MAJOR ARTICLE

Preoperative Statin Use and Infection after Cardiac Surgery: A Cohort Study

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Background. It has been suggested that the routine use of statins preoperatively would reduce the risk of postoperative infection. We conducted this study to explore whether preoperative statin use was associated with infection after cardiac surgery (recipients of which have a higher-than-average risk of postoperative infection).

Methods. We performed secondary analysis of data collected in a prospective cohort study of adults who underwent nontransplant cardiac surgery in a university hospital during the period January 1999 through December 2005. Outcomes were ascertained in a blinded and independent fashion.

Results. Of the 7733 patients, 2657 (34%) were taking statins preoperatively; the proportion increased from 16% during 1999–2000 to 53% during 2003–2005 ($P < .001$, by test for trend). There was no association between preoperative statin use and postoperative infection: 214 statin users (8.1%) versus 425 statin nonusers (8.4%) developed an infection within 30 days after surgery. Factors associated with increased risk of infection after cardiac surgery included diabetes mellitus, heart failure, chronic obstructive pulmonary disease, increasing age, elevated baseline creatinine level, and longer duration of cardiopulmonary bypass but not statin use (adjusted odds ratio, 1.08; 95% confidence interval, 0.89–1.31).

Conclusions. Preoperative statin use was not associated with a reduction in the rate of postoperative infection among patients who underwent cardiac surgery. This lack of apparent benefit for high-risk patients argues against the routine use of statins as a preoperative strategy for lower-risk patients and supports calls for randomized trials to define whether preoperative statin use influences postoperative rates of infection.

A recent analysis of administrative data suggested that the incidence of sepsis among patients hospitalized with ischemic coronary disease was reduced substantially with the use of statins [1]. In vitro studies have suggested that statins have beneficial immunomodulatory effects, which extend from their anti-oxidative and anti-inflammatory properties, including the suppression of G protein–mediated inflammation (which may also impede bacterial replication), the reduction of cytokine expression and acute phase reactants after coronary artery bypass, improvements in endothelial function and thrombomodulation, and reduction in the expression of the matrix metalloproteinases that impair host inflammatory response [2, 3]. However, other studies [4, 5] have raised questions about whether this apparent benefit against infection is real or merely associated with unmeasured confounders, and a recent systematic review [6] found that, although 6 of the 7 observational studies to have examined this topic reported that statin use reduced the risk of sepsis, these studies had a number of methodologic limitations that prevented definitive conclusions.

Although a number of randomized trials are currently testing whether statins improve patient outcome if they are administered to patients with sepsis or chronic viral infection [6], a related issue is whether statin treatment impacts the rate of postoperative infection [3, 7, 8]. Although >1 million individuals undergo surgery each year, there is a paucity of evidence from randomized, controlled trials addressing this is-

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sue. A search of http://clinicaltrials.gov (at the time, the most recent update was 31 October 2008) revealed no ongoing randomized, controlled trials of statins with postoperative infection as a primary outcome and just 1 randomized, controlled trial (target sample size, 70 patients) that will explore inflammatory response in surgical patients treated with statins as a primary outcome (NCT00656292). Thus, because no evidence from a randomized trial will be available for this topic in the near future, we designed this cohort study to examine the impact of preoperative use of statins on rates of postoperative infection among patients undergoing nontransplant cardiac surgery.

METHODS

Study Cohort

We prospectively enrolled all adult patients who underwent cardiac surgery at the University Hospital in Edmonton, Alberta, Canada, during the period from January 1999 through December 2005. We excluded 449 patients who had undergone heart or heart/lung transplantations. This project was conducted as a substudy of the Alberta Provincial Project for Outcome Assessment in Coronary Heart Disease (APPROACH) study [9], which was approved by the University of Alberta Health Research Ethics Board. Although the data collection for the APPROACH study is prospective, our investigation of the association between statin use and postoperative infection involves a retrospective examination of the APPROACH data.

Data Collection and Variables

Information on sociodemographic factors (sex, age, and residence in a metropolitan vs. nonmetropolitan area), coronary artery disease–specific variables, comorbid conditions, coronary anatomy (as determined using Heartview Software [Duke Clinical Research Center]), and preoperative medication use were collected through the APPROACH study, in which cardiologists assign all diagnoses, which are double-checked and entered into the database by specially trained cardiac nurses (table 1). A full description of these data sets (including the variables collected and definitions used) has been published elsewhere [9].

