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Impact of perioperative dexmedetomidine on long-term outcomes in older patients following cardiac surgery: follow-up of a randomized trial

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Abstract

Background Perioperative dexmedetomidine is reported to reduce complications and even in-hospital mortality after cardiac surgery. We therefore tested the hypothesis that perioperative dexmedetomidine may improve long-term outcomes after cardiac surgery.

Methods This was long-term follow-up of a randomized trial. We enrolled 285 patients aged 60 years or older who were scheduled for elective cardiac surgery. Patients were randomized to receive either dexmedetomidine or placebo (normal saline) during and early after surgery. Follow-up was conducted for up to 6 years post-surgery. The primary endpoint was overall survival. Secondary outcomes included major adverse cardiovascular events (MACE)-free and hospital-free survivals, as well as cognitive function and quality of life in 6-year survivors.

Results All 285 patients were included in final analysis. Median follow-up duration was 80 months (interquartile range 30 to 80). Overall survival did not differ between the two groups: there were 18 deaths (12.6%) with placebo versus 22 deaths (15.5%) with dexmedetomidine; hazard ratio (HR) 1.22, 95% CI 0.65 to 2.27, $p=0.418$. MACE-free survival was 23 (16.1%) with placebo versus 24 (16.9%) with dexmedetomidine; HR 1.03, 95% CI 0.58 to 1.83, $P=0.911$. Hospital-free survival was 39 (27.3%) with placebo versus 42 (29.6%) with dexmedetomidine; HR 1.04, 95% CI 0.67 to 1.61, $P=0.853$. Among 6-year survivors, the scores of cognitive function and quality of life were similar between groups.

Conclusions We found that, for older patients undergoing elective cardiac surgery, dexmedetomidine administered during and early after surgery did not alter overall and MACE-free survivals, as well as long-term cognitive function and quality of life. However, considering the underpowered sample size and non-negligible loss to follow-up rate, our results need further confirmation.

Trial registration ClinicalTrials.gov: NCT03289325 (September 20, 2017).

Keywords Older patients, Cardiac surgery, Dexmedetomidine, Perioperative period, Long-term outcomes

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Background

Dexmedetomidine is a highly selective α2-adrenergic agonist with anxiolytic, sedative, and analgesic effects [1, 2]. When given as a supplement during general anesthesia and/or postoperative analgesia, dexmedetomidine reduces opioid consumption and improves analgesia [3, 4]; it also relieves stress response and inflammation and preserved immune function after surgery [5]. These properties may provide organ protection and help to promote perioperative recovery. Indeed, available evidence indicated that perioperative dexmedetomidine improved sleep quality [6–9] and reduced delirium after surgery [10, 11]. Results of meta-analyses also showed that, in patients undergoing cardiac surgery, perioperative dexmedetomidine reduced acute kidney injury [12–14], myocardial injury [15, 16] and atrial fibrillation [17, 18]; dexmedetomidine even reduced perioperative mortality, although not universally [11, 14].

Considering the sustained harmful effects of the above complications [19–21], it is reasonable to suppose that dexmedetomidine may have favorable impact on long-term outcomes. However, data in this aspect is limited. In a 3-year follow-up of 700 patients who otherwise were randomized to low-dose dexmedetomidine or placebo during intensive care unit (ICU) stay after noncardiac surgery, those given dexmedetomidine had higher overall survival within 2 years [22, 23]. A recent 3-year follow-up of a randomized trial reported similar results; among 720 older patients undergoing major non-cardiac surgery, those who were randomized to receive intraoperative dexmedetomidine during the underlying trial had improved recurrence-free survival [24, 25]. Long-term effects of perioperative dexmedetomidine were also investigated in cardiac patients. In a retrospective study of 2068 patients undergoing cardiac surgery, dexmedetomidine use was associated with improved 5-year survival [26]. But neutral results were reported in another retrospective analysis [27].

In our initial randomized trial, 285 older patients who were scheduled for major cardiac surgery with or without cardiopulmonary bypass were randomized to receive either dexmedetomidine or placebo during anesthesia and early postoperative period [28]. Herein we report the median 80-month follow-up results of these patients. Our primary endpoint was overall survival. Our secondary endpoint was survival without major adverse cardiovascular events which included myocardial infarction, revascularization, stroke, and cardiovascular death.

Methods

Study design

This was a long-term follow-up of patients enrolled in a previously conducted randomized trial [28]. The study protocol for this follow-up was approved by the Biomedical Research Ethics Committee of Peking University First Hospital (2016–1188 and 2021–203) and participating center and registered with clinicaltrials.gov (NCT03289325; September 20, 2017). As all participants gave written informed consents during the underlying trial and no new intervention was required, the Ethics Committees agreed to waive written consents during the follow-up contacts. However, all patients and/or their family members were informed of the current study, and oral consents were obtained via telephone before data collection. The manuscript adheres to the Consolidated Standards of Reporting Trials (CONSORT) guidelines.

