ORIGINAL ARTICLE

Statin Use and the Risk of Surgical Site Infections in Elderly Patients Undergoing Elective Surgery

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Objective: To examine whether preoperative statin use is associated with a reduced risk of surgical site infections.

Design, Setting, and Patients: Population-based retrospective cohort study of all elderly patients undergoing elective surgery in Ontario from April 1, 1992, through March 31, 2006. Preoperative statin use was identified using provincewide pharmacy records. Procedure and patient characteristics were derived from hospital and physician claims databases within Canada's single-payer universal health care system.

Main Outcome Measure: The 30-day risk of surgical site infection was derived from the initial admission, outpatient consultations, and hospital readmissions.

Results: The cohort included 469 349 distinct elderly patients undergoing elective surgery, of whom 68 387 (14.6%) were statin users. The primary analysis included 53 565 statin users matched to 53 565 statin nonusers undergoing the same procedure in the same hospital by the same surgeon. Unadjusted analysis revealed a slight increase in the risk of surgical site infection among statin users compared with nonusers (8.9% vs 8.7%; $P < .001$), which disappeared after adjustment for demographics, health care utilization variables, comorbidities, and concurrent medication therapy (odds ratio, 1.00; 95% confidence interval, 0.95-1.04; $P = .85$). A similar lack of association was seen when matching was extended to include propensity scores (odds ratio, 0.99; 95% confidence interval, 0.94-1.05; $P = .82$). The lack of association persisted across pharmacologic, patient, and procedure subgroups.

Conclusions: Statin use is not associated with an altered risk of surgical site infection. Prevention efforts should be directed toward other evidence-based strategies.

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WOUND INFECTIONS are an unwanted complication of surgical care. On average, each wound infection is associated with 1 week of increased hospital length of stay,[1-3] $4000 in increased health care costs,[4-7] substantial patient suffering, and a doubling of mortality.[2,8,9] In the United States alone, more than 8000 deaths per year are attributable to surgical site infections and, not surprisingly, surgical site infections have become a central focus of the patient safety movement.[10,11] The cause of these infections involves a complex interaction of pathogen, procedure, and patient characteristics.[12,13] Strategies to prevent these infections include preoperative, intraoperative, and postoperative interventions.[14,15]

There is substantial uncertainty regarding the contribution of long-term medication therapy to the risk of postoperative wound infections.[14] One common class of long-term medications, hydroxymethylglutaryl-CoA reductase inhibitors (statins), may prevent wound infection based on their effects on inflammation and immunity[16-18] and on possible direct antibacterial activity through inhibition of isoprene biosynthesis.[19,20] Statins have been associated with an unanticipated benefit in several infectious syndromes in animal models[21-23] and in human observational studies.[24-32]

If the benefits of statins extend to surgical site infections, these medications might provide a simple, inexpensive means for improving surgical outcomes. Three previous studies have not detected a protective association, but each had insufficient power to exclude even a 50% reduction in the risk of wound infection.[33-35] Therefore, the objective of this population-based cohort study was to explore whether patients who receive statins are less likely

to develop surgical site infections than their counterparts undergoing the same elective procedure in the same institution by the same surgeon.

METHODS

STUDY DESIGN

We identified a provincewide cohort of all elderly patients admitted for elective surgery in Ontario from April 1, 1992, through March 31, 2006, via the Canadian Institute for Health Information database. We included elderly patients because they were the most frequent users of statins and because universal prescription data were only available for this group in Ontario. We limited the study to elective surgical procedures because, by definition, they allow time for medical optimization. Same-day surgical procedures were excluded because of low predicted event rates, and repeated procedures were excluded to avoid duplicate patients. We also excluded cases missing a valid encrypted health card number or procedure duration information.