Exposure

The exposure variable of interest was the use of statins at the time of surgery (i.e., a statin was listed in the admission medication list). Although we did not have information on statin dosing or on the specific agent used, previous studies locally and nationally have documented that >90% all statin prescriptions were for simvastatin, pravastatin, or atorvastatin during the period of our study [5, 10]. Of note, antibiotics are routinely administered to all persons who undergo cardiac surgery at our institution; intravenous cephalexin (or vancomycin for penicillin-allergic patients) is specified in our institutional preoperative care map.

Outcomes

Postoperative infections. Specially trained infection-control nurses perform routine postoperative wound surveillance for all cardiac surgery patients at our hospital. Surveillance includes a daily review of surgical wounds and the hospital chart until discharge from the hospital and assessment of any patients who are readmitted to the hospital ⩽30 days after surgery, with use of standard Centers for Disease Control and Prevention definitions for nosocomial and wound infections, as part of the Canadian Nosocomial Infection Surveillance Program [11]. The infection-control nurses were independent of our study and blinded to the hypothesis of this study. They collected information on wound infections (subdivided into superficial sternal, superficial saphenous vein graft site, or deep/organ space infection), urinary tract infections, and documented bacteremia.

Mortality. At our institution, 30-day mortality rates for all cardiac surgery patients are collected by specially trained cardiac nurses who review the medical records of all patients who have undergone an operation. Prespecified, standardized definitions are used for classifying types of death.

Statistical Analyses

We compared baseline characteristics and use of medications for patients who were exposed versus those who were not exposed to statins preoperatively using the χ^2 test for dichotomous variables and Student's t test for continuous variables. We examined the annual use of preoperative statins (1999–2005) and our perioperative outcomes of interest (death or infection) over time (1999–2005). In our crude analyses, we examined the association between statin use and the postoperative outcomes of interest (table 2). In addition, we used multiple logistic regression analysis to determine which preoperative and operative variables were associated with postoperative infection and examined whether statin use was associated with postoperative infection after adjustment for baseline imbalances between the groups. We considered for inclusion in our multivariate models any factors in table 1 that were imbalanced between arms ($P < .2$), had a prevalence of ⩾1%, and were associated (on bivariate analysis) with postoperative infection in our data set or were believed to be important to include on the basis of prior literature and/or clinical experience (including year of surgery). We selected the variables for our models using the backward stepwise selection technique, with an entry P value of ⩽.25 and an exit P value of .05 (table 2). We examined all first-order interaction terms in the model, and none achieved a level of significance of $P \leqslant .10$. All analyses were conducted with SPSS, version 13.0 (SPSS).

Table 1. Characteristics of 7733 patients undergoing nontransplant cardiac surgery, stratified by preoperative statin use.

Characteristic	Statin users (n = 2657)	Statin nonusers (n = 5076)	P
Age, mean years ± SD	65.0 ± 10.3	64.8 ± 11.3	.41
Male sex	2128 (80)	3789 (75)	<.001
Residence in a metropolitan area[a]	1659 (67)	3095 (65)	.09
Procedure			<.001
Isolated CABG	2058 (77)	3030 (60)	
CABG plus another procedure	420 (16)	762 (15)	
Other	179 (7)	1284 (25)	
Priority			<.001
Elective	673 (25)	1491 (29)	
Urgent	1601 (60)	2885 (57)	
Emergent	105 (4)	160 (3)	
Unknown	278 (10)	540 (11)	
Myocardium at risk, mean Duke Jeopardy score ± SD	49.7 ± 36.2	46.5 ± 38.7	.001
Comorbidity			
Prior myocardial infarction	1250 (47)	1860 (37)	<.001
Prior CABG	116 (4)	202 (4)	.42
Hypertension	1862 (70)	2970 (59)	<.001
Diabetes mellitus	771 (29)	1187 (23)	<.001
Hyperlipidemia	2303 (87)	2726 (54)	<.001
Peripheral vascular disease	281 (11)	532 (10)	.91
Cerebrovascular disease	237 (9)	419 (8)	.32
Chronic kidney disease	116 (4)	165 (3)	.01
Hemodialysis	51 (2)	85 (2)	.47
Heart failure	387 (15)	923 (18)	<.001
Smoking history			
Current smoker	747 (28)	1249 (25)	.001
Any history of smoking	1220 (46)	2278 (45)	.38
Chronic pulmonary disease	318 (12)	628 (12)	.61
Malignancy for <5 years	71 (3)	127 (3)	.65
Liver or gastrointestinal disease	127 (5)	186 (4)	.02
Creatinine level, mean μmol/L ± SD	108 ± 79	110 ± 84	.43
Other medications received before operation[b]			
Aspirin	1307 (62)	2679 (64)	.04
Ticlopidine and/or clopidogrel	174 (8)	522 (13)	<.001
ACE inhibitor	641 (30)	1231 (30)	.59
β-Blocker	1854 (88)	2820 (68)	<.001
Steroids	14 (0.7)	38 (0.9)	.30
Bypass data			
Time in operating room, mean min ± SD	219.2 ± 56.9	224.0 ± 63.2	.07
Duration of cardiopulmonary bypass, mean min ± SD	108.1 ± 40.9	114.9 ± 46.4	<.001
Duration of controlled cardiac ischemia, cross clamp time, mean min ± SD	72.0 ± 36.1	78.4 ± 39.3	<.001
Median no. of diseased coronary vessels (IQR)	3 (2–3)	3 (2–3)	.07

