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Review Article

# Cardiovascular and Respiratory Safety of Sedation Strategies Used in Transesophageal Echocardiography: A Systematic Review Incorporating Network Meta-Analysis

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TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) is carried out in various clinical settings, with an increasing importance, and sedation usually is required to perform it. Several sedative agents are available, and the authors aimed to compare the cardiovascular and respiratory safety of the strategies used for sedation in TEE through a systematic review with network meta-analysis (NMA). The MEDLINE, CENTRAL, EMBASE, and PsycInfo databases were searched in December 2020 for randomized clinical trials (RCTs) comparing sedation strategies for patients undergoing TEE. The authors assessed variations in systolic blood pressure (SBP), heart rate (HR), and peripheral oxygen saturation ($SpO_2$), along with the incidences of hypotension, bradycardia, and desaturation. A random-effect meta-analysis was performed. Nine RCTs (N = 881 patients) with 20 active arms (5 dexmedetomidine; 4 propofol; 4 midazolam; 3 midazolam + opioid; 2 ketamine + propofol; 1 midazolam + ondansetron; 1 midazolam + metoclopramide) and 1 placebo arm were included. Dexmedetomidine was associated with decreases in SBP (mean difference [MD] = -18.78 mmHg; 95% CI [-26.27 to -11.28]) and HR (MD = -11.15 beats/min; 95% CI [-16.15 to -6.15]). Dexmedetomidine significantly reduced the HR compared with ketamine + propofol (-16.90 beats/min; 95% CI: -33.21 to -0.58]) and midazolam + opioid (-24.15 beats/min; 95% CI: -42.67 to -5.63). Midazolam was found to reduce SBP (-12.09 mmHg; 95% CI: -20.43 to -3.74) and was shown to reduce $SpO_2$ compared with the placebo (-1.00%; 95% CI -1.74 to -0.26). Based on the NMA, the drugs with a higher likelihood of decreasing both SBP and HR were dexmedetomidine and midazolam. All of the drugs led to a small decrease (only statistically significant for midazolam) in $SpO_2$, with the systematic use of supplemental $O_2$ in some trials. The risks of hypotension, bradycardia, or desaturation were not significantly different among the evaluated drugs.


*Key Words:* transesophageal echocardiography; sedation; premedication; systematic review; network meta-analysis

TRANSESOPHAGEAL ECHOCARDIOGRAPHY (TEE) is an important cardiovascular imaging method in several clinical contexts due to the detailed morphologic and functional information that this examination provides. Moderate sedation usually is

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required to ease the TEE probe insertion, improve patient comfort, reduce gag reflex, and minimize hemodynamic changes.[1,2]

The guidelines for procedural sedation and analgesia in adults by the European Society of Anesthesiology (ESA)[3] have stated that this moderate sedation involves the use of hypnotic and/or analgesic medications to enable the effective performance of diagnostic or therapeutic procedures. This preserves the airway patency and spontaneous ventilation despite depressed levels of consciousness. Optimal sedation has the potential to improve the time to recovery and to hospital discharge; however, challenges exist in the patients at a high risk of adverse events; namely, older patients with multiple comorbidities. Therefore, the optimal drug profile for the patients' sedation in those undergoing TEE should comprise a rapid onset, short duration of action, and should have adequate hypnotic and analgesic properties, with a favorable hemodynamic and respiratory profile.

The British Society of Echocardiography, American Society of Echocardiography (ASE), and European Society of Cardiology all agree that benzodiazepines are the most commonly used sedative agents, with midazolam being the usual choice. The British Society of Echocardiography has stated that there is a wide variation in the sedation practice between cardiac units in the United Kingdom, and that a single agent is preferred over a combination of drugs.[4] The ASE has added that opioids often are used as adjuvant drugs to the procedure,[2] and the European Society of Cardiology has asserted that other sedatives or analgesics (eg, opioids) may be used instead.[5]

Although midazolam is administrated commonly for sedation in TEE procedures, its use is still a matter of debate, particularly due to its safety profile, and some studies[6-8] have been done comparing other pharmacologic strategies for TEE sedation.

In this review, the authors aimed to systematically assess all of the published data related to the different pharmacologic strategies used for sedation in the patients who have underwent TEE in order to compare safety in terms of cardiovascular and respiratory adverse events.

## Methods

### *Protocol and Registration*

This systematic review was reported according to Preferred Reporting Items for Systematic Reviews and Meta-Analysis for Network Meta-Analysis guidance.[9] The protocol was registered in PROSPERO with the reference CRD42021236477.

### *Eligibility Criteria*

The authors considered eligible all of the randomized clinical trials (RCTs) that actively have compared 2 or more pharmacologic interventions, or interventions against placebo, aiming to sedate patients undergoing TEE, excluding intraoperative TEE and the patients who need interventions other than TEE (eg, electrical cardioversion). No restraints were placed on the study eligibility based on the baseline characteristics of the patients, drug class, dose, route, or duration of administration. Furthermore, there were no restrictions on the publication date or language.

The authors' outcomes of interest were the following: (1) blood pressure changes in terms of systolic blood pressure (SBP) and the incidence of hypotension episodes; (2) heart rate (HR) and bradycardia events; and (3) peripheral oxygen saturation ($SpO_2$) and oxygen desaturation episodes throughout the TEE. Due to data availability, the authors considered the continuous outcomes (SBP, HR, and $SpO_2$) as primary outcomes, and the lowest and highest values obtained throughout the procedure were compared with baseline measurements; for dichotomous events (hypotension, bradycardia, and oxygen desaturation), the authors retrieved their incidence, reported by investigators as an adverse event, complication, or the need for any intervention to prevent or manage them.

### *Information Sources and Search Strategy*

The authors searched the bibliographic databases of MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, and PsycInfo on December 8, 2020, from the database inception. They also searched in OpenGrey (a database that includes technical or research reports, doctoral dissertations, and conference papers, among other types of documents that were not formally published in sources, [eg, books or journal articles]), reference lists of included studies or other relevant publications, and consulted experts for their knowledge on published data. Search strategy details are provided in the appendix (Supplementary Table 1).

### *Study Selection, Data Collection Process, and Data Items*

The titles and abstracts yielded by the search process for eligibility, as well as those assessed in full-text after the first phase, were appraised independently by 2 reviewers (T.M.F. and D.C.). Disagreements or doubts were solved through consensus. The exclusion reasons were recorded during the full-text screening phase.