Patients, randomization, and intervention

From December 1, 2014, to July 19, 2015, 285 patients were enrolled in the underlying trial. We included patients aged ≥ 60 years who were scheduled for elective coronary artery bypass graft and/or valve replacement surgery. We excluded those who had previous history of schizophrenia, epilepsy, Parkinson disease, or severe dementia; had history of neurosurgery or brain trauma; were unable to communicate due to severe visual/auditory dysfunction or language barrier; had preoperative sick sinus syndrome, severe bradycardia (heart rate < 50 bpm), or second-degree or above atrioventricular block without pacemaker; or had severe hepatic or renal insufficiency.

During the underlying trial, center-stratified random numbers were generated in a 1:1 ratio with a block size of 4 by an independent biostatistician using the SAS statistical package version 9.3 (SAS Institute, Cary, NC, USA), and sealed in sequentially numbered envelops. Before anesthesia induction, study coordinators who otherwise were not involved in the trial and clinical managements opened the envelops, prepared the study drugs according to randomization results, and provided study drugs to the responsible anesthesiologists. In this way the enrolled patients were randomly assigned to receive either dexmedetomidine ($n = 142$; dexmedetomidine 0.6 μg/kg over 10 min, followed by a continuous infusion at a rate of 0.4 μg/kg/h until the end of surgery, and 0.1 μg/kg/h after surgery until the end of mechanical ventilation) or placebo ($n = 143$; normal saline infused at the same rate for the same duration). All patients, health-care team members including responsible anesthesiologists and surgeons, and investigators for data collection and follow-up were blinded to group assignment.

Long-term follow-up

Long-term follow-ups were performed by investigators (YZ and HH) who were not involved in the underlying trial [28] and were blinded to study group assignment.

They had been trained and qualified for follow-up data collection. Follow-ups were performed via telephone interview with patients and/or their family members and supplemented by in-patient and out-patient medical records. Lost to follow-up was defined as patients who could not be contacted for at least 5 attempts on 5 different days.

Data collected during each follow-up contact included the following: (1) occurrence of major adverse cardiovascular events (MACE) which included myocardial infarction, myocardial revascularization (percutaneous coronary intervention with or without stent implantation or second coronary artery bypass graft surgery), stroke, or cardiovascular death [29]; (2) any major medical events that required hospitalization; (3) all-cause death. For each confirmed event, the date of earliest occurrence was recorded.

For survivors at last follow-up (up to 6 years after surgery), cognitive function was assessed with the Telephone Interview of Cognitive Status-modified (TICS-m) [30], and quality of life was assessed with the Short Form-36 (SF-36) [31]. The TICS-m is a 12-item questionnaire that assesses global cognitive function via telephone; scores range from 0 to 50, with higher scores indicating better function [30]; a minimum difference of 0.5 SD was considered clinical meaningful [32]. The SF-36 is a 36-item questionnaire that assesses quality of life in eight domains, i.e., physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role emotional, and mental health. Score of each domain ranges from 0 to 100, with higher score indicating better function and a minimal difference of 0.5 SD [31, 33].

Our primary endpoint was overall survival after surgery, defined as time interval from index surgery to all-cause death. Secondary endpoints included MACE-free survival and hospital-free survival, as well as cognitive function and quality of life among long-term survivors. MACE-free survival was defined as time interval from index surgery to MACE; deaths from other causes were censored at the time of death. Hospital-free survival was defined as time interval from index surgery to MACE, any event that required hospitalization, or all-cause death, which ever came first. For patients who were lost to follow-up, censoring points were the time of their last hospital visits after surgery recorded in the in-patient or outpatient medical record system.

Statistical analysis

Outcome analysis was performed in all patients who were enrolled in the underlying trial included in long-term follow-up. Numeric variables were analyzed with independent-sample t or Mann–Whitney U tests. Ordinal data were analyzed with Mann Whitney U tests. Differences (and 95% CIs for the differences) between two

