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CLINICAL INVESTIGATION

Effects of Dexmedetomidine on Outcomes After Cardiac Surgery (DOCS): a randomised double-blind, placebo-controlled trial

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Abstract

Background: Organ dysfunction after cardiac surgery may be reduced by dexmedetomidine. We evaluated whether perioperative dexmedetomidine reduces complications after cardiac surgery with cardiopulmonary bypass.

Methods: In this randomised, double-blind, placebo-controlled trial conducted in nine Chinese hospitals, adults scheduled for cardiac surgery with cardiopulmonary bypass were randomly assigned to receive i.v. dexmedetomidine ($0.4 \mu\text{g kg}^{-1} \text{h}^{-1}$) or saline (placebo) for 12 h after the induction of anaesthesia. The co-primary outcomes were in-hospital mortality and major complications after surgery (including stroke, myocardial infarction, heart block, cardiac arrest), analysed by intention-to-treat. Secondary outcomes included individual complications.

Results: A total of 1073 participants (46% female; mean age: 54 yr [range: 47–63 yr]) completed the study after randomisation. Major complications occurred in 161/536 (30%) participants who received dexmedetomidine, compared with 169/537 (32%) who received saline (relative risk: 0.93 [95% confidence interval: 0.72–1.21]; $P=0.66$). In addition, 10/536 (1.9%) participants who received dexmedetomidine died in hospital, compared with 15/537 (2.8%) participants who received saline (odds ratio: 0.66 [95% confidence interval: 0.29–1.49]; $P=0.32$). Major complications, other than heart block, did not differ between participants who received dexmedetomidine, compared with participants who received saline. Safety outcomes and process measures did not differ between participants allocated to dexmedetomidine or saline.

Conclusions: Perioperative use of dexmedetomidine did not reduce death, complications, or both in adults undergoing cardiopulmonary bypass-assisted cardiac surgery.

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Clinical trial registration: ClinicalTrials.gov (NCT02237495).

Keywords: cardiac surgery; cardiopulmonary bypass; dexmedetomidine; major morbidity; mortality

Editor's key points

- Dexmedetomidine could potentially protect organs in cardiac surgery with cardiopulmonary bypass.
- This multicentre placebo-controlled RCT evaluated whether perioperative dexmedetomidine reduces complications after cardiac surgery with cardiopulmonary bypass.
- A total of 1100 adults scheduled for cardiac surgery with cardiopulmonary bypass were randomly assigned to receive either i.v. dexmedetomidine or normal saline for 12 h after induction of anaesthesia.
- Mortality and complication rates were similar between dexmedetomidine and placebo groups.
- Perioperative use of dexmedetomidine did not reduce organ dysfunction in adults undergoing cardiopulmonary bypass-assisted cardiac surgery.

Cardiac surgery is associated with high rates of postoperative mortality and morbidity,^{1,2} with major adverse events occurring in around 12% of cardiac surgical patients compared with 3% in other surgical populations.³ Major complications after valve and coronary artery bypass grafting (CABG) procedures can occur in up to 30% of patients.^{4,5} Consequently, healthcare costs increase substantially as a result of postoperative complications.⁶ Preventing these complications and enhancing survival rates in cardiac surgery patients remain challenging.

Dexmedetomidine, a selective α_2 -adrenergic receptor agonist, exerts anxiolytic, sedative, analgesic, and sympatholytic effects by inhibiting central sympathetic outflow through the blockade of α_2 -receptors in the brainstem. Dexmedetomidine offers potentially beneficial effects in surgical settings,^{7–10} particularly in cardiac surgery.^{2,11,12} A recent systematic review and meta-analysis of 23 studies found that perioperative dexmedetomidine use decreased 30-day mortality, and in-hospital and ICU stays, and reduced incidence of delirium and atrial fibrillation.¹³ However, no guidelines currently recommend its perioperative use.^{14,15} The heterogeneity among studies complicates the interpretation of its benefits, as another meta-analysis found no reduction in mortality or major complications from prophylactic α_2 -agonists.¹⁶

To address confounding biases in observational studies and insufficient power in small trials, we conducted a large multicentre randomised placebo-controlled trial to determine whether perioperative dexmedetomidine administration major complications in patients undergoing cardiopulmonary bypass (CPB)-assisted cardiac surgery.

Methods

Study design

Effects of Dexmedetomidine on Outcomes after Cardiac Surgery (DOCS) was an investigator-initiated, multicentre,

randomised, double-blind, parallel-arm, and placebo-controlled trial. The effect of perioperative dexmedetomidine on postoperative in-hospital all-cause mortality and major morbidities was assessed. Ethical approvals from the institutional review board and ethics committee at each site were obtained. Before randomisation, all participants or their surrogates provided written informed consent. The trial was registered at [ClinicalTrials.gov](https://clinicaltrials.gov) before the first enrolment (NCT02237495), and overseen by an independent steering committee, aligning with a prespecified protocol and statistical analysis plan ([Supplementary material](#)) with regular site visits. The study was conducted at nine cardiovascular surgical centres across China, led by Xijing Hospital ([Supplementary material](#)).

