Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-201 Remimazolam

Stand: August 2021

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Remimazolam
[zur Einleitung und Aufrechterhaltung der allgemeinen Anästhesie]

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“.
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	„nicht angezeigt“
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Es liegen keine Beschlüsse vor.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	Siehe systematische Literaturrecherche

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Remimazolam	Geplantes Anwendungsgebiet laut Beratungsantrag: Ein kurzwirksames Benzodiazepin zur Einleitung und Aufrechterhaltung der allgemeinen Anästhesie bei erwachsenen Patienten.
Propofol N01AX10 Propofol 1 %	Propofol 1 % (10 mg/1 ml) MCT Fresenius ist ein kurz wirkendes intravenöses Narkosemittel zur • **Einleitung und Aufrechterhaltung einer Narkose bei Erwachsenen, Jugendlichen und Kindern über 1 Monat** • Sedierung bei chirurgischen und diagnostischen Maßnahmen, allein oder in Kombination mit einer Lokal- oder Regionalanästhesie bei Erwachsenen, Jugendlichen oder Kindern über 1 Monat • Sedierung von beatmeten Patienten über 16 Jahre im Rahmen der Intensivbehandlung
Midazolam N05C D08 Midazolam B. Braun 1 mg/ml Injektions-/ Infusionslösung	Midazolam B. Braun ist ein kurz wirksames Sedativum mit folgenden Indikationen: Bei Erwachsenen • ANALGOSEDIERUNG (bei erhaltenem Bewusstsein) vor und während diagnostischer Verfahren oder therapeutischer Eingriffe mit oder ohne Lokalanästhesie • **ANÄSTHESIE** o Prämedikation vor Anästhesieeinleitung o Anästhesieeinleitung o Als sedierende Komponente bei Kombinationsnarkosen • SEDIERUNG AUF DER INTENSIVSTATION
Ketamin Ketamin Inresa Injektionslösung	Ketamin Inresa 10 ml ist ein Mittel zur Narkosedurchführung. Ketamin Inresa 10 ml wird angewendet: • **zur Einleitung und Durchführung einer Allgemeinanästhesie (Vollnarkose)**, ggf. in Kombination mit Schlafmitteln (Hypnotika), • zur Ergänzung bei Regionalanästhesien (örtliche Betäubung), • zur Anästhesie und Schmerzbekämpfung (Analgesie) in der Notfallmedizin, • zur Behandlung von häufigen und dauerhaften Anfällen von Atemnot (therapieresistenter Status asthmaticus), • zur Schmerzbekämpfung bei künstlicher Beatmung (Intubation)

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Esketamin Esketamin Ethypharm 25 mg/ml Injektions-/Infusionslösung	• **Zur Einleitung und Aufrechterhaltung einer Allgemeinanästhesie, als einziges Anästhetikum oder in Kombination mit einem anderen Anästhetikum.** • Zur Anästhesie und Schmerzbekämpfung (Analgesie) in der Notfallmedizin. • Zur Ergänzung einer Regional- oder Lokalanästhesie.
Sufentanil	<u>Intravenöse Anwendung</u> • Die intravenöse Anwendung von Sufentanil ist indiziert zur Anästhesie bei allen medizinischen Maßnahmen, bei denen endotracheale Intubation und Beatmung durchgeführt werden: als analgetische Komponente während Einleitung und Aufrechterhaltung von Kombinationsnarkosen • als Monoanästhetikum.
Thiopental Thiopental Inresa 0,5 g	Kurznarkose ohne Intubation (kurzzeitige Betäubung während einer Operation ohne Vorbereitungen für eine künstliche Beatmung). **Einleitung einer Allgemeinanästhesie mit oder ohne Intubation** (Einleitung einer längeren Betäubung für Operationen mit oder ohne Vorbereitungen für eine künstliche Beatmung). Hinweis: Bei Anästhesie mit diesem Arzneimittel ist wie bei allen Barbituraten die Gabe eines Analgetikums erforderlich.
Etomidat Etomidat-®Lipuro 2 mg/ml Emulsion zur Injektion	Etomidat-Lipuro ist indiziert zur Einleitung einer Allgemeinanästhesie bei Erwachsenen, Säuglingen und Kleinkindern ab 6 Monaten sowie Kindern und Jugendlichen. Zur Kurznarkose (nur in Verbindung mit einem Analgetikum).
Isofluran Isofluran Baxter	Isofluran Baxter ist ein flüchtiges, halogeniertes Inhalationsanästhetikum zur Einleitung und Aufrechterhaltung einer Vollnarkose.
Sevofluran Sevofluran Baxter	Einleitung und Aufrechterhaltung einer Vollnarkose bei Erwachsenen und Kindern.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Desfluran Desfluran Piramal 100 % (v/v) Flüssigkeit zur Herstellung eines Dampfs zur Inhalation	Desfluran Piramal ist angezeigt zur Einleitung und Aufrechterhaltung einer Allgemeinnarkose bei stationären und ambulanten Eingriffen an Erwachsenen sowie zur Aufrechterhaltung einer Allgemeinnarkose bei Kleinkindern und Kindern.
Distickstoff-monoxid Distickstoff-monoxid medicAL 100% (V/V)	Im Gemisch mit Sauerstoff: Zur Analgesie unter stationären Bedingungen in der klinischen Geburtshilfe. **Zur Anästhesie-Einleitung und im Rahmen einer Kombinationsnarkose.**
Xenon Xenon pro Anaesthesia 100 % (V/V)	Dieses Arzneimittel eignet sich zur Aufrechterhaltung einer Narkose in Kombination mit anderen volatilen Anästhetika und/oder Opioiden im Rahmen einer balanzierten Anästhesie bei Erwachsenen der ASA-Klassen I-III. Über den Einsatz dieses Arzneimittels bei Patienten mit koronarer Herzerkrankung und/oder schwer eingeschränkter kardialer Funktion liegen bisher keine ausreichenden Erkenntnisse vor.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2021-B-201 (Remimazolam)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	2. August 2021

Inhaltsverzeichnis

Abkürzungsverzeichnis

AKI	Acute kidney injury
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CABG	Coronary artery bypass grafting
CK-MB	Postoperative levels of creatine kinase
CPB	Cardiopulmonary bypass
CTnI	blood cardiac troponin I
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
HR	Hazard Ratio
ICU	Intensive care unit
INHA	inhalational
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV	intravenös
KI	Konfidenzintervall
LoE	Level of Evidence
MAP	Mean arterial pressure
MMSE	Mini-mental state examination
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
OVL	one lung ventilation
PACU	Postanaesthesia care unit
POCD	Postoperative cognitive dysfunction
POD	Postoperative delirium
PONV	Postoperative nausea and vomitting
RR	Relatives Risiko
SIGN	Scottish Intercollegiate Guidelines Network
SUCRA	Surface under the cumulative ranking curve
TIVA	Total intravenous anaesthesia
TRIP	Turn Research into Practice Database
TSA	Trial sequential analysis
VIMA	Volatile induction and maintenance anaesthesia
WHO	World Health Organization

1 Indikation

Einleitung und Aufrechterhaltung der allgemeinen Anästhesie bei erwachsenen Patienten.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Allgemeinanästhesie durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 13.07.2021 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1368 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 14 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA-Beschlüsse/IQWiG-Berichte

Es konnten keine G-BA-Beschlüsse und/ oder IQWiG-Berichte identifiziert werden.

3.2 Cochrane Reviews

Miller D et al., 2018 [7].

Intravenous versus inhalational maintenance of anaesthesia for postoperative cognitive outcomes in elderly people undergoing non-cardiac surgery (Review)

Fragestellung

To compare maintenance of general anaesthesia for elderly people undergoing non-cardiac surgery using propofol-based TIVA or inhalational anaesthesia on postoperative cognitive function, mortality, risk of hypotension, length of stay in the postanaesthesia care unit (PACU), and hospital stay.

Methodik

Population:

- Participants aged 60 years and above, undergoing surgery under general anaesthesia.

Intervention:

- maintenance of anaesthesia with propofol-based TIVA

Komparator:

- inhalational anaesthesia (inhalational maintenance anaesthesia included both inhalational and IV induction of anaesthesia)

Endpunkte:

- Postoperative delirium; Postoperative cognitive dysfunction; Mortality at 30 days; Intraoperative hypotension as defined by the study authors (for example, mean arterial pressure (MAP) < 65 mmHg, drop in MAP > 20% from baseline value); Length of stay in the PACU (measured as minutes); Length of hospital stay (measured as days).

Recherche/Suchzeitraum:

- Bis November 2017 (u.a. Cochrane Register, Medline)

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 28 RCTs (n= 4507 participants)

Charakteristika der Population:

- 75% of participants were > 60 years of age

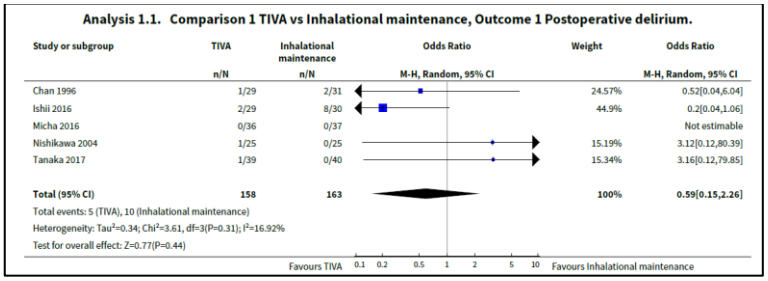
- Unterschiedliche Operationen: vascular surgery; laparoscopic surgery:; abdominal surgery; orthopaedic surgery; ophthalmic surgery
- All studies compared total intravenous anaesthesia (TIVA) using propofol versus maintenance anaesthesia using inhalational agents.
  - Ten studies described propofol anaesthesia using target-controlled infusion (TCI)
  - Nineteen studies compared TIVA versus maintenance using sevoflurane
  - Eight studies compared TIVA versus maintenance using isoflurane
  - Three studies compared TIVA versus maintenance using desflurane
  - One study described the comparator as volatile induction and maintenance anaesthesia (VIMA) and did not report details of the anaesthetic agents

Qualität der Studien:

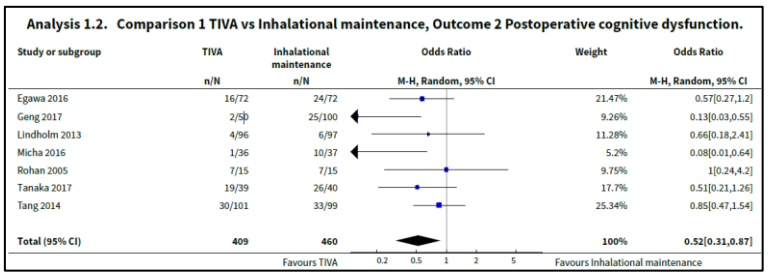
- We found insufficient reporting of randomization methods in many studies and all studies were at high risk of performance bias because it was not feasible to blind anaesthetists to study groups. Thirteen studies described blinding of outcome assessors. Three studies had a high of risk of attrition bias, and we noted differences in the use of analgesics between groups in six studies, and differences in baseline characteristics in five studies. Few studies reported clinical trials registration, which prevented assessment of risk of selective reporting bias.

Studienergebnisse:

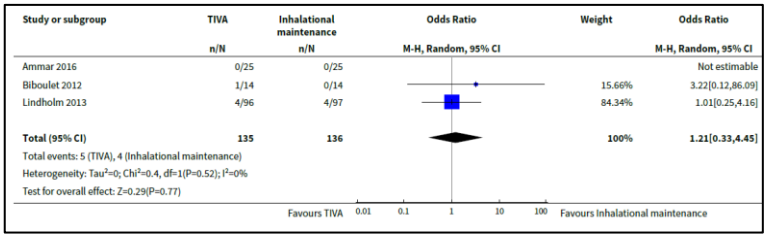
- Comparison 1 TIVA vs Inhalational maintenance, Outcome 1 Postoperative delirium. (n=5 Studien)



- Comparison 1 TIVA vs Inhalational maintenance, Outcome 2 Postoperative cognitive dysfunction (n=7 Studien)



- Comparison 1 TIVA vs Inhalational maintenance, Outcome 3 Mortality (n=3)



- We found little or no difference in postoperative delirium according to the type of anaesthetic maintenance agents from five studies (321 participants). We found that fewer people experienced postoperative cognitive dysfunction when TIVA with propofol was used in seven studies (869 participants). We excluded one study from analysis of this outcome because study authors had used methods to anaesthetize people which were not standard.
- We found little or no difference in the number of deaths from three studies (271 participants). We did not combine data for low blood pressure during the operation or length of stay in the PACU because we noted differences in studies, which may be explained by differences in patient management (for low blood pressure), and differences in how length of stay in the PACU is defined in each study . We found little or no difference in length of hospital stay from four studies (175 participants).

Anmerkung/Fazit der Autoren

We are uncertain whether maintenance with propofol-based total intravenous anaesthesia (TIVA) or with inhalational agents affect incidences of postoperative delirium, mortality, or length of hospital stay. We identified 28 studies, which assessed the effect of propofol-based TIVA versus inhalational maintenance in elderly surgical patients. Few of the included studies reported the effect on postoperative delirium.

We found no evidence of a difference in postoperative delirium according to type of anaesthetic agents used and we judged this evidence to be very low certainty. We found low-certainty evidence that propofol-based TIVA may reduce postoperative cognitive dysfunction (POCD). We were unable to ascertain any effect on length of stay in postanaesthesia care unit (PACU); we judged this evidence to be very low certainty, and we were unable to ascertain any effect on intraoperative hypotension for which we judged the evidence to be low certainty. We found little or no evidence of a difference in mortality and length of hospital stay, but this evidence was very low certainty.

3.3 Systematische Reviews

Cui Y et al., 2020 [5].

The effect of perioperative anesthetics for prevention of postoperative delirium on general anesthesia: A network meta-analysis

Fragestellung

Postoperative delirium (POD) is a common neurological system disorder in surgical patients. Anesthesia providers have a wide choice of sedative agents involving different mechanisms in clinical practice, and the incidence of POD varies regarding which sedative agent administered. This network meta-analysis aimed to comprehensively analyze the safety and efficacy of each choice for patients.

Methodik

Population:

- adults (≥18 years and older without sex restriction) without a history of delirium, severe dementia, Alzheimer's disease, schizophrenia, or moderate to severe depression undergoing general anesthesia

Intervention/ Komparator:

- sevoflurane, desflurane, isoflurane, dexmedetomidine, propofol, midazolam, and ketamine were enrolled in this meta-analysis. In our study, placebo referred to normal saline.

Endpunkte:

- incidence of POD, perioperative hypotension, bradycardia and postoperative nausea and vomiting

Recherche/Suchzeitraum:

- September 2018 (u.a. PubMed, Cochrane)

Qualitätsbewertung der Studien:

- Cochrane Collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 39 RCTs (5991 patients)

Charakteristika der Population:

- Overall, 4166 subjects were randomly assigned to an active anesthetic and 1825 to placebo.
- 12 were cardiac surgery [13,15,30,35,38–40,43–46,59], and 27 noncardiac surgery RCTs [8,12,14,31–34,36,37,41,42,47–58,60–62] which included thoracic surgery, spine surgery, total hip arthroplasty, major abdominal surgery, laparoscopic surgery, and other elective non-cardiac surgery under general anesthesia
- Isoflurane was not enrolled in the final analysis because of no relevant RCT.

