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Perioperative dexmedetomidine and 5-year survival in patients undergoing cardiac surgery

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Abstract

Background: Dexmedetomidine sedation has been associated with favourable outcomes after surgery. We aimed to assess whether perioperative dexmedetomidine use is associated with improved survival after cardiac surgery.
Methods: This retrospective cohort study included 2068 patients undergoing on-pump coronary artery bypass grafting and/or valve surgery. Among them, 1029 patients received dexmedetomidine, and 1039 patients did not. Intravenous dexmedetomidine infusion of 0.007 μg kg^{-1} min^{-1} was initiated before or immediately after cardiopulmonary bypass and lasted for < 24 h. The primary outcome was 5-year survival after cardiac surgery. The propensity scores matching (PSM), inverse probability of treatment weighting (IPTW), and overlap weighting approaches were used to minimise bias. Survival analyses were performed with Cox proportional-hazard models.
Results: The median age was 63 yr old and the male to female ratio was 71:29 in both groups. Baseline covariates were balanced between groups after adjustment using PSM, IPTW, or overlap weighting. Patients receiving dexmedetomidine in cardiac surgical procedures had higher survival during postoperative 5 yr in unadjusted analysis (hazard ratio [HR]=0.63; 95% confidence interval [CI], 0.51–0.78; *P*<0.001), and after adjustment with PSM (HR=0.63; 95% CI, 0.45–0.89; *P*=0.009), IPTW (HR=0.70; 95% CI, 0.51–0.95; *P*=0.023), or overlap weighting (HR=0.67; 95% CI, 0.51–0.89; *P*=0.006). The 5-yr mortality rate after cardiac surgery was 13% and 20% in the dexmedetomidine and non-dexmedetomidine groups, respectively (PSM adjusted odds ratio=0.61; 95% CI, 0.42–0.89; *P*=0.010).
Conclusion: Perioperative dexmedetomidine infusion was associated with improved 5-yr survival in patients undergoing cardiac surgery.

Keywords: cardiac surgery; complications; dexmedetomidine; long-term survival; postoperative outcomes

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Editor's Key Points

- Morbidity and mortality are common complications of cardiac surgery.
- Dexmedetomidine has shown promise as a sedative in critically ill patients, but whether it has advantages over alternative sedatives after cardiac surgery is unknown.
- This observational study, using sophisticated matching techniques in an attempt to balance groups, found that dexmedetomidine use was associated with markedly superior outcomes including less death up to 5 yr after cardiac surgery.
- Despite the impressive statistical methods, we must remain sceptical about substantial benefit attributable merely to the choice of sedative agent after cardiac surgery, and rigorous prospective trials are needed to assess these provocative findings.

Based on the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database, morbidity and mortality are common within the first few months to years after cardiac surgery.[1] For patients undergoing isolated coronary artery bypass grafting (CABG), each postoperative complication, such as atrial fibrillation, prolonged ventilation, reoperation, renal failure, stroke and deep sternal wound infection, substantially increased the healthcare costs.[2]

Dexmedetomidine is a highly selective α2-adrenergic agonist that produces sedative, analgesic, and sympatholytic properties and anti-inflammatory and organ protective effects.[3–5] Previous studies showed that perioperative use of dexmedetomidine was associated with improved postoperative outcomes and 1-year mortality after cardiac surgery.[6,7] Specifically, patients who received dexmedetomidine infusion, compared with those who did not, had fewer overall postoperative complications (47% vs. 54%) and a lower 1-year mortality rate (3% vs. 8%).[6] To date, the effect of dexmedetomidine on postoperative long-term outcomes after cardiac surgical procedures has been investigated, but has not been fully elucidated.[8,9]

Therefore, we aimed to evaluate the effects of perioperative dexmedetomidine infusion on postoperative morbidity and long-term survival up to 5 yr after surgery in a large cohort of patients who underwent cardiac surgery. We hypothesized that the use of dexmedetomidine would be associated with reduced postoperative major complications and improved 5-yr survival after cardiac surgery.

Methods

This is a single-centre, retrospective, cohort study involving 2452 consecutive patients who underwent cardiac surgery at a tertiary university hospital (UC Davis Medical Center) from January 1, 2004 to April 30, 2014. The study protocol was approved by the local Institutional Review Board and then registered at ClinicalTrials.gov (identifier: NCT01683448). The inclusion criteria of this study were: on-pump CABG, valve surgery or both with or without other procedures. The exclusion criteria were: emergency surgery, off-pump or robotic assisted surgery, thoracic aorta surgery, or other procedures other than CABG, valve surgery or both.