Inclusion criteria

Patients ≥ 18 yr who underwent elective cardiac surgeries (i.e. isolated CABG, isolated valve, or concomitant CABG or valve surgery) with CPB were screened.

Exclusion criteria

We excluded emergency surgeries, participation in other trials within 30 days, refusal to consent, pregnancy, expected deep hypothermic circulatory arrest during surgery, myocardial infarction (MI) 30 days before the surgery, preoperative left ventricular ejection fraction $< 30\%$ or severe heart failure, sick sinus or Wolff–Parkinson–White syndromes, sinus bradycardia (heart rate < 50 beats min^{-1}), second degree or greater atrioventricular block without pacemaker, severe hepatic dysfunction (Child–Pugh class C), renal dysfunction (requiring renal replacement therapy [RRT]), known adverse responses to α_2 -agonists, and α_2 -agonist exposure 30 days before the surgery.

Randomisation and masking

Randomisation was conducted using computer-generated permuted blocks with unknown sizes, stratified by site. Participants were assigned to receive either i.v. dexmedetomidine or placebo (saline) in a 1:1 ratio. Allocation was encrypted via a web-based central randomisation service. Trained research nurses prepared study drugs and were not involved in other aspects of the trial. All personnel, including patients, surgeons, anaesthesiologists, intensivists, and statisticians, were blinded.

Study intervention

Dexmedetomidine (200 μg 2 ml^{-1} ; Jiangsu Hengrui Medicine Co., Ltd.) and saline were provided in identical, pre-packed masked bottles. Independent drug encoding was handled by Jiangsu Hengrui Medicine Co., Ltd. In emergencies, treatment allocation could be unmasked by attending anaesthesiologists or intensivists to adjust doses or interrupt infusion, with all

procedures documented. Study medications were diluted with saline to 50 ml before administration. Dexmedetomidine at 8 $\mu\text{g ml}^{-1}$ concentration, or the same volume of saline, was continuously infused at 0.05 $\text{ml kg}^{-1} \text{h}^{-1}$ (0.4 $\mu\text{g kg}^{-1} \text{h}^{-1}$) i.v. The intervention commenced after anaesthesia induction and lasted for 12 h.

Clinical care

Perioperative monitoring and management followed the routine procedures of each centre and were at the discretion of the attending anaesthesiologists, with a general goal of maintaining mean arterial pressure (MAP) >65 mm Hg, central venous pressure 8–10 mm Hg, and cardiac index >2.2 $\text{L min}^{-1} \text{m}^{-2}$. Haemodynamics were closely monitored with transoesophageal echocardiography, central venous or pulmonary artery catheters, and radial artery catheter. Anaesthesia was maintained with volatile agents or propofol, and neuromuscular blocking agents used included rocuronium or cisatracurium. Traditional midline sternotomy open-heart procedure or thoracoscopy-assisted mini-invasive intercostal incision procedure were considered. CPB was supported by a membrane oxygenator and maintained MAP of 65–75 mm Hg. Dexmedetomidine infusion rates could be adjusted by anaesthesiologists or ICU physicians, with sedatives allowed, but no other α_2 -agonists.

Primary outcome

The co-primary outcomes were postoperative in-hospital mortality and major morbidities, including permanent or transient stroke, coma, perioperative MI, heart block, and cardiac arrest (details in Supplementary material).

Secondary outcomes

Secondary outcomes were each individual complication included in the co-primary outcome, plus new atrial fibrillation, acute kidney injury (AKI, defined by Kidney Disease: Improving Global Outcomes group), renal failure (stage 3 and AKI requiring RRT), and infections. Other prespecified outcomes include postoperative length of hospital stay (LOS), length of ICU stay, and incidence of respiratory failure (defined as the need for mechanical ventilation over 48 h).

Safety outcomes

We recorded episodes of hypotension and bradycardia (heart rate <50 beats min^{-1}) that required intervention or treatment.

Exploratory outcomes

We also recorded 30-day and 1-yr complications such as mortality, major complications, atrial fibrillation, unplanned re-operation, and postoperative delirium (assessed with Confusion Assessment Method for ICU). Follow-ups were made by phone calls at 30 days and 1-yr. For patients lost to follow-up, their families, attending general practitioners, or surgeons were contacted by telephone or e-mail.

Sample size

Sample sizes were calculated for each endpoint independently, with the final sample size determined based solely on in-hospital mortality estimates, owing to its lower event rate.

