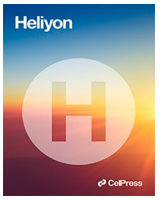
Heliyon 10 (2024) e38274

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon



Research article

Comparison of efficacy and safety of etomidate with other anesthesia induction drugs for patients undergoing cardiac surgery: A systematic review and meta-analysis of randomized controlled trials

Zhiqiu Xia [a], Kajal Kamra [a], Jianghu Dong [b,e], Kimberly A. Harp [c], Ying Xiong [b], Steven J. Lisco [a], Irving H. Zucker [d], Han-Jun Wang [a,*]

[a] Department of Anesthesiology, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[b] Department of Biostatistics, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[c] McGoogan Health Sciences Library, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[d] Department of Cellular and Integrative Physiology, University of Nebraska Medical Center, Omaha, NE, 68198, USA
[e] Division of Nephrology, University of Nebraska Medical Center, Omaha, NE, 68198, USA

A B S T R A C T

Introduction: Etomidate is commonly used to induce anesthesia in cardiac surgery patients due to its favorable cardiovascular profile. Sedative-hypnotic effects are mediated by gammaaminobutyric acid (GABA) receptor complexes in the central nervous system. There are numerous studies in which etomidate and other drugs are compared in terms of their clinical outcomes. The relative efficacy and safety of etomidate, however, remains inconclusive. In this study, we performed a systematic analysis of randomized controlled trials to assess the impact of etomidate, on patients undergoing cardiac surgery, with respect to patient outcome and adverse events.

Methods: A systematic review was conducted of all existing clinical trials exploring the safety and efficacy of etomidate in patients undergoing cardiac surgery. Randomized controlled trials (RCTs) that compared etomidate with other drugs during induction in adult cardiac surgery assessing hemodynamic parameters and clinical outcomes were included, while studies involving non-cardiac or pediatric surgery and those lacking relevant outcome data were excluded. Primary outcomes were all-cause 30-day mortality. Secondary outcomes included duration of tracheal intubation, duration of intensive care unit (ICU) stay, duration of hospital stay, systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), heart rate (HR) and other hemodynamic parameters, vasopressor requirements after induction and intubation, cortisol levels, and incidence of myoclonus.

Results: Sixteen randomized controlled trials involving 1162 patients were included. Etomidate did not affect the all-cause 30-day mortality of patients undergoing cardiac surgery compared to comparator drugs (RR, 0.96; 95 % CI, 0.26 to 3.49; P = 0.95). There were no significant differences in the duration of tracheal intubation (MD, −0.08 h; 95 % CI, −1.96 to 1.81; P = 0.94), the duration of ICU stay (MD, −2.07 h; 95 % CI, −8.09 to 3.96; P = 0.50) or the duration of hospital stay (MD, −0.62 d; 95 % CI, −2.25 to 1.00; P = 0.45) when etomidate was compared to comparator drugs. Patients receiving etomidate demonstrated a more stable hemodynamic profile after induction and intubation compared to those receiving comparator drugs. The requirement of a vasopressor after induction and intubation was significantly reduced with etomidate compared with those with comparator drugs (RR, 0.37; 95 % CI, 0.25 to 0.56; P < 0.00001).

Conclusions: This systematic meta-analysis found a significant heterogeneity among included studies. In addition, most studies focused only on the hemodynamic profile of etomidate. Thus, efficacy and safety of etomidate could not be answered within this context. Nevertheless, for patients undergoing cardiac surgery, etomidate seems to offer a minimal beneficial cardiovascular profile in comparison with other agents during induction

* Corresponding author. Department of Anesthesiology, University of Nebraska Medical Center, Omaha, NE, 68198, USA.
E-mail address: hanjunwang@unmc.edu (H.-J. Wang).

https://doi.org/10.1016/j.heliyon.2024.e38274
Received 10 August 2023; Received in revised form 2 September 2024; Accepted 20 September 2024
Available online 21 September 2024

and intubation. However, improved hemodynamics did not improve clinical outcomes as Etomidate did not affect mortality, duration of tracheal intubation, the length of stay in ICU and hospital. Finally, infectious side effects as one important trigger for increased mortality in ICU patients due to the use of Etomidate could not be analyzed as data were mostly missing.

1. Introduction

Safe management of the induction of anesthesia for cardiac surgical procedures requiring coronary artery bypass grafting (CABG) and cardiac valve repair or replacement is essential, especially for critically ill patients with compromised cardiac performance or unstable hemodynamics. Etomidate is commonly used to induce anesthesia in adult patients undergoing cardiac surgery due to its favorable cardiovascular profile and minimal respiratory depression. Etomidate is a short-acting sedative-hypnotic whose action is mediated by the gamma-aminobutyric acid (GABA) receptor complex in the central nervous system. It has been shown that etomidate causes adrenocortical suppression by blocking 11β-hydroxylase, which plays a critical role in the biosynthesis of cortisol [1,2]. Numerous clinical studies have examined etomidate compared to other drugs to determine if hemodynamic stability during anesthesia induction with etomidate outweigh the potential harm from transient adrenal suppression in patients undergoing cardiac surgery. The increased mortality was first identified by Ledingham et al. in critically ill multiple trauma patients in 1983 [1]. Some clinical studies suggest that etomidate is associated with an increased risk for cardiac morbidity and mortality after cardiac surgery [2,3]. In contrast, other studies demonstrate that etomidate does not worsen clinical outcomes such as duration of tracheal intubation, duration of ICU stay, duration of hospital stay, or mortality in patients undergoing cardiac surgery [4,5]. In 2021, Yao et al. conducted a meta-analysis to evaluate the use of etomidate in cardiac surgery [6]. They observed that a single dose of etomidate administered during anesthetic induction was associated with improved hemodynamic stability, and although it led to a higher incidence of adrenal insufficiency (AI), it did not result in worsened clinical outcomes. Nevertheless, it is worth noting that their review encompassed a diverse population comprising both adult and pediatric patients undergoing cardiac surgery. Given the inherent distinctions in etiological and pathological factors between pediatric and adult cardiac patients, our study deliberately focused on the adult population. We hypothesized that etomidate was associated with better clinical outcomes of patients undergoing cardiac surgery. Our aim was to conduct a comprehensive analysis between etomidate and comparator drugs with respect to clinical outcomes, hemodynamic alterations, as well as potential side effects and adverse events in cardiac surgical patients.

2. Materials and methods

2.1. Search strategy

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [7], including registration with PROSPERO (CRD42023310081). We searched bioscience and biomedical databases, including Medline via PubMed, Embase, the Cumulative Index of Nursing and Allied Health (CINAHL), and Scopus for pertinent articles and research. The results were limited to randomized controlled trials (RCT). The results were not limited to a publication date range. To minimize bias, we applied a broad search strategy that focused on all adult cardiac surgery patients regardless of patient history, gender, race, orientation, or ability. The search strategy, designed by an experienced academic medical librarian, combined controlled vocabulary terms and free-text words on the concepts of etomidate and cardiac surgery. The search was last performed on March 30, 2022. The complete search strategies are included in the supplemental material. References of relevant articles were also reviewed for any additional studies. The search resulted in 509 articles. These articles were then appraised and ascertained for meeting the inclusion and exclusion criteria. Articles pertaining to children or pediatric populations were excluded (see Fig. 1).

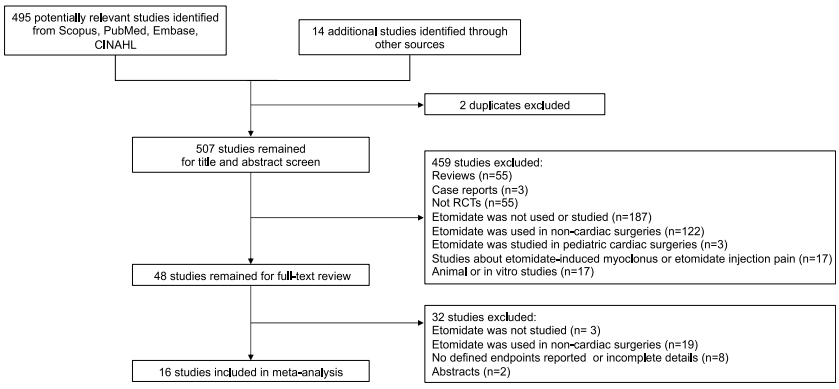


Fig. 1. Flowchart of the literature search.

2.2. Study selection

RCTs that met each of the following items were included:

(1) the study compared etomidate with comparator drugs during induction in cardiac surgery.
(2) outcomes included heart rate (HR), systolic blood pressure (SBP), diastolic blood pressure (DBP), mean arterial pressure (MAP), and other hemodynamic parameters during induction, use of vasopressors, incidence of myoclonus, cortisol levels, incidence of adrenal insufficiency, duration of ICU stay, duration of hospital stay, duration of tracheal intubation, modality, and mortality.

We excluded studies if:

(1) etomidate was used in non-cardiac surgery,
(2) etomidate was used in pediatric surgery, and
(3) outcomes of interest comparing etomidate and comparator drugs were lacking.

2.3. Data extraction

Two reviewers independently extracted data. Any disagreement in opinion was resolved through discussion with all investigators. The following data were extracted from the included studies: publication year, country, patient population, number of patients, and intervention including etomidate and comparator drugs patients received.

