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Does Dexmedetomidine Reduce the Risk of Atrial Fibrillation and Stroke After Adult Cardiac Surgery? A Systematic Review and Meta-analysis of Randomized Controlled Trials

META-ANALYSIS

ABSTRACT

Background: Postoperative atrial fibrillation is a common consequence of cardiac surgery with increased stroke complications and mortality. Although dexmedetomidine is thought to prevent postoperative atrial fibrillation and stroke because of its sympatholytic and anti-inflammatory properties, data from different studies show the effect of dexmedetomidine on postoperative atrial fibrillation and stroke uncertain in adult patients with cardiac surgery.

Methods: A database including EMBASE, PubMed, and Cochrane CENTRAL was searched for randomized controlled trials comparing dexmedetomidine with placebo or other anesthetic drugs in adult cardiac surgery. The primary outcome was the incidence of postoperative atrial fibrillation. The secondary outcomes were the incidence of postoperative stroke, mechanical ventilation duration, intensive care unit length of stay, hospital length of stay, and mortality.

Results: Eighteen trials with a total of 2933 patients were enrolled in the meta-analyses. Compared with controls, dexmedetomidine significantly reduced the incidence of postoperative atrial fibrillation [odds ratio, 0.82; 95% CI, 0.69-0.98; $P = .03$]. There was no significant difference between groups in stroke (odds ratio, 1.36; 95% CI, 0.59-3.16; $P = .47$), mechanical ventilation duration [weighted mean difference, −0.17; 95% CI, −0.35 to 0.14; $P = .39$], intensive care unit length of stay (weighted mean difference, −0.03; 95% CI, −0.93 to 0.87; $P = .95$), hospital length of stay (weighted mean difference, −0.04; 95% CI, −0.40 to 0.32; $P = .83$) and mortality (odds ratio, 0.72; 95% CI, 0.32-1.60; $P = .42$).

Conclusion: Perioperative dexmedetomidine reduced the incidence of postoperative atrial fibrillation in adult patients undergoing cardiac surgery. But there was no significant difference in the incidence of stroke, mechanical ventilation duration, intensive care unit length of stay, hospital length of stay, and mortality.

Keywords: Dexmedetomidine, atrial fibrillation, stroke, cardiac surgery, meta-analyses

INTRODUCTION

Postoperative atrial fibrillation (POAF) is often observed in adult patients who underwent cardiac surgery with the reported incidence ranging from 15% to 40%.[1] POAF is associated with an increased incidence of postoperative stroke complications and results in not only prolonged hospital length of stay (LOS), but also increased hospital costs and mortality.[2] The mechanism of POAF is complex and remains poorly understood. It might be triggered by postoperative factors such as inflammation, oxidative stress, pre-existing clinical characteristics including age, hypertension, and surgical procedure.[3] Pre-admission interventions and rate and rhythm control were thought to be the main strategies to prevent POAF in heart surgery patients. Although amiodarone or beta-blocker is used after cardiac surgery to prevent POAF as recommended by the European Society of Cardiology (ESC)/European Association of Cardio-Thoracic Surgery (EACTS) Guidelines,[4] the POAF incidence has remained largely constant over the past few decades. Furthermore, overcoming POAF remains a challenge.

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Dexmedetomidine (DEX) is a novel type of highly selective α2-adrenergic receptor agonist and has been used as a sedative or adjuvant anesthetic drug to maintain more stable hemodynamic parameters for patients undergoing cardiac surgery.[5] The original application for DEX was the short-term sedation for adult patients in the intensive care unit (ICU) who were receiving invasive mechanical ventilation. Then DEX received approval for monitored anesthesia care in adults in 2008. Based on its favorable effects from some randomized controlled studies, there is growing interest in the use of DEX for cardiac surgery. Now DEX has been a popular and assumed first-line sedation medication in cardiac surgery patients, especially for patients with hemodynamic instability, or patients with high risk for organ injury, arrhythmia, and delirium during the perioperative period. Based on the sympatholytic effect, DEX was thought to be pharmacologic prophylaxis for POAF. However, most of the present studies have some limitations because of the small number of patients or single-center study designs. Eventually, different points of view on the influence of DEX on AF occurrence emerged. Some studies have focused on this issue and show that perioperative DEX could reduce the POAF,[6,7] but some others have drawn opposite results.[8-20] The evidence on DEX for POAF remains unclear.

AF, especially postoperative new-onset AF (NOAF), has been described as a predictive risk of stroke after heart surgery. A study comprising 3008 patients showed NOAF is a significant risk factor for long-term stroke after cardiac surgery. Patients with POAF had a significantly higher incidence of postoperative stroke compared with the patients without POAF.[21] If DEX could reduce the incidence of POAF, the incidence of the postoperative stroke in theory will be lower owing to the DEX use after heart surgery. Although there were no studies mainly focused on the issue, some studies about the effect of DEX on other outcomes showed the incidence of postoperative stroke and the results were inconsistent.[8,11,14,17,22] Therefore, we performed a systemic review and meta-analyses to evaluate the effect of perioperative DEX on POAF and stroke in adult heart surgery patients.

METHODS

Ethical Statement

Since this was a meta-analysis, ethical approval was not required under the arrangements of the Institutional Review Board in our hospital.

HIGHLIGHTS

- Perioperative dexmedetomidine reduced the risk of atrial fibrillation after adult cardiac surgery.
- The effect of dexmedetomidine for postoperative atrial fibrillation (POAF) seemed to be obvious in female patients undergoing coronary artery bypass grafting (CABG) at a younger age.
- Dexmedetomidine use did not decrease the incidence of stroke.

Search Strategy and Study Criteria

According to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) guidelines, we conducted a systematic search in PubMed (1997 to July 2021), EMBASE (1997 to July 2021), and the Cochrane's Library (Cochrane Center Register of Controlled Trials) databases (1997 to July 2021). A full electronic search strategy for PubMed was performed as follows: "dexmedetomidine[tiab]" AND ("cardiac surgery[tiab]" OR "coronary artery bypass grafting[tiab]" OR "heart surgery[tiab]" OR "heart valve[tiab]" OR "cardiopulmonary bypass[tiab]") AND ("random*[tiab]" OR "prospective[tiab]" OR "clinical[tiab]" OR "controlled[tiab]" OR "multicenter[tiab]" OR "blind*[tiab]" OR "placebo[tiab]"). Various combinations of keywords and different search strategies were used for another two databases. All eligible studies met the following conditions: (1) study design: English-published randomized controlled trials (RCTs); (2) study population: adult patients (age ≥ 18 years) undergoing heart surgery with or without cardiopulmonary bypass; (3) intervention: DEX; (4) comparison: placebo or other drugs; (5) outcome measure: the incidence of POAF and stroke. Exclusion criteria were as follows: retrospective study, observational study, reviews, animal studies, studies involving pediatric population, and studies without reporting the incidence of POAF and stroke.