Qualität der Studien:

- Concerning the blinding of patients, investigators, and assessors, 22 trials were rated as low risk with double- or triple-blinded and 11 RCTs were ranked as a high or unclear risk because the blinding was either open-label or not mentioned. Small study bias or any publication bias was not observed in comparison-adjusted funnel plot

Studienergebnisse:

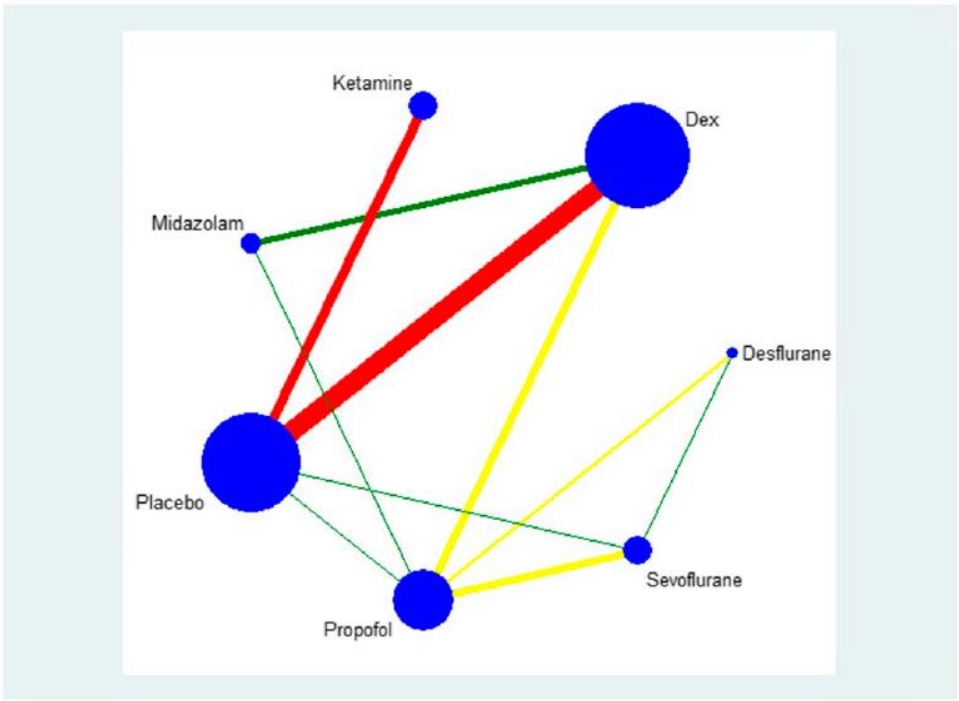


Fig. 2. The network geometry (the incidence of delirium) using colored edges according to blinding estimated as the level of bias in most of the trials and weighted according to the number of studies in each comparison. Width of the lines was the number of trials comparing pairwise intervention. Size of every blue circle was the proportion of sample size. Green, yellow and red colors were used to denote pairwise meta-analyses of low, unclear and high risk of bias. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

Postoperative delirium (POD)

- Midazolam (OR 5.97; 95% CI 2.63 to 13.56), propofol (OR 3.79; 95% CI 1.81 to 7.91), desflurane (OR 3.81; 95% CI 1.08 to 13.43) and sevoflurane (OR 5.62; 95% CI 2.00 to 15.80) were not as effective at reducing POD as dexmedetomidine. Compared with placebo, dexmedetomidine was associated with a lower incidence of delirium (OR 0.44; 95% CI 0.30 to 0.64), whereas midazolam was associated with a significantly higher number of patients with delirium (OR 2.62; 95% CI 1.07 to 6.43). Additionally, ketamine was superior (OR 0.30; 95% CI 0.09 to 0.99) to midazolam for the prevention of POD.
- To reduce bias, we performed subgroup analysis according to different clinical scenarios, i.e., focusing on choice of primary anesthetic agent, intraoperative adjuncts that are administered in addition to the primary anesthetic agent or sedation in the intensive care unit, respectively. Compared with placebo, dexmedetomidine had a lower incidence of POD (OR 1.83; 95% CI 1.21 to 2.77) when it was used as an intraoperative adjunct in addition to primary agents. There were no significant differences among propofol, sevoflurane and desflurane when they were used as the primary anesthesia agent.
- Dexmedetomidine was better than midazolam (OR 0.09; 95% CI 0.02 to 0.35), propofol (OR 0.03; 95% CI 0.00 to 0.34), and placebo (OR 0.45; 95% CI 0.27 to 0.73) at reducing POD when they were used as postoperative sedative agents

Perioperative hypotension, bradycardia and postoperative nausea and vomiting

- There were 17 studies which included 3301 subjects that reported perioperative hypotension [8,12,14,16,31,32,34–36,38,39,41,49, 51,54,59,60]. The result revealed that placebo had a lower incidence of perioperative hypotension (OR 0.76; 95% CI 0.61 to 0.95 and OR 0.32; 95% CI 0.15 to 0.68 respectively) than midazolam and propofol. There was no significant difference among the rest of the sedative agents
- Of the 39 enrolled studies, 15 studies listed the incidence of bradycardia [8,14,16,31,32,34–36,38,39,41,49,51,54,60]. Overall, the incidence of bradycardia was significantly higher when propofol or midazolam was given compared to placebo (OR 0.63, 95% CI 0.49–0.81; OR 0.32, 95% CI 0.16–0.65, respectively) (Fig. 6). Moreover, there was no significant difference among enrolled sedative agents in the occurrence of PONV

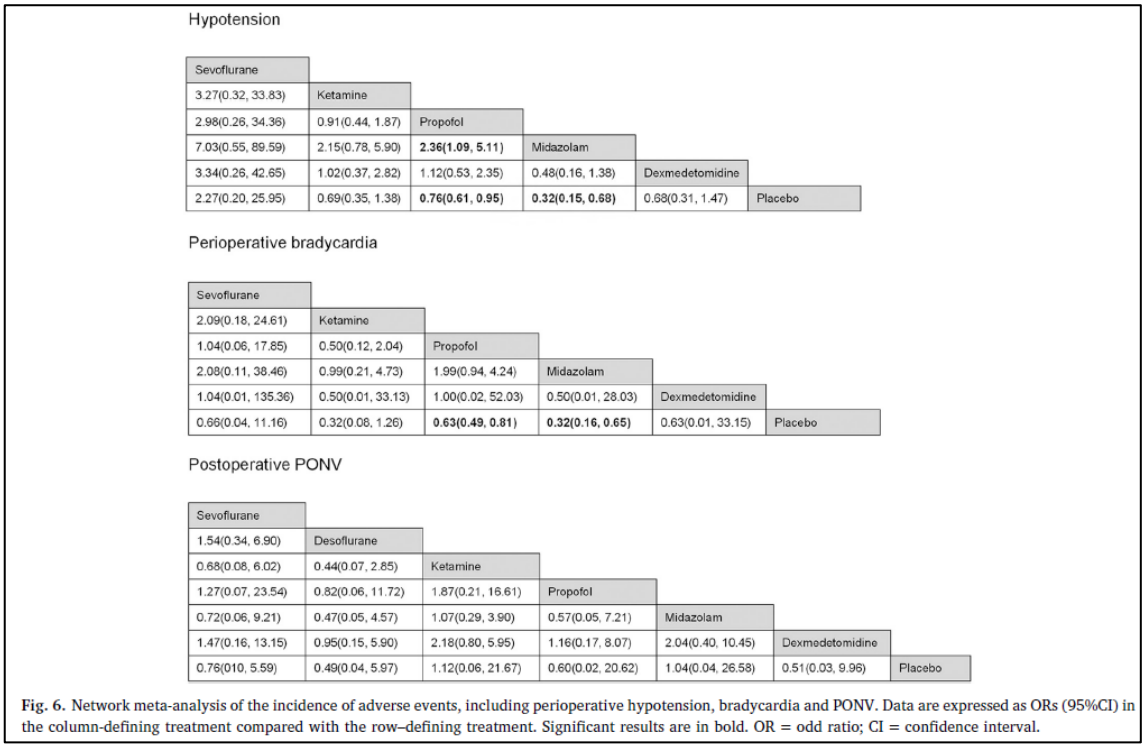


Fig. 6. Network meta-analysis of the incidence of adverse events, including perioperative hypotension, bradycardia and PONV. Data are expressed as ORs (95%CI) in the column-defining treatment compared with the row–defining treatment. Significant results are in bold. OR = odd ratio; CI = confidence interval.

Ranking probabilities

In the ranking probability plot (Fig. 7), dexmedetomidine seemed to be the best agent among all the treatments. The SUCRA values provided the hierarchy for the seven treatments; 64.6%, 98.2%, 15.5%, 41.4%, 73.0%, 39.7%, 17.8% for placebo, dexmedetomidine, midazolam, propofol, ketamine, desflurane, sevoflurane, respectively. We also adjusted the results from a network meta-regression accounting for small study effects, and the variance of the log-odds ratios was used as the covariate. However, no significant rankings change was observed. However, for cardiac patients, ketamine was the best agent based on the estimated probabilities (Desflurane: 27.5%; Dexmedetomidine: 79.3%; Ketamine: 96.7%; Midazolam: 18.6%; Placebo: 47.6%; Propofol: 30.6%) (Fig. 8). For non-cardiac patients, dexmedetomidine was the best choice among all treatments

Anmerkung/Fazit der Autoren

In summary, we used a scientific approach to provide evidence that dexmedetomidine could be considered as a safe and effective sedative agent to reduce POD without obvious

adverse events. However, the results should be interpreted cautiously due to the limitations of the enrolled studies. Clinical practitioners should weigh the pros and cons before choosing a sedative agent for each patient.

Beverstock J et al., 2021 [1].

A Comparison of Volatile Anesthesia and Total Intravenous Anesthesia (TIVA) Effects on Outcome From Cardiac Surgery: A Systematic Review and Meta-Analysis

Fragestellung

The primary objective of this study was to compare one-year mortality in patients undergoing cardiac surgery with volatile anesthesia or total intravenous anesthesia (TIVA). Secondary objectives were to compare in-hospital and 30-day mortality, postoperative levels of creatine kinase (CK-MB) and cardiac troponin, and durations of tracheal intubation, intensive care unit (ICU) and hospital stays.

Methodik

Population:

- Adults patients undergoing heart surgery

Intervention:

- Volatile anesthesia

Komparator:

- TIVA

Endpunkte:

- (1) mortality (in-hospital, at 30 days and at one year); (2) 24-hour postoperative blood cardiac troponin I (CTnI) levels; (3) 24-hour postoperative blood CK-MB levels as markers of a myocardial adverse event; (4) duration of tracheal intubation; and (5) ICU and (6) hospital stays.

Recherche/Suchzeitraum:

- until October 13, 2020 (u.a. Medline)

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions method.

Ergebnisse

Anzahl eingeschlossener Studien:

- 40 RCTs

Charakteristika der Population:

- Six papers reported on mortality one year after surgery and mortality after 30 days
- 11 papers on duration of tracheal intubation
- 11 papers on CK-MB level 24 hours
- 12 papers on duration of hospital stay
- 14 papers on in-hospital mortality

- 16 papers on duration of ICU stay
- 25 papers on CTnI level 24 hours postoperatively

Qualität der Studien:

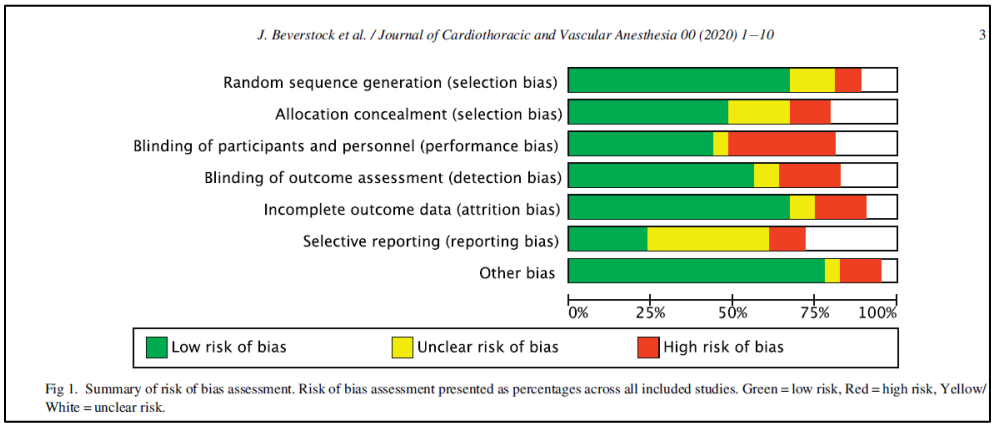


Fig 1. Summary of risk of bias assessment. Risk of bias assessment presented as percentages across all included studies. Green = low risk, Red = high risk, Yellow/White = unclear risk.

Studienergebnisse:

- Nineteen RCTs reported mortality after surgery over three different time periods—during the hospital stay and 30 days and one year after surgery. Six RCTs (n = 6,440) reported mortality one year after cardiac surgery. At one year after surgery, there were 175 deaths (5.42%) among the group of patients who were administered TIVA, compared with 140 deaths (4.36%) in the patients who received volatile anesthesia. Meta-analysis found no significant difference between the two groups in mortality at one year after cardiac surgery, with a low level of heterogeneity
- Six RCTs (n = 1,478) reported 30-day mortality after cardiac surgery. Thirty-two deaths occurred in the group of patients who were administered TIVA (4.35%), and 30 in those who received volatile anesthesia (4.04%). Meta-analysis found no significant difference between the two groups in mortality 30 days after cardiac surgery, with a low level of heterogeneity
- Although 14 RCTs reported in-hospital mortality, 11 had zero event rates and could not be included in the meta-analysis. As a result, only three RCTs (n = 676) were included in the meta-analysis. There were seven deaths in the TIVA group (2.35%) and nine in the volatile anesthesia group (2.38%). The meta-analysis found that there was no significant difference between the two groups, with a low level of heterogeneity
- Blood levels of CTnI measured 24 hours after surgery were reported in 25 RCTs (n = 3,127) (Fig 7). The meta-analysis found no significant difference in the level of CTnI 24 hours after surgery between patients receiving TIVA and volatile anesthesia, and the levels of heterogeneity were high.
- Eleven RCTs (n = 1,214) reported postoperative blood levels of CK-MB at 24 hours. The meta-analysis found that there was no statistically significant difference in CK-MB levels 24 hours postoperatively between TIVA and volatile anesthesia, and there was a high level of heterogeneity (Fig 8).
- Eleven RCTs reported the time from the end of surgery until tracheal extubation. One study was excluded from the metaanalysis, as there was an institutional policy requiring tracheal extubation to be delayed until the morning after surgery. As a result, only 10 RCTs (n = 1,059) were included in the metaanalysis, which found no statistically significant difference in the time to tracheal extubation between the two groups, with a high level of heterogeneity (Fig 9).

- Sixteen RCTs (n = 2,003) reported the duration of stay in ICU. Meta-analysis found a significant decrease in the duration of ICU stay associated with volatile anesthesia compared with TIVA, but with a high level of heterogeneity (Fig 10).
- Twelve RCTs (n = 1,241) reported on the duration of hospital stay in days. Meta-analysis found that compared with TIVA, volatile anesthesia was associated with a significantly shorter duration of hospital stay with a low level of heterogeneity (Fig 11).

Anmerkung/Fazit der Autoren

In conclusion, in patients undergoing cardiac surgery, the choice of volatile anesthesia or TIVA had no significant impact upon mortality, postoperative release of CTnI or CKMB, or time to tracheal extubation. However, compared with TIVA, volatile anesthesia was associated with shorter hospital and ICU stays after cardiac surgery.

Jiao X-F et al., 2019 [6].

Volatile anesthetics versus total intravenous anesthesia in patients undergoing coronary artery bypass grafting: An updated metaanalysis and trial sequential analysis of randomized controlled trials

Fragestellung

The benefits of volatile anesthetics in coronary artery bypass grafting (CABG) patients remain controversial. We aimed to conduct an updated meta-analysis to assess whether the use of volatile anesthetics during CABG could reduce mortality and other outcomes.

Methodik

Population:

- Patients undergoing general anesthesia for CABG

Intervention:

- an anesthesia plan that included a volatile anesthetic (such as halothane, sevoflurane, desflurane, isoflurane, enflurane, or ether) without restrictions in times and doses of administration

Komparator:

- TIVA (such as propofol, fentanyl, sufentanil, midazolam, thiopental, or etomidate)

Endpunkte:

- the primary outcomes were operative mortality and one-year mortality. The secondary outcomes included length of stay in ICU, length of stay in hospital, and postoperative safety outcomes (myocardial infarction, heart failure, arrhythmia, stroke, delirium, postoperative cognitive impairment, acute kidney injury, the use of intra-aortic balloon pump (IABP), and the use of other mechanical circulatory support).

Recherche/Suchzeitraum:

- Bis Juni 2019 (u.a. PubMed, Embase)

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 89 RCTs (14,387 patients)

Charakteristika der Population:

- The volatile anesthetic used in the included RCTs varied: 39 RCTs used sevoflurane, 23 RCTs used isoflurane, 8 RCTs used desflurane, 6 RCTs used enflurane, and 13 RCTs used more than one volatile anesthetics. Detailed characteristics of the included RCTs

Qualität der Studien:

- Overall, 5 (6%) RCTs were rated at low risk of bias, 12 (13%) RCTs were rated at high risk of bias, and the remaining RCTs were rated at unclear risk of bias.

Studienergebnisse:

Operative mortality

- A total of 44 RCTs reported operative mortality. There was no statistically significant difference between the volatile anesthetics and TIVA groups in operative mortality (RR = 0.92, 95% CI: 0.68–1.24, p = 0.59), and no heterogeneity (I2 = 0%)

One-year mortality

- Five RCTs reported one-year mortality. There was no statistically significant difference between the volatile anesthetics and TIVA groups in one-year mortality (RR = 0.64, 95% CI: 0.32–1.26, p = 0.19), with moderate heterogeneity (I2 = 51%). Sensitivity analysis did not change the result for one-year mortality (RR = 0.92, 95% CI: 0.68–1.25, p = 0.61, I2 = 0%)

Length of stay in ICU

- A total of 43 RCTs reported length of stay in ICU, which was shorter in the volatile anesthetics group than in the TIVA group (MD = -4.14 h, 95% CI: -5.63– -2.66 h, p<0.00001), with high heterogeneity (I2 = 98%). After sensitivity analysis, there was no statistically significant difference between the volatile anesthetics and TIVA groups in length of stay in ICU (MD = -0.01 h, 95% CI: -0.04–0.01 h, p = 0.38), with mild heterogeneity (I2 = 38%)

Length of stay in hospital

- A total of 34 RCTs reported length of stay in hospital, which was shorter in the volatile anesthetics than in the TIVA group (MD = -1.22 d, 95% CI: -1.81– -0.62 d, p <0.0001), with high heterogeneity (I2 = 95%). After sensitivity analysis, the length of hospital stay in the volatile anesthetics group was shorter than in the TIVA group (MD = -0.16 d, 95% CI: -0.28–-0.04 d, p = 0.008), with mild heterogeneity (I2 = 26%)

Myocardial infarction

- A total of 28 RCTs reported myocardial infarctions. There was no statistically significant difference between the volatile anesthetics and TIVA groups in the incidence of myocardial infarctions (RR = 0.94, 95% CI: 0.73–1.21, p = 0.64), without heterogeneity (I2 = 0%)

Heart failure

- A total of 4 RCTs reported heart failures. There was no statistically significant difference between the volatile anesthetics and TIVA groups in the incidence of heart failures (RR = 0.39, 95% CI: 0.08–2.01, p = 0.26), without heterogeneity (I_2 = 0%)

Arrhythmia

- A total of 29 RCTs reported arrhythmias. There was no statistically significant difference between the volatile anesthetics and TIVA groups in the incidence of arrhythmias (RR = 0.89, 95% CI: 0.77–1.03, p = 0.11), without heterogeneity (I2 = 0%)

Stroke

- A total of 2 RCTs reported strokes. There was no statistically significant difference between the volatile anesthetics and TIVA groups in the incidence of strokes (RR = 1.46, 95% CI: 0.76– 2.81, p = 0.25), without heterogeneity (I2 = 0%) (Table 2).

