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Association of Perioperative Statin Use With Mortality and Morbidity After Major Noncardiac Surgery

Martin J. London, MD; Gregory G. Schwartz, MD, PhD; Kwan Hur, PhD; William G. Henderson, MPH, PhD

IMPORTANCE The efficacy of statins in reducing perioperative cardiovascular and other organ system complications in patients undergoing noncardiac surgery remains controversial. Owing to a paucity of randomized clinical trials, analyses of large databases may facilitate informed hypothesis generation and more efficient trial design.

OBJECTIVE To evaluate associations of early perioperative statin use with outcomes in a national cohort of veterans undergoing noncardiac surgery.

DESIGN, SETTING, AND PARTICIPANTS This retrospective, observational cohort analysis included 180 478 veterans undergoing elective or emergent noncardiac surgery (including vascular, general, neurosurgery, orthopedic, thoracic, urologic, and otolaryngologic) who were admitted within 7 days of surgery and sampled by the Veterans Affairs Surgical Quality Improvement Program (VASQIP). Patients were admitted to Department of Veterans Affairs hospitals and underwent 30-day postoperative follow-up. Data were collected from October 1, 2005, to September 30, 2010, and analyzed from November 28, 2013, to October 31, 2016.

EXPOSURE Statin use on the day of or the day after surgery.

MAIN OUTCOMES AND MEASURES All-cause 30-day mortality (primary outcome) and standardized 30-day cardiovascular and noncardiovascular outcomes captured by VASQIP. Use of statins and other perioperative cardiovascular medications was ascertained from the Veterans Affairs Pharmacy Benefits Management research database.

RESULTS A total of 180 478 eligible patients (95.6% men and 4.4% women; mean [SD] age, 63.8 [11.6] years) underwent analysis, and 96 486 were included in the propensity score–matched cohort (96.3% men; 3.7% women; mean [SD] age, 65.9 [10.6] years). At the time of hospital admission, 37.8% of patients had an active outpatient prescription for a statin, of whom 80.8% were prescribed simvastatin and 59.5% used moderate-intensity dosing. Exposure to a statin on the day of or the day after surgery based on an inpatient prescription was noted in 31.5% of the cohort. Among 48 243 propensity score–matched pairs of early perioperative statin-exposed and nonexposed patients, 30-day all-cause mortality was significantly reduced in exposed patients (relative risk, 0.82; 95% CI, 0.75-0.89; $P < .001$; number needed to treat, 244; 95% CI, 170-432). Of the secondary outcomes, a significant association with reduced risk of any complication was noted (relative risk, 0.82; 95% CI, 0.79-0.86; $P < .001$; number needed to treat, 67; 95% CI, 55-87); all were significant except for the central nervous system and thrombosis categories, with the greatest risk reduction (relative risk, 0.73; 95% CI, 0.64-0.83) for cardiac complications.

CONCLUSIONS AND RELEVANCE Early perioperative exposure to a statin was associated with a significant reduction in all-cause perioperative mortality and several cardiovascular and noncardiovascular complications. However, the potential for selection biases in these results must be considered.

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Invited Commentary
Supplemental content

Author Affiliations: Author affiliations are listed at the end of this article.

Corresponding Author: Martin J. London, MD, Department of Anesthesia and Perioperative Care, Department of Veterans Affairs Medical Center, 4150 Clement St, San Francisco, CA 94121 (martin.london@ucsf.edu).

A recent analysis of the National Health and Nutrition Examination Survey reported that as of 2012, statins were the most commonly prescribed medication class in the United States.[1] With the release of updated national guidelines for cholesterol management in 2014,[2] the use of statins is expected to increase even further. Early safety concerns regarding perioperative statin treatment have been largely dispelled.[3,4] However, evidence for efficacy of perioperative statin treatment in reducing adverse perioperative cardiovascular and noncardiovascular outcomes remains inconclusive, with most current data derived from studies in cardiac or vascular surgery[5,6] and very limited data in other categories that constitute most surgical procedures.[5,7,8]

Current perioperative guidelines focus primarily on continuation of existing therapy in long-term statin users, with weak recommendations of potential efficacy in reducing cardiovascular complications.[9,10] Controversy regarding the the academic integrity of several randomized clinical trials of perioperative statins complicate interpretation of the existing literature.[11] An early large observational analysis[12] limited to inpatient billing and administrative data reported an adjusted odds ratio (OR) of 0.62 (95% CI, 0.58-0.67) for reduction of in-hospital mortality with inpatient statin use. Iannuzzi et al[13] used the American College of Surgery National Surgical Quality Improvement Program database to evaluate the association of preoperative statin use with several noncardiac postoperative complications in patients at a single center and reported reduction in an aggregate of complications but not overall mortality. More recently, Berwanger et al,[14] in a subanalysis of a multinational cohort of patients undergoing noncardiac surgery, reported that preoperative statin treatment was associated with significant reduction in all-cause postoperative mortality, myocardial injury, and stroke. However, whether statin treatment in the immediate perioperative period influences the risk for complications after noncardiac surgery remains unknown. Herein, we report on associations of early perioperative statin exposure with perioperative mortality and cardiovascular and noncardiovascular outcomes in a national cohort of US veterans. Secondary analyses considered associations of statin dosing, perioperative patterns of use, subgroup interactions, and potential selection biases with outcome.

Key Points

Question Is exposure to a statin in the early perioperative period associated with reduced postoperative complications after noncardiac surgery?

Findings This observational cohort analysis of veterans linked risk and outcome data from the Veterans Affairs Surgical Quality Improvement Program database to statin prescriptions in 180 478 patients and evaluated the associations of early statin exposure on 30-day mortality. After adjustment for risk, other medications used, and potential selection biases, 30-day mortality was significantly reduced in the statin-exposed group.

Meaning Perioperative statin use may be beneficial in reducing 30-day mortality, although the effects of selection biases cannot be excluded.