On the basis of previous studies^{2,17,18} we estimated that the in-hospital mortality would be 4.5% of the patients in the placebo group. We calculated that a sample size of 550 in each group (1100 patients in total) would provide 90% power to detect a 3.2% absolute reduction in the risk of in-hospital mortality (decreasing to 1.3%, corresponding to Cohen's $d=0.2$)² in the dexmedetomidine group compared with the placebo group, using a two-sided alpha of 0.05. This calculation accounted for a 10% dropout rate. No interim analysis was planned.

Statistical analysis

Continuous data were described as mean (standard deviation [SD]) or median (interquartile range [IQR]), with comparisons using t-tests, Mann–Whitney tests, or Kruskal–Wallis tests. Normality was assessed using the Shapiro–Wilk test. Categorical data were presented as counts (percentages) (n [%]), and compared using Fisher's exact or χ^2 tests. Variables with between-group absolute standardised differences (ASDs) >0.12 were considered imbalanced and was adjusted in analyses, derived from the formula $1.96 \times \sqrt{[(550+550)/(550 \times 550)]}$.

In accordance with the prespecified statistical plan (Supplementary material), the primary analysis utilised a modified intention-to-treat population, including randomised patients who underwent the planned surgery, irrespective of the actual intervention received, unless consent was withdrawn. The co-primary endpoints were compared using two-tailed χ^2 tests or Fisher's exact test, as appropriate, and were expressed as risk differences (RDs) with 95% confidence intervals (CIs). The intervention effect was estimated using log-binomial or logistic regression as appropriate and expressed with odds ratios (ORs) or relative risks (RRs), with 95% CIs. To ensure the robustness of the results, prespecified sensitivity analyses included an assessment of treatment effect heterogeneity across participating centres using the Cochran–Mantel–Haenszel test and mixed-effect models. For secondary outcomes, proportions were compared using the same methods as in the primary analyses. The intervention effects on continuous variables (length of hospital and ICU stays) were estimated using linear regression, with the coefficient and 95% CIs reported. These were further treated as time-to-event variables where hazard ratios (HRs) and 95% CIs were derived from Cox proportional hazards models.

Subgroup and exploratory analyses are detailed in Supplementary material and Supplementary Figure 1.

No missing values were imputed. Statistical significance was required for both co-primary endpoints ($\alpha=0.05$ for each, without multiplicity adjustment). No multiple comparisons adjustment was made for secondary endpoints, and therefore should be interpreted as exploratory. All analyses were performed in R 4.1.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

From April 2014 to March 2017, from a total of 3642 patients screened for eligibility, 1100 were enrolled. After randomisation, 14 participants randomised to receive dexmedetomidine, and 12 participants randomised to placebo, had their surgeries cancelled, changed, or they withdrew consent to participate. The modified intention-to-treat population included 1073 participants (Table 1, Fig. 1), with 911

Table 1 Participant characteristics. Data are reported as median (interquartile range) or *n* (%). *Intraoperative complications include hypotension (SBP ≤ 90 mm Hg or a $>30\%$ decrease from baseline), hypertension (SBP ≥ 180 mm Hg or a $>30\%$ increase from baseline), bradycardia (HR <50 beats min^{-1}), tachycardia (HR >120 beats min^{-1}), hypoxia (partial pressure of arterial oxygen <60 mm Hg), new-onset arrhythmia requiring intervention or treatment, need for mechanical circulatory support (including IABP, extracorporeal membrane oxygenation, VAD, such as Impella, or permanent pacemaker), cardiac dysfunction with unsuccessfully weaning from cardiopulmonary bypass, requiring reinitiation of CPB, massive bleeding, thrombotic events, intraoperative death, and any other adverse events or complications. CABG, coronary artery bypass grafting; CK-MB, creatine kinase-myocardial band; COPD, chronic obstructive pulmonary disease; CPB, cardiopulmonary bypass; Dex, dexmedetomidine group; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; Hb, haemoglobin; HR, heart rate; IABP, intra-aortic balloon pump; MAP, mean arterial pressure; MI, myocardial infarction; Non-Dex, non-dexmedetomidine group; SBP, systolic blood pressure; VAD, ventricular assist device.

