Effects of volatile anesthetics on mortality and postoperative pulmonary and other complications in patients undergoing surgery: A systematic review and meta-analysis

SUPPLEMENTAL DIGITAL CONTENT FILE 1

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Table 1: PRISMA Checklist

Section/Topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Table S2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-7

Table 1: PRISMA Checklist continued

Section/Topic	#	Checklist item	Reported on page #
METHODS			
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	6-7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	6-7
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	7-8
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	6-7
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	7-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	9 + Fig.1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	9-10, Table 1 and Table S6
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	10, Fig.3 and Table S7
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	10-12, Fig. 4-9, S1-6
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	10-12, Fig. 4-9, S1-S6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	10, Fig. 3 +S1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	10-12, Fig. 4-9, S2-S6
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	13
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	16-17

Table 1: PRISMA Checklist continued

Section/Topic	#	Checklist item	Reported on page #
DISCUSSION			
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

Table 2: Search String

MEDLINE via Ovid	1 randomized controlled trial.pt. 2 controlled clinical trial.pt. 3 randomized.ab. 4 placebo.ab. 5 clinical trials as topic.sh. 6 randomly.ab. 7 trial.ti. 8 Or/1-7 9 exp animals/ not humans.sh. 10 8 not 9 11 sevoflurane/ OR sevoflurane.mp. OR sevoran*.mp. 12 desflurane/ OR desflurane.mp. OR supran*.mp. 13 isoflurane/ OR isoflurane.mp. OR foren*.mp. 14 inhalation anesthetic agent/ OR inhalation anesthetic.mp. 15 (volatile anesthetics or gas anesthetics).mp. 16 or/11-15 17 surgery/ OR surgery.mp. OR surgical*.mp. 18 (operation or operative or postoperative).mp. 19 interven*.mp. 20 general anesthesia/ OR general anesthesia.mp. 21 balanced anesthesia/ OR balanced anesthesia.mp. 22 or/ 17-21 23 10 AND 16 AND 22 24 case report.tw. 25 letter/ 26 historical article/ 27 or/ 24-26 28 23 not 27
CENTRAL via Cochrane Library	1 sevoflurane 2 desfluran* 3 suprane 4 isofluran* 5 volatile anesthetic* 6 gas anesthetic* 7 inhalation anesthestic* 8 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7) 9 surgery OR surgical* 10 operation or operative or postoperative 11 interven* 12 general anesthesia 13 balanced anesthesia 14(#9 OR #10 OR #11 OR #12 OR #13) 15 (#8 AND #14)

Table 2: Search String continued

EMBASE via Ovid (SIGN search filter)	1 Clinical trial/ 2 Randomized controlled trial/ 3 Randomization/ 4 Single blind procedure/ 5 Double blind procedure/ 6 Crossover procedure/ 7 Placebo/ 8 Randomi?ed controlled trial$.tw. 9 Rct.tw. 10 Random allocation.tw. 11 Randomly allocated.tw. 12 Allocated randomly.tw. 13 (allocated adj2 random).tw. 14 Single blind$.tw. 15 Double blind$.tw. 16 (treble or triple) adj (blind$).tw. 17 Placebo$.tw. 18 Or/1-17 19 animal/ 20 human/ 21 19 not (19 and 20) 22 18 not 21 23 sevoflurane/ OR sevoflurane.mp. OR sevoran*.mp. 24 desflurane/ OR desflurane.mp. OR supran*.mp. 25 isoflurane/ OR isoflurane.mp. OR foren*.mp. 26 inhalation anesthetic agent/ OR inhalation anesthetic.mp. 27 (volatile anesthetics or gas anesthetics).mp. 28 or/23-27 29 surgery/ OR surgery.mp. OR surgical*.mp. 30 (operation or operative or postoperative).mp. 31 interven*.mp. 32 general anesthesia/ OR general anesthesia.mp. 33 balanced anesthesia/ OR balanced anesthesia.mp. 34 or/ 29-33 35 22 AND 28 AND 34 36 case report.tw. 37 letter/ 38 historical article/ 39 or/ 36-38 40 35 not 39 41 limit 40 to exclude medline journals

Reference List of Manual Search

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Table 3: Definitions of pulmonary postoperative complications (PPCs)

PPCs were defined according to the definition of the authors of the respective manuscript or the following:

Hypoxemia[1] PaO_2 < 60 mmHg or SpO_2 < 90% in room air, but responding to supplemental oxygen (excluding hypoventilation) or Need for non–invasive or invasive mechanical ventilation or a PaO_2 < 60 mmHg or SpO_2 < 90% despite supplemental oxygen (excluding hypoventilation)
Bronchospasm[1] Defined as newly detected expiratory wheezing treated with bronchodilators
Suspected pulmonary infection[1] In case patient receives antibiotics and meets at least one of the following criteria: new or changed sputum, new or changed lung opacities on chest X–ray when clinically indicated, timpanic temperature > 38·3°C, WBC count > 12 x10^9/L
Pulmonary infiltrate[1] Chest X–ray demonstrating monolateral or bilateral infiltrate
Aspiration pneumonitis[1] Defined as respiratory failure after the inhalation of regurgitated gastric contents
Acute Respiratory Distress Syndrome[1,2,3] By the consensus criteria or Berlin definition (only in case of non–invasive or invasive mechanical ventilation)
Atelectasis[1] Suggested by lung opacification with shift of the mediastinum, hilum, or hemidiaphragm towards the affected area, and compensatory overinflation in the adjacent nonatelectatic lung
Pleural effusion[1] Chest X–ray demonstrating blunting of the costophrenic angle, loss of the sharp silhouette of the ipsilateral hemidiaphragm in upright position, evidence of displacement of adjacent anatomical structures, or (in supine position) a hazy opacity in one hemi–thorax with preserved vascular shadows
Pulmonary oedema caused by cardiac failure[1] Defined as clinical signs of congestion, including dyspnea, edema, rales and jugular venous distention, with the chest X–ray demonstrating increase in vascular markings and diffuse alveolar interstitial infiltrates
Pneumothorax[1] Defined as air in the pleural space with no vascular bed surrounding the visceral pleura
Óther PPCs[4, 5] Such as prolonged mechanical ventilation (depending on the usual time of mechanical ventilation per study cohort, eg. >24 hours), reintubation

PaO_2: arterial partial oxygen pressure, SpO_2: pulseoxymetric measured oxygen saturation

References Table 4:

1. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384: 495-503
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Anesthetic-induced improvement of the inflammatory response to one-lung ventilation. Anesthesiology 2009; 110: 1316-26

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Table 4: Definitions of other postoperative complications

Other postoperative complications were defined according to the definition of the authors of the respective manuscript or the following:

Acute myocardial infarction[1,2] Detection of rise and/or fall of cardiac markers (preferably troponin) with at least one value above the 99th percentile of the upper reference limit, together with: symptoms of ischemia, ECG changes indicative of new ischemia, development of pathological Q-waves, or imaging evidence of new loss of viable myocardium or new regional wall motion abnormality, or: sudden unexpected cardiac death, involving cardiac arrest with symptoms suggestive of cardiac ischemia (but death occurring before the appearance of cardiac markers in blood)
Overall cardiac events[3,4] Including acute myocardial infarction, congestive herat failure, arrhythmia requiring hospitalization, postoperative need for intraaortic balloon pump or other cardiac events as defined by the authors of the respective manuscript
SIRS, sepsis, severe sepsis and septic shock[5] according to consensus definition
Extrapulmonary infection[1] Wound infection or any other infection
Neurological complications[1] Coma (Glasgow Coma Score < 8 in the absence of therapeutic coma or sedation) or stroke
Acute renal failure (ARF)[1,6] Renal failure documented as follows: Risk: increased creatinine x1.5 or glomerular filtration rate (GFR) decrease > 25% or urine output (UO) < 0·5 ml/kg/h x 6 h; Injury: increased creatinine x2 or GFR decrease > 50% or UO < 0·5 ml/kg/h x 12 hr; Failure: increase creatinine x3 or GFR decrease > 75% or UO < 0·3 ml/kg/h x 24 hr or anuria x 12 hrs; Loss: persistent ARF = complete loss of kidney function > 4 weeks
Disseminated intravascular coagulation (DIC)[1,7] DIC score documented as follows: Platelet count < 50 (2 points), < 100 (1 point), or ≥ 100 (0 points); D–dimer > 4 µg/ml (2 points), > 0·39 µg/ml (1 point) or ≤ 0·39 µg/ml (0 points); Prothrombin time > 20·5 seconds (2 points), > 17·5 seconds (1 point) or ≤ 17·5 seconds (0 points); if ≥ 5 points: overt DIC
Hepatic failure[1] Serum bilirubin level > 34 µmol/L with elevation of the transaminase and lactic dehydrogenase levels above twice normal values
Gastro–intestinal failure[1,8] Gastro–intestinal bleeding Gastro–intestinal failure (GIF) score documented as follows: 0 = normal gastrointestinal function; 1 = enteral feeding with under 50% of calculated needs or no feeding 3 days after abdominal surgery; 2 = food intolerance (FI) or intra–abdominal hypertension (IAH); 3 = FI and IAH; and 4 = abdominal compartment syndrome (ACS)

ECG: electrocardiography, GIF: gastro–intestinal failure, FI: food intolerance, IAH: intra–abdominal hypertension, ACS: abdominal compartment syndrome, GFR: glomerular filtration rate, UO: urine output

References Table 5:

1. PROVE Network Investigators for the Clinical Trial Network of the European Society of Anaesthesiology, Hemmes SN, Gama de Abreu M, Pelosi P, Schultz MJ: High versus low positive end-expiratory pressure during general anaesthesia for open abdominal surgery (PROVHILO trial): a multicentre randomised controlled trial. Lancet 2014; 384: 495-503
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Table 5: Reference list of included trials

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Table 5: Reference list of included trials continued

Author	Reference
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Table 5: Reference list of included trials continued

Author	Reference
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Table 5: Reference list of included trials continued

Author	Reference
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Table 5: Reference list of included trials continued

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Table 5: Reference list of included trials continued

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Table 5: Reference list of included trials continued

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Table 5: Reference list of included trials continued

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Detailed information regarding number of patients enrolled in the manuscripts reporting pospoperative pulmonary and other complications

Beside mortality, 26 randomized controlled trials (RCTs) reported PPCs including 2,306 patients comparing in 25 trials (2,232 patients) volatile anesthetics (sevoflurane n=708, desflurane n=111, isoflurane n=322) to TIVA (n=1,091) and in one trial (74 patients; included in network meta-analysis) sevoflurane (n=37) vs. desflurane (n=37). Out of those trials 15 RCTs recruited 1,630 patients undergoing cardiac surgery (sevoflurane n=475, desflurane n=287, isoflurane n=61, TIVA n=807) and 11 RCTs with 602 patients undergoing non-cardiac surgery (sevoflurane n=233, desflurane n=35, isoflurane n=50, TIVA n=284).

