Randomized Trial of Atorvastatin for Reduction of Myocardial Damage During Coronary Intervention

Results From the ARMYDA (Atorvastatin for Reduction of MYocardial Damage during Angioplasty) Study

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Background—Small myocardial infarctions after percutaneous coronary intervention have been associated with higher risk of cardiac events during follow-up. Observational studies have suggested that statins may lower the risk of procedural myocardial injury. The aim of our study was to confirm this hypothesis in a randomized study.

Methods and Results—One hundred fifty-three patients with chronic stable angina without previous statin treatment were enrolled in the study. Patients scheduled for elective coronary intervention were randomized to atorvastatin (40 mg/d, n=76) or placebo (n=77) 7 days before the procedure. Creatine kinase-MB, troponin I, and myoglobin levels were measured at baseline and at 8 and 24 hours after the procedure. Detection of markers of myocardial injury above the upper normal limit was significantly lower in the statin group versus the placebo group: 12% versus 35% for creatine kinase-MB (P=0.001), 20% versus 48% for troponin I (P=0.0004), and 22% versus 51% for myoglobin (P=0.0005). Myocardial infarction by creatine kinase-MB determination was detected after coronary intervention in 5% of patients in the statin group and in 18% of those in the placebo group (P=0.025). Postprocedural peak levels of creatine kinase-MB (2.9±3 versus 7.5±18 ng/mL, P=0.007), troponin I (0.09±0.2 versus 0.47±1.3 ng/mL, P=0.0008), and myoglobin (58±36 versus 81±49 ng/mL, P=0.0002) were also significantly lower in the statin than in the placebo group.

Conclusions—Pretreatment with atorvastatin 40 mg/d for 7 days significantly reduces procedural myocardial injury in elective coronary intervention. These results may influence practice patterns with regard to adjuvant pharmacological therapy before percutaneous revascularization. (Circulation. 2004;110:674-678.)

Key Words: angioptasy ■ trials ■ myocardial infarction ■ stents ■ angina

Myocardial necrosis, assessed by creatine kinase-MB (CK-MB) elevation, is relatively frequent after coronary intervention, occurring in up to 40% of cases.1-4 Although most patients remain asymptomatic with no changes in cardiac function, even a mild release of CK-MB is associated with higher mortality during follow-up.2,3,5 Many treatment strategies have been proposed to address this issue, but procedural ischemic myocardial injury remains the most frequent complication after coronary angioplasty.4

Several randomized studies demonstrated the beneficial effects of therapy with HMG-CoA reductase inhibitors (statins) in patients with coronary disease or in normal subjects with hypercholesterolemia,6-8 and retrospective observational studies have suggested that pretreatment with statins might reduce the incidence of myocardial infarction after coronary intervention.9-11 To date, there is no randomized, controlled study to evaluate the effects of statins given before coronary intervention on preventing myocardial injury.

Thus, we have performed the first randomized, placebo-controlled trial of pretreatment with atorvastatin before elective coronary intervention. In particular, we evaluated the effects of atorvastatin 40 mg/d, started 1 week before the procedure, on release of markers of cardiac damage (CK-MB, troponin I, and myoglobin) after percutaneous revascularization in patients with stable angina.