	Overall (n=1073)	Dex (n=536)	Non-Dex (n=537)
Patient characteristics			
Age, mean (range) (yr)	54.4 (48.0–63.0)	54.2 (47.0–63.0)	54.6 (48.0–63.0)
Sex			
Male	579 (54.0)	292 (54.5)	287 (53.4)
Female	494 (46.0)	244 (45.5)	250 (46.6)
Systolic blood pressure (mm Hg)	129 (115–148)	130 (115–150)	128 (116–146)
Diastolic blood pressure (mm Hg)	74.0 (65.0–82.0)	73.0 (65.0–83.0)	74.0 (66.0–82.0)
Weight (kg)	62.6 (11.1)	62.4 (11.2)	62.8 (11.1)
BMI (kg m^{-2})	22.8 (19.0–28.1)	22.4 (19.0–28.1)	23.1 (19.1–28.7)
Current smoking	456 (33.2)	182 (34.0)	174 (32.4)
Baseline lab tests			
Creatinine (μM)	83.0 (67.0–95.0)	83.0 (67.0–96.0)	82.0 (66.0–94.9)
CK-MB (U L^{-1})	12.3 (10.0–16.0)	12.3 (10.0–16.0)	12.5 (10.0–16.0)
Cardiac history			
Angina	148 (13.8)	69 (12.9)	79 (14.7)
Congestive heart failure	71 (6.62)	37 (6.90)	34 (6.33)
Previous MI	55 (5.13)	28 (5.22)	27 (5.03)
Atrial fibrillation	343 (32.0)	168 (31.3)	175 (32.6)
Previous cardiac surgery	43 (4.01)	22 (4.10)	21 (3.91)
EuroSCORE II	1.04 (0.80–1.51)	1.02 (0.80–1.58)	1.10 (0.80–1.50)
Other medical history			
Stroke	86 (8.01)	40 (7.46)	46 (8.57)
Diabetes mellitus	91 (8.48)	38 (7.09)	53 (9.87)
Hypertension	271 (25.3)	132 (24.6)	139 (25.9)
Dyslipidaemia	44 (4.10)	19 (3.54)	25 (4.66)
Peptic ulcer disease	32 (2.98)	16 (2.99)	16 (2.98)
Previous gastrointestinal bleed	7 (0.65)	1 (0.19)	6 (1.12)
Peripheral arterial disease	20 (1.86)	8 (1.49)	12 (2.23)
Chronic renal failure	1 (0.09)	0 (0.00)	1 (0.19)
Any coagulopathy	9 (0.84)	1 (0.19)	8 (1.49)
COPD	20 (1.86)	10 (1.87)	10 (1.86)
Preoperative status			
Preoperative inotropes or vasopressors	32 (2.98)	17 (3.17)	15 (2.79)
Preoperative IABP or VAD	1 (0.09)	0 (0.00)	1 (0.19)
Surgical incision			
Median sternotomy	938 (87.4)	467 (87.1)	471 (87.7)
Minimally invasive intercostal incision	125 (11.6)	65 (12.1)	60 (11.2)
Surgical procedure			
Isolated single valve	458 (42.7)	225 (41.9)	233 (43.5)
Aortic valve	207 (19.3)	100 (18.7)	107 (19.9)
Mitral valve	231 (21.5)	117 (21.8)	114 (21.2)
Tricuspid valve	18 (1.68)	8 (1.49)	10 (1.86)
Isolated CABG	114 (10.6)	59 (11.0)	55 (10.3)
Multiple valves	419 (39.0)	215 (40.0)	204 (38.1)
Combined valve+CABG	73 (6.80)	33 (6.15)	40 (7.46)
Other	8 (0.75)	5 (0.93)	3 (0.56)
Missing	1 (0.09)	0 (0.00)	1 (0.19)
Intraoperative adverse events			
Intraoperative complications*	50 (4.66)	23 (4.29)	27 (5.03)
Death	1 (0.09)	0 (0.00)	1 (0.19)
CPB information			
Total CPB time (min)	119 (89.0–152)	120 (91.0–153)	118 (88.8–148)
Cross-clamp time (min)	69.0 (51.0–93.0)	69.0 (50.0–93.0)	70.0 (51.0–92.2)
Lowest Hb during CPB (g dl^{-1})	7.90 (7.10–8.88)	8.00 (7.10–9.00)	7.90 (7.00–8.80)
Lowest MAP during CPB (mm Hg)	45.0 (40.0–51.0)	45.0 (40.0–53.0)	44.0 (39.0–50.0)
Lowest temperature during CPB ($^{\circ}\text{C}$)	31.2 (30.0–32.8)	31.2 (30.0–32.9)	31.1 (30.0–32.7)
Antifibrinolytic use	1068 (99.5)	532 (99.3)	536 (99.8)