Primary outcomes were all-cause 30-day mortality. Secondary outcomes included duration of tracheal intubation, duration of ICU stay, duration of hospital stay, SBP, DBP, MAP, HR, cardiac output (CO), cardiac index (CI), stroke volume (SV), stroke volume index (SVI), central venous pressure (CVP), systemic vascular resistance (SVR), systemic vascular resistance index (SVRI), mean pulmonary arterial pressure (MPAP), pulmonary capillary wedge pressure (PCWP), pulmonary vascular resistance (PVR), vasopressor

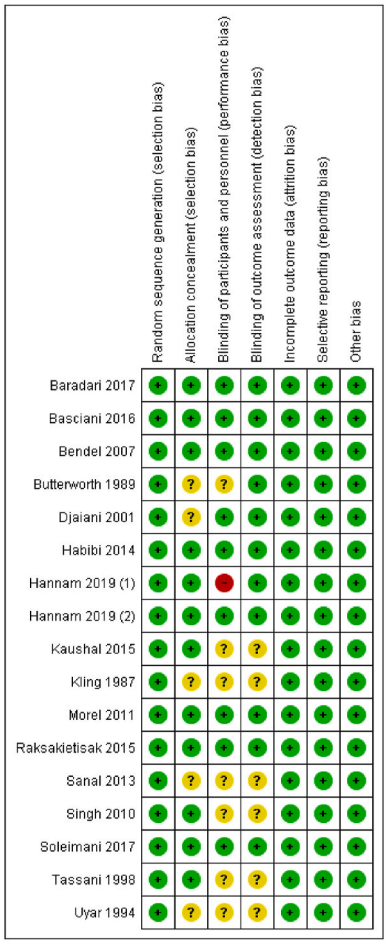


Fig. 2. Risk of bias.

requirements after induction and intubation, cortisol levels, and incidence of myoclonus.; For continuous outcomes (duration of tracheal intubation, duration of ICU stays, duration of hospital stays, SBP, DBP, MAP, HR, CO, CI, SV, SVI, CVP, SVR, SVRI, MPAP, PCWP, PVR, cortisol levels), mean differences (MDs) with 95 % confidence intervals (CIs) were calculated. For categorical outcomes (mortality, vasopressor requirements after induction and intubation, and incidence of myoclonus), relative risks (RR) with 95 % CIs were calculated.

To demonstrate the effect of etomidate on hemodynamic parameters and cortisol levels across time, we calculated the combined means and SDs for SBP, DBP, MAP, HR, and cortisol levels. These calculations were performed using online statistical calculators available at https://atozmath.com.

2.4. Quality assessment

The Cochrane risk of bias tool was used to assess the risk of bias for all included trials [8]. The risk of bias was considered high, low, or unclear based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases (see Fig. 2).

2.5. Data analysis

All parameters and units were normalized for comparison. All analyses were based on a random-effects model. Heterogeneity between studies was evaluated using a chi-squared test, and a P value of <0.10 was indicative of significant heterogeneity. Publication bias was assessed by funnel plot using vasopressor requirement after induction and intubation as an end point. Data analyses were done with ReviewManager [RevMan] version 5.4, (Nordic Cochrane Centre, Copenhagen, Denmark). For studies where no events were observed, RevMan automatically added 0.5 to each cell in a 2×2 table where such issues arose. A P value of <0.05 was considered significant in the analysis. Figures depicting the temporal changes in means and SDs for SBP, DBP, MAP, HR, and cortisol levels were generated using GraphPad Prism 9.0 (GraphPad Software, San Diego, California).

3. Results

3.1. Eligible studies

The initial search retrieved 509 publications. After excluding 2 duplicates, 507 distinct articles were identified for initial title and abstract screen (Fig. 1). Of these, 459 articles were excluded, of which 55 were reviews, 3 were case reports, 55 were not RCTs, 187 did not use or study etomidate, 122 were non-cardiac surgery, 3 were pediatric cardiac surgery, 17 focused on the etomidate-induced myoclonus or etomidate injection pain, and 17 were animal or in vitro studies.

After meticulously examining 48 full-text studies, we further proceeded with a comprehensive evaluation to identify those that conformed to our inclusion criteria. Thirty-two were excluded, of which 3 did not use, or study etomidate, 19 were non-cardiac surgery, 8 did not report defined endpoints, and 2 were abstracts. Therefore, 16 studies were included in this analysis (Table 1) [2–5,9–20].

3.2. Characteristics of studies included in the meta-analysis

The main characteristics of the included studies are summarized in Table 1. All studies were published between years 1989–2019. The comparator drugs included sedative-hypnotics, inhalational anesthetics, opioids, or a combination of them (Table 1). For the studies in which two types of surgeries (CABG and valve surgery) were analyzed [4], in which two different phases of clinical trials (open-label phase and blinded phases) were conducted [20], and in which etomidate was compared with more than two comparator drugs [3,9,13,15,19], each individual comparison was listed as a separate study (Table 1).

4. Primary outcomes

4.1. All-cause 30-day mortality

All-cause 30-day mortality was reported in three trials (Fig. 3) [3,4,14]. No difference was found between patients receiving etomidate and comparator drugs (RR, 0.96; 95 % CI, 0.26 to 3.49; P = 0.95).

5. Secondary outcomes

5.1. Duration of tracheal intubation

Two trials reported the effects of etomidate on the duration of tracheal intubation compared with comparator drugs (Fig. 4A) [4,5]. The combined data suggested that there was no difference in the duration of tracheal intubation among patients receiving etomidate and comparator drugs (MD, −0.08 h; 95 % CI, −1.96 to 1.81; P = 0.94).

Table 1
Main characteristics of clinical trials in the meta-analysis.

	Study	Year	Country	Surgery	Age	Sex	No of patients (Etomidate/control)	Etomidate Dosage (mg/kg)	N	Control Drug and dosage (mg/kg)	N	Maintainance	Duration of surgery (min)	Duration of aortic cross-clamp (min)	CPB time (min)	Use of vasopressors	Clinical Trials Registry
1	Baradari	2017	Iran	CABG	Etomidate: 62.23±6.3 Control: 58.71±9.2	Etomidate: 70.0% Control: 61.0%	40/41	0.2 mg/kg	40	Ketamine: 1 mg/kg and propofol: 1.5 mg/kg	41	NA	Etomidate: 189.36±26.51 Control: 193.48 ±22.35	Etomidate: 42.80 ±7.79 Control: 41.22 ±7.85	Etomidate: 65.38 ±9.25 Control: 66.07 ±8.95	If the blood pressure decreased to less than 20% of a patient's baseline, ephedrine (10 mg) was administered.	Iranian Registry of Clinical Trials Database (IRCT201207184365N14; http://www.irct.ir)
2	Basciani (1)	2016	Switzerland	CABG	Etomidate: 67±6 Control: 67±9	Etomidate: 90.0% Control: 83.3%	30/30	0.15 mg/kg	30	Propofol: 1.5 mg/kg	30	NA	NA	Etomidate: 46±20 Control: 56±23	Etomidate: 77±41 Control: 91±38	To maintain MAP within the range of 60 to 80mmHg, noradrenaline (5-10ug bolus) was administered.	NCT 00415701
2	Basciani (2)	2016	Switzerland	MVS	Etomidate: 60±10 Control: 65±11	Etomidate: 85.0% Control: 75.0%	20/20	0.15 mg/kg	20	Propofol: 1.5 mg/kg	20	NA	NA	Etomidate: 74±20 Control: 84±39	Etomidate: 98±20 Control: 123±78	To maintain MAP within the range of 60 to 80mmHg, noradrenaline (5-10ug bolus) was administered.	NCT 00415701
3	Bendel	2007	Finland	AVR	Etomidate: 67±9 Control: 63±9	Etomidate: 53.3% Control: 63.3%	30/30	13±10 mg (range, 4-20 mg)	30	Propofol: 77±36 mg (range, 40-400 mg)	30	NA	NA	NA	NA	If MAP decreased below 70 mmHg for more than 30 s, a minimum of 0.05 mg of phenylephedrine was given.	NA
4	Butterworth	1989	US	CABG	Etomidate: 56±7 Control: 61±9	Etomidate: 88.9% Control: 63.6%	9/11	0.4 mg/kg	9	Sufentanil: 5 ug/kg	11	Sufentanil (a total dose of 10 ug/kg, IV) supplemented with metocurine and/or pancuronium, lorazepam, 2 mg, IV, and enflurane.	NA	NA	NA	Hypotension to 65% or less of the baseline MAP (or to a systolic pressure < 90 mmHg) were treated with phenylephrine.	NA
5	Habibi	2014	Iran	CABG	Etomidate: 62.52±8.49 Control: 59.82±7.72	Etomidate: 70.0% Control: 58.0%	50/50	0.2 mg/kg	50	Ketamine: 1mg/kg and thiopental sodium: 3 mg/kg	50	NA	NA	NA	NA	If the blood pressure decreased to less than 20% of patient's baseline, ephedrine (10 mg) was administered.	Iranian Registry of Clinical Trials Database (IRCT201309242883N4).
6	Hannam (1)	2019	New Zealand	CABG, valve surgery, CABG+valve surgery, thoracic aorta surgery	Etomidate: 65 (range, 45-83) Control: 64 (range, 43-83)	Etomidate: 66.7% Control: 72.5%	36/40	0.19±0.09 mg/kg	36	Propofol: 1.1±1.3 mg	40	Before CBP, anaesthesia was maintained using volatile an aesthetics. Propofol was subsequently administered as an infusion starting with onset of CPB until the end of each case and to maintain sedation during transfer to the postoperative care unit.	NA	NA	NA	After induction, blood pressure was supported to a level determined by the anaesthetist as appropriate for the patient using bolus doses of metaraminol (0.25-0.5 mg) or ephedrine (3-6 mg).	Australian New Zealand Clinical Trials Registry (ACTRN12614000717651)

