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Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome
The SECURE-PCI Randomized Clinical Trial

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IMPORTANCE The effects of loading doses of statins on clinical outcomes in patients with acute coronary syndrome (ACS) and planned invasive management remain uncertain.

OBJECTIVE To determine if periprocedural loading doses of atorvastatin decrease 30-day major adverse cardiovascular events (MACE) in patients with ACS and planned invasive management.

DESIGN, SETTING, AND PARTICIPANTS Multicenter, double-blind, placebo-controlled, randomized clinical trial conducted at 53 sites in Brazil among 4191 patients with ACS evaluated with coronary angiography to proceed with a percutaneous coronary intervention (PCI) if anatomically feasible. Enrollment occurred between April 18, 2012, and October 6, 2017. Final follow-up for 30-day outcomes was on November 6, 2017.

INTERVENTIONS Patients were randomized to receive 2 loading doses of 80 mg of atorvastatin (n = 2087) or matching placebo (n = 2104) before and 24 hours after a planned PCI. All patients received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication.

MAIN OUTCOMES AND MEASURES The primary outcome was MACE, defined as a composite of all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization through 30 days.

RESULTS Among the 4191 patients (mean age, 61.8 [SD, 11.5] years; 1085 women [25.9%]) enrolled, 4163 (99.3%) completed 30-day follow-up. A total of 2710 (64.7%) underwent PCI, 333 (8%) underwent coronary artery bypass graft surgery, and 1144 (27.3%) had exclusively medical management. At 30 days, 130 patients in the atorvastatin group (6.2%) and 149 in the placebo group (7.1%) had a MACE (absolute difference, 0.85% [95% CI, −0.70% to 2.41%]; hazard ratio, 0.88; 95% CI, 0.69-1.11; *P* = .27). No cases of hepatic failure were reported; 3 cases of rhabdomyolysis were reported in the placebo group (0.1%) and 0 in the atorvastatin group.

CONCLUSIONS AND RELEVANCE Among patients with ACS and planned invasive management with PCI, periprocedural loading doses of atorvastatin did not reduce the rate of MACE at 30 days. These findings do not support the routine use of loading doses of atorvastatin among unselected patients with ACS and intended invasive management.

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Supplemental content

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Large randomized clinical trials have established the efficacy and safety of statins (3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors) for both primary and secondary cardiovascular disease prevention.[1-4] The effects of statins in reducing major cardiovascular events have largely been attributed to reduction of low-density lipoprotein cholesterol.[4] Mechanistic studies have suggested that loading doses of statins in acute coronary syndrome (ACS) may attenuate the inflammatory cascade and promote stability of coronary lesions vulnerable to rupture.[5,6] Previous trials and systematic reviews also have investigated the effect of loading doses of statins[7-13] before and after percutaneous coronary intervention (PCI). These studies have suggested that there may be a reduction in periprocedural myocardial infarction (MI),[7-13] which is an outcome known to be independently associated with higher subsequent mortality.[14]

The effect of loading doses of statins in patients with ACS is uncertain because the evidence is limited to studies with low numbers of events and different statin doses and regimens.[12,13] Thus, the SECURE-PCI (Statins Evaluation in Coronary Procedures and Revascularization) trial was designed to assess the effect of loading doses of atorvastatin on clinical outcomes in patients with ACS and planned invasive management.

Key Points

Question Do 2 loading doses of atorvastatin reduce 30-day major adverse cardiovascular events (MACE) in patients with acute coronary syndrome (ACS) and planned invasive management with percutaneous coronary intervention?

Findings In this randomized clinical trial of 4191 patients with ACS and planned invasive management, the rate of 30-day MACE was 6.2% among patients who received loading doses of atorvastatin and 7.1% among patients who received placebo, a nonsignificant difference.

Meaning Loading doses of atorvastatin in patients with ACS and planned invasive management did not reduce MACE at 30 days.

Methods

Study Design and Oversight

The study protocol was approved by the institutional review board from each site, and all patients provided written informed consent. The study design was previously published,[15] and the full protocol and statistical analysis plan are available in Supplement 1 and Supplement 2. Briefly, this trial was a randomized, double-blind, multicenter clinical trial conducted in Brazil in which patients with ACS were randomized to loading doses of 80 mg of atorvastatin or matching placebo before and 24 hours after a planned PCI. If patients did not undergo PCI, the second dose could have been administered 24 hours after the first dose. The follow-up period for the primary outcome was 30 days, with ongoing follow-up to 12 months for the assessment of clinical outcomes through additional exploratory analysis.

The trial was coordinated by the Research Institute-Heart Hospital and the Brazilian Clinical Research Institute in São Paulo, Brazil.

