Effect of Dose and Timing of Preoperative Statins on Mortality After Coronary Artery Bypass Surgery

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Background. **Preoperative statin administration is associated with reduced mortality risk after a coronary artery bypass graft operation. However, the optimal dose and timing are unknown.**

Methods. **We retrospectively reviewed data from 3,025 primary isolated coronary artery bypass graft surgery patients at our institution. Patients were divided into three groups, according to timing of their preoperative statin: 24 hours or less (n = 1,788), 24 to 72 hours (n = 452), or more than 72 hours before operation or no dose (n = 781). We then grouped patients by preoperative dose: no statin (n = 739), 20 mg or less (n = 920), or more than 20 mg (n = 1,284) atorvastatin or equivalent. Primary outcome was 30-day all-cause postoperative mortality.**

Results. **Thirty-day all-cause mortality was significantly lower for patients taking a statin 24 hours or less preoperatively (1.7%) compared with 24 to 72 hours (2.9%), more than 72 hours, or no dose (3.8%). Multivariate analysis of a propensity-matched cohort showed taking statins 24 hours or less preoperatively was associated with reduced 30-day all-cause mortality (odds ratio 0.52, 95% confidence interval: 0.28 to 0.98, $p = 0.04$) versus more than 24 hours or no dose. For preoperative statin dose, 30-day all-cause mortality was significantly lower when taking 20 mg or less(1.8%) or more than 20 mg atorvastatin or equivalent (2.1%) than when taking none (3.8%). In multivariate analysis of the propensity-matched cohort, more than 20 mg preoperative dose was associated with a 68% reduction of 30-day all-cause mortality (odds ratio 0.32, 95% confidence interval: 0.13 to 0.82, $p = 0.02$) compared with no preoperative statin. However, a 20 mg or less preoperative dose showed no mortality reduction.**

Conclusions. **Both statin use 24 hours or less preoperatively and preoperative statin dose of more than 20 mg were independently associated with decreased 30-day all-cause mortality after coronary artery bypass graft surgery.**

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Since their approval by the Food and Drug Administration in 1987, statins have played a substantial role in the management of cardiovascular disease. Studies have shown decreased cardiovascular mortality for patients with elevated cholesterol who received statin therapy [1, 2]. Several investigations [2–4] have shown that statins can be used for primary prevention of acute cardiovascular events, even for patients with average cholesterol. Such investigations include the Justification for the Use of Statin in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial, which demonstrated the importance of decreasing high-sensitivity C-reactive protein levels with statin therapy [4], suggesting antiinflammatory properties of statin therapy.

Given this knowledge, investigators such as those in the Atorvastatin for Reduction of Myocardial Damage During Angioplasty-Acute Coronary Syndromes (ARMYDA-ACS) trial have evaluated perioperative statin use. These studies revealed that statins reduced mortality or postoperative complications after percutaneous coronary intervention or cardiac surgery [5–12]. Therefore, current guidelines from the European Society of Cardiology, American College of Cardiology, and American Heart Association recommend all patients undergoing coronary artery bypass graft (CABG) operations should receive statin treatment unless contraindicated [13, 14].

Given these findings, it seems reasonable to hypothesize that the timing and dose of statin therapy may affect perioperative outcomes. However, to date there has been little investigation into these nuances of statin therapy. To determine whether preoperative statin dose or timing independently affects 30-day all-cause mortality, we retrospectively reviewed data from 3,025 patients undergoing CABG at our institution. Specifically, we performed a multivariate stepwise logistic regression analysis followed by propensity-based matching, controlling for patient demographics, medications, and perioperative risk factors.

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Patients and Methods

Study Design

In this retrospective cohort study, we reviewed records from 3,025 consecutive patients undergoing primary isolated CABG surgery with cardiopulmonary bypass between July 2005 and May 2011 at the Texas Heart Institute, Catholic Health Initiatives St. Luke's Health-Baylor St. Luke's Medical Center. Patients undergoing redo sternotomy, concomitant valve, or other cardiac procedures, including septal defect repair or ventricular aneurysm repair, were excluded. The study was approved by the Institutional Review Board at Baylor St. Luke's Medical Center.

Patients (n = 3,021) were first grouped according to the timing of their last statin dose before operation: (1) 24 hours or less (n = 1,788); (2) between 24 and 72 hours (n = 452); and (3) more than 72 hours preoperatively or no statin (n = 781). The patients in the group between 24 and 72 hours comprised 398 patients who received a statin 24 to 48 hours before operation and 54 patients who received statins more than 48 hours and 72 hours or less before operation. We excluded 4 patients because the timing of their last statin dose was unknown.

