


## Effect of dexmedetomidine for prevention of acute kidney injury after cardiac surgery: an updated systematic review and meta-analysis

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### ABSTRACT

**Background:** Acute kidney injury (AKI) is a serious complication related to cardiac surgery. Several studies have been conducted to investigate the effect of dexmedetomidine administration on AKI prevention.

**Objective:** To assess if dexmedetomidine is associated with a protective effect of renal function after cardiac surgery. And the aim of conducting this meta-analysis is to summarize the literature and determine the clinical utility of dexmedetomidine administration in patients undergoing cardiac surgery.

**Methods:** PubMed, Cochrane Library, and EMBASE databases were comprehensively searched for all randomized controlled trials (RCTs) published before 1 December, 2021 that investigated the effect of dexmedetomidine on AKI prevention.

**Results:** Our analysis included 16 studies involving 2148 patients. Compared with the control group, dexmedetomidine administration significantly reduced AKI incidence (OR, 0.47; 95% CI, 0.36–0.61;  $p < 0.00001$ ;  $I^2 = 26\%$ ) and the length of stay in the intensive care unit (ICU) but did not alter mortality rate, length of stay in the hospital, and mechanical ventilation time. Furthermore, the incidence of delirium among patients treated with dexmedetomidine was significantly decreased.

**Conclusion:** Dexmedetomidine administration has a positive effect on preventing AKI and postoperative delirium after cardiac surgery and significantly reduces the length of stay in the ICU.

### ARTICLE HISTORY

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### KEYWORDS

Dexmedetomidine; cardiac surgery; renal function; meta-analysis

## Introduction

Acute kidney injury (AKI) is a serious complication of cardiac surgery with an estimated incidence of 20% [1,2]. It is the second most common type of AKI in the intensive care unit, following sepsis-related AKI [3]. Coronary artery bypass graft and cardiac valve replacement can cause AKI because they are always accompanied by renal ischemia-reperfusion injury (I/R), elevated sympathetic activity, and hemodynamic instability. Despite steps to prevent AKI, a standard for preventing AKI after cardiac surgery is lacking.





Dexmedetomidine, an  $\alpha_2$ -adrenoreceptor agonist, has been widely used in anesthesia procedures and intensive care. It inhibits inflammation, alleviates postoperative delirium, and exhibits neuroprotective effects. AKI incidence decreases after the use of dexmedetomidine


in cardiac surgery. However, it remains unclear if dexmedetomidine can ameliorate the harmful effects of cardiac surgery on renal function. Six additional single-center randomized controlled trials have been concluded since the previous meta-analysis was published. Therefore, the present meta-analysis was conducted to provide updated information on the efficacy of dexmedetomidine on renal function after cardiac surgery.

## Methods

### Search strategy and selection criteria

This systematic review and meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and is registered at the International Prospective Register of Systematic

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Reviews (Number CRD42021253836). PubMed, EMBASE, and Cochrane Library were searched for relevant studies since inception to 1 December 2021 with no language restrictions. The following combined text and MeSH terms were used: 'Dexmedetomidine', 'Cardiac surgical procedures', and 'Renal insufficiency'. All the searched RCTs were included without bias of gender and age. Studies not reporting AKI incidence were excluded. In addition, reference lists of key published articles were manually searched.

### Study selection and data extraction

Two independent investigators (LX and HQX) reviewed the published studies and extracted data. If there were disagreements, the third investigator (CQX) resolved. RCTs involving cardiac surgery and treatment with dexmedetomidine during the perioperative period and reporting AKI incidence, regardless of the criteria AKIN, KDIGO, and RIFLE, were considered eligible for inclusion. Observational or retrospective studies were excluded. If there was more than one comparison eligible for inclusion criteria in one study, all of the comparisons would be included and defined as different groups. The Cochrane risk of bias tool was used for assessing the quality of the included studies. The following data were extracted from selected studies: total number of patients and their characteristics (age, sex, proportion of patients with diabetes, and proportion of hypertension), cardiac surgical procedures, cardiopulmonary bypass (CPB) time, control drugs, and the dosage of dexmedetomidine. The primary outcome was AKI incidence after cardiac surgery within 7 days. Secondary outcomes were as follows: all-cause mortality (within 30 days), mechanical ventilation (MV) duration, and the length of stay in ICU and hospital.

### Statistical analysis

The incidence of AKI after cardiac surgery, mortality, mechanical ventilation duration, the length of stay in ICU, and the length of stay in the hospital were analyzed. Data were pooled from all eligible RCTs and the Mantel–Haenszel method was used to calculate the risk ratio (RR) with 95% confidence intervals (CIs) for these dichotomous outcomes. A pooled estimate of RR was computed using the DerSimonian and Laird random-effects model. This model provides an appropriate assessment of the average treatment effect when studies are statistically heterogeneous, and it typically yields relatively wide CIs resulting in a more conservative statistical claim.

