Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 49, No. 12, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.02.025

Atorvastatin Pretreatment Improves Outcomes in Patients With Acute Coronary Syndromes Undergoing Early Percutaneous Coronary Intervention

Results of the ARMYDA-ACS Randomized Trial

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Objectives This study sought to investigate potential protective effects of atorvastatin in patients with acute coronary syndromes (ACS) undergoing percutaneous coronary intervention (PCI).

Background Randomized studies have shown that pretreatment with atorvastatin may reduce periprocedural myocardial infarction in patients with stable angina during elective PCI; however, this therapy has not been tested in patients with ACS.

Methods A total of 171 patients with non–ST-segment elevation ACS were randomized to pretreatment with atorvastatin (80 mg 12 h before PCI, with a further 40-mg preprocedure dose [n = 86]) or placebo (n = 85). All patients were given a clopidogrel 600-mg loading dose. All patients received long-term atorvastatin treatment thereafter (40 mg/day). The main end point of the trial was a 30-day incidence of major adverse cardiac events (death, myocardial infarction, or unplanned revascularization).

Results The primary end point occurred in 5% of patients in the atorvastatin arm and in 17% of those in the placebo arm (p = 0.01); this difference was mostly driven by reduction of myocardial infarction incidence (5% vs. 15%; p = 0.04). Postprocedural elevation of creatine kinase-MB and troponin-I was also significantly lower in the atorvastatin group (7% vs. 27%, p = 0.001 and 41% vs. 58%, p = 0.039, respectively). At multivariable analysis, pretreatment with atorvastatin conferred an 88% risk reduction of 30-day major adverse cardiac events (odds ratio 0.12, 95% confidence interval 0.05 to 0.50; p = 0.004).

Conclusions The ARMYDA-ACS trial indicates that even short-term pretreatment with atorvastatin may improve outcomes in patients with ACS undergoing early invasive strategy. These findings may support routine use of high-dose statins before intervention in patients with ACS. (J Am Coll Cardiol 2007;49:1272–8) © 2007 by the American College of Cardiology Foundation

The ARMYDA (Atorvastatin for Reduction of MYocardial Damage During Angioplasty) trial (1) has shown that a 7-day pretreatment with atorvastatin is associated with an 81% risk reduction of periprocedural myocardial infarction in patients with stable angina undergoing elective percutaneous coronary intervention (PCI); attenuation of endothelial activation may explain this protective role at least in part (2). The efficacy of atorvastatin pretreatment in patients with acute coronary syndromes undergoing early PCI has not been investigated. Observational data (3) have suggested that patients with acute coronary syndromes who were already receiving statins at the time of intervention have a lower incidence of periprocedural myonecrosis and a better cardiac event-free survival at 6 months; however, patients were treated with different types of statins, variable doses, and unknown duration of previous treatment, and those findings have not been validated in a randomized trial.

Thus, the ARMYDA study group (1,2,4,5) has performed a randomized, placebo-controlled trial evaluating the effects of pretreatment with a specific statin load on 30-day clinical outcomes after PCI in patients with acute coronary syndromes.

Methods

Study population and design. The ARMYDA-ACS (Atorvastatin for Reduction of MYocardial Damage During

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Manuscript received February 10, 2007; revised manuscript received February 23, 2007, accepted February 23, 2007.

