Lack of Association between Preoperative Statin Use and Respiratory and Neurologic Complications after Cardiac Surgery

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ABSTRACT

Background: Statins may reduce the risk of pulmonary and neurologic complications after cardiac surgery.

Methods: The authors acquired data for adults who had coronary artery bypass graft, valve surgery, or combined procedures. The authors matched patients who took statins preoperatively to patients who did not. First, the authors assessed the association between preoperative statin use and the primary outcomes of prolonged ventilation (more than 24 h), pneumonia (positive cultures of sputum, transtracheal fluid, bronchial washings, and/or clinical findings consistent with the diagnosis of pneumonia), and in-hospital all-cause mortality, using logistic regressions. Second, the authors analyzed the collapsed composite of neurologic complications using logistic regression. Intensive care unit and hospital length of stay were evaluated with Cox proportional hazard models.

Results: Among 14,129 eligible patients, 6,642 patients were successfully matched. There was no significant association between preoperative statin use and prolonged ventilation (statin: 408/3,321 [12.3%] *vs.* nonstatin: 389/3,321 [11.7%]), pneumonia (44/3,321 [1.3%] *vs.* 54/3,321 [1.6%]), and in-hospital mortality (52/3,321 [1.6%] *vs.* 43/3,321 [1.3%]). The estimated odds ratio was 1.06 (98.3% CI, 0.88 to 1.27) for prolonged ventilation, 0.81 (0.50 to 1.32) for pneumonia, and 1.21 (0.74 to 1.99) for in-hospital mortality. Neurologic outcomes were not associated with preoperative statin use (53/3,321 [1.6%] *vs.* 56/3,321 [1.7%]), with an odds ratio of 0.95 (0.60 to 1.50). The length of intensive care unit and hospital stay was also not associated with preoperative statin use, with a hazard ratio of 1.04 (0.98 to 1.10) for length of hospital stay and 1.00 (0.94 to 1.06) for length of intensive care unit stay.

Conclusions: Preoperative statin use did not reduce pulmonary or neurologic complications after cardiac surgery. **(Anesthesiology 2017; 126:799-809)**

3-HYDROXY-3-METHYLGLUTARYL coenzyme A reductase inhibitors (statins) are widely prescribed for hypercholesterolemia,[1] and large randomized trials show them to reduce cardiovascular mortality and morbidity in nonsurgical patients.[1–6] Statins are also associated with reduced postoperative mortality.[7–10] The benefits of statins for cardiovascular complications and mortality are thus well established. During the past two decades, investigators have proposed that statins may benefit noncardiovascular conditions. These pleiotropic effects, which are not mediated by the drugs' lipid-lowering effects,[11] include antioxidant properties, normalization of endothelial function, and attenuation of inflammation and reperfusion injury[12–14]—all of which can provide direct organ protection and contribute to improved postoperative outcomes.

Pulmonary complications after cardiac surgery are common, with an incidence of 10 to 25%.[15] These complications cause considerable mortality and morbidity, as well as increased hospital length of stay and costs.[16] Systemic inflammatory response and ischemia reperfusion injury with endothelial dysfunction are thought to be important pathways for postoperative pulmonary complications.[15,17–20] In nonsurgical settings, as might be expected from their antiinflammatory and immunomodulatory effects, statins provide protection[21,22] and survival benefit[21,23–25] from community-acquired pneumonia, as well as reduction in hospitalization

What We Already Know about This Topic

- Previous studies have demonstrated statins are associated with reduced cardiovascular postoperative mortality
- This study determined whether statins reduce pulmonary or neurologic complications after cardiac surgery

What This Article Tells Us That Is New

- Preoperative statin use did not reduce pulmonary or neurologic complications after cardiac surgery

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for asthma.[26] Considering the similar pathophysiologic mechanisms,[27] statins might also be expected to provide favorable effects on pulmonary outcomes in cardiac surgical settings. The incidence of postoperative pneumonia[28] and prolonged mechanical ventilation[29–31] have been reported in cardiac surgical populations. However, the true effect size of the statin–pulmonary complication association has not been established due to a paucity of data that yielded inconclusive results.[8,28–32]

Neurologic complications are also common after cardiac surgery, with delirium being the most common and stroke the most feared. Both are associated with increased morbidity, mortality, and longer hospitalization.[33] Decreasing embolic burden and restricting systemic inflammatory response are thought to prevent severe neurologic adverse events.[34] In nonsurgical settings, statin use reduces the incidence of stroke and other major vascular events in patients with high atherosclerosis burden[35,36]—which is common in cardiac surgical patients. However, studies investigated incidences of stroke,[9,29,37,38] encephalopathy,[37] and cognitive dysfunction[39] do not consistently demonstrate protective effects of statins.

We, therefore, tested the primary hypothesis that adult cardiac surgical patients who chronically use statins have a reduced incidence of pneumonia, prolonged ventilation (more than 24 h), and in-hospital mortality than those who do not. Secondarily, we tested the hypotheses that patients who take statins preoperatively have (1) a reduced incidence of a composite of neurologic complications; (2) shorter intensive care unit (ICU) stays; and (3) shorter hospitalizations.