Another 47 RCTs (5,376 patients) described other postoperative comlications in addition to mortality. Forty-four trials (5,169 patients) compared volatile anesthetics (total n=2,746, sevoflurane n=1,506, desflurane n=688, isoflurane n=552) to TIVA (n=2,423) and three trials investigated VOLs (total n=207, sevoflurane n=177, desflurane n=58, isoflurane n=153) without a TIVA group (included in network meta-analysis). Cardiac surgical patients were recruited in 32 trials (4,038 patients) comparing volatile anesthetics (total n=2,173, sevoflurane n=1,018, desflurane n=628, isoflurane n=527) to TIVA (n=1,865). Twelve RCTs (1,131 patients) with TIVA control group recruited patients from surgical fields other than cardiac surgery (sevoflurane n=488, desflurane n=60, isoflurane n=25, TIVA n=558).

Table 6: Detailed trial information

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Alvarez[1]	1990	single	mitral valve surgery with non-ischemic etiology, mean pulmonary artery pressure > 30 mmHg	aortic valve pathology	Premedication: clorazepate, Induction: diazepam, fentanyl, pancuronium, Maintenance: isoflurane, fentanyl (n=13)	Premedication: clorazepate, Induction: diazepam, fentanyl, pancuronium, Maintenance: high dose fentanyl (n=17)	not defined	hemodynamic parameters, cardiac index, gas exchange
Amr[2]	2010	single	2-3 coronary heart disease, (ejection fraction between 40% and 50%)	unstable angina; recent myocardial infarction (<1 month); prior CABG surgery; hepatic, renal, or pulmonary disease; concurrent valve repair or insufficiency; left bundle branch block or conduction defect; and treatment with oral hypoglycemic sulfamide (antagonist of K_{ATP} channels) and nicorandil (agonist of K_{ATP} channels) within 5 days before surgery	Premedication: diazepam, Induction: midazolam, sufentanil, pancuronium, Maintenance: isoflurane (preconditioning 10 mins), midazolam, sufentanil (n=15)	Premedication: diazepam, Induction: midazolam, sufentanil, pancuronium, Maintenance: midazolam, sufentanil (n=15)	not defined	hemodynamic data, cardiac troponin I, cardiac fraction of creatine kinase, cardiac function, cardiac events within 1 year
Baki[3]	2013	dual	coronary artery disease and scheduled for elective CABG	Left ventricular ejection fraction <30%, need for emergency coronary revascularization, acute reanl failure, hepatic failure, autoimmune disease, collagen tissue disease, systemic inflammatory disease, cerebrovascular disease within last 6 months	Premedication: midazolam, Induction: etomidate, fentanyl, rocuronium, Maintenance: desflurane, remifentanil (n=20)	Premedication: midazolam, Induction: etomidate, fentanyl, rocuronium, Maintenance: propofol, remifentanil (n=20)	not defined	cytokines (tumor necrosis factor-α, interleukin 6, interleukin 8), hemodynamic data, S100 beta level

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, K_{ATP}: adenosine triphosphate dependent potassium channels.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Ballester[4]	2011	single	age > 18 years, elective surgery and ASA III or less	history of allergy to propofol, previous cardiac surgery, combined surgery, severe valve insufficiency, myocardial infarction within the previous 6 weeks, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >150U/l), renal failure (creatinine concentration >1.5mg/dl), severe chronic obstructive pulmonary disease(forced expiratory volume in 1 second, FEV1 <50%), preoperative antioxidant therapy and pregnancy	Premedication: n/r, Induction: midazolam, fentanyl, cis-atracurium Maintenance: sevoflurane, fentanyl (n=18)	Premedication: n/r, Induction: midazolam, fentanyl, cis-atracurium, Maintenance: propofol, fentanyl (n=20)	intraoperative myocardial oxidative stress represented by the level of F2-isoprostanes in coronary sinus blood	hemodynamic data, cardiac troponin I, cardiac fraction of creatine kinase, lactate level, cardiac function, clinical outcome
Beck-Schim-mer[6]	2012	single	age >18 years, scheduled for liver resection (benign or malignant tumors) were eligible for the study	non-German speaking, laparoscopic liver resection (minor resection), emergency surgery (safety concerns), experienced coagulopathy (platelets <50,000/mL and/or international normalized ratio >1.5), or presented with liver cirrhosis (histologically confirmed)	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: sevoflurane (postconditioning circa 30mins), fentanyl, remifentanil (n=48)	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: propofol, fentanyl+remifentanil (n=17)	aspartate transaminase level	alanine transaminase, other blood liver synthesis and function parameters, postoperative complications
Beck-Schim-mer[5]	2008	single	consecutive patients undergoing elective liver resection with inflow occlusion	age <18 years, liver cirrhosis, additional ablation therapies (cryosurgery or radiofrequency),living donors, and liver resections without inflow occlusion	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: sevoflurane, fentanyl+remifentanil (n=40)	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: propofol, fentanyl+remifentanil (n=34)	aspartate transaminase level	alanine transaminase, other blood liver synthesis and function parameters, postoperative complications

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, FEV1: forced expiratory volume in one second, n/r: not reported.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Bein[7]	2005	single	elective minimal invasive CABG surgery single-vessel coronary artery disease (i.e., LAD stenosis). preoperative left ventricular ejection fraction >40%	unstable angina, acute myocardial infarction < 4 weeks ago, valvular heart disease, intracardiac shunts, severe pulmonary disease, pathologies of the esophagus or stomach, emergency cases	Premedication: midazolam, Induction: propofol, remifentanil, rocuronium, Maintenance: sevoflurane, remifentanil (n=24)	Premedication: midazolam, Induction: propofol, remifentanil, rocuronium, Maintenance: propofol, remifentanil (n=26)	myocardial performance index	myocardial cell damage (cardiac troponin T, cardiac fraction of creatine kinase, echocardiography variables, hemodynamic data
Bharti[8]	2008	single	elective CABG surgery, ASA I-III	Patients with severely impaired left ventricular function (EF <30%, LVEDP >18), renal or liver impairment, recent myocardial infarction (<6 weeks), associated valvular lesion or heart block, gross obesity (BMI >30%), anticipated difficult intubation, repeated coronary surgery, concurrent valve repair, or aneurysmal resection	Premedication: diazepam, Induction: sevoflurane, fentanyl, vecuronium, Maintenance: sevoflurane, fentanyl (n=15)	Premedication: diazepam, Induction: propofol, fentanyl, vecuronium, Maintenance: propofol, fentanyl (n=15)	incidence of bradycardia	feasibility of volatile induction and maintenance technique, hemodynamic data, gas exchange, postoperative complications
Biboulet[9]	2012	single	age > 75 years, ASA III or IV with severe cardiac comorbidities, hip fracture, undergoing hip nailing or partial hip replacement	contraindication to spinal anesthesia, allergy to any of the anesthetic drugs used, and total hip replacement.	Premedication:n/r, Induction: sevoflurane, remifentanil, lidocaine local vocal cord anesthesia, Maintenance: sevoflurane, remifentanil (n=14)	Premedication:n/r, Induction: propofol, remifentanil, lidocaine local vocal cord anesthesia, Maintenance: propofol, remifentanil (n=14)	number of hypotensive episodes	total dose of ephedrine administered, maximal decrease in mean arterial pressure, creatinine and serum urea nitrogen level, hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, ASA: American Society of Anesthesiology physical status, LAD: left anterior descendend coronary artery, LVEDP: left ventricular end-diastolic pressure, EF: left ventrucular ejection fraction, BMI: body mass index.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Bignami [10]	2012	single	coronary artery disease, scheduled for elective mitral valve surgery, age > 18 years, signed the written informed consent, at least one coronary vessel with a stenosis > 50% at the coronary angiogram	Patients were excluded in the case of previous unusual response to an anaesthetic, use of sulfonylurea, theophylline, or allopurinol, elevated pre-operative cardiac troponin I.	Premedication: diazepam, Induction: propofol,fentanyl,rocuronium, Maintenance: sevoflurane, fentanyl (n=50)	Premedication: diazepam, Induction: propofol,fentanyl,rocuronium, Maintenance: propofol, fentanyl (n=50)	cardiac troponin I	mortality
Braz[11]	2013	single	ASA I, age 18-50 years, minimally invasive elective otorhinological surgeries	smokers, alcoholics, obese, any medication, vitamins, antioxidants or radiation therapy within last 30 days	Premedication: midazolam, Induction: propofol,fentanyl,rocuronium, Maintenance: isoflurane, fentanyl (n=15)	Premedication: midazolam, Induction: propofol,fentanyl,rocuronium, Maintenance: propofol, fentanyl (n=15)	not defined	plasma Interleukin 6 level, plasma malondialdehyde level, hemodynamic parameters
Cavalca [12]	2008	single	stable angina, left ventricular ejection fraction > 40%, age 60–80 years	aortic valve stenosis, angina on arrival in the operating room, and acute myocardial infarction during the past 7 days	Premedication: morphine, Induction: thiopental, remifentanil, pancuronium, succinylcholine, Maintenance: sevooflurane, fentanyl (n=21)	Premedication: morphine, Induction: thiopental, remifentanil, pancuronium, succinylcholine, Maintenance: propofol, fentanyl (n=22)	plasma γ-tocopherol level	plasma Interleukin 10 level, plasma malondialdehyde level, α-tocopherol level, hemodynamic parameters

