Impact of Statin Use on Outcomes After Coronary Artery Bypass Graft Surgery

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Background—The benefits of statins have been demonstrated for patients with a remote history of coronary artery bypass grafting (CABG); however, no investigation to date has evaluated whether initiation of statin therapy in the early months after surgery improves clinical outcomes.

Methods and Results—A retrospective cohort of 7503 Medicare patients ≥65 years of age who underwent CABG (1995–2003) was assembled by use of linked hospital and pharmacy claims data. Rates of all-cause mortality and major adverse cardiovascular events were compared between patients who were (n=1745) and were not (n=5788) prescribed statins within 1 month of CABG discharge. Additional analyses evaluated the impact of statin initiation between 1 and 6 months after surgery. Multivariable and propensity score analysis demonstrated that statin use within 1 month of CABG discharge independently reduced the risk of all-cause mortality (adjusted hazard ratio 0.82, 95% confidence interval 0.72 to 0.94) compared with no statin use. Similarly, statin use within 1 month of CABG discharge independently reduced the risk of major adverse cardiovascular events (adjusted hazard ratio 0.89, 95% confidence interval 0.81 to 0.98). Initiation of statin therapy between 1 and 6 months after CABG discharge was also associated with reductions in major adverse cardiovascular events and mortality; however, outcome rates between early (≤1 month after CABG) and delayed (1 to 6 months after CABG) statin initiation were not significantly different.

Conclusions—Statin therapy initiated in the early months after hospital discharge independently reduces all-cause mortality and major adverse cardiovascular events after CABG. These findings validate the widespread practice of prescribing long-term statin therapy after CABG. (***Circulation*. 2008;118:1785-1792.**)

Key Words: coronary disease ■ surgery ■ lipids ■ morbidity ■ mortality

Coronary artery bypass graft surgery (CABG) is an effective treatment for ischemic heart disease; however, the long-term results after CABG are compromised by the progression of atherosclerosis in native coronary arteries and saphenous vein bypass grafts.[1,2] Only 60% of vein grafts remain patent 10 years after surgery, and 50% of those that are patent have clinically important stenosis.[1,2] As a result, patients are at high risk for subsequent ischemic events after CABG, including death, myocardial infarction, and stroke.[1,2]

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Strong evidence is available to support the use of statins to reduce the risk of recurrent cardiovascular events and improve survival in patients with native coronary artery disease[3]; however, less is known about the benefits of statins after CABG. The current American Heart Association/American College of Cardiology secondary prevention clinical guidelines[4] and the National Cholesterol Education Program Adult Treatment Panel III guidelines[5,6] recommend statin treatment to achieve low-density lipoprotein levels <100 mg/dL for all patients with previous CABG. These recommendations are based primarily on the results of the Post-CABG Trial, a study that evaluated aggressive cholesterol treatment with lovastatin 40 mg/d compared with moderate cholesterol treatment with lovastatin 5 mg/d. Published in 1997, the Post-CABG Trial enrolled 1351 low-risk male patients ≤65 years of age who had undergone surgery 1 to 11 years previously. The Post-CABG Trial demonstrated that aggressive cholesterol treatment with lovastatin reduced the progression of vein graft disease and cardiovascular morbidity and mortality.[7–9]

In contrast to the patients enrolled in the Post-CABG Trial, CABG patients in the current era are older, have more coexisting conditions, and are increasingly likely to be

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female.[10] Moreover, the Post-CABG Trial enrolled patients several years after they had undergone surgery (55% of patients had undergone surgery >5 years previously), with saphenous vein graft atherosclerosis likely already in progress.[7] Whether postoperative outcomes are improved by the administration of statins in the early months after coronary surgery has not been investigated specifically. To clarify the role of statin therapy in this context, we conducted a retrospective cohort study of CABG patients in typical practice and compared all-cause mortality and freedom from major adverse cardiovascular events (MACE) in patients who did and did not receive statins within 1 month of hospital discharge after CABG.

Methods

Setting and Design

We assembled the present cohort by linking Medicare files to data from the Pennsylvania Pharmaceutical Assistance Contract for the Elderly (PACE) and the New Jersey Pharmaceutical Assistance to the Aged and Disabled (PAAD) programs. Both PACE and PAAD provide prescription drug benefits to lower-middle-income individuals ≥65 years of age whose yearly earnings are above the threshold to qualify them for Medicaid. Participants pay copayments between $5 and $10 per prescription without any deductibles. The programs cover all medications that require a prescription and do not restrict which medications can be prescribed (ie, the programs do not use formularies, preferred drug lists, or prior authorization programs).

Data from PACE, PAAD, and Medicare were incorporated into a relational database that consisted of data for all filled prescriptions, procedures, physician encounters, hospitalizations, long-term care admissions, and deaths for the patients in the present cohort. These data sources have been used extensively to study population-based health outcomes.[11–13] All traceable person-specific identifying factors were transformed into anonymous coded study numbers to protect subjects' privacy. This study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, Mass.

Cohort

We included patients who were discharged alive from the hospital after undergoing CABG (International Classification of Diseases, 9th Revision codes 36.1x or 36.2x) between January 1, 1995, and December 31, 2003. We excluded patients who died or were readmitted to the hospital within 30 days after CABG discharge, patients who were not active users of either drug benefit program, and patients who received prescriptions for cerivastatin, because this drug was withdrawn from the market. Thirty days after the date of CABG discharge was considered the index date for the study analysis (ie, start of follow-up). Follow-up terminated at December 31, 2004.