Angioplasty-Acute Coronary Syndromes) trial is a multicenter, randomized, prospective, double-blind clinical trial performed in 3 Italian institutions (Campus Bio-Medico University of Rome, Vito Fazzi Hospital of Lecce, and University La Sapienza of Rome) (Fig. 1). Inclusion criteria were the presence of a non–ST-segment elevation acute coronary syndrome (unstable angina or non–ST-segment elevation acute myocardial infarction) sent to early (<48 h) coronary angiography. Exclusion criteria were a ST-segment elevation acute myocardial infarction; non–ST-segment elevation acute coronary syndrome with high-risk features warranting emergency coronary angiography (6); any increase in liver enzymes (aspartate amino transferases/alanine amino transferases); left ventricular ejection fraction <30%; renal failure with creatinine >3 mg/dl; history of liver or muscle disease; or previous or current treatment with statins. Between January 3, 2005, and December 21, 2006, a total of 771 patients fulfilling the inclusion criteria were initially evaluated; 451 patients were excluded because of previous or current treatment with statins, 41 for non–ST-segment elevation acute coronary syndrome requiring emergency invasive approach, 43 because of low ejection fraction, 30 because of contraindications to statin treatment (liver or muscle disease), and 15 because of renal failure. Eligible patients (n = 191) were randomized to receive placebo or atorvastatin (80-mg loading dose given a mean of 12 h before coronary angiography, with a further 40-mg dose approximately 2 h before the procedure). Patients were assigned to the study arm using an electronic spreadsheet indicating the group assignment by random numbers; randomization blocks were created and distributed to the 3 centers. After coronary angiography, 20 patients (10 in each randomization arm) who did not receive angioplasty were excluded from the study (8 were treated medically and 12 with bypass surgery); thus, 171 patients (86 randomized to atorvastatin and 85 to placebo) with significant coronary artery disease deemed responsible for the clinical instability and undergoing PCI immediately after diagnostic angiography were enrolled and represent the study population. Physicians performing the procedure and the follow-up assessment were not aware of the randomization assignment.

Abbreviations and Acronyms

CRP = C-reactive protein

MACE = major adverse cardiac event

PCI = percutaneous coronary intervention

All interventions were performed with a standard technique. According to protocol, patients were pretreated before intervention with aspirin (100 mg/day) and clopidogrel (600-mg loading dose at least 3 h before the

