Preoperative statin therapy is associated with reduced cardiac mortality after coronary artery bypass graft surgery

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Objective: Statin therapy in ambulatory populations is associated with a significant reduction in adverse cardiovascular events, including death and myocardial infarction. Much less is known about the beneficial effects of statins on acute perioperative cardiovascular events. The purpose of this study was to determine whether preoperative statin therapy is associated with a reduced risk of early cardiac death or nonfatal, in-hospital postoperative myocardial infarction after primary, elective coronary artery bypass graft surgery requiring cardiopulmonary bypass.

Methods: The Multicenter Study of Perioperative Ischemia (*McSPI*) Epidemiology II Study was a prospective, longitudinal study of 5436 patients undergoing coronary artery bypass graft surgery between November 1996 and June 2000 at 70 centers in 17 countries. The present study consisted of a pre-specified subset of these subjects divided into patients receiving (n = 1352) and not receiving (n = 1314) preoperative statin therapy. To control for potential bias related to use of statin therapy, the study estimated propensity scores by logistic regression to determine the predicted probability of inclusion in the "statin" group. Multivariate, stepwise logistic regression was then performed, controlling for patient demographics, medical history, operative characteristics, and propensity score to determine whether preoperative statin therapy was independently associated with a reduction in the risk of early (DOS-POD3) cardiac death and/or nonfatal, in-hospital postoperative myocardial infarction.

Results: Preoperative statin therapy was independently associated with a significant reduction (adjusted odds ratio [OR] 0.25; 95% confidence intervals [CI] 0.07-0.87) in the risk of early cardiac death after primary, elective coronary bypass surgery (0.3% vs 1.4%; $P < .03$), but was not associated with a reduced risk of postoperative nonfatal, in-hospital myocardial infarction (7.9% vs 6.2%; P = not significant). Discontinuation of statin therapy after surgery was independently associated with a significant increase in late (POD4-discharge) all-cause mortality (adjusted OR 2.64; 95% CI 1.32-5.26) compared with continuation of statin therapy (2.64% vs 0.60%; $P < .01$). This was true even when controlling for the postoperative discontinuation of aspirin, β-blocker, or angiotensin-converting enzyme inhibitor therapy. Discontinuation of statin therapy after surgery was also independently associated with a significant increase in late cardiac mortality (adjusted OR 2.95; 95% CI 1.31-6.66) compared with continuation of statin therapy (1.91% vs 0.45%; $P < 0.01$).

Conclusions: Preoperative statin use is associated with reduced cardiac mortality after primary, elective coronary artery bypass grafting. Postoperative statin discontinuation is associated with increased in-hospital mortality. Although further randomized trials are needed to confirm these findings, these data suggest the importance of perioperative statin administration.

Administration of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) inhibitors or "statins" to ambulatory patients reduces low-density lipoprotein (LDL), total cholesterol levels, and the risk of adverse cardiovascular events, including death, myocardial infarction (MI), and stroke.[1-11] Moreover, the beneficial effects of statin therapy are not limited to patients with hypercholesterolemia. Even in patients with normal total and LDL cholesterol levels, long-term statin administration reduces the incidence of adverse cardiovascular outcomes and decreases the need for coronary angioplasty or coronary artery bypass graft (CABG) surgery.[4-6]

Although the mechanisms by which statins reduce cardiovascular events have yet to be fully elucidated, statins have several important, non–lipid-mediated effects. For example, the metabolite of HMG-CoA reductase, mevalonic acid, is a precursor of the cholesterol and the isoprenoid intermediates, farnesyl and geranylgeranyl pyrophosphate, which are essential for the posttranslational modification of intracellular G-proteins that regulate endothelial, platelet, and leukocyte function.[12] Statins have also been shown to modulate vascular remodeling through inhibition of cellular matrix metalloproteases and transcription factors, such as nuclear factor-κB.[12] Thus, statins exert pleiotropic effects, independent of cholesterol reduction, that result in direct antiatherosclerotic, antithrombotic, and anti-inflammatory properties.[12-14]