Covariates

We determined patient comorbidities by searching physician service claims and hospitalization records for relevant diagnostic codes in the 1-year period before the index date. In this manner, the following characteristics were identified: age at index date, year of surgery, gender, race, length of hospital stay, previous myocardial infarction or acute coronary syndrome, hypertension, diabetes mellitus, congestive heart failure, stroke, peripheral vascular disease, previous CABG, previous percutaneous coronary intervention, chronic kidney disease, and chronic obstructive pulmonary disease. We assessed statin prescription rates (ie, prescriptions that were filled) in the 1-year period before CABG, as well as within 30 days after the CABG discharge date. We also determined the use of the following concurrent medications in the 1-year period before and 30 days after CABG: angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers, β-blockers, calcium channel blockers, fibrates, diuretics, nitrates, digoxin, warfarin, and clopidogrel.

We identified the hospital and surgeon for all CABG procedures. Hospitals that were accredited with the Association of American Medical Colleges were classified as teaching hospitals. All other hospitals were classified as nonteaching hospitals. We classified the "operating surgeon" as the cardiac, cardiothoracic, or thoracic surgeon who submitted a claim for CABG on the date of surgery using Medicare Part B claims. Records that contained invalid provider identification numbers were excluded from further analysis. If 2 or more surgeons were identified for an individual patient, then we defined the most responsible surgeon as the surgeon who submitted the most claims for that specific patient after surgery. The annualized volume of Medicare CABG patients treated by each surgeon was estimated by dividing the total number of Medicare CABG patients for each surgeon during the study time period by the number of years that each surgeon treated 1 or more cases. Surgeons were ranked in order of annualized volume and were then categorized into high-, medium-, and low-volume surgeon tertiles of equal size. The annual volume of the hospital from which each patient was discharged was determined in a similar manner as for surgeon volume, and high-, medium-, and low-volume hospital tertiles were subsequently created.

Statistical Analysis

The 2 outcomes assessed in the present study were freedom from all-cause mortality and freedom from MACE, beginning 30 days after CABG discharge. Event rates were compared between patients who did and did not fill statin prescriptions within 1 month of surgical discharge. MACE was defined as hospital admission for myocardial infarction or unstable angina, stroke, coronary artery revascularization (redo CABG or percutaneous coronary intervention), or out-of-hospital coronary death (death outside of the hospital without previous diagnosis of cancer [International Classification of Diseases, 9th Revision code 140.X to 208.X] or human immunodeficiency virus [International Classification of Diseases, 9th Revision code 042] within 1 month of death). Baseline characteristics between statin users and nonusers were compared with unpaired 2-sided Student t tests, Fisher exact tests, or χ^2 trend tests, as appropriate. Statistical significance was defined as $P<0.05$. Nonparametric estimates of freedom from all-cause mortality and freedom from MACE were determined for statin users and nonusers by the Kaplan-Meier method, and groups were compared with a log-rank test. Patients were censored at the end of follow-up or if they developed the outcome of interest.

Independent predictors of freedom from all-cause mortality and MACE after CABG discharge were identified with multivariable Cox proportional hazards models. Factors of clinical relevance thought to impact postoperative outcomes were incorporated into the models: age, gender, race, year of surgery, peripheral vascular disease, preoperative stroke, previous myocardial infarction or acute coronary syndrome, diabetes mellitus, postoperative β-blocker use, postoperative clopidogrel use, postoperative ACE inhibitor or angiotensin II receptor blocker use, teaching hospital, hospital volume, and surgeon volume. Because the rates of preoperative statin use were markedly different between the 2 patient groups, the multivariable Cox proportional hazards models were stratified on preoperative statin use. We also assessed for possible interactions between preoperative and postoperative statin use in the multivariable Cox proportional hazards models. Hazard ratios (HRs) are reported along with SEs or 95% confidence intervals (CIs). The validity of the Cox proportional hazard model assumptions was assessed in 2 ways. First, an interaction term between time and statin exposure was included in the multivariable models and evaluated for statistical significance. Second, the follow-up time was divided into nonoverlapping 6-month intervals, and interval-specific HRs for the impact of statin treatment on study outcomes were compared. All analyses were performed with SAS version 8.2 (SAS Institute, Cary, NC).

Sensitivity Analysis

To assess the robustness of our results, we repeated our analyses but additionally censored patients if they switched statin medications, changed statin doses, or discontinued statin therapy. We also performed an analysis whereby patients who required long-term care after surgery (rehabilitation or nursing home) were removed from the cohort. Additionally, we performed a propensity score–based analysis in which we calculated each patient's likelihood of receiving a postoperative statin prescription using a logistic regression model that included patient-, surgeon-, and hospital-related characteristics. Patients were then ranked in order of their propensity score and categorized into deciles of equal size. The propensity score deciles were added as categorical variables to the multivariable Cox proportional hazards models described above. To explicitly test whether early statin initiation improved outcome rates compared with slightly delayed statin therapy, we compared patients who initiated statins within 1 month of CABG discharge with those who started statins between 1 and 6 months after discharge. Finally, we performed an analysis with censoring at the end of each year to assess how much follow-up time needed to accrue before statin therapy (within 1 month of CABG discharge) would be associated with statistically significant reductions in mortality and MACE.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results

Patient Cohort

The present study cohort consisted of 7503 patients who underwent CABG between 1995 and 2003. The mean age of the cohort was 75.6±5.4 years, and 65.0% of the patients were women. The majority of patients underwent CABG at teaching hospitals (75.6%), and the mean length of stay after CABG was 8.3±5.7 days. During the 1-year period before CABG surgery, 31.8% of patients received a statin prescription. In contrast, 23.3% of CABG patients were prescribed statins within 1 month of CABG discharge. The median follow-up for the entire cohort was 4.0 years (maximum 9.9 years). Overall, 2324 patients died in the present study cohort, and 3686 patients developed MACE.

