Clinical Benefit of Statin Pretreatment in Patients Undergoing Percutaneous Coronary Intervention: A Collaborative Patient-Level Meta-Analysis of 13 Randomized Studies

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Clinical Benefit of Statin Pretreatment in Patients Undergoing Percutaneous Coronary Intervention

A Collaborative Patient-Level Meta-Analysis of 13 Randomized Studies

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Background—Previous studies suggested that statin pretreatment reduces cardiac events in patients undergoing percutaneous coronary intervention. However, most data were observational, and single randomized trials included limited numbers of patients.

Methods and Results—We performed a collaborative meta-analysis using individual patient data from 13 randomized studies in which 3341 patients received either high-dose statin (n=1692) or no statin/low-dose statin (n=1649) before percutaneous coronary intervention, with all patients receiving statin therapy after intervention. Occurrence of periprocedural myocardial infarction, defined as postintervention creatine kinase–MB increase ≥3 times the upper limit of normal, and 30-day major adverse cardiac events (death, myocardial infarction, target-vessel revascularization) was evaluated. Incidence of periprocedural myocardial infarction was 7.0% in the high-dose statin versus 11.9% in the control group, which corresponds to a 44% risk reduction in the active-treatment arm (odds ratio by fixed-effects model 0.56, 95% confidence interval, 0.44 to 0.71, $P<0.00001$). The rate of major adverse cardiac events at 30 days was significantly lower in the high-dose statin group (7.4% versus 12.6%, a 44% risk reduction; $P<0.00001$), and 1-month major adverse cardiac events, excluding periprocedural events, were also reduced (0.6% versus 1.4%; $P=0.05$). The benefit of high-dose statins was realized irrespective of clinical presentation (P for interaction=0.43) and was maintained across various subgroups but appeared greater in the subgroup with elevated baseline C-reactive protein levels (n=734; 68% risk reduction for periprocedural myocardial infarction versus 31% in those 1861 patients with normal CRP; P for quantitative interaction=0.025).

Conclusions—High-dose statin pretreatment leads to a significant reduction in periprocedural myocardial infarction and 30-day adverse events in patients undergoing percutaneous coronary intervention. This strategy should be considered in all patients with planned percutaneous coronary intervention. **(*Circulation*. 2011;123:1622-1632.)**

Key Words: statins, HMG-CoA ■ outcomes assessment ■ protective agents ■ meta-analysis ■ stents

Percutaneous coronary intervention (PCI) represents the prevalent revascularization strategy in patients with coronary artery disease. Although this procedure is safe and is associated with low rates of severe complications, periprocedural myocardial infarction, as assessed by cardiac marker elevation, occurs in 5% to 40% of patients, depending on the definition applied, antithrombotic approaches, and clinical/angiographic risk profile,[1–4] and it is well known that this complication may negatively impact clinical outcome after intervention.[2,3,5] Thus, various strategies, usually focused on

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improvement of antithrombotic therapy, have been evaluated to decrease the incidence of cardiac ischemic events during PCI (use of glycoprotein IIb/IIIa antagonists, β-blockers, optimization of clopidogrel loading, and new antiplatelet agents).[6–10]

Clinical Perspective on p 1632

In the last few years, experimental studies demonstrated that statins have cardioprotective effects in the animal model of ischemia/reperfusion,[11,12] and clinical data indicated that pretreatment with statins may significantly reduce periprocedural complications and major adverse cardiac events (MACE) in patients undergoing PCI[13–15]; however, those data mainly derive from observational studies, whereas single randomized trials on this topic included a limited number of patients and were not powered to evaluate post-PCI events.[16–28] It may be difficult to reach definitive conclusions on the basis of the results of individual studies; thus, we performed a collaborative patient-level meta-analysis of randomized, controlled trials that evaluated the clinical benefit of statin pretreatment in the setting of PCI to quantify the effect of such therapy on the reduction of periprocedural myocardial infarction and MACE at 30 days.

