot gives an estimated SMD of −0.82 (95% CI −1.24 to −0.39). For trials with data available as means and SDs, the MD is −0.90 (95% CI −1.49 to −0.30; Analysis 1.27). For trials judged as at low risk of bias for blinding of outcome assessment, the SMD is −0.86 (95% CI −1.87 to 0.15).

7. Haemodynamic support (in hospital)

7a. Hypotension or need for vasopressor boluses

From 17 trials with 870 participants, epidural analgesia may increase the risk of hypotension and/or the need for vasopressor boluses (RD 0.21, 95% CI 0.09 to 0.33; Analysis 1.28). Egger's regression intercept showed the possibility of a small-study effect (P = 0.01; two-tailed). Correcting the asymmetry of the funnel plot gives an estimated RD of 0.13 (95% CI 0.02 to 0.24). We judged that only one trial was at low risk of bias for blinding of the outcome assessor (RD −0.07, 95% CI −0.17 to 0.04). From an incidence of 30% in the systemic analgesia group, the number needed to harm is 4 (95% CI 3 to 12). From an incidence of 30%, 480 participants (240 per group) would be required in a large trial to eliminate a 25% increase in incidence (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality by two levels for risk of bias and rated it as low.

7b. Inotropic or vasopressor infusions

From 23 trials with 1821 participants, epidural analgesia makes little or no difference in the need for vasopressor or inotropic infusions (RD 0.00, 95 CI −0.06 to 0.07; Analysis 1.29). Criteria used by study authors are provided in Table 6. We found no evidence of a small-study effect. Correcting the asymmetry of the funnel plot gives an estimated RD of 0.05 (95% CI −0.02 to 0.12). For trials judged as at low risk of bias for binding of outcome assessment, the RD is −0.06 (95% CI −0.17 to 0.05). From an incidence of 34%, 396 participants (198 per group) would be required in a large trial to eliminate a 25% increase in incidence (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality by two levels for risk of bias and rated it as low.

Comparison 2: epidural analgesia compared with peripheral nerve blocks

Primary outcomes

1. Risk of mortality

From one trial with 145 participants, epidural analgesia makes little or no difference for mortality at 0 to 30 days (RD −0.03, 95% CI −0.08 to 0.02; Analysis 2.1). We judged this trial as having low risk of bias for blinding of outcome assessment. We downgraded the quality by one level for risk of bias and by two levels for imprecision. We judged the quality as very low.

We found no data for this outcome at six months nor at one year.

Secondary outcomes

1. Risk of myocardial infarction (0 to 30 days)

Two trials with 76 participants compared epidural analgesia versus paravertebral blockade for off-pump cardiac surgery. Results show no myocardial infarction at 0 to 30 days (RD 0.00, 95% CI −0.07 to 0.07; Analysis 2.2; Summary of findings 2). We judged the two trials as having low risk of bias for blinding of outcome assessment. Based on a 4% rate of myocardial infarction, 5640 participants (2820 per group) would be required in a large trial to eliminate a 30% difference (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality of evidence by one level for risk of bias and by two levels for imprecision, and we rated the quality as very low.

2. Risk of pulmonary complications

2a. Respiratory depression (0 to 30 days)

We found no data for this outcome.

2b. Pneumonia (0 to 30 days)

We found no data for this outcome.

3. Risk of atrial fibrillation or atrial flutter during surgery and within two weeks after surgery

We found no data for this outcome.

4. Risk of neurological complications

4a. Cerebrovascular accident (0 to 30 days)

From one trial with 145 participants, epidural analgesia makes little or no difference in the risk of cerebrovascular accident at 0 to 30 days (RD 0.00, 95% CI −0.03 to 0.03). We judged this trial as at low risk of bias for blinding of outcome assessment.

4b. Risk of serious neurological complications from epidural analgesia or epidural haematoma (0 to 30 days)

Mehta 2008 reported two participants with epidural analgesia who experienced transient numbness and no participants with epidural haematoma. Dohle 2001 reported that one participant reported pain at the epidural catheter insertion site and no complications of paravertebral blockade. For epidural haematoma, the RD is 0.00 (95% CI −0.03 to 0.03; four trials with 271 participants; Analysis 2.4; Summary of findings 2). For trials judged as at low risk of bias for blinding of outcome assessment, the RD is 0.00 (−0.03 to 0.03). We downgraded the quality by two levels for imprecision and rated the quality as low.

5. Duration of tracheal intubation

Four trials with 271 participants compared epidural analgesia versus paravertebral blockade or erector spinae plane blockade. We did not find a difference for time to tracheal extubation (MD −0.08 hour, 95% CI −0.54 to 0.38 hour; Analysis 2.5; Summary of findings 2). We found no evidence of a small-study effect. Correcting the asymmetry of the funnel plot gives an estimated MD of −0.05 hour (95% CI −0.50 to 0.40). For trials judged as at low risk of bias for blinding of outcome assessment, the MD is −0.18 hour (95% CI −1.41 to 1.05). We downgraded the quality of evidence by one for risk of bias and by two levels for imprecision, and we rated the quality as very low.

6. Pain

6a. Pain at six to eight hours

Pain at rest at six to eight hours

From two trials with 90 participants, epidural analgesia makes little or no difference in pain at rest at six to eight hours (MD 0.12, 95% CI −0.42 to 0.66; Analysis 2.6). For the trial judged as at low risk of bias for blinding of outcome assessment, the MD is 0.80 (95% CI −0.61 to 2.21). We downgraded the quality by one level for risk of bias and by two levels for imprecision and rated it as very low.

Pain on movement or coughing at six to eight hours

From two trials with 90 participants, epidural analgesia makes little or no difference in pain on movement at six to eight hours (MD −0.15, 95% CI −0.69 to 0.39; Analysis 2.6). For the trial judged as at low risk of bias for blinding of outcome assessment, the MD is −0.40 (95% CI −1.57 to 0.77).

6b. Pain at 24 hours

Pain at rest at 24 hours

From three trials with 231 participants, epidural analgesia makes little or no difference in pain at rest at 24 hours (MD 0.11, 95% CI −0.41 to 0.63; Analysis 2.8). We found no evidence of a small-study effect. Correcting the asymmetry of the funnel plot gives an estimated MD of 0.29 (95% CI −0.25 to 0.82). For the two trials judged as at low risk of bias for blinding of outcome assessment, the MD is −0.10 (95% CI −0.51 to 0.31).

Pain on movement or coughing at 24 hours

From two trials with 86 participants, epidural analgesia makes little or no difference in pain on movement or coughing (MD 0.31, 95% CI −0.62 to 1.24). For the trial judged as at low risk of bias, the MD is −0.24 (95% CI −1.11 to 0.63).

6c. Pain at 48 hours

Pain at rest at 48 hours

From two trials with 195 participants, epidural analgesia makes little or no difference in pain at rest at 48 hours after surgery (MD 0.51, 95% CI −0.77 to 1.80). For the trial judged as at low risk of bias for blinding of outcome assessment, the MD is -0.11 (95% CI −0.15 to -0.77).

Pain on movement or coughing at 48 hours

From one trial with 50 participants, pain on movement or on coughing at 48 hours may be greater with epidural analgesia than with bilateral erector spinae block (MD 1.36, 95% CI 0.76 to 1.96). We judged this trial to be at unclear risk of bias for blinding of outcome assessment.

6d. Pain at 72 hours

Pain at rest at 72 hours

We found no data for this outcome.

Pain on movement or coughing at 72 hours

We found no data for this outcome.

7. Haemodynamic support (in hospital)

7a. Hypotension or need for vasopressor boluses

From one trial with 40 participants, epidural analgesia makes little or no difference in risk of hypotension (RD 0.05, 95% CI −0.08 to 0.18). We judged this trial to be at low risk of bias for blinding of outcome assessment. From an incidence of 5% with epidural analgesia, 1720 participants per group would be required in a large trial to eliminate a 25% decrease with peripheral nerve block (alpha 0.05; beta 0.2; one-sided test). We downgraded the quality by two levels for imprecision and rated it as low.

7b. Inotropic or vasopressor infusions

We found no data for this outcome.

Comparison 3: epidural analgesia compared with intrapleural analgesia

Primary outcomes

1. Risk of mortality

We found no data for this outcome at 0 to 30 days, at six months, or at one year.

Secondary outcomes

1. Risk of myocardial infarction (0 to 30 days)

One small trial with 50 participants reported no myocardial infarction in either group (RD 0.00, 95% CI −0.07 to 0.07; Analysis 3.1; Summary of findings 3; Mehta 1998). We judged this trial to be at low risk of bias for blinding of outcome assessment. We downgraded the evidence by two levels for imprecision and rated it as low.

2. Risk of pulmonary complications

2a. Respiratory depression (0 to 30 days)

We found no data for this outcome.

2b. Pneumonia (0 to 30 days)

We found no data for this outcome.

3. Risk of atrial fibrillation or atrial flutter during surgery and up to two weeks after surgery

We found no data for this outcome.

4. Risk of neurological complications

4a. Cerebrovascular accident (0 to 30 days)

We found no data for this outcome.

4b. Risk of serious neurological complications from epidural analgesia or epidural haematoma (0 to 30 days)

One trial with 50 participants reported no epidural haematoma (RD 0.00, 95% CI −0.07 to 0.07; Analysis 3.2; Summary of findings 3; Mehta 2008). We judged this trial to be at low risk of bias for blinding of outcome assessment. We downgraded the quality by two levels for imprecision and rated the quality as low.

5. Duration of tracheal intubation

One small trial with 50 participants reported that 17 in the epidural analgesia group and 14 in the intrapleural analgesia group were extubated in the operating room, and the remainder were extubated in the post-anaesthesia care unit after a mean time of 3.8 ± 1.13 hours (mean ± SD) of ventilation in the epidural group and 4.1 ± 0.59 hours in the intrapleural group (MD −0.30 hour, 95% CI −1.20 to 0.60 hour; 15 participants; Analysis 3.3; Summary of findings 3; Mehta 2008). We judged this trial as being at low risk of bias for blinding of outcome assessment. We downgraded the quality by one level for risk of bias and by two levels for imprecision, and we rated the quality as very low.

6. Pain

6a. Pain at six to eight hours

Pain at rest at six to eight hours after surgery

From one trial with 50 participants, pain may be greater with epidural analgesia compared with paravertebral blockade for off-pump surgery (MD 0.84, 95% CI 0.31 to 1.37). We judged this trial to be at low risk of bias for blinding of outcome assessment. We downgraded the quality by two levels for imprecision, and we rated the quality as low.

Pain on movement or coughing at six to eight hours after surgery

We found no data for this outcome.

6b. Pain at 24 hours

We found no data for this outcome.

6c. Pain at 48 hours

We found no data for this outcome.

6d. Pain at 72 hours

We found no data for this outcome.

7. Haemodynamic support (in hospital)

We found no data for this outcome.

Comparison 4: epidural analgesia compared with wound infiltration

Primary outcomes

1. Risk of mortality

We found no data for this outcome at 0 to 30 days, at six months, or at one year.

Secondary outcomes

1. Risk of myocardial infarction (0 to 30 days)

We found no data for this outcome.

2. Risk of pulmonary complications

2a. Respiratory depression (0 to 30 days)

We found no data for this outcome.

2b. Pneumonia (0 to 30 days)

We found no data for this outcome.

3. Risk of atrial fibrillation or atrial flutter during surgery and up to two weeks after surgery

We found no data for this outcome.

4. Risk of neurological complications

4a. Cerebrovascular accident (0 to 30 days)

We found no data for cerebrovascular accident.

4b. Risk of serious neurological complications from epidural analgesia or epidural haematoma (0 to 30 days)

We found no data for this outcome.

5. Duration of tracheal intubation

One small trial with 37 participants published as a conference abstract reported no difference in time to tracheal extubation between epidural analgesia and intravenous patient-controlled analgesia plus wound infusion (Cheng-Wei 2017). Data were not suitable for extraction (Summary of findings 4). We judged this trial to be at low risk of bias for blinding of outcome assessment. We

downgraded the quality by one level for risk of bias and by two levels for imprecision and rated the quality as very low.

6. Pain

6a. Pain at six to eight hours

One small trial with 37 participants and judged as at unclear risk of bias for blinding of outcome assessment reported: "Both groups achieved satisfactory pain relief postoperatively. However, thoracic patient-controlled epidural analgesia further reduced the verbal analogue pain scores both at rest and during motion significantly as compared to continuous local infusion combined with patient controlled analgesia". Data were unsuitable for extraction.

6b. Pain at 24 hours

We found no suitable data for extraction for this outcome.

6c. Pain at 48 hours

We found no suitable data for extraction for this outcome.

6d. Pain at 72 hours

We found no suitable data for extraction for this outcome.

7. Haemodynamic support (in hospital)

We found no data for this outcome

DISCUSSION

Summary of main results

There may be no difference in mortality between epidural analgesia and systemic analgesia. Review authors found that the number of participants included was insufficient to exclude a difference in mortality between epidural analgesia and systemic analgesia, particularly at one year after surgery (Analysis 1.3). This is important because if indeed epidural analgesia would reduce the mortality rate at one year by half or more (three events for 423 participants for epidural analgesia, or 71 per 10,000 surgeries vs nine events for 426 participants for systemic analgesia or 211 events per 10,000 surgeries; Analysis 1.3), then a risk of three spinal haematomas per 10,000 epidural blocks could be justified (Landoni 2015). Although collecting enough participants to demonstrate a reduced mortality rate at one year may prove difficult (Choi 2009), a satisfactory answer to that important question could possibly be obtained with large well-designed retrospective trials (propensity score analysis).

There may be a difference in the risk of myocardial infarction. This is similar to what we found for patients undergoing abdominal aortic surgery (Guay 2016b). Although both populations shared many risk factors, in the present review, a vast majority of participants were undergoing coronary artery bypass grafting. Therefore, these participants should have had improved coronary artery blood flow after surgery, which may have offered a certain degree of protection that was added to any potential advantages of epidural analgesia. Many of the patients who undergo heart surgery have coronary artery bypass grafting (CABG) surgery, which may be protective against myocardial infarction.

Epidural analgesia reduces the risk of respiratory depression, but we did not find a difference for risk of pneumonia (Analysis 1.6). Reduced risk of respiratory depression was however more evident for participants undergoing cardiac surgery with cardiopulmonary bypass - a procedure usually performed through a median sternotomy; off-pump surgery may be performed by a mini-thoracotomy. The clinical relevance of this finding is unclear because all these patients are usually closely monitored during the period of higher risk for respiratory depression, no matter the mode of postoperative analgesia used.

Epidural analgesia also reduces the risk of atrial fibrillation or atrial flutter after surgery. However, one trial compared four treatment groups: epidural analgesia with or without amiodarone versus no epidural analgesia with or without amiodarone (Nygard 2004). Researchers administered amiodarone at 1800 mg orally the day before surgery and 900 mg IV per 24 hours started after anaesthesia induction and continued for three days. From the morning of the first postoperative day, 24-hour Holter recordings were obtained by a standard three-channel tape recorder, and this continued for five days. The incidence of new-onset atrial fibrillation requiring treatment was 20/48 (42%; 95% confidence interval (CI) 28 to 57%) for control, 22/44 (50%; 95% CI 35 to 65%) for epidural analgesia, 10/36 (28%; 05% CI 14 to 45%) for amiodarone, and 10/35 (29%; 95% CI 14 to 46%) for epidural analgesia plus amiodarone. This small trial suggests that epidural analgesia might not add much to a potent prophylaxis such as the one that can be obtained with amiodarone or other drugs (De Oliveira 2012). The Healthcare Improvement Scotland Committee recommended against the use of epidural analgesia for the sole purpose of decreasing the incidence of atrial fibrillation: "The choice of anaesthetic agent or technique and analgesia should be based on factors other than atrial fibrillation prophylaxis" (Healthcare Improvement Scotland Committee 2018).

We did not find an increase in the incidence of epidural haematoma, but the number of participants included in the analysis is clearly insufficient to evaluate this (Analysis 2.4; Summary of findings for the main comparison). Furthermore, pooling results from small randomized controlled trials (RCTs) to evaluate the risks of a rare event might not be appropriate. Small trials including such a severe complication might have been terminated and never published. From other authors (Landoni 2015), the risk of epidural haematoma in patients undergoing cardiac surgery would be 3 per 10,000 compared with 1 per 10,000 for the general population (Moen 2004). In its latest recommendation, the American Society of Regional Anesthesia (ASRA) (joint recommendation with the European Society of Anaesthesiology) stated: "Currently, insufficient data and experience are available to determine if the risk of neuraxial haematoma is increased when combining neuraxial techniques with the full anticoagulation of cardiac surgery" (Horlocker 2018). The ASRA also recommends the following precautions if a neuraxial block is performed in this specific population: "1) Neuraxial blocks should be avoided in a patient with known coagulopathy from any cause. 2) Surgery should be delayed 24 hours in the event of a traumatic tap. 3) Time from instrumentation to systemic heparinization should exceed 60 minutes. 4) Heparin effect and reversal should be tightly controlled (smallest amount of heparin for the shortest duration compatible with therapeutic objectives). 5) Epidural catheters should be removed when normal coagulation is restored, and patients should be closely monitored postoperatively for signs and symptoms of hematoma formation" (Chaney 1997; Horlocker 2018). It is noteworthy that these recommendations also apply to paravertebral blockade (a deep block). The ASRA considers that precautions for any block performed at a "non-compressible" site should be identical to

those followed for neuraxial blocks. Numerous cases of substantial internal haemorrhage (some with poor prognosis) have been reported when deep blocks (including paravertebral blockade) are performed in individuals with altered haemostasis/coagulation (Horlocker 2018; Thomas 1999). Bilateral erector spinae plane analgesic blocks have been proposed for postoperative analgesia after cardiac surgery through median sternotomy (Tsui 2018; Nagaraja 2018). However, this block is not without complications in itself (Ueshima 2018), and more randomized clinical trials will be required before an opinion can be made on the usefulness of this new block for cardiac surgery. Although intrapleural analgesia may sound attractive (Mehta 1998), it cannot be used for patients without pleural drainage and might be less effective in patients with large postoperative blood loss (more than 200 mL/h through the intercostal chest tube for the first five hours postoperatively; Mehta 1998).

Epidural analgesia reduces the duration of tracheal intubation, but this effect is more evident in older trials ($P < 0.0001$ for the meta-regression effect size vs year of publication), making epidural analgesia less likely to have an important beneficial impact on costs in 2018 for patients undergoing cardiac surgery (Fillinger 2002). This might be related to a change in clinical practice. Fast-track protocols including more systematic use of co-analgesic drugs, favouring short-acting drugs over long-acting ones and promoting early tracheal extubation, are used more often nowadays. Furthermore, other modalities of postoperative pain treatment such as peripheral nerve blocks (Analysis 2.5; Summary of findings 2), intrapleural analgesia (Analysis 3.3; Summary of findings 3), or wound infusion (Summary of findings 4) might be equally effective in reducing the duration of tracheal intubation.

Overall completeness and applicability of evidence

The number of participants included in the review is insufficient to eliminate a difference in mortality between epidural analgesia and systemic analgesia. The number of trials comparing epidural analgesia versus other techniques of regional anaesthesia is very limited.

Quality of the evidence

We rated the quality of evidence as moderate for reduction of respiratory depression, reduction of atrial fibrillation or atrial flutter, duration of tracheal intubation, and pain reduction. We rated the quality of evidence as low for no difference in mortality, reduced risk of myocardial infarction, no difference in risk of pneumonia, and haemodynamic support requirements, and as very low for uncertainty of differences in cerebrovascular accidents.

Potential biases in the review process

Conclusions of this review are limited by an insufficient number of participants/trials to eliminate a difference in mortality between epidural analgesia and systemic analgesia. Although the exact content of solutions infused varied widely, all but three studies included a local anaesthetic, and all were performed at the thoracic (or low cervical) level. It seems therefore unlikely that variations in techniques/drugs used in included trials could explain the lack of effect of epidural analgesia on most of the studied outcomes.

We found no published protocol for any of the included trials. Therefore, we were unable to judge whether or not trialists adhered to their protocol.

The three ongoing trials may change the results of this review.

Agreements and disagreements with other studies or reviews

In agreement with epidural analgesia for abdominal aortic surgery, epidural analgesia for cardiac surgery may reduce the risk of postoperative myocardial infarction (Guay 2016b). Many of the patients undergoing heart surgery are having coronary artery bypass graft (CABG) surgery, which may in itself be protective against myocardial infarction.

Others have also reported a reduction in the risk of arrhythmia (Barbosa 2016; Zhang 2015).

While reviewing randomized and case-matched studies, Landoni and colleagues reported a reduction in all-cause mortality at the longest follow-up available (risk ratio (RR) 0.65, 95% CI 0.48 to 0.86; 57 trials including 6383 participants; Landoni 2015). Inclusion of non-randomized trials, which are expected to be at higher risk of bias, and lack of a clear time point for mortality may explain in part the differences between their results and ours.

AUTHORS' CONCLUSIONS

Implications for practice

Compared with systemic analgesia, epidural analgesia may reduce the risk of myocardial infarction, respiratory depression, atrial fibrillation/atrial flutter, duration of tracheal intubation, and pain in adults undergoing cardiac surgery. There might be little or no difference in mortality, pneumonia, and epidural haematoma. Effects on risks of cerebrovascular accident are uncertain. Evidence is insufficient to show the effects of epidural analgesia compared with peripheral nerve blocks, intrapleural analgesia, or wound infiltration.

Implications for research

It is actually unclear whether benefits of epidural analgesia justify its potential risk for adults undergoing cardiac surgery. The risk of spinal haematoma might be higher than in the general population (3 per 10,000 vs 1 per 10,000; Landoni 2015; Moen 2004). Although rare, this complication can be devastating, with more than 75% of patients who experience it suffering permanent neurological damage. This potential increase in complications could however be justified if epidural analgesia would reduce postoperative mortality. The number of participants included in our review is clearly insufficient to justify any statement on the effects of epidural analgesia on mortality at one year. Collecting data for a large randomized controlled trial on epidural analgesia is difficult, if possible at all (Choi 2009). Therefore, large well-designed retrospective trials evaluating potential differences in mortality between epidural analgesia and systemic analgesia at one year would be useful (Analysis 1.3).

Trials comparing superficial regional anaesthetic techniques versus systemic analgesia for postoperative pain, risk of respiratory depression, myocardial infarction, arrhythmia, and duration of tracheal intubation could be interesting (Horlocker 2018; Nagaraja 2018; Tsui 2018). As opposed to deep blocks (non-compressible sites), superficial blocks offer the advantage of being performed at a compressible site, thus potentially limiting the consequences of inadvertent vascular puncture in heparinized patients. Erector

spinae blocks might be one of these "superficial blocks" deserving further exploration (Nagaraja 2018; Tsui 2018).

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aguero-Martinez 2012

Methods	Parallel RCT Ethics committee: approved by the institutional ethics committee Informed consents: written informed consents obtained Site: Surgical-Clinic Hermanos Ameijeiras Hospital, Cuba, Havana Setting: university hospital Dates of data collection: between September 2008 and March 2010 Funding: departmental Registration: RPCEC00000131 2012
Participants	Adults undergoing off-pump CABG; mean age: 60.2; sex distribution: 11 females and 49 males **Inclusion criteria** 1. No previous cardiac surgery 2. LVEF > 45% 3. No intra-aortic balloon pump support 4. Dysrhythmias or neurological disease 5. Urine output > 0.5 mL/kg and creatinine < 132 mmol/L 6. Normal chest x-ray **Exclusion criteria** 1. Not consenting 2. Absolute contraindication to regional anaesthesia 3. Myocardial infarction within the last 30 days 4. Inotropic drug

Aguero-Martinez 2012 *(Continued)*

5. Heart failure
6. Pulmonary hypertension or chronic obstructive lung disease

Interventions	**Intervention** 1. Single injection epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Premedication: IV midazolam 0.05 mg/kg Induction: midazolam, fentanyl, lidocaine, and atracurium Maintenance: propofol, isoflurane, and atracurium Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of in-hospital pulmonary complications (respiratory insufficiency) 4. Risk of atrial fibrillation or atrial flutter during surgery 5. Pain scores 6. Haemodynamic variables **Others** 1. Complications related to regional anaesthesia 2. ICU length of stay 3. Hospital length of stay 4. Costs
Notes	Correspondence: information received from study authors Conflict of interest: no conflict of interest DOI: n/a The trial also contains a third group with intrathecal analgesia not retained in the review

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized with a computer-generated table
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "patients were not blinded"
Blinding of outcome assessment (detection bias)	Low risk	Quote: "blinded"

Aguero-Martinez 2012 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	No failed epidural reported
Other bias	Unclear risk	The group given systemic analgesia included more aged participants

Bach 2002

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: University of Saarland, Homburg/Saarland, Germany Setting: university hospital Dates of data collection: unspecified Funding: supported in part by the industry Registration: unspecified
Participants	40 participants: mean age 63.0 years; sex distribution: 12 females and 28 males **Inclusion criteria** 1. Patients scheduled for elective coronary artery bypass grafting surgery **Exclusion criteria** 1. Impaired coagulation 2. Allergies to local anaesthetics 3. Corticoid medication 4. Preoperative signs of infection 5. Renal or liver failure 6. Diabetes mellitus 7. Impaired left ventricular function (LVEF < 50%)
Interventions	**Intervention** 1. Epidural analgesia (N = 13) **Comparator** 1. Systemic analgesia (N = 27) Premedication: 1 mg of flunitrazepam orally on the day of surgery Induction: fentanyl 10 mcg/kg, midazolam 40 mcg/kg, etomidate 0.15 mg/kg, and pancuronium 0.1 mg/kg Maintenance: fentanyl/midazolam infusion (10/75 mcg/kg/h) and pancuronium

Bach 2002 *(Continued)*

	Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Haemodynamic variables **Others** 1. Inflammatory response 2. Splanchnic perfusion
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: supported in part by the industry DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "drawing lots"
Allocation concealment (selection bias)	Unclear risk	Assigned the day before surgery; "randomizing box' contained 20 lots of each group"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant died at 8 hours after surgery, as included in the review
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Control group consisted of 27 participants; 13 of them received a dopexamine infusion Supported in part by the industry

Bakhtiary 2007

Methods	Parallel RCT Ethics committee: approved by the institutional review board Informed consents: written informed consents obtained Site: Johann Wolfgang Goethe University Hospital, Main, Germany

Bakhtiary 2007 *(Continued)*

	Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: not reported
Participants	132 participants; mean age 65 years; sex distribution: 20 females and 112 males **Inclusion criteria** 1. Patients with symptomatic coronary artery disease **Exclusion criteria** 1. History of atrial arrhythmias 2. Undergoing emergency operations 3. Requiring intraoperative inotropic support
Interventions	**Intervention** 1. TEA (N = 66) **Comparator** 1. Systemic analgesia (N = 66) Premedication: oral midazolam 7.5 mg Induction: propofol, remifentanil, and cisatracurium Maintenance: propofol, remifentanil, and cisatracurium Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of atrial fibrillation or atrial flutter during surgery 4. Haemodynamic variables **Other** 1. Catecholamine blood concentrations
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: 10.1016/j.jtcvs.2007.03.043

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized to receive either GA or combined GATEA
Allocation concealment (selection bias)	Unclear risk	Not reported

Bakhtiary 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No failed epidural reported Groups had similar demographic data

Barrington 2005

Methods	Parallel randomized controlled trial Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: St. Vincent's Hospital, Melbourne, Australia Setting: university hospital Dates of data collection: from December 1999 to March 2002 Funding: grants from the Australian Society of Anaesthetists and the Australian and New Zealand College of Anaesthetists Registration: unspecified
Participants	120 participants scheduled for elective coronary artery bypass grafting surgery; mean age 62.5 years; sex distribution: 16 females and 104 males **Inclusion criteria** 1. Patients scheduled for elective CABG surgery (using cardiopulmonary bypass (CPB)) were eligible **Exclusion criteria** 1. Emergency or repeat CABG surgery 2. Combined valve and CABG surgery 3. Aspirin ingestion within 6 days of surgery 4. Platelet count 150 × 10^9/L 5. International normalized ratio 1.1 6. Active neurological disease 7. Cutaneous disorders at the epidural insertion site
Interventions	**Intervention** 1. Epidural analgesia (N = 60)

Barrington 2005 *(Continued)*

	Comparator 1. Systemic analgesia (N = 60) Premedication: temazepam, ranitidine, and morphine Induction: midazolam, fentanyl, propofol, and rocuronium Maintenance: propofol Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications 4. Risk of atrial fibrillation or atrial flutter 5. Risk of neurological complications (cerebrovascular accident) 6. Tracheal extubation 7. Pain scores 8. Haemodynamic variables **Others** 1. Arterial blood PaO_2 and $PaCO_2$
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: 10.1213/01.ANE.0000146437.88485.47

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Patients were randomized the day before surgery to 2 groups. The random allocation sequence was computer-generated in permuted blocks of 4 and was enclosed in sequentially numbered opaque sealed envelopes
Allocation concealment (selection bias)	Low risk	Opaque sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Twelve-lead ECGs were recorded before surgery and on postoperative days 1 and 5 and were assessed by 2 observers blinded to group allocation and postoperative clinical course. No mention of blinding for any other outcome
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up. Two participants with failed epidural were kept in the analysis
Selective reporting (reporting bias)	Low risk	All prespecified outcomes were reported

Barrington 2005 *(Continued)*

Other bias	Unclear risk	All participants were included in the intention-to-treat analysis. Prevalence of cerebrovascular and peripheral vascular disease was more frequent in the epidural group

Bektas 2015

Methods	Parallel RCT Ethics committee: approved by the Turkey High Education and Research Hospital Ethics Committee Informed consents: written informed consents obtained Site: Turkiye Yuksek Ihtisas Education and Research Hospital, Ankara, Turkey Setting: university hospital Dates of data collection: between 15 February 2009 and 10 August 2011 Funding: departmental/institutional Registration: not registered
Participants	34 participants; mean age: 55 years; sex distribution: 10 females and 24 males **Inclusion criteria** 1. ASA II to III 2. Ejection fraction > 50% 3. Not previously undergone CABG 4. Did not have any contraindications for epidural anaesthesia 5. Scheduled for elective CABG **Exclusion criteria** 1. Contraindication for epidural catheter 2. Abnormal coagulation parameters (APTT > 40 s, INR > 1.25, fibrinogen concentration < 1 g/L) 3. Renal or hepatic failure 4. Local anaesthetic or opioid allergy
Interventions	**Intervention** 1. TEA (N = 17) **Comparator** 1. Systemic analgesia (N =17) Premedication: midazolam Induction: fentanyl, midazolam, and rocuronium Maintenance: fentanyl, midazolam, and rocuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of neurological complications (epidural haematoma)

Bektas 2015 *(Continued)*

	4. Pain scores 5. Haemodynamic variables **Others** 1. Rescue analgesia
Notes	Correspondence: information received from study authors Conflict of interest: "the authors declare that there is no conflict of interests regarding the publication of this paper" DOI: org/10.1155/2015/658678

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote. "randomly divided into 2 groups"
Allocation concealment (selection bias)	Unclear risk	Quote. "patient selection, data collection and evaluation were performed by separate workers unaware of each other"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Quote: "patient selection, data collection and evaluation were performed by separate workers unaware of each other"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "outcomes were evaluated by another doctor"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural Groups had similar demographic data

Berendes 2003

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: Munster, Germany Setting: university hospital Dates of data collection: from 1 February 2000 through 31 August 2000

Berendes 2003 *(Continued)*

	Funding: supported in part by grant Be-1-1-1/97-5 to the Faculty of Medicine, Westfalische Wilhelms-Universitat Munster, Innovative Medizinische Forschung, Munster, Germany Registration: unspecified
Participants	73 participants: mean age 60.0 years; sex distribution: 20 females and 53 males **Inclusion criteria** 1. Patients scheduled for CABG who had left ventricular ejection fraction ≥ 50% **Exclusion criteria** 1. Pre-existing endocrinological disease 2. Renal insufficiency 3. Coagulation disorders 4. Right and/or left ventricular dysfunction 5. Concomitant disorders of heart valves 6. Having undergone cardiac surgical procedures 7. Acute myocardial infarction 8. Heart failure
Interventions	**Intervention** 1. Epidural analgesia (N = 36) **Comparator** 1. Systemic analgesia (N = 37) Induction: midazolam, sufentanil, and pancuronium Maintenance: propofol and sufentanil Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications **Others** 1. Left ventricular function 2. Brain and atrial natriuretic peptides
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: 10.1001/archsurg.138.12.1283

Risk of bias

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

Berendes 2003 *(Continued)*

Allocation concealment (selection bias)	Low risk	Administered through a sequential opaque envelope technique
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "blinded for primary outcome measure: echographic examination for global and regional myocardial function
Incomplete outcome data (attrition bias) All outcomes	Low risk	No lost to follow-up
Selective reporting (reporting bias)	Low risk	All pre-specified outcomes reported
Other bias	Low risk	No failed epidural Groups had similar demographic characteristics

Brix-Christensen 1998

Methods	Parallel RCT Ethics committee: approved by the Regional Ethical Committee on Human Research Informed consents: informed consents were obtained from each patient Site: Aarhus University Hospital, 8000 Aarhus C, Denmark Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	16 participants; mean age: 58.5 years; sex distribution: not reported **Inclusion criteria** 1. Elective CABG **Exclusion criteria** 1. Diabetes mellitus 2. Cancer
Interventions	**Intervention** 1. Epidural analgesia (N = 8) **Comparator** 1. Systemic analgesia (N = 8)

Brix-Christensen 1998 *(Continued)*

	Premedication: morphine, scopolamine, and diazepam Induction: midazolam, fentanyl, and pancuronium Maintenance: midazolam, enflurane, and fentanyl (group systemic analgesia only) or epidural analgesia Surgery: CABG with CPB using a hollow fibre oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of neurological complications (epidural hematoma): intraoperative and postoperative course was uneventful for all participants **Others** 1. Inflammatory response to surgery
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomly allocated to 2 groups; no details were provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural mentioned Groups had similar demographic data

Caputo 2011

Methods	Parallel RCT

Caputo 2011 *(Continued)*

	Ethics committee: approved by the Central and South Bristol Research Ethics Committee (registration number E5471) Informed consents: written informed consents were obtained Site: Yale School of Medicine, New Haven, CT, USA; and University of Bristol, Bristol, UK; and Clinica Montevergine, Mercogliano, Italy Setting: university hospital Dates of data collection: August 2003 to November 2007 Funding: funded by the British Heart Foundation Registration: unspecified
Participants	226 participants; mean age 65.7 years; sex distribution: 22 females and 204 males **Inclusion criteria** 1. Adult (≥ 16 years) participants 2. Undergoing non-emergent off-pump CABG **Exclusion criteria** 1. Intravenous heparin, warfarin, or clopidogrel at the time of surgery 2. Suffered from bleeding diathesis
Interventions	**Intervention** 1. Epidural analgesia (N = 109) **Comparator** 1. Systemic analgesia (N = 117) Premedication: benzodiazepines Induction: fentanyl, propofol, and pancuronium or vecuronium Maintenance: isoflurane or propofol Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications 4. Risk of atrial fibrillation or atrial flutter 5. Risk of neurological complications 6. Pain scores 7. Haemodynamic variables **Others** 1. Length of hospital stay
Notes	Correspondence: information received from study authors Conflict of interest: none declared DOI: 10.1093/icvts/ivt001

Caputo 2011 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized treatment allocations were generated using Stata version 8. Participants were stratified by the consultant team via 1:1 allocation using blocks of varying sizes
Allocation concealment (selection bias)	Low risk	Allocation details were concealed in sequentially numbered, opaque sealed envelopes. These were prepared by the clinical trials and evaluation unit
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open"
Incomplete outcome data (attrition bias) All outcomes	Low risk	All randomized participants were included in the analysis No participants withdrew from the trial
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Unclear risk	Intention-to-treat Epidural anaesthesia: 18 not performed and 9 failed epidural Systemic analgesia: 3 participants received epidural analgesia Groups had similar demographic characteristics, except that lung disease/chronic obstructive airways disease was more common in the epidural group (23% vs 12%)

Celik 2015

Methods	Parallel RCT Ethics committee: approved by the hospital scientific committee Informed consents: obtained Site: Kardiyovasküler Cerrahi Kliniği, İstanbul, Türkiye Setting: university hospital Dates of data collection: 2009 Funding: institutional/departmental Registration: not registered
Participants	40 participants; mean age; 58 years; sex distribution: 12 females and 28 males **Incusion criteria**

Celik 2015 *(Continued)*

1. ASA III adults undergoing elective CABG
2. Age < 70 years

Exclusion criteria

1. Use of steroids
2. Coagulopathy
3. Non-steroid anti-inflammatory drugs (NSAIDs) or anticoagulant drugs
4. Left ventricular ejection fraction (LVEF) < 40%
5. Cervicothoracic arthritis
6. Concomitant valvular heart disease
7. Chronic renal failure
8. Endocrine system insufficiency
9. Morbid obesity (body mass index (BMI) > 35)

Interventions	**Intervention** 1. Epidural analgesia (N = 20) **Comparator** 1. Systemic analgesia (N = 20) Induction: fentanyl, midazolam, and pancuronium Maintenance: fentanyl and propofol Surgery: CABG, classified as with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction (postoperative troponin I and CK-MB values) 3. Risk of atrial fibrillation or atrial flutter (numbers in Table taken as numbers of participants) 4. Tracheal extubation 5. Pain scores after surgery 6. Haemodynamic variables **Others** 1. Supplemental analgesia 2. ICU length of stay 3. Hospital length of stay 4. Postoperative blood losses 5. Intraoperative and postoperative blood transfusions
Notes	Conflict of interest: no conflict of interest Correspondence: information received from study authors DOI: 10.4274/haseki.2163

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Prospectively randomized; no details

Celik 2015 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Quote: "only the anaesthesiologist knew the treatment group"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was not blinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the study was not blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results provided
Other bias	Low risk	Analysed in intention-to-treat Groups well balanced

Cheng-Wei 2017

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Far Eastern Memorial Hospital, New Taipei City, Taiwan Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	37 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Undergoing minimally invasive cardiac surgery **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 18) **Comparator** 1. Wound local anaesthetic infusion plus IV PCA (N = 19) Induction and maintenance: not reported

Cheng-Wei 2017 *(Continued)*

	Surgery: off-pump CABG or valve surgery
Outcomes	**Relevant to this review** 1. Tracheal extubation 2. Pain scores **Others** 1. ICU length of stay 2. Hospital length of stay
Notes	Conflict of interest: not reported Correspondence: email sent 16 March 2018; no reply DOI: n/a Conference abstract, limited information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly allocated"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Conference abstract; limited details provided
Selective reporting (reporting bias)	Low risk	Conference abstract; limited details provided
Other bias	Unclear risk	Conference abstract; limited details provided

de Vries 2002

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: obtained Site: Groningen, The Netherlands Setting: university hospital

de Vries 2002 *(Continued)*

	Dates of data collection: January 1996 to January 1999 Funding: departmental/institutional Registration: not registered
Participants	90 participants, for the 2 groups included in this review: mean age: 58.5 years; sex distribution: 18 females and 42 males **Inclusion criteria** 1. Scheduled for elective minimally invasive direct single coronary artery bypass surgery through anterolateral thoracotomy **Exclusion criteria** 1. Requiring emergency surgery 2. Patients with known coagulation disorders, including intravenous heparin therapy and treatment with low-molecular-weight heparin 12 hours before epidural puncture
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia and immediate tracheal extubation (N = 30) Induction: midazolam and sufentanil Maintenance: sufentanil and isoflurane or propofol Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Respiratory depression (pneumonia) 4. Pain scores 5. Haemodynamic variables **Others** 1. Length of hospital stay
Notes	Correspondence: information received from study authors Conflict of interest: no conflict of interest DOI: 10.1053/jcan.2002.29645 The trial includes a third group not retained for this review: high opoid dose and mandatory postoperative mechanical ventilation for a specific duration

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "90 patients were randomly divided into 3 groups"; "computer-generated table"

de Vries 2002 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Five participants were excluded from analysis: 3 for surgical reasons and 2 because the epidural technique failed
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Low risk	Not in intention-to-treat Groups had similar demographic data

Dohle 2001

Methods	Parallel RCT Ethics committee: approved Informed consents: obtained Site: New Delhi, India Setting: university hospital Dates of data collection: not reported Funding: unspecified Registration: unspecified
Participants	41 participants, for participants included in the analysis: mean age: 56 years; sex distribution: 7 females and 33 males **Inclusion criteria** 1. Consenting patients undergoing minimally invasive direct coronary artery bypass surgery **Exclusion criteria** 1. Ejection fraction 35%, with an anomaly of the vertebral column 2. Receiving heparin 3. Receiving antiplatelet medications within the last week 4. With significant respiratory disease 5. Requiring inotropic support or intra-aortic balloon counterpulsation
Interventions	**Intervention** 1. Thoracic epidural analgesia (N = 21)

Dohle 2001 *(Continued)*

	Comparator 1. Paravertebral blockade (N = 20) Premedication: lorazepam and morphine Induction and maintenance: midazolam, fentanyl (total dose 5 mcg/kg), nitrous oxide, isoflurane, and vecuronium Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Tracheal extubation 3. Risk of serious neurological complications from epidural analgesia 4. Pain scores 5. Haemodynamic variables **Others** 1. Respiratory function
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: 10.1053/jcan.2001.23271

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized study"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "an independent observer who was blinded to the analgesia technique recorded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One failed epidural
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Not in intention-to-treat Groups had similar demographic data

El-Baz 1987

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Chicago, IL, USA Setting: university hospital Dates of data collection: not reported Funding: unspecified Registration: unspecified
Participants	60 participants: mean age: 59 years; sex distribution: not reported **Inclusion criteria** 1. Patients, aged 34 to 76 years 2. After CABG (1 to 4 grafts) **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Induction: thiopental and succinylcholine Maintenance: nitrous oxide, halothane, and pancuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Pain scores 3. Haemodynamic variables **Others** 1. Rescue analgesia 2. Respiratory function 3. Stress markers
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a
Risk of bias	

El-Baz 1987 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote. "patients were randomly divided into two equal groups of 30 patients"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural mentioned Groups had similar demographic characteristics

El-Morsy 2012

Methods	Parallel RCT Ethics committee: approved by the institutional ethics committee Informed consents: written informed consents obtained Site: Mansoura University, Egypt Setting: university hospital Dates of data collection: unspecified Funding: departmental resources Registration: unspecified
Participants	50 participants; mean age: 69 years; sex distribution: 5 females and 45 males **Inclusion criteria** 1. Aged 65 to 75 years; ASA II and III scheduled for elective CABG **Exclusion criteria** 1. Local infection at the site of puncture or septicaemia 2. Pre-existing coagulopathy 3. Redo open heart surgery 4. Endocarditis

El-Morsy 2012 *(Continued)*

5. Neurological disorder
6. Hepatic disease
7. Pulmonary disease
8. Heart failure

Interventions	**Intervention** 1. Epidural analgesia (N = 25) **Comparator** 1. Systemic analgesia (N = 25) Premedication with midazolam and tramadol Induction: fentanyl, thiopental, and pancuronium Maintenance: sevoflurane, fentanyl, and pancuronium Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Respiratory depression (lower $PaCO_2$ values, better forced vital capacity and forced expiratory volume in 1 second for TEA participants as measured up to 24 hours) 2. Risk of neurological complications (mentioned as recorded in the method sections; none reported) 3. Tracheal extubation 4. Pain scores 5. Haemodynamic variables **Others** 1. Analgesic requirements 2. Pulmonary function tests 3. ICU length of stay 4. Hospital length of stay
Notes	Conflict of interest: none declared Correspondence: email sent 16 March 2018; no reply DOI: 10.4103/1658-354X.93048

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly enrolled (sealed envelope)
Allocation concealment (selection bias)	Low risk	Participants were randomly enrolled (sealed envelope)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias)	Unclear risk	Not mentioned

El-Morsy 2012 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural analgesia mentioned Participants in both groups were comparable with regard to demographic data, number of grafts, and time of surgery

El-Shora 2018

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: Egypt Setting: 2 centres from university hospital Dates of data collection: from March 2016 to March 2017 Funding: departmental/institutional Registration: PACTR201603001502110 (www.pactr.org).
Participants	145 participants: mean age 43.5 years; sex distribution: 68 females and 77 males **Inclusion criteria** 1. Patients who underwent elective cardiac surgery for valvular or coronary artery disease through full median sternotomy as a primary procedure **Exclusion criteria** 1. Refused to participate in the research 2. With preoperative coagulopathy 3. Severe organ insufficiency (e.g. serum creatinine > 3 mg and/or liver dysfunction) 4. Needed reoperation within 24 hours
Interventions	**Intervention** 1. Epidural analgesia (N = 75) **Comparator** 1. Bilateral paravertebral (N = 70) Induction: midazolam, fentanyl, propofol, lidocaine, and pancuronium Maintenance: isoflurane and pancuronium Surgery: valve or CABG with CPB
Outcomes	**Relevant to this review**

El-Shora 2018 *(Continued)*

1. Risk of mortality
2. Risk of neurological complications
3. Pain scores
4. Tracheal extubation

Others

1. Urinary retention
2. Vomiting
3. Acute kidney injury
4. Re-exploration for bleeding
5. ICU length of stay
6. Hospital length of stay

Notes	Correspondence: email sent 18 November 2018; study authors asked us to extract the information from the trial Conflict of interest: none DOI: 10.1055/s-0038-1668496

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Blocked stratified randomization was used to assign participants to 2 groups via 1:1 allocation Randomization sequence was generated randomly online using https://www.randomizer.org/; block size ranged from 4 to 6 participants. Randomization was stratified by participating centres
Allocation concealment (selection bias)	Low risk	On the day before surgery, participants were sorted to 1 of the 2 groups based on blocked single-blinded randomization
Blinding of participants and personnel (performance bias) All outcomes	High risk	Single-blinded
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Single-blinded Cardiac anaesthesia specialist, not participating in data collection or patient follow-up, performed the block designated for each participant (either bilateral thoracic paravertebral or thoracic epidural block) A nurse collected the data without pre-knowledge of participants' assigned groups
Incomplete outcome data (attrition bias) All outcomes	Low risk	5 participants were excluded from the paravertebral group: 3 for in-hospital mortality and 2 for reoperation within 24 hours One participant in the epidural group died in hospital, but data for this participant were included in the analysis
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Low risk	Groups well balanced