The data from the individual studies identified for inclusion were extracted to a prepiloted form. The retrieved information included the study design, setting, patient demographic data (age, sex, weight, TEE indication), study interventions, and stated outcomes of interest. The data from the studies' plots were extracted using Webplotdigitizer V.4.4.[10]

### *Risk of Bias Within Individual Studies*

The risk of bias of the selected studies independently was evaluated using the Revised Cochrane risk-of-bias tool for randomized trials (RoB 2).[11] The RoB 2 evaluates the following 6 domains: (1) the randomization process, (2) the deviations from the intended interventions (effect of assignment to intervention), (3) missing outcome data, (4) bias in the measurement of the outcome, (5) bias in the selection of the reported result, and (6) overall bias. For each domain, the authors would assess the risk of bias as "low," "some concerns," or "high"

based on responses to several signaling questions. The overall risk of bias in the included studies was categorized as "low risk," "some concerns," or "high risk of bias." The risk of bias graph was derived from this tool.

### *Data Synthesis and Statistical Analysis*

The R 4.0.0 (The R Foundation for Statistical Computing) and RevMan 5.4 (The Cochrane Collaboration) platforms were used to synthesize the results.

For continuous outcomes, such as SBP, HR, and $SpO_2$, the authors plotted the individual study estimates using the reported mean difference (MD) with their 95% CIs. If 95% CIs were not possible to derive from standard error or p values, the authors imputed the CI, assuming similarity to the trials with similar sample sizes. These data were pooled to provide the effect of each drug during (pre/post) the trials, using the inverse-variance method and random-effects model.

For both continuous and dichotomous outcomes, assuming the homogeneity, transitivity, and consistency of the data, the authors performed a random-effects models frequentist network meta-analysis (NMA). In this method, they aimed to simultaneously evaluate all of the available drugs regarding cardiovascular and respiratory safety outcomes.

In the NMA evaluation, the following drugs were used preferentially as reference: placebo, midazolam, and propofol. For continuous data, the results were expressed as MD with their 95% CI; and for dichotomous data, these were reported as relative risks (RR) with 95% CI.

## Results

### *Study Selection and Characteristics*

The authors' electronic search found 138 records. After removing the duplicates, screening titles, and abstracts for eligibility, 17 articles were selected for full-text review (Fig 1). After assessment, 9 RCTs with, overall, 881 patients undergoing pharmacologic sedation for TEE were selected to be included.[6-8,12-17] A detailed descriptions of 8 full-text excluded articles are available in the appendix (Supplementary Table 2).

The main characteristics of the included studies are depicted in Table 1. Among the selected studies, the main indications for TEE were emboli source search and evaluation of atrial septal defects. Study publication dates ranged from 1998 to 2020, with sample sizes between 21-to-192 patients. There were a total of 20 active arms (5 dexmedetomidine; 4 propofol; 4 midazolam; 3 midazolam + opioid; 2 ketamine + propofol; 1 midazolam + ondansetron; 1 midazolam + metoclopramide) and 1 placebo arm in the studies.

Some clinical heterogeneity was found among subgroups of interventions, especially concerning drug dosages used for TEE sedation. Only the Sruthi et al[6] study arms did not receive topical oropharyngeal anesthesia. Some intervention arms had supplemental oxygen being given or normal saline being infused. Supplementary Table 3 organizes study arms by their intervention strategy and can be consulted in the appendix.

### *Network Structure and Geometry*

The study authors made different networks of interventions and meta-analyses, one for each outcome, based on the available results of each RCT. Not all of the interventions contributed to every network. Network diagrams and league tables with pair-wise and NMA are available in the appendix.

### *Risk of Bias Within Individual Studies*

The overall risk of bias within included studies was low. Only the Aeschbacher et al,[12] Toman et al,[17] and Schelling et al[15] studies raised "some concerns" due to the lack of methods of randomization report. Aeschbacher et al[12] and Schelling et al[15] also raised "some concerns" regarding deviations from intended interventions and missing outcome data. The Toman et al[17] study did not report methods of blinding, but there was no evidence that the assessment of outcomes used in this review (hemodynamic parameters and adverse events) was influenced by knowledge of intervention received.

The authors' assessment is displayed by domain and overall judgments in the appendix (Supplementary Figure 1).

### *Cardiovascular and Respiratory Safety: Pre/Post Effects*

#### *Systolic Blood Pressure*

The evaluation of hemodynamic changes regarding SBP by subgroups of intervention showed that midazolam use was associated with a decrease in SBP (MD = -12.09 mmHg; 95% CI [-20.43 to -3.74]; p = 0.005). Dexmedetomidine also was accompanied with SBP drop from baseline (MD = -18.78 mmHg; 95% CI [-26.27 to -11.28]; $p < 0.00001$). The analysis showed substantial statistical heterogeneity in the midazolam ($Tau^2$ = 34.77; $I^2$ = 66%) and propofol ($Tau^2$ = 69.83; $I^2$ = 70%) subgroups (Fig 2). This could be explained by the use of different sedation protocols.

#### *Heart Rate*

In terms of HR changes, from the subgroup analysis, only dexmedetomidine use was associated with a significant variation in HR from a baseline of -11.15 beats/min (95% CI [-16.15 to -6.15]; $p < 0.0001$). The other pharmacologic sedations were not associated with a significant change in HR (Fig 3). Heterogeneity was not substantial in the propofol subgroup ($Tau^2 = 24.51$; $I^2 = 53\%$).

#### *Peripheral Oxygen Saturation*

Very few studies could be pooled together due to a lack of $SpO_2$ monitoring data (Fig 4). In Banihashem et al,[16] patients in both arms received supplemental oxygen, in addition to pharmacologic sedation, and that could explain the uncertainty about the mean estimate and the high heterogeneity ($Tau^2$ = 1.26; $I^2$ = 89%) found among the 3 pooled studies[12,13,16] in the midazolam subgroup.

The usage of either ondansetron or metoclopramide, in addition to midazolam, led to a decrease in $O_2$ peripheral saturation

