Reviews

Effects of Perioperative Dexmedetomidine on Postoperative Mortality and Morbidity: A Systematic Review and Meta-analysis

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ABSTRACT

Purpose: Major postoperative complications translate into increased health care resource utilization, prolonged hospital stays, and increased mortality. We aimed to assess the effects of perioperative dexmedetomidine use on postoperative mortality and the prevalence of major complications after cardiac and noncardiac surgery.

Methods: We searched the PubMed, EMBASE, and Cochrane databases to analyze all published evidence from randomized controlled trials (RCTs) and cohort studies comparing perioperative dexmedetomidine use versus no dexmedetomidine use in adult patients undergoing cardiac and noncardiac surgery. The primary outcome was postoperative mortality. Secondary outcomes were the durations of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay, and the prevalence of major complications.

Findings: Twenty-three studies in cardiac surgery (n = 7635) and 8 studies in noncardiac surgery (n = 1805) were included. In cardiac surgery, dexmedetomidine use reduced postoperative 30-day mortality (risk ratio [RR], 0.35 [95% CI, 0.24 to 0.51]); durations of mechanical ventilation (mean difference [MD], −1.56 h [−2.52 to −0.60]), ICU stay (MD, −0.22 day [−0.35 to −0.08]), and hospital stay (MD, −0.65 day [−1.12 to −0.18]); and the prevalences of delirium (RR, 0.50 [0.36 to 0.69]), atrial fibrillation (RR, 0.74 [0.57 to 0.97]), and cardiac arrest (RR, 0.34 [0.13 to 0.87]). In noncardiac surgery, dexmedetomidine use was associated with decreases in the durations of mechanical ventilation and hospital stay, with a trend toward a lower prevalence of delirium (RR, 0.57 [0.32 to 1.01]). The prevalence of bradycardia was increased in dexmedetomidine-treated patients undergoing cardiac surgery (RR, 1.70 [1.19 to 2.44]) and noncardiac surgery (RR, 1.64 [1.05 to 2.58]).

Implications: Dexmedetomidine use may help to reduce postoperative 30-day mortality, durations of mechanical ventilation, ICU stay, and hospital stay, and the prevalences of delirium, atrial fibrillation, and cardiac arrest in patients who undergo cardiac surgery. The majority of the benefits of dexmedetomidine were not significant in patients undergoing noncardiac surgery. An increased risk for bradycardia should be taken into consideration when prescribing dexmedetomidine. International Prospective Register of Systematic Reviews identifier: CRD42017070791. (*Clin Ther*. 2019;41:138–154) © 2018 Elsevier Inc. All rights reserved.

Keywords: complications, dexmedetomidine, meta-analysis, mortality, surgery.

INTRODUCTION

Globally, an estimated 312.9 million surgical operations took place in 2012, representing a 33.6% increase over 8 years [1,2]. Major postoperative complications associated with surgical procedures include myocardial infarction, heart block, cardiac arrest, acute respiratory failure, acute renal failure, delirium, stroke, gastrointestinal bleeding, and

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infection [3–6]. These complications translate into increased health care resource utilization, prolonged hospital stay, and increased mortality.

The α_2-adrenergic agonist dexmedetomidine (DEX) has a range of beneficial effects for surgical patients, including sedative, analgesic, sympatholytic, opioid-sparing, and anesthetic-sparing properties [7]. Previous studies have indicated that DEX use during cardiac surgery was associated with a reduced prevalence of complications and a decrease in postoperative mortality [4,8,9]. Consistent with these clinical findings, animal studies have shown that DEX had myocardial- and brain-protective effects [10–13]. Thus, DEX use may lead to better postoperative outcomes in surgical patients, including a lower prevalence of complications and improved survival. However, a recent report suggested that intraoperative DEX use did not reduce delirium in elderly patients undergoing noncardiac surgery [14]. Therefore, the impact of perioperative DEX use on outcomes of surgical patients, and whether these effects differ between cardiac and noncardiac surgical procedures, remain to be elucidated.

In this meta-analysis, we analyzed all published evidence, including randomized controlled trials (RCTs) and observational cohort studies, to test the hypotheses that perioperative DEX use in surgical patients: (1) reduces postoperative mortality; and (2) provides cardiac, renal, pulmonary, and neurologic protection with a decreased prevalence of major complications. Since cardiac surgery and noncardiac surgery vary with respect to patients' clinical characteristics and the risk for postoperative mortality, outcomes assessed were stratified by cardiac or noncardiac surgery.

MATERIALS AND METHODS

The protocol for this systematic review and meta-analysis is registered on the International Prospective Register of Systematic Reviews (registration number: CRD42017070791). The study was performed and is reported according to the recommendations of the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [15,16].

Search

Two reviewer–authors (K.P. and H.-Y.L.) independently searched the PubMed, EMBASE, and Cochrane databases from inception to August 2018 using specific search strategies (see Supplemental Table I in the online version at https://doi.org/10.1016/j.clinthera.2018.10.022). A manual search of reference lists from relevant articles was also conducted.

Study Selection

Two reviewer–authors (K.P. and H.-Y.L.) independently screened titles and abstracts using a priori selection criteria and reviewed full-text articles to identify eligible studies. Disagreements about study selection were resolved by group discussion until consensus was reached.

Inclusion criteria were: (1) study design: RCTs or observational cohort studies; (2) participants: adult surgical patients; (3) comparison: perioperative DEX use versus no perioperative DEX use (from anesthesia induction to 48 h postoperatively); and (4) outcomes measures: postoperative mortality and complications.

Exclusion criteria were: (1) studies that reported insufficient data; (2) duplicate datasets; and (3) reviews, letters, abstracts, or editorials.

Data Extraction

Two reviewer–authors (K.P. and H.Y.L.) independently extracted relevant data from each eligible study, including first author, publication date, country, health care setting, study period, interventions, number of patients, patient age, and main outcomes. Disagreements about data extraction were resolved by group discussion until consensus was reached.

Primary and Secondary Outcomes

The primary outcomes measure was postoperative mortality, including in-hospital, 30-day, and 1-year mortality. Secondary outcomes measures were the durations of mechanical ventilation, intensive care unit (ICU) stay, and hospital stay, and the prevalence of complications (delirium, stroke, coma, myocardial infarction, atrial fibrillation, cardiac arrest, heart block, the need for intra-aortic balloon pump assistance, acute kidney injury or failure, gastrointestinal bleeding, wound infection, hypotension, and bradycardia), reoperation, and readmission.

Quality Assessment

Two reviewer–authors (K.P. and H.-Y.L.) independently evaluated the risk for bias in RCTs using the Cochrane Collaboration's tool and the methodologic quality of observational studies using the Newcastle–Ottawa Scale criteria [17,18]. The Cochrane Collaboration's tool assesses the risk for bias in 6 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcomes assessment, incomplete data on outcomes, and selective reporting. Risk for bias was categorized as high (high risk for bias in one or more domains), low (low risk for bias in all domains), or otherwise unclear. The Newcastle–Ottawa Scale considers the selection of study cohorts, comparability of the cohorts, and outcomes ascertainment using a 9-star system. Risk for bias was categorized as low (score 8 or 9), moderate (score 6 or 7), or high (score <6). Disagreements about quality assessment were resolved by group discussion until consensus was reached.

