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Perioperative Dexmedetomidine Improves Outcomes of Cardiac Surgery

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Abstract

Background—Cardiac surgery is associated with a high risk of cardiovascular and other complications that translate into increased mortality and healthcare costs. This retrospective study was designed to determine whether the perioperative use of dexmedetomidine could reduce the incidence of complications and mortality following cardiac surgery.

Methods and Results—1,134 patients who underwent CABG and CABG plus valvular and/or other procedures were included. 568 received intravenous dexmedetomidine infusion and 566 did not. Data were adjusted with propensity scores and multivariate logistic regression was used. The primary outcomes measured included mortality and postoperative major adverse cardiocerebral events (MACE: stroke, coma, perioperative myocardial infarction, heart block or cardiac arrest). Secondary outcomes included renal failure, sepsis, delirium, postoperative ventilation hours, length of hospital stay and 30-day readmission. Dexmedetomidine use significantly reduced postoperative in-hospital [1.23% vs. 4.59%; adjusted odds ratio (OR), 0.34; 95% confidence intervals (CI), 0.192 to 0.614; P < 0.0001], 30-day (1.76% vs. 5.12%; adjusted OR, 0.39; 95% CI, 0.226 to 0.655; P <0.0001) and 1-year (3.17% vs. 7.95%; adjusted OR, 0.47; 95% CI, 0.312 to 0.701; P = 0.0002) mortalities. Perioperative dexmedetomidine therapy also reduced the risk of overall complications (47.18 vs. 54.06%; adjusted OR, 0.80, 95% CI, 0.68 to 0.96; p= 0.0136) and delirium (5.46% vs. 7.42%; adjusted OR, 0.53; 95% CI, 0.37 to 0.75; p=0.0030).

Conclusions—Perioperative dexmedetomidine use was associated with a decrease in postoperative mortality up to one year and decreased incidence of postoperative complications and delirium in patients undergoing cardiac surgery.

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Conflict of Interest Disclosures: None.

Keywords

Dexmedetomidine; Mortality; Complication; Cardiac surgery

There are approximately 7 million invasive cardiovascular procedures are performed worldwide each year.[1] The major complication rates for valve and coronary artery bypass graft (CABG) procedures are as high as 30.1% in Society of Thoracic Surgeons (STS) reports.[2] Postoperative delirium, infection, acute renal failure (ARF) and major adverse cardiocerebral events (MACE) which includes permanent or transient stroke, coma, perioperative myocardial infarction (MI), heart block and cardiac arrest represent major postoperative complications.[3-5] These complications translate into increased mortality and prolonged hospital stays with estimated costs exceeding $20 billion annually.[6] The etiologies of these adverse events are multifactorial, but one major contributing factor is the surgical stress response that results in increasing plasma levels of epinephrine and norepinephrine with consequent myocardial oxygen supply demand imbalance and myocardial ischemia. [7] More than 50% of all perioperative complications are related to adverse cardiovascular events.[8]

The alpha-2 receptor agonists (clonidine, dexmedetomidine) currently used in clinical practice have many desirable effects including analgesia, anxiolysis, inhibition of central sympathetic outflow and reduction of systemic norepinephrine release that improve hemodynamic stability, positively affect myocardial oxygen supply and demand and may provide myocardial protection. [9,10] The most widely studied alpha-2 agonist is clonidine, a long-acting partial agonist with an alpha-2 to alpha-1 selectivity ratio of 39:1. Dexmedetomidine is a highly selective, shorter-acting intravenous alpha-2 agonist with an alpha-2 to alpha-1 selectivity ratio of 1600:1.[11] At our institution, dexmedetomidine is used to transition cardiac surgical patients from the operating room to the intensive care unit (ICU) and provide sedation prior to extubation. Studies evaluating the hemodynamic stabilizing and sympatholytic effects have shown that alpha-2 agonists can potentially reduce postoperative cardiovascular complications. These include studies of clonidine in cardiac surgery patients and dexmedetomidine in vascular and non-cardiac surgery patients.[12-15] However, no studies to date have explored the impact of the alpha-2 agonists on perioperative outcomes of MI or cardiac death following cardiac surgery. Multiple studies have reported that dexmedetomidine has a protective effect on specific organs including the heart, brain, kidney and lungs.[16-20] In addition, dexmedetomidine has been shown to have anti-inflammatory properties, decreasing mortality and attenuating plasma cytokine concentrations in laboratory animals exposed to endotoxin in a dose-dependent fashion.[21] Therefore, in addition to investigating the more definitive endpoints of myocardial infarction and death, this study also examined the potential impact of dexmedetomidine on other major endpoints such as congestion heart failure (CHF), myocardial ischemia, arrhythmia, stroke, delirium, infection and acute renal failure (ARF) during the post-operative period for patients undergoing cardiac surgery. We hypothesized that dexmedetomidine may provide cardiac, brain, renal and immune function protection for cardiac surgical patients. The specific aim of this study was to investigate whether the perioperative use of dexmedetomidine was associated with improved outcomes and a decreased incidence in postoperative MACE or other complications in patients undergoing open-heart surgery.

Methods

Study Design

This study was a single center, retrospective and cohort study involving 1260 consecutive patients who underwent cardiac surgery at a university medical center from January 1, 2006 to December 31, 2011. The study was reviewed and approved by the local Institutional Review Board. Patients included in this study met the following criteria: CABG and/or valve surgery, CABG and/or valve surgery combined with other procedures. Patients excluded were: emergency surgery, off-pump or robotic surgery, surgery requiring deep hypothermic circulatory arrest or involving the thoracic aorta (Figure 1). 1,134 patients met the inclusion criteria and were divided into two groups: those who received dexmedetomidine (DEX group, n=568, 50.08%) or those who did not receive dexmedetomidine (Non-DEX group, n=566, 49.92%) during the perioperative period (Figure 1).

Data Collection

The patient data were collected and organized following the template of the Society of Thoracic Surgeons (STS) National Adult Cardiac Surgery Database and the hospital medical records and included demographics, patient history, medical record information, preoperative risk factors, preoperative medications, intraoperative data, postoperative MACE, ARF and in-hospital, 30-day and 1-year all cause mortality. Independent investigators prospectively collected the data on each patient during the course of the hospitalization.