In contrast to the widely described long-term benefits of statins in ambulatory patients, much less is known about the effects of statins on acute postoperative cardiovascular events.[14-18] Recently, statins were shown to be independently associated with a reduced risk of postoperative mortality in patients undergoing major, noncardiac vascular surgery.[15] Further, preoperative statin therapy has been independently associated with a significant reduction in the risk of all-cause mortality in patients undergoing CABG surgery.[16,17] The aim of the current study was to determine whether preoperative statin therapy is independently associated with a reduced incidence of early (date of surgery–postoperative day 3 [DOS-POD3]) cardiac death or nonfatal, in-hospital postoperative MI using the international Multicenter Study of Perioperative Ischemia (*McSPI*) Epidemiology II Study of patients undergoing primary, elective CABG surgery.[18] Additionally, we hypothesized that discontinuation of statins in the postoperative period is independently associated with an increased risk of late (POD4-discharge), in-hospital cardiac mortality, even when controlling for the discontinuation of preoperative aspirin β-blocker, or angiotensin-converting enzyme (ACE) inhibitor therapy.

Abbreviations and Acronyms

ACE = angiotensin-converting enzyme 4
ACS = acute coronary syndromes
CABG = coronary artery bypass graft
CI = confidence intervals
CPB = cardiopulmonary bypass
DOS = date of surgery
HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A
IREF = Ischemia Research and Education Foundation
LDL = low-density lipoprotein
McSPI = Multicenter Study of Perioperative Ischemia
MI = myocardial infarction
MIRACL = Myocardial Ischemia Reduction with Acute Cholesterol Lowering
OR = odds ratios
POD = postoperative day

Methods

Study Design

The *McSPI* Epidemiology II Study was prospective and longitudinal, consisting of 5436 patients with coronary artery disease scheduled to undergo CABG surgery with the use of cardiopulmonary bypass (CPB) at one of 70 medical institutions in 17 countries in North America, South America, Europe, the Middle East, and Asia. Enrollment began in November 1996 and ended in June 2000.[18] After institutional review board approval and written informed consent had been obtained from each patient, 100 patients were prospectively enrolled at each institution according to a systematic sampling scheme.[18] Patients were excluded from the present analysis if they (1) underwent emergency or urgent CABG surgery (n = 952); (2) had repeat CABG surgery (n = 306); or (3) had CABG surgery with concomitant valve or other cardiac surgery (n = 827). Additionally, patients were excluded (n = 685) from the present analysis for the following reasons: had a known history of hepatitis B or C, cancer, hematologic disorder, previous organ transplantation, alcohol or intravenous drug abuse, religious beliefs precluding transfusion, prior chemotherapy or immunosuppressive therapy; were currently HIV seropositive; pregnant, or had some other extraordinary characteristic (eg, history of depression, mental illness, associated cardiac anomalies, or severe aortic, thromboembolic, or neurologic disease). After application of the exclusion criteria, the remaining patients (n = 2666) were classified into 2 groups: patients receiving preoperative statin therapy (n = 1352) and patients not receiving any preoperative antihyperlipidemic therapy (n = 1314) at the time of admission. Commercially available statins screened for in this study included cerivastatin, fluvastatin, simvastatin, atorvastatin, lovastatin, and pravastatin.

Study Data

Data on more than 7500 variables, including patient demographics, preoperative risk factors, and the incidence of adverse postoperative outcomes, were collected on each enrolled patient by independent investigators during the course of the hospitalization for the CABG surgery (the index hospitalization). Data were adjudicated centrally (IREF, San Francisco, Calif), with all data for each patient examined for completeness and accuracy before the database was closed.

Measurement of Outcomes

All outcomes were pre-specified, defined by the protocol, and adjudicated by investigators at each site who were unaware of treatment-group assignment. Cardiac death was defined as death occurring secondary to an MI, heart failure, or arrhythmia. A diagnosis of MI was made if there were new Q waves (Minnesota code 1-1-1 to 1-2-7), new persistent ST-segment or T-wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2) and elevated values for the myocardial band isoenzyme of creatine kinase, or evidence of acute MI at autopsy.[18] A diagnosis of heart failure was made if a ventricular assist device was used, if continuous inotropic support was required for at least 24 hours, or if there was evidence of heart failure on autopsy.[18] "Early" death was defined as death occurring in hospital between DOS-POD3. "Late" death was defined as death occurring in hospital between POD4-discharge.