Methods

Data Sources and Selection Criteria

The MEDLINE and PubMed databases (from 1996 to 2010) were searched, and cited references were reviewed to identify prospective randomized trials that compared the clinical outcome of high-dose versus no statin or low-dose statin pretreatment in patients undergoing PCI. Search keywords were "statins," "statin," "atorvastatin," "rosuvastatin," "cerivastatin," "simvastatin," "pravastatin," "lovastatin," and "hydroxymethylglutaryl-CoA," combined with the words "angioplasty," "stent," "coronary," and "randomized." No restriction on subheadings was applied. Presentations at major cardiology congresses (meetings of the European Society of Cardiology, American College of Cardiology, and American Heart Association) were checked through meetings proceedings, official Web sites, and direct attendance at the meetings. All references of relevant trials were also reviewed.

Data Collection

We included 13 clinical trials; full descriptions of the study designs, sample characteristics, treatment protocols, and outcome findings have been reported elsewhere.[16–28] No identified studies were excluded. Principal investigators of each of the 13 trials were invited to send the requested patient-level data regarding main clinical and procedural features in the study population, as well as individual outcome data, including levels of creatine kinase–MB (CK-MB) and troponin before and after intervention; periprocedural high-sensitivity C-reactive protein (CRP) levels; and occurrence of death, stent thrombosis, unplanned target-vessel revascularization, myocardial infarction up to 30 days, or relevant drug-related side effects. Of the 13 studies, 12 agreed to participate in the patient-level analysis and 1 declined.[22] An electronic form that contained those data fields to be completed for individual patients was sent to the principal investigators who agreed to participate. All data were verified thoroughly for consistency (logical checking and checking against the original publications). Any disagreements were resolved, and final database entries were verified by the responsible trial investigator.

Quality of the Studies

Studies were evaluated for the adequacy of allocation concealment and performance of the analysis according to the intention-to-treat principle. Criteria previously described by Altman and Schulz[29] were used to determine adequate concealment of the treatment allocation. We did not perform weighting of the studies by quality scores because this practice has been discouraged previously in controlled clinical trials.[30]

End-Point Definitions

Individual data were pooled for comparison of the incidence of periprocedural myocardial infarction and MACE at 30 days in the 2 arms (high-dose statin pretreatment versus control). The control group included patients who received either no statin or low-dose statin before PCI.

For the purpose of this meta-analysis, to allow optimal comparability, a standard definition of periprocedural infarction was applied for all studies according to the universal definition,[31] even if the study used a different definition of periprocedural myocardial infarction: In patients with stable angina or non–ST-segment elevation acute coronary syndrome (ACS), periprocedural infarction was defined as a postintervention CK-MB increase ≥3 times the upper limit of normal (ULN), whereas in patients with ST-segment elevation myocardial infarction, it was defined as a ≥20% increase from the baseline value in CK-MB or troponin levels in the second sample drawn after 3 to 6 hours. A secondary analysis of periprocedural myocardial injury was defined as any postintervention elevation of troponin levels >1×ULN. Other exploratory definitions of periprocedural myocardial ischemic events included post-PCI CK-MB raise >1×ULN and troponin elevation ≥3×ULN. We also report data according to the "per trial" definition of periprocedural myocardial infarction.

The composite end point of the analysis was incidence of MACE, defined as death, myocardial infarction, or target-vessel revascularization, by 30 days. Other MACE end points were evaluated for consistency, including death, myocardial infarction, target-vessel revascularization, or stent thrombosis by 30 days, as well as both MACE end points using only spontaneous myocardial infarction rather than both spontaneous infarction and periprocedural infarction. The components of the MACE end points were also evaluated individually.

Outcome data were available through 30 days for all patients of the included studies, except those by Bozbas et al,[24] Jia et al,[26] and Cay et al,[28] which collected data only on in-hospital events. In addition, the study by Veselka et al,[22] who did not participate in the patient-level meta-analysis, did not evaluate the 30-day clinical outcome. For those 4 studies, which comprised 820 patients, in-hospital events were used for the MACE end point. Periprocedural high-sensitivity CRP level variation (postintervention CRP minus baseline CRP) was evaluated in the 2 groups when those data were available, as was the incidence of periprocedural infarction according to baseline CRP levels.

Statistical Analysis

A patient-level pooled analysis was performed to evaluate the effect of pretreatment with high-dose statin on outcome measures. The analysis was performed according to the intention-to-treat strategy. Percentages are presented for discrete variables and mean±SD or median (with 25th and 75th percentiles) for continuous variables. Continuous variables were compared with the Wilcoxon rank sum test. Differences between randomized groups for categorical variables were compared with a χ^2 test or Fisher exact test, as appropriate. Treatment effects were estimated from logistic regression models and reported as odds ratio (OR) with 95% confidence intervals (CIs). Subgroup analysis was performed in subjects by index event of stable angina versus ACS and by use of glycoprotein IIb/IIIa inhibitors, as well as according to other features (age, sex, diabetes mellitus versus no diabetes, single-vessel versus multivessel intervention, and presence or absence of elevated CRP).

