REVIEW

Can dexmedetomidine reduce atrial fibrillation after cardiac surgery? A systematic review and meta-analysis

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Purpose: Cardiac surgery patients always present with atrial fibrillation (AF) after admission to the intensive care unit, leading to high mortality and lengthy hospitalization. Dexmedetomidine (DEX) is a popular medication used for sedation in the intensive care unit; however, whether it can reduce AF needs to be analyzed.

Materials and methods: Three primary databases, Medline, Embase (Ovid SP) and the Cochrane Central Register of Controlled Trials (CENTRAL), were searched. All English language and randomized control designed clinical publications comparing DEX to control medicines for sedation after elective cardiac surgery were included. Two independent colleagues conducted the data extraction and quality assessments. The subgroup analysis was performed according to the medicine used, age, AF history, and whether previous beta-blocker premedication and cardiopulmonary bypass (CPB) were applied. The overall incidence of AF was analyzed.

Results: A total of 1,295 patients in nine studies met the selection criteria among 2,587 studies screened from the database. After quantitative synthesis, our results revealed that the DEX group was not associated with a decreased incidence of AF compared with the placebo (risk ratio [RR] 0.76, 95% CI 0.37, 1.55, P=0.44) and morphine groups (RR 0.86, 95% CI 0.56, 1.31, P=0.48). Subgroup analysis also indicated that the DEX vs propofol comparison exhibited no difference: 1) for patients of age >60 years (P=0.69) or ≤60 years (P=0.69); 2) under CPB surgery (P=0.45) or without CPB surgery (P=0.88); 3) with beta-blocker premedication (P=0.32) or without beta-blocker premedication (P=0.90); and 4) with AF history (RR 1.07, 95% CI 0.85, 1.36, P=0.57) or without AF history (P=0.30).

Conclusion: This meta-analysis revealed that DEX could not reduce the incidence of AF compared to control medicines following cardiac surgery. DEX may have an increased influence on AF occurrence if patients had a history of AF. However, cautious interpretation should be made due to high clinical heterogeneity.

Keywords: dexmedetomidine, sedation, cardiac surgery, atrial fibrillation

Introduction

Postoperative arrhythmias, which are included among various complications, are complications that can occur following cardiac surgery. Atrial tachyarrhythmia occurs most frequently and includes postoperative atrial fibrillation (POAF).[1]

It has also been reported that up to 40%–50% of patients will develop POAF during hospitalization among those undergoing cardiac surgery.[2] The occurrence of atrial fibrillation (AF) not only prolongs hospitalization but also increases the cost.[3] Furthermore, overcoming these arrhythmias remains a challenge due to ineffective

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antiarrhythmic therapies and significant adverse effects of existing drugs. The development of antiarrhythmic drugs has always been challenging and limited. Most importantly, some prophylactic therapy drugs are usually used, except for some conventional antiarrhythmic medicines and overdrive pacing, which include amiodarone, statin and colchicine.

Dexmedetomidine (DEX) is a highly selective α-2 receptor agonist that is currently applied safely and efficiently in perioperative cardiac surgery. Since its approval by the US Food and Drug Administration,[4] DEX has been a popular medication for cardiac surgery patients. Based on some randomized controlled studies, DEX was demonstrated to provide safe and effective sedation,[5,6] facilitate extubation,[5] and reduce delirium[7,8] and renal[9] and myocardial injury.[10] Some reviews also indicated that use of this drug was safe and efficient with post-cardiac surgery patients.[11,12]

Ettema et al thought that preadmission interventions was necessary to prevent postoperative complications via pre-admission interventions for older cardiac surgery patients.[13] Based on their theory, rate and rhythm control strategies are usually the focus for prevention of AF. As an assumed first-line sedation medicine,[14] DEX seems to be a promising candidate for postoperative cardiac patients; however, most of the present studies have some limitations because of small numbers of patients or single-center study designs. Eventually, different points of view on the influence of DEX on AF occurrence emerged.[5,7,15,16] Some randomized controlled trials (RCTs) and observation studies asserted that DEX could reduce the incidence of AF,[15,17–19] but some others drew a higher incidence in the control group.[5,7,16] Therefore, efforts must be taken to include enough data to draw a conclusion, and the lack of relevant reviews regarding this aspect is noteworthy.

Materials and methods

We searched the electronic database and performed a handy search to identify literatures that compared the incidence of AF between DEX and control drugs, including morphine, propofol and placebo. All procedures were based on the Cochrane Review Methods.

Search strategy

Two independent coworkers searched the Embase (Ovid SP), the Cochrane Central Register of Controlled Trials (CENTRAL) and Medline databases. All eligible articles written in English were chosen between 1966 and May 2017. The search strategy used the words "Dexmedetomidine", "Adrenergic alpha-Agonists", "Precedex", "Thoracic Surgery", "Cardiac Surgical Procedures", "cardiac Surgery", "Arrhythmias, Cardiac" and "Atrial Fibrillation". Various

combinations of free words were also used, and different search strategies were developed for each database. The deadline for the search was June 2017 with two new interesting reports were found for further review.

Eligible studies

All eligible studies had to meet the following criteria: 1) RCTs of valve replacement surgery or coronary artery bypass surgery with or without cardiopulmonary bypass (CPB) that compared DEX to control drugs; 2) sedation time <48 h in the intensive care unit (ICU) since admission, regardless of when the sedation began and 3) patients older than 18 years. Non-RCT studies, American Society of Anesthesiologists ≥IV and deep hypothermic circulatory arrest surgery were excluded from this study.

Data extraction and quality control

After retrieving the full articles, two independent coworkers conducted quality assessment using Cochrane Risk Bias Assessment Tool in Cochrane Handbook for Systematic Reviews of Interventions.[20] The assessment included the following: random sequence generation, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, allocation concealment, selective reporting and other biases. The risk of bias for each study was presented in the percentage form. The third operator intervened if a conflict occurred. The main outcome was the incidence of AF, and the GRADE system was applied to evaluate the quality of the grade.