Methods

Patient Population and Study Design

This was a randomized, prospective, double-blind, placebo-controlled trial performed in 2 institutions. Inclusion criteria were presence of typical stable effort angina, positive stress test (either ECG, nuclear scan, or stress echocardiogram), and indication for coronary angioplasty. Exclusion criteria were acute myocardial infarction (<3 months); unstable angina; any increase in CK-MB, troponin I, or myoglobin above upper normal limit at the time of randomization; any increase in liver enzymes (AST/ALT); left ventricular ejection fraction <30%; renal failure with creatinine >3
mg/dL; history of liver or muscle disease; or previous treatment with statins. Patients undergoing current therapy with statins were also excluded. Between September 1, 2002, and March 1, 2004, a total of 912 patients underwent elective angioplasty for stable angina; 636 patients were excluded because of previous or current treatment with statins, 58 because of low ejection fraction, 39 because of contraindications to statin treatment (liver or muscle disease), and 26 because of renal failure. Thus, a total of 153 patients (age 64±10 years, 107 men) fulfilling the inclusion criteria were scheduled for elective coronary intervention and were included in the study; 77 patients were randomized to placebo and 76 to atorvastatin (40 mg/d) starting 7 days before the planned intervention. Patients were randomized independently of their lipid levels. According to our standard protocol, all patients without contraindications were pretreated with aspirin (100 mg/d) and ticlopidine 250 mg BID at least 3 days before the procedure or with clopidogrel 300 mg at least 6 hours before the procedure. All patients continued ticlopidine 250 mg BID or clopidogrel 75 mg/d for 1 month (6 months for patients treated with drug-eluting stents). Before intervention, patients received weight-adjusted intravenous heparin with a target activated clotting time >300 seconds in the absence of glycoprotein Ib/IIa inhibitor therapy and 200 to 300 seconds with glycoprotein Ib/IIa, which was allowed at the operator’s discretion. Procedural success was defined as a reduction of stenosis to <30% residual narrowing. Blood samples were taken before and at 8 and 24 hours after the procedure to assay CK-MB (mass), troponin I (mass), and myoglobin; additional determinations were performed if any patient developed postprocedural symptoms suggestive of myocardial ischemia. Measurements of CK-MB, troponin I, and myoglobin were obtained with the Access 2 Immunochemiluminometric assay (Beckman Coulter).12 The upper normal limits were defined as the 99th percentiles of the normal population, with a total imprecision of <10%, according to Joint European Society of Cardiology/American College of Cardiology guidelines.13 Normal limits were =54 ng/mL for CK-MB, =0.08 ng/mL for troponin I, and 80 ng/mL for myoglobin. C-reactive protein levels were assessed before coronary intervention (1 week after randomization) and at 24 hours after the procedure in 98 patients (50 in the statin group and 48 in the placebo group). C-reactive protein was determined by the KRIPTOR ultrasensitive immunofluorescent assay (BRAHMS), with a detection limit of 0.06 mg/L. One-month clinical follow-up was obtained by office visit in all patients. Each patient gave informed consent to the study. The study was not supported by any external source of funding.

**End Points**

The primary end point was occurrence of myocardial infarction, defined as a postprocedural increase of CK-MB >2 times above the upper normal limit, according to the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction.13 Secondary end points included (1) any postprocedural increase of other markers of myocardial injury (CK-MB, troponin I, and myoglobin) above upper normal limits; (2) mean peak values of CK-MB, troponin I, and myoglobin after intervention; and (3) occurrence of all major adverse cardiac events (death, myocardial infarction, or need for unplanned revascularization) from the time of the procedure until 1 month of follow-up.

**Statistical Analysis**

According to recent observational studies, previous treatment with statins can be associated with a reduction of peri-procedural myocardial infarction of 50% to 90%.9 We expected an incidence of postprocedural CK-MB elevation of ~10% in the placebo group and 10% in the treatment group. Thus, a sample size of 120 patients (with 60 in each group) would provide 80% power to detect a difference with an alpha (probability value) of 0.05. Continuous variables between groups were compared by t test for normally distributed values (age, left ventricular ejection fraction); otherwise, the Mann-Whitney U test was applied (in particular, for CK-MB, troponin I, and myoglobin values). Proportions were compared by χ² test or Fisher’s exact test when appropriate. ORs and 95% CIs assessing the risk of peri-procedural myocardial infarction associated with different factors were assessed by multiple logistic regression, adjusted for age; sex; use of β-blockers, ACE inhibitors, or glycoprotein Ib/IIa inhibitors; diabetes; dyslipidemia; systemic hypertension; type of lesion (A/B1 versus B2/C); multivessel intervention; stent length; use of direct stenting; duration of balloon inflations; and use of high pressure after dilation. A probability value <0.05 (2 tailed) was considered significant. Analysis was performed with GB-STAT version 6 software. Results are expressed as mean±SD, unless otherwise specified.

**Results**

**Study Population**

Clinical and procedural variables in the atorvastatin and placebo groups are shown in Table 1 and Table 2, respectively. The 2 groups were similar with regard to age, sex, cardiovascular risk factors, clinical presentation (all patients had stable angina by study design), left ventricular function, renal function, and medical therapy at the time of the procedure. Coronary anatomy, lesion type, procedural characteristics (including total ischemia time), use of drug-eluting stents, diameter and length of implanted stents, and use of Ib/IIa inhibitors were also similar. Procedural success was achieved in all patients of the placebo group and in all but 1 patient (99%) of the atorvastatin group (in 1 patient, a total chronic occlusion could not be crossed with the wire); no patient had no-reflow phenomenon or significant (>2 mm) side-branch closure during the procedure. There were no in-hospital major complications (death or need for urgent revascularization). An increase above the upper normal limit of liver enzymes (AST/ALT) was observed in 1 patient in the atorvastatin group on admission for coronary intervention. In this patient, the drug was then discontinued; however, all patients completed the 7-day pretreatment period with ator-