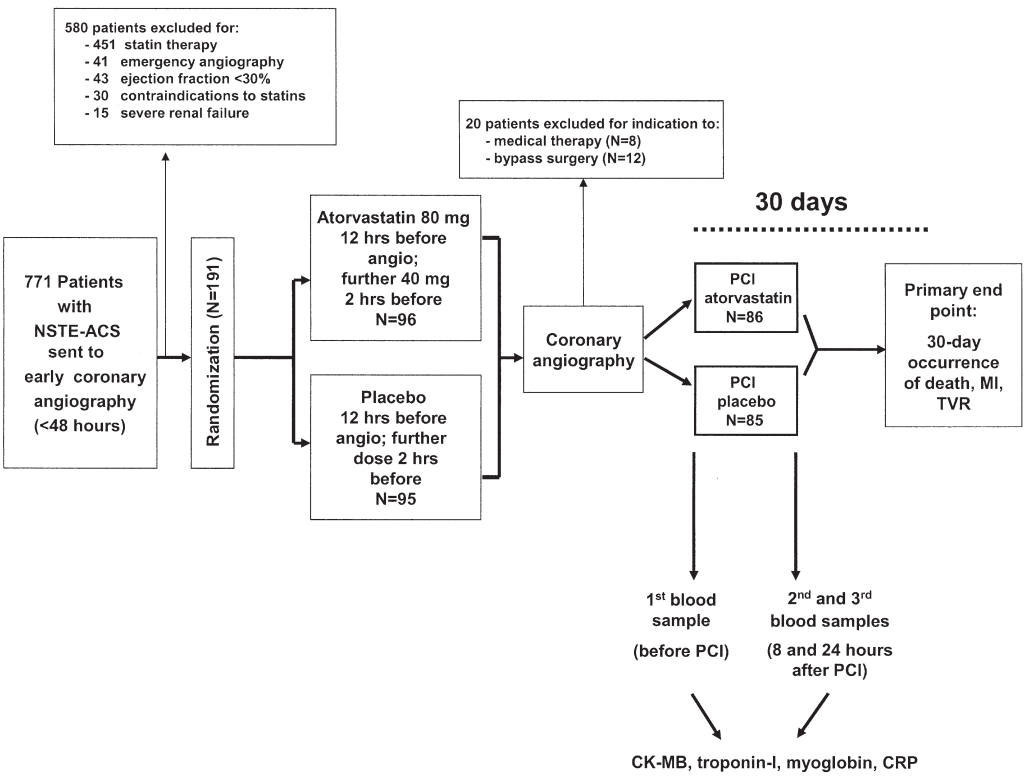

Figure 1 Study Design of the ARMYDA-ACS Trial

ARMYDA-ACS = Atorvastatin for Reduction of MYocardial Damage During Angioplasty—Acute Coronary Syndromes; CK-MB = creatine kinase-MB; CRP = C-reactive protein; MI = myocardial infarction; NSTE-ACS = non–ST-segment elevation acute coronary syndrome; PCI = percutaneous coronary intervention; TVR = target vessel revascularization.

procedure) (4). Glycoprotein IIb/IIIa inhibitors were used at the operator's discretion. Before intervention, patients received weight-adjusted intravenous heparin with a target activated clotting time of >300 s in the absence of glycoprotein IIb/IIIa inhibitor therapy and 200 to 300 s with glycoprotein IIb/IIIa. Procedural success was defined as reduction of stenosis to <30% residual narrowing. After PCI, aspirin (100 mg/day) was continued indefinitely, whereas clopidogrel (75 mg/day) was administered for at least 6 months; after intervention, all patients were treated with atorvastatin (40 mg/day) irrespective of the initial randomization assignment.

In all 171 patients, blood samples were collected before and at 8 and 24 h after PCI to measure creatine kinase-MB (mass), troponin-I (mass), and myoglobin levels; further measurements were performed in case of postprocedural symptoms suggestive of myocardial ischemia. Levels of creatine kinase-MB, troponin-I, and myoglobin were detected using the Access 2 immunochemiluminometric assay (Beckman Coulter, Brea, California) (7). Upper limits of normal were defined as the 99th percentile of normal population with a total imprecision of <10%, according to Joint European Society of Cardiology/American College of Cardiology guidelines (8). Normal limits were ≤4 ng/ml for creatine kinase-MB, ≤0.08 ng/ml for troponin-I, and 80 ng/ml for myoglobin. The C-reactive protein (CRP) levels were also measured before PCI and at 8 and 24 h after intervention. The CRP was assayed by the Kriptor ultrasensitive immunofluorescent assay (Brahms, Hennigsdorf/Berlin, Germany), with a detection limit of 0.06 mg/l. One-month clinical follow-up was performed by office visit in all study patients. Each patient gave informed consent to the study. The study was approved by the institutional review boards of the institutions involved. The trial was not supported by any external source of funding.

End points. The primary end point of the ARMYDA-ACS trial was occurrence of major adverse cardiac events (MACE) (death, myocardial infarction, target vessel revascularization) from the procedure up to 30 days. In patients with normal baseline levels of creatine kinase-MB, myocardial infarction was defined as a postprocedural increase of creatine kinase-MB >2 times above the upper limit of normal, according to the consensus statement of the Joint European Society of Cardiology/American College of Cardiology Committee for the Redefinition of Myocardial Infarction for clinical trials on coronary intervention (1,8). In patients with elevated baseline levels of creatine kinase-MB, myocardial infarction was defined as a subsequent increase of more than 2-fold in creatine kinase-MB from baseline value (9). Target vessel revascularization included bypass surgery or repeat PCI of the target vessel(s).

Secondary end points of the study were: 1) any postprocedural increase of markers of myocardial injury above upper limits of normal (creatine kinase-MB, troponin-I, myoglobin); and 2) postprocedural variations from baseline CRP levels in the 2 arms.