6	Hannam (2)	2019	New Zealand	CABG, valve surgery, CABG+valve surgery, thoracic aorta surgery	Etomidate: 61 (range, 20-87) Control: 62 (range, 36-84)	Etomidate: 82.1% Control: 74.3%	39/35	0.6±1.2 mg/kg	39	Propofol: 1.2±1.3 mg	35	Before CBP, anaesthesia was maintained using volatile an aesthetics. Propofol was subsequently administered as an infusion starting with onset of CPB until the end of each case and to maintain sedation during transfer to the postoperative care unit.	NA	NA	NA	After induction, blood pressure was supported to a level determined by the anaesthetist as appropriate for the patient using bolus doses of metaraminol (0.25-0.5 mg) or ephedrine (3-6 mg).	Australian New Zealand Clinical Trials Registry (ACTRN12614000717651)
7	Kaushal	2015	India	CABG, MVR, AVR	Etomidate: 36±12.33 Control: 33.96±10.88	Etomidate: 53.3% Control: 50.0%	30/30	0.2 mg/kg	30	Propofol: 2 mg/kg	30	Anesthesia was maintained with isoflurane (0.2-2%) and injection 0.1 mg/kg vecuronium was administered as IV bolus followed by 0.02 mg/kg every 30-40 min.	Etomidate: 324±61.2 Control: 315 ±66.6	NA	NA	Hypotension was defined as fall of MAP of more then 10% on the base line. No details on when vasopressors were required or administered.	NA
8	Morel	2011	France	CABG, valve replacement, CABG+valve replacement	Etomidate: 66±10 Control: 68±9	Etomidate: 64.7% Control: 67.3%	51/49	0.3 mg/kg	51	Propofol: 0.5 mg/kg	49	Continuous infusion of sufentanil (1-2 ug/kg/h) and desflurane (0.8 MAC) that was switched to propofol (3-4 mg/kg/h) during CPB.	NA	Etomidate: 82±34 Control: 83±40	Etomidate: 112±38 Control: 114±50	If, despite fluid challenge, arterial pressure still remained under 55 mmHg, norepinephrine was titrated (by 0.05 ug/kg/min increments) to achieve a MAP of 55-70 mmHg.	NCT00451776
9	Raksakietisak	2015	Thailand	CABG, valvular repair or replacement, combined surgery (valve surgery + single vessel bypass graft), and myomectomy	Etomidate: 67.5±6.7 Control: 70.7±6.7	Etomidate: 69.2% Control: 54.5%	13/11	2 mg/ml, the study drug was given by titration 1-2 ml with syringe pump in order to achieve loss of consciousness	13	Thiopentone: 25 mg/ml, the study drug was given by titration 1-2 ml with syringe pump in order to achieve loss of consciousness	11	Sevoflurane, additional doses of fentanyl, rocuronium, and midazolam.	Etomidate: 251±105 Control: 270±65	Etomidate: 78±33 Control: 91±36	Etomidate: 113±41 Control: 113±45	Dobutamine and epinephrine were used as inotropic drugs. No details on when vasopressors were required or administered.	NCT01495949
10	Sanal (1)	2013	Turkey	CABG	Etomidate: 59±10 Control: 60±9	Etomidate: 90.0% Control: 80.0%	20/20	0.2-0.5 mg/kg	20	Thiopental sodium: 3-7 mg/kg	20	NA	NA	NA	NA	Ephedrine was used as a vasopressor. No details on when it was required or administered.	NA

10	Sanal (2)	2013	Turkey	CABG	Etomidate: 59±10 Control: 60±9	Etomidate: 90.0% Control: 80.0%	20/20	0.2-0.5 mg/kg	20	Propofol: 1-2.5 mg/kg	20	NA	NA	NA	NA	Ephedrine was used as a vasopressor. No details on when it was required or administered.	NA
10	Sanal (3)	2013	Turkey	CABG	Etomidate: 59±10 Control: 61±8	Etomidate: 90.0% Control: 75.0%	20/20	0.2-0.5 mg/kg	20	Midazolam: 0.1-0.4 mg/kg	20	NA	NA	NA	NA	Ephedrine was used as a vasopressor. No details on when it was required or administered.	NA
11	Singh (1)	2010	India	CABG	Etomidate: 56.7±10.4 Control: 53.7±7.1	Etomidate: 66.7% Control: 73.3%	15/15	0.2 mg/kg	15	Midazolam: 0.15 mg/kg	15	NA	NA	NA	NA	Only mentioned that hemodynamic changes; 20beats/ minute or 20 mmHg difference in heart rate and blood pressure respectively were considered to be significant. No details on when vasopressors were required or administered.	NA
11	Singh (2)	2010	India	CABG	Etomidate: 56.7±10.4 Control: 60.5±8.0	Etomidate: 66.7% Control: 80.0%	15/15	0.2 mg/kg	15	Thiopentone: 5 mg/kg	15	NA	NA	NA	NA	Only mentioned that hemodynamic changes; 20beats/ minute or 20 mmHg difference in heart rate and blood pressure respectively were considered to be significant. No details on when vasopressors were required or administered.	NA
11	Singh (3)	2010	India	CABG	Etomidate: 56.7±10.4 Control: 57.7±8.3	Etomidate: 66.7% Control: 73.3%	15/15	0.2 mg/kg	15	Propofol: 1.5 mg/kg	15	NA	NA	NA	NA	Only mentioned that hemodynamic changes; 20beats/ minute or 20 mmHg difference in heart rate and blood pressure respectively were considered to be significant. No details on when vasopressors were required or administered.	NA
12	Soleimani (1)	2017	Iran	CABG	Etomidate: 59.4 Control: 58.5	Etomidate: 70.0% Control: 62.0%	50/50	0.2 mg/kg	50	Propofol: 1.5 mg/kg	50	NA	NA	NA	NA	If the blood pressure decreased to less than 20% of a patient's baseline, ephedrine (10 mg) was administered.	Iranian Registry of Clinical Trials Database (IRCT2015082921669N2)
12	Soleimani (2)	2017	Iran	CABG	Etomidate: 59.4 Control: 59.3	Etomidate: 70.0% Control: 64.0%	50/50	0.2 mg/kg	50	Diazepam: 0.3 mg/kg	50	NA	NA	NA	NA	If the blood pressure decreased to less than 20% of a patient's baseline, ephedrine (10 mg) was administered.	Iranian Registry of Clinical Trials Database (IRCT2015082921669N2)
13	Tassani (1)	1998	Germany	CABG	Etomidate: 57.4±8.6 Control: 60.8±8.8	Etomidate: 84.0% Control: 96.0%	25/25	0.18 mg/kg; additional boli of 0.06 mg/kg	25	Eltanolone: 0.3 mg/kg; additional boli of 0.1 mg/kg	25	NA	NA	NA	NA	A critical decrease in blood pressure was defined as a 20% depression of MAP for at least 5 minutes. No details on what vasopressors were administered.	NA

13	Tassani (2)	1998	Germany	CABG	Etomidate: 57.4±8.6 Control: 60.7±9.4	Etomidate: 84.0% Control: 88.0%	25/25	0.18 mg/kg; additional boli of 0.06 mg/kg	25	Thiopental sodium: 1.8 mg/kg; additional boli of 0.6 mg/kg	25	NA	NA	NA	NA	A critical decrease in blood pressure was defined as a 20% depression of MAP for at least 5 minutes. No details on what vasopressors were administered.	NA
14	Djaiani	2001	UK	CABG	Etomidate: 62±8 Control: 61±9	Etomidate: 70.0% Control: 83.3%	10/12	0.2-0.3 mg/kg	10	Sevoflurane: 8%	12	Inhalation agents	NA	NA	NA	Hypotension (SAP < 90 mmHg) was initially treated by adjusting the depth of anesthesia and intravenous fluid challenges (colloid solution, 5-10 mL/kg). If hypotension persisted, boluses of metaraminol, 100-200 ug, were administered. No details on when vasopressors were required or administered.	NA
15	Uyar	1994	Turkey	CABG	Etomidate: 54.4±7.6 Control: 57.0±7.3	NA	15/15	0.25 mg/kg	15	Midazolam: 0.15 mg/kg	15	Inhalation agents	NA	NA	NA	NA	NA
16	Kling (1)	1987	Germany	CABG	NA	NA	10/10	0.3 mg/kg	10	Midazolam: 0.15 mg/kg	10	NA	NA	NA	NA	NA	NA
16	Kling (2)	1987	Germany	CABG	NA	NA	10/10	0.3 mg/kg	10	Thiopental: 5 mg/kg	10	NA	NA	NA	NA	NA	NA
16	Kling (3)	1987	Germany	CABG	NA	NA	10/10	0.3 mg/kg	10	Propofol: 2 mg/kg	10	NA	NA	NA	NA	NA	NA
16	Kling (4)	1987	Germany	CABG	NA	NA	10/10	0.3 mg/kg	10	Methohexital: 1 mg/kg	10	NA	NA	NA	NA	NA	NA

CABG, coronary artery bypass graft; MAP, mean arterial pressure; CPB, cardiopulmonary bypass; MVS, mitral valve surgery; AVR, aortic valve replacement; MVR, mitral valve replacement; MAC, minimum alveolar concentration; SAP, systolic arterial pressure.