Statistical analysis

Review Manager (version 5.3)[21] was used to pool and analyze the eligible studies when studies reported the outcomes of interest. A random-effects model was applied throughout the whole analysis, and the Mantel–Haenszel method was used to calculate the risk ratio (RR) of each study. The fixed-effect model was used only in the absence of clinically and statistically significant heterogeneity ($P>0.1$, $I^2<50\%$). RR was chosen as the effect measure for dichotomous outcomes. Subgroup analysis based on medication, age, administration of beta-blocker medicine and coexisting AF and CPB was used ahead of the analysis. We used funnel plots to check for publication bias for the incidence of AF. Sensitivity analyses were also performed by removing low-quality and small sample size studies to confirm the stability of the results after the analyses. Following meta-analysis of all of the outcomes, a summary of the findings for each outcome was created with the GRADE system to evaluate the quality of evidence.

Results

Included studies

The study flow was based on the PRISMA criteria. Two thousand five hundred and eighty records were discovered in the electronic databases, which included Medline (104), Embase (449) and CENTRAL (2,027). The other seven studies were identified through the reference list. After checking for duplication with endnote X7, 2,427 records remained for screening. Of these, 2,141 records were removed due to the titles or abstracts being totally incompatible with our criteria. Two hundred and twenty-three records were excluded for not being pertinent to the subject matter. The remaining 63 full-text articles were retrieved from a database purchased by our own unit. Fifty-four articles were excluded due to various reasons. Finally, the remaining nine studies were included in the qualitative and quantitative analyses[5–10,15–17] (Figure 1).

Basic characteristics of the studies

Nine studies were included in this review. The total number of patients was 1,295, and the included patients across all studies ranged from 11 to 152 (Table 1). The main characteristics included age, surgery type, patient number and DEX intervention (Table 1). All studies were screened with the RCTs criteria. There were seven studies (449 in the DEX group, 461 in the control group) that compared DEX to propofol,[5–7,10,15–17] accounting for ~70% of the patients. One study compared DEX to morphine[8] and placebo,[9] respectively. Five studies had completed cardiac surgery without a CPB assistant,[5,6,9,10,16] while four studies used a CPB assistant.[7,8,15,17] Three studies adopted a bolus of ~0.4 µg/kg/h in volume when DEX was infused,[6,7,16] and two of these studies infused DEX before admission to ICU.[6,16] Intravenous infusion of DEX began primarily upon admission to ICU in six studies. Only one study adopted low infusion rate (0.04 µg/kg/h) without a bolus upon admission to ICU.[9] Only one study reported the main outcome of AF.[15]

Risk of bias

The ROB tool of the Cochrane library was adopted to identify the risk of bias in the nine studies (Figures 2 and 3).

According to the Cochrane handbook, a high risk of bias accounted for <25% for most of the included studies (Figure 2). Based on a detailed evaluation of the single
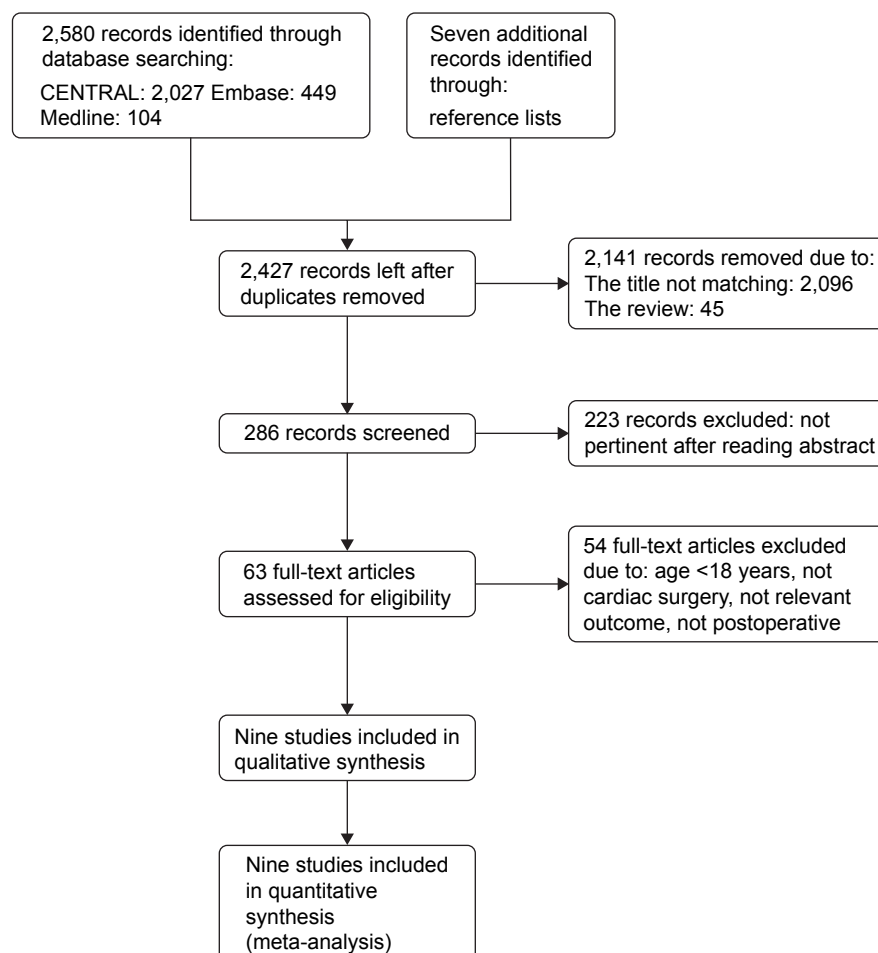

Figure 1 Study flow diagram.

