Preoperative Use of Statins Is Associated with Reduced Early Delirium Rates after Cardiac Surgery

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Background: Delirium is an acute deterioration of brain function characterized by fluctuating consciousness and an inability to maintain attention. Use of statins has been shown to decrease morbidity and mortality after major surgical procedures. The objective of this study was to determine an association between preoperative administration of statins and postoperative delirium in a large prospective cohort of patients undergoing cardiac surgery with cardiopulmonary bypass.

Methods: After Institutional Review Board approval, data were prospectively collected on consecutive patients undergoing cardiac surgery with cardiopulmonary bypass from April 2005 to June 2006 in an academic hospital. All patients were screened for delirium during their hospitalization using the Confusion Assessment Method in the intensive care unit. Multivariable logistic regression analysis was used to identify independent perioperative predictors of delirium after cardiac surgery. Statins were tested for a potential protective effect.

Results: Of the 1,059 patients analyzed, 122 patients (11.5%) had delirium at any time during their cardiovascular intensive care unit stay. Administration of statins had a protective effect, reducing the odds of delirium by 46%. Independent predictors of postoperative delirium included older age, preoperative depression, preoperative renal dysfunction, complex cardiac surgery, perioperative intraaortic balloon pump support, and massive blood transfusion. The model was reliable (Hosmer-Lemeshow test, $P = 0.3$) and discriminative (area under receiver operating characteristic curve = 0.77).

Conclusions: Preoperative administration of statins is associated with the reduced risk of postoperative delirium after cardiac surgery with cardiopulmonary bypass.

DELIRIUM is an important and widespread problem after cardiac surgery. The entity is defined as an acute deterioration of brain function characterized by fluctuating consciousness and an inability to maintain attention.[1] The prevalence of delirium after cardiac surgery is reported in a range of 3–47% of patients.[2-5] Delirium is associated with prolonged length of stay,[6-9] increased healthcare costs,[10,11] and higher mortality.[12,13] It has been estimated that about $6.9 billion of Medicare hospital expenditures are attributable to delirium.[14] Importantly, approximately 40% of delirium patients develop a chronic brain syndrome,[15] while only 4% of patients experience full resolution of symptoms of delirium at discharge.[16] The functional decline still persists 6 months after hospital discharge.[17]

The exact pathophysiologic mechanisms involved in the development of delirium after cardiac surgery are not well understood. It has been proposed that anatomical deficit and the imbalance of neurotransmitters are probably related to this condition.[18-20] However, the creation of animal models of delirium is problematic and therefore the pathophysiologic and anatomical aspects of delirium are extremely difficult to explore.

According to the neurotransmitter theory, delirium may be a result of reduced cholinergic function; excess release of dopamine, norepinephrine, and glutamate; and altered serotonergic and γ-aminobutyric activity.[20] These changes may be more pronounced in the presence of cerebral hypoperfusion, systemic inflammatory response, and cerebral embolism,[21-25] causing further impairment in microcirculation that may manifest itself as delirium.

Statin administration has been shown to decrease morbidity and mortality after cardiac[26] and major noncardiac[27] surgery. Animal and human studies have demonstrated a beneficial effect of statins in central neural system injury.[26,28,29] The antithrombotic, antiinflammatory, and immunomodulatory properties of statins are suggested to be responsible for these protective effects.[30,31] The objective of this study was to determine an association between preoperative administration of statins and early postoperative delirium in a large prospective cohort of patients undergoing cardiac surgery with cardiopulmonary bypass (CPB).

Materials and Methods

After Institutional Review Board approval (Toronto General Hospital, University Health Network, Toronto, Canada), we examined data collected prospectively as a part of the Toronto Anesthesia Perioperative Outcomes Database on 1,059 consecutive patients undergoing cardiac surgery with CPB from April 2005 to June 2006. Patients undergoing congenital or redo surgery, or requiring circulatory arrest, were excluded. As the Confu-

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sion Assessment Method (CAM) in the intensive care unit (ICU) was a part of standard clinical assessment, written informed consent was not requested.