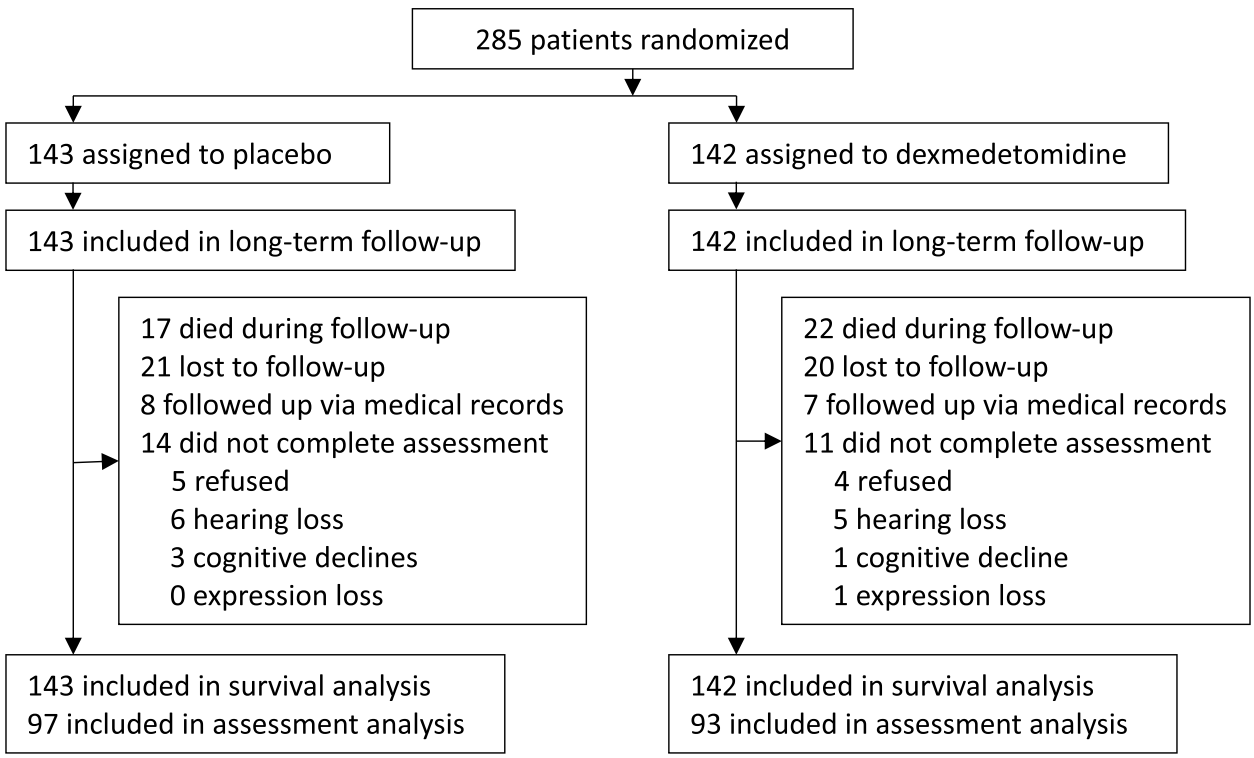

Fig. 1 Trial flowchart

Table 1 Baseline data

	All enrolled			Completed long-term assessments		
	Placebo ($n=143$)	Dexmedetomidine ($n=142$)	*P* value	Placebo ($n=83$)	Dexmedetomidine ($n=82$)	*P* value
Age (year)	67 ± 5	66 ± 5	0.076	66 ± 4	66 ± 5	0.161
Male sex	102 (71.3%)	95 (66.9%)	0.419	62 (74.7%)	55 (67.1%)	0.281
Body mass index (kg/m^2)	24.9 ± 2.8	25.3 ± 3.4	0.271	25.5 (23.7, 27.1)	24.9 (23.5, 27.9)	0.867
Education (year)	9 (5, 10)	9 (5, 12)	0.722	9 (6, 10)	9 (6, 12)	0.476
Preoperative comorbidity						
Stroke	33 (23.1%)	26 (18.3%)	0.321	17 (20.5%)	16(19.5%)	0.876
Hypertension	91 (63.6%)	89 (62.7%)	0.867	52 (62.7%)	53 (64.6%)	0.791
Arrhythmia	29 (20.3%)	32 (22.5%)	0.643	13 (15.7%)	18 (22.0%)	0.301
Acute myocardial infarction	11 (7.7%)	17 (12.0%)	0.225	3 (3.6%)	12 (14.6%)	**0.014**
Chronic obstructive pulmonary disease	4 (2.8%)	7 (4.9%)	0.350	2 (2.4%)	4 (4.9%)	0.666
Diabetes mellitus	49 (34.3%)	43 (30.3%)	0.472	29 (34.9%)	19 (23.2%)	0.096
Hyperlipidemia[a]	61 (42.7%)	38 (26.8%)	**0.005**	43 (51.8%)	22 (26.8%)	**0.001**
Chronic kidney disease[b]	7 (4.9%)	1 (0.7%)	0.075	1 (1.2%)	1 (1.2%)	> 0.999
History of tumor[c]	3 (2.1%)	7 (4.9%)	0.329	0 (0.0%)	3 (3.7%)	0.240
Charlson Comorbidity Index (point)	1 (0, 1)	0 (0, 1)	0.661	0 (0, 1)	0 (0, 1)	0.968
EuroSCORE (point) [d]	3 (2, 5)	3 (2, 5)	0.099	3 (2, 4)	3 (2, 4.25)	0.821
NYHA function class [e]	($n=132$)	($n=125$)	0.964			0.131
I	2 (1.5%)	2 (1.6%)		1 (1.3%)	2 (2.9%)	
II	92 (69.7%)	87 (69.6%)		54 (67.5%)	52 (74.3%)	
III	36 (27.3%)	33 (26.4%)		25 (31.3%)	14 (20.0%)	
IV	2 (1.5%)	3 (2.4%)		0 (0%)	2 (2.9%)	
ASA classification			0.827			0.205
II	2 (1.4%)	1 (0.7%)		1 (1.2%)	1 (1.2%)	
III	129 (90.2%)	128 (90.1%)		80 (96.4%)	74 (90.2%)	
IV	12 (8.4%)	13 (9.2%)		2 (2.4%)	7 (8.5%)	
Left ventricular ejection fraction (%)	65 (58, 71)	64 (56, 70)	0.274	65 (60, 71)	63 (56, 70)	0.132
Mini-Mental State Examination (point)[f]	29 (28, 30)	29 (28, 30)	0.216	30 (29, 30)	29 (28, 30)	0.208
Barthel Index (point)[g]	100 (95, 100)	100 (95, 100)	0.953	100 (95, 100)	100 (95, 100)	0.565

