The Association of Preoperative Statin Use and Acute Kidney Injury After Noncardiac Surgery

Maged Y. Argalious, MD, MBA*, Jarrod E. Dalton, MA,†‡ Thilak Sreenivasalu, MD,§ Jerome O'Hara, MD,* and Daniel I. Sessler, MD‡

BACKGROUND: Our objective was to examine the association between preoperative statin therapy and the incidence of postoperative acute kidney injury (AKI) in patients undergoing elective noncardiac surgery.

METHODS: We analyzed the electronic records of 57,246 patients who had elective noncardiac surgery at the Cleveland Clinic Main Campus between December 2004 and March 2010. Patients were divided into 2 groups depending on preoperative therapy with statin drugs. Our primary outcome was AKI, defined as "risk," "injury," or "failure" using the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) criteria. Secondary outcomes included postoperative dialysis and all-cause hospital mortality. Each statin user was matched to a nonuser based on propensity scores. The propensity scores were estimated using a multivariable logistic regression model, incorporating all available baseline potential confounders. After the propensity-matching procedure, we performed final analyses for the primary and secondary outcomes. For the primary analysis, we used a univariable logistic regression model to estimate the odds ratio (OR) (and 95% confidence intervals) for AKI, postoperative dialysis, and hospital mortality between matched statin users and nonusers.

RESULTS: Of the total group, 23,745 records were unusable because of missing data. Among the remaining 28,508 patients analyzed, the overall incidence of AKI was 6.1%. Three hundred sixty-one of 4805 statin users (7.5%) and 1377 of 23,703 nonusers (5.8%) experienced AKI. The incidence of postoperative dialysis was 0.05%. Six statin users (0.12%) and 8 nonusers (0.03%) required dialysis postoperatively. The incidence of hospital mortality was 0.62%. Mortality was observed for 47 patients (1.0%) and 130 patients (0.5%), respectively. Among 4172 matched pairs, the incidence (95% confidence interval) of AKI was 7.1% (6.2%, 8.1%) in the matched statin users and 8.0% (7.1%, 9.0%) in the nonusers, corresponding to an OR of 0.88 (0.75, 1.03), which was not statistically significant ($P = 0.12$, χ^2 test). The secondary outcomes were also not significantly different in matched statin users and nonusers. Postoperative dialysis was required for 0.10% (0.02%, 0.33%) and 0.12% (0.04%, 0.37%) of patients in the respective groups (OR = 0.80 [0.16, 3.70]; $P = 0.74$). Hospital mortality occurred in 1.0% (0.7%, 1.5%) and 1.3% (0.9%, 1.8%) of patients, respectively (OR = 0.76 [0.47, 1.20]; $P = 0.18$).

CONCLUSIONS: Our data did not support the hypothesis that preoperative statin therapy in doses routinely used to treat hypercholesterolemia is associated with a change in the incidence of AKI, postoperative dialysis, or hospital mortality in patients undergoing noncardiac surgery. (Anesth Analg 2013;117:916–23)

Acute kidney injury (AKI) occurs in 1% to 5% of patients having noncardiac surgery[1–3] and contributes to increased hospital mortality.[1,4] The predominant mechanism of perioperative AKI is thought to be impaired perfusion; the initial insult seems to be hypoxic, followed by production of reactive oxygen species and activation of inflammatory mechanisms during reperfusion.[5]

Statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) provide effective primary and secondary prevention against cardiovascular events in hyperlipidemic subjects[6,7] and in patients with chronic kidney disease not requiring dialysis,[8,9] which are independent of lipid lowering.[10,11] The vasodilatory, antiinflammatory, and antithrombotic effects of statins are mediated by increased endothelial nitric oxide synthase expression,[12] reduced expression of cytokines, chemokines, and adhesion molecules, and decreased C-reactive protein concentrations.[13]

Statins reduce endothelin secretion and rapidly increase nitric oxide production, thereby increasing flow-mediated vasodilation and endothelial function.[14] Statins also scavenge free radicals,[15] are antiinflammatory by blocking the infiltration of inflammatory cells and down-regulating the expression of inflammatory mediators, such as interleukin-6 and C-reactive protein,[16] and possess antithrombotic properties,[17] all of which were likely to be renal protective. As might thus be expected, animal models show that giving statins before an ischemic event significantly reduces AKI.[18–22]

From the *Department of General Anesthesia, §Anesthesiology Institute, and Departments of †Quantitative Health Science and ‡Outcomes Research, Cleveland Clinic, Cleveland, Ohio.

Accepted for publication November 21, 2012.

Supported by internal funds only.

This report was previously presented, in part, at the ASA meeting in October 2010 in abstract format.

The authors declare no conflicts of interest.

Reprints will not be available from the authors.

Address correspondence to Maged Y. Argalious, MD, MBA, Department of General Anesthesia, Anesthesiology Institute, Cleveland Clinic, 9500 Euclid Ave./G30, Cleveland, OH 44195. Address e-mail to argalim@ccf.org.

DOI: 10.1213/ANE.0b013e31828175ab

Compelling mechanistic evidence therefore suggests that statins might reduce postoperative kidney injury after noncardiac surgery. However, the extent to which statin use is associated with renal protection in noncardiac surgery remains unknown. We thus tested the hypothesis that preoperative statin use is independently associated with renal protection in noncardiac surgery patients. Secondarily, we sought to evaluate the relationship between statin use and new-onset postoperative dialysis and all-cause hospital mortality.