Anesthetic Management

All patients received premedication with 1 to 2 mg lorazepam 1 to 2 h before surgery. Anesthetic technique was standardized to include 10 to 20 mcg/kg fentanyl, 0.1 mg/kg midazolam, 0.15 to 0.20 mg/kg pancuronium, and 0.5 to 1.5% isoflurane. After surgery, patients were transferred to the ICU for postoperative ventilation. Sedation was achieved with 0.5 to 4 mg · kg^{-1} · h^{-1} propofol infusion and morphine boluses. Patients were extubated according to the following criteria: patient responsive and cooperative, arterial oxygen saturation > 94% with inspired oxygen fraction < 60%, complete reversal of neuromuscular blockade, Paco$_2$ 35–55 mmHg, stable hemodynamics, absence of uncontrolled arrhythmia, and nasopharyngeal temperature > 36°C. Statin therapy was restarted in all extubated patients within the first 2 postoperative days.

CPB Management

Anticoagulation was achieved with heparin to maintain an activated clotting time above 480 s. The CPB circuit was primed with 1.8 l Ringer's Lactate and 50 ml 20% mannitol. Albumin (25%) and synthetic colloids (Pentaspan®; Bristol-Myers Squibb, Montreal, Canada) were added to the circuit as needed. Management of CPB included systemic temperature drift to 34°C, α-stat pH management, targeted mean perfusion pressure between 50–70 mmHg, and pump flow rates of 2.0–2.4 l · min^{-1} · m^{-2}. Myocardial protection was achieved with intermittent antegrade, and occasionally retrograde, blood cardioplegia. After separation from CPB, heparin was neutralized with 1 mg protamine per 100 U of heparin, to achieve an activated clotting time within 10% of the baseline.

Delirium Assessment

Delirium was assessed with the CAM-ICU every 12 h postoperatively. The CAM-ICU allows the monitoring of delirium in both ventilated and extubated patients.[32] It is based on the Diagnostic and Statistical Manual of Mental Disorders criteria and includes a 4-step algorithm assessing the following: (1) an acute onset of changes or fluctuations in the course of mental status, (2) inattention, (3) disorganized thinking, and (4) an altered level of consciousness. The patient is determined to be delirious (CAM-positive) if he or she manifests both features (1) and (2), plus either feature (3) or (4).

The CAM-ICU measurements were performed by the cardiovascular ICU nurses. All nurses were educated and well trained in the application of the CAM-ICU in both ventilated and nonventilated patients. The training was provided by the nurse-educators, who used the introduction lecture and series of in-service sessions.

The nurses were unaware of the study goals.

Variables of Interest

Preoperative Variables Included. The preoperative variables included age, sex, diabetes mellitus, peripheral vascular disease, history of cerebrovascular accident or transient ischemic attack, hypertension, New York Heart Association class > 2, anemia (hemoglobin < 120 mg/dl), renal dysfunction (creatinine > 150 μM), depression, and statin administration. Diagnosis of preoperative depression was made on the basis of information provided by the referring physician and the patient's history.

Intraoperative Variables Included. The type of surgery (valve surgery, coronary artery bypass graft (CABG) surgery, or combined CABG/valve surgery), hematocrit < 19%, hyperglycemia (glucose > 9 mM), hyponatremia (sodium < 132 mEq/l), mean arterial blood pressure lower than 50 mmHg during CPB, duration of CPB, and the prevalence of massive blood transfusion (> 5 units of red blood cells).

Statistical Analysis

Univariate Analysis. Frequency analysis was performed for the variables of interest. Associations between the outcome and the independent variables (demographic characteristic and clinical factors) were assessed with the chi-square and Fisher exact test. Unadjusted odds ratios and 95% Wald CIs were also computed.

Multivariate Analysis. For multivariate analysis, ordinary logistic regression was used. A multistep model fitting procedure was performed to identify a number of significant covariates to adjust for in the logistic regression model while assessing the effect of statins. At the first step, the number of candidate covariates was reduced so that the number of observations with the less common outcome (patients with delirium) was equal to at least 10 times the number of predictors.[33] The selection was made based on univariate analysis, where, in addition to statins, covariates with lowest P values were kept.