Literature Review and Data Extraction

The literature review and data extraction were independently completed by two investigators (LXL and TZ). In case of duplicate records pertaining to a single study, we considered the PubMed database to take precedence. Disagreements were handled by discussion for consensus. Another two authors independently evaluated the quality of included studies, using the Cochrane risk of bias tool and the Jadad scale. Clinical characteristics such as age, the proportion of males, proportion with diabetes, proportion with history of myocardial infarction, proportion with hypertension, baseline left ventricular ejection fraction, β-blocker, and statin use were collected.

Postoperative Outcomes

The primary endpoint was the incidence of POAF. The secondary endpoints were the incidence of postoperative stroke, mechanical ventilation (MV) duration, ICU LOS, hospital LOS, and mortality.

Statistical Analyses

For dichotomous outcomes (reported with incidence), we calculated the risk ratio (RR) or odds ratio (OR) with a 95% CI. For continuous outcomes (reported as mean ± standard deviation, median and interquartile range, or median and range), we calculated mean differences for each study according to the statistical method of Hozo et al[23] and used weight (the inverse variance of the estimate) to pool the estimate (weighted mean difference, WMD) with 95% CI. Heterogeneity was assessed with the inconsistency statistic (I^2). Heterogeneity was assessed with the inconsistency statistic (I^2). Publication bias was assessed by Begg's test and

Egger's test. Meta-regression and subgroup analyses were conducted to explore the potential sources of significant heterogeneity and a *P*-value of < .1 was accepted. Sensitivity analyses were used to assess the robustness of our results by removing each included study at one time to obtain and evaluate the remaining overall estimates. $P < .05$ (2-sided) was considered to be statistically significant for hypothesis testing. All statistical analyses were performed using REVMAN (version 5.0; Cochrane Collaboration, Oxford, UK) and Stata (version 15.0; StataCorp LP).

RESULTS

Study Characteristics

The PRISMA flowchart for the RCTs screening and selection process is shown in Figure 1 in this study. Eighteen trials[6-20,22,24,25] with 19 groups of data enrolling 2933 patients were ultimately included and analyzed in the meta-analyses (Figure 1). Nine studies were for coronary artery bypass grafting (CABG), two for valve surgery, and nine were for combined cardiac surgery. Eight trials used placebo as a control, whereas 9 used propofol and 1 used morphine or remifentanil. DEX was continuously infused at a rate of 0.1-1.4 μg/kg/h after a loading dose (0.4-1.5 μg/kg) in five studies or infused at a rate of 0.04-1.5 μg/kg/h without a loading dose in 12.

For outcomes, POAF incidence was reported in 19 trials, postoperative stroke in 5, MV use in 12, ICU LOS in 12, hospital LOS in 10, and mortality in 4.

Study design and patient characteristics were summarized in Tables 1 and 2. Details on the quality assessment can be found in Table 3 and Figure 2.

Effect of DEX on Incidence of POAF

The POAF was reported in 2933 study participants, and the overall incidence was 22.50% (DEX group, 20.38%; control group, 24.64%). The POAF was significantly reduced by POAF (19 studies; RR, 0.82; 95% CI, 0.69-0.98; $P = .03$ $I^2 = 21\%$; Figure 3). There was no evidence of significant publication bias (Begg's test, $P = .213$; Egger's test, $P = .423$).

Subgroup analyses revealed similar trends to those of POAF outcomes based on different characteristics such as diabetes proportion (≥22% vs. <22%), CPB duration (≥98 minutes vs. <98 minutes), hypertension proportion (≥50% vs. <50%), loading dose (use or not), type of control (placebo vs. nonplacebo or propofol vs. others), administration timing (pre/intraoperative vs. postoperative), surgery type (combined surgery vs. CABG only), and Jadad score (Jadad ≥ 4 vs. Jadad < 4). There was a significant difference for the POAF in another two clinical subgroups according to age (≥ 63 vs. < 63 years, $P = .04$) and male proportion (≥ 70% vs. < 70%, $P = .04$) (Table 4).

Meta-regression analyses performed for the potential sources of significant heterogeneity were listed in Table 5, and there were no significant differences for POAF in all the subgroups.

Sensitivity analyses excluding each included study at a time revealed that all the studies were consistent with the

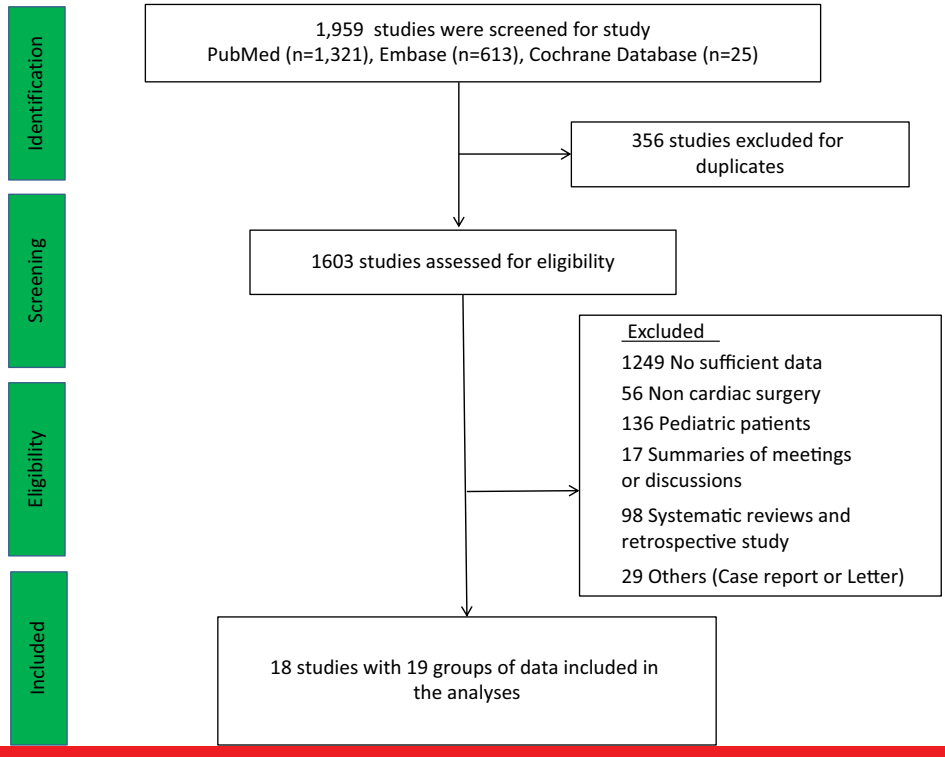

Figure 1. Flow diagram of studies included in meta-analyses.