Data are mean ± SD, median (interquartile range), or n (%). *P* values in bold indicate < 0.05

EuroSCORE European System for Cardiac Operative Risk Evaluation, *NYHA* New York Heart Association, *ASA* American Society of Anesthesiologists

[a] Serum total cholesterol > 5.18 mmol/L, triglyceride > 1.7 mmol/L, or low-density lipoprotein > 3.37 mmol/L

[b] Diagnosed according to the Kidney Disease: Improving Global Outcomes (KDIGO) criteria [34]

[c] Including breast cancer, lung cancer, gastric cancer, rectal cancer, and atrial myxoma

[d] A risk model to predict mortality after cardiac surgery, with score 1–2 indicating low risk (0.8%), 3–5 medium risk (3.0%), and 6 plus high-risk (11.2%)

[e] Excludes patients with acute myocardial infarction

[f] Score ranges from 0 to 30, with higher score indicating better function

[g] Score ranges from 0 to 100, with higher score indicating better function

medians were calculated with Hodges-Lehmann estimators. Categorical variables were analyzed with chi square, continuity-corrected chi square, or Fisher exact tests. Relative risks (and 95% CIs) were provided. Time-to-event variables were evaluated with Kaplan–Meier estimators, with differences between groups assessed with log-rank tests. Cox proportional hazard models were used to calculate hazard ratios (and 95% CIs). Missing data were not replaced. Two-tailed *P* values < 0.05 were considered statistically significant. Statistical analyses were performed on SPSS 25.0 software package (IBM SPSS, Chicago, IL).

Results

All 285 patients were included in this long-term follow-up, which was conducted from December 5, 2016, to May 3, 2022. Of these, 41 patients (14.4%) were lost to follow-up, including 21 (14.7%) in the placebo group and 20 (14.1%) in