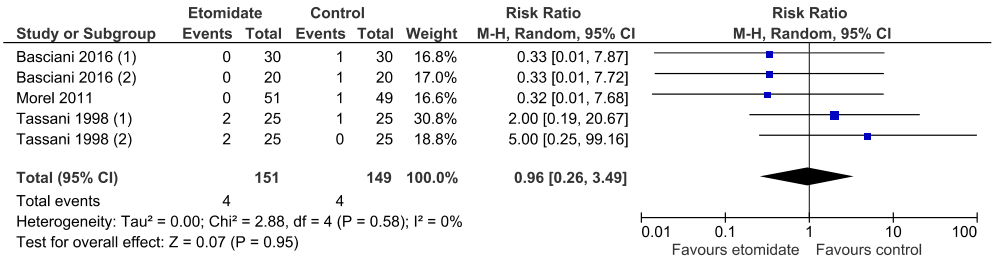


Fig. 3. Effect of etomidate on all-cause 30-day mortality.

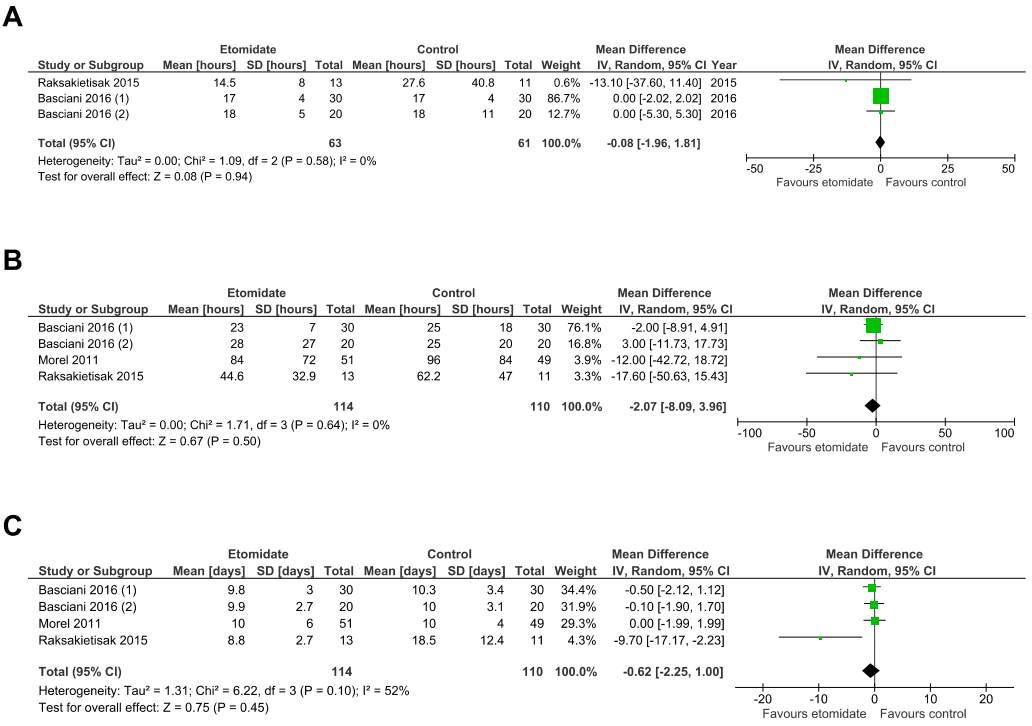


Fig. 4. Effect of etomidate on (A) duration of tracheal intubation in hours, (B) duration of ICU stay in hours, and (C) duration of hospital stay in days.

5.2. Duration of ICU stay

Three trials reported the effects of etomidate on the duration of ICU stay when compared to comparator drugs (Fig. 4B) [4,5,14]. The combined data suggested that there was no difference in the duration of ICU stay among patients receiving etomidate and comparator drugs (MD, −2.07 h; 95 % CI, −8.09 to 3.96; P = 0.50).

5.3. Duration of hospital stay

Three trials reported the effects of etomidate on the duration of hospital stay when compared to comparator drugs (Fig. 4C) [4,5,14]. The combined data suggested that there was no difference in the duration of hospital stay among patients receiving etomidate and comparator drugs (MD, −0.62 d; 95 % CI, −2.25 to 1.00; P = 0.45).

5.4. Hemodynamics and vasopressor requirement after induction and intubation

Ten studies reported the SBP, DBP, MAP, or HR before induction, before intubation, immediately after intubation, 1 min after intubation, 2 min after intubation or 3 min after intubation (Fig. 5) [2,3,9–11,13,16–19]. The SBP, DBP and HR of patients receiving

etomidate and comparator drugs were comparable before induction and before intubation. Immediately after intubation, the SBP, DBP and HR of the patients in the etomidate group were higher than that in the control groups (Fig. 5). The DBP and MAP of the patients receiving etomidate were also higher than those in the control groups at the time point of 1 min after intubation. However, at the time points of 2 min after intubation and 3 min after intubation, the MAP, SBP, and DBP of patients receiving etomidate and comparator drugs became similar. The HR was significantly lower in the etomidate group compared with the control at the time point of 3 min after intubation; for the rest of the other time points, the HR between the etomidate and control groups was comparable (Fig. 5). The calculation for other hemodynamic parameters is shown in Table 2.

Nine studies reported the use of vasopressors after induction and intubation of patients receiving etomidate compared with comparator drugs (Fig. 6) [2,3,11,12,15,17–20]. The requirement of vasopressors after induction and intubation was significantly reduced with etomidate compared with those with comparator drugs (RR, 0.37; 95 % CI, 0.25 to 0.56; $P < 0.00001$).

5.5. Cortisol levels and adrenal insufficiency

Three trials reported the cortisol levels of patients at different time points perioperatively [5,14,17]. The combined data showed that the cortisol levels were significantly lower in the patients with etomidate compared with those with comparator drugs during bypass until 12 h after induction (During bypass, MD, −5.46; 95 % CI, −6.69 to −4.23; $P < 0.00001$; after bypass, near the end of surgery, MD, −15.61; 95 % CI, −17.13 to −14.08; $P < 0.00001$; 8 h after induction, early period of induction, MD, −26.00; 95 % CI, −40.12 to −11.88; $P = 0.0003$; 12 h after induction, MD, −7.14; 95 % CI, −10.01 to −4.27; $P < 0.00001$) (See Fig. 7). The cortisol levels became comparable between patients receiving etomidate and comparator drugs beginning the first day post-surgery (Post--surgery day 1, MD, −2.88; 95 % CI, −6.54 to 0.78; $P = 0.12$; Post-surgery day 2, MD, −2.72; 95 % CI, −7.12 to 1.68; $P = 0.23$) (See Fig. 8).

Two studies reported the incidence of AI. Basciani et al. reported absolute AI, which was defined as a maximum serum cortisol concentration less than 500 nmol/L after ACTH stimulation, and relative AI, which was defined as an increase in serum cortisol concentration less than 248 nmol/L after ACTH stimulation irrespective of basal cortisol concentration [4]. They found that the incidence of relative AI was higher in patients receiving etomidate compared with propofol. The other study by Morel et al. reported adrenal insufficiency, which was defined as a cortisol response of less than 250 nmol/L after a 250 μg i. v. bolus of tetracosactide [14]. They found that the incidence of relative AI was higher in the etomidate group at 12 h and 24 h after anesthesia induction.

5.6. Adverse events

Perioperative adverse events were reported in several studies (Table 3). The reported adverse events were diverse and recorded at different time points following induction and intubation, and the definitions of AE in the included studies differed. Therefore, whether the use of etomidate is associated with an increased incidence of adverse events is inconclusive.

5.7. Myoclonus

Four studies included the incidence of myoclonus as an outcome of interest (Fig. 9) [13,16–18]. The analysis demonstrated that the use of etomidate tended to increase the risk of myoclonus compared with comparator drugs (RR, 5.00; 95 % CI, 0.91 to 27.56; $P = 0.06$) (see Fig. 10).

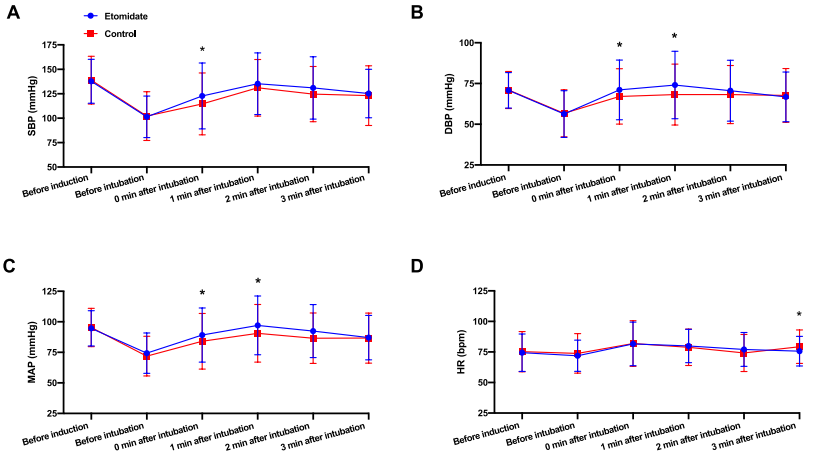


Fig. 5. Effect of etomidate on (A) systolic blood pressure in mmHg (SBP), (B) diastolic blood pressure (DBP) in mmHg, (C) mean arterial pressure (MAP) in mmHg, and (D) heart rate (HR) in bpm. Data are expressed as mean ± standard deviation (SD).