Materials and Methods

Our study was conducted with the Cleveland Clinic Institutional Review Board's (Cleveland, Ohio) approval and waived consent. From the Cardiothoracic Anesthesia Patient Registry and the Society of Thoracic Surgeons Adult Cardiac Surgery Database at the Cleveland Clinic, we acquired data for adults who had coronary artery bypass graft (CABG), valve surgery, or combined CABG/valve procedure requiring cardiopulmonary pump bypass at the Cleveland Clinic, from 2005 to 2013.

Data in both registries were prospectively collected in a standardized fashion according to strict definitions of preoperative characteristics, intraoperative information, and postoperative outcomes from medical records and physical assessment, anesthesia records, and clinical care notes. The registries include data validation procedures, and additional statistical validations were performed quarterly to identify any additional quality issues. Required supplemental demographic and clinical data available in other institutional databases were imported into the registry through manual and mechanized interfaces. All data were collected daily by experienced and specially trained research personnel concurrent with patient care.

Statistical Analysis

To control for potential confounding variables, we matched each patient who was on statins preoperatively (statins) to one patient who was not (nonstatins) using propensity score matching to control for observed potential confounding. Specifically, we first estimated the probability of preoperative statin use (*i.e.*, propensity score) for each patient using logistic regression with statins (*vs.* nonstatins) as the outcome and prespecified potential confounding variables (listed in table 1) as independent variables. Our prespecified list of potential confounding variables includes age, gender, race, body mass index, American Society of Anesthesiologists physical status, New York Heart Association classification, diabetes, carotid disease, congestive heart failure, chronic obstructive pulmonary disease, stroke, hypertension, dialysis, myocardial infarction, pulmonary hypertension, vascular disease, cardiogenic shock, smoking status, use of angiotensin blockers, calcium blockers, β blockers, angiotensin-converting enzyme inhibitors, and steroids, previous lung surgery, previous heart surgery, mitral valve stenosis, mitral valve insufficiency, aortic valve stenosis, aortic valve insufficiency, left ventricular ejection fraction, preoperative serum creatinine, preoperative hematocrit, duration of surgery, duration of cardiopulmonary bypass, duration of aortic clamping, and emergent case (*vs.* elective). We considered all the above variables as well as all possible two-way interactions for inclusion in the model for estimating the propensity score. In addition, for continuous predictors, both linear and quadratic terms were considered for inclusion in the model to accommodate a potential nonlinear relationship. To eliminate redundant predictors and avoid overfitting, we used the Least Absolute Shrinkage and Selection Operator modeling approach. Matching was then implemented through a greedy algorithm (SAS macro: gmatch; SAS Institute, USA), restricting successful matches to those with the same type of surgery and the same year of surgery and those whose estimated propensity score logits (*i.e.*, $\log\left(\frac{\check{p}}{1-\check{p}}\right)$, $\check{p}$: estimated propensity score) were within 0.2 propensity score logit SDs of each other.

Assessment of balance on the covariables used for the propensity score matching was performed using absolute standardized differences (*i.e.*, the absolute difference in means or proportions divided by the pooled SD). Imbalance was defined as a standardized difference greater than 0.10 in absolute value[40]; any such covariables were included in the models comparing statin and nonstatin patients on outcomes to reduce potential confounding. All of the analyses were based on this subset of matched patients.

Primary Outcomes

The primary outcomes were prolonged ventilation, pneumonia, and in-hospital mortality (appendix). We compared propensity score–matched statin users and nonusers on each of the primary outcomes, using a logistic regression

Table 1. Demographics and Baseline Characteristics for Patients with and without Preoperative Statin Use before and after Propensity Score Matching