Table 2 Intra- and postoperative data

	All enrolled			Completed long-term assessments		
	Placebo ($n=143$)	Dexmedetomidine ($n=142$)	*P* value	Placebo ($n=83$)	Dexmedetomidine ($n=82$)	*P* value
Intraoperative data						
Premedication						
Use of morphine	63 (44.1%)	67 (47.2%)	0.596	29 (34.9%)	29 (35.4%)	0.954
Use of estazolam	128 (89.5%)	133 (93.7%)	0.207	77 (92.8%)	78 (95.1%)	0.759
Duration of anesthesia (min)	256 (217, 300)	250 (220, 294)	0.889	248 (215, 300)	246 (218, 300)	0.957
Dose of anesthetics						
Use of midazolam	141 (98.6%)	139 (97.9%)	0.994	82 (98.8%)	80 (97.6%)	0.992
Propofol (mg)	600 (400, 920)	520 (300, 825)	0.098	550 (340, 850)	490 (285, 734)	0.241
Use of etomidate	61 (42.7%)	64 (45.1%)	0.681	42 (50.6%)	44 (53.7%)	0.694
Use of sufentanil	139 (97.2%)	140 (98.6%)	0.686	80 (96.4%)	80 (97.6%)	>0.999
Sufentanil (μg)	200 (150, 300)	225 (140, 300)	0.967	154 (250, 300)	250 (150, 348)	0.681
Use of fentanyl	4 (2.8%)	2 (1.4%)	0.686	3 (3.6%)	2 (2.4%)	>0.999
Average bispectral index[a]	45±6 [15]	42±5 [12]	**<0.001**	45±6 [10]	42±6 [9]	**0.016**
Duration of surgery	185 (157, 235)	180 (159, 225)	0.651	185 (155, 240)	180 (157, 228)	0.812
Type of surgery			0.731			0.526
Coronary artery bypass graft	103 (72.0%)	101 (71.1%)		65 (78.3%)	59 (72.0%)	
Valve replacement	19 (13.3%)	23 (16.2%)		10 (12.0%)	15 (18.3%)	
Combined	21 (14.7%)	18 (12.7%)		8 (9.6%)	8 (9.8%)	
Use of CPB	82 (57.3%)	82 (57.7%)	0.945	35 (42.2%)	37 (45.1%)	0.702
CPB duration (min)	101 (81, 130)	105 (84, 129)	0.979	103 (85, 136)	108 (84, 132)	0.946
Aortic cross clamping (min)	72 (49, 92)	71 (59, 91)	0.477	73 (54, 97)	76 (60, 95)	0.697
Hypothermia (min)	60 (40, 83)	59 (48, 77)	0.395	60 (40, 88)	61 (50, 77.5)	0.640
Postoperative data						
APACHE II at ICU admission (point)	8 (7, 11)	8 (6, 10)	0.099	8 (6, 10)	8 (6, 10)	0.190
Time to extubation (h)	14.0 (9.5, 19.0)	15.0 (9.5, 17.0)	0.368	14.0 (10.0, 18.0)	15.0 (11.9, 17.0)	0.940
Extubation within 24 h	122 (85.3%)	135 (95.1%)	**0.006**	76 (91.6%)	79 (96.3%)	0.338
Delirium or coma within 5 days	11 (7.7%)	7 (4.9%)	0.341	4 (4.8%)	2 (2.4%)	0.689
Major complications within 30 days [b]	76 (53.1%)	66 (46.5%)	0.260	39 (47.0%)	33 (40.2%)	0.382
Length of ICU stay after surgery (h)	46 (45, 47)	45 (43, 46)	0.788	43 (22, 67)	41 (27, 69)	0.726
Length of hospital stay after surgery (d)	9 (8, 10)	9 (8, 10)	0.826	8 (5, 11)	8 (6, 11)	0.793
Duration of long-term follow-up (m)	80 (25, 80)	80 (35, 80)	0.956	80 (80, 82)	80 (80, 82)	0.778

Data are n (%), median (interquartile range), or mean ± SD. *P* value in bold indicate < 0.05. Numbers in square brackets indicate patients with missing data

CPB cardiopulmonary bypass, *APACHE II* acute physiology and chronic health evaluation II (score ranges from 0 to 71, with higher score indicating more severe illness), *ICU* intensive care unit

[a] From end of anesthesia induction to end of surgery

[b] Defined as new-onset medical conditions that were deemed harmful and required therapeutic intervention, i.e., grade II or higher on the Clavien-Dindo classification [35]. Included stroke, new-onset arrhythmia, pulmonary complications, upper gastrointestinal bleeding, surgical bleeding, wound dehiscence or infection, and heart failure in the present study

the dexmedetomidine group ($p=0.788$); 39 patients (13.7%) died during the follow-up period. Among the 190 survivors who were contacted at last follow-up, 9 refused follow-up assessments (5 [3.5%] in the placebo group and 4 [2.8%] in the dexmedetomidine group) and 16 failed to complete assessments due to hearing loss, cognitive decline, or expression loss (9 [6.3%] in the placebo group and 7 [4.9%] in the dexmedetomidine group); the remaining 165 patients completed cognitive function and quality of life assessments (Fig. 1).