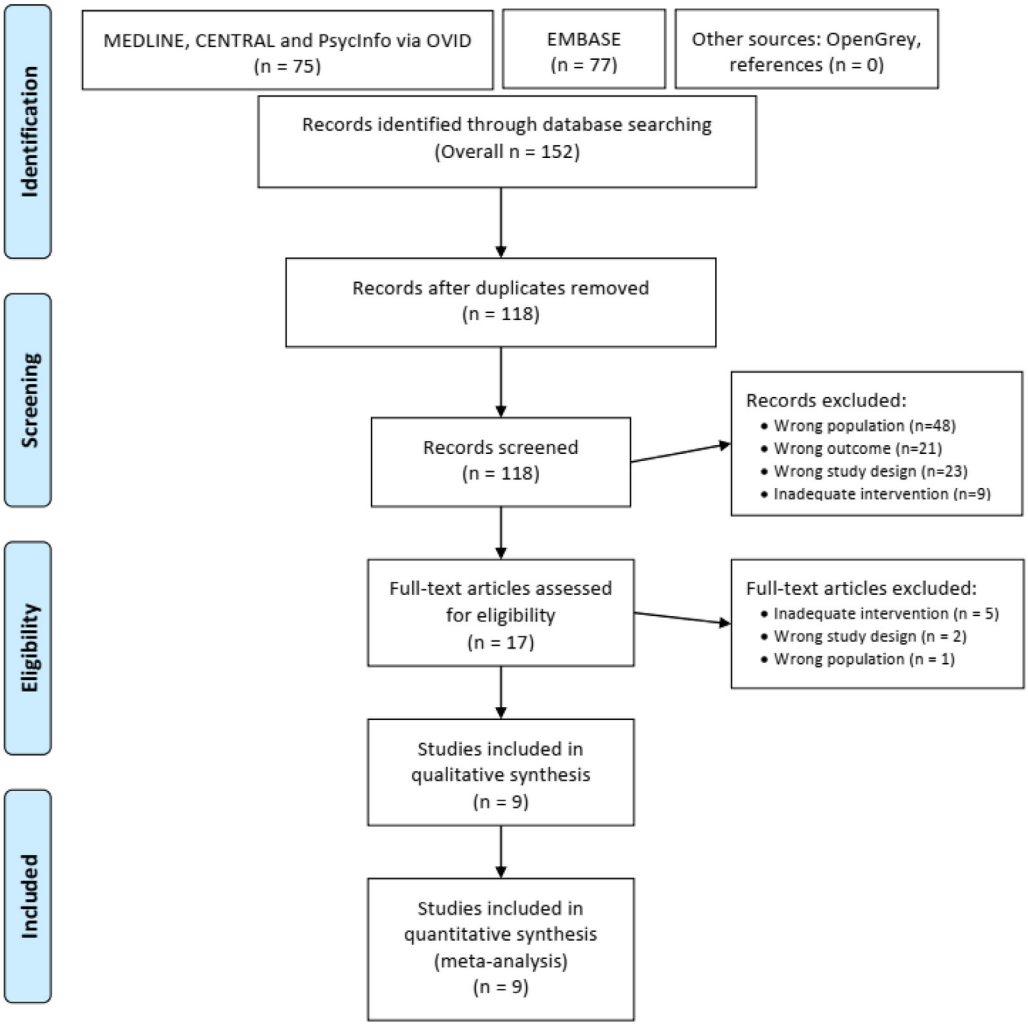


Fig 1. Preferred Reporting Items for Systematic Reviews and Meta-Analysis Flowchart of Studies Selection. OVID

of -1.8% (95% CI [-2.70 to -0.90]; $p < 0.0001$) in both interventions.

Pharmacologic sedation with propofol and midazolam + opioid in Schelling et al[15] led to a statistically significant increase in $SpO_2$ (MD = 1.05%; 95% CI [0.31-1.79]; p = 0.005 and MD = 0.85%; 95% CI [0.07-1.63]; p = 0.03, respectively); however, both arms during the procedure were under supplemental oxygen (2 L/min).

The usage of dexmedetomidine, despite oxygen supplementation,[16] also was associated with an $SpO_2$ drop of -1.38% (95% CI [-2.71 to -0.05]; p = 0.04).

### *Cardiovascular and Respiratory Safety: Relative Effects—NMA*

#### *Blood Pressure: Risk of Hypotension*

The network diagram of interventions being compared regarding the incidence of hypotension, reported as an adverse event, complication, or need for intervention by the investigators, is available in the appendix (Supplementary Figure 2), with propofol being the central element of comparison against midazolam + opioid, dexmedetomidine, and ketamine + propofol. Three studies,[7,8,15] with a total of 7 arms and 332 patients, were evaluated. There were 2 trials directly comparing propofol and dexmedetomidine. Using propofol as the reference, no intervention was significant for increased risk of hypotension (Fig 5). Significant clinical differences could not be excluded due to wide CIs.

The NMA RR estimates and their 95% CIs of hypotension between active sedation strategies can be seen in the appendix (Supplementary Table 4). The use of ketamine + propofol appeared to have a lower risk of hypotension than midazolam + opioid, propofol, and dexmedetomidine.

#### *Blood Pressure: Systolic Blood Pressure*

Supplementary Figure 3 shows the network of eligible comparisons for SBP change from baseline outcome. Midazolam and dexmedetomidine were the main contributors to direct evidence among studies. Midazolam was put head-to-head against placebo, midazolam + ondansetron, midazolam + metoclopramide, and dexmedetomidine. The latter was compared with propofol, midazolam + opioid, and ketamine + propofol. Seven RCTs,[6,7,12-16] with a total of 15 arms and 716 patients, were

Table 1
Characteristics of Studies Aimed at Comparing Pharmacologic Sedation Strategies for TEE