Statistics. If an overall incidence of MACE at 30 days of 13% is expected in the placebo arm (4) and, according to the results of the original ARMYDA study (1), a 81% risk reduction of adverse events is hypothesized in the atorvastatin arm, a total sample size of 171 patients would provide 80% power to detect this difference with an alpha level of 0.05. This expected clinical benefit is similar to that reported in a recent observational study describing a significantly lower incidence of MACE after PCI for an acute coronary syndrome in patients already taking statins (odds ratio 0.20) (3). Continuous variables between groups were compared by *t* test for normally distributed values, otherwise the Mann-Whitney *U* test was used. Proportions were compared by the Fisher exact test when the expected frequency was <5, otherwise the chi-square test (Yates corrected) was applied. Odds ratios and 95% confidence intervals assessing the risk of the primary end point according to potential confounding variables were assessed by logistic regression. The following parameters were evaluated first in a univariate model: age, gender, center of enrollment, use of beta-blockers, angiotensin-converting enzyme inhibitors, glycoprotein IIb/IIIa inhibitors, diabetes, dyslipidemia, systemic hypertension, cigarette smoking, left ventricular ejection fraction, type of lesion (A/B1 vs. B2/C), multivessel intervention, stent length, stent diameter, use of direct stenting, duration of balloon inflations, and use of high-pressure postdilatation. Variables with a p value <0.15 were then entered into a multivariable logistic regression analysis. Event-free survival analysis was performed by the Kaplan-Meier method with log-rank test group comparison. Results are expressed as mean ± SD unless otherwise specified. All calculations were performed using SPSS 12.0 (SPSS Inc., Chicago, Illinois), and p values <0.05 (2-tailed) were considered significant.

Results

Study population. Demographic/clinical and procedural features in the atorvastatin and placebo arms are indicated in Tables 1 and 2, respectively. The 2 groups were similar for age, gender, cardiovascular risk factors, clinical presentation, left ventricular function, blood creatinine levels, mean time to angiography, and medical therapy at the time of intervention. Coronary anatomy, lesion type, procedural characteristics, use of drug-eluting stents, diameter and length of implanted stents, and periprocedural infusion of glycoprotein IIb/IIIa inhibitors were also similar. Of note, patients receiving IIb/IIIa inhibitors had a significantly higher prevalence of diabetes mellitus, non–ST-segment elevation myocardial infarction, multivessel PCI, bifurcating lesions, and longer lesion length; these agents were used in a planned manner in 60% and in a bail-out manner in 40% of patients. Procedural success was obtained in all 171 patients; 4 patients (2 in each group) had no-reflow phenomenon, which significantly improved after administration of intracoronary nitrates and glycoprotein IIb/IIIa inhibitors. No patient had significant (≥2 mm) side branch

Table 1 Main Demographic/Clinical Features in the Atorvastatin and Placebo Groups

Variable	Atorvastatin (n = 86)	Placebo (n = 85)	p Value
Male gender	68 (79)	67 (79)	0.88
Age (yrs)	64 ± 11	67 ± 10	0.06
Diabetes mellitus	25 (29)	28 (33)	0.70
Systemic hypertension	63 (73)	63 (74)	0.96
Hypercholesterolemia	27 (31)	28 (33)	0.96
Current smoker	27 (31)	18 (21)	0.18
Family history of coronary disease	27 (31)	24 (28)	0.78
Previous myocardial infarction	20 (23)	19 (22)	0.97
Previous coronary intervention	9 (10)	9 (11)	0.82
Previous bypass surgery	2 (2)	3 (4)	0.99
Left ventricular ejection fraction (%)	55 ± 7	54 ± 8	0.38
Serum creatinine (mg/dl)	1.1 ± 0.3	1.1 ± 0.2	1
Clinical pattern			
Unstable angina	52 (60)	58 (68)	0.37
Non–ST-segment elevation myocardial infarction	34 (40)	27 (32)	0.37
Mean time to angiography (h)	23 ± 12	22 ± 10	0.56
Multivessel coronary artery disease	29 (34)	39 (46)	0.14
Therapy			
Aspirin	86 (100)	85 (100)	1
Clopidogrel	86 (100)	85 (100)	1
Beta-blockers	26 (30)	23 (27)	0.77
ACE inhibitors	67 (78)	65 (76)	0.97
Glycoprotein IIb/IIIa inhibitors	23 (27)	18 (21)	0.50