Table 1. Summarized Study Design of Included Randomized Trials

Study	Country	Surgery	Dexmedetomidine Dose	Control	Time and Duration of intervention or Control	No. of Patients	Clinical End Point	Follow-Up
Balkanay 2015 I	Turkey	On-PUMP CABG	0.04 μg/kg/h-0.05 μg/kg/h	Placebo	Start pre-CPB and last for 24 hours	31 vs. 28	AF, MV duration, ICU stay, Hospital stay	In hospital
Balkanay 2015 II	Turkey	On-PUMP CABG	0.04 μg/kg/h-0.05 μg/kg/h	Placebo	Start pre-CPB and last for 24 hours	29 vs. 28	AF, MV duration, ICU stay, Hospital stay	In hospital
Corbett 2005	United States	On-PUMP CABG	1 μg/kg 0.4 μg/kg/h	Propofol	Start postsurgery until the end of MV	43 vs. 46	AF, VF, MV duration, ICU stay	In hospital
Alparslan 2020	USA	Combined	0.1 μg/kg/h-0.4 μg/kg/h	Placebo	Started before the surgical incision and last for 24 hours	398 vs. 396	AF, Stroke, Mortality, ICU stay, Hospital stay	90 days after surgery
Djaiani 2016	Canada	Combined	0.4 μg/kg 0.2-0.7 μg/kg/h	Propofol	Start postsurgery and last for 24 hours	91 vs. 92	AF, Stroke, Mortality, MV duration, ICU stay, Hospital stay	In hospital
Balachundhar 2019	USA	Combined	0.5-1 μg/kg 0.1-1.4 μg/kg/h	Propofol	Start during chest closure last for up to 6 hours postoperatively	29 vs. 31	AF, Mortality, ICU stay, Hospital stay	In hospital
Herr 2003	USA	On-PUMP CABG	0.5 μg/kg 0.2-0.8 μg/kg/h	Propofol	Start postsurgery and last for 24 hours	148 vs. 147	AF, VT	In hospital
Shi 2019	China	Combined	0.4-0.6 μg/kg/h	Propofol	NA	84 vs. 80	AF, MV duration, ICU stay, Hospital stay	In hospital
Jalonen 1997	Finland	On-PUMP CABG	50ng/kg/min	Placebo	Start preCPB and last until the end of surgery	40 vs. 40	AF, VT	In hospital
Liu 2016	China	Combined	< 1.5 μg/kg/h	Propofol	Start after surgery and last until the end of MV	44 vs. 44	AF, Mortality, MV duration, ICU stay, Hospital stay	In hospital
Park 2014	Korea	Combined	0.5 μg/kg 0.2-0.8 μg/kg/h	Remifentanil	Start after surgery and last until extubation	67 vs. 75	AF, Stroke, MV duration, ICU stay, Hospital stay	In hospital
Shehabi 2009	Australia	Combined	0.1-0.7 μg/kg/mL	Morphine	Start within 1 hour of adminssin to CICU until the removal of chest drains	152 vs. 147	AF, Stroke, Mortality, MV duration, ICU stay, Hospital stay	In hospital
Zi 2020	China	Off-PUMP CABG	0.2-1 μg/kg/h	Propofol	Start from analepsia until the end of ICU	62 vs. 61	AF, MV duration, ICU stay	In hospital
Karaman 2015	Turkey	On-PUMP CABG	0.6 μg/kg/h, 0.2-1.0 μg/kg/h	Propofol	Start after surgery and last until extubation	31 vs. 33	AF, MV duration	30 days after surgery
Zhai 2017	China	valve surgery	0.6 μg/kg 0.2 μg/kg/h	Placebo	before anesthesia and last until the end of operation			

(*Continued*)

Table 1. Summarized Study Design of Included Randomized Trials (*Continued*)

Study	Country	Surgery	Dexmedetomidine Dose	Control	Time and Duration of intervention or Control	No. of Patients	Clinical End Point	Follow-Up
Ren 2013	China	On-PUMP CABG	0.2-0.5 μg/kg/h	Placebo	Following the first vascular anastomosis grafting and last until CCU for 12 hours	81 vs. 81	AF, VT,	In hospital
Seongsu 2021	Korea	Thoracic aortic surgery	0.4 mg/mL	Placebo	After the induction until 12 hours after ACC-off	26 vs. 25	AF, Stroke, MV duration, ICU stay, Hospital stay	In hospital
Göksedef 2013	NA	On-PUMP CABG	NA	NA	NA	49 vs. 37	AF	In hospital
Liu 2017	China	valve surgery	<1.5 μg/kg/h	Propofol	Start after surgery and last until the end of MV	29 vs. 32	AF, Mortality, MV duration, ICU stay, Hospital stay	In hospital
Ghasem Soltani 2017	Iran	Off-PUMP CABG	0.5 mcg/kg/h	Placebo	Start preCPB and last until the end of surgery	38 vs. 38	AF, VT, VF,	In hospital

AF, atrial fibrillation; VF, ventricular fibrillation; VT, ventricular tachycardia; CABG, coronary artery bypass graft; CPB, cardiopulmonary bypass; ICU, intensive care unit; CICU, cardiac intensive care unit, MV, mechanical ventilation; NA, not available.