Table 2
Effects of etomidate on hemodynamic parameters.

Outcome	Time points	Studies	Participants	Statistical method	Effect estimate
Cardiac output (CO, L/min)	Before induction	4	182	MD (IV, random, 95 % CI)	0.04 [-0.43, 0.50]
	Before intubation	4	182	MD (IV, random, 95 % CI)	0.28 [-0.00, 0.57]
	0 min after intubation	2	82	MD (IV, random, 95 % CI)	0.07 [-0.22, 0.35]
	2 min after intubation	2	100	MD (IV, random, 95 % CI)	0.72 [-0.26, 1.70]
Cardiac index (CI, L/min/m^2)	Before induction	13	440	MD (IV, random, 95 % CI)	0.12 [-0.07, 0.30]
	Before intubation	8	300	MD (IV, random, 95 % CI)	0.16 [0.05, 0.27]
	0 min after intubation	2	90	MD (IV, random, 95 % CI)	0.04 [-0.13, 0.20]
	1 min after intubation	7	170	MD (IV, random, 95 % CI)	0.43 [0.16, 0.71]
	2 min after intubation	3	120	MD (IV, random, 95 % CI)	0.38 [-0.05, 0.80]
Stroke volume (SV, mL)	Before induction	4	190	MD (IV, random, 95 % CI)	−2.78 [-8.49, 2.92]
	Before intubation	3	130	MD (IV, random, 95 % CI)	2.90 [-3.33, 9.13]
	0 min after intubation	1	30	MD (IV, random, 95 % CI)	−1.00 [-12.47, 10.47]
	2 min after intubation	2	100	MD (IV, random, 95 % CI)	2.56 [-8.22, 13.34]
Stroke volume index (SVI, mL/beat/m^2)	Before induction	8	190	MD (IV, random, 95 % CI)	0.87 [-2.24, 3.97]
	Before intubation	4	110	MD (IV, random, 95 % CI)	1.10 [-1.47, 3.67]
	1 min after intubation	7	170	MD (IV, random, 95 % CI)	3.48 [-0.19, 7.15]
	2 min after intubation	1	20	MD (IV, random, 95 % CI)	0.00 [-6.87, 6.87]
Central venous pressure (CVP, mmHg)	Before induction	9	322	MD (IV, random, 95 % CI)	0.44 [-0.08, 0.97]
	Before intubation	9	322	MD (IV, random, 95 % CI)	0.65 [0.16, 1.14]
	0 min after intubation	3	112	MD (IV, random, 95 % CI)	−0.34 [-0.86, 0.18]
	1 min after intubation	3	90	MD (IV, random, 95 % CI)	0.24 [-1.85, 2.32]
	2 min after intubation	3	120	MD (IV, random, 95 % CI)	1.05 [0.06, 2.04]
Systemic vascular resistance (SVR, dyne·s/cm^5)	Before induction	5	212	MD (IV, random, 95 % CI)	−1.50 [-148.32, 145.31]
	Before intubation	5	212	MD (IV, random, 95 % CI)	70.68 [-24.40, 165.76]
	0 min after intubation	3	112	MD (IV, random, 95 % CI)	−69.51 [-263.54, 124.52]
	2 min after intubation	2	100	MD (IV, random, 95 % CI)	63.93 [-84.92, 212.77]
Systemic vascular resistance index (SVRI, dyne·s/cm^5/m^2)	Before induction	5	170	MD (IV, random, 95 % CI)	−0.27 [-211.24, 210.70]
	Before intubation	4	110	MD (IV, random, 95 % CI)	138.99 [-270.51, 548.48]
	1 min after intubation	3	90	MD (IV, random, 95 % CI)	365.67 [135.78, 595.56]
	2 min after intubation	1	20	MD (IV, random, 95 % CI)	−300.00 [-1014.39, 414.39]
Mean pulmonary arterial pressure (MPAP, mmHg)	Before induction	3	120	MD (IV, random, 95 % CI)	1.20 [-0.56, 2.95]
	Before intubation	3	120	MD (IV, random, 95 % CI)	1.58 [-0.47, 3.63]
	2 min after intubation	3	120	MD (IV, random, 95 % CI)	2.25 [0.56, 3.95]
Pulmonary capillary wedge pressure (PCWP, mmHg)	Before induction	6	272	MD (IV, random, 95 % CI)	0.65 [-0.37, 1.66]

(*continued on next page*)

Table 2 (*continued*)

Outcome	Time points	Studies	Participants	Statistical method	Effect estimate
	Before intubation	5	212	MD (IV, random, 95 % CI)	1.88 [1.26, 2.50]
	0 min after intubation	3	112	MD (IV, random, 95 % CI)	0.73 [-0.04, 1.50]
	2 min after intubation	2	100	MD (IV, random, 95 % CI)	1.60 [0.14, 3.20]
Pulmonary vascular resistance (PVR, dyne·s/cm^5)	Before induction	4	190	MD (IV, random, 95 % CI)	14.40 [2.37, 26.44]
	Before intubation	4	190	MD (IV, random, 95 % CI)	9.99 [-0.79, 20.77]
	0 min after intubation	2	90	MD (IV, random, 95 % CI)	7.41 [-1.99, 16.81]
	2 min after intubation	2	100	MD (IV, random, 95 % CI)	2.97 [-22.32, 28.25]

MD, mean difference; IV, inverse variance; CI, confidence interval.

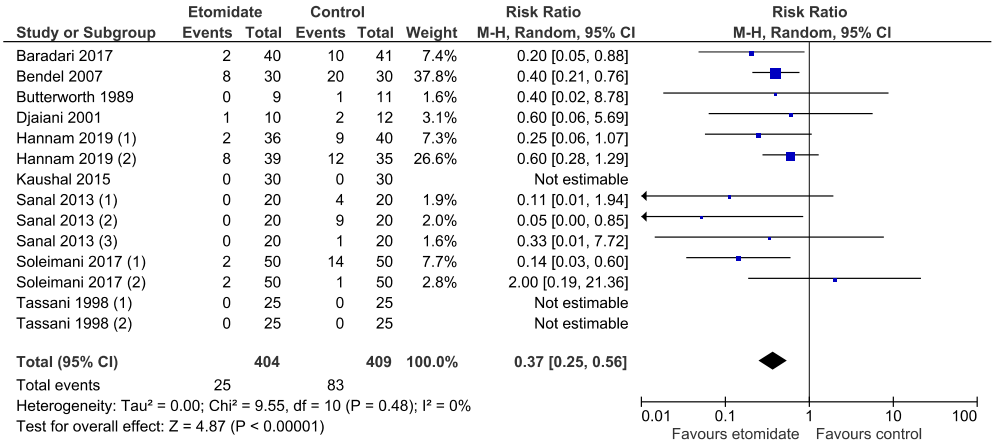


Fig. 6. Effect of etomidate on vasopressor requirement after induction and intubation.

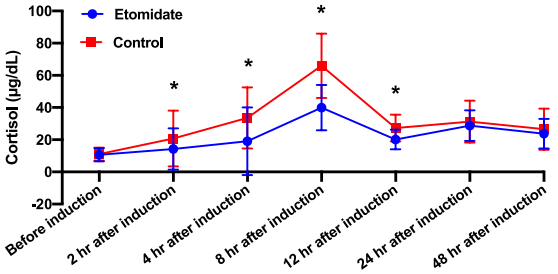


Fig. 7. Effect of etomidate and control on cortisol levels in µg/dL. Data are expressed as mean ± standard deviation (SD).

6. Discussion

This meta-analysis showed that etomidate did not affect the mortality of patients undergoing cardiac surgery compared with comparator drugs. There was no difference in the duration of tracheal intubation, the length of stay in ICU and hospital between etomidate and comparator drugs. The patients with etomidate demonstrated more stable hemodynamics after induction and intubation compared with those with comparator drugs. The requirement of vasopressor agents after induction and intubation was significantly reduced with etomidate compared with those with comparator drugs. Cortisol levels were significantly lower in the patients with etomidate compared with those with comparator drugs during bypass until 12 h after induction. The cortisol levels