| Study | Design | Common intervention | Comparison | No | Mean Age | Males | Weight (kg) | TEE Indication | Endpoints |
|---|---|---|---|---|---|---|---|---|---|
| Aeschbacher et al. 1998[12] | DB, RCT | TOA: tetracaine (4 mg) + lidocaine<br>As needed: 2.5 mg midazolam or placebo | Midazolam *v* Placebo (≤50 kg to 2 mg; 50, 80 kg [-2.5 mg; ≥80 kg to 3 mg]) | 184<br>(MDZ: 93; PBO: 91) | MDZ: 56 ± 15<br>PLC: 54 ± 16 | MDZ: 57%<br>PLC: 64% | MDZ: 74 ± 14<br>PLC: 75 ± 14 | Source of embolism (59%)<br>Infective endocarditis (16%)<br>Native valve disease (9%)<br>Other (16%) | Efficiency and safety of MDZ sedation (side effects and hemodynamic data) |
| Aydin et al. 2010[13] | DB, RCT | TOA: lidocaine + 2 mg midazolam<br>As needed: midazolam | Ondansetron: 4 mg<br>*v*<br>Metoclopramide: 10 mg<br>*v*<br>Midazolam | 156<br>(52 each) | MDZ + OND: 44.4 ± 12<br>MDZ + MET: 42.5 ± 11.4<br>MDZ: 44.2 ± 11.7 | MDZ + OND: 51%<br>MDZ + MET: 56%<br>MDZ: 56% | MDZ+ OND: 70.4 ± 9.9<br>MDZ + MET: 70.5 ± 10.7<br>MDZ: 70.4 ± 9.5 | Congenital heart defect assessment (38%)<br>Source of embolism (23%)<br>Artificial heart valve assessment (17%)<br>Other (22%) | Assess whether OND would improve patient comfort, reduce the need for sedation, and increase tolerance during TEE |
| Cooper et al. 2011[14] | TB, RCT | TOA: lidocaine + 1 mg midazolam<br>As needed: 1 mg midazolam + 25 μg opioid and increasing the rate of infusion up to 0.7 μg/kg/h | Dexmedetomidine: 1 μg/kg + 0.2 μg/kg/h<br>*v*<br>Midazolam + Opioid | 21<br>(MDZ + OP: 10; DEX: 11) | DEX: 50.6 ± 3.8<br>MDZ + OP: 51.6 ± 2.8 | DEX: 64%<br>MDZ + OP: 40% | DEX: 82.9 ± 7.2<br>MDZ + OP: 85.7 ± 6.6 | N/A | Primary endpoint: adequacy of sedation, followed by patient satisfaction |
| Schelling et al. 2015[15] | SB, RCT | TOA: lidocaine + $O_2$ (2 L/min) | Propofol <50 y: 50-60 mg (+ 20-30 mg PRF as needed)<br>>50 y: 30-40 mg<br>(+ 10-20 mg PRF as needed)<br>*v*<br>Midazolam: 1-2 mg + Opioid: 25mg<br>(+ 1 mg MDZ as needed) | 192<br>(PRF: 95; MDZ + OP: 97) | PRF: 66.9 ± 13.3<br>MDZ + OP: 64.2 ±13.6 | PRF: 61%<br>MDZ + OP: 64% | PRF: 27.8 ± 5.8*<br>MDZ +OP: 27.2 ± 5.3*<br>*BMI (kg/m2) | N/A | Primary endpoint: reduction in blood pressure. Secondary endpoints: side effects and patient comfort |
| Banihashem et al. 2015[16] | DB, RCT | TOA: lidocaine + $O_2$ | Dexmedetomidine: 1 μg/kg + 0.2 μg/kg/h<br>*v*<br>Midazolam: 2 mg | 48<br>(24 each) | DEX: 46.88 ± 16.10<br>MDZ: 50.38 ± 16.58 | DEX: 42%<br>MDZ: 46% | DEX: 72.83 ± 9.41<br>MDZ: 69.38 ± 10.42 | Source of embolism after transient ischemic attacks | Patients' sedation level, degree of analgesia, patients' satisfaction, vital signs and readiness for discharge from the recovery room |
| Toman et al. 2016[17] | N/A, RCT | TOA: lidocaine + 0.9% saline infusion | Midazolam: 2.5 mg<br>(+1 mg MDZ [max total 8 mg at 5 min intervals])<br>*v*<br>Midazolam: 1 mg + Opioid: 5 μg/kg<br>(+ 1 mg MDZ + 25 μg OP; + 0.5 mg MDZ [max total 5 mg] + 2.55 μg/kg OP [max total 1000 μg at 5 min intervals])<br>*v*<br>Propofol: 0.5 mg/kg (+ 0.5 mg/kg PRF; + 0.25 mg/kg PRF [max total 300 mg]) | 90<br>(30 each) | MDZ: 42.8 ± 15.2<br>MDZ + OP: 44.3 ± 16.9<br>PRF: 48.8 ± 18.7 | MDZ: 43%<br>MDZ + OP: 40%<br>PRF: 43% | MDZ: 72.1 ± 13.3<br>MDZ + OP: 68.5 ± 13.6<br>PRF: 68.7 ± 13.4 | N/A | Ease of procedure, hemodynamic response, efficacy, side effects and duration of hospital stay |
| Sruthi et al. 2018[6] | DB, RCT | $O_2$ (4 L/min) + ringer's lactate at 10 ml/kg/h | Dexmedetomidine: 10 μg/ml bolus until RSS≥3 + 0.5 μg/kg/h<br>*v*<br>Ketofol (3.2 mg/ml [K] + 9.5 mg/ml [PRF]): bolus until RSS ≥3 + 0.05 ml/kg/h | 50<br>(25 each) | DEX: 32.16 ± 10.8<br>KF: 32.28 ± 9.83 | DEX: 44%<br>KF: 44% | DEX: 55.84 ± 11.53<br>KF: 58.28 ± 13.82 | Atrial septal defect (46%)<br>Mitral stenosis (32%)<br>Mitral regurgitation (14%)<br>Others (8%) | Primary endpoint: time to achieve RSS ≥3. Secondary endpoints: hemodynamic parameters, need for rescue sedation, complications, and patient and cardiologist satisfaction |
| Alizadehasl et al. 2019[7] | SB, RCT | TOA: lidocaine | Dexmedetomidine: 1 μg/kg + 0.1-0.5 μg/kg/h according to RSS<br>*v* | 65<br>(P: 31; D: 34) | PRF: 41.8 ± 16.4<br>DEX: 45.2 ± 14.6 | PRF: 45%<br>DEX: 41% | PRF: 69.9 ± 11.2<br>DEX: 73.2 ± 16.9 | N/A | Assess and compare sedation level, hemodynamic stability, recovery time and patient, |

(*continued on next page*)

**Table 1** (*continued*)

| Study | Design | Common intervention | Comparison | No | Mean Age | Males | Weight (kg) | TEE Indication | Endpoints |
|---|---|---|---|---|---|---|---|---|---|
| | | | Propofol: 0.1 mg/kg + 25-75 μg/kg/min according to RSS | | | | | | cardiologist and anesthesiologist satisfaction |
| El Mourad et al. 2020[8] | DB, RCT | TOA: lidocaine + 1 mg midazolam + $O_2$ (2 L/min) | Propofol: 0.5 mg/kg + 25-75 μg/kg/min<br>v<br>Dexmedetomidine: 1 μg/kg + 0.2-0.7 μg/kg/h<br>v<br>Ketofol (2 mg/ml [K] + 4mg/ml [PRF]): 0.125 ml/kg + 0.05-0.125 ml/kg/h<br>(Maintenance dose according to BIS level + 10 mg PRF as needed) | 75<br>(25 each) | PRF: 23.20± 4.40<br>DEX: 23.16± 4.39<br>KF: 22.96± 4.64 | PRF: 10/15<br>DEX: 12/13<br>KF: 11/14 | PRF: 24.20 ± 3.18*<br>DEX: 25.07 ± 2.26*<br>KF: 24.28 ± 2.69*<br>*BMI (kg/m2) | Ventricular septal defect (48%)<br>Atrial septal defect (41%)<br>Patent ductus arteriosus (11%) | Primary endpoint: time to reach targeted sedation level.<br>Secondary endpoints: hemodynamic parameters, incidence of desaturation, procedure duration, time of recovery, and cardiologist's satisfaction |

Abbreviations: BIS, bispectral index; BMI, body mass index; DB, double-blinded; DEX, dexmedetomidine; K, ketamine; KF, ketofol (ketamine + propofol); MDZ, midazolam; MET, metoclopramide; N/A, not available; OND, ondansetron; OP, opioid (Cooper: Fentanil; Schelling: Pethidine; Toman: Alfentanil); PLC, placebo; PRF, propofol; RCT, randomized controlled trial; RSS, Ramsay sedation score; SB, single-blinded; TB, triple-blinded; TEE, transesophageal echocardiography; TOA, topical oropharyngeal anaesthesia (10% lidocaine in all but Cooper,which was 2%).

assessed. There were no significant differences in terms of SBP changes when comparing active interventions against placebo using the random effects model (Fig 6).

Pairwise and NMA estimates and their 95% CI regarding SBP change mean differences between interventions can be seen in the appendix (Supplementary Table 5).