Table 2. Summarized Patient Characteristic of the Included Randomized Trials

Study	Age	Male (%)	DM (%)	HP (%)	PreMI (%)	LVEF (%)	CPB Duration (min)	Anesthetics	β-Blocker (%)	Statins (%)
Balkanay 2015 I	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Balkanay 2015 II	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Corbett 2005	63	82	NA	NA	NA	NA	NA	NA	NA	NA
Alparslan 2020	62.5	69.6	20.8	67.1	10.8	60	NA	NA	49.1	55
DjaianiG 2016	72.55	75.4	21.9	75.4	16.4	NA	98.99	Isoflurane	68.85	72.55
Balachundhar 2019	67.1	83.3	NA	NA	NA	NA	NA	NA	NA	88.3
Herr 2003	62.2	NA	NA	NA	NA	NA	NA	NA	44	NA
Shi 2019	74.5	72.6	NA	NA	NA	NA	112.9	NA	54.3	79.9
Jalonen 1997	55.4	83.8	NA	NA	53.8	NA	92.5	NA	80	NA
Liu 2016	54.75	39.8	12.5	29.5	NA	65	71.15	Sevoflurane	NA	54.75
Park 2014	53.81	55.6	9.15	27.5	NA	61.87	166.75	Sevoflurane	NA	53.81
Shehabi 2009	71.25	75.3	29.5	80.1	36.6	NA	98.98	Sevoflurane	NA	71.25
Zi 2020	65.4	67.5	46.3	64.2	16.3	NA	NA	NA	NA	NA
Karaman 2015	57.25	76	68	82	NA	NA	66.2	Isoflurane	56	57.25
Ren 2013	58.1	50	30.7	48.7	8.6	52.9	NA	NA	NA	58.1
Seongsu 2021	61.5	54.9	11.8	68.6	13.7	63	NA	NA	23.5	NA
Göksedef 2013	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Liu 2017	54	41	8.2	26.2	NA	62	90.6	NA	NA	NA
Ghasem Soltani 2017	59.85	NA	40.75	68.35	1.3	51.45	NA	NA	NA	NA

Values are given as means unless otherwise specified.
DM, diabetes mellitus; HP, hypertension; PreMI, previous myocardial infarction; LVEF, left ventricular ejection fraction; CPB, cardiopulmonary bypass; NA, not available.

Table 3. Summarized Quality Assessment of Included Randomized Trials

Study	Random Sequencegeneration	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessment	Attrition Bias	Selective Reporting	JADAD
Balkanay 2015	Low risk	Unclear	Low risk	Low risk	Unclear	Unclear	4
Corbett 2005	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	3
Alparslan 2020	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	7
DjaianiG 2016	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	5
Balachundhar 2019	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	7
Herr 2003	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
Shi 2019	Unclear	Unclear	Low risk	Unclear	Unclear	Unclear	3
Jalonen 1997	Low risk	Unclear	Unclear	Unclear	Unclear	Unclear	3
Liu 2016	Low risk	Low risk	High risk	High risk	Low risk	Low risk	4
Park 2014	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
Shehabi 2009	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Zi 2020	Low risk	Unclear	Low risk	Unclear	Unclear	Unclear	4
Karaman 2015	Unclear	Unclear	Unclear	Unclear	Low risk	Low risk	2
Ren 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	1
Seongsu 2021	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	6
Göksedef 2013	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	2
Liu 2017	Low risk	Unclear	Unclear	Unclear	Low risk	Low risk	4
Ghasem Soltani 2017	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk	6

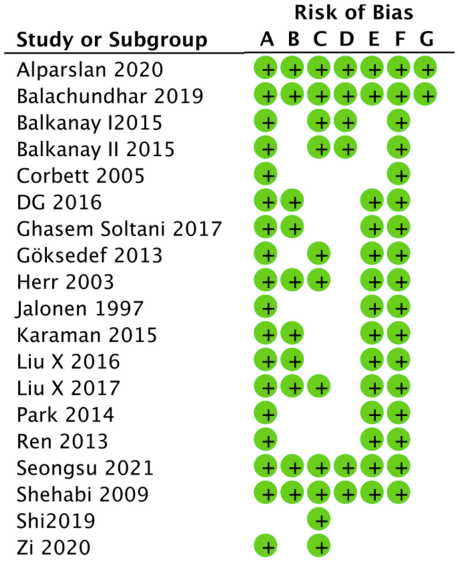

Figure 2. Quality Assessment of studies included in meta-analyses.

direction and size of the overall AF-reducing effect of dexmedetomidine (*P* for all < .05) except Liu et al[6] and Zi et al.[7]

Effect of DEX on Incidence of Stroke and Mortality

The stroke was reported in five studies including 1525 study participants,[8,11,14,17,22] and the overall incidence was 1.51% (DEX group, 1.71%; control group, 1.31%). There was no statistically significant reduction in stroke owing to perioperative DEX (five studies; OR, 1.36; 95% CI, 0.59-3.16; $P = .47$; $I^2 = 0\%$; Figure 4).

The mortality was reported in four studies enrolling 1504 study participants, and the overall incidence was 1.60% (DEX group, 1.33%; control group, 1.87%). There was no statistically significant reduction in mortality owing to perioperative DEX (four studies; OR, 0.72; 95% CI, 0.32-1.60; $P = .42$; $I^2 = 0\%$; Figure 5).

Effect of Dexmedetomidine on MV Duration, ICU LOS, and Hospital LOS

There was no statistically significant reduction of postoperative MV duration (12 studies WMD, −0.17; 95% CI, −0.35 to 0.14; $P = .39$; $I^2 = 76\%$; Figure 6), ICU LOS (12 studies; WMD, −0.03; 95% CI, −0.93 to 0.87; $P = .95$; $I^2 = 8\%$; Figure 7), and hospital LOS (10 studies; WMD, −0.04; 95% CI, −0.40 to 0.32; $P = .83$; $I^2 = 60\%$; Figure 8) by DEX.