	Before Matching			After Matching		
Variable	Statin (n = 7,993)	Nonstatin (n = 6,136)	ASD*	Statin (n = 3,321)	Nonstatin (n = 3,321)	ASD*
Demographics						
Age, yr	67 ± 11	61 ± 15	0.46	67 ± 12	66 ± 12	0.06
Gender, female, n (%)	2,356 (29)	2,240 (37)	0.15	1,184 (36)	1,156 (35)	0.02
Race, n (%)			0.04			0.01
Caucasian	7,044 (88)	5,488 (89)		2,991 (90)	2,989 (90)	
African American	475 (6)	319 (5)		152 (5)	156 (5)	
Other	474 (6)	329 (5)		178 (5)	176 (5)	
BMI, kg/m^2	28 (25–32)	27 (24–31)	0.31	28 (25–31)	27 (24–31)	0.06
ASA physical status, n (%)			0.25			0.07
I	1 (< 1)	2 (< 1)		0 (0)	0 (0)	
II	12 (< 1)	39 (1)		9 (< 1)	11 (< 1)	
III	1,138 (14)	1,442 (24)		563 (17)	651 (20)	
IV	6,791 (85)	4,614 (75)		2,724 (82)	2,640 (79)	
V	51 (1)	39 (1)		25 (1)	19 (1)	
NYHA classification, n (%)			0.17			0.02
I	1,605 (20)	1,760 (29)		813 (24)	868 (26)	
II	3,821 (48)	2,673 (44)		1,547 (47)	1,490 (45)	
III	2,137 (27)	1,427 (23)		819 (25)	830 (25)	
IV	430 (5)	276 (5)		142 (4)	133 (4)	
Medical history, yes, n (%)						
Diabetes mellitus			0.44			0.08
None	4,921 (62)	4,972 (81)		2,432 (73)	2,551 (77)	
Insulin independent	1,918 (24)	720 (12)		583 (18)	499 (15)	
Insulin dependent	1,154 (14)	444 (7)		306 (9)	271 (8)	
Carotid disease	1,823 (23)	603 (10)	0.36	600 (18)	568 (17)	0.03
Congestive heart failure	2,306 (29)	1,693 (28)	0.03	979 (29)	922 (28)	0.04
COPD	1,394 (17)	1,024 (17)	0.02	564 (17)	565 (17)	< 0.01
Stroke	737 (9)	428 (7)	0.08	273 (8)	241 (7)	0.04
Hypertension	6,674 (84)	3,920 (64)	0.46	2,525 (76)	2,417 (73)	0.07
Dialysis	169 (2)	110 (2)	0.02	59 (2)	53 (2)	0.01
Myocardial infarction	2,986 (37)	1,012 (16)	0.48	710 (21)	631 (19)	0.06
Pulmonary hypertension	1,396 (17)	1,351 (22)	0.11	733 (22)	748 (23)	0.01
Vascular disease	1,050 (13)	574 (9)	0.12	358 (11)	330 (10)	0.03
Cardiogenic shock	120 (2)	78 (1)	0.02	50 (2)	34 (1)	0.04
Smoking	3,850 (48)	2,057 (34)	0.30	1,338 (40)	1,351 (41)	0.01
Use of angiotensin blockers	742 (9)	481 (8)	0.05	323 (10)	304 (9)	0.02
Use of calcium blockers	1,927 (24)	1,054 (17)	0.17	718 (22)	658 (20)	0.04
Use of β blockers	5,478 (69)	2,192 (36)	0.70	1,740 (52)	1,758 (53)	0.01
Use of ACE inhibitors	3,922 (49)	1,643 (27)	0.47	1,279 (39)	1,293 (39)	0.01
Use of steroids	672 (8)	432 (7)	0.05	284 (9)	285 (9)	< 0.01
Previous lung surgery	74 (1)	34 (1)	0.04	43 (1)	24 (1)	0.06
Previous heart surgery	1,819 (23)	1,146 (19)	0.10	714 (22)	679 (20)	0.03
Mitral valve stenosis, n (%)	213 (3)	217 (4)	0.05	120 (4)	131 (4)	0.02
Mitral valve insufficiency, n (%)			0.51			0.01
None	2,242 (28)	979 (16)		679 (20)	698 (21)	
1+	2,956 (37)	1,747 (28)		1,064 (32)	1,041 (31)	
2+	1,051 (13)	677 (11)		418 (13)	400 (12)	
3+	708 (9)	680 (11)		385 (12)	350 (11)	
4+	1,036 (13)	2,053 (33)		775 (23)	832 (25)	
Aortic valve stenosis, n (%)	2,318 (29)	1,309 (21)	0.18	1,100 (33)	1,026 (31)	0.05
Aortic valve insufficiency, n (%)			0.19			0.05
None	4,619 (58)	3,054 (50)		1,614 (49)	1,704 (51)	
1+	1,922 (24)	1,613 (26)		885 (27)	860 (26)	

(Continued)

Table 1. *(Continued)*

Variable	Before Matching			After Matching		
	Statin (n = 7,993)	Nonstatin (n = 6,136)	ASD*	Statin (n = 3,321)	Nonstatin (n = 3,321)	ASD*
2+	883 (11)	601 (10)		454 (14)	366 (11)	
3+	331 (4)	350 (6)		201 (6)	180 (5)	
4+	238 (3)	518 (8)		167 (5)	211 (6)	
LVEF, n (%)			0.27			0.01
> 60	2,756 (34)	2,788 (45)		1,430 (43)	1,432 (43)	
50–59	3,098 (39)	2,306 (38)		1,243 (37)	1,259 (38)	
46–49	56 (1)	39 (1)		19 (1)	20 (1)	
41–45	447 (6)	265 (4)		140 (4)	149 (4)	
35–40	680 (9)	312 (5)		199 (6)	189 (6)	
< 35	956 (12)	426 (7)		290 (9)	272 (8)	
Perioperative characteristics						
Serum creatinine, mg/dL	1.0 (0.9–1.2)	1.0 (0.8–1.1)	0.19	1.0 (0.8–1.2)	1.0 (0.8–1.2)	< 0.01
Hematocrit (%)	39 ± 6	39 ± 6	0.04	39 ± 6	39 ± 6	0.02
Duration of surgery, h	6.4 (5.5–7.5)	5.9 (5.0–7.1)	0.30	6.0 (5.1–7.2)	5.9 (5.1–7.1)	0.01
CPB time, min	93 (73–119)	89 (68–116)	0.10	90 (69–117)	89 (69–116)	0.01
Aortic clamping time, min	72 (56–93)	67 (52–88)	0.15	68 (52–90)	69 (52–90)	0.00
Emergent case, yes, n (%)	64 (1)	68 (1)	0.03	27 (1)	28 (1)	< 0.01
Year of surgery, n (%)			0.27			0.00
2005	848 (11)	557 (9)		367 (11)	367 (11)	
2006	805 (10)	506 (8)		328 (10)	328 (10)	
2007	981 (12)	548 (9)		370 (11)	370 (11)	
2008	966 (12)	668 (11)		424 (13)	424 (13)	
2009	1,274 (16)	658 (11)		435 (13)	435 (13)	
2010	1,237 (15)	751 (12)		480 (14)	480 (14)	
2011	416 (5)	494 (8)		205 (6)	205 (6)	
2012	757 (9)	1,009 (16)		348 (10)	348 (10)	
2013	709 (9)	945 (15)		364 (11)	364 (11)	
Type of surgery			0.81			0.00
CABG	3,236 (40)	871 (14)		564 (17)	564 (17)	
Valve	2,565 (32)	4,212 (69)		1,966 (59)	1,966 (59)	
CABG plus valve	2,192 (27)	1,053 (17)		791 (24)	791 (24)	