Group Characteristics

Table 1 describes the characteristics of the patients who did (n=1745) and did not (n=5788) fill prescriptions for statins within 1 month of CABG discharge. Postoperative statin users were more likely to have received statins before surgery than nonusers ($P<0.0001$). Postoperative statin users were also more likely to have taken other cardiac medications both before and after surgery (all $P<0.05$). Although statin users were more likely to be women and to have diabetes mellitus, nonstatin users were more likely to be older, to have longer hospital stays, and to have preoperative congestive heart failure or chronic obstructive pulmonary disease (all $P<0.05$). Statin users were more likely to have had surgery in recent years ($P<0.0001$), although nonstatin users were more likely to have had surgery at teaching hospitals and at high-volume hospitals (all $P<0.05$). The median follow-up for statin users was 3.4 years; the median follow-up for nonstatin users was 4.4 years.

Impact of Postoperative Statins on Mortality and MACE

Freedom from all-cause mortality at 1, 5, and 9 years in patients who received postoperative statins within 1 month of

Table 1. Baseline Characteristics for Patients Treated With and Without Statins 1 Month After CABG Discharge

Characteristic	Nonstatin Users (n=5758)	Statin Users (n=1745)
Demographics		
Age, mean±SD	75.8±5.4	75.0±5.4*
Women, %	64.4	67.0*
White race, %	93.0	93.1
Comorbid conditions, %		
Prior myocardial infarction	15.8	14.2
Congestive heart failure	50.7	45.3*
Stroke	15.2	13.6
Peripheral vascular disease	6.1	5.7
Hypertension	87.8	92.1*
Diabetes mellitus	46.8	51.9*
Chronic kidney disease	26.1	26.5
Chronic obstructive pulmonary disease	32.4	27.5*
Previous stent/PTCA	9.1	10.1
Preoperative medication use, %		
Prior statin	20.4	69.6*
ACE inhibitor or angiotensin II receptor blocker	38.2	53.4*
Clopidogrel	8.5	19.3*
β-Blocker	51.7	73.9*
Calcium channel blocker	46.7	50.7*
Digoxin	14.6	17.9*
Diuretics	7.0	9.0*
Fibrate	3.4	3.7
Nitrates	50.7	63.1*
Warfarin	10.5	12.5*
Postoperative medication use, %		
ACE inhibitor or angiotensin II receptor blocker	19.5	36.9*
Clopidogrel	2.5	8.9*
β-Blocker	35.9	63.3*
Calcium channel blocker	13.8	17.6*
Digoxin	13.1	18.6*
Diuretics	2.0	4.4*
Fibrate	0.6	0.7
Nitrates	9.8	12.8*
Warfarin	9.4	11.5*
Hospital characteristics		
Teaching hospital, %	76.3	73.4*
Annual volume of hospital, %		
High (≥54 patients/y)	79.9	73.8
Medium (3–53 patients/y)	18.0	23.6*
Low (≤2 patients/y)	2.1	2.7
Annual volume of surgeon, %		
High (≥20 patients/year)	72.4	70.3
Medium (3–19 patients/year)	22.7	24.8
Low (≤2 patients/year)	4.9	4.9
Length of stay, mean±SD, d	8.7±6.2	7.2±3.5*

PTCA indicates percutaneous transluminal coronary angioplasty.
*$P<0.05$.

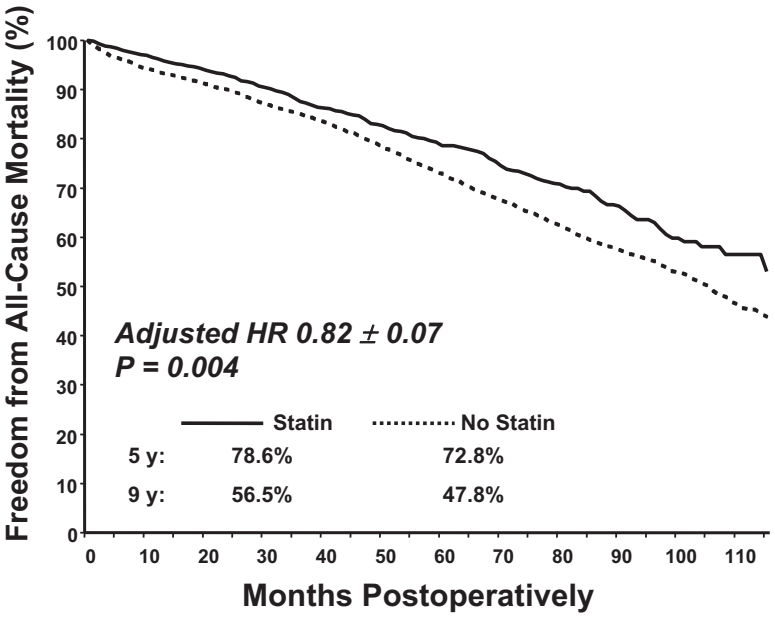

Figure 1. Freedom from all-cause mortality after CABG, stratified by statin use within 1 month of surgery discharge.