Statistical Analysis

Statistical analyses were performed with SAS, version 8.12 (SAS Institute, Cary, NC). Patients' preoperative and intraoperative demographics, risk factors, and medications were first compared between groups by univariate (χ^2) analysis (Tables 1 and 2). To control for selection bias related to statin use, the study estimated a propensity score for each patient using unconditional logistic regression to determine the predicted probability of inclusion in the preoperative "statin" group. Variables used to determine the propensity score included age, gender, ethnicity, body mass index, educational level, tobacco use, medications, and preoperative history of diabetes, hypercholesterolemia, cardiovascular, renal, neurologic, or hematologic disease. The propensity score and all predictor variables significant at a 2-tailed nominal $P < .15$ in the univariate analysis were then entered into a multivariate stepwise logistic regression model to determine whether preoperative statin therapy was independently associated with a reduction in the risk of early cardiac death or nonfatal, in-hospital postoperative MI after primary, elective CABG surgery. Only those variables significant at a 2-tailed nominal $P < .05$ were retained within the model. To ascertain the effect of postoperative statin discontinuation on late, in-hospital mortality, multivariate analysis was also performed as described above on the group of patients who received preoperative statin therapy, comparing patients in whom statin therapy was discontinued with those in whom it was not. Odds ratios (OR) and corresponding 95% confidence intervals (CI) are reported, with associated P values.

Results

Patient preoperative and intraoperative demographics are presented in Tables 1 and 2, respectively. Patients receiving preoperative statin therapy were significantly more likely to have a history of hyperlipidemia ($P = .001$), smoking ($P = .01$), coronary stent placement ($P = .002$), and percutaneous transluminal coronary angioplasty ($P = .001$) than were patients not receiving preoperative antihyperlipidemia therapy. Additionally, significant differences in statin usage between geographic regions were observed (Table 1).

The incidence of all-cause mortality, cardiac mortality, and in-hospital MI is presented in Figure 1. Multivariate analysis, including controlling for propensity score, showed that preoperative statin therapy was independently associated with a significant reduction in the risk of early all-cause mortality ($P < .04$) and cardiac death ($P < .04$) after elective, primary CABG surgery requiring CPB (Figure 2). Note that all early (DOS–POD3) deaths were cardiac in origin. Other significant independent predictors of early all-cause mortality *(A)* and cardiac mortality *(B)* are shown in Figure 2. Preoperative statin therapy was not independently associated with a significant reduction in the risk of nonfatal, in-hospital MI ($P = .08$). Only preoperative heparin or warfarin use was found to be a significant, independent predictor of postoperative nonfatal, in-hospital MI ($P < .01$). No significant differences between the commercially available statins were observed with respect to the incidence of all-cause mortality, cardiac mortality, and in-hospital MI.

Although preoperative statin therapy was independently associated with a significant reduction in the risk of early (DOS-POD3) cardiac death, the incidence of all-cause, in-hospital (DOS-discharge) mortality did not significantly differ between groups (1.9% vs 2.4%; $P =$ not significant). However, multivariate analysis controlling for the postoperative discontinuation of preoperative statin, aspirin, β-blocker, or ACE inhibitor therapy revealed that discontinuation of statin therapy was independently associated with an increased risk of late (POD4-discharge) in-hospital all-cause mortality compared with continuation of statins postoperatively (2.64% vs 0.6%; $P < .01$; Figure 3). Similarly, discontinuation of statin therapy was independently associated with an increased risk of late in-hospital cardiac mortality compared continuation of statins postoperatively (1.91% vs 0.45%; $P < .01$; Figure 3). In contrast, discontinuation of preoperative aspirin, β-blocker, or ACE inhibitor therapy was *not* independently associated with an increased risk of late, in-hospital all-cause mortality (Note that postoperative discontinuation of aspirin bordered on significance; $P = .054$).

Discussion

These data suggest that preoperative statin therapy is independently associated with a reduced risk of early (DOS-POD3) cardiac mortality after elective, primary CABG surgery requiring CPB, even after adjusting for patient demographics, risk factors, medications, and statin propensity score. Moreover, discontinuation of statin therapy in the immediate postoperative period is independently associated with an increased risk of late (POD4-discharge), all-cause in-hospital mortality, even after adjusting for the postoperative discontinuation of preoperative β-blocker, aspirin, and ACE inhibitor therapy. Preoperative statin therapy is not independently associated with a reduced risk of nonfatal, in-hospital postoperative MI, whereas it is associated with