DISCUSSION

This meta-analysis showed that perioperative DEX was associated with a significant reduction in POAF in adult patients

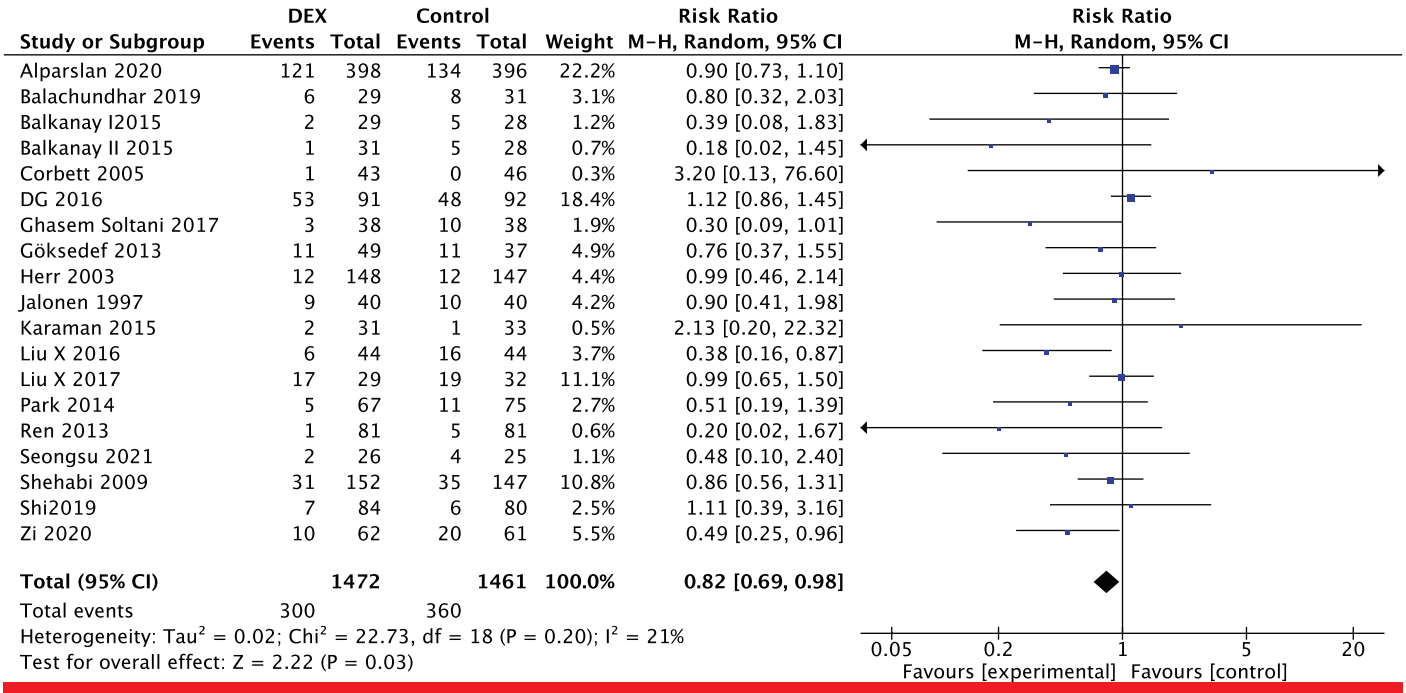

Figure 3. DEX reduced the incidence of POAF.

who underwent cardiac surgery. However, we demonstrated that DEX did not result in a decrease in stroke, mortality, MV duration, ICU, and hospital LOS.

POAF is one of the most common complications after cardiac surgery. Although sometimes transient, POAF could result in an increased risk of complications such as stroke, heart failure, and acute kidney injury.[26,27] The cardiac surgery patients with POAF had a double risk of death according to the research conducted by Almassi et al.[28] For this reason, strategies to lower the incidence of POAF are of high interest to clinicians.

The possible antiarrhythmic mechanism of DEX included activating vagus nerve,[29,30] reducing myocardial ischemia–reperfusion injury[31-34] and inhibiting the inflammatory response.[35,36] Some randomized controlled studies indicated that DEX might prevent POAF after cardiac surgery. However, there were also controversial or negative studies pertaining to the antiarrhythmic effect of DEX. A few meta-analyses and reviews have evaluated the effect of DEX on POAF after cardiac surgery. Early meta-analyses performed before 2018 indicated that DEX was not associated with the reduction in POAF,[37,38] while recent studies showed the prevention of DEX on POAF.[39,40] Compared with the latest meta-analyses performed by Peng et al[40] from 15 RCTs with 2733 patients, our analyses included three more studies and 200 more patients, especially one was a new published study and one more strengthened study with negative results of DEX for POAF. Also, meta-regression analyses were performed to explore the potential sources of heterogeneity. Besides only age and gender which were evaluated in the study of Peng et al[40], other factors for POAF during the perioperative period were collected and accessed in our meta-analyses, such as proportion with history of myocardial infarction, the proportion with hypertension, baseline left ventricular ejection fraction, β-blocker, and statin use. Our study showed a more convincing conclusion about the influence of DEX on POAF and added stroke, MV duration, ICU LOS, hospital LOS, and mortality as new outcomes after cardiac surgery. Compared with another study from 13 RCTs with 1684 patients,[39] our meta-analysis was an updated research and included 5 more studies and nearly double the sample size of patients, especially 5 were newly published studies and two more strengthened studies with negative results of DEX for POAF. Also, we added stroke as a new outcome after cardiac surgery. DEX is a useful and attractive drug, and we routinely used it in carefully selected patients undergoing cardiac surgery to reduce adverse events such as hypotension, bradycardia, or cardiac arrest. However, the antiarrhythmic mechanism of DEX is not completely understood, and clinical experience with DEX has only been shown in the pediatric population for the treatment of tachyarrhythmias.[41] Current data support its use only for short-term sedation and analgesic adjuvant in the adult population. Certain extended applications of DEX for anti-arrhythmias and anti-delirium require further evaluation.