Data Analysis

Statistical analysis was performed using RevMan software version 5.3 (Cochrane Collaboration, Copenhagen, Denmark). $P < 0.05$ denoted statistical significance. Mean differences (MDs) and corresponding 95% CIs were calculated for continuous outcomes, and risk ratios (RRs) with 95% CIs were calculated for dichotomous outcomes. Heterogeneity between studies was evaluated using the *I* [2] statistic [19]. Given the expected clinical and methodologic heterogeneity in this meta-analysis, which would have been reflected in variant estimated effect sizes across studies, a random-effects model was used [15,20–22].

Since the postoperative complications and mortality associated with cardiac surgery and noncardiac surgery have very different pathophysiology, we investigated the main outcomes in subgroup analyses stratified according to cardiac versus noncardiac surgery. In addition, subgroup analyses stratified by RCT versus non-RCT were performed for several outcomes measures to further assess the source of heterogeneity across included studies.

RESULTS

The initial literature search identified 871 articles. After removing duplicates and screening the titles and abstracts, 74 studies remained. After examining the full text of 74 articles, 43 studies were excluded, and 31 studies were finally included in this meta-analysis (Figure 1) [4,14,23–35].

Table I summarizes the characteristics of included studies. Twenty-three studies (n = 7635) included patients undergoing cardiac surgery [4,23–31,36–48], and 8 studies (n = 1805) included patients undergoing noncardiac surgery [14,32–35,49–51]. Of the 23 RCTs [14,23,26,28–30,34–46,48–51], the risk for bias was low in 16 trials and unclear in 7 trials. For the 8 non-RCTs [4,24,25,27,31–33,47], the methodologic quality was moderate to high (see Supplemental Tables II and III in the online version at https://doi.org/10.1016/j.clinthera.2018.10.022).

Primary and secondary outcomes are shown in Supplemental Table IV (see the online version at https://doi.org/10.1016/j.clinthera.2018.10.022). In cardiac surgery, perioperative DEX use reduced postoperative 30-day mortality (RR, 0.35 [CI, 0.24 to 0.51]; $P < 0.00001$; *I* [2] = 0), the duration of mechanical ventilation (MD, –1.56 h [−2.52 to –0.60]; $P = 0.001$; *I* [2] = 89), ICU stay (MD, –0.22 days [−0.35 to –0.08]; $P = 0.002$; $I^2 = 89$), and hospital stay (MD, –0.65 days [−1.12 to –0.18]; $P = 0.007$; *I* [2] = 70) (Figure 2), and the prevalences of delirium (MD, 0.50 [0.36 to 0.69]; $P < 0.0001$; *I* [2] = 30), atrial fibrillation (MD, 0.74 [0.57 to 0.97]; $P = 0.03$; *I* [2] = 44), and cardiac arrest (MD, 0.34 [0.13 to 0.87]; $P = 0.02$; *I* [2] = 19) versus no perioperative DEX use (Figure 3). Postoperative 30-day mortality was much higher in cardiac patients (39 of 1553 patients [2.51%] who received DEX and 83 of 1259 patients [6.59%] who did not receive DEX) compared to noncardiac patients (4 of 509 [0.79%] and 5 of 509 [0.98%]). In noncardiac surgery, perioperative DEX use reduced the durations of mechanical ventilation (MD, –2.30 days [−2.52 to –2.08]; $P < 0.00001$; *I* [2] = 0) and hospital stay (MD, –0.60 days [−1.07 to –0.13]; $P = 0.01$; *I* [2] = 83), with a trend toward a lower prevalence of delirium (MD, 0.57 [0.32 to 1.01]; $P = 0.05$; *I* [2] = 65) versus no perioperative DEX use.

There were no significant differences in the prevalences of stroke, coma, myocardial infarction, heart block, intra-aortic balloon pump assistance, acute kidney injury or failure, gastrointestinal bleeding, wound infection, reoperation, or readmission between groups (see Supplemental Table IV in the online version at https://doi.org/10.

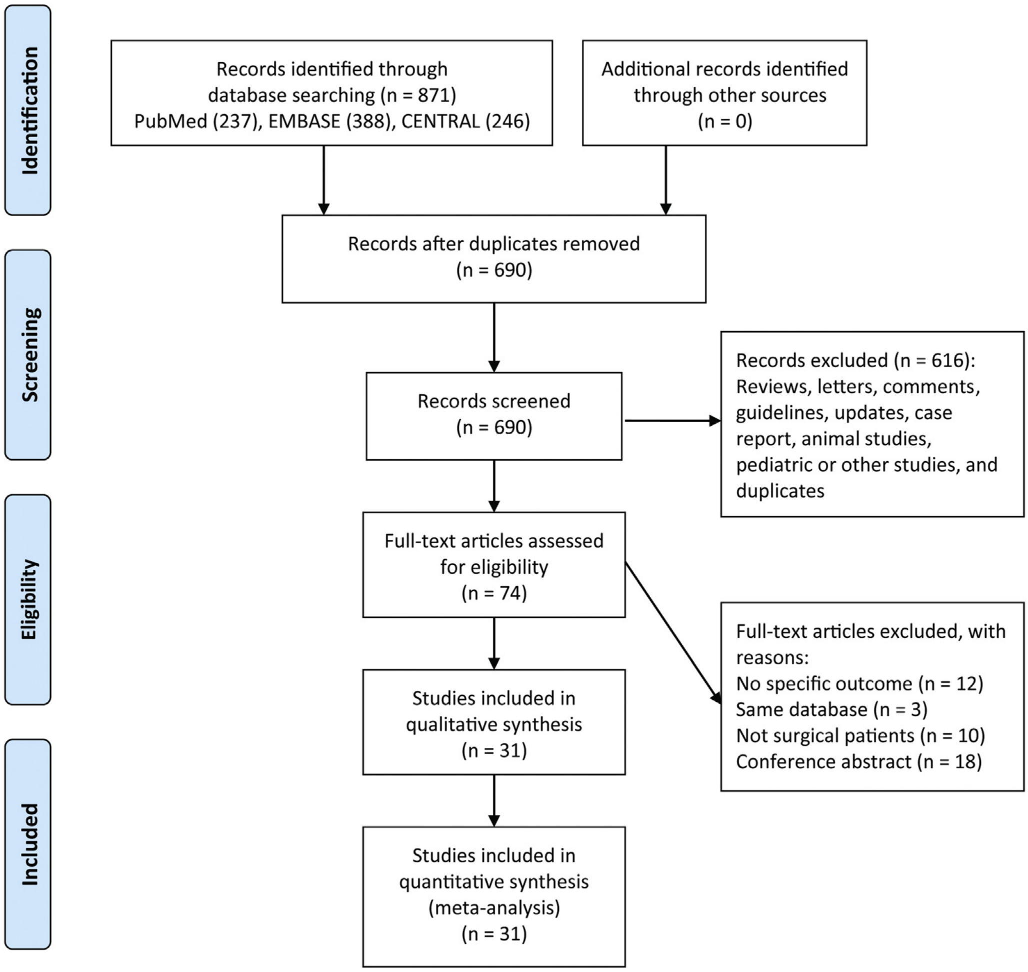

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram.