### *Heart Rate: Risk of Bradycardia*

The network diagram of bradycardia's reported incidence is formed by a closed loop of interventions between propofol, dexmedetomidine, and ketamine + propofol, the last 2 of which were compared directly twice (Supplementary Figure 4). Only 2 RCTs,[6,8] with an overall sample size of 125 patients and 5 arms, contributed to the analysis.

Sedation with dexmedetomidine appeared to increase the risk of bradycardia (RR = 6.80; 95% CI [0.90-51.19]) when compared to sedation with propofol (Fig 7). Pairwise and NMA pointed to dexmedetomidine as the sedation associated with more risk of bradycardia despite no certainty (Supplementary Table 6).

### *Heart Rate: Heart Rate*

Dexmedetomidine was compared directly with all interventions except placebo, making it the central point of the network diagram of interventions regarding HR change from baseline outcome (Supplementary Figure 5). Those interventions were midazolam + opioid, midazolam, ketamine + propofol, and propofol. Dexmedetomidine was compared 2 times with ketamine + propofol and with propofol alone. Seven studies, [6-8,12,14-16] comprising 15 arms and 634 patients, were considered. When compared with placebo, no sedation intervention showed a significant decrease or an increase in HR (Fig 8).

The NMA was able to narrow some CIs from pairwise meta-analysis, and showed that dexmedetomidine use for sedation in TEE was associated with a statistically significant decrease in HR when compared to ketamine + propofol (MD = -16.90 beats/min; 95% CI [-33.21 to -0.58]) and to midazolam + opioid (MD = -24.15 beats/min; 95% CI [-42.67 to -5.63]) (Supplementary Table 7).

### *Respiratory: Risk of Oxygen Desaturation*

The relative risk of oxygen desaturation among interventions was assessed using the network of interventions available in the appendix (Supplementary Figure 6). Interventions assessed for this outcome were propofol, dexmedetomidine, ketamine + propofol, midazolam + opioid, midazolam, and placebo. A total of 349 patients from 8 arms of 3 trials[8,12,17] were used in the analysis. The random-effects model, using placebo as a reference, did not show a statistically significant increase in the risk of oxygen desaturation when pharmacologically sedating patients for TEE (Fig 9). However, despite their broad 95% CI, all point estimates pointed toward an increased relative risk of oxygen desaturation.

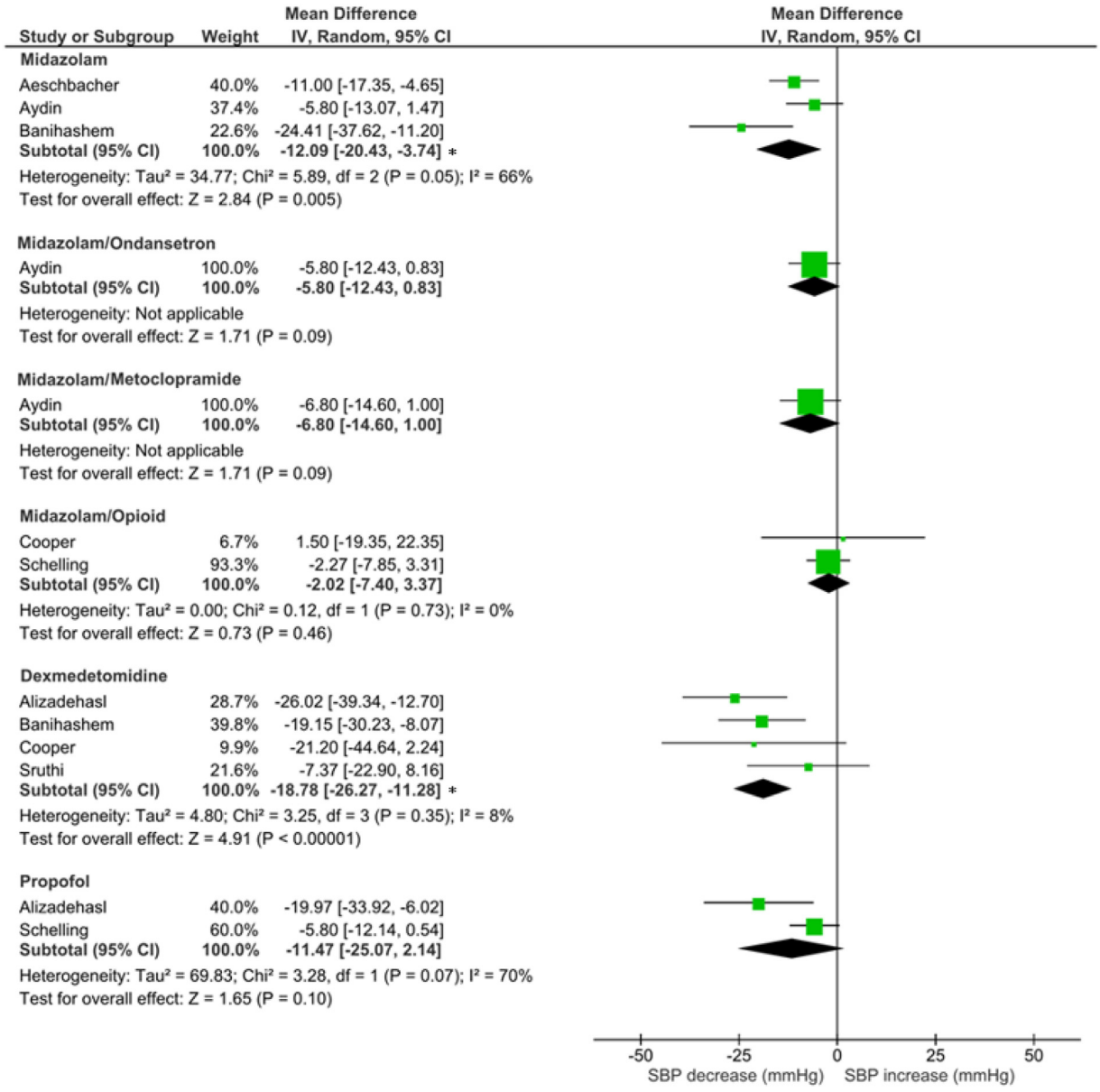


Fig 2. Subgroup forest plot comparing systolic blood pressure change from baseline. SBP, systolic blood pressure; IV, inverse variance.
*Statistically significant.

The NMA's league table concerning the relative risk of oxygen desaturation can be consulted in the appendix (Supplementary Table 8).

### *Respiratory: Peripheral $O_2$ Saturation*

The $SpO_2$ change from the baseline outcome's network diagram is shown in the appendix (Supplementary Figure 7). The network allows comparison among propofol, dexmedetomidine, midazolam + opioid, midazolam, midazolam + metoclopramide, midazolam + ondansetron, and placebo. Six RCTs[7,12-16] contributed to a pairwise meta-analysis, with 666 patients and 13 arms. The use of midazolam alone showed an average decrease in $SpO_2$ of -1.00% (95% CI [-1.74 to -0.26]) when compared with placebo (Fig 10).