*Absolute standardized difference (ASD): the absolute difference in means or proportions divided by the pooled SD; any covariables with ASD ≥ 0.10 after the propensity score matching were adjusted for in the analyses.[40]

ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; BMI = body mass index; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

model. The significance criterion for the three primary outcomes was $P < 0.017$ (*i.e.*, 0.05/3); thus, 98.3% CIs were reported.

In addition, we estimated the average relative effect across the three individual outcomes (average of the three log-odds ratios), using a generalized estimating equation multivariate model with an unstructured covariance matrix. In contrast to the more common collapsed composite method that compares groups on whether any (*vs.* none) of the outcomes were observed for a patient, the average relative effect generalized estimating equation method that we used captures complete information on each outcome for each patient, adjusts for the correlation among outcomes, and is not driven by component(s) with the highest frequency.

Secondary Outcomes

Within the propensity score–matched subset of statin and nonstatin patients, we also assessed the association between statin use and (1) composite of Society of Thoracic Surgeons'-defined serious neurologic complications including stroke, transient ischemic attack, coma more than 24 h, paralysis, paralysis less than 24 h (appendix); (2) length of initial ICU stay; and (3) duration of hospitalization.

A logistic regression model was built to analyze the collapsed composite of postoperative neurologic complications. As for the length of ICU stay and duration of hospitalization, we used separate Cox proportional hazard models to estimate the effect of preoperative statin use. The outcome event in the survival analysis (Cox model) was discharged alive, which indicates that patients who died in the hospital

were considered as never having the event by assigning a censoring time 1 day more than the observed longest duration of the hospitalization among those discharged alive. A Bonferroni correction was used to adjust for multiple testing to control the overall type I error at 0.05 for secondary outcomes. Thus, 98.3% CIs were reported, and the significance criterion for the three secondary outcomes was $P < 0.017$ (*i.e.*, 0.05/3). SAS software version 9.4 (SAS Institute) was used for all statistical analysis.

Results

We identified 14,129 patients who met inclusion and exclusion criteria, including 7,993 (57%) statin and 6,136 (43%) nonstatin patients. The usage of statin was based on an indicator variable in the database. Among the 2,935 statin patients with type of statin information collected, 61% had atorvastatin, 23% simvastatin, 8% rosuvastatin, 4% pravastatin, 3% lovastatin, and 1% fluvastatin. Based on demographic and baseline characteristics, we successfully matched 3,321 nonstatin patients (54% of 6,136 nonstatin patients) to 3,321 statin patients. Specifically, the statin and nonstatin patients were exactly matched on year and type of surgery and were much better balanced on other covariates as a result of propensity score matching (table 1; fig. 1). Since no covariates had an absolute standardized difference greater than 0.10 between the matched groups, we did not adjust for them when comparing the two groups on primary and secondary outcomes.

Primary Outcomes

Within the subset of matched patients, 408 (of 3,321, 12.3%) taking statins had prolonged ventilation more than 24 h, which was not significantly different from that in 389 (of 3,321, 11.7%) not taking statins, giving an odds ratio (statin *vs.* nonstatin) of 1.06 (98.3% CI, 0.88 to 1.26), $P = 0.47$. The incidence of pneumonia was 44 (1.3%) in the statin group *versus* 54 (1.6%) in the nonstatin group, again giving a nonsignificant odds ratio (statin *vs.* nonstatin) of 0.81 (0.50, 1.32), $P = 0.31$. Similarly, no significant difference was found in in-hospital mortality between the matched statin group (52, 1.6%) and nonstatin group (43, 1.3%) with an odds ratio (statin *vs.* nonstatin) of 1.21 (0.74 to 1.99) ($P = 0.35$, table 2). The average relative effect across the three outcomes was estimated as 1.02 (95% CI, 0.80 to 1.28) for statin *versus* nonstatin. Our sensitivity analyses adjusting for the estimated propensity score provided the same conclusions and very similar effect estimates (table 2). We also conducted a *post hoc* sensitivity analysis using data before 2011, given the fact that we observed a change in the proportion of patients who were on statin in 2011. All results were consistent with our primary analysis (table 2).