Whether or not a patient would receive dexmedetomidine as an anaesthetic adjuvant was at the discretion of the attending anaesthesiologist. The use of dexmedetomidine was to provide better sedation, analgesia, and anti-inflammation for patients who underwent cardiac surgery. An i.v. infusion of dexmedetomidine 0.007 μg kg^{-1} min^{-1}, without a loading dose, was initiated before or immediately after cardiopulmonary bypass and continued until extubation or for < 24 h. The dose of dexmedetomidine used for each patient was adjusted based on the patient's haemodynamic responses. In addition, the practice of dexmedetomidine use was consistent over the period of this study. Perioperative monitoring and anaesthesia management were left to the discretion of the attending anaesthesiologists.

Data collection

Two authors independently screened hospital medical records and the institutional STS National Adult Cardiac Surgery Database to extract the following data for each patient: patient characteristics, medical history, preoperative medications, procedural characteristics, and clinical outcomes. Investigators who were not involved in this study prospectively collected the data of patients during the hospitalization period. Outcomes were ascertained by the STS Adult Cardiac Surgery Database Data Specifications and data were collected by using the Data Collection Form.[10,11]

Patient characteristics included age, sex, body mass index (BMI), and race. Medical history data included status of current smoking, coronary artery disease, chronic lung disease, cerebrovascular disease, peripheral vascular disease, diabetes, hypercholesterolaemia, hypertension, renal failure, dialysis, atrial fibrillation, chronic heart failure, myocardial infarction (MI), ejection fraction, and last preoperative creatinine concentration. Data on preoperative medications included the use of angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), aspirin, beta blockers, antiplatelet agents, warfarin, inotropes, nitrates, and lipid lowering drugs. Procedural characteristics included status of surgery (urgent or elective), cardiopulmonary bypass time, cross clamp time, use of intra-aortic balloon pump (IABP), surgery type (CABG, valve or both with or without other), and vessels bypassed.

Study outcomes

The primary outcome of this study was postoperative 5-yr survival after cardiac surgery. All-cause death after surgery was determined based on the STS database, hospital medical records, and the Social Security Death Index.[12,13] The survival time was defined as the time from the day of cardiac surgery to the day when postoperative death occurred or the patient was censored (death did not occur until 5 yr after surgery).[14]

The secondary outcomes included the incidence of any complication, perioperative myocardial infarction (MI), heart block, cardiac arrest, stroke, coma, major adverse cardiovascular events (MACE, a composite outcome of perioperative MI, heart block, cardiac arrest, stroke, and coma), delirium, sepsis, new-onset atrial fibrillation, gastrointestinal complications, postoperative dialysis, renal failure, multiorgan failure, reoperation, ICU readmission, and 30-day readmission, as well as mechanical ventilation time, length of ICU stay, and length of

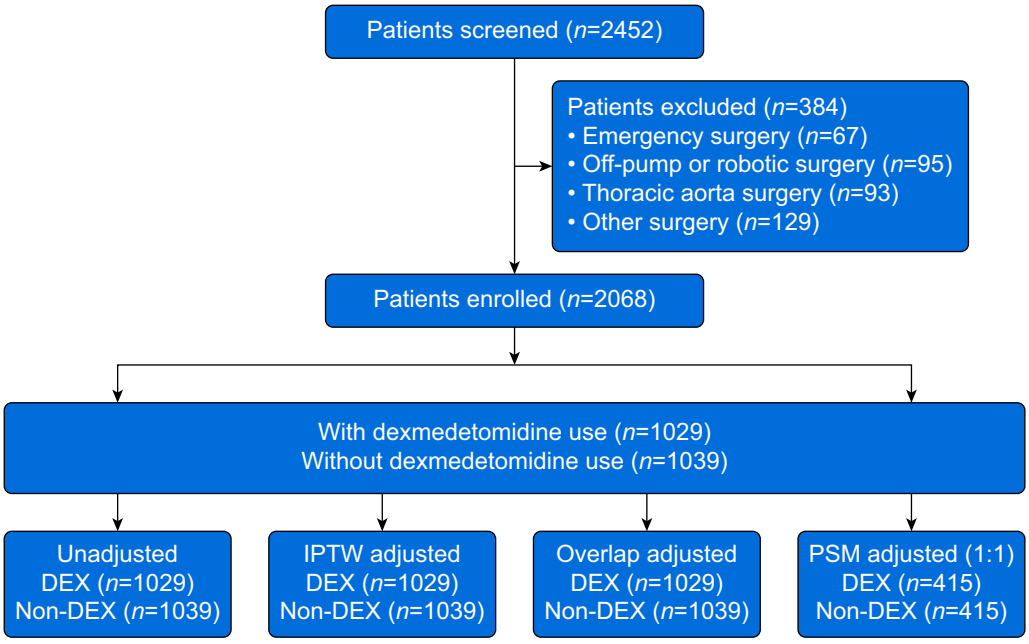

Fig 1. Study flow diagram. DEX, dexmedetomidine; IPTW, inverse probability of treatment weighting; PSM, propensity score matching.

postoperative hospital stay. The outcomes were defined by the STS national criteria (Supplementary Table S1).[11]