At the second step, a backward and stepwise automated model selection procedure was performed, with initial set of predictors those selected at the first step, and with keeping statins forced into the model. The significance of statins as independent predictor of delirium was evaluated based on its significance in the best-fitted multivariate model.

Covariate Effect. The significance of the covariate effect was assessed with the use of a Wald test, with low P values indicating a significant effect. The coefficient of the covariate was returned, as well as the odds ratios and the 95% CIs.

Interaction Effect. Interaction effects between statins and other covariates or between pairs of other covariates were not investigated because of the large number of potential covariates and possible interactions. Such investigation would require a large number of additional tests of significance for those interaction terms,

Table 1. Demographic Data and Surgical Characteristics

	Delirium Group (n = 122)	No Delirium Group (n = 937)	OR (95% CI)	P Value
Preoperative				
Age ≥ 60 yr	101 (83%)	573 (58.5%)	3.41 (2.09, 5.56)	< 0.0001
Sex (men)	79 (65%)	673 (72%)	1.39 (0.39, 2.07)	0.1
Hypertension	83 (68%)	556 (59%)	1.45 (0.97, 2.18)	0.06
DM	39 (32%)	237 (25%)	1.39 (0.92, 2.09)	0.1
PVD	23 (18.8%)	133 (14.2%)	1.40 (0.86, 2.24)	0.1
CVA, TIA	19 (15.6%)	81 (8.6%)	1.95 (1.13, 3.34)	0.014
NYHA class > 2	89 (73%)	570 (60%)	1.74 (1.14, 2.64)	0.009
Hb < 12 g/dl	112 (93%)	907 (97%)	0.36 (0.16, 0.78)	0.007
Creatinine > 150 μM	52 (43%)	144 (15%)	4.09 (2.74, 6.1)	< 0.0001
Depression	11 (9%)	29 (3%)	3.12 (1.52, 6.42)	0.004
Statins	73 (59%)	603 (64%)	0.83 (0.56, 1.21)	0.3
Intraoperative				
Combined CABG/valve surgery	41 (33%)	135 (14%)	3.01 (1.98, 4.57)	< 0.0001
CPB Ht < 19%	17 (14%)	91 (10%)	1.51 (0.86, 2.62)	0.14
CPB BG > 9 mM	29 (24%)	165 (17.6%)	1.46 (0.93, 2.29)	0.09
CPB Na$^+$ < 132 mEq/l	34 (27.8%)	248 (26.5%)	1.07 (0.7, 1.6)	0.7
CPB > 90 min	84 (68.9%)	510 (54.4%)	1.85 (1.24, 2.77)	0.0025
IABP support	15 (12%)	22 (2%)	3.84 (1.72, 8.57)	< 0.0001
RBC > 5 units	48 (42%)	115 (12%)	5.12 (3.4, 7.7)	< 0.0001

BG = blood glucose; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; CVA = cerebrovascular accident; DM = diabetes mellitus; Hb = hemoglobin; Ht = hematocrit; IABP = intraaortic balloon pump; NYHA = New York Heart Association; OR = odds ratio; PVD = peripheral vascular disease; RBC = red blood cells; TIA = transient ischemic attack.

with doubtful inference. Lack of previous evidence of such interaction effects justified this decision.

Goodness of Fit. The fit of the optimal selected model was assessed with various tests including a Likelihood Ratio test, a Wald test, and a Score test. These tests compare the selected model with the model without any covariate (intercept only). Low P values indicate that the selected model is fitting the data significantly better than the intercept-only model. An additional test for the fit of the model was done using a Hosmer-Lemeshow test,[34] where actual event frequencies are compared with the expected ones, given the selected model. Low P values indicate a large deviation and therefore a bad fit to the data. Finally, outlier and extreme influential observations were identified by visual inspection of residual plots and potentially removed to give a better fit to the model.