El-Shora 2018 *(Continued)*

	"intention-to-treat" principle

Fawcett 1997

Methods	Parallel RCT Ethics committee: approved by the Local Research Ethics Committee Informed consents: written informed consents obtained Site: St. George's Hospital Medical School, Cranmer Terrace, London, UK, and Queen's Medical Centre, University of Nottigham, Nottingham, UK Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	16 male participants; mean age: 61.5 years; sex distribution: 16 males **Inclusion criteria** 1. Scheduled for elective CABG **Exclusion criteria** 1. Aspirin within 10 days 2. Receiving warfarin or heparin or with abnormal coagulation study results 3. BMI > 30 kg/m^2 4. Neurological disease 5. Poor LVEF 6. Reversible airway obstruction
Interventions	**Intervention** 1. Epidural analgesia (N = 8) **Comparator** 1. Systemic analgesia (N = 8) Premedication: morphine and hyoscine Induction: fentanyl, thiopentone, and suxamethonium Maintenance: nitrous oxide, pancuronium, and midazolam Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Tracheal extubation 2. Pain scores 3. Haemodynamic variables **Others** 1. Catecholamine blood levels

Fawcett 1997 *(Continued)*

	2. Lung function tests
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly assigned"; no details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	No failed epidural Groups well balanced except for CPB time: 107 minutes for TEA vs 78 minutes for no epidural

Fillinger 2002

Methods	Parallel RCT Ethics committee: approved by the Dartmouth College Committee for Protection of Human Subjects (institutional review board) Informed consents: written, informed consents were obtained from all participants Site: Dartmouth-Hitchcock Medical Center, Lebanon; and Dartmouth Medical School, Hanover, NH, USA Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	60 participants; mean age: 62.8 years; sex distribution: 10 females and 50 males

Fillinger 2002 *(Continued)*

	Inclusion criteria 1. Scheduled for elective CABG **Exclusion criteria** 1. Absence of any specific contraindication to the use of heparin or warfarin anticoagulation 2. Pre-existing coagulopathy 3. Infection at insertion site 4. Septicaemia
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Premedication: fentanyl and midazolam Induction: fentanyl, midazolam, thiopental, and pancuronium or vecuronium Maintenance: isoflurane Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of atrial fibrillation or atrial flutter 4. Risk of neurological complications (cerebrovascular accidents) 5. Tracheal extubation 6. Pain scores **Others** 1. Length of hospital stay
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: 10.1053/jcan.2002.29639

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "computerized randomization" (as classified by previous review authors)
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "nonblinded"

Fillinger 2002 *(Continued)*

Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "nonblinded" Except for ECG: recordings were reviewed by one of the study authors and a cardiologist, both of whom were blinded to treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	Two participants in the epidural group were withdrawn from treatment in the operating room: 1 because of inability to place the catheter and 1 because of intravascular migration of an initially functioning catheter Both were included in subsequent analyses as intention-to-treat Groups had similar demographic data, except that 11 participants in the epidural group had a history of myocardial infarction within the 3 months immediately preceding surgery compared with 2 participants in the systemic analgesia group (P < 0.005)

Greisen 2012

Methods	Parallel RCT Ethics committee: approved by the regional ethics committee and the Danish Medicines Agency Informed consents: written as well as oral information was obtained Site: Department of Anaesthesiology and Intensive Care, Aarhus University Hospital-Skejby, Denmark Setting: university hospital Dates of data collection: from 1 March 2007 to 31 March 2009 Funding: departmental resources Registration: EudraCT 2005-000617-35
Participants	42 participants; mean age: 71.4 years; sex distribution: 17 females and 25 males **Inclusion criteria** 1. Aged 65 to 80; scheduled for elective CABG, aortic valve replacement, or combined surgery **Exclusion criteria** 1. Ejection fraction < 0.3 2. Myocardial infarction within last 4 weeks 3. Diagnosed diabetes 4. Severe pulmonary or arterial hypertension 5. Contraindication for epidural catheter 6. Ongoing antiplatelet therapy 7. Without preoperative optimal echocardiographic imaging
Interventions	**Intervention**

Greisen 2012 *(Continued)*

	1. Epidural analgesia (N = 21) **Comparator** 1. Systemic analgesia (N = 21) Premedication: benzodiazepine and paracetamol Maintenance: propofol or sevoflurane Surgery: CABG or valve replacement or both with CPB
Outcomes	**Relevant to this review** 1. Risk of neurological complications 2. Pain scores **Others** 1. Blood glucose
Notes	Conflict of interest: none Correspondence: letter sent 16 March 2018; no reply DOI: 10.1111/j.1399-6576.2012.02731.x

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomized by standard envelope method
Allocation concealment (selection bias)	Low risk	Randomized by standard envelope method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No participants had displaced catheters when they arrived for surgery All participants in both groups completed the study
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Low risk	All participants who intended to receive an epidural catheter had an epidural catheter successfully placed Groups well balanced

Gurses 2013

Methods	Parallel RCT Ethics committee: approved by the Ethics Committee of the Medical School, Pamukkale University Informed consents: written informed consent was received from each individual before entry into the study Site: School of Medicine, Pamukkale University, Denizli, Turkey Setting: university hospital Dates of data collection: between July 2010 and January 2011 Funding: funded solely by the institution of the authors Registration: unspecified
Participants	64 participants; mean age: 62.3; sex distribution: 18 females and 46 males **Inclusion criteria** 1. ASA II or III 2. Aged 40 to 79 years 3. Scheduled for elective CABG **Exclusion criteria** 1. Hypersensitivity towards any of the chemicals to be used 2. Contraindication for epidural anaesthesia (dermal infection, nervous system disease, severe hypovolaemia, high intracranial pressure, severe aorta stenosis, severe mitral stenosis, etc.) 3. History of vertebral surgery 4. Cervical or thoracic vertebral arthritis 5. Morbid obesity (BMI > 35), coagulopathy, < 40% ejection fraction, and preoperative inotropic agent usage
Interventions	**Intervention** 1. Epidural analgesia (N = 32) **Comparator** 1. Systemic analgesia (N = 32) Induction: thiopental and rocuronium Maintenance: sevoflurane and rocuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of neurological complications (epidural haematoma) 2. Risk of atrial fibrillation or atrial flutter 3. Tracheal extubation 4. Haemodynamic variables **Others** 1. Analgesic requirements 2. Blood transfusion requirement 3. ICU length of stay

Gurses 2013 *(Continued)*

	4. Hospital length of stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: no conflict of interest DOI: 10.12659/MSM.883861

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned to study groups by the closed envelope method
Allocation concealment (selection bias)	Low risk	Randomly assigned to study groups by the closed envelope method
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results provided
Other bias	Low risk	Study groups were similar in terms of demographic variables

Hansdottir 2006

Methods	Parallel RCT Ethics committee: the Human Ethics Committee of the Sahlgrenska Academy, Goteborg University, Goteborg, Sweden, approved the study protocol Informed consents: all participants gave written informed consent Site: Goteberg, Sweden Setting: university hospital Dates of data collection: from 1 April 2002 to 31 December 2003 Funding: support was provided solely from institutional and/or departmental sources Registration: unspecified
Participants	113 participants; mean age: 66.5 years; sex distribution: 37 females and 76 males **Inclusion criteria**

Hansdottir 2006 *(Continued)*

1. Patients undergoing elective cardiac surgery (CABG, cardiac valve procedures, combined CABG and valve procedures, or the Maze procedure, with or without CABG)

Exclusion criteria

1. Contraindications to epidural anaesthesia
2. Abnormal coagulation tests (i.e. partial thromboplastin time > 45 s or prothrombin time (international normalized ratio) > 1.5 or platelet count < 80,000)
3. Recent (1 week) treatment with thrombolytic or potent antiplatelet drugs (streptokinase, alteplase, clopidogrel, abciximab, tirofiban, integrelin)

Aspirin treatment was not considered a contraindication to placement of a thoracic epidural catheter

Interventions	**Intervention** 1. Epidural analgesia (N = 55) **Comparator** 1. Systemic analgesia (N = 55) Premedication: midazolam Induction and maintenance: propofol, remifentanil, and atracurium Surgery: CABG, valve procedures, or both with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Myocardial infarction 2. Risk of atrial fibrillation or atrial flutter 3. Risk of neurological complications: cerebrovascular accident 4. Pain scores **Others** 1. Sedation scores 2. Lung function 3. Quality recovery score 4. Length of hospital stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned the day before surgery to 1 of 2 regimens
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	The infusion bag (250 mL) of the patient-controlled analgesia pump was changed only once during the postoperative treatment period (72 h) by the nursing team, which was neither blinded to treatment nor involved in assessment of patients

Hansdottir 2006 *(Continued)*

		The decision to allow hospital discharge was made by the surgical team not blinded to treatment
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Atelectasis was defined as new area(s) of lobar or sublobar atelectatic consolidation with an air bronchogram by a radiologist blinded to treatment Evaluation of quality of recovery score, level of mobilization, pain, degree of sedation, lung function, and eligibility for hospital discharge was performed between 1:00 and 3:00 PM each day by either of two investigators. These investigators were blinded to the assigned treatment The blinded investigators were not involved in nursing of the participants Less than 5% of epidural participants revealed by mistake to the blinded observer the presence of the epidural catheter
Incomplete outcome data (attrition bias) All outcomes	Low risk	113 participants were randomized, 110 participants received allocated treatment, and 97 participants were eventually analysed
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Unclear risk	Three participants were excluded because of inability to place the epidural catheter. In 1 of these participants, the catheter was positioned intradurally, and another participant did not co-operate. A malfunctioning epidural catheter was considered in 7 participants after extubation. Three of these participants had the epidural catheter replaced in the ICU, and 4 were treated with intravenous patient-controlled analgesia with morphine These 7 participants were analysed on an intention-to-treat basis Groups had similar demographic data, except for a higher incidence of off-pump CABG in the epidural group and a longer cardiopulmonary bypass time in the systemic analgesia group

Heijmans 2007

Methods	Parallel RCT Ethics committee: the study was approved by the authors' hospital's Medical Ethics Committee Informed consents: written informed consents were obtained Site: Maastricht, The Netherlands Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	60 participants; mean age: 60 years; sex distribution: not reported **Inclusion criteria** 1. Undergoing elective cardiac surgery **Exclusion criteria**

Heijmans 2007 *(Continued)*

1. Left ventricular ejection fraction < 25%
2. Hypothermic circulatory arrest
3. Recent myocardial infarction
4. Preoperative inotropic or intra-aortic balloon pump metabolic
5. Neurological diseases

Interventions	**Intervention** 1. Epidural analgesia (N = 15) **Comparator** 1. Systemic analgesia (N = 45) Premedication: midazolam Induction and maintenance: propofol, remifentanil, or alfentanil and pancuronium Surgery; CABG with CPB using a hollow-fibre membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of atrial fibrillation or atrial flutter 3. Risk of neurological complications (cerebrovascular accident) **Others** 1. Inflammation markers
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: 10.1053/j.jvca.2007.02.008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "60 patients scheduled to undergo coronary artery bypass surgery were randomized"; no details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was blinded for the opioid infusion, except in the thoracic epidural group"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the study was blinded for the opioid infusion, except in the thoracic epidural group"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned

Heijmans 2007 *(Continued)*

Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Low risk	No failed epidural mentioned Groups had similar demographic data

Huh 2004

Methods	Parallel RCT Ethics committee: approved by the clinical committee Informed consents: unspecified Site: Ulsan University College of Medicine, Asan Medical Center, Seoul, Korea Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	56 participants; mean age: 57.8; sex distribution: 13 females and 43 males **Inclusion criteria** 1. ASA II or III adults 2. Undergoing open heart surgery **Exclusion criteria** 1. Hypoxaemia 2. Hypercapnia 3. Chronic pain 4. Use of pain medication 5. History of coagulation disorders 6. Age 70 years or older 7. Left ventricle ejection fraction ≤ 40% or inability to communicate
Interventions	**Intervention** 1. Epidural analgesia (N = 27) **Comparator** 1. Systemic analgesia (N = 29) Premedication: midazolam Induction: midazolam, fentanyl, and vecuronium Maintenance: vecuronium Surgery: various cardiac surgery with CPB
Outcomes	**Relevant to this review**

Huh 2004 *(Continued)*

1. Risk of neurological complications (epidural haematoma)
2. Tracheal extubation
3. Pain scores

Others

1. Nausea and vomiting
2. Pulmonary function tests
3. Patient satisfaction on a score from 1 (very good) to 5 (enough to regret the procedure)

Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: 10.4097/kjae.2004.47.4.521

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized; no details
Allocation concealment (selection bias)	Unclear risk	Not mentioned
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Pain scores were evaluated by a blinded observer
Incomplete outcome data (attrition bias) All outcomes	Low risk	60 participants enrolled, 27 and 29 analysed for TEA and control groups, respectively
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Groups well balanced

Hutchenson 2006

Methods	Parallel RCT Ethics committee: approved by the Human Review Committee of the University of Goettingen (N* 15 II 94) Informed consents: written informed consent obtained Site: University of Goettingen, Germany, and Department of Anaesthesia and Perioperative Medicine, Medical University Charleston, SC, USA Setting: university hospital

Hutchenson 2006 *(Continued)*

	Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	20 participants: mean age 61.0; sex distribution 20 males **Inclusion criteria** 1. ASA II or III male participants 2. Scheduled for coronary artery bypass **Exclusion criteria** 1. Aged over 70 years 2. History of congestive heart failure 3. Ejection fraction < 40% 4. Valvular heart disease 5. Liver disease 6. Metabolic disorders 7. Platelet count < 120,000 8. Partial thromboplastin time > 40 s and thrombin time > 22 s 9. Baseline neurological deficits 10. Infection at the site of epidural insertion
Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. Systemic analgesia (N = 10) Premedication: flunitrazepam 2 mg orally Induction: sufentanil, midazolam, and pancuronium Maintenance: midazolam, sufentanil Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of neurological complications (epidural haematoma) 3. Haemodynamic variables **Others** 1. Blood gas 2. Myocardial blood flow
Notes	Correspondence: email sent 16 March 2018; no reply Email: riekeh@musc.edu Conflict of interest: none DOI: n/a

Risk of bias

Hutchenson 2006 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly assigned (envelope method)
Allocation concealment (selection bias)	Low risk	Randomly assigned (envelope method)
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Jakobsen 2012

Methods	Parallel RCT Ethics committee approval: approved by the Central Denmark Region Committee on Biomedical Research Ethics and the Danish Medicine Agency Informed consents: written informed consents were obtained from all participants Site: Aarhus University Hospital, Skejby, Aarhus, Denmark Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: Eudra CT 2005-000617-35
Participants	60 participants; mean age: 71.3 years; sex distribution: 21 females and 39 males **Inclusion criteria** 1. Low- to moderate-risk participants between the ages of 65 and 80 years scheduled for CABG with or without AVR **Exclusion criteria** 1. Ejection fraction < 0.3 2. Myocardial infarction within the last 4 weeks 3. Diabetes

Jakobsen 2012 *(Continued)*

4. Severe pulmonary or arterial hypertension
5. Contraindication for TEA
6. No preoperative optimal echocardiographic imaging

Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Induction and maintenance: propofol or sevoflurane, sufentanil, and rocuronium Surgery: CABG, valve procedure, or both with CPB, using a hollow-fibre membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of neurological complication: cerebrovascular accident 4. Time to tracheal extubation 5. Haemodynamic variables **Others** 1. Rescue analgesics 2. Acute kidney injury: renal function expressed as changes in s-creatinine: fewer TEA patients (13.3% vs 36.7%; P = 0.074, Chi^2 test) developed acute kidney injury 3. ICU length of stay (hours from arrival in the ICU to discharge to the surgical ward) 4. Time to eligible to ICU discharge (predefined scoring system evaluated at regular intervals) 5. Hospital length of stay
Notes	Conflict of interest: study authors declare that they have no competing interests Correspondence: email sent 16 March 2018; no reply DOI: 10.1053/j.jvca.2012.05.007 and 10.1053/j.jvca.2012.05.008

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization by the standard envelope method with blocks of 20 participants was performed immediately before insertion of the epidural catheter the day before surgery
Allocation concealment (selection bias)	Low risk	Randomization by the standard envelope method with blocks of 20 participants was performed immediately before insertion of the epidural catheter the day before surgery
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Jakobsen 2012 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Sixty-three patients were approached; 2 declined, and 1 was excluded because surgery was changed to off-pump CABG surgery
Selective reporting (reporting bias)	Unclear risk	Quote: "there were no significant differences in blood loss, urine output, administration of crystalloids and adverse events (not shown)"
Other bias	Low risk	Groups well balanced for preoperative characteristics One participant in the TEA group did not receive a functional epidural, but because the protocol was based on an intention-to-treat principle, this participant was analysed in the TEA group

Kendall 2004

Methods	Parallel RCT Ethics committee: approved by local research ethics committee Informed consents: obtained Site: Liverpool, UK Setting: university hospital Dates of data collection: not reported Funding: this work was entirely funded by The Cardiothoracic Centre, Thomas Drive, Liverpool, L14 3PE Registration: unspecified
Participants	30 participants: mean age: 64.1 years; sex distribution: 8 females and 22 males **Inclusion criteria** 1. Patients undergoing off-pump coronary artery bypass grafting **Exclusion criteria** 1. Patients undergoing emergency surgery 2. Unstable angina 3. Plasma creatinine values > 160 mmol/L 4. Patients taking anticoagulant therapy 5. Any other contraindication to insertion of a thoracic epidural
Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. Systemic analgesia (N = 20) Premedication: diazepam Induction: etomidate or propofol and fentanyl Maintenance: isoflurane (N = 10) or propofol (N = 10) Surgery: off-pump CABG

Kendall 2004 *(Continued)*

	General anaesthesia: propofol or isoflurane or epidural: isoflurane with bupivacaine
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Tracheal extubation 4. Haemodynamic variables **Other** 1. Return to operating room
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: 10.1111/j.1365-2044.2004.03713.x

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly allocated to 1 of 3 groups, using a shuffled, sealed envelope technique
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "single-blinded"; no sham block mentioned
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "single-blinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "three patients were excluded from the study and further analysis. Their treatment was re-randomized and reallocated, providing 30 complete data sets for analysis"
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Not in intention-to-treat: (quote): "two participants required cardiopulmonary bypass to complete arterial revascularization, one in the isoflurane group and one in the epidural group. Two participants were found to have inadequate postoperative epidural analgesia. One participant in the propofol group had incomplete troponin T data. These participants were excluded from the study and further analysis" Groups had similar demographic characteristics

Kilickan 2006

Methods	Parallel RCT

Kilickan 2006 *(Continued)*

	Ethics committee: approved by the institutional review committee Informed consents: patient consents were obtained Site: Kocaeli University School of Medicine, Kocaeli, Turkey Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	80 participants; mean age: 59.9 years; sex distribution: 16 females and 64 males **Inclusion criteria** 1. Undergoing elective CABG with CPB **Exclusion criteria** 1. Compromised coagulation (thromboplastin time < 80%, prothrombin time > 40 seconds, or platelets < 100 nL)
Interventions	**Intervention** 1. Epidural analgesia with LVEF ≤ 0.4 (N = 20) or > 0.4 (N = 20) **Comparator** 1. Systemic analgesia with LVEF ≤ 0.4 (N = 20) or > 0.4 (N = 20) Premedication: midazolam Induction: midazolam, fentanyl, and vecuronium Maintenance: nitrous oxide, propofol, and fentanyl Suregry: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of atrial fibrillation or atrial flutter 4. Tracheal extubation 5. Pain scores 6. Haemodynamic variables **Other** 1. Right atrial biopsies
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly distributed sealed envelopes
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Kilickan 2006 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural Groups well balanced

Kilickan 2008

Methods	Parallel RCT Ethics committee: approved by the institutional review committee Informed consents: unspecified Site: Istanbul Bilim University School of Medicine, Istanbul, Turkey Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	60 participants: mean age: 61.8 years; sex distribution: 15 females and 45 males **Inclusion criteria** 1. Undergoing elective CABG surgery with CPB **Exclusion criteria** 1. Left ventricular ejection fraction < 0.40 2. Diabetes 3. Active gastropathy disorder 4. Preoperative use of steroids and contraindications to steroid administration 5. Contraindications to the epidural technique (e.g. pre-existing coagulopathy, anticoagulation (i.e. full therapeutic doses of standard or low-molecular-weight heparin, warfarin, thrombolytic drugs or potent antiplatelet drugs)) 6. Systemic or local infection 7. Preoperative signs of infection (white blood cell count > 12 000 µL, body temperature > 38°C, C-reactive protein > 5 mg/dL) 8. Chronic inflammatory disease 9. Treatment with cyclo-oxygenase inhibitors, ticlopidine, or other drugs

Kilickan 2008 *(Continued)*

	10.Drugs inhibiting thrombocyte function within the last 7 days before the operation
Interventions	**Interevention** 1. Epidural analgesia with (N = 15) or without steroids (N = 15) **Comparator** 1. Systemic analgesia with (N = 15) or without steroids (N = 15) Premedication: midazolam Induction: midazolam, fentanyl, and vecuronium Maintenance: nitrous oxide, propofol, and fentanyl Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Tracheal extubation **Other** 1. Hospital length of stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomly allocated; no details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural mentioned Groups well balanced

Kirno 1994

Methods	Parallel RCT Ethics committee: approved Informed consents: obtained Site: Goteberg, Sweden Setting: university hospitals Dates of data collection: unspecified Funding: this work was supported by grants from the Swedish Medical Research Council (No. 08682,09047, and 09720), the Medical Faculty at the University of Goteborg, the Medical Society of Goteborg, and the Swedish Heart-Lung Foundation Registration: unspecified
Participants	20 participants: mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Patients undergoing coronary artery bypass grafting 2. All patients had a history of stable ischaemic heart disease with 2- or 3-vessel coronary artery disease 3. Ejection fraction > 50% **Exclusion criteria** 1. Patients with coexisting valvular anomaly, arrhythmias, or diabetes mellitus
Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. Systemic analgesia (N = 10) Induction: thiopental, pancuronium, and fentanyl Maintenace: nitrous oxide in oxygen and fentanyl Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Haemodynamic variables **Others** 1. Regional myocardial oxygen consumption 2. Myocardial ischaemia 3. Noradrenaline spillover (sympathetic nervous system activation)
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Kirno 1994 *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Participants were randomized to 2 groups; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Unclear risk	No failed epidural reported No details on preoperative groups' demographic data

Kirov 2011

Methods	Parallel RCT Ethics committee: study protocol and informed consent form were approved by the Ethics Committee of Northern State Medical University, Arkhangelsk, Russian Federation Informed consents: written informed consent was obtained from every patient Site: Northern State Medical University, Troitsky Avenue 51, Arkhangelsk, 163000, Russian Federation; University of Tromsø, MH-Breivika, Tromsø, 9038, Norway; and University Hospital of North Norway, Sykehusveien 38, Tromsø, 9038, Norway Setting: university hospital Dates of data collection: from January 2008 to September 2009 Funding: supported by a grant from the Government of Arkhangelsk region, “Young Pomor scientists”, and departmental funds Registration: NCT01384175
Participants	93 participants; for the participants included in the analysis, mean age: 55.6 years; sex distribution: 42 females and 48 males **Inclusion criteria** 1. ASA III adult patients with coronary artery disease

Kirov 2011 *(Continued)*

	2. ASA III and scheduled for elective off-pump coronary artery bypass grafting **Exclusion criteria** 1. Age < 18 years 2. Severe valve dysfunction 3. Peripheral vascular disease 4. Simultaneous interventions (carotid endarterectomy, aneurysm repair, etc.) 5. Transfer to CPB during surgery
Interventions	**Intervention** 1. Epidural analgesia as a continuous infusion (N = 31) or as PCEA (N = 31) **Comparator** 1. Systemic analgesia (N = 31) Premedication: diazepam Induction: fentanyl, propofol, and pipecuronium Maintenance: propofol, fentanyl, and pipecuronium Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality at 28 days 2. Risk of myocardial infarction (troponin-T) 3. Risk of atrial fibrillation or atrial flutter (no difference between groups) 4. Tracheal extubation 5. Pain scores 6. Haemodynamic variables **Others** 1. Sedation scores 2. ICU length of stay 3. Hospital length of stay
Notes	Correspondence: information received from study authors Conflict of interest: study authors declare that they have no competing interests DOI: 10.1186/1471-2253-11-17

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized to 3 groups, using the envelope method
Allocation concealment (selection bias)	Low risk	Participants were randomized to 3 groups, using the envelope method
Blinding of participants and personnel (performance bias)	High risk	Not blinded

Kirov 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was withdrawn from analysis in each group due to protocol violation (transfer to CPB)
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Konishi 1995

Methods	Parallel RCT Ethics committee: unspecified Informed consents: unspecified Site: New Tokyo Hospital, Matsudo, Japan Setting: university hospital Dates of data collection: October 1993 to March 1994 Funding: unspecified Registration: unspecified
Participants	97 participants: mean age 64 years: sex distribution: not reported **Inclusion criteria** 1. Heart surgery patients with average age of 64 years **Exclusion criteria** 1. Not available from the partial translation
Interventions	**Intervention** 1. Epidural analgesia with butorphanol (N = 31) or morphine (N = 31) **Comparator** 1. Systemic analgesia (N = 35) Induction and maintenance: low-dose fentanyl, nitrous oxide, and isoflurane Surgery: mainly CABG with CPB
Outcomes	**Relevant to this review** 1. Tracheal extubation 2. Haemodynamic variables

Konishi 1995 *(Continued)*

	Others 1. Rescue analgesia 2. Blood gas 3. ICU length of stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote. "divided"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	No failed epidural mentioned Some participants had laparotomy to take the gastroepiploic artery used for coronary grafting

Kundu 2007

Methods	Parallel RCT Ethics committee: approved by institutional ethics committee Informed consents: informed written consents were taken from all participants Site: National Institute of Cardiovascular Diseases (NICVD), Dhaka, Bangladesh Setting: university hospital Dates of data collection: between July 2006 and March 2007 Funding: unspecified

Kundu 2007 *(Continued)*

	Registration: unspecified
Participants	40 participants: mean age: 51.2; sex distribution: 6 females and 34 males **Inclusion criteria** 1. ASA II or III patients 2. Aged between 40 and 65 years 3. LVEF ≥ 40% 4. Scheduled for off-pump CABG **Exclusion criteria** 1. Left main artery coronary disease 2. Any contraindication to neuraxial block or catheter placement 3. Hypersensitivity to any drugs used in the study 4. Taking antiplatelet and anticoagulant drugs within 3 to 5 days before operation
Interventions	**Intervention** 1. Epidural analgesia (N = 20) **Comparator** 1. Systemic analgesia (N= 20) Premedication: diazepam Induction: midazolam, morphine, and pancuronium bromide Maintenance: halothane, midazolam, morphine, and pancuronium bromide Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of atrial fibrillation or atrial flutter 3. Haemodynamic variables **Other** 1. Myocardial ischaemia
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly selected and divided in two groups"
Allocation concealment (selection bias)	Unclear risk	Not reported

Kundu 2007 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	All results reported
Selective reporting (reporting bias)	Low risk	No loss to follow-up
Other bias	Low risk	No failed epidural mentioned Groups well balanced

Kunstyr 2001

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Department of Cardiology at General University Hospital, Medical Faculty of Charles University, Prague, Czech Republic Setting: university hospital Dates of data collection: from autumn 1998 to spring 1999 Funding: unspecified Registration: unspecified
Participants	81 participants; mean age: 61.6 years; sex distribution: 5 females and 76 males **Inclusion criteria** 1. LVEF > 40% **Exclusion criteria** 1. Significant preoperative pulmonary or renal dysfunction 2. Scheduled for CABG under CPB
Interventions	**Intervention** 1. Epidural analgesia (N = 20) **Comparator 1** 1. Postoperative analgesia with a mixture of ketamine 400 mg and sufentanil 100 mcg in 50 mL syringe, administered in a continuous infusion; rate of infusion 0.5 mL/h to 3.5 mL/h (N = 20) **Comparator 2**

Kunstyr 2001 *(Continued)*

	1. Nurse-administered morphine (N = 21) **Comparator 3** 1. IV PCA with morphine (N = 20) Premedication: morphine; atropine, and midazolam Induction: sufentanil, midazolam, and pipecuronium Maintenance: isoflurane, sufentanil, and midazolam Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of pulmonary complications (respiratory depression) 2. Tracheal extubation 3. Pain scores 4. Haemodynamic variables **Others** 1. Lung function tests 2. Sedation
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were withdrawn from the study and were excluded from analysis in the "ketamine" group due to diplopia, 2 were excluded due to TEA catheter dislodgement, and 3 for technical PCA pump problems (low battery)
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Not in intention-to-treat

Kunstyr 2001 *(Continued)*

	Groups well balanced

Lenkutis 2009

Methods	Parallel RCT Ethics committee: approved by the local Ethics Committee of Kaunas Medical University Informed consents: obtained the day before surgery Site: Clinic of Cardiothoracic and Vascular Surgery, Kaunas University Hospital, Kaunas, Lithuania Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	60 participants; mean age: 65.4 years; sex distribution: 27 females and 33 males **Inclusion criteria** 1. New York Heart Association class II to III and ASA class III participants, 2. Presenting with double- or triple-vessel disease 3. LVEF > 50% 4. Undergoing CABG surgery with CPB. **Exclusion criteria** 1. Pulmonary or neuromuscular disease 2. Abnormal preoperative chest radiograph or preoperative respiratory status
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Premedication: midazolam and morphine Induction: fentanyl, midazolam, etomidate, and rocuronium Maintenance: sevoflurane, midazolam, and fentanyl for the systemic analgesia group Surgery: CABG with CPB using a hollow-fibre membranous oxygenator
Outcomes	**Relevant to this review** 1. Tracheal extubation **Others** 1. Global end-diastolic volume index 2. Intrathoracic blood volume index 3. Extravascular lung water index
Notes	Correspondence: email sent 16 March 2018; no reply

Lenkutis 2009 *(Continued)*

Conflict of interest: not reported

DOI: 10.1177/0267659109348724

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Randomized; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Liem 1992

Methods	Parallel RCT Ethics committee: approved by the hospital ethics committee. Informed consents: oral informed consents obtained Site: Nijmegen, The Netherlands Setting: university hospital Dates of data collection: not reported Funding: supported by a grant from the Janssen Research Foundation, Beerse, Belgium Registration: unspecified
Participants	54 participants; mean age: 59.6 years; sex distribution: 15 females and 39 males **Inclusion criteria** 1. Patients scheduled for elective coronary artery bypass surgery 2. Normal or only moderately impaired left ventricular (LV) function (ejection fraction > 40%) as assessed by preoperative LV cineangiography and LV end-diastolic pressure < 18 mmHg

Liem 1992 *(Continued)*

	Exclusion criteria 1. Patients who had a myocardial infarction in the 7 days preceding surgery 2. Pre-existing haemorrhagic diathesis, or valvular heart disease
Interventions	**Intervention** 1. Epidural analgesia (N = 27) **Comparator** 1. Systemic analgesia (N = 27) Induction: midazolam, sufentanil, etomidate, and pancuronium Maintenance: midazolam, sufentanil, and pancuronium Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications (respiratory depression) 4. Pain scores 5. Haemodynamic variables **Others** 1. Time to awakening 2. Arrhythmias (tachycardia) 3. Adrenergic responses
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported other than the grant received DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	On the day before surgery, participants were assigned randomly to an epidural or systemic analgesia group; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the x-rays were reviewed for atelectasis in a double blind manner"

Liem 1992 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	Re-sternotomy was necessary in 2 participants (1 in each group). In 1 TEA group participant, the epidural catheter was dislocated. These participants were excluded from the study
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Not in intention-to-treat With the exception of time of surgery and number of mammary artery bypasses, no significant differences were observed

Loick 1999

Methods	Parallel RCT Ethics committee: approved by the local ethical committee Informed consents: all study participants gave written consent Site: Munster, Germany Setting: university hospital Dates of data collection: unspecified Funding: departmental/institutional Registration: unspecified
Participants	70 participants, for the participants included in this review: mean age: 61.9 years; sex distribution: 9 females and 37 males **Inclusion criteria** 1. Patients scheduled for elective coronary artery bypass grafting **Exclusion criteria** 1. Disorders of the intestine and liver 2. Gastritis 3. Ulcera ventriculi and duodeni 4. Autonomic neuropathy 5. Diabetes mellitus (patients receiving insulin or oral hypoglycaemic drugs)
Interventions	**Intervention** 1. Epidural analgesia (N = 25) **Comparator** 1. Systemic analgesia (N = 21) Induction: sufentanil, propofol, and pancuronium Maintenance: sufentanil and propofol Surgery: CABG with CPB using hollow fibre oxygenator
Outcomes	**Relevant to this review**

Loick 1999 *(Continued)*

	1. Risk of mortality 2. Risk of myocardial infarction 3. Haemodynamic variables **Other** 1. Stress markers
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a The trial contains a third group given IV clonidine and not retained for analysis

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote. "The patients were randomly allocated to one of the following three study groups"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	"Post hoc, two patients in the control group, who underwent repeat thoracotomy due to surgical bleeding, were excluded from the study"
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Epidural blockade was performed successfully in all participants without any observed complications The groups were comparable with respect to previous myocardial infarction, preoperative medication of β-blockers, and vasoactive substances. All participants had 2- to 3-vessel coronary artery disease, and all, except 1 in each group, received a left internal mammary artery graft to bypass stenosis of the left descending artery

Lundstrom 2005

Methods	Parallel RCT Ethics committee: approved by the local ethics committee Informed consents: written informed consents obtained

Lundstrom 2005 *(Continued)*

	Site: Rigshospitalet, Copenhagen, Denmark Setting: university hospital Dates of data collection: from 3 January 2000 to 12 December 2000 Funding: this research was supported by The Danish Heart Foundation, Copenhagen, Denmark, by research grants No. 99-2-3-79-22764 and 99-1-5-92-22709 Registration: unspecified
Participants	50 participants; mean age: 64.6 years; sex distribution: not reported **Inclusion criteria** 1. Undergoing elective CABG 2. Age greater than 18 years 3. Sinus rhythm on preoperative ECG 4. Written and oral informed consent **Exclusion criteria** 1. Oral anticoagulation and coagulopathy
Interventions	**Intervention** 1. Epidural analgesia (N = 26) **Comparator** 1. Systemic analgesia (N = 24) Induction: midazolam, fentanyl, and pancuronium Maintenance: midazolam, pancuronium, and fentanyl or epidural analgesia Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of in-hospital pulmonary complications (respiratory depression) **Other** 1. Episodic hypoxaemia
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The randomization list was generated from a table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported

Lundstrom 2005 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Quote: "the data analyses were blinded in relation to any clinical information"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All prespecified outcomes reported
Other bias	Low risk	No failed epidural reported No statistically significant differences between demographic data for the 2 groups

Lyons 1998

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Harefield Hospital, Middlesex, UK Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	20 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. NYHA II or Ill participants with LVEF > 50% undergoing CABG **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. Systemic analgesia (N = 10) Induction and maintenance: propofol and isoflurane plus fentanyl or epidural Surgery: CABG with CPB

Lyons 1998 *(Continued)*

Outcomes	**Relevant to this review** 1. Risk of myocardial infarction **Other** 1. Haemodynamic parameters
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a Conference abstract; limited information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote. "randomized"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Conference abstract; limited information

Mehta 1998

Methods	Parallel RCT Ethics committee: approved Informed consents: written informed consents obtained Site: New Delhi, India Setting: university hospital Funding: unspecified

Mehta 1998 *(Continued)*

	Registration: unspecified
Participants	50 participants: mean age 54.4 years; sex distribution: 3 females and 47 males **Inclusion criteria** 1. Elective mini-invasive CABG **Exclusion criteria** 1. Absence of consent
Interventions	**Intervention** 1. Epidural analgesia (N = 25) **Comparator** 1. Intrapleural analgesia (N = 25) Premedication: lorazepam and morphine Induction: morphine, diazepam, vecuronium bromide, and thiopentone sodium Maintenance: morphine dose of 0.15 mg/kg, nitrous oxide, isoflurane, and vecuronium Surgery: CABG; off-pump surgery performed with a 4- to 6-inch left anterior thoracotomy incision through the fourth intercostal space
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Complications 3. Tracheal intubation 4. Pain scores 5. Haemodynamic variables **Others** 1. Rescue analgesia 2. Sedation score 3. Respiratory function
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomly divided into two groups using computer-generated random numbers"
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias)	Unclear risk	Not reported

Mehta 1998 *(Continued)*
All outcomes

Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All analgesic dosing was administered based on the VAS score, as noted by the blinded nurse observer" Myocardial infarction was assessed by a cardiologist blinded to the treatment group allocation
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups had similar demographic data

Mehta 2008

Methods	Parallel RCT Ethics committee: approved by institutional review board Informed consents: informed consents obtained Site: Escorts Heart Institute and Research Centre, New Delhi, India Setting: university hospital Dates of data collection: 2006 to 2007 Funding: departmental Registration: not registered
Participants	36 participants; mean age: 53.9; sex distribution: 2 females and 34 males **Inclusion criteria** 1. Patients undergoing elective robotic-assisted CABG **Exclusion criteria** 1. LVEF < 35% 2. Anomaly of the vertebral column 3. Receiving heparin and antiplatelet medication within the preceding week 4. With significant respiratory disease 5. Requiring preoperative inotropic support or intra-aortic balloon counterpulsation
Interventions	**Intervention** 1. Epidural analgesia (N = 19) **Comparator** 1. Paravertebral blockade (N = 17) Premedication: oral lorazepam 2 mg and morphine sulphate 0.1 mg/kg with glycopyrrolate 0.2 mg IM

Mehta 2008 *(Continued)*

	Induction: midazolam, fentanyl Maintenance: isoflurane in oxygen and air, and vecuronium bromide Surgery: off-pump robotic-assisted CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications (respiratory depression and pneumonia) 4. Risk of atrial fibrillation or atrial flutter 5. Risk of neurological complications (cerebrovascular accident or epidural hematoma) 6. Tracheal extubation 7. Pain scores 8. Haemodynamic variables **Others** 1. Rescue analgesia 2. Lung function tests 3. Re-exporation 4. Hospital length of stay
Notes	Correspondence: information received from study authors Conflict of interest: none DOI: 10.4103/0971-9784.41576

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote. "randomised"; "chit system"
Allocation concealment (selection bias)	Unclear risk	Unclear
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Unclear
Blinding of outcome assessment (detection bias) All outcomes	Low risk	An independent observer who was blinded to the analgesic techniques recorded visual analogue scale scores
Incomplete outcome data (attrition bias) All outcomes	Low risk	All results reported
Selective reporting (reporting bias)	Low risk	No loss to follow-up
Other bias	Low risk	Analysed in intention-to-treat Groups had similar demographic data

Mehta 2010

Methods	Parallel RCT Ethics committee: approved by institutional ethics board Informed consents: written informed consents obtained Site: Indraprastha Apollo Hospital, New Delhi, India Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	62 participants; mean age: 58.3 years; sex distribution: 5 females and 57 males **Inclusion criteria** 1. ASA II or III participants 2. Chronic obstructive pulmonary disease 3. Undergoing off-pump CABG **Exclusion criteria** 1. Emergency surgery 2. Combined procedures (e.g. CABG with valve replacement), CABG on CPB 3. Very severe chronic obstructive pulmonary disease (FEV_1/FVC < 70% and FEV_1 < 30% of predicted) or cor pulmonale
Interventions	**Intervention** 1. Epidural analgesia (N = 31) **Comparator** 1. Systemic analgesia (N = 31) Premedication: lorazepam, pantoprazole, inhaled levo-salbutamol sulphate, and ipratropium bromide Induction: midazolam, fentanyl, thiopental, and pancuronium bromide Maintenance: midazolam, fentanyl, and pancuronium bromide Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of in-hospital pulmonary complications (respiratory depression, pneumonia) 4. Risk of neurological complications (epidural haematoma) 5. Tracheal extubation 6. Pain scores 7. Haemodynamic variables **Others** 1. Rescue analgesia

Mehta 2010 *(Continued)*

	2. Pulmonary function tests 3. ICU length of stay (no difference) 4. Hospital length of stay (no difference)
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "An independent observer who was blinded to the analgesic techniques recorded visual analogue scale"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural Groups well balanced

Mishra 2004

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: All India Institute of Medical Sciences, New Delhi, India Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	31 participants; mean age: not reported; sex distribution: not reported

Mishra 2004 *(Continued)*

	Inclusion criteria 1. Patients undergoing fast-track CABG **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 17) **Comparator** 1. Systemic analgesia (N =15) Induction and maintenance: not reported Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of in-hospital pulmonary complications (respiratory insufficiency or pneumonia) 2. Risk of neurological complications (epidural haematoma) 3. Tracheal extubation 4. Haemodynamic variables **Others** 1. Analgesic requirement 2. Patient satisfaction 3. Awareness
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a Conference abstract, limited information

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Mishra 2004 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No indication of other bias

Moore 1995

Methods	Parallel RCT Ethics committee: approved by the ethics committee (reference No. 90/3496) Informed consents: written informed consents obtained Site: Hammersmith Hospital, London, UK Setting: university hospital Dates of data collection: not reported Funding: financial support for this study from Hammersmith and Acton Special Trustees and Hammersmith and Queen Charlotte's Special Health Authority Registration: unspecified
Participants	18 participants: mean age: 57.1 years; sex distribution: 1 female and 16 males and 1 unclear **Inclusion criteria** 1. Patients undergoing elective coronary artery bypass grafting **Exclusion criteria** 1. History of metabolic or endocrine disease 2. Abnormal bleeding time
Interventions	**Intervention** 1. Epidural analgesia (N = 9) **Comparator** 1. Systemic analgesia (N = 9) Premedication: diazepam, papaveretum, and hyoscine Induction: sufentanil, thiopentone, and pancuronium Maintenance: sufentanil Surgery: CABG with CPB using a bubble oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Haemodynamic variables **Others**

Moore 1995 *(Continued)*

	1. Plasma catecholamines 2. Plasma cortisol 3. Serum insulin and growth hormone
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were allocated by selection of a sealed envelope
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant had a severe haemorrhage; data from this participant were not presented
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Not in intention-to-treat Groups had similar demographic data

Nagaraja 2018

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: Departments of Cardiac Anaesthesiology and CTVS, Sri Jayadeva Institute of Cardiovascular Sciences and Research, Bengaluru, Karnataka, India Setting: university hospital Dates of data collection: not reported Funding: departmental/institutional Registration: unspecified

Nagaraja 2018 *(Continued)*

Participants	50 participants undergoing cardiac surgery; mean age 47.5 years; sex distribution: 22 females and 28 males **Inclusion criteria** 1. Adult elective cardiac surgical patients underwent median sternotomy **Exclusion criteria** 1. Emergency surgery; left main coronary artery disease 2. Left ventricular ejection fraction < 40% 3. Spinal abnormalities; blood or cerebrospinal fluid tap during the procedure 4. Failed blocks 5. Patient on anticoagulants; bleeding diathesis 6. Patients who expired before extubation
Interventions	**Interevention** 1. Epidural analgesia (N = 25) **Comparator** 1. Bilateral erector spinae plane block (N = 25) Standardized general anaesthesia Surgery: CABG through median sternotomy
Outcomes	**Relevant to this review** 1. Tracheal extubation 2. Pain scores **Others** 1. Intensive care unit length of stay 2. Lung function
Notes	Correspondence: email sent 18 November 2018; no reply Conflict of interest: none DOI: 10.4103/aca.ACA_16_18

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Randomization was performed to two groups of 25 each using the closed envelope method"
Allocation concealment (selection bias)	Low risk	"Randomization was performed to two groups of 25 each using the closed envelope method"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias)	Unclear risk	Not reported

Nagaraja 2018 *(Continued)*

All outcomes		
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Groups well balanced

Neskovic 2013

Methods	Parallel RCT Ethics committee: obtained Informed consents: not reported Site: Clinic for Anesthesiology and Intensive Care, Military Medical Academy, Belgrade, Serbia; Faculty of Medicine of the Military Medical Academy, University of Defence, Belgrade, Serbia; and Dedinje Cardiovascular Institute, Belgrade, Serbia Setting: university hospital Dates of data collection: February 2002 to October 2005 Funding: departmental (academic trial; part of a PhD thesis) Registration: not registered
Participants	82 participants; mean age: 54.8 years; sex distribution: 13 females and 68 males and 1 unclear **Inclusion criteria** 1. Scheduled for coronary artery bypass surgery (more than 1 graft) 2. LVEF > 30% 3. No contraindication to TEA **Exclusion criteria** 1. Acute infection 2. Immunological disease 3. Myocardial infarction up to 1 month before surgery 4. Diabetes mellitus type 1 5. Acute or chronic renal failure 6. Chronic lung disease 7. Stroke or transitory ischaemic attack 8. Coagulation disorders
Interventions	**Intervention** 1. Epidural analgesia with off-pump CABG (N = 17) or CABG with CPB (N = 18) **Comparator** 1. Systemic analgesia and off-pump CABG (N = 19) or CABG with CPB (N = 27) Induction: midazolam, propofol, fentanyl, and pancuronium

Neskovic 2013 *(Continued)*

	Maintenance: propofol, fentanyl, and pancuronium Surgery: CABG with or without CPB
Outcomes	**Relevant to this review** 1. Risk of mortality **Others** 1. Blood loss and transfusion requirements 2. ICU length of stay 3. Hospital length of stay
Notes	Correspondence: information received from study authors Conflict of interest: none DOI: 10.2298/VSP1305439N

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization
Allocation concealment (selection bias)	Low risk	Allocation concealment was done by: (quote) "envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "open label study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "open label study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One of the participants had incomplete data and was excluded from further statistical analysis
Selective reporting (reporting bias)	Unclear risk	Initially, the study was designed for a larger number of participants, but for technical reasons, enrolment of patients was stopped earlier (82 participants) Otherwise, all results were reported
Other bias	Unclear risk	Not in intention-to-treat: there were 3 conversions from off-pump to standard surgery and cardiopulmonary bypass; these participants were assigned to different groups according to the anaesthetic technique applied Groups well balanced except for LVEF

Nygard 2004

Methods	Parallel RCT

Nygard 2004 *(Continued)*

	Ethics committees: approved by the Scientific Ethics Committees for Copenhagen and Frederiksberg (KF 02-124/98), the Danish Data Protection Agency, and the Danish Medicines Agency Informed consents: written informed consents obtained Site: Copenhagen, Denmark Setting: university hospital Dates of data collection: not reported Funding: supported by The Danish Heart Foundation (grant no. 99-2-3-79-22764 and no. 99-1-5-92-22709) and an unrestricted grant from AstraZeneca, Denmark Registration: unspecified
Participants	163 participants; mean age: 64.4 years; sex distribution: 18 females and 145 females **Inclusion criteria** 1. Patients scheduled for elective CABG; sinus rhythm **Exclusion criteria** 1. Off-pump surgery 2. Implanted pacemaker 3. Use of amiodarone within 4 months of enrolment 4. History of amiodarone toxicity 5. Known thyroid disease 6. Liver disease 7. Uncontrolled heart failure 8. Resting heart rate < 50 beats/min in the absence of medical therapy known to slow the heart rate 9. Anticoagulant medication with warfarin 10. Coagulopathy 11. Pregnancy 12. Use of antiarrhythmic drugs other than alpha$_1$-receptor antagonists 13. Calcium channel antagonists 14. Digoxin.
Interventions	**Intervention** 1. Epidural analgesia with (N = 35) or without amiodarone (N = 44) **Comparator** 1. Systemic analgesia with (N = 36) or without amiodarone (N = 48) Induction: midazolam, fentanyl, and pancuronium Maintenance: isoflurane and fentanyl or epidural analgesia Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of atrial fibrillation or atrial flutter 3. Haemodynamic variables **Other**