Delirium

- A total of 3 RCTs reported delirium. There was no statistically significant difference betweene the volatile anesthetics and TIVA groups in the incidence of delirium (RR = 0.96, 95% CI: 0.71–1.29, p = 0.78), without heterogeneity (I2 = 0%) (Table 2).

Postoperative cognitive impairment

- A total of 8 RCTs reported postoperative cognitive impairment. There was no statistically significant difference between the volatile anesthetics and TIVA groups in the incidence of postoperative cognitive impairment (RR = 1.20, 95% CI: 0.74–1.94, p = 0.46), with moderate heterogeneity (I2 = 59%). Sensitivity analysis did not change the result for postoperative cognitive impairment (RR = 1.37, 95% CI: 0.94–1.98, p = 0.1, I2 = 36%).

Anmerkung/Fazit der Autoren

A total of 89 RCTs comprising 14,387 patients were included. There were no significant differences between the volatile anesthetics and TIVA groups in operative mortality (relative risk (RR) = 0.92, 95% confidence interval (CI): 0.68–1.24, p = 0.59, I2 = 0%), one-year mortality (RR = 0.64, 95% CI: 0.32–1.26, p = 0.19, I2 = 51%), or any of the postoperative safety outcomes. The lengths of stay in the ICU and hospital were shorter in the volatile anesthetics group than in the TIVA group. TSA revealed that the results for operative mortality, one-year mortality, length of stay in the ICU, heart failure, stroke, and the use of IABP were inconclusive.

Conventional meta-analysis suggests that the use of volatile anesthetics during CABG is not associated with reduced risk of mortality or other postoperative safety outcomes when compared with TIVA. TSA shows that the current evidence is insufficient and inconclusive. Thus, future large RCTs are required to clarify this issue.

Bonanni A et al., 2020 [2].

Volatile Anesthetics versus Propofol for Cardiac Surgery with Cardiopulmonary Bypass Meta-analysis of Randomized Trials

Fragestellung

The aim of this systematic review and meta-analysis was to assess the effect of anesthesia maintenance with volatile agents compared with propofol on both short- and long-term mortality (primary outcomes) and major clinical events in adults undergoing cardiac surgery with cardiopulmonary bypass.

Methodik

Population:

- adults (at least 18 yr old) undergoing cardiac surgery with CPB and anesthesia maintenance

Intervention:

- Volatile Anesthetics

Komparator:

- Propofol

Endpunkte:

Primary outcomes
First coprimary outcome: short-term mortality (in hospital or within 30 days)
Second coprimary outcome: 1-yr mortality
Secondary outcomes
In-hospital myocardial infarction, by using investigators' definitions
Area under the curve for cardiac troponin for at least postoperative 24 h; if not reported, area under the curve was calculated from tabulated data or graphs (trapezoidal rule)
Cardiac index (l/min/m^{-2}) or cardiac output (l/min) from postcardiopulmonary bypass (usually 15 min) to 3–6 h after intensive care unit admission
Inotropic medications (milrinone, dobutamine, dopamine, epinephrine) from postcardiopulmonary bypass to 12 h after intensive care unit admission
In-hospital atrial fibrillation
In-hospital acute kidney injury, defined according to AKIN,[29] RIFLE,[30] or KDIGO criteria[31]or to comparable ones
In-hospital renal replacement therapy
Extubation time (h)
Length of intensive care unit stay (days)
Length of hospital stay (days)

Recherche/Suchzeitraum:

- Bis September 2019 (u.a. PubMed)

Qualitätsbewertung der Studien:

- Cochrane risk of bias criteria

Ergebnisse

Anzahl eingeschlossener Studien:

- Finally, 36 studies reported in 37 full-text articles were included

Charakteristika der Population:

Reference	No. of Patients (VA/P)	Surgery Type	Follow-up	Anesthetics (Maintenance)	Age, yr	Male, %	eGFR ml/min	DM %	EF < 25–40%, %	EF, % ± SD	Aortic X Clamping (min)
Sorbara *et al.*[33]	15/15	EIC	1 week	I *vs.* P	60	77	*	*	0	*	67
Engoren *et al.*[34]	35/35	EIC	In hospital	I *vs.* P	61	77	*	*	26.5	*	*
Story *et al.*[35]/Parker *et al.*[40]	236/118	EIC	In hospital	I or S *vs.* P	66	82	≥ 30	*	6.5	*	*
De Hert *et al.* (I)[36]	10/10	EIC	36 h	S *vs.* P	63	80	*	1	0†	64 ± 7.1	42
El Azab *et al.*[37]	10/10	EIC	In hospital	S *vs.* P	61	75	≥ 30	*	0†	*	67
De Hert *et al.* (II)[38]	30/15	EIC	36 h	D or S *vs.* P	75	87	*	27	0	41 ± 5	47
De Hert *et al.* (III)[11]	160/80	EIC	In hospital	D or S *vs.* P	67	82	≥ 45	28	0	67.3 ± 11.3	30
De Hert *et al.* (IV)[39]	50/50	EIC	In hospital	S *vs.* P	66	79	≥ 45	22	0	63.5 ± 12	30
Cromheecke *et al.*[41]	15/15	EIV	In hospital	S *vs.* P	69	57	≥ 30	10	0	67 ± 11.5	68
Lorsomradee *et al.*[42]	160/160	EIC	In hospital	S *vs.* P	67	80	≥ 45	28	0†	67.5 ± 11	30
Xia *et al.*[43]	18/36	EIC	In hospital	I *vs.* P	64	69	≥ 90	13	0	52 ± 4.3	84
Tritapepe *et al.*[44]	75/75	EIC	30 days	D *vs.* P	65	82	≥ 30	21	Some	51.5 ± 11.8	67
Cavalca *et al.*[45]	21/22	ECS	In hospital	S *vs.* P	67	65	≥ 30	14	0†	60.8 ± 7.6	81
De Hert *et al.* (V)[47]	269/145	EIC	30 days/1 yr	D or S *vs.* P	67	81	*	23	0	67 ± 13.3	*
Yildirim *et al.*[46]	40/20	EIC	30 days	I or S *vs.* P	68	75	≥ 45	30	0	44.3 ± 4.3	2
Flier *et al.*[48]	41/43	EIC	30 days/1 yr	I *vs.* P	67	79	≥ 45	30	5	*	53
Huang *et al.*[49]	30/30	EIC	In hospital	I *vs.* P	61	83	≥ 45	20	0	54 ± 8	*
Royse *et al.*[50]	90/89	EIC	In hospital	D *vs.* P	63	85	≥ 30	76	7	*	73
Bignami *et al.*[51]	50/50	ECS	In hospital/1 yr	S *vs.* P	67	76	≥ 30	6	Some	55.1 ± 12.9	80
Imantalab *et al.*[52]	20/20	EIC	In hospital	I *vs.* P	*	75	*	38	0†	*	41
Jovic *et al.*[53]	11/11	EIV	In hospital	S *vs.* P	63	59	≥ 30	14	0	57.5 ± 8	68
Kottenberg *et al.*[54]	19/19	EIC	In hospital	I *vs.* P	65	84	≥ 45	0†	*	*	72
Soro *et al.*[55]	36/37	EIC	In hospital	S *vs.* P	69	78	≥ 30	44	0	57.8 ± 13	48
Koç *et al.*[56]	20/20	EIC	In hospital	S *vs.* P	55	*	*	1	0	*	51
Landoni *et al.*[57]	100/100	ECS	30 days/1 yr	S *vs.* P	69	68	*	*	Some	50.8 ± 14.8	94
Yoo *et al.*[58]	56/56	EIV	In hospital	S *vs.* P	58	46	≥ 45	14	0†	64.2 ± 10.7	69
Jerath *et al.*[59]	67/74	EIC‡	In hospital	I or S *vs.* P	64	93	≥ 30	28	0†	*	*
Kapoor *et al.*[60]	40/36	EIV	30 days	D *vs.* P	40	*	≥ 90	0†	0†	*	64
Sirvinskas *et al.*[61]	36/36	EIC	In hospital	S *vs.* P	67	78	≥ 15	0†	0†	*	*
Likhvantsev *et al.*[62]	437/431	EIC	30 days/1 yr	S *vs.* P	62	88	*	17	0	54.5 ± 6.5	44
Hofland *et al.*[64]	165/166	EIC	In hospital	S *vs.* P	64	86	≥ 45	30	0†	*	66
Hou *et al.*[65]	45/45	EIV	48 h	S *vs.* P	54	66	> 60	*	0†	*	*
Yang *et al.*[63]	36/37	EIV	In hospital	S *vs.* P	51	47	*	0†	0†	56.5 ± 5.5	63
Oh *et al.*[66]	78/78	EIV	In hospital	S *vs.* P	60	45	*	8	0	64.2 ± 7.3	108
Moscarelli *et al.*[67]	31/31	EIV	In hospital	S *vs.* P	65	45	≥ 45	0†	10	58.6 ± 7.4	92.3
Landoni *et al.* (I)[68]‖	1,709/1,721	EIC	30 days/1 yr	D or I or S *vs.* P	62	81	≥ 45	28	< 5	57 ± 3.7	*

*Not reported. †Exclusion criteria; ‡10% off pump. §EuroSCORE II. ‖In the Landoni (I) study among reported outcomes, only 30-day and 1-yr mortality are selectively reported for the on-pump procedure.

AF, atrial fibrillation; AKI, acute kidney injury; AUC, area under the curve for 24–72 h; CI, cardiac index; cTn, cardiac troponin; D, desflurane; DM, diabetes mellitus; ECS, elective concomitant surgery; EF, left ventricular ejection fraction; eGFR, estimated glomerular filtration rate; EIC, elective isolated coronary artery bypass graft; EIV, elective isolated valve surgery; I, isoflurane; ICU, intensive care unit; Inotr., inotropic medications; MI, myocardial infarction; P, propofol; RRT, renal replacement therapy; S, sevoflurane; VA, volatile anesthetics; X clamping, cross clamping time.

Qualität der Studien:

- Most included studies resulted at “low” risk of bias for almost all items investigated. Only in case of allocation concealments did the judgment result frequently “unclear” because methods to protect against bias were not sufficiently reported.

Studienergebnisse:

Mortality

- Short-term mortality data were available from 30 articles (37 studies) in which 127 deaths were registered among 7,743 patients.
- Short-term mortality was not modified by volatile anesthetics either as a class (odds ratio, 1.04 [95% CI, 0.73 to 1.49]; P = 0.820; I2 = 0%] or as individual agents. Visual inspection of funnel plot and Egger’s test did not reveal asymmetry
- Six studies reported mortality at 1 yr in 5,096 patients with 311 deaths registered (6.1%; fig. 2). Volatile anesthetics were associated with a lower mortality (5.5%) relative to propofol (6.8%; odds ratio, 0.76 [95% CI, 0.60 to 0.96]; P = 0.023; I2 = 0%). On the contrary, in the same studies short-term mortality in volatile anesthetics was similar (2.2%) to propofol

MI (myocardial infarction)

- MI incidence was recorded in 22 articles (27 studies totalling 3,037 patients) and occurred in 3.2% of patients
- Volatile anesthetics were associated with a lower MI incidence (odds ratio, 0.60 [95% CI, 0.39 to 0.92]; P = 0.020; I2 = 0%). Although the subgroup of desflurane or sevoflurane was associated with a lower incidence of MI (odds ratio, 0.54 [95% CI, 0.34 to 0.86]; P = 0.009; I2 = 0%), isoflurane was not (odds ratio, 1.38 [95% CI, 0.46 to 4.13]; P = 0.562; I2 = 0%). Univariate and multiple analysis did not reveal a role for study era, surgery type, and aortic cross clamp time on volatile anesthetics effect on MI incidence

Extubation Time, ICU, and Hospital Stays

- The class of volatile anesthetics compared with propofol was associated with lower extubation time (standardized mean difference, −0.35 [95% CI, −0.68 to −0.02]; P = 0.038), and with higher cardiac index/output (standardized mean difference, 0.70 [95% CI, 0.37 to 1.04]; P < 0.0001). The class of volatile anesthetics was not associated with changes in short-term mortality (1.63 vs. 1.65%; odds ratio, 1.04 [95% CI, 0.73 to 1.49]; P = 0.820) and acute kidney injury (odds ratio, 1.25 [95% CI, 0.77 to 2.03]; P = 0.358).

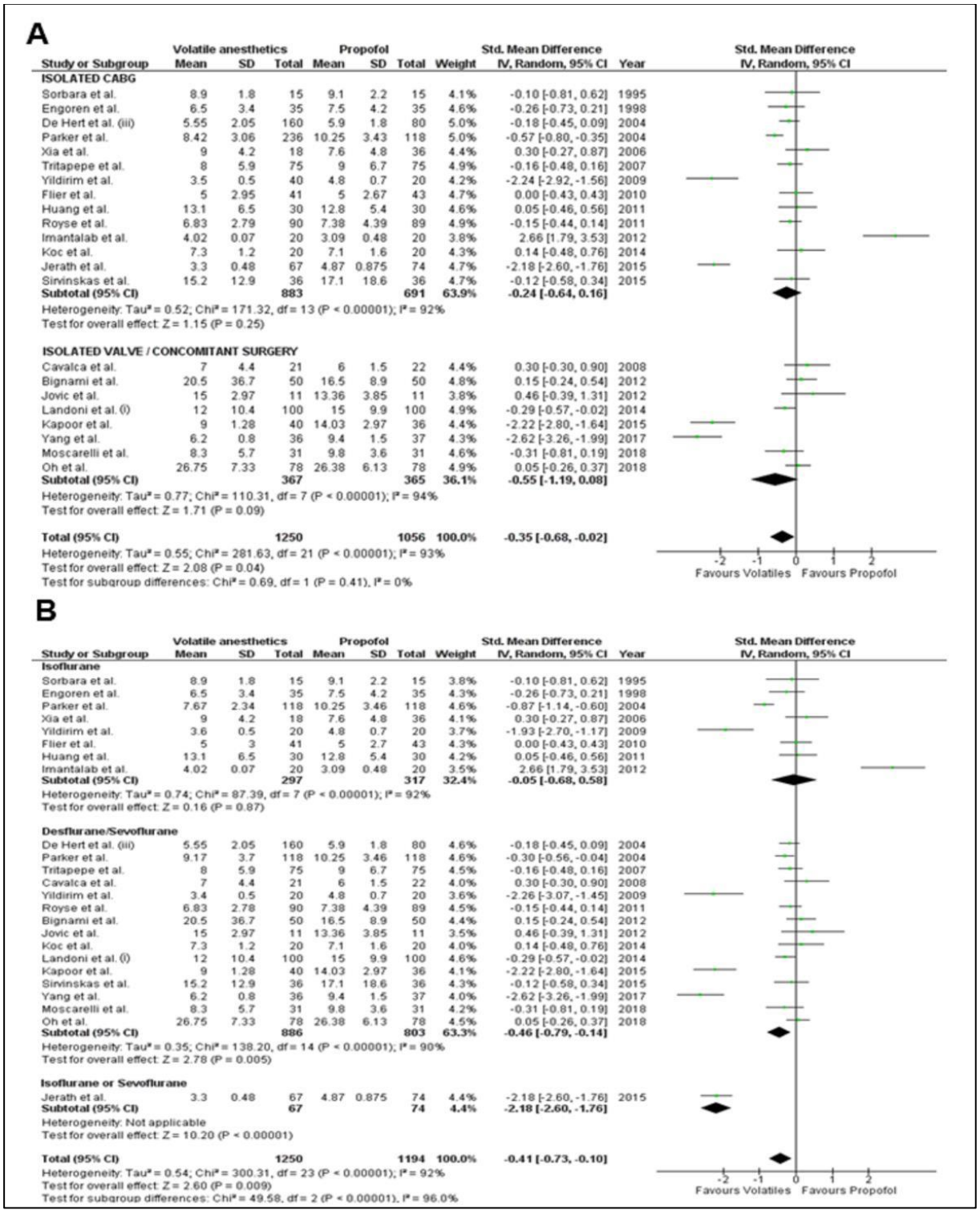


Figure 8: Forest plot for the effects of volatile anesthetics (A) as a class and (B) as subgroups versus propofol on the extubation time (hours) in adults undergoing cardiac surgery with cardiopulmonary bypass. Subgroup analysis: in (A) isolated coronary artery bypass graft versus isolated valve/concomitant surgery, and in (B) isoflurane versus desflurane or sevoflurane. Std. Mean difference: standardized mean difference. IV : inverse variance