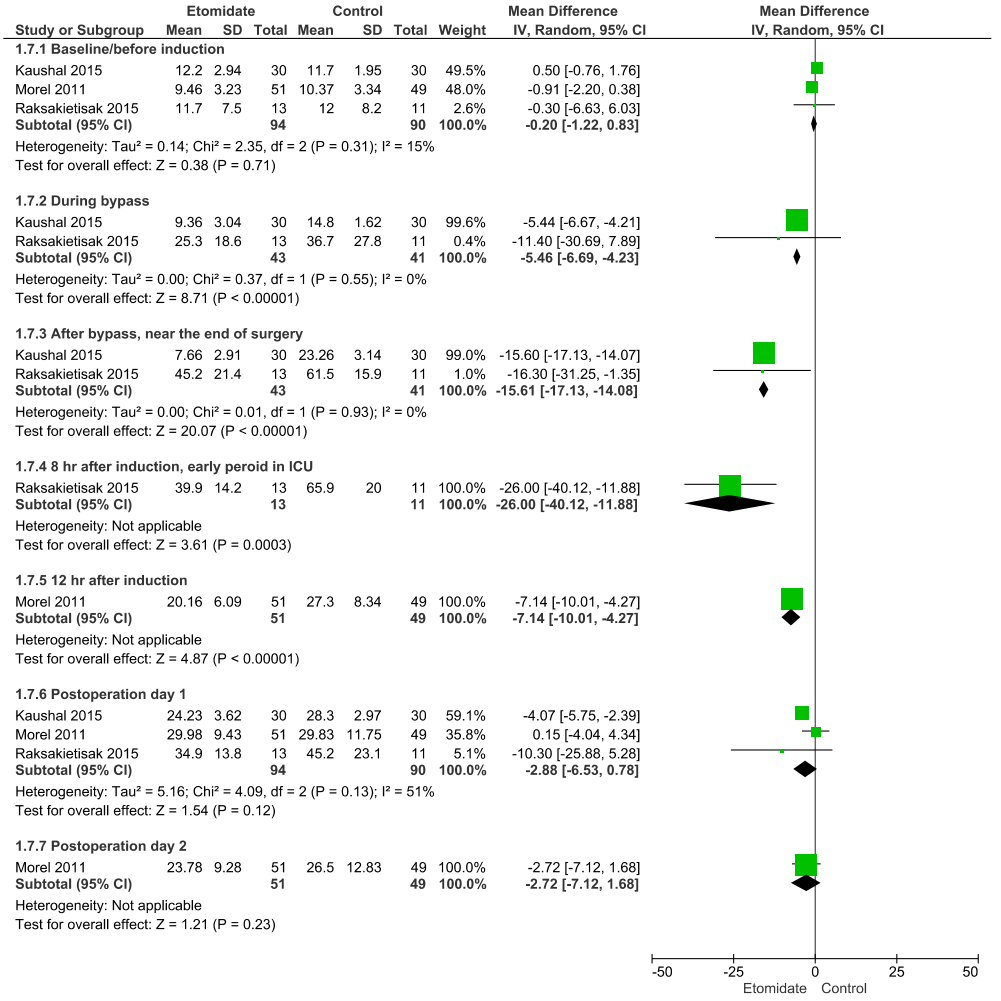


Fig. 8. Effect of etomidate on cortisol levels in μg/dL.

became comparable between patients with etomidate and comparator drugs from the first day post-surgery. The use of etomidate tended to increase the risk of myoclonus compared with comparator drugs.

Etomidate, an imidazole derivative, first introduced into clinical practice in 1972, causes peripheral vasoconstriction, which contributes to its cardiovascular stability. Etomidate does not inhibit myocardial contractility in the clinical concentration ranges and has little effects on heart rate and blood pressure in patients with cardiovascular diseases or under the condition of hemorrhagic shock [21–23].

Post-induction hypotension has been associated with adverse outcomes, including extended duration of ICU stays, and post-operative ventilation requirement, and increased morbidity [24,25]. Patients with a compromised cardiovascular system and a need for cardiac surgery demand sufficient sympathetic tone to maintain their blood pressure and cardiac output. Because of its benign hemodynamic effects, etomidate has been one of the hypnotic drugs of choice for general anesthetic induction in patients undergoing cardiac surgery, in those with poor cardiac function, and in those who are critically ill. Whether etomidate offers long-term beneficial effects needs further clinical investigation.

Adverse effects associated with etomidate include pain on injection, postoperative nausea and vomiting, and myoclonus during induction [26,27]. The major concern with the clinical use of etomidate is its ability to suppress adrenal steroidogenesis through inhibition of the enzyme 11β-hydroxylase, which lasts 48 h after a single induction does in critically ill patients without sepsis [28]. The clinical relevance of adrenal suppression after a single dose of etomidate for induction is controversial. In addition, whether etomidate impairs patient outcome depends on different clinical scenarios. A multicenter RCT that included patients that needed sedation for emergency intubation demonstrated that there was no difference in the mean maximum sequential organ failure assessment (SOFA) score, or the intubation conditions between the etomidate and ketamine groups; however, the incidence of adrenal

Table 3
Adverse events reported in the included clinical trials.

Event	Study	Etomidate		Control		Timepoint	Manifestations of adverse events
		Events	Total	Events	Total		
Myocardial ischemia	Butterworth 1989	3	9	0	11	Following induction and intubation	ST segment depression, or a large, new V wave during pulmonary artery balloon occlusion
	Butterworth 1989	4	8	6	9	Following operation	ST segment changes
	Tassani 1998 (1)	0	25	0	25	From baseline to 5 min after intubation	Based on ST-segment analysis and PCWP pressure tracing
	Tassani 1998 (2)	0	25	0	25	From baseline to 5 min after intubation	Based on ST-segment analysis and PCWP pressure tracing
Myocardial infarction	Butterworth 1989	2	8	0	9	Following operation	A new Q wave
Acute coronary syndrome	Morel 2011	4	51	6	49	Following operation	New Q waves or ST-segment elevation on a 12-lead electrocardiogram
Cardiovascular complications	Morel 2011	0	51	3	49	Following operation	Refractory cardiogenic shock, or ventricular arrhythmia with cardiogenic shock and cerebral stroke
Acute respiratory failure	Morel 2011	1	51	1	49	Following operation	NA
Acute renal failure	Morel 2011	1	51	1	49	Following operation	NA
Postoperative complications	Morel 2011	1	51	4	49	Following operation	Mediastinitis, or acute mediastinal bleeding
Atrial fibrillation	Raksakietisak 2015	3	13	3	11	Following operation	NA
	Sanal 2013 (1)	0	20	1	20	From baseline to 15 min after intubation	NA
Bradycardia	Raksakietisak 2015	0	13	1	11	Following operation	Bradycardia requiring permanent pacemaker
	Sanal 2013 (2)	0	20	1	20	From baseline to 15 min after intubation	NA
Cardiogenic pulmonary edema	Raksakietisak 2015	0	13	1	11	Following operation	NA
Ventricular extra systole	Sanal 2013 (1)	0	20	3	20	From baseline to 15 min after intubation	NA
Tachycardia	Sanal 2013 (1)	1	20	0	20	From baseline to 15 min after intubation	NA
	Sanal 2013 (2)	1	20	0	20	From baseline to 15 min after intubation	NA
	Sanal 2013 (3)	1	20	0	20	From baseline to 15 min after intubation	NA
Ventricular ectopic beats	Sanal 2013 (2)	0	20	1	20	From baseline to 15 min after intubation	NA
Adrenal crisis (unexplained hypotension, hyponatremia, hyperkalemia, or hypoglycemia)	Raksakietisak 2015	0	13	0	11	NA	NA
Delirium	Raksakietisak 2015	1	13	0	11	Following operation	NA

PCWP, pulmonary capillary wedge pressure.

insufficiency was significantly higher in the etomidate group [29]. Regarding septic patients whose adrenal cortical function may already be insufficient, a meta-analysis in 2012 that included randomized controlled trials and observational studies found that administration of etomidate for rapid sequence intubation is associated with higher rates of adrenal insufficiency and mortality in patients with sepsis [30]. To patients with a compromised cardiovascular system who are scheduled for cardiac surgery, it is important to maintain stable hemodynamics peri-operatively because of limited cardiac functional reserve, myocardial ischemic risk, or valvular heart disease. A prospective cohort study that included 120 elective cardiopulmonary bypass patients showed that 88 % of patients

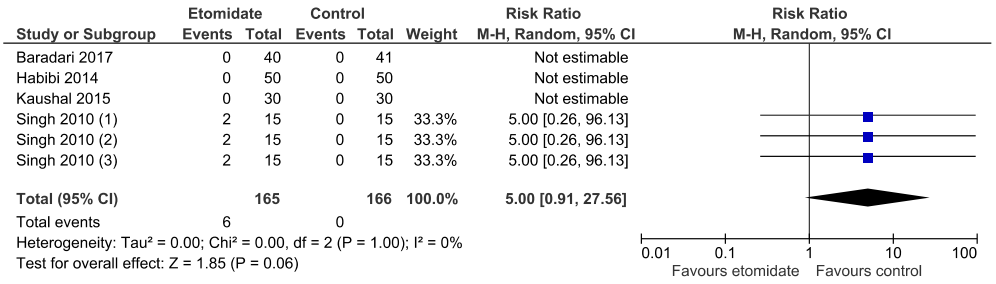


Fig. 9. Effects of etomidate on incidence of myoclonus.

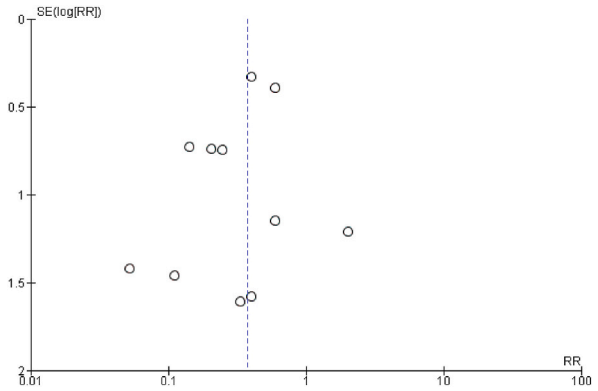


Fig. 10. Funnel plot.

that received etomidate developed relative adrenal insufficiency [31]. A retrospective cohort study that included 8978 patients who underwent CABG, valve, or combined valve/surgery, found that etomidate was not associated with increased incidence of post-operative atrial arrhythmia or increased intensive care unit or hospital stay [32]. In our study, the calculation demonstrated that cortisol levels were significantly lower in the patients with etomidate compared with those with comparator drugs until the first post-surgery day. These results align with the outcomes reported in a meta-analysis conducted by Yao et al., in 2021 [6].