STATIN THERAPY

Preoperative statin use was obtained by linkage to the Ontario Drug Benefits database, which provided prescription information for all outpatient drugs dispensed to Ontario's 1.6 million elderly residents. The database is comprehensive (the Ontario Drug Benefits program provides universal drug coverage for all senior citizens in the province) and accurate (concordance with pharmacy chart review exceeds 99%).[36] During the corresponding years of this study, the following 7 statins were licensed in Ontario: atorvastatin (1997-2006), cerivastatin (1999-2001), fluvastatin (1995-2006), lovastatin (1992-2006), pravastatin (1992-2006), rosuvastatin (2003-2006), and simvastatin (1992-2006).

A *statin user* was defined as an individual who received at least 2 statin prescriptions in the 12 months before surgery, of which at least 1 prescription was dispensed in the 90 days immediately preceding surgery. All other patients were classified as *statin nonusers*. This definition was identical to that used in previous research[27] and was designed to increase the likelihood that patients were receiving statins at the time of operation (because no information was available regarding inpatient medications or outpatient adherence to treatment).

OUTCOME ASCERTAINMENT

The primary outcome in this study was the risk of a surgical site infection, which included any infection of the surgical incision or surgically manipulated structures that developed within 30 days of the operative procedure.[37] Because more than half of surgical site infections are diagnosed after discharge from the hospital,[38,39] we gathered information from a combination of inpatient data, outpatient visits, and hospital readmissions. A *surgical site infection* was defined as any hospital discharge diagnosis of surgical site infection (during the index stay or readmission) or any physician claim for surgical wound infection (inpatient or outpatient). A spectrum of secondary outcome definitions was used to capture earlier and potentially more severe surgical site infections, including infections during the index admission according to the hospital or the physician database, infections during the index admission according to the hospital database only, and infections during the index admission also associated with reoperation or death.

Diagnoses were coded using the *International Classification of Diseases, Ninth Revision* (*ICD-9*) before April 1, 2002, and using the *International Statistical Classification of Diseases, 10th Revision* (*ICD-10*) beginning April 1, 2002. Under both of these systems, some hospital diagnostic codes represent surgical site infection after any surgical procedure (eg, 998.5 in *ICD-9* and T 81.4 in *ICD-10*), whereas other codes reflect surgical site infection after specific subcategories of procedures (eg, intracranial abscess after neurosurgery). Similar diagnostic algorithms have achieved sensitivities exceeding that of active clinical surveillance[40] and specificities of 97% to 99%.[41,42] Enhanced sensitivity of outcome detection in this study was provided by linkage with the Ontario Health Insurance Plan database, which contains inpatient and outpatient physician service billing claims paid for by Ontario's universal health care system.

RISK FACTORS

From the hospital database, we abstracted procedure risk factors, including year of surgery, institution, attending surgeon, and exact procedure code. Procedures were coded according to the Canadian Classification of Procedures before April 1, 2002, and according to the Canadian Classification of Health Interventions beginning April 1, 2002. Surgical data are among the most accurate and precise components of the Canadian Institute for Health Information database,[43] with more than 4975 distinct procedure codes (1904 in the Canadian Classification of Procedures and 3701 in the Canadian Classification of Health Interventions). For the purpose of this study we have also developed a novel method for measuring surgical duration from administrative data (using anesthesiology physician claims, which are recorded in 15-minute increments) that demonstrated high concordance with the medical record review (Pearson $r = 0.94$; $P < .001$).[44]

Patient risk factors were abstracted from hospital and physician database records from the 3 years before surgery. Demographic risk factors included patient age, sex, neighborhood income quintile, and rural residence (2001 Canadian census agglomeration areas with a population of <10 000). Markers of health care utilization included residence in a long-term care facility, the number of physician encounters (distinct days associated with Ontario Health Insurance Plan claims in the preceding year), recent hospitalizations, and the use of home health care services. The impact of overall patient comorbidity was assessed using the Deyo-Charlson Comorbidity Index and data on 15 individual conditions; concurrent medications (12 cardiac classes and 18 noncardiac classes) were abstracted from the Ontario Drug Benefits database.[45]