TABLE 1. Preoperative demographic variables and risk factors in patients receiving preoperative statin therapy and patients not receiving preoperative antihyperlipidemic therapy

Patient demographics and preoperative risk factors (%, [n])	No statin therapy (n = 1314)	Statin therapy (n = 1352)	*P* value
Age (y)	63.4 ± 0.26	61.9 ± 0.26	<.001
Female gender	18 (232)	19 (263)	.23
College graduate	18 (238)	18 (245)	.99
Body mass index	27.1 ± 0.12	27.5 ± 0.11	.04
Diabetes mellitus type I	8 (102)	7 (98)	.61
Hyperlipidemia	54 (707)	92 (1251)	<.001
History of smoking	65 (860)	70 (952)	.01
Pulmonary disease	19 (246)	16 (210)	.03
Renal disease	15 (196)	14 (183)	.30
Hypertension	65 (855)	65 (886)	.84
Prior MI	51 (668)	53 (712)	.36
Angina	91 (1196)	92 (1251)	.19
Previous coronary stent	4 (59)	8 (105)	.002
Previous PTCA	12 (153)	18 (238)	<.001
Dysrhythmias	16 (211)	14 (191)	.15
Atrial fibrillation	6 (83)	6 (82)	.79
Valvular disease	9 (124)	7 (93)	.02
Carotid disease	10 (136)	12 (161)	.19
Ejection fraction > 55%	63 (751)	65 (794)	.80
Ejection fraction < 44%	14 (181)	14 (184)	.90
Congestive heart failure	29 (385)	29 (390)	.81
Aortic vascular disease	1 (8)	1 (13)	.30
Peripheral vascular disease	15 (201)	15 (197)	.59
Syncope	6 (79)	5 (74)	.55
Transient ischemic attack	5 (71)	5 (69)	.73
Stroke	6 (75)	6 (76)	.95
Gastrointestinal disease	24 (320)	27 (365)	.12
Hematologic disease	4 (57)	3 (42)	.09
Hepatic disease	8 (99)	7 (90)	.36
Preoperative medications			
β-Blockers	68 (889)	76 (1023)	<.001
Aspirin	60 (795)	67 (905)	<.001
IABP	1 (9)	0.5 (6)	.41
Antiarrhythmics	10 (131)	10 (142)	.65
ACE inhibitors	42 (556)	43 (577)	.85
Ca^{2+} channel blockers	35 (460)	39 (522)	.05
Diuretics	25 (328)	21 (278)	.007
Intravenous inotropes	5 (67)	2 (26)	<.001
Nonaspirin platelet inhibitors	1 (16)	1 (17)	.93
Vasodilators	12 (156)	8 (107)	<.001
Warfarin or heparin	26 (338)	23 (311)	.10
Antifibrinolytics	0.15 (2)	0.52 (7)	.10
Region			
Asia	13 (168)	5 (61)	<.001
Canada	6 (82)	8 (107)	.09
Europe	43 (558)	36 (488)	.001
Middle East	2 (22)	2 (24)	.84
South America	6 (77)	4 (59)	.08
United Kingdom	8 (103)	20 (268)	<.001
United States	23 (304)	26 (345)	.15

Mean ± SEM. *MI*, Myocardial infarction; *PTCA*, percutaneous transluminal coronary angioplasty; *IABP*, intra-aortic balloon pump; *ACE*, angiotensin-converting enzyme.

TABLE 2. Intraoperative demographic variables and risk factors in patients receiving preoperative statin therapy and patients not receiving preoperative antihyperlipidemic therapy

Intraoperative demographics and risk factors (%, [n])	No statin therapy (n = 1314)	Statin therapy (n = 1352)	*P* value
Crossclamp time (min)	59.7 ± 0.71	58.4 ± 0.72	.21
Total bypass time (min)	96.9 ± 0.96	93.5 ± 0.97	.01
Crossclamp used > 1 time	2 (29)	6 (82)	.001
Side-biter clamp used > 1 time	21 (274)	22 (288)	.70
Number of CABGs ≥ 3	74 (967)	74 (1006)	.63
Arterial filter used during CPB	80 (1048)	83 (1112)	.07
Membrane oxygenator	96 (1262)	99 (1343)	<.001
Lowest temperature actively cooled (C°)	30.9 ± 0.08	31.0 ± 0.08	.32
Highest temperature actively warmed (C°)	36.9 ± 0.02	37.0 ± 0.02	.003
Ventricular vent	92 (1210)	91 (1233)	.41
Intraoperative intravenous inotropes	69 (913)	71 (956)	.49
Intraoperative IABP	1 (18)	1 (19)	.94
Intraoperative antifibrinolytics	69 (904)	72 (978)	.15
Return to CPB	3 (42)	3 (42)	.89
Intraoperative VAD	0 (0)	1 (1)	>.999

