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Lipid-lowering effect of preoperative statin therapy on postoperative major adverse cardiac events after coronary artery bypass surgery

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Objective: Statins are powerful lipid-lowering drugs that have been proved effective in the prevention of coronary artery disease, clearly reducing the risk of mortality and cardiovascular events. Whether hyperlipidemic patients undergoing coronary artery bypass grafting profit from the lipid-lowering beneficial effects of statins is as yet uncertain. We sought to determine whether preoperative statin therapy may have an effect on outcome among hyperlipidemic patients undergoing coronary artery bypass grafting.

Methods: From January 2000 through March 2006, prospectively recorded clinical data from 3346 consecutive patients undergoing isolated first-time elective coronary artery bypass grafting were analyzed for major adverse cardiac events and all-cause in-hospital mortality. Of these, 167 patients had preoperative statin-untreated hyperlipidemia (group 1), 2592 had statin-treated hyperlipidemia (group 2), and 587 had statin-untreated normolipidemia (group 3).

Results: Risk-adjusted multivariate logistic regression analysis revealed statin-treated hyperlipidemia (odds ratio, 0.42; 95% confidence interval, 0.26-0.69; $P = .0007$) and statin-untreated normolipidemia (odds ratio, 0.42; confidence interval, 0.26-0.69; $P = .0007$) to be independently associated with reduced in-hospital major adverse cardiac events but not with in-hospital mortality. To further control for selection bias, a computed propensity score matching based on 14 major preoperative risk factors was performed. After propensity matching, conditional logistic regression analysis confirmed statin-treated hyperlipidemia and statin-untreated normolipidemia to be strongly related to reduced in-hospital major adverse cardiac events (odds ratio, 0.41; 95% confidence interval, 0.24–0.71 [$P = .0013$] and odds ratio, 0.23; 95% confidence interval, 0.11–0.48 [$P = .0001$]) but not with in-hospital mortality (odds ratio, 1.18; 95% confidence interval, 0.36–3.87 [$P = .79$] and odds ratio, 1.10; 95% confidence interval, 0.32–4.41 [$P = .80$]) after coronary artery bypass grafting surgery.

Conclusions: Hyperlipidemic, but not normolipidemic, patients have an increased risk for in-hospital major adverse cardiac events and therefore clearly benefit from preoperative statin therapy before coronary artery bypass grafting surgery.

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Hyperlipidemia is known as one of the major risk factors associated with vascular endothelial injury, causing atherosclerotic plaque formation and coronary artery disease (CAD) that result in recurrent ischemic cardiovascular events.[1] Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase, statins, are recognized as powerful lipid-lowering drugs that have been proved highly effective in primary and secondary prevention of CAD, decreasing low-density lipoprotein cholesterol (LDL-C) levels and thereby reducing the risk of mortality and cardiovascular adverse events in hyperlipidemic and normocholester-

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Abbreviations and Acronyms
CAD = coronary artery disease
CI = confidence interval
LCOS = low cardiac output syndrome
LDL-C = low-density lipoprotein cholesterol
MACE = major adverse cardiac event
PMI = perioperative myocardial infarction
OR = odds ratio

olemic patients.[2] In terms of surgical intervention, preoperative statin therapy has recently been shown to reduce the risk of early mortality in noncardiac[3-5] and cardiac[6-9] operations, suggesting early beneficial effects of statin treatment, irrespective of hyperlipidemia. To further differentiate lipid-dependent early beneficial statin effects, we sought to determine whether preoperative statin therapy might be associated with a reduced risk of postoperative death or major adverse cardiac events (MACEs) in patients with hyperlipidemia undergoing CABG and whether statin-untreated normolipidemic patients might have in turn an increased risk for postoperative death and MACEs after CABG.