STATISTICAL ANALYSIS

In the primary analysis, the statin users were matched one-to-one to nonusers undergoing the same surgical procedure by the same surgeon in the same hospital. This matching was intended to equalize important procedural determinants of wound infection and unmeasured institutional characteristics such as infection control infrastructure and discharge coding practices.[46] Multivariable logistic regression was performed to adjust for other procedure and patient covariates and generalized estimating equations were used to account for the paired data.[47]

As a secondary analysis, statin users were matched to statin nonusers with an equivalent propensity score for statin use (±1 SD), in addition to matching on the procedure, surgeon, and institution. Logistic regression was performed with statin use as the dependent variable; in this manner, we developed a predictive equation for the likelihood of statin therapy that was contingent on the other covariates (demographic data, health care utilization data, comorbidities, and concurrent medical therapies). We were therefore able to assign each patient (statin users and nonusers) a propensity score based on that person's

predicted likelihood of receiving statins. The goal of propensity matching was to further minimize bias by indication, with the trade-off being reduced sample size.[48]

In a further analysis, the impact of statins on surgical wound infection was evaluated in the overall elective surgery cohort without any matching procedures. The advantage of this analysis was increased sample size, but the disadvantage was a lack of adjustment for surgeon and institution and more limited adjustment for procedure detail (procedures were lumped into the 12 anatomical categories of abdominal, retroperitoneal, breast and skin, cardiac, head and neck, musculoskeletal, neurosurgical, ophthalmologic, thoracic, urologic/gynecologic, vascular, or unclassified).

All analyses were performed using commercially available statistical software (SAS, version 9.1; SAS Institute, Cary, North Carolina). Patient confidentiality was maintained via encrypted health card numbers using protocols of the Institute for Clinical Evaluative Sciences. The study was approved by the ethics review boards of Sunnybrook Health Sciences Centre and the University of Toronto, Toronto, Ontario, Canada. Access to data was limited to the 3 study authors.

RESULTS

COHORT CHARACTERISTICS

During the 14-year study period, there were 12 861 108 surgical admissions in Ontario, of which 7 685 515 (59.8%) involved same-day procedures; 2 026 323 (15.8%), urgent or emergent procedures; and 3 149 270 (24.5%), elective procedures requiring admission. Of elective surgical procedures requiring admission, 850 459 (27.0%) involved elderly patients. One patient was excluded owing to an invalid encrypted health care number, 242 256 were excluded because they represented repeated procedures during the study period, and 138 853 were excluded owing to missing data on procedure duration. Therefore, the study cohort included 469 349 individuals.

These operations involved a large number of institutions (n=193), attending surgeons (n=2726), and procedure types (n=4975). Procedure duration ranged from 15 minutes to 11.1 hours (median, 1.75 hours). The most common surgical procedures were abdominal (107 581 procedures [22.9%]), urologic/gynecologic (103 592 [22.1%]), and musculoskeletal (101 392 [21.6%]), with other body systems each accounting for less than 10% of the elective surgery cohort. The patients spanned a broad range of ages (66-107 years; median age, 73 years) and included approximately similar numbers of men and women. The most common comorbidities were lung disease (21.5%), diabetes mellitus (22.3%), coronary artery disease (12.5%), and renal insufficiency (9.7%).

In total, 38 131 patients (8.1%) developed a surgical site infection within 30 days of surgery, of which approximately half (18 855 [4.0%]) received a diagnosis during the index hospitalization and the others (19 276 [4.1%]) after discharge.

STATIN USERS AND NONUSERS

Statins were the seventh most common drugs prescribed to elderly patients undergoing elective surgery (after nonsteroidal anti-inflammatory drugs, gastric acid suppressants, calcium channel blockers, β-blockers, nitrates, and benzodiazepines). Overall, 68 387 patients undergoing elective surgery (14.6%) were statin users, and 400 962 (85.4%) were nonusers. Statin prevalence increased substantially during the study period and, by fiscal year 2005, represented the most common prescription medication in the cohort (34.5% of patients).