To evaluate the robustness of the findings and the impact of the 1 study that declined to participate in the patient-level analysis, we conducted a trial-level meta-analysis using the event rates in the high-dose statin and control arms for each trial. The meta-analysis was performed of the relative odds based on fixed-effects models. A

test of heterogeneity, which evaluates variability in the treatment effects, was performed by the Mantel-Haenszel method. The possibility of publication bias was assessed by funnel plot analysis.[32] A 2-sided $P<0.05$ was considered statistically significant. With the exception of the trial-level meta-analysis, all other statistical analyses were performed with Stata/SE, version 9.2 (StataCorp, College Station, TX). The trial-level meta-analysis was performed with Review Manager 4.2.10 software (available from The Cochrane Collaboration at http//www.cochrane.org). Thirty-day cardiac event analysis was performed by the Kaplan-Meier method with log-rank test group comparison.

Results

Main Features of Included Studies

Data from the aforementioned 13 prospective randomized trials[16–28] that evaluated the effects of high-dose statin pretreatment on clinical outcome in patients undergoing PCI were analyzed (Table 1); 3341 patients were included in the analysis, 1692 of whom were randomized to high-dose statin and 1649 to low-dose or no statin therapy (control group).

The clinical presentation of the patients included in the studies and the drug assignment before PCI are indicated in Table 1. Patients with severe renal failure or with liver or muscle diseases were excluded. All studies except 2 (ARMYDA-RECAPTURE [Atorvastatin for Reduction of Myocardial Damage During Angioplasty Recapture Trial][20] and the study by Hara et al[27]) included statin-naive patients. In all studies, patients received statin therapy after the intervention irrespective of the initial randomization assignment (Table 1).

The pre-PCI bolus of unfractionated heparin was similar: 5000 IU in the studies by Yun et al[19] and Jia et al,[26] 50 to 80 IU/kg in the study by Veselka et al,[22] 70 to 100 IU/kg in the studies by Bozbas et al[24] and Cay et al,[28] 100 IU/kg in the study by Hara et al,[27] and 70 IU/kg in the 3 ARMYDA trials,[16,18,20] the 2 studies by Briguori et al,[17,21] and the study by Kinoshita et al.[25] In STATIN STEMI (Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction),[23] weight-adjusted unfractionated heparin was given to achieve a target activated clotting time of >300 seconds in the absence of glycoprotein IIb/IIIa inhibitors and 200 to 300 seconds with glycoprotein IIb/IIIa inhibitors. Bivalirudin was used instead of unfractionated heparin in 10% of patients in ARMYDA-RECAPTURE[20] and enoxaparin in 37% of those in the study by Yun et al.[19] Patients in all studies were pretreated with aspirin; the ARMYDA trials and STATIN STEMI[16,18,20,23] used 600 mg of clopidogrel as a loading dose, 5 studies[19,21,22,24,28] used a 300-mg loading dose, 3 studies[17,25,26] used either ticlopidine or clopidogrel (75 mg/d) starting ≥3 days before PCI, and ticlopidine or cilostazol was given in the study by Hara et al.[27] Glycoprotein IIb/IIIa inhibitors were not used in 4 studies,[22,24,25,27] whereas such agents were administered, at the discretion of the operator, in the following proportions of patients in the other studies: 52% in the studies by Briguori et al,[17] 24% in ARMYDA-ACS,[18] 20% in ARMYDA[16] and in the study by Jia et al,[26] 14% in NAPLES (Novel Approaches for Preventing or Limiting Events) II[21] and in the study by Cay et al,[28] 12% in ARMYDA-RECAPTURE,[20] 7% in the study by Yun et al,[19] and 22% in STATIN STEMI.[23] There were no differences in periprocedural antithrombotic therapies between high-dose statin pretreatment and control groups in any of the studies.

Main demographic, clinical, and procedural features in the overall population are reported in Table 2. The prevalence of patients with age ≥65 years was approximately 50%; 39% of patients had ACS, and 28% had diabetes mellitus.