NOTE. Data are no. (%) of patients, unless otherwise indicated. Only 2 patients were taking angiotensin receptor blockers pre- or postoperatively and thus angiotensin receptor blockers are not included in this table. ACE, angiotensin-converting enzyme; CABG, coronary artery bypass; IQR, interquartile range.

[a] Data were unknown for 489 patients.

[b] Data on other preoperative medications were available for only 6277 patients (2118 statin users and 4159 statin nonusers); thus, listed percentages reflect these denominators.

RESULTS

In total, 7733 patients underwent nontransplant cardiac surgery during the period from January 1999 through December 2005; 5088 (66%) underwent isolated coronary artery bypass surgery. The baseline characteristics of these patients are summarized in table 1. A total of 2657 patients (34%) had been taking statins preoperatively. Statin users were more likely to be male, to have atherosclerotic risk factors and/or a prior history of myocardial infarction, and to be about to undergo isolated coronary artery bypass surgery. Although statin users and nonusers had a similar number of diseased vessels noted by angiography, statin users had higher Duke Jeopardy scores, indicating that a larger volume of their myocardium was at risk (table 1). Statin users were more likely than nonusers to be treated with β-blockers and less likely to be treated with antiplatelet agents preoperatively (table 1). Of note, statin use increased over time (figure 1), from 16% in 1999–2000 to 53% in 2003–2005 ($P < .001$, by test for trend).

Although the 30-day infection rate decreased over time (from 11% in 1999–2000 to 8% in 2003–2005; $P = .005$, by test for trend) (figure 1), there was no association between preoperative statin use and postoperative infection: 214 statin users (8.1%) versus 425 statin nonusers (8.4%) had an infection within 30 days after surgery, as adjudicated by the infection control nurses at our institution (adjusted OR, 1.08; 95% CI, 0.89–1.31) (table 2). The rate of postoperative infection did not statistically differ

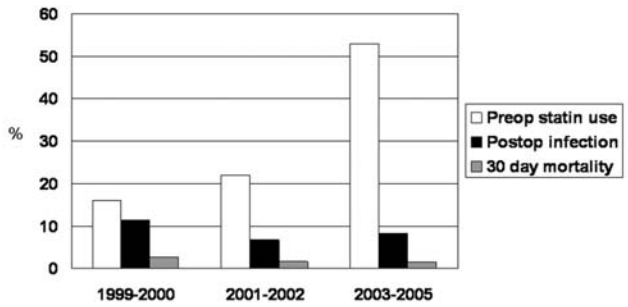

Figure 1. Changes over time in preoperative (Preop) statin use and outcomes. Postop, postoperative.

for statin users versus nonusers during any year of our study. The rate of specific infections (note that 1 patient could contribute >1 infection type to the following totals) was as follows: saphenous vein graft site infection, 87 statin users (3.3%) and 146 nonusers (2.9%; $P = .39$); superficial sternal infection, 72 statin users (2.7%) and 135 nonusers (2.7%; $P = .98$); bacteremia, 34 statin users (1.3%) and 99 nonusers (1.9%; $P = .11$); urinary tract infection, 34 statin users (1.3%) and 71 nonusers (1.4%; $P = .62$); and deep sternal/organ space infection 16 statin users (0.6%) and 54 nonusers (1.1%; $P = .04$). Multivariate analysis revealed that postoperative infections were associated with a history of diabetes, chronic obstructive pulmonary disease, heart failure, older age, longer cardiopulmonary bypass

Table 2. Postoperative outcomes within 30 days, stratified by preoperative statin use.