For these surgical patients, after standard monitoring, general anesthesia was induced with midazolam, propofol/etomidate, fentanyl/sufentanil, lidocaine, and rocuronium and maintained with oxygen and sevoflurane according to patient's hemodynamic responses. Ventilation was controlled to an end tidal CO_2 of 35–45 mm Hg by adjusting tidal volume and respiratory rate. Arterial catheter, pulmonary artery catheter and transesophageal echocardiography were used for hemodynamic and cardiac function monitoring. Perioperative dexmedetomidine use was defined as an intravenous infusion (0.24 to 0.6mcg/kg/hr) initiated after cardiopulmonary bypass (CPB) and continued for less than 24 hours postoperatively in the ICU. Infusion rate of dexmedetomidine was adjusted according to the manufactures package insert and adjusted in response to the patients' hemodynamic changes in response to stimulation.

Major outcomes of this study were in-hospital, 30-day and 1-year all cause of mortality, and a composite outcome – MACE, which included permanent or transient stroke, coma, perioperative MI, heart block and cardiac arrest.[5] Secondary outcomes included postoperative length of mechanical ventilation, postoperative renal failure or new dialysis requirement, length of ICU stay, length of hospital stay (LOS) and 30-day readmission. Based on the STS criteria, the following definitions were used: permanent stroke -a postoperative stroke (any confirmed neurological deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 hours, transient stroke or transient ischemic attack (TIA) - a loss of neurological function that was abrupt in onset but with complete return of function within 24 hours, coma - a new postoperative coma that persisted for at least 24 hours secondary to anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event or cerebral bleed, delirium - illusions, confusion and cerebral excitement in the post-operative period and having a comparatively short course, perioperative MI - (< 24 hours post operation): creatine phosphokinase-MB (CK-MB) or CK if MB not available, greater than or equal to 5 times the upper limit of normal, with or without new Q waves present in two or more contiguous electrocardiograph (ECG) leads, no

symptoms required; or (> 24 hours post operation): at least one of the following criteria: evolutionary ST- segment elevations, development of new Q- waves in two or more contiguous ECG leads, new left bundle branch block (LBBB) pattern on the ECG, CK-MB (or CK if MB not available) greater than or equal to 3 times the upper limit of normal, heart block - new onset requiring the implantation of a permanent pacemaker of any type prior to discharge, postoperative renal failure - acute or worsening renal failure resulting in one or more of the following: increase in serum creatinine >2.0 mg/dL or two-fold increase of most recent preoperative serum creatinine or a new requirement for dialysis, sepsis - A systemic inflammatory response syndrome is present when at least two of the following criteria are present: hypo- or hyperthermia (>38.5 or <36.0), tachycardia or bradycardia, tachypnea, leukocytosis or leukopenia, and thrombocytopenia. Any complication included all postoperative complications occurring during the hospitalization, including the entire postoperative period up to discharge, even if over 30 days (Supplemental Table 1).

Statistical Methods

Continuous and categorical variables were reported as mean ± SD or percentages, and compared with the *t* test or chi-square test (two tailed), respectively. Univariate and multivariate logistic regressions were performed to assess associations of demographic, therapeutic and clinical outcome variables. To mitigate selection bias in patients who received a dexmedetomidine infusion, we computed the propensity score that is the conditional probability of each patient receiving dexmedetomidine, with a multivariable logistic regression model that included patient demographic and clinical risk factors (Table 1, Supplemental Figure 1).

To achieve model parsimony and stability, the backward selection procedure was applied with the drop-out criterion P > 0.1. The candidate risk factors were selected on the basis of the literature reviews, clinical plausibility and variables collected in the database. The candidate independent variables included: age, gender, race, status of procedure, body mass index (BMI), creatinine level, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of coronary artery disease, diabetes, hypertension, hypercholesterolemia, dyslipidemia, renal failure, dialysis, MI, CHF, Intra-aortic balloon pump (IABP), beta blockers, angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, ADP inhibitors, nitrates, anticoagulants, anti-platelet drugs, Coumadin, inotropes, steroids, aspirin, lipid lowering drugs, GPIIb/IIIa inhibitors, surgery type, ejection fraction (EF), perfusion time, cross clamp time, and year of surgery. The parsimonious multivariable propensity model for dexmedetomidine use included status of procedure, preoperative family history of CAD, preoperative CHF, surgery type, ejection fraction and year of surgery (Figure 2). We then created a propensity-weighted logistic regression model for 1-year mortality in which we used the inverse (estimated) propensity score as weights for patients who received dexmedetomidine and the inverse of 1 minus the propensity score for patients who did not receive dexmedetomidine and then added dexmedetomidine as an independent factor to the model. All models fit analysis was evaluated with the Hosmer-Lemeshow goodness-of-fit statistic. The C statistic was reported as a measure of predictive power. Based on the propensity of dexmedetomidine use we classified all patients into quintile where quintile 1 contained patients with lowest propensity scores and quintile 5 contained patients with the highest propensity scores. Then, with a general linear model, we compared the propensity weighted and risk adjusted 1 –year mortality between the cohort of dexmedetomidine used and the cohort of no dexmedetomidine used for each propensity matched quintile. The results are reported as percentages and odds ratios (OR) and with 95% confidence intervals (CI).

Furthermore, we performed survival analysis and present Kaplan-Meier curves for patients who received dexmedetomidine vs. those who did not receive dexmedetomidine. A parsimonious Cox proportional hazards model was created to evaluate the effect of dexmedetomidine for 1-year survival. All reported p values were 2-sided, and p values < 0.05 were considered to be statistically significant. Statistical analysis was performed with SAS version 9.3 for Windows (SAS Inc., Cary, NC).

Results

Baseline and intraoperative parameters

Demographic and clinical data of the patients who did and did not receive perioperative dexmedetomidine therapy are presented in Table 1. There were no significant differences between two groups with respect to age, gender, race, BMI, medical history (smoking, cerebrovascular disease, chronic lung disease, peripheral vascular disease, diabetes or hypertension) and preoperative medical therapy (beta blockers, nitrates, anti-platelet drugs, Coumadin, inotropes or aspirin). However, the patients in the DEX group presented with a greater incidence of a history of previous MI (43.46% vs. 32.57, p=0.0002), CHF (31.51 vs. 7.42%, p<0.0001), low EF (49.7 ±13.6 vs. 52.5 ±12.8, p=0.0004), renal failure (5.46% vs. 2.47%, p=0.010), dyslipidemia (67.61% vs. 44.70%, p<0.0001) and the use of lipid lowering medications (65.49 vs.52.30%, p<0.0001).