Patients

We included patients aged 18 years or older with ACS (with or without ST-segment elevation)[2,3,16] who had invasive management planned within the next 7 days (detailed inclusion and exclusion criteria are shown in eAppendix 1 in Supplement 3).[16] Planned invasive management was considered the strategy of systematic evaluation for coronary revascularization through routine coronary angiography in centers with PCI capability. In hospitals where diagnostic angiography and PCI were performed in a staged fashion, sites could have waited for diagnostic angiography results to randomize patients before PCI. However, in centers where PCI was routinely performed at the same time as diagnostic angiography, patient randomization was performed before the angiography. Because of the pragmatic nature of the trial, the decision regarding use of revascularization or not and the type of revascularization were defined by the local team at each site.

Key exclusion criteria were use of any fibrate in the 24 hours previous to the loading dose and use of any statin at a maximum dose in the 24 hours previous to the loading dose. Maximum doses of statins were considered as follows: atorvastatin, 80 mg; rosuvastatin, 40 mg; simvastatin, 80 mg; pravastatin, 40 mg; and fluvastatin, 80 mg.

Randomization and Study Treatments

Randomization was performed through a 24-hour central web-based automated system in permuted blocks of 4, stratified according to site. Patients were randomized (1:1) to receive either two 80-mg loading doses of atorvastatin or matching placebo (**Figure 1**).

The timing of study medication administration varied according to type of ACS. For patients with ACS without ST-segment elevation, the first dose was administered between 2 and 12 hours before angiography and PCI. For patients with ST-segment elevation MI (STEMI), the first loading dose was administered as soon as possible before primary PCI. In both cases, the second dose of 80-mg atorvastatin or matching placebo was administered 24 hours after the first dose.

Coronary angiography, and PCI if appropriate, were strongly recommended[2,15] in the first 48 hours for non-ST-segment elevation (NSTE) ACS. Percutaneous coronary intervention was performed according to standard of care (including access site and type of stent) in each center. For patients who were randomized and received the first dose of study medication but did not undergo PCI within 24 hours, 2 strategies were recommended for subsequent dosing of study medication depending on the planned timing of PCI. If PCI was delayed for more than 24 hours, patients received an additional loading dose before the procedure. However, if PCI was not performed following the diagnostic coronary angiography, patients could receive another 80-mg dose of

atorvastatin (or placebo) at the discretion of the investigator (the second loading dose was recommended in the protocol for cases in which coronary artery disease was present on the angiogram).

Evidence-based treatments for ACS were recommended according to current clinical practice guidelines.[2,3] All patients in both groups were to receive 40 mg/d of atorvastatin after the procedure through 30 days, starting on the day after the administration of the second loading dose of atorvastatin or placebo. After 30 days, statin use and regimen were defined by the site investigators according to local practice.

Clinical Outcomes

The primary outcome was major adverse cardiovascular events (MACE) at 30 days, which was defined as the composite of all-cause mortality, acute MI, stroke, and unplanned coronary revascularization at 30 days. Secondary outcomes at 30 days included individual components of the primary outcome as well as cardiovascular death, stent thrombosis, and target vessel revascularization.

Cardiac biomarkers including creatine kinase-MB fraction and/or troponin were measured before PCI and 6 to 12 hours and 18 to 24 hours after PCI to systematically evaluate periprocedural MI. The detailed definitions of spontaneous and periprocedural MI as well as other clinical outcomes are described in eAppendix 2 in Supplement 3. Clinical outcomes were adjudicated according to criteria prespecified by a clinical events committee whose members were blinded to study drug assignment.

Statistical Analysis

Assuming an event rate for MACE of approximately 12.3% based on previous trials and systematic reviews[12,13,17] and a relative risk reduction of 25% also based on previous randomized evidence,[12,13] a power of 90% and a 2-tailed α=.05, the required sample size was determined to be 4192 patients. The assumption for the study sample size was that approximately 70% of the study population would undergo PCI, which would also provide approximately 80% power for the primary analysis of the study in the PCI-treated patients, assuming a relative risk reduction in MACE of 25% in this subgroup.

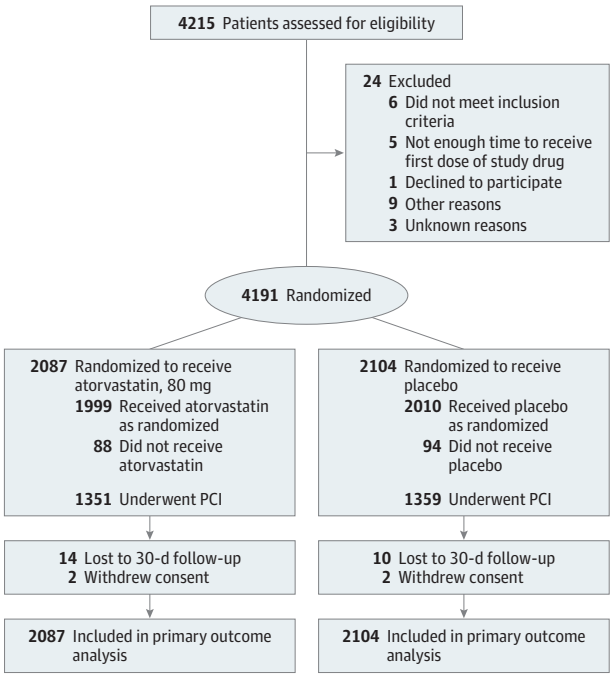
Continuous variables are reported as means and standard deviations or medians and interquartile ranges as appropriate. Categorical variables are summarized as frequencies.