Cochran's Q test and Higgins'  $I^2$  statistical test were used to assess the statistical heterogeneity of the pooled results [4]. If  $0\% \leq I^2 < 25\%$ , the results showed no heterogeneity; if  $25\% \leq I^2 < 50\%$ , the results showed a low level of heterogeneity; if  $50\% \leq I^2 < 75\%$ , the results showed a medium level of heterogeneity; if  $75\% \leq I^2 \leq 100\%$ , the results showed a high level of heterogeneity. Risk of bias assessment was done using the Cochrane Collaboration tool (Cochrane, London, UK).

Begg's test and Egger's test were used to determine publication bias, and a  $p$ -value  $< 0.1$  indicated significant bias. Trim-and-fill computation was performed to estimate the effect of publication bias on the interpretation of the results.  $p < 0.05$  (two-sided) indicated statistical significance. We used REVMAN (version 5.4; Cochrane Collaboration, Oxford, UK) and Stata (version 12.0; Stata Corp LP) for statistical analyses.

## Results

### Study characteristics

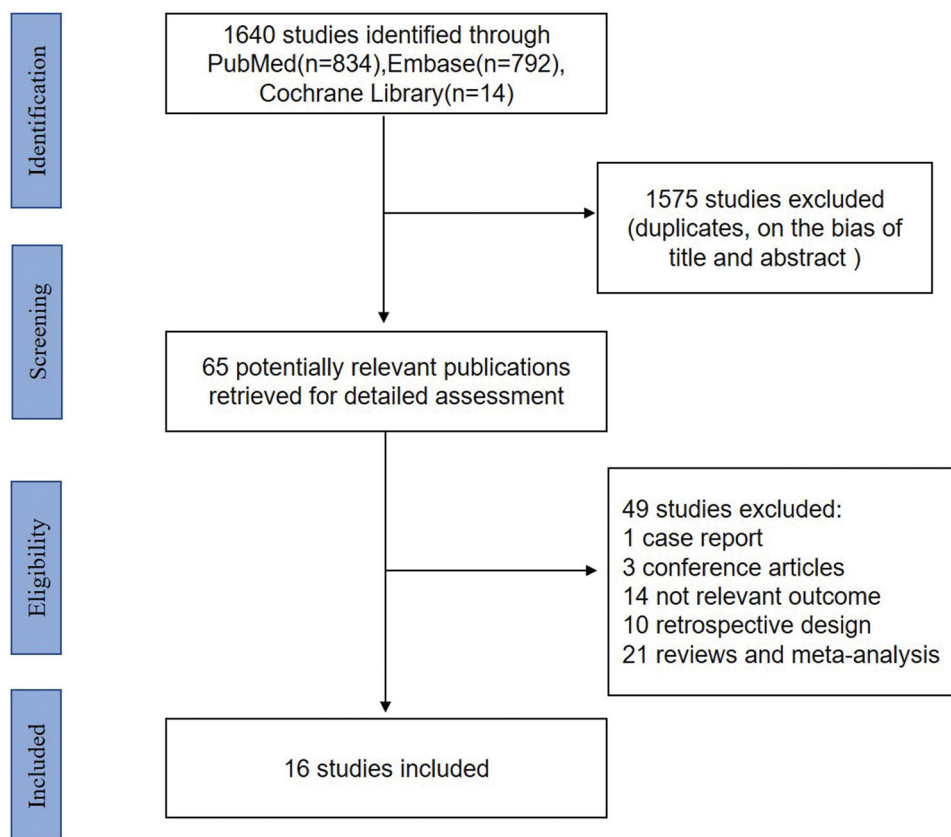
The literature search identified 1640 articles of which 16 articles [5–20] ultimately met the inclusion criteria (Figure 1). The characteristics of the 16 studies that involved 2148 participants are summarized in Tables 1 and 2. For postoperative outcomes, AKI incidents were reported in all studies. AKI was defined based on three definitions, including RIFLE [6,10,12,20], AKIN [8,13,18], KDIGO [7,11,12,16], and a diagnostic criterion of  $Cr > 115 \mu\text{mol/L}$  [17]. Four studies did not mention the specific criteria used to define AKI [5,9,15,19].

The risk of bias graph (Figure 2) shows two studies rated as high risk for attrition bias, in which complete outcome data were not available. Supplementary Figure 3 shows no significant asymmetry in the funnel plot, which means no significant publication bias.