In addition, etomidate may increase the risk of postoperative infections and sepsis, which is a fundamental concern for clinicians. A higher rate of hospital-acquired pneumonia was observed with the use of etomidate for anesthesia induction in trauma patients [33]. A large RCTs published in 2022 reported that, compared with propofol, more patients in the etomidate group developed pneumonia when used for induction and maintenance of general anesthesia in older patients undergoing abdominal surgery [34]. A recent retrospective study found that a single dose of etomidate, compared to propofol, is not statistically associated with higher post-operative sepsis rates in cardiac surgery but is associated with more hospital-acquired pneumonia [35]. However, after a thorough review of all included studies, we found that only two studies reported data on this aspect. Morel et al. reported that several patients died of postoperative mediastinitis but provided no further details [14]. Bendel et al. reported no differences in the incidence of infections after cardiac surgery between patients receiving propofol and those receiving etomidate [12]. Future RCTs on etomidate should include postoperative infections and sepsis as standardized endpoints, as defined by the Standardized Endpoints in Perioperative Medicine (StEP) initiative [36]. Future RCTs should consider reporting adverse effects, especially postoperative infections and sepsis, as well as providing a complete anesthesia protocol, including the actual etomidate doses, vasopressor use in the ICU, and steroid supplements post-surgery.

Several limitations should be pointed out when interpreting the results of the meta-analysis. First, heterogeneity was detected for some of the secondary outcomes. Types of cardiac surgeries, the clinical profiles of the included patients, severity of cardiovascular diseases, type of comparative drugs, and differences in clinical practice and anesthetic protocol varied across the included studies. In addition, although we incorporated the findings of all pertinent RCTs, our conclusion was derived from a relatively limited number of trials, which may potentially result in our study being underpowered to detect any concealed yet statistically significant differences between etomidate and comparator drugs, making the findings of no significant difference prone to a Type II error. Theoretically, an ideal RCT would require at least 4000 patients to detect a 10 % difference in mortality between the etomidate and comparator groups, based on our analysis. In summary, there is insufficient evidence to show that etomidate leads to worse outcomes, such as increased mortality, in patients undergoing cardiac surgery. However, this finding is based on a limited number of studies. Although the cortisol levels were lower in patients with etomidate until the first-day post-surgery, the incidence of adverse events was not increased compared with comparator drugs. Regarding that the requirement of vasopressors after induction and intubation was reduced with

etomidate compared with those with comparator drugs, and etomidate offered a more stable hemodynamic profile. Although this difference was statistically significant, it may not be clinically relevant given the lack of effect on all-cause 30-day mortality, ICU length of stay, and hospital length of stay, and these findings were based on a relatively small sample size. Larger, high-quality randomized trials of etomidate are needed for further investigation, with a focus on long-term mortality, and requirement of vasopressors in ICU.

In summary, this systematic meta-analysis found a significant heterogeneity among included studies. In addition, most studies focused only on the hemodynamic profile of etomidate. Thus, efficacy and safety of etomidate could not be answered within this context. Nevertheless, for patients undergoing cardiac surgery, etomidate seems to offer a minimal beneficial cardiovascular profile in comparison with other agents during induction and intubation. However, improved hemodynamics did not improve clinical outcomes as Etomidate did not affect mortality, duration of tracheal intubation, the length of stay in ICU and hospital. Finally, infectious side effects as one important trigger for increased mortality in ICU patients due to the use of Etomidate could not be analyzed as data were mostly missing.

Data availability statement

The data associated with the study has not been deposited into a publicly available repository. Our data is included in article/supp. material/referenced in the article. Raw data is available upon request.

Funding statement

This study was supported by NIH grant 2R01 HL126796 and partially supported by 1R01 HL-152160, 1R01HL-171602 and 1R01 HL-169205. Dr. Hanjun Wang is also supported by Margaret R. Larson Professorship in Anesthesiology. Dr. Irving H. Zucker is supported in part by the Theodore F. Hubbard Professorship for Cardiovascular Research. Dr. Steven J. Lisco is supported in part by the Myrna Newland, MD Professorship in Anesthesiology.

Ethics declarations

Not applicable because our study is a systematic review of randomized controlled trials to assess the impact of etomidate on patients undergoing cardiac surgery.

CRediT authorship contribution statement

Zhiqiu Xia: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Kajal Kamra:** Writing – review & editing, Methodology, Formal analysis, Data curation. **Jianghu Dong:** Writing – review & editing, Validation, Supervision, Methodology, Formal analysis, Data curation. **Kimberly A. Harp:** Writing – review & editing, Software, Methodology, Formal analysis, Data curation. **Ying Xiong:** Writing – review & editing, Validation, Software, Methodology, Formal analysis, Data curation. **Steven J. Lisco:** Writing – review & editing, Supervision, Resources, Conceptualization. **Irving H. Zucker:** Writing – review & editing, Visualization, Resources, Conceptualization. **Han-Jun Wang:** Writing – review & editing, Visualization, Supervision, Resources, Project administration, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:Hanjun Wang reports financial support was provided by National Institutes of Health. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2024.e38274.

References

[1] I.M. Ledingham, I. Watt, Influence of sedation on mortality in critically ill multiple trauma patients, Lancet 1 (1983) 1270, https://doi.org/10.1016/s0140-6736(83)92712-5.

[2] J.F.t. Butterworth, V.E. Bean, R.L. Royster, Sufentanil is preferable to etomidate during rapid-sequence anesthesia induction for aortocoronary bypass surgery, J. Cardiothorac. Anesth. 3 (1989) 396–400, https://doi.org/10.1016/s0888-6296(89)97219-0.

[3] P. Tassani, K. Martin, U. Janicke, S.O. Olsson, E. Ott, Induction of anesthesia by titration of eltanolone compared with thiopental and etomidate for coronary artery bypass grafting, J. Clin. Anesth. 10 (1998) 114–119, https://doi.org/10.1016/s0952-8180(97)00254-7.

[4] R.M. Basciani, A. Rindlisbacher, E. Begert, L. Brander, S.M. Jakob, R. Etter, T. Carrel, B. Eberle, Anaesthetic induction with etomidate in cardiac surgery: a randomised controlled trial, Eur. J. Anaesthesiol. 33 (2016) 417–424, https://doi.org/10.1097/eja.0000000000000434.

[5] M. Raksakietisak, C. Ngamlamiad, T. Duangrat, S. Soontarinka, K. Raksamani, The changes in cortisol levels during cardiac surgery: a randomized double-blinded study between two induction agents etomidate and thiopentone, J. Med. Assoc. Thai. 98 (2015) 775–781.

[6] Y.T. Yao, L.X. He, N.X. Fang, J. Ma, Anesthetic induction with etomidate in cardiac surgical patients: a PRISMA-compliant systematic review and meta-analysis, J. Cardiothorac. Vasc. Anesth. 35 (2021) 1073–1085, https://doi.org/10.1053/j.jvca.2020.11.068.

[7] D. Moher, A. Liberati, J. Tetzlaff, D.G. Altman, Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement, Ann. Intern. Med. 151 (2009) 264–269, https://doi.org/10.7326/0003-4819-151-4-200908180-00135, w264.

[8] J.P.T. Higgins, D.G. Altman, J.A.C. Sterne, in: J.P.T. Higgins, R. Churchill, J. Chandler, M.S. Cumpston (Eds.) Cochrane Handbook for Systematic Reviews of Interventions Version 5.2.0 (updated June 2017), Cochrane2017.

[9] D. Kling, H. Laubenthal, U. Börner, J. Boldt, G. Hempelmann, [Comparative hemodynamic study of anesthesia induction with propofol (Diprivan), thiopental, methohexital, etomidate and midazolam in patients with coronary disease], Anaesthesist 36 (1987) 541–547.

[10] M. Uyar, F.Z. Askar, B. Ulusoy, L. Erel, A. Certug, The hemodynamic effects of etomidate and midazolam during induction of anaesthesia for coronary artery bypass grafting surgery, Turk Anesteziyoloji ve Reanimasyon 22 (1994) 137–141.

[11] G.N. Djaiani, J. Hall, S. Pugh, R.T. Peaston, Vital capacity inhalation induction with sevoflurane: an alternative to standard intravenous induction for patients undergoing cardiac surgery, J. Cardiothorac. Vasc. Anesth. 15 (2001) 169–174, https://doi.org/10.1053/jcan.2001.21940.

[12] S. Bendel, E. Ruokonen, P. Pölönen, A. Uusaro, Propofol causes more hypotension than etomidate in patients with severe aortic stenosis: a double-blind, randomized study comparing propofol and etomidate, Acta Anaesthesiol. Scand. 51 (2007) 284–289, https://doi.org/10.1111/j.1399-6576.2006.01206.x.

[13] R. Singh, M. Choudhury, P.M. Kapoor, U. Kiran, A randomized trial of anesthetic induction agents in patients with coronary artery disease and left ventricular dysfunction, Ann. Card Anaesth. 13 (2010) 217–223, https://doi.org/10.4103/0971-9784.69057.