Table 1 Characteristics of included studies

Author (year)	Age, years	Patient number	Surgery type	Main outcomes	DEX intervention	Control infusion
Herr et al[6] (2003)	61.9	295	CABG	No significant differences in RSS between groups during assisted ventilation (4.5, DEX vs 4.7, propofol; P=0.259) (P>0.05); no significant differences between the groups in median times to weaning, extubation and mean heart rates (P>0.05); DEX group required significantly less morphine (P<0.05)	1.0 µg/kg induced, then 0.2–0.7 µg/kg/h maintained	Propofol used, but no detailed data
Corbett et al[16] (2005)	63.6	89	CABG	Propofol Ramsay level 4.00 (95% CI 3.62–4.19) greater than DEX 3.67 (95% CI 3.00–4.15; P=0.021), the same incidence of fibrillation and delirium	1 µg/kg induced, maintained by 0.4 µg/kg/h	Propofol: 0.2–0.7 µg/kg/h
Shehabi et al[8] (2009)	71.5	306	On-pump cardiac surgery[a]	Delirium incidence was comparable between DEX 13 (8.6%) and morphine 22 (15.0%) (RR 0.571, 95% CI 0.256, 1.099, P=0.088); DEX showed no more benefits in sedation and pain levels and extubation time, except more earlier extubation and higher incidence of bradycardia	0.1–0.7 µg/kg/h	Morphine: 10–70 µg/kg/h
Göksedef et al[9] (2013)	58	100	CABG	AF, extubation time and mortality between two groups have no difference	0.04 µg/kg/h	Placebo
Ren et al[10] (2013)	60	162	CABG	The blood pressure, heart rate, postoperative arrhythmic events (including AF, ventricular tachycardia), duration of mechanical ventilation and ICU residence time in DEX were shorter than those in the control group (P<0.05)	0.2–0.5 µg/kg/h	Propofol: 2–4 mg/kg/h
Karaman et al[5] (2015)	62.5	64	CABG	DEX showed priority in extubation times, RSS and patient satisfaction; no difference for bradycardia and AF	0.2–1.0 µg/kg/h	Propofol: 1.0–3.0 mg/kg/h
Djaiani et al[7] (2016)	72.7	183	On-pump cardiac surgery[a]	POD was present in 16/91 (17.5%) and 29/92 (31.5%) patients in DEX and propofol groups, respectively (odds ratio, 0.46, 95% CI 0.23, 0.92, P=0.028) (P<0.05); onset and duration of POD show statistical difference	0.4 µg/kg bolus followed by 0.2–0.7 µg/kg/h	Propofol: 25–50 µg/kg/min
Liu et al[15] (2016)	62.5	90	On-pump cardiac surgery[a]	AF occurred in 6/44 patients (13.6%) in the DEX group compared to 16/44 patients (36.4%) in the propofol group (P=0.025); the DEX group had shorter length of ICU stay and high incidence of hypotension	0.2–1.5 µg/kg/h	Propofol: 0.3–3 mg/kg/h
Liu et al[17] (2017)	53	61	On-pump cardiac surgery[a]	Four hours after ICU admission, median changes in perfused small-vessel density and the De Backer score from baseline were significantly greater in the DEX group than in the propofol group (1.3 vs 0 mm/mm^2, P=0.025; 0.9 vs −0.1/mm, P=0.005, respectively)	0.2–1.5 µg/kg/h	Propofol: 5–50 µg/kg/min

Note: [a]On-pump cardiac surgery including valve surgery or/and CABG.
Abbreviations: CABG, coronary artery bypass grafting; DEX, dexmedetomidine; ICU, intensive care unit; POD, postoperative delirium; RR, risk ratio; RSS, Ramsay Sedation Scores.
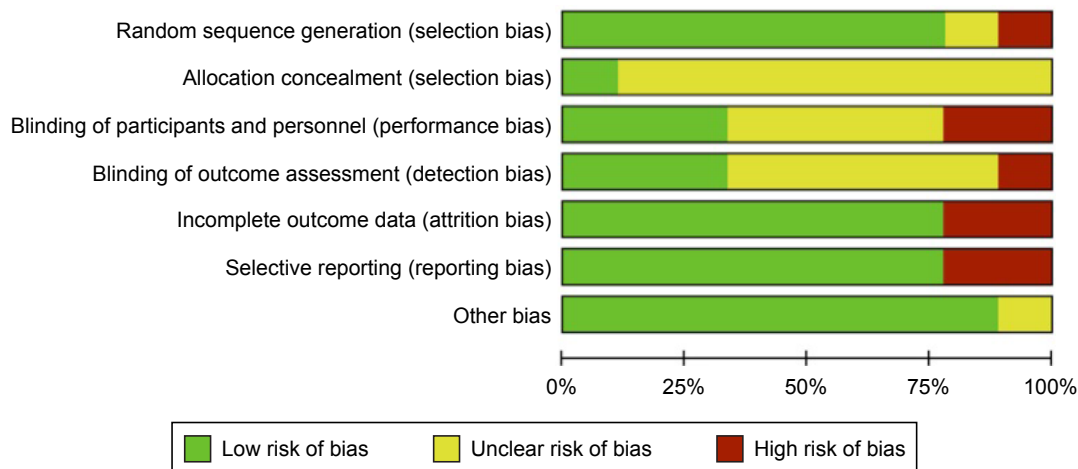

Figure 2 Risk of bias presented as percentages for all included studies.

Figure 3 Risk of bias: author's judgment for all included studies.

Figure 4 Funnel plot of included studies for the incidence of AF.
Abbreviation: AF, atrial fibrillation.

was applied for imprecision bias due to a small number of studies with wide CIs (Table 2).

Outcomes analysis

After meta-analysis of the nine included studies, the incidence of AF was aggregated with 1,295 participants. The RR for AF in the DEX group was 0.76 (Mantel-Haenszel [M–H], random 95% CI 0.37, 1.55) compared to the placebo group (Figure 5) and 0.86 (M–H, random 95% CI 0.56, 1.31) compared to the morphine group (Figure 6). For the propofol group, which contained the majority of the participants, it was difficult to draw a conclusion because of the complex clinical heterogeneity before performing subgroup analysis.