surgery discharge was 96.2%, 78.6%, and 56.5%, respectively. Freedom from all-cause mortality at 1, 5, and 9 years among patients who did not receive postoperative statins within 1 month of surgery discharge was 93.5%, 72.8%, and 47.8%, respectively (Figure 1). On univariate analysis, freedom from all-cause mortality was significantly better among patients who received postoperative statins within 1 month of surgery discharge (HR 0.75, 95% CI 0.67 to 0.84). After adjustment for patient-, surgeon-, and hospital-related characteristics in the multivariable analysis, postoperative statin use within 1 month of surgery discharge was independently associated with better freedom from all-cause mortality (HR 0.82, 95% CI 0.72 to 0.94). Other factors independently associated with all-cause mortality are outlined in Table 2. There was no significant interaction term between time and statin use in this analysis ($P=0.43$), and thus the proportional hazards assumption was valid. No significant interaction was found between preoperative and postoperative statin use in the multivariable model for mortality ($P=0.25$).

Freedom from the composite MACE outcome at 1, 5, and 9 years in patients who received postoperative statins within 1 month of surgery discharge was 82.3%, 52.3%, and 34.9%, respectively. Freedom from MACE at 1, 5, and 9 years among patients who did not receive postoperative statins within 1 month of surgery discharge was 81.0%, 47.1%, and 26.7%, respectively (Figure 2). On univariate analysis, freedom from MACE was significantly better among patients who received postoperative statins within 1 month of surgery discharge (HR 0.88, 95% CI 0.81 to 0.95). In the multivariable analysis, postoperative statin use within 1 month of surgery discharge was independently associated with better freedom from MACE (HR 0.89, 95% CI 0.81 to 0.98). Other factors independently associated with MACE are outlined in Table 2. Although a significant interaction was found between time and statin use in this model ($P=0.02$), the interval-specific HRs were virtually identical (ie, <0.001 absolute difference in HRs over a 5-year interval), and therefore, no meaningful violation of the proportional hazards assumption occurred. No significant interaction was present between preoperative and postoperative statin use in the multivariable model for MACE ($P=0.28$).

Sensitivity Analysis

Sensitivity analysis yielded similar results to those presented above (Table 3). After adjustment for propensity scores, postoperative statin use within 1 month of surgery discharge was independently associated with better freedom from all-cause mortality (propensity-adjusted HR 0.77, 95% CI 0.68 to 0.88) and better freedom from MACE (propensity-adjusted HR 0.84, 95% CI 0.76 to 0.93). With removal from the analyses of those patients who were discharged to long-term care facilities after CABG (n=2076), postoperative statin use within 1 month of surgery discharge was associated with nonsignificant trends toward better freedom from all-cause mortality (adjusted HR 0.87, 95% CI 0.75 to 1.02) and better freedom from MACE (adjusted HR 0.92, 95% CI 0.82 to 1.03).

The analysis with yearly censoring led to a diminishing cohort size: 5048 patients at 1 year, 4905 at 2 years, 4706 at 3 years, 4515 at 4 years, 4327 at 5 years, and 4152 at 6 years. At a median follow-up time of 4 years, postoperative statin therapy within 1 month of surgery discharge was associated with nonsignificant trends toward better freedom from all-cause mortality (adjusted HR 0.83, 95% CI 0.67 to 1.03) and better freedom from MACE (adjusted HR 0.90, 95% CI 0.79 to 1.02). After the accrual of 6 years of postoperative follow-up data, the benefit of statin therapy within 1 month of CABG surgery discharge reached statistical significance, with significantly better freedom from all-cause mortality (adjusted HR 0.83, 95% CI 0.70 to 1.00) and better freedom from MACE (adjusted HR 0.89, 95% CI 0.80 to 1.00) at that time point.

Patients who delayed initiation of statins until 1 to 6 months after CABG had a nonsignificant reduction in all-cause mortality (adjusted HR 0.86, 95% CI 0.73 to 1.02) and

Table 2. Predictors of Death and MACE After CABG

Characteristic	HR for Death (95% CI)	HR for MACE (95% CI)
Univariate analysis		
Postoperative statin within 1 month	0.75 (0.67–0.84)	0.88 (0.81–0.95)
Multivariate analysis*		
Postoperative statin within 1 month	0.82 (0.72–0.94)	0.89 (0.81–0.98)
Preoperative characteristics		
Patient age (per additional year)	1.04 (1.04–1.05)	1.01 (1.01–1.02)
Male gender	1.28 (1.17–1.39)	0.88 (0.82–0.94)
White race	1.12 (0.94–1.32)	0.81 (0.71–0.91)
Year of surgery (per additional year)	0.99 (0.97–1.01)	0.98 (0.97–1.00)
Prior myocardial infarction	1.01 (0.90–1.14)	1.16 (1.06–1.27)
Diabetes mellitus	1.52 (1.40–1.65)	1.21 (1.13–1.29)
Peripheral vascular disease	1.72 (1.49–1.98)	1.30 (1.14–1.49)
Congestive heart failure	2.01 (1.84–2.19)	1.40 (1.31–1.50)
Stroke	1.40 (1.26–1.55)	1.57 (1.44–1.71)
Surgeon and hospital characteristics		
Teaching hospital	0.89 (0.80–0.98)	0.99 (0.92–1.07)
Medium-volume vs low-volume hospital	1.13 (0.82–1.55)	1.02 (0.80–1.29)
High-volume vs low-volume hospital	1.06 (0.78–1.45)	1.05 (0.83–1.33)
Medium-volume vs low-volume surgeon	0.94 (0.77–1.13)	0.87 (0.74–1.01)
High-volume vs low-volume surgeon	0.88 (0.73–1.06)	0.83 (0.71–0.96)
Postoperative medications		
Postoperative β-blocker	0.88 (0.81–0.97)	0.95 (0.89–1.02)
Postoperative clopidogrel	0.91 (0.69–1.20)	1.07 (0.88–1.30)
Postoperative ACE inhibitor or angiotensin II receptor blocker	1.14 (1.03–1.25)	1.06 (0.98–1.14)