The main analysis was performed based on the intention-to-treat principle (ie, including patients in the groups to which they were randomized). Time-to-event outcomes are presented using Kaplan-Meier survival curves. The treatment effect of loading doses of 80 mg of atorvastatin vs placebo was assessed using Cox regression analysis and expressed by hazard ratios (HRs) and 95% confidence intervals. Proportional hazard assumptions were checked by visual inspection and a weighted residuals test and all criteria were met. All events were considered in a time-to-event analysis, in which patients who were lost to follow-up at 30-day visits were censored at hospital discharge, including those who withdrew consent. We did not use any method of data imputation. We evaluated the effect of treatment on the incidence of bleeding and rhabdomyolysis at 7 days or until hospital discharge with a χ^2 test. Risk ratios were expressed using the Wald likelihood ratio to calculate 95% confidence intervals.

We performed subgroup analyses according to sex, age, type of ACS, previous use of statin, PCI, and type of stent, analyzed by interaction terms in the Cox regression. Sensitivity analyses were performed for the primary outcome excluding patients who did not receive a loading dose (overall population and patients who underwent PCI only), excluding patients with clinical events before loading dose (overall population and patients who underwent PCI only), and excluding patients with clinical events before PCI. We also performed post hoc analyses testing the interaction between PCI and type of ACS (STEMI and NSTEMI) and using a frailty Cox proportional hazard model considering sites as random effects (overall population and patients who underwent PCI only).

All analyses considered a 2-tailed α=.05 as the level for determining statistical significance and were performed using R software, version 3.3.3 (R Foundation for Statistical Computing).[18] For the secondary outcomes, the potential for type I error due to multiple comparisons was not accounted for; thus, these outcomes should be interpreted as exploratory.

Figure 1. Flow of Participants Through the Statins Evaluation in Coronary Procedures and Revascularization Trial



PCI indicates percutaneous coronary intervention. Considering the pragmatic nature of the study, not all sites collected complete and detailed information of patients who would be eligible but not randomized because of lack of adequate time to obtain informed consent. Patients who were lost to 30-day follow-up or withdrew consent were censored at hospital discharge in the time-to-event analysis.

Table 1. Baseline Participant Characteristics

Characteristics	No. /Total No. (%)[a] Atorvastatin (n = 2087)	Placebo (n = 2104)
Age, mean (SD), y	61.7 (11.3)	61.9 (11.7)
Male	1581/2087 (75.8)	1525/2104 (72.5)
Initial diagnosis		
STEMI	495/2031 (24.4)	517/2049 (25.2)
NSTEMI	1241/2031 (61.1)	1236/2049 (60.3)
Unstable angina	295/2031 (14.5)	296/2049 (14.4)
Previous long-term use of statin therapy (6 mo before randomization)	608/2085 (29.2)	600/2102 (28.5)
Medical history		
Hypertension	1475/2085 (70.7)	1499/2102 (71.3)
Hypercholesterolemia	755/2085 (36.2)	764/2102 (36.3)
Diabetes	653/2084 (31.3)	673/2102 (32.0)
Tobacco use	564/2085 (27.1)	618/2102 (29.4)
Previous MI	342/2085 (16.4)	320/2102 (15.2)
Previous PCI	258/2085 (12.4)	261/2102 (12.4)
Previous CABG surgery	128/2085 (6.1)	102/2101 (4.9)
Previous stroke	74/2085 (3.5)	76/2101 (3.6)
Renal impairment	60/2085 (2.9)	73/2102 (3.5)
Obesity	324/2085 (15.5)	339/2102 (16.1)
Initial treatment strategy		
PCI	1351/2085 (64.8)	1359/2102 (64.7)
CABG surgery	162/2085 (7.8)	171/2102 (8.1)
Medical management	572/2085 (27.4)	572/2102 (27.2)
Time from randomization to study drug administration, h	n=2034	n=2050
Mean (SD)	6.1 (31.2)	5.2 (24.3)
Median (IQR)	0.1 (0-0.5)	0.2 (0-0.6)
Time from hospital admission to PCI, h	n=1351	n=1359
Mean (SD)	47.8 (66.6)	45.3 (63.8)
Median (IQR)	20 (3-72)	19 (3-64)
Time from randomization to PCI, h	n=1351	n=1359
Mean (SD)	7.2 (88.8)	9.1 (59.2)
Median (IQR)	3 (1-6)	3 (1-6)
Reason PCI was not performed		
Clinical treatment	450/734 (61.3)	472/743 (63.5)
CABG	162/734 (22.1)	171/743 (23.0)
Not a final diagnosis of ACS	109/734 (14.9)	88/743 (11.8)
Unknown	13/734 (1.8)	12/743 (1.6)
Other medical therapy		
Aspirin	1880/2085 (90.2)	1883/2102 (89.6)
Clopidogrel, ticagrelor, or prasugrel	1775/2085 (85.1)	1766/2102 (84.0)
β-blockers	1606/2085 (77.0)	1599/2102 (76.1)
ACE inhibitors or ARAs	1484/2085 (71.2)	1444/2102 (68.7)