Subgroup analysis and sensitivity analysis

Subgroup analysis also indicated that DEX vs the propofol subgroup had similar RR (RR 0.90, 95% CI 0.54, 1.51, I^2=43%) for patients of age >60 years (Figure 7) and (RR 0.89, 95% CI 0.52, 1.54) ≤60 years (Figure 8); under CPB surgery (RR 0.81, 95% CI 0.47, 1.39, I^2=69%; Figure 9) and without CPB surgery (RR 0.94, 95% CI 0.45, 1.97, I^2=4%; Figure 10); for beta-blocker premedication (RR 0.72, 95% CI 0.37, 1.39, I^2=66%; Figure 11) and without beta-blocker premedication (RR 0.97, 95% CI 0.57, 1.63, I^2=0%; Figure 12); and for AF history (RR 1.07, 95% CI 0.85, 1.36, I^2=0%; Figure 13) and without AF history (RR 0.67, 95% CI 0.32, 1.43, I^2=33%; Figure 14).

Sensitivity analysis was carried out based on the high statistical heterogeneity for AF under CPB surgery (I^2=69%; Figure 9) and beta-blocker premedication (I^2=66%; Figure 11). After excluding the low-quality and small-sample studies, the heterogeneity disappeared, and similar results affirmed the incidence of AF with beta-blocker premedication (Figure 15) and CPB surgery (I^2=0%; Figure 16), respectively.

studies, we observed that four studies in this review could be considered as high quality because no high risk of bias was found.[6–8,16] There was an "unknown risk" that came from some nonspecific details of randomization or insufficient information for confirmation. Three studies exhibited moderate quality due to incomplete data that caused disproportionate data loss.[9,10,17] For example, one study had obvious high-risk bias because of the mentioned "respiratory function" indicators in the methods while providing no results in the later sections.[9] The remaining two studies were classified as low quality because of multiple "high risk of bias" due to lack of randomization, attrition balance or intention-to-treat.[5,15]

Publication bias was visualized through funnel plots, and no significant publication bias was found (Figure 4).

Summary of findings by the GRADE system

The main outcomes of AF were graded according to the GRADE system standard. Incomplete data and disproportionate data loss occurred in two studies, which equaled one level of risk of bias downgrade,[5,15] while another level of downgrade
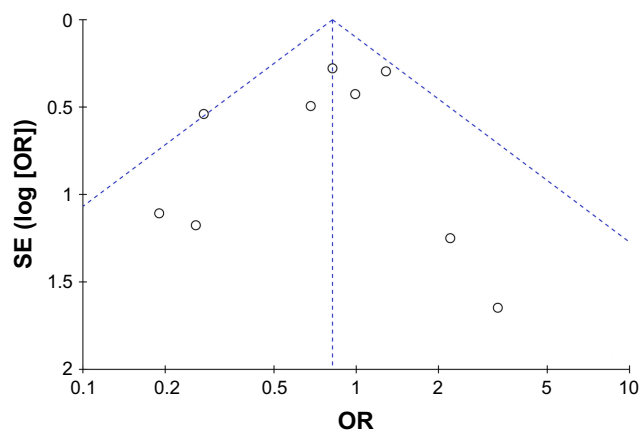
Table 2 The quality of evidence for AF by GRADE

DEX compared to control drugs for AF after cardiac surgery						
Patient or population: patients with incidence of AF after cardiac surgery **Setting:** ICU **Intervention:** DEX **Comparison:** control drugs						
Outcomes	Illustrative comparative risks[a] (95% CI)		Relative effect (95% CI)	No of participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control drugs	DEX				
AF	Study population		RR 0.82	1,295	⊕⊕⊝⊝	
	206 per 1,000	169 per 1,000 (124–227)	(0.6, 1.1)	(9 studies)	Low[b,c]	
	Moderate					

Notes: [a]The basis for the assumed risk (eg, the median control group risk across studies). The corresponding risk (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE working group grades of evidence are as follows: high quality: further research is very unlikely to change our confidence in the estimate of effect; moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate; low quality (⊕⊕⊝⊝): further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate; and very low quality: we are very uncertain about the estimate. [b]Attrition bias happened due to incomplete data or no ITT. [c]Some small sample studies with very wide CIs.
Abbreviations: AF, atrial fibrillation; DEX, dexmedetomidine; ICU, intensive care unit; ITT, intention-to-treat; RR, risk ratio.

Study or subgroup	DEX Events	Total	Placebo Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Göksedef et al,[9] 2013	11	49	11	37	100	0.76 (0.37, 1.55)	
Total (95% CI)		**49**		**37**	**100**	**0.76 (0.37, 1.55)**	
Total events	11		11				
Heterogeneity: not applicable							
Test for overall effect: Z=0.77 (P=0.44)							
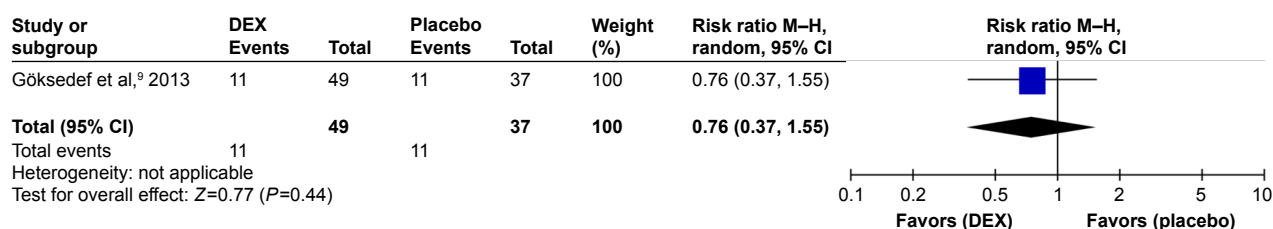
Figure 5 Forest plot: the incidence of AF between DEX and placebo groups.
Abbreviations: AF, atrial fibrillation; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Morphine Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Shehabi et al,[8] 2009	31	152	35	147	100	0.86 (0.56, 1.31)	
Total (95% CI)		**152**		**147**	**100**	**0.86 (0.56, 1.31)**	
Total events	31		35				
Heterogeneity: not applicable							
Test for overall effect: Z=0.71 (P=0.48)							
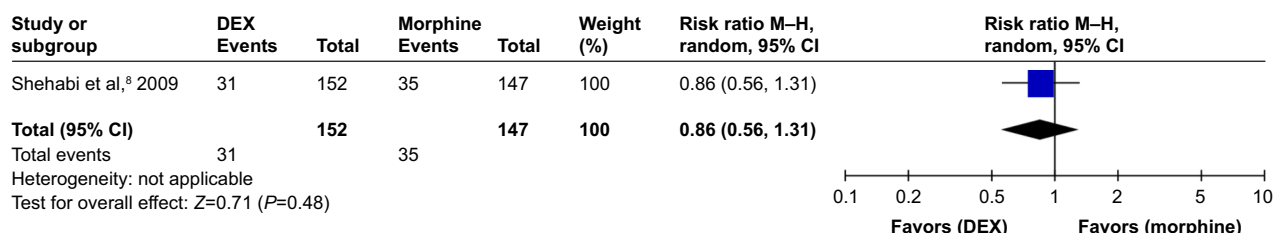
Figure 6 Forest plot: the incidence of AF between DEX and morphine groups.
Abbreviations: AF, atrial fibrillation; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Corbett et al,[16] 2005	1	43	0	46	2.5	3.20 (0.13, 76.60)	
George et al,[7] 2016	53	91	48	92	46.4	1.12 (0.86, 1.45)	
Herr et al,[6] 2003	12	148	12	147	24.5	0.99 (0.46, 2.14)	
Karaman et al,[5] 2015	2	31	1	33	4.5	2.13 (0.20, 22.32)	
Liu et al,[15] 2016	6	44	16	44	22.1	0.38 (0.16, 0.87)	
Total (95% CI)		**357**		**362**	**100**	**0.90 (0.54, 1.51)**	
Total events	74		77				
Heterogeneity: τ^2=0.13; χ^2=7.01, df=4 (P=0.14); I^2=43%							
Test for overall effect: Z=0.39 (P=0.69)							