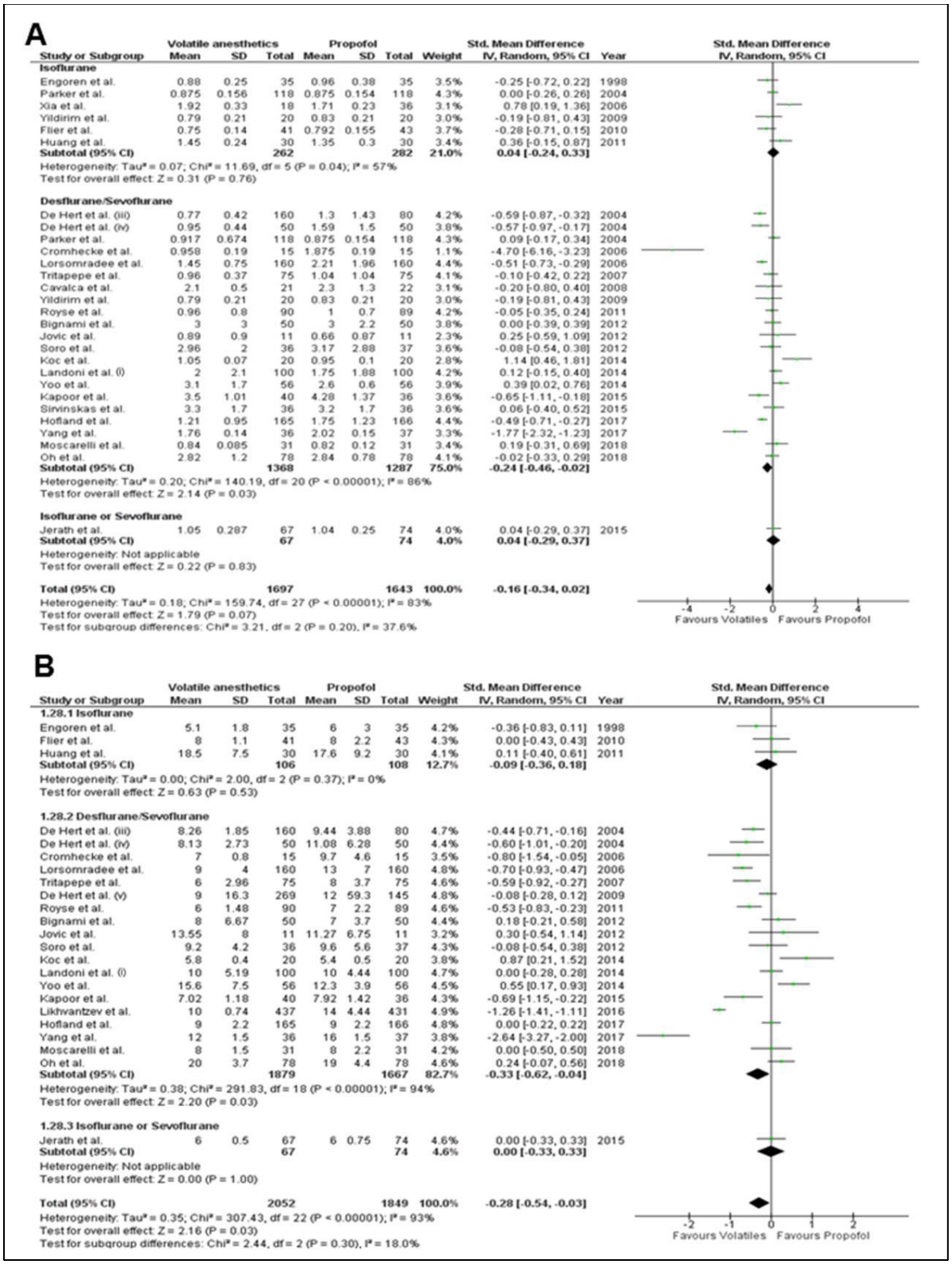


Figura 9: Forest plot for the effects of volatile anesthetics subgroups versus propofol on (A) Intensive Care Unit (days) and (B) Hospital Stay (days) in adults undergoing cardiac surgery with cardiopulmonary bypass . Subgroup analysis: isoflurane versus desflurane or sevoflurane. M-H: Mantel-Haenszel

Anmerkung/Fazit der Autoren

This meta-analysis has several important clinical results. In adults undergoing cardiac surgery with CPB (both CABG and valve or complex surgery), the class of volatile anesthetics compared with propofol was associated with a similar short-term mortality but with a lower 1-yr mortality. In addition, volatile anesthetics were associated with cardioprotection, whereas no renoprotection was found. Cardioprotection is evident from lower MI incidence, cardiac troponin release, the need for inotropic medications, and preserved cardiac index. The desflurane or sevoflurane subgroup was associated also with reduced extubation time, ICU, and hospital stays.

In adults undergoing cardiac surgery with cardiopulmonary bypass, the class of volatile anesthetics was superior to propofol with regard to long-term mortality, as well as to many secondary outcomes indicating myocardial protection.

Chen L et al., 2019 [3].

Safety and efficacy of combined use of propofol and etomidate for sedation during gastroscopy

Fragestellung

The aim of the study, therefore, was to conduct a systematic review and meta-analysis of randomized controlled trials (RCTs) to investigate the safety and efficacy of the combined use of propofol and etomidate for patients undergoing gastroscopy.

Methodik

Population:

- patients in whom gastroscopy was indicated

Intervention:

- etomidate plus propofol or propofol plus etomidate

Komparator:

- etomidate or propofol alone

Endpunkte:

- recovery time, mean arterial pressure (MAP), hypotension, bradycardia, heart rate (HR), pulse oxygen saturation (SPO2), apnea or hypoxemia, myoclonus, nausea and vomiting, body movements, and injection pain

Recherche/Suchzeitraum:

- Bis August 2018 (u.a. Medline, Cochrane)

Qualitätsbewertung der Studien:

- Cochrane Handbook for Systematic Reviews of Interventions version 5.1.0

Ergebnisse

Anzahl eingeschlossener Studien:

- 15 RCTs (2973 participants)

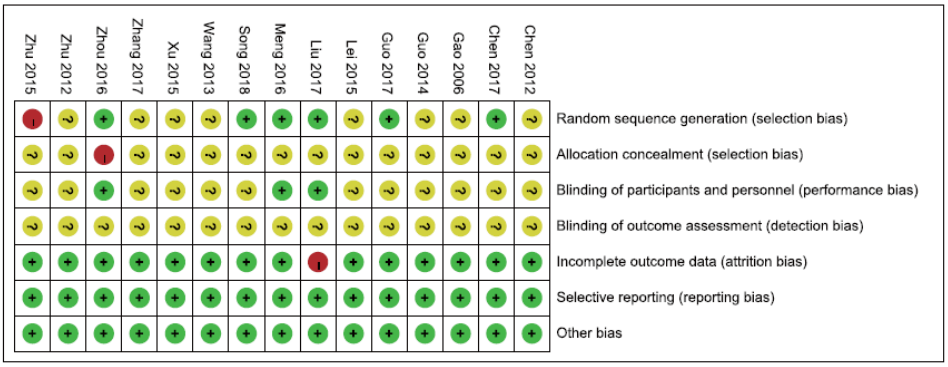
Charakteristika der Population:

The characteristics of the included studies.

Author (year)	Sample size: Treatment group P + E	Sample size: Treatment group E + P	Sample size: Control group P	Sample size: Control group E	Outcomes
Chen, 2012	–	30	30	30	a, b, c, e, h, i, j, k
Chen, 2017	–	60	60	60	a, b, d, e, f, g, h, j
Gao, 2006	80	–	80	80	a, c, h, i
Guo, 2014	40	–	40	40	b, c, e, h, i, k
Guo, 2017	60	–	60	60	d, e, i, j, k
Lei, 2015	60	–	60	–	c, h
Liu, 2017	218	–	73	72	e, i, j
Meng, 2016	50	50	50	50	a, d, e, f, g, i, j, k
Song, 2018	–	40	40	40	a, b, c, e, h, i, j, k
Wang, 2013	40	–	–	40	a, b, c, e, h, i
Xu, 2015	100	–	100	100	a, b, e, h, k
Zhang, 2017	100	–	–	100	a, d, e, g, k
Zhou, 2016	200	–	200	–	a, d, e, f, g, i, k
Zhu, 2012	100	–	100	–	a, d, e, i
Zhu, 2015	–	60	60	60	a, c, e, h, i, j, k

P = propofol; E = etomidate; –: no report; LP = low-dose propofol; MP = middle-dose propofol; HP = high-dose propofol.
[Outcomes]: a: recovery time; b: MAP; c: SPO_2; d: apnea or hyoxemia; e: myoclonus; f: hypotension; g: bradycardia; h: heart rate; i: nausea vomiting; j: body movements; k: injection pain.

Qualität der Studien:



Studienergebnisse:

Primary outcomes: recovery time

- **A:** Compared with propofol alone, co-administration of propofol and etomidate increased the recovery time of patients undergoing gastroscopy, but subgroup analyses showed no significant difference between propofol plus etomidate and propofol alone. The test for heterogeneity of 11 studies demonstrated no heterogeneity, and the fixed-effect model was used. Based on our analysis, the pooled estimate of SMD was 0.14, and the 95% CI was 0.04–0.24 (P=.005)
- **B:** no significant difference was found between propofol plus etomidate or etomidate plus propofol and etomidate alone (SMD=-0.22; 95% CI, -0.44–0.01; P=.06)

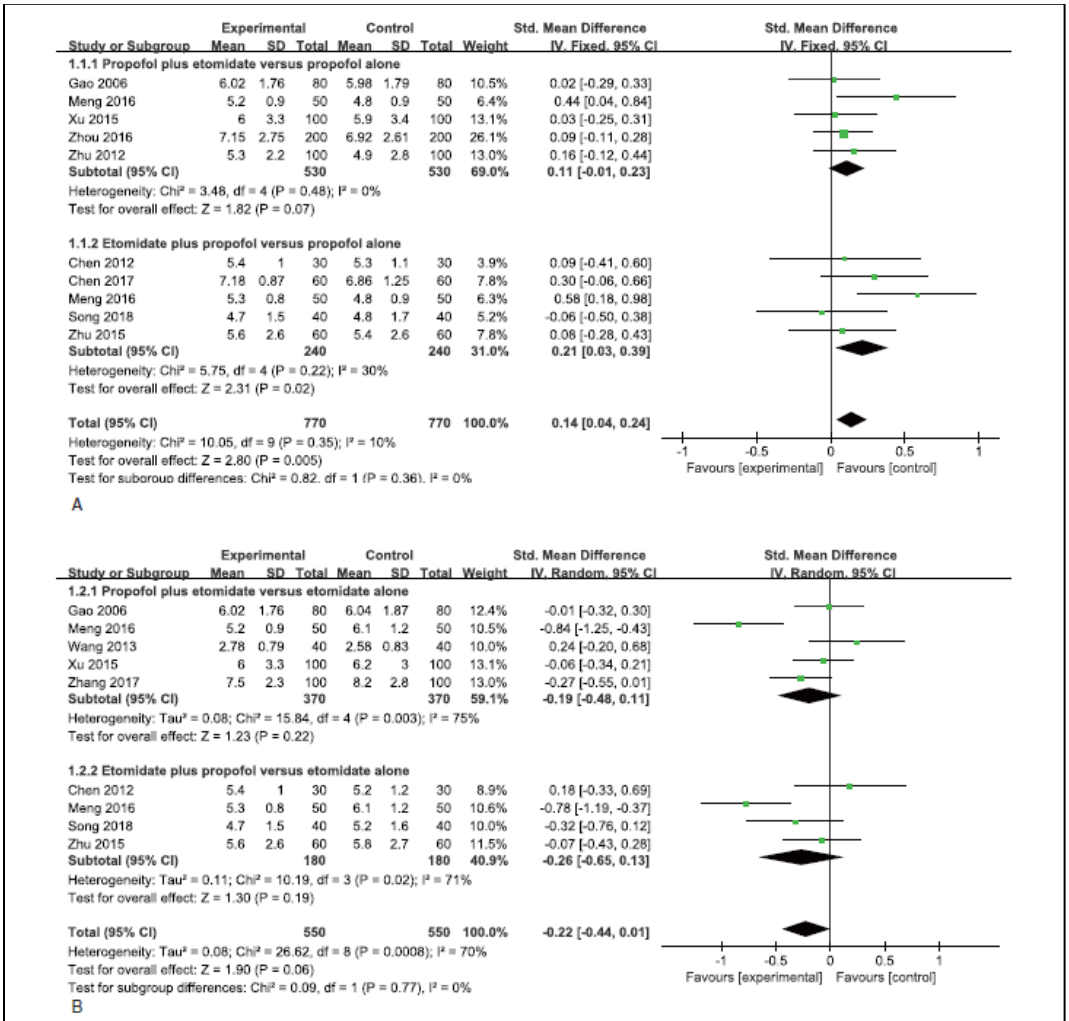


Figure 3. Meta-analysis of the of recovery time (min). (A) Recovery time of patients received co-administration of propofol and etomidate vs propofol alone, fixed-effect model; (B) recovery time of patients received co-administration of propofol and etomidate vs etomidate alone, random-effect model.

On circulation system

- **A:** The time point of MAP was determined at 0 to 2minutes after the patients received anesthetics in different included studies. Following the treatment of the combined use of propofol and etomidate vs propofol alone, there was a significant difference of MAP after the patients received anesthetic (SMD=1.32; 95% CI, 0.38–2.26; P=.006; Fig. 4A) compared with propofol alone. There was significant heterogeneity existed for MAP after the patients received co-administration of propofol and etomidate vs propofol alone (x2=27.07, P<.001, I2=85%).
- **B:** Therefore, a random-effect model was adopted for statistical analysis. On other hand, there was no significant difference of MAP after the patients received combination of propofol and etomidate vs etomidate alone (SMD=-0.02; 95% CI, -0.19–0.16; P=.83). The test for heterogeneity of this comparison demonstrated no heterogeneity, and the fixed-effect model was performed.
- These results suggest that co-administration of propofol and etomidate had few effects on MAP of patients undergoing gastroscopy and was safer and more effective compared to propofol alone. Etomidate is associated with hemodynamic stability, which is similar to co-administration of propofol and etomidate. In addition, the results show that a combination of etomidate and propofol can result in favorable hemodynamic stability.

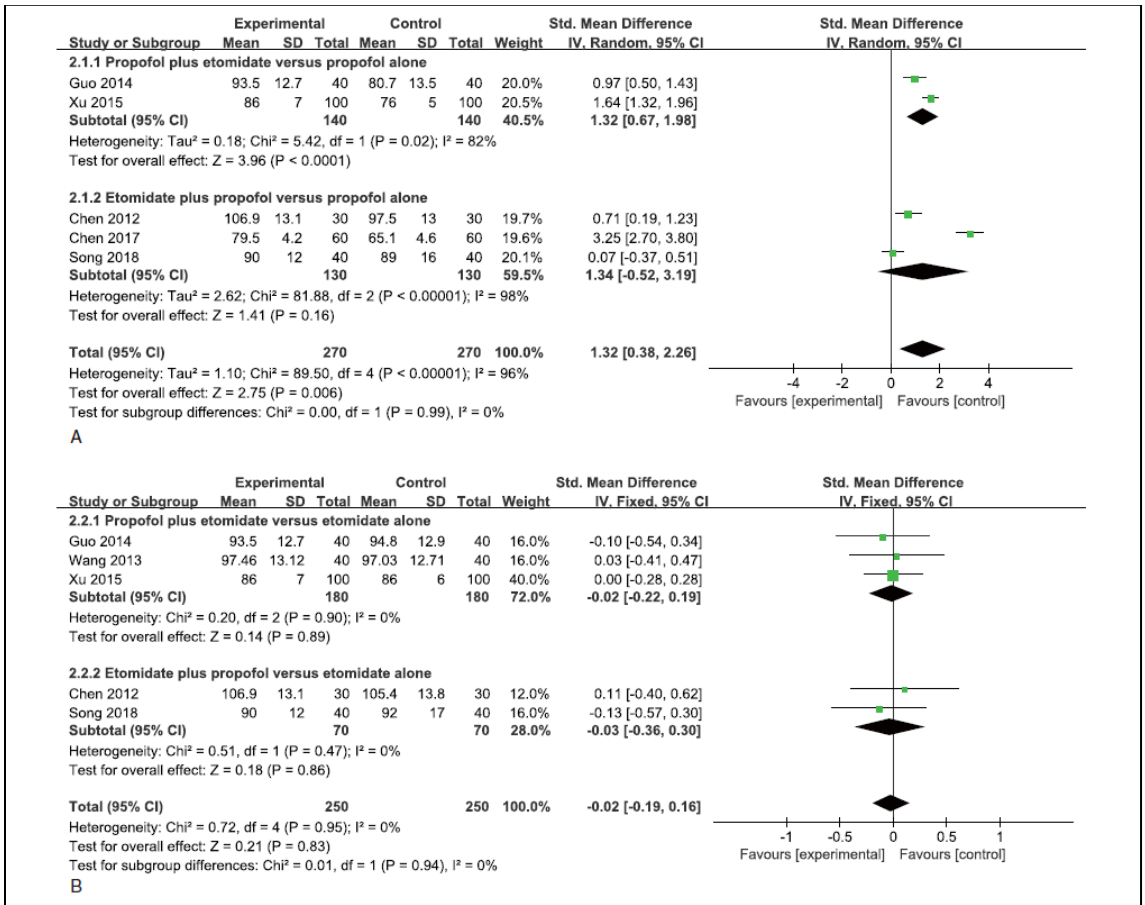


Figure 4. Meta-analysis of the MAP (mmHg). (A) MAP after the patients received co-administration of propofol and etomidate vs propofol alone, random-effect model; (B) MAP after the patients received co-administration of propofol and etomidate vs etomidate alone, fixed-effect model.

Hypotension

- Three studies totaling 780 patients provided data on hypotension after the patients received anesthetic. The combined use of propofol and etomidate was associated lower risk of hypotension compared with propofol alone (OR=0.05, 95% CI=0.01–0.19; P<.001; with significant heterogeneity, x2=14.23, P=.003, I2=79%)

Bradycardia

- Four studies totaling 980 patients provided data on bradycardia after the patients received anesthetic. The combined use of propofol and etomidate was associated lower risk of bradycardia compared with propofol alone (OR=0.53, 95% CI=0.31–0.89; P=.02; without heterogeneity. The combined use of propofol and etomidate showed no difference in hypotension and bradycardia with etomidate alone.

Heart rate (HR)

- Nine studies totaling 1430 patients provided data on heart rate (HR). The time point ofHRwas determined at 0 to 2minutes after the patients received anesthetics in different included studies.
- Compared to propofol or etomidate alone, thecombined use of propofol and etomidate showed no difference in HR.