Materials and Methods

Study Design

This study was a retrospective single-center cohort study including 3346 consecutive patients who underwent first-time isolated elective CABG at the West German Heart Center Essen between January 2000 and March 2006. Patients were included in and classified into one of 3 groups, depending on whether they had statin-untreated hyperlipidemia (group 1), statin-treated hyperlipidemia (group 2), or statin-untreated normolipidemia (group 3) before CABG surgery. The most recent levels of total cholesterol, LDL-C, high-density lipoprotein cholesterol, and triglyceride in serum within 1 month before surgical intervention were recorded. Hyperlipidemia was defined as a serum total cholesterol level of 200 mg/dL or greater and/or a low-density lipoprotein level of 130 mg/dL or greater and/or use of lipid-lowering statin therapy with a history of hyperlipidemia. Preoperative statin therapy consisted of one the following statins before CABG: pravastatin, simvastatin, fluvastatin, atorvastatin, cerivastatin, or lovastatin. Surgical revascularization was routinely performed as previously described[10] in all patients by using a median sternotomy, a standard CPB technique with ascending aortic and 2-stage venous cannulation, mild hypothermia (>32°C), and cold crystalloid cardioplegic arrest. Off-pump coronary operations, emergency or urgent surgical intervention, previous myocardial infarction (<4 weeks) before CABG, reoperative procedures, or concomitant operations were the exclusion criteria. The institutional review board approved the study. All of the patients had previously granted permission for use of their medical records for research purposes.

Data Collection

Data used in this analysis were retrieved from the West German Heart Center cardiovascular surgical database. This database prospectively collects a comprehensive list of prespecified data points, with more than 1800 data items per patient for all of the consecutive patients undergoing CABG surgery at our institution, including demographic, clinical, and outcome data. Within the database, patients were coded as having statin-untreated hyperlipidemia, statin-treated hyperlipidemia, or statin-untreated normolipidemia.

Outcome Measures

All outcome measures used in this analysis were prespecified. Given the subject nature of many clinical outcomes, we only prespecified all-cause in-hospital mortality after CABG as the primary study end point. The prespecified secondary end point was the MACE rate, including sudden cardiac death, cardiac death, low cardiac output syndrome (LCOS), and perioperative myocardial infarction (PMI), during the postoperative hospitalization period. An independent review of the medical records of the patients who died after CABG operations was performed, and cardiac versus noncardiac cause of death was adjudicated.

Definitions

In-hospital death was defined as death after CABG during the index hospitalization. A PMI was considered to have occurred if one of the following diagnostic criteria were present: (1) a cardiac troponin I level of greater than 10.5 ng/mL after CABG, as previously described[11]; (2) a creatine kinase–MB level 3 times greater than the upper normal level; (3) new persistent ST-segment or T-wave changes (Minnesota code 4-1, 4-2, 5-1, 5-2, or 9-2); or (4) the development of new Q-waves (Minnesota code 1-1-1 to 1-2-7). LCOS was supposed with a cardiac index of less than 2.0 $L \cdot min^{-1} \cdot m^{-2}$ or a systolic arterial pressure of less than 90 mm Hg, despite high-dose inotropic support (intravenous dopamine, ≥ 8 $\mu g \cdot kg^{-1} \cdot min^{-1}$; dobutamine, ≥ 6 $\mu g \cdot kg^{-1} \cdot min^{-1}$; epinephrine, >0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$; or norepinephrine, >0.1 $\mu g \cdot kg^{-1} \cdot min^{-1}$). Death was considered cardiac if it was caused by PMI, significant cardiac arrhythmias, or refractory LCOS. Sudden unexpected death occurring without another explanation was defined as sudden cardiac death.

Statistical Analysis

Descriptive statistics are summarized for categoric variables as frequencies (percentages) and compared between groups by using the Pearson χ^2 exact test. Continuous variables, expressed as means $\pm$ standard deviations or as medians (interquartile ranges), were compared between groups by using the Kruskal–Wallis test. When a significant overall effect was detected, 2 group comparisons were performed with the Fisher exact test or the Mann–Whitney *U* test. Univariate and multivariate logistic regression were performed to identify preoperative independent predictors for in-hospital mortality and MACEs. Those variables identified by means of univariate regression analysis with a *P* value of .05 or less for at least 1 study end point were added to the multivariate logistic regression model. Propensity score matching was performed to control for selection bias as a result of nonrandom assignment to the 3 groups.[12] The propensity scores were calculated separately, comparing group 1 versus group 2 and group 1 versus group 3. The following patient characteristics and major preoperative risk factors were used to calculate propensity scores: age, sex, diabetes, hypertension, hyperlipidemia, left ventricular