Statistical analysis

For adjusting between-group differences, the propensity scores were developed to reflect the probability of each patient receiving dexmedetomidine, with the use of multivariable logistic regression based on patients' characteristics and clinical risk factors.[15] Three adjustment approaches based on propensity scores were used, including inverse probability of treatment weighting (IPTW), overlap weighting, and propensity scores matching (PSM).[16] The IPTW or overlap weighting method was used to assess the average intervention effect in the study patients. For IPTW, we applied the inverse propensity score as weights for patients who received dexmedetomidine and the inverse of 1 minus the propensity score for patients who did not. For overlap weighting, we applied 1 minus the propensity score as weights for patients who received dexmedetomidine and the propensity score for those who did not. In addition, the PSM approach was used to estimate the intervention effect for the specific groups of one to one matching patients, with a greedy matching algorithm (a caliper width of 0.2 of the pooled standard deviation [SD]). The successful balance of covariates after adjustment was confirmed by using a bootstrap method and propensity score histograms.

Continuous variables are presented as median (interquartile range, IQR) or mean (SD), and categorical variables are shown as n (%). Patients' demographic, clinical, and procedural characteristic data were analysed using the Wilcoxon rank-sum test or the Pearson chi-square test. Postoperative outcomes were analysed using univariate logistic regression or generalised linear models. Data were then adjusted with IPTW, overlap weighting, or PSM based on the propensity score. Furthermore, we performed Kaplan-Meier curves and survival analyses with the use of Cox proportional-hazard models to demonstrate the effects of dexmedetomidine on long-term survival after cardiac surgery. Because the data of mechanical ventilation time, length of ICU stay, and length of postoperative hospital stay appear to be over-dispersed, the studentized Breusch-Pagan test was performed to assess the heteroskedasticity. We did not perform adjustment for multiple testing of secondary outcomes, and we reported these results only as point estimates with unadjusted 95% confidence interval (CI).[17] Hence, there should be no definite clinical inferences from the secondary outcomes.

Difference, odds ratio (OR), or hazards ratio (HR) with 95% CIs are used to show the effect size of a comparison. All statistical analyses were conducted with the SAS software (version 9.4, SAS Institute Inc., Cary, NC, USA) and R statistical software (version 3.6.0, R Foundation for Statistical Computing, Vienna, Austria). A two-tailed P value <0.05 was considered statistically significant.

Results

A total of 2068 patients were finally included in this study (Fig. 1). Among them, 1029 patients received dexmedetomidine infusion during the perioperative period, and 1039 patients did not. The two groups had similar patient characteristics (Table 1). However, several clinical characteristics including medical history, preoperative medication, and procedures differed significantly between the two groups. A greater number of patients in the dexmedetomidine group had history of chronic heart failure, whereas more patients in the Non-dexmedetomidine group had history of current smoking, coronary artery disease, renal failure, and MI. Preoperative

Table 1 Patient characteristic, clinical, and procedural characteristics. Data are median (inter-quartile range), mean (standard deviation), or *n* (%). ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; DEX, dexmedetomidine; IABP, intra-aortic balloon pump; smd, standardised mean difference.

