Statins Are Associated With a Reduced Incidence of Perioperative Mortality After Coronary Artery Bypass Graft Surgery

Wei Pan, MD; Tatjana Pintar, MD; James Anton, MD; Vei-Vei Lee, MS; William K. Vaughn, PhD; Charles D. Collard, MD

Background—Statin therapy in nonsurgical patient populations is associated with a significant reduction in adverse cardiovascular events, including death, myocardial infarction (MI), and stroke. Recently, statin therapy was shown to be associated with a reduced incidence of postoperative mortality in patients undergoing major noncardiac vascular surgery. We investigated the influence of preoperative statin therapy on adverse outcomes after primary coronary artery bypass graft (CABG) surgery.

Methods and Results—A retrospective cohort study of patients undergoing primary CABG surgery with cardiopulmonary bypass (CPB) (n=1663) between January 1, 2000 and December 31, 2001 at the Texas Heart Institute was performed. Patients were classified into 2 groups: patients receiving preoperative statin therapy (n=943) and patients not receiving preoperative antihyperlipidemic therapy (n=720). To determine if preoperative statin therapy was independently associated with a reduction in the risk of adverse postoperative outcomes, multivariate stepwise logistic regression was performed controlling for patient demographics, medical history, and preoperative medications. Multivariate logistic regression analysis demonstrated that preoperative statin therapy was independently associated with a significant reduction (≈50%) in the risk of 30-day all-cause mortality (3.75% versus 1.80%; P<0.05). The adjusted odds ratio for early mortality in patients receiving preoperative statin therapy compared with patients not receiving antihyperlipidemic agents was 0.53 (95% CI, 0.28 to 0.99). Statin therapy was not independently associated with a reduced risk of postoperative MI, cardiac arrhythmias, stroke, or renal dysfunction. In an attempt to further control for selection bias related to the choice of therapy, multivariate analysis of a propensity-matched cohort of 1362 patients revealed that preoperative statin therapy was independently associated with a significant reduction in the composite endpoint of 30-day all-cause mortality and stroke (7.1% versus 4.6%; P<0.05).

Conclusions—Preoperative statin therapy may reduce the risk of early mortality after primary CABG surgery with CPB. (Circulation. 2004;110[suppl II]:II-45–II-49.)

Key Words: surgery ■ cardiopulmonary bypass ■ inflammation ■ coronary disease ■ prevention

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dministration of 3-hydroxy-3-methylglutaryl coenzyme A inhibitors or “statins” to ambulatory patient populations is associated with a reduced incidence of adverse cardiovascular events, including death, myocardial infarction (MI), stroke, and renal dysfunction.1–10 However, the beneficial effects of statin therapy on adverse cardiovascular events in the acute perioperative period are largely unknown.11–13 Recently, statins were shown to be associated with a reduced incidence of perioperative mortality in patients undergoing major noncardiac vascular surgery.11 Additionally, the 1-year mortality rate after coronary artery bypass graft (CABG) surgery in a small patient series from a single institution was shown to be significantly lower in patients receiving preoperative statin therapy compared with nonstatin-treated patients.12 However, this relatively underpowered study (n=≈300 patients) was unable to demonstrate an independent association between preoperative statin therapy and a reduction in the risk of acute postoperative death, MI, or stroke. The aim of the current study was to determine whether preoperative statin therapy is independently associated with a reduced incidence of acute (<30 days) adverse outcomes after primary CABG surgery. To this end, multivariate stepwise logistic regression analysis was performed on >1650 consecutive patients undergoing primary CABG surgery at the Texas Heart Institute, controlling for patient demographics, medical history, and preoperative medications.

Methods

Study Design

A retrospective cohort study of all consecutive patients undergoing primary CABG surgery with cardiopulmonary bypass (CPB) (n =1663) between January 1, 2000 and December 31, 2001 at the Texas Heart Institute was performed. Patients were classified into 2
groups: patients receiving preoperative statin therapy (n=943) and patients not receiving preoperative antihyperlipidemic therapy (n=720) at the time of admission. Patients undergoing primary CABG surgery along with concomitant valve or other cardiac surgery (eg, atrial septal defect repair, ventricular aneurysm resection) were excluded from the analysis. Commercially available statins screened for in this study included cerivastatin, fluvastatin, simvastatin, atorvastatin, lovastatin, pravastatin, and simvastatin.