Methods

Perioperative risk, process, and outcome data from patients undergoing noncardiac surgical procedures in 7 surgical subspecialties (neurosurgery and vascular, general, orthopedic, thoracic, urologic, and otolaryngologic surgery) were derived from the Veterans Affairs (VA) Surgical Quality Improvement Program (VASQIP) database as previously described.[15] These data were supplemented with discharge and treatment codes from the *International Classification of Diseases, Ninth Revision, Clinical Modification*. The discharge and treatment codes were extracted from the Veterans Health Administration (VHA) outpatient care and patient treatment files; prescription data, from the outpatient and inpatient Pharmacy Benefit Management databases (eTables 1 and 2 in the Supplement).[16] Databases were linked by scrambled Social Security numbers. The data collection period spanned October 1, 2005, to September 30, 2010. Surgical procedures performed during the first 90 days or last 30 days of this interval were excluded so that 90-day preoperative statin treatment and 30-day postoperative outcomes could be assessed uniformly in all subjects. This study was approved by the US VHA Office of Patient Care Services and the institutional review boards of the San Francisco and Denver Veterans Affairs Medical Centers, who waived the need for informed consent.

We considered patients undergoing elective or emergent surgery who were admitted to hospital on the day of or within 7 days of surgery, with a hospital stay lasting at least through the day after surgery. Patients who died on the day of or the day after surgery were excluded. For patients with multiple records in the VASQIP database within this time frame, one was chosen randomly.

Prescription data grouped by VA National Formulary Drug Class are shown in eTable 1 in the Supplement. We subcategorized prescriptions in the antilipemic class by individual statins and the dose prescribed, allowing categorization by statin intensity groups (low, moderate, or high) per the American College of Cardiology/American Heart Association guidelines.[2] We also coded nonstatin drugs included in this class. Combinations of a statin and nonstatin were coded as statin combinations, with the statin intensity coded as described above. We coded the percentage of days within 90 days of hospital admission that a prescription was available, its maximum intensity, and whether it was active at the time of hospital admission. We also categorized new prescriptions starting within 14 days of hospital admission as a potential marker of prophylactic administration. Data were grouped by the presurgery inpatient period, day of surgery, day after surgery, the remainder of the hospital stay, and the time from hospital discharge until 30 days after surgery (if applicable). Relevant covariate medications were also coded. The revised cardiac risk index component variables were coded as previously reported (eTable 3 in the Supplement).[15,17]

Study Outcomes

We analyzed the association of statin exposure on the day of and/or the day after surgery with the primary outcome of death

from any cause within 30 days of surgery. Secondary outcomes included the following groupings of complications: cardiac (cardiac arrest, myocardial infarction), central nervous system (stroke, coma >24 hours), thrombotic (deep vein thrombosis, pulmonary embolus, and graft or prosthesis failure), infection (sepsis, organ space infection, and deep wound infection), respiratory (failure to wean from mechanical ventilation, pneumonia, and reintubation), renal (acute renal failure, renal insufficiency), or a composite of any of these secondary outcomes. Pneumonia was tested as a component of the respiratory or the infection category (discussed below). Events occurring within the 2-day exposure period were excluded from the analysis, with the exception of organ space and deep wound infection, for which dates of occurrence were not available in our data set.

Statistical Analysis

Data were analyzed from November 28, 2013, to October 31, 2016. To control for potential treatment-selection bias, we performed a propensity score–matched analysis.[18] The propensity score estimated the probability of statin exposure during the first 2 perioperative days using a nonparsimonious logistic regression model (omitting any statin use variables) as previously described and imputing missing values for preoperative laboratory values and body mass index using multiple imputation, constrained within plausible ranges.[15,19,20] We eliminated 430 patients with missing categorical variables used in the regression model. Statin exposure on the day of surgery or day after surgery was regressed on risk or process variables that we considered associated with statin exposure or any outcome with prevalence in the data set of at least 1% (eTable 4 in the Supplement). To adjust for potential regional effects, we included a variable for each of 21 administrative geographical regions in the VA health system. To avoid immortal time bias, we performed a landmark analysis, eliminating patients who died or sustained any of the secondary morbidity outcomes during the exposure period.[21]

Propensity score–matching (1:1) was conducted by matching pairs of patients with statin exposure and no exposure with a greedy matching algorithm and a caliper width of 0.2 SD of the log odds of the estimated propensity score.[22] Covariate balance between matched pairs for continuous and dichotomous categorical variables was assessed using the standardized difference, with values equal to or less than 10% indicating minimal imbalance.[23] We used the McNemar test to compare the frequency of the primary and secondary outcomes between the matched groups.[24] Relative risks (RRs) were computed using methods appropriate for paired data and are presented with their 95% CIs. Numbers needed to treat were calculated as the inverse of the absolute risk reduction estimated in the propensity score–matched sample. Details of sensitivity analyses for the primary and secondary outcomes are presented in the eMethods and eResults in the Supplement.

Continuous and categorical variables were compared using parametric or nonparametric methods as appropriate. We calculated RRs or ORs with 95% CIs. Categorical trends were assessed using the Cochran-Armitage trend test. We used SAS software (version 9.4; SAS Institute Inc) for all analyses, with 2-tailed $P < .05$ considered significant.

Results

The initial VASQIP cohort of patients undergoing surgery in our selected surgical subgroups consisted of 334 130 patients. We excluded 153 652 patients after adjustment for (1) the 90-day prehospital admission and 30-day postoperative assessment periods (n = 13 010); (2) admission more than 7 days before surgery (n = 12 541); (3) minimum length of stay criteria (n = 54 877) (including 468 patients dying on the day of or the day after surgery); (4) random exclusion of patients undergoing multiple surgical procedures in the assessment period (n = 34 088); (5) admission after the date of surgery (n = 2648); and (6) patients undergoing an assessed operation within 30 days of another procedure and combinations of any of the above criteria (n = 36 488). The final cohort consisted of 180 478 patients at 104 VHA hospitals (95.6% men and 4.4% women; mean [SD] age, 63.8 [11.6] years). Of these, 52 642 (29.2%) were admitted before the day of surgery and 127 836 (70.8%) on the day of surgery. The propensity score–matched cohort included 96 486 patients (96.3% men and 3.7% women; mean [SD] age, 65.9 [10.6] years).