Secondary Outcomes

Within the subset of matched patients, there was no significant association between preoperative use of statins and any of the secondary outcomes (table 3). The observed incidence of the composite of neurologic outcomes was 1.6% in the statin group and 1.7% in the nonstatin group; the corresponding estimated odds ratio was 0.95 (98.3% CI, 0.60 to 1.50; $P = 0.77$; statin *vs.* nonstatin). In the statin group, 52 (1.6%) patients died in the hospital, of which 9 died in the ICU; in the nonstatin group, 43 (1.3%) patients died in the hospital, of which 5 died in the ICU. Discharges for those patients were considered as nonevents and censored at the longest observed length of stay. The estimated median durations of hospitalization from the Kaplan–Meier curve were 8 (first to third quartile: 5.4, 13) days for statin patients and 7.4 (5.3, 12.7) days for nonstatin patients. The estimated median durations of ICU stay were 1.3 (first to third quartile: 1, 3) days for both groups. The hazard ratio (statin *vs.* nonstatin) was 1.04 (0.98, 1.10) for length of hospital stay ($P = 0.12$) and 1.01 (0.97, 1.06) for length of ICU stay ($P = 0.59$).

Discussion

Pulmonary complications after cardiac surgery vary in severity from atelectasis to acute respiratory distress syndrome and are among the leading causes of morbidity in this population.[17] We restricted our analysis to two important pulmonary complications, pneumonia and prolonged mechanical ventilation, both of which were specifically defined and evaluated concurrent with patient care. The overall pneumonia rate was 1%, and 12% of our patients experienced prolonged ventilation. The reported incidence of pneumonia after cardiac surgery varies from 0.7 to 22%,[17,41] and the incidence of prolonged mechanical ventilation varies from 3 to 23%.[42] Our results are thus generally consistent with previous literature.[43] The incidence of neurologic complications in the current study was 2%, which is also consistent with previous literature,[9,44] thus suggesting that our registry reliably collected information about measured outcomes.

We found no association between the preoperative use of statins and pneumonia or prolonged ventilation. Coleman *et al.*[28] and Hartholt *et al.*[32] showed that statins reduce the incidence of infections after cardiac surgery, with half of the reported infections being pneumonia. However, risk reduction in pneumonia did not reach statistical significance due to the small sample sizes. Similarly, Le Manach *et al.*[8] showed that postoperative pneumonia was not prevented by preoperative statin treatment in 1,674 patients who had aortic reconstruction (adjusted relative risk: 0.88; 95% CI, 0.62 to 1.25; $P = 0.48$).

Prolonged mechanical ventilation can be considered a general marker for severe pulmonary complications. Similar to our results, Ali and Buth [29] and Subramaniam *et al.*[31] showed no benefit of statin use in matched populations with cardiac surgery. Chello *et al.*[30] randomized 40 patients to treatment with atorvastatin or placebo, 3 weeks before CABG procedure. Atorvastatin patients had lower inflammatory marker concentrations, whereas prolonged postoperative ventilation rates were similar. All of these studies suffer