Abbreviations: ACE, angiotensin-converting enzyme; ACS, acute coronary syndrome; ARA, angiotensin II receptor antagonist; CABG, coronary artery bypass graft; IQR, interquartile range; MI, myocardial infarction; NSTEMI, non–ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

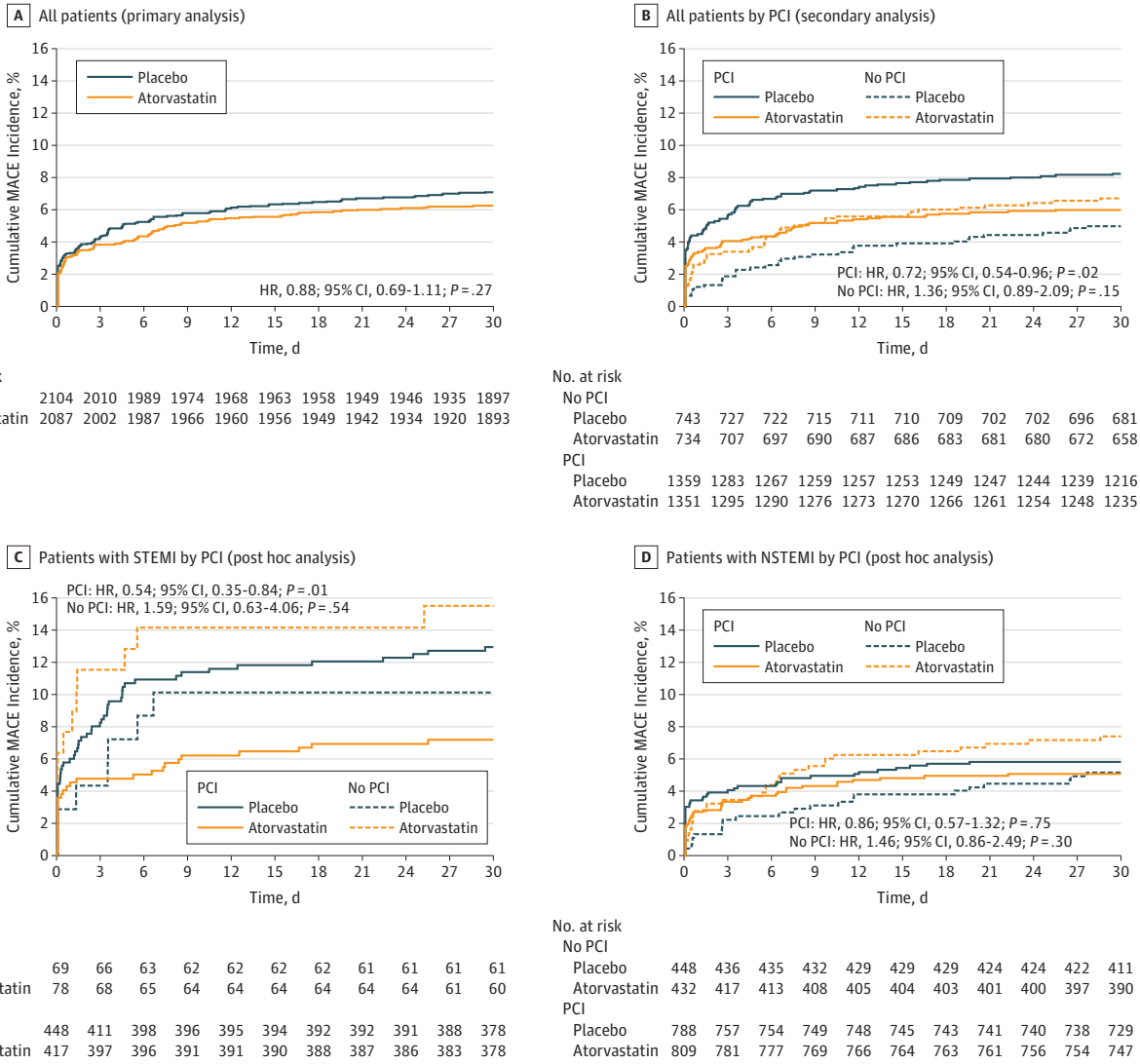
[a] Data are expressed as No./total No. (%) unless otherwise indicated.