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Conno[13]	2009	single	ASA status I–III, scheduled to undergo elective thoracic surgery with lung resection performed through thoracotomy or thoracoscopy, and requiring OLV during surgery	ongoing treatment with any dose of systemic or topical steroids, acute pulmonary or extra-pulmonary infections (elevated C-reactive protein > 10 ng/ml [reference range<5 ng/ml] or leukocytosis > 10 x 10^3/ l [reference range 3.0–9.6 x 10^3/ l]), severe chronic obstructive pulmonary disease (Gold stage 2–4), history of recurrent pneumothoraces, pneumonectomy, and/or lung volume–reduction surgery	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: sevoflurane, fentanyl+remifentanil (n=27)	Premedication: midazolam, Induction: propofol, fentanyl, atracurium, Maintenance: propofol, fentanyl+remifentanil (n=27)	lung cytokines	pulmonary infections necessitating antibiotic treatment, pneumonia, atelectasis, pleural effusion, fistula, reintubation, systemic inflammatory response syndrome, sepsis, acute respiratory distress syndrome, surgical revision, and death
Conzen [14]	2003	single	one vessel or two-vessel coronary artery disease suitable for repair without cardiopulmonary bypass (off-pump coronary artery bypass surgery), informed consent, age greater than 18 years, elective surgery, body mass index below 150% of ideal, and ASA II–IV	previous unusual response to an anesthetic, an experimental drug within 28 days before surgery, severe accompanying disease (hepatic, renal), previous surgical coronary artery repair, severe cardiac dysrhythmias or an ejection fraction below 0.3 preoperative cardiac catheterization), and combined surgery involving a second organ (e.g., carotid endarterectomy), oral glibenclamide or other sulfonylurea drugs	Premedication: midazolam, Induction: etomidate, sufentanil, pancuronium, Maintenance: sevoflurane, sufentanil (n=10)	Premedication: midazolam, Induction: propofol, sufentanil, pancuronium, Maintenance: propofol, sufentanil (n=10)	troponin I level	intraoperative hemodynamic data, creatine kinase, myocardial fraction of creatine kinase, Interleukin 6

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, OLV: one lung ventilation, ASA: American Society of Anesthesiology physical status.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Cromheecke [15]	2006	single	elective aortic valve replacement for aortic stenosis	Previous coronary surgery or valve replacement, combined operations (simultaneous valve repair and coronary surgery, carotid endarterectomy, or left ventricular aneurysm repair), critical aortic stenosis (aortic valve area <0.5 cm^2, unstable angina, occurrence of coronary stenosis on coronary angiography, documented myocardial infarction within the previous 6 wk, active congestive heart failure, hemodynamic instability with the need for medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase _150 U/L), renal insufficiency (creatinine concentration >1.5 mg/dL), severe chronic obstructive pulmonary disease (forced expired volume in 1 s <0.8 L), or history of neurologic disturbance	Premedication: n/s, Induction: sevoflurane,remifentanil, pancuronium, Maintenance: sevoflurane, remifentanil (n=15)	Premedication: n/s, Induction: propofol,remifentanil,pancuronium, Maintenance: propofol, remifentanil (n=15)	cardiac troponin I level, maximum rate of pressure development (dP/dt) post - CPB	intraoperative hemodynamic data,
De Hert [20]	2009	dual	elective isolated coronary artery bypass grafting with CPB were included	documented evidence for a recent (< 7 days) or ongoing myocardial infarction, combined surgical procedures or redo operations	Premedication: n/s, Induction: n/s, Maintenance: sevoflurane (n=132) desflurane (n=137), opiod n/s	Premedication: n/s, Induction: n/s, Maintenance: propofol (n=145), opiod n/s	troponin T level	mortality, clinical outcome

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CPB: cardiopulmonary bypass, ASA: American Society of Anesthesiology physical status, n/s: not specified in study protocol.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
De Hert[17]	2003	single	age >70 years with three-vessel disease and with a preoperative ejection fraction less than 50%	repeat coronary surgery, concurrent valve repair, or aneurysm resection, unstable angina or with valve insufficiency	Premedication: n/r, Induction: group 1 (n=15): sevoflurane, remifentanil, pancuronium, group 2 (n=15): diazepam, remifentanil, pancuronium, Maintenance: sevoflurane, remifentanil (group 1), desflurane, remifentanil (group 2)	Premedication: n/r, Induction: propofol, remifentanil, pancuronium, Maintenance: propofol, remifentanil (n=15)	cardiac troponin I level, maximum rate of pressure development (dP/dt) post - CPB	hemodynamic data
De Hert[16]	2002	single	elective CABG surgery, preoperative ejection fraction of more than 40% were included	repeat coronary surgery, concurrent valve repair, or aneurysm resection, unstable angina or valve insufficiency, None of the patients included in this study had oral antidiabetic medication or were treated with theophylline	Premedication: n/r, Induction: sevoflurane, remifentanil, pancuronium, Maintenance: sevoflurane, remifentanil (n=10)	Premedication: n/r, Induction: propofol, remifentanil, pancuronium, Maintenance: propofol, remifentanil (n=10)	cardiac troponin I level	hemodynamic data
De Hert[18]	2004	single	elective coronary surgery with CPB	previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy, or LV aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability with the need for medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase > 150 U/l), renal insufficiency (creatinine concentration > 1.5 mg/dl), severe chronic obstructive pulmonary disease (forced expired volume in 1 s < 0.8 l), or history of neurologic disturbances	Premedication: lorazepam, fentanyl, Induction: propofol, remifentanil, pancuronium, Maintenance: sevoflurane (three different durations of administration), remifentanil (n=150, 50 per group)	Premedication: lorazepam, fentanyl Induction: propofol, remifentanil, pancuronium, Maintenance: propofol, remifentanil (n=50)	cardiac troponin I level	hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CPB: cardiopulmonary bypass, CABG: coronary artery bypass graft, LV: left ventricular.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
De Hert II[19]	2004	single	elective coronary surgery with cardiopulmonary bypass	previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy, or LV aneurysm repair), unstable angina, valve insufficiency, documented myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynamic instability requiring medical or mechanical support, severe hepatic disease (alanine aminotransferase or aspartate aminotransferase >150 U/l), renal insufficiency (creatinine concentration >1.5 mg/dl), severe chronic obstructive pulmonary disease (forced expired volume in 1 s <50% of predicted or <2.0 l), or history of neurologic disturbances	Premedication: lorazepam, fentanyl Induction: group 1 and 2 (n=160) midazolam, remifentanil, pancuronium, Maintenance: group 1 sevoflurane, remifentanil (n=80), group 2 desflurane, remifentanil (n=80)	Premedication: lorazepam, fentanyl Induction: group 3 (n=80) midazolam, remifentanil, pancuronium, group 4 (n=80) propofol, remifentanil, pancuronium Maintenance: group 3 midazolam, remifentanil (n=80), group 4 propofol, remifentanil (n=80)	hospital and ICU length of stay	cardiac troponin I level, hemo-dynmanic data
Deegan[21]	2010	single	18 to 85 years and scheduled for mastectomy and axillary node clearance or wide local tumor excision without known extension beyond the breast and axillary nodes (ie, believed to be tumor stages I-III, nodes 0-2)	previous breast cancer surgery (except diagnostic biopsy), inflammatory breast cancer, ASA IV or greater, any contraindication to paravertebral anesthesia (including coagulopathy and abnormal anatomy), and any contraindication to midazolam, propofol, sevoflurane, fentanyl, or morphine	Premedication: n/r, Induction: propofol, fentanyl, Maintenance: sevoflurane, morphine (n=17)	Premedication: n/r, Induction: propofol, fentanyl, Maintenance: propofol, fentanyl, paravertebral block (n=15)	not defined	systemic inflammatory response/plasma cytokine levels

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, LV: left ventricular, ASA: American Society of Anesthesiology physical status.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Eremeev [22]	2011	single	CAD, elective off-pump CABG, EF>30%, no contraindication regional anesthesia, ability to assess pain, scale 1-10, ability to use PCA	valvular disease concomittant, severe atriosclerosis, damage peripherial vessels, simultant porcedure with valve or carotid endarteiocetomy, necessity of CPB	Premedication: phenazepam, phenobarbital, omeprazol, promedol, Induction: midazolam, fentanyl, pipercuronium, Maintenance: sevoflurane, fentanyl (n=12)	Premedication: phenazepam, phenobarbital, omeprazol, promedol, Induction: midazolam, fentanyl, pipercuronium, Maintenance: propofol, fentanyl (n=12)	not defined	hemodynamic data, postoperative pain
Flier[23]	2010	single	elective CABG with the use of CPB	emergency surgery; combined or re-do procedures; diagnosis of any hormone disorder other than diabetes, chronic inflammatory disease, malignancy, or current infections, preoperative treatment with steroids; and participation in another study that might interfere with the endpoints of the current trial.	Premedication: midazolam, Induction: midazolam, sufentanil, pancuronium, Maintenance: isoflurane, sufentanil (n=41)	Premedication: midazolam, Induction: midazolam,sufentanil,pancuronium, Maintenance: propofol, sufentanil (n=43)	cardiac troponin I level	clinical outcome, in-hospital morbidity and mortality
Fräßdorf[24]	2009	single	isolated coronary revascularization (CABG)	ASA status 4 or 5, angina during the previous 72 hours, unstable angina, acute myocardial infarction, ejection fraction lower than 40%, congestive heart failure, emergency procedures, former CABG surgery, concurrent valve repair, oral antidiabetics, or theophylline therapy	Premedication: diazepam, Induction: propofol, sufentanil, pancuronium, Maintenance: sevoflurane, sufentanil (n=20)	Premedication: diazepam, Induction: propofol, sufentanil, pancuronium, Maintenance: propofol, sufentanil (n=10)	cardiac troponin I level	clinical outcome, hemodynamic data, creatine kinase, myocardial fraction of creatine kinase
Fudickar[25]	2014	single	elective surgical treatment of peripheral occlusive arterial disease with clamping of the femoral artery under general anesthesia	skin disease rendering NIRS impossible and patients with amputation of the leg opposite to the side of surgery were excluded from the study.	Premedication:midazolam, Induction: propofol, remifentanil, rocuronium, Maintenance: sevoflurane (preconditioning), propofpl, remifentanil (n=20)	Premedication:midazolam, Induction: propofol, remifentanil, rocuronium, Maintenance: propofol, remifentanil (n=20)	leg muscle tissue oxygen saturation	clinical outcome, blood gas analysis data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CAD: Coronary artery disease, CPB: cardiopulmonary bypass, CABG: coronary artery bypass graft, ASA: American Society of Anesthesiology physical status, PCA: patient controlled anesthesia, EF: ejection fraction,NIRS: near infrared spectroscopy.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Garcia[26]	2005	Multi-center	elective CABG surgery	concomitant aortic or valvular surgery, elevated cardiac enzymes <24 h before surgery, unstable angina, angina <24 h before surgery, hemodynamic instability requiring inotropic support and administration of diazoxide, nicorandil, sulfonylurea or theophylline	Premedication: n/r Induction: propofol, etomidate, opioide+NMBA n/s, Maintenance: sevoflurane, opioide n/s (n=37)	Premedication: n/r Induction: propofol, etomidate, opioide+NMBA n/s, Maintenance: propofol, opioide n/s (n=35)	not defined	transcript levels of platelet–endothelial cell adhesion molecule-1, cardiac troponin I, NTproBNP, clinical outcome
Gaszynski[27]	2011	single	morbid obesity (body mass index >40 kg/m^2), ASA ≤ II, NYHA ≤ II	coexisting cardiovascular diseases, except for well-controlled hypertension	Premedication: n/r Induction: midazolam, propofol,fentanyl, atracurium, Maintenance: sevoflurane, fentanyl (n=41)	Premedication: n/r Induction: midazolam, propofol,fentanyl, atracurium, Maintenance: propofol, fentanyl (n=40)	not defined	hemodynamic data
Godet[28]	1990	single	were undergoing surgical repairs of the descending thoracic aorta that did not necessitate one lung ventilation	none	Premedication: n/r Induction: flunitrazepam, fentanyl, pancuronium, Maintenance: isoflurane, fentanyl (n=10)	Premedication: n/r Induction: flunitrazepam, fentanyl, pancuronium, Maintenance: high dose fentanyl (n=10)	not defined	hemodynamic data, blood gas analysis data, oxygen consumption and delivery
Gravel[29]	1999	single	age >18 and <75 yr, left ventricular ejection fraction >40%, normal hepatic and renal function	Emergency surgery, allergy to study medication, drug or alcohol abuse, gastro-esophageal reflux, obesity (body mass index >32), anticipated difficult intubation	Premedication: lorazepam, morphine Induction: sevoflurane, sufentanil, cis-atracurium, Maintenance: sevoflurane, sufentanil (n=15)	Premedication: lorazepam, morphine Induction: midazolam, sufentanil, cis-atracurium, Maintenance: propofol, sufentanil (n=15)	not defined	hemodynamic data, clinical outcome