Nygard 2004 *(Continued)*

	1. Length of hospital stay
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none other than the grants received DOI: 10.1053/j.jvca.2004.08.006

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomly assigned to 4 groups; randomization was 1:1:1:1. Randomization list was generated from a computerized table of random numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was conducted in an open manner"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the study was conducted in an open manner"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Of the 196 patients included, 163 were evaluated: 18 patients had surgery cancelled, and 4 patients had a change in surgical procedure. One withdrew consent preoperatively, and 6 withdrew consent postoperatively. One patient had a stroke before surgery, and in 1 patient placement of the epidural catheter was unsuccessful. Two patients were excluded because of protocol violations
Selective reporting (reporting bias)	Low risk	Appears to be free of other sources of bias. Sample size calculation stated
Other bias	Unclear risk	Not in intention-to-treat Groups had similar demographic data

Obersztyn 2018

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: Medical University of Silesia in Katowice, Poland Setting: university hospital Dates of data collection: 18-month period Funding: departmental/institutional Registration: unspecified

Obersztyn 2018 *(Continued)*

Participants	80 participants: mean age 59.6 years; sex distribution: 20 females and 60 males **Inclusion criteria** 1. Patients scheduled for low-risk CABG with or without CPB **Exclusion criteria** 1. Contraindications for epidural anaesthesia (i.e. purulent skin lesions, significant spine deformations, abnormal basic haemostasis parameters) 2. With no informed consent 3. With chronic metabolic disease (except diabetes); with advanced respiratory, renal, or hepatic insufficiency 4. With symptoms of circulatory insufficiency or unstable coronary disease and urgent qualification for the procedure 5. Advanced respiratory insufficiency (forced expiratory volume 1 s < 50% of normal volume and/or presence of respiratory insufficiency in a preoperative arterial blood gas analysis) 6. Study was discontinued if the following complications occurred: myocardial insufficiency requiring placement of an intra-aortic balloon pump or other methods of mechanical support, symptoms of acute myocardial ischaemia, requirement for increased doses of inotropic drugs (dopamine and/or dobutamine up to 5 mcg/kg/min was acceptable), cumulative time of extracorporeal circulation exceeding 180 minutes, marked drainage, deterioration in blood gases or other problems requiring elective extubation, and other circumstances not listed in the protocol that could affect postoperative sedation or elective extubation. For patients with any complications mentioned above, only the operation period was analysed
Interventions	**Intervention** 1. Epidural analgesia (N = 40) **Comparator** 1. Systemic analgesia (N = 40) Premedication: oral midazolam Induction: etomidate, fentanyl, and pancuronium Maintenance: isoflurane, fentanyl, and 1 dose of morphine before wound closure Surgery: CABG with or without CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications: respiratory depression 4. Risk of neurological complications: risk of serious neurological complications from epidural analgesia (lasting > 3 months), sensory or motor deficit, or epidural haematoma 5. Time to tracheal extubation 6. Haemodynamic variables **Others** 1. Rescue analgesia 2. Arterial blood gases 3. Intensive care unit length of stay 4. Hospital length of stay 5. Reoperation

Obersztyn 2018 *(Continued)*

Notes	Correspondence: email sent 18 November 2018; no reply Conflict of interest: none DOI: 10.5114/kitp.2018.76471

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"Patients were assessed by the anaesthesiologists at least 12 hours before transfer to the operating theatre. Randomization was performed at this stage, by tossing a coin"
Allocation concealment (selection bias)	Low risk	From the information above, group treatment was unknown at enrolment
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Study was discontinued if the following complications occurred: myocardial insufficiency requiring placement of an intra-aortic balloon pump or other methods of mechanical support, symptoms of acute myocardial ischaemia, requirement for increased doses of inotropic drugs (dopamine and/or dobutamine up to 5 mcg/kg/min was acceptable), cumulative time of extracorporeal circulation exceeding 180 minutes, marked drainage, deterioration in blood gases or other problems requiring elective extubation, and other circumstances not listed in the protocol that could affect postoperative sedation or elective extubation. For patients with any complications mentioned above, only the operation period was analysed Analysis of the postoperative period was performed for 39 participants in each group because 2 participants were excluded from participation in the study according to the methodology In group I, 1 participant (operated on with the use of extracorporeal circulation) was excluded because of a serious haemorrhage that occurred immediately after transfer from the surgical theatre and required reoperation One exclusion occurred in group II (also in a participant operated on with the use of extracorporeal circulation) because of perioperative myocardial infarction diagnosed both in ECG and with elevated serum enzymes
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Groups well balanced

Onan 2011

Methods	Parallel RCT Ethics committee: approved

Onan 2011 *(Continued)*

	Informed consents: obtained Site: Kocaeli, Turkey Setting: university hospital Dates of data collection: not reported Funding: unspecified Registration: unspecified
Participants	30 participants; mean age: 59.0 years; sex distribution: 3 females and 27 males **Inclusion criteria** 1. Patients with documented 3-vessel coronary artery disease who were scheduled for elective coronary artery bypass graft surgery **Exclusion criteria** 1. Decreased ventricular function (ejection fraction 40%) 2. Emergency operation 3. Previous cardiothoracic operation 4. Unstable angina 5. Resting bradycardia (< 60 beats/min) 6. Critical left main coronary artery disease (50% stenosis) 7. Contraindications to the epidural technique including pre-existing coagulopathy 8. Preoperative anticoagulation (full therapeutic doses of standard or low–molecular-weight heparin, warfarin, thrombolytic drugs, or potent antiplatelet drugs) 9. Systemic or local infection 10. Previous cervical or upper thoracic operation 11. Vertebral deformity 12. Drug hypersensitivity
Interventions	**Intervention** 1. Epidural analgesia (N = 15) **Comparator** 1. Systemic analgesia (N = 15) Premedication: midazolam Induction: midazolam, fentanyl, and rocuronium Maintenance: nitrous oxide, propofol, fentanyl, and rocuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction **Others** 1. Immunoreactivity 2. Graft blood flow
Notes	Correspondence: email sent 16 March 2018; no reply

Onan 2011 *(Continued)*

Conflict of interest: not reported

DOI: 10.1053/j.jvca.2011.06.004

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed immediately before surgery using sealed envelopes
Allocation concealment (selection bias)	Low risk	Randomization was performed immediately before surgery using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups had similar demographic data

Onan 2013

Methods	Parallel RCT Ethics committee: approved by the Institutional Ethics Committee Informed consents: informed written consents were obtained from each patient Site: Istanbul Florence Nightingale Hospital, Istanbul, Turkey Setting: unspecified Dates of data collection: between April 2009 and March 2010 Funding: unspecified Registration: unspecified
Participants	40 participants; mean age: 58.5 years; sex distribution: 4 females and 36 males **Inclusion criteria** 1. Patients with ischaemic heart disease scheduled for elective CABG **Exclusion criteria**

Onan 2013 *(Continued)*

1. LEVF < 40%
2. Emergency operation
3. Previous cardiothoracic operation
4. Unstable angina
5. Resting bradycardia (< 60 beats/min)
6. Critical left main coronary artery disease (> 50% stenosis)
7. Contraindications for the epidural technique including preexisting coagulopathy
8. Preoperative anticoagulation (full therapeutic doses of standard or low-molecular-weight heparin, warfarin, thrombolytic drugs, or potent antiplatelet drugs)
9. Systemic or local infection
10. Previous cervical or upper thoracic operation
11. Vertebral deformity
12. Drug hypersensitivity
13. Long-term use of non-steroidal anti-inflammatory drugs
14. Use of tranquillizers
15. Inability to express themselves verbally
16. Inability to fill out the questionnaires

Interventions	**Intervention** 1. Epidural analgesia (N = 20) **Comparator** 1. Systemic analgesia (N = 20) Premedication: midazolam Induction: midazolam, fentanyl, and rocuronium Maintenance: nitrous oxide, rocuronium, propofol, and fentanyl Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of pulmonary complications (pneumonia) 3. Risk of atrial fibrillation or atrial flutter 4. Risk of neurological complications (cerebrovascular accident or epidural haematoma or abscess) 5. Tracheal intubation 6. Pain scores **Others** 1. Acute kidney injury 2. ICU length of stay 3. Hospital length of stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: study authors acknowledge no conflict of interest in the submission DOI: 10.1111/jocs.12086

Risk of bias

Bias	Authors' judgement	Support for judgement

Onan 2013 *(Continued)*

Random sequence generation (selection bias)	Low risk	Randomization was performed immediately before surgery using sealed envelopes
Allocation concealment (selection bias)	Low risk	Randomization was performed immediately before surgery using sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Palomero 2008

Methods	Parallel RCT Ethics committee: approved by the La Paz Hospital Human Research Ethics Committee Informed consents: written informed consents were obtained from all patients Site: La Paz University Hospital, Madrid, Spain; and Gregorio Marañon University Hospital, Madrid, Spain Setting: university hospital Dates of data collection: not reported Funding: departmental Registration: unspecified
Participants	22 participants; mean age: 65.3 years; sex distribution: 4 females and 18 males **Inclusion criteria** 1. Patients undergoing elective coronary artery bypass graft surgery **Exclusion criteria** 1. History of inflammatory disease 2. Recent infection 3. Autoimmune disease 4. Corticoid treatment 5. Immunosuppressant treatment

Palomero 2008 *(Continued)*

6. Recent preoperative procedure
7. Recent emergency procedure
8. Concurrent valvular surgery or presence of valvular disease
9. Ejection fraction (EF) < 45%
10. Older than 85 years

Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. No epidural (N = 12) Induction: propofol, fentanyl, and vecuronium Maintenance: propofol, sevoflurane, and fentanyl or epidural analgesia Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of atrial fibrillation or atrial flutter 3. Risk of neurological complications (cerebrovascular accident or epidural haematoma or abscess) 4. Tracheal extubation 5. Haemodynamic variables **Others** 1. Markers of inflammation 2. Blood transfusion requirement
Notes	Correspondence: information received from study authors Conflict of interest: no conflict of interest DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "assigned a computer-generated randomization code"
Allocation concealment (selection bias)	Low risk	Quote: "final randomization was performed by a physician not belonging to the hospital team the day before surgery, using the randomization code"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "the study was not blinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "the study was not blinded"
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

Palomero 2008 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced, except Euroscore was higher in the TEA group (5.4 vs 3.8)

Petrovski 2006

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Special Hospital for Cardiac Surgery Filip II, Skopje, Macedonia Setting: private hospital Dates of data collection: between March 2003 and March 2004 Funding: unspecified Registration: unspecified
Participants	110 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Patients undergoing off-pump CABG **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 56) **Comparator** 1. Systemic analgesia (N = 54) Induction: not reported Maintenance: not reported Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Pain scores 2. Tracheal extubation **Others** 1. Time to first mobilization 2. Hospital length of stay

Petrovski 2006 *(Continued)*

Notes	Correspondence: email sent 18 November 2018; no reply Conflict of interest: not reported DOI: n/a Conference abstract

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly selected"; no details
Allocation concealment (selection bias)	Unclear risk	"not reported"
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	"not reported"
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	"not reported"
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up mentioned
Selective reporting (reporting bias)	Unclear risk	"conference abstract"; "limited information"
Other bias	Unclear risk	"conference abstract"; "limited information"

Priestley 2002

Methods	Parallel RCT Ethics committee: approved by the local hospital Research and Ethics Committee Informed consents: all participants gave written informed consent Site: Westmead Hospital, Westmead, Australia Setting: university hospital Dates of data collection: unspecified Funding: this study was supported by the Australian and New Zealand College of Anaesthetists Registration: unspecified
Participants	100 participants; mean age: 59 years; sex distribution: 14 females and 86 males **Inclusion criteria** 1. Patients scheduled for elective CABG

Priestley 2002 *(Continued)*

	Exclusion criteria 1. Contraindications to the epidural technique (e.g. preexisting coagulopathy, anticoagulation (i.e. full therapeutic doses of standard or low-molecular-weight heparin, warfarin, thrombolytic drugs, or potent antiplatelet drugs), systemic or local infection) 2. Arthritis of the thoracic or cervical spine with a history of associated neurological deficit 3. Coexisting surgery (e.g. valvular, carotid, aortic surgery) 4. Contraindications to any of the intended drugs in the treatment protocol 5. Significant alcohol or other substance abuse 6. Cognitive impairment 7. Other reason for inability to comply with treatment as assessed by investigators
Interventions	**Intervention** 1. Epidural analgesia (N = 50) **Comparator** 1. Systemic analgesia (N = 50) Premedication: lorazepam, morphine, and midazolam Induction: fentanyl, propofol, and pancuronium Maintenance: fentanyl, propofol, and pancuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of neurological complications 4. Tracheal extubation 5. Pain scores **Others** 1. Pain scores 2. Lung function 3. Length of hospital stay 4. Mobilization goals
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Block randomization via sealed envelopes was used; participants at high risk were randomized separately
Allocation concealment (selection bias)	Low risk	Sealed envelopes

Priestley 2002 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "blinding of participants or investigators was not considered feasible"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "blinding of participants or investigators was not considered feasible"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Fifty participants were enrolled into each group, and data were analysed on an intention-to-treat basis. A per-protocol analysis was also performed, and 12 participants were excluded from such analysis: 4 failed epidural blocks, 3 surgical complications required reoperation (2 systemic analgesia, 1 epidural analgesia), 1 underwent reintubation (epidural) for respiratory failure, and 4 had protocol violations (3 systemic analgesia and 1 epidural analgesia)
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Groups had similar demographic data

Rein 1989

Methods	Parallel RCT Ethics committee: approved by the ethical committee of the hospital Informed consents: obtained from all participants Site: Trondheim, Norway Setting: university hospital Dates of data collection: unspecified Funding: this study was supported by a grant from the Norwegian Council for Cardiovascular Diseases Registration: unspecified
Participants	16 participants: age: 60.3 years; sex distribution: 16 males **Inclusion criteria** 1. Male patients 2. Requiring CABG with extracorporeal circulation **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 8) **Comparator** 1. Systemic analgesia (N = 8) Premedication: morphine and scopolamine

Rein 1989 *(Continued)*

	Induction: thiopentone and pancuronium Maintenance: nitrous oxide, diazepam, and fentanyl or epidural analgesia Surgery: CABG with CPB using a bubble oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Haemodynamic variables **Others** 1. Postoperative haemodynamics
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "16 male patients were allocated at random to two groups"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant died 9 hours postoperatively and was excluded from final analyses
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Not in intention-to-treat Groups had similar demographic data

Royse 2003

Methods	Parallel RCT Ethics committee: approved by institutional ethics committee Informed consents: informed written consents obtained

Royse 2003 *(Continued)*

	Site: Melbourne, Victoria, Australia Setting: university hospital Dates of data collection: between 1998 and 2001 Funding: the study is supported by grants from the National Heart Foundation of Australia; Australian Society of Anaesthetists; and AstraZeneca Pty, Ltd Registration: unspecified
Participants	76 participants; mean age: 64.7 years; sex distribution: 16 females and 60 males **Inclusion criteria** 1. Patients receiving elective CABG with cardiopulmonary bypass **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 37) **Comparator** 1. Systemic analgesia (N = 39) Induction and maintenance: midazolam, propofol, and alfentanil Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of pulmonary complications (respiratory depression) 3. Risk of atrial fibrillation or atrial flutter 4. Risk of neurological complications (cerebrovascular accident) 5. Pain scores 6. Haemodynamic variables **Others** 1. Physiotherapy co-operation 2. Depression and post-traumatic stress 3. Somatosensory sensitization 4. Lung function
Notes	Correspondence: information received from study authors Conflict of interest: none other than the grant received DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"; no details provided

Royse 2003 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	Four participants were withdrawn: 1 withdrew from the study after randomization, deciding not to participate in research; 2 had failed epidurals; and 1 from the control group requested the epidural
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Unclear risk	Not in intention-to-treat Epidural group had significantly longer cardiopulmonary bypass time Supported in part by the industry

Scott 2001

Methods	Parallel RCT Ethics committee: the hospital ethics committee approved the study Informed consents: all participants gave written informed consent Site: Glasgow, Scotland, UK Setting: university hospital Dates of data collection: unspecified Funding: departmental/institutional Registration: unspecified
Participants	408 participants; mean age: 59 years; sex distribution: 56 females and 352 males **Inclusion criteria** 1. Patients undergoing elective CABG 2. Normal coagulation screen 3. LVEF > 35% **Exclusion criteria** 1. Abnormal preoperative coagulation screen that included prothrombin time, international normalized ratio, fibrinogen, platelet count, and activated partial thromboplastin time
Interventions	**Intervention** 1. Epidural analgesia (N = 206)

Scott 2001 *(Continued)*

	Comparator 1. Systemic analgesia (N = 202) Premedication: temazepam, ranitidine, and metoclopramide Induction and maintenance: propofol, alfentanil, and pancuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications (respiratory depression or pneumonia) 4. Risk of neurological complications (cerebrovascular accident) **Others** 1. Acute confusion 2. Significant bleeding 3. Renal failure 4. Incidence of major organ complications
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "patients were randomized to one of two regimens...by using cards drawn from a sealed envelope"
Allocation concealment (selection bias)	Low risk	Sealed envelope
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was conducted in an open manner; therefore, neither the anaesthesiologists nor the nurses taking measurements were blinded to participants' treatment
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was conducted in an open manner; therefore, neither the anaesthesiologists nor the nurses taking measurements were blinded to participants' treatment
Incomplete outcome data (attrition bias) All outcomes	Low risk	12 participants had insufficient data
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	In intention-to-treat for remaining 408 participants Groups had similar demographic data

Sen 2017

Methods	Parallel RCT Ethics committee: approved by the ethical committee of the hospital Informed consents: obtained Site: Amrita Institute of Medical Sciences, Amrita Vishwa Vidyapeetham, Kochi, Kerala, India Setting: university hospital Dates of data collection: unspecified Funding: departmental resources Registration: unspecified
Participants	60 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Male 2. ASA III participants 3. Aged 45 to 70 years 4. Posted for CABG surgery for triple-vessel disease 5. APTT ≤ 45 seconds prothrombin time (PT) (international normalized ratio (INR) ≤ 1.5), platelets ≥ 80,000/dL 6. Good left ventricular systolic function ejection fraction (EF) > 50% 7. Had discontinued aspirin and clopidogrel 7 days preoperatively **Exclusion criteria** 1. Patient refusal 2. Infection at puncture site 3. APTT ≥ 45 seconds 4. PT (INR) = 1.5 5. Platelets ≤ 80,000/dL 6. Clopidogrel within last 7 days of the procedure 7. Coexisting liver disease
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Fentanyl infusion (N = 30) Premedication: lorazepam, ranitidine, allopurinol, vitamin C, vitamin A, and vitamin E Induction and maintenance: fentanyl, midazolam, and pancuronium Surgery: CABG with CPB using a membrane oxygenator
Outcomes	**Relevant to this review** 1. Risk of pulmonary complications (respiratory depression) 2. Risk of neurological complications (serious neurological complications from epidural analgesia) 3. Pain scores 4. Haemodynamic variables

Sen 2017 *(Continued)*

	Others 1. Rescue analgesia 2. Sedation scores 3. Co-operation to physiotherapy
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: no conflicts of interest DOI: 10.4103/0259-1162.186613

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomly allocated to 2 equal groups by computer-generated random sequence of numbers
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	High risk	Study was a prospective, randomized, non-blinded comparative study
Blinding of outcome assessment (detection bias) All outcomes	High risk	Study was a prospective, randomized, non-blinded comparative study
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Sharma 2010

Methods	Parallel RCT Ethics committee: approved by the institutional ethical review board Informed consents: informed written consents obtained Site: Indraprastha Apollo Hospitals, New Delhi, India Setting: university hospital Dates of data collection: unspecified Funding: departmental/institutional

Sharma 2010 *(Continued)*

	Registration: unspecified
Participants	60 participants; mean age: 58.1 years; sex distribution: 4 females and 56 males **Inclusion criteria** 1. Obese patients 2. Between 40 and 70 years age 3. Body mass index > 30 kg/m^2 4. Physical status ASA II and III 5. Scheduled for elective off-pump CABG **Exclusion criteria** 1. Emergency surgery 2. LVEF ≤ 35% 3. Chronic obstructive airway disease (to avoid confounding effects on pulmonary function test) 4. Coagulopathy 5. Sepsis 6. Neurological disorder 7. CABG on CPB 8. Significant left main coronary artery disease
Interventions	**Intervention** 1. Epidural analgesia (N = 30) **Comparator** 1. Systemic analgesia (N = 30) Premedication: lorazepam and pantoprazole Induction: midazolam, fentanyl, propofol, and vecuronium Maintenamce: isoflurane Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Pain scores **Others** 1. Lung function
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none declared DOI: 10.4103/0971-9784.58831

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized into two groups of 30 each"; no details

Sharma 2010 *(Continued)*

Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Any untoward complications of epidural analgesia such as paresis, hypotension, urinary retention (after removal of Foley's catheter), respiratory depression, and pruritus were noted every-4-hourly by a blinded observer Pain assessment was done using a 10-cm visual analogue scale at rest and on coughing (10 cm = maximum pain and 0 = no pain) by a blinded observer Richter scale was observed by a blinded radiologist
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups had similar characteristics

Stenseth 1994

Methods	Parallel RCT Ethics committee: approved by the Ethics Committee of the University of Trondheim Informed consents: obtained Site: Trondheim, Norway Setting: university hospital Dates of data collection: unspecified Funding: departmental/institutional Registration: unspecified
Participants	28 participants: mean age: 54.9 years; sex distribution: 28 males **Inclusion criteria** 1. Male 2. ASA III patients 3. < 65 years 4. LVEF > 50% 5. Undergoing CABG for double-vessel or triple-vessel disease **Exclusion criteria** 1. Not reported

Stenseth 1994 *(Continued)*

Interventions	**Intevention** 1. Epidural analgesia and high- (N = 10) or low-dose fentanyl (N = 8) **Comparator** 1. Systemic analgesia (N = 10) Premedication: morphine and scopolamine Induction: thiopentone and pancuronium Maintenance: fentanyl, diazepam, and nitrous oxide Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Haemodynamic variables **Others** 1. Use of vasoactive drugs
Notes	Correspondence: data no longer available Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"; no details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were excluded from the final analysis due to surgical problems
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Not in intention-to-treat Groups had similar demographic data

Stenseth 1996

Methods	Parallel RCT Ethics committee: approved by the Ethics Committee of the University of Trondheim Informed consents: obtained Site: Trondheim, Norway Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	52 participants: mean age: 55.2 years; sex distribution: 52 males **Inclusion criteria** 1. Male 2. New York Heart Association class III patients 3. Age < 65 years 4. LVEF > 50% 5. Scheduled for CABG for double- or triple-vessel disease **Exclusion criteria** 1. Pulmonary or neuromuscular disease 2. Abnormal preoperative standard chest radiographs 3. Preoperative respiratory status
Interventions	**Intervention** 1. Epidural analgesia (N = 26) **Comparator** 1. Systemic analgesia (N = 26) Premedication: morphine and scopolamine Induction and maintenance: diazepam, thiopentone, nitrous oxide, and pancuronium Surgery: CABG with CPB using a bubble oxygenator
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of neurological complications (cerebrovascular accident) 4. Tracheal extubation **Others** 1. Lung function
Notes	Correspondence: data are no longer available Conflict of interest: not reported

Stenseth 1996 *(Continued)*

DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized into two groups"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	Two participants were excluded from the analysis because of complications experienced
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Not in intention-to-treat Groups had similar demographic data

Stritesky 2006

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: written informed consents obtained Site: Cardiovascular Clinic, Prague, Czech Republic Setting: private clinic Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	30 participants: mean age 69 years; sex distribution: 9 females and 21 males **Inclusion criteria** 1. Patients scheduled for elective CABG with CPB **Exclusion criteria** 1. Left ventricular ejection fraction < 40%,

Stritesky 2006 *(Continued)*

2. Diabetes mellitus,
3. Coagulation abnormalities, anti-aggregation therapy (< 4 days before surgery), anticoagulation therapy, pathology in the spine
4. Sepsis
5. CPB time > 130 minutes
6. Serious intraoperative complications not related to anaesthesia (e.g. bleeding revision).

Interventions	**Intervention** 1. Epidural analgesia (N = 15) **Comparator** 1. Systemic analgesia (N = 15) Premedication: midazolam, morphine, and atropine Induction: fentanyl, midazolam, thiopental, and atracurium Maintenance: midazolam, nitrous oxide, isoflurane, sufentanil or epidural anaesthesia, and atracurium Surgery: CABG with CPB with a membrane oxygenator
Outcomes	**Relevant to this review** 1. Tracheal extubation 2. Pain scores 3. Haemodynamic variables **Others** 1. First walk 2. Hospital length of stay
Notes	Correspondence: email sent 18 Novembre 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	"randomly divided"; no details
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias)	Low risk	No loss to follow-up

Stritesky 2006 *(Continued)*
All outcomes

Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Groups well balanced, except for pulmonary disease

Svircevic 2011

Methods	Parallel: 2-centre RCT Ethics committee: local human research ethics committees of the 2 participating centres (METC Isala Clinics, Zwolle, The Netherlands; and METC MST, Enschede, The Netherlands) approved of the study Informed consents: written informed consent was obtained from all participants Site: Utrecht, The Netherlands Setting: university hospitals Dates of data collection: from March 2004 to September 2007 Funding: the health renewal project provided from institutional sources: Isala Clinics Hospital 02/19. Registration number: 100000461 Registration: ISRCTN50434243
Participants	654 participants; mean age: 64.5 years; sex distribution: 111 females and 543 males Patients scheduled for elective cardiac surgery, including off-pump procedures
Interventions	**Intervention** 1. Epidural analgesia N = 325 **Comparator** 1. Systemic analgesia N = 329 Induction: remifentanil, etomidate, and pancuronium Maintenace: propofol or sevoflurane and remifentanil Surgery: CABG with or without CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of myocardial infarction 3. Risk of pulmonary complications 4. Risk of atrial fibrillation or atrial flutter 5. Risk of neurological complications (cerebrovascular accident) **Other** 1. Length of hospital stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: none reported

Svircevic 2011 *(Continued)*

DOI: 10.1097/ALN.0b013e318201d2de

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The random allocation sequence was concealed and computer-generated in permuted unequal blocks, accessible through an Internet site
Allocation concealment (selection bias)	Low risk	The random allocation sequence was concealed
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "It was not possible for either the patient or the care providers to be blinded for treatment allocation"
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Quote: "All components of the primary endpoint were evaluated by an independent event committee blinded for randomization, consisting of a cardiologist, cardiothoracic surgeon, nephrologist, pulmonologist, and a neurologist"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was excluded because his surgery was cancelled, and one participant withdrew his consent after randomization
Selective reporting (reporting bias)	Low risk	All results were reported
Other bias	Low risk	Intention-to-treat Groups had similar demographic data

Tenenbein 2008

Methods	Parallel RCT Ethics committee: approved by the Ethics Review Board of the University of Manitoba Health Sciences Centre Informed consents: all participants gave written informed consent Site: University of Manitoba, Canada Setting: university hospital Dates of data collection: between July 1, 2003, and June 30, 2004 Funding: supported by the Health Sciences Centre Research Foundation Registration: not registered
Participants	50 participants; mean age: 60.5 years; sex distribution: not reported **Inclusion criteria** 1. Patients younger than 80 years of age 2. Deemed appropriate for their facilitated recovery programme 3. Undergoing CABG surgery

Tenenbein 2008 *(Continued)*

	Exclusion criteria 1. Age 80 years or older 2. Previous cardiac surgery 3. Combined procedures 4. Serum creatinine > 150 mmol/L 5. Pre-existing coagulopathy 6. Use of antiplatelet agents other than aspirin 7. Active liver disease 8. Severe spinal deformity 9. Ejection fraction < 30% 10. Body mass index > 35 kg/m^2
Interventions	**Intervention** 1. Epidural analgesia (N = 25) **Control** 1. Systemic analgesia (N = 25) Premedication: diazepam Induction: sufentanil, sodium thiopental, or propofol and rocuronium Maintenance: isoflurane Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Risk of pulmonary complications (respiratory depression, pneumonia) 3. Risk of atrial fibrillation or atrial flutter 4. Risk of neurological complications (cerebrovascular accident, serious neurological complications from epidural analgesia) 5. Tracheal extubation 6. Pain scores **Others** 1. Rescue analgesia 2. Lung function tests
Notes	Correspondence: information received from study authors Conflict of interest: no conflicts of interest DOI: 10.1007/BF03021489

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "prospective, randomized, controlled trial"; "Randomization occurred immediately after enrolment"; "assigned a sealed envelope that contained the group assignment"

Tenenbein 2008 *(Continued)*

Allocation concealment (selection bias)	Low risk	Quote: "assigned a sealed envelope that contained the group assignment"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "this was not a blinded study"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "this was not a blinded study"
Incomplete outcome data (attrition bias) All outcomes	Low risk	Quote: "Due to incomplete data collection, two patients were excluded from each group"; "unable to insert an epidural in one patient, and the epidural was not use, postoperatively in another patient, because of quadriparesis on emergence"
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Quote: "intention to treat principle" Preoperatively, groups were similar, except for higher mean ejection fractions in the control group (59.1 ± 8.9% vs 52.9 ± 7.5%; P < 0.01)

Tenling 1999

Methods	Parallel RCT Ethics committee: approved by the ethics committee of Uppsala University Informed consents: obtained Site: Uppsala, Sweden Setting: university hospital Dates of data collection: not reported Funding: the study was supported by grants from the Swedish Medical Research Council (5315), the E. K. G. Selander Foundation, the Uppsala County Association Against Heart and Lung Diseases, and Uppsala University Registration: unspecified
Participants	29 participants: mean age: 61.6 years; sex distribution: 1 female and 28 males **Inclusion criteria** 1. Patients scheduled for CABG 2. Stable angina pectoris 3. LVEF > 40% **Exclusion criteria** 1. Significant lung, kidney, liver, or neurological disease 2. Insulin-dependent diabetes mellitus 3. Significant valve disease or bleeding diathesis

Tenling 1999 *(Continued)*

	4. Receiving heparin or heparin fragments
Interventions	**Intervention** 1. Epidural analgesia (N = 14) **Comparator** 1. Systemic analgesia (N = 14) Premedication: morphine and scopolamine Induction: fentanyl, thiopental, and pancuronium Maintenance: nitrous oxide, isoflurane, and fentanyl or epidural analgesia Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of mortality 2. Tracheal extubation **Others** 1. Ventilation/perfusion mismatch
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: none reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Quote: "randomization was achieved with sealed envelopes"
Allocation concealment (selection bias)	Low risk	Sealed envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Quote: "unblinded"
Blinding of outcome assessment (detection bias) All outcomes	High risk	Quote: "unblinded"
Incomplete outcome data (attrition bias) All outcomes	Low risk	One participant was excluded from the analyses (reoperation)
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Not in intention-to-treat

Tenling 1999 *(Continued)*

	Groups had similar demographic data

Usui 1990

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Japan Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	20 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Patients undergoing CABG due to myocardial infarction or unstable angina **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 10) **Comparator** 1. Systemic analgesia (N = 10) Induction: morphine and pancuronium Maintenance: nitrous oxide, morphine, and pancuronium Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of neurological complications (serious neurological complications from epidural analgesia) 2. Time to tracheal extubation 3. Haemodynamic variables **Others** 1. Postoperative sedation requirements
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Usui 1990 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "divided randomly"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Unclear risk	Groups had similar demographic data Additional co-analgesia for the systemic analgesia group only

Volk 2003

Methods	Parallel RCT Ethics committee: approved Informed consents: written informed consents obtained Site: Germany Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	26 participants; mean age: 66 years; sex distribution: 5 females and 21 males **Inclusion criteria** 1. Patients undergoing CABG for stable anginal with 3-vessel disease **Exclusion criteria** 1. LVEF < 0.4; left ventricular end diastolic pressure ≥ 17 mmHg 2. Clinically significant preexisting pulmonary diseases (determined by clinical examination, chest radiography, lung function tests, and blood gas analyses) 3. Insulin-dependent diabetes mellitus 4. Clinically relevant renal, hepatic, or cerebrovascular disease

Volk 2003 *(Continued)*

5. Patients with preoperative signs of infection (white cell blood count > 12,000/microlitre, body temperature > 38 degrees C, C-reactive protein > 5 mg/dL), chronic inflammatory disease
6. Patients treated with cyclo-oxygenase inhibitors, ticlopidine, or other drugs inhibiting thrombocyte functions within the last 7 days before the operation
7. Emergencies

Interventions	**Intervention** 1. Epidural analgesia (N = 13) **Comparator** 1. Systemic analgesia (N = 13) Premedication: oral midazolam 0.1 mg/kg Induction: etomidate 0.2 mg/kg Maintenance: midazolam, sufentanil, and pancuronium Surgery: CABG with CPB with a membrane oxygenator
Outcomes	**Relevant to this review** 1. Pain scores 2. Haemodynamic variables **Others** 1. Inflammatory response 2. Stress response
Notes	Correspondence: email sent 18 November 2018; no reply Conflict of interest: not reported DOI: 10.1016/S1043-4666(03)00090-5

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Randomization was performed using computer-generated random numbers
Allocation concealment (selection bias)	Low risk	Sealed opaque envelopes
Blinding of participants and personnel (performance bias) All outcomes	High risk	Not blinded
Blinding of outcome assessment (detection bias) All outcomes	High risk	Not blinded
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up

Volk 2003 *(Continued)*

Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Groups well balanced, except perhaps for sex distribution

Yang 1996

Methods	Parallel RCT Ethics committee: unspecified Informed consents: unspecified Site: Baogang Hospital, Baotou, China Setting: university hospital Dates of data collection: unspecified Funding: unspecified Registration: unspecified
Participants	21 participants; mean age: not reported; sex distribution: not reported **Inclusion criteria** 1. Patients with non-cyanotic congenital heart disease 2. Age > 15 years old 3. Weight > 35 kg 4. Undergoing CPB for open heart surgery **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural (N= 10) **Comparator** 1. Systemic analgesia (N= 11) Premedication: morphine and scopolamine Induction: thiopental, fentanyl, and pancuronium Maintenance: enflurane, pancuronium, and fentanyl or epidural analgesia Surgery: heart surgery for congenital heart disease with CPB
Outcomes	**Relevant to this review** 1. Haemodynamic variables **Others** 1. Markers of stress response (catecholamines)
Notes	Correspondence: letter sent 16 March 2018; no reply

Yang 1996 *(Continued)*

	Conflict of interest: not reported
	DOI:n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote:"randomly divided"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural mentioned Groups similar for preoperative cathecholamine values

Yilmaz 2007

Methods	Parallel RCT Ethics committee: approved by the ethics committee Informed consents: not reported Site: Yeditepe University Hospital, Department of Anesthesiology and Reanimation Anabilim; Psychiatry Ersek Chest Cardiovascular Center; Anesthesia Clinic and Special Swiss Hospital Breast Cardiovascular Anesthesiology, Turkey Setting: university hospital Dates of data collection: not reported Funding: unspecified Registration: unspecified
Participants	34 participants; mean age: 55.7 years; sex distribution: 7 females and 27 males **Inclusion criteria** 1. ASA II to III

Yilmaz 2007 *(Continued)*

	2. Aged < 70 years 3. LVEF > 40% 4. Undergoing elective CABG **Exclusion criteria** 1. Not reported
Interventions	**Intervention** 1. Epidural analgesia (N = 17) **Comparator** 1. Systemic analgesia (N = 17) Premedication: atropine and midazolam Induction: fentanyl, midazolam, and pancuronium Maintenance: fentanyl, midazolam, and isoflurane Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of pulmonary complications (pneumonia) 2. Time to tracheal extubation 3. Risk of neurological complications (serious neurological complications from epidural analgesia) 4. Pain scores 5. Haemodynamic variables **Others** 1. Rescue analgesia 2. Lung function tests
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"; no details provided
Allocation concealment (selection bias)	Unclear risk	Quote: "randomized"; no details provided
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Yilmaz 2007 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural mentioned Groups well balanced

Yung 1997

Methods	Parallel RCT Ethics committee: not reported Informed consents: obtained Site: Veterans General Hospital-Taipei and National Yang-Ming University School of Medicine, Taipei, Taiwan, ROC Setting: university hospital Dates of data collection: from June 1995 to December 1995 Funding: unspecified Registration: unspecified
Participants	40 participants; mean age: 66.6 years; sex distribution: 5 females and 35 males **Inclusion criteria** 1. Scheduled for CABG **Exclusion criteria** 1. LVEF < 30% 2. Previously prescribed digitalis and beta-blocker medications
Interventions	**Intervention** 1. Epidural analgesia (N = 20) **Comparator** 1. Systemic analgesia (N = 20) Induction and maintenance: etomidate, vecuronium, fentanyl, and isoflurane Surgery: CABG with CPB
Outcomes	**Relevant to this review** 1. Risk of pulmonary complications (respiratory depression) 2. Risk of neurological complications (risk of serious neurological complications from epidural analgesia) 3. Tracheal extubation 4. Pain scores

Yung 1997 *(Continued)*

	Others 1. Rescue analgesia
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: not reported DOI: n/a

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomly selected and randomly divided into two groups"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported
Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported Groups well balanced

Zawar 2015

Methods	Parallel RCT Ethics committee: approved by hospital research ethics committee Informed consents: written informed consents obtained Site: Institute of Critical Care Anesthesiology, Medanta - The Medicity, Gurgaon, Haryana, India Setting: tertiary care hospital Dates of data collection: between December 2011 and November 2014 Funding: departmental resources Registration: unspecified
Participants	81 participants; mean age: 74.6 years; sex distribution: 9 females and 72 males

Zawar 2015 *(Continued)*

	Inclusion criteria 1. Comorbidities (diabetes mellitus, chronic obstructive pulmonary disease, cerebrovascular disease, peripheral vascular disease, renal dysfunction) 2. Aged ≥ 70 years 3. Undergoing primary off-pump CABG **Exclusion criteria** 1. Infection over the spine 2. Coagulation disorders 3. Emergency cases 4. Unstable angina 5. Left main stem disease 6. Dysrhythmia 7. Undergoing combined procedures 8. On intra-aortic balloon counter-pulsation 9. On antiplatelet agent 10. Low-molecular-weight heparin 11. Heparin infusion
Interventions	**Intervention** 1. Epidural analgesia (N = 35) **Comparator** 1. Systemic analgesia (N = 46) Premedication: lorazepam and pantoprazole Induction: thiopentone sodium, fentanyl sulfate, and midazolam Maintenance: isoflurane, fentanyl, midazolam, and pancuronium or vecuronium bromide Surgery: off-pump CABG
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of neurological complications (cerebrovascular accident) 3. Tracheal extubation 4. Pain scores **Others** 1. Rescue analgesia 2. Markers of inflammation 3. Markers of stress response 4. Blood transfusion requirements 5. Time to mobilization 6. Acute kidney injury 7. ICU length of stay 8. Hospital length of stay
Notes	Correspondence: email sent 16 March 2018; no reply Conflict of interest: no conflicts of interest

Zawar 2015 *(Continued)*

DOI: 10.4103/0971-9784.159810

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Participants were randomized by computer-generated numbers
Allocation concealment (selection bias)	Low risk	Quote: "sealed envelopes"
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was a non-blinded study
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was a non-blinded study
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Five protocol violations were reported in participants allocated to the study group. Two epidural catheters were accidentally dislodged during shifting of the participant; 1 participant developed severe hypotension requiring a bolus of epinephrine during catheter placement without any clinical consequences; 1 off-pump CABG was converted to open CABG due to haemodynamic instability during surgery; and 1 participant withdrew consent from the trial. None of the participants had (quote:) “bloody tap” during epidural catheter placement
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	Not in intention-to-treat Groups well balanced

Zhou 2010

Methods	Parallel RCT Ethics committee: not reported Informed consents: not reported Site: Shandong University, Jinan, China Setting: university hospital Dates of data collection: from July 2007 to July 2009 Funding: departmental resources Registration: unspecified
Participants	30 participants; mean age: not reported; sex distribution: 11 females and 19 males **Inclusion criteria** 1. Patients undergoing cardiac thoracotomy

Zhou 2010 *(Continued)*

2. Aged 20 to 75 years old
3. Weighing 45 to 75 kg
4. ASA physical status I or II

Exclusion criteria

1. Allergic to opioids
2. Receiving long-term opioid treatment due to chronic pain and for other preoperative reasons
3. Needing postoperative mechanical ventilation
4. Preoperative forced vital capacity
5. Forced expiratory volume in 1 second
6. Peak expiratory flow < 80% of predicted value

Interventions	**Intervention** 1. Epidural analgesia (N = 15) **Comparator** 1. Systemic analgesia (N = 15) Induction and maintenance: not reported Surgery: unclear if surgeries were performed with or without cardiopulmonary bypass, classified as with CPB
Outcomes	**Relevant to this review** 1. Risk of myocardial infarction 2. Risk of pulmonary complications (respiratory depression) 3. Haemodynamic variables **Others** 1. Nausea and vomiting
Notes	Correspondence: letter sent 16 March 2018; no reply Conflict of interest: no conflict of interest DOI: 10.16252/j .cnki .issn1004-0501-2010.03.021

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Quote: "randomized"; no details provided
Allocation concealment (selection bias)	Unclear risk	Not reported
Blinding of participants and personnel (performance bias) All outcomes	Unclear risk	Not reported
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not reported

Zhou 2010 *(Continued)*

Incomplete outcome data (attrition bias) All outcomes	Low risk	No loss to follow-up
Selective reporting (reporting bias)	Low risk	All results reported
Other bias	Low risk	No failed epidural reported No significant differences between the 2 groups in general characteristics (P > 0.05)

APTT: activated partial thromboplastin time; ASA: American Society of Anesthesiologists; AVR: aortic valve replacement; BMI: body mass index; CABG: coronary artery bypass grafting; CK-MB: creatine kinase muscle/brain; CPB: cardiopulmonary bypass; ECG: electrocardiogram; EF: ejection fraction; FEV_1: forced expiratory volume in one second; FVC: forced vital capacity; GA: general anaesthesia; GATEA: general anaesthesia plus thoracic epidural analgesia; ICU: intensive care unit; INR: international normalized ratio; kg/m^2: kilogram per square meter; IM: intramuscularly; IV: intravenously; LVEF: left ventricular ejection fraction; n/a: not available; NSAID: non-steroidal anti-inflammatory drug; NYHA: New York Heart Association; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PCA: patient-controlled analgesia; PCEA: patient-controlled epidural analgesia; PT: prothrombin time; RCT: randomized controlled trial; TEA: thoracic epidural analgesia.

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

Study	Reason for exclusion
Amat-Santos 2012	Different study design: not an RCT: "depending on the preference of the anaesthesiologist responsible for the case"
Anderson 2005	Different study design: not an RCT: "the lack of randomization is a limitation"
Casalino 2006	Different study design: not an RCT: case series of 144 patients
Chae 1998	Different study design: classified as "no adequate sequence generation" by original review authors
Chakravarthy 2005	Different study design: prospective audit of cases conducted over a 13-year period
Crescenzi 2009	Different study design: not an RCT: case-matched, non-randomized study
Djaiani 2000	No original data
El-Morsy 2012a	Different study population: children
Jideus 2001	Different study design: classified as not randomized by previous review authors
Joachimsson 1989	Different study design: not an RCT: "two groups of consecutive patients meeting the inclusion criteria were investigated"
Kaunienė 2016	No outcome of interest measured
Kessler 2002	Different study design: not an RCT and different intervention: "use of TEA alone was applied in awake patients with multi-vessel coronary artery disease who underwent CABG via median sternotomy"
Kessler 2005	Different study design: classified as "no adequate sequence generation" by previous review authors

Study	Reason for exclusion
Kunstyr 2008	Different study population: pulmonary endarterectomy with cardiopulmonary bypass
Kurtoglu 2009	Different intervention: compares general vs epidural anaesthesia for minimally invasive direct coronary artery bypass
Lagunilla 2006	Different intervention: "In the post-operative period, 0.2% ropivacaine with 5 mg/ml fentanyl was used for analgesia in all patients, employing a patient controlled system"
Liang 2012	Different intervention: comparison between epidural anaesthesia perioperatively and postoperatively
Liem 1998	Different study design: not an RCT: case report
Martinez 2012	Different intervention: general anaesthesia compared with epidural anaesthesia or intrathecal morphine for beating heart surgery
Novikov 2011	Different study population: aorto-femoral bypass
Olivier 2005	Different intervention: comparison of 3 different epidural solutions
Orsolya 2015	Different study population: robot-assisted laparoscopic urogenital surgery
Ortega 2011	Different intervention: all participants had epidural analgesia with bupivacaine alone or bupivacaine plus morphine
Ovezov 2011	Different intervention: all participants had epidural analgesia
Rao 2016	Different intervention: all participants had epidural anaesthesia
Salman 2012	Different study design: not an RCT: "retrospective study"
Salvi 2004	Different study design: not an RCT: retrospective review of prospectively collected data
Schmidt 2005	Different intervention: all participants had epidural analgesia
Stenger 2013	Different study design: not an RCT: retrospective cohort study of prospectively registered data using population-based healthcare databases
Stenseth 1993	Different intervention: all participants had epidural analgesia and were randomized to light or deep general anaesthesia
Thorelius 1996	Different study design: not an RCT: classified as "no adequate sequence generation" by previous review authors
Thorelius 1997	Different study design: not an RCT
Toda 2013	Different study design: not an RCT: "in this prospective non-randomized study"
Turfrey 1997	Different study design: not an RCT: "Using computerised patient medical records, we analysed the frequency of respiratory, neurological, renal, gastrointestinal, haematological and cardiovascular complications in these two groups"
Yashiki 2005	Different intervention: TEA vs general anaesthesia

RCT: randomized controlled trial; TEA: thoracic epidural analgesia.