Results

Patients

Of the 4191 patients randomized from April 2012 through October 2017, a total of 4 patients (0.1%) withdrew consent after randomization and 24 (0.6%) were lost to follow-up at 30 days (Figure 1). Baseline characteristics are shown in **Table 1**. Groups were well balanced at baseline. The mean age was 61.8 (SD, 11.5) years and 1085 (25.9%) were women. Among the index ACS events, 24.8% were STEMI, 60.7% were NSTEMI, and 14.5% were unstable angina. Regarding treatment strategy, 2710 patients (64.7%) underwent PCI, 333 (8%) underwent coronary artery bypass graft surgery, and 1144 (27.3%) were exclusively medically managed. The median time from admission to PCI was 20 (interquartile

Figure 2. Cumulative Incidence of the Primary Outcome



HR indicates hazard ratio; NSTEMI, non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. The combined primary outcome of major adverse cardiovascular events (MACE) included all-cause mortality, acute myocardial infarction, stroke, and unplanned coronary revascularization occurrence in all patients. Panels B-D show primary outcome occurrence in patients who underwent percutaneous coronary intervention (PCI) and in patients who did not undergo PCI. There were 4 patients (2 in each group) for whom information regarding PCI could not be obtained. These patients were not included in the subgroup analyses (PCI and no PCI subgroups). *P*=.04 for interaction between PCI and non-PCI and *P*=.13 for interaction between groups in panels C and D.

range, 3-68) hours. A total of 4093 patients (97.8%) received a first loading dose and 3216 (76.8%) received a second loading dose (eTable 1 in Supplement 3). The study drug administration and protocol adherence according to initial diagnosis is detailed in eTable 2 in Supplement 3. Procedural characteristics are presented in eTable 3 in Supplement 3. Among patients undergoing PCI, 98% (n=2643) received a stent, with bare-metal stents used more commonly than drug-eluting stents in both treatment groups. The mean percentages of days within the 30-day follow-up period that 40-mg atorvastatin pills were taken according to protocol were 85.1% (SD, 34.1%) in the atorvastatin group and 87.0% (SD, 32.1%) in the placebo group (eTable 1).

Primary Outcome

The primary outcome (MACE) at 30 days occurred in 130 (6.2%) of 2087 patients in the atorvastatin group, compared with 149 (7.1%) of 2104 patients in the placebo group (absolute difference, 0.85% [95% CI, −0.70% to 2.41%]; HR,0.88; 95% CI, 0.69-1.11; *P* = .27) (**Figure 2**A).

Components of the Primary Outcome

At 30 days, MI had occurred in 2.9% of the atorvastatin group and 3.7% of the placebo group (HR, 0.80; 95% CI, 0.57-1.11; *P* = .18), stroke had occurred in 0.5% of patients in both groups (HR, 0.92; 95% CI, 0.39-2.16; *P* = .85), and 3.2% of patients in the atorvastatin group and 3.3% of patients in the

Table 2. 30-Day Outcomes Overall and in Patients Undergoing and Not Undergoing PCI