METHODS

Data from 57,246 patients undergoing noncardiac surgery at the Cleveland Clinic between December 8, 2004 and March 8, 2010 (most recent operation per patient) were obtained from the Anesthesia Institute's Perioperative Health Documentation System database. This database is approved for research by our IRB.

We included patients who had an ASA physical status ≤IV. Patients who had outpatient procedures or emergency surgery were excluded. We also excluded patients who had a previous kidney transplant, who already required renal replacement therapy, and patients with end-stage renal disease, which included those having arteriovenous fistula surgery, nephrectomy of a sole remaining kidney, or a baseline serum creatinine of ≥5.0 mg/dL.

Our primary outcome was AKI based on the RIFLE (Risk, Injury, Failure, Loss, and End-stage Kidney) criteria.[23] The RIFLE criteria were used to categorize patients into 3 groups: (1) patients at risk of renal injury (as defined by a maximal postoperative plasma creatinine concentration ≥1.5 mg/dL but less than twice the preoperative concentration); (2) patients with renal injury (maximal postoperative plasma creatinine concentration ≥2 mg/dL but less than 3 times the preoperative concentration); and (3) patients with renal failure (maximal postoperative plasma creatinine concentration >4 mg/dL with an increase of at least 0.5 mg/dL, or maximal preoperative creatinine at least 3 times the preoperative concentration).

The primary exposure of interest was routine preoperative statin use, determined by querying patients' active medication list in the database for the presence of any commercially available statin drugs. With the exception of angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, patients at our institution are normally instructed to take routine medications, including statins, on the morning of surgery.

Propensity scores for statin use were estimated using a multivariable logistic regression model, incorporating all available baseline potential confounders (listed in the top panel of Table 1). Each statin user was matched to a nonuser based on the propensity scores; specifically, we used exact matching on propensity score to within 0.01 units. The data were randomly permuted before matching.

We adjusted for severity of surgery (in terms of risk of postoperative AKI) by estimating for each procedure type the overall incidence of AKI; the resulting measure of procedural risk for AKI was then used as a potential confounder during our propensity-matching analysis. Procedure codes were defined using the United States Agency for Healthcare Research and Quality's single-level Clinical Classifications Software for *International Classification of Diseases, Ninth Revision, Clinical Modification* procedure code.[a]

Balance between statin users and nonusers on the available baseline potential confounders was assessed using standard univariable summary statistics (e.g., means and standard deviations, percentages, or medians and quartiles) and absolute standardized differences. The absolute standardized difference is a useful measure of balance between 2 groups on a covariate, and is equal to the absolute value of the difference in means, mean ranks, or proportions divided by a pooled measure of standard deviation. Thus, the absolute standardized difference approximately represents the number of standard deviations apart 2 groups are on a covariate. An absolute standardized difference value ≥0.1 generally suggests slight imbalance between the groups, which could be potentially confounding depending on the degree of association between the baseline variable in question and the outcome.

After the propensity-matching procedure, we performed final analyses for the primary outcome and the secondary outcomes. For the primary analysis, we used a univariable logistic regression model to estimate the odds ratio (OR) for AKI between matched statin users and nonusers and its associated 95% confidence interval. The null hypothesis of no relationship between statin use and AKI was evaluated using a standard χ^2 test; the type I (false-positive) error rate for this primary hypothesis was fixed at 0.05. Similar analyses were performed for the secondary outcomes; however, for these analyses, we used the Bonferroni correction to control the overall type I error rate at 0.05 for the secondary outcomes.

R software version 2.12.1 for Windows (The R Foundation for Statistical Computing, Vienna, Austria) and SAS software version 9.2 for Windows (SAS Institute, Cary, NC) were used for all statistical analyses. Patients were propensity matched using the R package "Matching."[24]

RESULTS

Among the 57,246 patients identified through the Perioperative Health Documentation System database, who had noncardiac surgery, 4993 (8.7%) did not meet our inclusion/exclusion criteria (Fig. 1). Statin use, baseline serum creatinine, and/or the AKI outcome were unavailable for 23,745 patients, generally because postoperative serum creatinine analysis was not clinically indicated; thus, 28,508 patients were analyzed. A comparison of baseline characteristics between patients included in the study and patients excluded because of unavailable data on the primary exposure and outcome is provided in Appendix 1.

Baseline serum albumin and body mass index were excluded from the model estimating propensity scores because many values were missing (43% and 30%, respectively). Furthermore, 881 patients with missing values for ≥1 of the other baseline variables included in the model estimating propensity scores were removed. Our propensity-matching procedure yielded successful matches for 4172 (87%) of the statin users; therefore, our analyzed dataset consisted of 8344 propensity-matched patients.

[a] HCUP Clinical Classifications Software (CCS) for ICD-9-CM. Available at: http://www.hcup-us.ahrq.gov/toolssoftware/ccs/ccs.jsp. Accessed January 7, 2011.

Table 1. Baseline and Intraoperative Patient Characteristics, Before and After Propensity Score Matching on the Baseline Characteristics (Intraoperative Characteristics Were Not Used for the Matching)

	All patients		Matched patients	
	Non-statins (*n* = 23,703)	Statins (*n* = 4805)	Non-statins (*n* = 4172)	Statins (*n* = 4172)
Baseline factors				
To-come-in admission (versus inpatient), %	85.6	79.5	79.3	80.3
Age, y, mean ± SD	58 ± 16	67 ± 12	67 ± 13	66 ± 12
Body mass index, kg/m^2, median (quartiles)	28 (24, 33)	28 (25, 33)	28 (25, 33)	28 (25, 33)
Female gender, %	52.5	43.4	44.2	44.4
Race, %				
Caucasian	86.0	87.1	87.2	87.0
African American	10.3	9.8	9.9	9.7
Other	3.8	3.1	2.8	3.3
Creatinine, mg/dL, median (quartiles)	0.9 (0.7, 1.0)	0.9 (0.8, 1.2)	0.9 (0.8, 1.1)	0.9 (0.8, 1.1)
Hematocrit, %, mean ± SD	40.8 ± 4.9	40.2 ± 5.1	40.3 ± 5.2	40.3 ± 5.1
Albumin, mg/dL, median (quartiles)	4.3 (4.0, 4.5)	4.2 (3.8, 4.5)	4.2 (3.8, 4.4)	4.2 (3.9, 4.5)
History of acute renal failure, %	2.8	5.0	4.6	4.6
Chronic kidney disease, %	2.9	5.8	4.9	5.4
Diabetes mellitus, %				
None	85.1	70.5	74.4	73.4
Oral	13.0	19.4	18.4	18.1
Insulin	1.9	10.2	7.2	8.5
Hypertension, %	48.2	76.7	76.3	74.5
Congestive heart failure, %	4.0	9.6	8.0	8.8
Myocardial infarction, %	4.6	15.0	11.8	12.9
Valvular heart disease, %	3.2	4.5	4.8	4.4
History of coronary artery bypass grafting, %	3.9	13.8	10.5	11.3
History of percutaneous coronary intervention, %	4.3	12.6	9.7	10.9
Chronic obstructive pulmonary disease, %	10.1	10.7	10.8	10.5
History of deep venous thrombosis, %	1.7	2.7	2.9	2.5
History of supraventricular arrhythmia, %	2.7	3.4	3.2	3.4
History of ventricular arrhythmia, %	1.2	2.5	2.2	2.1
Use of β-blockers, %	14.8	49.2	45.9	44.5
Use of ACE inhibitors, %	10.3	37.8	34.6	33.7
Use of ARBS, %	4.6	15.5	14.1	14.5
Use of Ca-channel blockers, %	7.2	21.8	21.5	20.2
Use of steroids, %	6.2	13.6	13.7	12.8
Use of diuretics, %	6.1	22.1	18.8	19.4
Use of aspirin, %	5.0	27.0	19.7	22.0
ASA physical status, %				
I	3.0	0.2	0.1	0.3
II	42.5	23.1	25.4	25.3
III	48.8	66.2	64.9	64.9
IV	5.6	10.5	9.7	9.5
Intraoperative factors, median (quartiles)				
Case duration, min	251 (188, 330)	255 (188, 336)	253 (190, 337)	255 (189, 336)
Estimated blood loss, mL	200 (75, 400)	200 (100, 400)	200 (100, 450)	200 (100, 450)
Crystalloids, mL	2700 (2000, 3700)	2700 (1900, 3700)	2700 (1800, 3712)	2700 (1900, 3700)
Colloids, mL	500 (0, 1000)	500 (0, 1000)	500 (0, 1000)	500 (0, 1000)
Red blood cell transfusion, mL	0 (0, 0)	0 (0, 0)	0 (0, 0)	0 (0, 0)
Urine output, mL	300 (105, 600)	300 (120, 600)	300 (115, 600)	300 (120, 600)

SD = standard deviation; ACE = angiotensin-converting enzyme; ARBS = angiotensin II receptor blockers; Ca = calcium; ASA = American Society of Anesthesiologists.

Before matching, statin users were generally older and sicker than nonusers in baseline characteristics (Table 1). After matching, none of the baseline potential confounders exhibited absolute standardized difference scores >0.2 (Fig. 2). Although serum albumin and body mass index were not considered in the matching, they were nonetheless well balanced among the matched patients with available measurements. Thus, the propensity-matching procedure was successful in balancing baseline potential confounders. Intraoperative characteristics such as case duration and fluid volumes, also not used for propensity matching, were nonetheless similar among the matched patients (Table 1).

The incidence (95% confidence interval) of AKI was 7.1% (6.2%, 8.1%) in the matched statin users and 8.0% (7.1%, 9.0%) in the nonusers, corresponding to an OR of 0.88 (0.75, 1.03), which was not statistically significant ($P = 0.12$, χ^2 test).

The secondary outcomes were also not significantly different between matched statin users and nonusers. Postoperative dialysis was required for 0.10% (0.02%, 0.33%) and 0.12% (0.04%, 0.37%) of patients in the matched groups (OR = 0.80 [0.16, 3.70]; $P = 0.74$). In-hospital mortality occurred in 1.0% (0.7%, 1.5%) and 1.3% (0.9%, 1.8%) of the matched patients, respectively (OR = 0.76 [0.47, 1.20]; $P = 0.18$). A summary of the incidence of primary and

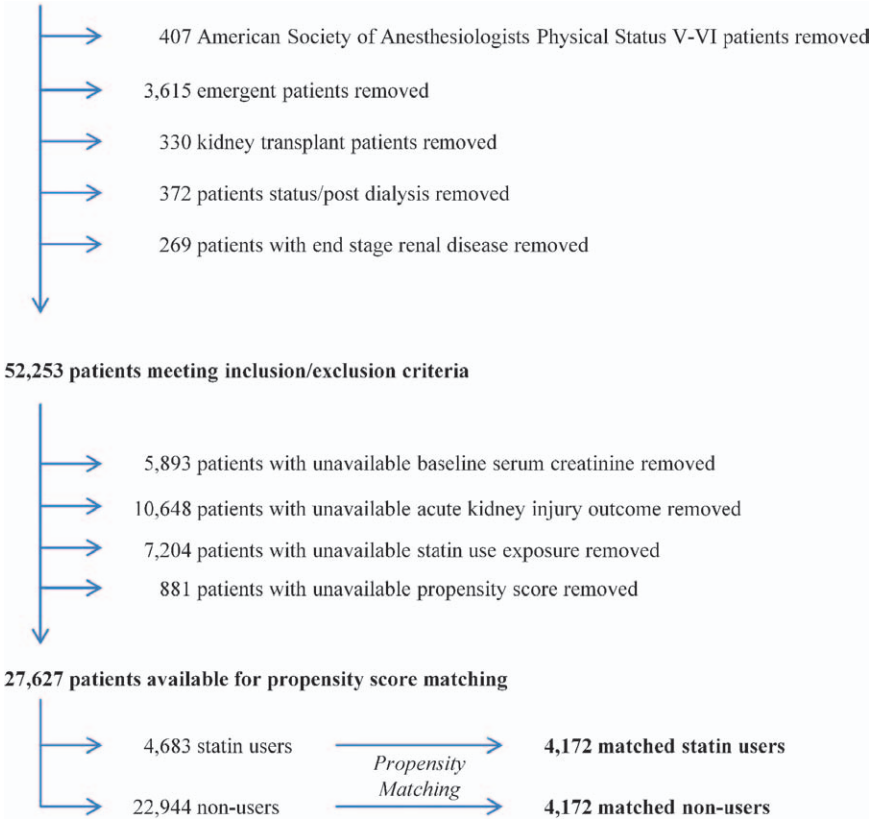

Figure 1. Summary of inclusion/exclusion criteria and results of the propensity score matching procedure. TCI = to-come-in.

secondary outcomes among statin users and nonusers (both before and after matching) is provided in Table 2.

DISCUSSION

Our principal finding is that preoperative statin therapy does not seem to be associated with a reduced risk of AKI in patients undergoing noncardiac surgery (although, as our confidence interval for the primary comparison of interest indicates, we could not exclude from possibility a reduction in the odds of AKI as large as 25%). This result is similar to that reported in patients having noncardiac[25] and cardiac surgery.[26] In contrast, Molnar et al.[27] reported an association between preoperative statin use and a reduced risk of AKI in patients having major elective surgery. However, their study cohort was restricted to patients older than 65 years of age. Furthermore, they combined patients having cardiac and noncardiac surgery, although pathophysiologic mechanisms for AKI probably differ.[5,28] Most importantly, however, Molnar et al. used AKI diagnostic codes based on the *International Classification of Diseases, Ninth Revision* classification system, which has only 28% sensitivity for AKI.[29]

We also found no evidence supporting the idea that preoperative statin use is associated with a reduced incidence of new-onset dialysis or hospital mortality. The same results were reported in a single-center, albeit smaller, retrospective study by Kor et al.[25] in patients undergoing major vascular surgery. A recent study associating statin use with a lower incidence of new-onset dialysis also reported an absence of association between statin use and reduced dialysis dependence 90 to 120 days postoperatively, making a significant long-term renoprotective effect of statin drugs in current clinical doses highly unlikely.[27]

Our study results contrast with those reported by Lindenauer et al.,[30] in a large retrospective study cohort based on administrative data from 328 hospitals. In their propensity-matched cohort, hospital mortality after major noncardiac surgery was 2.2% in patients treated with lipid-decreasing medications compared with 3.2% in patients who did not receive lipid-decreasing therapy or in whom treatment was initiated after the second day of hospitalization ($P < 0.001$). In contrast, this study is a retrospective, single tertiary care center study based on clinical and not administrative data and included only patients receiving statin therapy (and not other lipid-decreasing medications). In addition, all noncardiac procedures were included in this report (and not only major noncardiac surgery), which explains the decrease in hospital mortality reported in this study: 1.0% in the statin propensity-matched group and 1.3% in the no statin group; OR (95% confidence interval): 0.76 (0.47, 1.20) ($P = 0.18$).

A "healthy user effect" referring to the phenomenon in which patients who adhere to a medication schedule also engage in a healthy lifestyle, resulting in better overall health,[31] can explain the reduction in hospital mortality reported by Lindenauer et al. in patients receiving a lipid-decreasing drug. Another explanation is that the sample size of this study was not large enough to detect a difference between the 2 groups. A post hoc sample size calculation suggests that approximately 27,000 patients per group would be necessary to exclude a type II error in assessing

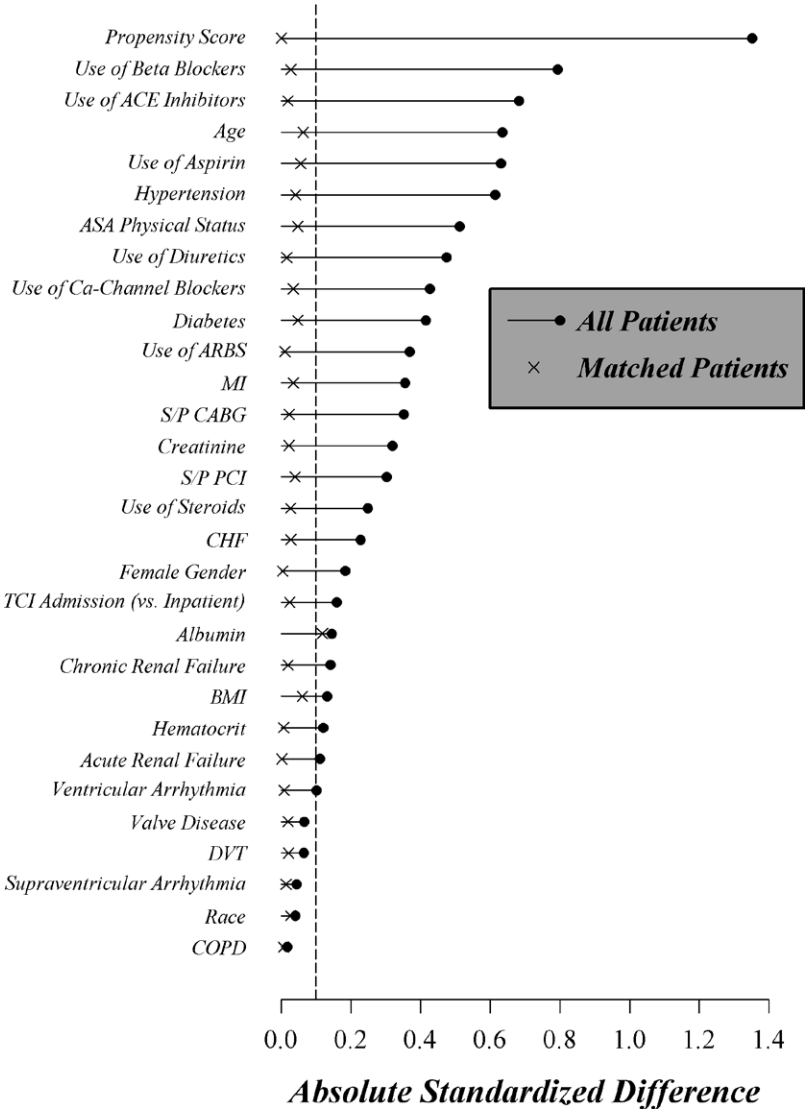

Figure 2. Balance of patient characteristics before and after exact matching on propensity score (rounded to the nearest percentage), as characterized by absolute standardized differences (ASDs). The ASD, equal to the difference in means, mean rankings, or proportions divided by the pooled standard deviation, is a measure of statistical distance between 2 groups on a characteristic; values >0.2 are indicative of imbalance between the 2 groups (and thus potentially confounding on the relationship of interest). ACE = angiotensin-converting enzyme; Ca = calcium; ARBS = angiotensin II receptor blockers; MI = myocardial infarction; S/P = status/post; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; CHF = congestive heart failure; TCI = to-come-in; BMI = body mass index; DVT = deep vein thrombosis; COPD = chronic obstructive pulmonary disease.

Table 2. Incidence of Acute Kidney Injury (and Components of Acute Kidney Injury as Defined by the RIFLE Criteria), Dialysis, and In-Hospital Mortality Among 28,508 Patients Included in the Study and Among a Subset of 8344 Propensity-Matched Patients

All patients	**No Statins (*n* = 23,703)**	**Statins (*n* = 4805)**		
Acute kidney Injury	1377 (5.8%)	361 (7.5%)		
Risk	940 (4.0%)	226 (4.7%)		
Injury	278 (1.2%)	81 (1.7%)		
Failure	159 (0.7%)	54 (1.1%)		
Dialysis	8 (0.03%)	6 (0.12%)		
Mortality	130 (0.5%)	47 (1.0%)		
Propensity-matched patients	**No Statins (N=4172)**	**Statins (N=4172)**	**Odds ratio (95% CI)**	**P Value**
Acute kidney Injury	334 (8.0%)	296 (7.1%)	0.88 (0.75, 1.03)	0.12
Risk	211 (5.1%)	192 (4.6%)		
Injury	79 (1.9%)	63 (1.5%)		
Failure	44 (1.1%)	41 (1.0%)		
Dialysis*	5 (0.12%)	4 (0.10%)	0.80 (0.16, 3.70)	0.74
Mortality*	54 (1.3%)	41 (1.0%)	0.76 (0.47, 1.20)	0.18

Odds ratios, 95% confidence intervals, and *P* values testing the hypothesis of association between statin use and the respective outcomes are presented for the matched subset.

*A Bonferroni-adjusted significance criterion of 0.025 was used for these secondary outcomes.

the effects of statin therapy on hospital mortality (assuming 90% power and an OR of ≤0.7).

Available evidence suggests that routine preoperative statin use has little if any renoprotective effect.[25,26,32] In fact, there are currently no known effective and safe drugs that prevent ischemic renal injury.[33–36] Maintaining adequate arterial blood pressure might thus be the best clinical approach at this time.[37] It remains possible, however, that current doses of statins, mainly used to treat hypercholesterolemia, are insufficient in attenuating AKI. Consistent with this theory, Verma et al.[38] demonstrated attenuation of cell injury with pravastatin, but only at high serum concentrations of the drug.[11]

Although statin drugs are restarted on the first postoperative day according to an institutional protocol, the possibility of late reinstitution of statin drugs in some patients (because of postoperative ileus or surgical team preference) cannot be excluded and may have potentially masked a protective effect of statins. "Statin withdrawal" can occur when the drugs are discontinued postoperatively, or reinstituted >48 hours after surgery. Statin withdrawal is thought to augment the risk of AKI, new-onset dialysis, and hospital mortality.[25] Le Manach et al.[39] also reported that postoperative statin withdrawal for at least 4 days is an independent predictor of postoperative cardiac myonecrosis.

Our registry does not include specific statin formulations, doses, or preoperative duration of use. Potency varies among statins and molecules that cause comparable lipid decreasing may differ considerably in their antiinflammatory characteristics and ability to prevent atrial fibrillation and provide other cardiac benefits.[40] It thus remains plausible that adequate doses of certain statins could provide substantial protection against AKI, but this will be determined only by focused, prospective, randomized, controlled studies.

As with any observational study, our results are subject to potential selection bias, confounding, and measurement bias.[31] In addition, 40% of our patients were excluded because of missing data (Fig. 1).We attempted to limit these sources of error by using propensity matching. Because the Perioperative Health Documentation System is mostly based on clinical (rather than administrative) records, it is fairly dense and includes many known predictors of AKI. Nonetheless, it remains likely that at least some unknown confounders impaired our analysis. Intraoperative hemodynamic variables may have differed between the 2 groups and could have influenced the incidence of AKI.[36] We note, however, that important confounding factors mostly increase the likelihood of spurious associations, rather than cause lack of association as we found.

In summary, we did not identify an independent association between preoperative statin therapy at current clinical doses used for treatment of hypercholesterolemia and risk of AKI, postoperative dialysis, or hospital mortality in patients having noncardiac surgery.

Appendix 1: Baseline and Intraoperative Patient Characteristics for 28,508 Patients Included in the Study and 23,745 Patients Excluded from the Study

Baseline factors	Included in the study (*n* = 28,508)	Unavailable baseline statin use, baseline serum creatinine, and/or acute kidney injury outcome (*n* = 23,745)
To-come-in admission (versus inpatient), %	84.6	77.7
Age, y, mean ± SD	59 ± 15	57 ± 16
Body mass index, kg/m^2, median (quartiles)	28 (24, 33)	28 (24, 33)
Female gender, %	50.9	54.7
Race, %		
Caucasian	86.2	84.5
African American	10.2	11.7
Other	3.6	3.8
Creatinine, mg/dL, median (quartiles)	0.9 (0.7, 1.1)	0.9 (0.7, 1.0)
Hematocrit, %, mean ± SD	40.7 ± 4.9	39.3 ± 5.5
Albumin, mg/dL, median (quartiles)	4.3 (3.9, 4.5)	4.2 (3.6, 4.5)
Acute renal failure, %	3.2	4.0
Chronic renal failure, %	3.4	4.4
Diabetes, %		
None	82.6	83.6
Oral	14.1	13.8
Insulin	3.3	2.6
Hypertension, %	53.0	46.0
CHF, %	4.9	4.3
MI, %	6.3	4.7
Valve disease, %	3.4	3.8
S/P CABG, %	5.6	5.0
S/P PCI, %	5.7	4.4
COPD, %	10.2	10.0
DVT, %	1.9	1.9
Supraventricular arrhythmia, %	2.8	2.7
Ventricular arrhythmia, %	1.4	1.5
Use of β-blockers, %	20.6	12.9
Use of ACE inhibitors, %	14.9	11.2
Use of ARBS, %	6.5	4.6

(*Continued*)

Appendix 1: (Continued)

Baseline factors	Included in the study (*n* = 28,508)	Unavailable baseline statin use, baseline serum creatinine, and/or acute kidney injury outcome (*n* = 23,745)
Use of Ca-channel blockers, %	9.6	6.9
Use of steroids, %	7.5	5.6
Use of diuretics, %	8.8	5.6
Use of aspirin, %	8.7	5.2
ASA physical status, %		
I	2.6	3.0
II	39.3	40.2
III	51.8	50.2
IV	6.4	6.5
Case duration, min, median (quartiles)	252 (188, 331)	206 (142, 287)
EBL, mL, median (quartiles)	200 (75, 400)	100 (20, 200)
Crystalloids, mL, median (quartiles)	2700 (1900, 3700)	2000 (1200, 2900)
Colloids, mL, median (quartiles)	500 (0, 1000)	0 (0, 500)
RBC transfusion, mL, median (quartiles)	0 (0, 0)	0 (0, 0)
Urine output, mL, median (quartiles)	300 (110, 600)	120 (0, 400)

CHF = congestive heart failure; MI = myocardial infarction; S/P = status/post; CABG = coronary artery bypass graft; PCI = percutaneous coronary intervention; COPD = chronic obstructive pulmonary disease; DVT = deep vein thrombosis; ACE = angiotensin-converting enzyme; ARBS = angiotensin II receptor blockers; Ca = calcium; EBL = estimated blood loss; RBC = red blood cell.

DISCLOSURES

Name: Maged Y. Argalious, MD, MBA.
Contribution: This author helped design the study, conduct the study, analyze the data, and write the manuscript.
Attestation: Maged Argalious has seen the original study data, reviewed the analysis of the data, approved the final manuscript, and is the author responsible for archiving the study files.
Name: Jarrod E. Dalton, MA.
Contribution: This author helped analyze the data and write the manuscript.
Attestation: Jarrod Dalton has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Thilak Sreenivasalu, MD.
Contribution: This author helped conduct the study.
Attestation: Thilak Sreenivasalu has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
Name: Jerome O'Hara, MD.
Contribution: This author helped conduct the study.
Attestation: Jerome O'Hara has seen the original study data and approved the final manuscript.
Name: Daniel I. Sessler, MD.
Contribution: This author helped write the manuscript.
Attestation: Daniel I. Sessler has seen the original study data, reviewed the analysis of the data, and approved the final manuscript.
This manuscript was handled by: Sorin J. Brull, MD, FCARCSI (Hon).

REFERENCES

1. Mehta RL, Kellum JA, Shah SV, Molitoris BA, Ronco C, Warnock DG, Levin A; Acute Kidney Injury Network. Acute Kidney Injury Network: report of an initiative to improve outcomes in acute kidney injury. Crit Care 2007;11:R31
2. Kheterpal S, Tremper KK, Englesbe MJ, O'Reilly M, Shanks AM, Fetterman DM, Rosenberg AL, Swartz RD. Predictors of postoperative acute renal failure after noncardiac surgery in patients with previously normal renal function. Anesthesiology 2007;107:892–902
3. Hou SH, Bushinsky DA, Wish JB, Cohen JJ, Harrington JT. Hospital-acquired renal insufficiency: a prospective study. Am J Med 1983;74:243–8
4. Xue JL, Daniels F, Star RA, Kimmel PL, Eggers PW, Molitoris BA, Himmelfarb J, Collins AJ. Incidence and mortality of acute renal failure in Medicare beneficiaries, 1992 to 2001. J Am Soc Nephrol 2006;17:1135–42
5. Devarajan P. Update on mechanisms of ischemic acute kidney injury. J Am Soc Nephrol 2006;17:1503–20
6. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, Caulfield M, Collins R, Kjeldsen SE, Kristinsson A, McInnes GT, Mehlsen J, Nieminen M, O'Brien E, Ostergren J; ASCOT Investigators. Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial–Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 2003;361:1149–58
7. Randomised trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). Lancet 1994;344:1383–9
8. Tonelli M, Isles C, Curhan GC, Tonkin A, Pfeffer MA, Shepherd J, Sacks FM, Furberg C, Cobbe SM, Simes J, Craven T, West M. Effect of pravastatin on cardiovascular events in people with chronic kidney disease. Circulation 2004;110:1557–63
9. Chonchol M, Cook T, Kjekshus J, Pedersen TR, Lindenfeld J. Simvastatin for secondary prevention of all-cause mortality and major coronary events in patients with mild chronic renal insufficiency. Am J Kidney Dis 2007;49:373–82
10. Campese VM, Park J. HMG-CoA reductase inhibitors and the kidney. Kidney Int 2007;71:1215–22
11. Epstein M, Campese VM. Pleiotropic effects of 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibitors on renal function. Am J Kidney Dis 2005;45:2–14
12. Liao JK. Effects of statins on 3-hydroxy-3-methylglutaryl coenzyme a reductase inhibition beyond low-density lipoprotein cholesterol. Am J Cardiol 2005;96:24F–33F
13. Albert MA, Danielson E, Rifai N, Ridker PM; PRINCE Investigators. Effect of statin therapy on C-reactive protein levels: the pravastatin inflammation/CRP evaluation (PRINCE)—a randomized trial and cohort study. JAMA 2001;286:64–70
14. Kalinowski L, Dobrucki LW, Brovkovych V, Malinski T. Increased nitric oxide bioavailability in endothelial cells contributes to the pleiotropic effect of cerivastatin. Circulation 2002;105:933–8
15. Suzumura K, Yasuhara M, Tanaka K, Odawara A, Narita H, Suzuki T. An in vitro study of the hydroxyl radical scavenging property of fluvastatin, and HMG-CoA reductase inhibitor. Chem Pharm Bull 1999;47:1010–2
16. Crisby M, Nordin-Fredriksson G, Shah PK, Yano J, Zhu J, Nilsson J. Pravastatin treatment increases collagen content and decreases lipid content, inflammation, metalloproteinases, and cell death in human carotid plaques: implications for plaque stabilization. Circulation 2001;103:926–33

17. Tsiara S, Elisaf M, Mikhailidis DP. Early vascular benefits of statin therapy. Curr Med Res Opin 2003;19:540–56
18. Sharyo S, Yokota-Ikeda N, Mori M, Kumagai K, Uchida K, Ito K, Burne-Taney MJ, Rabb H, Ikeda M. Pravastatin improves renal ischemia-reperfusion injury by inhibiting the mevalonate pathway. Kidney Int 2008;74:577–84
19. Gueler F, Rong S, Park JK, Fiebeler A, Menne J, Elger M, Mueller DN, Hampich F, Dechend R, Kunter U, Luft FC, Haller H. Postischemic acute renal failure is reduced by short-term statin treatment in a rat model. J Am Soc Nephrol 2002;13:2288–98
20. Gueler F, Park JK, Rong S, Kirsch T, Lindschau C, Zheng W, Elger M, Fiebeler A, Fliser D, Luft FC, Haller H. Statins attenuate ischemia-reperfusion injury by inducing heme oxygenase-1 in infiltrating macrophages. Am J Pathol 2007;170:1192–9
21. Sabbatini M, Pisani A, Uccello F, Serio V, Serù R, Paternò R, Cianciaruso B, Fuiano G, Andreucci M. Atorvastatin improves the course of ischemic acute renal failure in aging rats. J Am Soc Nephrol 2004;15:901–9
22. Joyce M, Kelly C, Winter D, Chen G, Leahy A, Bouchier-Hayes D. Pravastatin, a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor, attenuates renal injury in an experimental model of ischemia-reperfusion. J Surg Res 2001;101:79–84
23. Uchino S, Bellomo R, Goldsmith D, Bates S, Ronco C. An assessment of the RIFLE criteria for acute renal failure in hospitalized patients. Crit Care Med 2006;34:1913–7
24. Sekhon JS. Multivariate and propensity score matching software with automated balance optimization: the matching package for R. J Stat Softw 2011;42:1–52
25. Kor DJ, Brown MJ, Iscimen R, Brown DR, Whalen FX, Roy TK, Keegan MT. Perioperative statin therapy and renal outcomes after major vascular surgery: a propensity-based analysis. J Cardiothorac Vasc Anesth 2008;22:210–6
26. Argalious M, Xu M, Sun Z, Smedira N, Koch CG. Preoperative statin therapy is not associated with a reduced incidence of postoperative acute kidney injury after cardiac surgery. Anesth Analg 2010;111:324–30
27. Molnar AO, Coca SG, Devereaux PJ, Jain AK, Kitchlu A, Luo J, Parikh CR, Paterson JM, Siddiqui N, Wald R, Walsh M, Garg AX. Statin use associates with a lower incidence of acute kidney injury after major elective surgery. J Am Soc Nephrol 2011;22:939–46
28. Pathi VL, Morrison J, MacPhaden A, Martin W, McQuiston AM, Wheatley DJ. Alterations in renal microcirculation during cardiopulmonary bypass. Ann Thorac Surg 1998;65:993–8
29. Waikar SS, Wald R, Chertow GM, Curhan GC, Winkelmayer WC, Liangos O, Sosa MA, Jaber BL. Validity of International Classification of Diseases, Ninth Revision, clinical modification codes for acute renal failure. J Am Soc Nephrol 2006;17:1688–94
30. Lindenauer PK, Pekow P, Wang K, Gutierrez B, Benjamin EM. Lipid-lowering therapy and in-hospital mortality following major noncardiac surgery. JAMA 2004;291:2092–9
31. Beattie WS, Wijeysundera DN. Statins and the "healthy user bias" in cardiac surgery. Anesth Analg 2010;111:261–3
32. Argalious MY, Dalton JE, Cywinski JB, Seif J, Abdelmalak M, Sessler DI. Association between preoperative statin therapy and postoperative change in glomerular filtration rate in endovascular aortic surgery. Br J Anaesth 2012;109:161–7
33. Bellomo R, Chapman M, Finfer S, Hickling K, Myburgh J. Low-dose dopamine in patients with early renal dysfunction: a placebo-controlled randomised trial. Australian and New Zealand Intensive Care Society (ANZICS) Clinical Trials Group. Lancet 2000;356:2139–43
34. Doi K, Ogawa N, Suzuki E, Noiri E, Fujita T. Mannitol-induced acute renal failure. Am J Med 2003;115:593–4
35. Morelli A, Ricci Z, Bellomo R, Ronco C, Rocco M, Conti G, De Gaetano A, Picchini U, Orecchioni A, Portieri M, Coluzzi F, Porzi P, Serio P, Bruno A, Pietropaoli P. Prophylactic fenoldopam for renal protection in sepsis: a randomized, double-blind, placebo-controlled pilot trial. Crit Care Med 2005;33:2451–6
36. Hersey P, Poullis M. Does the administration of mannitol prevent renal failure in open abdominal aortic aneurysm surgery? Interact Cardiovasc Thorac Surg 2008;7:906–9
37. Liu YL, Prowle J, Licari E, Uchino S, Bellomo R. Changes in blood pressure before the development of nosocomial acute kidney injury. Nephrol Dial Transplant 2009;24:504–11
38. Verma S, Rao V, Weisel RD, Li SH, Fedak PW, Miriuka S, Li RK. Novel cardioprotective effects of pravastatin in human ventricular cardiomyocytes subjected to hypoxia and reoxygenation: beneficial effects of statins independent of endothelial cells. J Surg Res 2004;119:66–71
39. Le Manach Y, Godet G, Coriat P, Martinon C, Bertrand M, Fléron MH, Riou B. The impact of postoperative discontinuation or continuation of chronic statin therapy on cardiac outcome after major vascular surgery. Anesth Analg 2007;104:1326–33
40. Kourliouros A, De Souza A, Roberts N, Marciniak A, Tsiouris A, Valencia O, Camm J, Jahangiri M. Dose-related effect of statins on atrial fibrillation after cardiac surgery. Ann Thorac Surg 2008;85:1515–20