	Unadjusted		P-value	Matched		P-value	SMD
	DEX (*n*=1029)	Non-DEX (*n*=1039)		DEX (*n*=415)	Non-DEX (*n*=415)		
Patient characteristics							
Age, yr	63 (55, 71)	63 (55, 72)	0.5624	64 (56, 72)	62 (56, 72)	0.2068	0.050
Male	730 (71%)	733 (71%)	0.8819	302 (73%)	299 (72%)	0.8766	0.016
BMI, kg m^{-2}	29.0 (5.9)	29.5 (7.1)	0.2553	29.2 (5.8)	29.3 (6.4)	0.7660	0.016
White race	692 (67%)	690 (66%)	0.7197	294 (71%)	271 (65%)	0.1014	0.119
Medical history							
Current smoking	362 (35%)	572 (55%)	<0.0001	197 (48%)	205 (49%)	0.6268	0.039
History of coronary artery disease	228 (22%)	314 (30%)	<0.0001	108 (26%)	99 (24%)	0.5210	0.050
Chronic lung disease	181 (18%)	152 (15%)	0.0765	72 (17%)	70 (17%)	0.9266	0.013
Cerebrovascular disease	164 (16%)	180 (17%)	0.4310	67 (16%)	73 (18%)	0.6430	0.039
Peripheral vascular disease	117 (11%)	141 (14%)	0.1477	53 (13%)	61 (15%)	0.4803	0.056
Diabetes mellitus	379 (37%)	379 (37%)	0.9032	146 (35%)	146 (35%)	1.0000	<0.001
Hypercholesterolaemia	787 (77%)	760 (73%)	0.0899	317 (76%)	326 (79%)	0.5063	0.052
Hypertension	793 (77%)	772 (74%)	0.1577	315 (76%)	322 (78%)	0.6220	0.040
History of renal failure	36 (4%)	69 (7%)	0.0016	27 (7%)	29 (7%)	0.8899	0.019
Dialysis	44 (4%)	32 (3%)	0.1840	17 (4%)	16 (4%)	1.0000	0.012
Atrial fibrillation	161 (16%)	145 (14%)	0.3074	55 (13%)	44 (11%)	0.2842	0.082
Chronic heart failure	428 (42%)	357 (34%)	0.0008	156 (38%)	143 (35%)	0.3856	0.065
Preoperative myocardial infarction	345 (34%)	400 (39%)	0.0210	142 (34%)	138 (33%)	0.8257	0.020
Ejection fraction, %	53 (13)	51 (13)	0.0001	52 (13)	53 (13)	0.9766	0.018
Last creatinine level, mg dl^{-1}	1.3 (1.2)	1.2 (0.9)	0.7209	1.3 (1.1)	1.3 (1.1)	0.9467	0.001
Preoperative medication							
ACEI/ARB	395 (38%)	564 (54%)	<0.0001	195 (47%)	217 (52%)	0.1449	0.106
Aspirin	753 (73%)	761 (73%)	1.0000	305 (74%)	309 (75%)	0.8124	0.022
Beta blockers	676 (66%)	680 (65%)	0.9426	279 (67%)	281 (68%)	0.9409	0.010
Antiplatelets	159 (16%)	199 (19%)	0.0303	105 (25%)	112 (27%)	0.6355	0.038
Warfarin	67 (7%)	62 (6%)	0.6742	32 (8%)	17 (4%)	0.0392	0.154
Inotropes	11 (1%)	15 (1%)	0.5705	4 (1%)	3 (1%)	1.0000	0.026
Nitrates	32 (3%)	58 (6%)	0.0081	18 (4%)	14 (3%)	0.5886	0.050
Lipid lowering	767 (75%)	670 (65%)	<0.0001	297 (72%)	301 (73%)	0.8165	0.021
Procedural characteristics							
Urgent	495 (48%)	595 (57%)	<0.0001	209 (50%)	222 (54%)	0.4045	0.063
Cardiopulmonary bypass time, min	180.8 (75.7)	205.8 (81.5)	<0.0001	194.4 (80.1)	194.2 (80.6)	0.9703	0.003
Cross clamp time, min	123.8 (54.8)	152.0 (59.2)	<0.0001	139.3 (62.0)	138.8 (58.0)	0.7758	0.007
IABP	80 (8%)	162 (16%)	<0.0001	41 (10%)	43 (10%)	0.9084	0.016
Surgery type							0.096
CABG only	483 (47%)	584 (56%)	<0.0001	219 (53%)	227 (55%)	0.8236	
CABG + other	55 (5%)	60 (6%)	0.7410	23 (6%)	22 (5%)	0.8164	
CABG + valve	185 (18%)	232 (22%)	0.0159	84 (20%)	92 (22%)	0.3541	
Valve + (valve + other)	306 (30%)	163 (16%)	<0.0001	89 (21%)	74 (18%)	0.7351	
Vessels bypassed, n	2.1 (2.0)	3.1 (1.9)	<0.0001	2.9 (2.0)	2.9 (2.0)	0.7456	0.034
Year of surgery							0.044
2004 to 2008	170 (17%)	799 (77%)	<0.0001	169 (41%)	178 (43%)	0.5735	
2009 to 2014	859 (83%)	240 (23%)		246 (59%)	237 (57%)		
Surgeons							0.380
Surgeon A	179 (17%)	54 (5%)	<0.0001	3 (1%)	30 (7%)	<0.0001	
Surgeon B	131 (13%)	29 (3%)	<0.0001	18 (4%)	28 (7%)	0.1721	
Surgeon C	133 (13%)	32 (3%)	<0.0001	41 (10%)	31 (8%)	0.2670	
Surgeon D	20 (2%)	190 (18%)	<0.0001	18 (4%)	18 (4%)	1.0000	
Surgeon E	307 (30%)	438 (42%)	<0.0001	188 (45%)	162 (39%)	0.0789	
Surgeon F	165 (16%)	61 (6%)	<0.0001	67 (16%)	57 (14%)	0.3808	
Surgeon G	94 (9%)	235 (23%)	<0.0001	80 (19%)	89 (21%)	0.4905	

ejection fraction and use of lipid-lowering medication were higher in the dexmedetomidine group, whereas use of ACEI/ARB, antiplatelets, and nitrates were higher in the non-dex medetomidine group. In terms of procedural characteristics, the dexmedetomidine group underwent more valve procedures with or without other procedures, whereas the non-dexmedetomidine group had more urgent surgery and IABP use, longer cardiopulmonary bypass and aortic cross clamp time, and a greater number of CABG only and CABG combined with valve procedures. Year of surgery and attending surgeons also differed significantly between the two groups.