Figure 7 Forest plot: the subgroup analysis for age >60 years.
Abbreviations: DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Liu et al,[17] 2017	17	59	19	59	100	0.89 (0.52, 1.54)
Total (95% CI)		59		59	100	0.89 (0.52, 1.54)
Total events	17		19			

Heterogeneity: not applicable
Test for overall effect: Z=0.40 (P=0.69)

Favors (DEX)   Favors (propofol)

Figure 8 Forest plot: the subgroup analysis for age ≤60 years.
Abbreviations: DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Propofol Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Djaiani et al,[7] 2016	53	91	48	92	44.6	1.12 (0.86, 1.45)
Liu et al,[15] 2016	6	44	16	44	22.5	0.38 (0.16, 0.87)
Liu et al,[17] 2017	17	59	19	59	32.9	0.89 (0.52, 1.54)
Total (95% CI)		194		195	100	0.81 (0.47, 1.39)
Total events	76		83			

Heterogeneity: τ^2=0.15; χ^2=6.47, df=2 (P=0.04); I^2=69%
Test for overall effect: Z=0.76 (P=0.45)

Favors (DEX)   Favors (propofol)

Figure 9 Forest plot: the subgroup analysis for CPB surgery.
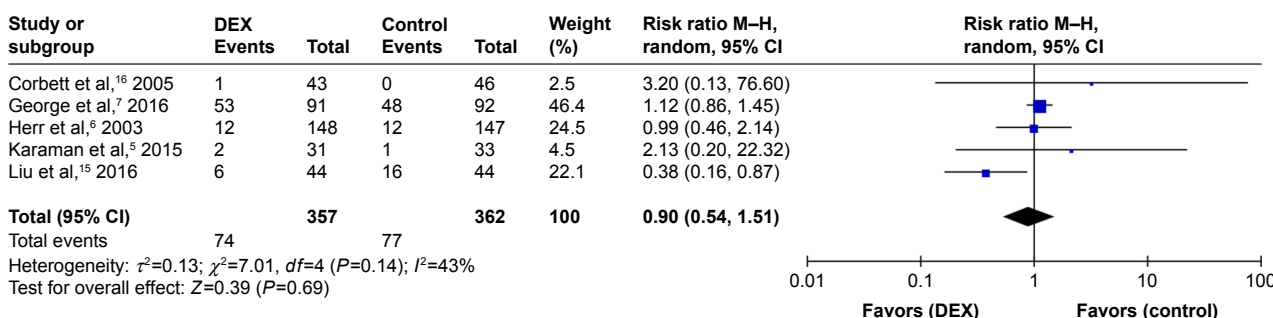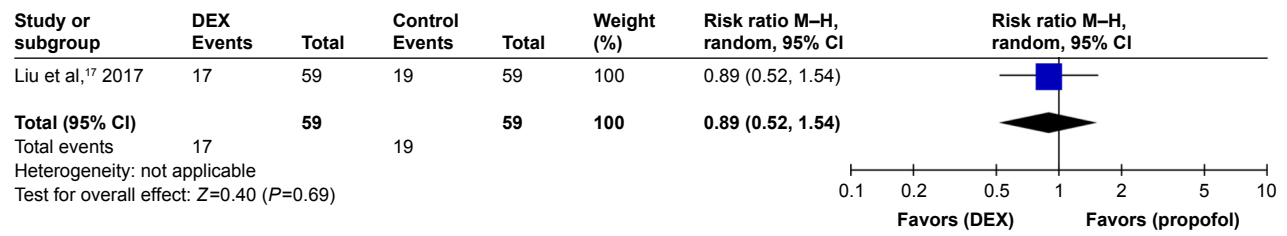**Abbreviations:** CPB, cardiopulmonary bypass; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Propofol Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Corbett et al,[16] 2005	1	43	0	46	5.3	3.20 (0.13, 76.60)
Herr et al,[6] 2003	12	148	12	147	73.6	0.99 (0.46, 2.14)
Karaman et al,[5] 2015	2	31	1	33	9.5	2.13 (0.20, 22.32)
Ren et al,[10] 2013	1	81	5	81	11.6	0.20 (0.02, 1.67)
Total (95% CI)		303		307	100	0.94 (0.45, 1.97)
Total events	16		18			