Statin users were more often younger, male, and living in an urban locale (**Table 1**). Statin users were more likely to have diabetes mellitus, atherosclerosis (coronary or cerebral), and complications of vascular disease (congestive heart failure, renal failure, or hemodialysis requirement). However, several other important comorbidities were less prevalent among statin users, including alcoholism, liver disease, malignant neoplasm, myopathies, dementia, and Parkinson disease. Statin users underwent a different distribution of surgical procedures than their counterparts who did not use statins, including a disproportionate number of cardiac and vascular procedures (Table 1).

For the primary study analysis, statin users were matched one-to-one with statin nonusers undergoing the same surgical procedure at the same institution by the same attending surgeon. Exact matches were obtained for 53 565 of statin users (78.3%), yielding a total matched cohort of 107 130 patients. By design, matching eliminated differences in the distribution of surgical procedures that the patients underwent (Table 1). In addition, matching narrowed the demographic and comorbidity differences between statin users and nonusers. In the propensity-based secondary analysis, 32 475 statin users (47.5% of all statin users) were successfully matched to nonusers, yielding a total propensity matched cohort of 64 950 patients. Differences in apparent baseline patient and procedure characteristics were further diminished within the propensity cohort.

STATIN USE AND SURGICAL SITE INFECTION

The univariate analysis of the matched cohort showed a slight increase in risk of surgical site infection among statin users compared with nonusers (8.9% vs 8.7%; $P<.001$). After multivariable adjustment for patient demographics, health utilization variables, comorbidities, and concurrent medication therapy, no significant difference in postoperative wound infection rates was apparent (odds ratio [OR], 1.00; 95% confidence interval [CI], 0.95-1.04; $P=.85$). Extending the matching to include propensity scores showed no association of statin use on wound infection rates in univariate analysis (OR, 0.99; 95% CI, 0.94-1.05; $P=.82$). In contrast, the unmatched cohort showed a marginally decreased risk of surgical site infection among statin users (OR, 0.96; 95% CI, 0.93-0.99; $P=.004$).

A consistent lack of statin benefit or harm was apparent across a spectrum of surgical site infection definitions in the primary and propensity matched cohorts (**Table 2**). In the overall cohort, there was apparent increased benefit among earlier and more severe surgical site infections. Whereas statin use had no impact on wound infections in the matched cohort, these medications were associated with decreased mortality on univariate (OR, 0.85; 95% CI, 0.77-0.94; $P<.001$) and multivariable analysis in this cohort (OR, 0.80; 95% CI, 0.80-0.99; $P=.04$).

Table 1. Baseline Patient and Procedure Characteristics in Overall, Matched, and Propensity Cohorts