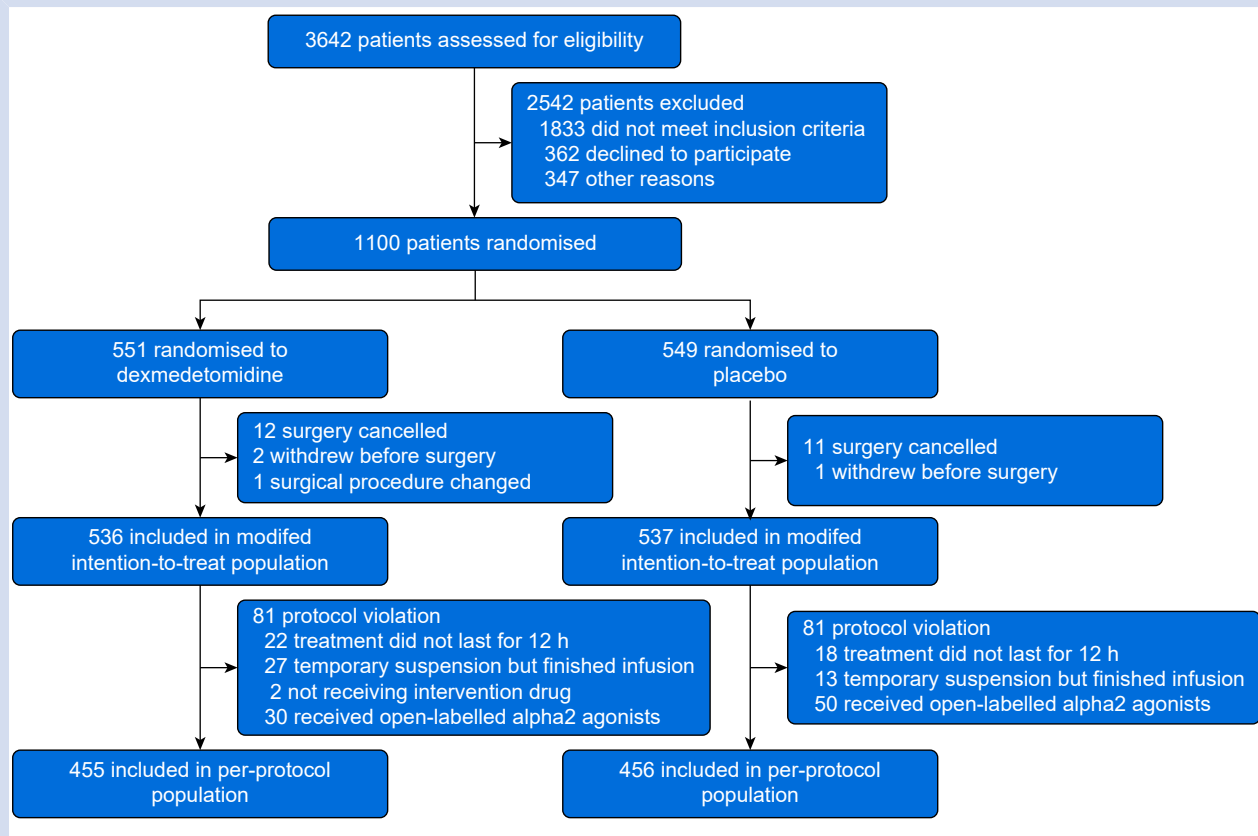


Fig 1. Study flowchart. A total of 1100 participants were randomised, and 1073 patients received the allocated study medication were included in the full analysis set, and 911 patients completed the study were included in the per-protocol set.

Table 2 Primary and secondary outcomes. Data are reported as median (interquartile range) or n (%). *Major morbidities include stroke, MI, coma, heart block, and cardiac arrest. [†]RR estimated via log-binomial regression as rate is greater than 30%. [‡]Both LOS and ICU stay are estimated as continuous variables, where the RD column reports the mean difference and OR column refers to the β -coefficient of log-transformed linear regression. CI, confidence interval; Dex, dexmedetomidine group; LOS, length of stay; Non-Dex, non-dexmedetomidine group; OR, odds ratio; RD, risk difference; RR, relative risk.

	Overall (n=1073)	Dex (n=536)	Non-Dex (n=537)	RD (95% CI) (%)	OR/RR (95% CI)	P-value
Primary outcome						
Death	25 (2.33)	10 (1.87)	15 (2.79)	-0.92 (-2.73 to 0.88)	0.66 (0.29–1.49)	0.421
Major morbidities*	330 (30.8)	161 (30.0)	169 (31.5)	-1.43 (-6.96 to 4.09)	0.93 (0.72–1.21) [†]	0.658
Secondary outcomes						
Stroke	8 (0.75)	4 (0.75)	4 (0.74)	0.00 (-1.03 to 1.03)	1.00 (0.25–4.03)	1.000
Myocardial infarction	298 (27.8)	145 (27.1)	153 (28.5)	-1.44 (-6.80 to 3.92)	0.94 (0.72–1.22) [†]	0.674
Coma	4 (0.37)	2 (0.37)	2 (0.37)	0.00 (-0.73 to 0.73)	1.00 (0.14–7.09)	1.000
Heart block	32 (2.98)	10 (1.86)	22 (4.10)	-2.23 (-4.26 to -0.20)	0.46 (0.22–0.95)	0.048
Cardiac arrest	19 (1.77)	9 (1.68)	10 (1.87)	-0.18 (-1.76 to 1.40)	0.90 (0.37–2.17)	0.997
New-onset atrial fibrillation	55 (5.13)	22 (4.10)	33 (6.15)	-2.04 (-4.68 to 0.60)	0.65 (0.38–1.14)	0.171
Acute kidney injury	416 (38.8)	197 (36.8)	219 (40.8)	-4.03 (-9.85 to 1.80)	0.85 (0.66–1.08) [†]	0.205
Renal failure	25 (2.33)	11 (2.05)	14 (2.61)	-0.55 (-2.36 to 1.25)	0.79 (0.35–1.75)	0.700
Infection	311 (29.0)	166 (31.0)	145 (27.0)	3.97 (-1.46 to 9.39)	1.22 (0.94–1.59) [†]	0.154
Respiratory failure	77 (7.18)	37 (6.90)	40 (7.45)	-0.55 (-3.63 to 2.54)	0.92 (0.58–1.47)	0.826
Postoperative LOS (days) [‡]	11.0 (9.0–15.0)	11.0 (9.0–15.0)	11.0 (9.00–14.0)	0.00 (-1.00 to 1.00)	-0.02 (-0.04 to 0.07)	0.703
Postoperative ICU stay (h) [‡]	43.0 (37.0–65.5)	43.0 (30.8–63.2)	44.0 (38.0–67.0)	-1.21 (-251.19 to 248.78)	-1.21 (-12.11 to 9.69)	0.226