After adjustment with the use of PSM, IPTW, or overlap weighting method, the baseline covariates were balanced between groups (Table 1, Supplementary Table S2,

Table 2 Postoperative mortality in unadjusted and matched cohorts. Date are n (%). CI, confidence interval; DEX, dexmedetomidine.

	Unadjusted			P-value	Matched			P-value
	DEX (*n*=1029)	Non-DEX (*n*=1039)	Odds ratio (95% CI)		DEX (*n*=415)	Non-DEX (*n*=415)	Odds ratio (95% CI)	
30-Day mortality	28 (3%)	48 (5%)	0.58 (0.36, 0.92)	0.023	6 (1%)	22 (5%)	0.26 (0.10, 0.61)	0.004
1-Yr mortality	74 (7%)	102 (10%)	0.71 (0.52, 0.97)	0.033	24 (6%)	41 (10%)	0.56 (0.33, 0.94)	0.030
2-Yr mortality	92 (9%)	119 (11%)	0.76 (0.57, 1.01)	0.060	33 (8%)	50 (12%)	0.63 (0.39, 1.00)	0.051
3-Yr mortality	104 (10%)	150 (14%)	0.67 (0.51, 0.87)	0.003	38 (9%)	60 (14%)	0.60 (0.38, 0.91)	0.019
4-Yr mortality	119 (12%)	181 (17%)	0.62 (0.48, 0.79)	<0.001	45 (11%)	68 (16%)	0.62 (0.41, 0.93)	0.021
5-Yr mortality	136 (13%)	210 (20%)	0.60 (0.47, 0.76)	<0.001	56 (13%)	84 (20%)	0.61 (0.42, 0.89)	0.010

Supplementary Fig. S1). The propensity score histograms show that the distribution of propensity score is well balanced after PSM adjustment (Fig. S2).

Primary outcome

The unadjusted analysis shows that perioperative dexmedetomidine infusion was associated with significantly reduced mortality from 30 days to 5 yr after surgery (Table 2). The postoperative 5-year mortality was 13% in the dexmedetomidine group compared with 20% in the non-dexmedetomidine group (OR=0.60; 95% CI, 0.47–0.76; $P<0.001$). After PSM adjustment, postoperative 5-year mortality was still significantly lower in the dexmedetomidine group (OR=0.61; 95% CI, 0.42–0.89; $P=0.010$). The details of the unmatchable patients in the PSM adjusted analysis are shown in Supplementary Table S3. Moreover, the improved 5-year mortality was also evident after adjustment with IPTW (OR=0.67; 95% CI, 0.48–0.94; $P=0.022$) or overlap weighting (OR=0.65; 95% CI, 0.48–0.88; $P=0.006$) (Supplementary Table S4).

In the Kaplan-Meier survival plot, the dexmedetomidine group had a significantly higher survival rate during 5 yr after surgery, with the use of a Cox proportional-hazard model unadjusted analysis (HR=0.63; 95% CI, 0.51–0.78; $P<0.0001$; Fig. 2a) and adjustment with PSM (HR=0.63; 95% CI, 0.45–0.89; $P=0.0085$; Fig. 2b). The improved 5-year survival in the dexmedetomidine group was also evident using the Cox model in IPTW adjusted analysis (HR=0.70; 95% CI, 0.51–0.95; $P=0.0227$) and overlap weighting adjusted analysis (HR=0.67; 95% CI, 0.51–0.89; $P=0.0058$) (Supplementary Fig. S3).

Secondary outcomes

The secondary outcomes are shown in Table 3. The incidence of heart block was 3% in the dexmedetomidine group vs. 6% in the non-dexmedetomidine group in the unadjusted cohort, but the two groups are similar (3% vs. 3%) in the matched cohort. Again, the incidence of MACE was 6% in the dexmedetomidine group vs. 9% in the non-dexmedetomidine group before adjustment, but became similar (6% vs. 7%) in matched patients.

In the matched cohort, the dexmedetomidine group had reduced incidences of delirium (5% vs. 9%), sepsis (1% vs. 3%), reintubation (3% vs. 6%), 30-day readmission (15% vs. 19%), and any complication (45% vs. 51%), and a reduced mechanical ventilation time (difference is -11.2 h) after cardiac surgery. By using the studentized Breusch-Pagan test, we did not find significant heteroskedasticity in mechanical ventilation time ($P=0.7774$), length of ICU stay ($P=0.5952$), and length of postoperative hospital stay ($P=0.2981$) in the matched cohort.

Discussion

In this cohort of 2068 patients undergoing cardiac surgery, we found that perioperative dexmedetomidine infusion was associated with an improved survival rate up to 5 yr after surgery. After several statistical adjusting approaches for differences between patients who received perioperative dexmedetomidine and those who did not, the association between dexmedetomidine use and postoperative long-term survival remained evident.