The 30-day all-cause mortality rate for the entire cohort was 2.2% (n = 3975). Mortality varied significantly by surgical subgroup (vascular, 2.6%; general, 3.2%; orthopedic, 1.5%; and aggregated remaining specialties, 1.8%; $P < .001$ for differences among categories).

Pertinent demographic and clinical characteristics before and after propensity score matching are presented in **Table 1** and **Table 2**. Before matching, the statin-exposed group was older and more likely to be male and had a higher burden of existing cardiovascular risk factors, a greater prevalence of established cardiovascular disease, more revised cardiac risk index factors, a higher American Society of Anesthesiology physical status classification, and a greater likelihood of undergoing vascular or orthopedic surgery.

Analyses of Statin Exposure

The distribution of statin exposure and covariate medication use are presented in **Table 3** in the entire and propensity score–matched cohorts. In the entire cohort, any outpatient statin prescription within the 90-day preadmission period was identified among 47.2% of patients, including 37.8% with an active prescription at the time of hospital admission. A similar percentage of use (169 patients [36.1%]) was noted among the 468 patients who died within the exposure period and were excluded from the cohort based on a landmark analysis. A new prescription for a statin within 14 days of admission was issued in only 0.9% of patients. The most commonly prescribed statin was simvastatin (80.8%). Moderate-intensity dosing was most common (59.5% of statin users). Statin availability at the time of admission increased monotonically during the 5 fiscal years from 35.5% to 39.1% ($P < .001$). Prescription of high- and moderate-intensity doses relative to low-intensity doses increased from year 1 (high, 7.1%; moderate, 21.7%; and low, 6.7%) to year 5 (high, 10.6%; moderate, 22.7%; and low, 5.8%) ($P < .001$). Significant differences in outpatient statin use were noted among patients undergoing vascular surgery (53.9%), general surgery (33.4%), orthopedic

Table 1. Study Cohort Characteristics[a]

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Propensity Score–Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (N = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
Demographic								
Age, mean (SD), y	66.2 (10.0)	62.7 (12.1)	<.001	63.8 (11.6)	65.8 (10.0)	66.0 (11.1)	.001	65.9 (10.6)
Race								
White	68.3	64.4	<.001	65.6	67.4	67.4	.80	67.4
Black	12.5	16.3		15.1	13.2	13.0		13.1
Other	1.5	1.6		1.6	1.5	1.5		1.5
Unknown	17.7	17.7		17.7	17.8	18.0		18.0
Sex								
Male	96.6	95.1	<.001	95.6	96.3	96.3	.85	96.3
Female	3.4	4.9		4.4	3.7	3.7		3.7
Body mass index, mean (SD)[a]	29.3 (5.6)	28.2 (5.6)	<.001	28.6 (5.7)	29.2 (5.5)	29.1 (5.8)	.38	29.1 (5.7)
Preoperative Risk Variables								
Cardiovascular								
VASQIP								
Angina within 30 d	2.1	1.1	<.001	1.4	1.8	1.8	.74	1.8
MI within 6 mo	1.0	0.4	<.001	0.6	0.8	0.6	<.001	0.7
Previous PTCA or PCI	14.2	5.5	<.001	8.3	11.1	10.8	.10	10.9
Previous cardiac surgery	16.2	6.3	<.001	9.4	12.8	12.3	.02	12.6
Congestive heart failure within 30 d	1.6	0.9	<.001	1.1	1.4	1.4	.81	1.4
Hypertension with medication	83.7	63.5	<.001	69.9	81.2	82.1	<.001	81.7
Revascularization or amputation PVD	9.5	4.5	<.001	6.1	8.0	7.9	.55	8.0
Rest pain/gangrene within 30 d	6.4	3.3	<.001	4.3	5.5	5.5	.92	5.5
ICD-9-CM and PTF or OPC								
Conduction disorders	6.4	3.6	<.001	4.5	5.7	5.6	.65	5.6
Dysrhythmias	17.3	12.8	<.001	14.2	16.4	16.6	.27	16.5
Peripheral vascular disease	23.6	12.6	<.001	16.1	20.6	20.6	.96	20.6
Congestive heart failure within 1 y	15.8	9.0	<.001	11.1	13.9	13.9	.87	13.9
Ischemic heart disease within 1 y	40.0	18.5	<.001	25.3	33.8	32.7	<.001	33.3
Cerebrovascular or CNS								
CVA with neurologic deficit	5.7	3.3	<.001	4.1	5.2	4.9	.05	5.1
CVA with no deficit	4.9	2.7	<.001	3.4	4.2	4.3	.05	4.3
Hemiplegia	3.5	2.2	<.001	2.6	3.3	3.0	.03	3.1
History of TIAs	5.7	2.8	<.001	3.7	4.7	4.6	.33	4.6
Impaired sensorium	1.3	1.1	<.001	1.2	1.2	1.2	.84	1.2
Preoperative coma	0.03	0.1	.06	0.05	0.03	0.1	.06	0.04
CNS tumor	1.0	0.9	.33	0.9	1.0	0.9	.13	0.9
Quadraplegia	0.3	0.5	<.001	0.4	0.3	0.3	.29	0.3
Paraplegia	0.9	1.1	.02	1.0	0.9	1.0	.48	0.9
General Variables								
ASA physical status classification								
I	0.1	1.0	<.001	0.7	0.1	0.1	.55	0.1
II	13.1	22.6		19.6	15.0	14.9		14.9
III	72.7	65.2		67.6	71.7	71.9		71.8
IV	13.9	10.9		11.8	13.0	12.9		13.0
V	0.2	0.2		0.2	0.2	0.2		0.2