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

CTRI/2012/04/002608

Trial name or title	Non-analgesic benefits of combined thoracic epidural analgesia in elderly off-pump coronary artery bypass grafting patients
Methods	Randomized by sealed opaque envelope; blinded participants
Participants	Participants undergoing off-pump coronary artery bypass grafting Inclusion criteria: comorbidities Exclusion criteria: patient refusal, signs of infection over the spine, coagulation disorders, on antiplatelet agent, low-molecular-weight heparin or heparin infusion, emergency cases, unstable angina, left main stem disease, dysrhythmias, on steroids, undergoing combined procedures, on intra-aortic, balloon pulsation, on rosuvastatin
Interventions	Intervention: epidural analgesia (5 to 15 mL of ropivacaine 0.75% followed by 6 to 14 mL as an infusion) Comparator: unspecified
Outcomes	1. Stress response 2. Hypercoagulability
Starting date	Registered: 27 April 2012 Last refreshed: 14 January 2019 Status: opened to recruitment
Contact information	Dr. Bhanu Prakash Medanta - The Medicity, Sec-38, Haryana, Gurgaon, 122001, Sonipat, Hatyana, India Email: doctorbhanu@yahoo.in
Notes	Found 6 February 2019 Funded by Industry (AstraZeneca Pharma India Ltd,, Avishkar, PB No. 2483, Bellary Road, Hebbal, Bangalore 560024)

CTRI/2018/05/013902

Trial name or title	A study of central and mixed venous oxygen saturation with outcomes in open heart surgery patients between two groups conventional general anaesthesia and combined with perioperative thoracic epidural or intravenous analgesia
Methods	Randomized (computer generated; open list of random numbers; participant, investigator and outcome assessor blinded)
Participants	80 adults with coronary artery disease aged from 40 to 70 years Inclusion criteria: requiring off-pump open heart bypass surgery

CTRI/2018/05/013902 *(Continued)*

	Exclusion criteria: abnormal coagulation profiles, requiring salvage coronary artery bypass grafting, cardiogenic shock, heart valve pathology, antiplatelet therapy continuing local infection; renal, metabolic, neurological, or psychiatric disorders
Interventions	Intervention: epidural analgesia (10 mL bupivacaine 025%) Comparator: intravenous analgesia
Outcomes	1. Central venous and mixed venous oxygen saturation during intraoperative period and time for extubation and length of postoperative intensive care unit stay 2. Stress response, inotropic/vasodilatory support, pain outcome, and analgesia requirements 3. New arrhythmia, postoperative blood loss, perioperative myocardial infarction, neurological events, infective complication, if present 4. Any other adverse effects during the study period
Starting date	Started: 26 March 2013 Completed: 25 November 2013 Trial registered retrospectively: 5 May 2018 Unpublished results
Contact information	Dr. Chaitali Sen Professor and Head Institute of Post Graduate Medical Education & Research, Kolkata Department of Cardiac Anesthesiology IPGMER and SSKM Hospital, 242 A J C Bose Road Kolkata, West Bengal, 700020, India Email: chaitali03@rediffmail.com
Notes	Found on 6 February 2019

NCT03719248

Trial name or title	Thoracic epidural reduces risks of increased left ventricular mass index during coronary artery bypass graft surgery
Methods	Open-label, parallel, randomized controlled trial
Participants	80 ASA II to IV adults (65 to 75 years old) Inclusion criteria: aortic valve replacement with or without coronary artery bypass grafting Exclusion criteria: ejection fraction 0.3, myocardial infarction within the last 4 weeks, diabetes, severe pulmonary or arterial hypertension, a contraindication for epidural analgesia, administration of ticlopidine within 15 days before surgery and administration of platelet glycoprotein IIb/IIIa inhibitor, significant aortic insufficiency, emergency surgery, poor acoustic windows for adequate echocardiographic assessment, and/or did not undergo an echocardiogram before the operation
Interventions	Intervention: thoracic epidural Comparator: unspecified
Outcomes	1. Cardiac function 2. Other haemodynamic variables

NCT03719248 *(Continued)*	3. Myocardial ischaemia
Starting date	Started: 1 January 2017 Registered: 15 October 2018 Completed
Contact information	Not available
Notes	Found 6 February 2019

ASA: American Society of Anesthesiologists physical status.

DATA AND ANALYSES

Comparison 1. Epidural analgesia compared with systemic analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 0 to 30 days	38	3418	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.01]
1.1 With cardiopulmonary bypass	28	1844	Risk Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
1.2 Off-pump surgery	8	729	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.02]
1.3 With and without cardiopulmonary bypass	3	845	Risk Difference (IV, Fixed, 95% CI)	0.00 [-0.01, 0.01]
2 Mortality at 6 months	7	407	Risk Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.03]
2.1 With cardiopulmonary bypass	7	407	Risk Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.03]
3 Mortality at 1 year	5	849	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.00]
3.1 With cardiopulmonary bypass	4	197	Risk Difference (M-H, Fixed, 95% CI)	-0.02 [-0.07, 0.03]
3.2 With and without cardiopulmonary bypass	1	652	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.03, 0.01]
4 Myocardial infarction (0 to 30 days)	26	2713	Risk Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, 0.00]
4.1 With cardiopulmonary bypass	16	1153	Risk Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 Off-pump surgery	8	713	Risk Difference (IV, Fixed, 95% CI)	-0.01 [-0.03, 0.01]
4.3 With and without cardiopulmonary bypass	3	847	Risk Difference (IV, Fixed, 95% CI)	-0.00 [-0.03, 0.02]
5 Respiratory complications: respiratory depression (0 to 30 days)	21	1736	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.05, -0.01]
5.1 With cardiopulmonary bypass	15	1246	Risk Difference (M-H, Fixed, 95% CI)	-0.04 [-0.07, -0.01]
5.2 Off-pump surgery	5	299	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.05, 0.02]
5.3 With and without cardiopulmonary bypass	2	191	Risk Difference (M-H, Fixed, 95% CI)	0.01 [-0.06, 0.08]
6 Respiratory complications: pneumonia (0 to 30 days)	10	1107	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.07, 0.01]
6.1 With cardiopulmonary bypass	7	677	Risk Difference (M-H, Random, 95% CI)	-0.03 [-0.09, 0.04]
6.2 Off-pump surgery	3	322	Risk Difference (M-H, Random, 95% CI)	-0.02 [-0.07, 0.04]
6.3 With and without cardiopulmonary bypass	1	108	Risk Difference (M-H, Random, 95% CI)	-0.05 [-0.12, 0.01]
7 Atrial fibrillation or flutter within 2 weeks	18	2431	Risk Difference (M-H, Random, 95% CI)	-0.06 [-0.10, -0.01]
7.1 With cardiopulmonary bypass	11	1118	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.08, 0.00]
7.2 Off-pump surgery	6	551	Risk Difference (M-H, Random, 95% CI)	-0.09 [-0.22, 0.03]
7.3 With and without cardiopulmonary bypass	2	762	Risk Difference (M-H, Random, 95% CI)	-0.04 [-0.11, 0.03]
8 Neurological complications: cerebrovascular accident (0 to 30 days)	18	2232	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.01, 0.01]
8.1 With cardiopulmonary bypass	13	1067	Risk Difference (M-H, Fixed, 95% CI)	-0.01 [-0.02, 0.01]
8.2 Off-pump surgery	4	403	Risk Difference (M-H, Fixed, 95% CI)	-0.00 [-0.03, 0.03]
8.3 With and without cardiopulmonary bypass	2	762	Risk Difference (M-H, Fixed, 95% CI)	0.00 [-0.01, 0.01]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9 Neurological complications: epidural haematoma (0 to 30 days)	53	3982	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
9.1 With cardiopulmonary bypass	39	2231	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
9.2 Off-pump surgery	10	841	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.02, 0.02]
9.3 With and without cardiopulmonary bypass	4	910	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.01, 0.01]
10 Duration of tracheal intubation	40	3353	Std. Mean Difference (Random, 95% CI)	-0.78 [-1.01, -0.55]
10.1 Cardiopulmonary bypass	27	1570	Std. Mean Difference (Random, 95% CI)	-0.75 [-1.03, -0.47]
10.2 Off-pump surgery	11	943	Std. Mean Difference (Random, 95% CI)	-0.90 [-1.38, -0.41]
10.3 With and without cardiopulmonary bypass	3	840	Std. Mean Difference (Random, 95% CI)	-0.60 [-1.42, 0.23]
11 Duration of tracheal intubation in hours (for studies for which means and standard deviations could be extracted)	33	2062	Mean Difference (IV, Random, 95% CI)	-2.91 [-3.61, -2.21]
11.1 With cardiopulmonary bypass	23	1249	Mean Difference (IV, Random, 95% CI)	-3.23 [-4.30, -2.17]
11.2 Off-pump surgery	9	627	Mean Difference (IV, Random, 95% CI)	-1.87 [-3.36, -0.37]
11.3 With and without cardiopulmonary bypass	2	186	Mean Difference (IV, Random, 95% CI)	-4.42 [-5.62, -3.22]
12 Pain at rest at 6 to 8 hours after surgery	10	502	Std. Mean Difference (Random, 95% CI)	-1.35 [-1.98, -0.72]
12.1 With cardiopulmonary bypass	7	320	Std. Mean Difference (Random, 95% CI)	-0.83 [-1.16, -0.50]
12.2 Off-pump surgery	3	182	Std. Mean Difference (Random, 95% CI)	-2.99 [-5.37, -0.60]
13 Pain at rest at 6 to 8 hours: data available as means and standard deviations	5	272	Mean Difference (IV, Random, 95% CI)	-2.26 [-4.84, 0.32]
13.1 With cardiopulmonary bypass	2	90	Mean Difference (IV, Random, 95% CI)	-1.59 [-3.15, -0.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
13.2 Off-pump surgery	3	182	Mean Difference (IV, Random, 95% CI)	-2.74 [-6.36, 0.88]
14 Pain on movement/coughing at 6 to 8 hours	5	342	Std. Mean Difference (Random, 95% CI)	-1.39 [-2.16, -0.62]
14.1 With cardiopulmonary bypass	3	220	Std. Mean Difference (Random, 95% CI)	-1.41 [-2.65, -0.17]
14.2 Off-pump surgery	2	122	Std. Mean Difference (Random, 95% CI)	-1.43 [-2.36, -0.50]
15 Pain on movement/coughing at 6 to 8 hours: data available as means and standard deviations	3	162	Mean Difference (IV, Random, 95% CI)	-2.46 [-4.37, -0.54]
15.1 With cardiopulmonary bypass	1	40	Mean Difference (IV, Random, 95% CI)	-5.5 [-6.47, -4.53]
15.2 Off-pump surgery	2	122	Mean Difference (IV, Random, 95% CI)	-1.01 [-1.24, -0.78]
16 Pain at rest at 24 hours after surgery	22	2033	Std. Mean Difference (Random, 95% CI)	-0.93 [-1.22, -0.65]
16.1 With cardiopulmonary bypass	15	837	Std. Mean Difference (Random, 95% CI)	-0.80 [-1.06, -0.54]
16.2 Off-pump surgery	5	432	Std. Mean Difference (Random, 95% CI)	-2.06 [-3.15, -0.97]
16.3 With and without cardiopulmonary bypass	2	764	Std. Mean Difference (Random, 95% CI)	-0.24 [-0.38, -0.09]
17 Pain at rest at 24 hours: data available as means and standard deviations	15	875	Mean Difference (IV, Random, 95% CI)	-1.53 [-2.51, -0.55]
17.1 With cardiopulmonary bypass	10	526	Mean Difference (IV, Random, 95% CI)	-1.42 [-2.11, -0.73]
17.2 Off-pump surgery	4	239	Mean Difference (IV, Random, 95% CI)	-2.30 [-5.16, 0.56]
17.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	-0.17 [-0.78, 0.44]
18 Pain scores on movement/coughing at 24 hours	12	842	Std. Mean Difference (Random, 95% CI)	-0.83 [-1.18, -0.49]
18.1 With cardiopulmonary bypass	9	610	Std. Mean Difference (Random, 95% CI)	-0.90 [-1.25, -0.55]
18.2 Off-pump surgery	2	122	Std. Mean Difference (Random, 95% CI)	-1.03 [-1.69, -0.38]

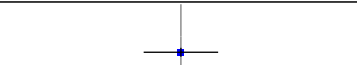
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
18.3 With and without cardiopulmonary bypass	1	110	Std. Mean Difference (Random, 95% CI)	0.22 [-0.15, 0.60]
19 Pain scores on movement/coughing at 24 hours: data available as means and standard deviations	9	582	Mean Difference (IV, Random, 95% CI)	-1.74 [-2.63, -0.86]
19.1 With cardiopulmonary bypass	6	350	Mean Difference (IV, Random, 95% CI)	-2.20 [-3.30, -1.10]
19.2 Off-pump surgery	2	122	Mean Difference (IV, Random, 95% CI)	-1.20 [-2.06, -0.34]
19.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	0.38 [-0.26, 1.02]
20 Pain at rest at 48 hours after surgery	15	1649	Std. Mean Difference (Random, 95% CI)	-1.01 [-1.37, -0.64]
20.1 With cardiopulmonary bypass	9	510	Std. Mean Difference (Random, 95% CI)	-0.76 [-1.08, -0.44]
20.2 Off-pump surgery	4	375	Std. Mean Difference (Random, 95% CI)	-2.11 [-3.17, -1.05]
20.3 With and without cardiopulmonary bypass	2	764	Std. Mean Difference (Random, 95% CI)	-0.25 [-0.39, -0.10]
21 Pain at rest at 48 hours after surgery: data available as means and standard deviations	11	692	Mean Difference (IV, Random, 95% CI)	-1.31 [-1.99, -0.64]
21.1 With cardiopulmonary bypass	7	400	Mean Difference (IV, Random, 95% CI)	-1.05 [-1.73, -0.37]
21.2 Off-pump surgery	3	182	Mean Difference (IV, Random, 95% CI)	-2.38 [-4.07, -0.70]
21.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	-0.26 [-0.83, 0.31]
22 Pain scores on movement/coughing at 48 hours	10	700	Std. Mean Difference (Random, 95% CI)	-0.83 [-1.31, -0.35]
22.1 With cardiopulmonary bypass	7	468	Std. Mean Difference (Random, 95% CI)	-0.78 [-1.22, -0.34]
22.2 Off-pump surgery	2	122	Std. Mean Difference (Random, 95% CI)	-1.56 [-3.09, -0.03]
22.3 With and without cardiopulmonary bypass	1	110	Std. Mean Difference (Random, 95% CI)	0.33 [-0.05, 0.70]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
23 Pain scores on movement/coughing at 48 hours: data available as means and standard deviations	9	582	Mean Difference (IV, Random, 95% CI)	-1.30 [0.00, -0.60]
23.1 With cardiopulmonary bypass	6	350	Mean Difference (IV, Random, 95% CI)	-1.61 [-2.56, -0.65]
23.2 Off-pump surgery	2	122	Mean Difference (IV, Random, 95% CI)	-1.22 [-1.99, -0.45]
23.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	0.64 [-0.09, 1.37]
24 Pain at rest at 72 hours after surgery	12	897	Std. Mean Difference (Random, 95% CI)	-1.09 [-1.57, -0.62]
24.1 With cardiopulmonary bypass	7	412	Std. Mean Difference (Random, 95% CI)	-0.99 [-1.66, -0.33]
24.2 Off-pump surgery	4	375	Std. Mean Difference (Random, 95% CI)	-1.54 [-2.14, -0.94]
24.3 With and without cardiopulmonary bypass	1	110	Std. Mean Difference (Random, 95% CI)	-0.01 [-0.38, 0.37]
25 Pain at rest at 72 hours after surgery: data available as means and standard deviations	10	624	Mean Difference (IV, Random, 95% CI)	-1.02 [-1.41, -0.63]
25.1 With cardiopulmonary bypass	6	332	Mean Difference (IV, Random, 95% CI)	-1.09 [-1.71, -0.46]
25.2 Off-pump surgery	3	182	Mean Difference (IV, Random, 95% CI)	-1.27 [-1.96, -0.59]
25.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	-0.01 [-0.47, 0.45]
26 Pain scores on movement/coughing at 72 hours	9	654	Std. Mean Difference (Random, 95% CI)	-0.62 [-1.13, -0.11]
26.1 With cardiopulmonary bypass	6	422	Std. Mean Difference (Random, 95% CI)	-0.40 [-0.90, 0.09]
26.2 Off-pump surgery	2	122	Std. Mean Difference (Random, 95% CI)	-1.69 [-3.32, -0.07]
26.3 With and without cardiopulmonary bypass	1	110	Std. Mean Difference (Random, 95% CI)	0.09 [-0.28, 0.47]
27 Pain scores on movement/coughing at 72 hours: data available as means and standard deviations	7	454	Mean Difference (IV, Random, 95% CI)	-0.90 [-1.49, -0.30]

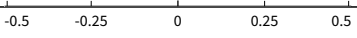
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
27.1 With cardiopulmonary bypass	4	222	Mean Difference (IV, Random, 95% CI)	-1.02 [-2.05, 0.02]
27.2 Off-pump surgery	2	122	Mean Difference (IV, Random, 95% CI)	-1.17 [-1.93, -0.42]
27.3 With and without cardiopulmonary bypass	1	110	Mean Difference (IV, Random, 95% CI)	0.19 [-0.57, 0.95]
28 Hypotension or vasopressor bolus during surgery	17	870	Risk Difference (M-H, Random, 95% CI)	0.21 [0.09, 0.33]
28.1 With cardiopulmonary bypass	14	637	Risk Difference (M-H, Random, 95% CI)	0.22 [0.08, 0.36]
28.2 Off-pump surgery	2	153	Risk Difference (M-H, Random, 95% CI)	0.09 [-0.30, 0.48]
28.3 With and without cardiopulmonary bypass	1	80	Risk Difference (M-H, Random, 95% CI)	0.3 [0.15, 0.45]
29 Needed vasopressor/inotropic infusion	23	1821	Risk Difference (M-H, Random, 95% CI)	0.00 [-0.06, 0.07]
29.1 With cardiopulmonary bypass	16	1237	Risk Difference (M-H, Random, 95% CI)	0.04 [-0.05, 0.13]
29.2 Off-pump surgery	6	506	Risk Difference (M-H, Random, 95% CI)	-0.08 [-0.21, 0.04]
29.3 With and without cardiopulmonary bypass	1	78	Risk Difference (M-H, Random, 95% CI)	0.0 [-0.05, 0.05]

Analysis 1.1. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 1 Mortality at 0 to 30 days.

Study or subgroup	Epidural n/N	Control n/N	Risk Difference IV, Fixed, 95% CI	Weight	Risk Difference IV, Fixed, 95% CI
1.1.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		0.39%	0[-0.11,0.11]
Onan 2013	0/20	0/20		0.53%	0[-0.09,0.09]
Fillinger 2002	1/30	0/30		0.59%	0.03[-0.05,0.12]
Kirno 1994	0/10	0/10		0.15%	0[-0.17,0.17]
Rein 1989	1/8	0/8		0.06%	0.13[-0.16,0.41]
El-Baz 1987	0/30	0/30		1.15%	0[-0.06,0.06]
Stenseth 1996	1/27	0/26		0.47%	0.04[-0.06,0.13]
Liem 1992	0/27	0/27		0.94%	0[-0.07,0.07]
Stenseth 1994	0/18	0/10		0.22%	0[-0.14,0.14]
Brix-Christensen 1998	0/8	0/8		0.1%	0[-0.21,0.21]
Barrington 2005	0/60	2/60		1.51%	-0.03[-0.09,0.02]



Study or subgroup	Epidural n/N	Control n/N	Risk Difference IV, Fixed, 95% CI	Weight	Risk Difference IV, Fixed, 95% CI
Jakobsen 2012	0/30	1/30		0.59%	-0.03[-0.12,0.05]
Berendes 2003	0/36	0/37		1.67%	0[-0.05,0.05]
Lundstrom 2005	0/26	0/24		0.81%	0[-0.07,0.07]
Bach 2002	0/13	1/27		0.28%	-0.04[-0.17,0.09]
Onan 2011	0/15	0/15		0.31%	0[-0.12,0.12]
Moore 1995	0/9	0/9		0.12%	0[-0.19,0.19]
Tenenbein 2008	0/25	0/25		0.81%	0[-0.07,0.07]
Kilickan 2006	0/40	1/40		1.02%	-0.02[-0.09,0.04]
Heijmans 2007	0/15	0/45		0.55%	0[-0.09,0.09]
Celik 2015	0/20	0/20		0.53%	0[-0.09,0.09]
Priestley 2002	1/50	0/50		1.57%	0.02[-0.03,0.07]
Nygard 2004	0/79	2/84		2.84%	-0.02[-0.06,0.02]
Royse 2003	0/37	1/39		0.95%	-0.03[-0.09,0.04]
Palomero 2008	1/10	0/12		0.09%	0.1[-0.13,0.33]
Neskovic 2013	1/18	0/27		0.26%	0.06[-0.08,0.19]
Tenling 1999	0/14	0/14		0.27%	0[-0.13,0.13]
Scott 2001	1/206	2/202		16.33%	-0.01[-0.02,0.01]
Subtotal (95% CI)	**898**	**946**		**35.12%**	**-0.01[-0.02,0.01]**
Total events: 7 (Epidural), 10 (Control)					
Heterogeneity: Tau^2=0; Chi^2=8.11, df=27(P=1); I^2=0%					
Test for overall effect: Z=0.89(P=0.37)					
1.1.2 Off-pump surgery					
Sharma 2010	0/30	0/30		1.15%	0[-0.06,0.06]
Mehta 2010	0/31	0/31		1.22%	0[-0.06,0.06]
Kendall 2004	0/10	0/20		0.23%	0[-0.14,0.14]
Bakhtiary 2007	0/66	0/66		5.32%	0[-0.03,0.03]
Neskovic 2013	0/17	0/19		0.43%	0[-0.1,0.1]
Kirov 2011	1/62	0/31		1.38%	0.02[-0.04,0.07]
de Vries 2002	0/30	0/60		1.82%	0[-0.05,0.05]
Caputo 2011	1/109	0/117		7.44%	0.01[-0.02,0.03]
Subtotal (95% CI)	**355**	**374**		**19%**	**0[-0.01,0.02]**
Total events: 2 (Epidural), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.47, df=7(P=1); I^2=0%					
Test for overall effect: Z=0.61(P=0.54)					
1.1.3 With and without cardiopulmonary bypass					
Hansdottir 2006	1/58	0/55		2.03%	0.02[-0.03,0.06]
Svircevic 2011	2/325	1/329		41.94%	0[-0.01,0.01]
Obersztyn 2018	0/39	0/39		1.9%	0[-0.05,0.05]
Subtotal (95% CI)	**422**	**423**		**45.88%**	**0[-0.01,0.01]**
Total events: 3 (Epidural), 1 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=0.71(P=0.48)					
Total (95% CI)	**1675**	**1743**		**100%**	**0[-0.01,0.01]**
Total events: 12 (Epidural), 11 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.56, df=38(P=1); I^2=0%					
Test for overall effect: Z=0.22(P=0.83)					
Test for subgroup differences: Chi^2=1.62, df=1 (P=0.44), I^2=0%					



Favours intervention

Favours comparator

Analysis 1.2. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 2 Mortality at 6 months.

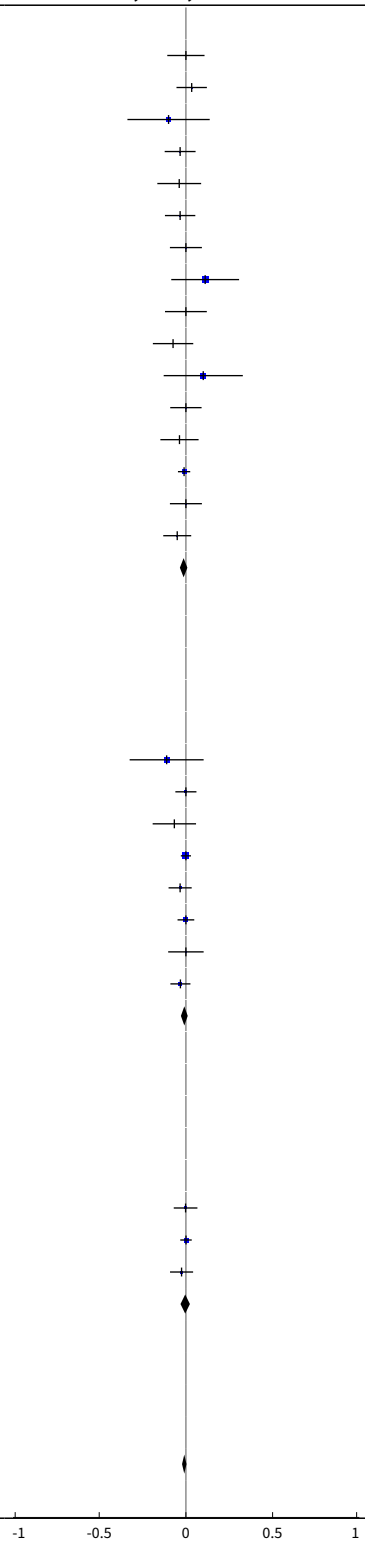
Study or subgroup	Epidural n/N	Control n/N	Risk Difference IV, Fixed, 95% CI	Weight	Risk Difference IV, Fixed, 95% CI
1.2.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		7.45%	0[-0.11,0.11]
Onan 2013	0/20	0/20		10.1%	0[-0.09,0.09]
Loick 1999	0/25	1/45		15.84%	-0.02[-0.1,0.05]
Berendes 2003	0/36	2/37		11.3%	-0.05[-0.14,0.03]
Celik 2015	0/20	0/20		10.1%	0[-0.09,0.09]
Tenenbein 2008	0/25	0/25		15.41%	0[-0.07,0.07]
Priestley 2002	1/50	0/50		29.8%	0.02[-0.03,0.07]
Subtotal (95% CI)	**193**	**214**		**100%**	**-0[-0.03,0.03]**
Total events: 1 (Epidural), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.3, df=6(P=0.89); I^2=0%					
Test for overall effect: Z=0.25(P=0.81)					
Total (95% CI)	**193**	**214**		**100%**	**-0[-0.03,0.03]**
Total events: 1 (Epidural), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.3, df=6(P=0.89); I^2=0%					
Test for overall effect: Z=0.25(P=0.81)					

Analysis 1.3. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 3 Mortality at 1 year.

Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.3.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		4%	0[-0.11,0.11]
Berendes 2003	0/36	2/37		8.6%	-0.05[-0.14,0.03]
Celik 2015	0/20	0/20		4.71%	0[-0.09,0.09]
Tenenbein 2008	0/25	0/25		5.89%	0[-0.07,0.07]
Subtotal (95% CI)	**98**	**99**		**23.2%**	**-0.02[-0.07,0.03]**
Total events: 0 (Epidural), 2 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.18, df=3(P=0.76); I^2=0%					
Test for overall effect: Z=0.83(P=0.41)					
1.3.2 With and without cardiopulmonary bypass					
Svircevic 2011	3/325	7/327		76.8%	-0.01[-0.03,0.01]
Subtotal (95% CI)	**325**	**327**		**76.8%**	**-0.01[-0.03,0.01]**
Total events: 3 (Epidural), 7 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.27(P=0.2)					
Total (95% CI)	**423**	**426**		**100%**	**-0.01[-0.03,0]**
Total events: 3 (Epidural), 9 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.14, df=4(P=0.89); I^2=0%					
Test for overall effect: Z=1.51(P=0.13)					
Test for subgroup differences: Chi^2=0.09, df=1 (P=0.76), I^2=0%					

Analysis 1.4. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 4 Myocardial infarction (0 to 30 days).

Study or subgroup	Epidural n/N	Control n/N	Risk Difference IV, Fixed, 95% CI	Weight	Risk Difference IV, Fixed, 95% CI
1.4.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		1.43%	0[-0.11,0.11]
Fillinger 2002	1/30	0/30		2.15%	0.03[-0.05,0.12]
Lyons 1998	0/10	1/10		0.29%	-0.1[-0.34,0.14]
Barrington 2005	3/60	5/60		2.07%	-0.03[-0.12,0.06]
Stenseth 1996	1/26	2/26		1.03%	-0.04[-0.16,0.09]
Jakobsen 2012	0/30	1/30		2.15%	-0.03[-0.12,0.05]
Onan 2013	0/20	0/20		1.94%	0[-0.09,0.09]
Stenseth 1994	2/18	0/10		0.43%	0.11[-0.08,0.31]
Onan 2011	0/15	0/15		1.13%	0[-0.12,0.12]
Liem 1992	0/27	2/27		1.21%	-0.07[-0.19,0.04]
Palomero 2008	1/10	0/12		0.32%	0.1[-0.13,0.33]
Heijmans 2007	0/15	0/45		2.02%	0[-0.09,0.09]
Neskovic 2013	0/18	1/27		1.36%	-0.04[-0.15,0.07]
Scott 2001	6/206	8/202		13.16%	-0.01[-0.05,0.02]
Celik 2015	0/20	0/20		1.94%	0[-0.09,0.09]
Kilickan 2006	0/40	2/40		2.53%	-0.05[-0.13,0.03]
Subtotal (95% CI)	**562**	**591**		**35.15%**	**-0.01[-0.03,0.01]**
Total events: 14 (Epidural), 22 (Control)					
Heterogeneity: Tau^2=0; Chi^2=7.05, df=15(P=0.96); I^2=0%					
Test for overall effect: Z=1.19(P=0.23)					
1.4.2 Off-pump surgery					
Kendall 2004	0/8	2/18		0.36%	-0.11[-0.32,0.1]
Mehta 2010	0/31	0/31		4.46%	0[-0.06,0.06]
Aguero-Martinez 2012	1/30	3/30		1.05%	-0.07[-0.19,0.06]
Bakhtiary 2007	0/66	0/66		19.38%	0[-0.03,0.03]
de Vries 2002	0/30	2/60		3.71%	-0.03[-0.1,0.03]
Zawar 2015	0/35	0/46		7.09%	0[-0.05,0.05]
Neskovic 2013	0/17	0/19		1.58%	0[-0.1,0.1]
Caputo 2011	4/109	8/117		4.93%	-0.03[-0.09,0.03]
Subtotal (95% CI)	**326**	**387**		**42.55%**	**-0.01[-0.03,0.01]**
Total events: 5 (Epidural), 15 (Control)					
Heterogeneity: Tau^2=0; Chi^2=3.41, df=7(P=0.84); I^2=0%					
Test for overall effect: Z=0.91(P=0.36)					
1.4.3 With and without cardiopulmonary bypass					
Hansdottir 2006	2/58	2/55		3.54%	-0[-0.07,0.07]
Svircevic 2011	16/325	16/329		15.05%	0[-0.03,0.03]
Obersztyn 2018	0/40	1/40		3.71%	-0.02[-0.09,0.04]
Subtotal (95% CI)	**423**	**424**		**22.3%**	**-0[-0.03,0.02]**
Total events: 18 (Epidural), 19 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=0.29(P=0.77)					
Total (95% CI)	**1311**	**1402**		**100%**	**-0.01[-0.02,0]**
Total events: 37 (Epidural), 56 (Control)					



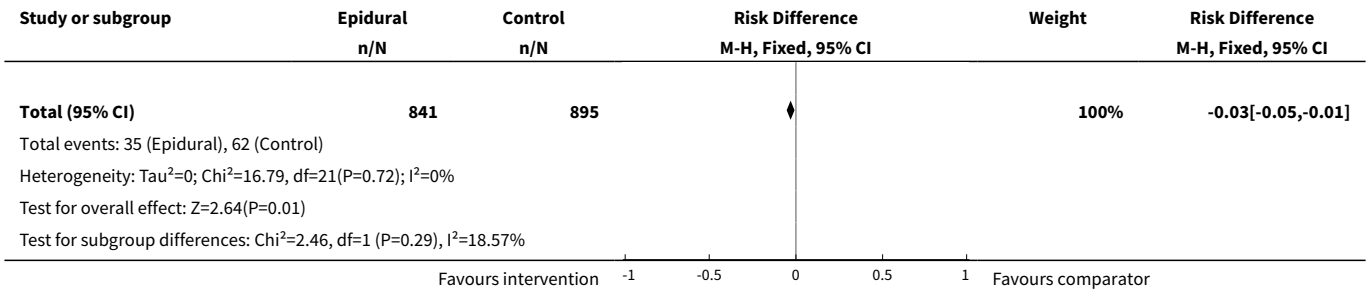
Study or subgroup	Epidural n/N	Control n/N	Risk Difference IV, Fixed, 95% CI	Weight	Risk Difference IV, Fixed, 95% CI
Heterogeneity: Tau²=0; Chi²=11.19, df=26(P=0.99); I²=0%					
Test for overall effect: Z=1.44(P=0.15)					
Test for subgroup differences: Chi²=0.27, df=1 (P=0.88), I²=0%					

Favours intervention -1 -0.5 0 0.5 1 Favours comparator

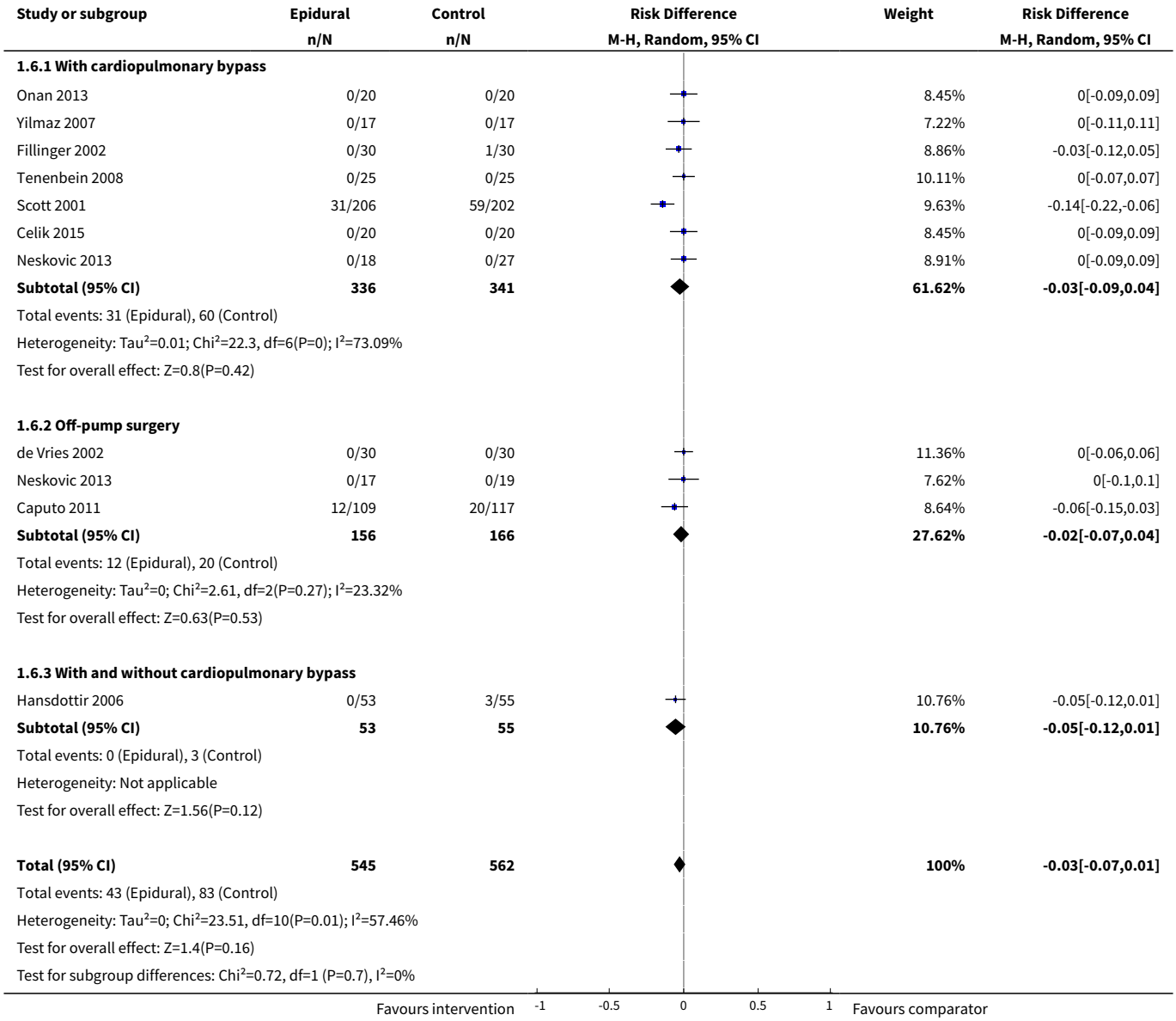
Analysis 1.5. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 5 Respiratory complications: respiratory depression (0 to 30 days).

Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.5.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		1.99%	0[-0.11,0.11]
El-Baz 1987	0/30	4/30		3.51%	-0.13[-0.27,-0]
Berendes 2003	0/36	2/36		4.21%	-0.06[-0.14,0.03]
Lundstrom 2005	1/25	2/21		2.67%	-0.06[-0.2,0.09]
Barrington 2005	1/60	2/60		7.01%	-0.02[-0.07,0.04]
Liem 1992	0/27	0/27		3.16%	0[-0.07,0.07]
Fillinger 2002	1/30	1/30		3.51%	0[-0.09,0.09]
Yung 1997	2/20	2/20		2.34%	0[-0.19,0.19]
Kunstyr 2001	0/20	2/61		3.52%	-0.03[-0.11,0.05]
Royse 2003	2/37	8/39		4.44%	-0.15[-0.3,-0]
Sen 2017	0/30	0/30		3.51%	0[-0.06,0.06]
Scott 2001	22/206	29/202		23.84%	-0.04[-0.1,0.03]
Tenenbein 2008	0/25	0/25		2.92%	0[-0.07,0.07]
Neskovic 2013	0/18	3/27		2.52%	-0.11[-0.25,0.03]
Celik 2015	0/20	0/20		2.34%	0[-0.09,0.09]
Subtotal (95% CI)	**601**	**645**		**71.47%**	**-0.04[-0.07,-0.01]**
Total events: 29 (Epidural), 55 (Control)					
Heterogeneity: Tau²=0; Chi²=12.28, df=14(P=0.58); I²=0%					
Test for overall effect: Z=2.77(P=0.01)					
1.5.2 Off-pump surgery					
Aguero-Martinez 2012	0/30	0/30		3.51%	0[-0.06,0.06]
Mehta 2010	0/31	0/31		3.62%	0[-0.06,0.06]
Neskovic 2013	0/17	0/19		2.1%	0[-0.1,0.1]
de Vries 2002	0/30	2/30		3.51%	-0.07[-0.17,0.04]
Zawar 2015	0/35	0/46		4.65%	0[-0.05,0.05]
Subtotal (95% CI)	**143**	**156**		**17.38%**	**-0.01[-0.05,0.02]**
Total events: 0 (Epidural), 2 (Control)					
Heterogeneity: Tau²=0; Chi²=1.71, df=4(P=0.79); I²=0%					
Test for overall effect: Z=0.77(P=0.44)					
1.5.3 With and without cardiopulmonary bypass					
Hansdottir 2006	6/58	5/55		6.6%	0.01[-0.1,0.12]
Obersztyn 2018	0/39	0/39		4.56%	0[-0.05,0.05]
Subtotal (95% CI)	**97**	**94**		**11.16%**	**0.01[-0.06,0.08]**
Total events: 6 (Epidural), 5 (Control)					
Heterogeneity: Tau²=0; Chi²=0.1, df=1(P=0.75); I²=0%					
Test for overall effect: Z=0.21(P=0.83)					

Favours intervention -1 -0.5 0 0.5 1 Favours comparator



Analysis 1.6. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 6 Respiratory complications: pneumonia (0 to 30 days).

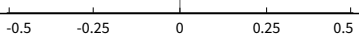


Analysis 1.7. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 7 Atrial fibrillation or flutter within 2 weeks.

Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.7.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		7.16%	0[-0.11,0.11]
Onan 2013	0/20	0/20		7.9%	0[-0.09,0.09]
Fillinger 2002	7/30	7/30		3.45%	0[-0.21,0.21]
Barrington 2005	16/60	20/60		4.85%	-0.07[-0.23,0.1]
Priestley 2002	11/50	10/50		4.98%	0.02[-0.14,0.18]
Royse 2003	12/37	14/39		3.47%	-0.03[-0.25,0.18]
Scott 2001	21/206	45/202		8.99%	-0.12[-0.19,-0.05]
Palomero 2008	2/10	1/12		2.15%	0.12[-0.18,0.41]
Neskovic 2013	4/18	10/27		2.53%	-0.15[-0.41,0.12]
Nygard 2004	32/79	30/84		5.36%	0.05[-0.1,0.2]
Tenenbein 2008	6/25	9/25		2.73%	-0.12[-0.37,0.13]
Subtotal (95% CI)	**552**	**566**		**53.59%**	**-0.04[-0.08,0]**
Total events: 111 (Epidural), 146 (Control)					
Heterogeneity: Tau^2=0; Chi^2=10.68, df=10(P=0.38); I^2=6.39%					
Test for overall effect: Z=1.86(P=0.06)					
1.7.2 Off-pump surgery					
Aguero-Martinez 2012	0/30	8/30		4.86%	-0.27[-0.43,-0.1]
Kundu 2007	0/20	2/20		5.21%	-0.1[-0.25,0.05]
Bakhtiary 2007	2/66	18/66		6.79%	-0.24[-0.36,-0.13]
de Vries 2002	3/28	2/29		5.44%	0.04[-0.11,0.19]
Caputo 2011	22/109	41/117		6.81%	-0.15[-0.26,-0.03]
Neskovic 2013	4/17	0/19		3.51%	0.24[0.02,0.45]
Subtotal (95% CI)	**270**	**281**		**32.63%**	**-0.09[-0.22,0.03]**
Total events: 31 (Epidural), 71 (Control)					
Heterogeneity: Tau^2=0.02; Chi^2=23.24, df=5(P=0); I^2=78.49%					
Test for overall effect: Z=1.43(P=0.15)					
1.7.3 With and without cardiopulmonary bypass					
Hansdottir 2006	11/53	13/55		5.09%	-0.03[-0.19,0.13]
Svircevic 2011	156/325	173/329		8.7%	-0.05[-0.12,0.03]
Subtotal (95% CI)	**378**	**384**		**13.79%**	**-0.04[-0.11,0.03]**
Total events: 167 (Epidural), 186 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.85); I^2=0%					
Test for overall effect: Z=1.21(P=0.23)					
Total (95% CI)	**1200**	**1231**		**100%**	**-0.06[-0.1,-0.01]**
Total events: 309 (Epidural), 403 (Control)					
Heterogeneity: Tau^2=0.01; Chi^2=38.87, df=18(P=0); I^2=53.69%					
Test for overall effect: Z=2.3(P=0.02)					
Test for subgroup differences: Chi^2=0.58, df=1 (P=0.75), I^2=0%					

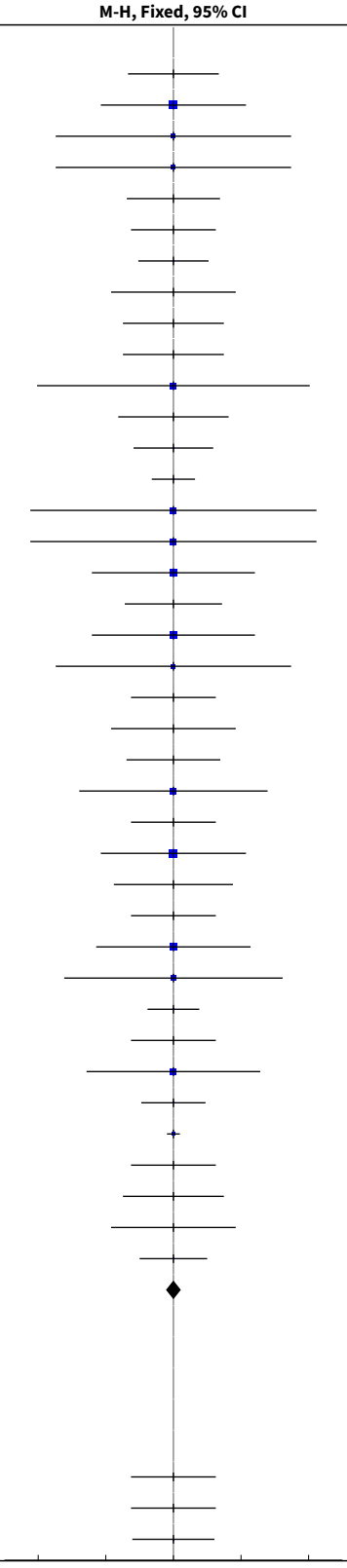
Analysis 1.8. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 8 Neurological complications: cerebrovascular accident (0 to 30 days).

Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.8.1 With cardiopulmonary bypass					
Bektas 2015	0/17	0/17		1.54%	0[-0.11,0.11]
Stenseth 1996	1/26	0/26		2.35%	0.04[-0.06,0.14]
Jakobsen 2012	1/30	0/30		2.71%	0.03[-0.05,0.12]
Barrington 2005	0/60	1/60		5.42%	-0.02[-0.06,0.03]
Onan 2013	0/20	0/20		1.81%	0[-0.09,0.09]
Fillinger 2002	1/30	1/30		2.71%	0[-0.09,0.09]
Neskovic 2013	0/18	0/27		1.95%	0[-0.09,0.09]
Palomero 2008	0/10	0/12		0.99%	0[-0.16,0.16]
Royse 2003	0/37	0/39		3.43%	0[-0.05,0.05]
Celik 2015	0/20	0/20		1.81%	0[-0.09,0.09]
Tenenbein 2008	0/25	0/25		2.26%	0[-0.07,0.07]
Scott 2001	2/206	6/202		18.43%	-0.02[-0.05,0.01]
Heijmans 2007	0/15	0/45		2.03%	0[-0.09,0.09]
Subtotal (95% CI)	**514**	**553**		**47.44%**	**-0.01[-0.02,0.01]**
Total events: 5 (Epidural), 8 (Control)					
Heterogeneity: Tau^2=0; Chi^2=2.97, df=12(P=1); I^2=0%					
Test for overall effect: Z=0.63(P=0.53)					
1.8.2 Off-pump surgery					
Aguero-Martinez 2012	1/30	0/30		2.71%	0.03[-0.05,0.12]
Neskovic 2013	0/17	1/19		1.62%	-0.05[-0.19,0.09]
Caputo 2011	2/117	2/109		10.2%	-0[-0.04,0.03]
Zawar 2015	0/35	0/46		3.59%	0[-0.05,0.05]
Subtotal (95% CI)	**199**	**204**		**18.13%**	**-0[-0.03,0.03]**
Total events: 3 (Epidural), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=1.12, df=3(P=0.77); I^2=0%					
Test for overall effect: Z=0.03(P=0.98)					
1.8.3 With and without cardiopulmonary bypass					
Hansdottir 2006	1/53	2/55		4.88%	-0.02[-0.08,0.04]
Svircevic 2011	2/325	1/329		29.55%	0[-0.01,0.01]
Subtotal (95% CI)	**378**	**384**		**34.43%**	**0[-0.01,0.01]**
Total events: 3 (Epidural), 3 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0.62, df=1(P=0.43); I^2=0%					
Test for overall effect: Z=0.03(P=0.98)					
Total (95% CI)	**1091**	**1141**		**100%**	**-0[-0.01,0.01]**
Total events: 11 (Epidural), 14 (Control)					
Heterogeneity: Tau^2=0; Chi^2=5.91, df=18(P=1); I^2=0%					
Test for overall effect: Z=0.5(P=0.62)					
Test for subgroup differences: Chi^2=0.3, df=1 (P=0.86), I^2=0%					

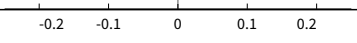


Analysis 1.9. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 9 Neurological complications: epidural haematoma (0 to 30 days).

Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
1.9.1 With cardiopulmonary bypass					
Huh 2004	0/27	0/29		1.42%	0[-0.07,0.07]
Bektas 2015	0/17	0/17		0.86%	0[-0.11,0.11]
Usui 1990	0/10	0/10		0.51%	0[-0.17,0.17]
Hutchenson 2006	0/10	0/10		0.51%	0[-0.17,0.17]
Kunstyr 2001	0/20	0/61		1.53%	0[-0.07,0.07]
Kilickan 2008	0/30	0/30		1.52%	0[-0.06,0.06]
Berendes 2003	0/36	0/37		1.85%	0[-0.05,0.05]
Onan 2013	0/20	0/20		1.02%	0[-0.09,0.09]
El-Morsy 2012	0/25	0/25		1.27%	0[-0.07,0.07]
Lundstrom 2005	0/25	0/25		1.27%	0[-0.07,0.07]
Moore 1995	0/8	0/9		0.43%	0[-0.2,0.2]
Loick 1999	0/25	0/21		1.16%	0[-0.08,0.08]
Gurses 2013	0/32	0/32		1.62%	0[-0.06,0.06]
Barrington 2005	0/60	0/60		3.05%	0[-0.03,0.03]
Brix-Christensen 1998	0/8	0/8		0.41%	0[-0.21,0.21]
Rein 1989	0/8	0/8		0.41%	0[-0.21,0.21]
Zhou 2010	0/15	0/15		0.76%	0[-0.12,0.12]
Stenseth 1996	0/26	0/26		1.32%	0[-0.07,0.07]
Onan 2011	0/15	0/15		0.76%	0[-0.12,0.12]
Kirno 1994	0/10	0/10		0.51%	0[-0.17,0.17]
El-Baz 1987	0/30	0/30		1.52%	0[-0.06,0.06]
Yung 1997	0/20	0/20		1.02%	0[-0.09,0.09]
Liem 1992	0/27	0/27		1.37%	0[-0.07,0.07]
Stenseth 1994	0/20	0/10		0.68%	0[-0.14,0.14]
Jakobsen 2012	0/30	0/30		1.52%	0[-0.06,0.06]
Yilmaz 2007	0/17	0/17		0.86%	0[-0.11,0.11]
Greisen 2012	0/21	0/21		1.07%	0[-0.09,0.09]
Fillinger 2002	0/30	0/30		1.52%	0[-0.06,0.06]
Mishra 2004	0/17	0/15		0.81%	0[-0.11,0.11]
Palomero 2008	0/10	0/12		0.55%	0[-0.16,0.16]
Priestley 2002	0/50	0/50		2.54%	0[-0.04,0.04]
Heijmans 2007	0/30	0/30		1.52%	0[-0.06,0.06]
Tenling 1999	0/14	0/14		0.71%	0[-0.13,0.13]
Kilickan 2006	0/40	0/40		2.03%	0[-0.05,0.05]
Scott 2001	0/206	0/202		10.35%	0[-0.01,0.01]
Sen 2017	0/30	0/30		1.52%	0[-0.06,0.06]
Tenenbein 2008	0/25	0/25		1.27%	0[-0.07,0.07]
Celik 2015	0/20	0/20		1.02%	0[-0.09,0.09]
Royse 2003	0/37	0/39		1.93%	0[-0.05,0.05]
Subtotal (95% CI)	**1101**	**1130**		**55.98%**	**0[-0.01,0.01]**
Total events: 0 (Epidural), 0 (Control)					
Heterogeneity: Tau²=0; Chi²=0, df=38(P=1); I²=0%					
Test for overall effect: Not applicable					
1.9.2 Off-pump surgery					
Aguero-Martinez 2012	0/30	0/30		1.52%	0[-0.06,0.06]
Sharma 2010	0/30	0/30		1.52%	0[-0.06,0.06]
Mehta 2010	0/31	0/31		1.57%	0[-0.06,0.06]

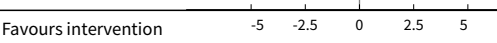


Study or subgroup	Epidural n/N	Control n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
Kendall 2004	0/10	0/20		0.68%	0[-0.14,0.14]
Kundu 2007	0/20	0/20		1.02%	0[-0.09,0.09]
Bakhtiary 2007	0/66	0/66		3.35%	0[-0.03,0.03]
Caputo 2011	0/109	0/117		5.73%	0[-0.02,0.02]
Kirov 2011	0/60	0/30		2.03%	0[-0.05,0.05]
de Vries 2002	0/30	0/30		1.52%	0[-0.06,0.06]
Zawar 2015	0/35	0/46		2.02%	0[-0.05,0.05]
Subtotal (95% CI)	**421**	**420**		**20.96%**	**0[-0.02,0.02]**
Total events: 0 (Epidural), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=9(P=1); I^2=0%					
Test for overall effect: Not applicable					
1.9.3 With and without cardiopulmonary bypass					
Svircevic 2011	0/325	0/329		16.6%	0[-0.01,0.01]
Hansdottir 2006	0/48	0/49		2.46%	0[-0.04,0.04]
Obersztyn 2018	0/39	0/39		1.98%	0[-0.05,0.05]
Neskovic 2013	0/35	0/46		2.02%	0[-0.05,0.05]
Subtotal (95% CI)	**447**	**463**		**23.06%**	**0[-0.01,0.01]**
Total events: 0 (Epidural), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=3(P=1); I^2=0%					
Test for overall effect: Not applicable					
Total (95% CI)	**1969**	**2013**		**100%**	**0[-0.01,0.01]**
Total events: 0 (Epidural), 0 (Control)					
Heterogeneity: Tau^2=0; Chi^2=0, df=52(P=1); I^2=0%					
Test for overall effect: Not applicable					
Test for subgroup differences: Not applicable					

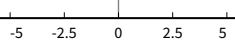


Analysis 1.10. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 10 Duration of tracheal intubation.

Study or subgroup	Epidural N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.10.1 Cardiopulmonary bypass						
Barrington 2005	60	60	-0.7 (0.189)		2.33%	-0.74[-1.11,-0.37]
Berendes 2003	36	37	-1.7 (0.275)		2.18%	-1.74[-2.28,-1.2]
Celik 2015	20	20	-0.7 (0.325)		2.08%	-0.68[-1.32,-0.04]
El-Baz 1987	30	30	-2.2 (0.326)		2.08%	-2.18[-2.82,-1.54]
El-Morsy 2012	25	25	-0.5 (0.287)		2.16%	-0.46[-1.02,0.1]
Fawcett 1997	8	8	-1.8 (0.597)		1.5%	-1.85[-3.02,-0.68]
Fillinger 2002	30	30	1.1 (0.276)		2.18%	1.05[0.51,1.59]
Gurses 2013	32	32	-1.5 (0.281)		2.17%	-1.45[-2.01,-0.9]
Huh 2004	27	29	-1.5 (0.301)		2.13%	-1.46[-2.05,-0.87]
Jakobsen 2012	30	30	0.1 (0.259)		2.22%	0.15[-0.36,0.65]
Kilickan 2006	20	20	-1.4 (0.351)		2.03%	-1.35[-2.04,-0.67]
Kilickan 2006	20	20	0.3 (0.318)		2.1%	0.3[-0.33,0.92]
Kilickan 2008	15	15	-0.5 (0.371)		1.98%	-0.5[-1.23,0.22]



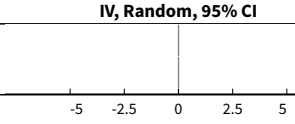
Study or subgroup	Epidural N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Kilickan 2008	15	15	-0.4 (0.37)		1.99%	-0.44[-1.17,0.28]
Konishi 1995	31	18	-0.6 (0.302)		2.13%	-0.59[-1.18,0]
Konishi 1995	31	18	-0.8 (0.308)		2.12%	-0.83[-1.44,-0.23]
Kunstyr 2001	7	20	-0.1 (0.439)		1.84%	-0.06[-0.92,0.8]
Kunstyr 2001	7	20	-0.3 (0.441)		1.83%	-0.31[-1.18,0.55]
Kunstyr 2001	7	21	0.1 (0.437)		1.84%	0.1[-0.75,0.96]
Lenkutis 2009	30	30	0.7 (0.266)		2.2%	0.68[0.16,1.2]
Liem 1992	25	25	-2 (0.331)		2.07%	-1.95[-2.6,-1.31]
Loick 1999	25	21	-0.7 (0.305)		2.12%	-0.72[-1.32,-0.12]
Neskovic 2013	18	27	-0.4 (0.308)		2.12%	-0.43[-1.03,0.17]
Onan 2013	20	20	-1.6 (0.361)		2.01%	-1.56[-2.27,-0.86]
Palomero 2008	10	12	-0.1 (0.429)		1.86%	-0.15[-0.99,0.69]
Priestley 2002	58	60	-0.7 (0.19)		2.33%	-0.74[-1.12,-0.37]
Royse 2003	37	39	-1 (0.243)		2.24%	-0.99[-1.47,-0.51]
Stenseth 1996	26	26	-1.8 (0.334)		2.06%	-1.83[-2.48,-1.17]
Stritesky 2006	15	15	-0.9 (0.386)		1.95%	-0.9[-1.65,-0.14]
Tenenbein 2008	25	25	0.2 (0.283)		2.17%	0.18[-0.38,0.73]
Tenling 1999	14	14	-2 (0.462)		1.79%	-1.98[-2.89,-1.08]
Yilmaz 2007	17	17	-1.1 (0.369)		1.99%	-1.12[-1.85,-0.4]
Subtotal (95% CI)					**65.81%**	**-0.75[-1.03,-0.47]**
Heterogeneity: Tau²=0.54; Chi²=206.24, df=31(P<0.0001); I²=84.97%						
Test for overall effect: Z=5.29(P<0.0001)						
1.10.2 Off-pump surgery						
Aguero-Martinez 2012	29	30	-1.6 (0.297)		2.14%	-1.62[-2.2,-1.03]
Bakhtiary 2007	66	66	-0.3 (0.175)		2.35%	-0.3[-0.64,0.05]
Caputo 2011	109	117	-0.4 (0.135)		2.41%	-0.44[-0.71,-0.18]
de Vries 2002	28	29	-0.7 (0.272)		2.19%	-0.66[-1.19,-0.12]
Kendall 2004	5	10	-0.5 (0.555)		1.59%	-0.49[-1.58,0.6]
Kendall 2004	5	10	-0.4 (0.552)		1.59%	-0.38[-1.46,0.7]
Kirov 2011	30	15	-0.7 (0.324)		2.08%	-0.67[-1.3,-0.03]
Kirov 2011	30	15	-0.5 (0.32)		2.09%	-0.48[-1.1,0.15]
Mehta 2010	31	31	-0.9 (0.266)		2.2%	-0.89[-1.41,-0.37]
Neskovic 2013	17	19	-0.4 (0.337)		2.06%	-0.37[-1.03,0.29]
Petrovski 2006	56	54	-4.4 (0.355)		2.02%	-4.35[-5.05,-3.66]
Sharma 2010	30	30	-0.9 (0.27)		2.19%	-0.86[-1.39,-0.33]
Zawar 2015	35	46	-0.2 (0.225)		2.28%	-0.21[-0.65,0.23]
Subtotal (95% CI)					**27.19%**	**-0.9[-1.38,-0.41]**
Heterogeneity: Tau²=0.69; Chi²=132.2, df=12(P<0.0001); I²=90.92%						
Test for overall effect: Z=3.63(P=0)						
1.10.3 With and without cardiopulmonary bypass						
Hansdottir 2006	53	55	-0.4 (0.194)		2.33%	-0.36[-0.74,0.02]
Obersztyn 2018	39	39	-1.6 (0.26)		2.21%	-1.56[-2.07,-1.05]
Svircevic 2011	325	329	0 (0.078)		2.46%	0.04[-0.11,0.2]
Subtotal (95% CI)					**7%**	**-0.6[-1.42,0.23]**
Heterogeneity: Tau²=0.5; Chi²=36.65, df=2(P<0.0001); I²=94.54%						
Test for overall effect: Z=1.42(P=0.16)						
Total (95% CI)					**100%**	**-0.78[-1.01,-0.55]**
Heterogeneity: Tau²=0.54; Chi²=424.81, df=47(P<0.0001); I²=88.94%						



Favours intervention

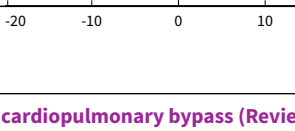
Favours comparator

Study or subgroup	Epidural N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Test for overall effect: Z=6.73(P<0.0001)						
Test for subgroup differences: Chi²=0.44, df=1 (P=0.8), I²=0%						



Analysis 1.11. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 11 Duration of tracheal intubation in hours (for studies for which means and standard deviations could be extracted).

Study or subgroup	Intervention N	Intervention Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.11.1 With cardiopulmonary bypass							
El-Baz 1987	30	9 (3)	30	18 (5)		2.58%	-9[-11.09,-6.91]
Liem 1992	25	7.7 (6.6)	25	19 (4.8)		1.97%	-11.28[-14.48,-8.08]
Konishi 1995	31	6.6 (3.7)	18	9.2 (5.4)		2.17%	-2.6[-5.41,0.21]
Konishi 1995	31	5.8 (3.1)	18	9.2 (5.4)		2.22%	-3.4[-6.12,-0.68]
Stenseth 1996	26	5.4 (2)	26	10.8 (3.6)		2.86%	-5.4[-6.98,-3.82]
Fawcett 1997	8	5.8 (1)	8	9.2 (2.4)		2.74%	-3.4[-5.2,-1.6]
Tenling 1999	14	3.6 (0.5)	14	8 (3.1)		2.83%	-4.35[-5.98,-2.72]
Loick 1999	25	10 (2.7)	21	14.6 (9.2)		1.57%	-4.65[-8.7,-0.6]
Kunstyr 2001	7	6.1 (2.9)	20	6.3 (3.4)		2.26%	-0.19[-2.83,2.45]
Kunstyr 2001	7	6.1 (2.9)	21	5.8 (2.4)		2.4%	0.26[-2.13,2.65]
Kunstyr 2001	7	6.1 (2.9)	20	7 (3)		2.32%	-0.93[-3.47,1.61]
Fillinger 2002	30	10.7 (1.4)	37	9.5 (0.8)		3.28%	1.2[0.64,1.76]
Berendes 2003	36	3.4 (1.9)	37	9.2 (4.3)		2.89%	-5.8[-7.32,-4.28]
Royse 2003	37	2.6 (2.5)	39	5.4 (3.1)		3.02%	-2.8[-4.06,-1.54]
Huh 2004	27	4.6 (4.8)	29	13.4 (7)		2.01%	-8.82[-11.94,-5.7]
Kilickan 2006	20	10 (5.3)	20	8.5 (4.7)		2.01%	1.48[-1.64,4.6]
Kilickan 2006	20	7.6 (6.1)	20	14.6 (4.2)		1.95%	-7.05[-10.28,-3.82]
Yilmaz 2007	17	7.4 (1.4)	17	9.4 (2)		3.08%	-1.93[-3.07,-0.79]
Tenenbein 2008	25	0.3 (0.6)	25	0.2 (0.2)		3.34%	0.09[-0.17,0.35]
Kilickan 2008	15	5 (3.2)	15	6.6 (4)		2.29%	-1.6[-4.19,0.99]
Kilickan 2008	15	5.5 (2.6)	15	7 (3.3)		2.56%	-1.5[-3.63,0.63]
Palomero 2008	10	11.7 (7.5)	12	12.5 (2.4)		1.28%	-0.8[-5.65,4.05]
Lenkutis 2009	30	6 (0.6)	30	11.1 (1.6)		3.26%	-5.02[-5.64,-4.4]
El-Morsy 2012	25	7.3 (6.4)	25	10.7 (8.2)		1.56%	-3.4[-7.48,0.68]
Neskovic 2013	18	6.7 (4.7)	27	8.8 (5.3)		2.11%	-2.16[-5.09,0.77]
Onan 2013	20	2.9 (1.1)	20	4.7 (1.2)		3.24%	-1.8[-2.51,-1.09]
Gurses 2013	32	4.1 (1.7)	32	6.8 (2)		3.17%	-2.7[-3.61,-1.79]
Celik 2015	20	7.2 (1.8)	20	11.7 (2)		3.05%	-4.5[-5.69,-3.31]
Subtotal * **	**608**		**641**			**70.02%**	**-3.23[-4.3,-2.17]**
Heterogeneity: Tau²=6.87; Chi²=582.93, df=27(P<0.0001); I²=95.37%							
Test for overall effect: Z=5.95(P<0.0001)							
1.11.2 Off-pump surgery							
de Vries 2002	28	0.2 (0.1)	29	0.2 (0.1)		3.35%	-0.07[-0.12,-0.02]
Kendall 2004	5	5.3 (4.1)	10	6.6 (3.1)		1.56%	-1.3[-5.38,2.78]
Kendall 2004	5	5.3 (4.1)	10	6.9 (2.8)		1.6%	-1.6[-5.59,2.39]
Petrovski 2006	56	3.5 (0.8)	54	6.8 (0.7)		3.33%	-3.3[-3.58,-3.02]
Bakhtiary 2007	66	6 (2.3)	66	7 (4.2)		3.07%	-1[-2.16,0.16]



Study or subgroup	Intervention N	Intervention Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Sharma 2010	30	9.3 (2.2)	30	11.7 (3)		2.98%	-2.34[-3.69,-0.99]
Mehta 2010	31	10.8 (3.2)	31	13.5 (2.9)		2.9%	-2.7[-4.21,-1.19]
Aguero-Martinez 2012	29	4.5 (2.8)	30	7.8 (5.2)		2.55%	-3.31[-5.45,-1.17]
Neskovic 2013	17	4.4 (4.3)	19	5.8 (3.5)		2.3%	-1.43[-4.01,1.15]
Zawar 2015	35	14.2 (8.2)	46	15.5 (3.9)		2.1%	-1.3[-4.24,1.64]
Subtotal ***	**302**		**325**			**25.74%**	**-1.87[-3.36,-0.37]**
Heterogeneity: Tau²=4.62; Chi²=524.23, df=9(P<0.0001); I²=98.28%							
Test for overall effect: Z=2.45(P=0.01)							
1.11.3 With and without cardiopulmonary bypass							
Hansdottir 2006	53	2.3 (1.1)	55	7.3 (19.2)		1.21%	-5[-10.08,0.08]
Obersztyn 2018	39	3.6 (2.6)	39	8 (2.9)		3.03%	-4.38[-5.62,-3.15]
Subtotal ***	**92**		**94**			**4.24%**	**-4.42[-5.62,-3.22]**
Heterogeneity: Tau²=0; Chi²=0.05, df=1(P=0.82); I²=0%							
Test for overall effect: Z=7.23(P<0.0001)							
Total ***	**1002**		**1060**			**100%**	**-2.91[-3.61,-2.21]**
Heterogeneity: Tau²=3.78; Chi²=1261.01, df=39(P<0.0001); I²=96.91%							
Test for overall effect: Z=8.17(P<0.0001)							
Test for subgroup differences: Chi²=6.88, df=1 (P=0.03), I²=70.94%							

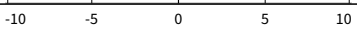
Analysis 1.12. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 12 Pain at rest at 6 to 8 hours after surgery.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.12.1 With cardiopulmonary bypass						
Bektas 2015	17	17	-0.7 (0.355)		10.04%	-0.7[-1.39,-0]
Fillinger 2002	32	32	-0.9 (0.262)		10.63%	-0.86[-1.38,-0.35]
Onan 2013	20	20	-1.7 (0.377)		9.88%	-1.75[-2.49,-1.01]
Greisen 2012	21	21	-1.1 (0.343)		10.12%	-1.13[-1.8,-0.46]
El-Morsy 2012	25	25	-0.3 (0.285)		10.5%	-0.29[-0.85,0.27]
Sen 2017	30	20	-0.5 (0.293)		10.44%	-0.48[-1.05,0.1]
Celik 2015	20	20	-0.9 (0.332)		10.19%	-0.85[-1.51,-0.2]
Subtotal (95% CI)					**71.79%**	**-0.83[-1.16,-0.5]**
Heterogeneity: Tau²=0.1; Chi²=11.79, df=6(P=0.07); I²=49.12%						
Test for overall effect: Z=4.94(P<0.0001)						
1.12.2 Off-pump surgery						
Sharma 2010	30	30	-0.9 (0.272)		10.57%	-0.91[-1.44,-0.38]
Mehta 2010	31	31	-1.1 (0.274)		10.56%	-1.1[-1.64,-0.57]
Aguero-Martinez 2012	30	30	-7.4 (0.744)		7.08%	-7.39[-8.85,-5.93]
Subtotal (95% CI)					**28.21%**	**-2.99[-5.37,-0.6]**
Heterogeneity: Tau²=4.21; Chi²=69.22, df=2(P<0.0001); I²=97.11%						
Test for overall effect: Z=2.46(P=0.01)						
Total (95% CI)					**100%**	**-1.35[-1.98,-0.72]**

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Heterogeneity: Tau²=0.9; Chi²=88.56, df=9(P<0.0001); I²=89.84%						
Test for overall effect: Z=4.21(P<0.0001)						
Test for subgroup differences: Chi²=3.09, df=1 (P=0.08), I²=67.61%						

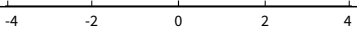
Analysis 1.13. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 13 Pain at rest at 6 to 8 hours: data available as means and standard deviations.

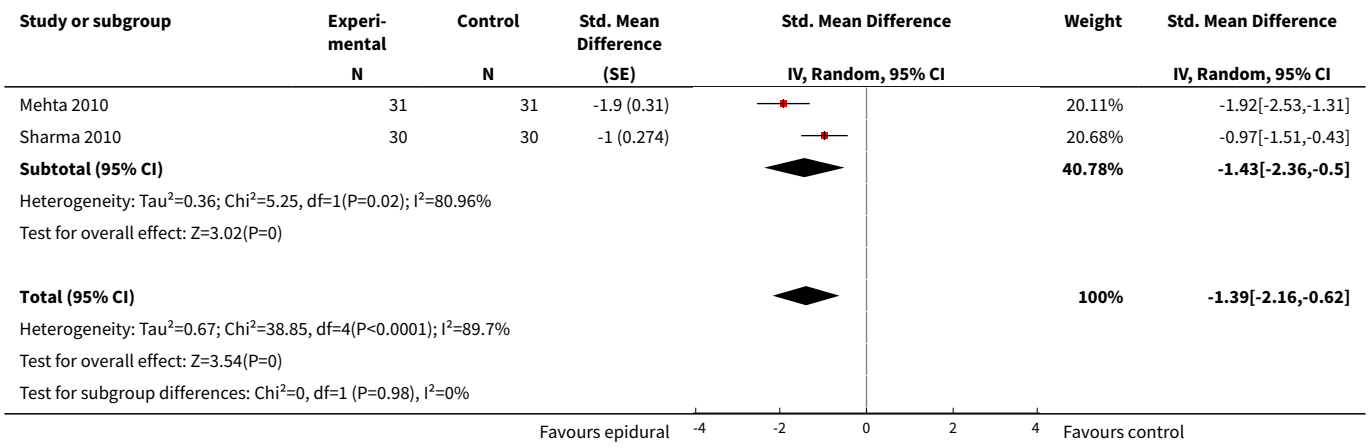
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.13.1 With cardiopulmonary bypass							
El-Morsy 2012	25	3 (3)	25	3.7 (1.5)		19.32%	-0.7[-2.01,0.61]
Onan 2013	20	0.1 (0.3)	20	2.4 (1.8)		19.95%	-2.3[-3.1,-1.5]
Subtotal ***	**45**		**45**			**39.27%**	**-1.59[-3.15,-0.03]**
Heterogeneity: Tau²=0.97; Chi²=4.15, df=1(P=0.04); I²=75.92%							
Test for overall effect: Z=2(P=0.05)							
1.13.2 Off-pump surgery							
Sharma 2010	30	2.5 (0.9)	30	3.2 (0.7)		20.24%	-0.73[-1.13,-0.33]
Mehta 2010	31	4 (0.7)	31	4.7 (0.5)		20.28%	-0.67[-0.97,-0.37]
Aguero-Martinez 2012	30	0 (0)	30	6.8 (1.3)		20.21%	-6.83[-7.29,-6.37]
Subtotal ***	**91**		**91**			**60.73%**	**-2.74[-6.36,0.88]**
Heterogeneity: Tau²=10.18; Chi²=533.12, df=2(P<0.0001); I²=99.62%							
Test for overall effect: Z=1.48(P=0.14)							
Total ***	**136**		**136**			**100%**	**-2.26[-4.84,0.32]**
Heterogeneity: Tau²=8.5; Chi²=537.43, df=4(P<0.0001); I²=99.26%							
Test for overall effect: Z=1.72(P=0.09)							
Test for subgroup differences: Chi²=0.33, df=1 (P=0.57), I²=0%							



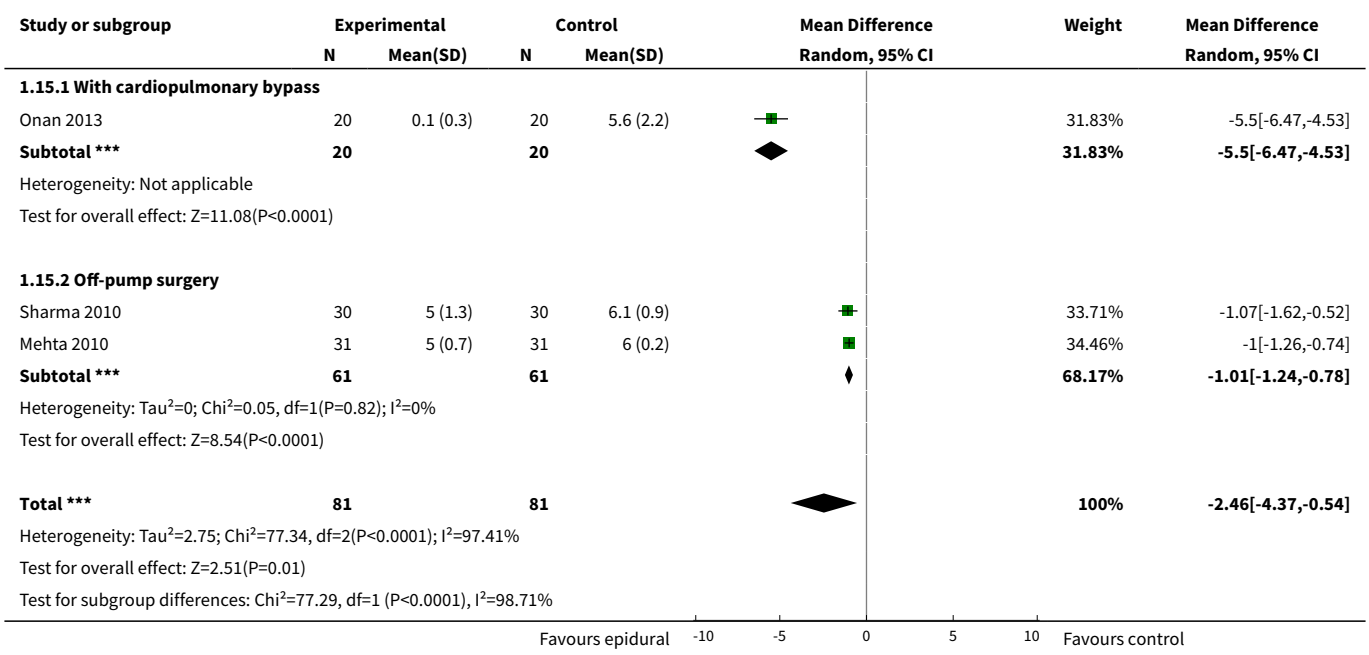
Analysis 1.14. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 14 Pain on movement/coughing at 6 to 8 hours.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.14.1 With cardiopulmonary bypass						
Barrington 2005	60	60	-0.7 (0.189)		21.82%	-0.73[-1.1,-0.36]
Onan 2013	20	20	-3.4 (0.513)		16.52%	-3.43[-4.44,-2.43]
Sen 2017	30	30	-0.4 (0.261)		20.87%	-0.38[-0.89,0.13]
Subtotal (95% CI)					**59.22%**	**-1.41[-2.65,-0.17]**
Heterogeneity: Tau²=1.09; Chi²=28.97, df=2(P<0.0001); I²=93.1%						
Test for overall effect: Z=2.23(P=0.03)						
1.14.2 Off-pump surgery						

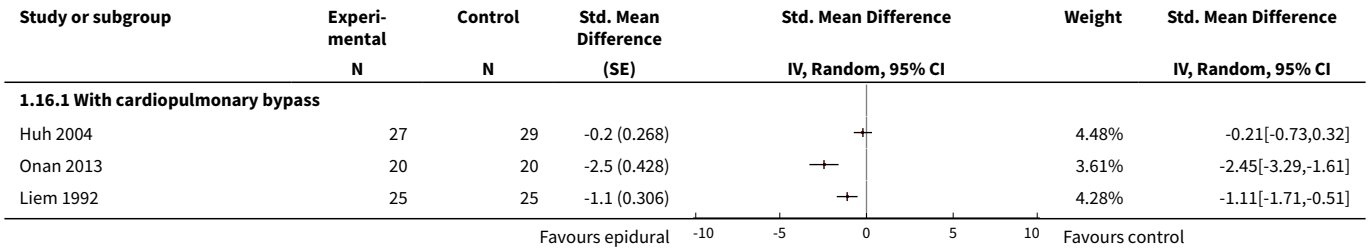


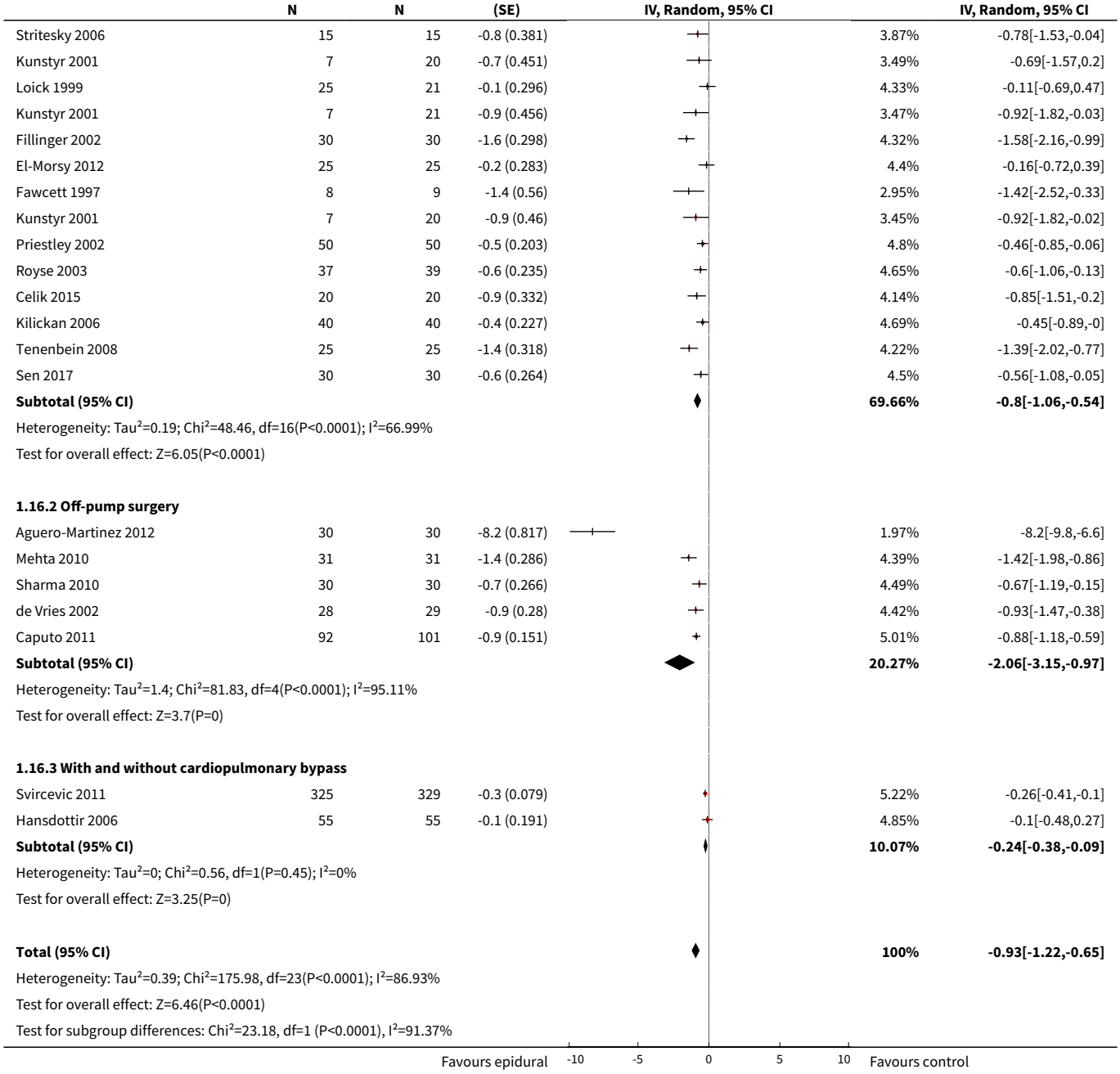


Analysis 1.15. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 15 Pain on movement/coughing at 6 to 8 hours: data available as means and standard deviations.

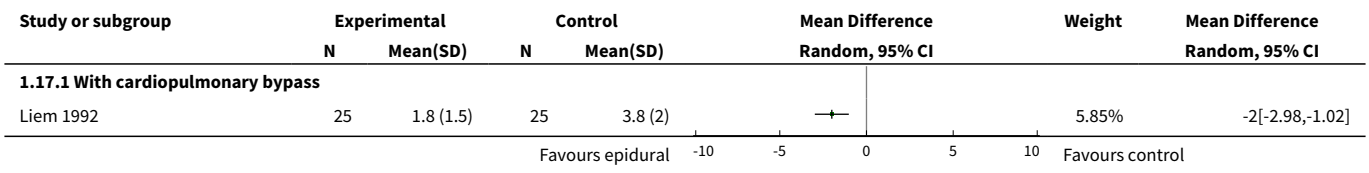


Analysis 1.16. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 16 Pain at rest at 24 hours after surgery.

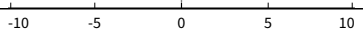




Analysis 1.17. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 17 Pain at rest at 24 hours: data available as means and standard deviations.



Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Fawcett 1997	8	1.2 (0.6)	8	5 (0.9)		6%	-3.8[-4.55,-3.05]
Loick 1999	25	1.2 (1.1)	21	1.3 (1)		6.07%	-0.12[-0.74,0.5]
Kunstyr 2001	7	3.1 (1.5)	21	4.2 (1.3)		5.65%	-1.12[-2.36,0.12]
Kunstyr 2001	7	3.1 (1.5)	20	3.9 (1.3)		5.65%	-0.87[-2.11,0.37]
Kunstyr 2001	7	3.1 (1.5)	20	4.1 (1.2)		5.67%	-1.07[-2.29,0.15]
Fillinger 2002	30	2.7 (0.5)	30	3.5 (0.5)		6.19%	-0.8[-1.05,-0.55]
Royse 2003	37	0 (0.2)	39	0.8 (1.8)		6.09%	-0.78[-1.35,-0.21]
Huh 2004	27	3.1 (2.6)	29	3.8 (3.9)		5.21%	-0.7[-2.42,1.02]
Tenenbein 2008	25	0.8 (1.2)	25	2.8 (1.6)		5.98%	-2[-2.78,-1.22]
El-Morsy 2012	25	2.9 (3)	25	2.4 (3)		5.27%	0.5[-1.16,2.16]
Onan 2013	20	0.1 (0.1)	20	3.6 (2)		5.92%	-3.54[-4.42,-2.66]
Subtotal ***	**243**		**283**			**69.54%**	**-1.42[-2.11,-0.73]**
Heterogeneity: Tau²=1.22; Chi²=107.86, df=11(P<0.0001); I²=89.8%							
Test for overall effect: Z=4.02(P<0.0001)							
1.17.2 Off-pump surgery							
de Vries 2002	28	3 (1.6)	29	4.6 (1.8)		5.92%	-1.6[-2.48,-0.72]
Mehta 2010	31	3.1 (0.9)	31	4.1 (0.4)		6.17%	-1[-1.35,-0.65]
Sharma 2010	30	2.3 (0.9)	30	2.8 (0.7)		6.15%	-0.56[-0.98,-0.14]
Aguero-Martinez 2012	30	0.1 (0.6)	30	6.1 (0.9)		6.16%	-6.03[-6.4,-5.66]
Subtotal ***	**119**		**120**			**24.39%**	**-2.3[-5.16,0.56]**
Heterogeneity: Tau²=8.42; Chi²=513.55, df=3(P<0.0001); I²=99.42%							
Test for overall effect: Z=1.58(P=0.11)							
1.17.3 With and without cardiopulmonary bypass							
Hansdottir 2006	55	0.9 (1.6)	55	1.1 (1.6)		6.07%	-0.17[-0.78,0.44]
Subtotal ***	**55**		**55**			**6.07%**	**-0.17[-0.78,0.44]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.55(P=0.58)							
Total ***	**417**		**458**			**100%**	**-1.53[-2.51,-0.55]**
Heterogeneity: Tau²=4.02; Chi²=746.32, df=16(P<0.0001); I²=97.86%							
Test for overall effect: Z=3.07(P=0)							
Test for subgroup differences: Chi²=8.24, df=1 (P=0.02), I²=75.73%							



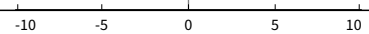
Analysis 1.18. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 18 Pain scores on movement/coughing at 24 hours.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.18.1 With cardiopulmonary bypass						
Huh 2004	27	29	-0.6 (0.273)		7.55%	-0.56[-1.1,-0.03]
Barrington 2005	60	60	-0.7 (0.189)		8.35%	-0.73[-1.1,-0.36]
Loick 1999	25	21	-0.1 (0.296)		7.31%	-0.14[-0.72,0.44]
Kunstyr 2001	7	21	-0.8 (0.452)		5.73%	-0.82[-1.71,0.07]
Kunstyr 2001	7	20	-0.6 (0.447)		5.78%	-0.56[-1.43,0.32]
Onan 2013	20	20	-2.2 (0.407)		6.18%	-2.17[-2.97,-1.37]

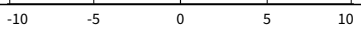
Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Kunstyr 2001	7	20	-1 (0.462)		5.64%	-0.96[-1.87,-0.06]
Kilickan 2006	40	40	-0.4 (0.227)		8.01%	-0.45[-0.89,-0]
Tenenbein 2008	25	25	-2.1 (0.36)		6.65%	-2.14[-2.84,-1.43]
Sen 2017	30	30	-0.5 (0.263)		7.66%	-0.52[-1.03,-0]
Royse 2003	37	39	-1.3 (0.252)		7.76%	-1.26[-1.75,-0.76]
Subtotal (95% CI)					**76.62%**	**-0.9[-1.25,-0.55]**
Heterogeneity: Tau²=0.25; Chi²=38.21, df=10(P<0.0001); I²=73.83%						
Test for overall effect: Z=5.04(P<0.0001)						
1.18.2 Off-pump surgery						
Mehta 2010	31	31	-1.4 (0.284)		7.44%	-1.37[-1.93,-0.82]
Sharma 2010	30	30	-0.7 (0.267)		7.62%	-0.7[-1.23,-0.18]
Subtotal (95% CI)					**15.06%**	**-1.03[-1.69,-0.38]**
Heterogeneity: Tau²=0.15; Chi²=2.96, df=1(P=0.09); I²=66.2%						
Test for overall effect: Z=3.08(P=0)						
1.18.3 With and without cardiopulmonary bypass						
Hansdottir 2006	55	55	0.2 (0.191)		8.33%	0.22[-0.15,0.6]
Subtotal (95% CI)					**8.33%**	**0.22[-0.15,0.6]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.15(P=0.25)						
Total (95% CI)					**100%**	**-0.83[-1.18,-0.49]**
Heterogeneity: Tau²=0.33; Chi²=68.71, df=13(P<0.0001); I²=81.08%						
Test for overall effect: Z=4.76(P<0.0001)						
Test for subgroup differences: Chi²=21.68, df=1 (P<0.0001), I²=90.77%						

Analysis 1.19. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 19 Pain scores on movement/coughing at 24 hours: data available as means and standard deviations.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.19.1 With cardiopulmonary bypass							
Loick 1999	25	3.4 (2.1)	21	3.7 (2.1)		8.8%	-0.3[-1.52,0.92]
Kunstyr 2001	7	3.2 (1.5)	20	4 (1.6)		8.6%	-0.89[-2.19,0.41]
Kunstyr 2001	7	3.2 (1.5)	20	4.5 (1.4)		8.7%	-1.39[-2.65,-0.13]
Kunstyr 2001	7	3.2 (1.5)	21	4.6 (1.8)		8.46%	-1.49[-2.85,-0.13]
Royse 2003	37	1.2 (1.7)	39	4.4 (3.1)		9.04%	-3.2[-4.32,-2.08]
Huh 2004	27	4.8 (2)	29	6.4 (3.4)		8.22%	-1.61[-3.06,-0.16]
Tenenbein 2008	25	1.6 (1.4)	25	5.6 (2.2)		9.26%	-4[-5.02,-2.98]
Onan 2013	20	0.1 (0.2)	20	4.6 (2.9)		8.66%	-4.55[-5.82,-3.28]
Subtotal * **	**155**		**195**			**69.74%**	**-2.2[-3.3,-1.1]**
Heterogeneity: Tau²=2.1; Chi²=44.19, df=7(P<0.0001); I²=84.16%							
Test for overall effect: Z=3.93(P<0.0001)							
1.19.2 Off-pump surgery							
Sharma 2010	30	4.6 (1.2)	30	5.4 (0.9)		10.16%	-0.77[-1.32,-0.22]

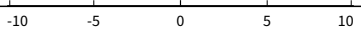


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Mehta 2010	31	4 (1.6)	31	5.7 (0.5)		10.09%	-1.65[-2.24,-1.06]
Subtotal ***	**61**		**61**			**20.25%**	**-1.2[-2.06,-0.34]**
Heterogeneity: Tau²=0.3; Chi²=4.6, df=1(P=0.03); I²=78.27%							
Test for overall effect: Z=2.73(P=0.01)							
1.19.3 With and without cardiopulmonary bypass							
Hansdottir 2006	55	3.8 (1.7)	55	3.4 (1.7)		10.01%	0.38[-0.26,1.02]
Subtotal ***	**55**		**55**			**10.01%**	**0.38[-0.26,1.02]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.17(P=0.24)							
Total ***	**271**		**311**			**100%**	**-1.74[-2.63,-0.86]**
Heterogeneity: Tau²=1.92; Chi²=97.56, df=10(P<0.0001); I²=89.75%							
Test for overall effect: Z=3.87(P=0)							
Test for subgroup differences: Chi²=19.01, df=1 (P<0.0001), I²=89.48%							



Analysis 1.20. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 20 Pain at rest at 48 hours after surgery.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.20.1 With cardiopulmonary bypass						
Huh 2004	27	29	-0.5 (0.272)		6.17%	-0.51[-1.04,0.03]
Loick 1999	25	21	0.2 (0.297)		6.02%	0.23[-0.35,0.82]
Onan 2013	20	20	-2 (0.397)		5.36%	-2.04[-2.82,-1.26]
Kunstyr 2001	7	21	-0.9 (0.455)		4.97%	-0.88[-1.77,0.01]
Liem 1992	25	25	-1.2 (0.311)		5.93%	-1.25[-1.85,-0.64]
Kunstyr 2001	7	20	-0.7 (0.451)		5%	-0.69[-1.57,0.2]
Kunstyr 2001	7	20	-0.9 (0.46)		4.94%	-0.92[-1.82,-0.02]
Stritesky 2006	15	15	-0.7 (0.38)		5.48%	-0.75[-1.49,-0]
Kilickan 2006	40	40	-0.4 (0.227)		6.44%	-0.45[-0.89,-0]
Royse 2003	37	39	-0.6 (0.234)		6.39%	-0.56[-1.02,-0.1]
Tenenbein 2008	25	25	-1 (0.302)		5.99%	-1[-1.59,-0.41]
Subtotal (95% CI)					**62.67%**	**-0.76[-1.08,-0.44]**
Heterogeneity: Tau²=0.18; Chi²=27.89, df=10(P=0); I²=64.14%						
Test for overall effect: Z=4.64(P<0.0001)						
1.20.2 Off-pump surgery						
Mehta 2010	31	31	-2.7 (0.357)		5.63%	-2.7[-3.4,-2]
Sharma 2010	30	30	-1.2 (0.282)		6.11%	-1.19[-1.74,-0.64]
Aguero-Martinez 2012	30	30	-3.6 (0.43)		5.14%	-3.64[-4.48,-2.79]
Caputo 2011	92	101	-1.1 (0.155)		6.79%	-1.11[-1.41,-0.8]
Subtotal (95% CI)					**23.66%**	**-2.11[-3.17,-1.05]**
Heterogeneity: Tau²=1.07; Chi²=43.65, df=3(P<0.0001); I²=93.13%						
Test for overall effect: Z=3.9(P<0.0001)						
1.20.3 With and without cardiopulmonary bypass						



Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Svircevic 2011	325	329	-0.3 (0.079)		7.04%	-0.26[-0.41,-0.1]
Hansdottir 2006	55	55	-0.2 (0.191)		6.62%	-0.17[-0.54,0.21]
Subtotal (95% CI)					**13.66%**	**-0.25[-0.39,-0.1]**
Heterogeneity: Tau²=0; Chi²=0.19, df=1(P=0.67); I²=0%						
Test for overall effect: Z=3.38(P=0)						
Total (95% CI)					**100%**	**-1.01[-1.37,-0.64]**
Heterogeneity: Tau²=0.48; Chi²=152.47, df=16(P<0.0001); I²=89.51%						
Test for overall effect: Z=5.45(P<0.0001)						
Test for subgroup differences: Chi²=18.94, df=1 (P<0.0001), I²=89.44%						

Favours epidural -10 -5 0 5 10 Favours control

Analysis 1.21. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 21 Pain at rest at 48 hours after surgery: data available as means and standard deviations.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.21.1 With cardiopulmonary bypass							
Liem 1992	25	2.3 (1)	25	4.3 (2)		7.52%	-2[-2.88,-1.12]
Loick 1999	25	1.6 (1.3)	21	1.3 (1)		7.94%	0.28[-0.39,0.95]
Kunstyr 2001	7	3.7 (1.1)	20	4.1 (1.2)		7.41%	-0.44[-1.37,0.49]
Kunstyr 2001	7	3.7 (1.1)	21	4.2 (1.3)		7.36%	-0.49[-1.44,0.46]
Kunstyr 2001	7	3.7 (1.1)	20	3.9 (1.3)		7.34%	-0.24[-1.2,0.72]
Royse 2003	37	0.1 (0.4)	39	1.2 (2.7)		7.56%	-1.1[-1.96,-0.24]
Huh 2004	27	2.8 (2.3)	29	4.1 (2.6)		6.55%	-1.27[-2.56,0.02]
Tenenbein 2008	25	0.5 (0.9)	25	1.7 (1.4)		7.97%	-1.2[-1.85,-0.55]
Onan 2013	20	0.1 (0.1)	20	3.2 (2.1)		7.43%	-3.08[-4,-2.16]
Subtotal ***	**180**		**220**			**67.08%**	**-1.05[-1.73,-0.37]**
Heterogeneity: Tau²=0.87; Chi²=44.33, df=8(P<0.0001); I²=81.96%							
Test for overall effect: Z=3.01(P=0)							
1.21.2 Off-pump surgery							
Mehta 2010	31	1.8 (0.6)	31	3.3 (0.5)		8.49%	-1.51[-1.78,-1.24]
Sharma 2010	30	1.6 (0.9)	30	2.5 (0.7)		8.37%	-0.93[-1.32,-0.54]
Aguero-Martinez 2012	30	1.1 (1.7)	30	5.9 (0.7)		7.96%	-4.8[-5.46,-4.14]
Subtotal ***	**91**		**91**			**24.81%**	**-2.38[-4.07,-0.7]**
Heterogeneity: Tau²=2.16; Chi²=101.75, df=2(P<0.0001); I²=98.03%							
Test for overall effect: Z=2.77(P=0.01)							
1.21.3 With and without cardiopulmonary bypass							
Hansdottir 2006	55	0.9 (1.5)	55	1.1 (1.5)		8.11%	-0.26[-0.83,0.31]
Subtotal ***	**55**		**55**			**8.11%**	**-0.26[-0.83,0.31]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.89(P=0.37)							
Total ***	**326**		**366**			**100%**	**-1.31[-1.99,-0.64]**
Heterogeneity: Tau²=1.38; Chi²=176.15, df=12(P<0.0001); I²=93.19%							
Test for overall effect: Z=3.81(P=0)							

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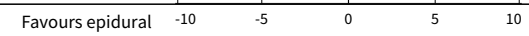
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for subgroup differences: Chi²=7.13, df=1 (P=0.03), I²=71.93%							

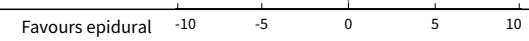
Analysis 1.22. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 22 Pain scores on movement/coughing at 48 hours.