*Models stratified by preoperative statin use.

a borderline-significant reduction in MACE (adjusted HR 0.88, 95% CI 0.79 to 1.00) compared with statin nonusers. Early statin users ($\leq$1 month after discharge) were nonsignificantly less likely to die (adjusted HR 0.89, 95% CI 0.73 to 1.10) or to have MACE (adjusted HR 0.91, 95% CI 0.79 to 1.05) than patients who began using statins 1 to 6 months after CABG discharge.

Discussion

Clinical trials have consistently demonstrated that statins reduce the risk of recurrent cardiovascular events and improve survival in patients with native coronary artery disease.[3] The benefits of statin treatment appear to be applicable to men and women, as well as to older and younger patients[3]; however, less is known about the benefits of statins after CABG. The current clinical guidelines recommend cholesterol treatment to achieve low-density lipoprotein levels $<$100 mg/dL for all patients after CABG.[4–6,14] These recommendations are based primarily on studies published more than 10 years ago that enrolled low-risk patients several years after surgical coronary revascularization.[7,15] Whether these data are applicable to representative patients who currently present for CABG has not been evaluated recently. Compared with previous years, CABG patients in the current era are older, sicker, and increasingly likely to be women.[10] Moreover, to the best of our knowledge, no study to date has investigated the clinical impact of statin therapy initiated in the early months after CABG.

In the present study of patients discharged from the hospital after CABG, we demonstrated that statin therapy initiated within 1 month of CABG discharge is independently associated with a lower risk of all-cause mortality and MACE, even after adjustment for patient, hospital, and surgeon characteristics. These results support existing practice guidelines and confirm that in the absence of serious contraindications, essentially all patients should be prescribed long-term statin therapy after CABG. Despite the presence of these guidelines, however, we found that few patients receive statin therapy after CABG, in keeping with our earlier work.[12]

Previous clinical trials have evaluated the use of lipid-lowering agents for the prevention of saphenous vein graft disease and adverse cardiovascular events late after CABG. Blankenhorn et al[15,16] published the results of a randomized, placebo-controlled trial in 1987 that investigated the effect of colestipol and niacin therapy on the progression of atherosclerosis. One hundred sixty-two patients with a mean age of 54.2 years were enrolled, on average 3.6 years after CABG. In an era before the routine use of postoperative antiplatelet therapy, this study illustrated that the combination of colestipol and niacin lowered serum low-density lipoprotein levels from 160 to 97 mg/dL ($P<0.001$) and significantly reduced the occurrence of vein graft occlusion by 16% after 2 years of therapy.[15,16] Similar findings were reported by the larger Post-CABG Trial that involved 1351 patients who had surgery 1 to 11 years previously.[7–9] Compared with patients randomized to lovastatin 5 mg/d, patients randomized to lovastatin 40 mg/d had a lower incidence of vein graft occlusive disease and less cardiovascular morbidity and mortality 4 years after randomization.[7–9]

The 2 studies described above enrolled relatively healthy male patients under the age of 65 years who had undergone surgery several years earlier.[7,15] The results of the present study confirm those of the previous trials and extend the benefits of statins to a cohort of patients that is representative of today's CABG population. In contrast to the practice of the randomized trials in which lipid-lowering agents were administered several years after CABG, the present study focused on statin prescription in the early months after surgical revascularization. The present analysis did not find a statistically significant benefit to the initiation of statin therapy within 1 month of CABG discharge compared with starting statin therapy between postoperative months 1 and 6; however, a trend was found in the direction of benefit. Although we had $>$90% power to detect a 9% reduction in the hazard

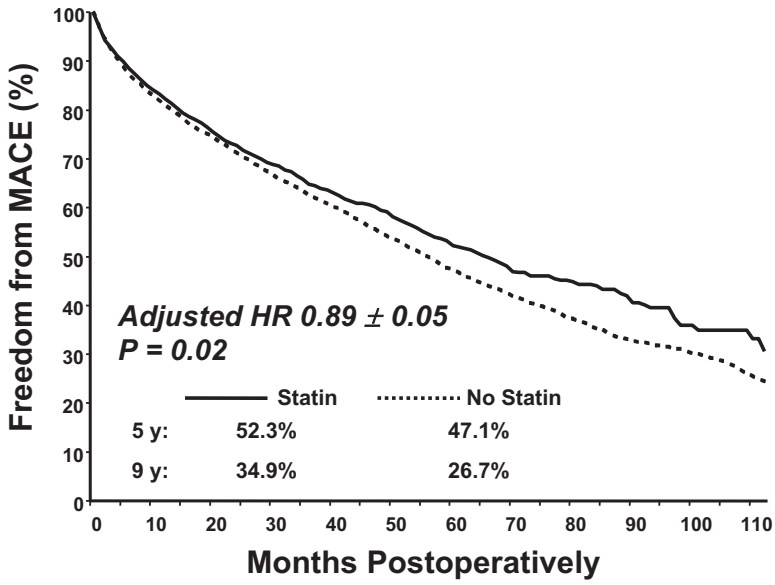

Figure 2. Freedom from MACE after CABG, stratified by statin use within 1 month of surgery discharge.