Characteristic	Overall Cohort		Matched Cohort		Propensity Cohort	
	Statin Users (n=68 387)	Statin Nonusers (n=400 962)	Statin Users (n=53 565)	Statin Nonusers (n=53 565)	Statin Users (n=32 475)	Statin Nonusers (n=32 475)
Age, mean (SD), y	72.6 (5.1)	73.9 (6.1)	72.6 (5.0)	73.6 (5.8)	72.7 (5.0)	72.8 (5.3)
Sex, %						
Male	55.5	50.5	55.9	55.0	56.2	58.1
Top income quintile, %	19.2	19.4	19.4	20.1	19.9	20.0
Urban residence, %	87.7	86.4	87.7	87.0	87.2	87.9
Deyo-Charlson Comorbidity Index ≥2, %	30.1	28.7	29.3	28.4	26.2	26.1
Comorbidities, %						
Alcoholism	1.5	1.8	1.5	2.0	1.6	1.7
CAD	17.0	7.3	16.4	10.3	12.2	13.3
CHF	8.0	5.4	13.5	10.6	6.0	6.7
Dementia	3.4	4.8	3.2	4.3	3.0	2.9
Diabetes mellitus	28.7	15.8	27.5	18.6	21.6	22.0
Dialysis	0.7	0.2	0.5	0.3	0.3	0.3
HIV	0.0	0.0	0.0	0.0	0.0	0.0
Liver disease	0.7	1.3	0.7	1.0	0.7	0.6
Lung disease	22.3	20.0	21.7	21.0	20.5	21.4
Malignant neoplasm	25.4	28.4	25.0	25.8	22.7	21.9
Muscle disorder	0.3	0.5	0.3	0.4	0.3	0.3
Neutropenia	0.2	0.3	0.2	0.3	0.2	0.3
Parkinson disease	1.0	1.4	1.0	1.2	1.0	1.0
Renal disease	11.6	7.7	10.4	9.2	8.6	8.9
Stroke	3.7	2.8	3.6	2.9	3.2	3.4
Transplant	0.4	0.2	0.4	0.2	0.2	0.2
Trauma	8.5	3.6	6.6	6.7	5.2	4.9
Time with OHIP physician claims in past year, median (SD), d	24 (16.2)	20 (17)	23 (15)	21 (16)	22 (15)	21 (16)
No. of hospitalizations in preceding 3 y, mean (SD)	0.7 (1.3)	0.7 (1.6)	0.7 (1.2)	0.7 (1.2)	0.6 (1.2)	0.7 (1.2)
Fiscal year of index procedure, %						
1992-1999	30.4	67.9	34.3	37.8	41.0	41.4
2000-2005	69.6	32.1	65.7	62.2	59.0	58.6
Procedure category, %						
Abdominal	18.0	23.8	17.6	17.6	15.2	15.2
Breast and skin	4.0	5.3	3.9	3.9	3.5	3.5
Cardiac	17.9	5.6	16.7	16.7	18.0	18.0
Head and neck	3.1	3.5	2.3	2.3	1.5	1.5
Musculoskeletal	18.8	22.0	20.0	20.0	21.8	21.8
Neurosurgical	1.7	1.8	1.6	1.6	1.4	1.4
Ophthalmologic	1.9	5.4	2.1	2.1	2.3	2.3
Retroperitoneal	1.6	1.4	1.2	1.2	0.7	0.7
Thoracic	2.6	2.6	2.5	2.5	2.1	2.1
Urologic/gynecologic	19.0	22.7	21.2	21.2	22.6	22.6
Vascular	11.2	5.8	10.9	10.9	10.8	10.8
Unclassified	0.2	0.2	0.1	0.1	0.1	0.1
Procedure duration, median (SD), h	1.5 (1.1)	1.1 (0.9)	1.5 (1.0)	1.5 (1.0)	1.3 (1.0)	1.3 (1.0)

Abbreviations: CAD, coronary artery disease; CHF, congestive heart failure; HIV, human immunodeficiency virus; OHIP, Ontario Health Insurance Plan.

When assessed individually, no specific statin showed a significantly decreased risk of surgical site infection, including atorvastatin (OR, 1.02; 95% CI, 0.95-1.09), lovastatin (OR, 0.89; 95% CI, 0.79-1.00), pravastatin (0.97; 0.87-1.09), simvastatin (1.03; 0.94-1.12), or other less common statins (1.11; 0.96-1.07). The lack of association was consistent across prespecified statin dose categories, procedure categories, and patient subgroups (**Figure**). Although one analysis suggested a possible harm among male patients and another suggested a possible benefit among early study years, these isolated anomalies were not statistically significant after Bonferroni adjustment for multiple comparisons.