Stroke remains a devastating complication after cardiac surgery, with reported incidences between 0.4% and 13.8%.[42] Risk factors of postoperative stroke include advanced age, diabetes mellitus, cerebrovascular disease, atherosclerotic disease, and perioperative AF.[43,44] A study conducted by Wang et al[21] indicated that patients who developed new-onset AF had an increased risk of postoperative stroke (OR, 1.53; 95% CI, 1.08-2.18; $P = .017$) and higher mortality (HR, 1.49; 95% CI, 1.22-1.81; $P < .001$) compared with patients without AF after cardiac surgery.[21] The key question is: if we were able to reduce the incidence of POAF through DEX use, would we

Table 4. Subgroup Analyses for the Potential Sources of Heterogeneity

Subgroup	Endpoint	No. of Comparisons	OR WMD	95% CI	*P*	I^2 (%)	$P_{Difference}$
1. Age (years)	AF	11	0.83	0.63–1.09	.17	35	.04
≥ 63		5	1.05	0.85–1.29	.68	0	
< 63		6	0.59	0.35–0.98	.04	49	
2. Gender (male)	AF	14	0.87	0.73–1.03	.10	17	.04
≥ 70		7	1.03	0.84–1.26	.79	0	
< 70		7	0.69	0.50–0.95	.02	42	
3. Previous DM (%)	AF	10	0.80	0.64–1.01	.06	45	.97
≥ 22		5	0.78	0.50–1.21	.26	48	
< 22		5	0.78	0.58–1.06	.12	34	
4. HP (%)	AF	11	0.78	0.62–0.99	.04	45	.09
≥ 50		6	0.92	0.75–1.14	.47	26	
< 50		5	0.56	0.33–0.95	.03	53	
5. CPB duration(minutes)	AF	9	0.83	0.63–1.09	.19	46	.43
≥ 98		5	0.91	0.65–1.27	.57	33	
< 98		4	0.70	0.41–1.20	.19	46	
6. Loading dose use	AF	18	0.82	0.68–0.98	.03	25	.41
Yes		9	0.91	0.66–1.24	.54	11	
No		9	0.77	0.60–0.98	.03	34	
7. Control drugs	AF	19	0.82	0.69–0.98	.03	21	.34
Placebo		8	0.71	0.51–0.99	.04	20	
Others		11	0.86	0.68–1.08	.20	24	
8. Control drugs	AF	19	0.82	0.69–0.98	.03	21	.13
Propofol		9	0.83	0.61–1.15	.26	27	
Others		10	0.61	0.43–0.80	.007	4	
9. DEX administration	AF	16	0.82	0.68–0.98	.03	25	.43
Pre/Intraoperation		6	0.68	0.45–1.05	.08	27	
Postoperation		10	0.83	0.66–1.05	.12	30	
10. Surgery type	AF	19	0.82	0.69–0.98	.03	21	.08
CABG		10	0.65	0.46–0.91	.01	3	
Other surgery		9	0.91	0.77–1.13	.21	46	
11. Jadad	AF	19	0.82	0.69–0.98	.03	21	.76
Jadad ≥ 4		11	0.78	0.62–0.98	.04	45	
Jadad < 4		8	0.83	0.58–1.19	.32	0	

AF, atrial fibrillation; RR, risk ratio; DM, diabetes mellitus; CPB, cardiopulmonary bypass; DEX, dexmedetomidine; CABG, coronary artery bypass graft.

then lower the incidence of postoperative stroke? As far as we know, there were no studies that considered the effect of DEX for postoperative stroke after heart surgery as their principal objective of the research. Although some studies show the incidence of postoperative stroke not as the primary outcome, previous meta-analyses focused on POAF did not assess the effect of DEX on the postoperative stroke. Our study enrolling 1525 patients showed that there was no statistically significant difference in postoperative stroke owing to DEX use. Unlike our study, in some experimental studies, neuroprotective effect of DEX was proposed.[45] The difference between theory and the results of clinical studies may be ascribed to small sample size and publication bias which no studies was primarily designed to evaluate the effect of DEX on stroke. Future high quality research mainly focused on the DEX for postoperative stroke are required to elucidate the relationship between DEX and stroke.

Subgroup analyses were used to explore the potential sources of significant heterogeneity. Risk factors for AF are reported as age, gender, hypertension, and diabetes mellitus.[46] In our study, the subgroup with younger age (≤63 years) or less male proportion (≤70%) showed a more significant reducing effect on POAF. The possible mechanism includes the loss of myocardial fibers, increased fibrosis, and collagen deposition in the atria in male patients with advanced age.[47]

To date, when to start DEX and the optimal dose of DEX to prevent POAF after cardiac surgery is emerging as important consideration. Research conducted by Liu et al[6] implied that DEX started after cardiac surgery rather than at induction had a 72% decrease in POAF. Another study performed by

Table 5. Meta-regression for the Potential Sources of Heterogeneity

	Regression Coefficient	95% CI	*P*
1. Age (years)	0.017	−0.003 to 0.037	.102
2. Gender (male %)	0.009	−0.005 to 0.022	.200
3. Previous DM (%)	−0.006	−0.027 to 0.015	.578
4. CPB duration (minutes)	−0.002	−0.014 to 0.011	.801
5. HP (%)	0.006	−0.007 to 0.019	.367
6. PreMI	0.008	−0.013 to 0.030	.455
7. LVEF	0.047	−0.072 to 0.166	.440
8. Propofol	0.360	−0.123 to 0.719	.131
9. Betablockers	0.007	−0.021 to 0.036	.612
10. Statins	0.014	−0.012 to 0.040	.298
11. Loading dose use	0.179	−0.482 to 0.840	.596
12. Time of DEX administration (Pre/Intraoperation)	−0.126	−0.555 to 0.304	.566
13. Surgery type	−0.419	−0.803 to −0.304	.061
14. Jadad score	0.046	−0.041 to 0.156	.310

DM, diabetes mellitus; CPB, cardiopulmonary bypass; HP, hypertension; PreMI, previous myocardial infarction; DEX, dexmedetomidine; LVEF, left ventricular ejection fraction.

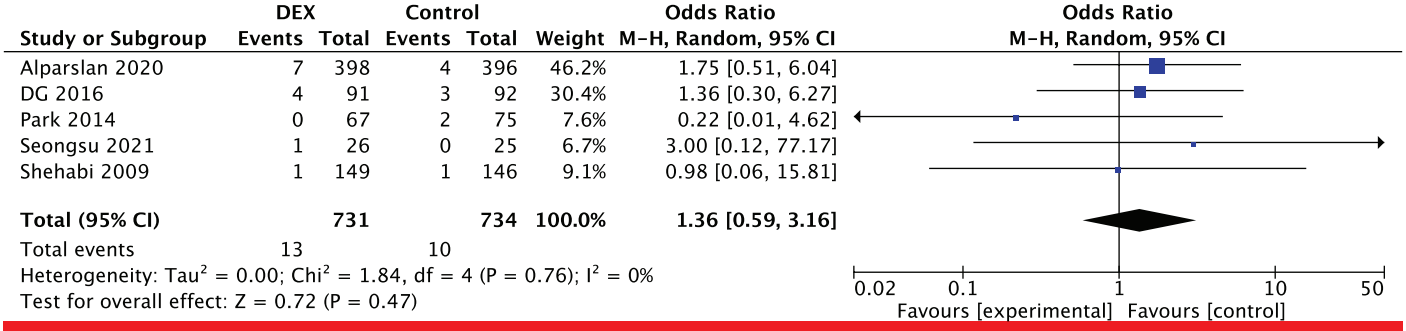

Figure 4. Forest plot for postoperative stroke.