### Effect of dexmedetomidine on AKI

In a pooled analysis of all 16 studies, the overall incidence of AKI was 13.78% (dexmedetomidine group, 105/1077; control group, 191/1071). The incidence of AKI was significantly reduced after perioperative dexmedetomidine treatment (OR, 0.47; 95% CI, 0.36–0.61;  $p < 0.00001$ ;  $I^2 = 26\%$ . Figure 3). No publication bias was noted according to Begg's test ( $p > 0.1$ ) and Egger's test ( $p > 0.1$ ).

Subgroup analyses to identify the effect of a potential source of heterogeneity on AKI were performed by classifying these included studies according to gender (proportion of male  $\geq 50$  vs.  $< 50\%$ ), age (year,  $\geq 60$  vs.  $< 60$ ), duration of CPB (min,  $\leq 80$  vs.  $> 80$ ), control drugs



**Figure 1.** Study selection process.

(placebo vs nonplacebo), loading dose (using or not), continuous infusion dose ( $>0.4$  vs.  $0.4 \leq \mu\text{g/kg/h}$ ), time of dexmedetomidine administration (pre/intraoperation vs. post-operation), diabetes ( $\geq 25$  vs.  $<25\%$ ), hypertension ( $\geq 50$  vs.  $<50\%$ ), and surgical procedures (CABG only vs combined surgery), as shown in Table 2. The results indicated no significant differences in the AKI incidence.

#### **Mortality rate after dexmedetomidine treatment**

A mortality rate of 1.5% was reported (dexmedetomidine group, 6/651; control group, 14/648). No significant difference was noted between the two groups (OR, 0.48; 95%CI, 0.19–1.24;  $p = 0.13$ ;  $I^2 = 0\%$ , Figure 4)

#### **The length of stay in ICU, MV duration, and length of stay in hospital after dexmedetomidine treatment**

Perioperative dexmedetomidine treatment could significantly reduce the length of stay in ICU (OR,  $-2.04$ ; 95%CI,  $-3.60$  to  $-0.49$ ;  $p = 0.01$ ;  $I^2 = 100\%$ , Supplementary Figure 1). MV duration in ICU and hospital stay did no significantly differ between the two groups.

#### **Effect of dexmedetomidine on the incidence of adverse events during the perioperative period**

The incidence of delirium was significantly reduced by administration of dexmedetomidine ( $p < 0.001$ ), while no significant change in the incidence of arrhythmias ( $p = 0.06$ ), bradycardia ( $p = 0.08$ ), hypotension ( $p = 0.41$ ), and stroke ( $p = 1.00$ ) was observed (Figure 5).

#### **Discussion**

The present meta-analysis indicated that the administration of dexmedetomidine can reduce AKI incidence during the perioperative period in cardiac patients. Compared with previous meta-analysis [21], our subgroup analysis indicated no significant differences in age and the usage time of dexmedetomidine. Perioperative dexmedetomidine treatment significantly reduced the length of stay in the ICU. Mortality rate and MV duration did not differ significantly between the groups. Moreover, dexmedetomidine treatment significantly reduce the incidence of delirium, but the incidence of arrhythmias, bradycardia, hypotension, and stroke in the perioperative period was not significantly altered.