Heterogeneity: τ^2=0.04; χ^2=3.12, df=3 (P=0.37); I^2=4%
Test for overall effect: Z=0.15 (P=0.88)
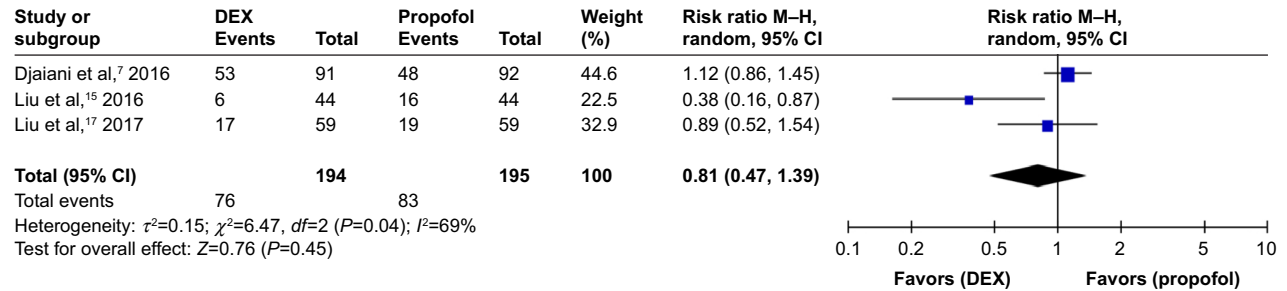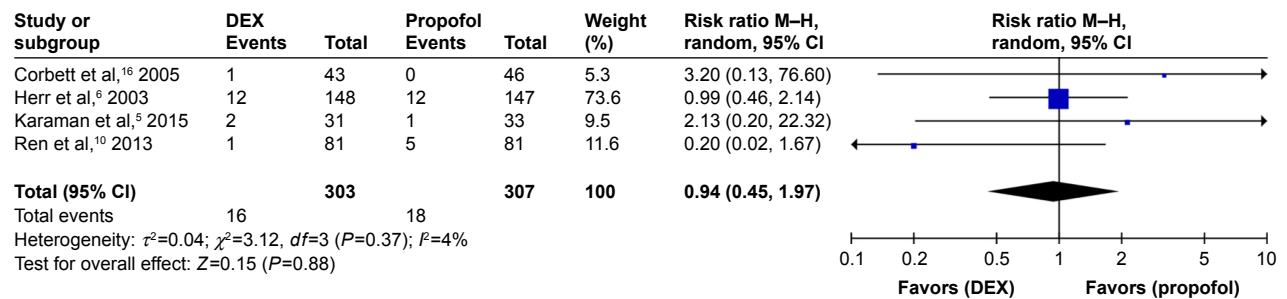
Favors (DEX)   Favors (propofol)

Figure 10 Forest plot: the subgroup analysis without CPB surgery.
Abbreviations: CPB, cardiopulmonary bypass; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Propofol Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI
Djaiani et al,[7] 2016	53	91	48	92	40.0	1.12 (0.86, 1.45)
Herr et al,[6] 2003	12	148	12	147	27.0	0.99 (0.46, 2.14)
Liu et al,[15] 2016	6	44	16	44	25.2	0.38 (0.16, 0.87)
Ren et al,[10] 2013	1	81	5	81	7.8	0.20 (0.02, 1.67)
Total (95% CI)		364		364	100	0.72 (0.37, 1.39)
Total events	72		81			

Heterogeneity: τ^2=0.26; χ^2=8.85, df=3 (P=0.03); I^2=66%
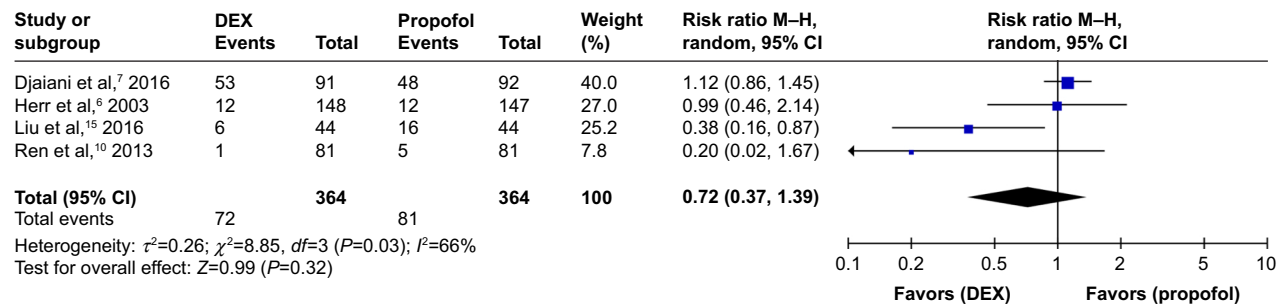Test for overall effect: Z=0.99 (P=0.32)

Favors (DEX)   Favors (propofol)

Figure 11 Forest plot: the subgroup analysis for beta-blocker premedication.
Abbreviations: DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Corbett et al,[16] 2005	1	43	0	46	2.7	3.20 (0.13, 76.60)	
Karaman et al,[5] 2015	2	31	1	33	5.0	2.13 (0.20, 22.32)	
Liu et al,[17] 2017	17	59	19	59	92.3	0.89 (0.52, 1.54)	
Total (95% CI)		**133**		**138**	**100**	**0.97 (0.57, 1.63)**	
Total events	20		20				

Heterogeneity: $\tau^2=0.00$; $\chi^2=1.08$, $df=2$ ($P=0.58$); $I^2=0\%$
Test for overall effect: $Z=0.12$ ($P=0.90$)