Values are given as number of patients (%) or mean ± SD.
ACE = angiotensin-converting enzyme.

closure during intervention. An increase above the upper normal limit of liver enzymes (aspartate amino transferases/alanine amino transferases) was observed in 1 patient of the atorvastatin arm after the procedure, in whom the drug was then discontinued; however, all patients received the study assignment drug (atorvastatin or placebo) before PCI.

Primary end point. The primary end point was evaluated at 30 days (Table 3). The composite primary end point of death, myocardial infarction, and target vessel revascularization occurred in 5% of patients (4 of 86) in the atorvastatin arm and in 17% (14 of 85) of those in the placebo arm ($p = 0.01$). The incidence of MACE at 1 month was mostly driven by postprocedural myocardial infarction (5% vs. 15%, $p = 0.04$). No patient in either arm died; an abrupt vessel closure caused by coronary dissection occurred in 1 patient (2%) of the placebo group the day after the index procedure and was successfully treated with re-intervention and implantation of another stent; this patient had no creatine kinase-MB elevation fulfilling the criteria for myocardial infarction. Kaplan-Meier curves confirmed a significantly better event-free survival at 30 days in the treatment arm (Fig. 2).

Secondary end points. The prevalence of patients with preprocedural elevation of cardiac markers above the upper limit of normal was similar in the atorvastatin and placebo groups (creatine kinase-MB 5% vs. 8%, $p = 0.52$; troponin-I 35% vs. 33%, $p = 0.92$; myoglobin 29% vs. 26%, $p = 0.77$). After PCI, the proportion of patients with elevated levels of creatine kinase-MB and troponin-I was significantly lower in the atorvastatin arm (creatine kinase-MB 7% vs. 27%, $p = 0.001$; troponin-I 41% vs. 58%, $p = 0.039$); no difference was observed in the prevalence of patients with elevated myoglobin levels after intervention (45% vs. 42%, $p = 0.81$). Distribution of creatine kinase-MB and troponin-I levels in the 2 groups is shown in Figure 3.

The CRP levels at the time of the procedure were not significantly different in the 2 groups before (7.8 ± 18 mg/l in the atorvastatin vs. 4.8 ± 13 mg/l in the placebo group, $p = 0.21$) or after PCI (10 ± 8 mg/l vs. 7.5 ± 13 mg/l, $p = 0.13$); however, the average percent increase of CRP levels from baseline was significantly lower in the statin arm (63 ± 114% vs. 147 ± 274%, $p = 0.01$).

Multivariable analysis. Multivariable analysis (Fig. 4) identified pretreatment with atorvastatin as a predictor of decreased risk of MACE at 30 days (odds ratio 0.12, 95% confidence interval 0.05 to 0.50; $p = 0.004$); patients requiring periprocedural use of glycoprotein IIb/IIIa inhibitors had an increased risk of events, as well as those with left ventricular ejection fraction ≤40%. Therapy with beta-blockers or angiotensin-converting enzyme inhibitors at the time of PCI was not associated with risk reduction.

Discussion

The ARMYDA-ACS trial is a randomized trial showing that short-term pretreatment with atorvastatin reduces the incidence of cardiac events in patients with acute coronary syndromes undergoing early PCI; this benefit is essentially driven by a significant reduction of periprocedural myocardial infarction.