After excluding studies with supplemental oxygen in all arms, the number of available comparisons was lower, but the overall results were similar (Supplemental Figure 8).

According to the authors' NMA point estimates, propofol seemed to decrease $SpO_2$ the most among the available sedation strategies. However, given its wide 95% CI, there is low certainty (Supplementary Table 9).

### *Cardiovascular and Respiratory Safety: Summary of Findings*

Supplementary Table 10 summarizes results from pre/post and NMA evaluation regarding continuous (SBP, HR, and $SpO_2$ change from baseline) and dichotomous outcomes (hypotension, bradycardia, and $O_2$ desaturation) for each sedation strategy, reported respectively as MD (95% CI) and RR (95% CI).

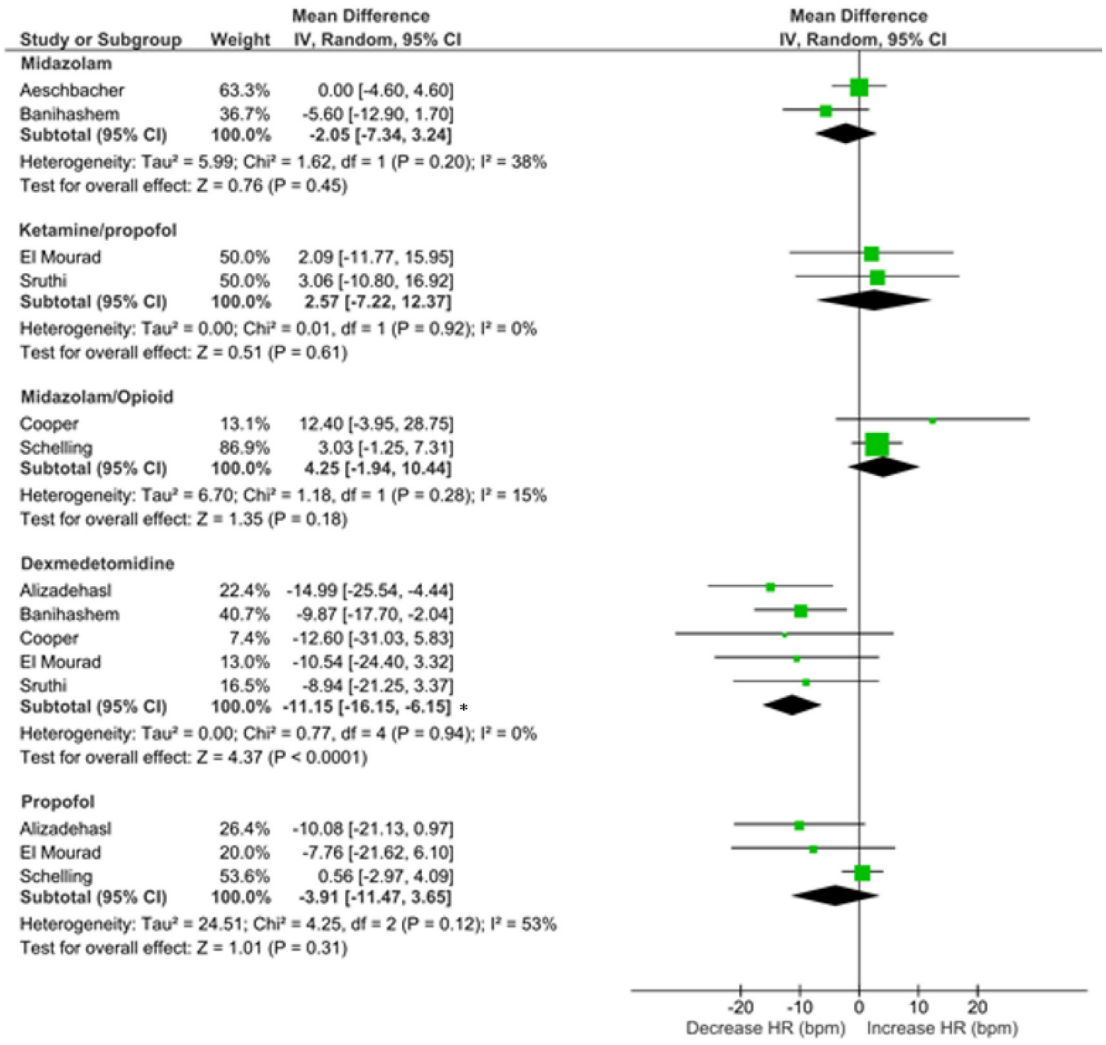


Fig 3. Subgroup forest plot comparing heart rate change from baseline.HR, heart rate; IV, inverse variance
*Statistically significant.

*Exploration for Inconsistency*

Inconsistency was evaluated for each outcome's network. No pair-wise comparison was found to be statistically significant for inconsistency (Supplementary Tables 11-16).

## Discussion

The TEE is a semiinvasive procedure and, therefore, requires moderate sedation. There are many pharmacologic options for this purpose, midazolam being the most used, but alternatives such as dexmedetomidine, propofol alone, and in association with ketamine, also are considered, as well as other pharmacologic adjuvants that might be added to reduce midazolam dosages, such as ondansetron, metoclopramide, or opioids. In clinical practice, the clinicians' choice among multiple sedatives may become difficult when only some of the available sedatives have undertaken head-to-head comparisons by investigators. All of the sedatives are different in their safety profiles. Therefore, a systematic review incorporating NMA can be useful because it allows for simultaneous comparisons of multiple interventions against each other.

The authors' review showed that midazolam and dexmedetomidine use for TEE sedation were associated with a statistically significant SBP decrease. In terms of HR, dexmedetomidine also was associated with statistically significant HR lowering. These results, however, were not statistically significant when compared with placebo sedation in the authors' NMA. On the other hand, their NMA showed that dexmedetomidine use for sedation in TEE was associated with a statistically significant greater decrease in HR when compared to ketamine + propofol and to midazolam + opioid, providing valuable information for decision-making about the preferred sedation depending on the patient's characteristics or clinical condition.