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, ASA: American Society of Anesthesiology physical status, NYHA: New York Heart Association, NTproBNP: N-terminal prohormone of brain natriuretic peptide, n/r: not reported, n/s: not specified in study protocol, NMBA: neuromuscular blocking agent.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Guarracino [30]	2006	multicenter	elective CABG surgery with the OPCAB; isolated coronary revascularization were eligible if referred for an elective procedure, were 18 years old, and if an OPCAB procedure was deemed technically feasible technique	case of CABG with CPB, myocardial infarction during the preceding 6 weeks, valve insufficiency, active congestive heart failure, any other surgical procedure during current admission, previous unusual response to an anesthetic, and use of any experimental drugs within 28 days before surgery. Patients taking sulfonylurea, theophylline, or allopurinol were also excluded.	Premedication: diazepame, morphine, scopolamine, Induction: midazolam, fentanyl, pancuronium, Maintenance: desflurane, fentanyl (n=57)	Premedication: diazepame, morphine, scopolamine, Induction: midazolam, fentanyl, pancuronium, Maintenance: desflurane, fentanyl (n=55)	cardiac troponin I level	postoperative morbidity, length of hospital stay
Helman [31]	1992	single	elective CABG surgery, EF>30%, stenosis grade coronary artery >70% for RIVA, RCX, RCA or >50% main stem	uninterpretable ECG (pacermaker, left bundle branch block), esophageal disease precluding TEE probe insertion	Premedication: midazolam, morphine, Induction: thiopental, sufentanil, pancuronium or vecuronium, Maintenance: desflurane, sufentanil (n=100)	Premedication: midazolam, morphine, Induction: thiopental, sufentanil, pancuronium or vecuronium, Maintenance: midazolam during CPB+ high dose sufentanil (n=100)	not defined	myocardial ischemia events, hemodynamic and echocardiographic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, OPCAB: off-pump coronary artery bypass, CPB: cardiopulmonary bypass, ECG: electrocardiography, EF: ejection fraction, RIVA: Ramus interventricularis anterior of the left coronary artery, RCX, Ramus circumflexus of the left coronary artery, RCA: right coronary artery, TEE: transesophagic echocardiography.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Howie[32]	1996	single	undergo elective mitral valve repair or replacement surgery who had a mean pulmonary artery pressure equal to or more than 25 mmHg written, informed consent	Pregnancy, left main coronary artery stenosis, significant left ventricular dysfunction with a left ventricular ejection fraction ~40% as measured by radiographic angiography, significant cardiac dysrhythmias as defined by the cardiologist in the catheterization report, prior myocardial infarction within 48 h before surgery, CABG surgery, significant liver or kidney disease as defined by serum levels of aminotransferase exceeding three times normal, bilirubin > 2 mg/dL, and creatinine > 2.5 mg/d.	Premedication: lorazepam, morphine, Induction: thiopental, vecuronium or pancuronium, Maintenance: isoflurane, fentanyl (n=23)	Premedication: lorazepam, morphine, Induction: thiopental, vecuronium or pancuronium, Maintenance: high dose fentanyl (n=21)	not defined	hemodynamic data
Huang[33]	2011	single	primary elective CABG	emergency revascularization for unstable angina, previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy or left ventricular aneurysm repair), preoperative myocardial infarction within the last 4 weeks or ongoing myocardial infarction, poor ventricular function (ejection fraction 0.30), preoperative haemodynamic instability with the need for medical or mechanical support, severe hepatic disease, (alanine aminotransferase or aspartate aminotransferase>150 units/l), renal insufficiency (creatinine concentration>1.5 mg/dl), severe chronic obstructive pulmonary disease (forced expiratory volume in 1 s) >0.8 L, severe coagulation abnormalities, history of neurological disturbances	Premedication: morphine, scopolamine, Induction: etomidate, fentanyl, pancuronium, Maintenance: isoflurane, fentanyl (n=30)	Premedication: morphine, scopolamine, Induction: etomidate, fentanyl, pancuronium, Maintenance: group 1 propofol + fentanyl (n=30), group 2 midazolam + fentanyl (n=29)	not defined	cardiac troponin I, postoperative morbidity, hemodynamic data, inflammatory cytokine levels

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Jovic[34]	2012	single	elective AVR due to severe aortic stenosis, aortic valve area <1 cm^2, with cardiopulmonary bypass	previous heart surgery (coronary, valvular or aortic reconstructive surgery), concomitant: coronary or valvular disease, aortic valve insufficiency, acute congestive heart failure, renal insufficiency (creatinine concentration >1.5 mg/dL), as well as presented carotid artery disease (stenosis >50%), severe hepatic disease (alanine or aspartate aminotransferase >150 U/L) and severe chronic obstructive pulmonary disease	Premedication: midazolam, morphine, atropine Induction: midazolam, sufentanil, pancuronium, Maintenance: sevoflurane, sufentanil (n=11)	Premedication: midazolam, morphine, atropine, Induction: propofol, sufentanil, pancuronium, Maintenance: propofol, sufentanil (n=11)	not defined	protein levels and transcriptional levels of mitochondrial enzymes, hemodynamic data
Kendall[35]	2004	single	elective OPCAB	Patients undergoing emergency surgery and those with unstable angina were excluded from the study.Patients with plasma creatinine values > 160 mmol.l) were excluded from the study; troponin T levels can be difficult to interpret in the presence of renal impairment. Patients taking anticoagulant therapy and those with any other contraindication to the insertion of a thoracic epidural were also excluded.	Premedication: n/r, Induction: etomidate, fentanyl, vecuronium, Maintenance: isoflurane, fentanyl (n=10)	Premedication: n/r, Induction: propofol, fentanyl, vecuronium, Maintenance: propofol, fentanyl (n=10)	not defined	troponin T levels, hemodynamic data
Kirov[36]	2007	single	coronary artery disease, scheduled for elective OPCAB	age < 18 years, simultaneous interventions (carotid endarterectomy, aneurysm repair, etc.) and severely stenosed femoral arteries	Premedication: diazepam, Induction: midazolam, fentanyl, pipecuronium, Maintenance: isoflurane, fentanyl (n=12)	Premedication: diazepam Induction: midazolam, fentanyl, pipecuronium, Maintenance: group 1 midazolam, fentanyl (n=12), group 2 propofol, fentanyl (n=10)	not defined	hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, OPCAB: off-pump coronary artery bypass, AVR: aortic valve replacement.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Ko[38]	2010	single	liver donors undergoing right hepatectomy	Patients undergoing re-operation, those contraindicated to spinal injection of morphine sulfate (e.g. skin infection at the site of injection) or those with a known allergy to any of the drugs used in this study were excluded	Premedication: none, Induction: thiopental, remifentanil,vecuronium, Maintenance: sevoflurnae, remifentanil,morphine intrathecal (n=37)	Premedication: none, Induction: thiopental, remifentanil, vecuronium, Maintenance: isoflurane, remifentanil,morphine intrathecal (n=37)	ALAT	liver markers (ASAT, albumin), prothrombin time, blood urea nitrogen, creatinine
Ko[37]	2008	single	patients undergoing right donor hepatectomy	known allergy to eggs, propofol, or any of the drugs used in this study.	Premedication: n/r Induction: thiopental, opiod n/r,vecuronium, Maintenance: desflurane, opiod n/r (n=35)	Premedication: n/r Induction:propofol, remifentanil,vecuronium, Maintenance: desflurane, remifentanil (n=35)	not defined	liver markers (ALAT, ASAT, total bilirubin, prothrombin time, albumin), blood urea nitrogen, creatinine, postsurgical morbidity
Kortekaas[39]	2014	single	severe mitral regurgitation due to degenerative mitral valve disease	left ventricular dysfunction, (ejection fraction below 35%), minimal invasive or emergency, procedures, previous cardiac surgery, and the use of ketamine,aprotinin, corticosteroids, and volatile sevoflurane perioperatively	Premedication: lorazepam, Induction: propofol, remifentanil, NMBA: n/r, Maintenance: sevolfurane during CPB, propofol, remifentanil (n=11)	Premedication: lorazepam, Induction: propofol, remifentanil, NMBA: n/r, Maintenance: propofol, remifentanil (n=10)	not defined	cardiac troponin I, cytokine levels