Procedural Characteristics

Procedural characteristics, including the number of vessels bypassed, types of surgery were similar in both groups. In contrast, CPB time (181.8 ±76.6 vs. 199.8 ±81.6, p=0.001) and aortic cross-clamp time (128.9 ±63.9 vs.144.8±62.5, p<0.0001) were significantly longer in Non-DEX group as was the incidence of IABP use (6.87 vs.14.13%, p<0.0001). All surgeries were performed by 1 of 4 experienced cardiovascular surgeons (Table 2).

Postoperative complications and mortality

Univariate Analysis—Thirty-three of the total 1,134 patients (3.3%) died in hospital, 39 patients (3.4%) died within 30-days and 63 patients (5.6%) died within 1-year after cardiac surgery. Perioperative infusion of dexmedetomidine was associated with significantly reduced in-hospital, 30-day and 1-year mortalities. In-hospital mortality was 1.23% in the DEX group vs. 4.59% in the Non- DEX group (OR, 0.26; 95% CI, 0.11 to 0.60; p = 0.008). 30-day mortality was 1.76% in the DEX group vs. 5.12% in the Non-DEX group (OR, 0.33; 95%CI, 0.16 to 0.67; p = 0.002). 1-year mortality was 3.17% in the DEX group vs. 7.95% in the Non-DEX group (OR, 0.38; 95%CI, 0.22 to 0.66; p = 0.0004) (Figure 3). The perioperative use of dexmedetomidine was associated with a significantly reduced incidence of postoperative sepsis (0.7% vs.2.1%, OR, 0.33; 95%CI, 0.11 to 1.02; P= 0.043) and any complication (47.18 vs. 54.06%, OR, 0.76; 95% CI, 0.60 to 0.96; p= 0.0205). No differences were seen in the incidence of MACE, delirium, post-operative ventilation time (hours), total ICU length of stay (hours) or LOS (Figure 3, Table 3).

Propensity and Multivariate Analysis—The final multivariate model assessing MACE included the propensity score, age, body mass index (BMI), diabetes, current smoking, surgical type, IABP use and family history of CAD before surgery. The multivariate model assessing any complication included the propensity score, age, status of procedure, BMI, creatinine level, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of CAD, diabetes, hypertension, renal failure, MI, CHF, IABP, beta blockers, angiotensin-converting enzyme inhibitors, anticoagulants, anti-platelet drugs, steroids, aspirin, surgical type, EF, perfusion time, and year of surgery. The multivariate model assessing delirium included the propensity score, age, smoking, diabetes and surgical

type. The multivariate model assessing postoperative RF included propensity score, age, status of procedure, family history of CAD, diabetes, hypertension, surgical type and angiotensin-converting enzyme. The multivariate model assessing in-hospital, 30-day, 1-year mortalities included the propensity score, age, status of procedure, family history of CAD, surgical type and perfusion time. The model was calibrated among deciles of observed and expected risks for 1-year mortality (Hosmer-Lemeshow $\chi 2$: 13.1039, c= 0.796, P =0.1083) and dexmedetomidine use (Hosmer-Lemeshow $\chi 2$: 29.9369; c=0.788, P =0.0002). Results of the multivariate analysis are summarized in Figure 3. The observed reduction in-hospital (adjusted OR, 0.34; 95% CI, 0.19 to 0.61; p<0.0001), 30-day (adjusted OR, 0.39; 95% CI, 0.23 to 0.66; p<0.0001) and 1-year (adjusted OR, 0.47; 95% CI, 0.31 to 0.70; p=0.0002) mortalities in patients receiving perioperative dexmedetomidine persisted after propensity adjustment. The adjusted rates of any postoperative complication (adjusted OR, 0.80; 95% CI, 0.68 to 0.96; p=0.0136,) and delirium (adjusted OR, 0.53; 95% CI, 0.37 to 0.75; p= 0.0030) were also statistically significant between the DEX and Non-DEX groups. There is a significant increase in the rate of postoperative RF (adjusted OR, 1.5; 95% CI, 1.12 to 2.51; p=0.00945) in patients receiving perioperative dexmedetomidine. However, there were no statistical differences in the incidence of cardiac arrest (adjusted OR, 0.64; 95% CI, 0.19 to 2.14; p=0.4681), sepsis (adjusted OR, 0.70; 95% CI, 0.34 to 1.45; p= 0.3349) between groups after adjusting for differences between groups although the OR point estimates favor perioperative dexmedetomidine use (Figure 3).

1-year Mortality and Survival Analysis

Based on the propensity of dexmedetomidine use we classified all patients into quintiles where quintile 1 contained patients with lowest propensity scores and quintile 5 contained patients with the highest propensity scores. Patients who received dexmedetomidine in quintile 1, 3, 5 were significantly lower with respect to 1-year mortality compared to the patients in the Non-DEX group (4.99% vs.10.39, p=0.0495; 2.87% vs.7.89%, p=0.0009; 3.05% vs.9.88%, p=0.0002, respectively) (Table 4).

Survival probability was calculated using Kaplan–Meier methods and compared with the use of a Log-rank test (p=0.001). For the duration of 1 year there were significant differences in survival between the DEX and Non-DEX groups (propensity adjusted: 96.74% vs.91.70%, p<0.0001). The absence of overlapping curves from beginning to end suggests that there are obvious differences in survival between the DEX and Non-DEX groups (Figure 4).

After risk adjustment, a Cox proportional hazard model analysis revealed that older patients (age>65 years), urgent surgery and perfusion time significantly increase the 1-year mortality, whereas perioperative dexmedetomidine infusion, CABG only and CABG plus valve surgery reduced the risk of death during the first year. Preoperative family history of CAD had no relationship with 1-year mortality. Patients who received dexmedetomidine during the perioperative period had a significantly reduced hazard of death (Hazard ratio, 47.8%; 95% CI, 0.28 to 0.81; p=0.007) compared to those in Non-DEX group at any time within 1-year after cardiac surgery when controlling for other risk factors (Table 4, Figure 5).