OTHER PREDICTORS OF SURGICAL SITE INFECTION

Although statin use was not associated with surgical site infection risk, multiple other procedure and patient predictors were identified (**Table 3**). The risk of surgical site infection increased linearly with increasing duration of surgery (OR, 1.20 per hour; 95% CI, 1.20-1.20), and this relationship persisted across the full spectrum of operative times. With musculoskeletal surgical procedures used as the reference standard, abdominal operations were associated with the greatest risk of wound infection, whereas ophthalmologic operations were as-

Table 2. Perioperative Statin Use and Rates of Surgical Site Infection Across a Spectrum of Administrative Definitions

Surgical Site Infection	Impact of Statins, OR (95% CI)		
	Matched Cohort	Propensity Match	Overall Cohort
Primary outcome			
Infection within 30 d of surgery, CIHI or OHIP	1.00 (0.95-1.04)	0.99 (0.94-1.05)	0.96 (0.93-0.99)
Secondary outcomes			
Infection during index admission, CIHI or OHIP	0.98 (0.92-1.04)	0.94 (0.87-1.03)	0.92 (0.88-0.96)
Infection during index admission, CIHI only	0.98 (0.89-1.08)	Missing[a]	0.88 (0.83-0.93)
Infection during index admission, CIHI only, plus reoperation or death	0.92 (0.67-1.30)	Missing[a]	0.79 (0.65-0.96)

Abbreviations: CI, confidence interval; CIHI, Canadian Institute for Health Information Discharge abstract database; OHIP, Ontario Health Insurance Plan database; OR, odds ratio.

[a]Statistical models failed to converge owing to collinearity.

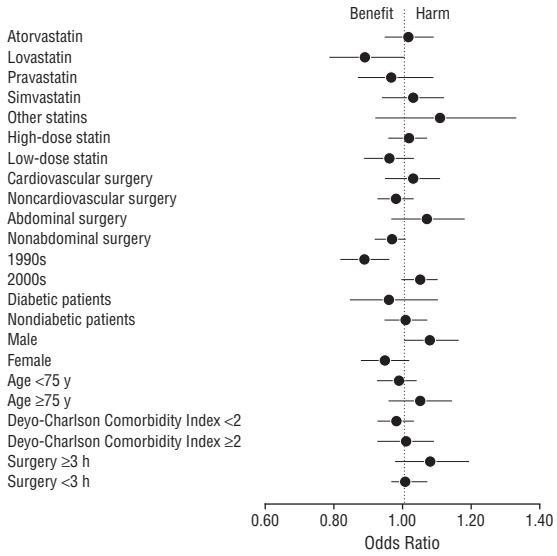

Figure. Lack of association of perioperative statin use and risk for surgical site infection across pharmacologic, patient, and procedure subgroups.

sociated with the lowest risk. Upper income quintile and advanced age were associated with a decreased risk of surgical site infection, whereas rural residence, use of home care health services, and previous physician contacts were associated with an increased risk. We also observed an increased risk associated with higher overall comorbidity, as well as additional risks associated with several individual comorbidities (Table 3).

SEQUELAE OF SURGICAL SITE INFECTIONS

Patients with infections, compared with their uninfected counterparts, had a longer median length of stay in the hospital (7 vs 4 days; $P<.001$) and higher rates of reoperation (3.5% vs 1.3%; $P<.001$), readmission (2.0% vs 0.7%; $P<.001$), and 30-day mortality (3.1% vs 1.5%; $P<.001$) (**Table 4**). Even after multivariable adjustment for potential confounders (demographic, health care utilization, comorbidity, and procedure variables), patients with surgical site infection remained more likely to develop these adverse sequelae (Table 4). Among the 38 131 patients with surgical site infection, statin users had a decreased risk of adverse sequelae, including a significantly decreased risk of death (2.6% vs 3.2%; adjusted OR, 0.83; $P=.04$) and a trend toward decreased reoperation (2.2% vs 3.7%; adjusted OR, 0.93; $P=.33$) and readmission (1.6% vs 2.1%; adjusted OR, 0.89; $P=.23$).