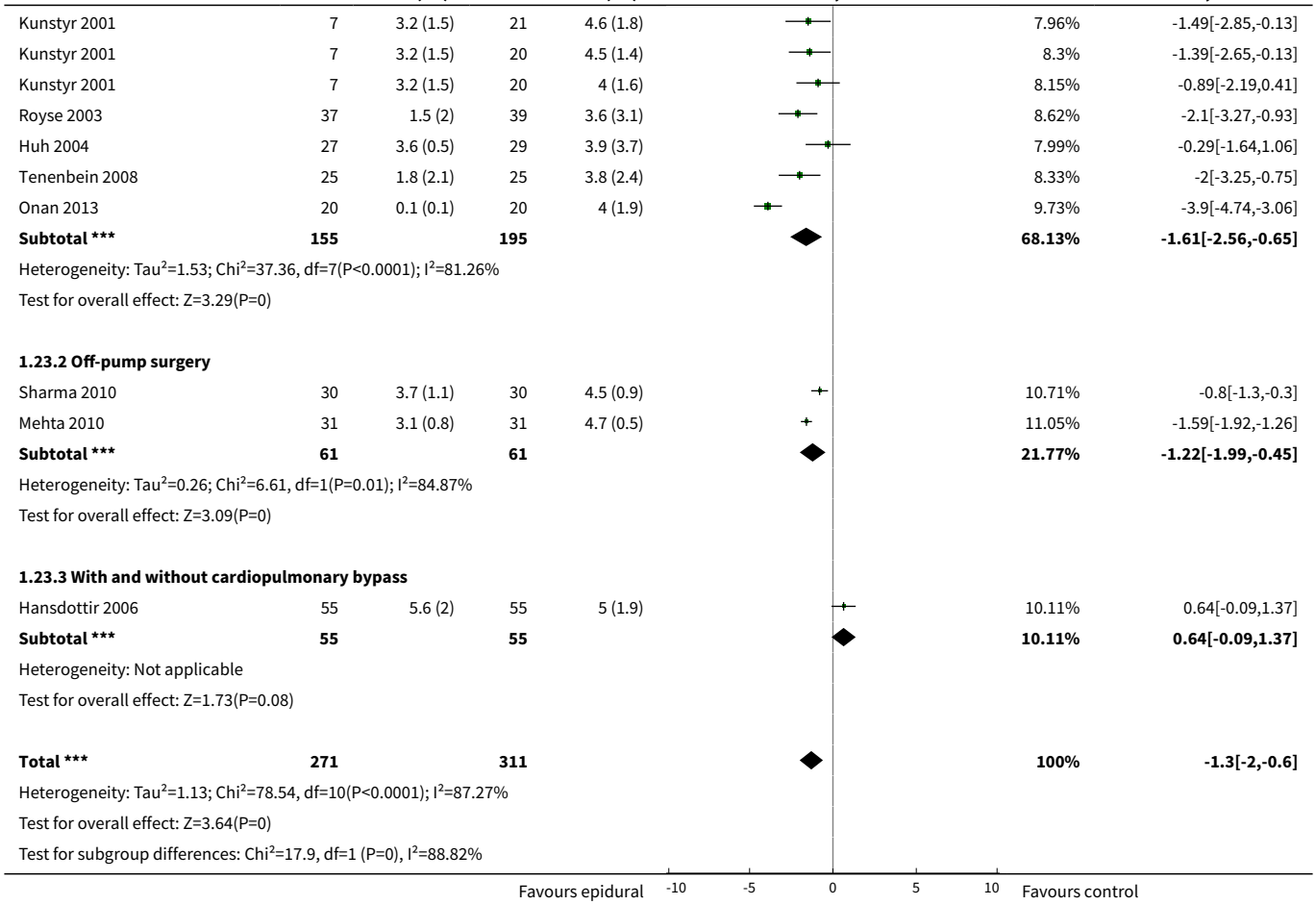
Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.22.1 With cardiopulmonary bypass						
Huh 2004	27	29	-0.1 (0.268)		10.12%	-0.11[-0.63,0.42]
Onan 2013	20	20	-2.8 (0.458)		8.23%	-2.81[-3.7,-1.91]
Barrington 2005	60	60	-0.7 (0.189)		10.77%	-0.73[-1.1,-0.36]
Loick 1999	25	21	-0.3 (0.297)		9.85%	-0.27[-0.85,0.32]
Tenenbein 2008	25	25	-0.9 (0.297)		9.85%	-0.87[-1.46,-0.29]
Kilickan 2006	40	40	-0.4 (0.227)		10.48%	-0.45[-0.89,-0]
Royse 2003	37	39	-0.8 (0.239)		10.37%	-0.79[-1.26,-0.32]
Subtotal (95% CI)					**69.67%**	**-0.78[-1.22,-0.34]**
Heterogeneity: Tau²=0.27; Chi²=29.92, df=6(P<0.0001); I²=79.95%						
Test for overall effect: Z=3.47(P=0)						
1.22.2 Off-pump surgery						
Mehta 2010	31	31	-2.4 (0.335)		9.48%	-2.35[-3.01,-1.7]
Sharma 2010	30	30	-0.8 (0.269)		10.11%	-0.8[-1.32,-0.27]
Subtotal (95% CI)					**19.59%**	**-1.56[-3.09,-0.03]**
Heterogeneity: Tau²=1.12; Chi²=13.16, df=1(P=0); I²=92.4%						
Test for overall effect: Z=2(P=0.05)						
1.22.3 With and without cardiopulmonary bypass						
Hansdottir 2006	55	55	0.3 (0.192)		10.74%	0.33[-0.05,0.7]
Subtotal (95% CI)					**10.74%**	**0.33[-0.05,0.7]**
Heterogeneity: Not applicable						
Test for overall effect: Z=1.7(P=0.09)						
Total (95% CI)					**100%**	**-0.83[-1.31,-0.35]**
Heterogeneity: Tau²=0.53; Chi²=81.65, df=9(P<0.0001); I²=88.98%						
Test for overall effect: Z=3.37(P=0)						
Test for subgroup differences: Chi²=17.24, df=1 (P=0), I²=88.4%						



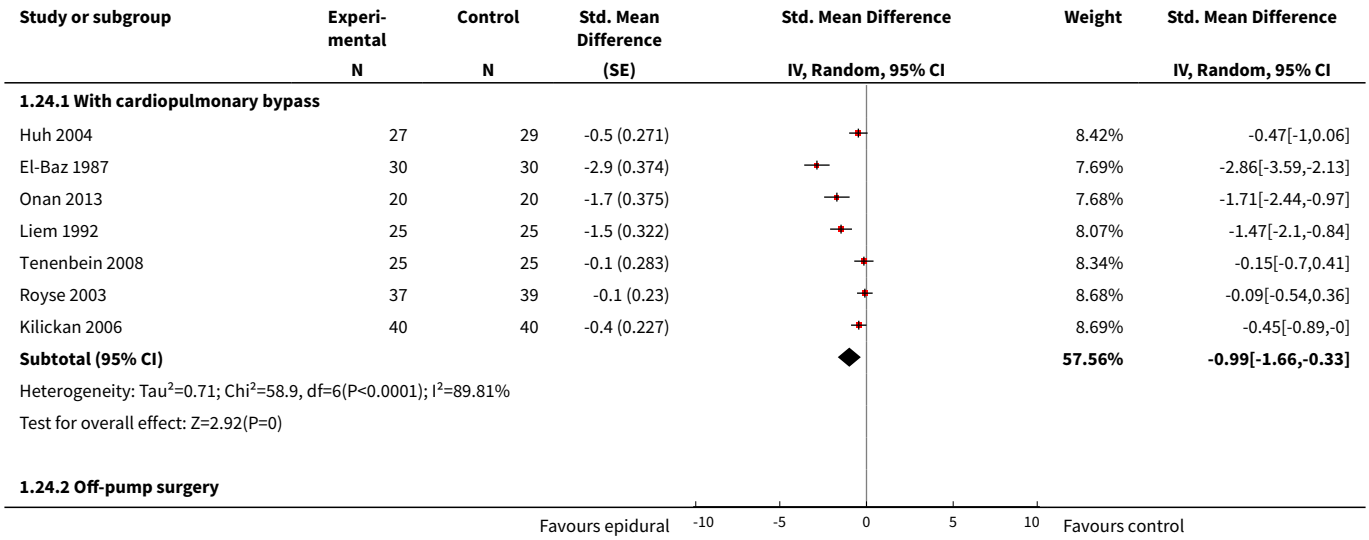
Analysis 1.23. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 23 Pain scores on movement/coughing at 48 hours: data available as means and standard deviations.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.23.1 With cardiopulmonary bypass							
Loick 1999	25	2.9 (2.1)	21	3.4 (1.5)		9.06%	-0.5[-1.54,0.54]

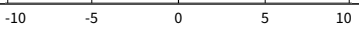




Analysis 1.24. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 24 Pain at rest at 72 hours after surgery.

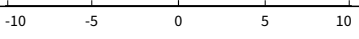


Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
Aguero-Martinez 2012	30	30	-1.7 (0.304)		8.19%	-1.7[-2.3,-1.11]
Sharma 2010	30	30	-0.9 (0.272)		8.41%	-0.91[-1.44,-0.37]
Mehta 2010	31	31	-2.5 (0.347)		7.89%	-2.54[-3.22,-1.86]
Caputo 2011	92	101	-1.2 (0.156)		9.06%	-1.18[-1.48,-0.87]
Subtotal (95% CI)					**33.55%**	**-1.54[-2.14,-0.94]**
Heterogeneity: Tau²=0.31; Chi²=17.04, df=3(P=0); I²=82.39%						
Test for overall effect: Z=4.99(P<0.0001)						
1.24.3 With and without cardiopulmonary bypass						
Hansdottir 2006	55	55	-0 (0.191)		8.89%	-0.01[-0.38,0.37]
Subtotal (95% CI)					**8.89%**	**-0.01[-0.38,0.37]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.04(P=0.97)						
Total (95% CI)					**100%**	**-1.09[-1.57,-0.62]**
Heterogeneity: Tau²=0.62; Chi²=115.49, df=11(P<0.0001); I²=90.48%						
Test for overall effect: Z=4.51(P<0.0001)						
Test for subgroup differences: Chi²=20.06, df=1 (P<0.0001), I²=90.03%						

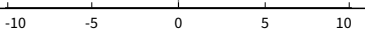


Analysis 1.25. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 25 Pain at rest at 72 hours after surgery: data available as means and standard deviations.

Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.25.1 With cardiopulmonary bypass							
El-Baz 1987	30	2.3 (0.6)	30	3.5 (0.1)		12.48%	-1.17[-1.37,-0.97]
Liem 1992	25	1.4 (1)	25	3.3 (1.5)		9.07%	-1.9[-2.61,-1.19]
Royse 2003	37	0.2 (1)	39	0.3 (1.1)		10.86%	-0.1[-0.57,0.37]
Huh 2004	27	2.7 (2)	29	3.7 (2.1)		6.47%	-0.98[-2.06,0.1]
Tenenbein 2008	25	0.7 (1.5)	25	0.9 (1.1)		8.9%	-0.2[-0.93,0.53]
Onan 2013	20	0.1 (0.1)	20	2.5 (1.9)		8.09%	-2.35[-3.19,-1.52]
Subtotal ***	**164**		**168**			**55.87%**	**-1.09[-1.71,-0.46]**
Heterogeneity: Tau²=0.49; Chi²=36.95, df=5(P<0.0001); I²=86.47%							
Test for overall effect: Z=3.41(P=0)							
1.25.2 Off-pump surgery							
Sharma 2010	30	1.1 (0.7)	30	1.7 (0.6)		11.83%	-0.6[-0.93,-0.27]
Mehta 2010	31	1.2 (0.4)	31	2.2 (0.4)		12.5%	-1.03[-1.23,-0.83]
Aguero-Martinez 2012	30	3 (2)	30	5.5 (0.6)		8.86%	-2.5[-3.23,-1.77]
Subtotal ***	**91**		**91**			**33.2%**	**-1.27[-1.96,-0.59]**
Heterogeneity: Tau²=0.32; Chi²=21.79, df=2(P<0.0001); I²=90.82%							
Test for overall effect: Z=3.63(P=0)							
1.25.3 With and without cardiopulmonary bypass							
Hansdottir 2006	55	0.7 (1.3)	55	0.7 (1.2)		10.94%	-0.01[-0.47,0.45]
Subtotal ***	**55**		**55**			**10.94%**	**-0.01[-0.47,0.45]**
Heterogeneity: Not applicable							

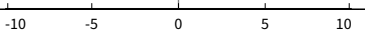


Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
Test for overall effect: Z=0.04(P=0.97)							
Total ***	**310**		**314**			**100%**	**-1.02[-1.41,-0.63]**
Heterogeneity: Tau²=0.31; Chi²=76.61, df=9(P<0.0001); I²=88.25%							
Test for overall effect: Z=5.15(P<0.0001)							
Test for subgroup differences: Chi²=12.29, df=1 (P=0), I²=83.72%							



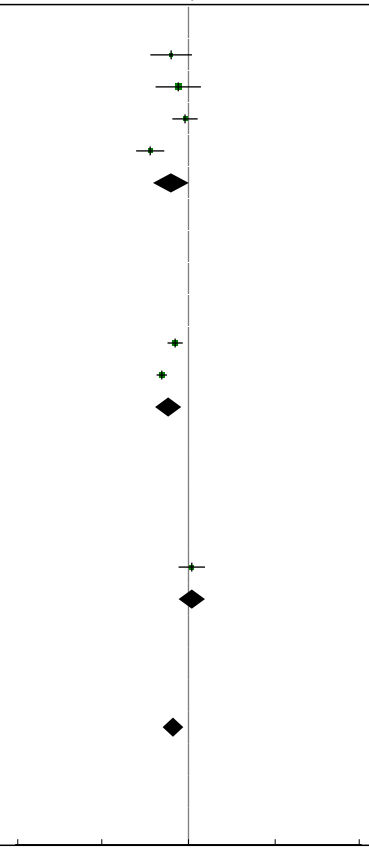
Analysis 1.26. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 26 Pain scores on movement/coughing at 72 hours.

Study or subgroup	Experimental N	Control N	Std. Mean Difference (SE)	Std. Mean Difference IV, Random, 95% CI	Weight	Std. Mean Difference IV, Random, 95% CI
1.26.1 With cardiopulmonary bypass						
Huh 2004	27	29	-0.2 (0.268)		11.1%	-0.23[-0.76,0.3]
Onan 2013	20	20	-1.7 (0.372)		10.02%	-1.66[-2.38,-0.93]
Barrington 2005	60	60	-0.7 (0.189)		11.81%	-0.73[-1.1,-0.36]
Kilickan 2006	40	40	0.4 (0.227)		11.49%	0.45[0,0.89]
Tenenbein 2008	25	25	-0.1 (0.283)		10.96%	-0.06[-0.61,0.5]
Royse 2003	37	39	-0.4 (0.232)		11.45%	-0.37[-0.82,0.08]
Subtotal (95% CI)					**66.83%**	**-0.4[-0.9,0.09]**
Heterogeneity: Tau²=0.31; Chi²=30.12, df=5(P<0.0001); I²=83.4%						
Test for overall effect: Z=1.59(P=0.11)						
1.26.2 Off-pump surgery						
Mehta 2010	31	31	-2.5 (0.346)		10.3%	-2.53[-3.21,-1.86]
Sharma 2010	30	30	-0.9 (0.271)		11.08%	-0.88[-1.41,-0.35]
Subtotal (95% CI)					**21.37%**	**-1.69[-3.32,-0.07]**
Heterogeneity: Tau²=1.28; Chi²=14.19, df=1(P=0); I²=92.95%						
Test for overall effect: Z=2.04(P=0.04)						
1.26.3 With and without cardiopulmonary bypass						
Hansdottir 2006	55	55	0.1 (0.191)		11.79%	0.09[-0.28,0.47]
Subtotal (95% CI)					**11.79%**	**0.09[-0.28,0.47]**
Heterogeneity: Not applicable						
Test for overall effect: Z=0.49(P=0.63)						
Total (95% CI)					**100%**	**-0.62[-1.13,-0.11]**
Heterogeneity: Tau²=0.54; Chi²=77.97, df=8(P<0.0001); I²=89.74%						
Test for overall effect: Z=2.39(P=0.02)						
Test for subgroup differences: Chi²=6.08, df=1 (P=0.05), I²=67.09%						



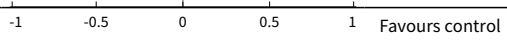
Analysis 1.27. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 27 Pain scores on movement/coughing at 72 hours: data available as means and standard deviations.

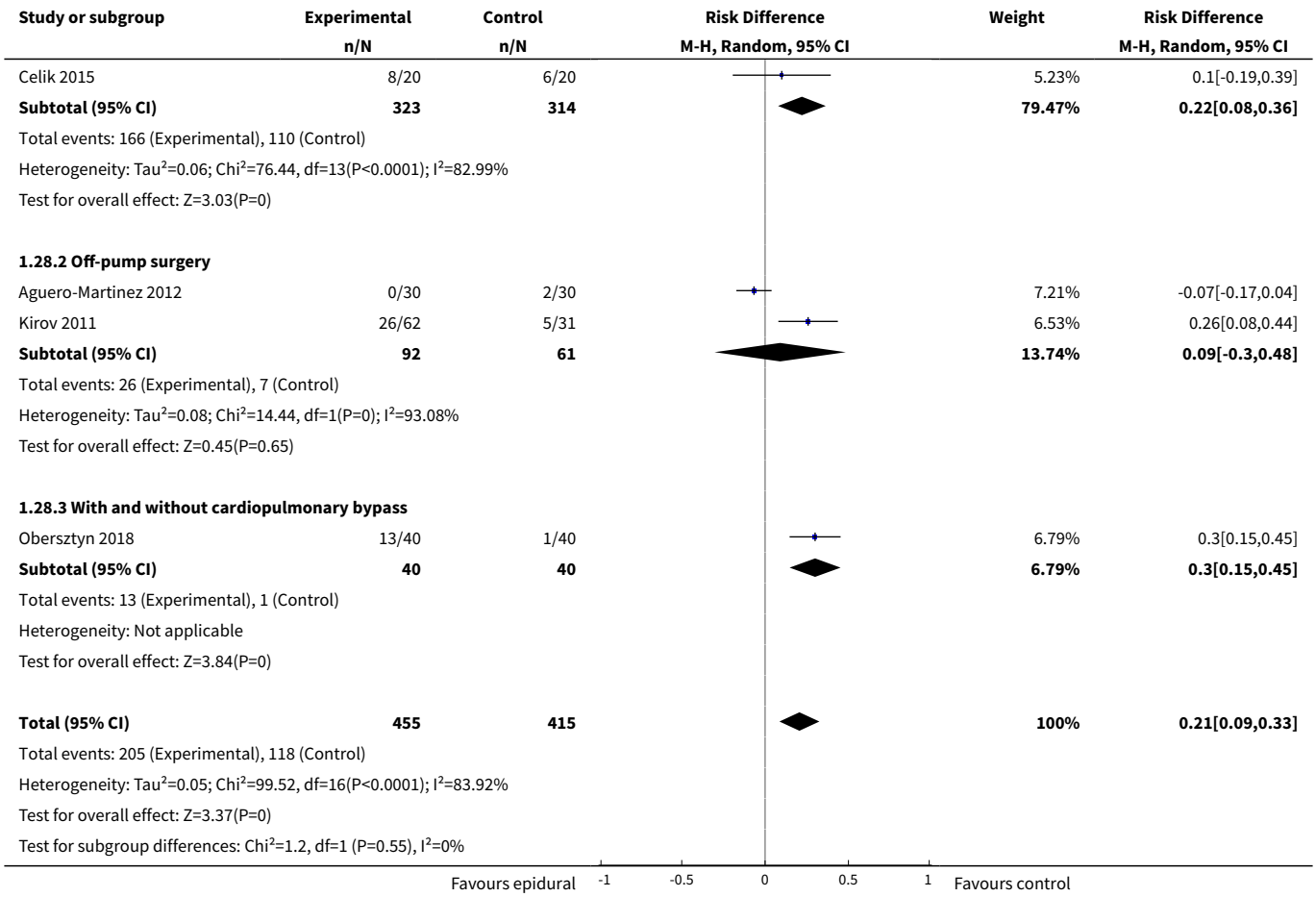
Study or subgroup	Experimental N	Experimental Mean(SD)	Control N	Control Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
1.27.1 With cardiopulmonary bypass							
Royse 2003	37	1.7 (2.3)	39	2.7 (3)		10.79%	-1[-2.2,0.2]
Huh 2004	27	3.6 (2)	29	4.2 (2.9)		9.97%	-0.59[-1.9,0.72]
Tenenbein 2008	25	0.7 (1.5)	25	0.9 (1.1)		14.88%	-0.2[-0.93,0.53]
Onan 2013	20	0.1 (0.1)	20	2.3 (1.8)		14.14%	-2.21[-3.02,-1.4]
Subtotal ***	**109**		**113**			**49.78%**	**-1.02[-2.05,0.02]**
Heterogeneity: Tau^2=0.84; Chi^2=13.53, df=3(P=0); I^2=77.83%							
Test for overall effect: Z=1.93(P=0.05)							
1.27.2 Off-pump surgery							
Sharma 2010	30	3 (1)	30	3.8 (0.8)		17.35%	-0.77[-1.21,-0.33]
Mehta 2010	31	2.2 (0.6)	31	3.8 (0.6)		18.27%	-1.54[-1.84,-1.24]
Subtotal ***	**61**		**61**			**35.62%**	**-1.17[-1.93,-0.42]**
Heterogeneity: Tau^2=0.26; Chi^2=8.1, df=1(P=0); I^2=87.65%							
Test for overall effect: Z=3.05(P=0)							
1.27.3 With and without cardiopulmonary bypass							
Hansdottir 2006	55	6.3 (1.9)	55	6.1 (2.2)		14.6%	0.19[-0.57,0.95]
Subtotal ***	**55**		**55**			**14.6%**	**0.19[-0.57,0.95]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.49(P=0.62)							
Total ***	**225**		**229**			**100%**	**-0.9[-1.49,-0.3]**
Heterogeneity: Tau^2=0.48; Chi^2=35.15, df=6(P<0.0001); I^2=82.93%							
Test for overall effect: Z=2.95(P=0)							
Test for subgroup differences: Chi^2=6.98, df=1 (P=0.03), I^2=71.36%							



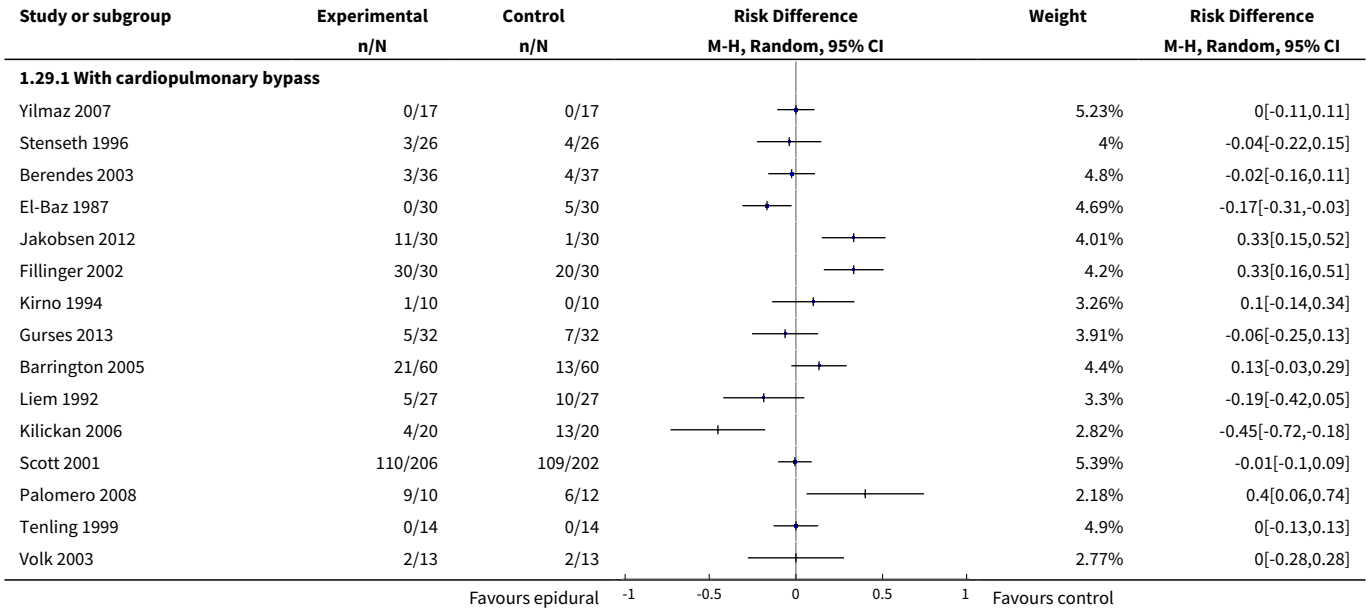
Analysis 1.28. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 28 Hypotension or vasopressor bolus during surgery.

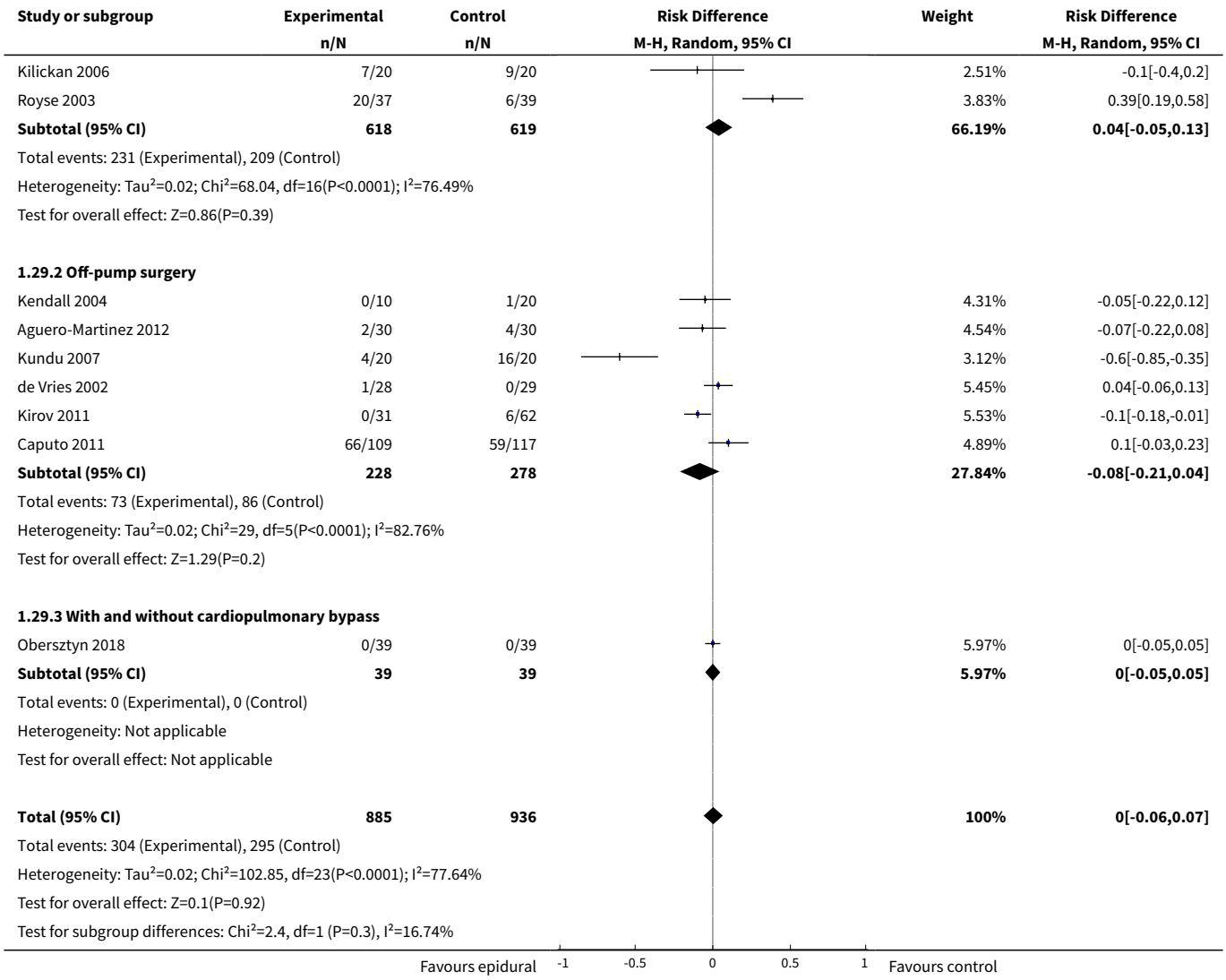
Study or subgroup	Experimental n/N	Control n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
1.28.1 With cardiopulmonary bypass					
Liem 1992	5/27	7/27		6.06%	-0.07[-0.29,0.15]
Gurses 2013	4/32	7/32		6.48%	-0.09[-0.28,0.09]
Stenseth 1994	17/20	4/10		4.71%	0.45[0.11,0.79]
Fillinger 2002	21/30	19/30		5.87%	0.07[-0.17,0.3]
Stenseth 1996	14/26	0/26		6.35%	0.54[0.34,0.73]
Barrington 2005	45/60	53/60		6.95%	-0.13[-0.27,0]
Moore 1995	4/8	0/9		4.59%	0.5[0.15,0.85]
Kirno 1994	6/10	1/10		4.56%	0.5[0.14,0.86]
Greisen 2012	9/21	0/21		6.12%	0.43[0.21,0.64]
Yilmaz 2007	0/17	0/17		7.19%	0[-0.11,0.11]
Jakobsen 2012	17/30	5/30		6.05%	0.4[0.18,0.62]
Fawcett 1997	3/8	1/8		4.07%	0.25[-0.16,0.66]
Tenling 1999	13/14	7/14		5.23%	0.43[0.13,0.72]





Analysis 1.29. Comparison 1 Epidural analgesia compared with systemic analgesia, Outcome 29 Needed vasopressor/inotropic infusion.





Comparison 2. Epidural analgesia compared with peripheral nerve blocks

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality at 0 to 30 days	1	145	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
1.1 With cardiopulmonary bypass	1	145	Risk Difference (M-H, Fixed, 95% CI)	-0.03 [-0.08, 0.02]
2 Myocardial infarction (0 to 30 days)	2	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
2.1 Off-pump surgery	2	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3 Neurological complications: cerebrovascular accident (0 to 30 days)	1	145	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
3.1 With cardiopulmonary bypass	1	145	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
4 Neurological complications: epidural haematoma (0 to 30 days)	4	271	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
4.1 With cardiopulmonary bypass	2	195	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.03, 0.03]
4.2 Off-pump surgery	2	76	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
5 Duration of tracheal intubation (hours)	4	271	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.54, 0.38]
5.1 With cardiopulmonary bypass	2	195	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.53, 0.44]
5.2 Off-pump surgery	2	76	Mean Difference (IV, Fixed, 95% CI)	-0.35 [-1.70, 0.99]
6 Pain scores at rest at 6 to 8 hours	2	90	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.42, 0.66]
6.1 With cardiopulmonary bypass	1	50	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.59, 0.59]
6.2 Off-pump surgery	1	40	Mean Difference (IV, Fixed, 95% CI)	0.8 [-0.61, 2.21]
7 Pain scores on movement/coughing at 6 to 8 hours	2	90	Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.69, 0.39]
7.1 With cardiopulmonary bypass	1	50	Mean Difference (IV, Fixed, 95% CI)	-0.08 [-0.69, 0.53]
7.2 Off-pump surgery	1	40	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.57, 0.77]
8 Pain at rest at 24 hours	3	231	Mean Difference (IV, Random, 95% CI)	0.11 [-0.41, 0.63]
8.1 With cardiopulmonary bypass	2	195	Mean Difference (IV, Random, 95% CI)	0.28 [-0.34, 0.91]
8.2 Off-pump surgery	1	36	Mean Difference (IV, Random, 95% CI)	-0.54 [-1.38, 0.30]
9 Pain on movement/coughing at 24 hours	2	86	Mean Difference (IV, Random, 95% CI)	0.31 [-0.62, 1.24]
9.1 With cardiopulmonary bypass	1	50	Mean Difference (IV, Random, 95% CI)	0.72 [0.22, 1.22]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.2 Off-pump surgery	1	36	Mean Difference (IV, Random, 95% CI)	-0.24 [-1.11, 0.63]
10 Pain at rest at 48 hours	2	195	Mean Difference (IV, Random, 95% CI)	0.51 [-0.77, 1.80]
10.1 With cardiopulmonary bypass	2	195	Mean Difference (IV, Random, 95% CI)	0.51 [-0.77, 1.80]
11 Pain at rest on movement/coughing at 48 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	1.36 [0.76, 1.96]
12 Hypotension or need for vasopressor	1	40	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.08, 0.18]
12.1 Off-pump surgery	1	40	Risk Difference (M-H, Random, 95% CI)	0.05 [-0.08, 0.18]

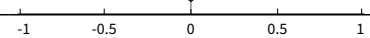
Analysis 2.1. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 1 Mortality at 0 to 30 days.

Study or subgroup	Epidural analgesia n/N	Paravertebral blockade n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.1.1 With cardiopulmonary bypass					
El-Shora 2018	1/75	3/70		100%	-0.03[-0.08,0.02]
Subtotal (95% CI)	**75**	**70**		**100%**	**-0.03[-0.08,0.02]**
Total events: 1 (Epidural analgesia), 3 (Paravertebral blockade)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.07(P=0.28)					
Total (95% CI)	**75**	**70**		**100%**	**-0.03[-0.08,0.02]**
Total events: 1 (Epidural analgesia), 3 (Paravertebral blockade)					
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%					
Test for overall effect: Z=1.07(P=0.28)					

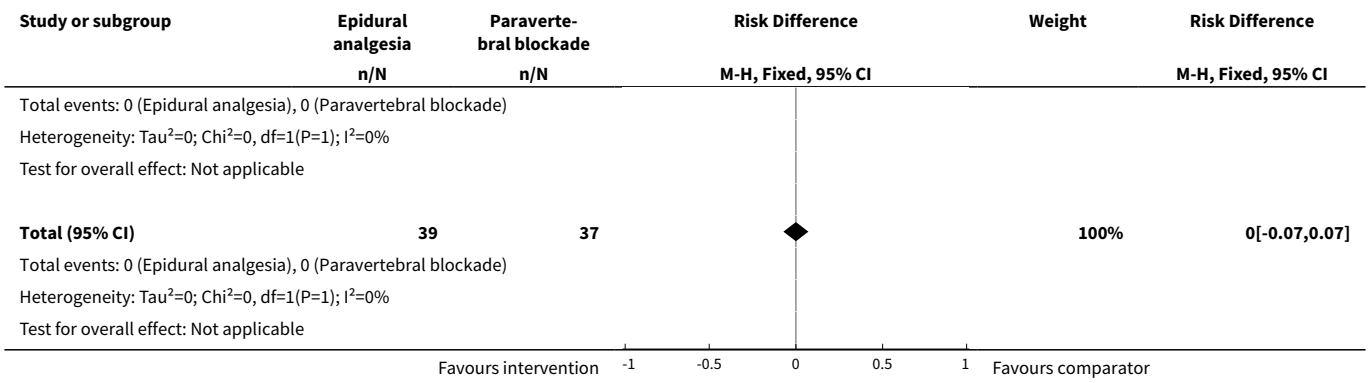
Favours epidural — Favours control

Analysis 2.2. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 2 Myocardial infarction (0 to 30 days).

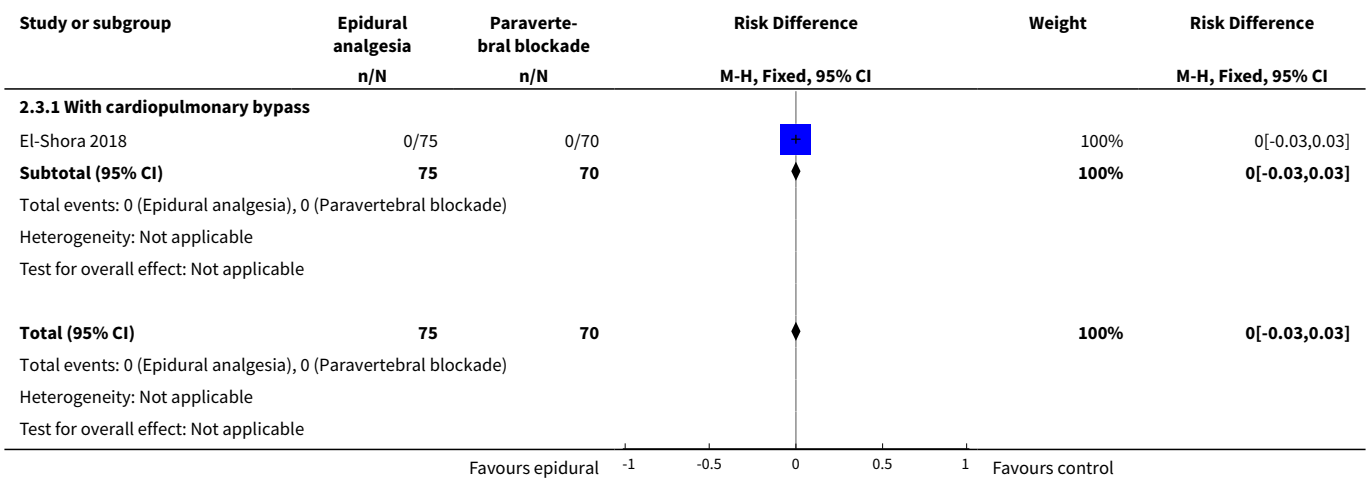
Study or subgroup	Epidural analgesia n/N	Paravertebral blockade n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
2.2.1 Off-pump surgery					
Dohle 2001	0/20	0/20		52.71%	0[-0.09,0.09]
Mehta 2008	0/19	0/17		47.29%	0[-0.1,0.1]
Subtotal (95% CI)	**39**	**37**		**100%**	**0[-0.07,0.07]**



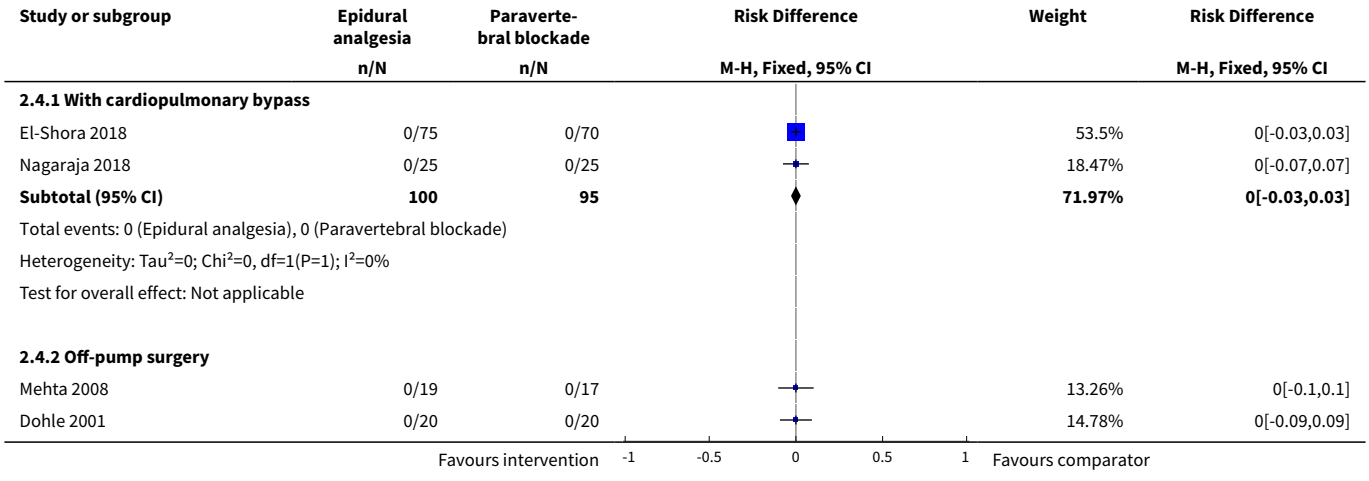
Favours intervention — Favours comparator

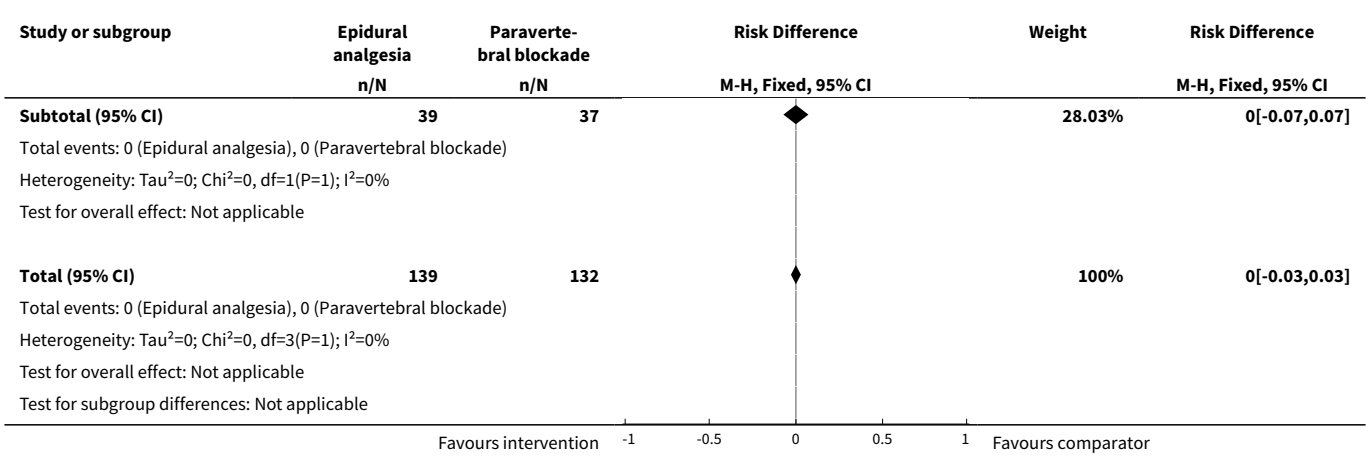


Analysis 2.3. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 3 Neurological complications: cerebrovascular accident (0 to 30 days).