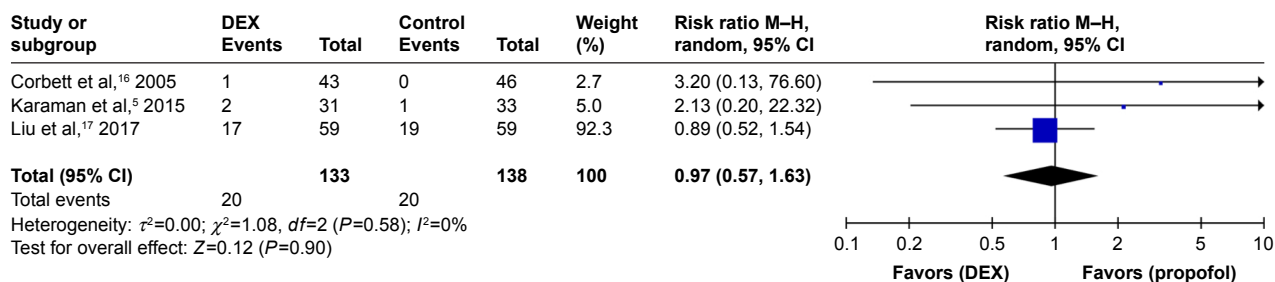Favors (DEX)   Favors (propofol)

Figure 12 Forest plot: the subgroup analysis without beta-blocker premedication.
Abbreviations: DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Propofol Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
George et al,[7] 2016	53	91	48	92	81.3	1.12 (0.86, 1.45)	
Liu et al,[17] 2017	17	59	19	59	18.7	0.89 (0.52, 1.54)	
Total (95% CI)		**150**		**151**	**100**	**1.07 (0.85, 1.36)**	
Total events	70		67				

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.53$, $df=1$ ($P=0.47$); $I^2=0\%$
Test for overall effect: $Z=0.57$ ($P=0.57$)

Favors (DEX)   Favors (propofol)

Figure 13 Forest plot: the subgroup analysis with AF history.
Abbreviations: AF, atrial fibrillation; DEX, dexmedetomidine; M–H, Mantel-Haenszel.
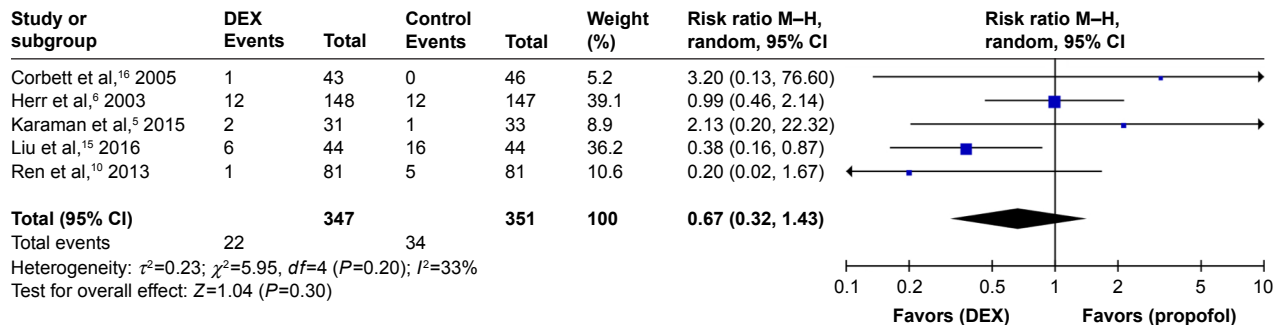
Study or subgroup	DEX Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Corbett et al,[16] 2005	1	43	0	46	5.2	3.20 (0.13, 76.60)	
Herr et al,[6] 2003	12	148	12	147	39.1	0.99 (0.46, 2.14)	
Karaman et al,[5] 2015	2	31	1	33	8.9	2.13 (0.20, 22.32)	
Liu et al,[15] 2016	6	44	16	44	36.2	0.38 (0.16, 0.87)	
Ren et al,[10] 2013	1	81	5	81	10.6	0.20 (0.02, 1.67)	
Total (95% CI)		**347**		**351**	**100**	**0.67 (0.32, 1.43)**	
Total events	22		34				

Heterogeneity: $\tau^2=0.23$; $\chi^2=5.95$, $df=4$ ($P=0.20$); $I^2=33\%$
Test for overall effect: $Z=1.04$ ($P=0.30$)

Favors (DEX)   Favors (propofol)

Figure 14 Forest plot: the subgroup analysis without AF history.
Abbreviations: AF, atrial fibrillation; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Control Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
George et al,[7] 2016	53	91	48	92	81.3	1.12 (0.86, 1.45)	
Liu et al,[17] 2017	17	59	19	59	18.7	0.89 (0.52, 1.54)	
Total (95% CI)		**150**		**151**	**100**	**1.07 (0.85, 1.36)**	
Total events	70		67				

Heterogeneity: $\tau^2=0.00$; $\chi^2=0.53$, $df=1$ ($P=0.47$); $I^2=0\%$
Test for overall effect: $Z=0.57$ ($P=0.57$)

Favors (DEX)   Favors (propofol)

Figure 15 Forest plot: the sensitivity analysis for beta-blocker premedication.
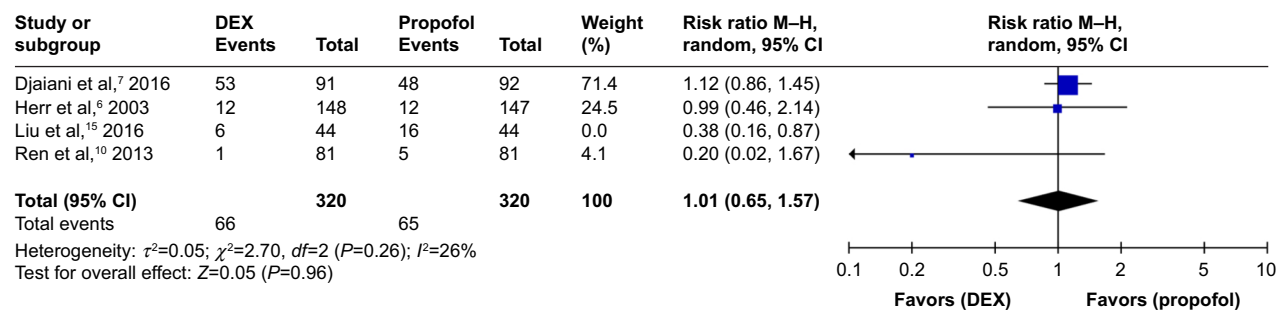**Abbreviations:** DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Study or subgroup	DEX Events	Total	Propofol Events	Total	Weight (%)	Risk ratio M–H, random, 95% CI	Risk ratio M–H, random, 95% CI
Djaiani et al,[7] 2016	53	91	48	92	71.4	1.12 (0.86, 1.45)	
Herr et al,[6] 2003	12	148	12	147	24.5	0.99 (0.46, 2.14)	
Liu et al,[15] 2016	6	44	16	44	0.0	0.38 (0.16, 0.87)	
Ren et al,[10] 2013	1	81	5	81	4.1	0.20 (0.02, 1.67)	
Total (95% CI)		**320**		**320**	**100**	**1.01 (0.65, 1.57)**	
Total events	66		65				