Discussion

In this analysis of consecutive patients undergoing cardiac surgery at our institution, we found that perioperative dexmedetomidine use is associated with improved survival. We observed significant reductions in-hospital (1.23% vs. 4.59%), 30-day (1.76% vs. 5.12%) and 1-year (3.17% vs. 7.95%) mortalities in the patients who had received dexmedetomidine during the perioperative period. This improvement in survival persisted after statistical adjustment, which included the propensity to have received perioperative dexmedetomidine

use. Our results further suggest that perioperative dexmedetomidine use is associated with a reduced incidence of delirium and overall complications after cardiac surgery. We did not observe an associated statistically significant incremental benefit of perioperative dexmedetomidine use on postoperative major adverse cerebrovascular events (MACE) and sepsis, however, the OR point estimates for these outcomes favored perioperative dexmedetomidine use. Our analysis likely lacked sufficient power to detect statistically significant differences in these outcomes measure after statistical adjustment. This is the first report of a beneficial effect on outcomes associated with the perioperative use of dexmedetomidine in cardiac surgery patients.

Cardiac surgery is associated with high risks of cardiovascular and other complications, with a reported incidence of 30% for combined valve and CABG procedures that increases up to as high as 86% in higher risk populations.[2, 22] These reported postoperative complications include stroke (1.4-4.6%), cardiac arrest (5.0%), sepsis (4.1%), MI (3.1%) and ARF (3.7-7.1%). [2,4,5,23-25] These complications consequently increase overall morbidity and mortality. The mean of in-hospital mortality in our study (3.41%) is in agreement with previous reports (2.76-4.4%), [26,27] however, in-hospital, 30-day and 1-year mortalities were significantly lower in patients who received dexmedetomidine in our study.

Dexmedetomidine is widely used for anesthetic premedication, sedation, anxiolysis and analgesia.[11] Alpha-2 agonists have been show to be beneficial in the setting of noncardiac surgery where they significantly reduce mortality in patients with coronary artery disease. An investigation found 17% of non-cardiac surgery patients received dexmedetomidine in preoperatively or intraoperatively between 2007 and 2008.[28] 11.7% of cardiac surgery patients received intravenous infusion sedation after surgery from 2001 to 2007.[29] The perioperative use of dexmedetomidine continues to increase, especially in patients with cardiac disease. In this study more than 50% of the cardiac surgery patients received dexmedetomidine. A meta-analysis has indicated that alpha-2 agonists may reduce cardiac risk, especially during vascular surgery.[13] It would be reasonable to postulate that perioperative dexmedetomidine use might also confer an early postoperative benefit for cardiac surgical patients given the well-proven benefits of sympatholysis, anti-inflammatory and anti-delirium effects in the setting of cardiac surgery.

Although, there is not enough evidence to prove the beneficial effect of dexmedetomidine on myocardial function in our study, the trend of MACE supports this effect. Studies have shown dexmedetomidine provides protective effects on the myocardium. Alpha 2-adrenergic agonists have protective effects against myocardial ischemia by increasing the cAMP level and enhancing adenosine-induced coronary vasodilatation effect.[30-32] Dexmedetomidine preconditioning has been shown to attenuate myocardial I/R injury by activating pro-survival kinases. [33]

Surgery and other forms of trauma can activate the sympathetic nervous system initiating systemic inflammatory responses that can disrupt the function of the CNS.[34] Proinflammatory cytokines have been shown to play a key role in mediating surgery-induced neuroinflammation and subsequent postoperative cognitive changes.[35] Dexmedetomidine attenuates isoflurane-induced neurocognitive impairment and reduces the prevalence of delirium.[19] In a multi-center ICU sedation study, dexmedetomidine-treated patients spent less time on the ventilator and experienced less delirium.[36] Our study also found those who received dexmedetomidine use had significant lower incidence of delirium after cardiac surgery even though the prevalence of delirium in our study was lower than most reported results.[37] This may be because we only included patients with hyperactive delirium in this analysis. Delirium has been observed at higher rates after cardiac surgery, especially older patients, but the rate of hyperactive delirium seen is far lower than

emotional delirium. [37] Pandharipande and colleagues recently suggested that the prevalence of pure hyperactive delirium was only 1% in surgical ICU patients whereas the majority of patients had either a mixed (9%) or hypoactive (73%) delirium.[38]

By stabilizing the sympathetic nervous system, exerting anti-inflammatory effects and attenuating I/R injury, dexmedetomidine produces its protective effects on the functions of heart, brain, lung, kidney, intestine and immune system.[16-20,27,30,31] Because CPB has adverse effects on all of these same organs, complications inevitably occur after cardiac surgery. Our results indicate just over 50% of patients experienced some postoperative complications. Dexmedetomidine reduced the overall incidence of any complication, a measure that includes all postoperative events that occurred during the hospitalization. But use of dexmedetomidine in this study was associated with an increase in the incidence of postoperative renal dysfunction. Renal protective effects have been reported for alpha2-adrenoceptor agonists.[18] The contrary results association in this study might reflect the timing of dexmedetomidine administration since the beneficial administered the drug prior to the renal insult.[39] In addition, in this study the incidence of preoperative renal failure was greater in the DEX group. Further studies to confirm this result are required.

Limitations

There are several limitations of this investigation. First, this is an observational cohort study. Multivariate regression in combination with propensity score adjustments was applied to this study population to reduce evident biases, however, the potential confounding biases associated with a non-randomized study remain. Second, cardiac surgical patients share common risks of postoperative complications involving the heart, brain and kidneys despite the widely varying types of surgery. Dexmedetomidine, may impact the common pathway responsible for these complications by its sympatholytic and anti-inflammatory effects, however, further studies to analyze its impact on different types of cardiac surgery are required and could provide more definitive information about the potential benefits of dexmedetomidine in this setting. Thirdly, although the rate of dexmedetomidine use was much higher in patients undergoing cardiac surgery among this cohort than previous cohort study, [28] further prospective, multicenter randomized studies are required to confirm the benefit demonstrated in this study. Finally, because the data of our study was extracted from STS, which is a voluntary database, the possibility of underreporting or forging adverse outcomes in data submitted to STS is a concern. However, the STS guarantees strict confidentiality, which removes much of the motivation for event underreporting. Moreover, underreporting would unlikely preferentially affect those who were indicated as having received dexmedetomidine compared with those who were not. Recently, the investigations of data quality and outcomes in the STS have demonstrated remarkable similarity between voluntary STS data (e.g. percent, age, missing data, incidence, and trend analyses) with audited data and mandatory cardiac databases.[40-42]