On respiration system

- Six studies including a total of 950 patients provided data on SPO2.
- Following co-administration of propofol and etomidate vs propofol alone, there was significant difference in SPO2 after the patients received anesthetics (SMD=0.99, 95%

CI=0.43–1.55; P < .001), with high heterogeneity among these studies (x2=52.67, P < .001, I2=91%).

- no significant difference in SPO2 after the patients received treatment with the co-administration of propofol and etomidate vs etomidate alone (SMD=-0.09, 95%CI=-0.16–0.34; P=.49
- These results show that the combined use of propofol and etomidate causes minimal respiratory depression vs propofol alone, preserves spontaneous respirations in patients undergoing gastroscopy. These results showed that the combined use of propofol and etomidate and etomidate or propofol alone have the same effect on HR.

Adverse Events

- Six studies including a total of 1420 patients provided data on apnea or hypoxemia.
- Compared with propofol alone, the combined use of propofol and etomidate was associated with significantly reduced apnea or hypoxemia; the pooled estimate of OR was 0.16, and the 95% CI was 0.08–0.33. (P < .001)
- no significant difference between the combined use of propofol with etomidate and etomidate alone (OR=1.18, 95% CI=0.53–2.59; P=.69). These results showed that co-administration of propofol and etomidate had fewer effects on respiration in patients undergoing gastroscopy than did propofol alone, and the treatment was as safe as etomidate alone.
- Thirteen studies including a total of 2513 patients provided data on myoclonus. Based on our analysis of the combined use of propofol and etomidate vs propofol alone, the pooled estimate of OR was 3.07 and the 95% CI was 1.73–5.44 (P<.001). This revealed that the combined use of propofol and etomidate might increase the risk for myoclonus-realted adverse events in patients undergoing gastroscopy. On the other hand, compared to etomidate alone, the combined use of propofol and etomidate was associated with significantly reduced myoclonus in patients undergoing gastroscopy (OR=0.15, 95% CI=0.11–0.22; P <.001). These results showed that co-administration of propofol and etomidate had few effects on myoclonus in patients undergoing gastroscopy than did etomidate alone; however, it was not safer than propofol alone.

Anmerkung/Fazit der Autoren

Fifteen studies with 2973 participants were included in the analysis. Compared to propofol alone, the combined use of propofol and etomidate possibly increased recovery time (SMD=0.14, 95% CI=0.04–0.24; P=.005), and the risk formyoclonus (OR=3.07, 95% CI=1.73–5.44; P<.001), injection pain, and nausea and vomiting. Furthermore, compared to propofol alone, the combination of propofol and etomidate produced an apparent beneficial effect formean arterial pressure (MAP) after anesthesia (SMD=1.32, 95%CI=0.38–2.26; P=.006), SPO2 after anesthesia (SMD=0.99, 95% CI=0.43–1.55; P<.001), apnea or hypoxemia (OR=0.16, 95% CI=0.08–0.33; P<.001), injection pain, and bodymovement. Further, compared to etomidate alone, the combination of propofol and etomidate reduced the risk for myoclonus (OR=0.15, 95% CI=0.11–0.22; P<.001), body movement, and nausea and vomiting.

The combination of propofol and etomidate might increase recovery time vs that associated with propofol, but it had fewer side effects on circulation and respiration in patients undergoing gastroscopy. The combined use of propofol and etomidate can improve and produce an apparent beneficial effect on the adverse effects of propofol or etomidate alone, and it was safer and more effective than propofol or etomidate alone.

Choi GJ et al., 2018 [4].

Etomidate versus propofol sedation for electrical external cardioversion: a meta-analysis

Fragestellung

To compare the efficacy and safety of etomidate vs propofol sedation for electrical cardioversion.

Methodik

Population:

- patients with hemodynamic stability (>18 Jahre)

Intervention:

- Etomidate

Komparator:

- propofol sedation

Endpunkte:

- electrical cardioversion

Recherche/Suchzeitraum:

- Update: January 2018 (u.a. Medline, Embase)

Qualitätsbewertung der Studien:

- risk of bias" tool (Cochrane)

Ergebnisse

Anzahl eingeschlossener Studien:

- n=9 RCTs

Charakteristika der Population:

Table 1. Study characteristics.

Reference, Publication year	G	*n* (M/F)	Age (Mean ± SD, year)	Sedation regimen	
				Induction	Maintenance
Desai *et al.*[14], 2015	E	30 (13/17)	38.8 ± 11.2	0.1 mg/kg	0.05 mg/kg
	P	30 (12/18)	38.2 ± 11.2	1 mg/kg	0.5 mg/kg
Kalogridaki *et al.*[16], 2011	E	21 (12/9)	61.2 ± 9.2	0.1 mg/kg	4 mg
	P	25 (18/7)	67.0 ± 8.3	0.5 mg/kg	20 mg
Siedy *et al.*[12], 2010	E	50 (35/15)	60.1 ± 10.7	0.15 mg/kg	0.03 mg/kg
	P	50 (37/13)	63.3 ± 10.9	1 mg/kg	0.2 mg/kg
Akcaboy *et al.*[15], 2007	E	20 (12/8)	65.2 ± 5.85	0.1 mg/kg	2 mg
	P	20 (11/9)	63.9 ± 7.45	0.5 mg/kg	10 mg
Herregods *et al.*[11], 2003	E	25 (19/6)	57.6 ± 9.0	0.2 mg/kg	NR
	P			1 mg/kg	
Kick *et al.*[18], 1996	E	20 (14/7)	56.2 ± 14	0.25 mg/kg	0.03 mg/kg
	P	20 (14/6)	57.7 ± 15.6	1.5 mg/kg	0.25 mg/kg
Hullander *et al.*[13], 1993	E	20 (13/7)	63 ± 15	8 mg/min	20 mcg/kg/min
	P	20 (14/6)	67 ± 14	50 mg/min	100 mcg/kg/min
Canessa *et al.*[10], 1991	E	10 (7/3)	54.5 ± 10.8	0.15 mg/kg	NR
	P	12 (7/5)	56.9 ± 7.4	1.5 mg/kg	
Mitterschiffthaler *et al.*[17], 1990	E	20	61 ± 15	0.2 mg/kg	NR
	P	28	57 ± 12	1.2 mg/kg	

Abbreviations: G, group; *n*, number of participants; M/F, male/female; SD, standard deviation; E, etomidate sedation; P, propofol sedation; NR, not reported.

Qualität der Studien:

Table 2. Risk of bias proposed by the Cochrane collaboration.

Study	Random sequence generation	Allocation concealment	Blinding of participants	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Desai *et al.*[14], 2015	Low	Low	Unclear	High	Unclear	Unclear
Kalogridaki *et al.*[16], 2011	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Siedy *et al.*[12], 2010	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Akcaboy *et al.*[15], 2007	Unclear	Low	Low	Unclear	Unclear	Unclear
Herregods *et al.*[11], 2003	Unclear	Low	Unclear	Unclear	Low	Unclear
Kick *et al.*[18], 1996	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Hullander *et al.*[13], 1993	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Canessa *et al.*[10], 1991	High	Unclear	Unclear	Unclear	Unclear	Unclear
Mitterschiffthaler *et al.*[17], 1990	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear

Studienergebnisse:

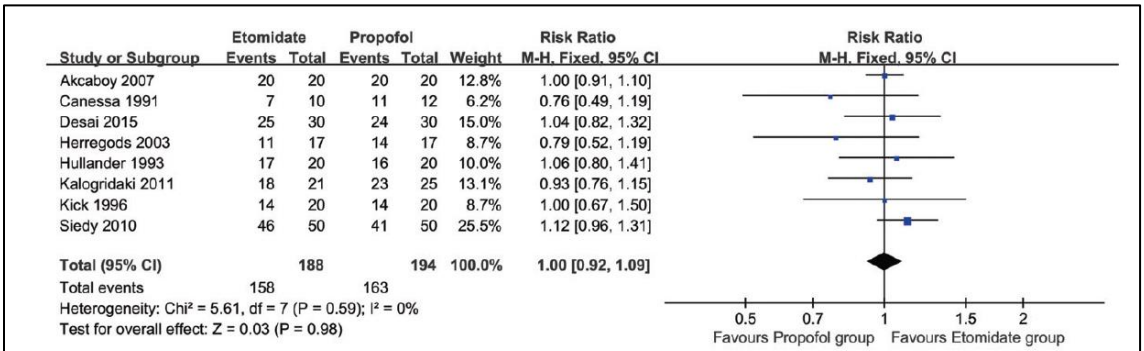


Figure 2. Forest plot of overall success rate of cardioversion: etomidate vs propofol sedation.

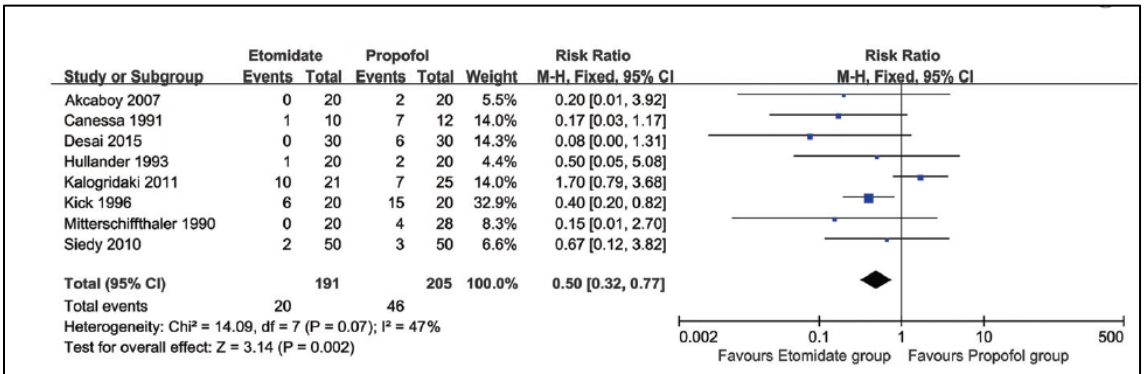


Figure 3. Forest plot of the incidence of respiratory depression: etomidate vs propofol sedation.

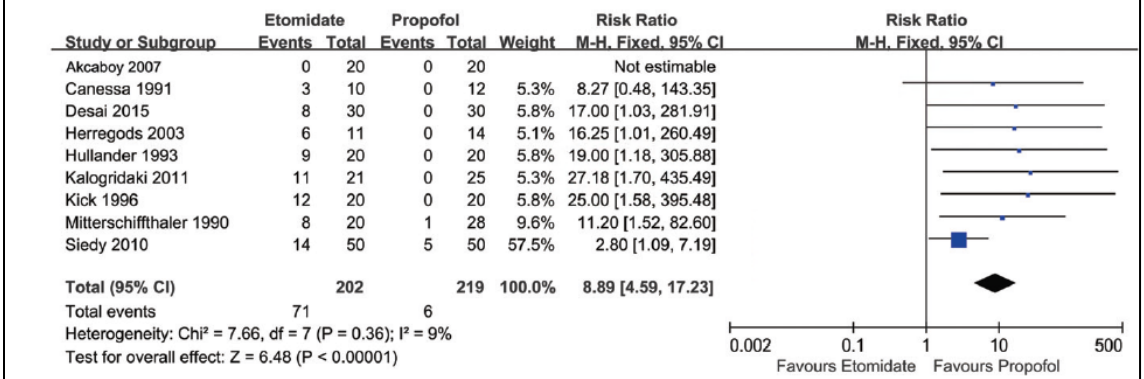


Figure 4. Forest plot of the incidence of myoclonus: etomidate vs propofol sedation.

Anmerkung/Fazit der Autoren

A total of nine studies, involving a total of 430 patients, were included. Induction and recovery time, success rate, number of shocks, and cumulative energy were similar. The incidences of hypotension and respiratory depression were significantly higher in the propofol group than in the etomidate group (risk ratio [RR] 0.11, 95% confidence interval (CI) 0.02–0.74, I2 0%; RR 0.50, 95% CI 0.32–0.77, I2 47%, respectively). The incidences of myoclonus and nausea or vomiting were significantly higher in the etomidate group than in the propofol group (RR 8.89, 95% CI 4.59–17.23, I2 9%; RR 5.13, 95%CI 1.72–15.31, I2 31%, respectively).

Issues affecting efficacy, including induction and recovery time, success rate, number of shocks, and cumulative energy, were comparable between etomidate and propofol sedation. Regarding safety issues, propofol sedation resulted in hypotension and respiratory depression more frequently; however, initiation of positive pressure ventilat on was comparable. Etomidate sedation caused myoclonus and nausea or vomiting more frequently.

Pang Q-Y et al., 2018 [9].

Effects of inhalation and intravenous anesthesia on intraoperative cardiopulmonary function and postoperative complications in patients undergoing thoracic surgery

Fragestellung

we conducted this systematic review and meta-analysis to compare the effects of inhalation anesthesia and intravenous anesthesia on pulmonary or cardiac function and postoperative complications in patients undergoing thoracic surgery with OLV, and we attempted to determine the optimal anesthesia regimen for thoracic surgery

Methodik

Population:

- adult patients (>18 years old), elective thoracic surgery with OLV, including lung resection and esophagectomy

Intervention:

- inhalation oder inhalation combined with local anesthesia

Komparator:

- intravenous anesthesia oder intravenous anesthesia combined with local anesthesia

Endpunkte:

- pulmonary or cardiac function and postoperative complications

Recherche/Suchzeitraum:

- January 2018 (u.a. PubMed, Cochrane)

Qualitätsbewertung der Studien:

- Cochrane Collaboration (Risk of Bias)

Ergebnisse

Anzahl eingeschlossener Studien:

- 23 RCTs (n=1349 Patienten)

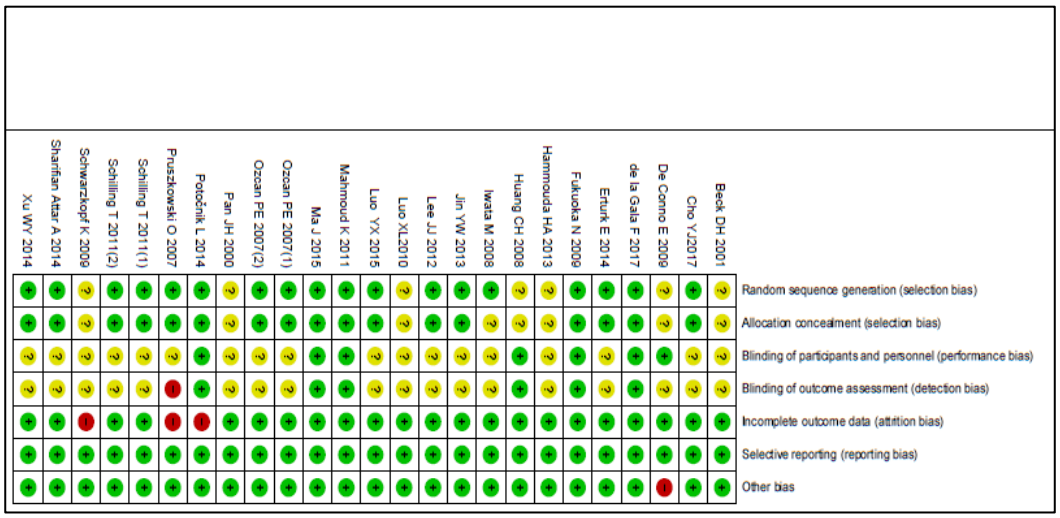
Charakteristika der Population:

TABLE I.—*Characteristics of the trials.*[2-4, 6, 7, 13-30]