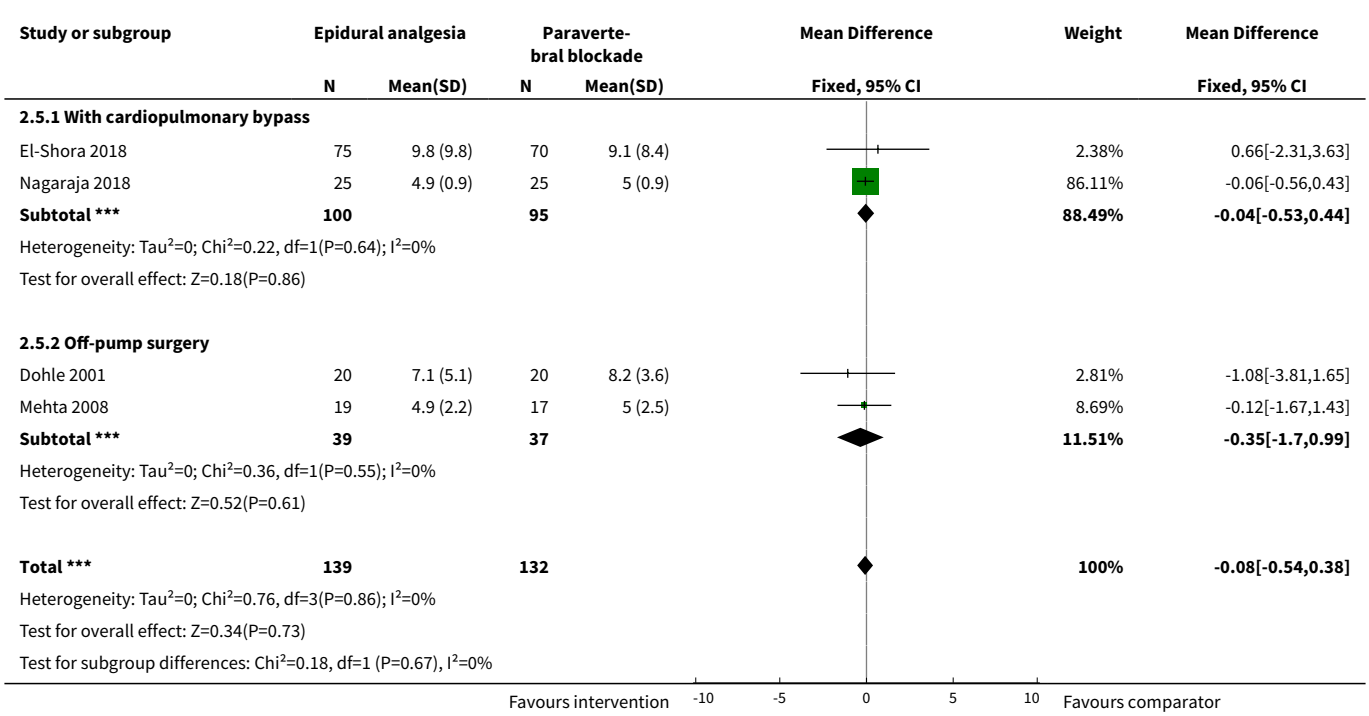


Analysis 2.4. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 4 Neurological complications: epidural haematoma (0 to 30 days).

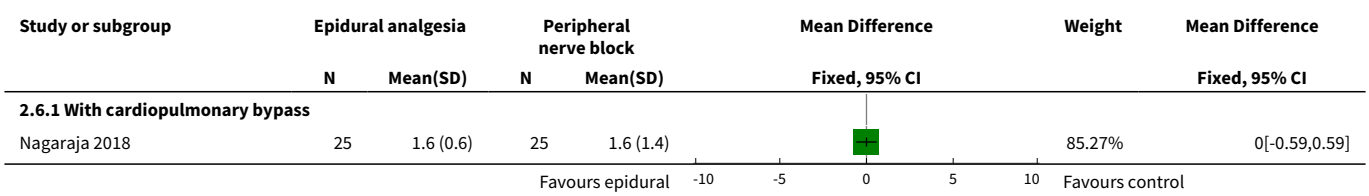


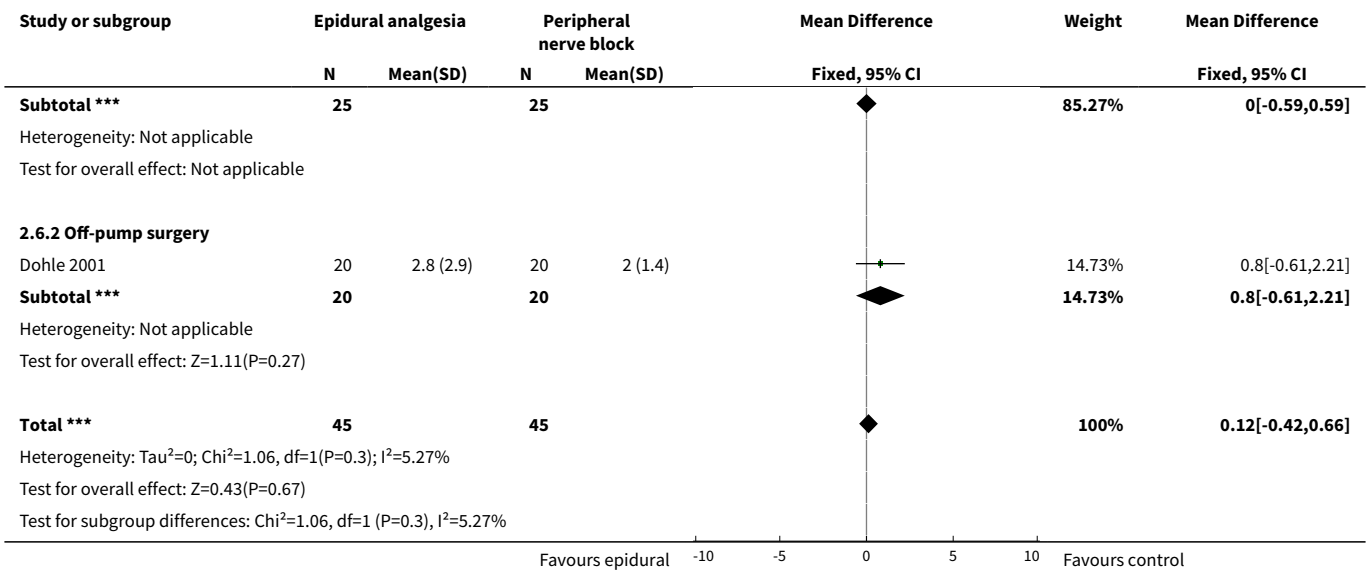


Analysis 2.5. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 5 Duration of tracheal intubation (hours).

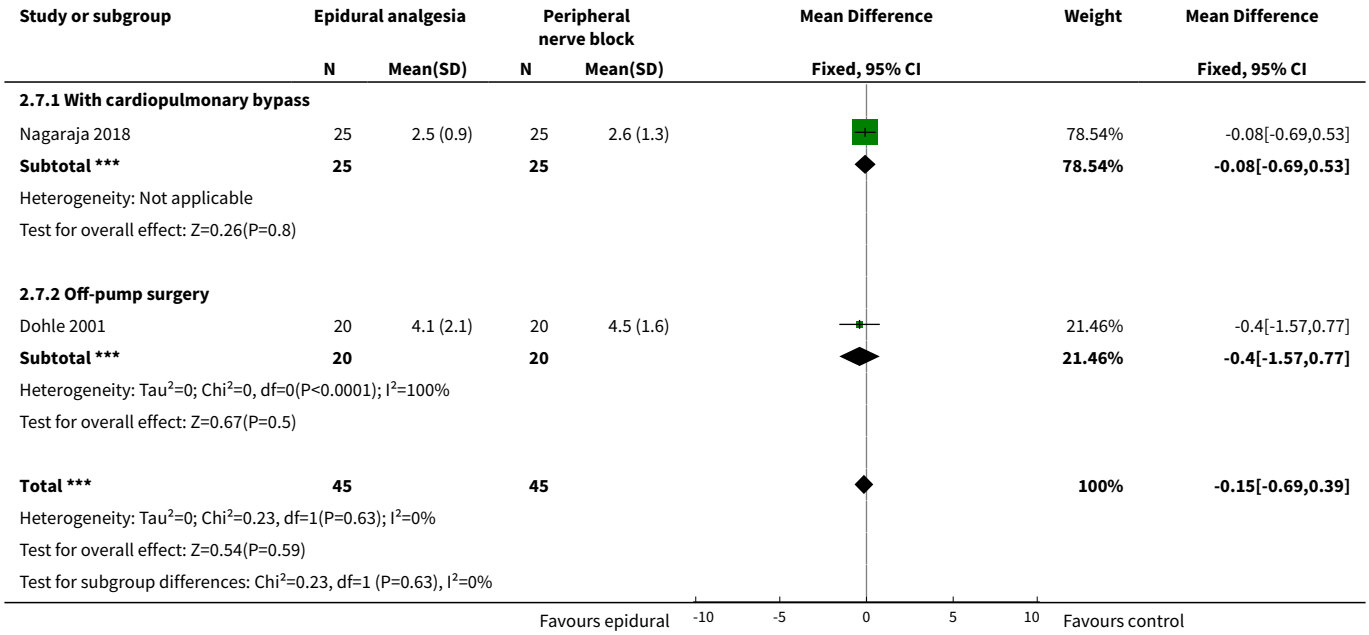


Analysis 2.6. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 6 Pain scores at rest at 6 to 8 hours.



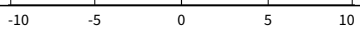


Analysis 2.7. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 7 Pain scores on movement/coughing at 6 to 8 hours.



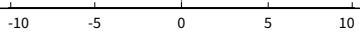
Analysis 2.8. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 8 Pain at rest at 24 hours.

Study or subgroup	Epidural analgesia		Paraverte-bral blockade		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.8.1 With cardiopulmonary bypass							
El-Shora 2018	75	1.9 (0.2)	70	1.9 (0.2)		44.74%	0[-0.05,0.05]
Nagaraja 2018	25	2.1 (0.6)	25	1.4 (0.9)		34.6%	0.64[0.22,1.06]
Subtotal ***	**100**		**95**			**79.34%**	**0.28[-0.34,0.91]**
Heterogeneity: Tau^2=0.18; Chi^2=8.66, df=1(P=0); I^2=88.45%							
Test for overall effect: Z=0.89(P=0.37)							
2.8.2 Off-pump surgery							
Mehta 2008	19	0.8 (1.2)	17	1.3 (1.4)		20.66%	-0.54[-1.38,0.3]
Subtotal ***	**19**		**17**			**20.66%**	**-0.54[-1.38,0.3]**
Heterogeneity: Not applicable							
Test for overall effect: Z=1.26(P=0.21)							
Total ***	**119**		**112**			**100%**	**0.11[-0.41,0.63]**
Heterogeneity: Tau^2=0.16; Chi^2=10.29, df=2(P=0.01); I^2=80.57%							
Test for overall effect: Z=0.41(P=0.68)							
Test for subgroup differences: Chi^2=2.38, df=1 (P=0.12), I^2=58.06%							



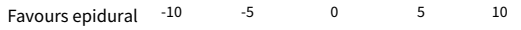
Analysis 2.9. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 9 Pain on movement/coughing at 24 hours.

Study or subgroup	Epidural analgesia		Peripheral nerve block		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	Random, 95% CI		Random, 95% CI
2.9.1 With cardiopulmonary bypass							
Nagaraja 2018	25	3.1 (0.7)	25	2.4 (1.1)		57.06%	0.72[0.22,1.22]
Subtotal ***	**25**		**25**			**57.06%**	**0.72[0.22,1.22]**
Heterogeneity: Not applicable							
Test for overall effect: Z=2.82(P=0)							
2.9.2 Off-pump surgery							
Mehta 2008	19	1.8 (1.3)	17	2.1 (1.3)		42.94%	-0.24[-1.11,0.63]
Subtotal ***	**19**		**17**			**42.94%**	**-0.24[-1.11,0.63]**
Heterogeneity: Tau^2=0; Chi^2=0, df=0(P<0.0001); I^2=100%							
Test for overall effect: Z=0.54(P=0.59)							
Total ***	**44**		**42**			**100%**	**0.31[-0.62,1.24]**
Heterogeneity: Tau^2=0.33; Chi^2=3.53, df=1(P=0.06); I^2=71.7%							
Test for overall effect: Z=0.65(P=0.52)							
Test for subgroup differences: Chi^2=3.53, df=1 (P=0.06), I^2=71.7%							



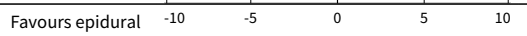
Analysis 2.10. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 10 Pain at rest at 48 hours.

Study or subgroup	Epidural analgesia N	Epidural analgesia Mean(SD)	Peripheral nerve block N	Peripheral nerve block Mean(SD)	Mean Difference Random, 95% CI	Weight	Mean Difference Random, 95% CI
2.10.1 With cardiopulmonary bypass							
El-Shora 2018	75	1.5 (0.1)	70	1.7 (0.1)		52.48%	-0.11[-0.15,-0.07]
Nagaraja 2018	25	2 (1.3)	25	0.8 (0.6)		47.52%	1.2[0.62,1.78]
Subtotal * **	**100**		**95**			**100%**	**0.51[-0.77,1.8]**
Heterogeneity: Tau^2=0.82; Chi^2=19.93, df=1(P<0.0001); I^2=94.98%							
Test for overall effect: Z=0.78(P=0.44)							
Total * **	**100**		**95**			**100%**	**0.51[-0.77,1.8]**
Heterogeneity: Tau^2=0.82; Chi^2=19.93, df=1(P<0.0001); I^2=94.98%							
Test for overall effect: Z=0.78(P=0.44)							



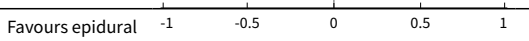
Analysis 2.11. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 11 Pain at rest on movement/coughing at 48 hours.

Study or subgroup	Epidural analgesia N	Epidural analgesia Mean(SD)	Paraverte-bral blockade N	Paraverte-bral blockade Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Nagaraja 2018	25	2.7 (1.4)	25	1.4 (0.7)		100%	1.36[0.76,1.96]
Total * **	**25**		**25**			**100%**	**1.36[0.76,1.96]**
Heterogeneity: Not applicable							
Test for overall effect: Z=4.42(P<0.0001)							



Analysis 2.12. Comparison 2 Epidural analgesia compared with peripheral nerve blocks, Outcome 12 Hypotension or need for vasopressor.

Study or subgroup	Epidural analgesia n/N	Paraverte-bral blockade n/N	Risk Difference M-H, Random, 95% CI	Weight	Risk Difference M-H, Random, 95% CI
2.12.1 Off-pump surgery					
Dohle 2001	1/20	0/20		100%	0.05[-0.08,0.18]
Subtotal (95% CI)	**20**	**20**		**100%**	**0.05[-0.08,0.18]**
Total events: 1 (Epidural analgesia), 0 (Paravertebral blockade)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					
Total (95% CI)	**20**	**20**		**100%**	**0.05[-0.08,0.18]**
Total events: 1 (Epidural analgesia), 0 (Paravertebral blockade)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.77(P=0.44)					

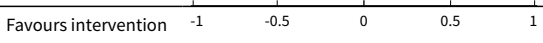


Comparison 3. Epidural analgesia compared with intrapleural analgesia

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Myocardial infarction (0 to 30 days)	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
1.1 Off-pump surgery	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
2 Neurological complications: epidural haematoma (0 to 30 days)	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
2.1 Off-pump surgery	1	50	Risk Difference (M-H, Fixed, 95% CI)	0.0 [-0.07, 0.07]
3 Duration of tracheal intubation (hours)	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.20, 0.60]
3.1 Off-pump surgery	1	15	Mean Difference (IV, Fixed, 95% CI)	-0.30 [-1.20, 0.60]
4 Pain scores at rest at 6 hours	1	50	Mean Difference (IV, Fixed, 95% CI)	0.84 [0.31, 1.37]
4.1 Off-pump surgery	1	50	Mean Difference (IV, Fixed, 95% CI)	0.84 [0.31, 1.37]

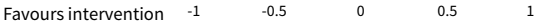
Analysis 3.1. Comparison 3 Epidural analgesia compared with intrapleural analgesia, Outcome 1 Myocardial infarction (0 to 30 days).

Study or subgroup	Intervention n/N	Comparator n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
3.1.1 Off-pump surgery					
Mehta 1998	0/25	0/25		100%	0[-0.07,0.07]
Subtotal (95% CI)	**25**	**25**		**100%**	**0[-0.07,0.07]**
Total events: 0 (Intervention), 0 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**25**	**25**		**100%**	**0[-0.07,0.07]**
Total events: 0 (Intervention), 0 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



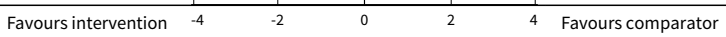
Analysis 3.2. Comparison 3 Epidural analgesia compared with intrapleural analgesia, Outcome 2 Neurological complications: epidural haematoma (0 to 30 days).

Study or subgroup	Intervention n/N	Comparator n/N	Risk Difference M-H, Fixed, 95% CI	Weight	Risk Difference M-H, Fixed, 95% CI
3.2.1 Off-pump surgery					
Mehta 1998	0/25	0/25		100%	0[-0.07,0.07]
Subtotal (95% CI)	**25**	**25**		**100%**	**0[-0.07,0.07]**
Total events: 0 (Intervention), 0 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**25**	**25**		**100%**	**0[-0.07,0.07]**
Total events: 0 (Intervention), 0 (Comparator)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



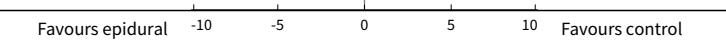
Analysis 3.3. Comparison 3 Epidural analgesia compared with intrapleural analgesia, Outcome 3 Duration of tracheal intubation (hours).

Study or subgroup	Intervention N	Intervention Mean(SD)	Comparator N	Comparator Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.3.1 Off-pump surgery							
Mehta 1998	8	3.8 (1.1)	7	4.1 (0.6)		100%	-0.3[-1.2,0.6]
Subtotal ***	**8**		**7**			**100%**	**-0.3[-1.2,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.66(P=0.51)							
Total ***	**8**		**7**			**100%**	**-0.3[-1.2,0.6]**
Heterogeneity: Not applicable							
Test for overall effect: Z=0.66(P=0.51)							



Analysis 3.4. Comparison 3 Epidural analgesia compared with intrapleural analgesia, Outcome 4 Pain scores at rest at 6 hours.

Study or subgroup	Epidural N	Epidural Mean(SD)	Control N	Control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
3.4.1 Off-pump surgery							
Mehta 1998	25	4.5 (1.1)	25	3.7 (0.8)		100%	0.84[0.31,1.37]
Subtotal ***	**25**		**25**			**100%**	**0.84[0.31,1.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.1(P=0)							
Total ***	**25**		**25**			**100%**	**0.84[0.31,1.37]**
Heterogeneity: Not applicable							
Test for overall effect: Z=3.1(P=0)							



ADDITIONAL TABLES

Table 1. Postoperative analgesia

Study	Regional blockade	Comparator
Aguero-Martinez 2012	TEA (T3-T4) with 10 mL bupivacaine 0.5% and morphine 5 mg administered at least 1 hour before IV heparin	Low doses of opioids
Bach 2002	TEA (T12-L1) inserted the evening before surgery Bupivacaine 0.25% 10 mL Bupivacaine 0.25% ((body height (cm) − 100) × 10^{-1} = mL/h) for 18 hours Catheter removed on the second or third day after surgery when coagulation parameters had returned to normal range	Not reported
Bakhtiary 2007	TEA (T1-T3; soft multi-port) inserted the day before surgery 6 mL ropivacaine 0.16% plus sufentanil 1 mcg/mL Ropivacaine 0.16% plus sufentanil 1 mcg/mL at 2 to 5 mL/h started before surgery and continued for 3 days after surgery	Metamizole and pir-itramide
Barrington 2005	TEA (T1-T3) (20-gauge; Portex, Hythe, Kent, UK) inserted 4 cm cephalad the day before surgery using a midline approach and a loss of resistance to saline technique Ropivacaine 1% 5 mL and fentanyl 50 mcg (adjusted for T1 to T6 sensory block) Ropivacaine 0.2% and fentanyl 2 mcg/mL 5 mL/h started 1 hour after induction and continued until morning of postoperative day 3 (adjusted on pain scores)	IV morphine infusion and infiltration of chest drain sites
Bektas 2015	TEA (T2-T4) inserted 5 cm into the epidural space 1 day before surgery Lidocaine 60 mg Levobupivacaine 0.25% 0.1 mL/kg/min and fentanyl 2 mcg/kg/min bolus for T1-L2 sensory block Levobupivacaine 0.25% 0.1 mL/kg/h and fentanyl 2 mcg/mL	IV PCA with morphine for 24 hours
Berendes 2003	TEA (C7-T1) with a median approach and a hanging drop technique inserted the day before surgery 2 mL of 0.5% bupivacaine with epinephrine Bupivacaine 0.5% at 6 to 12 mL/h plus sufentanil 15 to 25 mcg started just before surgery and kept for 4 days	Not reported
Brix-Christensen 1998	TEA (T3-T4) inserted at least 12 hours before surgery Bupivacaine 0.5% 8 mL 30 minutes before induction of anaesthesia Continuous infusion with bupivacaine 2 mg/mL and fentanyl 5 mcg/mL at 5 mL/h during and after surgery until the second postoperative day	IV morphine
Caputo 2011	TEA (T2-T4) inserted before surgery	IV PCA with morphine

Table 1. Postoperative analgesia *(Continued)*

	Bupivacaine 0.5% 5 + 5 mL Bupivacaine 0.125% plus clonidine 0.0003% 10 mL/hour started after induction and continued for 72 hours (adjusted for T1 to T10 sensory block and on pain scores)	
Celik 2015	TEA (T5-T6) inserted the day before surgery Levobupivacaine 2 mcg/mL and fentanyl 10 mcg/mL started at ICU admission at 5 mL/h and maintained for 24 hours	IV fentanyl infusion at 8 mcg/kg/h for 24 hours
Cheng-Wei 2017	TEA PCEA with 0.075% bupivacaine and 2 mcg/mL fentanyl	Wound infusion with 0.15% bupivacaine infused continuously at 2 mL/h through a catheter embedded in the wound plus IV PCA
de Vries 2002	TEA (T3-T4) placed immediately before induction of anaesthesia Test dose with 3 to 4 mL of lidocaine 2% with epinephrine 1:200,000 8 to 10 mL bupivacaine 0.25% with sufentanil 25 mcg/10 mL Bupivacaine 0.125% and sufentanil 25 mcg/50 mL given at 8 to 10 mL/h	Piritramide 0.2 mg/kg intramuscularly on request
Dohle 2001	TEA (T4-T5) 18G, midline approach, catheter advanced 3 cm past the needle tip Test dose with 3 mL 2% lidocaine Loading with 8 mL 0.5% bupivacaine injected through the catheter, followed by infusion of 0.25% bupivacaine at the rate of 6 mL/h	Paravertebral blockade, left T4 to T5, loss of resistance with saline, catheter advanced 3 cm past the needle tip Test dose with 3 mL 2% lidocaine Loading with 8 mL 0.5% bupivacaine injected through the catheter, followed by an infusion of 0.25% bupivacaine at the rate of 6 mL/h
El-Baz 1987	TEA (T3-T4), epidural catheter (American Pharmaseal Labs, Glendale, CA, USA) inserted by lateral approach Position of the catheter in the epidural space was confirmed by the catheter advancement test (El-Baz 1984; "After eliciting a lack of resistance to the injection of air through the epidural needle, the ability to advance 20 cm of a soft epidural catheter, without stylet, beyond the vertebral lamina with minimal resistance was indicative of a successful epidural catheterization. After a successful advancement with minimal resistance, the epidural catheter was withdrawn 17-18 cm leaving 2 -3 cm of the catheter in the epidural space and the tip near the spinal segment (T4 - 5) that corresponded to the site of surgical incision. Subdural and intravascular catheterization were excluded by placing the proximal end of the epidural catheter below the site of injection for gravity drainage to assure the absence of cerebrospinal fluid or blood flow through the catheter") Morphine 0.1 mg/h started in ICU	IV morphine on request
El-Morsy 2012	TEA (T3-T4) inserted at least 2 hours before heparinization (change of level if blood in the needle or catheter)	IV tramadol on demand

Table 1. Postoperative analgesia *(Continued)*

	Test dose with 3 mL 1.5% lidocaine 0.125% bupivacaine with 1 mcg/mL fentanyl at 5 mL/h and continued until 24 hours postoperatively	
El-Shora 2018	TEA (T6-T7) catheter inserted through a 17G Tuohy needle with loss of resistance technique Bupivacaine 0.125% plus fentanyl 1 mcg/mL 12 mL followed by 12 mL/h for 48 hours and started after surgery	Ultrasound-guided bilateral paravertebral blockade at T6-T7 Bupivacaine 0.125% plus fentanyl 1 mcg/mL 6 mL per side followed by 6 mL/h for 48 hours and started after surgery
Fawcett 1997	TEA (T2-T4) inserted in operating room 15 mL bupivacaine 0.5% after CPB Bupivacaine 0.375% at 5 to 8 mL/h for 24 hours	IV morphine infusion for 24 hours
Fillinger 2002	TEA (T3-T10), catheter inserted before induction of anaesthesia through an 18G Hustead needle using loss of resistance to saline technique and leaving 3 cm of catheter in the epidural space Test dose with 3 mL 1.5% lidocaine with 1:200,000 epinephrine Loading with morphine 20 mcg/kg and 0.5% bupivacaine in 5-mg increments, to a total loading dose of 25 to 35 mg bupivacaine 0.5% bupivacaine with morphine 25 mcg/mL at 4 to 10 mL/h beginning after induction of anaesthesia (adjusted on haemodynamic parameters) Epidural catheters removed on the first postoperative day	Intravenous morphine, intravenous meperidine, and oral oxycodone
Greisen 2012	TEA (T2-T4) inserted the day before surgery 5 to 7 mL 5.0 mg/mL bupivacaine (Marcaine, Astra, Södertälje, Sweden) together with sufentanil 2.5 mcg/mL Bupivacaine 2.5 mg/mL and sufentanil 1 mcg/mL 4 to 6 mL/h, by discretion of the attending anaesthesiologist, until end of surgery Changed to bupivacaine 1 mg/mL together with sufentanil 1 mcg/mL in ICU and continued after discharge from ICU until second postoperative day	Not reported
Gurses 2013	CEA (C6-C7) (Braun Perifix 20 G) inserted 3 to 4 cm caudally (T2-T4) at least 1 hour before heparin injection 0.075 mg/kg levobupivacaine hydrochloride (Chirocaine 5 mg/mL, Abbott Lab, Istanbul, Turkey) + 2 mcg/kg fentanyl (fentanyl citrate 50 mcg/mL, Abbott Lab, Istanbul, Turkey) in total 10 mL bolus 0.0375 mg/kg/h levobupivacaine + 0.5 mcg/kg/h fentanyl epidural infusion started with patient-controlled analgesia instrument (Abbott Pain Management Provider, Abbott Laboratoires, North Chicago, IL, USA)	Intramuscular diclofenac sodium (Diklоron 75 mg 10 amp, Mefar Drug Ltd, Istanbul, Turkey)
Hansdottir 2006	TEA (T2-T5) inserted the day before surgery using median hanging drop or loss of resistance technique, 3 to 5 cm into the epidural space Test dose with 4 mL lidocaine 1%	IV PCA with morphine

Table 1. Postoperative analgesia *(Continued)*

	PCEA with bupivacaine 0.1% and fentanyl 2 mcg/mL	
Heijmans 2007	TEA (C7-T1) by median approach and hanging drop technique Test dose of 2 mL lidocaine 2% Loading dose of 10 mL bupivacaine 0.25% with 2.5 mg morphine infused over 1 hour Bupivacaine 0.125% and morphine 0.2 mg/mL at 1.5 mL/h for 48 hours	IV piritramide 0.15 mg/kg
Huh 2004	TEA (T4-T5) inserted the day before surgery Test dose with 3 mL lidocaine 2% and epinephrine 5 to 7 mL bupivacaine 0.15% and fentanyl 50 mcg before skin incision Bupivacaine 0.15% and fentanyl 10 mcg/mL through PCEA for 3 days after surgery	IV meperidine, tramadol, and NSAIDs
Hutchenson 2006	TEA (T2-T4) inserted 3 cm the day before surgery with fluoroscopic guidance Bupivacaine 0.5% 200 mcg/cm body height Bupivacaine 0.25% 200 mcg/cm body height per hour	Not reported
Jakobsen 2012	TEA (T3-T4) Test dose of 3 mL 2% lidocaine Bolus dose of 5 to 7 mL, guided by primary patient heights, of 0.5% bupivacaine (Marcaine; Astra, Södertälje, Sweden) and sufentanil 2.5 mcg/mL Bupivacaine 2.5 mg/mL/sufentanil 1 mcg/mL, 4 to 6 mL/h during surgery Bupivacaine 1 mg/mL and sufentanil 1 mcg/mL postoperatively and continued after discharge from ICU until second postoperative day	Participants in both groups received intravenous morphine or alfentanil according to the department's general guidelines (i.e. morphine 0.05 mg/kg, or alfentanil 25 mcg, if rapid pain relief was needed) All participants in both groups received additional oral or intravenous paracetamol 1 g every 6 hours
Kendall 2004	TEA (T1-T4) inserted after induction through a paramedian approach and loss of resistance technique 2 mL 0.5% bupivacaine plus epinephrine 0.1 mL/kg 0.1% bupivacaine plus fentanyl 5 mcg/mL followed by infusion at 0.1 mL/kg/h kept for 48 hours	IV PCA with morphine
Kilickan 2006	TEA (T1-T5) inserted the day before surgery (3 attempts only) Test dose with 3 to 4 mL 2% lidocaine, position confirmed with injection of contrast material and X-ray Bupivacaine 20 mg after anaesthesia induction Bupivacaine 0.125% 4 to 10 mL/h intraoperatively and postoperatively for 3 days, adjusted for a sensory blockade from T1 to T10	IV PCA with morphine
Kilickan 2008	TEA (T1-T5) inserted the day before surgery (3 attempts only)	IV PCA with Dolantin

Table 1. Postoperative analgesia *(Continued)*

	Test dose with 3 to 4 mL 2% lidocaine, position confirmed with injection of contrast material and X-ray Bupivacaine 20 mg 60 minutes before induction of anaesthesia Bupivacaine 20 mg/h intraoperatively and postoperatively for 3 days	
Kirno 1994	TEA (T3-T4; Perifix, B. Braun, Melsungen AG, Germany) at least 12 hours before surgery Mepivacaine 20 mg/mL (Carbocain, Astra, Södertälje, Sweden) was injected to achieve a T1-T5 block	Not reported
Kirov 2011	TEA (T2-T4) Test dose of 1 mL 2% lidocaine Ropivacaine 0.75% 1 mg/kg and fentanyl 1 mcg/kg for surgery Ropivacaine 0.2% and fentanyl 2 mcg/mL at 3 to 8 mL/h (VAS score < 30 mm at rest) or via PCEA after surgery	IV fentanyl 10 mcg/mL at 3 to 8 mL/h
Konishi 1995	TEA (T7-T10) inserted the day before surgery Butorphanol 0.5 to 1.0 mg or Morphine 2.5 mg	Fentanyl, pentazocine, and minor tranquillizers
Kundu 2007	TEA (C7-T2) inserted 3 to 4 cm cephaladly before anaesthesia induction with hanging drop technique in left lateral decubitus position Lidocaine 1% 5 mL Bupivacaine 0.25% 5 mL plus fentanyl 10 mcg Bupivacaine 0.25% 5 mL plus fentanyl 10 mcg every 2 hours	Not reported
Kunstyr 2001	TEA (T1-T5) inserted at least 60 minutes before heparinization 10 mL bupivacaine 0.5% Bupivacaine 0.125% plus sufentanil 1 mcg/mL infused at 3 to 8 mL/h after surgery	1. Postoperative analgesia with a mixture of ketamine 400 mg and sufentanil 100 mcg in 50 mL syringe, administered in a continuous infusion; rate of infusion 0.5 to 3.5 mL/h 2. Nurse administered morphine on request 3. IV PCA with morphine
Lenkutis 2009	TEA (T1-T2) Lidocaine 2% 7 to 8 mL Bupivacaine 0.25% at 8 mL/h during surgery Bupivacaine 0.25% and fentanyl 5 mcg/mL at 5 to 7 mL/h for at least 84 hours postoperatively	IM/IV pethidine 0.1 to 0.4 mg/kg
Liem 1992	TEA (T1-T2) inserted the day before surgery by paramedian approach and hanging drop technique Test dose with 2 mL 2% lidocaine	IV nicomorphine

Table 1. Postoperative analgesia *(Continued)*

	Loading with 0.375% bupivacaine plus sufentanil 5 mcg/mL at a dose of 0.05 mL/cm body length administered over a 10-minute period 0.125% bupivacaine plus sufentanil 1 mcg/mL at 0.05 mL/cm body length/h started before induction and continued for 72 hours	
Loick 1999	TEA (C7-T1) inserted the day before surgery by median approach and hanging drop technique Test dose with 2 mL bupivacaine 0.5% with adrenaline Loading before induction with 8 to 12 mL bupivacaine 0.375% and 16 to 24 mcg sufentanil into the epidural space in increments to block the somatosensory level C7-T6 PCEA with bupivacaine 0.75% plus sufentanil 1 mcg/mL if < 65 years of age, and without adjuvant if ≥ 65 years (duration unclear, possibly 48 hours)	PCA with piritramide
Lundstrom 2005	TEA (T1-T3) inserted the day before surgery by median approach using hanging drop technique Test dose with 2 mL 2% lidocaine Loading with 8 to 10 mL bupivacaine 0.5% (adjusted for sensory block T1-T8) before induction Bupivacaine 0.125% and morphine 25 mcg/mL at 5 mL/h plus 4 mL every hour started after induction Bupivacaine 0.25% 4 mL on request after surgery (adjusted for T1-T8) Catheters removed on day 4 or 5	Morphine IV for 24 hours, then orally
Lyons 1998	TEA (C7-T1) Bupivacaine 0.5% 0.1 mL/kg Bupivacaine 0.1% and fentanyl 2 mcg/mL, infusion for 72 hours	Not reported
Mehta 1998	TEA (T4-T5 or T5-T6) 16G, median approach, loss of resistance to saline, catheter inserted 3 to 4 cm past the needle tip On first demand for pain relief, participants in the TEA group received 8 mL 0.25% bupivacaine hydrochloride Maximum of 3 doses was given over the next 12 hours, if required	Intrapleural catheter: 16G epidural catheter inserted in intercostal space 6 to 7 cm in left anterior axillary line by the operating surgeon, 6 to 8 cm in intrapleural space, directed posteriorly and anchored with a skin suture before thoracotomy closure On first demand for pain relief, participants in the intrapleural group received 20 mL 0.25% bupivacaine hydrochloride Before injection of intrapleural bupivacaine, participants were positioned supine with a

Table 1. Postoperative analgesia *(Continued)*

		one-third left lateral tilt and with the intercostal chest tube clamped after exclusion of any air leak. The chest tube was kept clamped for 20 minutes after the injection Maximum of 3 doses was given over the next 12 hours, if required
Mehta 2008	TEA (C7-T1) hanging drop technique in the sitting position, catheter inserted 4 cm beyond needle tip Lidocaine 2% 3 mL Bupivacaine 0.5% 8 mL Bupivacaine 0.25% at 0.1 mL/kg/h	Paravertebral blockade Loss of resistance to saline at left T4-T5 Lidocaine 2% 3 mL Bupivacaine 0.5% 8 mL Bupivacaine 0.25% at 0.1 mL/kg/h
Mehta 2010	TEA (C7-T1) using hanging drop technique in sitting position inserted at least 2 hours before heparinization; intervention postponed in cases of bloody tap 3 mL 2% lidocaine without epinephrine; adequacy and level of the block established by confirming loss of pin-prick sensation and warm/cold discrimination 8 to 10 mL 0.25% bupivacaine (aim at T4 sensory block) Bupivacaine infusion (0.125%) with fentanyl citrate (1 mcg/mL) at the rate of 5 mL/h was commenced and continued until postoperative day 3 to provide intraoperative and postoperative analgesia	Not reported
Mishra 2004	No details available	Not reported
Moore 1995	TEA (T1-T5) Bupivacaine 0.5% in 2 mL increments for sensory block from T1 to L2 Bupivacaine 0.375% at 5 to 8 mL/h started before induction Bupivacaine 0.25% at 5 to 8 mL/h for at least 24 hours	IV papaveretum
Nagaraja 2018	TEA (C7-T1) inserted (3 to 4 cm caudally) the day before surgery through an 18G Tuohy needle 0.25% plain bupivacaine 15 mL before surgery followed by 0.125% plain bupivacaine at 0.1 mL/kg/h for 48 hours post extubation	`Ultrasound-guided` (in-plane) erector spinae plane lock Catherer inserted 5 cm cephaladly the day before surgery through an 18G Tuohy needle. 3 cm lateral to T6 spinous process (T5 transverse process) with hydrodissection below the erector spinae muscle with 5 mL normal saline,

Table 1. Postoperative analgesia *(Continued)*

		0.25% plain bupivacaine, 15 mL in each catheter before surgery, followed by 0.125% plain bupivacaine at 0.1 mL/kg/h for 48 hours post extubation, through each catheter
Neskovic 2013	TEA (T2-T4) inserted 30 minutes before surgery and at least 2 hours before the first dose of heparin Test dose 10 to 15 mL 0.125 or 0.25% bupivacaine with fentanyl 0.125 or 0.25% bupivacaine with fentanyl at 5 to 10 mL/h	Not reported
Nygard 2004	TEA (T1-T3) inserted the day before surgery by the median approach and hanging drop technique Test dose with 2 mL 2% lidocaine Loading with 8 to 10 mL bupivacaine 05% before induction (adjusted for T1 to T8) Bupivacaine 0.125% with morphine 25 mcg/mL at 5 mL/h started after induction and continued for 4 days Additional bolus doses of 4 mL bupivacaine 0.5% hourly during the operation	Morphine IV for 24 hours, then orally
Obersztyn 2018	TEA (T1-T3) with hanging drop technique, catheters inserted 3 to 4 cm into the epidural space at least 6 hours before surgery Before surgery: 9 to 11 mL 0.25% bupivacaine with fentanyl in a concentration of 10 mcg/mL, followed by 0.19% (more exactly, 0.1875%) bupivacaine and fentanyl at 6 mL/h during surgery and 0.125% bupivacaine plus fentanyl 6.25 mcg/mL at 2 to 8 mL/h after surgery until discharge fro the ICU (mean 18.8 hours)	IV morphine
Onan 2011	TEA (T2-T4; side-holed 18 G epidural catheter) by using a median approach and a loss of resistance technique with saline solution Test dose with 3 to 4 mL 2% lidocaine 20 mg bolus 0.25% bupivacaine through the epidural catheters 1 hour before surgery 0.25% bupivacaine infused at a rate of 20 mg/h during surgery 0.125% bupivacaine at 4 to 10 mL/h after surgery (adjusted for T1-T10) Epidural catheters removed at 24 hours postoperatively	Not reported
Onan 2013	TEA (T1-T5) inserted the night before surgery 3 cm into epidural space Test dose with 3 to 4 mL 2% lidocaine Sensory blockade tested with ice plus X-ray after injection of contrast material Bolus of 20 mg 0.25% bupivacaine 1 hour before surgery 20 mg/h 0.25% bupivacaine intraoperatively	Acetaminophen (500 mg) and tramadol (1 mg/kg) used as rescue medications

Table 1. Postoperative analgesia *(Continued)*

	Bupivacaine 0.25% 10 to 20 mL/h during first 24 hours after surgery (adjusted according to pain scores)	
Palomero 2008	TEA (T3-T6) inserted the day before surgery Bolus of 6 to 8 mL 0.33% bupivacaine 0.175% bupivacaine 6 to 8 mL/h for 48 hours Catheter withdrawn after check of coagulation status	Morphine 0.5 to 1 mL/h
Petrovski 2006	TEA; no details	Not reported
Priestley 2002	TEA (T1-T4; 18G side-holed epidural catheter) inserted the evening before surgery Test dose with 2% lidocaine 3 to 4 mL Loading with 4 mL ropivacaine 1% and fentanyl 100 mcg (adjusted for T1-T6) Ropivacaine 1% and fentanyl 5 mcg/mL at 3 to 5 mL/h started before induction and continued for 48 hours	Continuous morphine infusion for 24 hours, followed by PCA with morphine
Rein 1989	TEA (T4-T5) Bupivacaine 0.5% 10 mL at induction of anaesthesia and 4 mL every hour during surgery Bupivacaine 0.5% at 4 mL/h for 24 hours	Morphine
Royse 2003	TEA (T1-T3) inserted the night before the operation 8 mL bupivacaine 0.5% with fentanyl 20 mcg before induction Ropivacaine 0.2% with fentanyl 2 mcg/mL at 5 to 14 mL/h (for T1-T10 sensory block) and continued until postoperative day 3, 6H00 AM	PCA with morphine
Scott 2001	TEA (T2-T4) inserted before induction Loading with bupivacaine 0.5% 2 boluses of 5 mL (for T1-T10) Bupivacaine 0.125% and 0.0006% clonidine at 10 L/h started after induction and continued for 96 hours (adjusted on pain scores and sensory block)	Target controlled infusion of alfentanil for 24 hours followed by PCA with morphine for another 48 hours (adjusted on pain scores)
Sen 2017	TEA (T2-T4) inserted 4 to 6 cm into epidural space the day before surgery Lidocaine 2% with epinephrine 5 mcg/mL 3 mL Bupivacaine 0.1% and fentanyl 2 mcg/mL at 0.1 mL/kg/h started after induction	IV fentanyl 0.5 to 2 mcg/kg/h IV tramadol 100 mg as rescue analgesia
Sharma 2010	TEA (C7-T2) inserted at least 2 hours before heparinization and using hanging drop technique via midline approach Test dose 3 mL 2% lignocaine without epinephrine Loading with 8 to 10 mL bupivacaine 0.25% (for sensory block until at least T4) before induction Bupivacaine 0.125% with 1 mcg/mL fentanyl citrate at 5 mL/h started after induction and continued until third postoperative day	IV continuous infusion of tramadol

Table 1. Postoperative analgesia *(Continued)*

Stenseth 1994	TEA (T4-T6) inserted the day before surgery Test dose with lidocaine 10 mL bupivacaine 0.5% before induction 4 mL bupivacaine 0.5% hourly during surgery Bupivacaine 0.5% at 3 mL/h plus 4 mL every 4 hours after surgery	IV morphine on request
Stenseth 1996	TEA (T4-T6) inserted the day before surgery Test dose with lidocaine 10 mL bupivacaine 0.5% before induction (for at least T1-T2 block) 4 mL bupivacaine 0.5% hourly during surgery Bupivacaine 0.5% at 3 mL/h plus 4 mL every 4 hours after surgery Morphine epidurally 4 to 6 mg 3 to 4 times a day for the next 2 days, supplemented with bupivacaine 5 mg/mL when needed until third postoperative day	IV morphine on request
Stritesky 2006	TEA (T2-T4) 1 hour before surgery with an 18G Tuohy needle and hanging drop or loss of resistance technique, with catheter inserted 4 cm past the needle tip 10 mL bupivacaine 0.25% plus fentanyl 100 mcg for loading (half through the needle and half through the catheter) Bupivacaine 0.25% and fentanyl 1 mcg/mL at 8 to 12 mL/h during surgery and for 48 hours	Not reported
Svircevic 2011	TEA (T2-T4) at least 4 hours before heparinization Test dose with lidocaine 2% 3 mL 0.1 mL/kg administered of a solution of 0.08 mg/mL morphine and 0.125% bupivacaine, followed by continuous infusion of 4 to 8 mL/h of the same solution started before induction Epidural catheter removed before transfer to the general ward (median 22 hours)	Morphine IV infusion
Tenenbein 2008	TEA (T2-T5) inserted at least 4 hours before systemic heparinization 2.5 mL test dose of 2% lidocaine, with 1:200,000 epinephrine on insertion 3 mL test dose of 2% lidocaine before surgery 0.75% ropivacaine 5 mL with hydromorphone 200 mcg followed by an infusion of ropivacaine 0.75% at 5 mL/h during surgery 0.2% ropivacaine with hydromorphone 15 mcg/mL for 48 hours after surgery	IV PCA with morphine Indomethacin suppositories (100 mg) postoperatively, and twice-daily naproxen (500 mg)
Tenling 1999	TEA (T3-T5; 16G), inserted the day before surgery through the lateral approach and loss of resistance technique with saline 0.9% Test dose of 2 to 3 mL lidocaine 1% 8 to 12 mL bupivacaine 0.5% the morning of the operation (for T1-T8 sensory block) Bupivacaine 0.5% at 4 to 8 mL/h until ICU admission	IV ketobemidone

Table 1. Postoperative analgesia *(Continued)*

	Bupivacaine 0.2% and sufentanil 1 mcg/mL at 3 to 7 mL/h from arrival to ICU until the day after the operation	
Usui 1990	TEA (T6-T7) inserted 4 cm past needle tip 24 hours before surgery and kept for 1 or 2 days after extubation Morphine 3 mg given after surgery and repeated as required	Morphine 10 mg IV as required Additional co-analgesia as required
Volk 2003	TEA (C7-T3) inserted the day before surgery Lidocaine 2% for T1-T6 sensory block Bupivacaine 0.5% 6 to 10 mL hourly during surgery Bupivacaine 0.25% at 6 to 12 mL/h for at least 24 hours	IV patient-controlled analgesia with pir-itramide
Yang 1996	TEA (T4-T5) inserted 3 cm cephalad in the right lateral decubitus position Lidocaine 2% 3 mL Bupivacaine 0.375% and fentanyl 5 mcg/mL 0.06 mL/cm of body length Bupivacaine 0.25% with fentanyl 5 mcg/mL 0.03 mL/cm of body length every hour	Not reported
Yilmaz 2007	TEA (T3-T6) inserted cranially 3 to 4 cm 16 to 24 hours before systemic he-parinization (Perifix 18G, Braun) Loading with morphine 5 mcg/kg and 6 mL bupivacaine 0.25% at least 45 min-utes before surgical incision 6 mL bupivacaine 0.12% with fentanyl 2.5 mcg/kg every 6 hours for 48 hours, after which catheters were withdrawn	IV fentanyl 0.7 mcg/kg/h
Yung 1997	TEA or upper lumbar epidural inserted 24 hours before surgery Lidocaine 1.5% 25 to 30 mL with ketamine 15 mg, morphine 1 mg/10 kg for surgery Morhine 1 mg in 10 mL normal saline every 12 hours for 5 days for postopera-tive analgesia	IV meperidine HCl
Zawar 2015	TEA (C7-T2) catheters inserted 4 to 5 cm cranially using hanging drop tech-nique If a “bloody tap” was to occur, the operation was postponed for 24 hours and participant was excluded from the study Bolus of 6 to 14 mL ropivacaine 0.75% for T1-T10 sensory block (sensory loss to cold pack and needle prick) Infusion of 5 to 15 mL/h ropivacaine 0.2% for 72 hours after surgery	IV tramadol hydrochlo-ride 100 mg 8 hourly
Zhou 2010	TEA (T4-T6) inserted in lateral decubitus position the day before surgery Bolus 8 to 20 mL lidocaine 1% PCEA with ropivacaine 0.125% and fentanyl 2 mcg/mL at 4 mL/h plus 2 mL bo-lus (lockout time 20 minutes)	IV PCA with fentanyl

CEA: cervical epidural analgesia; CPB: cardiopulmonary bypass; ICU: intensive care unit; NSAIDs: non-steroidal anti-inflammatory drugs; PCA: patient-controlled analgesia; PCEA: patient-controlled epidural analgesia; TEA: thoracic epidural analgesia; VAS: visual/verbal analogical pain score.