(continued)

Table 1. Study Cohort Characteristics[a] (continued)

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Propensity Score–Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (N = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
Alcohol intake >2 drinks/d	6.3	9.5	<.001	8.5	6.9	6.9	.83	6.9
DNR status	1.3	1.4	.06	1.4	1.3	1.4	.41	1.4
Functional health status								
Independent	89.4	90.0	<.001	89.8	89.5	89.4	.61	89.4
Partially or totally dependent	10.6	10.0		10.2	10.6	10.5		10.5
Current smoking	30.5	36.6	<.001	34.7	31.5	31.0	.17	31.2
Hepatobiliary								
Esophageal varices	0.2	0.4	<.001	0.3	0.1	0.2	.009	0.2
Ascites	0.3	1.1	<.001	0.9	0.4	0.5	<.001	0.4
Hepatitis	2.9	7.4	<.001	5.9	3.3	3.2	.22	3.2
Nutritional, Immune, or Other								
Diabetes								
None	65.4	80.9	<.001	76.0	69.5	69.5	.87	69.5
Oral hypoglycemic use	20.2	11.3		14.1	18.1	18.0		18.1
Insulin use	14.4	7.9		9.9	12.4	12.4		12.4
Disseminated cancer	1.4	2.7	<.001	2.2	1.5	1.5	.60	1.5
Wound infection	7.3	5.4	<.001	6.0	6.8	6.6	.32	6.7
Preoperative corticosteroid use within 30 d	2.3	2.5	.05	2.4	2.4	2.4	.87	2.4
Weight loss >10% within 6 mo	2.7	4.6	<.001	4.0	2.9	2.9	.91	2.9
Bleeding disorder	6.1	4.5	<.001	5.0	5.4	5.2	.24	5.3
Preoperative RBC transfusion >4 U within 72 h	0.1	0.3	<.001	0.2	0.2	0.2	.01	0.2
Preoperative chemotherapy for cancer within 30 d	0.5	1.0	<.001	0.8	0.5	0.6	.25	0.5
Preoperative radiotherapy for cancer within 90 d	0.5	1.2	<.001	1.0	0.5	0.5	.69	0.5
Preoperative sepsis within 48 h	1.7	2.5	<.001	2.2	1.8	1.8	.58	1.8
Pulmonary								
Preoperative ventilator dependency within 48 h	0.3	0.5	<.001	0.4	0.3	0.4	.006	0.4
Current pneumonia	0.5	0.7	<.001	0.7	0.5	0.6	.04	0.5
Severe COPD	17.5	15.0	<.001	15.8	17.0	17.1	.82	17.0
Asthma, *ICD-9-CM* diagnosis	3.3	2.7	<.001	2.9	3.2	3.3	.61	3.2
Renal								
Acute renal failure	0.5	0.6	<.001	0.6	0.5	0.6	.11	0.5
Preoperative dialysis within 2 wk	1.5	1.0	<.001	1.2	1.5	1.4	.20	1.4
Revised Cardiac Risk Index Variables								
Congestive heart failure	16.1	9.2	<.001	11.4	14.3	14.2	.88	14.2
Cerebrovascular disease	14.8	8.6	<.001	10.5	13.0	13.0	.95	13.0
Diabetes with insulin use	15.7	8.7	<.001	10.9	13.5	13.7	.59	13.6
Diabetes with insulin or oral medication use	36.7	20.5	<.001	25.6	32.4	32.5	.66	32.4
Ischemic heart disease	43.2	20.8	<.001	27.9	36.7	36.1	.06	36.4
High-risk surgery	27.9	46.0	<.001	40.3	30.8	31.2	.13	31.0
Renal insufficiency	5.0	3.7	<.001	4.1	4.7	4.6	.51	4.7
Laboratory Measurements								
Serum albumin level, mean (SD), g/dL	3.9 (0.6)	3.9 (0.6)	<.001	3.9 (0.6)	3.9 (0.6)	3.9 (0.6)	.13	3.9 (0.6)
Alkaline phosphatase level, mean (SD), mU/mL	87.2 (45.0)	91.2 (57.9)	<.001	89.9 (54.2)	87.5 (46.8)	88.0 (41)	.09	87.7 (44)

(continued)

Table 1. Study Cohort Characteristics[a] (continued)

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Propensity Score–Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (N = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
Total bilirubin level, mean (SD), mg/dL	0.7 (0.4)	0.8 (0.8)	<.001	0.8 (0.4)	0.8 (0.4)	0.8 (0.4)	.53	0.8 (0.4)
Serum urea nitrogen level, mean (SD), mg/dL	19.1 (10.4)	17.0 (9.7)	<.001	17.7 (10)	18.6 (10.2)	18.6 (10.1)	.89	18.6 (10.2)
Serum creatinine level, mean (SD), mg/dL	1.23 (0.8)	1.15 (0.8)	<.001	1.17 (0.8)	1.21 (0.8)	1.21 (0.9)	.37	1.21 (0.9)
Hematocrit reading, mean (SD), %	39.8 (5.4)	40.1 (5.5)	<.001	40.0 (5.5)	39.9 (5.4)	39.9 (5.4)	.86	39.9 (5.4)
Platelet count, mean (SD), ×1000/μL	241 (83)	250 (92)	<.001	247 (90)	243 (84)	244 (86)	.66	243 (85)
International normalized ratio, mean (SD)	1.1 (0.2)	1.1 (0.2)	0.002	1.1 (0.2)	1.1 (0.2)	1.0 (0.2)	.86	1.0 (0.2)
Partial thromboplastin time, mean (SD), s	30.8 (7.8)	30.5 (6.4)	<.001	30.6 (6.9)	30.7 (7.5)	30.6 (7.0)	.52	30.6 (7.2)
Serum glutamic oxaloacetate level, mean (SD), mU/mL	27.9 (18.8)	30.9 (29.3)	<.001	29.9 (26.5)	28.1 (19.6)	28.4 (19.7)	.03	28.3 (19.6)
Serum sodium level, mean (SD), mEq/L	139 (3.2)	138 (3.3)	<.001	139 (3.3)	139 (3)	139 (3)	.47	139 (3)
White blood cell count, mean (SD), ×1000/μL	8.2 (3.8)	8.3 (4.4)	<.001	8.3 (4.2)	8.2 (3.9)	8.2 (4.4)	.87	8.2 (4.2)