for mortality or MACE in the primary analysis (entire study cohort), our analyses of early versus delayed statin initiation were underpowered to exclude similarly sized outcome reductions (ie, we had 87% and 70% power to exclude a 9% reduction in the hazard for mortality and MACE analysis, respectively). That being said, the present analysis was sufficiently powered to exclude a 20% reduction in the hazard for mortality and MACE in the comparison of early versus delayed statin initiation. Nevertheless, a delay in statin therapy until several months after hospital discharge may be associated with poorer long-term adherence and may result in fewer patients achieving target low-density lipoprotein levels.[17–20] Moreover, in the present analysis, no statistically significant reduction from statin therapy was seen until 6 years after discharge. This may be related to the development of saphenous vein graft atherosclerosis and occlusion, a process that, although slowed by statin therapy,[7–9] typically manifests clinically 5 to 10 years after CABG.[1,2]

Several investigators have previously demonstrated that preoperative statin therapy improves clinical outcomes after CABG, including a reduced risk of death, myocardial infarction, and arrhythmias in the first 60 days after surgery.[21–24] With a focus on preoperative statin use, none of these studies specifically assessed the use of statins after surgery. In the present analysis, we concentrated on postoperative statin use and adjusted for clinical factors in the multivariable models, including stratification on preoperative statin use. Although preoperative statin use may be important for the reduction of perioperative morbidity,[25] we believe that preoperative statin administration may not directly reduce long-term adverse events after CABG but rather may predict those patients who are more likely to receive statins after surgery.[12]

Table 3. Adjusted HRs for Death and MACE After CABG

Analysis	Adjusted HR for Death (95% CI) for Statin Therapy vs No Statin Therapy	Adjusted HR for MACE (95% CI) for Statin Therapy vs No Statin Therapy
Intention-to-treat analysis*	0.82 (0.72–0.94)	0.89 (0.81–0.98)
Medication change analysis†	0.34 (0.22–0.51)	0.76 (0.64–0.90)
Propensity-matched analysis‡	0.77 (0.68–0.88)	0.84 (0.76–0.93)
Long-term care analysis§	0.87 (0.75–1.02)	0.92 (0.82–1.03)

*Intention-to-treat analysis with censoring at the time of outcome or at the end of follow-up (as in Table 2).

†Medication change analysis with censoring of patients upon statin discontinuation, switching of statins, statin dose change, and at the time of outcome or the end of follow-up.

‡Propensity-matched analysis with propensity score deciles added as categorical variables to the multivariable Cox proportional hazards models.

§Patients who required long-term care after surgery (rehabilitation or nursing home) were removed from the cohort for this analysis.

Additional findings of the present study include the association of postoperative β-blocker therapy with lower rates of all-cause mortality and the association of postoperative angiotensin-converting enzyme inhibitors or angiotensin II receptor blocker with higher rates of all-cause mortality. In the only randomized controlled trial to evaluate the long-term use of β-blocker therapy after CABG, the MACB (Metoprolol After Coronary Bypass) study demonstrated that 100 mg of metoprolol twice per day for 2 years after surgery did not reduce the incidence of repeat revascularization, unstable angina, nonfatal myocardial infarction, or death compared with placebo.[26] Two randomized, controlled trials have studied the use of ACE inhibitors after CABG. The QUO VADIS (Quinapril on Clinical Outcome After Coronary Artery Bypass Grafting) study of 149 patients documented a reduction in the composite outcome of angina, death, myocardial infarction, repeat revascularization, stroke, or transient ischemic attacks in patients who received quinapril for 1 year after CABG compared with placebo (3.5% versus 15%, quinapril versus placebo, $P=0.02$).[27] However, these findings were not confirmed in the larger multicenter IMAGINE (Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting Enzyme) trial of 2204 patients, which showed quinapril to have no benefit compared with placebo when administered after CABG.[28,29]

The present results should be interpreted in the context of several limitations. First, this research focused specifically on

elderly patients enrolled in Medicare and the PACE and PAAD prescription drug benefit plans. Because the average age of CABG patients in the present cohort was 75.6 years, and 65% of patients were female, our results may not be generalizable to patients with other demographic or clinical characteristics. Second, the administrative data used do not contain information on over-the-counter medication such as aspirin use, detailed clinical information such as cholesterol levels, or the reasons for physicians' prescription choices. As an example, statins may have been prescribed preferentially to patients with higher baseline cholesterol levels. Despite the statistical adjustments applied to control for potential selection bias (including propensity score analysis), it is possible that unmeasured or unknown confounders may have influenced the results. For instance, statin users could have been systematically healthier or more health-seeking than patients who did not receive statins, and thus, the results of the present study could be biased by the "healthy user effect."[30] This may have been a factor explaining the lack of statistical significance for postoperative statin use in the multivariable models once we excluded from the analyses those patients who were discharged to long-term care facilities; however, the HR point estimates in this analysis were similar to those obtained from our other models. Moreover, the above finding could simply reflect insufficient statistical power after the exclusion of the 2076 patients discharged to long-term care facilities. Finally, the present study is limited by the lack of power to fully assess the impact of initiating statins early after surgery (within 1 month of CABG discharge) compared with delayed administration (1 to 6 months after discharge).