Outcomes	No. /Total No. (%)		Absolute Difference, % (95% CI)[a]	Hazard Ratio (95% CI)	*P* Value
	Atorvastatin	Placebo			
Primary Outcome at 30 d					
MACE	130/2087 (6.2)	149/2104 (7.1)	0.85 (−0.70 to 2.41)	0.88 (0.69-1.11)	.27
Components of Primary Outcomes at 30 d					
Death	67/2087 (3.2)	70/2104 (3.3)	0.12 (−1.01 to 1.24)	0.97 (0.69-1.35)	.84
Cardiovascular death	59/2087 (2.8)	61/2104 (2.9)	0.07 (−0.99 to 1.13)	0.98 (0.68-1.40)	.90
Myocardial infarction	61/2087 (2.9)	77/2104 (3.7)	0.74 (−0.39 to 1.86)	0.80 (0.57-1.11)	.18
Peri-PCI	42/2087 (2.0)	54/2104 (2.6)	0.55 (−0.40 to 1.51)	0.78 (0.52-1.17)	.23
Non-PCI-related	20/2087 (1.0)	26/2104 (1.2)	0.28 (−0.40 to 0.96)	0.77 (0.43-1.39)	.39
Coronary revascularization	11/2087 (0.5)	14/2104 (0.7)	0.14 (−0.38 to 0.65)	0.79 (0.36-1.75)	.57
Urgent or target vessel	5/2087 (0.2)	9/2104 (0.4)	0.19 (−0.21 to 0.58)	0.56 (0.19-1.67)	.30
Stroke	10/2087 (0.5)	11/2104 (0.5)	0.04 (−0.43 to 0.51)	0.92 (0.39-2.16)	.85
Stent thrombosis	7/2087 (0.3)	15/2104 (0.7)	0.38 (−0.11 to 0.86)	0.47 (0.19-1.15)	.10
Exploratory Analysis at 7 d or Hospital Discharge					
Bleeding	8/2087 (0.4)	11/2104 (0.5)	0.14 (−0.31 to 0.59)	0.84 (0.50-1.43)[b]	.65
Rhabdomyolysis	0	3/2104 (0.1)	0.14 (−0.07 to 0.35)		.25
Exploratory Analysis at 30 d in Subgroup of Patients Undergoing PCI					
MACE	81/1351 (6.0)	112/1359 (8.2)	2.25 (0.24 to 4.25)	0.72 (0.54-0.96)	.02
Death	31/1351 (2.3)	43/1359 (3.2)	0.87 (−0.43 to 2.17)	0.72 (0.46-1.15)	.17
Cardiovascular death	28/1351 (2.1)	37/1359 (2.7)	0.65 (−0.58 to 1.88)	0.76 (0.46-1.24)	.27
Myocardial infarction	48/1351 (3.6)	70/1359 (5.2)	1.60 (−0.01 to 3.21)	0.68 (0.47-0.99)	.04
Peri-PCI	41/1351 (3)	54/1359 (4)	0.94 (−0.52 to 2.40)	0.76 (0.51-1.14)	.18
Non-PCI-related	8/1351 (0.6)	19/1359 (1.4)	0.81 (−0.01 to 1.63)	0.42 (0.18-0.96)	.04
Coronary revascularization	8/1351 (0.6)	12/1359 (0.9)	0.29 (−0.43 to 1.01)	0.67 (0.27-1.63)	.38
Urgent or target vessel	3/1351 (0.2)	7/1359 (0.5)	0.29 (−0.24 to 0.82)	0.43 (0.11-1.66)	.22
Stroke	4/1351 (0.3)	8/1359 (0.6)	0.29 (−0.28 to 0.87)	0.50 (0.15-1.66)	.26
Stent thrombosis	7/1351 (0.5)	15/1359 (1.1)	0.59 (−0.16 to 1.33)	0.47 (0.19-1.14)	.10
Exploratory Analysis at 30 d in Subgroup of Patients Not Undergoing PCI					
MACE	49/734 (6.7)	37/743 (5.0)	−1.70 (−4.22 to 0.83)	1.36 (0.89-2.09)	.15
Death	36/734 (4.9)	27/743 (3.6)	−1.27 (−3.47 to 0.93)	1.36 (0.83-2.25)	.22
Cardiovascular death	31/734 (4.2)	24/743 (3.2)	−0.99 (−3.06 to 1.07)	1.32 (0.78-2.25)	.31
Myocardial infarction	13/734 (1.8)	7/743 (0.9)	−0.83 (−2.14 to 0.49)	1.91 (0.76-4.79)	.17
Peri-PCI	1/734 (0.1)	0	−0.14 (−0.54 to 0.27)		
Non-PCI-related	12/734 (1.6)	7/743 (0.9)	−0.69 (−1.98 to 0.59)	1.76 (0.69-4.47)	.23
Coronary revascularization	3/734 (0.4)	2/743 (0.3)	−0.14 (−0.87 to 0.59)	1.54 (0.26-9.25)	.63
Urgent or target vessel	2/734 (0.3)	2/743 (0.3)	0.00 (−0.54 to 0.53)	1.03 (0.15-7.31)	.98
Stroke	6/734 (0.8)	3/743 (0.4)	−0.41 (−1.34 to 0.52)	2.05 (0.51-8.18)	.31
Stent thrombosis	0	0			

Abbreviations: MACE, major adverse cardiovascular events; PCI, percutaneous coronary intervention.

[a] Positive values favor atorvastatin.

[b] Effect estimate is risk ratio instead of hazard ratio.

placebo group had died (HR, 0.97; 95% CI, 0.69-1.35; *P* = .84) (**Table 2**). Other secondary outcomes are listed in Table 2.

Subgroups

The main results of the trial were consistent among different subgroups, and there was not statistical evidence of interaction except in the PCI group (*P* = .02 for interaction) (**Figure 3**).