Variable	No. (%) of statin users ($n = 2657$)	No. (%) of statin nonusers ($n = 5076$)	Impact of statin use on outcome		Covariates associated with outcome and adjusted for in multivariate analyses
			Crude OR (95% CI)	Adjusted OR[a] (95% CI)	
Any infection	214 (8.1)	425 (8.4)	0.94 (0.79–1.12)	1.08 (0.89–1.31)	Diabetes mellitus (OR, 1.65; 95% CI, 1.39–1.98), COPD (OR, 1.53; 95% CI, 1.23–1.91), history of heart failure (OR, 1.46; 95% CI, 1.19–1.78), age (OR per year, 1.03; 95% CI, 1.02–1.04), cardiopulmonary bypass time (OR per min, 1.006; 95% CI, 1.004–1.008), baseline creatinine level (OR per μmol/L, 1.001; 95% CI, 1.000–1.003)
All-cause death	42 (1.6)	95 (1.9)	0.84 (0.58–1.22)	1.24 (0.83–1.87)	Age (OR per year, 1.06; 95% CI, 1.04–1.08), cardiopulmonary bypass time (OR per min, 1.02; 95% CI, 1.01–1.02), prior myocardial infarction (OR, 1.46; 95% CI, 1.02–2.10)
Death due to infection	12 (0.5)	29 (0.6)	0.79 (0.40–1.55)	1.11 (0.54–2.28)	Age (OR per year, 1.07; 95% CI, 1.03–1.10), diabetes mellitus (OR, 1.86; 95% CI, 0.99–3.53), cardiopulmonary bypass time (OR per min, 1.013; 95% CI, 1.009–1.017)

NOTE. COPD, chronic obstructive pulmonary disease.

[a] In addition to the clinical covariates listed in the final column, adjustment was made for the year of surgery in all 3 multivariate models.

time, elevated baseline creatinine level, and year of surgery (table 2). Analyses of each type of infection individually demonstrated no differences between statin users and nonusers for all types of infection, including septicemia: 1.1% of statin users had positive blood culture results, compared with 1.5% of statin nonusers (adjusted OR, 0.87; 95% CI, 0.55–1.36).

Similarly, although the all-cause mortality rate for the first 30 days after surgery decreased over time (from 2.7% in 1999–2000 to 1.4% in 2003–2005; $P = .003$, by test for trend) (figure 1), it was not associated with preoperative statin use (1.6% and 1.9% of statin users and nonusers, respectively, died; adjusted OR, 1.24; 95% CI, 0.83–1.87) (table 2). The rate of death due to infection also did not differ between statin users (0.5%) and nonusers (0.6%; adjusted OR, 1.11; 95% CI, 0.54–2.28). Analyses restricted to the 5310 patients who underwent nonemergent coronary artery bypass surgery confirmed no association between preoperative statin use and postoperative infections (166 [7.7%] of 2162 statin users and 279 [8.9%] of 3148 statin nonusers experienced postoperative infection; adjusted OR, 0.92; 95% CI, 0.66–1.30).