In summary, statin therapy initiated within the first few months after hospital discharge independently reduces all-cause mortality and MACE after CABG. These results confirm those of earlier studies within a contemporary surgical population and support the current clinical guidelines. Although it appears that statins are underutilized after surgical coronary revascularization, the present findings endorse the view that essentially all patients should be prescribed long-term statin therapy after CABG.

Disclosures

None.

References

1. Fitzgibbon GM, Kafka HP, Leach AJ, Keon WJ, Hooper GD, Burton JR. Coronary bypass graft fate and patient outcome: angiographic follow-up of 5,065 grafts related to survival and reoperation in 1,388 patients during 25 years. *J Am Coll Cardiol*. 1996;28:616–626.
2. Motwani JG, Topol EJ. Aortocoronary saphenous vein graft disease: pathogenesis, predisposition, and prevention. *Circulation*. 1998;97:916–931.
3. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A, Sourjina T, Peto R, Collins R, Simes R. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet*. 2005;366:1267–1278.
4. Smith SC Jr, Allen J, Blair SN, Bonow RO, Brass LM, Fonarow GC, Grundy SM, Hiratzka L, Jones D, Krumholz HM, Mosca L, Pasternak RC, Pearson T, Pfeffer MA, Taubert KA. AHA/ACC guidelines for secondary prevention for patients with coronary and other atherosclerotic vascular disease: 2006 update: endorsed by the National Heart, Lung, and Blood Institute. *Circulation*. 2006;113:2363–2372.
5. Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA*. 2001;285:2486–2497.
6. Grundy SM, Cleeman JI, Merz CN, Brewer HB Jr, Clark LT, Hunninghake DB, Pasternak RC, Smith SC Jr, Stone NJ. Implications of recent clinical trials for the National Cholesterol Education Program Adult Treatment Panel III guidelines. *Circulation*. 2004;110:227–239.
7. The Post Coronary Artery Bypass Graft Trial Investigators. The effect of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation on obstructive changes in saphenous-vein coronary-artery bypass grafts. *N Engl J Med*. 1997;336:153–162.
8. White CW, Gobel FL, Campeau L, Knatterud GL, Forman SA, Forrester JS, Geller NL, Herd JA, Hickey A, Hoogwerf BJ, Hunninghake DB, Rosenberg Y, Terrin ML. Effect of an aggressive lipid-lowering strategy on progression of atherosclerosis in the left main coronary artery from patients in the Post Coronary Artery Bypass Graft Trial. *Circulation*. 2001;104:2660–2665.
9. Knatterud GL, Rosenberg Y, Campeau L, Geller NL, Hunninghake DB, Forman SA, Forrester JS, Gobel FL, Herd JA, Hickey A, Hoogwerf BJ, Terrin ML, White C; Post CABG Investigators. Long-term effects on clinical outcomes of aggressive lowering of low-density lipoprotein cholesterol levels and low-dose anticoagulation in the post coronary artery bypass graft trial. *Circulation*. 2000;102:157–165.
10. Ferguson TB Jr, Hammill BG, Peterson ED, DeLong ER, Grover FL. A decade of change–risk profiles and outcomes for isolated coronary artery bypass grafting procedures, 1990–1999: a report from the STS National Database Committee and the Duke Clinical Research Institute. Society of Thoracic Surgeons. *Ann Thorac Surg*. 2002;73:480–489.
11. Choudhry NK, Levin R, Winkelmayer WC. Statins in elderly patients with acute coronary syndrome: an analysis of dose and class effects in typical practice. *Heart*. 2007;93:945–951.
12. Kulik A, Levin R, Ruel M, Mesana TG, Solomon DH, Choudhry NK. Patterns and predictors of statin use after coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. 2007;134:932–938.
13. Solomon DH, Schneeweiss S, Glynn RJ, Kiyota Y, Levin R, Mogun H, Avorn J. Relationship between selective cyclooxygenase-2 inhibitors and acute myocardial infarction in older adults. *Circulation*. 2004;109:2068–2073.
14. Smith SC Jr, Blair SN, Bonow RO, Brass LM, Cerqueira MD, Dracup K, Fuster V, Gotto A, Grundy SM, Miller NH, Jacobs A, Jones D, Krauss RM, Mosca L, Ockene I, Pasternak RC, Pearson T, Pfeffer MA, Starke RD, Taubert KA. AHA/ACC scientific statement: AHA/ACC guidelines for preventing heart attack and death in patients with atherosclerotic cardiovascular disease: 2001 update: a statement for healthcare professionals from the American Heart Association and the American College of Cardiology. *Circulation*. 2001;104:1577–1579.
15. Blankenhorn DH, Nessim SA, Johnson RL, Sanmarco ME, Azen SP, Cashin-Hemphill L. Beneficial effects of combined colestipol-niacin therapy on coronary atherosclerosis and coronary venous bypass grafts. *JAMA*. 1987;257:3233–3240.
16. Blankenhorn DH, Alaupovic P, Wickham E, Chin HP, Azen SP. Prediction of angiographic change in native human coronary arteries and aortocoronary bypass grafts: lipid and nonlipid factors. *Circulation*. 1990;81:470–476.
17. Fonarow GC, Gawlinski A, Moughrabi S, Tillisch JH. Improved treatment of coronary heart disease by implementation of a Cardiac Hospitalization Atherosclerosis Management Program (CHAMP). *Am J Cardiol*. 2001;87:819–822.
18. Simpson E, Beck C, Richard H, Eisenberg MJ, Pilote L. Drug prescriptions after acute myocardial infarction: dosage, compliance, and persistence. *Am Heart J*. 2003;145:438–444.
19. Butler J, Arbogast PG, BeLue R, Daugherty J, Jain MK, Ray WA, Griffin MR. Outpatient adherence to beta-blocker therapy after acute myocardial infarction. *J Am Coll Cardiol*. 2002;40:1589–1595.
20. Muhlestein JB, Horne BD, Bair TL, Li Q, Madsen TE, Pearson RR, Anderson JL. Usefulness of in-hospital prescription of statin agents after angiographic diagnosis of coronary artery disease in improving continued compliance and reduced mortality. *Am J Cardiol*. 2001;87:257–261.
21. Dotani MI, Elnicki DM, Jain AC, Gibson CM. Effect of preoperative statin therapy and cardiac outcomes after coronary artery bypass grafting. *Am J Cardiol*. 2000;86:1128–1130, A6.
22. Pan W, Pintar T, Anton J, Lee VV, Vaughn WK, Collard CD. Statins are associated with a reduced incidence of perioperative mortality after