Model Validation. Various aspects of the automatic model selection procedure were validated internally using bootstrap.[35] For each bootstrap sample, a stepwise model selection procedure was performed, leading to potentially different models (while statins was always forced in the models). The robustness of this procedure was evaluated by the consistency of the selected covariates in the optimal model. In addition, the bootstrap CI of the odds ratio of statins was calculated (using the bootstrap-t method[36]) and compared with the one produced by the whole sample. Finally, the predictive strength of the model selected by this procedure was evaluated by the area under the receiver operating characteristic curve, using the nonparametric ".632" estimate. This estimate is equal to $0.368*apparent + 0.632*average(test)$, where $apparent$ is the estimate us-

ing the whole data set, and $test$ is the estimate from the patients not selected in the bootstrap sample.[35,37] One thousand bootstrap samples were used for the validation. External validation, although desirable, was not performed because of the lack of external data.

All statistical analyses were performed with SAS version 9.1 software (SAS Institute, Inc., Cary, NC) and R version 2.5.0 software (The R Foundation for Statistical Computing, Vienna, Austria) under the Microsoft Windows XP Professional (Version 2002, Service Pack 2; Microsoft Corporation, Redmond, WA) operating system.

Results

All patients included in the study had the CAM-ICU assessment every 12 h during their cardiovascular ICU admission. Five hundred sixty-nine patients had 1 CAM-ICU assessment, 186 patients had 3 CAM-ICU assessments, and 304 patients had 5 or more CAM-ICU assessments. Postoperative delirium was present in 11.5% of patients (122 of 1,059) at any time during their cardiovascular ICU stay. A total of 63 patients (52%) were CAM-ICU-positive on the first postoperative day. Another 25 patients (21%) developed delirium on the second postoperative day. Twenty-four patients (20%) were CAM-ICU-positive between postoperative Days 3 and 5. The remaining 10 patients (8%) developed delirium between postoperative Days 6 and 12.

Demographic data and surgical characteristics in patients with and without delirium are reflected in table 1. There was no difference regarding perioperative benzodiazepine and narcotic analgesic use between the two groups.
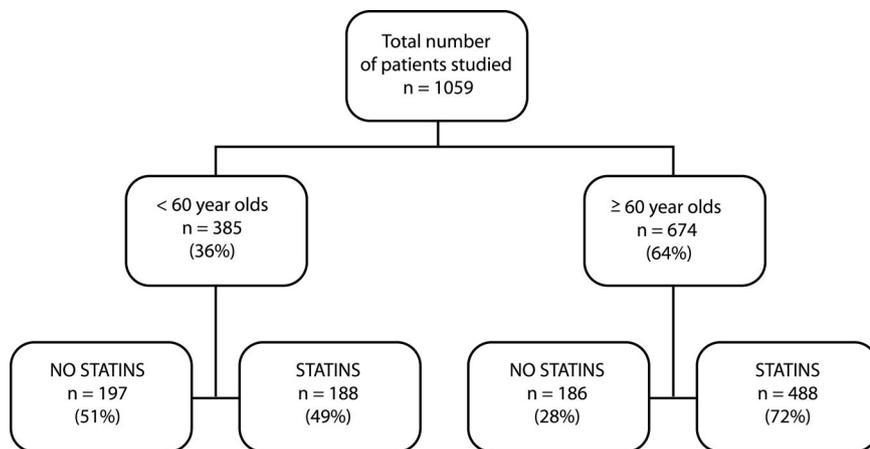
Fig. 1. Schematic of preoperative administration of statins stratified by patients' age.