Data Collection
Patient demographics, preoperative risk factors, and the incidence of adverse postoperative outcomes were obtained from the Texas Heart Institute cardiac surgical database. Measured adverse outcomes included 30-day all-cause mortality, MI, cardiac arrhythmias, stroke, and renal dysfunction. 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), elevated levels of the muscle-brain (MB) isoenzyme of creatine kinase, or evidence of acute MI on autopsy. A diagnosis of stroke was made if there was clinical evidence or evidence of a focal or global defect on computed tomography, magnetic resonance imaging, or autopsy. Renal dysfunction was defined as a serum creatinine level of at least 2.0 mg/dL accompanied by an increase of at least 0.7 mg/dL from baseline, renal failure requiring dialysis, or evidence of renal failure on autopsy.

Statistical Analysis
All statistical analyses were performed using SAS statistical software (SAS Institute). Patient preoperative demographics, risk factors, and preoperative medications were first compared between groups by univariate (χ²) analysis (Table 1). All predictor variables significant at a 2-tailed nominal P<0.15 in the univariate analysis were then entered into a multivariate logistical model, and stepwise logistic regression was performed to determine if preoperative statin therapy was independently associated with a reduction in the risk of adverse postoperative outcomes after primary CABG surgery. Only those variables significant at a 2-tailed nominal P<0.05 were retained within the model. Odds ratios and corresponding 95% CI are reported with associated P values.

In an attempt to further control for selection bias related to the choice of therapy, propensity scores were also estimated using unconditional logistic regression to determine the predicted probability of inclusion in the “statin” group for each of the 1663 patients. The 23 variables used in the initial model are shown in Table 2. Patients receiving preoperative statin therapy (n=943) and patients not receiving preoperative antihyperlipidemic therapy (n=720) were then matched 1-to-1 on these variables, resulting in successful matching of 1362 patients. All predictor variables significant at a 2-tailed nominal P<0.05 in the univariate analysis were then entered into a multivariate logistical model, and stepwise logistic regression was performed to determine if preoperative statin therapy was independently associated with a reduction in the risk of adverse postoperative outcomes after primary CABG surgery in propensity score-matched subjects.

Results
Patient preoperative demographics and risk factors are presented in Table 1. As expected, the incidence of a history of hyperlipidemia was significantly greater in patients receiving preoperative statin therapy compared with patients not receiving antihyperlipidemic therapy (P=0.01). The preoperative incidence of hypertension was also significantly greater in patients receiving preoperative statin therapy compared with patients not receiving antihyperlipidemic therapy (P=0.01). Patients receiving preoperative statin therapy were also more likely to be receiving preoperative β-blockers (P=0.001) or aspirin (P=0.003). Although the groups did not significantly differ with respect to the incidence of patients with a preoperative ejection fraction <50%, the incidence of a history of congestive heart failure was significantly greater in patients not receiving preoperative antihyperlipidemic therapy compared with patients receiving statin therapy (P=0.01). Of note, the groups did not significantly differ with respect to age older than 65 years, gender, diabetes, history of smoking, renal insufficiency, severity of coronary artery disease, previous MI, stroke, or, intraoperative CPB, and aortic cross-clamp times.

The adverse postoperative outcome incidence is presented in Table 3. Within the total combined patient population, perioperative cardiovascular complications were the primary cause of death in 28 (64%) patients; 4 (9%) had a fatal MI, 18 (41%) had a fatal arrhythmia, 3 (7%) had fatal cardiogenic shock, and 3 (7%) patients had fatal stroke. The most common nonvascular causes of death were sepsis (3 cases, 7%), stroke (3 cases, 7%), and multigorgan dysfunction syndrome (5 cases, 11%). Univariate analysis revealed that the incidence of 30-day all-cause death was 50% lower in patients receiving preoperative statin therapy compared with patients not receiving antihyperlipidemic therapy (1.8% ver-
No significant differences between groups were observed with respect to the incidence of postoperative MI, cardiac arrhythmias, stroke, or renal dysfunction.