Almost all of the sedation strategies have been associated with some degree of decrease in $SpO_2$ (irrespective of the statistical significance), whereas the supplemental oxygen delivery seemed to maintain or even raise $SpO_2$ from baseline. Midazolam was associated with a statistically significant $SpO_2$ decrease when compared with placebo, despite $O_2$

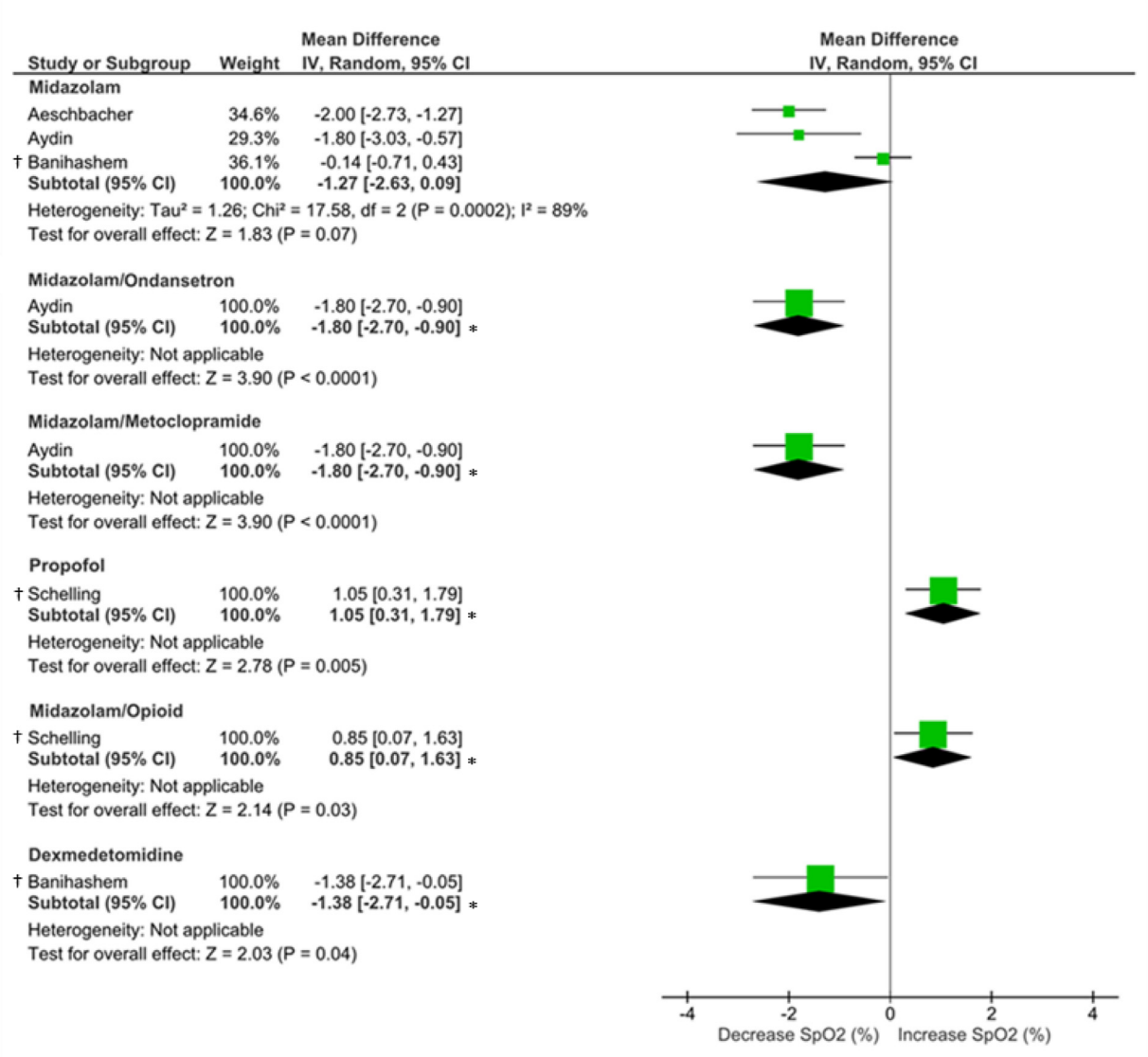


Fig 4. Subgroup forest plot comparing peripheral oxygen saturation change from baseline. IV, inverse variance.
*Statistically significant. †Supplemental $O_2$ was given.

supplementation in one study[16] included in the analysis. Overall, the studies that administered supplemental oxygen were associated with lower rates of desaturation episodes, so routine administration of low $O_2$ rates during TEE seems reasonable. Also, for those patients with reduced respiratory reserve or at risk for hypoxia and respiratory failure, noninvasive ventilation through masks that allow for endoscopic probe insertion might be a viable option.[18]

The evaluation of the risk of hypotension, bradycardia, and desaturation seems to complement the authors' continuous outcomes, although not all studies have contributed equally with their data. For example, the data from SBP change from baseline

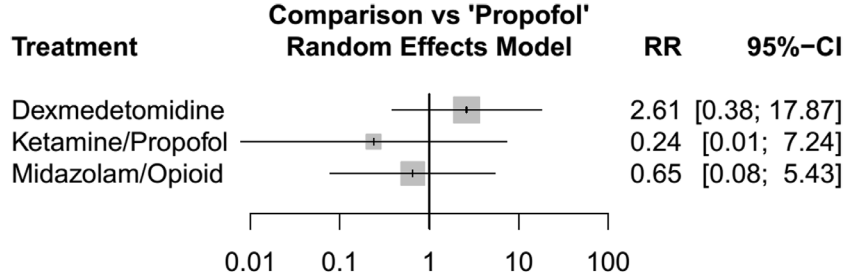


Fig 5. Relative risk of hypotension among interventions. Propofol was used as the reference. RR, relative risk.

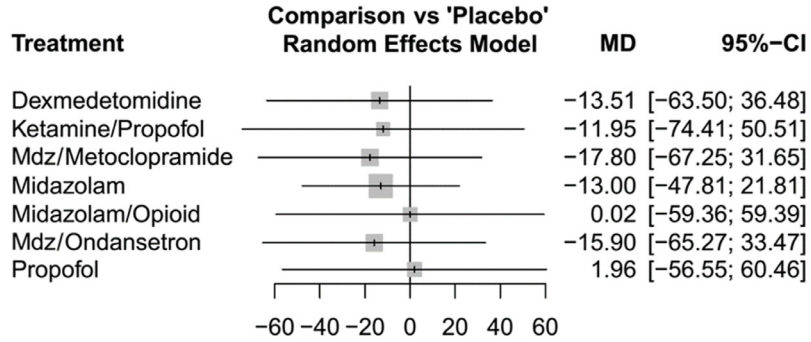


Fig 6. Mean difference in systolic blood pressure change among interventions. Placebo was used as the reference. MD, mean difference.

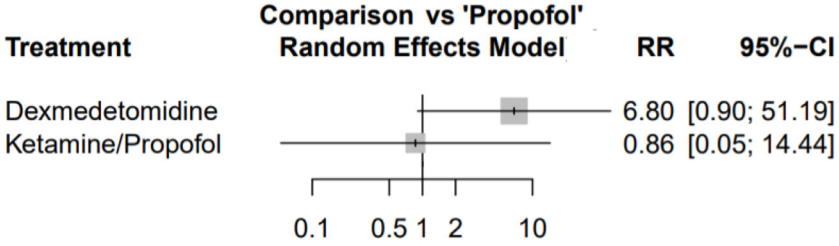


Fig 7. Relative risk of bradycardia between interventions. Propofol was used as the reference. RR, relative risk.