Conclusions

This study is the first to demonstrate that cardiac surgical patients who received an intravenous dexmedetomidine infusion after CPB were more likely to have better in-hospital, 30-day and 1-year survival. The perioperative use of dexmedetomidine is also associated with a significant decrease in the incidence of postoperative overall complications and delirium. There was no evidence of adverse hemodynamic side effects of dexmedetomidine in patients undergoing cardiac surgery. A prospective, multicenter randomized study focused on the use of dexmedetomidine in cardiac surgery patients is indicated to confirm these findings.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Clinical Commentary

There are approximately 7 million invasive cardiovascular procedures performed worldwide each year. Cardiac surgery is associated with a high risk of cardiovascular and other complications that translate into increased mortality and healthcare costs. In this single-centered analysis of consecutive patients undergoing cardiac surgery, the perioperative dexmedetomidine use is associated with improved survival. We observed significant reductions delirium, overall complications, in-hospital, 30-day and 1-year mortalities after cardiac surgery in the patients who had received dexmedetomidine during the perioperative period. At the same time, there was no evidence of adverse hemodynamic side effects of dexmedetomidine in patients undergoing cardiac surgery. Dexmedetomidine is a commercially available medication and has been used extensively for sedation. Use of dexmedetomidine as an anesthesia adjuvant was associated with better outcomes in patients undergoing cardiac surgery. This further suggested that the use of dexmedetomidine played an important role in mortality and morbidity reduction after cardiac surgery and should be part of the perioperative medication regiment in this patient population.

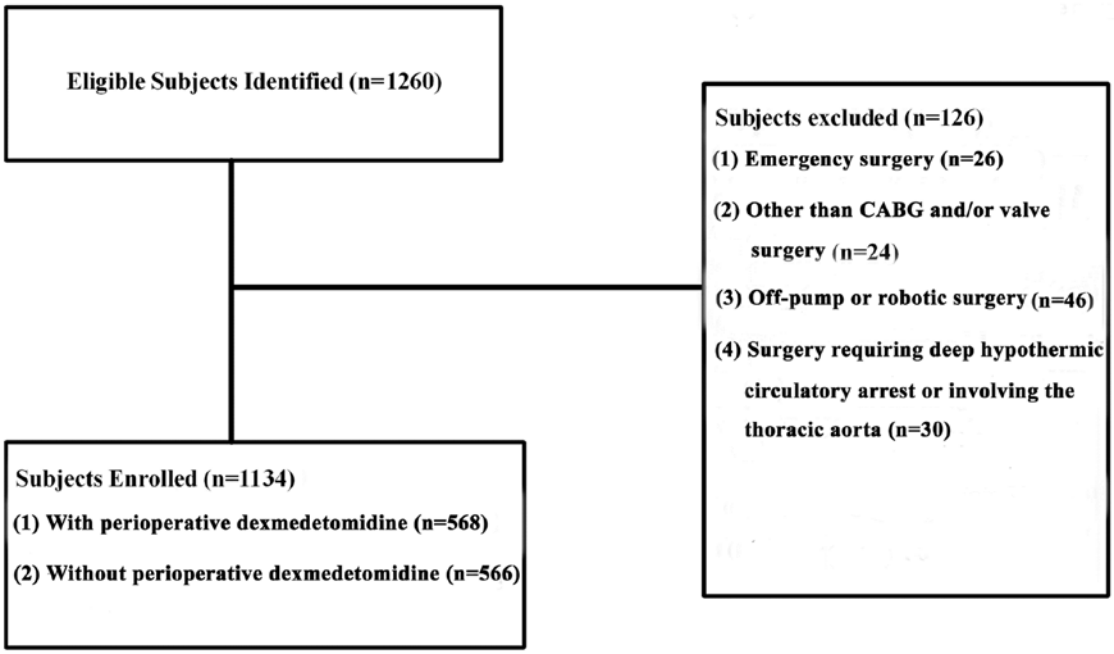


Figure 1.
Study population recruitment summary.