To determine whether preoperative statin therapy is independently associated with a significant reduction in the risk of early mortality after primary CABG surgery, multivariate analysis of all-cause early mortality was performed controlling for patient demographics, preoperative risk factors, and intraoperative variables (Figure 1). Multivariate analysis revealed that preoperative statin therapy is independently associated with a significant reduction in the risk of early mortality after primary CABG surgery (3.75% versus 1.8%, \( P < 0.05 \)). The adjusted odds ratio for early mortality in patients receiving preoperative statin therapy compared with patients not receiving antihyperlipidemic agents was 0.53 (95% CI, 0.28 to 0.99). Other significant predictors of early mortality included a preoperative history of congestive heart failure or renal insufficiency and the need for emergency surgery (Figure 1). In contrast to early mortality, statin therapy was not independently associated with a reduced risk of MI, cardiac arrhythmias, stroke, or renal dysfunction by multivariate analysis. Although multivariate analysis was performed on multiple different composite outcomes (eg, MI and stroke), preoperative statin therapy was only shown to be independently associated with a reduced risk of MI, cardiac arrhythmias, stroke, or renal dysfunction by multivariate analysis. Although multivariate analysis was performed on multiple different composite outcomes (eg, MI and stroke), preoperative statin therapy was only shown to be independently associated with a reduced risk of MI, cardiac arrhythmias, stroke, or renal dysfunction by multivariate analysis. Although multivariate analysis was performed on multiple different composite outcomes (eg, MI and stroke), preoperative statin therapy was only shown to be independently associated with a reduced risk of MI, cardiac arrhythmias, stroke, or renal dysfunction by multivariate analysis. Although multivariate analysis was performed on multiple different composite outcomes (eg, MI and stroke), preoperative statin therapy was only shown to be independently associated with a reduced risk of MI, cardiac arrhythmias, stroke, or renal dysfunction by multivariate analysis.

In an attempt to further control for selection bias related to the choice of therapy, stepwise logistic regression was also performed on a propensity score-matched cohort of 1362 patients. Table 2 lists the variables used to determine each subject’s propensity score and demonstrates that no significant differences existed between the patients receiving preoperative statin therapy and patients not receiving preoperative antihyperlipidemic therapy in the propensity-matched cohort.

NYHA indicates New York Heart Association.

No significant differences between groups were observed with respect to the incidence of postoperative MI, cardiac arrhythmias, stroke, or renal dysfunction.

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Note that there are no significant differences in preoperative risk factors between patients receiving preoperative statin therapy and patients not receiving preoperative antihyperlipidemic therapy in the propensity-matched cohort.

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operative statin therapy and patients not receiving antihyperlipidemic agents in the propensity-matched cohort. Even after controlling for propensity score, preoperative statin therapy was found to be independently associated with a significant reduction in the risk of the composite outcome of stroke and early mortality (7.1% versus 4.6%; P < 0.05). Although there was ≈40% reduction in 30-day all-cause mortality in patients receiving preoperative statin therapy (4%) compared with patients not receiving antihyperlipidemic agents (2.4%) in the propensity-matched cohort, preoperative statin therapy was not found to be an independent predictor of early mortality alone (P < 0.08). It is clear that the percentage reduction in early mortality in both the propensity and multivariate analyses are very similar (≈50%), indicating little change associated with propensity score adjustment. The loss in statistical significance in 30-day all-cause mortality alone with propensity analysis is thus probably attributable to the loss of statistical power associated with the ≈20% reduction in the total original sample size after propensity matching. Nonetheless, preoperative statin therapy is independently associated with a significant reduction in the risk of the composite outcome of stroke and early mortality, even after controlling for propensity score.

### Discussion

Cardiac surgical mortality remains a problem of significant medical and socioeconomic significance, with estimates ranging as high as 3% to 6%. Our data suggest that preoperative statin therapy may significantly reduce the risk of early mortality after primary CABG surgery with CPB, even after adjusting for patient demographics, preoperative risk factors, and medications. Thirty-day all-cause mortality was ≈50% lower in patients receiving preoperative statin therapy compared with patients not receiving preoperative antihyperlipidemic therapy. Although preoperative statin therapy was not shown to be independently associated with a reduced risk of postoperative MI, cardiac arrhythmias, stroke, or renal dysfunction, a significant reduction (≈30% to 35%) in the risk of the composite outcome of stroke and 30-day all-cause mortality was observed by multivariate analysis, even when controlling for propensity score. Together, these data suggest that preoperative statin therapy may be beneficial in reducing acute postoperative cardiac surgical morbidity and mortality.