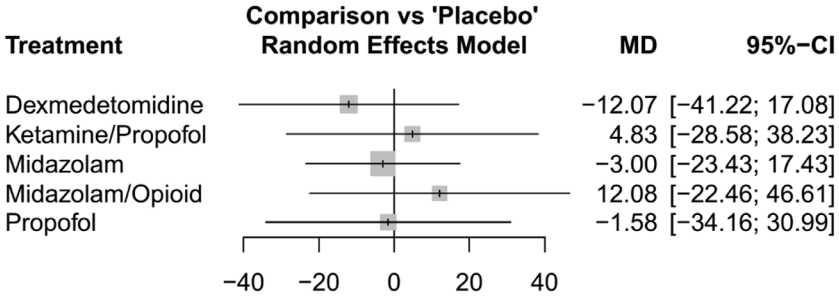


Fig 8. Mean difference in heart rate change among interventions. Placebo was used as the reference. MD, mean difference.

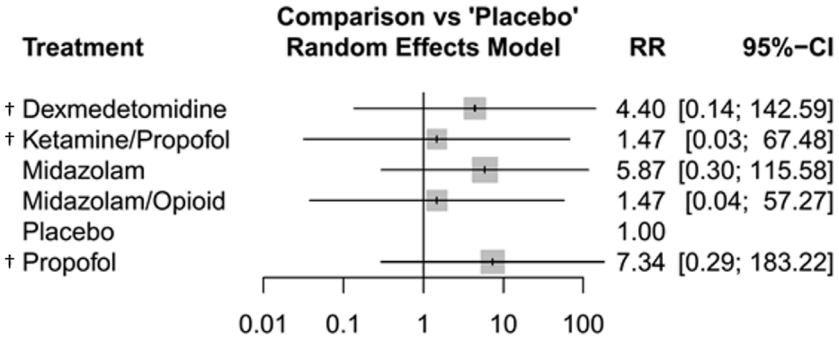


Fig 9. Relative risk of oxygen desaturation among interventions. Placebo was used as the reference.
*Supplemental $O_2$ was given in at least one of the studies included in analysis. RR, relative risk.

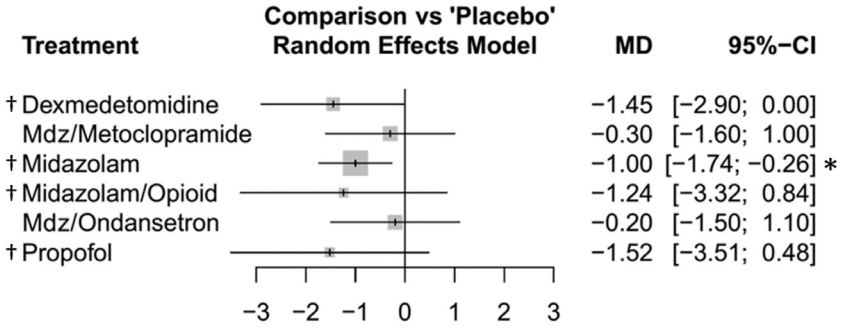


Fig 10. Mean difference in peripheral oxygen saturation change among interventions. Placebo was used as the reference.
*Statistically significant. †Supplemental $O_2$ was given in at least one of the studies included in analysis. MD, mean difference.

was obtained for all 7 available interventions, whereas the incidence of hypotension was only available for 4 interventions.

The RR of hypotension and bradycardia was higher with dexmedetomidine, although not statistically significant, but consistent with the SBP and HR decrease association. The RR of desaturation, as for $SpO_2$ change, might have been underestimated due to supplemental oxygen in various interventions' arms, but there were not any significant increases in the desaturation risk.

The use of ondansetron or opioids in addition to midazolam has appeared to be useful in comparison with the use of midazolam alone. Both of these drugs seemed to improve patient comfort, and were associated with a decrease in the midazolam dose required for optimal sedation.[13,17] This can be important because midazolam was found to reduce SBP and $SpO_2$. Despite low confidence, overall, the usage of these adjuncts seemed to have a favorable hemodynamic profile over midazolam alone. In the authors' NMA, the use of midazolam alone showed a tendency toward greater SBP, HR, and $SpO_2$ decreases, as well as a greater relative risk of bradycardia when compared to sedation with midazolam + opioid, but no statistical significance was found.

Propofol is known to lower HR and blood pressure, and is associated with desaturation due to respiratory depression in a dose-dependent manner.[19] Despite being biased by $O_2$ supplementation, the authors' analysis showed a tendency toward greater respiratory depression when compared to placebo and others. However, it failed to show significant decreases in SBP, HR, and $SpO_2$, probably due to the low doses given to achieve only moderate sedation. In the authors' NMA estimates, propofol appeared to be the less hypotensive sedation strategy, noticing that there was no statistical significance when compared to other strategies.

The authors' safety cardiovascular and respiratory data were important, not only for the drug decision process, but also to plan the discharge of patients who underwent the TEE as outpatients, as the European Society of Anesthesiology[3] and ASE[2] have recommended the assessment of the Modified Aldrete Score[20] before discharge, which necessarily includes the evaluation of parameters such as breathing, circulation, and oxygenation.

Several limitations in this review need to be acknowledged. There were few RCTs available, with small numbers of patients. The interventions used did not allow direct or indirect comparisons in all of them. Monitoring data regarding SBP, HR, and $SpO_2$ were not available in all of the studies despite being measured. Among the available RCTs, the incidences of cardiovascular and respiratory events, such as bradycardia, hypotension, or desaturation was low, and certain studies were not designed to account for them, which may explain the authors' wide CIs. The definition of these dichotomous outcomes also was inconsistent among the studies. Pooling data from the studies with different designs also should be considered a potential limitation.

Nevertheless, this systematic review incorporating NMA increased the power and external validity of the obtained data regarding cardiovascular and respiratory safety of sedations used for TEE. The studies incorporated were only RCTs mainly with a low risk of bias. The authors' network diagrams may be useful to guide further investigation. The standardization of monitoring and sedation strategies should be considered to reduce clinical heterogeneity, especially concerning drug dosage.

In conclusion, this study showed that sedation with midazolam was associated with a decrease in SBP, and when compared with placebo sedation, a greater decrease in $SpO_2$ was found. Dexmedetomidine's hemodynamic profile also was consistent with decreases in SBP and HR, showing reduction in HR more than ketamine + propofol and midazolam + opioid. Adverse events of hypotension, bradycardia, and desaturation should be monitored closely when performing TEE with SBP, HR, and $SpO_2$ measurements, regardless of which sedative is used. Further studies are needed to increase confidence in the results.

## Conflict of Interest

None.

## Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:10.1053/j.jvca.2022.07.003.

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