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Table 2 Procedural Features in the Atorvastatin and Placebo Groups

Variable	Atorvastatin (n = 86)	Placebo (n = 85)	p Value
Vessel treated			
Left main	—	1 (1)	0.97
Left anterior descending	51 (50)	54 (49)	0.94
Left circumflex	31 (30)	28 (25)	0.56
Right coronary artery	20 (19)	26 (24)	0.56
Saphenous vein grafts	1 (1)	1 (1)	0.51
Restenotic lesions	1 (1)	2 (2)	0.99
Lesion type B2/C	73 (85)	71 (84)	0.97
Multivessel intervention	17 (20)	25 (29)	0.20
Type of intervention			
Balloon only	1 (1)	1 (1)	0.48
Stent	85 (99)	84 (99)	0.48
Bifurcations with kissing balloon	8 (9)	8 (9)	0.81
No. of stents per patient	1.4 ± 0.6	1.5 ± 0.9	0.40
Stent diameter (mm)	3.1 ± 0.4	3.1 ± 0.3	0.90
Total stent length (mm)	16.7 ± 5.7	16.9 ± 5.5	0.82
Use of drug-eluting stents	55 (64)	47 (55)	0.32
Direct stenting	41 (48)	36 (42)	0.59
No. of predilatations	2.1 ± 1.4	2.2 ± 1.7	0.68
Stent deployment pressure (atm)	11.2 ± 4.1	11.6 ± 2.7	0.44
Duration of stent deployment (s)	16 ± 7	16 ± 5	1
Total ischemia >120 s	17 (20)	17 (20)	0.88
Use of postdilatation	12 (14)	22 (26)	0.08

Values are given as number of patients (%) or mean ± SD.

Previous randomized studies have shown that long-term therapy with statins improves prognosis in subjects with hypercholesteremia and in patients with stable coronary artery disease (10,11); data on the effects of statins in the setting of acute coronary syndromes are more limited. Observational studies on patients with acute myocardial infarction have suggested that statin initiation within 24 h is associated with a significantly lower occurrence of early complications, a reduced infarct size, and better in-hospital survival (12,13). Nonrandomized studies on early use of statins in patients with a variety of acute coronary syndromes have shown conflicting results; a number of them (14,15) have shown a lower occurrence of cardiovascular events, but a recent post-hoc analysis on 12,365 patients has indicated no benefit in terms of death, myocardial infarction, or recurrent ischemia at 90 days (16). Indeed, a recent meta-analysis evaluating the outcomes for up to 4 months of patients from 12 randomized trials that compared early (<14 days) statin therapy with placebo or usual care after an acute coronary syndrome showed that statins do not decrease the incidence of death, myocardial infarction, or stroke, with a trend toward a reduction of unstable angina (17). However, this meta-analysis has included studies enrolling mostly patients treated with a conservative strategy, without early coronary intervention.

Table 3 Individual and Combined Outcome Measures of the Primary End Point at 30 Days in the Atorvastatin and Placebo Groups

	Atorvastatin (n = 86)	Placebo (n = 85)	p Value
Death	—	—	
Myocardial infarction	4 (5)	13 (15)	0.04
Target vessel revascularization	—	1 (2)	1
Total MACE	4 (5)	14 (17)	0.01

Values are given as number of patients (%).
MACE = major adverse cardiac events.

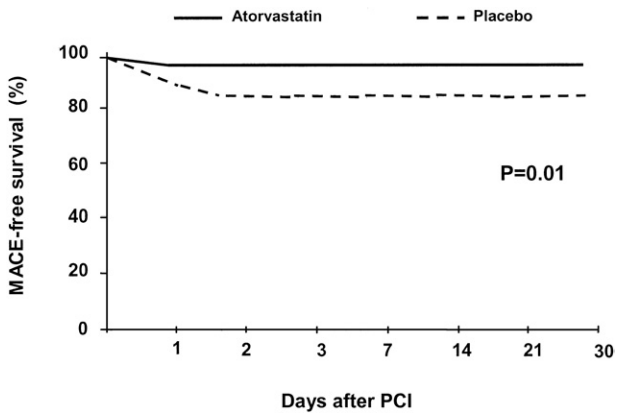

Figure 2 ARMYDA-ACS Survival Curves

Actuarial curves of 30-day major adverse cardiac event (MACE)-free survival in the 2 arms. PCI = percutaneous coronary intervention.