Among all enrolled patients, baseline data were generally well balanced except that the proportion with hyperlipidemia was lower in the dexmedetomidine group than in the placebo group (Table 1); the average bispectral index during surgery was lower but the proportion of extubation within 24 h after surgery was higher in the dexmedetomidine group than in the control group (Table 2). Among long-term survivors who completed cognitive function and quality-of-life assessments, the

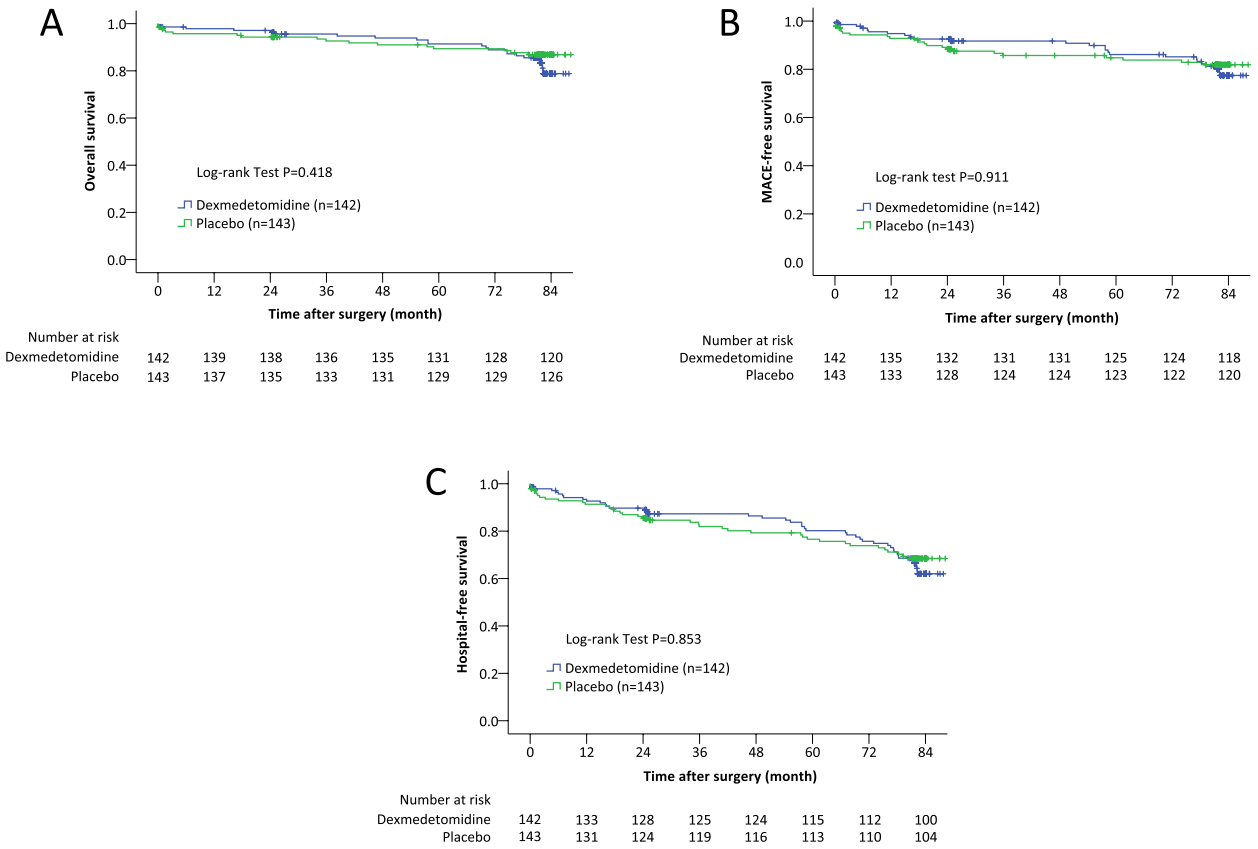

Fig. 2 The Kaplan–Meier curves for overall (**A**), MACE-free (**B**), and hospital-free survivals (**C**) after cardiac surgery. MACE, major adverse cardiovascular events. Crosses indicate censored patients

proportion with preoperative acute myocardial infarction was higher, whereas the proportion with hyperlipidemia was lower in the dexmedetomidine group than in the placebo group (Table 1); the average bispectral index during surgery were lower in the dexmedetomidine group than that in the placebo group (Table 2).

The median follow-up duration was 80 (interquartile range [IQR] 30 to 80) months. At the end of follow-up, there were 18 deaths (12.6%) in the placebo group and 22 deaths (15.5%) in the dexmedetomidine group. Overall survival did not differ between the two groups: hazard ratio (HR) 1.22, 95% CI 0.65 to 2.27, $P=0.418$; Fig. 2A). There was no significant difference in MACE-free survival between the two groups: 23 events (16.1%) with placebo versus 24 events (16.9%) with dexmedetomidine; HR 1.03, 95% CI 0.58 to 1.83, $P=0.911$; Fig. 2B). There was also no significant difference in hospital-free survival between the two groups: 39 events (27.3%) with placebo vs. 42 events (29.6%) with dexmedetomidine; HR 1.04, 95% CI 0.67 to 1.61, $P=0.853$; Fig. 2C; Table 3).