Preoperative statins were administered in 63.8% of patients (676 of 1,059). Older patients ($\geq$ 60 yr of age) were more likely to receive preoperative statins ($P <$ 0.0001, fig. 1). Univariate analysis showed that administration of statins was associated with reduced postoperative delirium rates in patients $\geq$ 60 yr of age (fig. 2). After univariate analysis, the following predictors, along with statins, were selected for multivariate model selection (with the lowest P values): sex, older age, preoperative depression, preoperative renal dysfunction, hypertension, peripheral vascular disease, New York Heart Association class > 2, preoperative anemia, diabetes, preoperative history of cerebrovascular accident and transient ischemic attack, prolonged cardiopulmonary bypass, intraoperative anemia and hyperglycemia, complex cardiac surgery, perioperative intraaortic balloon pump support, and massive blood transfusion. After applying automated model selection, the following variables remained in the best-fitted model: older age, preoperative depression, preoperative renal dysfunction, complex cardiac surgery, perioperative intraaortic balloon pump support, and massive blood transfusion. Adjusting for those variables, administration of statins had a statistically significant protective effect, reducing the odds of delirium by 46% (table 2). The model fitted well, with the likelihood ratio test being significant (chisquare = 126.2520 at 7 df, P value $< .0001$). The Hosmer-Lemeshow test indicated good calibration (chisquare = 7.8787 at 7df, P value = 0.3434). The c statistic, estimate of the area under the receiver operating characteristic curve, as calculated by PROC LOGISTIC in SAS [3], was equal to 0.774.

Validation using bootstrap showed a satisfactory consistency in the covariates remaining in the multivariate model after the automatic model selection procedure. Each one of the six covariates (along with statins) selected in the model using the whole dataset appeared in at least 75% of the repetitions, while the next in-order covariate (history of cerebrovascular accident or transient ischemic attack) appeared in only 43% of the models (table 3). This validates the procedure followed for the model selection. In addition, the bootstrap CI of the odds ratio of statin against the delirium outcome was (0.346, 0.891), only slightly wider than the interval generated by the model using the whole data set (0.350, 0.847).

Finally, the ".632" estimate of area under the receiver operating characteristic curve was equal to 0.368*0.774 + 0.632* 0.730 = 0.746, suggesting a good discriminative power.

Discussion

In this prospective observational study, we found that the perioperative therapy with statins was associated with decreased delirium rates in patients after cardiac surgery with CPB. This effect was particularly apparent in patients $\geq$ 60 yr of age. The overall postoperative delirium rate was 11.5%. However, in patients $\geq$ 60 yr of age with and without statins, the delirium rates were 13.1% and 19.9%, respectively ($P = 0.03$).

To better understand the reason why statins became significant in the final multivariate model while it was
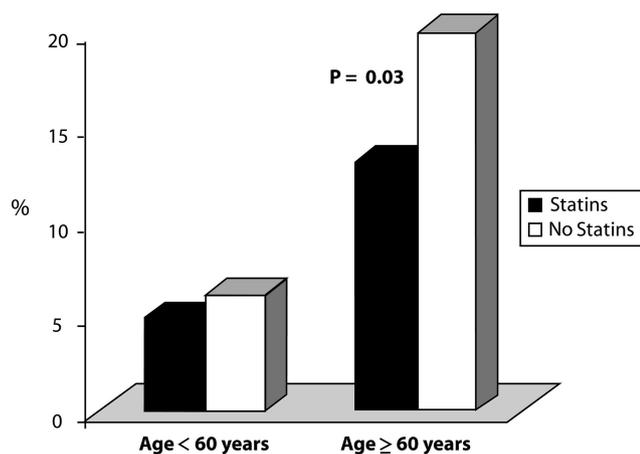

Fig. 2. Delirium rates according to age stratification and administration of statins. Age < 60 yr. Odds ratio (95% CI), 0.78 (0.32, 1.88); $P = 0.57$. Age $\geq$ 60 yr. Odds ratio (95% CI), 0.61 (0.39, 0.95); $P = 0.03$.