The ARMYDA trial (1) was a randomized study showing the clinical benefit of pretreatment with statins in patients undergoing PCI; however, this study enrolled only patients with stable angina, and the protocol used (1-week pretreatment with atorvastatin) could not be applied to unstable patients requiring an early invasive strategy. Therefore, the ARMYDA study group has designed the ARMYDA-ACS trial to assess whether an acute loading with high-dose atorvastatin improves clinical outcome in patients with acute coronary syndromes (unstable angina or non–ST-segment elevation myocardial infarction) treated

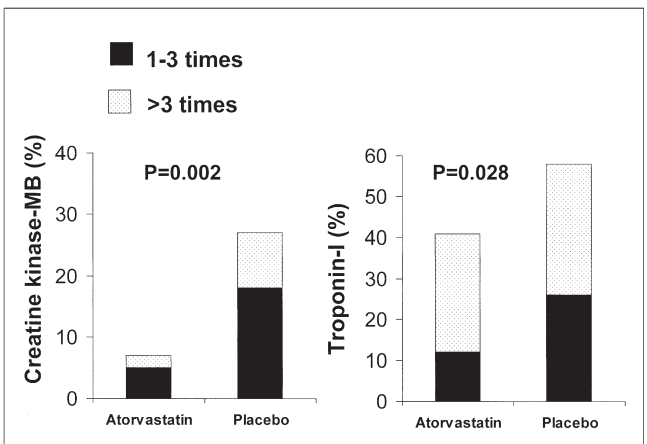

Figure 3 ARMYDA-ACS: Cardiac Marker Elevations

Incidence of postprocedural increase of creatine kinase-MB and troponin-I 1 to 3 times and >3 times above the upper limits of normal.

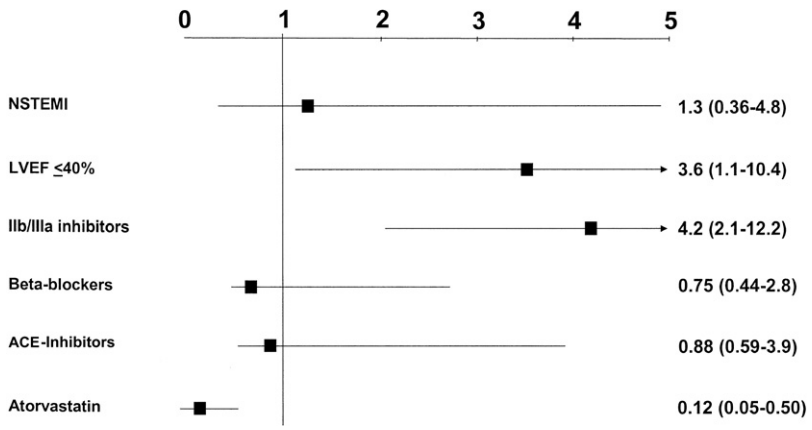

Figure 4 **ARMYDA-ACS: Odds Ratios for 30-Day MACE**

Results of multivariable analysis showing 88% major adverse cardiac event (MACE) risk reduction at 30 days with atorvastatin (odds ratio 0.12, 95% confidence interval 0.05 to 0.50; p = 0.004). ACE = angiotensin-converting enzyme; LVEF = left ventricular ejection fraction; NSTEMI = non–ST-segment elevation myocardial infarction.