In a separate analysis, we grouped patients (n = 2,943) by statin dose: (1) no statin preoperatively (n = 739); (2) 20 mg or less atorvastatin or equivalent (n = 920); and (3) more than 20 mg atorvastatin or equivalent (n = 1,284). We excluded 82 patients because of incomplete records regarding statin dose. Equivalents to atorvastatin were defined according to Food and Drug Administration recommendations [15].

Data Collection

We obtained information on patient demographics, perioperative risk factors and medications, and 30-day all-cause mortality from the cardiac surgical database at Texas Heart Institute. Preoperative pulmonary disease was defined as a patient having been diagnosed preoperatively with chronic obstructive pulmonary disease, pulmonary embolism or infarction, emphysema, asthma, or tuberculosis. The timing and dose of statins were collected from patients' charts if available. For those admitted to the hospital on the day of operation, we used the preoperative medication questionnaire to obtain the time and dose of statin administered. For those who were inpatients, the nursing administration record was used to gather this information.

Statistical Analysis

All statistical analyses were performed by the Division of Biostatistics and Epidemiology at Texas Heart Institute with the use of SAS statistical software (v9.1; SAS Institute, Cary, NC). Categoric (frequency) variables are expressed as percentages, and continuous variables are expressed as mean ± SD. To determine whether statin timing or dose was independently associated with a reduction in the risk of 30-day all-cause mortality after CABG, we performed multivariate stepwise logistic regressions in the timing-based and dose-based groups. Odds ratio (OR) and corresponding 95% confidence interval (CI) are reported with associated p values.

To further control for selection bias, we created propensity-matched populations for separate analyses using 28 perioperative variables. After successful matching, we performed a multivariate stepwise logistic regression to determine whether statin timing and dose were independently associated with a reduction in the risk of 30-day all-cause mortality after primary CABG surgery.

Results

We grouped 3,025 consecutive patients undergoing primary isolated CABG between July 2005 and May 2011 by timing of administration of preoperative statin: 59% (n = 1,788) had taken a statin 24 hours or less before operation, 15% (n = 452) between 24 and 72 hours preoperatively, and 26% (n = 781) had no statin or took it more than 72 hours before operation. Perioperative demographics and risk factors for patients grouped by statin timing are shown in Table 1.

For patients stratified by preoperative statin timing, the incidence of 30-day all-cause mortality was 3.8% for those not taking statin or whose last dose was more than 72 hours before operation, 2.9% for those who took a statin 24 to 72 hours preoperatively, and 1.7% for those who took a statin 24 hours or less before operation. We found no significant difference among the groups in cardiovascular outcomes such as incidence of postoperative myocardial infarction, stroke, lethal arrhythmias, or cardiac arrest. The 30-day all-cause mortality was 2.5% in 2005 to 2006, 2.4% in 2007 to 2008, and 2.4% in 2009 to 2011.

We then performed multivariate stepwise logistic regression on the same data. Statin administration within 24 hours showed a significant independent mortality benefit (OR 0.38, 95% CI: 0.22 to 0.66, $p < 0.01$; Fig 1). However, last statin administration between 24 and 72 hours preoperatively did not show a significant independent effect on mortality (OR 0.63, 95% CI: 0.31 to 1.29, $p = 0.21$). Other significant independent predictors of mortality included age more than 65 years ($p = 0.03$), being female ($p = 0.02$), anticoagulant use ($p < 0.01$), dialysis ($p < 0.01$), peripheral vascular disease ($p < 0.01$), renal insufficiency ($p < 0.01$), previous myocardial infarction ($p < 0.01$), and history of cancer ($p = 0.03$).

Lastly, to control better for selection bias related to the type of therapy, we used 28 variables to create propensity-matched populations (Table 2). Statin administration 24 hours or less before operation (n = 1,035) versus any other timing or no statin (n = 1,035) significantly decreased 30-day all-cause mortality (OR 0.52, 95% CI: 0.28 to 0.98, $p = 0.04$; Table 3).

For the analysis focusing on the effect of preoperative statin dose on 30-day all-cause mortality, we reviewed the records of the 2,943 patients undergoing elective CABG surgery for whom complete statin dosage was documented. Of these patients, 31% (n = 920) were taking 20 mg or less atorvastatin or equivalent, 44% (n = 1,284)