Mean ± SEM. *CABG*, Coronary artery bypass graft; *CPB*, cardiopulmonary bypass; *IABP*, intra-aortic balloon pump; *VAD*, ventricular assist device.

early cardiac mortality. Although randomized trials are still needed, these data suggest that preoperative statin therapy is associated with a reduced risk of acute postoperative cardiac surgical mortality. Moreover, discontinuation of statins after cardiac surgery is associated with an increased risk of late in-hospital mortality.

Long-term statin administration in ambulatory patients is associated with a reduced risk of adverse cardiovascular events, including death, MI, stroke, atrial fibrillation, and renal dysfunction.[1-11] However, recent evidence suggests that statins may also reduce the risk of acute adverse outcomes after invasive cardiovascular procedures.[15,19-25] For

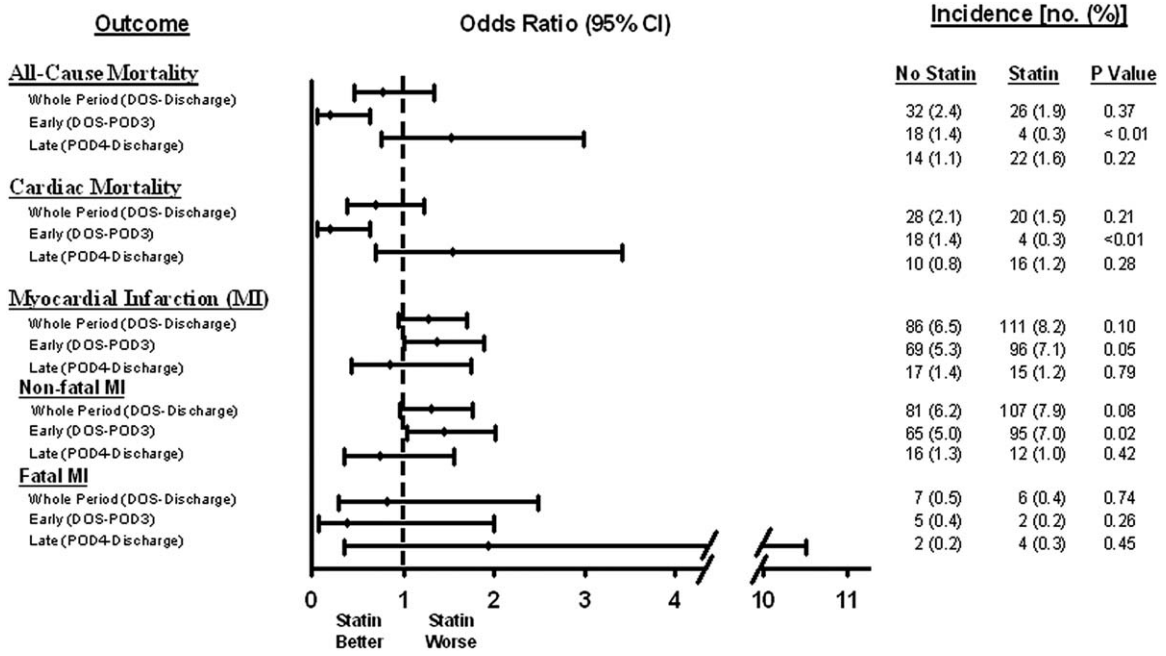

Figure 1. Univariate analysis of all-cause mortality, cardiac mortality, and nonfatal, in-hospital myocardial infarction (MI). The incidence, associated odds ratios, and 95% confidence intervals *(CI)* of all-cause mortality, cardiac mortality, and nonfatal, in-hospital MI in patients receiving preoperative statin therapy (n = 1352) and patients who did not (n = 1314) are shown. *DOS,* Day of surgery; *POD,* postoperative day.