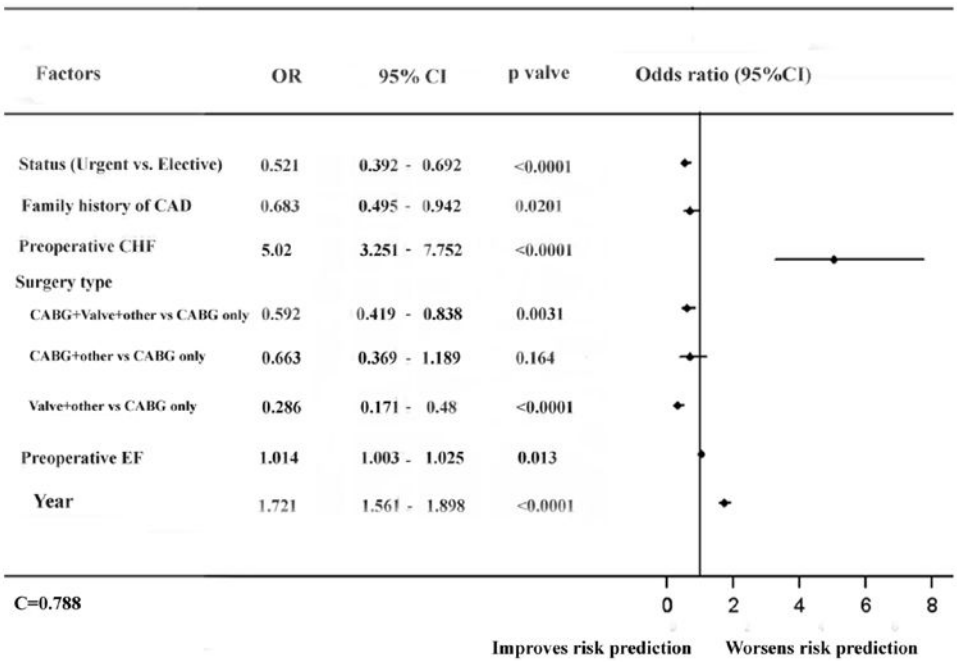
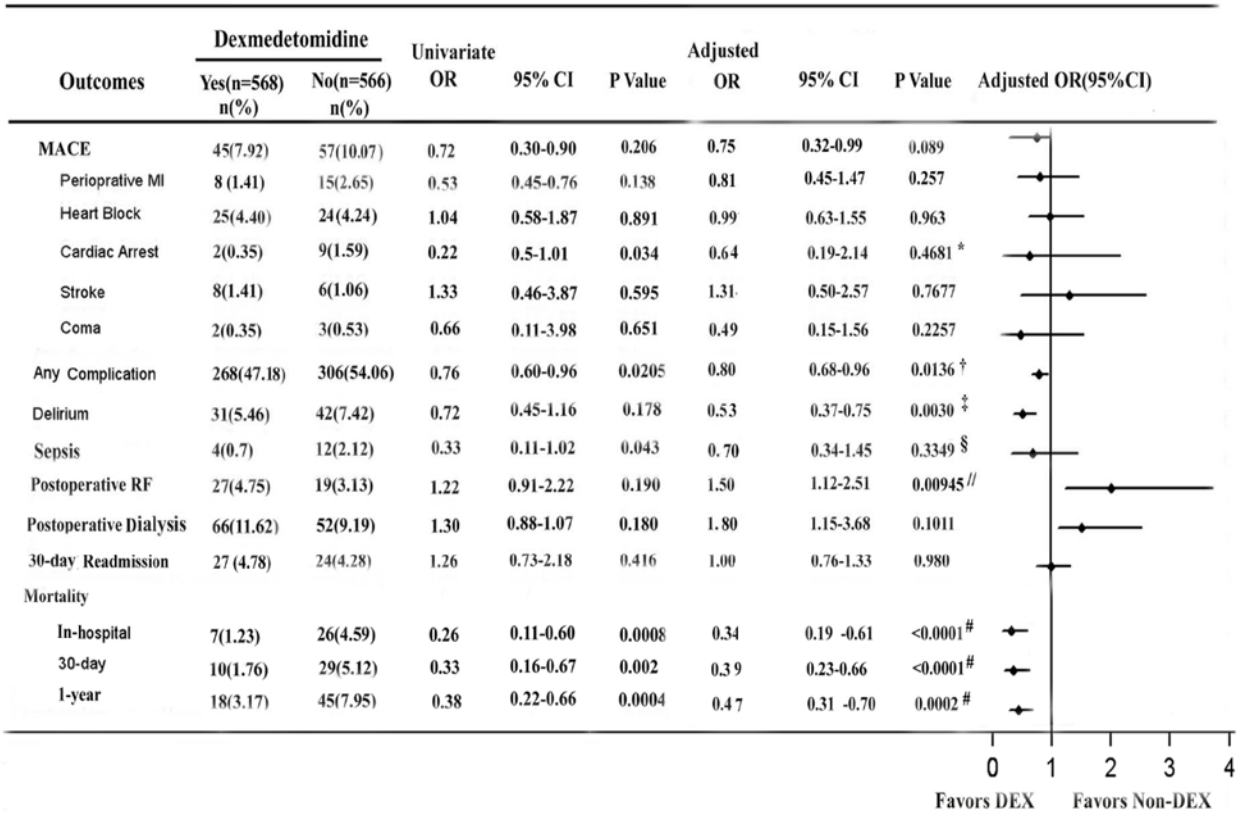


Figure 2.

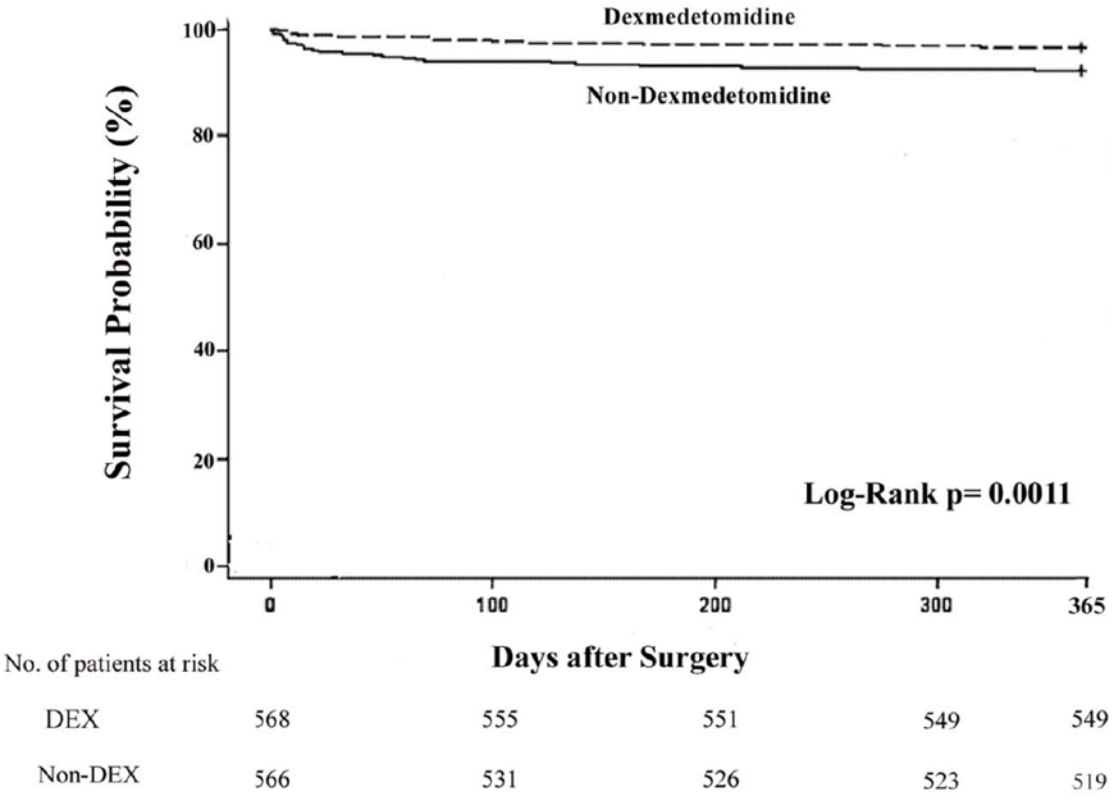
Parsimonious multi variable propensity model for dexmedetomidine use. OR, odds ratio; CI, confidence interval; Family history of CAD, preoperative family history of coronary artery disease; PreOp CHF, preoperative congestive heart failure; CABG, coronary artery bypass graft; PreOp EF, preoperative ejection fraction.