Abbreviations: ASA, American Society of Anesthesiologists; CNS, central nervous system; COPD, chronic obstructive pulmonary disease; CVA, cerebrovascular accident; DNR, do not resuscitate; *ICD-9-CM*, *International Classification of Diseases, Ninth Revision, Clinical Modification*; MI, myocardial infarction; OPC, outpatient care file; PCI, percutaneous coronary intervention; PTCA, percutaneous transluminal angioplasty; PTF, patient treatment file; PVD, peripheral vascular disease; RBC, red blood cell; TIA, transient ischemic attack; VASQIP, Veterans Affairs Surgical Quality Improvement Program.

SI conversion factors: To convert albumin to grams per liter, multiply by 10; alkaline phosphatase to microkatals per liter, multiply by 0.0167; bilirubin to micromoles per liter, multiply by 17.104; creatinine to micromoles per liter, multiply by 88.4; hematocrit to a proportion of 1, multiply by 0.01; platelet count to $\times 10^9$ per liter, multiply by 1; serum urea nitrogen to millimoles per liter, multiply by 0.357; sodium to millimoles per liter, multiply by 1.0; and white blood cell count to $\times 10^9$ per liter, multiply by 0.001.

[a] Calculated as weight in kilograms divided by the height in meters squared.

surgery (37.6%), and the aggregated remainder (35.9%) ($P < .001$). Patients in the statin-exposed group had significantly greater concurrent use of nonstatin agents to lower lipid levels and other types of cardiovascular medications. In the propensity score–matched cohort, differences in statin use persisted but with no significant differences in the use of nonstatin medications.

Of the entire cohort, regardless of their outpatient status, 31.5% were exposed to a statin on the day of or the day after surgery. Exposure rates differed significantly between surgical subgroups (vascular surgery, 50.1%; general surgery, 18.6%; orthopedic surgery, 38.8%; and aggregated remainder, 29.7%; $P < .001$). Of patients with an active outpatient prescription at the time of admission, 62.0% were exposed to a statin on the day of and/or the day after surgery and 38.0% were not exposed. The exposure rate varied significantly between surgical subgroups (vascular surgery, 66.6%; general surgery, 41.2%; orthopedic surgery, 78.1%; and aggregated remainder, 62.0%; $P < .001$). Of patients without an active statin prescription on admission, 13.1% were exposed to statin on the day of and/or the day after surgery (vascular surgery, 30.9%; general surgery, 7.3%; orthopedic surgery, 15.4%; and aggregated remainder, 11.6%; $P < .001$). Patients in the statin-exposed group had significantly greater concurrent use of nearly all of covariate medications considered in this analysis (Table 3).

Association of Statin Exposure With Outcomes

The primary and secondary outcomes for the entire cohort and the matched cohort are presented in **Table 4**. The propensity score–matched analyses for the primary and secondary outcomes are presented in **Table 5**. For the primary outcome, we matched 96 486 patients, corresponding to 71.9% of all patients in the cohort with an active statin prescription on admission. Mean standardized differences before and after matching are presented in eTable 5 in the Supplement. All mean standardized differences were less than 10%, which is consistent with an adequate balance of covariates. Statin exposure on the day of or the day after surgery was associated with a reduced 30-day all-cause mortality (RR, 0.82; 95% CI, 0.75-0.89; $P < .001$; number needed to treat, 244; 95% CI, 170-432). Significant risk reductions were noted for each of the secondary outcomes (RR for any, 0.82; 95% CI, 0.79-0.86; $P < .001$; number needed to treat, 67; 95% CI, 55-87), with the exception of central nervous system and thrombosis categories. The greatest risk reduction (RR, 0.73; 95% CI, 0.64-0.83) was noted for cardiac complications. Considering pneumonia as a component of the respiratory or infection categories did not alter statistical significance of either group. The number needed to treat for the aggregate of any complication was 67.

Of the 1659 patients identified as having a new prescription with 14 days of admission, we noted a high unadjusted, primary outcome event rate (198 [11.9%]) vs 3777 (2.1%) in the remaining 178 819 patients (RR, 6.28; 05% CI, 5.39-7.31; $P < .001$). New use was significantly higher in the vascular surgery group (1.5%) compared with the general surgery (1.0%) and orthopedic surgery (0.7%) groups and the aggre-

Table 2. Surgical Details of the Study Population

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Propensity Score–Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (n = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
Surgery specialty								
General	16.9	34.2	<.001	28.7	19.4	19.4	.58	19.4
Neurosurgery	9.5	8.0		8.5	9.5	9.4		9.4
Orthopedic	35.0	25.5		28.5	34.0	34.1		34.0
Otolaryngology	2.6	3.7		3.3	2.9	2.8		2.8
Thoracic	5.4	6.4		6.1	5.9	6.0		5.9
Urology	11.5	13.6		12.9	12.3	12.7		12.5
Vascular	19.1	8.8		12.0	16.0	15.7		15.9
Work portion Medicare RVU, mean (SD)	19.7 (7.0)	20.3 (8.2)	<.001	20.1 (7.8)	19.8 (7.1)	19.9 (7.5)	.12	19.8 (7.3)
Emergency procedure	6.3	10.0	<.001	8.8	6.7	6.6	.65	6.7
Laparoscopic procedure	7.8	12.1	<.001	10.7	8.9	8.7	.48	8.8
Endovascular procedure	3.0	1.2	<.001	1.7	2.4	2.4	.58	2.4
Duration of surgery, mean (SD), h	2.56(1.6)	2.76 (1.8)	<.001	2.7 (1.7)	2.6 (1.6)	2.6 (1.6)	.71	2.6 (1.6)
Principal anesthesia technique								
General	85.5	90.7	<.001	89.0	86.5	86.5	.75	86.5
Spinal or epidural alone	11.2	7.3		8.5	10.5	10.6		10.6
Other	3.3	2.1		2.5	3.0	2.9		3.0
Wound classification								
Clean or clean contaminated	92.0	89.9	<.001	90.6	91.9	91.9	.79	93.8
Contaminated or infected	8.0	10.1		9.4	8.1	8.1		8.1
RBCs transfused, median (IQR), U	0 (0-35)	0 (0-60)	<.001	0 (0-60)	0 (0-35)	0 (0-24)	.18	0 (0-35)
Total hospital LOS, median (IQR), d	5 (2-382)	6 (2-375)	<.001	5 (2-282)	5 (2-382)	5 (2-373)	<.001	5 (2-373)