Table 2. Independent Predictors of Postoperative Delirium

Variable	Coefficient Estimate	Odds Ratio Point Estimate	95% CI	P Value
Red blood cell transfusion, (> 5 units)	0.5967	3.29	2.09–5.19	< 0.0001
Perioperative intraaortic balloon pump support	0.673	3.84	1.72–8.56	0.001
Preoperative depression	0.559	3.06	1.36–6.90	< 0.01
Preoperative creatinine >150 mm	0.544	2.96	1.9–4.63	< 0.001
Age ≥ 60 yr	0.451	2.47	1.43–4.23	0.001
Combined CABG and valvular surgery	0.309	1.86	1.16–2.98	0.01
Preoperative administration of statins	−0.3	0.54	0.35–0.84	< 0.01

CABG = coronary artery bypass graft; CI = confidence interval.

not significant univariately, we investigated the confounding effects on statins from each one of older age, preoperative depression, preoperative renal dysfunction, complex cardiac surgery, perioperative intraaortic balloon pump support, and massive blood transfusion as predictors. To do this we compared the univariate coefficient and P value of statins with those from logistic regression models with two predictors, statins and one of the variables listed above. We found that adding age into the univariate model caused the biggest discrepancy in the effect of statins on delirium. We investigated this further by contingency tables analysis (table 4), stratifying by older age. The results showed an association between age and statins, where older patients were more likely to take statins, as compared with younger patients (odds ratio = 2.75). In addition, delirium rates were higher in older patients (14.99%) than younger ones (5.45%). In the marginal table, the tendency of reducing delirium is small, because of the fact that patients who take statins are more likely to be older, and

older patients are more likely to have delirium, so the statins effect is diluted. On the other hand, the conditional association controlling for age shows a strong tendency for patients who take statins to reduce the risk of delirium, and the effect is stronger for older patients. This explains the low significance of statins in the univariate (marginal) analysis, which becomes high when age is controlled for.

Our findings were similar to recent studies by Bucerius et al.[5] and Kazmirski et al.,[38] who reported the prevalence of delirium in a range of 8.4–11.5% after cardiac surgery. Furthermore, our study confirmed a number of previous reports[4,5,38–41] identifying that preoperative depression, older age, renal dysfunction, complex surgery, and massive blood transfusion were independent predictors of postoperative delirium.

The combined CABG and valve surgery, intraaortic balloon pump support, massive blood transfusion, and postoperative renal dysfunction are likely a reflection of complexity of surgery and inflammatory response leading to multiorgan dysfunction, resulting in delirium. There is a growing body of evidence suggesting that older patients have higher levels of circulating cytokines and acute phase proteins that may be involved in pathophysiology of postoperative delirium. Ageing is characterized by up to four-fold increase in the blood levels of cytokines and acute phase proteins.[42] The "agitated" inflammatory status in the elderly may explain why the antiinflammatory and antithrombotic effects of statins are particularly prominent in this patient population. This concept has also been suggested in reducing the risk of cognitive impairment in nonsurgical population

Table 3. Consistency in the Covariates Remaining in the Multivariate Model after Validation with the Bootstrapping Method

Variable	Appearance in Optimal Model (%)
Intercept	100
Preoperative statins administration	100
Preoperative creatinine > 150 μm	99.4
RBC > 5 units	98.2
IABP support	91.9
Age ≥ 60 yr	91.2
Depression	80.5
Combined CABG/valve surgery	75.7
History of CVA, TIA	42.9
CPB > 90 min	34.2
Hb < 12 g/dl	29.4
Hypertension	22.2
CPB Ht < 19%	19.9
NYHA class > 2	16.2
CPB BG > 9 mm	16
Sex	14.5
PVD	12
DM	9.4

BG = blood glucose; CABG = coronary artery bypass graft; CPB = cardiopulmonary bypass; CVA = cerebrovascular accident; DM = diabetes mellitus; Hb = hemoglobin; Ht = hematocrit; IABP = intraaortic balloon pump; NYHA = New York Heart Association; PVD = peripheral vascular disease; RBC = red blood cells; TIA = transient ischemic attack.