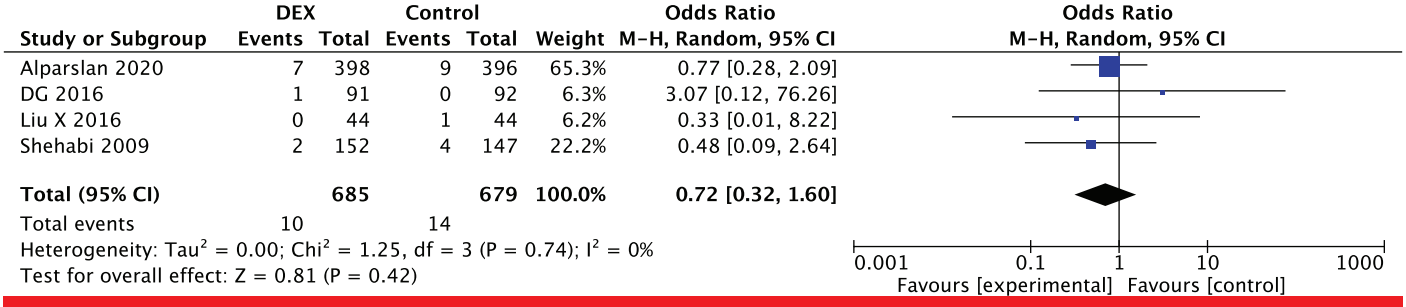

Figure 5. Forest plot for mortality.

Zi et al[7] showed a similar result and DEX use during ICU stay was associated with a significant reduction in POAF. However, the small sample size in the two studies makes their results highly fragile. Our meta-analyses included 2933 patients and 660 events indicated that DEX might be more effective in preemptive strategy compared with postoperative administration, although there was no significant difference ($P=.09$). Yet there has been very little research into the optimal dose of DEX for POAF. We found that DEX infusion without loading dose appeared to be possibly more safe and effective for antiarrhythmia by avoiding unstable hemodynamics compared to those with loading dose ($P=.09$). Most of the adverse events associated with DEX occur during or shortly after a loading infusion. We recommended that DEX should be infused in a slow titration to maintain the infusion rate without the administration of a loading dose to reduce the incidence of side effects.

The incidence of POAF varied according to the cardiac surgery type and occur almost 30% after CABG, 30%-40% after valve replacement surgery, and 40%-60% after combined surgical procedures.[1,48,49] Our study showed the incidence of

Study or Subgroup	DEX Mean	DEX SD	DEX Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Balkanay I2015	12.4	4.9	31	10.6	4.5	28	13.2%	1.80 [-0.60, 4.20]
Balkanay II 2015	12.9	4.8	29	10.6	4.5	28	13.1%	2.30 [-0.11, 4.71]
Corbett 2005	10.2	12.8	43	8.97	7.69	46	6.7%	1.23 [-3.19, 5.65]
DG 2016	5.4	23.3	91	5.9	33.5	92	2.4%	-0.50 [-8.85, 7.85]
Karaman 2015	4.4	0.72	31	5.4	0.65	33	21.6%	-1.00 [-1.34, -0.66]
Liu X 2016	21	9.47	44	21.2	9.81	44	7.6%	-0.20 [-4.23, 3.83]
Liu X 2017	18.9	7.25	29	21	8	32	8.2%	-2.10 [-5.93, 1.73]
Park 2014	22.72	26.36	67	18.6	19.74	75	2.8%	4.12 [-3.61, 11.85]
Seongsu 2021	15.2	10.2	26	16.4	9.4	25	5.1%	-1.20 [-6.58, 4.18]
Shehabi 2009	14	26.7	31	15	37.1	35	0.8%	-1.00 [-16.47, 14.47]
Shi2019	10.9	16.6	84	77.3	156.3	80	0.2%	-66.40 [-100.83, -31.97]
Zi 2020	11.7	3	62	11.8	4.2	61	18.4%	-0.10 [-1.39, 1.19]
Total (95% CI)			**568**			**579**	**100.0%**	**0.13 [-1.25, 1.51]**

Heterogeneity: Tau² = 2.26; Chi² = 30.16, df = 11 (P = 0.001); I² = 64%
Test for overall effect: Z = 0.18 (P = 0.86)

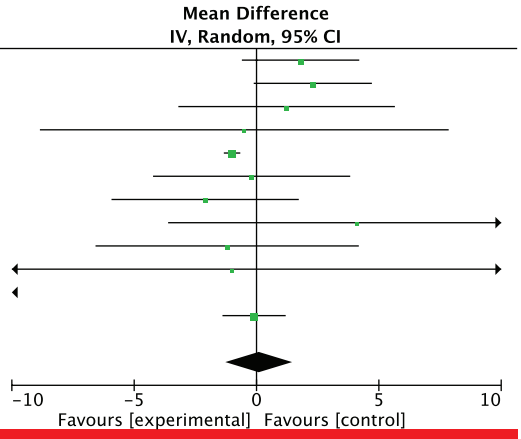

Figure 6. Forest plot for MV duration.