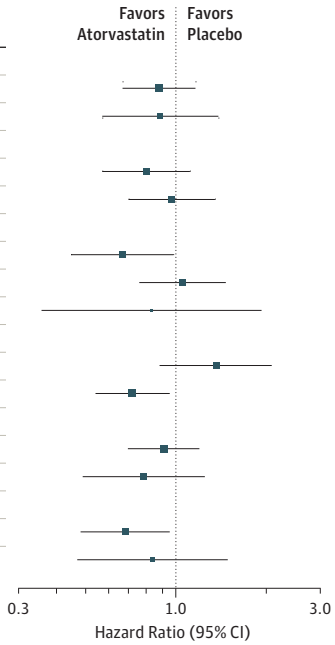
Among 2710 patients (64.7% of the overall population) who underwent PCI, MACE at 30 days occurred in 81 (6.0%) of 1351 patients in the atorvastatin group compared with 112 (8.2%) of 1359 in the placebo group (HR, 0.72; 95% CI, 0.54-0.96; *P* = .02). In 1477 patients (35.2% of the overall population) who did not undergo PCI, MACE at 30 days occurred in 49 (6.7%) of 734 patients in the atorvastatin group compared with 37 (5.0%) of 743 patients in the placebo group (HR, 1.36; 95% CI, 0.89-2.09; *P* = .15) (Table 2).

Exploratory Analyses

Total cholesterol, low-density lipoprotein cholesterol, and triglycerides did not differ significantly at baseline, but at 30 days there was a difference between groups for low-density lipoprotein cholesterol, with mean values of 79.6 (SD, 56.4) mg/dL (2.06 [SD, 1.46] mmol/L) in the atorvastatin group and 75.8 (SD, 34.7) mg/dL (1.96 [SD, 0.90] mmol/L) in the placebo group (*P* = .04) (eTable 4 in Supplement 3).

Figure 3. Subgroup Analysis of the Primary Outcome

	No. With Primary Outcome/Total No. (%)				
	Atorvastatin (n = 2087)	Placebo (n = 2104)	Hazard Ratio (95% CI)	Favors Atorvastatin / Favors Placebo	*P* Value for Interaction
Sex					
Male	95/1581 (6.0)	104/1525 (6.8)	0.88 (0.66-1.16)		.96
Female	35/506 (6.9)	45/579 (7.8)	0.89 (0.57-1.38)		
Age, y					
≤65	62/1320 (4.7)	77/1314 (5.9)	0.80 (0.57-1.11)		.41
>65	68/767 (8.9)	72/790 (9.1)	0.97 (0.70-1.35)		
Type of acute coronary syndrome					
STEMI	42/495 (8.5)	65/517 (12.6)	0.66 (0.45-0.98)		.21
NSTEMI	73/1241 (5.9)	69/1236 (5.6)	1.05 (0.76-1.46)		
Unstable angina	10/295 (3.4)	12/296 (4.1)	0.83 (0.36-1.93)		
Percutaneous cornary intervention					
No	49/734 (6.7)	37/743 (5.0)	1.36 (0.89-2.09)		.02
Yes	81/1351 (6.0)	112/1359 (8.2)	0.72 (0.54-0.96)		
Previous use of statin					
No	98/1477 (6.6)	109/1502 (7.3)	0.91 (0.69-1.20)		.58
Yes	32/608 (5.3)	40/600 (6.7)	0.78 (0.49-1.24)		
Type of stent[a]					
Bare-metal stent only	56/1013 (5.5)	82/1020 (8.0)	0.68 (0.48-0.95)		.18
≥1 Drug-eluting stent	21/298 (7.0)	26/312 (8.3)	0.83 (0.47-1.48)		



NSTEMI indicates non–ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction. Size of the data markers indicates size of hazard ratios. *P* values were calculated by interaction parameters in the Cox regression model.

[a] Among patients undergoing PCI, 2643 (98%) received a stent.

Sensitivity Analyses

Sensitivity analyses are presented in eTable 5 in Supplement 3. Overall, the results of the sensitivity analyses were consistent with the main findings of the study.

Post Hoc Analyses

The results in the STEMI and NSTEMI subgroups were also explored according to treatment with PCI or not. In the subgroup of patients with STEMI (Figure 2C), MACE at 30 days occurred in 30 of 417 patients in the atorvastatin group and in 58 of 448 patients in the placebo group who underwent PCI (HR, 0.54; 95% CI, 0.35-0.84; *P* = .01) and occurred in 12 of 78 patients in the atorvastatin group and in 7 of 69 patients in the placebo group who did not undergo PCI (HR, 1.59; 95% CI, 0.63-4.06; *P* = .54) (*P* = .04 for interaction). In the NSTEMI subgroup (Figure 2D), MACE at 30 days occurred in 41 of 809 patients in the atorvastatin group and in 46 of 788 patients in the placebo group who underwent PCI (HR, 0.86; 95% CI, 0.57-1.32; *P* = .75) and occurred in 32 of 432 patients in the atorvastatin group and in 23 of 448 patients in the placebo group who did not undergo PCI (HR, 1.46; 95% CI, 0.86-2.49; *P* = .30) (*P* = .13 for interaction).

Adverse Events

No cases of rhabdomyolysis or hepatic failure were reported in the atorvastatin group. Creatine phosphokinase and aminotransferases levels were not significantly different in patients treated with atorvastatin vs placebo (eTable 3 in Supplement 3).