with PCI. Multivariable analysis indicates an 88% risk reduction of MACE at 1 month in the treated arm. This is a much greater effect than that observed in other large studies using a high dose of statins in acute coronary syndromes, albeit without early invasive strategy, such as MIRACL (Myocardial Ischemia Reducation with Aggressive Cholesterol Lowering; 16% risk reduction of the composite primary cardiac end point) (18), A to Z (Aggrastat to Zocor; 25% risk reduction) (19) or PROVE-IT (Pravastatin or Atorvastatin Evaluation and Infection Therapy; 28% risk reduction) (20), all with a longer follow-up period. Our study shows 70% reduction in the incidence of periprocedural myocardial infarction: according to these data, 10 patients should be treated with atorvastatin to avoid 1 case of myocardial infarction. Indeed, a significant prevention of periprocedural myocardial injury, as measured by any postprocedural increase of cardiac markers (creatine kinase-MB and troponin-I), has been observed.

The possible mechanism(s) underlying the early protective effect of atorvastatin are unclear, but unlikely attributable to cholesterol-lowering effects, which require a longer duration of treatment (21). Experimental evidence indicates various lipid-independent, pleiotropic effects of acute atorvastatin treatment, such as improvement of endothelial function (22), vasodilation of coronary microvessels (23), and direct antithrombotic effect (24); atorvastatin bolus also reduces infarct size in a mouse model of ischemia-reperfusion through a direct protective effect on myocardial cells (25). Finally, a prospective subanalysis on patients of the ARMYDA trial has shown a significant attenuation of post-PCI increase of adhesion molecule levels in the atorvastatin arm (2). In addition, anti-inflammatory actions of statins are well documented both in vitro (26) and in vivo (27); in patients with acute coronary syndromes, atorvastatin significantly decreases levels of CRP during the acute phase (28,29) and enhances the decline in inflammation during follow-up (30). In the present study, atorvastatin did not reduce the postprocedural increase of CRP values in the whole study population, but mostly in patients with higher baseline levels of such markers; this suggests that the anti-inflammatory effects of atorvastatin may be stronger in patients with an enhanced baseline inflammatory status.

Our study included patients with non–ST-segment elevation acute coronary syndromes requiring interventional treatment; these results cannot be extrapolated directly to patients with ST-segment elevation myocardial infarction, or to those with unstable syndromes treated medically or receiving surgical revascularization. Furthermore, the ARMYDA-ACS trial included patients sent to an early invasive strategy, but not those undergoing emergency revascularization; thus, it is unknown whether an immediate single loading dose of atorvastatin may confer a protective effect also in the latter patients. Finally, patients on current therapy with statins were excluded by study design; it is unclear whether patients on chronic statin treatment may have a clinical benefit similar to that observed with acute administration. Indeed, in a rat model of ischemia/reperfusion, the acute protective effect of atorvastatin on myocardial injury wanes with a longer treatment, but this effect can be recaptured by a "reloading" given immediately before ischemia/reperfusion (31).

In the ARMYDA-ACS trial, only 24% of patients were treated with glycoprotein IIb/IIIa antagonists, reflecting practice patterns in the participating centers, whereas all patients received a 600-mg loading dose of clopidogrel before the procedure. The benefit of atorvastatin was independent of use of glycoprotein IIb/IIIa inhibitors, although patients requiring such drugs had a significantly higher occurrence of adverse events at 30 days, probably because of their higher risk profile. On the other hand, the 5% incidence of myocardial infarction in the treated arm of the ARMYDA-ACS trial, similar to that observed in the treatment arm of the more stable population of the original

ARMYDA trial, may be caused by the protective effects of the higher clopidogrel loading dose (4).

In conclusion, the present trial shows that a short-term atorvastatin pretreatment before PCI improves clinical outcomes in patients with unstable angina and non–ST-segment elevation myocardial infarction. If confirmed by larger additional randomized studies, these findings may support the indication of "upstream" administration of high-dose statins in patients with acute coronary syndromes treated with an early invasive strategy.

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APPENDIX

For a list of investigators who participated in the ARMYDA-ACS trial, please see the online version of this article.