Study or Subgroup	DEX Mean	DEX SD	DEX Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alparslan 2020	58	47.6	398	50	38.7	396	2.2%	8.00 [1.97, 14.03]
Balachundhar 2019	32.7	14.5	29	36.5	21.4	31	0.9%	-3.80 [-13.00, 5.40]
Balkanay I2015	43.4	6.1	31	44.1	8.6	28	5.1%	-0.70 [-4.54, 3.14]
Balkanay II 2015	42.6	3.1	29	44.1	8.6	28	6.5%	-1.50 [-4.88, 1.88]
Corbett 2005	23	10.75	43	23	11.5	46	3.6%	0.00 [-4.62, 4.62]
DG 2016	43	49.5	91	29.4	156.7	92	0.1%	13.60 [-20.00, 47.20]
Liu X 2016	69.6	44.7	44	84	73.1	44	0.1%	-14.40 [-39.72, 10.92]
Park 2014	67.71	48.41	67	61.25	30.57	75	0.4%	6.46 [-7.04, 19.96]
Seongsu 2021	66.9	39.6	26	60.1	22	25	0.3%	6.80 [-10.69, 24.29]
Shehabi 2009	45	15.7	152	45	16.7	147	5.6%	0.00 [-3.68, 3.68]
Shi2019	28.9	10.5	84	29.8	9.1	80	8.0%	-0.90 [-3.90, 2.10]
Zi 2020	3.4	0.8	62	3.4	0.8	61	67.2%	0.00 [-0.28, 0.28]
Total (95% CI)			**1056**			**1053**	**100.0%**	**-0.03 [-0.93, 0.87]**

Heterogeneity: Tau² = 0.29; Chi² = 11.97, df = 11 (P = 0.37); I² = 8%
Test for overall effect: Z = 0.06 (P = 0.95)

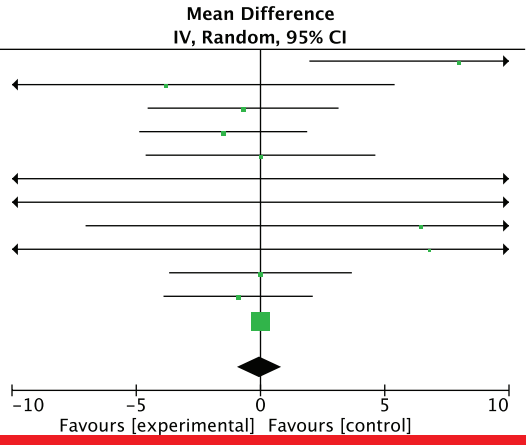

Figure 7. Forest plot for ICU LOS.

Study or Subgroup	DEX Mean	DEX SD	DEX Total	Control Mean	Control SD	Control Total	Weight	Mean Difference IV, Random, 95% CI
Alparslan 2020	6.4	2.2	398	6	1.5	396	25.6%	0.40 [0.14, 0.66]
Balachundhar 2019	7.6	2.3	29	8.4	3.9	31	4.3%	-0.80 [-2.41, 0.81]
Balkanay I2015	7.5	1.7	31	7.9	1.7	28	10.9%	-0.40 [-1.27, 0.47]
Balkanay II 2015	8.4	1.6	29	7.9	1.7	28	11.0%	0.50 [-0.36, 1.36]
DG 2016	7	5.16	91	7	11.67	92	1.8%	0.00 [-2.61, 2.61]
Liu X 2016	13.5	1.43	44	14	1.5	44	15.9%	-0.50 [-1.11, 0.11]
Park 2014	19.96	11.76	67	18.37	8.45	75	1.1%	1.59 [-1.81, 4.99]
Seongsu 2021	15.6	7.7	26	18.4	10.2	25	0.5%	-2.80 [-7.77, 2.17]
Shehabi 2009	8	0.67	152	8	0.67	147	28.1%	0.00 [-0.15, 0.15]
Shi2019	23.8	14	84	29.1	11.6	80	0.8%	-5.30 [-9.23, -1.37]
Total (95% CI)			**951**			**946**	**100.0%**	**-0.04 [-0.40, 0.32]**

Heterogeneity: Tau² = 0.11; Chi² = 22.68, df = 9 (P = 0.007); I² = 60%
Test for overall effect: Z = 0.22 (P = 0.83)

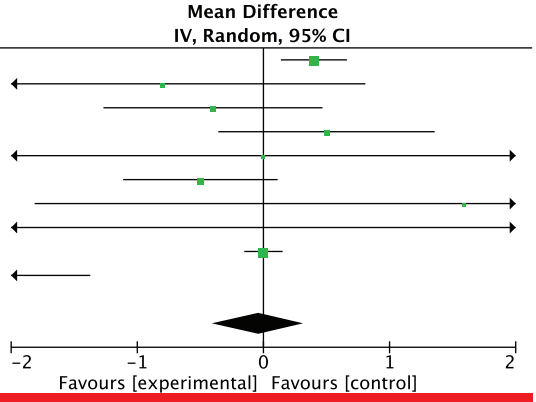

Figure 8. Forest plot for hospital LOS.

POAF was 12% in subgroup CABG, 37.5% in subgroup valve surgery, and 28.2% in subgroup combined surgery. Perioperative DEX was associated with a significant reduction of POAF in patients undergoing CABG ($P = .01$). However, there was no statistically significant difference between subgroup CABG and subgroup others ($P = .08$).

Several disadvantages also exist in our meta-analyses. First, although the method of pooling data from different studies was performed to reduce the risk of a false negative finding, there was potential heterogeneity among these trials, which may limit the quality of the results. Second, among the 19 included trials, only 3 were primarily designed to evaluate the effect of DEX on POAF. Third, with the primary outcome of POAF, this meta-analysis may be underpowered to detect the difference in other outcomes, including stroke, mortality, MV duration, ICU LOS, and hospital LOS. Fourthly, the sample size in the study is relatively small. Lastly, many design differences among these studies made it difficult to reduce clinical heterogeneity. Future large and well-designed multicenter

studies with larger sample sizes are required to confirm the effect of DEX on POAF as well as a more appropriate dose and time of DEX.

CONCLUSIONS

This meta-analysis reveals evidence that perioperative administration of DEX reduces the incidence of POAF in adult cardiac surgery. The reduction of POAF seems to be obvious in female patients undergoing CABG at a younger age. There is no significant difference in the incidence of stroke, mortality, MV duration, ICU LOS, and hospital LOS.

Data Availability Statement: The data used to support the findings of this study are included within the supplementary information file.

Ethics Committee Approval: Ethical committee approval was not required under the arrangements of the Ethics Committee of Beijing Shijitan Hospital, Capital Medical University.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept – C.J., M.Q.G.; Design – C.J., M.Q.G.; Supervision – M.Q.G.; Fundings – Y.L.L., L.F.; Materials – Y.L.L., L.F.; Data collection &/or processing – L.L., T.Z.; Analysis &/or interpretation – L.L., T.Z.; Literature search – L.L., T.Z.; Writing – C.J., Y.L.L., L.F.; Critical review – C.J., M.Q.G.

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