Abbreviations: IQR, interquartile range; LOS, length of stay; RVU, relative value unit.

gated remainder (0.9%) ($P < .001$). The results of the sensitivity analyses are presented in the eMethods and eResults in the Supplement.

Discussion

The present analysis indicates that statin use on the day of and/or the day after noncardiac surgery as defined by an active inpatient prescription is associated with lower 30-day all-cause mortality and reduction in a variety of postoperative complications (most notably cardiac), compared with nonuse during this period. Subanalyses indicate that patients with ischemic heart disease or diabetes, those younger than 75 years, those undergoing high-risk surgery, and those receiving intensive statin therapy may have greater risk reduction with perioperative statin treatment and that perioperative withdrawal of statin treatment may be associated with adverse outcomes.

Although earlier literature suggested a perioperative benefit of statin therapy in noncardiac surgery, that conclusion was based on limited data from randomized clinical trials and predominantly small, single-center observational analyses.[25,26] Meta-analyses provide conflicting evidence, depending on inclusion or exclusion of observational analyses along with randomized clinical trials or the inclusion of controversial analyses from the Erasmus University group.[11] Sanders et al[7] performed a meta-analysis (excluding trials from the Erasmus University group[27]) and concluded that the evidence was insufficient to support an effect of perioperative statin use on all-cause or cardiovascular mortality or safety outcomes. In contrast, Antoniou et al[8] considered 4 randomized clinical trials and 20 observational cohort analyses (including several from the Erasmus University group) and reported significant associations with all-cause perioperative mortality (OR, 0.54; 95% CI, 0.38-0.78), myocardial infarction (OR, 0.62; 95% CI, 0.45-0.87), stroke (OR, 0.51; 95% CI, 0.39-0.67), and their composite (OR, 0.45; 95% CI, 0.29-0.70), with no reduction in cardiovascular mortality or renal injury.

Berwanger et al[14] correlated preoperative statin use (2845 users matched with 4492 controls) with cardiovascular and all-cause mortality from the Vascular Events in Noncardiac Surgery Patients Cohort Evaluation (VISION) multinational prospective cohort.[28] This analysis is notable for inclusion of a wide variety of noncardiac operations, routine troponin surveillance, and evaluation of outcomes at 30 days after surgery. Statin use was

Table 3. Medication Data

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (N = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
Statin Use								
Active outpatient prescription on admission								
Any statin	74.2	21.0	<.001	37.8	73.3	28.2	<.001	50.8
Atorvastatin calcium	1.5	0.5	<.001	0.8	1.4	0.9	<.001	1.1
Fluvastatin sodium	0.9	0.3	<.001	0.5	0.9	0.4	<.001	0.6
Lovastatin	4.3	1.1	<.001	2.1	4.4	1.3	<.001	2.9
Pravastatin sodium	2.5	0.8	<.001	1.3	2.5	1.0	<.001	1.8
Rosuvastatin calcium	4.3	1.5	<.001	2.4	3.8	2.6	<.001	3.2
Simvastatin	61.0	16.5	<.001	30.5	60.6	21.6	<.001	41.1
Combination agent	2.0	1.0	<.001	1.3	1.8	1.7	.50	1.7
Nonstatin agent	3.1	1.8	<.001	2.2	2.8	2.8	.98	2.8
New statin prescription within 14 d of admission	1.8	0.5	<.001	0.9	1.8	0.7	<.001	1.2
Intensity of dose								
None	0	100	<.001	68.5	0	100	<.001	50
Low	15.2	0		4.8	16.0	0		8.0
Moderate	59.5	0		18.8	60.3	0		30.2
High	25.3	0		8.0	23.7	0		11.8
Inpatient prescription for any statin from POD2 to discharge	85.1	7.6	<.001	32.0	84.8	10.4	<.001	47.6
Outpatient prescription from discharge to POD 30	80.4	22.8	<.001	41.0	79.8	30.6	<.001	5.2
Preoperative Covariate Medications								
Any β-blocker	53.0	31.8	<.001	38.5	47.9	47.6	.34	47.7
Atenolol	17.0	11.8	<.001	13.5	16.2	16.5	.11	16.4
Bisoprolol fumarate	0.02	0.03	.70	0.03	0.01	0.04	.02	0.03
Carvedilol	3.3	1.4	<.001	2.0	2.6	2.6	.52	2.6
Metoprolol tartrate	27.7	15.4	<.001	19.3	24.6	24.5	.77	24.5
Metoprolol succinate	4.9	2.2	<.001	3.0	4.0	3.8	.14	3.9
Other β-blocker	2.0	2.0	.63	2.0	2.0	1.9	.13	1.9
ACE-I/ARB	53.9	32.8	<.001	39.5	49.4	49.7	.45	49.5
Diuretic	43.9	31.5	<.001	35.4	41.5	42.0	.11	41.7
CEB-dihydropyridine	22.3	15.8	<.001	17.9	21.1	21.2	.63	21.1
CEB-nondihydropyridine	5.7	4.4	<.001	4.8	5.7	5.7	.93	5.7
Clonidine	2.5	1.9	<.001	2.1	2.4	2.4	.56	2.4
Other antihypertensive	2.3	1.3	<.001	1.6	2.0	2.0	.80	2.0
Anticoagulant or antiplatelet	41.0	28.6	<.001	32.5	38.4	38.2	.58	38.3
Digoxin or antiarrhythmics	4.4	2.6	<.001	3.1	4.0	4.0	.92	4.0
Oral hypoglycemic	27.0	14.0	<.001	18.1	23.8	22.7	<.001	23.3
Rosiglitazone maleate	2.5	1.1	<.001	1.6	2.1	2.1	>.99	2.1
Insulin	13.0	6.6	<.001	8.7	11.0	10.9	.64	11.0
Bronchodilator	19.2	16.0	<.001	17.0	18.5	18.6	.65	18.6