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CPB: cardiopulomanry bypass, NMBA: neuromuscular blocking agent, ALAT: alanine aminotransaminase, ASAT: aspartate aminotransferase, n/r: not reported.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Kottenberg [40]	2012	single	three-vessel coronary artery disease scheduled for CABG surgery,>18 years of age, who were scheduled for elective isolated first-time CABG surgery for three-vessel coronary artery disease were eligible	any type of diabetes mellitus (controlled by diet, oral drugs, or insulin), renal insufficiency (serum creatinine >2 mg/dl), peripheral vascular disease affecting the upper limbs, acute coronary syndrome, acute or recent myocardial infarction, preoperative inotropic support before induction of anesthesia, any kind of mechanical assist device, those with any condition potentially increasing preoperative troponin I concentration, e.g., coronary interventions within the previous 6 weeks, or those having received any type of emergency surgery, combined CABG/valve surgery, or those with any previous cardiac operations were excluded. Patients receiving chronic treatment with acetylsalicylic acid and/or clopidogrel	Premedication: flunitrazepam, Induction: etomidate, sufentanil, rocuronium, Maintenance: isoflurane, sufentanil (n=39)	Premedication: flunitrazepam, Induction: etomidate, sufentanil, rocuronium, Maintenance: propofol, sufentanil (n=33)	cardiac troponin I level	creatinine level, anesthetic and surgical data
Landoni[41]	2007	single	mitral valve surgery for mitral valve repair age > 18 years, written informed consent.	preoperative cardiac troponin I values 0.04 ng/mL; previous unusual response to an anesthetic; or use of sulfonylurea, theophylline, or allopurinol	Premedication: morphine, scopolamine Induction: propofol, fentanyl, atracurium, Maintenance: isoflurane, fentanyl (n=59)	Premedication: morphine, scopolamine Induction: propofol, fentanyl, atracurium, Maintenance: isoflurane, fentanyl (n=61)	cardiac troponin I peak level	postoperative morbidity, length of hospital stay

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft.*: References are listed in table 5 in the supplemental digital content file 1. ,

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Lee, J. [43]	2012	single	ASA I to II patients aged 40 to 70 years old and undergoing an elective Ivor Lewis operation primary squamous cell or adenocarcinoma of the esophagus	persistent tobacco abuse, a high body temperature (above 37°C), increased levels of C-reactive protein and white blood cells, an administration of nonsteroidal anti-inflammatory agent or corticosteroid within 3 months, and a vital capacity or peak expiratory volume at one minute 50% of expected	Premedication:n/r Induction: thiopental, rocuronium, Maintenance: sevoflurane, fentanyl (n=24)	Premedication:n/r Induction: propofol, remifentanil, rocuronium, Maintenance: propofol, remifentanil (n=24)	interleukin 6 level	pulmonary complications and inflammatory response
Lee,M-C. [42]	2006	single	with stable angina and multi-vessel disease undergoing elective CABG surgery	Patients with acute (1 week) myocardial infarction, unstable angina, left ventricular aneurysm or very poor left ventricular function (ejection fraction 25%), significant valvular disease, chronic obstructive pulmonary disease, advanced renal or hepatic dysfunction and those taking sulphonylurea anti-diabetic drugs or theophylline preparations	Premedication:n/r Induction: diazepam, fentanyl, pancuronium Maintenance: isoflurane, fentanyl (n=20)	Premedication:n/r Induction: diazepam, fentanyl, pancuronium Maintenance: propofol, midazolam, fentanyl (n=20)	not defined	cardiac troponin I level, hemodynmanic data, perioperative pharmacological inotropic support, clinical outcome
Leung[44]	1991	single	elective CABG	none	Premedication: diazepam, morphine Induction: diazepam, thiopental, fentanyl, NMBA n/s Maintenance: isoflurane, fentanyl (n=64)	Premedication: diazepam, morphine Induction: diazepam, thiopental, sufentanil, NMBA n/s Maintenance: midazolam, sufentanil (n=126)	not defined	hemodynamic data, ischemic episodes, clincial outcome

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, NMBA: neuromusular blocking agent, CABG: coronary artery bypass graft, ASA: American Society of Anesthesiology physical status.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Lindholm[45]	2013	single	Consecutive patients with abdominal aortic aneurysm and/or aortic arteriosclerosis obliterans scheduled for open abdominal aortic surgery	<18 yr of age, included in other pharmaceutical studies, abuse of opioids, benzodiazepines, antiepileptic drugs, alcohol, and α2-agonists, pregnant and breastfeeding women, familiar history of malignant hyperthermia, known hypersensitivity for opioids, propofol, or volatile anesthetics, serious arrhythmias; ventricular fibrillation/tachycardia or tachycardia >100 beats/min (atrial fibrillation/flutter <100 beats/min was acceptable), severe valvular diseases requiring surgical repair before major noncardiac surgery,uncontrolled hypertension, serious psychiatric disease, unstable angina pectoris or myocardial infarction 30 days before inclusion, acute abdominal aortic surgery (acute dissection or rupture), planned laparoscopic abdominal aortic aneurysm surgery	Premedication: paracetamol, Induction: thiopental, fentanyl, vecuronium, Maintenance: sevoflurane, fentanyl (n=97)	Premedication: paracetamol, Induction: thiopental, fentanyl, vecuronium, Maintenance: propofol, sufentanil (n=96)	cardiac troponin I level	postoperative morbidity, diuresis, anesthetic and surgical data
Lorsomradee[46]	2006	single	elective coronary artery bypass graft (CABG) surgery with CPB	previous coronary or valvular heart surgery, combined operations (simultaneous valve repair, carotid endarterectomy, or left-ventricular aneurysm repair), unstable angina, valvular insufficiency>grade II/IV, documented myocardial infarction within the previous 6 weeks, preoperative ejection fraction <50%, elevated troponin levels before surgery, active congestive heart failure, hemodynamic instability requiring medical or mechanical support, hepatic disease (serum glutamic pyruvic transaminase or serum glutamic oxaloacetic transaminase >150 U/L), or renal insufficiency (serum creatinine concentration >1.5 mg/ dL)	Premedication: lorazepam, fentanyl, droperidol, Induction: sevoflurane, remifentanil, cis-atracurium, Maintenance: sevoflurane, fentanyl (n=160)	Premedication: lorazepam, fentanyl, droperidol, Induction: sevoflurane, remifentanil, cis-atracurium, Maintenance: propofol, fentanyl (n=160)	serum glutamic oxaloacetic trans-aminase	cardiac troponin I, liver enzymes, renal function, hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, CPB: cardiopulmonary bypass.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Lurati Buse[47]	2012	multicenter	proven coronary artery disease +planned for major surgery /general anesthesia or ≥ 2 risk factors for CAD + major vascular surgery/general anesthesia	current medication with sulfonylurea derivatives or theophylline unless stopped ≥2 days before surgery because these drugs reportedly inhibit anesthetic preconditioning; current congestive heart failure; current unstable angina pectoris; preoperative hemodynamic instability, defined as the use of vasopressors; hepatic disease, defined as alanine aminotransferase and/or aspartate aminotransferase values >100 U/L; renal insufficiency, defined as creatinine clearance <30 mL/min; emergent surgery; severe chronic obstructive pulmonary disease, defined as forced expiratory volume in the first second of expiration <1 L; prior enrollment in the study; concurrent enrollment in another RCT; pregnancy; or absence of written informed consent.	Premedication: n/s Induction:etomidate, opiods + NMBAs n/s, Maintenance: sevoflurane, opioids n/s (n=184)	Premedication: n/s Induction:etomidate, opiods + NMBAs n/s, Maintenance: propofol, opioids n/s (n=201)	ischemic episodes (composite of troponin T elevation and/or ischemia in ECG)	ECG recordings, hemodynamic variables, N-terminal prohormone of brain natriuretic peptide
Mahmoud[48]	2011	single	adult ASA I-III patients undergoing elective open thoracic surgery using one-lung ventilation	significant lung diseases forced expiratory volume in 1 s or vital capacity < 50% of the predicted values, heart failure or mean pulmonary artery pressure >30mmHg, coagulation disorders or a history of preoperative immuno-suppressant medications	Premedication: midazolam Induction:propofol, fentanyl, cis-atracurium, Maintenance: isoflurane, fentanyl, TEA (n=25)	Premedication: midazolam Induction:propofol, fentanyl, cis-atracurium, Maintenance: propofol, fentanyl, TEA (n=25)	alveolar and plasma cytokine level (interleukin 8, tumor necrosis factor alpha)	arterial blood gas and respiratory parameters, postoperative morbidity
Mazoti[49]	2013	single	ASA I adults, scheduled for elective otorhinological surgery >120 min	smokers, alcoholics, obese, infection/inflammatory diseases, any medication or radiation therapy within last 30 days	Premedication: n/s Induction:propofol, fentanyl, rocuronium, Maintenance: isoflurane, fentanyl (n=16)	Premedication: n/s Induction:propofol, fentanyl, rocuronium, Maintenance: propofol, fentanyl, (n=18)	plasma pro-inflammatory cytokines	hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, CAD: coroanry artery disease, RCT: randomized controlled trial, TEA: thoracic epidural anesthesia, ECG: electrocardiography, NMBA: neuromuscular blocking agent, n/s: not specified in study protocol.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Meco[50]	2007	single	patients undergoing elective coronary artery bypass grafting	concomitant aortic or valvular surgery, elevated troponin I concentration within 24 h before surgery, unstable angina, angina within 24 h before surgery, hemodynamic instability with the need for medical or mechanical inotropic support, administration of adenosine-triphosphate-sensitive potassium channel agonists or antagonist such as diazoxide, nicorandil, sulfonylurea, or theophylline, left main disease, reintervention, preoperative values of creatinine > 1.7 mg/dl, chronic obstructive pulmonary disease, age over 70 years, preoperative ejection fraction inferior to 40%, preoperative hepatopathy, emergencies	Premedication: n/s Induction: propofol, midazolam, fentanyl, pancuronium, Maintenance: desflurane, propofol, midazolam, fentanyl (n=14)	Premedication: n/s Induction: propofol, midazolam, fentanyl, pancuronium, Maintenance: propofol, midazolam, fentanyl (n=14)	cardiac troponin I and N-terminal prohormone of brain natriuretic peptide level	tissue doppler imaging data, hemodynamic data
Ndoko[51]	2007	single	patients scheduled for elective cardiac surgery with CPB	consumption of sulfonylurea medications or nitric oxide donors, heart transplantation or implantation of ventricular assistance devices, emergency cardiac surgery with acute myocardial ischemia, unstable angina, or recent (<6 weeks) documented myocardial infarction, suspected or confirmed endocardial sepsis, preoperative hemodynamic instability requiring inotropic support, severe hepatic disease resulting from right ventricular dysfunction	Premedication: hydroxyzine Induction: propofol, sufentanil, pancuronium, Maintenance: desflurane, propofol, sufentanil (n=128)	Premedication: hydroxyzine Induction: propofol, sufentanil, pancuronium, Maintenance: desflurane, propofol, sufentanil (n=124)	postoperative dobutamine requirements	cardiac troponin I level, postoperative morbidity
Parsons[52]	1994	single	ASA II and III patients undergoing coronary artery bypass surgery	35< Age > 80 years, weight > 125 kg, preexisting neurological disease, pregnancy, preoperative medication affecting central nervous system, participant in other trial within 28 days before surgery, Left ventricular ejection fraction < 35%, packed cell volume < 25%, unstable cardiovascular status	Premedication: morphine, hyoscine Induction: thiopental, fentanyl, pancuronium, Maintenance: desflurane, fentanyl (n=25)	Premedication: morphine, hyoscine Induction: thiopental, fentanyl, pancuronium, Maintenance: midazolam, fentanyl (n=25)	not defined	hemodynamic, anesthestic and surgical data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, CPB: cardiopulmonary bypass.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Piriou[53]	2007	dual	patients (18-79 years) undergoing elective coronary artery bypass grafting	left ventricular ejection fraction <40%, treatment with oral hypoglycaemic sulfamide (antagonist of K_{ATP} channels), and nicorandil (agonist of K_{ATP} channels) within 5 days before surgery, emergency surgery, myocardial infarction, or clinical angina within 7 days before surgery, history of serious adverse event, or serious allergy, or any contraindication to sevoflurane, propofol, midazolam or opioids, and major coagulation disorders	Premedication: hydroxyzine Induction:propofol, sufentanl, cis-atracurium, Maintenance: sevoflurane, propofol, sufentanil (n=36)	Premedication: hydroxyzine Induction:propofol, sufentanl, cis-atracurium, Maintenance: propofol, sufentanil (n=36)	cardiac troponin I level	hemodynamic data and tissular enzymes
Rex[54]	2009	multicenter	ASA I-III patients (20-65 years) undergoing 2-5 h GA with NMBA use for surgery	neuromuscular disorder affecting NMB; anatomical malformation that predicts difficult intubation; history of malignant hyperthermia, significant renal dysfunction, or allergy to medications used during general anesthesia; concurrent use of medications known to interfere with NMBAs (*e.g.*, antibiotics anticonvulsants, magnesium salts); and women who were pregnant, breastfeeding, or of childbearing potential and not using an adequate method of contraception	Premedication: n/s Induction: propofol, opioids n/s, rocuronium, Maintenance: sevoflurane, opioids n/s (n=26)	Premedication: n/s Induction: propofol, opioids n/s, rocuronium, Maintenance: sevoflurane, opioids n/s (n=25)	time to recovery of train of four	clinical effect of sugammadex
Royse[55]	2011	single	patients >18years scheduled for elective CABG under CPB without add. procedure, able to sufficiently speak english	dialysis dependent renal failure, liver transaminases more than 1.5 times normal, pre-existing diagnosis of schizophrenia, dementia, recent stroke, known disorder affecting cognition, severe anxiety states, recent alcohol abuse or a history of chronic opioid or other psychotropic drug use	Premedication: n/s Induction: midazolam, fentanyl, rocuronium, Maintenance: sevoflurane, fentanyl (n=91)	Premedication: n/s Induction: midazolam, fentanyl, rocuronium, Maintenance: propofol, fentanyl (n=89)	postopertive cognitive dysfunction	postoperative morbidity