Among long-term survivors, the scores of TICS-m (mean difference [MD] 0, 95% CI −1 to 1, $P=0.655$) and SF-36 (physical functioning: MD 5, 95% CI −2 to 12, $P=0.146$; role-physical: MD 2, 95% CI −11 to 15, $P=0.717$; bodily pain: MD 3, 95% CI −3 to 9, $P=0.355$; general health: MD 2, 95% CI −6 to 10, $P=0.624$; vitality: MD −1, 95% CI −6 to 3, $P=0.590$; social functioning: MD 5, 95% CI −2 to 12, $P=0.168$ role emotional: MD 4, 95% CI −5 to 13, $P=0.337$; mental health: MD 1, 95% CI −2 to 5, $P=0.456$) were similar between the two groups (Table 3).

Discussion

Our long-term follow-up results showed that, for older patients undergoing elective cardiac surgery, dexmedetomidine administration during anesthesia and early postoperative period did not change overall, MACE-free, and hospital-free survival for up to 6 years after surgery, nor did it change cognitive function and quality of life in long-term survivors.

Along with increasing life expectancy and ageing population, the number of older patients who undergo cardiac surgery is also increasing [38, 39]. The progress of perioperative medicine has improved early and long-term outcomes after cardiac surgery [39, 40], with reported

Table 3 Long-term outcomes

	Placebo ($n=143$)	Dexmedetomidine ($n=142$)	Estimated effects (95% CI)	*P* value
Primary endpoints				
Overall survival, number of deaths	18 (12.6%)	22 (15.5%)	HR = 1.22 (0.65, 2.27)	0.418
Secondary endpoints				
MACE-free survival, number of events	23 (16.1%)	24 (16.9%)	HR = 1.03 (0.58, 1.83)	0.911
Individual component of MACE				
Myocardial infarction [a]	8 (5.6%)	6 (4.2%)	HR = 0.74 (0.26, 2.12)	0.568
Myocardial revascularization [b]	3 (2.1%)	3 (2.1%)	HR = 0.99 (0.20, 4.93)	0.994
Stroke [c]	4 (2.8%)	10 (7.0%)	HR = 2.51 (0.79, 8.01)	0.120
Cardiovascular death [d]	9 (6.3%)	7 (4.9%)	HR = 0.78 (0.29, 2.08)	0.612
Hospital-free survival, number of events	39 (27.3%)	42 (29.6%)	HR = 1.04 (0.67, 1.61)	0.853
For long-term survivors	($n=97$)	($n=93$)		
Cognitive function (point) [e]	34 ± 4 [14]	34 ± 3 [11]	MD = 0 (−1, 1)	0.655
Quality of life (point) [f]	[14]	[11]		
Physical functioning	65 ± 25	70 ± 19	MD = 5 (−2, 12)	0.146
Role-physical	70 ± 43	72 ± 41	MD = 2 (−11, 15)	0.717
Bodily pain	84 ± 21	87 ± 19	MD = 3 (−3, 9)	0.355
General health	66 ± 27	68 ± 27	MD = 2 (−6, 10)	0.624
Vitality	56 ± 13	54 ± 17	MD = −1 (−6, 3)	0.590
Social functioning	90 ± 24	95 ± 21	MD = 5 (−2, 12)	0.168
Role emotional	85 ± 31	89 ± 26	MD = 4 (−5, 13)	0.337
Mental health	78 ± 11	80 ± 108	MD = 1 (−2, 5)	0.456

Data are n (%) or mean ± SD. Numbers in square brackets indicate patients with missing data (refused or failed to complete assessments)

HR hazard ratio, *MACE* major adverse cardiovascular events, *MD* mean difference

[a] Defined as a clinical (or pathologic) event in the setting of myocardial ischemia in which there is evidence of myocardial injury or necrosis [36, 37]

[b] Included percutaneous coronary intervention and coronary artery bypass graft surgery

[c] Included ischemic stroke and hemorrhagic stroke

[d] Included sudden cardiac death, myocardial infarction-related death, and stroke-related death

[e] Assessed with the Telephone Interview of Cognitive Status-modified (TICS-m), score ranges from 0 to 50, with higher scores indicating better function

[f] Assessed with Short Form-36 (SF-36), a 36-item questionnaire that consists of eight health concepts or scales. Each scale is made up of a number of distinct questionnaire items and reported as a score from 0 to 100, with higher score indicating better function

survival rate ranged from 80.2% to 85.8% at 5 years [41, 42] and from 58.0% to 67.8% at 10 years [43, 44]. In the present study, the estimated 5-year overall survival rate was 90.2% in the placebo group and 91.2% in all our patients, slightly higher than the previous results. Potential reasons contributing to the relatively higher survival rate in our patients may include the following. Firstly, we only enrolled patients who were scheduled for elective cardiac surgery in the underlying trial, whereas patients requiring emergency surgery were usually in a critical state. Secondly, we excluded patients with severe comorbidities which might have negative impact on long-term survival. Our patients might be healthier than those in previous observational studies [41–44].