Table 2. Diagnostic criteria for myocardial infarction

Study	Criteria
Aguero-Martinez 2012	New pathological Q wave (duration ≥ 0.04 second and depth ≥ 25% of the R wave or QRS complex) in more than 1 derivation. Non-specific changes that included elevation of the ST segment > 1.5 mm from the isoelectric line in 2 or more leads of the same region, ST depression > 2 mm in the precordial leads, or reversal of the T wave for longer than 48 hours; absence of R wave in the precordial leads. Ventricular or atrioventricular conduction defects Enzymatic criteria: 5 times normal values: troponin > 1 mcg/mL, CK > 250 U/L, CK-MB > 133 U/L, LDH > 800 U/L, LDH 1/LDH 2 > 1 in blood samples collected between postoperative days 2 and 3, and GOT > 90 U/L Echocardiographic criteria: new segmental motility disorders Anatomopathological criteria: in dead patients
Bakhtiary 2007	Unspecified
Barrington 2005	Transmural infarction defined as new Q waves
Bektas 2015	1. Cardiac biomarkers (with troponins preferred) rise > 10 times 99% upper reference limit (URL) from normal preoperative level 2. New pathological Q waves or new left bundle branch block (LBBB) and/or imaging or angiographic evidence of new occlusion of native vessels or grafts, new regional wall motion abnormality, or loss of viable myocardium
Caputo 2011	New Q waves of 0.04 ms and/or reduction in R waves > 25% in at least 2 contiguous leads on ECG
Celik 2015	ECG monitored (ST analysis); CK-MB and troponin I levels measured at fourth and 24th hours
de Vries 2002	Myocardial infarction defined as a new Q wave on ECG and CK 180 U/L with CK-MB 10% of total
Dohle 2001	Myocardial infarction assessed by ECG changes and CK-MB values
Fillinger 2002	New Q waves of at least 0.04 second duration or postoperative elevation of serum creatine phosphokinase confirmed by creatine phosphokinase isoenzyme pattern
Hansdottir 2006	New Q waves or CK-MB isoenzyme concentration ≥ 50
Heijmans 2007	Myocardial infarction not mentioned in the report
Jakobsen 2012	Perioperative myocardial infarction, defined as new Q waves of 0.04 ms and/or reduction in R waves > 25% in at least 2 contiguous leads on ECG
Kendall 2004	ECG changes (new Q wave, or loss of R wave progression, or new permanent left bundle branch block) and increase in creatinine kinase myocardial fraction (CK-MB) to > 120 units per litre
Kilickan 2006	Unspecified
Liem 1992	CK-MB values ≥ 80 IU/L and evidence of new Q waves or bundle branch block on postoperative ECG
Loick 1999	Unclear

Table 2. Diagnostic criteria for myocardial infarction *(Continued)*

Lyons 1998	Unclear
Mehta 1998	Incidence of perioperative myocardial infarction also analysed by an independent cardiologist, as per the appearance of new Q waves in the ECG and increase in creatine phosphokinase-myocardial band isoenzyme (CPK-MB) levels to > 70 ng/mL in the first 12 hours postoperatively
Mehta 2010	2-lead ECG and CPK, CPK-MB levels
Neskovic 2013	New ECG changes with positive enzymes (CK-MB and troponin)
Obersztyn 2018	ECG and elevated serum enzymes
Onan 2011	Unspecified
Onan 2013	Unspecified
Palomero 2008	Myocardial infarction defined by analysis of the ECG (new Q waves or increases in ST segment > 3 mm)
Priestley 2002	New Q waves (assessed by the blinded cardiologist) on a 12-lead ECG on days 0, 1, 2, and 4 and assessment of venous blood levels of troponin T and creatine kinase-MB fraction on arrival in the ICU, and again at 4, 12, and 24 hours and on postoperative day 2
Scott 2001	Q waves, ST segment increase of 3 mm, and a myocardial specific serum creatinine kinase level ≥ 60 ng/mL
Stenseth 1994	Unspecified
Stenseth 1996	Unspecified
Svircevic 2011	Creatine kinase muscle–brain isoenzymes > 75 units per litre (5 times upper limit of normal level) and peak creatine kinase muscle–brain isoenzyme/creatine kinase ratio > 10% or new Q wave infarction
Zawar 2015	Myocardial infarction defined as developing ECG changes, new Q waves on postoperative ECG ≥ 0.03 second in duration in 2 or more adjacent leads lasting until discharge, rise in creatine `phosphokinase-MB` and troponin I, and new regional wall motion abnormalities

CK: creatinine kinase; CK-MB: creatinine kinase muscle brain; ECG: electrocardiogram; GOT: glutamic-oxaloacetic transaminase; LBBB: left bundle branch block; LDH: lactate dehydrogenase; URL: upper reference limit.

Table 3. Diagnostic criteria for pulmonary complications

Study	Criteria
Aguero-Martinez 2012	Respiratory depression
Barrington 2005	Respiratory depression: reintubation
Berendes 2003	Respiratory depression: need of ICU 24 hours due to intermittent respiratory insufficiency
Caputo 2011	Pneumonia: presence of purulent sputum associated with fever and requiring antibiotic therapy according to positive sputum culture

Table 3. Diagnostic criteria for pulmonary complications *(Continued)*

Celik 2015	Respiratory depression: $PaCO_2$ and PO_2 measurements at baseline and at first, sixth, and 12th hours were followed Pneumonia: fever, C-reactive protein, leukocyte values, and chest radiography were assessed
de Vries 2002	Respirarory depression: respiratory acidosis Pneumonia: criteria of the Centers for Disease Control and Prevention
El-Baz 1987	Respiratory depression: respiratory insufficiency requiring intubation and ventilatory support
Fillinger 2002	Respiratory depression: need for mechanical ventilation for 24 hours after surgery or clinical decision to initiate mechanical ventilation after initial tracheal extubation Pneumonia: positive sputum culture and chest radiograph changes
Hansdottir 2006	Respiratory depression: postoperative mechanical ventilation for longer than 24 hours or need for non-invasive positive-pressure ventilation Pneumonia: defined as pulmonary infiltrate with positive microbial cultures from sputum or fever, high leukocyte count, or high levels of C-reactive protein
Kunstyr 2001	Respiratory depression: 8 or fewer breaths per minute and $PaCO_2$ > 55 kPa
Liem 1992	Respiratory depression: no details provided
Lundstrom 2005	Respiratory depression: constant hypoxaemia on third night after surgery
Mehta 2010	Respiratory depression: no details provided
Neskovic 2013	Respiratory depression: need for re-intubation Pneumonia: febrile state, with new chest radiography findings
Obersztyn 2018	Respiratory depression: need for respiratory support after extubation
Onan 2013	Pneumonia: no details provided
Royse 2003	Respiratory depression: need for non-invasive respiratory support or re-intubation
Scott 2001	Respiratory depression: respiratory failure requiring tracheal re-intubation or prolonged mechanical ventilation (> 24 hours) Pneumonia: combination of increased white cell count, pyrexia, productive sputum, radiological signs, and positive bacterial growth on culture
Tenenbein 2008	Respiratory depression: no details provided Pneumonia: no details provided
Yilmaz 2007	Pneumonia: respiratory infection
Yung 1997	Respiratory depression: re-intubation
Zawar 2015	Respiratory depression: re-intubation

ICU: intensive care unit; kPa: kilopascal; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen.

Table 4. Diagnostic criteria for neurological complications: cerebrovascular accident

Study	Neurological complication
Aguero-Martinez 2012	Neurological complication: any new-onset psychiatric or neurological disorder with altered consciousness with or without focalization
Barrington 2005	Stroke
Bektas 2015	Stroke: All participants were postoperatively managed in the cardiac surgery intensive care unit. Postoperative stroke was suspected when a patient showed focal neurological deficits or delayed recovery of mental status after surgery. Such patients were referred to stroke neurologists and were evaluated by computed tomography. Post coronary artery bypass grafting, stroke was diagnosed as: 1) newly developed neurological deficits within 14 days of coronary artery bypass grafting; and 2) Low-density lesions on postoperative computed tomography that were not observed preoperatively. Strokes that occurred within 24 hours after coronary artery bypass grafting were defined as immediate, whereas all others were considered delayed
Caputo 2011	Stroke/transient ischaemic attack: diagnosis of stroke was made if evidence showed new neurological deficit with morphological substrate confirmed by computed tomography or nuclear magnetic resonance imaging
Celik 2015	Stroke: neurological findings of participants (hemiparesis, hemiplegia, etc.) were followed
Fillinger 2002	Neurological event: new sensorimotor neurological events
El-Shora 2018	Stroke
Hansdottir 2006	Stroke: defined as a new central neurological deficit
Heijmans 2007	Stroke
Jakobsen 2012	Transitory Ischaemic attack lasting less than 24 hours
Neskovic 2013	Stroke: new motor or sensory deficit after surgery
Onan 2013	Cerebrovascular accident
Palomero 2008	Focal neurological dysfunction defined as a sensory or motor deficit affecting 1 or more limbs appearing 5 days after surgery
Royse 2003	Stroke
Scott 2001	Cerebrovascular accident defined as a new motor or sensory deficit affecting 1 or more limbs and present on awakening from anaesthesia or occurring within the next 5 days
Stenseth 1996	Hemiparesis
Svircevic 2011	Stroke: a new motor or sensory deficit of central origin, persisting longer than 24 hours, preferably confirmed by computed tomography, resulting in a drop of 2 points on the Rankin scale
Tenenbein 2008	Stroke or transient ischaemic attack
Zawar 2015	Stroke was documented if diagnosed on computed tomography scan or magnetic resonance imaging

Table 5. Criteria for tracheal extubation

Study	Criteria
Aguero-Martinez 2012	Adequate response to verbal commands, pulse oximetry 95% with FiO_2 0.5, $PaCO_2$ 45 mmHg in spontaneous respiration, respiratory rate between 10 and 20/min, regular thoracic movements with tidal volume > 5 mL/kg, temperature > 36°C, stable haemodynamic parameters, and no surgical complications
Bakhtiary 2007	Not reported
Barrington 2005	Anaesthesiologist tracheally extubated participants in the operating room if extubation criteria—respiratory rate 10 to 20 breaths/min, responsiveness to voice, end-tidal CO_2 50 mmHg, SaO_2 94% with a fraction of inspired oxygen of 1.0, haemodynamic stability, minimal chest drain output (not requiring transfusion or consideration for surgical re-exploration), and temperature 35.9°C—were achieved within 30 minutes. For participants not extubated in the operating room, postoperative management of ventilation and extubation followed existing unit guidelines. Participants were required to respond appropriately to voice, have an acceptable ventilatory pattern and arterial blood gas analysis, and be haemodynamically stable
Berendes 2003	Weaning the participant from the respirator and extubation were performed according to standard procedures
Caputo 2011	Not reported
Celik 2015	Not reported
de Vries 2002	Extubation criteria were normothermia, haemodynamic stability, ability to respond to verbal commands, and respiratory rate of at least 8 breaths/min with peripheral oxygen saturation of at least 94%
Dohle 2001	Extubated whenever they qualified for extubation
El-Baz 1987	Not reported
El-Morsy 2012	Extubation criteria included an adequate level of consciousness and muscle strength, stable cardiovascular status, normothermia, adequate pulmonary function (PaO_2 > 80 mmHg with fraction of inspired oxygen ≤ 0.4), and minimal thoracotomy tube output
Fillinger 2002	Endotracheal extubation was managed by ICU staff following standardized criteria. ICU extubation criteria included an adequate level of consciousness and muscle strength, stable cardiovascular status, normothermia, adequate pulmonary function (PaO_2 80 mmHg with fraction of inspired oxygen 0.4), and minimal thoracostomy tube output
Gurses 2013	Participants were extubated when they completely recovered and regained muscular power (Aldrete's recovery score = 9, $PaCO_2$ < 45 mmHg, PaO_2 > 100 mmHg, FiO_2 = 0.4, and pH between 7.35 and 7.45, together with stable haemodynamic and metabolic parameters)
Hansdottir 2006	Participants underwent extubation when they fulfilled the following criteria. 1. Responsive to verbal commands. 2. Body temperature > 36.5°C. 3. Chest tube drainage < 100 mL/h. 4. Arterial PaO_2 ≥ 70 mmHg at an FiO_2 < 0.5. 5. Arterial $PaCO_2$ < 50 mmHg and respiratory rate ≤ 20 at pressure support ventilation of 10 cm H_2O.

Table 5. Criteria for tracheal extubation *(Continued)*

	6. Haemodynamic stability (i.e. not requiring significant inotropic support).
Huh 2004	Participants were extubated when they were awake (eyes opened and able to follow orders), were haemodynamically stable, and had normal arterial blood gases with $FiO_2 \leq 0.3$
Jakobsen 2012	Extubation was performed when the participant was awake and without pain following objective criteria such as a spontaneous respiratory rate of 10 to 16, a core temperature of 36°C, a normal acid/base balance with pH between 7.34 and 7.45, PaO_2 of 10 kPa with FiO_2 40% and maximum positive end-expiratory pressure 5 cm H_2O, $PaCO_2$ 6 kPa, drainage 100 mL/h in the 2 following hours, together with stable haemodynamics, which were considered present with 20% change in cardiac index, SvO_2, and mean arterial pressure over the last hour
Kendall 2004	Intermittent positive-pressure ventilation was continued until the participant met the following minimum criteria for extubation: haemodynamic stability with blood loss < 120 mL/h, core temperature > 36°C, responsive, co-operative, and pain-free
Kilickan 2006	Participants were extubated when they met set criteria as assessed by the ICU nursing staff: not in pain or agitated, cardiovascular stability without inotropes, systolic pressure > 90 mmHg, core temperature > 36.4°C, spontaneous ventilation with PaO_2 > 12 kPa on FiO_2 < 0.4 and $PaCO_2$ < 7 kPa, blood loss from chest drains < 60 mU/h, urine output > 1 mL/kg/h
Kilickan 2008	Participants were extubated when they met set criteria as assessed by the ICU nursing staff: not in pain or agitated, cardiovascular stability without inotropes, systolic pressure > 90 mmHg, core temperature > 36.4°C, spontaneous ventilation with PaO_2 > 12 kPa on FiO_2 < 0.4 and $PaCO_2$ < 7 kPa, blood loss from chest drains < 60 mU/h, urine output > l mL/kg/h
Kirov 2011	Extubation criteria were the following: a co-operative, alert participant; adequate muscular tone; SpO_2 > 95% with FiO_2 0.5; $PaCO_2$ < 45 mmHg; stable haemodynamics without inotrope/vasopressor support; absence of arrhythmias; and body temperature > 35°C. Temporary pacing was not regarded as a contraindication to extubation
Konishi 1995	Not reported in partial translation
Kunstyr 2001	Not reported
Lenkutis 2009	Participants were extubated according to conventional clinical criteria: bleeding < 50 mL/h, stable haemodynamics, SpO_2 > 95% on FiO_2 50%, awake enough to follow commands
Liem 1992	Participants were extubated when they fulfilled the following criteria: responsive to verbal stimuli; respiratory rate per minute ≥ 10 and ≤ 25; $SaO_2 \geq 95\%$; breathing adequately via endotracheal tube with 5 L/min of oxygen (pH 7.30 to 7.40; $PaO_2 \geq 10$ kPa; $PaCO_2 \leq 6.5$ kPa); rectal temperature ≥ 36°C and temperature "p" ("p" not defined in report) ≥ 31°C; haemodynamically stable; chest and mediastinal tube output ≤ 2 mL/kg/h; and urine output ≥ 0.5 mL/kg/h
Loick 1999	Participants were tracheally extubated as soon as they fulfilled extubation criteria: sufficient spontaneous ventilation, existing protective reflexes
Mehta 1998	Not reported
Mehta 2008	After surgery, participants were transferred to the recovery room and were extubated when they qualified for extubation
Mehta 2010	Extubation criteria included haemodynamic stability with systolic blood pressure ≥ 100 mmHg (without inotropes and/or vasopressors), core temperature ≥ 36°C, spontaneous ventilation with $PaO_2 \geq 100$ mmHg on $FiO_2 = 0.4$ and $PaCO_2 \leq 40$ mmHg, blood loss from chest drains < 50 mL/h, and urine output > 1 mL/kg/h

Table 5. Criteria for tracheal extubation *(Continued)*

Onan 2013	All participants were extubated in the ICU after rewarming and haemodynamic stabilization. Participants were extubated using clinical criteria together with analytical criteria (PaO_2) with the participant breathing through a T piece. The decision was made by the consultant on call
Palomero 2008	Extubation time was calculated starting from the moment the participant was transferred to the ICU
Petrovski 2006	Not reported
Priestley 2002	Participants in the ICU were weaned from positive-pressure ventilation and were extubated when they met set criteria as assessed by the ICU nursing staff: participant responsive to voice, oxygen saturation > 94% on inspired oxygen concentration < 50%, respiratory rate < 20 breaths/min and no obvious respiratory distress, $PaCO_2$ < 50 mmHg, pH > 7.3, tidal volume > 7 mL/kg on pressure support < 12 cm H_2O above end-expiratory pressure, temperature > 36.0°C, chest tube drainage < 100 mL/h, haemodynamic stability (i.e. not requiring significant inotropic support and no uncontrolled arrhythmia)
Royse 2003	Extubation was performed when the participant was awake, co-operative, normothermic (core body temperature 36°C), pH 7.3, and PaO_2 > 75 mmHg on 40% inspired oxygen
Sharma 2010	Once participants were awake with adequate spontaneous ventilation and a stable haemodynamic state, they were weaned off the ventilator and the trachea was extubated. Extubation criteria were as follows: haemodynamic stability with mean arterial pressure > 60 mmHg (without or with minimal inotropes and/or vasopressors), core temperature ≥ 36°C, spontaneous ventilation with PaO_2 > 100 mmHg on FiO_2 ≤ 0.4 and $PaCO_2$ < 40 mmHg, blood loss from chest drains < 50 mL/h, and urine output > 1 mL/kg/h
Stenseth 1996	Participants were extubated when awake, with adequate spontaneous ventilation ($PaCO_2$ < 6 kPa, PaO_2 > 10 kPa at FiO_2 = 0.6), and when in a stable haemodynamic state
Svircevic 2011	Participants were extubated as soon as extubation criteria were met: core temperature > 36°C, difference core/skin temperature < 5°C, haemodynamic stability without the use of major doses of vasoactive medication, chest drain output < 1.5 mL/kg/h, presence of deglutition reflex, breathing minute volume > 80 mL/kg/min, breathing frequency > 10/min and < 20/min, oxygen saturation > 94% with FiO_2 ≤ 40%
Tenenbein 2008	Postoperatively, participants' tracheas were extubated when they were haemodynamically stable, awake, and able to follow commands, with oxygen saturation ≥ 97%, FiO_2 ≤ 60%, and end-tidal CO_2 ≤ 50
Tenling 1999	Participants were tracheally extubated when they were awake and haemodynamically stable and had carbon dioxide tension < 5.5 kPa while spontaneously breathing, oxygen tension > 10 kPa, FiO_2 < 0.45, and body temperature > 37.0°C
Usui 1990	Extubation was considered once participants demonstrated the ability to breathe under continuous positive airway pressure
Yilmaz 2007	Criteria for tracheal extubation were: stayed awake without stimulation, respiratory rate < 30 breaths/min, PaO_2 > 100 mmHg with FiO_2 ≤ 40% and $PaCO_2$ < 45 mmHg, stable haemodynamic and metabolic variables, and drainage < 100 mL/h
Zawar 2015	Not reported

cm H_2O: centimetre of water; CO_2: carbon dioxide; FiO_2: fraction of inspired oxygen; ICU: intensive care unit; kPa: kilopascal; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; pH: acidity or alkalinity of a solution on a logarithmic scale on which 7 is neutral; SaO_2: oxygen saturation; SpO_2: pulse oximetry; SvO_2: venous oxygen saturation.

Table 6. Criteria for hypotension or use of inotropics/vasopressors

Study	Definition
Aguero-Martinez 2012	Change > 20% of basal value after local anaesthetic injection
Bach 2002	Mean arterial blood pressure < 55 mmHg
Barrington 2005	Mean arterial blood pressure < 65 mmHg
Berendes 2003	Unspecified
Celik 2015	Intraoperative hypotension
de Vries 2002	Mean arterial blood pressure < 60 mmHg
Fawcett 1997	Mean arterial blood pressure < 60 mmHg
Dohle 2001	Unspecified
Fillinger 2002	Unspecified
Greisen 2012	Unspecified
Gurses 2013	Mean arterial blood pressure < 50 mmHg
Jakobsen 2012	Mean arterial blood pressure < 60 mmHg
Kendall 2004	Variation > 20% from baseline
Kilickan 2006	Systolic arterial blood pressure < 80 mmHg
Kirno 1994	Unspecified
Kirov 2011	Mean arterial blood pressure < 60 mmHg
Kundu 2007	Unspecified
Liem 1992	Change in mean arterial blood pressure ≥ 20% of baseline value
Moore 1995	Mean blood arterial pressure < 50 mmHg
Palomero 2008	Mean blood arterial pressure < 50 mmHg
Royse 2003	Systolic arterial blood pressure ≤ 100 mmHg
Scott 2001	Mean arterial blood pressure ≤ 40 mmHg
Stenseth 1994	Mean arterial blood pressure < 65 mmHg
Stenseth 1996	Mean arterial blood pressure ≤ 65 mmHg
Tenling 1999	Mean arterial blood pressure decreased > 30% from baseline
Tenenbein 2008	Mean arterial blood pressure < 55 mmHg
Volk 2003	Unspecified

Table 6. Criteria for hypotension or use of inotropics/vasopressors *(Continued)*

Yilmaz 2007	Mean arterial blood pressure < 50 mmHg

APPENDICES

Appendix 1. Search strategies

Search date 19 November 2018

Cochrane Central Register of Controlled Trials: November 2018, Issue 11 of 12

#1 MeSH descriptor: [Analgesia, Epidural] explode all trees 1909
#2 MeSH descriptor: [Anesthesia, Epidural] explode all trees 1918
#3 (epidural* or peridural* or subarachnoid* or extradural* or neuraxial*) 13410
#4 (#1 or #2 or #3) 13538
#5 MeSH descriptor: [Cardiac Surgical Procedures] explode all trees 12271
#6 MeSH descriptor: [Cardiopulmonary Bypass] explode all trees 2615
#7 MeSH descriptor: [Coronary Artery Bypass] explode all trees 5206
#8 ((coronary or bypass or heart or cardio* or cardiac* or valve) next (surg* or graft* or bypass or plasty or replacement)) or cabg 21798
#9 (#5 or #6 or #7 or #8) 26170
#10 (#9 and #4) 306 (242 trials)
#11 #10 Publication Year from 2012 to 2018 = 69

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 (Cardiac Surgical Procedures or cardiopulmonary bypass or Coronary Artery Bypass or ((coronary or heart or cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)) or cabg).af. (288226)
2 (Epidural* or peridural* or extradural* or subarachnoid* or neuraxial* or (Anesthesia, Epidural or Analgesia, Epidural)).af. (83065)
3 (randomized controlled trial or controlled clinical trial or randomi? or placebo or drug therapy or randomly or trial or groups).af. (4258550)
4 1 and 2 and 3 (429)
5 limit "2012 -Current" (106)

Embase <1974 to 19 November 2018>

1 (heart surgery) or (cardiopulonary bypass) or (heart valve surgery) or ((coronary) or (heart) or (cardio* or cardiac* or valve) adj5 (surg* or graft* or bypass or plasty or replacement)) or (cabg) (541,226)
2 (epidural or peridural or extradural or subarachnoid or neuraxial) and (an?esth or analg) or (epidural anesthesia or epidural analgesia) (28,907)
3 (double blind procedure or single blind procedure) or (placebo) or (crossover procedure) or (controlled adj3 (study or design or trial)) or (allocat* or trial or random*) not ((exp animal or animal or nonhuman) not (exp human cell)) (2,347,081)
4 1 and 2 and 3 (775)
5 limit 4 to yr="2012 -Current" (256)

Cumulative Index to Nursing and Allied Health Literature (CINAHL, EBSCO host)

CINAHL, EBSCOhost S1	(MM "Heart Surgery+") OR (MM "Cardiopulmonary Bypass+") OR CABG OR ((coronary or heart or cardiac* OR cardio* or valve) N3 (surg* or graft* OR bypass OR shunt or plasty or replacement)))	63,212
S2	(MM "Analgesia, Epidural+") OR (MM "Anesthesia, Epidural+") OR (MM "Epidural Analgesia Administration (Iowa NIC)") OR (epidural* OR peridural* OR extradural* OR subarachnoid* OR neuraxial*)	18,984
S3	(MH "Placebos") OR ((MM "Randomized Controlled Trials") OR (MM "Random Assignment") OR (MH "Prospective Studies") OR (MH "Multicenter Studies") OR (MH "Clinical Trials") OR (MH "Single-Blind Studies") OR (MH "Triple-Blind	755,253

(Continued)

	Studies") OR (MH "Double-Blind Studies")) OR (placebo* or multicenter or prospective or ((random* or control*) and trial*))	
S4	S1 AND S2 AND S3	103
S5	S1 AND S2 AND S3 Published: 2012-2018	42

Web of Science (SCI/SSCI)

# 5	**101**	#4 *Timespan=2012-2018*
# 4	**331**	#3 AND #2 AND #1
# 3	**4,539,758**	TS= clinical trial* OR TS=research design OR TS=comparative stud* OR TS=evaluation stud* OR TS=controlled trial* OR TS=follow-up stud* OR TS=prospective stud* OR TS=random* OR TS=placebo* OR TS=(single blind*) OR TS=(double blind*)
# 2	**19,362**	TS=((epidural* OR peridural* OR extradural* OR subarachnoid* OR neuraxial*) AND (an?esth* or analg*))
# 1	**191,475**	TS=(((coronary or heart or cardio* or cardiac* or valve) NEAR/5 (surg* or graft* or bypass or plasty or replacement)) or cabg)

Appendix 2. List of reviews checked for additional trials

Baidya 2014

Baidya DK, Khanna P, Maitra S. Analgesic efficacy and safety of thoracic paravertebral and epidural analgesia for thoracic surgery: a systematic review and meta-analysis. Interactive Cardiovascular and Thoracic Surgery 2014;18(5):626-35. (DOI: 10.1093/icvts/ivt551; PubMed: 24488821)

Barbosa 2016

Barbosa FT, de Sousa Rodrigues CF, Castro AA, da Cunha RM, Barbosa TRBW. Is there any benefit in associating neuraxial anesthesia to general anesthesia for coronary artery bypass graft surgery? Revista Brasileira de Anestesiologia 2016;66(3):304-9. (DOI: 10.1016/j.bjane.2013.09.015; PubMed: 27108829)

Barbosa 2016a

Barbosa FT, da Cunha RM, da Silva Ramos FW, Camello de Lima FJ, Barros Rodrigues AK, do Nascimento Galvão AM, et al. Revista Brasileira de Anestesiologia 2016;66(2):183-193. (DOI: 10.1016/j.bjane.2014.05.012; PubMed: 25746164)

Bigeleisen 2015

Bigeleisen PE, Goehner N. Novel approaches in pain management in cardiac surgery. Current Opinion in Anaesthesiology 2015;28(1):89-94. (DOI: 10.1097/ACO.0000000000000147; PubMed: 25500688)

Bignami 2010

Bignami E, Landoni G, Biondi-Zoccai GG, Boroli F, Messina M, Dedola E, et al. Epidural analgesia improves outcome in cardiac surgery: a meta-analysis of randomized controlled trials. Journal of Cardiothoracic and Vascular Anesthesia 2010;24(4):586-97. (DOI: 10.1053/j.jvca.2009.09.015; PubMed: 20005129)

Bignami 2017

Bignami E, Castella A, Pota V, Saglietti F, Scognamiglio A, Trumello C, et al. Perioperative pain management in cardiac surgery: a systematic review. Minerva Anestesiologica 2017. (DOI: 10.23736/S0375-9393.17.12142-5; PubMed: 29027773)

Bracco 2007

Bracco D, Hemmerling T. Epidural analgesia in cardiac surgery: an updated risk assessment. Heart Surgery Forum 2007;10(4):E334-7.

Bracco 2008

Bracco D, Hemmerling TM. Thoracic epidural analgesia in cardiac surgery: impact on postoperative morbidity. Techniques in Regional Anesthesia and Pain Management 2008;12:32-40.

Chaney 2006

Chaney MA. Intrathecal and epidural anesthesia and analgesia for cardiac surgery. Anesthesia and Analgesia 2006;102:45-64. (MEDLINE: 16368803)

Chaparro 2013

Chaparro LE, Smith SA, Moore RA, Wiffen PJ, Gilron I. Pharmacotherapy for the prevention of chronic pain after surgery in adults. Cochrane Database of Systematic Reviews 2013;(7):CD008307. (PubMed: 23881791)

Gu 2012

Gu WJ, Wei CY, Huang DQ, Yin RX. Meta-analysis of randomized controlled trials on the efficacy of thoracic epidural anesthesia in preventing atrial fibrillation after coronary artery bypass grafting. BMC Cardiovascular Disorders 2012;12:67. (DOI: 10.1186/1471-2261-12-67; PubMed: 22900930)

Hemmerling 2013a

Hemmerling TM, Romano G, Terrasini N, Noiseux N. Anesthesia for off-pump coronary artery bypass surgery. Annals of Cardiac Anaesthesia 2013;16(1):28-39. (PubMed: 23287083)

Huang 2016

Huang AP, Sakata RK. Pain after sternotomy - review. Brazilian Journal of Anesthesiology 2016;66(4):395-401. (DOI: 10.1016/j.bjane.2014.09.013; PubMed: 27343790)

Jakobsen 2015

Jakobsen CJ. High thoracic epidural in cardiac anesthesia: a review. Seminars in Cardiothoracic and Vascular Anesthesia 2015;19(1):38-48. (PubMed: 25201889)

Konstantatos 2008

Konstantatos A, Silvers AJ, Myles PS. Analgesia best practice after cardiac surgery. Anesthesiology Clinics 2008;26(3):591-602. (PubMed: 18765224)

Kooij 2014

Kooij FO, Schlack WS, Preckel B, Hollmann MW. Does regional analgesia for major surgery improve outcome? Focus on epidural analgesia. Anesthesia and Analgesia 2014;119(3):740-4. (DOI: 10.1213/ANE.0000000000000245.; PubMed: 25137006)

Landoni 2015

Landoni G, Isella F, Greco M, Zangrillo A, Royse CF. Benefits and risks of epidural analgesia in cardiac surgery. British Journal of Anaesthesia 2015;115(1):25-32. (DOI: 10.1093/bja/aev201; PubMed: 26089444)

Liu 2004

Liu SS, Block BM, Wu CL. Effects of perioperative central neuraxial analgesia on outcome after coronary artery bypass surgery: a meta-analysis. Anesthesiology 2004;101:153-61. (MEDLINE: 15220785)

Mehta 2012

Mehta Y, Arora D, Vats M. Epidural analgesia in high risk cardiac surgical patients. HSR Proceedings in Intensive Care and Cardiovascular Anesthesia 2012;4(1):11-4. (PubMed: 23440670)

Mehta 2014

Mehta Y, Arora D. Benefits and risks of epidural analgesia in cardiac surgery. Journal of Cardiothoracic and Vascular Anesthesia 2014;28(4):1057-63. (DOI: 10.1053/j.jvca.2013.07.016; PubMed: 24315759)

Meissner 1997

Meissner A, Rolf N, Van Aken H. Thoracic epidural anesthesia and the patient with heart disease: benefits, risks, and controversies. Anesthesia and Analgesia 1997;85(3):517-28. (PubMed: 9296403)

Neskovic 2003

Nešković V, Milojević P. High thoracic epidural anesthesia for coronary artery bypass graft surgery [Visoka torakalna epiduralana anestezija u koronarnoj hirurgili]. Medicinski Pregled 2003;LVI(3-4):152-6.

Popping 2014

Popping DM, Elia N, Van Aken HK, Marret E, Schug SA, Kranke P, et al. Impact of epidural analgesia on mortality and morbidity after surgery: systematic review and meta-analysis of randomized controlled trials. Annals of Surgery 2014;259(6):1056-67. (DOI: 10.1097/SLA.0000000000000237; PubMed: 24096762)

Ronald 2006

Ronald A, Abdulaziz KA, Day TG, Scott M. In patients undergoing cardiac surgery, thoracic epidural analgesia combined with general anaesthesia results in faster recovery and fewer complications but does not affect length of hospital stay. Interactive Cardiovascular and Thoracic Surgery 2006;5(3):207-16. (DOI: 10.1510/icvts.2005.125054; PubMed: 17670549)

Royse 2009

Royse CF. High thoracic epidural anaesthesia for cardiac surgery. Current Opinion in Anaesthesiology 2009;22(1):84-7. (DOI: 1097/ACO.0b013e32831a40b6; PubMed: 19295296)

Ruppen 2006

Ruppen W, Derry S, McQuay HJ, Moore RA. Incidence of epidural haematoma and neurological injury in cardiovascular patients with epidural analgesia/anaesthesia: systematic review and meta-analysis. BMC Anesthesiology 2006;6:10. (DOI: 10.1186/1471-2253-6-10; PubMed: 16968537)

Scarfe 2016

Scarfe AJ, Schuhmann-Hingel S, Duncan JK, Ma N, Atukorale YN, Cameron AL. Continuous paravertebral block for post-cardiothoracic surgery analgesia: a systematic review and meta-analysis. European Journal of Cardio-Thoracic Surgery 2016;50(6):1010-8. (DOI: 10.1093/ejcts/ezw168; PubMed: 27242357)

Smith 2017

Smith LM, Cozowicz C, Uda Y, Memtsoudis SG, Barrington MJ. Neuraxial and combined neuraxial/general anesthesia compared to general anesthesia for major truncal and lower limb surgery: a systematic review and meta-analysis. Anesthesia and Analgesia 2017;124(6):1931-45. (DOI: 10.1213/ANE.0000000000002069; PubMed: 28537970)

Sondekoppam 2014

Sondekoppam RV, Arellano R, Ganapathy S, Cheng D. Pain and inflammatory response following off-pump coronary artery bypass grafting. Current Opinion in Anaesthesiology 2014;27(1):106-15. (DOI: 10.1097/ACO.0000000000000036; PubMed: 24322210)

Wardhan 2015

Wardhan R. Update on paravertebral blocks. Current Opinion in Anaesthesiology 2015;28(5):588-92. (DOI: 10.1097/ACO.0000000000000235; PubMed: 26308511)

Wei 2013

Wei G, Xuan Y, Zheng H, Wang J. Effectiveness and safety of thoracic epidural analgesia for postoperative complications after cardiac surgery: a systematic review. Chinese Journal of Evidence-Based Medicine 2013;13(10):1229-35. (DOI: 10.7507/1672-2531.20130211)

Williams 2002

Williams J. Thoracic epidural anaesthesia for cardiac surgery. Canadian Journal of Anesthesia 2002;49:7R.

Yeung 2016

Yeung JH, Gates S, Naidu BV, Wilson MJ, Gao Smith F. Paravertebral block versus thoracic epidural for patients undergoing thoracotomy. The Cochrane Database of Systematic Reviews 2016;2:CD009121. (DOI: 10.1002/14651858.CD009121.pub2.; PubMed: 26897642)

Zhang 2015

Zhang S, Wu X, Guo H, Ma L. Thoracic epidural anesthesia improves outcomes in patients undergoing cardiac surgery: meta-analysis of randomized controlled trials. European Journal of Medical Research 2015;20:25. (DOI: 10.1186/s40001-015-0091-y; PubMed: 25888937)

Appendix 3. Numbers needed to treat for additional beneficial outcome or harmful effect

1. Comparison 1: risk of respiratory complications: respiratory depression

Odds ratio: 0.56 (95% CI 0.37 to 0.86)

For the control group, there were 62 events out of 856 participants included for an incidence of 7.5%.

From Cates 2016:

NNTB = 32 (95% CI 22 to 102)

2. Comparison 1: risk of atrial fibrillation or atrial flutter during surgery and up to 2 weeks after surgery.

Odds ratio: 0.69 (95% CI 0.50 to 0.95)

For the control group, there were 403 events out of 1231 participants included for an incidence of 32.7%.

From Cates 2016:

NNTB = 14 (95% CI 8 to 90)

3. Comparison 1: hypotension or need for vasopressor

For the control group, there were 118 events out of 398 participants for an incidence of 30%.

Odds ratio: 3.16 (95% CI 1.49 to 6.71)

From Cates 2016:

NNTH = 4 (95% CI 3 to 12)

Appendix 4. Comparison 1: duration of tracheal intubation for trials for which means and standard deviations were available

Tracheal intubation Comparison 1: trials for which means and standard deviations were available

Study	Epidural analgesia			Systemic analgesia		
	Mean	SD	N	Mean	SD	N
El-Baz 1987	9.00	3.00	30	18.000	5.000	30
Liem 1992	7.72	6.58	25	19.000	4.830	25
Konishi 1995 (1)	6.60	3.70	31	9.200	5.400	18
Konishi 1995 (2)	5.80	3.10	31	9.200	5.400	18
Stenseth 1996	5.40	2.04	26	10.800	3.569	26
Fawcett 1997	5.80	1.00	8	9.200	2.400	8

(Continued)

Loick 1999	9.98	2.65	25	14.630	9.150	21
Tenling 1999	3.62	0.47	14	7.970	3.070	14
Kunstyr 2001 (4)	6.07	2.93	7	7.000	2.990	20
Kunstyr 2001 (5)	6.07	2.93	7	5.810	2.350	21
Kunstyr 2001 (6)	6.07	2.93	7	6.260	3.440	20
Fillinger 2002	10.70	1.40	30	9.500	0.800	30
Berendes 2003	3.40	1.90	36	9.200	4.300	37
Royse 2003	2.60	2.50	37	5.400	3.100	39
Huh 2004	4.61	4.75	27	13.430	7.010	29
Hansdottir 2006	2.30	1.10	53	7.300	19.200	55
Kilickan 2006 (7)	7.57	6.05	20	14.620	4.200	20
Kilickan 2006 (8)	10.00	5.32	20	8.520	4.720	20
Petrovski 2006	3.50	0.80	56	6.800	0.700	54
Yilmaz 2007	7.44	1.36	17	9.370	1.980	17
Tenenbein 2008	0.26	0.63	25	0.170	0.210	25
Kilickan 2008 (10)	5.00	3.20	15	6.600	4.000	15
Kilickan 2008 (11)	5.50	2.60	15	7.000	3.300	15
Palomero 2008	11.70	7.52	10	12.500	2.400	12
Lenkutis 2009	6.04	0.56	30	11.060	1.640	30
El-Morsy 2012	7.30	6.40	25	10.700	8.200	25
Onan 2013	2.90	1.10	20	4.700	1.200	20
Neskovic 2013 (12)	6.67	4.66	18	8.830	5.270	27
Gurses 2013	4.10	1.70	32	6.800	2.000	32
Celik 2015	7.20	1.82	20	11.700	2.020	20
de Vries 2002 (13)	0.15	0.08	28	0.220	0.120	29
Kendall 2004 (14)	5.30	4.10	5	6.900	2.800	10
Kendall 2004 (15)	5.30	4.10	5	6.600	3.100	10
Bakhtiary 2007	6.00	2.30	66	7.000	4.200	66

(Continued)

Sharma 2010	9.33	2.24	30	11.670	3.020	30
Mehta 2010	10.80	3.19	31	13.500	2.880	31
Aguero-Martinez 2012	4.52	2.84	29	7.830	5.240	30
Neskovic 2013 (16)	4.38	4.31	17	5.810	3.500	19
Zawar 2015	14.20	8.20	35	15.500	3.900	46
Obersztyn 2018	3.60	2.63	39	7.983	2.917	39

SD: standard deviation.

(1) Morphine
(2) Butorphanol
(3) For this analysis, only two groups were retained: epidural analgesia versus control
(4) Compared with intravenous infusion of sufentanil and ketamine
(5) Compared with nurse administered morphine
(6) Compared with intravenous patient controlled analgesia with morphine
(7) Poor ventricular function
(8) Good ventricular function
(9) Variances from Table 3 were entered as standard errors of the means
(10) Without steroids
(11) With steroids
(12) With cardiopulmonary bypass

(13) For this analysis only two groups were retained: epidural analgesia versus extubated

(14)Compared with isoflurane and systemic analgesia
(15) Compared with propofol and systemic analgesia

(16) Off-pump

	Epidural analgesia	Systemic analgesia
Mean (hours)	6.1	9.1
Std. deviation	3.0	4.0

Appendix 5. Pain scores at rest at 6 to 8 hours for trials with data available as means and SDs

Comparison 1

Study	Epidural analgesia			Systemic analgesia		
	Mean	SD	N	Mean	SD	N
El-Morsy 2012	3.00	3.000	25	3.70	1.50	25
Onan 2013	0.10	0.300	20	2.40	1.80	20

(Continued)

Mehta 2010	4.03	0.700	31	4.70	0.50	31
Sharma 2010	2.50	0.860	30	3.23	0.72	30
Aguero-Martinez 2012	0.00	0.001	30	6.83	1.29	30

	Epidural analgesia	Systemic analgesia
Mean	1.92	4.17
SD	1.80	1.70

N: number of participants; SD: standard deviation.

Comparison 2

Study	Epidural analgesia			Peripheral nerve block		
	Mean	SD	N	Mean	SD	N
Nagaraja 2018	1.64	0.64	25	1.64	1.35	25
Dohle 2001	2.75	2.88	20	1.95	1.43	20

	Epidural analgesia	Peripheral nerve block
Mean	2.195	1.795
SD	0.7849	0.2192

N: number of participants; SD: standard deviation.

WHAT'S NEW

Date	Event	Description
19 November 2018	New citation required and conclusions have changed	Conclusions unchanged for outcomes included in the previous version New conclusions provided for new outcomes, along with new comparisons

Date	Event	Description
19 November 2018	New search has been performed	Review updated in 2018 by new authors: Joanne Guay and Sandra Kopp Methodology updated 38 new trials included; 3 new comparisons and 3 outcomes (duration of tracheal intubation, pain, haemodynamic support requirements) added

HISTORY

Protocol first published: Issue 3, 2007
Review first published: Issue 6, 2013

Date	Event	Description
26 September 2017	New search has been performed	Review undertaken by 2 new review authors
22 September 2017	Amended	Change made to review authors Previous review authors replaced by Joanne Guay and Sandra Kopp
1 July 2013	Amended	Contact details for Geert J. van der Heijden amended

CONTRIBUTIONS OF AUTHORS

Conceiving the update: Joanne Guay (JG) and Sandra Kopp (SK)
Co-ordinating the review: JG
Undertaking manual searches: JG
Screening search results: JG and SK
Organizing retrieval of papers: JG
Screening retrieved papers against inclusion criteria: JG and SK
Appraising quality of papers: JG and SK
Abstracting data from papers: JG and SK
Writing to authors of papers for additional information: JG
Obtaining and screening data on unpublished studies: JG and SK
Managing data for the review: JG
Entering data into Review Manager (Review Manager 2014): JG
Analysing RevMan 5 statistical data: JG and SK
Performing other statistical analysis not using RevMan 5: JG
Interpreting data: JG and SK
Making statistical inferences: JG
Writing the review: JG and SK
Serving as guarantor for the review (one author): JG
Being responsible for reading and checking the review before submission: JG and SK

DECLARATIONS OF INTEREST

Joanne Guay: none known

Sandra Kopp: none known

SOURCES OF SUPPORT

Internal sources

- University of Sherbrooke, Canada.

  University of Sherbrooke granted access to databases and major medical journals
- Laval University, Canada.

  Laval University granted access to databases and major medical journals
- University of Quebec in Abitibi Temiscamingue, Canada.

  University of Quebec in Abitibi Temiscamingue granted access to databases and major medical journals

External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We made the following changes to the published review (Svircevic 2013).

1. Two new review authors (Joanne Guay and Sandra Kopp) replaced authors from the previously published version (Vesna Svircevic, Martijn M Passier, Arno P Nierich, Diederik van Dijk, Cor J Kalkman and Geert J van der Heijden).
2. We clarified that we are excluding observational studies, quasi-randomized trials, cross-over trials, and cluster-randomized trials.
3. We clarified that patients operated with or without cardiopulmonary bypass are included.
4. We clarified that studies in which investigators administered epidural analgesia as a single shot block or as a continuous infusion for any duration and containing a local anaesthetic alone (extended duration or not) or in combination with an opioid (extended duration or not) or an opioid alone were included.
5. For the comparator, we included all other modes of analgesia and divided them into the following: (1) all forms of systemic analgesia (opioid-based regimen or other) regardless of the route of administration (intravenous (with or without a self-administered patient-controlled device), intramuscular, or oral analgesia), (2) peripheral nerve blocks, (3) intrapleural analgesia, and (4) wound infiltration.
6. Some time points were changed, and we are now evaluating the following: (1) mortality at 0 to 30 days, six months, and one year, (2) myocardial infarction at 0 to 30 days, (3) respiratory complications at 0 to 30 days, (4) atrial fibrillation or atrial flutter at zero to two weeks, (5) neurological complications at 0 to 30 days, and (6) duration of tracheal intubation.
7. We have clarified that the definition used for myocardial infarction was the one used by study authors.
8. We added three outcomes.
   a. Duration of tracheal intubation: we think that resource utilization is an important factor in nowadays budgets.
   b. Pain scores: we wanted to quantify the differences between epidural analgesia and other modalities of pain treatment.
   c. Haemodynamic support: we wanted to quantify the additional risk or not of hypotensive episodes and the need for vasopressors or inotropic support.
9. We clarified supraventricular tachyarrhythmia as atrial fibrillation or atrial flutter.
10. We clarified respiratory complications as respiratory depression or pneumonia.
11. We clarified neurological complications as stroke or severe neurological complications from epidural analgesia.
12. We updated the methodology: provided clarification for use of fixed versus random effects models, use of risk difference for study with zero cells, a priori factors for heterogeneity exploration, numbers needed to treat for additional beneficial outcome, and rating of the quality of evidence as per the GRADE system.

INDEX TERMS

Medical Subject Headings (MeSH)

*Cardiac Surgical Procedures [adverse effects] [mortality]; Analgesia, Epidural [*adverse effects] [methods] [mortality]; Anesthesia, General [*adverse effects] [methods] [mortality]; Arrhythmias, Cardiac [prevention & control]; Coronary Artery Bypass [adverse effects] [mortality]; Myocardial Infarction [*etiology]; Randomized Controlled Trials as Topic; Respiration Disorders [etiology]; Stroke [*etiology]

MeSH check words

Adult; Humans