Continuative statin therapy after percutaneous coronary intervention improves outcome in coronary bypass surgery: A propensity score analysis of 2501 patients

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Objectives: A history of percutaneous coronary intervention increases the risk of death and complications of coronary artery bypass grafting. This retrospective multicenter study evaluated the impact of continuative use of statin on postoperative outcomes when subsequent elective coronary artery bypass grafting is required after percutaneous coronary intervention.

Methods: Among 14,575 patients who underwent isolated first-time coronary artery bypass grafting between January 2000 and December 2010, 2501 who had previous percutaneous coronary intervention with stenting and fulfilled inclusion criteria were enrolled. Continuative statin therapy was used in 1528 patients and not used in 973 patients. Logistic multiple regression and propensity score analyses were used to assess the risk-adjusted impact of statin therapy on in-hospital mortality and major adverse cardiac events. The Cox proportional hazards model was constructed to assess the effect of continuative statin therapy on 24-month outcome.

Results: At multivariate analysis, age more than 70 years, 3-vessel or 2-vessel plus left main coronary disease, multivessel percutaneous coronary intervention, ejection fraction 0.40 or less, diabetes mellitus, and logistic European System for Cardiac Operative Risk Evaluation 5 or greater were independent predictors of hospital mortality and major adverse cardiac events. After propensity score matching, conditional logistic regression analysis demonstrated that continuative statin therapy before coronary artery bypass grafting reduced the risk for hospital and 2-year mortality (odds ratio [OR], 0.27; 95% confidence interval [CI], 0.12-0. 57; $P = .004$ and OR, 0.6; 95% CI, 0.36-0.96; $P = .04$, respectively) and major adverse cardiac events (OR, 0.31; 95% CI, 0.18-0.78; $P = .003$ and OR, 0.5; 95% CI, 0.34-0.76; $P = .006$, respectively).

Conclusions: Long-term statin treatment after percutaneous coronary intervention improves early and midterm outcome when surgical revascularization will be required. (J Thorac Cardiovasc Surg 2014;148:1876-83)

See related commentary on pages 1884-6.

Recent studies indicate that 10% to 30% of the patients treated by percutaneous coronary intervention (PCI) for multivessel coronary disease require repeated coronary revascularization because of symptom recurrence and restenosis within 2 to 4 years after primary intervention.[1,2] When a subsequent coronary artery bypass grafting (CABG) is necessary, a history of PCI is associated with a higher incidence of perioperative adverse events.[3-7] Thus, in the setting of these high-risk patients, novel technical and pharmacologic strategies are required.

Recent guidelines suggest antiplatelet therapy for primary and secondary prevention before and after implantation of stents or in surgical patients to improve vein-graft patency after CABG.[8-11] Furthermore, robust evidence supports the early and aggressive therapy with inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase statins to reduce cardiovascular adverse events and repeat revascularization procedures after PCI.[12] In patients undergoing CABG, statin therapy exerts multiple pleiotropic effects associated with reduction of myocardial damage and better surgical results.[13-17] This overall efficacy of statins is reflected in the latest American College of Cardiology/American Heart Association guidelines. However, the effect of statin on postoperative outcome of patients with a history of PCI, subsequently referred to CABG, has not been evaluated until now.

Because of the important clinical implications, this study evaluated the impact of continuative statin treatment on early and midterm cardiac mortality and nonfatal major adverse cardiac events (MACE) in those patients who are finally referred to elective CABG after previous PCI by stenting.

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Abbreviations and Acronyms

CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
MACE = major adverse cardiac events
MI = myocardial infarction
NO = nitric oxide
OR = odds ratio
PCI = percutaneous coronary intervention

PATIENTS AND METHODS

The study was a retrospective multicenter cohort study designed according to the STROBE statement. Among a total of 14,575 patients who underwent first-time isolated CABG between January 2000 and February 2010, 2051 consecutive patients previously treated by PCI by stenting were evaluated. Additional cardiac procedures and urgent or emergency CABG were exclusion criteria. Patients were classified depending on whether they received (statin group) or did not receive (no statin group) continuous treatment with any kind of statins during the period between PCI and CABG surgery. Types of statin used and the usual dosages were as follows: atorvastatin 20 to 40 mg/d, rosuvastatin 10 to 20 mg/d, simvastatin 20 to 40 mg/d, pravastatin 20 to 40 mg/d, and fluvastatin 20 to 40 mg/d. All patients with suspected low adherence to statin therapy during the last 6 months before CABG were excluded. Adherence to therapy was assessed by rates of prescription refills as reported by Osterberg and Blaschke.[18] We measured statin adherence as the proportion of days covered. We defined patients as being "adherent" if the proportion of days covered was 80% or more. Change from one statin to another was considered adherence with therapy. A total of 1528 patients treated by continuative statin therapy were identified and compared with 973 patients who did not receive continuative statin treatment after PCI. In the statin group, the overall proportion of days covered was 86.4%.

