Effect of rosuvastatin pretreatment on myocardial damage after coronary surgery: A randomized trial

Vito A. Mannacio, MD,[a] Domenico Iorio, MD,[a] Vincenzo De Amicis, MD,[a] Francesco Di Lello, MD,[a] and F. Musumeci, MD[b]

Objective: Myocardial disease without evidence of myocardial infarction is a frequent complication after cardiac surgery during cardiopulmonary bypass. Statins might be protective, but their efficacy has not been established in randomized trials.

Methods: Two hundred patients undergoing coronary surgery were enrolled. They were randomized to rosuvastatin (20 mg/d, n = 100) or placebo (n = 100) starting 1 week before the operation. Troponin I, myoglobin, creatine kinase–MB mass, and high-sensitivity C-reactive protein were used as markers of myocardial injury, and their values were determined at baseline and at regular intervals after the operation. Electrocardiography and echocardiography were performed before and after the operation.

Results: Myocardial disease was diagnosed when troponin I, myoglobin, and creatine kinase–MB mass values were above the upper normal limit without evidence of electrocardiographic changes, echocardiographic changes, or both. The percentages of marker level increase indicative of myocardial disease were determined in the placebo versus statin groups and were as follows: troponin I, 35% versus 65% ($P < .0001$); myoglobin, 39% versus 72% ($P < .0001$); creatine kinase–MB mass, 22% versus 40% ($P = .0002$). Peak postoperative values of troponin I (0.16 ± 0.15 vs 0.32 ± 0.26 ng/mL, $P = .0008$), myoglobin (72.25 ± 25 vs 98.31 ± 31 ng/mL, $P < .0001$), and creatine kinase–MB mass (3.9 ± 3.3 vs 9.3 ± 8.1 ng/mL, $P < .0001$) were significantly higher in the placebo group. High-sensitivity C-reactive protein values were increased in 58% of pretreated versus 88% of the control patients (15.4 ± 2.5 vs 17.2 ± 3.4 mg/L, $P < .0001$). In high-risk patients myocardial disease was observed more frequently but significantly less in statin-pretreated patients.

Conclusions: Statin pretreatment reduces myocardial damage after coronary surgery and could improve both short- and long-term results.

Myocardial damage (MD), as assessed based on biochemical marker increase, occurs very frequently after coronary surgery.[1-4] Even if marker increase can be observed in more than 60% of patients, electrocardiographic abnormalities, echocardiographic abnormalities, or both suggestive of myocardial infarction (MI)[5,6] are detectable in only 1% to 3% of them. In most patients cardiac function remains unaltered, yet evidence of MD is a sensible predictor of early and late cardiovascular events.[4,7-9] Many clinical and intraoperative factors concur with the pathogenesis of this condition, and recently, the contribution of an inflammatory response has been demonstrated in the process leading to MD.[10-13]

Several clinical and experimental studies have suggested the usefulness of preoperative statin treatment in preventing MD after coronary artery bypass graft (CABG) surgery.[14,15] 3-hydroxy-3-methyl-glutaryl-CoA (HMG-CoA) reductase inhibitors have been shown to significantly reduce cardiovascular risk independently of their lipid-lowering effect[16,17] and to exert both a vasoprotective and an anti-inflammatory effect.[18] Rosuvastatin (RSV) is a new-generation statin with a highly effective lipid-lowering and antiatherosclerotic activity.[19,20] Its pharmacologic action has been shown at lower doses and with less collateral effects compared with other commonly used statins; however, only few data are available about its advantageous anti-inflammatory properties.[16,19]

We performed a randomized placebo-controlled trial of RSV pretreatment (20 mg/d) before elective coronary artery bypass surgery, investigating the possible effect of a 7-day preoperative statin treatment on reducing postoperative release of markers of MD.

MATERIALS AND METHODS

Patient Population and Study Design

This was a randomized, double-blind, placebo-controlled study. Between January 2005 and January 2007, 200 consecutive patients matching the study selection criteria were enrolled of a total of 1187 patients undergoing CABG surgery in the same period. Exclusion criteria were as follows to obtain as homogeneous a group as possible and therefore avoid any

From the Department of Cardiac Surgery,[a] University of Naples Federico II, Naples, Italy, and the Department of Cardiovascular Surgery,[b] Azienda Ospedaliera S. Camillo Forlanini, Rome, Italy.

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Address for reprints: Vito A. Mannacio, MD, Via S. Domenico 62, 80127 Naples, Italy (E-mail: vitomannacio2@libero.it).

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Abbreviations and Acronyms

AF = atrial fibrillation
CABG = coronary artery bypass grafting
CI = confidence interval
CPB = cardiopulmonary bypass
EF = ejection fraction
ILVM = indexed left ventricular mass
LOS = low output syndrome
LVEF = left ventricular ejection fraction
MD = myocardial damage
MI = myocardial infarction
NO = nitric oxide
OR = odds ratio
PAMI = postoperative acute myocardial infarction
RSV = rosuvastatin
WMSI = wall motion score index

misleading interference: emergency cardiac operation; associated cardiac surgery; acute MI (<3 months); poor cardiac function, as indicated by an ejection fraction (EF) less than 35%; increase in creatine kinase–MB mass (CK-MB mass), troponin I, or myoglobin values before the operation; high-sensitivity C-reactive protein (hsCRP) levels of greater than 5 mg/L as a marker of acute or chronic preoperative inflammatory response; moderate renal failure (creatinine clearance >2.0 mL $\cdot min^{-1} \cdot m^{-2}$); active liver disease or increased liver enzyme levels (alanine aminotransferase – aspartate aminotransferase); type 2 diabetes mellitus; contraindications to statin treatments (history of liver or muscle disease); previous recent (60 days) therapy with steroidal or nonsteroidal anti-inflammatory drugs; and previous recent (30 days) treatment with any kind of statins: all patients who could not suspend the therapy for at least 30 days before the planned operation were excluded. Diabetic patients were excluded as well because their chronic inflammatory status might have interfered with measured hsCRP values at baseline.[21,22] Patients undergoing surgical intervention for single- or quadruple-vessel disease were also excluded to avoid too high a variance between minimal and maximal cardiopulmonary bypass (CPB) time.[23] Patients with diffuse distal lesions of the left anterior descending coronary artery, a dominant right coronary artery, and/or a dominant circumflex artery were also excluded. All patients received complete myocardial revascularization. The study cohort was very homogeneous for age, sex, clinical features, and severity of coronary artery disease.