Discussion

In this randomized clinical trial of patients with ACS and planned invasive management, loading doses of atorvastatin, compared with placebo, did not reduce the rate of MACE at 30 days. Several small studies suggested that a loading dose of statin in the periprocedural setting can reduce myocardial infarction.[7-13] Pooled data from published studies showed an aggregate 44% relative risk reduction in MACE at 30 days in the group using an early and high dose of statin.[13] However, most of the evidence derives from studies including patients with stable coronary disease and elective PCI.[12,13] The small number of ACS patients with low absolute numbers of clinical events included in previous trials do not allow an adequate evaluation of the treatment effect of a loading dose of statin in this setting.[12,13]

In previous trials, the benefit of loading doses of statins among ACS patients was observed only in patients treated with PCI.[12,13] This study likewise did not show a reduction in MACE at 30 days in the overall ACS population. However, the significant reduction in MACE among patients undergoing PCI suggests a benefit of loading doses in the periprocedural setting. Considering that the reduction of MACE observed in this study occurred early and was related to PCI, the mechanism behind this potential effect is likely not the low-density lipoprotein cholesterol reduction. Mechanistic studies have suggested that statins have important pleotropic effects that can start early after statin initiation.[5,6] These effects include

regulation of nitric oxide synthesis, reducing metalloproteinase activity, and lowering circulating levels of proinflammatory biomarkers.[5,6,15]

The CANTOS trial[19] has shown that anti-inflammatory intervention reduces major cardiovascular outcomes in patients with coronary artery disease, which supports the hypothesis that the possible benefit of statin therapy could extend beyond a lipid-lowering effect. Considering that PCI may result in both local and embolic complications and also enhancement of inflammatory activity and atherosclerotic plaque instability,[20,21] these additional effects of statins have the potential to reduce the risk of clinical events, especially in patients undergoing a coronary intervention. Despite occurring among a postbaseline subgroup, the reduction of MACE found in the PCI-treated patients suggests that loading doses of statins might have a role in modifying adverse atherosclerotic events in patients with ACS undergoing PCI, particularly in patients with STEMI. However, this finding requires further investigation.

The current evidence-based guidelines already recommend routine use of high-dose statins among patients with ACS.[1,3] However, the ideal timing of statin initiation in the ACS setting remains uncertain, which is reflected by the fact that registries and quality improvement programs have been assessing the use of statins at discharge as the main process indicator of adherence to guidelines.[1,3] Thus, the findings of this study may help guide medical decision making regarding how to start statins in the very early phase of ACS, particularly in patients with STEMI undergoing an invasive strategy. Considering that after 48 hours both groups of patients in this study received the same statin regimen but early initiation of atorvastatin was safe and suggested some benefit in the prespecified group of patients undergoing PCI, use of a loading dose of statin in clinical practice may be a reasonable approach especially useful for hospitals that do not use this statin regimen in the first 24 to 48 hours. Importantly, in this study, in the subgroup of patients with STEMI undergoing primary PCI, with the very short time from loading-dose statin initiation to PCI, 80 mg of atorvastatin before and after the coronary intervention showed a significant reduction in MACE at 30 days. This early administration of statins before primary PCI is not recommended in evidence-based guidelines; thus, these findings may guide medical decision making in these critical scenarios.

Limitations

This study has several limitations. First, a heterogeneous population of patients with ACS was included. Patients who did not undergo PCI were represented in this trial because it was a more pragmatic approach to include patients before knowing their coronary anatomy, allowing study treatment to be given prior to the coronary procedure. However, considering that there is less of a rationale for potential benefit in patients without PCI, this may explain the reason for the lack of a significant treatment effect of a loading dose of atorvastatin in the overall population. Future studies enrolling exclusively patients undergoing PCI might yield different results than the overall findings of the present study. Second, despite that the analysis including only patients who underwent PCI was prespecified, the results for this postbaseline subgroup of patients should be interpreted with caution and should be considered as purely exploratory. In addition, although sensitivity analyses were performed with results consistent with the main findings, immortal time bias cannot be completely excluded when analyzing subgroups that are defined based on postbaseline characteristics.

Third, 3% of all patients included in this study did not have a confirmed ACS as their final diagnosis. Nevertheless, the sensitivity analyses excluding patients without ACS were robust and consistent with the overall study results. Fourth, the observed event rates were lower than the ones used in the sample size calculation, which were based on previous randomized evidence. Several factors—including that this study used broader and more pragmatic eligibility criteria than previous studies, that about one-third of patients in this study did not undergo PCI, and that more recent and specific criteria were used to adjudicate outcomes such as periprocedural MI—may partially account for the lower-than-expected event rates found in this study.

Conclusions

Among patients with ACS and planned invasive management with PCI, periprocedural loading doses of atorvastatin did not reduce the rate of MACE at 30 days. These findings do not support the routine use of loading doses of atorvastatin among unselected patients with ACS and intended invasive management.

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