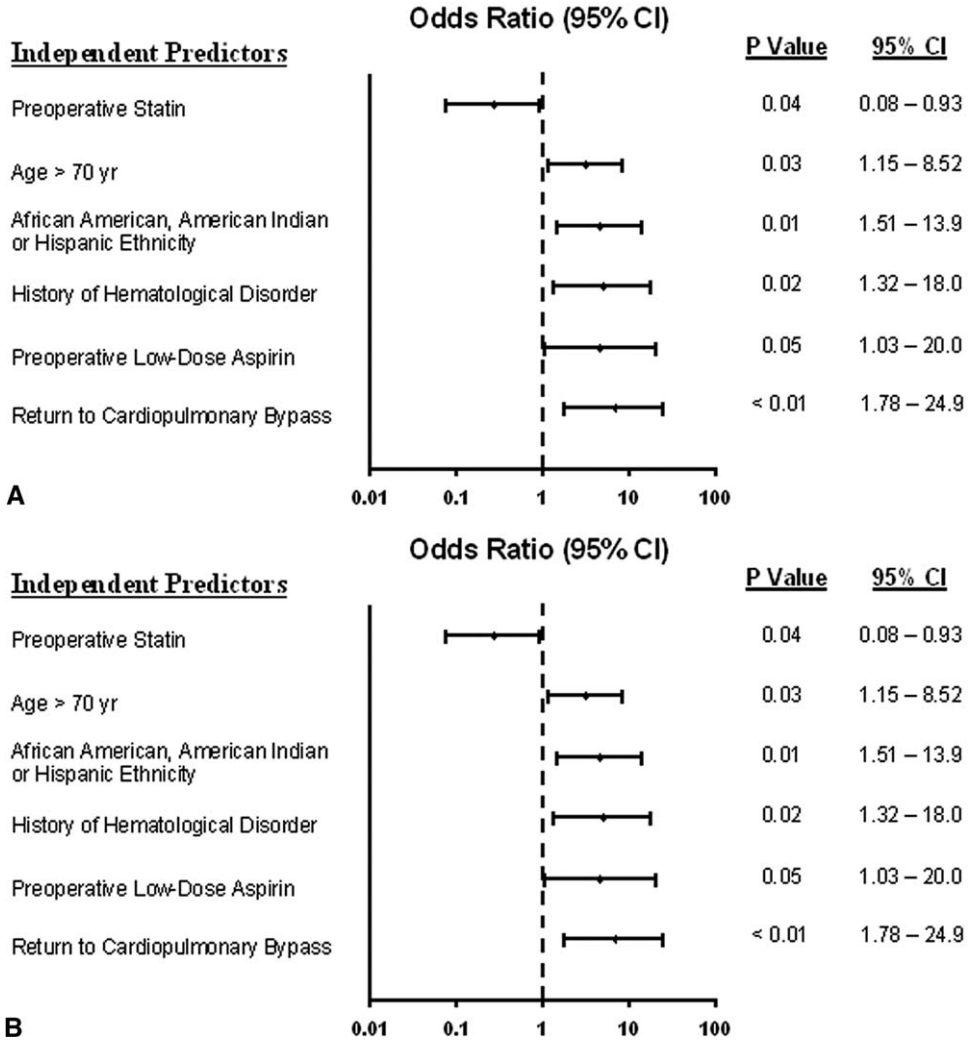

Figure 2. Multivariate analysis of early (DOS-POD3) all-cause mortality (A) and cardiac mortality (B) after elective, primary CABG surgery controlling for patient demographics, perioperative risk factors, medications, and statin propensity score. Significant, independent predictors of early all-cause mortality and cardiac mortality, along with their associated odds ratios and 95% confidence intervals *(CI)* are shown. Note that all deaths between DOS-POD 3 were cardiac in origin.

example, statin administration at the time of percutaneous transluminal coronary angioplasty is independently associated with improved 30-day and 6-month survival.[7] Statin use was also recently associated with a reduced risk of perioperative mortality in patients undergoing vascular or cardiac surgery.[15,16] We now demonstrate that preoperative statin therapy is not only independently associated with a reduced risk of early cardiac mortality, but that discontinuation of preoperative statin therapy in the immediate postoperative period is also independently associated with an increased risk of late in-hospital mortality after primary, elective CABG surgery.