Outcomes	Dexmedetomidine Yes(n=568) n(%)	Dexmedetomidine No(n=566) n(%)	Univariate OR	95% CI	P Value	Adjusted OR	95% CI	P Value
MACE	45(7.92)	57(10.07)	0.72	0.30-0.90	0.206	0.75	0.32-0.99	0.089
Perioprative MI	8 (1.41)	15(2.65)	0.53	0.45-0.76	0.138	0.81	0.45-1.47	0.257
Heart Block	25(4.40)	24(4.24)	1.04	0.58-1.87	0.891	0.99	0.63-1.55	0.963
Cardiac Arrest	2(0.35)	9(1.59)	0.22	0.5-1.01	0.034	0.64	0.19-2.14	0.4681 *
Stroke	8(1.41)	6(1.06)	1.33	0.46-3.87	0.595	1.31	0.50-2.57	0.7677
Coma	2(0.35)	3(0.53)	0.66	0.11-3.98	0.651	0.49	0.15-1.56	0.2257
Any Complication	268(47.18)	306(54.06)	0.76	0.60-0.96	0.0205	0.80	0.68-0.96	0.0136 †
Delirium	31(5.46)	42(7.42)	0.72	0.45-1.16	0.178	0.53	0.37-0.75	0.0030 ‡
Sepsis	4(0.7)	12(2.12)	0.33	0.11-1.02	0.043	0.70	0.34-1.45	0.3349 §
Postoperative RF	27(4.75)	19(3.13)	1.22	0.91-2.22	0.190	1.50	1.12-2.51	0.00945 //
Postoperative Dialysis	66(11.62)	52(9.19)	1.30	0.88-1.07	0.180	1.80	1.15-3.68	0.1011
30-day Readmission	27 (4.78)	24(4.28)	1.26	0.73-2.18	0.416	1.00	0.76-1.33	0.980
Mortality								
In-hospital	7(1.23)	26(4.59)	0.26	0.11-0.60	0.0008	0.34	0.19 -0.61	<0.0001 #
30-day	10(1.76)	29(5.12)	0.33	0.16-0.67	0.002	0.39	0.23-0.66	<0.0001 #
1-year	18(3.17)	45(7.95)	0.38	0.22-0.66	0.0004	0.47	0.31 -0.70	0.0002 #

Figure 3.

Effects of dexmedetomidine on postoperative complications and mortality in patients undergoing cardiac surgery. Values are numbers (%) for categorical variables. OR, odds ratio; CI, confidence interval; MACE, major adverse cardiocerebral events; MI, myocardial infarction; RF, renal failure; DEX, dexmedetomidine. *Adjusted for propensity score, age, body mass index, diabetes, current smoking, surgical type, IABP use and family history of CAD before surgery. †Adjusted for propensity score, age, status of procedure, BMI, creatinine level, smoking, chronic lung disease, cerebrovascular disease, peripheral vascular disease, family history of CAD, diabetes, hypertension, renal failure, MI, CHF, IABP, beta blockers, angiotensin-converting enzyme inhibitors, anticoagulants, anti-platelet drugs, steroids, aspirin, surgical type, EF, perfusion time, and year of surgery.‡Adjusted for propensity score, age, smoking, diabetes and surgical type; §, Adjusted for propensity score, age, diabetes perfusion time, and year of surgery. ‖ Adjusted for propensity score, age, status of procedure, family history of CAD, diabetes, hypertension, surgical type and angiotensin-converting enzyme. # Adjusted for propensity score, age, status of procedure, family history of CAD, surgical type and perfusion time.



No. of patients at risk					
DEX	568	555	551	549	549
Non-DEX	566	531	526	523	519

Figure 4.

Survival estimates after cardiac surgery. Survival probabilities were calculated with the use of Kaplan–Meier methods and compared with the use of a log-rank test (Log -Rank test, chi-square=10.734, p=0.0011). The dash line represents the survival probabilities of individuals who received dexmedetomidine; the solid line represents the survival probabilities of individuals who did not. DEX, dexmedetomidine.