**Table 1.** Characteristics of the included studies.

Study	Country	Surgery	Age	No. of Patients (Dex vs Control)	Loading DOSE	Dexmedetomidine dose	Control	Time and duration	AKI definition	Clinical End Point
Ammar 2016	Egypt	Combined	Adult	25 vs. 25	1 ug/kg	0.5 ug/kg/h	Placebo	Started 5min before CPB and continued 6 h after surgery	NA	AKI; MV duration; ICU stay; hospital stay; mortality
Balkanay (High dose) 2015	Turkey	CABG	Senior	29 vs. 28	NA	0.04–0.5 ug/kg/h	Placebo	Started after arrived ICU and last for a maximum of 24h	RIFLE	AKI; MV duration; ICU stay; hospital stay
Balkanay (Low dose) 2015	Turkey	CABG	Senior	31 vs. 28	NA	0.04–0.5 ug/kg/h	Placebo	Started after arrived ICU and last for a maximum of 24h	RIFLE	AKI; MV duration; ICU stay; hospital stay
Cho 2016	Korea	Combined	Senior	100 vs. 100	NA	0.4 ug/kg/h	Placebo	Started after anesthetic induction and continuing for 24 h after surgery and continued until extubation	AKIN	AKI; mortality
Djaiani 2016	Canada	Combined	Senior	91 vs. 92	0.4 ug/kg	0.2–0.7ug/kg/h	Propofol	Started upon arrival to ICU	NA	AKI; MV duration; ICU stay; hospital stay; mortality
Jo 2017	Korea	Atrial or ventricular defect repair	Pediatric	15 vs. 14	0.5 ug/kg	0.5 ug/kg/h	Placebo	Started after anesthesia induction and continued to the end of CPB	AKIN	AKI
Kim 2020	Korea	Combined	Pediatric	71 vs. 68	1 ug/kg	0.5 ug/kg/h	Placebo	Started after induction and continued until the end of surgery	KDIGO	AKI; MV duration; ICU stay; hospital stay
Leino 2011	Finland	CABG	Adult	35 vs. 31	NA	0.6ng/ml	Placebo	Start after anesthesia induction, and continued until 4h after arrival in the ICU	RIFLE	AKI; MV duration
Li 2017	China	Combined	Senior	142 vs. 143	NA	0.1–0.6 ug/kg/h	Placebo	Started before surgery and continued until the end of MV	KDIGO	AKI; MV duration; ICU stay; hospital stay; Mortality
Liu 2016	China	Combined	Adult	44 vs. 44	NA	≤1.5 ug/kg/h	Propofol	Started upon arrival at the ICU and continued before extubation	AKIN	AKI; MV duration; ICU stay; hospital stay
Park 2014	Korea	Combined	Adult	67 vs. 75	0.5 ug/kg	0.2–0.8 ug/kg/hr	Remifentani	Started upon return to the C ICU and maintained until extubation	NA	AKI; MV duration; ICU stay; hospital stay
Shehabi 2009	Australia	Combined	Senior	149 vs. 146	NA	0.1–0.7 ug/kg/ml	Morphine	Start within 1h of admission to the ICU until the removal of chest drains	NA	AKI; MV duration; ICU stay; hospital stay; mortality
Soh 2020	Korea	Combined	Senior	54 vs. 54	NA	0.4 ug/kg/h	Placebo	Started after anesthetic induction and continued for 24h	KDIGO	AKI; mortality
Soliman 2016	Egypt	Aortic vascular surgery	Adult	75 vs. 75	1 ug/kg	0.3 ug/kg/h	Placebo	Start before induction and maintained to the end of procedure	Cr > 115 μmol/L	AKI; mortality
Soliman 2017	Egypt	CABG	Adult	75 vs. 75	NA	0.4 ug/kg	Placebo	Started after induction and continued during the first 24 postoperative hours	RIFLE	AKI; ICU stay; hospital stay; mortality
Tang 2020	China	Cardiac valve replacement	Adult	38 vs. 37	1 ug/kg	0.3 ug/kg/h	Placebo	Started before induction and continued until the end of operation period	KDIGO	AKI; MV duration; ICU stay; hospital stay
Zhai 2017	China	Cardiac valve replacement	Adult	36 vs. 36	0.6 ug/kg	0.2 ug/kg/h	Placebo	Started before anesthesia and continued during the entire operation period	RIFLE	AKI; MV duration

**Table 2.** Subgroup analysis of the potential sources of heterogeneity.

Subgroup	Endpoint	No. of comparisons	OR WMD	95%CI	p Value	I <sup>2</sup>
Gender (males%)	AKI	17	0.47	0.36–0.61	0.161	26
≥50		13	0.50	0.37–0.68	0.084	38.6
<50		4	0.35	0.19–0.63	0.783	0.0
Age (years)	AKI	17	0.47	0.36–0.61	0.161	26
≥60		6	0.51	0.35–0.73	0.188	33
<60		11	0.43	0.29–0.63	0.198	26.8
DM (≥50%)	AKI	14	0.58	0.47–0.73	0.215	22.6
Yes		7	0.45	0.28–0.71	0.274	21.1
No		7	0.64	0.50–0.82	0.304	16.6
Hypertension (≥50%)	AKI	12	0.58	0.46–0.74	0.159	30.2
Yes		8	0.58	0.44–0.77	0.145	37.2
No		4	0.58	0.37–0.92	0.189	37.2
Surgical procedures (CABG ≥ 50%)	AKI	15	0.55	0.45–0.69	0.185	24.3
Yes		7	0.59	0.44–0.80	0.138	38.2
No		8	0.52	0.38–0.69	0.332	12.6
CPB time (minutes)	AKI	17	0.47	0.36–0.61	0.161	26
≥80		7	0.42	0.21–0.85	0.273	21.3
<80		10	0.47	0.36–0.63	0.125	35.3
Control drugs	AKI	17	0.47	0.36–0.61	0.161	26
Placebo		12	0.48	0.36–0.65	0.381	6.6
Others		5	0.42	0.24–0.73	0.053	57.2
Dexmedetomidine administration	AKI	17	0.47	0.36–0.61	0.161	26.0
Pre/intraoperation		11	0.42	0.32–0.56	0.107	37.7
Postoperation		6	0.92	0.43–1.97	0.774	0.0
Loading dose	AKI	17	0.47	0.36–0.61	0.161	26.0
Yes		10	0.56	0.48–0.80	0.311	14.7
No		7	0.37	0.25–0.55	0.226	26.5
Dexmedetomidine dose (≤0.4 μg/kg/h)	AKI	10	0.41	0.31–0.54	0.670	0.0
Yes		3	0.61	0.35–1.04	0.345	0.0
No		7	0.36	0.26–0.51	0.838	0.0