Cardiac surgery with cardiopulmonary bypass induces significant systemic inflammation, which leads to dysfunction of major organs.[18,19] In a recent study of 502 patients undergoing cardiac surgery with cardiopulmonary bypass, 142 patients (28%) developed systemic inflammatory reaction syndrome at 24 h after surgery and experienced more complicated morbidity postoperatively.[20] Over recent years, dexmedetomidine has been used as an anaesthesia adjuvant to help alleviate surgical stress, inflammatory responses, and immunosuppression induced by surgical trauma.[4] A recent meta-analysis of 67 studies including 4842 patients suggests that dexmedetomidine attenuates perioperative stress and inflammation and preserves immune function in patients undergoing surgery.[21] Experimental studies have also shown the organ protective effects of dexmedetomidine, through inhibiting inflammation,[22–24] limiting intracellular calcium overload,[25] and inhibiting cell apoptosis signalling pathways.[26] In this context, dexmedetomidine may be of benefit to cardiac surgical patients for improving clinical outcomes after surgery by alleviating stress and inflammatory responses.

A previous cohort study of 1134 patients reported that perioperative use of dexmedetomidine was associated with improvement in postoperative 1-year mortality and major complications following cardiac surgery.[6] In a recent meta-analysis, dexmedetomidine use in cardiovascular surgery was associated with reduced 30-day mortality, reduced length of ICU and hospital stay, and lower incidences of postoperative cardiac arrest, atrial fibrillation, and delirium.[8] The reduced 30-day mortality associated with dexmedetomidine was based on two observational studies,[6,27] and two small randomised trials.[28,29] Both observational data and randomised studies were included in this meta-analysis, and the dose, timing, and duration of dexmedetomidine use varied. Therefore, the heterogeneity among studies makes it difficult to interpret the