All patients underwent preoperative coronary angiography. Risk stratification was assessed by the logistic European System for Cardiac Operative Risk Evaluation. Low-density lipoprotein levels before the operation were 120 ± 28 mg/dL in the statin group and 159 ± 39 mg/dL in the no statin group ($P < .001$). The main demographic and clinical characteristics of the patients are shown in Table 1.

Troponin I values, assessed preoperatively, and at 8 and 12 hours after operation, and then on every postoperative day until hospital discharge, were collected as markers of myocardial damage. The dose of inotropic support, when required, was considered indicative of postoperative outcome. To avoid bias due to the different duration of follow-up, the last time point for postoperative evaluation was fixed at 24 postoperative months in all patients.

The study protocol was approved by the ethics committee of the University of Naples Federico II. All patients preliminarily granted permission for the use of their medical records for research purposes; thus, individual patient consent was waived for this study.

Perioperative Management

Patients receiving antiplatelet therapy before surgery were managed in accordance with the 2011 American College of Cardiology Foundation/American Heart Association Guideline for Coronary Artery Bypass Graft Surgery.[19] Standardized dual antiplatelet therapy was started when chest tube drainage was less than 20 mL/h.[9] Statins were given 24 hours after surgery and continued over all follow-up time in all patients.[16]

Outcome Measures and Definitions

The end points were (1) hospital mortality and major adverse cardiac events (MACE) and (2) 2-year mortality and MACE.

Hospital mortality was defined as death within 30 days or at any time after operation if the patient did not leave the hospital alive. MACE were defined as a composite end point of nonfatal perioperative myocardial infarction (MI), low output syndrome, significant cardiac arrhythmias, and need for repeat surgical or percutaneous revascularization.

Perioperative acute MI was diagnosed when the criteria indicated by the Joint European Society of Cardiology/American College of Cardiology Foundation/American Heart Association/World Heart Federation Task Force for the Universal Definition of Myocardial Infarction guidelines were fulfilled.[20] Troponin I leakage without electrocardiographic modifications, new loss of viable myocardium, and new regional wall motion abnormality were considered as myocardial damage.[16] Postoperative renal disease was defined as serum creatinine 2.5 mg/dL or greater. Low output syndrome was diagnosed as previously described.[21] High-dose inotropic support was defined when 7 $\mu g \cdot kg^{-1} \cdot min^{-1}$ or greater of dopamine or any dose of adrenaline was added.

Statistical Analysis

Descriptive statistics were summarized for categoric variables as percentages and compared using the chi-square exact test. Univariate logistic regressions were performed to identify preoperative independent predictors for hospital mortality and MACE based on the preoperative variables mentioned in Table 1. Multivariate logistic regression model included those variables with a probability value of .05 or less for association with at least 1 study end point.

To eliminate confounding bias due to unequal distribution of risk factors among groups, propensity score was performed to generate a subset of matched cases (statin therapy) and controls (no statin therapy) who had the same distribution of covariates. SAS/STAT logistic procedure and a SAS %GMATCH Macro program (SAS Institute Inc, Cary, NC) were used to match cases to controls. Variables listed in Table 1 were used to build a fully adjusted multivariable logistic regression model to compute a propensity score for each patient. The cases were matched with controls to create a 1-to-1 match. Matching was done without replacement, based on caliper matching within a prespecified distance of a maximum of 0.2 of the standard deviation of the logit of the propensity score. If more than 1 control matched equally to 1 case, the control was selected at random.

Comparisons between the 2 groups were performed by the chi-square test to confirm that the 2 groups were successfully matched. The c statistic was 0.89, indicating the good discriminatory power of the propensity model. Hospital mortality and MACE were compared between the 2 matched groups by the 2-tailed McNemar test. Multi-way analysis of variance with correction for serial measurements analyzed troponin I, inotropic support, and postoperative creatinine levels. A Cox proportional hazards model was constructed using the variables reported in Table 1 to evaluate the effect of continuative statin therapy on 24-month survival and MACE. All statistical analyses were performed with the SAS system, version 9.1 (SAS Institute Inc) or SPSS version 13.0 for Windows (SPSS Inc, Chicago, Ill).

RESULTS

All 2501 patients underwent CABG at a median of 38 months (interquartile range, 29-48) after a mean of 1.9 angioplasties by stenting. A total of 1211 patients (48.4%) underwent operation with cardiopulmonary bypass (CPB), and 1290 patients (51.6%) underwent operation off-pump. In patients who underwent on-pump CABG, mean CPB and mean aortic crossclamp times were 83.5 ± 25.2 minutes and 43.2 ± 13.2 minutes,