Xiao et al. revealed that dexmedetomidine administration can protect organs only if administered before ischemia sets in [22]. In our meta-analysis, pooled results of 10 studies indicated that preoperative or intraoperative administration of dexmedetomidine cannot reduce the incidence of AKI compared with postoperative administration of dexmedetomidine ( $p=0.06$ ). In addition, subgroup analysis suggested that the relatively low dose of dexmedetomidine ( $\leq 0.4 \mu\text{g}/\text{kg}/\text{min}$ ) had a similar protective effect to the high dose ( $>0.4 \mu\text{g}/\text{kg}/\text{min}$ ;  $p=0.46$ ). Moreover the previous meta-analysis suggested that the use of dexmedetomidine might reduce the incidence of AKI in adult patients [21,23]. However, they excluded children, which might conceal the true effect of dexmedetomidine on AKI, as the occurrence of AKI in children can also lead to adverse outcomes during the perioperative and postoperative periods. The present study showed no significant difference in the ability of dexmedetomidine to reduce AKI incidence between children and adults. Furthermore, both previous studies excluded trials involving patients with basic renal dysfunction, which might increase the heterogeneity among the studies. However, our results indicated that the inclusion of our

study did not significantly increase heterogeneity ( $I^2=26\%$  vs.  $I^2=8\%$ ). Linda et al. found that the increased prevalence of chronic kidney disease among elderly patients, excluding patients with renal dysfunction, might conceal the nephroprotective effect of dexmedetomidine in patients with CKD [24].

The current meta-analysis indicated that perioperative treatment with dexmedetomidine might reduce the incidence of delirium, consistent with the results of several other studies focusing on the incidence of delirium among patients undergoing cardiac surgery [25]. Lower rates of delirium have been reported in ICU patients sedated with dexmedetomidine than patients sedated with benzodiazepines and propofol [26,27]. Moreover, the incidences of arrhythmias, bradycardia, hypotension, and stroke were not significantly different in compared groups. These adverse events might prolong the length of stay in ICU and hospital and even increase the mortality rate. Hypotension and bradycardia are the most common adverse effects during the use of dexmedetomidine due to its inhibition of the sympathetic nervous system. Patients in the dexmedetomidine treatment group had a lower incidence of AKI despite more adverse hemodynamic events. However,