coronary artery bypass graft surgery. *Circulation*. 2004;110(suppl II):II-45–II-49.
23. Clark LL, Ikonomidis JS, Crawford FA Jr, Crumbley A III, Kratz JM, Stroud MR, Woolson RF, Bruce JJ, Nicholas JS, Lackland DT, Zile MR, Spinale FG. Preoperative statin treatment is associated with reduced postoperative mortality and morbidity in patients undergoing cardiac surgery: an 8-year retrospective cohort study. *J Thorac Cardiovasc Surg*. 2006;131:679–685.
24. Collard CD, Body SC, Shernan SK, Wang S, Mangano DT. Preoperative statin therapy is associated with reduced cardiac mortality after coronary artery bypass graft surgery. *J Thorac Cardiovasc Surg*. 2006;132:392–400.
25. Liakopoulos OJ, Choi YH, Haldenwang PL, Strauch J, Wittwer T, Dorge H, Stamm C, Wassmer G, Wahlers T. Impact of preoperative statin therapy on adverse postoperative outcomes in patients undergoing cardiac surgery: a meta-analysis of over 30 000 patients. *Eur Heart J*. 2008;29:1548–1559.
26. The MACB Study Group. Effect of metoprolol on death and cardiac events during a 2-year period after coronary artery bypass grafting. *Eur Heart J*. 1995;16:1825–1832.
27. Oosterga M, Voors AA, Pinto YM, Buikema H, Grandjean JG, Kingma JH, Crijns HJ, van Gilst WH. Effects of quinapril on clinical outcome after coronary artery bypass grafting (the QUO VADIS Study): QUinapril on Vascular Ace and Determinants of Ischemia. *Am J Cardiol*. 2001;87:542–546.
28. Warnica JW, Gilst WV, Baillot R, Johnstone D, Block P, Myers MG, Chocron S, Ave SD, Martineau P, Rouleau JL. Ischemia Management with Accupril post bypass Graft via Inhibition of angiotensin coNverting enzyme (IMAGINE): a multicentre randomized trial: design and rationale. *Can J Cardiol*. 2002;18:1191–1200.
29. Cleland JG, Coletta AP, Lammiman M, Witte KK, Loh H, Nasir M, Clark AL. Clinical trials update from the European Society of Cardiology meeting 2005: CARE-HF extension study, ESSENTIAL, CIBIS-III, S-ICD, ISSUE-2, STRIDE-2, SOFA, IMAGINE, PREAMI, SIRIUS-II and ACTIVE. *Eur J Heart Fail*. 2005;7:1070–1075.
30. Brookhart MA, Patrick AR, Dormuth C, Avorn J, Shrank W, Cadarette SM, Solomon DH. Adherence to lipid-lowering therapy and the use of preventive health services: an investigation of the healthy user effect. *Am J Epidemiol*. 2007;166:348–354.

CLINICAL PERSPECTIVE

Strong evidence is available to support the use of statins to reduce the risk of recurrent cardiovascular events in patients with native coronary artery disease; however, less is known about the benefits of statins after coronary artery bypass grafting (CABG). Previous randomized controlled trials investigating cholesterol reduction after CABG enrolled relatively healthy male patients <65 years of age who had undergone surgery several years earlier; however, CABG patients in the current era are older, have more coexisting conditions, and are increasingly likely to be women. We sought to clarify the role of statin therapy in this context and conducted a retrospective cohort study of 7503 CABG patients ≥65 years old who had and had not received statins within 1 month of hospital discharge after CABG. Our primary outcomes were all-cause mortality and freedom from major adverse cardiovascular events. Multivariable and propensity score–adjusted analysis demonstrated that statin use within 1 month of CABG discharge independently reduced the risk of all-cause mortality (adjusted hazard ratio 0.82, 95% confidence interval 0.72 to 0.94) and major adverse cardiovascular events (adjusted hazard ratio 0.89, 95% confidence interval 0.81 to 0.98) compared with nonuse. Thus, early statin therapy independently improved postoperative outcomes, and these results confirm those of earlier studies within a contemporary surgical population. Our findings endorse the view that essentially all patients should be prescribed long-term statin therapy after CABG.

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