1016/j.clinthera.2018.10.022). Perioperative DEX use did not increase the prevalence of hypotension but did increase the prevalence of bradycardia in patients undergoing cardiac surgery (MD, 1.70 [1.19 to 2.44]; $P = 0.004$; I [2] = 0) and noncardiac surgery (MD, 1.64 [1.05 to 2.58]; $P = 0.03$; I [2] = 43) versus no perioperative DEX use (Figure 4).

Table II summarizes the results of subgroup analyses according to the study design. In patients undergoing cardiac surgery, perioperative DEX use significantly decreased 30-day mortality, duration of hospital stay, and prevalence of atrial fibrillation in non-RCTs but not in RCTs, while the reduced durations of mechanical ventilation and ICU stay were significant in both non-RCTs and RCTs. DEX use reduced the prevalence of delirium in cardiac patients in RCTs. In patients undergoing noncardiac surgery, the DEX-induced significant decreases in the duration of mechanical ventilation and hospital stay were mainly based on findings from non-RCTs.

DISCUSSION

The findings from this comprehensive meta-analysis of current evidence suggest that perioperative DEX use may reduce postoperative 30-day mortality, the duration of mechanical ventilation, and ICU and hospital stay, and the prevalences of delirium, atrial fibrillation, and cardiac arrest in patients who undergo cardiac surgery. In noncardiac surgery, most of the benefits of DEX were not significant. Due to

Table I. Study characteristics.

Study	Procedure	Region	Design	Setting/Study Period	Groups	DEX Use	Outcomes Reported
Ammar et al. (2016) [23]	Cardiac	Egypt	RCT	University hospital, June 2012 to Feb 2014	DEX (n = 25; mean age, 55 y); Saline (n = 25; mean age, 59 y)	1 µg/kg before bypass, followed by 0.5 µg/kg/h until 6 h after surgery	30-d mortality, complications, mechanical ventilation, ICU stay, hospital stay
Bily et al. (2015) [24]	Cardiac	Slovak	Non-RCT	University hospital, April 2013 to Feb 2014	DEX (n = 250; mean age, 64 y); Non-DEX (n = 250; mean age, 65 y)	0.4 µg/kg during sternal wiring, followed by 0.25 µg/kg/h to <200 µg	In-hospital mortality, complications, mechanical ventilation, ICU stay, hospital stay
Brandão et al. (2016) [25]	Cardiac	Brazil	Non-RCT	University hospital, Jan 2003 to Apr 2011	DEX (n = 796; mean age, 56 y); Non-DEX (n = 506; mean age, 58 y)	0.5 µg/kg after induction, followed by 0.5 µg/kg/h intraoperatively	30-d mortality, complications, ICU stay
Cho et al. (2016) [26]	Cardiac	Korea	RCT	University hospital, Jun 2013 to Jan 2015	DEX (n = 100; mean age, 67 y); Saline (n = 100; mean age, 62 y)	0.4 µg/kg/h after induction, until 24 h after surgery	In-hospital mortality, complications, ICU stay
Corbett et al. (2005) [36]	Cardiac	US	RCT	University hospital, Oct 2002 to Apr 2004	DEX (n = 43; mean age, 63 y); Propofol (n = 46; mean age, 62 y)	1 µg/kg on ICU admission, followed by 0.4 µg/kg/h up to 1 h after extubation	In-hospital mortality, complications, mechanical ventilation, ICU stay
Curtis et al. (2013) [27]	Cardiac	US	Non-RCT	Community hospital, Dec 2008 to Oct 2010	DEX (n = 291; mean age, 67 y); Propofol (n = 291; mean age, 65 y)	Sedation in ICU, no other details	In-hospital mortality, mechanical ventilation, ICU stay, hospital stay
Djaiani et al. (2016) [37]	Cardiac	Canada	RCT	University hospital, Aug 2011 to Jul 2014	DEX (n = 91; mean age, 72 y); Propofol (n = 92; mean age, 72 y)	0.4 µg/kg on ICU admission, followed by 0.2–0.7 µg/kg/h until extubation	In-hospital mortality, complications, mechanical ventilation, ICU stay, hospital stay
Herr et al. (2003) [38]	Cardiac	US and Canada	RCT	Multicenter, not reported	DEX (n = 148; mean age, 61 y); Propofol (n = 147; mean age, 62 y)	1 µg/kg at sternal closure, followed by 0.2–0.7 µg/kg/h up to 2 h after extubation	Complications, mechanical ventilation
Jalonen et al. (1997) [39]	Cardiac	Finland	RCT	University hospital, Jun 1992 to Mar 1993	DEX (n = 40; mean age, 55 y); Saline (n = 40; mean age, 55 y)	50 ng/kg/min before induction, followed by 7 ng/kg/min intraoperatively	In-hospital mortality, complications

Table I. (*Continued*)