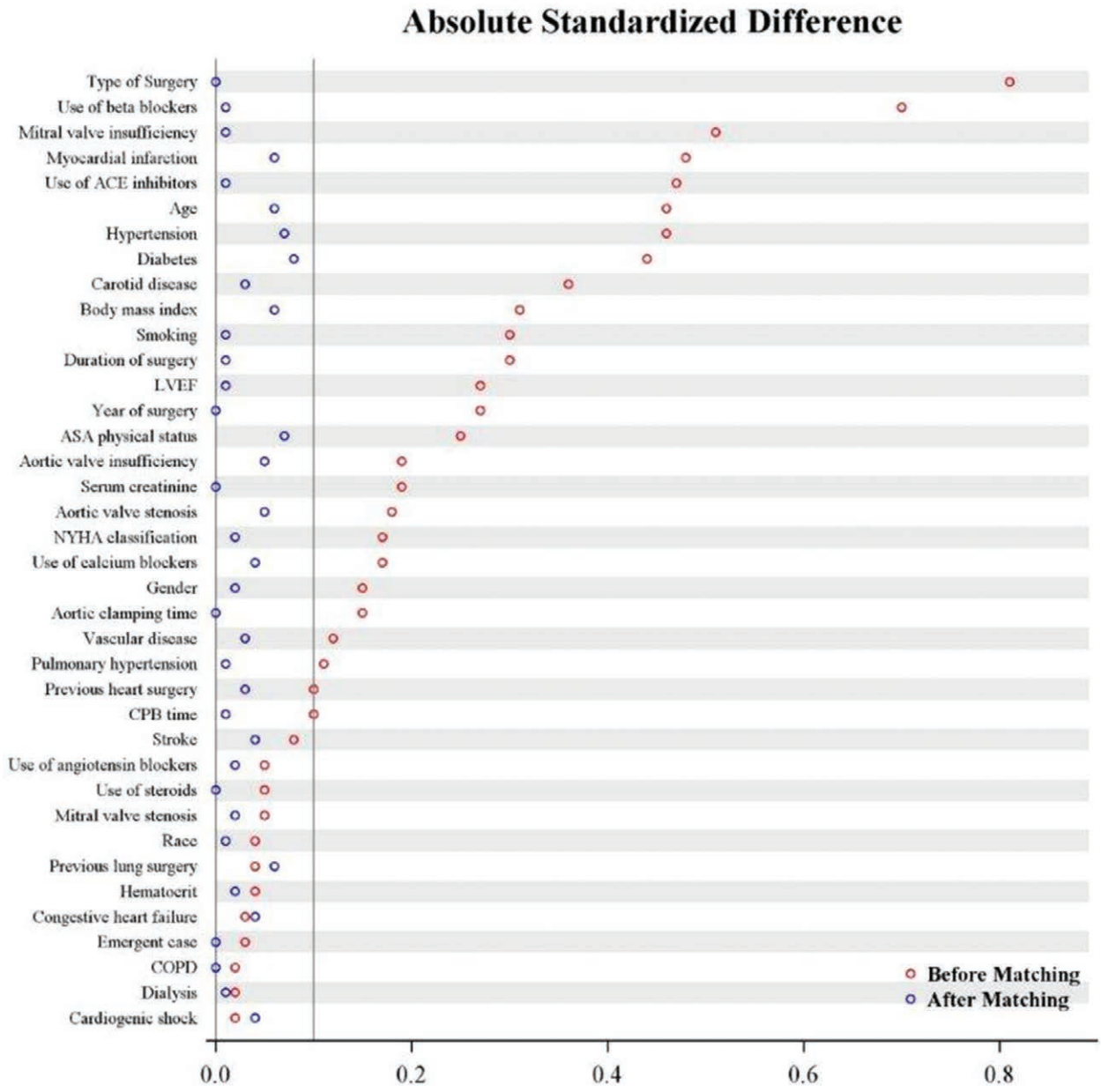

Fig. 1. Plot of absolute standardized difference (ASD) between statin and nonstatin groups on covariables before (*red circles*) and after (*blue circles*) the propensity score matching. ASD is absolute difference in means or proportions divided by the pooled SD. All the covariables were well balanced between the two groups after the propensity score matching; all ASDs were less than 0.10.[40] ACE = angiotensin-converting enzyme; ASA = American Society of Anesthesiologists; COPD = chronic obstructive pulmonary disease; CPB = cardiopulmonary bypass; LVEF = left ventricular ejection fraction; NYHA = New York Heart Association.

from insufficient power due to relatively small sample sizes and multiple comparisons.

That preoperative statins did not reduce pulmonary complications might be consequent to their multifactorial etiologies.[20,45] It is likely that perioperative risk factors other than inflammation and endothelial injury—for which we adjusted—contribute more to major postoperative pulmonary complications. Supporting this conclusion, minimizing systemic inflammation and endothelial pathologies by using off-pump cardiac surgery techniques also fails to reduce pulmonary risk after cardiac surgery.[46–48] Additionally, prolonged mechanical ventilation could be a clinical manifestation of multiple conditions including those unrelated to inflammatory response, such as atelectasis, surgical bleeding, or a prolonged residual anesthesia effect. Those contributions could dilute a plausible protective effect of statins (*i.e.*, antiinflammatory and immunomodulatory effect) and may make the benefit of statins less noticeable than on a homogeneous condition like pneumonia.

Table 2. Primary Results—Comparison of Statin and Nonstatin Patients on Prolonged Ventilation Pneumonia and In-hospital Mortality among Propensity Score–matched* Patients (n = 6,642)

Primary Outcome	Incidence n (%)		Odds Ratio† (98.3% CI) (Statin *vs.* Nonstatin)	*P* Value†
	Statin (n = 3,321)	Nonstatin (n = 3,321)		
Primary analysis—no adjustment for covariate‡				
Prolonged ventilation > 24 h	408 (12.3)	389 (11.7)	1.06 (0.88–1.27)	0.47
Pneumonia	44 (1.3)	54 (1.6)	0.81 (0.50–1.32)	0.31
In-hospital mortality	52 (1.6)	43 (1.3)	1.21 (0.74–1.99)	0.35
Average relative effect odds ratio§			1.02 (0.80–1.28)	0.90
Sensitivity analysis 1—adjusting for estimated propensity score				
Prolonged ventilation > 24 h	408 (12.3)	389 (11.7)	1.05 (0.88–1.26)	0.47
Pneumonia	44 (1.3)	54 (1.6)	0.81 (0.50–1.32)	0.30
In-hospital mortality	52 (1.6)	43 (1.3)	1.21 (0.74–1.99)	0.36
Average relative effect odds ratio§			1.01 (0.80–1.28)	0.91
Sensitivity analysis 2—including cases prior to 2011 only‖				
	n = 2,404	n = 2,404		
Prolonged ventilation > 24 h	301 (12.5)	303 (12.6)	0.99 (0.81–1.22)	0.93
Pneumonia	31 (1.3)	40 (1.7)	0.77 (0.43–1.37)	0.28
In-hospital mortality	41 (1.7)	31 (1.3)	1.33 (0.75–2.35)	0.24
Average relative effect odds ratio§			1.01 (0.77–1.32)	0.95

*Statin and nonstatin patients were exactly matched on both type of surgery and year of surgery and then propensity score matched on the all the potential confounding variables listed in table 1. †Significance criterion for the two individual components of the composite was $P < 0.017$ (*i.e.*, 0.05/3, Bonferroni correction). ‡Matched stain and nonstatin patients were well balanced on all *a priori* specified covariates with absolute standardized difference < 0.10; therefore, no further adjustment for covariate was needed.[40] §Estimated the average relative effect across the three individual outcomes (average of the three log-odds ratios), using a generalized estimating equation multivariate model with an unstructured covariance matrix. ‖*Post hoc* sensitivity analysis using data prior to 2011, given the fact that there was a change in the proportion of patients who were on statin at 2011. There were 60, 61, 64, 59, 66, and 62% patients on stains from 2005 to 2010, respectively; however, it dropped to 46% in 2011 and 43% in 2012 and 2013.