Table 3. Multivariable Predictors of Surgical Site Infection

Procedure or Patient Characteristic	Adjusted OR (95% CI)
Duration of surgery, per hour	1.20 (1.20-1.20)
Procedure category	
Abdominal	1.39 (1.35-1.43)
Breast and skin	1.15 (1.09-1.21)
Vascular	1.03 (0.99-1.07)
Musculoskeletal	1 [Reference]
Thoracic	0.98 (0.93-1.05)
Retroperitoneal	0.83 (0.76-0.91)
Cardiac	0.78 (0.74-0.81)
Neurosurgical	0.72 (0.66-0.78)
Urologic/gynecologic	0.68 (0.65-0.71)
Head and neck	0.66 (0.61-0.70)
Ophthalmologic	0.13 (0.11-0.15)
Age, per year >66 y	0.99 (0.99-0.99)
Highest income quintile	0.91 (0.88-0.94)
Rural residence	1.28 (1.24-1.31)
Physician contacts, per day of OHIP claims in previous year	1.004 (1.004-1.005)
Use of home health care services	1.20 (1.10-1.20)
Deyo-Charlson Comorbidity Index, per point	1.01 (1.10-1.20)
Alcoholism	1.11 (1.04-1.19)
Congestive heart failure	1.08 (1.04-1.13)
Lung disease	1.08 (1.05-1.11)
Diabetes mellitus	1.10 (1.06-1.14)
Liver disease	1.32 (1.22-1.42)
Malignant neoplasm	1.09 (1.05-1.12)
Previous trauma	2.06 (2.00-2.14)

Abbreviations: CI, confidence interval; OHIP, Ontario Health Insurance Plan; OR, odds ratio.

COMMENT

In this population-based retrospective cohort of nearly half a million elderly patients undergoing elective surgery, perioperative statin use was not associated with an increase or a decrease in the risk of surgical site infection. The lack of an association between the use of statin medications and the risk of surgical site infection was consistent across multiple analytic designs, outcome definitions, and subgroup analyses. Together, these results provide robust evidence that statins do not prevent surgical site infection and advance the theoretical understanding of statin therapy for preventing sepsis.

This study conflicts with some cellular, animal model, and human observational evidence of a statin benefit in models of infection. Statins have been shown to sometimes improve mortality after community-acquired pneumonia,[26]

Table 4. Adverse Outcomes Among Patients With Surgical Site Infection

	Patients With Surgical Site Infection, %	Patients Without Surgical Site Infection, %	Crude OR (95% CI)	Adjusted OR[a] (95% CI)
Reoperation	3.5	1.3	2.83 (2.66-3.00)	2.86 (2.69-3.04)
Readmission	2.0	0.7	2.98 (2.75-3.22)	3.34 (3.08-3.63)
Death at 30 d	3.1	1.5	2.11 (1.98-2.24)	1.28 (1.20-1.36)

Abbreviations: CI, confidence interval; OR, odds ratio.
[a] Adjusted for demographics, use of health care resources, comorbidities, and procedures.

bacteremia,[24,29] and sepsis[25] and have been found to be associated with lower rates of sepsis in high-risk patient groups.[25,27,30,31] However, these studies do not claim that statins prevent focal bacterial infection, but rather prevent an uncontrolled host inflammatory cascade. The theory of immune modulation is in keeping with the best-established mechanisms of statin pleiotropic benefit: namely, alteration of intracellular signaling, cytokines, chemokines, leukocyte function, and nitric oxide synthesis.[18]

Our study agrees with the literature that statins do not exert direct antibacterial activity. Recent reports[19,20] that statins have in vitro activity against *Staphylococcus aureus* and other bacteria are somewhat misleading because the minimum inhibitory concentrations of these statins far exceed the pharmacologic levels that can be achieved with usual doses in humans. We believe our study confirms that statins are not antibiotics, in that they fail to prevent the onset of surgical wound infections. Three previous small studies have corroborated a null effect of statins on surgical site infection,[33-35] but our study is the first, to our knowledge, that has been adequately powered to properly address this question.