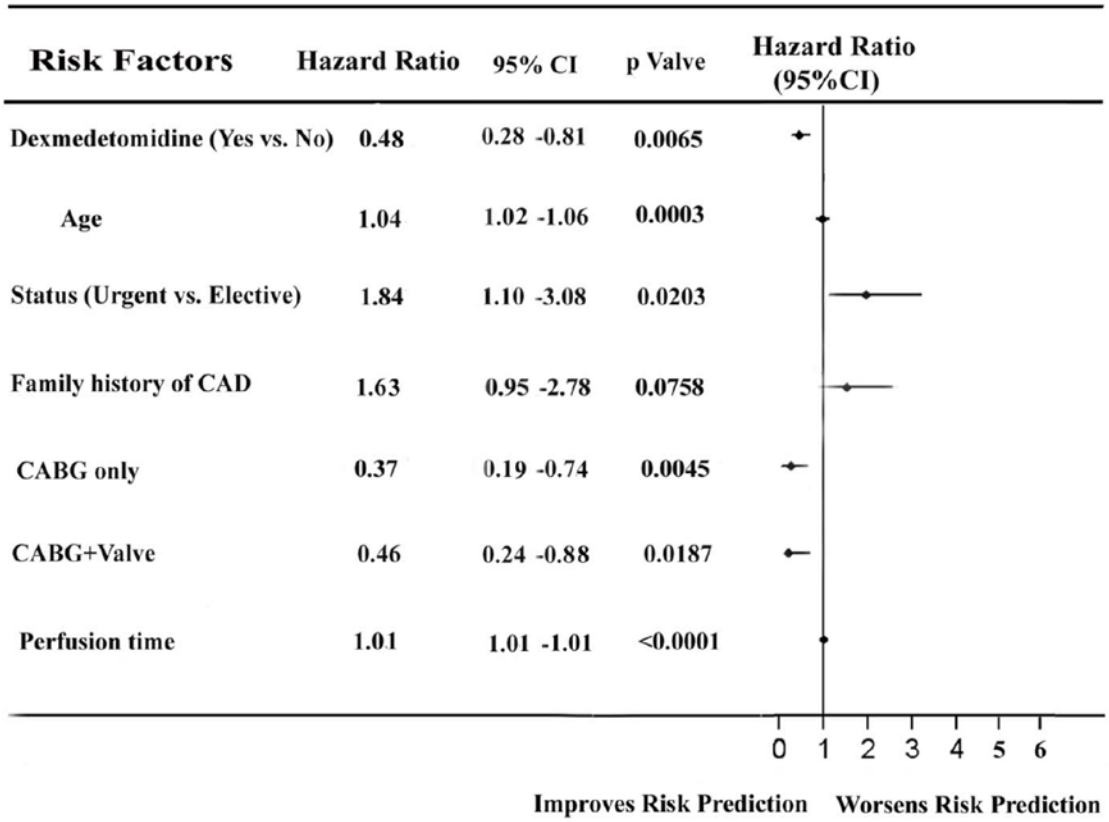


Figure 5.

Cox proportional hazard model for 1-year mortality following cardiac surgery. OR, odds ratio; CI, confidence interval; CAD, coronary artery disease; CABG, coronary artery bypass graft.

Table 1

Demographic and Clinical Characteristics

Characteristics	Dexmedetomidine		p-value
	Yes (N=568)	No (N=566)	
Age	63.0 (12.0)	63.5 (11.1)	0.524
Gender (F)	159 (27.99)	166 (29.33)	0.619
Race (White)	384(67.67)	383(67.61)	0.982
BMI	29.5 (6.3)	29.9 (6.9)	0.231
Past medical history			
Current smoking	107 (18.84%)	126 (22.26)	0.154
Chronic lung disease	490(86.27)	476(84.10)	0.711
Cerebrovascular disease	94(16.55)	94(19.61)	0.181
Peripheral vascular disease	80(14.08)	84(14.84)	0.717
Family history of CAD	109(19.19)	168(29.68)	<.0001
Diabetes	204(35.92)	204(31.27)	0.098
Hypertension	436(76.94)	437(77.03)	0.970
Dyslipidemia	384(67.61)	253(44.70)	<.0001
History of renal failure	31(5.460)	14(2.470)	0.010
Dialysis	19(3.35)	11(1.94)	0.142
Pre-op MI	245(43.46)	186(32.57)	0.0002
CHF	179(31.51)	42(7.42)	<.0001
EF %	49.7 (13.6)	52.5 (12.8)	0.0004
Preoperative Medication			
ACEI	285(50.18)	326(57.60)	0.012
Beta Blockers	394(69.54)	374(66.08)	0.212
Nitrates	16(2.82)	20(3.53)	0.492
Anti platelets	9(1.58)	6(1.06)	0.440
Coumadin	42(7.39)	37(6.54)	0.571
Inotropes	2(0.35)	7(1.24)	0.093
Aspirin	456(77.290)	439(80.570)	0.176
Lipid lowering	371(65.49)	296(52.30)	<.0001
Propensity score	0.627 (0.217)	0.376 (0.219)	<.0001

Values are n (%) for categorical variables and mean ±SD for continuous variables. BMI, Body Mass Index; CAD, Coronary Arterial Disease; Pre-op MI, preoperative myocardial infarction (MI); CHF, Chronic heart failure; IABP, Intra- aortic balloon pump; EF, ejection fraction; ACEI, angiotensin converting enzyme inhibitors

Table 2

Procedural Characteristics

Characteristics	Dexmedetomidine		p-valve
	Yes (N=568)	No (N=566)	
Perfusion time (min)	181.8 (76.6)	199.8 (81.6)	0.0001
Cross clamp time (min)	128.9 (63.9)	144.8 (62.5)	<0.0001
IABP used, no. (%)	39(6.87)	80(14.13)	<0.0001
Surgery type, no. (%)			
CABG Only	311(54.75)	304(53.70)	0.766
CABG+Valve	121(21.03)	116(20.49)	0.770
CABG+Other	39 (6.89)	29(5.110)	0.2158
Valve+(Valve+Other)	90(15.84)	107(20.77)	0.183
No. Vessels bypassed	3.92±1.16	4.01±1.08	0.337
Surgeon, no/no. (%)			
#1	610/686 (88.8)		
#2	229/254 (90.2)		
#3	203/247(82.2)		
#4	92/114 (80.7)		

Values are n (%) for categorical variables and mean ± SD for continuous variables. IABP, Intra- aortic balloon pump; CAB, Coronary arterial bypass; no/no, numbers of enrolled patients/total numbers of cardiac surgeries performed by one specific surgeon.

Table 3

Postoperative Ventilation, ICU and Hospital Stay Time

Outcomes	Unadjusted			Risk Adjusted		
Postoperative	**DEX (n=568)**	**Non-DEX (n=566)**	**p valve**	**DEX (n=568)**	**Non-DEX (n=566)**	**p valve**
Ventilation hours	30.0±83.4	41.5±135.3	0.0858	35.6	35.9	0.9612
ICU hours	110.2±162.9	112.8±159.2	0.7901	102.2	120.8	0.0509
LOS (days)	9.1±10.6	9.2±8.9	0.6683	8.8	9.6	0.1454

Unadjusted values are presented as mean±SD and risk adjusted values are presented as mean for continuous variables. ICU, intensive care unit; LOS, length of hospital stay; DEX, dexmedetomidine

Table 4

Predicted 1-Year Mortality by Quintile of Propensity Score

Quintile	Number		Propensity score		p-valve	Mortality		p-valve
	DEX	Non-DEX	DEX	Non-DEX		DEX	Non-DEX	
1	30	196	0.194	0.161	0.998	0.0499	0.1039	0.0495
2	89	145	0.342	0.316	0.99	0.0433	0.0631	0.7963
3	100	120	0.499	0.490	0.449	0.0287	0.0789	0.0009
4	165	62	0.670	0.662	0.215	0.0282	0.0607	0.2632
5	184	43	0.861	0.853	0.866	0.0305	0.0988	0.0002

Propensity score reflected mean propensity score; Mortality reflected mean predicted 1-year mortality; Quintile 1 contains patients with lowest propensity scores and quintile 5 contains patients with the highest propensity scores. DEX, dexmedetomidine.