Table 3. Secondary Results—Comparison of Statin and Nonstatin Patients on Secondary Outcomes using the Propensity Score–matched* Patients (n = 6,642)

Secondary Outcome	Incidence No. (%)		Odds Ratio (98.3% CI)† (Statin *vs.* Nonstatin)	*P* Value†
	Statin (n = 3,321)	Nonstatin (n = 3,321)		
Neurologic complication	53 (1.6)	56 (1.7)	0.95 (0.60–1.50)	0.77
	Hazard Ratio			
Length of postoperative hospital stay, days‡	8 (5.4–13)	7.4 (5.3–12.7)	1.04 (0.98–1.10)	0.12
Length of postoperative ICU stay, days‡	1.3 (1–3)	1.3 (1–3)	1.00 (0.94–1.06)	> 0.99

*Statin and nonstatin patients were exactly matched on both type of surgery and year of surgery and then propensity score matched on all the potential confounding variables listed in table 1. †Significance criterion was $P < 0.017$ for each of the secondary outcomes (*i.e.*, 0.05/3, Bonferroni correction). ‡Median, first quartile, and third quartile for the length of hospital stay and ICU stay were estimated from the Kaplan–Meier curves. In the statin group, 52 (1.6%) patients died in the hospital, of which nine died in the ICU; in the nonstatin group, 43 (1.3%) patients died in the hospital, of which five died in the ICU. The outcome event in the survival analysis (Cox model) was discharged alive, which indicated that patients who died in the hospital were considered as never having the event by assigning a censoring time 1 day more than the observed longest duration of the hospitalization among those discharged alive.
ICU = intensive care unit.

Unlike previous retrospective studies, we used a composite of neurologic complications that allowed us to include various important neurologic outcomes. Nevertheless, we found no association between preoperative statin use and a composite of neurologic complications after cardiac surgery. Consistent with our result, two previous randomized controlled trials[49,50] showed that preoperative statin therapy is not protective against postoperative stroke (odds ratio, 0.70; 95% CI, 0.14 to 3.63; $P = 0.67$).[51] However, these studies combined included 264 patients with only five stroke events and are thus seriously underpowered. In contrast, a retrospective study suggests a strong protective effect of statins against stroke and transient ischemic attack,[52] and meta-analyses of observational studies concluded that preoperative statin use reduces the risk of stroke after cardiac surgery.[9,44,53] However, all of those meta-analyses used unadjusted results of original studies, and inevitably they reported significant differences in baseline characteristics introducing a serious confounding effect. In fact, large retrospective studies[29,37,54] reported no significant benefit of statin use on postoperative stroke rate after adjustment. We could not assess the incidence of delirium due to unavailability of information in our database. One

proposed pathophysiology of delirium is neuroinflammation caused by hyperresponsiveness of cerebral immune cells from systemic inflammation.[55] In patients undergoing CABG with cardiopulmonary pump bypass, increased concentration of proinflammatory cytokines was associated with delirium. As might thus be expected, several studies have investigated the potential protective effect of statin on delirium, which resulted in inconsistent outcomes.[39,56,57] Multifactorial pathophysiology of delirium after cardiac surgery (*i.e.*, embolic events, low cardiac output, hypoxemia, and metabolic derangement) is likely to explain the inconsistent effect size of statins reported in various studies.

Given the lack of effect of statin use on major postoperative pulmonary and neurologic outcomes, it is perhaps unsurprising that there was no improvement in length of ICU or hospital stay in our matched cohort. A recent meta-analysis by Kuhn *et al.*[53] showed a reduction in length of stay in the ICU (weighted mean difference −0.14; 95% CI, −0.23 to −0.03; $P < 0.01$) and hospitalization (weighted mean difference −0.57; 95% CI, −0.76 to −0.38; $P < 0.01$). However, estimation of the independent effect of the statin is difficult, as meta-analyses mostly reported outcomes without consideration of confounding variables.

There are a number of limitations of our study. As with any retrospective analysis, our study may suffer from the type and quality of data collected and residual confounding. For example, we are unable to account for type, dose, and duration of preoperative statin use. Additionally, we selectively reported pulmonary and neurologic outcomes for the purpose of limiting the number of comparisons to reduce the risk of chance findings. Omission of cardiac outcomes could have confounded the incidence of prolonged ventilation that is often driven by cardiac condition. Further, requirement of tracheostomy, a clinically important consequence of respiratory complications, was not captured by our definition of prolonged intubation. Analyses combining both CABG and valve surgery did not allow assessment of the effect size of statins on outcomes in the two different patient populations. However, we adjusted for many baseline characteristics likely to influence outcomes. It is thus likely that the effect sizes we reported represent independent effects of preoperative statin use on the major respiratory and neurologic complications. We were only able to match 54% of the nonstatin patients, which is a potential loss of generalizability of our results. However, with 6,642 matched subjects, our sample size is still quite large. Also, the matching approach to control potential confounding variables isolates the average treatment effects for those treated (*i.e.*, taking statins). Finally, less severe complications, such as early cognitive dysfunction, were not included in our analyses. However, we show no difference in ICU and hospital length of stay; thus, we can assume that the clinical impact of such less severe complications was small.