Trial	Surgery	Group	Age (years)	Anesthesia	FiO_2 during OLV	Outcomes
De Conno (2009)[2]	Lung resection	TEA+sev (N.=27) TEA+prop (N.=27)	55±15 58±12	Sev: 1 MAC Prop: TCI	1	Pulmonary complications
Mahmoud (2011)[3]	Lung resection	TEA+iso (N.=25) TEA+prop (N.=25)	48.8±14 50.3±13	Iso: 1 MAC Prop: 4-6 mg/kg/h	0.8-1.0	OI, pulmonary complications
Schilling (2011)[4]	Lung resection	TEA+sev (N.=21) TEA+des (N.=21) TEA+prop (N.=21)	63 (29-78) 60 (24-83) 64 (21-78)	Sev: 1.6-1.8% Des: 5.2-5.6% Prop: 3.8-4.2 mg/kg/h	0.6-0.7	OI
Luo (2015)[6]	Esophagectomy	Sev (N.=46) Prop (N.=46)	Unclear	Sev: 1-3% Prop: 4-8 mg/kg/h	Unclear	OI, incidence of perioperative infections
Jin (2013)[7]	Lung resection	Sev (N.=20) Prop (N.=20)	62±11 59±13	Sev: 1-3% Prop: 6-10 mg/kg/h	1	Qs/Qt
Hammouda (2013)[13]	Lung resection	Sev (N.=20) Prop (N.=20)	54.5±12.4 52.9±9.8	Sev: 1-2 MAC Prop: 3-12 mg/kg/h	1	OI
Lee (2012)[14]	Esophagectomy	TEA+sev (N.=24) TEA+prop (N.=24)	60.4±7.5 63.2±7.5	Sev: 1-2.5% Prop: TCI BIS 30-50	The FiO_2 was set to achieve SpO_2≥95%	Cardiopulmonary complications
Xu (2014)[15]	Esophagectomy	Sev (N.=20) Prop (N.=20)	60.6±6.6 59.0±7.8	BIS: 40-60 BIS: 40-60	1	OI, Qs/Qt, CI, cardiopulmonary complications
Erturk (2014)[16]	Lung resection	Sev (N.=22) Prop (N.=22)	52.31±13.22 52.45±11.8	Sev: 1-2.5% +40/60% O_2/N_2O mixture Prop: 7.5-15 mg/kg/h	1	OI
Fukuoka (2009)[17]	Thoracic surgery	TEA+sev (N.=22) TEA+prop (N.=22)	67±11 69±9	Sev: 1.4-1.6% Prop: 3-5 mg/kg/h	1	OI
Huang (2008)[18]	Thoracic surgery	Iso (N.=15) Prop (N.=15)	40±11 44±7	Iso: 1-2% Prop: 8-10 mg/kg/h	1	OI
Iwata (2008)[19]	Lung resection	TEA+sev (N.=26) TEA+prop (N.=26)	63±8 61±9	BIS: 45-55 BIS: 45-55	0.5	OI
Potočnik (2014)[20]	Thoracic surgery	Sev (N.=17) Prop (N.=19)	52.7±14.6 60.9±9.4	Sev: 2-2.5% Prop: 4-6 mg/kg/h	0.6-0.7	Postoperative OI, pulmonary complications
Pruszkowski (2007)[21]	Lung resection	TEA+sev (N.=33) TEA+prop (N.=32)	62 (37-68) 57 (18-70)	BIS: 40-60 BIS: 40-60	1	OI
Schwarzkopf (2009)[22]	Thoracic surgery	Sev (N.=28) Prop (N.=26)	61±14 57±14	Sev: 1 MAC Prop: 4-6 mg/kg/h	0.9	OI
Ozcan (2007)[23]	Thoracotomy	Iso (N.=25) Prop (N.=25) TEA+iso (N.=25) TEA+prop (N.=25)	53±10 52±11 50±12 48±10	BIS: 40-50 BIS: 40-50 BIS: 40-50 BIS: 40-50	0.8	OI, Qs/Qt
Beck (2001)[24]	Lung resection	Sev (N.=20) Prop (N.=20)	58 (34-78) 62 (46-78)	Sev: 1.8% Prop: 6-9 mg/kg/h	0.5	Qs/Qt, OI, CI
Ma (2015)[25]	Esophagectomy	Sev (N.=30) Prop (N.=30)	62±11 60±8	Sev: 1-2.5% Prop: 1.5-3 μg/mL	0.8	OI, pulmonary complications
Sharifian Atter (2014)[26]	Lung resection	Iso (N.=30) Prop (N.=30)	41.93±18.38 40.52±19.20	Iso: 1.1% Prop: 6 mg/kg/h	1	OI
Cho (2017)[27]	Lung resection	Dev (N.=52) Prop (N.=51)	63±8 62±10	Des: 5-7% Prop: 3-4 μg/mL	1	OI, CI
Luo (2010)[28]	Esophagectomy	Iso (N.=14) Prop (N.=14)	48.6±12.4 50.2±10.8	AAI: 20-30 AAI: 20-30	1	Qs/Qt
Pan (2000)[29]	Thoracic surgery	Env (N.=15) Prop (N.=15)	57.23±8.64 57.23±8.64	En: 1.8% Prop: 6 mg/kg/h	Unclear	Qs/Qt, OI
de la Gala (2017)[30]	Lung resection	Sev (N.=86) Prop (N.=88)	64.5 (19-85) 62.4 (25-88)	BIS: 40-60 BIS: 40-60	0.6-1.0	OI, Qs/Qt, CI, cardiopulmonary complications

OLV: one-lung ventilation; TEA: thoracic epidural anesthesia; Sev: sevoflurane; Des: desflurane; Iso: isoflurane; En: enflurane; Prop: propofol; OI: Oxygenation Index; Qs/Qt: pulmonary shunt fraction; CI: Cardiac Index; FiO_2: fraction of inspiration O_2.

Qualität der Studien:



Studienergebnisse:

TABLE II.—*Summary of finding table for cardiopulmonary intraoperative function and postoperative complications under inhalation anesthesia vs. intravenous anesthesia.*

Outcomes	Illustrative comparative risks (95% CI)		Relative effect (95% CI)	N. participants (N. studies)	Quality of the evidence (GRADE)
	Assumed risk (intravenous anesthesia group)	Corresponding risk reduction in inhalation anesthesia group			
OI OLV≤30 min	The mean OI ranged across intravenous anesthesia groups from 114.00 to 295.05	The mean OI was 27.37 (10.82-43.92) lower in inhalation anesthesia groups		982 (16)	+ Very low
OI OLV>30 min	The mean OI ranged across intravenous anesthesia groups from 123.30 to 216.00	Not significantly different		432 (7)	+ Very low
Qs/Qt (%) OLV≤30 min	The mean Qs/Qt ranged across intravenous anesthesia groups from 20.56 to 32.4	The mean Qs/Qt was 5.40 (2.95-7.84) higher in inhalation anesthesia groups		183 (4)	++ Low
Qs/Qt (%) OLV>30 min	The mean Qs/Qt ranged across intravenous anesthesia groups from 18.3 to 26.1	The mean Qs/Qt was 6.02 (2.41-9.63) higher in inhalation anesthesia groups		98 (3)	+ Very low
Pulmonary complications	290 per 1000 patients	150 (70 to 240) events avoided per 1000 patients	RR: 0.47 (0.33 to 0.66)	554 (8)	+++ Moderate
CI	The mean CI ranged across intravenous anesthesia groups from 2.7 to 3.4	The mean CI was 0.19 (0.10-0.28) higher in inhalation anesthesia groups		355 (4)	++ Low
Cardiac adverse events	83 per 1000 patients	Not significantly different	RR: 1.11 (0.51 to 2.41)	262 (3)	+ Very low

OI: Oxygenation Index; Qs/Qt: pulmonary shunt fraction; CI: Cardiac Index; OLV: one-lung ventilation.

Anmerkung/Fazit der Autoren

In summary, inhalation anesthesia can preserve intraoperative cardiac function, and reduce postoperative pulmonary complications in patients undergoing thoracic surgery with OLV. Although it decreases intraoperative pulmonary function, inhalation anesthesia may be superior to intravenous anesthesia in thoracic surgery.

- Pooled analyses showed that compared with intravenous anesthesia, inhalation anesthesia significantly increased pulmonary shunt fraction, improved cardiac index, and decreased oxygenation index during OLV intraoperatively.
- Inhalation anesthesia could reduce postoperative pulmonary complications but did not reduce postoperative cardiac adverse events.
- More well-designed high-quality RCTs are needed to demonstrate the superiority of inhalation anesthesia in patients undergoing thoracic surgery with OLV.

Ren S-F et al., 2019 [10].

Inhalation versus intravenous anesthesia for adults undergoing heart valve surgery: a systematic review and meta-analysis

Fragestellung

we conducted this systematic review and meta-analysis to compare the effects of inhalation anesthesia and intravenous anesthesia on postoperative outcomes in adults undergoing heart valve surgery, and we attempted to provide an evidence-based anesthetic regimen for heart valve surgery.

Methodik

Population:

- population: adult patients (>18 years) undergoing heart valve surgery

Intervention:

- any volatile anesthetics without restriction in dose and time of administration

Komparator:

- TIVA

Endpunkte:

- mortality at 30 days and postoperative complications including postoperative arrhythmia, acute kidney injury (AKI), pulmonary complications (pneumonia, pulmonary edema or respiratory failure), neurological events (type Iincluding focal injury, stupor, or coma, or type IIincluding deterioration in intellectual function, memory deficit or seizures), reoperation for bleeding, myocardial infarction. Secondary outcomes focused on myocardial injury by the postoperative peak troponin release, hospital stay, Intensive Care Unit (ICU) stay and the ventilation time.

Recherche/Suchzeitraum:

- Bis Juni 2018 (u.a. Medline, Cochrane)

Qualitätsbewertung der Studien:

- Cochrane Collaboration risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 13 RCTs (n=962 patients), with 473 received inhalation anesthesia and 489 received TIVA were included in this meta-analysis

Charakteristika der Population:

- For inhalation group, nine trials administrated sevoflurane,[8,9,23-26,28,30,31] two administrated desflurane[6, 7] and further two used isoflurane.[27, 29]

TABLE I.—*Characteristics of included randomized controlled trials.*

Study	Sample size (Inhalation/ TIVA,n)	Mean age (y)	Male (%)	Surgical procedure	Volatile anesthetic	Administration
Bignami (2012)[23]	50/50	67/66	74/78	MVR	Sevo	Pre-CPB, post-CPB
Cavalca (2008)[24]	22/21	67.7/65.2	48/78	MVR, AVR, CABG, DVR, myxoma excision	Sevo	Pre-CPB, post-CPB
Cho (2009)[25]	15/15	57/48	20/20	MVR, AVR	Sevo	Whole procedure
Cromeecke (2006)[26]	15/15	67/71	60/53	AVR	Sevo	Whole procedure
Howie (1996)[27]	23/27	53/53	35/37	MVR	Iso	Whole procedure
Jovic (2012)[28]	11/11	63/63	45/73	AVR	Sevo	Whole procedure
Kapoor (2015)[6]	36/40	42/38	Not reported	AVR	Des	Whole procedure
Landoni (2007)[7]	59/61	62/59	59/50	MVR, MVP	Des	30 min before CPB
Landoni (2014)[8]	100/100	68/70	72/64	MVR/AVR/DVR+CABG	Sevo	Whole procedure
Moscarelli(2018)[9]	31/31	60.7/68.3	13/15	Min invasive MVP	Sevo	Whole procedure
Newman (1998)[29]	16/15/13	56/61/60	38/67/31	MVR, AVR, DVR	Iso	Whole procedure
Yang (2017)[30]	36/37	50.5/50.7	44/49	MVR, AVR, TVR, TVP	Sevo	Whole procedure
Yoo (2014)[31]	56/56	58.8/58.1	43/66	MVR, AVR, TVP, DVR, Bental	Sevo	whole procedure

MVR: mitral valve replacement; AVR: aortic valve replacement; CABG: coronary artery bypass grafting; DVR: dual valve replacement; MVP: mitral valvuloplasty; min invasive MVP: minimally invasive mitral valvuloplasty; TVR: tricuspid valve replacement; TVP: tricuspid valve plasty; Sevo: sevoflurane; Iso: isoflurane; Des: desflurane; CPB: cardiopulmonary bypass; MAC: minimum alveolar concentration; EEG: electroencephalography; TIVA: total intravenous anesthesia; cTnI: serum cardiac troponin I: CK-MB: creatine kinase-MB.

Qualität der Studien:

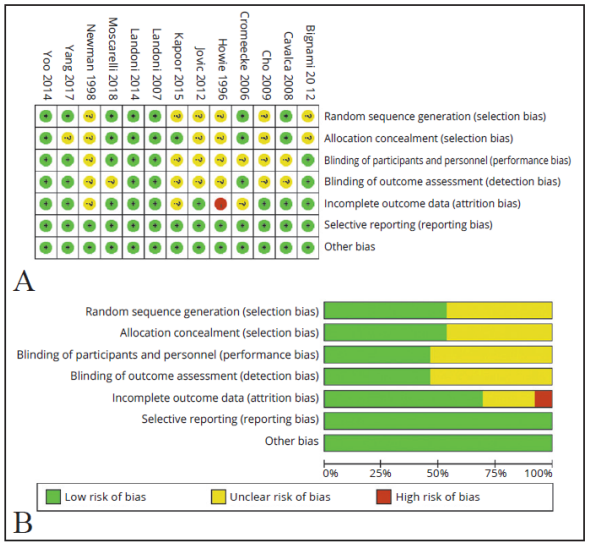


Figure 2.—Assessment of risk bias. A) A summary of bias for each included study; B) a graph with percentages for all included studies.[6-9, 23-31]

Studienergebnisse:

Meta-analysis comparing inhalation anesthesia versus TIVA

- Overall analysis comparing inhalation anesthesia (including sevoflurane, desflurane and isoflurane) with TIVA (including propofol, fentanyl and sufentanil) from 13 RCTs showed that, the rates of all major endpoints were comparable between the inhalation anesthesia and TIVA. Based on 496 participants reported from four RCTs, there was no statistically reduction with the use of inhalation anesthesia compared to TIVA in death within 30 days (12/249 [4.8%] vs. 13/247 [5.3%], RR=0.97; 95% CI: 0.45 to 2.09; P=0.93; P for heterogeneity=0.66, I2=0%; Figure 3).[6-8, 23]
- Rates of postoperative arrhythmia from six trials[6-9, 23, 25] (67/295 [22.7%] vs. 56/293 [19.1%], RR=1.19; 95% CI: 0.87 to 1.63; P=0.27; P for heterogeneity=0.77, I2=0%), AKI from six trials[7, 8, 23, 25, 28, 31] (61/291 [21.0%] vs. 44/293 [15.0%], RR=1.39; 95% CI: 0.79 to 2.43; P=0.25; P for heterogeneity=0.13, I2=41%), pulmonary complications from five trials[7, 8, 23, 25, 28] (10/235 [4.3%] vs. 7/237 [3.0%], RR=1.16; 95% CI: 0.42 to 3.23; P=0.77; P for heterogeneity=0.54, I2=0%), neurological events from five trials[7-9, 23, 29] (9/256 [3.5%] vs. 15/270 [5.6%], RR=0.66; 95% CI: 0.29 to 1.49; P=0.32; P for heterogeneity=0.78, I2=0%), reoperation for bleeding from three trials[9, 28, 31] (6/98 [6.1%] vs. 1/98 [1.0%], RR=3.51; 95% CI: 0.78 to 15.80; P=0.1; P for heterogeneity=0.98, I2=0%) and myocardial infarction from three trials[7, 8, 23] (8/209 [3.8%] vs. 10/211 [4.7%], RR=0.8; 95% CI: 0.32 to 2.00; P=0.64; P for heterogeneity=0.91, I2=0%) were not significantly different between the inhalation anesthesia and TIVA.
- Results from seven trial measuring myocardial injury by the postoperative peak troponin release[6-8,23,26,28,30] suggested no significant difference between the inhalation anesthesia and TIVA (SMD=-0.24; 95% CI: -0.61 to 0.12; P=0.19; P for heterogeneity=0.0001, I2=78%)
- Also, the hospital stay[6, 7, 9, 23, 24, 26, 28, 30, 31] (SMD=-0.13; 95% CI: -0.44 to 0.18; P=0.41; P for heterogeneity<0.0001, I2=77%, Figure 4), ICU stay6-9, 23, 24, 26, 28, 30, 31 (SMD=-0.43; 95% CI: -0.89 to 0.04; P=0.08; P for heterogeneity<0.00001, I2=90%) and the ventilation time (SMD=-0.52; 95% CI: -1.11 to 0.08; P=0.09; P for heterogeneity<0.00001, I2=93%)[6, 8, 9, 23, 24, 27, 28, 30, 31] were comparable between two groups.

Meta-analysis comparing sevoflurane versus propofol

- Eight of thirteen included studies compared sevoflurane with propofol in patients undergoing heart valve surgery.[8, 9, 23, 24, 26, 28, 30, 31]
- Same to the overall analysis, results of mortality from two trials, postoperative arrhythmia from three trials, AKI from four trials, pulmonary complications from three trials, neurological events from three trials, reoperation for bleeding from three trials and myocardial infarction from two trials were not significantly different. Also, pooled data of postoperative peak troponin release from five trials, hospital stay from seven trials, ICU stay from eight trials and ventilation time from eight trials were comparable between two groups

Meta-analysis comparing desflurane versus propofol

- Desflurane comparing with propofol was studied only in two RCTs with high heterogeneity in study design.
- Kapoor et al.[6] reported patients undergoing aortic valve replacement and administrated desflurane throughout the procedure, whereas Landoni et al.[7] studied patients received mitral surgery and only administrated desflurane 30 minutes before CPB. The pooled data of mortality, arrhythmia, peak troponin value, hospital/ICU stay showed no significant different

Meta-analysis comparing isoflurane versus fentanyl

- Newman et al. and Howie et al. conducted the study comparing isoflurane versus fentanyl.[27, 29]
- However, these two studies did not report the majority of outcomes. Newman et al. reported one neurological event in the isoflurane group and two in the fentanyl group, and Howie et al. reported the comparable ventilation time between two groups.

Anmerkung/Fazit der Autoren

Among patients undergoing heart valve surgery, the use of inhalation anesthesia compared with TIVA failed to demonstrate superiority for survival, cardioprotection, renal protection and other postoperative complications and the evidence was not enough to draw firm conclusions due to the limited sample size in this meta-analysis. A determination of equivalence or superiority between these two anesthetic regimens requires further researches.

- General anesthesia is routinely used in cardiac surgery. Many studies have found that volatile anesthetics are associated with improved clinical outcomes for adults undergoing CABG. However, the effect of volatile anesthetics for adults after heart valve surgery has been unclear.
- Evidence from 13 RCTs including 962 adult patients indicated that inhalation anesthesia and TIVA were associated with similar effect on cardioprotection, renal protection, survival, pulmonary complications, neuro-logical events, postoperative bleeding, ventilation time, hospital stay and ICU stay.
- The use of inhalation anesthesia com-pared with TIVA failed to demonstrate superiority for survival and major postoperative complications among patients undergoing heart valve surgery, and the evidence was in-sufficient to draw firm conclusions due to the limited sample size.
- A determination of equivalence or superiority between these two anesthetic regi-mens requires further researches.

Soltanizadeh S et al., 2017 [11].

Outcomes of cancer surgery after inhalational and intravenous anesthesia: A systematic review

Fragestellung

The aim of this systematic review was to investigate if there is a difference in overall mortality and postoperative complications in patients receiving INHA versus TIVA during cancer surgery.

Methodik

Population:

- patients undergoing cancer surgery

Intervention:

- TIVA

Komparator:

- INHA

Endpunkte:

- Overall mortality and postoperative complications

Recherche/Suchzeitraum:

- Update März 2017 (u.a. PubMed, Embase)

Qualitätsbewertung der Studien:

- Bias in non-randomized studies were evaluated with ACROBAT-NRSI (A Cochrane Risk Of Bias Assessment Tool for Non-Randomized Studies of Intervention)

Ergebnisse

Anzahl eingeschlossener Studien:

- N=8

Charakteristika der Population:

- Four studies reported overall mortality in cancer patients and four studies reported postoperative complications [17–24].