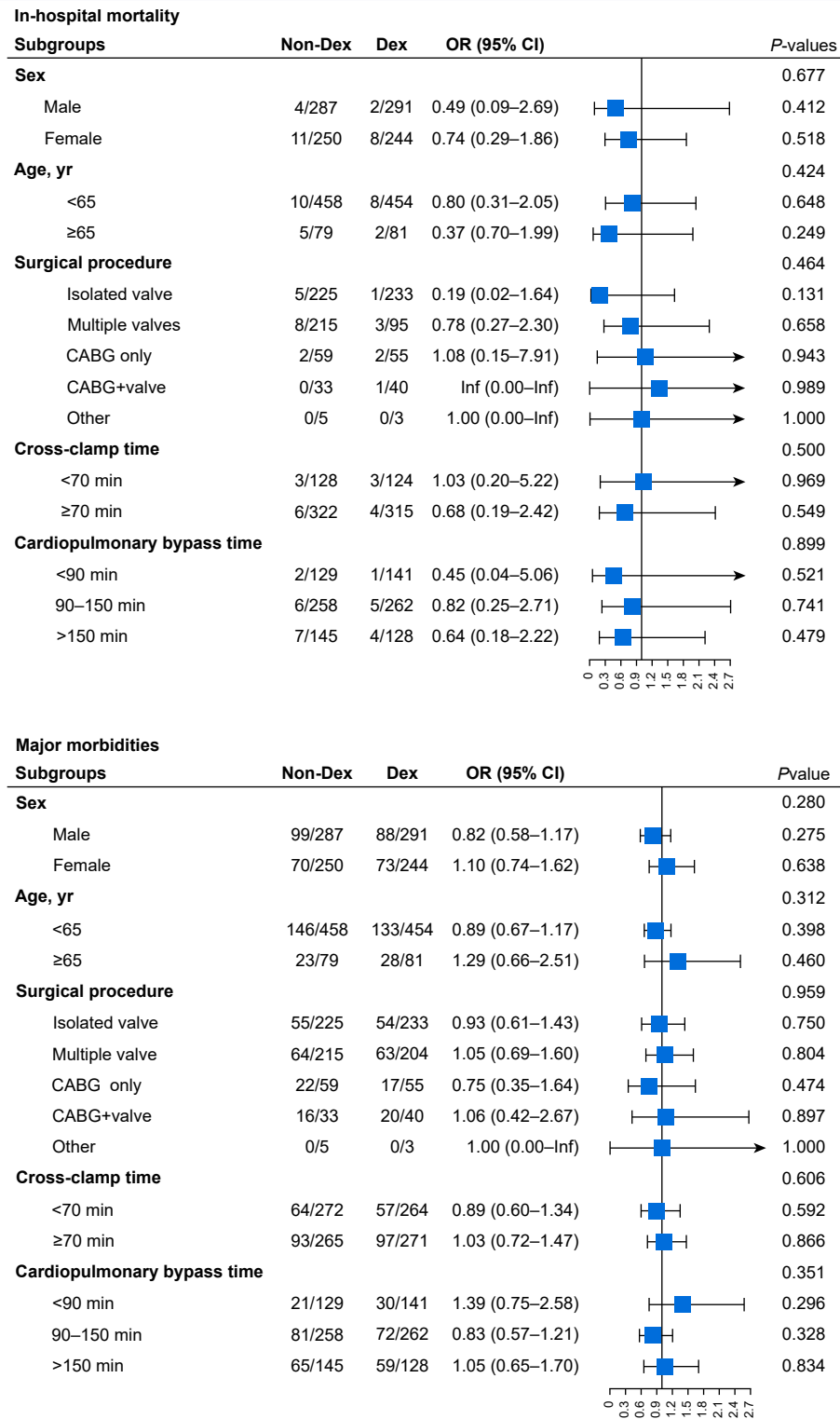


Fig 2. Prespecified subgroup analyses on sex, age, surgical procedure, cross-clamp time, and cardiopulmonary bypass time. Outcomes of in-hospital mortality and major morbidities, analysed separately. P-values refer to interaction effects across subgroups, and for each subgroup individually. CABG, coronary artery bypass grafting; CI, confidence interval; Dex, dexmedetomidine group; Non-Dex, non-dexmedetomidine group.

participants (84.9%) completing the trial without any protocol violations (Supplementary Tables 1 and 2).