Study	Procedure	Region	Design	Setting/Study Period	Groups	DEX Use	Outcomes Reported
Ji et al. (2013) [9]	Cardiac	US	Non-RCT	University hospital, Jan 2006 to Dec 2011	DEX (n = 568; mean age, 63 y); Non-DEX (n = 566; mean age, 63 y)	0.24–0.6 μg/kg/h after bypass, until <24 h in ICU	In-hospital, 30-d, 1-y mortality, mechanical ventilation, complications, ICU stay, hospital stay
Khalil et al. (2013) [40]	Cardiac	Saudi Arabia	RCT	University hospital, Jan 2008 to Sept 2008	DEX (n = 25; mean age, 58 y); Saline (n = 25; mean age, 58 y)	1 μg/kg after induction, followed by 0.5 μg/kg/h intraoperatively	In-hospital mortality, mechanical ventilation, ICU stay, hospital stay
Kim et al. (2014) [28]	Cardiac	Korea	RCT	University hospital, Sept 2012 to Feb 2013	DEX (n = 40; mean age, 63 y); Saline (n = 38; mean age, 65 y)	0.3–0.7 μg/kg/h after induction, until 24 h after surgery	1-y mortality, complications, ICU stay, hospital stay
Li et al. (2017) [29]	Cardiac	China	RCT	Two university hospitals, Sept 2012 to Feb 2013	DEX (n = 142; mean age, 66 y); Saline (n = 143; mean age, 67 y)	0.6 μg/kg before induction, 0.4 μg/kg/h during surgery, 0.1 μg/kg/h until extubation	30-d mortality, complications, mechanical ventilation, ICU stay, hospital stay
Liu et al. (2016) [30]	Cardiac	China	RCT	University hospital, Jan 2015 to Dec 2015	DEX (n = 44; mean age, 53 y); Propofol (n = 44; mean age, 56 y)	0.2–1.5 μg/kg/h from ICU admission until extubation	In-hospital mortality, complications, mechanical ventilation, ICU stay, hospital stay
Park et al. (2014) [41]	Cardiac	Korea	RCT	University hospital, Apr 2012 to Mar 2013	DEX (n = 67; mean age, 51 y); Remifentanil (n = 75; mean age, 54 y)	0.5 μg/kg on ICU admission, followed by 0.2–0.8 μg/kg/h until extubation	In-hospital mortality, complications, mechanical ventilation, ICU stay, hospital stay
Ren et al. (2013) [42]	Cardiac	China	RCT	University hospital, Jan 2010 to Jan 2011	DEX (n = 81; mean age, 60 y); Saline (n = 81; mean age, 58 y)	Intraoperative 0.2–0.5 μg/kg/h until transferred to ICU for 12 h	In-hospital mortality, complications
Shehabi et al. (2009) [43]	Cardiac	Australia	RCT	University hospital, Apr 2012 to Mar 2013	DEX (n = 152; mean age, 71 y); Morphine (n = 147; mean age, 71 y)	0.1–0.7 μg/kg/h from ICU admission until extubation	In-hospital mortality, complications, mechanical ventilation, ICU stay, hospital stay

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Table I. (*Continued*)

Study	Procedure	Region	Design	Setting/Study Period	Groups	DEX Use	Outcomes Reported
Soltani et al. (2017) [44]	Cardiac	Iran	RCT	University hospital, Jul 2016 to Jan 2017	DEX (n = 38; mean age, 60 y); Saline (n = 38; mean age, 59 y)	0.5 μg/kg after induction, followed by 0.5 μg/kg/h intraoperatively	Complications
Talke et al. (2000) [45]	Cardiac	US	RCT	University hospital, Jan 2010 to Jan 2011	DEX (n = 22; mean age, 65 y); Saline (n = 19; mean age, 66 y)	24 μg before induction, 0.15−0.8 μg/min until 48 h after surgery	30-d mortality, complications
Venn et al. (1999) [46]	Cardiac	UK	RCT	Multicenter, not reported	DEX (n = 66; mean age, 63 y); Saline (n = 53; mean age, 64 y)	1 μg/kg on ICU admission, followed by 0.2−0.7 μg/kg/h up to 24 h	In-hospital mortality, complications, mechanical ventilation
Wanat et al. (2014) [31]	Cardiac	US	Non-RCT	Academic hospital, Jan 2011 to Jul 2011	DEX (n = 33; mean age, 63 y); Propofol (n = 319; mean age, 68 y)	Sedation in ICU, 0.35−0.62 μg/kg/h until extubation	In-hospital mortality, mechanical ventilation complications, ICU stay, hospital stay
Xu et al. (2018) [47]	Cardiac	China	Non-RCT	University hospital, Jun 2012 to Sept 2012	DEX (n = 1077; mean age, 57 y); Non-DEX (n = 400; mean age, 58 y)	0.375−0.6 μg/kg/h after central venous catheter insertion, until extubation in ICU	In-hospital and 1-y mortality, mechanical ventilation, complications
Zhai et al. (2017) [48]	Cardiac	China	RCT	University hospital, Feb 2014 to Dec 2014	DEX (n = 36; mean age, 45 y); Saline (n = 36; mean age, 47 y)	0.6 μg/kg before induction, followed by 0.2 μg/kg/h intraoperatively	Complications, mechanical ventilation
Deiner et al. (2017) [14]	Noncardiac	US	RCT	Multicenter, Feb 2008 to May 2014	DEX (n = 189; mean age, 74 y); Saline (n = 201; mean age, 74 y)	0.5 μg/kg/h before induction, until 2 h into recovery	In-hospital mortality, complications, hospital stay
John et al. (2015) [32]	Noncardiac	US	Non-RCT	Urban academic hospital, Jan 2008 to Dec 2012	DEX (n = 35; mean age, 68 y); Propofol (n = 37; mean age, 68 y)	Sedation without intubation, no other details	In-hospital mortality, complications

Table I. (*Continued*)

Study	Procedure	Region	Design	Setting/Study Period	Groups	DEX Use	Outcomes Reported
Mei et al. (2018) [49]	Noncardiac	China	RCT	University hospital, Jun 2016 to Jun 2017	DEX (n = 148; mean age, 76 y); Propofol (n = 148; mean age, 74 y)	0.8−1 µg/kg, followed by 0.1−0.5 µg/kg/h intraoperatively	30-d mortality, complications, hospital stay
Seo et al. (2016) [33]	Noncardiac	Korea	Non-RCT	University hospital, May 2012 to Apr 2015	DEX (n = 48; mean age, 39 y); Non-DEX (n = 69; mean age, 34 y)	1 µg/kg, followed by 0.3−0.5 µg/kg/h intraoperatively	In-hospital mortality, complications, ICU stay, hospital stay
Su et al. (2016) [50]	Noncardiac	China	RCT	Two tertiary-care hospitals, Aug 2011 to Nov 2013	DEX (n = 350; mean age, >65 y); Saline (n = 350; mean age, >65 y)	0.1 µg/kg/h from ICU admission until postoperative day 1	In-hospital and 30-d mortality, complications, mechanical ventilation, ICU stay, hospital stay
Soliman et al. (2016) [34]	Noncardiac	Egypt	RCT	University hospital, May 2012 to Apr 2015	DEX (n = 75; mean age, 58 y); Saline (n = 75; mean age, 57 y)	1 µg/kg before induction, 0.3 µg/kg/h until end of surgery	In-hospital mortality, complications
Venn et al. (2001) [35]	Noncardiac	UK	RCT	University hospital, Not reported	DEX (n = 10; mean age, 65 y); Propofol (n = 10; mean age, 67 y)	0.4 µg/kg on ICU admission, followed by 0.2−0.25 µg/kg/h until extubation	In-hospital, 30-d mortality
Wu et al. (2018) [51]	Noncardiac	Taiwan, China	RCT	University hospital, Jul 2015 to Jun 2016	DEX (n = 30; mean age, 59 y); Saline (n = 30; mean age, 58 y)	0.5 µg/kg/h from before induction until the end of surgery	Complications, ICU stay, hospital stay

DEX = dexmedetomidine; ICU = intensive care unit; RCT = randomized controlled trial.

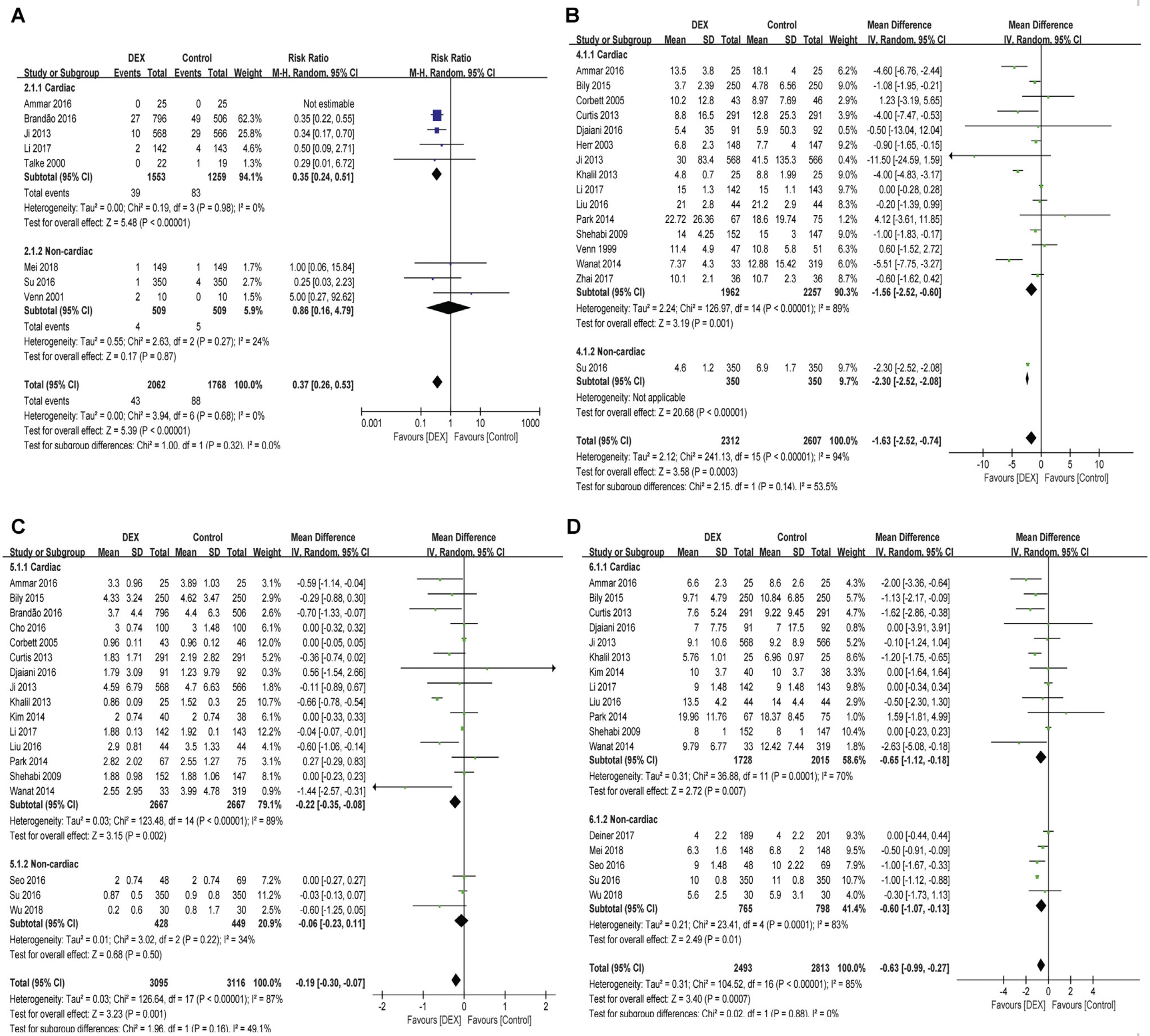

Figure 2. Outcomes with dexmedetomidine (DEX) versus control in adult surgical patients. A, 30-Day mortality. B, Duration of mechanical ventilation. C, Duration of intensive care unit (ICU) stay. D, Duration of hospital stay.

the lack of RCTs, some of the findings were significant only in cohort studies. Notably, the prevalence of bradycardia was increased in DEX-treated patients undergoing cardiac and noncardiac surgery.

Surgical manipulation and trauma activate the sympathetic nervous system and initiate systemic inflammatory responses [52,53]. DEX may have protective effects on the heart, brain, kidney, lung, intestine, and immune system by attenuating ischemia/reperfusion injury, exerting anti-inflammatory effects, and stabilizing the sympathetic nervous system [54–58]. In this study, we suggest a potential organ-protective effect of DEX in clinical use, as evidenced by the lower prevalence of delirium,

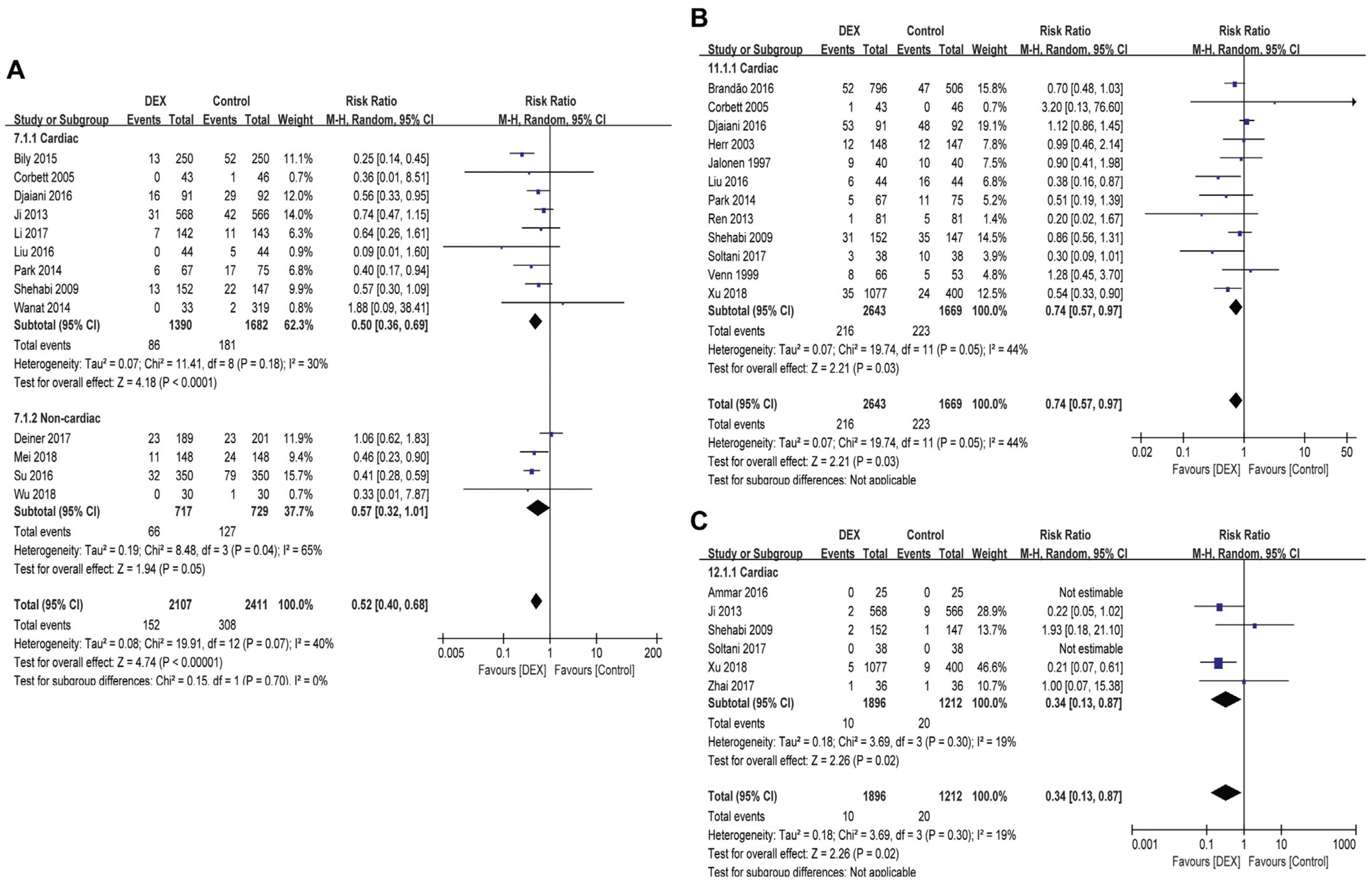

Figure 3. Prevalences of complications with dexmedetomidine (DEX) versus control in adult surgical patients. A, Delirium. B, Atrial fibrillation. C, Cardiac arrest.

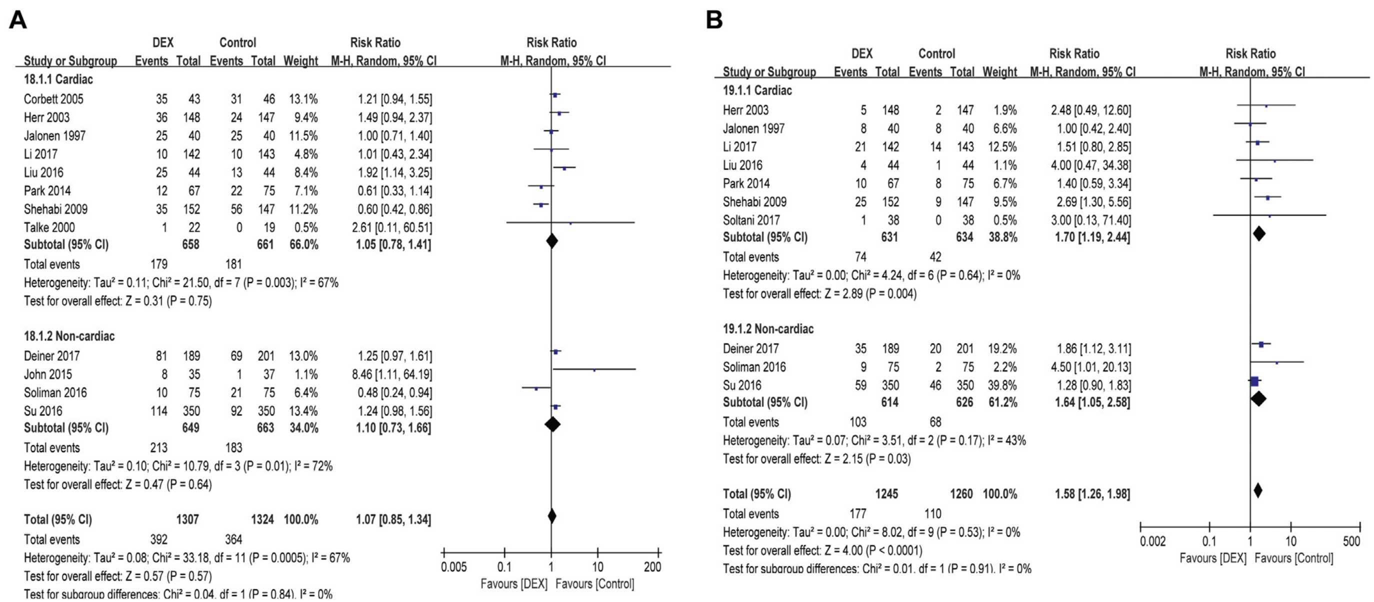

Figure 4. Prevalences of additional complications with dexmedetomidine (DEX) versus control in adult surgical patients. A, Hypotension. B, Bradycardia.

Table II. Subgroup analyses based on study design.

Subgroups	No. of Studies	No. of Patients	RR or MD (95% CI)	*P*	I^2 %	*P* Interaction
In-hospital mortality						
Cardiac						
RCT	9	1270	0.49 (0.19—1.29)	0.15	0	0.46
Non-RCT	5	4045	0.81 (0.33—2.00)	0.65	56	
Noncardiac						
RCT	4	1260	0.76 (0.21—2.68)	0.67	0	0.27
Non-RCT	2	189	2.11 (0.57—7.81)	0.26	0	
30-d Mortality						
Cardiac						
RCT	3	376	0.45 (0.10—1.96)	0.28	0	0.75
Non-RCT	2	2436	0.35 (0.24—0.51)	0.00001*	0	
Noncardiac						
RCT	3	1018	0.86 (0.16—4.79)	0.87	24	NA
1-y Mortality						
Cardiac						
RCT	1	114	0.37 (0.02—7.44)	0.51	0	0.70
Non-RCT	2	2611	0.70 (0.21—2.31)	0.56	81	
Mechanical ventilation, h						
Cardiac						
RCT	11	1651	−1.08 (−2.15 to −0.01)	0.05*	90	0.12
Non-RCT	4	2568	−3.81 (−7.05 to −0.57)	0.02*	82	
Noncardiac						
RCT	1	700	−2.30 (−2.52 to −2.08)	0.00001*	0	NA
ICU stay, d						
Cardiac						
RCT	10	1464	−0.17 (−0.31 to −0.02)	0.03*	92	0.10
Non-RCT	5	3870	−0.45 (−0.74 to −0.15)	0.003*	16	
Noncardiac						
RCT	2	760	−0.22 (−0.75 to 0.31)	0.41	66	0.46
Non-RCT	1	117	0.00 (−0.27 to 0.27)	0.99	0	
Hospital stay (d)						
Cardiac						
RCT	8	1175	−0.45 (−0.96 to 0.07)	0.09	72	0.19
Non-RCT	4	2568	−1.11 (−1.97 to −0.25)	0.01*	41	
Noncardiac						
RCT	4	1446	−0.50 (−1.07 to 0.07)	0.08	87	0.27
Non-RCT	1	117	−1.00 (−1.67 to −0.33)	0.003*	0	

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Table II. (*Continued*)

Subgroups	No. of Studies	No. of Patients	RR or MD (95% CI)	*P*	I^2 %	*P* Interaction
Delirium						
Cardiac						
RCT	6	1086	0.53 (0.37–0.74)	0.0002*	0	0.91
Non-RCT	3	1986	0.50 (0.19–1.32)	0.16	78	
Noncardiac						
RCT	4	1446	0.57 (0.32–1.01)	0.05	65	NA
Atrial fibrillation						
Cardiac						
RCT	10	1533	0.79 (0.58–1.09)	0.15	40	0.34
Non-RCT	2	2779	0.64 (0.47–0.87)	0.004*	0	
Bradycardia						
Cardiac						
RCT	7	1265	1.70 (1.19–2.44)	0.004*	0	NA
Noncardiac						
RCT	3	1240	1.64 (1.05–2.58)	0.03*	43	NA

MD = mean difference; RCT = randomized controlled trial; RR = risk ratio.
* Significant difference.

atrial fibrillation, and cardiac arrest after cardiac surgery in patients that received perioperative DEX compared to those that did not. Previously, we investigated the cardioprotective and neuroprotective effects of DEX in animal studies [10,11,13].

In cardiac surgery, our previous meta-analysis showed that perioperative DEX use reduced the risks for postoperative ventricular tachycardia and delirium; however, we did not evaluate postoperative mortality and other major complications [59]. In noncardiac surgery, a meta-analysis showed a trend toward improved cardiac outcomes associated with perioperative DEX use [60]. In contrast, another study suggested that perioperative DEX use in noncardiac surgery did not decrease the risk for cardiac complications or mortality and may increase the risk for hypotension and bradycardia [61]. The inconsistency between the results in cardiac and noncardiac surgery may have been the result of a higher potential for postoperative complications and mortality in cardiac surgery, where DEX was reported to provide protective effects by attenuating excessive inflammation. In addition, a recent meta-analysis indicated that prophylactic α_2-adrenergic agonists (DEX, clonidine, and mivazerol) did not reduce mortality or major cardiac complications [62]. However, the inclusion of clonidine and mivazerol in this study may have introduced some bias and hampered the interpretation of the effects of DEX. Another meta-analysis showed a lower prevalence of postoperative delirium in adult cardiac and noncardiac surgical patients who received DEX, but did not present data on mortality, duration of hospital stay, or other complications [63]. An additional meta-analysis did not reach a conclusion about the overall effects of perioperative DEX use on postoperative outcomes in surgical patients due to lack of evidence [64].

Our study had several strengths. First, to the authors' knowledge, this is the first meta-analysis that aimed to assess the impact of DEX on postoperative outcomes in a large population of surgical patients, covering both cardiac and noncardiac procedures. Second, we comprehensively reviewed the current literature and included recent and well-designed

RCTs as well as all available cohort studies. Third, we performed data analyses based on cardiac and noncardiac surgery and found that the reduced mortality rate and other benefits associated with DEX were mainly significant in cardiac procedures versus noncardiac procedures. Fourth, we performed subgroup analyses according to RCT versus non-RCT. Based on data from RCTs, we found that DEX use reduced the duration of mechanical ventilation, the duration of ICU stay, and the prevalence of delirium in cardiac surgery.

We also acknowledge several limitations. First, study-level data rather than patient-level data were considered; therefore, the cause of death for each patient could not be determined. Second, definitions of postoperative complications were based on the original reports and thus were not completely uniform across studies. Third, the number of studies in noncardiac surgery was small, and the types of surgery varied. Hence, this meta-analysis may have been underpowered to show the benefits of DEX for patients who underwent noncardiac surgery. Fourth, heterogeneity between studies was evident for some outcomes; these results should be interpreted with caution. Last, some of the results were significant only in cohort studies. Further RCTs that evaluate the effects of DEX in different types of surgery are required and could provide more definitive information about the potential benefits of DEX in surgical patients.

CONCLUSIONS

Overall, the findings from our meta-analysis of current evidence indicate that perioperative DEX use may improve patient outcomes after cardiac surgery. However, due to the small number of studies, most of the benefits of DEX were not significant for patients undergoing noncardiac surgery. Of note, an increased risk for bradycardia should be taken into consideration when using DEX in patients undergoing cardiac and noncardiac surgery.

CONFLICTS OF INTEREST

The authors have indicated that they have no conflicts of interest with regard to the content of this article.

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K. Peng, F.-H. Ji, and H.-Y. Liu contributed equally to this work. K. Peng and F.-H. Ji conceived and designed the study. K. Peng and H.-Y. Liu performed the search, study selection, data extraction, bias assessment, and statistical analysis. K. Peng and F.-H. Ji wrote the manuscript. J. Zhang, Q.-C. Chen, and Y.-H. Jiang helped to acquire, analyze, and interpret the data. All of the authors read the manuscript and approved the final version.

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APPENDIX. SUPPLEMENTARY DATA

Supplemental Table 1. Search strategies

PubMed
Searched on: Aug 1, 2018
Results: 237

Search	Query
#1	dexmedetomidine[tiab]
#2	mortality[tiab] OR death[tiab] OR died[tiab] OR fatality[tiab]
#3	morbidity[tiab] OR complication*[tiab]
#4	#2 OR #3
#5	surgery[tiab] OR surgical[tiab] OR perioperative[tiab] OR postoperative[tiab] OR intraoperative[tiab]
#6	randomized controlled trial[pt] OR controlled clinical trial[pt]
#7	random*[tiab] OR prospective[tiab] OR clinical[tiab] OR controlled[tiab] OR multicenter[tiab] OR blind*[tiab] OR placebo[tiab] OR observation*[tiab] OR retrospective[tiab] OR cohort[tiab]
#8	#6 OR #7
#9	#1 AND #4 AND #5 AND #8

EMBASE
Searched on: Aug 1, 2018
Results: 388

Search	Query
#1	dexmedetomidine:ab,ti
#2	mortality:ti,ab OR death:ti,ab OR died:ti,ab OR fatality:ti,ab
#3	morbidity:ti,ab OR complication*:ti,ab
#4	#2 OR #3
#5	perioperative:ti,ab OR postoperative:ti,ab OR intraoperative:ti,ab OR surgery:ti,ab OR surgical:ti,ab
#6	random*:ti,ab OR prospective:ti,ab OR clinical:ti,ab OR controlled:ti,ab OR multicenter:ti,ab OR blind*:ti,ab OR placebo:ti,ab OR observation*:ti,ab OR retrospective:ti,ab OR cohort:ti,ab
#7	#1 AND #4 AND #5 AND #6

CENTRAL
Searched on: Aug 1, 2018
Results: 246

Search	Query
#1	dexmedetomidine:ti,ab,kw
#2	(mortality OR death OR died OR fatality):ti,ab,kw
#3	(morbidity or complication*):ti,ab
#4	#2 OR #3
#5	(perioperative or postoperative or intraoperative or surgery or surgical):ti,ab
#6	#1 AND #4 AND #5