Demographic characteristics of included studies.

Study	Country	Year of participant enrolment	Study design	INHA (n=)	TIVA (n=)	Sex (M:F)	Mean age (±SD)	Volatile agent	Intravenous agent	Cancer site	Outcome
Long-term mortality studies											
Wigmore [17]	UK	2010–2013	Retrospective	3316	3714	2596:4434	57 (15.2) (INHA) 57 (14.4) (TIVA)	Sevoflurane/isoflurane	Propofol	Various cancer sites	Overall mortality
Enlund [18]	Sweden	1998–2010	Retrospective	1935	903	531:2307	[a]	Sevoflurane	Propofol	Brest, colon and rectum	Overall mortality
Sofra [19]	Italy	2010–2011	RCT	14	14	23:5	61.2 (10.8) (INHA) 63.2 (6.8) (TIVA)	Sevoflurane	Propofol	Bladder	Overall mortality
Lee [20]	Korea	2007–2008	Retrospective	152	173	-	50.5 (10.9) (INHA) 50.2 (9.7) (TIVA)	Sevoflurane	Propofol	Breast	Recurrence-free survival and overall mortality
Postoperative complication studies											
Chang [21]	Taiwan	2012–2013	Retrospective	87	69	147:9	52.4 (9.8)	Sevoflurane/desflurane	Propofol	Head and neck	Postoperative complications
Owusu-Agyemang [22]	USA	2011–2014	Retrospective	139	74	100:113	50.0 (14.1) (INHA) 52.5 (10.6) (TIVA)	Desflurane	Propofol	Various cancer sites	Postoperative complications
Lee [23]	Korea	From 2009	RCT	24	24	48:0	60.4 (7.5) (INHA) 63.2 (7.5) (TIVA)	Sevoflurane	Propofol	Esophagus	Postoperative complications
Liu [24]	China	2014	RCT	29	29	0:58	48.3 (9.8) (INHA) 45.9 (10.0) (TIVA)	Sevoflurane	Propofol	Uterus	Postoperative complications

RCT = randomized controlled trial.
- not reported.
[a] Reported age not applicable in table.

Qualität der Studien:

- Evidence was evaluated to be of moderate to serious risk of bias.

Studienergebnisse:

Overall mortality

- In the four studies reporting overall mortality, a total number of 10,221 patients were included.

Overall mortality rates of primary studies, Cox regression proportional Hazard Ratio (HR) in multivariate analysis.

Study	Event/no (%)				Overall mortality HR (CI 95%)		p-Value	Recurrence-free survival HR (CI 95%)		p-Value	Follow-up
	INHA		TIVA		INHA	TIVA		INHA	TIVA		
Wigmore [17]											2.66 years (median)
Breast cancer	52/603	(8.6)	103/1560	(6.6)	-	-	-	-	-	-	
GI cancer	223/504	(44.2)	137/418	(32.8)	-	-	-	-	-	-	
Gynecology	133/428	(31.1)	81/331	(24.5)	-	-	-	-	-	-	
Sarcoma	128/625	(20.5)	77/491	(15.7)	-	-	-	-	-	-	
Urology	41/432	(9.5)	41/670	(6.1)	-	-	-	-	-	-	
Other	179/724	(24.7)	65/244	(26.6)	-	-	-	-	-	-	
					1.47 (1.31–1.64)[a]	**1**	**<0.001**	-	-	-	
Enlund [18]											5 years
Colon cancer	243/516[b]	(47.1)	66/179[b]	(37.0)	1	0.94 (0.71–1.25)	n.s.	-	-	-	
Rectal cancer	67/202[b]	(33.0)	28/104[b]	(27.0)	1	0.83 (0.52–1.31)	n.s.	-	-	-	
Breast cancer	219/1217[b]	(18.0)	99/620[b]	(16.0)	1	1.33 (0.91–1.94)	n.s.	-	-	-	
					1	**0.85 (0.72–1.00)**[c]	**n.s.**	-	-	-	
Sofra [19]											–
Bladder cancer	5/14	(35.7)	2/14	(14.3)	-	-	-	-	-	-	-
Lee [20]											5 years
Breast cancer	11/152	(7.2)	9/173	(5.2)	-	-	n.s.	**1**	**0.48 (0.27–0.86)**	**0.014**[d]	

% was calculated by dividing event with intervention group size.
n.s. = not-significant.
Bold numbers indicate significance at 0.051.
- not reported.
[a] Multivariate analysis adjusted for age, sex, blood transfusion, epidural use, ASA-score, surgical severity and metastasis at surgery.
[b] Calculated from Table 3 [19].
[c] Analysis received from corresponding author and adjusted for age, sex and type of malignancy.
[d] Adjusted for tumor size, invasion grade of lymph nodes, histologic grade and postoperative endocrine-, radio- and chemotherapy.

Postoperative complications

- Postoperative complications during hospital stays were reported in four studies including a total of 475 patients.

Table 3
Overview of postoperative complications.

Intervention groups	Chang [21]			Owusu-Agyemang [22]			Lee [23]			Liu [24]		
	INHA (n = 87)	TIVA (n = 69)	p-Value	INHA (n = 139)	TIVA (n = 74)	p-Value	INHA (n = 24)	TIVA (n = 24)	p-Value	INHA (n = 29)	TIVA (n = 29)	p-Value
LOS (± SD)	23.6 (12.1)	20.5 (9.6)	n.s.	17.5 (13.0)	19.7 (27.0)	n.s.	13.0 (2.5)	16.6 (9.9)	n.s.	7.2 (1.5)	6.6 (1.4)	n.s.
Cardiovascular (%)	0 (0.0)	0 (0.0)		13 (9.4)	2 (2.7)	n.s.	3 (12.5)	3 (12.5)	n.s.	0 (0.0)	0 (0.0)	n.s.
Respiratory (%)	47 (54.0)	18 (26.1)	<0.001[†]	3 (2.2)	2 (2.7)	n.s.	16 (66.7)	15 (62.5)	n.s.	-	-	
Neurological (%)	0 (0.0)	0 (0.0)		1 (0.7)	1 (1.4)	n.s.	-	-		-	-	
Infections (%)	-	-		48 (34.3)[*]	24 (32.4)[*]	n.s.	2 (8.3)	0 (0.0)	n.s.	7 (24.1)[‡]	2 (6.9)[‡]	n.s.
Gastrointestinal (%)	-	-		45 (32.4)	27 (36.5)	n.s.	1 (4.2)	2 (8.3)	n.s.	0 (0.0)	0 (0.0)	n.s.
Renal (%)	-	-		3 (2.2)	6 (8.1)	n.s.	0 (0.0)	2 (8.3)	n.s.	-	-	
Hematological (%)	-	-		10 (7.2)	7 (9.5)	n.s.	-	-		-	-	
Multisystem organ (%)	-	-		0 (0.0)	1 (1.4)	n.s.	-	-		-	-	
Death (%)	2 (2.3)	0 (0.0)	n.s	1 (0.7)	0 (0.0)	-	0 (0.0)	0 (0.0)	n.s.	-	-	
Other (%)	21[a] (24.1)	19[a] (27.5)	n.s							9 (31.0)[b]	8 (27.6)[b]	n.s.

Cardiovascular: arrhythmia, deep venous thrombosis, pulmonary embolism, change in ECG/cardiac enzyme, coronary vessel stenosis.
Respiratory: atelectasis, respiratory failure, pneumonia, pulmonary edema.
Neurological: transient ischemic attack, stroke, delirium, cerebral edema.
Infections: wound infection, urinary tract infection, sepsis/septic shock, clostridium difficile, diarrhea.
Gastrointestinal: bleeding, ileus, anastomotic leak, enterocutaneous fistula, vomiting.
LOS: mean length of hospital stay, days.
% was calculated by dividing event with intervention group size, p-values based on chi-square test or Fisher's exact test.
- not reported.
[†] Odds ratio 0.41, 95% CI: 0.18–0.92, p = 0.031 in multivariate logistic regression, adjusted for anesthetic duration, mean central venous pressure, total urine output and volume of crystalloid and colloid administration.
[*] Pneumonia classified as infectious complication in this study.
[‡] Including urinary tract infection, vaginal cuff infection and febrile morbidity.
[a] Surgical complications including thrombosis, bleeding and reoperation due to graft failure.
[b] Bladder dysfunction.

Anmerkung/Fazit der Autoren

In conclusion, TIVA might lead to decrease of mortality and reduced postoperative pulmonary complications. However, current evidence is not convincing and large cancer-specific randomized studies are needed to eliminate known and unknown confounders.

Sun H et al., 2019 [12].

A systematic review: comparative analysis of the effects of propofol and sevoflurane on postoperative cognitive function in elderly patients with lung cancer.

Fragestellung

to compare the effects of propofol and sevoflurane anesthesia on postoperative cognitive function in elderly patients with lung cancer

Methodik

Population:

- population of > 60 years old, ASA class I to III patients who had scheduled for lung cancer surgeries

Intervention/Komparator:

- propofol or sevoflurane during anesthesia.

Endpunkte:

- postoperative mini-mental state examination (MMSE) scores at various time points; serum S100beta concentration 24 h after surgery

Recherche/Suchzeitraum:

- Embase, Pubmed, The Cochrane Library, Web of Science, and China National Knowledge Infrastructure (CNKI)
- From the database construction time to March 2018

Qualitätsbewertung der Studien:

- Cochrane Risk Bias Assessment Tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 14 studies, including 1404 patients, were included in the final meta-analysis

Charakteristika der Population:

Table 2 Characteristics of studies included in the meta-analysis

Author	Year	Country	Sex (M/F)	Age	Surgery	ASA grade	Outcomes	Propofol group		Sevoflurane group	
								Method	No.	Method	No.
Yu et al.	2012	China	44/36	68.8 ± 3.8	Lung cancer operation	I~II	①②③④⑤⑥	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: propofol	40	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: sevoflurane	40
Tang et al.	2014	China	38/32	70.0 ± 11.7	Lung cancer operation	I~II	①②③④⑤⑥	Induction: etomidate, midazolam, fentanyl, rocuronium; Maintain: propofol	35	Induction: etomidate, midazolam, fentanyl, rocuronium; Maintain: sevoflurane	35
Sun et al.	2014	China	77/29	72.2 ± 2.6	Lung cancer operation	N	①②③④⑤⑥	Induction: fentanyl and vecuronium bromide; Maintain: propofol 2~4 mg/kg/min	53	Induction: fentanyl and vecuronium bromide; Maintain: sevoflurane	53
Cui et al.	2015	China	94/76	69 ± 12.9	Lung cancer operation	N	①③⑤⑥	Induction: fentanyl, etomidate, vecuronium bromide; Maintain: propofol 2~4 mg/kg/min	80	Induction: fentanyl, etomidate, vecuronium bromide; Maintain: sevoflurane 1%~ 3%	80
Zhang et al.	2016	China	101/91	60.0 ± 6.4	Lung cancer operation	N	①③④⑥	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: propofol	96	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: sevoflurane	96
Wang H et al.	2015	China	41/31	73.5 ± 2.8	Lung cancer operation	I~II	①②③④⑤⑥	Induction: unified rapid induction; Maintain: propofol	36	Induction: unified rapid induction; Maintain: sevoflurane	36
Wang F et al.	2017	China	32/18	72.5 ± 3.0	Lung cancer operation	N	①②③④⑤⑥	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: propofol	50	Induction: midazolam, fentanyl, rocuronium, etomidate; Maintain: sevoflurane	50
Zhao et al.	2014	China	80/30	73.5 ± 2.0	Lung cancer operation	I~II	①②③④⑤⑥	Induction: fentanyl and vecuronium bromide; Maintain: propofol 2~4 mg/kg/min	50	Induction: fentanyl and vecuronium bromide; Maintain: sevoflurane	60
Chen et al.	2015	China	43/35	69.2 ± 3.2	Lung cancer operation	N	①②③④⑤⑥	Induction: midazolam, propofol, fentanyl and vecuronium bromide; Maintain: propofol 6~10 mg/kg/min	39	Induction: midazolam, propofol, fentanyl and vecuronium bromide; Maintain: sevoflurane	39
Huang et al.	2015	China	50/40	68.2 ± 1.3	Lung cancer operation	N	①②③④⑤⑥	Induction: rocuronium, fentanyl, midazolam, etomidate; Maintain: propofol	45	Induction: rocuronium, fentanyl, midazolam, etomidate; Maintain: sevoflurane	45
Lin et al.	2017	China	54/40	68.23 ± 1.32	Lung cancer operation	I~II	①②③④⑥	Induction: propofol, midazolam, vecuronium, fentanyl; Maintain: propofol	40	Induction: propofol, midazolam, vecuronium, fentanyl; Maintain: sevoflurane	54
Zhang et al.	2017	China	41/29	P: 74.8 ± 2.1; S: 74.3 ± 2.5	Lung cancer operation	I~II	②③④	Induction: fentanyl, etomidate, midazolam, rocuronium; Maintain: propofol	35	Induction: fentanyl, etomidate, midazolam, rocuronium; Maintain: sevoflurane	35
Yang et al.	2017	China	84/36	71.9 ± 2.5	Lung cancer operation	N	①②③④⑤⑥	Induction: unified rapid induction; Maintain: propofol	60	Induction: unified rapid induction; Maintain: sevoflurane	60
Tian et al.	2017	China	38/24	P: 68.3 ± 13.5; S: 65.5 ± 16.2	Lung cancer operation	I~II	①③⑥	Induction: midazolam, fentanyl, propofol; Maintain: propofol	31	Induction: midazolam, fentanyl, sevoflurane; Maintain: propofol	31

N Not mentioned, *ASA* American society of anesthesiology, ① = Preoperative MMSE score, ② = MMSE score at 6 h after surgery, ③ = MMSE score at 1 day after surgery, ④ = MMSE score at 3 day after surgery, ⑤ = MMSE score at 7 day after surgery, ⑥ = Plasma S100β protein level at 1 day after surgery, *P* Propofol, *S* Sevoflurane

Qualität der Studien:

Table 6 Study quality: review authors' judgments about each risk of bias item for each included study

Author	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Yu et al.	2012	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Tang et al.	2014	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Sun et al.	2014	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Cui et al.	2015	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Zhang et al.	2016	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Wang H et al.	2015	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Wang F et al.	2017	Random number table	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Zhao et al.	2014	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Chen et al.	2015	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Huang et al.	2015	Random number table	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Lin et al.	2017	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Zhang et al.	2017	Unclear risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Unclear risk	Unclear risk
Yang et al.	2017	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk
Tian et al.	2017	Low risk	Unclear risk	Unclear risk	Unclear risk	Low risk	Low risk	Unclear risk

Studienergebnisse:

- Results suggested that propofol has a greater adverse effect on cognitive function in the elderly patients with lung cancer than sevoflurane.
- There were significant differences in issues of MMSE 6 h (11 studies; SMD -1.391, 95% CI -2.024, − 0.757; p < 0.001), MMSE 24 h (14 studies; SMD -1.106, 95% CI -1.588, − 0.624; p < 0.001), MMSE 3d (11 studies; SMD -1.065, 95% CI -1.564, − 0.566; p < 0.001), MMSE 7d (10 studies; SMD -0.422, 95% CI -0.549, − 0.295; p < 0.001), and serum S100beta concentration at 1 day after surgery (13 studies; SMD 0.746, 95% CI 0.475, 1.017; p < 0.001).

Anmerkung/Fazit der Autoren

In summary, propofol has a more significant adverse effect on postoperative cognitive function in lung cancer patients than sevoflurane. In the included studies, some of the documents are of low quality and may affect the stability and reliability of the final results. Therefore, larger samples, more rigorous design, and higher quality tests are still needed for verification.

Kommentare zum Review

- The majority of included studies had been undertaken in Asian populations.

Xia Y et al., 2018 [13].

Clinical efficacy of xenon versus propofol. A systematic review and meta-analysis.

Fragestellung

to compare the clinical efficacy of xenon with that of propofol

Methodik

Population:

- Patients treated with xenon or propofol (siehe Tabelle zu den Charakteristika)

Intervention:

- xenon

Komparator:

- propofol

Endpunkte:

- time in the PACU, the influence of xenon on nondepolarizing muscular relaxants, BIS index, hemodynamic effects, and side effects, such as hypotension, bradycardia, hypertension and postoperative nausea and vomiting (PONV)

Recherche/Suchzeitraum:

- through December 2017 using various databases, including PubMed, Embase, and the Cochrane Library

Qualitätsbewertung der Studien:

- Cochrane collaboration's tool

Ergebnisse

Anzahl eingeschlossener Studien:

- thirteen trials that included a total of 817 patients

Charakteristika der Population:

Table 1

Basic characteristics of included studies.