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, GA: general anesthesia, NMBA: neuromuscular blocking agent, n/s: not specified in study protocol, CABG: coronary artery bypass graft, CPB: cardiopulmonary bypass, K_{ATP}: adenosine triphosphate dependent potassium channels.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Schoen[56]	2011	single	patients undergoing elective cardiac surgery with CPB	age below 18 yr, overt neurological diseases or dementia, significant stenosis of the carotid arteries, pregnancy, contraindications for sevoflurane, insufficient knowledge of the German language, and emergency indication	Premedication: n/s Induction:etomodate, sufentanil, pancuronium, Maintenance: sevoflurane, propofol, remifentanil (n=59)	Premedication: n/s Induction:etomodate, sufentanil, pancuronium, Maintenance: propofol, remifentanil (n=60)	cognitive function	postoperative morbidity, cardiac troponin I, creatine kinase, myocardial fraction of creatine kinase, anesthesia and surgical data
Searle[57]	1996	Multi-center	elective CAPB, ASA III-IV, NYHA I-II	significant valvular disease, , ejection fraction<30%, uninterpretible ECG (Left bundle branch block, atrioventricular block II and III), childbearing potenital, drug and alcohol abuse	Premedication: diazepam, morphine Induction:midazolam, fentanyl, vecuronium, Maintenance:isoflurane, fentanyl (n=133)	Premedication: diazepam, morphine Induction:midazolam, fentanyl, vecuronium, Maintenance: sevoflurane, fentanyl (n=140)	not defined	hemodynamic parameters, myocardial ischemia detected by ECG
Slogoff[58]	1989	single	elective CABG, 21-75 age	previous cardiac operation, emergency procedure, additional procedure to CABG, severe systemic non-cardiac disease other than diabetes, hypertension, history of allergy to any drug that might be administered, preop ECG diagnosis of ischemia (left bundle branch block) or failure to obtain consent	Premedication: n/r Induction:diazepam, fentanyl, pancuronium, Maintenance: isoflurane (n=253)	Premedication: n/r Induction:diazepam, fentanyl, pancuronium, Maintenance: high dose sufentanil (n=254)	not defined	intraoperative ischemia, intraoperative hemodynamic data, postoperative morbidity
Song, J-C.[59]	2010	single	ASA physical status I/II/III patients undergoing elective liver resection with inflow occlusion	Age <18 years, additional ablation therapies (cryosurgery or radiofrequency ablation), prior liver resection for donation or scheduled resection not requiring inflow occlusion	Premedication: midazolam, atropine Induction:sevoflurane, fentanyl, cis-atracurium, Maintenance: sevoflurane, TEA (n=50)	Premedication: midazolam, atropine Induction:propofol, fentanyl, cis-atracurium, Maintenance: propofol, TEA (n=50)	peak alanine transaminase level	hemodynamic data, liver enzymes (aspartate aminotransferase, total bilirubin, prothrombin time, albumin), postoperative morbidity

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, CABG: coronary artery bypass graft, CPB: cardiopulmonary bypass, NYHA: New York Heart Association classification, TEA: thoracic epidural anesthesia, ECG: electrocardiography.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Song, J-G.[60]	2012	single	ASAI–II patients (18–75 years) scheduled for thoracotomy during surgery for lung and oesophageal cancer	chronic opioid use, preexisting pain syndromes, neurological disorders, severe cardiovascular disease (NYHA III or IV), severe pulmonary disease, contraindications to epidural catheter placement (coagulopathy, infection or patient refusal)	Premedication: n/s Induction: etomidate, opioids n/s, rocuronium, Maintenance: sevoflurane, TEA (n=176)	Premedication: n/s Induction: etomidate, opioids n/s, rocuronium, Maintenance: propofol, remifentanil, TEA (n=177)	incidence of post-thoracotomy pain syndrome six month after surgery	anesthetic and surgical intraoperative data, postoperative morbidity, postoperative pain and analgesic use
Soro[61]	2012	single	patients (>18 years) scheduled for elective CABG and > 4 h of postoperative sedation	combined surgery, reintervention, valve dysfunction, preoperative troponin I more than 0.5 ng/ml, altered liver (serum aspartate transaminase or serum glutamate pyruvate transaminase concentration >150 IU/l) or kidney function (serum creatinine concentration >132mmol/l) and history of chronic alcoholism or neurological disease	Premedication: lorazepam Induction: etomidate, midazolam, fentanyl,cis-atracurium, Maintenance: sevoflurane, midazolam, remifentanil (n=36)	Premedication: lorazepam Induction: etomidate, midazolam, fentanyl, cis-atracurium, Maintenance: propofol, midazolam, remifentanil (n=37)	cardiac troponin I level	myocardial biomarkers, hemodynamic data, postoperative morbidity
Story[62]	2001	single	patients for CABG	Emergency surgery, valve surgery, obesity (body mass index >35 kg/m^2), preoperative renal dialysis, lung disease treated with oral corticosteroids	Premedication: papavaretum, scopolamine Induction: diazepam, fentanyl, pancuronium, Maintenance: isoflurane, fentanyl, morphine (n=120)	Premedication: papavaretum, scopolamine Induction: diazepam, fentanyl, pancuronium, Maintenance: propofol, fentanyl, morphine (n=120)	creatinine level	urea levels

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, CABG: coronary artery bypass graft, NYHA: New York Heart Association classification, TEA: thoracic epidural anesthesia, ECG: electrocardiography, n/s: not specified.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Thomson [63]	1991	single	elective CABG, LVEF >34%	BW>110kg, Hct<25%, 35°C>T>38°C, disease of central nervous system, chronic exposure to or abuse of alcohol or drugs, general anesthesia 7 days before surgery, adverse reaction to anesthetics or opioids, malignant hyperthermia, respiratory disease sufficient to alter inhaled anesthetic uptake, recent use of any experimental drug or device	Premedication: morphine im, scopolamine im, Induction: thiopental, fentanyl, pancuronium, Maintenance: isoflurane, midazolam, fentanyl, (n=20)	Premedication: morphine im, scopolamine im, Induction: thiopental, fentanyl, pancuronium, Maintenance: isoflurane, midazolam, fentanyl, (n=21)	not defined	ECG recordings, hemodynamic variables, myocardial ischemia markers (CK, CK-MB)
Tritapepe [64]	2007	multi-center	All subjects underwent isolated CABG and were eligible if referred for isolated elective coronary bypass surgery and were 18 yr of age.	CABG planned with the off-pump technique; any other surgical procedure during current admission; a Q-wave myocardial infarction in the preceding 6 weeks; valve insufficiency; active congestive heart failure; previous unusual response to an anesthetic; an experimental drug within 28 days before surgery; use of sulfonylurea, theophylline or allopurinol.	Premedication: diazepam, morphine, scopolamine, Induction: midazolam, fentanyl, pancuronium, Maintenance: desflurane, fentanyl (n=75)	Premedication: diazepam, morphine, scopolamine, Induction: midazolam, fentanyl, pancuronium, Maintenance: propofol, fentanyl (n=75)	cardiac troponin I level	postoperative morbidity, hemodynmaic data
Xu [65]	2014	single	undergoing an elective open-chest thoracotomy for esophagectomy were prospectively enrolled whose ASA physical status were I-II	cardiac disease, heart failure, arrhythmia, bronchial inflammation, coagulation disorders, hepatic and renal insufficiency	Premedication: n/r Induction: sevoflurane, remifentanil, cis-atracurium, Maintenance: sevoflurane, remifentanil (n=20)	Premedication: n/r Induction: propofol, remifentanil, cis-atracurium, Maintenance: propofol, remifentanil (n=20)	Not defined	hemodynamic data

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, ASA: American Society of Anesthesiology physical status, CABG: coronary artery bypass graft, ECG: electrocardiography, LVEF: left ventricular ejection fraction, CK: creatine kinase, CK-MB: myocardial fraction of creatine kinase, BW: body weigth, Hct: hemotocrit, T: temperature, n/r: not reported.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Yildirim[66]	2009	single	CABG	previous coronary or valve heart surgery, combined surgical procedures (valve repair etc), unstable angina, valve insuffiency, documented acute myocardial infarction within the previous 6 weeks, active congestive heart failure, hemodynmaic instability reqiureing medical or mechanical support, severe hepatic disease, renal insufficieny, severe chronic obstructive lung disease, or history of neurological disturbances	Premedication: diazepam Induction: midazolam, remifentanil, vecuronium, Maintenance: isoflurane, remifentanil (n=20)	Premedication: diazepam Induction: propofol, remifentanil, vecuronium, Maintenance: propofol, remifentanil (n=20)	not defined	hemodynamic data, cardiac troponin I, thiobarbiturate acid-reactive substance, nitrous oxide, glutathione peroxidase, superoxide dismutase levels
Yoo[67]	2014	single	valvular heart surgery	pre-existing renal insufficiency (serum creatinine level >1.5mg/dl in men or >1.3mg/dl in women),36 older than 80 years, coronary artery occlusive disease, hepatic or pulmonary, disease, active infective endocarditis, left ventricular ejection fraction o30%, myocardial infarction within 4 weeks, or with a history of hypersensitivity to propofol, surgery requiring hypothermic circulatory arrest	Premedication: n/r Induction: midazolam, sufentanil, rocuronium, Maintenance: sevoflurane, sufentanil (n=56)	Premedication: n/r Induction: propofol, sufentanil, rocuronium, Maintenance: propofol, sufentanil (n=56)	incidence of acute kidney injury	cystatin C, interleukin 1, interleukin 6, tumor necrosis factor alpha, cardiac fraction of creatine kinase, postoperative morbidity

VOL: volatile anesthetics, TIVA: total intravenous anesthesia, CABG: coronary artery bypass graft, n/r: not reported.*: References are listed in table 5 in the supplemental digital content file 1.

Table 6: Detailed trial information continued

Publication details			Population		Intervention		Outcome	
Author*	**Year**	**Centers**	**Inclusion criteria**	**Exclusion criteria**	**Treatment (VOL)**	**Control (TIVA or VOL)**	**Primary**	**Secondary**
Zangrillo[68]	2011	single	patients with a Lee index ≥2 scheduled for elective lung surgery and major peripheral vascular surgery, one-lung ventilation for lung (using either thoracotomic or thoracoscopic approach) or peripheral revascularization surgery, age> 18 years, written informed consent, and planned for general anesthesia	previous unusual response to an anesthetic use of sulfonylurea, theophylline, or allopurinol	Premedication: diazepam Induction: thiopental, fentanyl, atracurium, Maintenance: sevoflurane, fentanyl (n=44)	Premedication: diazepam Induction: thiopental, fentanyl, atracurium, Maintenance: sevoflurane, fentanyl (n=44)	cardiac troponin I	postoperative morbidity and mortality,

VOL: volatile anesthetics, TIVA: total intravenous anesthesia.*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Alvarez[1]	1990	no specific statement	high risk	randomized by even/ uneven days	high risk	randomized by even/ uneven days	high risk	no blinding	high risk	no blinding	high risk	no patient lost to follow-up	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Amr[2]	2010	none declared	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient lost to follow-up	low risk	only deaths reported	unclear risk	not pre-defined	low risk	none
Baki[3]	2013	no specific statement	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	only deaths reported	unclear risk	not pre-defined	low risk	none
Ballester[4]	2011	none declared	low risk	computer-generated	low risk	sealed envelopes	low risk	only surgeons blinded, not considered to increase risk of bias	unclear risk	no specific statement	low risk	2/40 excluded	low risk	mortality of all patients reported	unclear risk	not pre-defined	low risk	none
Beck-S.[6]	2012	none declared	low risk	computer-generated, stratified	low risk	concealed online	unclear risk	no specific statement	unclear risk	no specific statement	low risk	4/195 excluded, handling of missing data reported	low risk	mortality of all patients reported	low risk	AEs pre-defined	low risk	none
Beck-S.[5]	2008	grant by manufacturer (Abbott)	low risk	computer-generated, non-stratified	low risk	sealed envelopes	low risk	only surgeons blinded, not considered to increase risk of bias	unclear risk	no specific statement	low risk	6/70 excluded	low risk	mortality of all patients reported	low risk	AEs pre-defined	low risk	none
Bein[7]	2005	none declared	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	2/50 excluded	low risk	no death reported	unclear risk	not pre-defined	low risk	none

*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Bharti[8]	2008	no specific statement	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	only death reported	unclear risk	not pre-defined	low risk	none
Biboulet[9]	2012	none declared	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	2/45 excluded	low risk	mortality of all patients reported	low risk	AEs predefined	low risk	none
Bignami[10]	2012	none declared	low risk	computer-generated	low risk	sealed envelopes	low risk	participants blinded to intervention	low risk	outcome assesors blinded	low risk	all patients analyzed, ITT analysis performed	low risk	mortality of all patients reported	low risk	main AEs defined, definition of EPPC only partially reported	low risk	none
Braz[11]	2013	none declared	unclear risk	no specific statement	low risk	sealed envelopes	low risk	according to clinicaltrials.gov, participants were blinded to intervention	low risk	according to clinicaltrials.gov, investigators were blinded to intervention	low risk	none lost to follow up	low risk	all pateints survived	low risk	no AE obtained	low risk	none
Cavalca[12]	2008	no specific statement	low risk	computer-generated	low risk	intra-operative investigators blinded to treatment until the morning of surgery and after enrollment	unclear risk	no specific statement	unclear risk	no specific statement	low risk	1/44 excluded	low risk	all pateints survived	low risk	no major AE obtained	low risk	none
Conzen[13]	2003	financial support by departmental grant	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no information regarding mechanical ventilation settings and fluid therapy is provided

*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Crom-heecke[14]	2006	no specific statement	low risk	computer-generated random code	low risk	"The participant randomization assignment was concealed in an envelope until the start of anesthesia."	unclear risk	no specific statement	unclear risk	only one outcome assessor blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
De Conno[15]	2009	financial support by institutional grants and grant by manufacturer (Abbott)	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	high risk	16/70 patients excluded, due to intraoperative change of surgical procedure	low risk	all patients survived	low risk	pre-defined	low risk	none
De Hert[20]	2009	financial support by grants from manufacturer (Abbott, Baxter, GSK)	low risk	computerised block randomisation	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	high risk	free choice of the opioid and NMBAs
De Hert[17]	2003	financial support by governmental grant	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	only one outcome assessor blinded	low risk	no patient excluded	low risk	deaths reported	low risk	not pre-defined	low risk	none
De Hert[16]	2002	financial support by governmental grant	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	all patients survived	low risk	pre-defined	low risk	none
De Hert[18]	2004	none declared, financial support by institutional and departemental resources	low risk	computer-generated code	low risk	sealed envelopes	unclear risk	no specific statement regarding blinding of participants, data collectors blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	low risk	none

*: References are listed in table 5 in the supplemental digital content file 1. GSK: GaxoSmithKline, NMBAs: neuromuscular blockers.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
De Hert II[19]	2004	none declared, financial support by institutional and departemental resources	low risk	computer-generated code	low risk	sealed envelopes	unclear risk	no specific statement regarding blinding of participants, data collectors blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	low risk	none
Deegan[21]	2010	none declared, financial support by two independent research grants	low risk	secure web-based system	low risk	secure web-based system	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	paravertebral block intstead of opioid in TIVA group
Eremeev[22]	2011	none declared	unclear risk	no specific statement	unclear risk	no specific statement	high risk	no blinding	high risk	no blinding	low risk	no patients excluded	low risk	all patients survived	unclear risk	not pre-defined, only "serious adverse events assessed 3 days after surgery, at discharge, 30 days and one year after surgery" according to clinicaltrials.gov	unclear risk	different duration of surgical procedures between groups

*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details			Risk of Bias Assessment															
Author*	Year	Conflicts of interest/ financial support	Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Flier[23]	2010	none declared, financial support by grant from the European Association of Cardio-Thoracic Anaesthesiologists and departemental funds	unclear risk	no specific statement	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	unclear risk	no patient lost to follow-up, in 13/100 patients the intervention was discontinued	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Fräßdorf[24]	2009	financial support from manufacturer (Abbott) and governmental grant	unclear risk	no specific statement	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Fudickar[25]	2014	one author received lecture fees from Abbvie	low risk	block randomization, selfmade	low risk	sealed envelopes	high risk	no blinding reported	high risk	one outcome assesor was blindend to the primary otcome of the trial, no further blinding reported	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	high risk	ischemic pre-conditioning was performed in control group in addition to TIVA
Garcia[26]	2005	financial support from manufacturer (Abbott)	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement regarding blinding of participants, studypersonnel was blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	unclear risk	not pre-defined	unclear risk	no information regarding mechanical ventilation settings and fluid therapy is provided