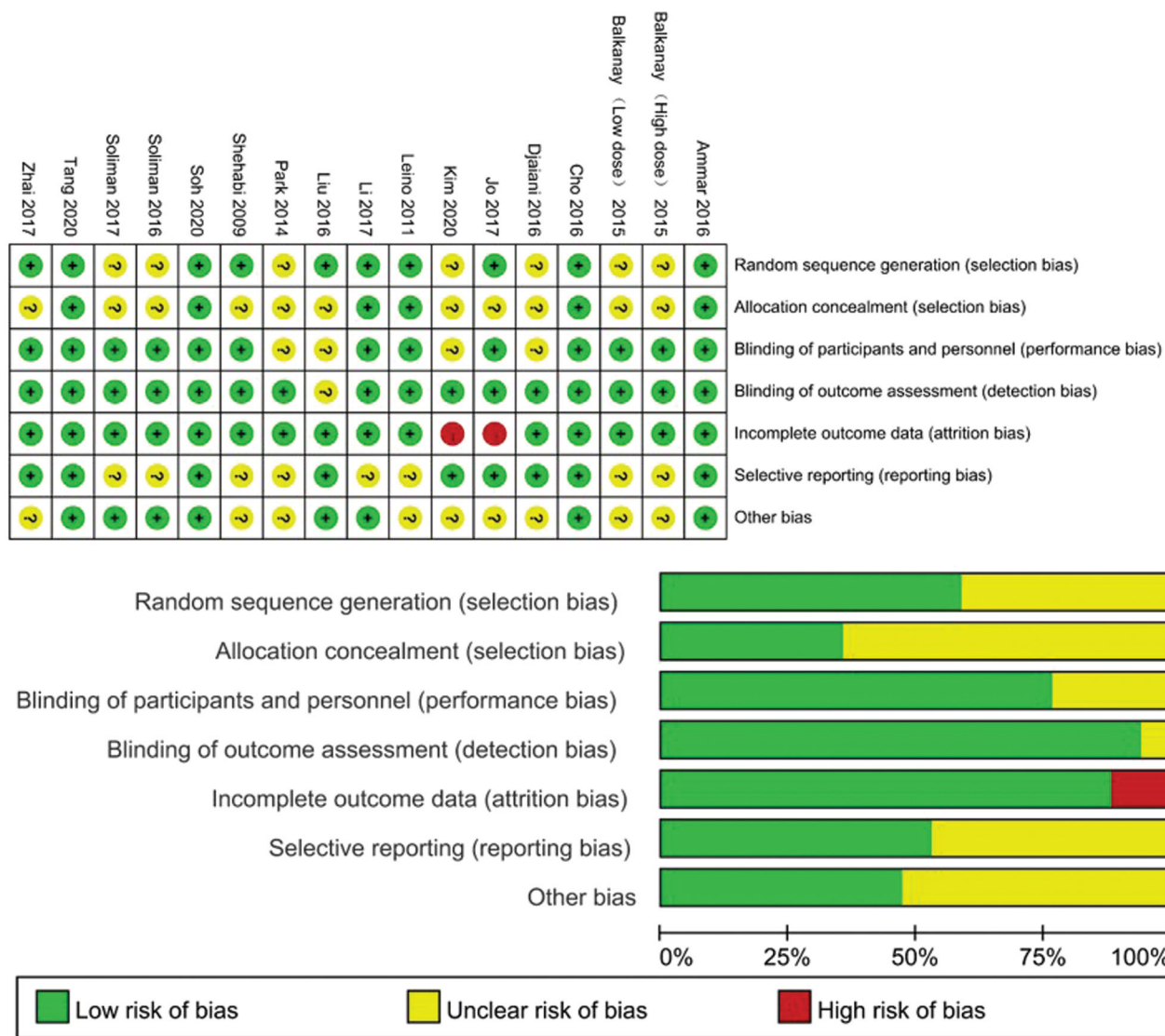


Figure 2. Risk of bias assessment of the included studies.

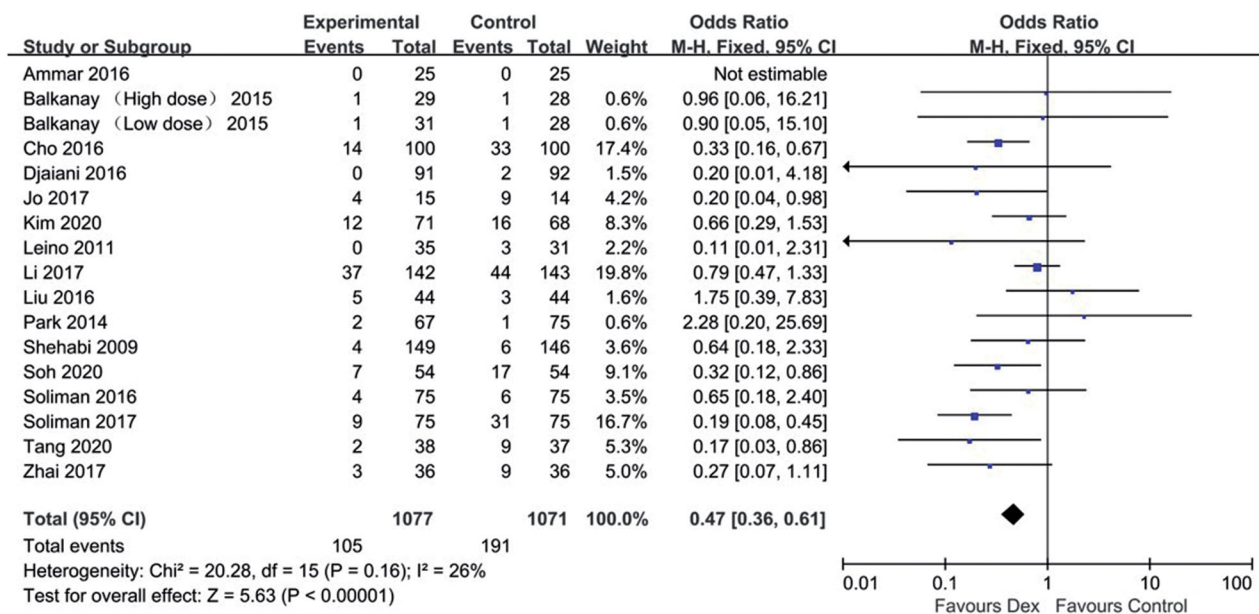


Figure 3. Forest plots for meta-analysis of AKI incidence in cardiac surgery patients.