Table 4. Contingency Table Analysis Reflecting Interaction between Preoperative Statin Administration and Postoperative Delirium According to Age Stratification

Age	Statins	Delirium		Incidence (%)
		Yes	No	
≥ 60 yr	Yes	64	424	13.1
	No	37	149	19.9
< 60 yr	Yes	9	179	4.8
	No	12	185	6.1
Total	Yes	73	603	10.8
	No	49	334	12.8

of elderly women taking statins.[43] Statins also reduced the risk of dementia in the elderly,[44,45] and its use was associated with decreased incidence of postoperative stroke after cardiac surgery.[26]

Statins competitively inhibit HMG-coA reductase, the rate-limiting step of cholesterol formation in the liver. Reduced hepatocytes' cholesterol causes higher expression of low-density lipoprotein receptors on the cell surface, resulting in increased extraction of cholesterol from the circulation. It has been proposed that the neuroprotective effects of statins relate to both their lipid-lowering ability as well as their complex effects on inflammation and endothelial function.[46] In various models of brain injury, acute and chronic administration of statins reduced the infarct size, increased cerebral blood flow in the ischemic penumbra, and improved the behavioral deficits.[28,30] It has also been shown that statins reduced the permeability of the human blood-brain barrier and restricted the transmigration of leukocytes.[47] In various laboratory and clinical studies, statins restrained inflammatory processes on multiple levels by affecting adhesion molecules, chemoattractant proteins, proinflammatory transcription factors, and proinflammatory enzymes.[31] They improved endothelial function, stabilized plaques, and stimulated neovascularization.[48] A recent report by Liakopoulos *et al.*[49] identified that preoperative administration of statins decreased the secretion of proinflammatory and up-regulated the release of anti-inflammatory cytokines in the early postoperative period after cardiac surgery. These findings were supported by another study showing that pretreatment with atorvastatin significantly reduced cytokine release and neutrophil adhesion to the venous endothelium in patients undergoing CABG surgery with cardiopulmonary bypass.[50] Although inflammation is considered to be one of the primary etiologic factors for postoperative cognitive dysfunction, Mathew *et al.*[51] showed that the preoperative statin therapy did not decrease the rate of cognitive decline after CABG surgery. There are several differences between our two studies that may explain the contradictory results. It is currently unknown whether the etiologies of postoperative cognitive decline and postoperative delirium are similar or different. Furthermore, the majority of patients (69%) in our study received atorvastatin *versus* only 22% of patients in the study by Mathew *et al.* The current study assessed the effect of statins in the early postoperative period, while Matthew *et al.*[51] evaluated cognitive function 6 weeks after surgery. It is noteworthy that 46% of the patients receiving preoperative statins were withdrawn from therapy postoperatively. It is possible that discontinuation of statins resulted in reduced cognitive performance in these patients. However, this hypothesis would need to be tested in future studies.

Our study has several limitations. First, our findings point to an association rather than a causal relationship between the statin therapy and reduced postoperative delirium rates. Consequently, a double-blind, randomized, placebo-controlled trial would be required to validate these findings. Second, although the majority of patients received atorvastatin, one-third of patients received a different type of statins. Furthermore, the type of statin therapy could not be determined in 8.5% of patients. Although the different types of statins may have a different ability to penetrate the brain-blood barrier,[52] there is currently no evidence linking the type of statins and outcomes after cardiac surgery. As a result, we did not measure the lipid levels during the perioperative period. Third, we did not screen patients for delirium preoperatively. However, the preoperative delirium rates are extremely low, and it is unlikely that they would have altered our current findings. Fourth, the CAM-ICU assessment was performed in the cardiovascular ICU and was not extended to the cardiac surgical floor. As a result, our findings can only be applied to early postoperative delirium. Further studies would be required to explore the delirium rates on the surgical floor before discharge from the hospital. Fifth, the diagnosis of preoperative depression was based on past medical history and not on screening scale or psychiatric evaluation, and therefore the incidence of preoperative depression could be underestimated. Last, our study mainly focused on pre- and intraoperative predictors, and did not include postoperative variables. Numerous postoperative factors such as hypotension, hypoxia, infection, sedatives, and narcotic analgesics could all play a role in development of delirium after cardiac surgery. A much larger sample size would be required to address these concerns.

In summary, to the best of our knowledge, this is the first report identifying an association between preoperative statin therapy and postoperative delirium in a cardiac surgical population. A double-blind, randomized, placebo-controlled clinical trial would be required to validate these findings.

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