Abbreviations: ACE-I, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; CEB, calcium entry blocker; POD, postoperative day.

significantly associated with reduced all-cause (RR, 0.58; 95% CI, 0.40-0.83) and cardiovascular (RR, 0.42; 95% CI, 0.23-0.76) mortality and a composite of all-cause mortality, myocardial injury, or stroke (RR, 0.83; 95% CI, 0.73-0.95) but not with myocardial infarction or stroke alone.

Among secondary outcomes, we found no significant associations of statin exposure with central nervous system or nonatherosclerotic thrombotic events. However, we found that perioperative statin exposure was associated with significant risk reduction in renal-, respiratory-, and infection-related complications. Our finding of a decreased risk for adverse renal outcomes is consistent with some, but not all, prior observational analyses in patients undergoing surgery.[13,29-32] Comparison among studies is complicated by varying data

Table 4. 30-Day Postoperative Outcomes

Variable	Statin Exposure, % of Patients							
	Entire Cohort				Matched Cohort			
	Exposed (n = 56 939)	Nonexposed (n = 123 539)	*P* Value	All (N = 180 478)	Exposed (n = 48 243)	Nonexposed (n = 48 243)	*P* Value	All (n = 96 486)
30-d All-cause mortality	1.8	2.4	<.001	2.2	1.8	2.3	<.001	2.0
Cardiac complications								
Cardiac arrest	0.7	0.8	.03	0.8	0.7	0.9	.001	0.8
Q-wave MI infarction	0.5	0.4	<.001	0.4	0.5	0.6	.02	0.5
Composite	0.8	1.0	.03	0.9	0.8	1.1	<.001	1.0
CNS complications								
Cerebrovascular accident	0.5	0.3	<.001	0.4	0.4	0.5	.39	0.5
Coma	0.1	0.2	.10	0.1	0.1	0.1	>.99	0.1
Composite	0.4	0.4	.60	0.4	0.4	0.4	.38	0.4
Thrombotic complications								
DVT or thrombophlebitis	0.7	0.7	.02	0.7	0.7	0.8	.06	0.7
Pulmonary embolism	0.5	0.6	.07	0.5	0.5	0.5	.48	0.5
Graft failure	0.3	0.2	<.001	0.2	0.3	0.3	.47	0.3
Composite	1.3	1.2	.19	1.3	1.2	1.3	.07	1.3
Infection complications								
Sepsis	2.0	2.9	<.001	2.6	2.1	2.5	<.001	2.3
Organ space	0.5	1.0	<.001	0.9	0.6	0.6	.33	0.6
Deep wound	0.8	1.1	<.001	1.0	0.8	0.9	.01	0.9
Composite	2.8	4.2	<.001	3.8	2.9	3.4	<.001	3.2
Respiratory complications								
Failure to wean	1.8	3.2	<.001	2.8	1.9	2.6	<.001	2.3
Pneumonia	2.2	3.2	<.001	2.9	2.3	2.9	<.001	2.6
Reintubation	2.2	2.9	<.001	2.7	2.2	3.0	<.001	2.6
Composite	3.4	5.1	<.001	4.6	3.5	4.5	<.001	4.0
Renal complications								
Acute renal failure	0.5	0.6	.002	0.6	0.5	0.6	.08	0.5
Progressive renal insufficiency	0.8	0.8	.74	0.8	0.8	0.9	.052	0.8
Composite	1.0	1.2	.009	1.1	1.0	1.2	.005	1.1
Any nonfatal complication	6.9	9.2	<.001	8.5	7.0	8.5	<.001	7.7

Abbreviations: CNS, central nervous system; DVT, deep vein thrombosis; LOS, length of stay; MI, myocardial infarction.

Table 5. Analysis of Primary and Secondary Outcomes

Outcome	Pairs	Statin Exposure, No. (%) of Patients With Outcome		RR (95% CI)	*P* Value	NNT (95% CI)
		Exposed	Unexposed			
Mortality	48 243	888 (1.8)	1086 (2.3)	0.82 (0.75-0.89)	<.001	244 (170-432)
Cardiac	47 950	385 (0.8)	528 (1.1)	0.73 (0.64-0.83)	<.001	335 (237-571)
CNS group	48 068	177 (0.4)	194 (0.4)	0.91 (0.75-1.12)	.40	
Thrombosis	48 080	581 (1.2)	645 (1.3)	0.9 (0.81-1.01)	.07	
Infection	48 012	1394 (2.9)	1655 (3.4)	0.84 (0.79-0.90)	<.001	184 (131-310)
Infection B[a]	47 893	2106 (4.4)	2532 (5.3)	0.83 (0.79-0.88)	<.001	112 (86-162)
Respiratory	47 261	1671 (3.5)	2106 (4.5)	0.79 (0.74-0.85)	<.001	109 (85-149)
Respiratory B[a]	47 371	1070 (2.3)	1435 (3.0)	0.75 (0.69-0.81)	<.001	130 (103-177)
Renal	48 059	490 (1.0)	577 (1.2)	0.85 (0.75-0.96)	.008	552 (319-2070)
Any complication	46 461	3252 (7.0)	3943 (8.5)	0.82 (0.79-0.86)	<.001	67 (55-87)

Abbreviations: CNS, central nervous system; infection B, with pneumonia; NNT, number needed to treat; respiratory B, without pneumonia; RR, relative risk.