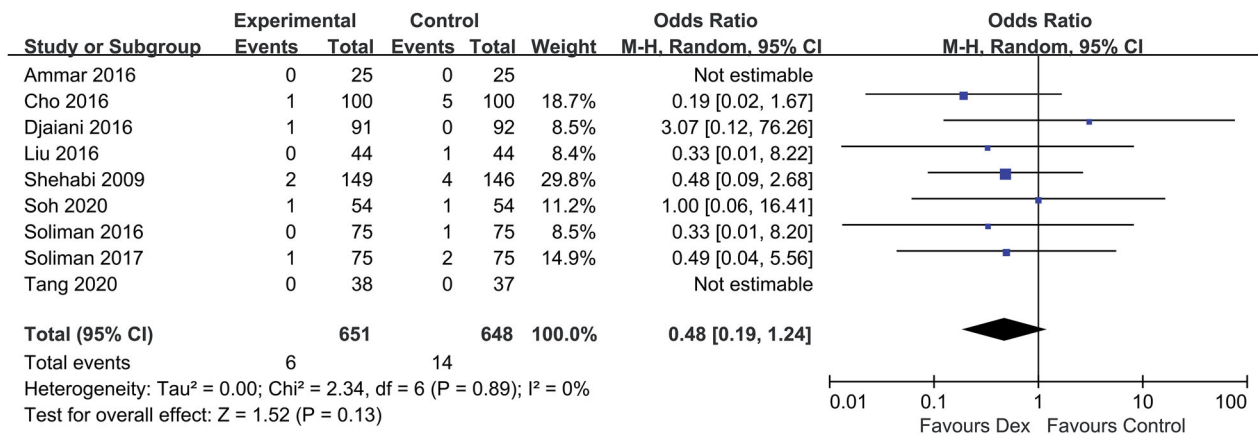


Figure 4. Forest plot for meta-analysis of mortality.

these adverse effects could be easily handled if the atropine or vasoactive agents were administered timely. Findings from our meta-analysis showed a protective effect of dexmedetomidine on renal function in patients undergoing cardiac surgery. We comprehensively reviewed RCTs designed to detect the effect of dexmedetomidine on cardiac surgery patients, pediatric patients, and patients with renal impairment. The heterogeneity was 26% for the primary outcome, which suggested that the interpretation of the current finding was reliable.

The mean blood pressure may relatively decrease during CPB in cardiac surgery, and the blood pressure may return to normal after the CPB procedure. The protective effect of dexmedetomidine on attenuating the I/R injury in mice was related to sirtuin 3 activation [28]. Zhao et al. indicated that dexmedetomidine might reduce kidney injury by increasing autophagy through inhibition of the PI3K/AKT/mTOR pathway in lipopolysaccharide-induced rat AKI models [29]. However, further studies are needed to understand the exact mechanisms of the nephroprotective effects of dexmedetomidine.

The current study extends the scope of our understanding by summarizing the effect of dexmedetomidine on renal function after cardiac surgery. Several limitations exist in this meta-analysis. First, a previous study revealed that a higher incidence of AKI in patients with a long duration of cardiac surgery [30]. The duration of operation and ischemia might differ because the trials included in the previous meta-analysis were conducted at different medical centers, which could greatly affect renal function. Subgroup analysis suggested no significant difference in the AKI incidence between CPB time of more than 3 h or not. More eligible trials are required to further investigate the exact influence of CPB duration on the protective effect of

dexmedetomidine. The same limitation was also noted for the length of MV duration, length of stay in ICU, and length of stay in hospital. Second, many factors could influence renal function, such as age, degree of hypertension, pulsatility of blood flow and central venous pressure during the surgery period, and drugs used for treating hypertension and diabetes mellitus; however, we only estimated the effect of dexmedetomidine. Further robust evidence is required to confirm the effect of dexmedetomidine on patients undergoing cardiac surgery. Third, based on the included data, there are four different definitions of AKI, including RIFLE, AKIN, KDIGO, and Cr >115  $\mu\text{mol/L}$ . There are still 4 studies that have not mentioned the definition of AKI. Indeed, a subgroup analysis based on AKI definition would be appropriate, but some of the subgroup analysis may only include 3 or less studies, too few studies might draw a misleading conclusion and this is a limitation of our study. Finally, some of the primary results were calculated based on the statistical methods of Luo et al. and Wan et al., which might influence the detection of differences in this study.