We present the largest cohort study to date with more than 14,000 patients and 6,642 matched subjects, having 90% power to detect clinically relevant differences in major outcomes. Our matching approach exactly matched on type and year of surgery and propensity score matched on a total of 36 potential confounding variables. As a single-center study, interpatient variability and heterogeneity were naturally low, which adds further strength. Therefore, our study adds further evidence that may help solve ongoing controversies with a notable strength from large sample size and methodology.

In summary, promising laboratory and epidemiologic evidence suggests that pleiotropic effects of statins may have various impact noncardiac complications after cardiac surgery. We nonetheless found no evidence that preoperative use of statins reduced either major respiratory or neurologic complications, possibly because these outcomes are overwhelmingly determined by other baseline and surgical factors.

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Competing Interests

The authors declare no competing interests.

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Appendix: Definition of Complications

Outcome	Data Field Intent	Field Name Clarification	Source Document
Prolonged ventilation (> 24 h)	Indicate whether the patient had prolonged pulmonary ventilator > 24 h. Include (but not limited to) causes such as adult respiratory distress syndrome (ARDS), pulmonary edema, and/or any patient requiring mechanical ventilation > 24 h postoperatively.	A total of 24 h, include initial and additional hours of mechanical ventilation. Extended ventilation may include, but is not limited to, the specific definitional reasons. Example: if a major stroke or coma occurred that required ventilation for life support, code as prolonged if > 24 h. Do not include the hours ventilated if a patient returns to the operating room suite and requires reintubation as part of general anesthesia.	Consultations Critical care notes Intensive care unit hemodynamic flow sheets or records Nursing notes Respiratory therapy flow sheets
Pneumonia	Indicate whether the patient had pneumonia diagnosed by any of the following: positive cultures of sputum, transtracheal fluid, bronchial washings, and/or clinical findings consistent with the diagnosis of pneumonia (which may include chest x-ray diagnostic of pulmonary infiltrates).	Diagnosis of pneumonia may be determined by multiple diagnostic tools, as listed in the definition manual. Diagnosis may also be determined solely on chest x-ray reports. Treatment therapies may be as minimal as increased or added inhalation therapies or reintubation and antibiotics. Positive cultures are not necessary if there are clinical findings consistent with the diagnosis of pneumonia. Please keep in mind that atelectasis and effusions do not necessarily indicate pneumonia. Pneumonia is most often diagnosed by chest x-ray. Make sure that pneumonia is present and documented so that you are not overcoding pneumonia.	Consultations Laboratory culture reports Physician progress reports Radiology reports (*i.e.*, chest x-ray, scans)
Stroke	Indicate whether the patient has a postoperative stroke (*i.e.*, any confirmed neurologic deficit of abrupt onset caused by a disturbance in cerebral blood supply) that did not resolve within 24 h.	Central events are caused by embolic or hemorrhagic events. Neurologic deficits such as confusion, delirium, and/or encephalopathic (anoxic or metabolic) events are not to be coded in this field.	Consultations Physician progress reports Radiology reports (*i.e.*, MRI, CT scan) Readmission and/or 30-day follow-up process
Transient ischemic attack	Indicate whether the patient had a postoperative TIA: loss of neurologic function that was abrupt in onset but with complete return of function within 24 h.	TIA events resolve within 24 h. Symptoms may include but are not limited to, visual, speech, memory or physical deficits. Patients who have suffered a TIA have an increased risk of peripheral and coronary artery atherosclerosis and an increased risk of subsequent heart attack and stroke.	Consultations Physician progress reports Radiology reports (*i.e.*, MRI, CT scan) Readmission and/or 30-day follow-up process
Coma (≥ 24 h)	Indicate whether the patient had a new postoperative coma that persists for at least 24 h secondary to anoxic/ischemic and/or metabolic encephalopathy, thromboembolic event, or cerebral bleed.	Do not code comas that are pharmacologically induced (anesthesia or intentionally drug induced). If the patient experiences a major permanent stroke where consciousness was never regained after the onset of a coma, stroke. If a postoperative paralysis or hemiplegia applies, code stroke and paralysis.	Consultations Physician progress reports Radiology reports Readmission and/or 30-day follow-up process
Paralysis	Indicate whether the patient had a new postoperative paralysis or paraplegia.	Paralysis is a loss of purposeful movement, usually as a result of a neurologic disease (*e.g.* stroke), drugs, or toxins. Loss of motor function may be complete (paralysis) or partial (paresis); unilateral (hemiplegic) or bilateral confined to the lower extremities (paraplegic) or present in all four extremities (quadriplegic); accompanied by increased muscular tension and hyperactive reflexes (spastic) or by loss of reflexes (flaccid).	Consultations Physical therapy report Physician progress reports Radiology reports Readmission and/or 30-day follow-up process

CT = computerized tomography; MRI = magnetic resonance imaging; TIA = transient ischemic attack.