[14] J. Morel, M. Salard, C. Castelain, M.C. Bayon, P. Lambert, M. Vola, C. Auboyer, S. Molliex, Haemodynamic consequences of etomidate administration in elective cardiac surgery: a randomized double-blinded study, Br. J. Anaesth. 107 (2011) 503–509, https://doi.org/10.1093/bja/aer169.

[15] S. Şanal Baş, M.Ö. Erdemli, Effects of thiopental, propofol, etomidate, midazolam on hemodynamic state in anesthesia induction and intubation of hypertensive patients in the coronary artery bypass grafting surgery, Gogus-Kalp-Damar Anestezi ve Yogun Bakim Dernegi Dergisi 19 (2013) 161–167, https://doi.org/10.5222/GKDAD.2013.161.

[16] M.R. Habibi, A.G. Baradari, A. Soleimani, A. Emami Zeydi, H.S. Nia, A. Habibi, N. Onagh, Hemodynamic responses to etomidate versus ketamine-thiopental sodium combination for anesthetic induction in coronary artery bypass graft surgery patients with low ejection fraction: a double-blind, randomized, clinical trial, J. Clin. Diagn. Res. 8 (2014) Gc01–5, https://doi.org/10.7860/jcdr/2014/10237.5006.

[17] R.P. Kaushal, A. Vatal, R. Pathak, Effect of etomidate and propofol induction on hemodynamic and endocrine response in patients undergoing coronary artery bypass grafting/mitral valve and aortic valve replacement surgery on cardiopulmonary bypass, Ann. Card Anaesth. 18 (2015) 172–178, https://doi.org/10.4103/0971-9784.154470.

[18] A.G. Baradari, A. Alipour, M.R. Habibi, S. Rashidaei, A. Emami Zeydi, A randomized clinical trial comparing hemodynamic responses to ketamine-propofol combination (ketofol) versus etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery, Arch. Med. Sci. 13 (2017) 1102–1110, https://doi.org/10.5114/aoms.2016.63193.

[19] A. Soleimani, N. Heidari, M.R. Habibi, F.H. Kiabi, M. Khademloo, A. Emami Zeydi, F.B. Sohrabi, Comparing hemodynamic responses to diazepam, propofol and etomidate during anesthesia induction in patients with left ventricular dysfunction undergoing coronary artery bypass graft surgery: a double-blind, randomized clinical trial, Med. Arch. 71 (2017) 198–203, https://doi.org/10.5455/medarh.2017.71.198-203.

[20] J.A. Hannam, S.J. Mitchell, D. Cumin, C. Frampton, A.F. Merry, M.R. Moore, C.J. Kruger, Haemodynamic profiles of etomidate vs propofol for induction of anaesthesia: a randomised controlled trial in patients undergoing cardiac surgery, Br. J. Anaesth. 122 (2019) 198–205, https://doi.org/10.1016/j.bja.2018.09.027.

[21] H.P. Gelissen, A.H. Epema, R.H. Henning, H.J. Krijnen, P.J. Hennis, A. den Hertog, Inotropic effects of propofol, thiopental, midazolam, etomidate, and ketamine on isolated human atrial muscle, Anesthesiology 84 (1996) 397–403, https://doi.org/10.1097/00000542-199602000-00019.

[22] T.J. Ebert, M. Muzi, R. Berens, D. Goff, J.P. Kampine, Sympathetic responses to induction of anesthesia in humans with propofol or etomidate, Anesthesiology 76 (1992) 725–733, https://doi.org/10.1097/00000542-199205000-00010.

[23] K.B. Johnson, T.D. Egan, J. Layman, S.E. Kern, J.L. White, S.W. McJames, The influence of hemorrhagic shock on etomidate: a pharmacokinetic and pharmacodynamic analysis, Anesth. Analg. 96 (2003) 1360–1368, https://doi.org/10.1213/01.Ane.0000055804.30509.69.

[24] R.S. Green, M.B. Butler, Postintubation hypotension in general anesthesia: a retrospective analysis, J. Intensive Care Med. 31 (2016) 667–675, https://doi.org/10.1177/0885066615597198.

[25] R.S. Green, A.F. Turgeon, L.A. McIntyre, A.E. Fox-Robichaud, D.A. Fergusson, S. Doucette, M.B. Butler, M. Erdogan, Postintubation hypotension in intensive care unit patients: a multicenter cohort study, J. Crit. Care 30 (2015) 1055–1060, https://doi.org/10.1016/j.jcrc.2015.06.007.

[26] B.I. Valk, M. Struys, Etomidate and its analogs: a review of pharmacokinetics and pharmacodynamics, Clin. Pharmacokinet. 60 (2021) 1253–1269, https://doi.org/10.1007/s40262-021-01038-6.

[27] S.A. Forman, Clinical and molecular pharmacology of etomidate, Anesthesiology 114 (2011) 695–707, https://doi.org/10.1097/ALN.0b013e3181ff72b5.

[28] M. Vinclair, C. Broux, P. Faure, J. Brun, C. Genty, C. Jacquot, O. Chabre, J.F. Payen, Duration of adrenal inhibition following a single dose of etomidate in critically ill patients, Intensive Care Med. 34 (2008) 714–719, https://doi.org/10.1007/s00134-007-0970-y.

[29] P. Jabre, X. Combes, F. Lapostolle, M. Dhaouadi, A. Ricard-Hibon, B. Vivien, L. Bertrand, A. Beltramini, P. Gamand, S. Albizzati, D. Perdrizet, G. Lebail, C. Chollet-Xemard, V. Maxime, C. Brun-Buisson, J.Y. Lefrant, P.E. Bollaert, B. Megarbane, J.D. Ricard, N. Anguel, E. Vicaut, F. Adnet, Etomidate versus ketamine for rapid sequence intubation in acutely ill patients: a multicentre randomised controlled trial, Lancet 374 (2009) 293–300, https://doi.org/10.1016/s0140-6736(09)60949-1.

[30] C.M. Chan, A.L. Mitchell, A.F. Shorr, Etomidate is associated with mortality and adrenal insufficiency in sepsis: a meta-analysis, Crit. Care Med. 40 (2012) 2945–2953, https://doi.org/10.1097/CCM.0b013e31825fec26.

[31] J.L. Iribarren, J.J. Jiménez, D. Hernández, L. Lorenzo, M. Brouard, A. Milena, M.L. Mora, R. Martínez, Relative adrenal insufficiency and hemodynamic status in cardiopulmonary bypass surgery patients. A prospective cohort study, J. Cardiothorac. Surg. 5 (2010) 26, https://doi.org/10.1186/1749-8090-5-26.

[32] R. Komatsu, N. Makarova, J. You, D.I. Sessler, D.G. Anthony, Y. Kasuya, E.G. Soltesz, A. Turan, Etomidate and the risk of complications after cardiac surgery: a retrospective cohort analysis, J. Cardiothorac. Vasc. Anesth. 30 (2016) 1516–1522, https://doi.org/10.1053/j.jvca.2016.04.022.

[33] K. Asehnoune, P.J. Mahe, P. Seguin, S. Jaber, B. Jung, C. Guitton, N. Chatel-Josse, A. Subileau, A.C. Tellier, F. Masson, B. Renard, Y. Malledant, C. Lejus, C. Volteau, V. Sébille, A. Roquilly, Etomidate increases susceptibility to pneumonia in trauma patients, Intensive Care Med. 38 (2012) 1673–1682, https://doi.org/10.1007/s00134-012-2619-8.

[34] Z. Lu, H. Zheng, Z. Chen, S. Xu, S. Chen, W. Mi, T. Wang, X. Chai, Q. Guo, H. Zhou, Y. Yu, X. Zheng, J. Zhang, Y. Ai, B. Yu, H. Bao, H. Zheng, W. Huang, A. Wu, X. Deng, H. Ma, W. Ma, L. Tao, X. Yang, J. Zhang, T. Liu, H.P. Ma, W. Liang, X. Wang, Y. Zhang, W. Du, T. Ma, Y. Xie, Y. Xie, N. Li, Y. Yang, T. Zheng, C. Zhang, Y. Zhao, R. Dong, C. Zhang, G. Zhang, K. Liu, Y. Wu, X. Fan, W. Tan, N. Li, H. Dong, L. Xiong, Effect of etomidate vs propofol for total intravenous anesthesia on major postoperative complications in older patients: a randomized clinical trial, JAMA Surg 157 (2022) 888–895, https://doi.org/10.1001/jamasurg.2022.3338.

[35] B. Weiss, F. Schiefenhövel, J.J. Grunow, M. Krüger, C.D. Spies, M. Menk, J. Kruppa, H. Grubitzsch, M. Sander, S. Treskatsch, F. Balzer, Infectious complications after etomidate vs. Propofol for induction of general anesthesia in cardiac surgery-results of a retrospective, before-after study, J. Clin. Med. 10 (2021), https://doi.org/10.3390/jcm10132908.

[36] J. Barnes, J. Hunter, S. Harris, M. Shankar-Hari, E. Diouf, I. Jammer, C. Kalkman, A.A. Klein, T. Corcoran, S. Dieleman, M.P.W. Grocott, M.G. Mythen, Systematic review and consensus definitions for the Standardised Endpoints in Perioperative Medicine (StEP) initiative: infection and sepsis, Br. J. Anaesth. 122 (2019) 500–508, https://doi.org/10.1016/j.bja.2019.01.009.