DISCUSSION

In summary, we found no difference in postsurgical infection rates between patients who were taking a statin preoperatively and patients who were not. Similar to previous studies [12–14], we did find that postoperative infections were more common among older patients and/or those with diabetes, chronic obstructive pulmonary disease, heart failure, prolonged cardiopulmonary bypass time, and chronic kidney disease, suggesting our cohort is comparable to previously reported populations. The risk factors for infection included in our multivariate models are also similar to those reported in the 2 earlier studies [3, 7] that suggested that infection rates are reduced among cardiac surgery patients who are pretreated with statins. So why, then, did we find no association between statin pretreatment and postoperative infection? One explanation may lie in the more rigorous ascertainment of infections in our study, because trained infection-control nurses who were blinded to the hypothesis of this study reviewed each and every patient postoperatively specifically for evidence of infection. Thus, we did not rely on the diagnosis of attending physicians or a review of medical records by hospital nosologists to define infection. Furthermore, we collected information on a number of clinical and perioperative factors for all patients and were therefore able to conduct more-rigorous multivariate analyses than earlier studies. Certainly, other investigators have demonstrated that, although statin use appears to be associated with a reduced risk of infection or septic sequelae in crude or minimally adjusted analyses, adjustment for more clinical detail in multivariate models negated this apparent benefit [5, 6, 15].

We also found no association between preoperative statin use and the 30-day mortality rate in our cohort of 7733 patients with 100% follow-up. This is in contrast to the findings of some earlier observational studies [7, 16–18] but in agreement with others [19–22]. Our 30-day mortality rates are very similar to those reported in a recent cohort from another Canadian university hospital [23] and by the Multicenter Study of Perioperative Ischemia investigators [20], who also found no association between statin use and in-hospital all-cause mortality (all-cause mortality rate, 1.9% and 2.4% for statin users and nonusers, respectively; crude OR, 0.79; 95% CI, 0.45–1.36). Our results are also consistent with the findings of the only 2 randomized trials of statin use for cardiac surgery patients; these studies demonstrated 30-day mortality rates <2%, with no significant difference between persons who were randomized to receive statin and those randomized to receive placebo [21, 24]. Indeed, a recent meta-analysis of randomized trials of persons with acute coronary syndromes failed to demonstrate a short-term mortality benefit of statin use and suggested that the benefits of statins were not apparent until 4 months after the acute coronary event [25].

Our study addressed several limitations in the current literature base [6, 8] on preoperative statin use and infectious outcomes in that we prospectively captured detailed perioperative data on all patients undergoing nontransplant cardiac surgery at our institution with 100% follow-up. Also, outcomes were collected by infection-control nurses who were blinded to the hypothesis of our study, and we included linkage to electronic records to minimize recall or ascertainment bias. Indeed, our "negative" findings redress the publication bias currently apparent in the literature on this topic and should serve to provide some balance to the debate about the role of statins as a preoperative intervention to reduce the risk of infection.

However, there are some limitations to our study. For one, although we conducted rigorous multivariate analyses, this is still an observational study, and as such, we can only explore associations and cannot attribute causation. That said, our findings should give pause to persons who have advocated the use of preoperative statins as a strategy to reduce the rate of postoperative infection and highlights the need for further study before exposing this very large number of patients to any therapy that has both potential harms and benefits. Second, we do not have data on dosing or duration of statin therapy before surgery or on preoperative low-density lipoprotein cholesterol levels and thus cannot examine whether these factors influenced outcomes. Third, we do not have data on postoperative use of statins after hospital discharge. However, we did focus on short-term outcomes (30 days) in this study. Fourth, we have data on preoperative statin use but no data on medications administered after admission to the hospital; thus, we cannot examine whether statins were stopped in some patients in the immediate

postoperative period and whether this obscured any mortality benefit of statin therapy. At least 1 study [20] has suggested that discontinuation of statins may increase the short-term risk of cardiovascular events in the immediate postoperative period. Fifth, we do not have data on the duration of the initial hospitalization for all patients, and although we have outcome data at 30 days for all patients, we were unable to adjust for the initial length of hospital stay in our analyses. Finally, we do not have any data on other potential confounders, such as perioperative glycemic control or EuroSCORE, in our cohort patients.

In summary, our analysis of 7733 patients who underwent nontransplant cardiac surgery showed no reduction in postoperative infection associated with preoperative statin use. We chose to study cardiac surgery patients because they are at high risk for postoperative infection, and thus, any potential benefits of statin use should be most apparent in this group; this makes our negative finding all the more striking. Although statins are clearly indicated for all patients with cardiovascular disease who do not have contraindications, we believe that it is premature to call for wider use of statins as a routine preoperative management strategy for patients without atherosclerotic disease on the basis of assumptions that statins will reduce the likelihood of postoperative infection. Randomized trials are needed to define the benefits and risks of preoperative statin use in patients without underlying atherosclerotic disease.

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