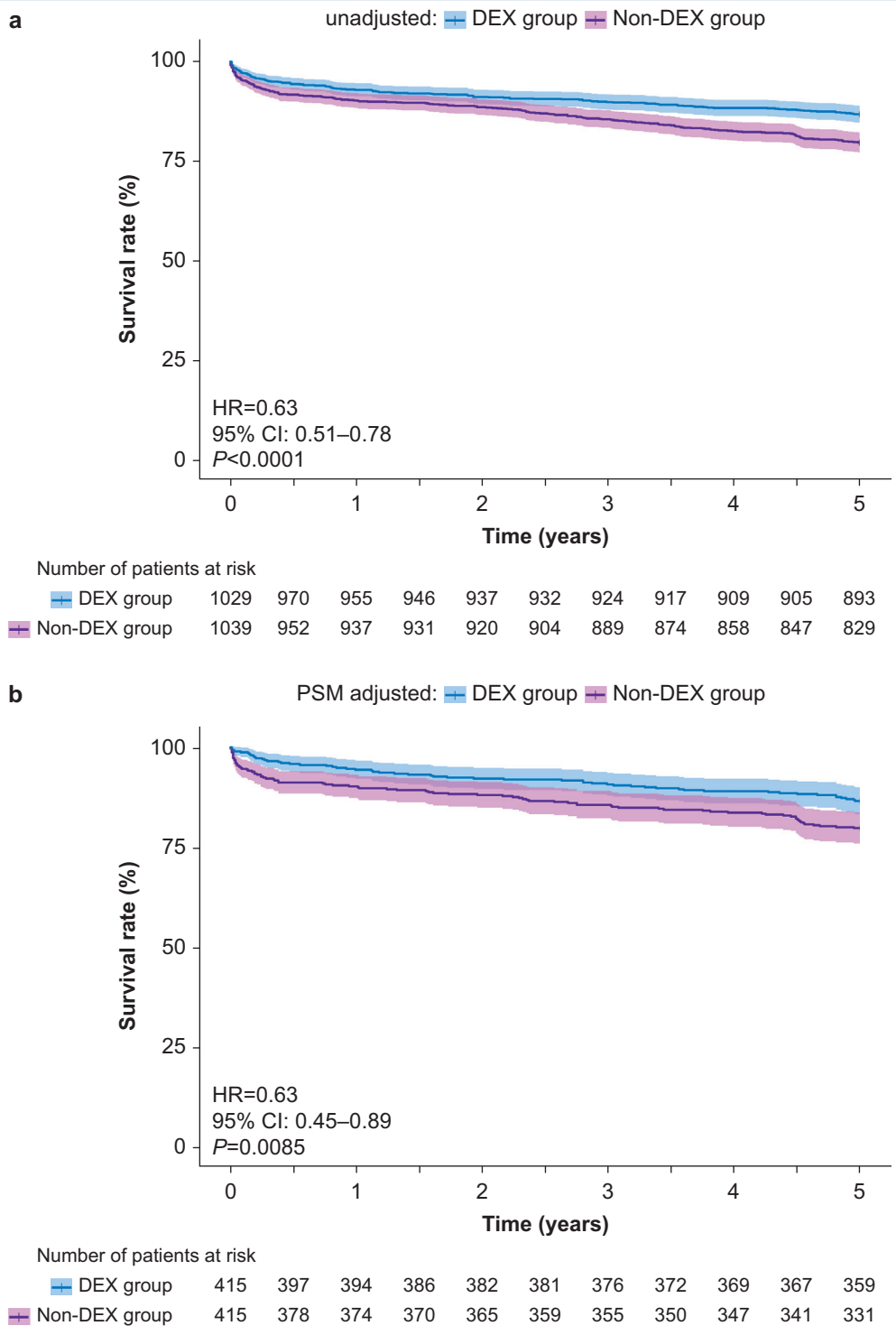

Fig 2. Survival rate during 5 yr after cardiac surgery: (a) unadjusted analysis, (b) PSM adjusted analysis. Survival curves are obtained by using the Kaplan–Meier method, and survival analysis is performed with the use of Cox proportional-hazard model (unadjusted or propensity score matching – PSM – method adjusted). CI, confidence interval; DEX, dexmedetomidine; HR, hazard ratio; PSM, propensity score matching.

true effect of dexmedetomidine. In addition, a recent randomised controlled study (DECADE) showed that dexmedetomidine did not reduce the incidence of atrial fibrillation or delirium after cardiac surgery, nor it had any significant impact on postoperative 90-day outcomes.[9] To date, whether dexmedetomidine provides long-term survival benefits after

Table 3 Secondary outcomes. Data are *n* (%) or median (inter-quartile range). CI, confidence interval; DEX, dexmedetomidine; MACE, major adverse cardiovascular events.

	Unadjusted		Matched		
	DEX (*n*=1029)	Non-DEX (*n*=1039)	DEX (*n*=415)	Non-DEX (*n*=415)	Odds ratio or difference (95% CI)
Perioperative myocardial infarction	18 (2%)	20 (2%)	9 (2%)	10 (2%)	0.90 (0.36, 2.23)
Heart block	34 (3%)	61 (6%)	12 (3%)	14 (3%)	0.85 (0.39, 1.87)
Cardiac arrest	19 (2%)	23 (2%)	4 (<1%)	6 (1%)	0.66 (0.19, 2.37)
Stroke	16 (2%)	16 (2%)	5 (1%)	4 (<1%)	1.25 (0.33, 4.70)
Coma	2 (<1%)	6 (<1%)	1 (<1%)	3 (<1%)	0.33 (0.03, 3.20)
MACE	65 (6%)	98 (9%)	25 (6%)	29 (7%)	0.85 (0.49, 1.48)
Delirium	45 (4%)	82 (8%)	22 (5%)	39 (9%)	0.54 (0.31, 0.93)
Sepsis	16 (2%)	40 (4%)	8 (1%)	19 (3%)	0.41 (0.18, 0.95)
New-onset of atrial fibrillation	230 (22%)	249 (24%)	103 (25%)	105 (25%)	0.97 (0.71, 1.33)
Gastrointestinal complications	35 (3%)	27 (3%)	6 (1%)	8 (2%)	0.75 (0.26, 2.17)
Postoperative dialysis	106 (10%)	146 (14%)	42 (10%)	51 (12%)	0.80 (0.52, 1.24)
Renal failure	40 (4%)	49 (5%)	19 (5%)	21 (5%)	0.90 (0.48, 1.70)
Multiorgan failure	16 (2%)	14 (1%)	3 (<1%)	4 (<1%)	0.75 (0.17, 3.36)
Reintubation	54 (5%)	70 (7%)	11 (3%)	26 (6%)	0.41 (0.20, 0.84)
Reoperation	29 (3%)	31 (3%)	7 (2%)	8 (2%)	0.87 (0.31, 2.43)
ICU readmission	30 (3%)	41 (4%)	9 (2%)	9 (2%)	1.00 (0.39, 2.54)
30-day readmission	146 (14%)	161 (16%)	61 (15%)	77 (19%)	0.76 (0.52, 1.09)
Any complication	458 (45%)	559 (54%)	187 (45%)	211 (51%)	0.79 (0.60, 1.04)
Mechanical ventilation time, h	5.8 (1.5, 23.8)	15.1 (7.8, 23.8)	4.1 (0, 14.6)	12.3 (6.3, 20.6)	-11.2 (-23.6, 1.1)
ICU stay, h	78.3 (50.3, 121.2)	70.1 (45.8, 114.9)	74.1 (48.1, 119.7)	69.0 (47.0, 101.3)	7.6 (-13.0, 28.2)
Postoperative hospital stay, days	7 (5, 10)	7 (5, 9)	7 (5, 10)	7 (5, 9)	0.2 (-1.1, 1.5)

cardiac surgery remains largely unknown. For the dexmedetomidine vs. non-dexmedetomidine groups in the prior study, the adjusted OR (95% CI) value is 0.39 (0.23–0.66) for 30-day mortality and 0.47 (0.31–0.70) for 1-year mortality.[6] In the present study, the PSM adjusted OR (95% CI) is 0.26 (0.10–0.61) for 30-day mortality and 0.56 (0.33–0.94) for 1-year mortality. Overall, the OR values increase over time in both the prior and the present studies. After postoperative 1 year, this study shows that the adjusted ORs remain at approximately 0.60.