*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details			Risk of Bias Assessment															
Author*	Year	Conflicts of interest/ financial support	Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Gasz-ynski[27]	2011	financial support by governmental grant	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	high risk	100 patients included, but only complete data from 81 patients is reported, without further specification why	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no information regarding mechanical ventilation settings and fluid therapy is provided
Godet[28]	1990	none declared	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	mortality of all patients reported	high risk	not pre-defined, PPCs only for patients who died reported	high risk	systemic nitroprussid infusion in the control group
Gravel[29]	1999	none declared	unclear risk	block randomization 3:3, not further specified	low risk	sealed envelopes	unclear risk	only participants blinded to intervention	high risk	outcome assessor not blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Guarra-cino[30]	2006	Provision of Desflurane for free by manufacturer (Baxter)	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	low risk	none
Helman[31]	1992	financial support from manufacturer (Anaquest)	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	mortality of all patients reported	unclear risk	not pre-defined	unclear risk	no information regarding mechanical ventilation settings and fluid therapy is provided

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Howie[32]	1996	none declared	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	high risk	6 patients from TIVA group excluded due to inability to maintain baseline hemodynamic stability	unclear risk	all patients survived, but severe hypotension occured in the excluded patients	unclear risk	not pre-defined	unclear risk	different neuromuscular blocking agents used
Huang[33]	2011	financial support by governmental grant	low risk	computer-generated random code	unclear risk	no specific statement	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	high risk	one patient was excluded due to severe intraoperative right coronary artery thrombosis, who died	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Jovic[34]	2012	financial support by governmental grant	unclear risk	"randomly allocated"	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded, only isoflurane and propfol group for the present meta-analysis analysed	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no information regarding mechanical ventilation settings and fluid therapy is provided
Kendall[35]	2004	financial support by intstitutional funds	low risk	shuffled envelopes	low risk	sealed envelopes	unclear risk	no explicit statement, only "single blind" reported	unclear risk	no explicit statement, only "single blind" reported	low risk	no patient excluded, only isoflurane and propfol group for the present meta-analysis analysed	low risk	all patients survived	unclear risk	not pre-defined	low risk	none

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Kirov[36]	2007	financial support by governmental grants and Pulsion Medical Systems (provided technical support)	unclear risk	only "randomized" statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	None
Ko[38]	2010	financial support by unrestricted educational institutional grant	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	low risk	outcome assesors blinded	low risk	no specific statement	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no data regarding mechincal ventilation settings reported
Ko[37]	2008	none declared	low risk	computer-generated list	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	high risk	no analgesic reported for desflurane group
Kortekaas[39]	2014	governmental grant	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	patients were blinded, no statement regarding blinding of study personnel	unclear risk	no statement regarding blinding	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	nothing reported regarding mechanical ventilation settings and fluid management

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Kotten-berg[40]	2012	none declared	low risk	computer-generated list	low risk	sealed envelopes	unclear risk	no statement reqarding blinidn of participants, study personnel partially blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	high risk	remote ischemic preconditioning was used in two groups additionally
Landoni[41]	2007	none declared	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	low risk	None
Lee, J.[43]	2012	intstitutional grant	low risk	computer generated list in ACTRN registered protocol	low risk	sealed envelopes	unclear risk	no specific statement	low risk	outcome assesors blinded	high risk	10/58 patients 5 in each group) were excluded after randomization due to incomplete data acquisition	low risk	mortality of all patients reported	low risk	pre-defined	low risk	none
Lee,M-C.[42]	2006	intstitutional grant	unclear risk	"randomized"	unclear risk	no specific statement	unclear risk	no specific statement	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	deaths reported	unclear risk	not pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Leung[44]	1991	financial support by governmental grants	high risk	"randomized" reported but group size was unequal (124 vs. 62 patients)	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	high risk	only cardiac deaths reported	unclear risk	not pre-defined	high risk	no data regarding mechanical ventilation and fluid management reported, high opioid anesthesia
Lindholm[45]	2013	institutional and departemental funding, First author received presentation fees from manufacturer (Baxter)	low risk	block randomization 1:1	low risk	sealed envelopes	unclear risk	participants not blinded, study personnel not blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	unclear risk	not pre-defined	unclear risk	different opioids used
Lorsomradee[46]	2006	not reported	low risk	computer-generated list	low risk	sealed envelopes	low risk	no specific statement on blinding of participants, but double-blind trial design;data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	low risk	none

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details			Risk of Bias Assessment															
Author*	Year	Conflicts of interest/ financial support	Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Lurati Buse[47]	2012	financial support by instituional grants and manufacturer (Abbott)	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	mortality of all patients reported	low risk	pre-defined	unclear risk	17/385 patients were erroneously randomized to the wrong group
Mahmoud[48]	2011	none declared	low risk	computer-generated list	low risk	statistician ensured "proper concealment"	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Mazoti[49]	2013	none declared	unclear risk	no specific statement	low risk	sealed envelopes	low risk	no specific statement	low risk	outcome assesors blinded	unclear risk	2/36 patients excluded after enrollment before randomization, becuase "critical data were missing"	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Meco[50]	2007	none declared	low risk	"The randomisation management was delegated to a person unconnected to the clinical experimentation"	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown

*: References are listed in table 5 in the supplemental digital content file 1.

Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Ndoko[51]	2007	none declared	unclear risk	sequence generation not further specified	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	high risk	28/280 patients were excluded from the analysis due to severe complications	unclear risk	mortality only reported from the patients not excluded from analysis	unclear risk	not pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown
Parsons[52]	1994	grant from manufacturer (Anaquest)	low risk	random number table	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	1/51 patients, excluded due to equipment failure	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Piriou[53]	2007	financial support by manufacturer (Laboratoire Abbott France)	low risk	blocked randomization stratified by center	low risk	sealed envelopes	unclear risk	no blinding, but the primary outcome is not likely to be influenced	low risk	outcome assesors blinded	low risk	8/72 patients excluded due to protocol deviations (all sevoflurane group), but data is reported in the intention-to-treat analysis	low risk	all patients survived	low risk	pre-defined	low risk	none
Rex[54]	2009	financial support by manufacturer (Schering-Plough)	low risk	central randomization list system	unclear risk	no specific statement	unclear risk	no specific statement	low risk	outcome assesors blinded	low risk	1/51 patients lost to follow-up	low risk	all patients survived	low risk	not pre-defined, but this trial was a safety study and all Aes and SAEs irregardless of causation were strictly monitored	low risk	none

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details		Conflicts of interest/ financial support	Risk of Bias Assessment															
Author*	Year		Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Royse[55]	2011	investigator initiated trial, financial support by manufacturer (Baxter)	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	3/182 patients lost to follow-up	low risk	mortality of all patients reported	low risk	pre-defined	low risk	None
Schoen[56]	2011	two authors recieved honoria for lectures from Coviedien, financial grant support by manufacturer (Abbott)	low risk	multiple randomization lists, stratified	low risk	investigators had no access to the randomization lists	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	11/128 patients lost to follow-up, but relevant data for this meta-analysis of these patients is reported	low risk	death reported	low risk	pre-defined	low risk	none
Searle[57]	1996	financial support by manufacturer (Abbott)	unclear risk	block randomization 1:1, no statement about sequence generation	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	only one outcome assessor blinded	unclear risk	11/284 patients excluded from analysis (different reasons mentioned)	low risk	mortality of all patients reported	unclear risk	not pre-defined	unclear risk	no data regarding mechincal ventilation settings reported
Slogoff[58]	1989	none declared	low risk	random number table	low risk	no specific statement	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	deaths reported	low risk	pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown
Song, J-C.[59]	2010	none declared, financial support by governmental grant	low risk	computer-generated list	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient lost to follow-up	low risk	all patients survived	low risk	pre-defined	low risk	none

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details			Risk of Bias Assessment															
Author*	Year	Conflicts of interest/ financial support	Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Song, J-G.[60]	2012	none declared	low risk	computer-generated list	unclear risk	no specific statement	unclear risk	no specific statement on blinding of participants, data collectors blinded	low risk	outcome assesors blinded	low risk	13/366 patients lost to follow-up and 10/183 deaths within six months	low risk	deaths reported	unclear risk	not pre-defined	low risk	None
Soro[61]	2012	none declared, no financial support declared	low risk	random number table generator	low risk	sealed envelopes	low risk	participants and study personnel blinded to intervention	low risk	double blind double dummy design	low risk	2/75 patients excluded because surgery was not carried out (propofol group)	low risk	deaths reported	low risk	pre-defined	low risk	none
Story[62]	2001	financial support from manufacturer (Abbott and AstraZeneca)	low risk	random number table	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	highr risk	34/360 patients excluded from intention-to-treat analysis	unclear risk	one patient who died was excluded from analysis and the reason for that is unclear. The patient possibly died intraoperatively.	low risk	pre-defined	low risk	none
Thomson[63]	1991	none declared	low risk	random number table generator	unclear risk	no specific statement	unclear risk	no specific statement	unclear risk	only one outcome assessor blinded	low risk	no specific statement	low risk	deaths reported	unclear risk	not pre-defined	unclear risk	no data regarding mechincal ventilation settings reported
Tritapepe[64]	2007	free provision of desflurane by manufacturer (Baxter)	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient lost to follow-up	low risk	mortality of all patients reported	low risk	daily evaluation of Aes	low risk	none

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Table 7: Detailed risk of bias assessment and conflict of interests continued

Publication details			Risk of Bias Assessment															
Author*	Year	Conflicts of interest/ financial support	Sequence generation (selection bias)		Allocation concealment (selection bias)		Blinding of participants, study personnel (performance bias)		Blinding of outcome assessment (detection bias)		Incomplete data (attrition bias)		Selective outcome reporting - primary outcome (attrition bias)		Selective outcome reporting - secondary outcome (attrition bias)		other	
Xu[65]	2014	none declared	unclear risk	no specific statement	low risk	sealed envelopes	unclear risk	no specific statement	unclear risk	no specific statement	low risk	no patient excluded	low risk	deaths reported	unclear risk	not pre-defined	low risk	none
Yildirim[66]	2009	none declared	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	no patient lost to follow-up	low risk	all patients survived	unclear risk	not pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown
Yoo[67]	2014	none declared	low risk	computer-generated list	low risk	sealed envelopes	unclear risk	blinding of participants not reported, study personnel blinded	low risk	outcome assesors blinded	low risk	no patient excluded	low risk	all patients survived	unclear risk	not pre-defined	low risk	none
Zangrillo[68]	2011	none declared	low risk	computer-generated list	low risk	sealed envelopes	low risk	participants and data collectors blinded to intervention	low risk	outcome assesors blinded	low risk	1/88 patients lost to follow-up	low risk	mortality of all patients reported	unclear risk	not pre-defined	unclear risk	no data reqarding intraoperative ventilation and fluid managemnt shown, postoperative complications all summarized

*: References are listed in table 5 in the supplemental digital content file 1.