Study	Year	Patients Age/ASA	Intervention (no.) Xenon	Intervention (no.) Propofol	Type(s) of surgery	Outcomes used in this meta-analysis
Abramo et al[3]	2012	18–60/I–II	60%–65% (0.8MAC) (no.10)	5 mg/kg/h (no. 10)	Roux-en-Y laparoscopic gastric bypass	
Baumert et al[5]	2008	≥40/III–IV	62%–68% (0.9MAC) (No.20)	5 mg/kg/h (no. 20)	Elective noncardiac surgery	BIS value, MAP, adverse events
Baumert et al[6]	2007	>40/III–IV	60%(0.8MAC) (no. 13)	5 mg/kg/h (no. 13)	Noncardiac, nonthoracic surgery	BIS value, MAP, HR
Baumert et al[4]	2005	>18/III–IV	60%–65% (0.8MAC) (no. 12)	3 mg/kg/h (no. 14)	Implantation of a cardioverter-defibrillator (ICD)	BIS value, HR, MAP
Bein et al[7]	2005	?/ III	55%–60% (0.8MAC) (no. 20)	3–8 mg/kg/h (no. 19)	Elective abdominal aortic aneurysm repair	HR, MAP
Bein et al[20]	2004	?/ III	60%(0.8MAC) (no. 20)	?(no. 19)	Aortic reconstruction	HR, MAP
Coburn et al[8]	2008	18–60/I–II	60%(0.8MAC) (no. 71)	0.1 mg/kg/min (no. 71)	Trauma/orthopedic, Otolaryngology, urology, gynaecology, plastic surgery, laparoscopy	Time in PACU, PONV
Coburn et al[9]	2005	18–60/I–II	60%(0.8MAC) (no. 63)	0.1–0.12 mg/kg/min (no. 53)	Any elective surgery	Time in PACU, PONV
Coburn et al[10]	2005	18–60/I–II	60%(0.8MAC) (no. 80)	0.1–0.12 mg/kg/min (no. 80)	Any elective surgery	Time in PACU, BIS value, adverse events, HR, MAP
Hanss et al[13]	2006	?/II–IV	60%(0.8MAC) (no. 22)	3–6 mg/kg/h (no. 22)	Abdominal aortic surgery	HR, MAP
Kunitz et al[16]	2005	18–60/I–II	60%(0.8MAC) (no. 21)	0.09–0.13 mg/kg/min (no. 21)	?	Neuromuscular monitoring (mivacurium)
Kunitz et al[15]	2004	18–60/I–II	60%(0.8MAC) (no. 20)	0.06–0.12 mg/kg/min (no. 20)	?	Neuromuscular monitoring (rocuronium)
Rasmussen et al[17]	2006	>60/I–II	50%–70% (0.8MAC) (no. 21)	3–5 mg/kg/h (no. 18)	Knee replacement	HR, MAP

ASA = American Society of Anesthesiologists, BIS = bispectral index, HR = heart rate, MAC = minimum alveolar concentration, MAP = mean arterial blood pressure, PACU = postanesthesia care unit, PONV = postoperative nausea and vomiting.

Qualität der Studien:

Table 2

Risk of bias in included studies.

Study	Year	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting
Abramo et al[5]	2012	Unclear	Unclear	High	Low	Low	Low
Baumert et al[5]	2008	Unclear	Unclear	High	Low	High	High
Baumert et al[6]	2007	Unclear	Unclear	High	Low	Low	High
Baumert et al[6]	2005	Unclear	Unclear	High	Low	High	High
Bein et al[7]	2005	Unclear	Unclear	High	Low	Low	Low
Bein et al[20]	2004	Low	Unclear	High	Low	Low	Low
Coburn et al[8]	2008	Low	Low	High	Low	Low	Low
Coburn et al[9]	2005	Unclear	Unclear	High	High	Low	Low
Coburn et al[10]	2005	Low	Low	High	Low	High	High
Hanss et al[13]	2006	Low	Unclear	Unclear	Low	Low	Low
Kunitz et al[16]	2005	Low	Low	High	High	Low	High
Kunitz et al[15]	2004	Low	Low	High	High	Low	High
Rasmussen et al[17]	2006	High	Unclear	High	Low	Low	Low

Studienergebnisse:

- Patients treated with xenon had a lower bispectral index (BIS) (weighted mean difference (WMD): -6.26, 95% confidence interval (CI): -11.33 to -1.18, P=.02), a higher mean arterial blood pressure (MAP) (WMD: 7.00, 95% CI: 2.32–11.68, P=.003) and a lower heart rate (HR) (WMD: -9.45, 95% CI: -12.28 to -6.63, P<0.00001) than propofol-treated patients.
- However, there were no significant differences between the 2 treatment groups in the effects of non-depolarizing muscular relaxants, the duration spent in the post anesthesia care unit (PACU) (WMD: -0.94, 95% CI: -8.79–6.91, P=.81), or the incidence of perioperative complications [assessed using the outcomes of postoperative nausea and vomiting (PONV) (relative risk (RR): 2.01, 95% CI: 0.79–5.11, P=.14), hypotension (RR: 0.62, 95% CI: 0.27 to 1.40, P=.25), hypertension (RR: 1.27, 95% CI: 0.73–2.21, P=.39) and bradycardia (RR: 1.00, 95% CI: 0.36–2.74, P=1.00)].

Anmerkung/Fazit der Autoren

In conclusion, xenon has been demonstrated to have good linical efficacy and safety with regard to recovery time, influence on neuromuscular blockers, and postoperative complications, and it may therefore be a good alternative to general anesthetics. In addition, clinicians must take the higher MAP, lower HR, and lower BIS values associated with xenon into consideration when using this drug instead of propofol as an anesthetic.

Kommentare zum Review

- Keine Spezifikation der Patientenpopulation

Zhang R et al., 2018 [14].

The Comparison of Midazolam and Propofol in Gastrointestinal Endoscopy: A Systematic Review and Meta-analysis.

Fragestellung

to compare the efficacy and safety of midazolam and propofol in gastrointestinal endoscopy.

Methodik

Population:

- patients undergoing gastrointestinal endoscopy;

Intervention:

- midazolam

Komparator:

- propofol

Endpunkte:

- endoscopist satisfaction scores and patient satisfaction scores, procedure time, hypotension, hypoxia, and bradycardia

Recherche/Suchzeitraum:

- PubMed, EMbase, Web of science, EBSCO, and Cochrane library databases

Qualitätsbewertung der Studien:

- Die Qualitätsbewertung der Primärliteratur wurde anhand der Jadad-Skala vorgenommen. Diese Bewertung ermöglicht keine umfassende Einschätzung des Verzerrungspotenzials.

Ergebnisse

Anzahl eingeschlossener Studien:

- Five randomized controlled trials involving 552 patients

Charakteristika der Population & Qualität der Studien:

TABLE 1. Characteristics of Included Studies

		Midazolam Group						Propofol Group					
No.	References	No.	Age (y)	Male (n)	Body Mass Index (kg/m²)	ASA Class 1 (n)	Methods	No.	Age (y)	Male (n)	Body Mass Index (kg/m²)	ASA Class 1 (n)	Methods	Jada Scores
1	Ominami et al[17]	66	70.1 ± 8.8	54	22.4 ± 3.3	7	An initial bolus of 3-4 mg of midazolam, and the increments of 2 mg until RSS 5-6 for endoscopic submucosal dissection for esophageal squamous cell carcinoma	66	69.5 ± 8.2	52	22.0 ± 3.0	7	1% propofol administered continuously for endoscopic submucosal dissection for esophageal squamous cell carcinoma	4
2	Fanti et al[16]	35	52.3 ± 18.1 in EGD, 58.6 ± 11.6 in CS	20 in EGD, 20 in CS	23.2 ± 4 in EGD, 23.2 ± 4.5 in CS	16 in EGD, 19 in CS	Fentanyl (1 μg/kg) + midazolam (0.03-0.04 mg/kg) or midazolam only for gastrointestinal endoscopy	35	47.8 ± 17.5 in EGD, 57.2 ± 13.8 in CS	22 in EGD, 22 in CS	24.3 ± 5 in EGD, 25.4 ± 6.4 in CS	18 in EGD, 20 in CS	Fentanyl (1 μg/kg) + propofol Target Controlled Infusion (1.2-1.6 μg/ml) or propofol target controlled infusion only for gastrointestinal endoscopy	5
3	Lera dos Santos et al[22]	100	52.14 ± 15.01	34	25.91 ± 4.54	63	Initial dose of 2-5 mg midazolam, 0.5-1.0 mg every 2-3 min, up to a maximum cumulative dose of 10 mg or 0.1 mg/kg of body weight for maintenance + fentanyl for upper gastrointestinal endoscopy	100	54.40 ± 15.44	29	27.39 ± 6.59	55	Initial dose of 0.25-0.5 mg/kg propofol, 10-20 mg bolus at 60 s intervals for maintenance + fentanyl for upper gastrointestinal endoscopy	4
4	Meining et al[23]	30	57, median	16	25.4, median	0	An initial dose of 1-2 mg, 1-2 mg boluses given until the patient reached a state of conscious sedation or until a maximum dosage of 5 mg for upper gastrointestinal endoscopy	30	59, median	13	25.5, median	0	Initial dose 0.5-1 mg/kg, further boluses of 10-20 mg until conscious sedation is achieved, up to a maximum dosage of 500 mg for upper gastrointestinal endoscopy	3
5	Carlsson and Grattidge[24]	45	43 ± 13	21	—	—	Initial dose of 0.06 mg/kg midazolam, followed by repeat doses of 50% of the initial dose, as required for upper gastrointestinal endoscopy	45	44 ± 12	18	—	—	Initial dose of 0. 6 mg/kg propofol, followed by repeat doses of 50% of the initial dose, as required for upper gastrointestinal endoscopy	4

ASA indicates American Society of Anesthesiologists risk class; CS, colonoscopy; EGD, upper endoscopy; RSS, Ramsay Sedation Score.

Studienergebnisse:

- Overall, compared with midazolam sedation during gastrointestinal endoscopy, propofol sedation results in higher endoscopist satisfaction scores during gastrointestinal endoscopy than midazolam [standard mean difference (Std. MD)=-0.71; 95"/o confidence interval (CI)=-l.05 to -0.37; P < 0.0001), but the comparison shows no remarkable influence on patient satisfaction scores between midazolam and propofol (Std. MD=-0.34; 95% CI=-0.88 to 0.20; P=0.21), procedure time (Std. MD=0.14; 95% CI=-0.13 to 0.42; P=0.31), hypoxia [risk ratio (RR)=0.86; 95% CI=0.53-1.38; P=0.53), and bradycardia (RR= 1.05; 95% CI= 0.54-2.06; P = 0.89).
- propofol shows higher incidence of hypotension than midazolam (RR=0.58; 95% CI=0.34-0.99; P=0.04).

Anmerkung/Fazit der Autoren

Propofol sedation may have some advantages to midazolam sedation during gastrointestinal endoscopy, and combination of propofol and opioids should be recommended with caution.

3.4 Leitlinien

Pajares MA et al., 2021 [8].

Guidelines for enhanced recovery after cardiac surgery. Consensus document of Spanish Societies of Anaesthesia (SEDAR), Cardiovascular Surgery (SECCE) and Perfusionists (AEP)

CONSENSUS STATEMENT

Zielsetzung/Fragestellung

To draw up evidence-based consensus recommendations to promote the development of ERACS programmes. To attempt to standardise perioperative care and adapt it to the guidelines of the enhanced recovery after cardiac surgery (ERACS) clinical pathway.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium unklar;
- Interessenkonflikte dargelegt und finanzielle Unabhängigkeit unklar;
- Systematische Suche, Auswahl und Bewertung der Evidenz nur limitiert dargestellt (es fehlen Angaben zur syst. Suche, Recherchezeitraum etc.;
- Formale Konsensusprozesse und externes Begutachtungsverfahren unklar;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität unklar.

Recherche/Suchzeitraum:

- A systematic review of the scientific literature relative to each recommendation was performed by searching Pubmed, Embase and Cochrane Library and reviewing various Clinical Practice Guidelines.

LoE

Table 2 Levels of evidence.

LEVEL OF EVIDENCE	
	Meaning
High	Future research is unlikely to change our recommendation
Moderate	Future research could change our recommendation
Low	Future research is highly likely to change our recommendation

GoR

Table 1 Grades of recommendation.

GRADE OF RECOMMENTATION		
	Meaning	**Implications**
Strong + (Level I)	The risk/benefit balance is clearly in favour of benefit	This recommendation should be followed in most patients, and it should therefore be adopted as a healthcare policy for most situations
Weak + (Level II)	The risk/benefit balance tends to be even, but slightly in favour of benefit	The evidence for and against the recommendation should be weighed up on a case by case basis before taking a decision
Weal	The risk/benefit balance tends to be even, but slightly in favour of riskt	The evidence for and against the recommendation should be weighed up on a case by case basis before taking a decision
Strong -	The risk/benefit balance is clearly in favour of risk	This intervention should be avoided in most patients, and it should not therefore be adopted as a healthcare policy

Note: the equivalence to the most commonly used scales would be: Strong +: grade 1 recommendation; Weak +: grade IIa and IIb recommendation; Weak and Strong -: grade III recommendation.

Sonstige methodische Hinweise

- Die Leitlinie erfüllt nicht ausreichend die methodischen Anforderungen. Aufgrund limitierter/fehlender höherwertiger Evidenz, wird die LL jedoch ergänzend dargestellt.

Empfehlungen - Induction

Anaesthesia induction can cause serious haemodynamic instability, and post-induction hypotension can increase both morbidity and mortality, especially in patients with heart disease. Therefore, induction must be carefully planned, using drugs with an appropriate safety profile and maximising haemodynamic stability. Propofol is a short-acting drug with hypnotic/anaesthetic action. It is used to induce and maintain general anaesthesia, and is also a powerful sedative that is used to prepare patients for mechanical ventilation. Haemodynamic changes after propofol administration, especially bolus, consist of low mean arterial pressure (MAP), low ejection fraction, low cardiac output, and the appearance of reflex tachycardia. Propofol has several direct and indirect adverse effects on cardiac function that can compromise haemodynamics, especially in patients with poor myocardial reserve and haemodynamic instability.[210-213] Etomidate, which has a safer haemodynamic profile than propofol, is the hypnotic of choice in patients with left ventricular dysfunction. Despite its tendency to cause adrenal suppression, this appears to be self-limiting after administration of the induction dose.[214,215.]

76. Etomidate has a safer haemodynamic profile than propofol, and is recommended for anaesthesia induction in patients with left ventricular dysfunction. Strong recommendation +. Moderate quality of evidence.

The use of benzodiazepines for preoperative anxiolysis and anaesthesia induction has been associated with delaye dawakening, late extubation, and a higher incidence of cognitive disorders and delirium in patients aged over 65 years.[213]

77. It is recommended to avoid the use of anxiolytic drugs, especially benzodiazepines, particularly inpatients aged over 65 years. *Strong recommendation -. Moderate quality of evidence.*

Ketamine preserves afterload, but its negative inotropic action can cause severe arterial hypotension in patients with catecholaminergic depletion, so it is advisable to avoid full doses in cardiac surgery.[215]

78. It is recommended to avoid full-dose ketamine in induction for cardiac surgery. *Strong recommendation -. Low quality of evidence.*

Empfehlungen - Maintenance

Studies have shown that volatile or inhalational anaesthetics, compared to propofol, are more effective in preserving cardiac function after CPB (lower troponin release), and are associated with lower mortality and fewer pulmonarycomplications.[216-219] However, the MYRIAD trial found no significant reduction in 30-day or 12-month mortality in patients undergoing elective CABG.[220] Therefore, several clinical guidelines suggest that these results should be applied to cardiac anaesthesia.[74,221] There is insufficient evidence to recommend the use of one volatile agent over another, since no differences have been found between sevoflurane and isoflurane.[222]

79. Given the cardioprotective effect of inhaled agents over propofol, it is recommended to maintain intra-operative anaesthesia with halogenated anaesthetics in oxygen-enriched air, although there is as yet no evidence that this reduces the risk of mortality in patients under-going CABG. *Strong recommendation +. High quality of evidence.*

Regarding the choice of intraoperative opioids, remifentanil appears to have the best pharmacokinetic profile and favours early extubation. If remifentanil is used, it must be factored into the postoperative analgesia strategy.[223]

80. Remifentanil can be considered the intraoperative opioid with the most suitable pharmacokinetic profile. *Weak recommendation +. Low quality of evidence.*

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4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 07 of 12, July 2021) am 08.07.2021

#	Suchfrage
1	MeSH descriptor: [Anesthesia, General] explode all trees
2	MeSH descriptor: [Anesthetics, General] explode all trees
3	(general NEAR (anesthe* OR anaesthe*)):ti,ab,kw
4	#1 OR #2 OR #3
5	#4 with Cochrane Library publication date from Jul 2016 to present, in Cochrane Reviews

Systematic Reviews in Medline (PubMed) am 08.07.2021

#	Suchfrage
1	anesthesia, general[MeSH Major Topic]
2	anesthetics, general[MeSH Terms]
3	general anesthe*[Title/Abstract] OR general anaesthe*[Title/Abstract]
4	#1 OR #2 OR #3
5	(#4) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab]

#	Suchfrage
	AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
6	(#5) AND ("2016/07/01"[PDAT] : "3000"[PDAT])
7	(#6) NOT "The Cochrane database of systematic reviews"[Journal]
8	(#7) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
9	(#8) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 08.07.2021

#	Suchfrage
1	anesthesia, general[MeSH Terms] OR anesthesia, cardiac procedures[MeSH Terms] OR anesthesia, intravenous[MeSH Terms] OR "Anesthesia"[Mesh:NoExp] OR deep sedation[MeSH Terms] OR conscious sedation[MeSH Terms]
2	anesthetics, general[MeSH Terms] OR anesthetics, combined[MeSH Terms] OR "Anesthetics"[Mesh:NoExp]
3	general anesthe*[Title/Abstract] OR general anaesthe*[Title/Abstract]
4	sedat*[Title]
5	((surger*[Title/Abstract] OR surgical[Title/Abstract]) AND (anesthesia[Title/Abstract] OR anaesthesia[Title/Abstract] OR anesthetic[Title/Abstract] OR anaesthetic[Title/Abstract])) NOT medline[sb]
6	#1 OR #2 OR #3 OR #4 OR #5
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	(#7) AND ("2016/07/01"[PDAT] : "3000"[PDAT])
9	(#8) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))
10	(#9) NOT (retracted publication [pt] OR retraction of publication [pt])

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Gemeinsamer Bundesausschuss

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO