CLINICAL RESEARCH STUDY

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Preoperative Statin Use and Postoperative Acute Kidney Injury

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ABSTRACT

BACKGROUND: Acute kidney injury is a frequent postoperative complication that confers increased mortality, morbidity, and costs. The purpose of this study was to evaluate whether preoperative statin use is associated with a decreased risk of postoperative acute kidney injury.

METHODS: We assembled a retrospective cohort of 98,939 patients who underwent a major open abdominal, cardiac, thoracic, or vascular procedure between 2000 and 2010. Statin users were pair-matched to nonusers on the basis of surgery type, baseline kidney function, days from admission until surgery, and propensity score based on demographics, comorbid conditions, and concomitant medications. Acute kidney injury was defined based on changes in serum creatinine measurements applying Acute Kidney Injury Network and Risk-Injury-Failure staging systems, and on the need for renal replacement therapy. Associations between statin use and acute kidney injury were estimated by conditional logistic regression.

RESULTS: Across various acute kidney injury definitions, statin use was consistently associated with a decreased risk: adjusted odds ratios (95% confidence intervals) varied from 0.74 (0.58-0.95) to 0.80 (0.71-0.90). Associations were similar among diabetics and nondiabetics, and across strata of baseline kidney function. The protective association of statins was most pronounced among patients undergoing vascular surgery and least among patients undergoing cardiac surgery.

CONCLUSIONS: Preoperative statin use is associated with a decreased risk of postoperative acute kidney injury. Future randomized clinical trials are needed to determine causality.

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KEYWORDS: Acute kidney injury; Acute renal failure; 3-Hydroxy-3-glutaryl Co-A reductase inhibitors; Perioperative complications; Statins; Surgery

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Acute kidney injury is a frequent postoperative complication and has important ramifications on in-hospital mortality, length of stay, and resource utilization, as well as long-term implications for renal outcomes and patient survival.[1-15] Considering these factors and the vast number of patients who undergo elective surgery annually (>230 million worldwide[16]), identification of effective prophylactic therapies is paramount.

A recent population-based cohort study from Ontario suggested that use of 3-hydroxy-3-glutaryl Co-A reductase inhibitors ("statins") was associated with a decreased risk of postoperative acute kidney injury.[17] Although grounded in a strong biological basis and rigorously conducted, the study relied on diagnostic codes to identify acute kidney injury, as well as chronic kidney disease, arguably the most compelling confounder and potential effect modifier of any association with acute kidney injury. Limited sensitivity of

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chronic kidney disease diagnostic codes may have led to residual confounding. Unclear operating characteristics of acute kidney injury diagnostic codes may have promoted misclassification bias and prevented consideration of acute kidney injury severity in gradations short of renal replacement therapy requirement.[18] Other studies have attempted to examine the association between statins and postoperative acute kidney injury among cardiac surgery patients, but were limited by heterogeneity in outcome definitions and relatively small sample sizes.[19-24]

To address some of the limitations of previous studies, we used data from a large cohort of patients undergoing abdominal, cardiac, vascular, and thoracic surgery with detailed laboratory information, allowing ascertainment of acute kidney injury outcomes using consensus definitions. We sought to evaluate whether preoperative statin use was associated with a decreased risk of postoperative acute kidney injury, and whether this association was modified by type of surgery, diabetes, or baseline estimated glomerular filtration rate (eGFR).

CLINICAL SIGNIFICANCE

- Preoperative statin use is associated with a 20%-26% reduction in the incidence of postoperative acute kidney injury.
- Benefits were equivalent among diabetics and nondiabetics and irrespective of preoperative glomerular filtration rate.
- Benefits were most pronounced among patients undergoing vascular surgery, intermediate among patients undergoing abdominal and thoracic surgery, and least among patients undergoing cardiac surgery.

METHODS

Study Sites and Participants

The study protocol was approved by the Partners Healthcare Institutional Review Board. We assembled a retrospective cohort of 98,939 unique adult patients who underwent a major open abdominal, cardiac, thoracic, or vascular procedure at Massachusetts General Hospital or Brigham and Women's Hospital between January 1, 2000 and December 31, 2010, had no prior diagnosis of end-stage renal disease, had not previously undergone dialysis or renal transplantation, and did not have acute kidney injury (AKIN- stage 1; see below) during the index hospitalization before or at the time of surgery. For patients who met eligibility criteria on more than one occasion, one procedure was selected at random to avoid within-subject clustering. In order to focus consideration on subjects admitted specifically for surgery, we excluded patients whose surgery occurred more than 3 days after hospital admission (n = 19,918). Because a current assessment of baseline serum creatinine is essential to accurately define acute kidney injury and baseline chronic kidney disease, we further excluded patients who did not have a baseline serum creatinine measured in either the 30-day period preceding hospital admission or in the hospital before surgery (n = 921).

Data, Exposure, and Outcomes

All study data were abstracted from Partners Healthcare Research Patient Data Registry, which has been utilized extensively in prior epidemiological studies.[25-29] The Research Patient Data Registry aggregates data on sociodemographics, diagnostic, and procedural claims, laboratory values, and medication use across all Partners Healthcare sites (inpatient and outpatient), including the 2 source hospitals considered in this study. Comorbid conditions were defined using medical records and claims. For example, diabetes was ascribed on the basis of International Classification of Disease-Ninth Revision codes 249.x and 250.x, Diagnosis-Related Groups 294 and 295, or record of diabetes on the subject's problem list. In addition, ischemic heart disease and cerebrovascular disease were additionally defined based on prior procedural interventions (eg, Current Procedural Technology code 35301, which codes for "Thromboendarterectomy, with or without patch graft; carotid, vertebral, subclavian, by neck incision," was interpreted as evidence of cerebrovascular disease). In order to respect time sequence, we considered only codes that preceded surgery. Baseline eGFR was based preferentially on the first serum creatinine during the index hospitalization, or on the latest serum creatinine measurement within 30 days preceding hospital admission; eGFR was calculated using 4-variable Modified Diet in Renal Disease Study equation.[30]

Medication use was assessed based on doses administered between the time of hospital admission and surgery. Data on prehospital medications were sparsely populated and thus could not be considered. Subjects were considered to be statin users if they received at least one dose of atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, or simvastatin during this period and as nonusers if they did not.

Subjects were considered at risk beginning at the time of surgery and remained at risk for the duration of hospitalization. Acute kidney injury was defined in terms of both the Acute Kidney Injury Network (AKIN) and Risk-Injury-Failure (RIFLE) staging systems as follows:[31,32]

- AKIN-stage 1: increase in serum creatinine ≥0.3 mg/dL or ≥50% over any 48-hour period
- RIFLE-R: increase in serum creatinine ≥50% or fall in eGFR ≥25% over any 48-hour period
- AKIN-stages 2,3 (identical to RIFLE-I,F): doubling of serum creatinine or increase in serum creatinine ≥0.5 mg/dL to a level ≥4 mg/dL over any 48-hour period

For patients in whom serum creatinine was not measured preoperatively in the hospital, the prehospital value was considered as the initial referent against which acute kidney injury was defined. Renal replacement therapy was defined based on procedural claims for hemodialysis, peritoneal dialysis, or continuous renal replacement therapy during the postoperative hospital course. The following primary composite outcomes (listed in order of increasing restrictiveness) were considered: composite AKIN-1 or renal replacement therapy; composite RIFLE-R or renal replacement therapy; composite AKIN-2,3 or renal replacement therapy. In secondary analyses, we also considered renal replacement therapy alone as an outcome, recognizing that statistical power would be limited due to low event rates.

Analysis

Continuous variables were examined graphically and summarized as means, standard deviations, medians, and interquartile ranges, as dictated by data type. Categorical variables were summarized as counts and proportions. Subject characteristics were compared across exposure groups in terms of standardized differences (difference in mean [or proportion] divided by the pooled SD);[33] standardized differences >10% are indicative of meaningful imbalance.[34] Thereafter, statin users were pair-matched to nonusers on the basis of type of surgery (abdominal, cardiac, thoracic, vascular), lag time between admission and surgery (0, 1, 2, 3 days), baseline eGFR (>60, 46-60, 31-45, ≤30 mL/min/1.73 m^2), and propensity score (nearest neighbor with caliper width not exceeding 0.005). Propensity score was estimated using a logistic model in which statin use was the dependent variable and predicted based on the remaining demographic factors, comorbid conditions, and concomitant medications (area under the receiver operating characteristic curve for propensity model was 0.83). Associations between statin use and outcomes were estimated using conditional logistic regression models grouped on matched pair assignment. Further statistical adjustment for year of surgery did not materially affect estimates. Interaction on the basis of diabetes, baseline eGFR, and surgery type was examined by likelihood ratio testing comparing nested models that did and did not contain 2-way factor-by-exposure cross-product terms; stratum-specific estimates were estimated by linear combination of regression coefficients.

We recognized that the perceived effect of statins may have been affected by the timing and acuity of surgery (particularly when surgery occurred on the date of admission) that, in turn, impacted the opportunity for in-hospital, preoperative statin receipt. We therefore compared effect estimates for statin use (vs nonuse) among patients who underwent surgery on hospital day 0 versus hospital days 1-3, and found no evidence of effect modification (*P*-interaction >0.20 for all acute kidney injury outcomes). Therefore, patients undergoing surgery on the date of hospital admission were retained in subsequent analyses.

Sensitivity Analyses

In order to provide insight as to whether the protective association of statins might be attributable to confounding on the basis of health-seeking behavior (ie, the healthy-user effect), we performed 2 additional analyses. First, if statin use is a marker of healthy behavior, then a protective association also should be observed for patients using other medications (compared with nonusers). We therefore examined the association of beta-blockers and serotonin selective reuptake inhibitors with acute kidney injury, which should not theoretically lower the risk of postoperative renal impairment. Methods were analogous to those used in the primary statin analysis. Second, we examined the association between statins and postoperative pneumonia, against which there was no cogent reason to suspect statins would be protective. Third, we repeated our analysis after limiting outcomes to acute kidney injury events occurring within 72 hours of surgery. All analyses were performed using Stata 10.0 SE (StataCorp LP, College Station, Tex).

RESULTS

Baseline Characteristics

The source cohort consisted of 78,100 subjects among whom mean age was 60.7 years; 45.6% were female, 86.1% were white, 54.4% had hypertension, 19.5% had diabetes, and 21.5% had baseline eGFR ≤60 mL/min/1.73 m^2. Respectively, 34.2%, 26.1%, 20.5%, and 19.2% underwent abdominal, cardiac, thoracic, and vascular surgery. Median (interquartile range) between hospital admission and surgery was 0 (0, 1) days.

There were 10,779 (13.8%) statin users and 67,321 (86.2%) statin nonusers in the source population. Compared with nonusers, statin users were older, more likely to be male; to have hypertension, diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, and eGFR 60 mL/min/1.73 m^2; to be treated with other classes of cardiovascular medication; and more likely to be undergoing cardiac or vascular surgery (**Table 1**). A total of 7971 statin users (73.9% of those in source cohort) were successfully pair-matched to a nonuser. In the matched analytical cohort, statin users and nonusers were well balanced on all covariates.

Association between Statin Use and Acute Kidney Injury

In the primary analysis, statin use was associated with a decreased risk of composite AKIN-1 or renal replacement therapy, composite RIFLE-R or renal replacement therapy, composite AKIN-2,3 or renal replacement therapy, and renal replacement therapy alone (**Table 2**, **Supplemental Table 1**). Results were essentially identical when

Table 1 Baseline Characteristics of Preoperative (In Hospital) Statin Users vs Nonusers in the Source and Matched Cohorts

	Source Cohort			Matched Cohort		
	Nonusers n = 67,321	Users n = 10,779	Std Diff (%)	Nonusers n = 7971	Users n = 7971	Std Diff (%)
Age, years	59.4 ± 15.9	68.6 ± 11.0	60.1*	68.3 ± 12.1	68.0 ± 11.2	−2.6
Female	47.3%	35.0%	−24.8*	34.5%	35.9%	2.9
Race						
White	85.8%	88.1%	6.7	89.3%	88.5%	−2.5
Black	3.8%	2.2%	−8.6	1.8%	2.4%	4.2
Other/unknown	10.5%	9.7%	−2.6	8.9%	9.1%	0.7
Hypertension	51.1%	74.8%	48.2*	71.7%	73.2%	3.9
Diabetes	17.5%	32.3%	37.6*	26.9%	29.4%	5.6
Congestive heart failure	18.3%	36.1%	44.4*	34.8%	32.8%	−4.2
Ischemic heart disease	45.2%	79.5%	70.6*	75.6%	74.5%	−2.5
Cerebrovascular disease	13.4%	27.0%	38.1*	28.7%	25.8%	−6.5
Angiotensin-converting enzyme inhibitor	3.2%	22.3%	84.9*	12.2%	13.6%	4.2
Angiotensin receptor blocker	1.1%	5.6%	34.8*	3.7%	4.1%	2.1
Beta-blocker	31.5%	70.2%	83.5*	62.6%	62.7%	0.2
Calcium channel blocker	5.5%	19.0%	52.5*	15.4%	15.5%	0.3
Loop diuretic	7.4%	21.0%	47.5*	18.8%	15.4%	−9.0
Thiazide diuretic	1.5%	7.1%	37.9*	4.8%	5.1%	1.4
Potassium-sparing diuretic	0.4%	1.2%	11.2*	1.0%	1.1%	1.0
Aspirin	0.5%	3.3%	30.0*	1.7%	2.2%	3.6
Other antiplatelet	0.8%	6.5%	46.2*	3.1%	3.5%	2.2
Nonsteroidal anti-inflammatory	13.0%	12.5%	−1.5	11.4%	11.8%	1.2
Type of surgery						
Abdominal	38.0%	10.8%	−58.5*	12.0%	12.0%	0%
Cardiac	21.9%	51.8%	70.1*	47.0%	47.0%	0%
Vascular	19.0%	30.0%	27.4*	32.9%	32.9%	0%
Thoracic	21.1%	7.5%	−34.8*	8.1%	8.1%	0%
Baseline eGFR, mL/min/1.73 m^2						
>60	80.1%	68.3%	−28.9*	71.1%	71.1%	0%
46-60	13.2%	20.3%	20.4*	19.6%	19.6%	0%
31-45	5.2%	9.2%	17.2*	8.2%	8.2%	0%
≤30	1.5%	2.3%	6.4	1.2%	1.2%	0%
Lag admission to surgery, days						
0	74.0%	32.0%	−94.9*	40.4%	40.4%	0%
1	17.8%	31.0%	33.5*	36.3%	36.3%	0%
2	5.1%	21.1%	62.9*	14.8%	14.8%	0%
3	3.1%	15.9%	60.8*	8.5%	8.5%	0%
Propensity score, %						
Mean ± SD	10.7 ± 12.7	32.9 ± 23.0		25.4 ± 18.3	25.4 ± 18.3	
Median [IQR] (min, max)	6.3 [2.6, 12.9] (0.6, 96.2)	27.0 [14.1, 48.5] (0.9, 98.4.2)		21.6 [11.0-34.5] (0.9, 93.3)	21.6 [11.0-34.5] (0.9, 92.9)	

eGFR = estimated glomerular filtration; IQR = interquartile range; Std Dif = standardized difference.
*Standardized differences >10%.

AKIN-1, AKIN-2,3, and RIFLE-R were considered as stand-alone endpoints (ie, not composited with renal replacement therapy). Estimates were similar when consideration was limited to acute kidney injury events occurring within 72 hours following surgery (**Supplemental Table 2**), although the 95% confidence interval for the statin-renal replacement therapy alone association was wide and included the null, possibly due to a low event rate.

To examine for a dose-response trend, we examined the association between statins and acute kidney injury among 1702 matched pairs in which the statin user was on a high-potency statin and 6102 pairs in which the statin user was on a low-potency statin. High-potency statins appeared more protective than low-potency statins, although formal tests for interaction were significant only for more permissive outcome definitions, probably based on issues of statistical power (**Table 3**).

Table 2 Adjusted ORs (95% CIs) between Preoperative Statin Use vs Nonuse and Postoperative Acute Kidney Injury in Matched Analytical Cohort*

	Number of Pairs Based on Incident Acute Kidney Injury among Statin User and Nonuser				
Acute Kidney Injury Definition	Neither	Both	Statin: without Control: with	Statin: with Control: without	Adjusted OR (95% CI)
AKIN-1 or renal replacement therapy	2896	1648	1935	1492	0.77 (0.72-0.82)
RIFLE-R or renal replacement therapy	4723	487	1541	1220	0.79 (0.73-0.85)
AKIN-2,3 or renal replacement therapy	6791	45	631	504	0.80 (0.71-0.90)
Renal replacement therapy alone	7707	1	151	112	0.74 (0.58-0.95)

AKIN = Acute Kidney Injury Network; CI = confidence interval; OR = odds ratio; RIFLE = Risk-Injury-Failure.

*Statin users and nonusers were pair-matched on the basis of type of surgery (abdominal, cardiac, vascular thoracic), lag time between admission and surgery (0, 1, 2, 3 days), baseline estimated glomerular filtration rate (>60, 46-60, 31-45, ≤30 mL/min/1.73 m^2), and propensity score (nearest neighbor with caliper width not exceeding 0.005), which was estimated on the basis of age, sex, race (Caucasian, African American, other/unknown), hypertension, diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, loop diuretics, thiazide-type diuretics, potassium-sparing diuretics, aspirin, nonaspirin antiplatelet agents, and nonsteroidal anti-inflammatory agents. Adjusted associations were estimated through conditional logistic regression models, which were grouped on matched-pair assignment.

Subgroup Analyses

The incidence of postoperative acute kidney injury according to baseline eGFR and statin exposure is given in **Supplemental Table 3**. The association between statin use and each acute kidney injury outcome was similar across strata of baseline eGFR (**Figure 1**). The incidence of postoperative acute kidney injury according to diabetic status and statin exposure is given in **Supplemental Table 4**. No effect

Table 3 Adjusted ORs (95% CIs) between Preoperative Statin Use vs Nonuse and Postoperative Acute Kidney Injury among 7804 Matched Pairs in whom Daily Statin Dose could be Identified*

	Number of Pairs Based on Incident Acute Kidney Injury among Statin User and Nonuser			
Acute Kidney Injury Definition	Statin: without Control: with	Statin: with Control: without	Stratum-specific aOR (95% CI)	P-Interaction by Dose
AKIN-1 or renal replacement therapy				<.001
• Low-dose statin†	1426	1170	0.82 (0.76-0.89)	
• High-dose statin‡	476	293	0.62 (0.53-0.71)	
RIFLE-R or renal replacement therapy				<.001
• Low-dose statin†	1152	975	0.85 (0.78-0.92)	
• High-dose statin‡	365	221	0.61 (0.51-0.72)	
AKIN-2,3 or renal replacement therapy				.13
• Low-dose statin†	476	393	0.83 (0.72-0.94)	
• High-dose statin‡	148	98	0.66 (0.51-0.85)	
Renal replacement therapy alone				.76
• Low-dose statin†	112	83	0.74 (0.56-0.98)	
• High-dose statin‡	37	25	0.68 (0.41-1.12)	

AKIN = Acute Kidney Injury Network; aOR = adjusted odds ratio; CI = confidence interval; RIFLE = Risk-Injury-Failure.

*Statin users and nonusers were pair-matched on the basis of type of surgery (abdominal, cardiac, vascular thoracic), lag time between admission and surgery (0, 1, 2, 3 days), baseline estimated glomerular filtration rate (>60, 46-60, 31-45, ≤30 mL/min/1.73 m^2), and propensity score (nearest neighbor with caliper width not exceeding 0.005), which was estimated on the basis of age, sex, race (Caucasian, African American, other/unknown), hypertension, diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, loop diuretics, thiazide type diuretics, potassium-sparing diuretics, aspirin, nonaspirin antiplatelet agents, and nonsteroidal anti-inflammatory agents. Adjusted associations were estimated through conditional logistic regression models which were grouped on matched pair assignment.

†Among matched pairs in which the statin user was on atorvastatin 10 mg/day or less, fluvastatin of any dose, pravastatin of any dose, simvastatin 40 mg/day or less, or rosuvastatin 5 mg/day or less.

‡Among matched pairs in which the statin user was on atorvastatin 20 mg/day or more, simvastatin 80 mg/day, or rosuvastatin 10 mg/day or more.

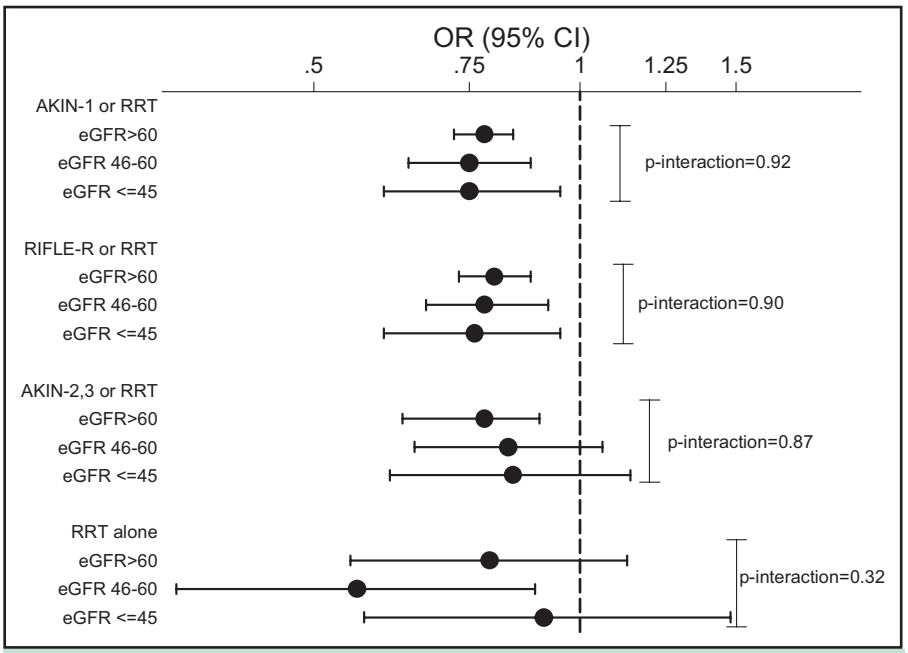

Figure 1 Adjusted odds ratios (ORs) (95% confidence intervals [CIs]) between preoperative statin use vs nonuse and postoperative acute kidney injury in matched cohort stratified on baseline estimated glomerular filtration rate (eGFR). [Note: eGFR ≤30 and 31-45 collapsed due to sparseness]. AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure; RRT = renal replacement therapy.

modification was observed of diabetes on statin-acute kidney injury associations (**Figure 2**).

The incidence of postoperative acute kidney injury according to type of surgery and statin exposure is given in **Supplemental Table 5**. The statin-acute kidney injury association was modified by surgery type when the outcomes of composite AKIN-1 or renal replacement therapy, composite RIFLE-R or renal replacement therapy, and composite AKIN-2,3 or renal replacement therapy were considered (**Figure 3**). In each case, statin use was most protective among patients undergoing vascular surgery, least protective (essentially null) among patients undergoing cardiac surgery, and bore intermediary associations among patients undergoing abdominal and thoracic surgery. Because few subjects undergoing abdominal and thoracic surgery required renal replacement therapy (n = 23 and 19, respectively) we limited subgroup analysis for this outcome to those undergoing cardiac and vascular surgery: adjusted odds ratios (ORs) (95% confidence intervals) were 0.92 (0.64-1.32) and 0.60 (0.40-1.14), respectively.

Tests of Healthy User Effects

Neither beta-blocker use nor serotonin selective reuptake inhibitors use was associated with a lower risk of acute kidney injury; beta-blockers were associated with a modestly increased risk (**Table 4**). As expected, no protective association of statin use with postoperative pneumonia was observed: adjusted OR 1.00 (95% confidence interval 0.88-1.14).

DISCUSSION

Acute kidney injury is a frequent complication of major surgery, with important ramifications for long-term renal function and survival. Our results suggest that preoperative statin use is associated with a decreased risk of postoperative acute kidney injury. The magnitude of risk reduction was similar (18%-22%) when more and less restrictive definitions of acute kidney injury were considered. Our findings, which used laboratory-based acute kidney injury definitions, complement results from a recent observational study using claims-based acute kidney injury definitions, helping to allay concerns about potential bias due to misclassification of nonrenal replacement therapy requiring acute kidney injury outcomes in that study.[17] Importantly, our large sample size allowed us to examine whether the association between statin use and acute kidney injury was modified by factors such as baseline eGFR and diabetes. In fact, the protective association of statins with acute kidney injury was similar across strata of these variables. Our findings add acute kidney injury to the growing list of potential beneficial effects of perioperative statin use, which currently includes postoperative atrial fibrillation and myocardial infarction.[35,36]

Animal models provide a biological basis for a putative causal benefit of statin use on acute kidney injury. In rat models of ischemia-reperfusion kidney injury, statin (vs vehicle) pretreatment blunts increase in serum creatinine, prevents monocyte and macrophage infiltration, decreases expression of intracellular adhesion molecule-1, type IV

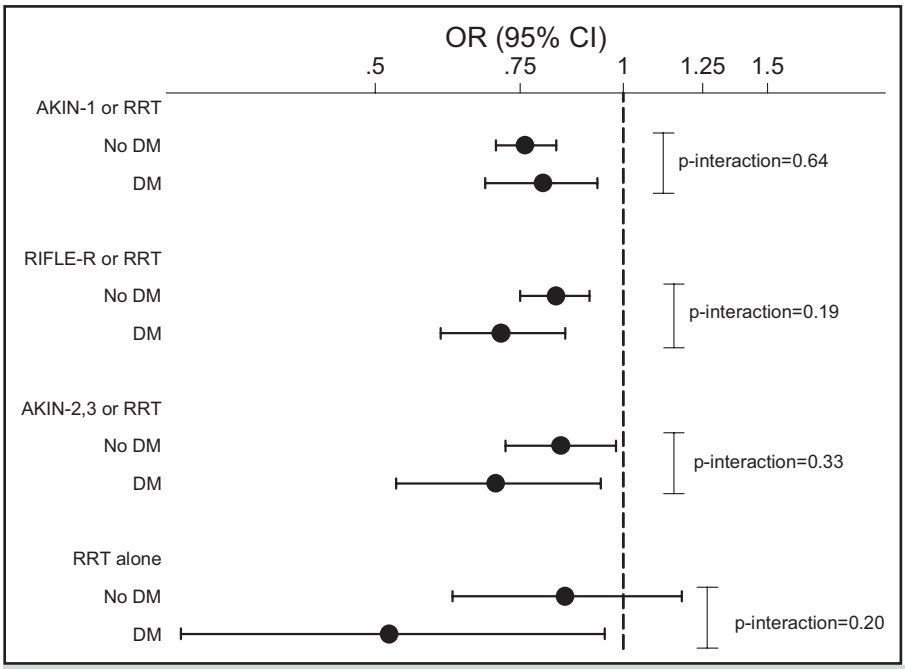

Figure 2 Adjusted odds ratios (ORs) (95% confidence intervals [CIs]) between preoperative statin use vs nonuse and postoperative acute kidney injury in matched cohort stratified on diabetes mellitus (DM). AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure; RRT = renal replacement therapy.

collagen, fibronectin, nuclear factor kappa-B, and activator protein-1, and abrogates histological changes of acute tubular necrosis.[37] Mechanistic studies suggest that these effects are mediated by favorable effects of statins on heme oxygenase-1 expression,[38] the mevalonate-isoprenoid pathway,[39] and nitric oxide synthesis.[40]

Several studies have estimated the association between statin use and postoperative acute kidney injury among patients undergoing cardiac surgery, with inconsistent findings. Virani et al reported that statin use was associated with a significant reduction in acute kidney injury defined as a clinically significant change in serum creatinine as determined by the treating clinician.[19] Huffmyer et al observed a protective association of statins on postoperative renal replacement therapy requirement, but not in terms of eGFR fall >50%.[20] Mithani et al observed point estimates similar to ours among high-dose (OR 0.79), but not low-dose statin users; however, the former did not achieve statistical significance, possibly due to limited statistical power.[21] Conversely, Argalious et al and Bolesta et al observed no protective association of statins.[22,23] A recent pilot randomized trial likewise showed no beneficial effect of statins, but was dramatically underpowered.[24] Interestingly, our data suggest that the protective effect of statins may be less robust among patients undergoing cardiac versus other types of surgery. This finding is reassuring: if the protective effect of statins was confounded by statin use being a marker of superior longitudinal medical care or of adherence, then this effect should be most pronounced among cardiac surgery patients among whom indications for statins are most prevalent; that the protective association of statins was least potent in this subgroup suggests that such bias did not drive the present findings. We were not able to directly assess why cardiac surgery patients derived lesser benefit from statins. We speculate that factors unique to cardiac surgery—such as cardioplegia, cardiopulmonary bypass, and myocardial suppression—may foster hemodynamic insults of sufficient magnitude so as to override the protective effects of statins in many instances. However, it is important to recognize that the study was not powered to detect statin effects within strata defined by surgery type. Thereby, it is notable that the effect estimate for statins trended in the protective direction across all combinations of surgery type and acute kidney injury definitions considered.

As with all observational studies, our data are subject to potential confounding. In terms of measured factors, statin users were older and less healthy. Therefore, confounding would tend to bias estimates towards making statins appear harmful. Empirically, this was the case: in unadjusted analyses, in the unmatched source cohort, statin use was associated with an increased risk of acute kidney injury outcomes (crude ORs ranged from 1.10 for renal replacement therapy alone to 1.91 for composite AKIN-1 or renal replacement therapy). However, adjustment for confounders can lead to biased estimates favoring statins if other unmeasured but favorable factors tend to aggregate among statin users. To examine for this healthy-user effect, we estimated the association between preoperative statin use and postoperative pneumonia, which is presumably not affected by statins, and observed no association. Moreover, we exam-

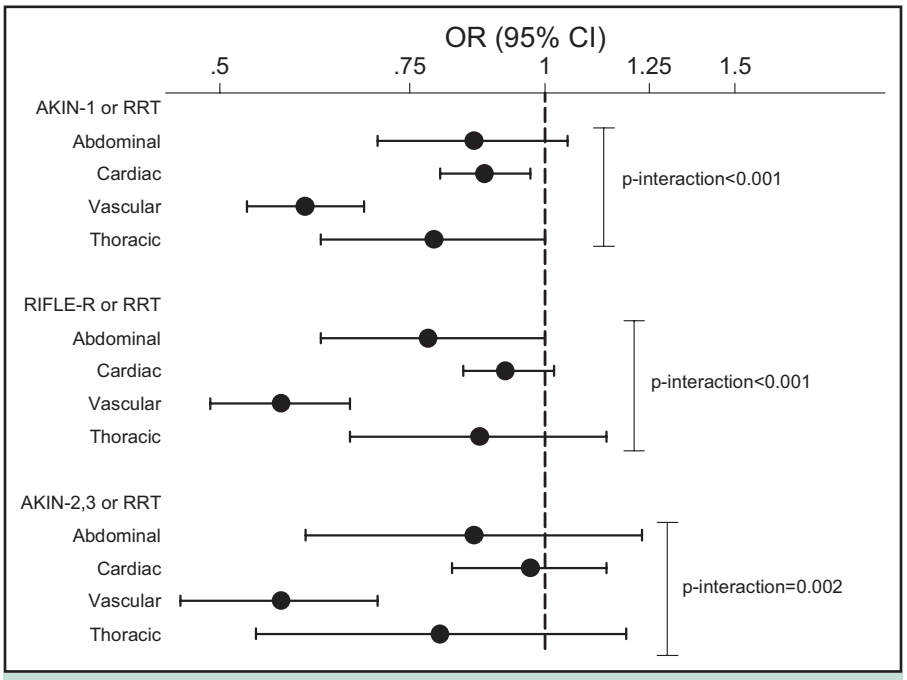

Figure 3 Adjusted odds ratios (ORs) (95% confidence intervals [CIs]) between preoperative statin use vs nonuse and postoperative acute kidney injury in matched cohort stratified on type of surgery. AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure; RRT = renal replacement therapy.

ined whether use of other medications such as beta-blockers and serotonin selective reuptake inhibitors, which might indicate healthier users (eg, greater access to medical care, better treatment adherence) but should not ameliorate renal outcomes, were associated with postoperative acute kidney injury, and again observed no protective association. In fact, beta-blocker use was associated with an increased risk of acute kidney injury, perhaps related to hemodynamic effects.[41] This finding warrants future directed study. Nonetheless, the absent protective association of beta-blockers allays concerns about potent healthy user bias.

Other limitations of the study also bear mention. Data on prehospital medication use were largely unavailable. However, most statin use during surgical admissions is likely to

Table 4 Association between Preoperative Statin, Beta-blocker, and Serotonin Selective Reuptake Inhibitor Use (Each vs Nonuse) and Postoperative Acute Kidney Injury*

Outcome	Statin	Beta-blocker	Serotonin Selective Reuptake Inhibitor
Propensity model ROC area	0.83	0.72	0.71
n, pairs	7971	20,830	2313
Matching efficiency	73.9%	72.4%	97.4%
aOR acute kidney injury			
● AKIN-1 or renal replacement therapy	0.77 (0.72-0.82)	1.15 (1.10-1.20)	0.93 (0.81-1.06)
● RIFLE-R or renal replacement therapy	0.79 (0.73-0.85)	1.10 (1.04-1.15)	0.99 (0.86-1.15)
● AKIN-2,3 or renal replacement therapy	0.80 (0.71-0.90)	1.11 (1.03-1.20)	1.08 (0.89-1.37)
● Renal replacement therapy alone	0.74 (0.58-0.95)	1.47 (1.24-1.75)	0.73 (0.46-1.17)

AKIN = Acute Kidney Injury Network; aOR = adjusted odds ratio; RIFLE = Risk-Injury-Failure; ROC = receiver operating characteristic.

*For each class of medication, users and nonusers were pair-matched on the basis of type of surgery (abdominal, cardiac, vascular thoracic), lag time between admission and surgery (0, 1, 2, 3 days), baseline estimated glomerular filtration rate (>60, 46-60, 31-45, ≤30 mL/min/1.73 m^2), and propensity score (nearest neighbor with caliper width not exceeding 0.005), which was estimated on the basis of age, sex, race (Caucasian, African American, other/unknown), hypertension, diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, loop diuretics, thiazide-type diuretics, potassium-sparing diuretics, aspirin, nonaspirin antiplatelet agents, and nonsteroidal anti-inflammatory agents. Adjusted associations were estimated through conditional logistic regression models which were grouped on matched pair assignment.

be carried over from the prehospital setting rather than de novo, and therefore represents ongoing exposure. Moreover, in-hospital statin use is more directly germane to perioperative bioavailability and therefore of greater biological relevance. In addition, we lacked histological data or other diagnostic indices of acute kidney injury type. It stands to reason that some cases of acute kidney injury were attributable to factors not susceptible to statin amelioration such as acute interstitial nephritis or obstructive uropathy. However, such cases presumably constitute only a minority of postoperative acute kidney injury events,[42,43] and would tend to bias estimates toward the null, thereby not accounting for the protective association of statins seen here. Finally, we note that our cohort was preponderantly white; given the known associations between race and renal susceptibility, caution should be exercised in generalizing to more racially mixed populations.

In conclusion, we found that preoperative statin use is associated with a decreased risk of postoperative acute kidney injury. Although future randomized clinical trials will be needed to make definitive recommendations, our findings support the continuation of statins among prevalent users in the perioperative period. Further studies are needed to confirm and generalize findings.

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Authorship: Dr Brunelli had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: Brunelli, Waikar, Choudhry; Acquisition of data: Brunelli; Analysis and interpretation of data: Brunelli, Waikar, Bateman, Chang, Lii, Garg, Winkelmayer, Choudhry; Drafting of the manuscript: Brunelli; Critical revision of the manuscript for important intellectual content: Brunelli, Waikar, Bateman, Chang, Lii, Garg, Winkelmayer, Choudhry; Statistical analysis: Brunelli, Lii; Obtained funding: Brunelli; Administrative, technical, or material support: Brunelli, Lii; Study supervision: Brunelli.

Supplemental Table 1 The Incidence of Postoperative Acute Kidney Injury Overall and by Statin Exposure in the Matched Analytical Cohort

	Overall	Statin Users	Statin Nonusers	Difference (Statin Users-Nonusers)
AKIN-1 or renal replacement therapy	42.2%	39.4%	45.0%	−5.6%
RIFLE-R or renal replacement therapy	23.4%	21.4%	25.4%	−4.0%
AKIN-2,3 or renal replacement therapy	7.7%	6.9%	8.5%	−1.6%
Renal replacement therapy alone	1.7%	1.4%	1.9%	−0.5%

AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure.

Supplemental Table 2 Adjusted ORs (95% CIs) between Preoperative Statin Use vs Nonuse and Postoperative Acute Kidney Injury in Matched Analytical Cohort Considering Only Acute Kidney Injury Events Occurring within 72 Hours of Surgery

	Number of Pairs Based on Incident Acute Kidney Injury among Statin User and Nonuser				
Acute kidney injury definition	Neither	Both	Statin: without Control: with	Statin: with Control: without	Adjusted OR (95% CI)
AKIN-1 or renal replacement therapy	3675	1099	1838	1359	0.74 (0.69-0.79)
RIFLE-R or renal replacement therapy	5441	303	1292	935	0.72 (0.67-0.79)
AKIN-2,3 or renal replacement therapy	7209	23	431	308	0.71 (0.62-0.83)
Renal replacement therapy alone	7859	0	64	48	0.75 (0.52-1.09)

AKIN = Acute Kidney Injury Network; CI = confidence interval; OR = odds ratio; RIFLE = Risk-Injury-Failure.

*Statin users and nonusers were pair matched on the basis of type of surgery (abdominal, cardiac, vascular thoracic), lag time between admission and surgery (0, 1, 2, 3 days), baseline estimated glomerular filtration rate (>60, 46-60, 31-45, ≤30 mL/min/1.73 m^2), and propensity score (nearest neighbor with caliper width not exceeding 0.005), which was estimated on the basis of age, sex, race (Caucasian, African American, other/unknown), hypertension, diabetes, ischemic heart disease, cerebrovascular disease, congestive heart failure, and use of angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, loop diuretics, thiazide type diuretics, potassium-sparing diuretics, aspirin, nonaspirin antiplatelet agents, and nonsteroidal anti-inflammatory agents. Adjusted associations were estimated through conditional logistic regression models, which were grouped on matched-pair assignment.

Supplemental Table 3 The Incidence of Postoperative Acute Kidney Injury according to Baseline eGFR Overall and by Statin Exposure in the Matched Analytical Cohort

	eGFR >60 mL/min/1.73 m^2 (n = 11,332)	eGFR 46-60 mL/min/1.73 m^2 (n = 3120)	eGFR ≤45 mL/min/1.73 m^2 (n = 1490)
AKIN-1 or renal replacement therapy			
Overall	36.6%	51.6%	64.6%
Statin users	33.9%	48.7%	61.7%
Statin nonusers	39.4%	54.6%	67.4%
Difference (statin users-nonusers)	−5.5%	−5.9%	−5.7%
RIFLE-R or renal replacement therapy			
Overall	21.5%	27.4%	29.7%
Statin users	19.6%	25.2%	27.0%
Statin nonusers	23.4%	29.7%	32.5%
Difference (statin users-nonusers)	−3.8%	−4.5%	−5.5%
AKIN-2,3 or renal replacement therapy			
Overall	6.8%	9.0%	11.4%
Statin users	6.1%	8.2%	10.5%
Statin nonusers	7.6%	9.7%	12.4%
Difference (statin users-nonusers)	−1.5%	−1.5%	−1.9%
Renal replacement therapy alone			
Overall	1.0%	2.5%	4.6%
Statin users	0.9%	1.8%	4.4%
Statin nonusers	1.2%	3.2%	4.8%
Difference (statin users-nonusers)	−0.3%	−1.4%	−0.4%

AKIN = Acute Kidney Injury Network; eGFR = estimated glomerular filtration rate; RIFLE = Risk-Injury-Failure.

Supplemental Table 4 The Incidence of Postoperative Acute Kidney Injury According to Diabetes Overall and by Statin Exposure in the Matched Analytical Cohort

	Nondiabetic (n = 11,450)	Diabetic (n = 4492)
AKIN-1 or renal replacement therapy		
Overall	41.0%	45.2%
Statin users	38.0%	42.9%
Statin nonusers	43.9%	47.8%
Difference (statin users-nonusers)	−5.9%	−4.9%
RIFLE-R or renal replacement therapy		
Overall	23.1%	24.4%
Statin users	21.5%	21.3%
Statin nonusers	24.6%	27.8%
Difference (statin users-nonusers)	−3.1%	−6.5%
AKIN-2,3 or renal replacement therapy		
Overall	8.0%	6.9%
Statin users	7.3%	6.0%
Statin nonusers	8.7%	7.8%
Difference (statin users-non users)	−1.4%	−1.8%
Renal replacement therapy alone		
Overall	1.7%	1.7%
Statin users	1.5%	1.2%
Statin nonusers	1.8%	2.1%
Difference (statin users-nonusers)	−0.3%	−0.9%

AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure.

Supplemental Table 5 The Incidence of Postoperative Acute Kidney Injury According to Type of Surgery Overall and by Statin Exposure in the Matched Analytical Cohort

	Abdominal (n = 1912)	Cardiac (n = 7490)	Vascular (n = 5246)	Thoracic (n = 1294)
AKIN-1 or renal replacement therapy				
Overall	26.8%	54.6%	31.9%	34.5%
Statin users	25.3%	53.2%	26.7%	32.0%
Statin nonusers	28.4%	56.1%	37.1%	37.1%
Difference (statin users-nonusers)	−3.1%	−2.9%	−10.4%	−5.1%
RIFLE-R or renal replacement therapy				
Overall	16.8%	28.9%	18.2%	22.8%
Statin users	15.1%	28.1%	14.1%	21.6%
Statin nonusers	18.5%	29.7%	22.2%	24.0%
Difference (statin users-nonusers)	−3.4%	−1.6%	−7.1%	−2.4%
AKIN-2,3 or renal replacement therapy				
Overall	6.8%	8.3%	7.0%	8.6%
Statin users	6.3%	8.1%	5.2%	7.7%
Statin nonusers	7.2%	8.4%	8.8%	9.4%
Difference (statin users-nonusers)	−0.9%	−0.3%	−3.6%	−1.7%
Renal replacement therapy alone				
Overall	1.2%	1.6%	2.0%	1.5%
Statin users	1.1%	1.5%	1.5%	1.1%
Statin nonusers	1.4%	1.7%	2.5%	1.9%
Difference (statin users-nonusers)	−0.3%	−0.2%	−1.0%	−0.8%

AKIN = Acute Kidney Injury Network; RIFLE = Risk-Injury-Failure.