Heterogeneity: τ^2=0.05; χ^2=2.70, df=2 (P=0.26); I^2=26%
Test for overall effect: Z=0.05 (P=0.96)

0.1 0.2 0.5 1 2 5 10
Favors (DEX)   Favors (propofol)

Figure 16 Forest plot: the sensitivity analysis for CPB surgery.
Abbreviations: CPB, cardiopulmonary bypass; DEX, dexmedetomidine; M–H, Mantel-Haenszel.

Discussion

With the popularity of DEX sedation for ICU patients, an increasing number of functions for this drug have been found; however, controversies exist that need to be solved. Our current meta-analysis with limited resources indicated that sedation with DEX following cardiac surgery not only could not reduce the incidence of AF compared with control drugs but may also promote the incidence of AF in patients with a history of AF.

Currently, the risk factors for postoperative arrhythmias have been proposed to include hypoxia, ischemia, trauma, inflammation, catecholamines and electrolyte abnormalities; however, some patients present with different features.[22] It is well known that tachyarrhythmias can lead to decreased diastolic filling time and reduced cardiac output, resulting in possible myocardial ischemia and hypotension. Related research has indicated that the excitation of the sympathetic nerve is the primary pathogenesis of tachyarrhythmia following cardiac surgery.[23] AF following cardiac surgery is a thoroughly studied postoperative tachyarrhythmia.[1,24–27] Specifically, new-onset AF has been the focus of current research.[25] According to Banach et al's meta-analysis, the incidence of AF in patients after cardiac surgery doubles the risk of death.[28] The ACCP Guidelines for the Prevention and Management of Postoperative Atrial Fibrillation After Cardiac Surgery was proposed by the American College of Chest Physicians in 2005.[29] Then, the updated recommendation for management of POAF appeared in 2016.[30] Possible mechanisms may be the activation of a systemic proinflammatory state, myocardial irritation and heightened sympathetic tone. Although various functional drugs are recommended, it remains unclear whether these drugs have definitive effects. Thus, clinical research is critical for the development of new drugs.

DEX is a highly selective, new-generation alpha-2 adrenergic receptor agonist, and it was applied safely far beyond sedation. It also exhibits anxiolytic, analgesic and sympatholytic properties.[31] By activating G-protein transmembrane alpha-2 receptors located within the brain, DEX can theoretically influence the transmission of sympathetic activity from the central nervous system to the peripheral nervous system and could play an antiarrhythmic role. This anti-epinephrine effect was already proven effective by Hayashi et al's research.[32] The activation of vagus nerve was also thought to be one of the mechanisms responsible for the antidysrhythmic effect several years later.[33] Additionally, studies have referred to DEX's multifunctional characteristics in cardiac surgery, which include reducing myocardial ischemia–reperfusion injury[10,34] and inhibiting the inflammatory response.[35,36] In conclusion, all of the above features seem to indicate that DEX has antiarrhythmic effects. However, AF prophylaxis is a controversial topic in different types of patients. Ai et al confirmed the ineffectiveness of DEX in lung cancer patients,[37] but Liu et al's study indicated a positive effect of DEX in the prevention of AF.[15] Some related reviews have also strived to clarify the incidence of AF risk factors and drug prevention strategies.[3,30]

Our meta-analysis studied possible factors for clinical statistical heterogeneity and concluded that DEX exhibited no effective antiarrhythmic quality compared to control drugs for AF. Moreover, this study was graded to have low quality of evidence (Table 2). On the other hand, the subgroup analysis under CPB exhibited obvious heterogeneity (I^2=69%), which was eliminated after sensitivity analysis by the removal of one study.[15] Subsequently, consistent results were found. The heterogeneity from the removed study was likely due to the young age of the sample (~50 years) and the shortened clamp-close time (~50 minutes) of the enrolled patients, and thus it differed from other studies. It is known that increasing age and clamp-close time are risk factors for POAF,[38–40] directly influencing the rate of AF and prognosis of patients. Another finding of this study was the 1.07 times increased incidence of AF in the DEX

subgroup compared to the control subgroup if patients were accompanied with history of AF. However, the specific reason for this was not within the scope of this study and thus deserves further study.

Several limitations were found in our meta-analysis, which are as follows:

- Due to the shortage of RCTs and poor quality, an inconclusive conclusion may be drawn, especially since only one study of the control drug was enrolled, which can lead to an inability to quantitatively merge the results.
- The main outcome was found in only one included study; therefore, it is possible that the tests had inadequate power, and the detection of AF could have been missed.
- Many design differences between the studies made it difficult to reduce clinical heterogeneity, including variations in the timing of DEX administration, the duration of DEX infusion, the presence or lack of a loading dose and the infusion drug dosage.

Conclusion

From this meta-analysis, we conclude with low-quality evidence that DEX cannot decrease the incidence of AF compared to control drugs after cardiac surgery. Furthermore, DEX may increase the incidence of AF when patients have existing history of AF. However, cautious interpretation should be exercised due to the clinical heterogeneity. More RCTs and high-quality studies are warranted in the future.

Acknowledgment

Disclosure

The authors report no conflicts of interest in this work.

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