Although the exact mechanisms underlying the observed association of preoperative statin therapy with reduced cardiac surgical mortality are unclear, accumulating evidence suggests that statins exert multiple effects independent of their effect on LDL cholesterol.[26-35] In patients with acute coronary syndromes (ACS) or idiopathic dilated cardiomyopathy, statin therapy has been shown to improve ventricular function and reduce markers of inflammation, including C-reactive protein, serum amyloid A, tumor necrosis factor α, interleukin 6, and brain natriuretic peptide levels.[27-29] Statins have also been shown to be protective against ischemia and reperfusion injury in the heart, lung, brain,

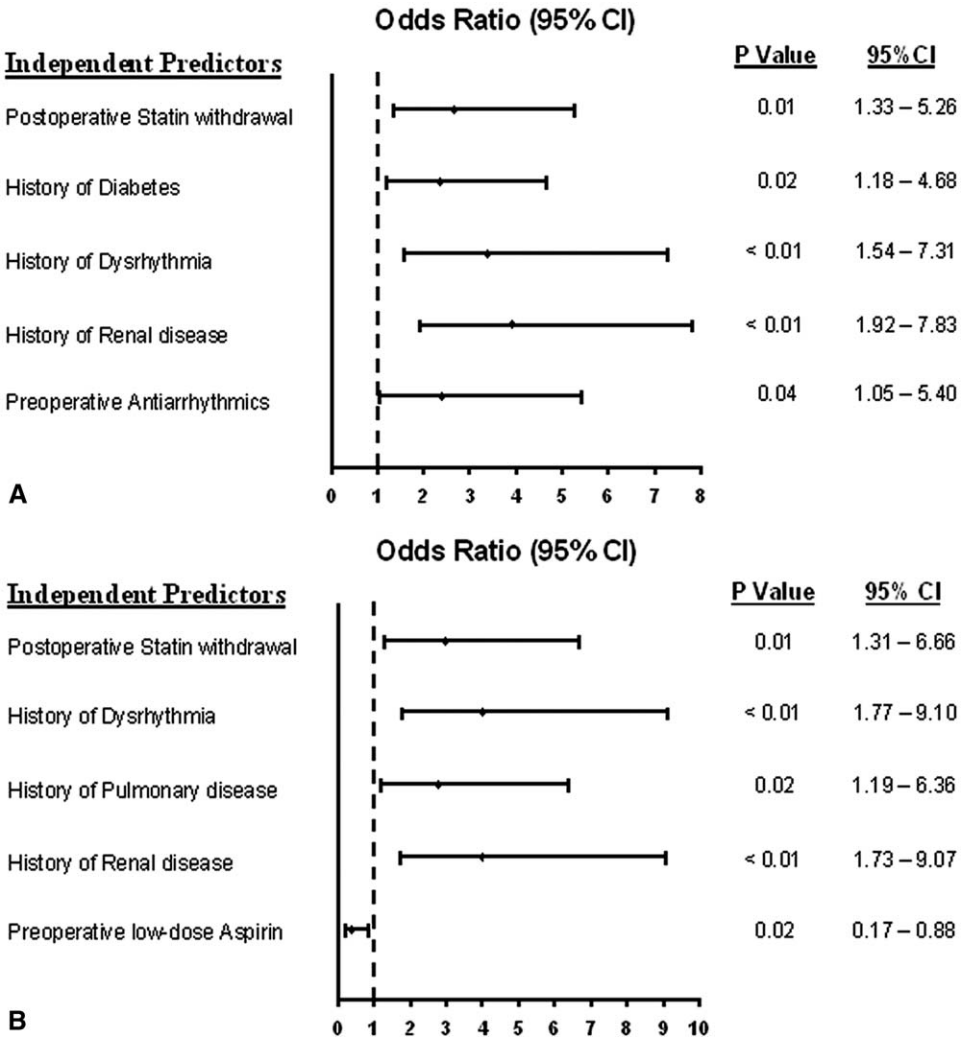

Figure 3. Multivariate analysis of late (POD4-discharge) all-cause mortality (A) and cardiac mortality (B) after elective CABG surgery controlling for the postoperative discontinuation of preoperative statin, aspirin, β-blocker, or angiotensin-converting enzyme inhibitor therapy. Significant, independent predictors of late all-cause mortality and cardiac mortality along with their associated odds ratios and 95% confidence intervals *(CI)* are shown. Only discontinuation of statin therapy independently predicted increased all-cause and cardiac mortality occurring on or after POD 4.