Co-primary outcomes

In-hospital mortality occurred in 10/536 (1.87%) participants who received dexmedetomidine, compared with 15/537 (2.79%) participants who received saline placebo (OR: 0.66 [95% CI: 0.29–1.49]; Table 2; Supplementary Figs 2 and 3). Major complications developed in 161/536 (30.0%) participants who received dexmedetomidine, compared with 169/537 (31.5%) participants who received saline placebo (RR: 0.93 [95% CI: 0.72–1.21]; $P=0.658$; Table 2). Similar results were found in the per-protocol and all sensitivity analyses (Supplementary Tables 3–6, Supplementary Figs 2–7).

Secondary outcomes

Major complications did not differ between participants who received dexmedetomidine, compared with participants who received saline placebo (Table 2). The incidence of heart block was higher in the participants who received the saline placebo.

Safety measures

Hypotension occurred in 41 participants (7.65%) who received dexmedetomidine, compared with 32 participants (5.96%) who received the saline placebo. The incidence of bradycardia was similar between both groups (Supplementary Table 7).

Subgroup analyses

Subgroup analyses, including 1-yr follow-up, mirrored the results of the co-primary and secondary outcome analyses (Fig. 2; Supplementary Fig. 8).

Discussion

In this multicentre trial, death and major complications did not differ between patients who randomly received dexmedetomidine compared with saline placebo. None of the co-primary endpoints—in-hospital all-cause mortality or major morbidities (including permanent or transient stroke, coma, MI, heart block, and cardiac arrest)—were different. Secondary outcomes were also comparable between groups. These data suggest that perioperative administration of dexmedetomidine does not reduce the incidence of in-hospital mortality or major morbidities after cardiac surgery with CPB.

Cardiac surgery with CPB can trigger significant systemic inflammation, leading to organ dysfunctions,^{19,20} and severe postoperative complications.²¹ Dexmedetomidine may help mitigate this by reducing the hypothalamic–pituitary–adrenal axis and sympathoadrenal tone, and alleviating surgical stress and inflammation,^{8,22} potentially protecting against myocardial, neuronal, pulmonary, and renal injury.^{12,22–24} These effects, together with its cytoprotective effects, may reduce postoperative complications such as AKI, delirium, and atrial fibrillation, which are linked to higher mortality.^{25–27}

Several observational studies and meta-analyses suggested reduced mortality and complications (AKI, delirium, and atrial fibrillation) with perioperative dexmedetomidine in cardiac surgical patients.^{2,11–13,28} However, DOCS indicated no statistically significant differences in in-hospital mortality between dexmedetomidine and placebo. The observed 1% difference

suggested that the study may have been underpowered to detect a survival effect. This can be attributed to the substantial reduction in observed mortality (2.33%) compared with the anticipated rate of 4.5%. Although this mortality is lower than previous reports,² it aligns with a more recent cardiac surgery study.²⁹ The observed mortality reduction may reflect improved perioperative care standards. Additionally, this may also reveal the heterogeneity in patient risk profile across participating centres (Xijing Hospital, 3.9% vs 1.4% in other centres).³⁰

To our knowledge, this is the largest randomised trial exploring perioperative use of dexmedetomidine in cardiac surgery, which helps to mitigate the fragility in smaller trials and enhances robust findings. However, the probability of a false negative finding remains owing to reduced statistical power, stemming from the lowered-than-expected event rate. The ACCEPT curve demonstrated that, at the prespecified unacceptable threshold of zero, the probability that dexmedetomidine is superior to placebo in reducing mortality was 84% (Supplementary Fig. 9), falling short of the 97.5% threshold (one-sided significance of 0.025). This further supports the negative results indicated by the primary analysis.

Previous studies reported that dexmedetomidine may lower mortality in cardiac surgery patients.^{2,11} However, no guidelines currently recommend its perioperative use.^{14,15} In observational studies, perioperative dexmedetomidine (0.24–0.6 $\mu\text{g kg}^{-1}$ per hour) administered after CPB and continued for <24 h decreased postoperative mortality in older patients (mean age 63).^{2,11,12} This inherent observational design rendered the study susceptible to selection bias, confoundings, and variability in dexmedetomidine dosage and duration. A previous meta-analysis of 48 studies also showed reduced postoperative mortality. However, it included both observational studies and randomised trials and the benefits disappeared after excluding non-randomised trials.