Previous studies showed that perioperative dexmedetomidine reduced complications and in-hospital mortality after cardiac surgery [11–18]. Theoretically, dexmedetomidine might also have favorable impact on long-term outcomes. However, studies investigating long-term effects of dexmedetomidine in cardiac surgery patients are limited. Retrospective studies of Ji and colleagues reported that perioperative dexmedetomidine was associated with improved 1-year [45, 46] and 5-year survivals after cardiac surgery [26]. Whereas a retrospective study of Xu and colleagues included 1477 patients following cardiac surgery but did not find associations between intraoperative dexmedetomidine and 1-year morbidity and mortality [27]. In the present study, 285 older patients who, for other reasons, were randomized to receive either dexmedetomidine or placebo during the perioperative period [28] were followed up for up to 6 years after cardiac surgery. We did not find significant differences in overall survival between the two groups. Considering the low number of all-cause deaths during

the follow-up period, the impacts of perioperative dexmedetomidine on long-term survival requires further investigation.

MACE are important reasons that lead to death or poor quality of life after cardiac surgery. According to available studies, the incidence of MACE ranged from 6.6% to 12.2% at 1 year [47, 48] and from 13.4% to 29.9% at 5 to 6 years after coronary artery bypass grafting (CABG) surgery [49–52]. In the present study, most of our patients (85.3%) underwent CABG surgery. MACE occurred in 10.0% of our placebo patients within 5 years, roughly within the reported ranges. We also did not find significant differences in MACE-free survival nor hospital-free survival between the two groups. But again, considering the limited number of endpoint events, more studies are required in these aspects. As can be expected, the cognitive function as assessed with the TICS-m and quality of life as assessed with the SF-36 were similar between groups in long-term survivors. In line with our results, a small sample size trial of 70 patients also reported that dexmedetomidine compared with propofol for ICU sedation did not improve quality of life (measured with SF-36) in older patients at 6 months after cardiac surgery [53].

This study was based on a rigorously conducted randomized trial; the subsequent long-term follow-up was performed in a double-blind way. Our results thus provide evidence of high quality. There are some limitations. Firstly, sample size of the underlying trial was estimated to detect difference in postoperative delirium rather than long-term outcomes. This follow-up study was underpowered to detect differences in overall, MACE-free, and hospital-free survivals. Secondly, 14.4% of our patients were lost during the long follow-up period; this may produce bias although the proportions of lost to follow-up were comparable in each group.

In summary, our long-term follow up study found that perioperative dexmedetomidine did not improve overall and MACE-free survivals among older patients after elective cardiac surgery. However, our results were underpowered considering the limited sample size and non-negligible loss to follow-up rate. Well-designed large sample size studies are needed to further clarify the impacts of dexmedetomidine on long-term outcomes in this patient population.

Abbreviations

MACE	Major adverse cardiovascular events
HR	Hazard ratio
ICU	Intensive care unit
CONSORT	Consolidated Standards of Reporting Trials
TICS-m	Telephone Interview of Cognitive Status-modified
SF-36	Short Form-36
CABG	Coronary artery bypass grafting
EuroSCORE	European System for Cardiac Operative Risk Evaluation
NYHA	New York Heart Association
ASA	American Society of Anesthesiologists.
KDIGO	Kidney Disease: Improving Global Outcomes
CPB	Cardiopulmonary bypass
APACHEII	Acute physiology and chronic health evaluation II
MD	Median difference

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Authors' contributions
HH, XL, JY, FXY, and DXW contributed to the study's conception and design. HH, XL, JY, YZ, and GYL contributed to material preparation and data collection. HH and DXW contributed to data analysis, results interpretation, and writing the first draft of the paper. All authors were involved in critical revision of the paper for important intellectual content. All authors approved the final version and publishment.

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Data availability
The datasets used and/or analyzed during the current study are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate
Ethics Committee approvals were obtained from the Biomedical Research Ethics Committee of Peking University First Hospital and Fuwai Hospital. Since participants had already provided written informed consents during the underlying trial and no additional interventions were required, the Ethics Committees approved the waiver of written consents for the follow-up contacts. However, all patients and/or their family members were informed about the current study, and oral consents was obtained via telephone prior to data collection.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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