kidney, and gut.[31-34,36] For example, simvastatin inhibited leukocyte-endothelial cell interactions in an isolated, perfused rat heart model, while preserving cardiac contractile function and coronary perfusion after myocardial ischemia and reperfusion.[32] In addition to promoting systemic antioxidant effects, statins have also been shown to modulate remodeling of the cardiac extracellular matrix and to inhibit synthesis of isoprenoids required for the posttranslational modification of important signaling molecules, such as Rho, Rac, and Ras.[29,30] Multiple mechanisms, independent of cholesterol reduction, may thus underlie the protective influence of preoperative statin therapy on acute cardiac surgical mortality.[12-14]

Depending on the statin type, the half-life of inhibitory activity for HMG-CoA reductase may range as high as 20 to 30 hours because of the contribution of active metabolites. However, acute discontinuation of statins in ambulatory patients with ACS has been shown to increase the risk of adverse cardiovascular outcomes. Heeschen and colleagues[37] demonstrated in ambulatory patients experiencing ACS that administration of statin therapy before the onset of symptoms was associated with a reduced incidence of 30-day all-cause mortality and nonfatal MI compared with nonuse of statins (adjusted OR 0.49, 95% CI 0.21-0.86; $P = .004$). Moreover, the incidence of 30-day all-cause mortality and nonfatal MI was significantly increased when statin

therapy was withdrawn compared with when statin therapy was continued (adjusted OR 2.93, 95% CI 1.64-6.27; $P = .005$). Both effects were independent of cholesterol levels, further supporting the non–lipid-mediated benefits of statin therapy. Finally, statin therapy was shown to be less effective in reducing the risk of death or nonfatal MI when initiated after the presentation of an ACS, compared with pretreatment before the onset of symptoms (14% vs 51% relative risk reduction). These results are consistent with our present findings in CABG surgical patients suggesting that postoperative discontinuation of statin therapy is associated with an increased risk of late, all-cause in-hospital mortality.

Despite guidelines by the American College of Cardiology and American Heart Association recommending statins for CABG patients with LDL concentrations greater than 100 mg/dL,[38] two thirds of eligible candidates may not be receiving statin therapy at discharge.[39] Explanations for not reinitiating statin therapy after CABG surgery may include patients' decreased tolerance of oral medications secondary to nausea and vomiting, transient renal dysfunction, concerns pertaining to hepatic toxicity or myositis, or failure of the responsible physician to reimplement preoperative medications. Educating physicians about the potential benefits of continuing statin therapy throughout the perioperative period may therefore be warranted.

Although this prospective cohort study extends the results of previous studies suggesting that preoperative statin therapy may be beneficial after major cardiovascular surgery,[15,16,19,20] the present study is not without limitations. Despite the use of propensity scoring and multivariate regression models to adjust for potential confounders that affect postoperative outcomes, immeasurable or unknown factors may still exist. Physician bias may have influenced patient selection, statin type, and dose. Indeed, randomized clinical trials of statin use in other settings such as ACS (eg, the Myocardial Ischemia Reduction with Acute Cholesterol Lowering [MIRACL] trial), while encouraging, have not always confirmed as marked a reduction in mortality as was seen in early observational studies.[40,41] Nonetheless, an intensive lipid-lowering statin regimen was recently shown to have greater protection against death and major cardiovascular events in ACS patients than a standard regimen,[42] suggesting that such patients may further benefit from early and continued lowering of LDL cholesterol to levels substantially below current target levels. There thus remains a need for a prospective, randomized study to investigate the influence of statins on adverse cardiac surgical outcomes and to determine which patients would benefit the most from perioperative statin therapy. Second, we were unable to determine the influence of the duration of preoperative statin therapy on the risk of postoperative outcomes. Although the duration of preoperative statin therapy was not measured or controlled in the present study, previous studies have shown that statin therapy improves endothelial function and lowers serum inflammatory markers as early as 6 to 16 weeks.[7,26,27,29] Finally, further study is needed to determine the effect of postoperative statin administration in patients not receiving preoperative statin therapy.

Conclusion

Preoperative statin therapy may reduce the risk of early cardiac mortality after primary, elective CABG surgery requiring CPB. Furthermore, discontinuation of statins after cardiac surgery is associated with an increased risk of late in-hospital mortality.

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E Appendix

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