## Conclusion

The perioperative administration of dexmedetomidine could reduce AKI incidence in patients undergoing cardiac surgery. Dexmedetomidine treatment may also reduce the length of stay in ICU and the incidence of postoperative delirium.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

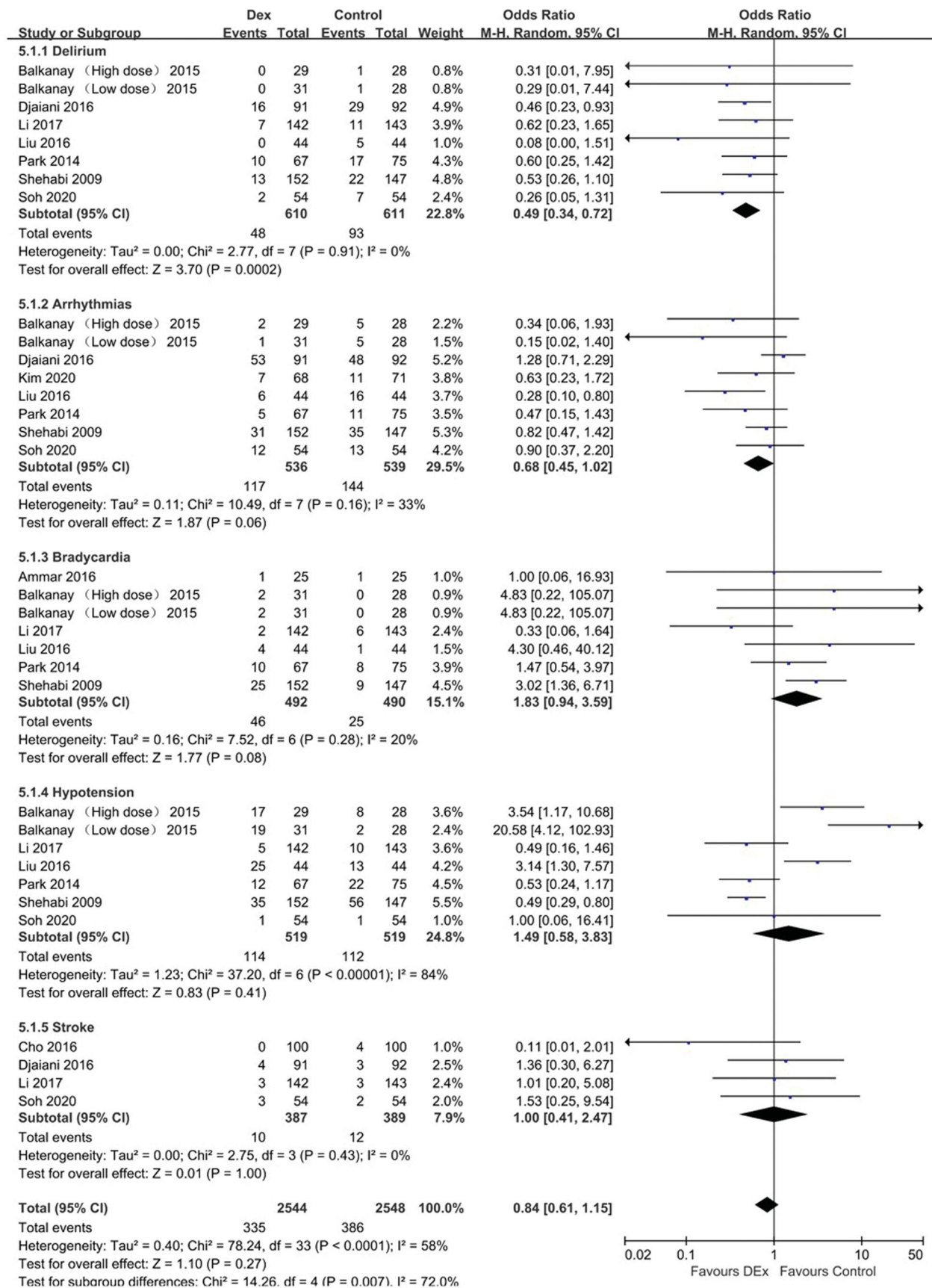


Figure 5. Forest plots for meta-analysis of adverse events (delirium, arrhythmias, bradycardia, hypotension, and stroke).



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