<table>
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<th>TABLE 1. Main Clinical Features in the Placebo and Atorvastatin Groups</th>
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<td>Characteristic</td>
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<td>Male sex, n (%)</td>
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<tr>
<td>Age, y</td>
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<tr>
<td>Diabetes mellitus, n (%)</td>
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<tr>
<td>Systemic hypertension, n (%)</td>
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<tr>
<td>Hypercholesterolemia, n (%)</td>
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<td>Current smokers, n (%)</td>
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<td>Family history, n (%)</td>
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<td>Previous myocardial infarction, n (%)</td>
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<td>Previous coronary intervention, n (%)</td>
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<tr>
<td>Previous bypass surgery, n (%)</td>
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<td>Left ventricular ejection fraction, %</td>
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<td>Multivessel coronary artery disease, n (%)</td>
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<td>Blood creatinine, mg/dL</td>
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<td>Aspirin, n (%)</td>
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<td>Ticlopidine/clopidogrel, n (%)</td>
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<td>β-Blockers, n (%)</td>
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markers of myocardial damage after coronary intervention included CK-MB, troponin I, and myoglobin. Several randomized trials have shown that statins have beneficial effects on the incidence of myocardial injury during coronary intervention compared with placebo; atorvastatin significantly reduced the risk of periprocedural CK-MB release (OR 0.19, 95% CI 0.05 to 0.57); use of B-blockers, glycoprotein IIb/IIIa inhibitors, or ACE inhibitors was not associated with risk reduction (Figure 3).

**Discussion**

This is the first randomized trial to demonstrate that pretreatment with atorvastatin decreases the incidence of myocardial injury during coronary intervention compared with placebo; indeed, atorvastatin significantly reduced release of all markers of myocardial damage after coronary intervention, including myoglobin, troponin I, and CK-MB. Several randomized trials have shown that statins have beneficial effects on the incidence of long-term cardiovascular events in subjects with hypercholester-
Asymptomatic myocardial injury, assessed by postprocedural CK-MB releases, is frequent during coronary intervention, occurring in 10% to 40% of cases.1 Use of β-blockers, glycoprotein IIb/IIIa inhibitors, or ACE inhibitors was not associated with risk reduction. MI indicates myocardial infarction.

Figure 3. Results of multivariate analysis showing that pretreatment with atorvastatin significantly reduced risk of periprocedural myocardial infarction (OR 0.19, 95% CI 0.05 to 0.57). Use of β-blockers, glycoprotein IIb/IIIa inhibitors, or ACE inhibitors was not associated with risk reduction. MI indicates myocardial infarction.

The mechanisms underlying the beneficial effects of atorvastatin are not completely clear. A previous observational study has suggested that the antiinflammatory effect of statins may play a role, showing that the benefit was higher in patients with high C-reactive protein.14 Statins have important antiinflammatory effects in vitro25 and in vivo,26 and inflammatory status before angioplasty is associated with higher risk of periprocedural myocardial necrosis14 and adverse cardiac events during follow-up.27,28 The antiinflammatory effect of statins might contribute to reduce myocardial necrosis due to microembolization during coronary intervention;
this is supported by experimental evidence showing protective effects of statins on a model of ischemia/reperfusion, possibly by effects on microcirculation and cell adhesion and platelet function, and by the trend toward reduced C-reactive protein levels observed in the present study. A recent study observed that even a single dose of statins may significantly improve endothelial function; thus, even short-term treatment with statin may have important effects on endothelial function and on inflammation.

In conclusion, the present study shows that pretreatment with atorvastatin 40 mg/d for 1 week before coronary intervention may reduce periprocedural myocardial injury in patients with stable angina. The low cost and very low risk of this therapy may support its routine use in patients undergoing percutaneous revascularization.

**Appendix**

The following investigators and institutions participated in the ARMYDA trial:

**Chairmen:**

Vincenzo Pasceri, Giuseppe Richichi, San Filippo Neri Hospital, Rome; Giuseppe Patti, Germano Di Sciascio, Campus Bio-Medico University, Rome.

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**References**


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