Long-term statin administration in ambulatory patient populations has been previously associated with a reduced risk of adverse cardiovascular events, including death, MI, stroke, and renal dysfunction. Furthermore, the beneficial effects of statin therapy are not limited to patients with hypercholesterolemia. Multiple randomized clinical trials have shown that even in patients with normal total and low-density lipoprotein cholesterol levels, long-term statin administration is associated with reduced incidence of adverse cardiovascular outcomes and a decreased need for coronary angioplasty or CABG surgery.

Although there is little doubt that statin therapy is associated with a reduced incidence of long-term adverse cardiovascular outcomes, recent evidence suggests that statins may also reduce the risk of acute adverse outcomes after invasive cardiovascular procedures. For example, statin therapy at the time of percutaneous coronary intervention was recently demonstrated to be an independent predictor of 30-day and 6-month survival. Statin use was also recently associated with a reduced risk of perioperative mortality in patients undergoing major noncardiac vascular surgery. Finally, the 1-year mortality rate after CABG surgery in a small patient series from a single institution was shown to be significantly lower in patients receiving preoperative statin therapy compared with nonstatin-treated patients.

Using a much larger patient series, we now extend this previous observation by demonstrating that preoperative statin therapy may reduce the risk of early (30-day) mortality after CABG surgery. Further, we demonstrate that preoperative statin therapy is independently associated with a significant reduction in the risk of the composite outcome of stroke and 30-day all-cause mortality, even when controlling for propensity score.

Although the exact mechanisms underlying the association of preoperative statin therapy and reduced cardiac surgical mortality are unclear in the present study, an accumulating body of evidence suggests that statins exert multiple antiinflammatory effects independent of their effect on low-density lipoprotein cholesterol. In patients with acute coronary syndromes or idiopathic dilated cardiomyopathy, statin therapy has been shown to reduce serum inflammatory marker levels, including C-reactive protein, serum amyloid A, tumor necrosis factor-α, interleukin-6, and brain natriuretic peptide. Along these same lines, the survival benefit of statin therapy in patients with angiographically significant CAD (>70% stenosis) was recently linked to a high incidence of cytomegalovirus seropositivity and increased serum C-reactive protein levels. Finally, an intensive lipid-lowering statin regimen was recently shown to have greater protection against death and major cardiovascular events in acute coronary syndromes patients than did a standard regimen, suggesting that such patients may further benefit from early and continued lowering of low-density lipoprotein cholesterol to levels substantially below current target levels.

Statins have also been shown to be protective against tissue injury in multiple models of ischemia/reperfusion, including the heart, lung, brain, kidney, and gut. For example, simvastatin in an isolated perfused rat heart model was shown...
to be a potent and effective cardioprotective agent that inhibited leukocyte–endothelial cell interactions and preserved cardiac contractile function and coronary perfusion after myocardial ischemia and reperfusion.\textsuperscript{20} In addition to their anti-inflammatory effects, statins have also been shown to promote systemic antioxidant effects, modulate remodeling of the cardiac extracellular matrix, and inhibit synthesis of isoprenoids required for the posttranslational modification of important signaling molecules such as Rho, Rac, and Ras.\textsuperscript{17,18} Thus, multiple mechanisms may underlie the protective influence of preoperative statin therapy on acute cardiac surgical mortality.

Although this retrospective cohort study extends the results of previous studies suggesting that preoperative statin therapy may be of benefit after major cardiovascular surgery,\textsuperscript{11–13} the present study is not without limitations. First, administration of preoperative statin therapy in our study was neither prospective nor randomized. Despite careful use of regression models to adjust for potential confounders that may affect postoperative outcomes, immeasurable factors may still exist. Physician bias may have influenced patient selection, statin type, and dose. Subsequent randomized clinical trials of statin use in other settings such as acute coronary syndromes (eg, the Myocardial Ischemia Reduction with Acute Cholesterol-Lowering [MIRACL]) trial), although encouraging, have not always confirmed as marked of a reduction in mortality as was seen in early observational studies.\textsuperscript{26,27} Thus, the need for a prospective randomized study of the influence of statin therapy on adverse cardiac surgical outcomes still exists. Second, we were unable to determine the influence of the duration of preoperative statin therapy on the risk of adverse 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.\textsuperscript{7,14,15,17} Finally, this study did not measure or control for the effect of postoperative statin administration.

Conclusion
Preoperative statin therapy may reduce the risk of early mortality after primary CAGB surgery with CPB. Although the mechanism underlying this association remains unclear, further investigation of early statin treatment within cardiac surgical patient populations is warranted.

References
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