In the present study, we focused on the primary outcome of postoperative long-term survival associated with dexmedetomidine. We did not perform multiple testing for the secondary outcomes, because these results including many postoperative complications are useful to illustrate if the adjustment strategy is more successful than as specific outcomes. For example, the incidence of heart block was 3% vs. 6% between the dexmedetomidine and non-dex medetomidine groups in the unadjusted cohort, but after PSM adjustment the two groups were similar (3% vs. 3%). The incidence of MACE was lower in the dexmedetomidine group before adjustment (6% vs. 9%), and became 6% vs. 7% in the matched cohort. Again, the between-group difference in the incidence of any complication (45% vs. 54%) was also reduced after adjustment (45% vs. 51%). Therefore, our adjustment strategy appears to be effective for minimising the confounding bias, and no definitive clinical inferences can be made from the secondary outcomes in this study.

This study has some strengths. First, we performed propensity score adjustment for a variety of potentially confounding factors, including patient characteristics, medical history, preoperative medications, procedure characteristics, year of surgery, and the attending surgeons. The propensity scores were developed using a multivariable logistic regression model, which was successfully used in our prior study and other recent studies.[6,13,30] Second, by using several adjusting methods based on propensity scores, all baseline covariates were balanced between the dexmedetomidine and Non-dexmedetomidine groups, and we were able to evaluate the current results in a more comprehensive way. Third, considering that IPTW in finite samples is known to undercorrect in the presence of strong selection even when the assumptions are true, we also applied adjustment with the PSM and overlap weighting methods.[31] Our study shows an increased 5-year survival associated with dexmedetomidine in all models (unadjusted: HR=0.63, 95% CI, 0.51–0.78, $P<0.0001$; PSM adjusted: HR=0.63, 95% CI, 0.45–0.89, $P=0.0085$; IPTW adjusted: HR=0.70, 95% CI, 0.51–0.95, $P=0.0227$; and overlap weighting adjusted: HR=0.67, 95% CI, 0.51–0.89, $P=0.0058$). Last, to the best of our knowledge, this is the first study to demonstrate the long-term survival benefits of dexmedetomidine for patients undergoing cardiac surgery.

This study also has several limitations. First, although the IPTW, overlap weighting, and PSM analyses were carried out to reduce selection bias between the dexmedetomidine and Non-dexmedetomidine groups, potential flaws may still exist in this nonrandomised study. Second, whether or not a patient would receive dexmedetomidine was at the discretion of the attending anaesthesiologist, so there were no specific indications for dexmedetomidine use for which we can apply adjustment in the propensity analysis. Third, more than half of the patients were unmatchable in the PSM adjusted analysis, mainly as a result of inconsistent data distribution in year of surgery and attending surgeons between the dexmedetomidine and non-dexmedetomidine groups. The temporal

pattern of dexmedetomidine use makes it unable to adjust for each year of the surgery, which should be considered as a potential confounder when interpreting the data. Fourth, based on the STS database, postoperative complications were recorded only during the hospitalization period, and thus we lacked long-term data of these outcomes. Fifth, we noticed a low delirium rate in our patients. One major reason is that delirium was diagnosed by a psychiatrist in our institution. Thus, only hyperactive delirium characterized by restlessness and agitation were recorded, excluding many cases of hypoactive delirium. Last, because this is a single-centre study, the generalisability of our findings may be limited. Further multicenter, prospective, randomised studies are encouraged to confirm the benefits of dexmedetomidine on postoperative complications and survival after cardiac surgery in the long-term follow-up.

In conclusion, a perioperative dexmedetomidine infusion in cardiac surgical procedures is associated with improved long-term survival. Although this finding is promising, the current data support future rigorous RCTs on the long-term benefits of dexmedetomidine in cardiac surgery.

Author's contributions

Designed the study: FHJ, HL Contributed to data extraction and acquisition: KP, HL Contributed to manuscript drafting: KP, YPS Contributed to statistical analysis: YPS, YYY, ZZ Contributed to interpretation of data: KP, RA, DAL, ZX, XMF, JPY, HL Contributed to revision of the manuscript: BK, VR, DB, RA, DAL, ZX, XMF, FHJ, HL

Declarations of interest

The authors declare that they have no conflicts of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bja.2021.03.040.

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