According to the study design, 100 patients were randomized to placebo and 100 to RSV; the 2 patient groups were homogeneous, with minimal interference of minor demographic variables. All patients in the RSV group received a dose of 20 mg/d starting 7 days before the planned operation, regardless of cholesterol level. The dose was determined in agreement with the clinical pharmacology service, aiming at a satisfactory preoperative blood level of the drug with the lowest possible chance of disturbing collateral effects. Selection of patients for placebo or RSV treatment was obtained on admission by means of a computer-generated algorithm. Randomization was fully blinded, without any account of clinical or demographic features.

Hemodynamic variables were recorded in all patients through a Swan–Ganz Combo pulmonary artery catheter and elaborated with a Vigilance CEDV monitor (Edwards Lifesciences, Irvine, Calif). All surgical operations were performed by the same staff of senior surgeons. During the period of study, standardized operative techniques were always used, and a shared strategy was established before the operation. All operations were performed through a median sternotomy and during CPB with hollow-fiber oxygenators (Capiox SX25RX; Terumo, Leuven, Belgium) and roller pumps. In all cases the ascending aorta and right atrium were cannulated. Pump flow was kept at approximately 2.5 L $\cdot min^{-1} \cdot m^{-2}$, providing an arterial pressure of approximately 70 mm Hg. Normothermia was always used, and cardioplegic arrest was achieved with intermittent cold hyperkalemic blood cardioplegia infused into the ascending aorta. Retrograde cardioplegia was never used. Heparin was administered to obtain an activated clotting time of longer than 500 seconds. At the end of CPB, protamine sulfate was administered to completely reverse the heparin effect. The number of grafts per patient was 2 to 3. The left internal thoracic artery was used in all cases and always to revascularize the left anterior descending artery. In 20 cases sequential grafting to the first diagonal artery was also performed. The right internal thoracic artery was also used in 70 patients younger than 60 years. Autologous saphenous veins were used in all other cases. The radial artery was never used. Graft flow was in all cases measured by means of a transit-time flowmeter (CardioMed CM 2005; MediStern AS, Oslo, Norway) to confirm graft patency at the end of the procedure: in 8 cases the distal anastomosis had to be redone because of an unsatisfactory measured flow. Shed mediastinal blood was never autotransfused. No associated procedures were ever required.

A standardized protocol was followed in the intensive care unit. Blood transfusions were administered when hemoglobin values decreased to less than 8 g/dL. Ticlopidine was started 48 hours after the operation at a dose of 250 mg/d in both randomized groups. Other drugs were administered after the operation, when clinically indicated.

Twelve-lead electrocardiograms were obtained before the operation, on admission to the intensive care unit, 12 hours later, and every day thereafter until hospital discharge. The electrocardiograms were analyzed blind to the assigned treatment.

Echocardiographic evaluation was also obtained blind to the assigned treatment and was performed by the same 2 physicians preoperatively, 24 hours and 48 hours postoperatively, and at hospital discharge: left ventricular EF (LVEF), wall motion score index (WMSI), and indexed left ventricular mass (ILVM) were calculated and recorded. An ILVM of greater than 125 g/m^2 was considered a marker of left ventricular hypertrophy. A 5% or greater postoperative reduction of LVEF was considered significant.[21]

Blood samples for assay of CK-MB mass, troponin I, and myoglobin were collected before the operation and at 8, 12, 16, and 24 hours after the operation and then on every postoperative day until hospital discharge. Further testing was performed when the clinical picture suggested myocardial ischemia. The upper normal limits for assayed markers were defined according to the Joint European Society of Cardiology/American College of Cardiology guidelines.[24] Upper normal limits were 5 ng/mL for CPK-MB, 0.08 ng/mL for troponin I, and 80 ng/mL for myoglobin. Troponin I, myoglobin, and CK-MB mass were assayed by means of a LIAISON kit (DiaSorin SpA, Saluggia, Italy), with a detection limit of less than 0.5 for myoglobin and CK-MB mass and less than 0.005 for troponin I.

hsCRP was assayed at baseline and at 24, 48, and 72 hours after the operation by means of immunonephelometry with a BN System (CardioPhase hs CRP–BN ProSpec; Dade Behring Marburg GmbH, Marburg, Germany). Levels of hsCRP of 3 mg/L or less were considered to be normal. When a value of greater than 5 mg/L was obtained, the test was repeated to avoid any inappropriate interpretation.

Two weeks after hospital discharge, all patients were followed up during an office visit.

Definition of Perioperative Data

Before starting the study, we proceeded to the necessary assessment of the concept and definition of postoperative acute myocardial infarction (PAMI) versus MD. As confirmed by several reports, high serum levels of cardiac enzymes can be detected in more than 60% of patients after cardiac surgery, even in the absence of electrocardiographic evidence, echocardiographic evidence, or both of MI. Therefore it was imperative for us to establish a cutoff level between PAMI and MD.