Supplemental Table II. Risk of bias of randomized trials

Studies	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)
Ammar 2016	Low	Low	Low	Low	Unclear[a]	Low
Cho 2016	Low	Low	Low	Low	Unclear[a]	Low
Corbett 2005	Low	Low	Low	Low	Low	Low
Deiner 2017	Low	Low	Low	Low	Low	Low
Djaiani 2016	Low	Low	Low	Low	Low	Low
Herr 2003	Low	Low	Low	Low	Low	Low
Jalonen 1997	Low	Low	Low	Low	Low	Low
Khalil 2013	Low	Low	Low	Low	Low	Low
Kim 2014	Low	Low	Low	Low	Low	Low
Li 2017	Low	Low	Low	Low	Low	Low
Liu 2016	Low	Low	Unclear[b]	Unclear[b]	Low	Low
Mei 2018	Low	Low	Low	Low	Low	Low
Park 2014	Low	Unclear[c]	Unclear[b]	Unclear[b]	Low	Low
Ren 2013	Low	Unclear[c]	Unclear[b]	Unclear[b]	Low	Low
Shehabi 2009	Low	Low	Low	Low	Low	Low
Soliman 2016	Low	Low	Unclear[b]	Unclear[b]	Unclear[a]	Low
Soltani 2017	Low	Low	Low	Low	Low	Low
Su 2016	Low	Low	Low	Low	Low	Low
Talke 2000	Low	Low	Low	Low	Low	Low
Venn 1999	Low	Low	Low	Low	Low	Low
Venn 2001	Low	Low	Low	Low	Unclear[a]	Low
Wu 2018	Low	Low	Low	Low	Low	Low
Zhai 2017	Low	Low	Low	Low	Low	Low

Cochrane tool: Risk of bias is categorized as high, low, or unclear

[a] No data on follow-up.

[b] No detail on blinding method.

[c] No detail on allocation concealment.

Supplemental Table III. Quality of observational studies

Studies	Selection				Comparability	Outcome			Total score
	Representative-ness of the exposed cohort	Selection of the non-exposed cohort	Ascertain-ment of exposure	Outcome not present at study start	Controlling important factors or confounding factors	Assessment of outcome	Follow-up long enough for outcomes to occur	Integrity of follow up	
Bily 2015	*	*	*	*		*	*	*	7
Brandão 2016	*	*	*	*		*	*	*	7
Curtis 2013	*	*	*	*		*	*	*	7
Ji 2013	*	*	*	*	**	*	*	*	9
John 2015	*	*	*	*		*	*	*	7
Seo 2016	*	*	*	*		*	*	*	7
Wanat 2014	*	*	*	*		*	*	*	7
Xu 2018	*	*	*	*	**	*	*	*	9

Newcastle-Ottawa Scale: the highest quality studies receive nine stars
How a star is earned in each domain:
Selection (4 points): consecutive patients truly representative of the cohort; ascertainment of exposure to implants with secure records; outcomes of interest were not present at start of study.
Comparability (2 points): propensity score adjustment or multivariate adjustment performed.
Outcome (3 points): assessment of outcome adjudicated by independent clinicians; follow up were adequate and long enough.

Supplemental Table IV. Main outcomes

Outcomes	Procedure	No. of studies	No. of patients	RR or MD [95% CI]	P value	I^2 (%)
In-hospital mortality	Cardiac	14	5,315	RR = 0.66 [0.37, 1.18]	.16	22
	Non-cardiac	6	1,449	RR = 1.24 [0.50, 3.09]	.64	0
30-day mortality	Cardiac	5	2,812	RR = 0.35 [0.24, 0.51]	.00001*	0
	Non-cardiac	3	1,018	RR = 0.86 [0.16, 4.79]	.87	24
1-year mortality	Cardiac	3	2,725	RR = 0.65 [0.24, 1.76]	.39	63
Mechanical ventilation (h)	Cardiac	15	4,219	MD = −1.56 [−2.52, −0.60]	.001*	89
	Non-cardiac	1	700	MD = −2.30 [−2.52, −2.08]	.00001*	0
ICU stay (d)	Cardiac	15	5,334	MD = −0.22 [−0.35, −0.08]	.002*	89
	Non-cardiac	3	877	MD = −0.06 [−0.23, 0.11]	.50	34
Hospital stay (d)	Cardiac	12	3,743	MD = −0.65 [−1.12, −0.18]	.007*	70
	Non-cardiac	5	1,563	MD = −0.60 [−1.07, −0.13]	.01*	83
Delirium	Cardiac	9	3,072	RR = 0.50 [0.36, 0.69]	.0001*	30
	Non-cardiac	4	1,446	RR = 0.57 [0.32, 1.01]	.05	65
Stroke	Cardiac	8	3,590	RR = 0.95 [0.57, 1.61]	.86	0
	Non-cardiac	1	304	RR = 0.36 [0.01, 8.67]	.53	0
Coma	Cardiac	3	2,896	RR = 0.69 [0.32, 1.47]	.33	0
Myocardial infarction	Cardiac	6	3,183	RR = 0.90 [0.54, 1.50]	.70	5
	Non-cardiac	2	454	RR = 0.77 [0.09, 6.53]	.81	23
Atrial fibrillation	Cardiac	12	4,312	RR = 0.74 [0.57, 0.97]	.03*	44
Cardiac arrest	Cardiac	6	3,108	RR = 0.34 [0.13, 0.87]	.02*	19
Heart block	Cardiac	4	2,737	RR = 0.98 [0.62, 1.53]	.91	0
IABP assistance	Cardiac	3	548	RR = 0.58 [0.27, 1.21]	.15	0
Acute kidney injury or failure	Cardiac	10	5,045	RR = 0.85 [0.65, 1.12]	.25	42
	Non-cardiac	2	454	RR = 0.67 [0.20, 2.27]	.52	0
Gastrointestinal bleeding	Cardiac	1	285	RR = 0.50 [0.09, 2.71]	.42	0
	Non-cardiac	1	304	RR = 1.07 [0.07, 16.92]	.96	0
Wound infection	Cardiac	4	599	RR = 1.35 [0.52, 3.49]	.54	45
	Non-cardiac	2	421	RR = 2.02 [0.16, 25.30]	.59	72
Hypotension	Cardiac	8	1,319	RR = 1.05 [0.78, 1.41]	.75	67
	Non-cardiac	4	1,312	RR = 1.10 [0.73, 1.66]	.64	72
Bradycardia	Cardiac	7	1,265	RR = 1.70 [1.19, 2.44]	.004*	0
	Non-cardiac	3	1,240	RR = 1.64 [1.05, 2.58]	.03*	43
Reoperation	Cardiac	5	3,461	RR = 0.89 [0.59, 1.34]	.58	0
Readmission	Cardiac	3	2,721	RR = 0.89 [0.61, 1.30]	.55	25

MD = mean difference; RCT = randomized controlled trial; RR = risk ratio.
* indicates a statistical difference.