The divergent results observed may be attributed to differences in patient profiles. In DOCS, a wide range of procedures (valve, CABG, and combined procedures) were included, resulting in a study population with a heterogeneous risk profile for postoperative complications. A retrospective study of CABG patients also reported no association between dexmedetomidine use and 30-day mortality, which is consistent with our findings.³¹ DOCS enrolled younger (mean age 55) and generally healthier patients, with fewer comorbidities, in China, compared with patients undergoing similar surgical procedures in Western countries. For example, in our previous observational study using US registry data,² the mean age was 63 yr old. Age-related changes in the pharmacokinetics and pharmacodynamics of dexmedetomidine may affect its response.^{32,33} This may translate into different responses to drug administration as demonstrated in the Early Sedation with Dexmedetomidine in Critically Ill Patients (SPICE III) trial, where mortality was reduced in older adults (median age >63.7) but increased in younger patients, highlighting age-dependent treatment effects.³⁴ Small RCTs in cardiac surgery patients had heterogeneous methodologies, making interpretation challenging. Even with recent evidence on reduced short-term mortality from a trial sequential analysis during 1990–2022,³⁵ variations in dosing, timing, and duration of administration remain. The short-acting nature of dexmedetomidine may limit its benefits after discontinuation, highlighting the need for optimal dosing protocols.^{36,37}

A positive association with dexmedetomidine was only seen for infusions longer than 12 h,^{2,10} whereas the timing of

administration also contributed to variability in postoperative outcomes.^{10,36,38,39} Many studies also reported decreased atrial fibrillation,^{13,28,40} delirium,^{41,42} AKI,^{9,12,43} ICU stay, and tracheal intubation by facilitating conscious sedation with no respiratory depression.⁴⁴ However, the more recently published DEXmedetomidine for reduction of Atrial fibrillation and Delirium after cardiac surgery (DECADE) suggested otherwise: dexmedetomidine infusion (started from anaesthetic induction and lasting for 24 h) did not reduce atrial arrhythmias or delirium in cardiac surgical patients,⁴⁵ consistent with our findings.

Our study has several limitations. First, the lower-than-expected event rate may reduce the statistical power of the findings. However, this potentially reflects improved perioperative care standards during the trial period. It may also reveal the heterogeneity in the risk profile for in-hospital mortality among the participating centres. Second, approximately 15% of participants met protocol violations. Although these violations reflect real-world clinical practice, they introduce potential biases, despite the robust results observed across different analytical sets. Among patients with protocol violations, a greater proportion in the dexmedetomidine group temporarily halted the infusion because of medical decisions based on haemodynamic instability, whereas more patients in the placebo group received open-label dexmedetomidine for ICU sedation. These findings reflect the haemodynamic and sedative effects of dexmedetomidine. Such violations may dilute the treatment effects and potentially lead to unblinding of ICU physicians. However, this is an inherent issue of clinical practice when comparing an active drug with a placebo. Outcome assessors were not involved in postoperative care. Third, DOCS primarily enrolled younger patients undergoing valve replacement for rheumatic heart disease, which differs from typical Western cardiac surgery.^{2,11,28,45} This may explain the lower-than-expected postoperative mortality.^{2,11,28} Despite these limitations, the DOCS trial provides valuable evidence regarding the adjunctive use of dexmedetomidine perioperatively in CPB-assisted cardiac surgery patients across China.

In summary, we found that perioperative adjunctive use of dexmedetomidine, starting at induction of anaesthesia and continued for 12 h, did not reduce in-hospital mortality or postoperative major morbidities in adults undergoing cardiopulmonary bypass-assisted cardiac surgery.

Authors' contributions

Conceptualised the study: CLei, HL, HD

Revised and finalised the protocol: CLei, ZZ, C. Li, JX, LW, HL, HD

Conducted the trial, screened patients and collected patients' data in each participating centre: CLei, JH, LW, WZ, SW, XG, TZ, J. Zhou, J. Zou, YT, XC, LQ, MX, XZ, WH, YC, MY, HW

Conducted standardised anaesthesia for the most cases: JH, LW, WZ, LH

Screened patients and conducted surgery: SY, JL, XX

Led the data analysis: ZZ, CL, JX, LW

Led data interpretation: CLei, ZZ, HL, HD

Conducted data analyses and visualised the data: ZZ

Drafted the first report and verified the underlying data: CLei and ZZ

Critically reviewed and revised the initial draft: HL, HD

Gave final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that

questions related to the accuracy and integrity of any part of the work are appropriately investigated and resolved: all authors

Declaration of interest

The authors declare that they have no conflicts of interest.

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Data availability statement

De-identified data may be requested for appropriate and approved study proposals from the corresponding author.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.bja.2025.09.026>.

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