[a] See the Study Outcomes subsection of the Methods section for details.

sources, outcome definitions, types of surgery, and preoperative vs perioperative statin use. Effects of statins on respiratory or infectious complications in medical patients are controversial, with limited data in the perioperative setting. Le Manach et al[30] reported no difference in postoperative pneumonia in a vascular cohort, and Yadav et al[33] reported no difference in rates of early postoperative adult respiratory distress syndrome in patients undergoing aortic vascular or thoracic surgery. However, Iannuzzi et al[13] reported a reduction in an aggregated respiratory (OR, 0.63; 95% CI, 0.50-0.79) and infection-related (OR, 0.65; 95% CI, 0.45-0.94) complication in statin users undergoing primarily noncardiac, nonvascular surgery.

In sensitivity analyses (presented in the eMethods and eResults in the Supplement), we found evidence that perioperative outcomes were favorably affected by moderate- to high-intensity dosing (relative to no or low-intensity dosing). This finding is concordant with observations in 5 randomized secondary prevention trials that more intensive statin therapy is associated with fewer cardiovascular events than less intensive therapy.[34] The present findings also align with a recent single-center trial of 500 patients with stable coronary artery disease receiving long-term statin therapy who underwent emergency noncardiac surgery.[35] Patients were randomized to continue their outpatient statin treatment or to undergo statin reloading with atorvastatin calcium, 80 mg 2 hours before surgery. The reloaded group had lower rates of 30-day major adverse cardiac events and atrial fibrillation and a shorter duration of hospitalization. Similar findings of improved outcomes with preoperative statin therapy intensification are suggested in the meta-analyses of patients undergoing percutaneous coronary intervention or cardiac surgery.[36,37] However, our observation of a possible association of high-intensity dosing with renal injury suggests the need for further study, particularly given similar associations in 2 recent trials studying patients undergoing cardiac surgery.[38,39]

Additional sensitivity analyses were performed to evaluate the potential for several types of selection bias that may confound statin use. These include the effect of prevalent (long-term) vs incident (new) statin use and of variables that may reflect socioeconomic status.[40-42] These analyses suggest a marginally favorable effect of longer-term use (6 months to 1 year before admission) on mortality and several complications. With regard to new users, our analysis suggests that most (78.1%) were actually prior users with variable adherence to the medication regimen. The strikingly higher event rate noted in this group suggests they belong to patient subgroups recently identified at higher risk for adverse long-term cardiovascular outcomes with discontinuation of statin and/or angiotensin-converting enzyme inhibitor therapy.[43,44] The complexities of quantifying variable patterns of statin therapy adherence for primary or secondary prevention, their clinical and socioeconomic predictors, and methods for prevention remain a focus of active research in the general medicine setting.[45-47] Analysis of available socioeconomic variables revealed unexpected favorable associations of nonwhite race and smoking with our primary outcome, whereas adverse associations with several of our secondary complications were more consistent with healthy user bias. Consideration of additional variables related to educational level, income, number of primary care visits, etc, might help to clarify whether selection bias in statin treatment might in turn have influenced the results of the present analysis.

A notable finding was the frequency with which outpatient statin prescriptions were not continued in the critical perioperative period. Similar findings have been reported by others and have been associated with adverse outcome.[48] Because statin exposure on the day of and the day after surgery was significantly associated with more favorable surgical outcomes, this observation suggests the need for medication reconciliation practices to minimize interruption of established statin therapy in patients undergoing surgery. With increased emphasis on such practices,[4] interruption of perioperative statin therapy may have become less frequent in years subsequent to the analysis period of this report.

Limitations

The limitations of our study include those common to pharmacoepidemiologic analyses where the indications for prescription are not specified and drug administration is not captured. The VASQIP criteria for myocardial infarction require the development of electrocardiographic Q waves and are considerably more specific and less sensitive than criteria that use cardiac biomarkers or ST-T changes. The VASQIP database does not capture postoperative atrial fibrillation, a complication that some studies suggest may be modified by statin treatment and may be linked to other forms of postoperative morbidity.[6,49] We were unable to evaluate the most commonly reported adverse effects of statins such as elevated levels of creatine kinase, myalgia, or liver transaminase due to lack of capture by VASQIP.[4] Our data do not allow us to relate measurements of serum lipid or inflammatory biomarker levels to statin use or outcomes; however, prior meta-analyses of nonsurgical cohorts indicate that the relative risk reduction afforded by statin treatment is similar across a wide range of baseline low-density lipoprotein cholesterol levels.[50]

Conclusions

Early perioperative exposure to a statin was associated with a significant reduction in all-cause perioperative mortality and several cardiovascular and noncardiovascular complications. However, the potential for selection biases in these results must be considered.

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Author Affiliations: Department of Anesthesia and Perioperative Care, University of California, San Francisco (London); Department of Anesthesia and Perioperative Care, Department of Veterans Affairs Medical Center, San Francisco, California (London); Cardiology Section, Department of Medicine, Department of Veterans Affairs Medical Center, Denver, Colorado (Schwartz); Center for Medication Safety, Pharmacy Benefits Management Services, Department of Veterans Affairs Medical

Center, Hines, Illinois (Hur); Department of Biostatistics, University of Colorado, Denver (Henderson); Adult and Child Center for Outcomes Research and Delivery Science (ACCORDS) and Department of Biostatistics and Informatics, Colorado School of Public Health, Aurora (Henderson).

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Study concept and design: London, Schwartz, Henderson.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: London.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: London, Hur, Henderson.
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