The dominant predictor of surgical wound infection in our study was the characteristic of the surgical procedure. Although the surgical procedure is partially determined by the patient's underlying surgical indication, these results may suggest that minimally invasive procedures should be performed when possible.[49] The duration of surgery is an important additional predictor of surgical site infection, which is partly determined by the complexity of the patient's anatomy and underlying disease.[50] Surgical duration is also partially modifiable and thus may be a potential target for risk reduction strategies.[51,52]

Patient risk factors for surgical site infection included lower income, rural residence, number of previous physician visits, use of home health care services, overall comorbidity level, alcoholism, diabetes mellitus, lung disease, liver disease, malignant neoplasm, and previous trauma. These factors may facilitate prediction of surgical site infection and may identify patients worthy of more targeted prevention strategies or intensive postoperative monitoring. In some cases, such as cessation of alcohol use, they may even offer potential avenues for reduction of surgical site infection risk. These factors might also be helpful in comparing rates at different hospitals by using risk-adjusted administrative report cards.

As expected, surgical site infections were common and associated with significant sequelae. The 8% infection rate in this study agrees with rates in previous studies (4.3%-30.2%) that have evaluated surgical site infection rates with diligent follow-up.[38,53-55] Although our rates exceed those of Centers for Disease Control and Prevention surveillance[56] (overall rate, 2.4%) and UK surveillance[2] (overall rate, 4.2%), these networks are limited primarily to in-hospital observation. Our secondary analysis of surgical site infections diagnosed during the index hospitalization yielded an estimate in line with those of the Centers for Disease Control and Prevention[56] and UK networks.[2] Wound infections in our study were associated with a 3-day prolongation of median hospital stay, a 3-fold increased risk of reoperation or readmission, and a 30% increase in adjusted mortality. Widespread approaches to risk reduction are needed.

As with all noninterventional research, the lack of randomization allows for potential selection bias. In particular, this study may be subject to bias by indication, in that statin users differ systematically from statin nonusers in important respects.[57] Statin users were more likely to have significant vascular disease and complications, more likely to be undergoing cardiovascular procedures, and more likely to be receiving concomitant medications. We attempted to reduce selection bias by matching for procedure risk and adjusting for an extensive list of cofactors. It is still possible, however, that some unmeasured comorbidity, if loaded against statin users, may have obscured a small potential benefit of statin therapy.

This retrospective analysis of administrative data may also have been influenced by information bias. First, there may have been misclassification of the primary predictor variable (statin use). Although the Ontario Drug Benefits database has an accuracy exceeding 99%,[36] some patients may not have been adhering to their medication regimens. Moreover, statin use was extrapolated from the outpatient setting to the inpatient setting, and we have no data regarding temporary discontinuation of statin therapy in the immediate perioperative period. For example, there may have been some intentional discontinuation of statin therapy by physicians worried about hepatitis risk or high rates of unanticipated discontinuation owing to postoperative ileus.[58]

The surgical site infection outcome was also derived from administrative data and thus may be prone to misclassification, despite similar algorithms demonstrating sensitivities exceeding that of active surveillance in some settings.[59] Any misclassification of surgical site infection should be nondifferential (with equal rates among statin users and nonusers) because the predictor and outcome variables are derived from independent computer databases. Moreover, variations in institutional coding practices would not have biased our results because statin users were matched

to nonusers undergoing surgery at the same hospital. Finally, administrative data sets lack information on some clinical variables that may alter wound infection risk, such as smoking, obesity, and antibiotic prophylaxis.

In summary, our data suggest that statins do not offer a clinically significant prospect of surgical site infection prevention. The decision of whether or not to continue statin therapy, therefore, should be determined by other statin benefits (eg, vascular protection and sepsis prevention) and risks (eg, hepatitis and rhabdomyolysis). Meanwhile, efforts to prevent surgical site infection should be directed toward other preoperative, intraoperative, and postoperative strategies. Although statin pleiotropy is not the answer, other innovative methods are needed to reduce the burden of these iatrogenic infections.

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