Periprocedural Outcome

Patient-level analysis demonstrated that overall, periprocedural myocardial infarction occurred in 6.8% of patients in the high-dose statin pretreatment group versus 11.9% of those in the control group, which corresponds to a 46% relative reduction in the active-treatment arm (OR, 0.54, 95% CI, 0.42 to 0.70; $P<0.00001$). When data from the study by Veselka et al[22] were added in a trial-level analysis, the findings for periprocedural myocardial infarction were consistent: 7.0% versus 11.9%, a 44% relative risk reduction (OR, 0.56, 95% CI, 0.44 to 0.71; $P<0.00001$; Table 3; Figure 1). There was no evidence of significant heterogeneity among the 13 trials ($P=0.62$, $I^2=0\%$), and funnel plot analysis did not suggest the presence of publication bias (Figure 1). High-dose statin pretreatment was also associated with a significantly lower incidence of periprocedural myocardial infarction per trial definition (6.8% versus 15.1% in the control arm; OR, 0.40, 95% CI, 0.32 to 0.51; $P<0.00001$).

Moreover, after high-dose statin pretreatment, there was a decreased incidence of periprocedural myocardial injury (defined as any post-PCI elevation of troponin levels above the ULN): 34.9% versus 47.7% in the control group (OR, 0.59, 95% CI, 0.51 to 0.68; $P<0.00001$). When data from the study by Veselka et al[22] were added in a trial-level analysis, the findings for periprocedural myocardial injury were consistent: 35.8% versus 47.9% (OR, 0.57, 95% CI, 0.49 to 0.67; $P<0.00001$; Table 3). Results according to other exploratory definitions of periprocedural myocardial ischemic events are indicated in Table 3. Maximum CK-MB/ULN ratio and maximum troponin/ULN ratio after PCI were also significantly lower in the high-dose statin group (CK-MB: median 0.7 ng/mL, interquartile range 0.4 to 1.1 ng/mL versus 0.8 ng/mL, interquartile range 0.5 to 1.6 ng/mL [$P=0.00001$]; troponin: median 0.4 ng/mL, interquartile range 0.1 to 1.8 ng/mL versus 0.8 ng/mL, interquartile range 0.2 to 3.8 ng/mL [$P=0.00001$]).

Adverse Events at 30 Days

The proportion of patients with MACE (including periprocedural myocardial infarction) at 30 days was lower in the high-dose statin pretreatment group (7.4% versus 12.6%; OR, 0.56, 95% CI, 0.44 to 0.71; $P<0.00001$; Table 3; Figure 2); this outcome was mainly driven by periprocedural events in either arm (Figure 3). There was no evidence of significant heterogeneity among the trials with regard to outcome data through 1 month ($P=0.54$, $I^2=0\%$; Figure 2). However, when only spontaneous myocardial infarctions (ie, not periprocedural infarctions) were counted, rates of MACE were 0.6% in the high-dose statin group versus 1.4% in the control arm, with an OR of 0.44 (95% CI, 0.19 to 1.01; $P=0.05$), consistent with the overall

Table 1. Main Descriptors of the 13 Trials Included

Trials	Patients, n	Type of Population	Clinical Presentation	Type of Statin	Statin Regimen Before PCI	Statin Regimen After PCI*	Follow-Up
ARMYDA[16]	153	Statin naive	Stable angina	Atorvastatin	7-Day pretreatment with 40 mg/d vs placebo	Atorvastatin 40 mg/d	30 d
ARMYDA-ACS[18]	171	Statin naive	NSTE-ACS	Atorvastatin	80 mg 12 h before PCI+40 mg 2 h before PCI vs placebo	Atorvastatin 40 mg/d	30 d
ARMYDA-RECAPTURE[20]	383	Statin-treated	53% Stable angina; 47% NSTE-ACS	Atorvastatin	80 mg 12 h before PCI+40 mg 2 h before PCI vs placebo	Atorvastatin 40 mg/d	30 d
Briguori et al[17]	451	Statin naive	92% Stable angina/asymptomatic; 8% unstable angina	39% Simvastatin; 29% atorvastatin; 29% pravastatin; 3% fluvastatin	≥3-Day pretreatment (average 17 days) vs no statin pretreatment	The same statin as before PCI in the statin group and atorvastatin 20 mg/d in the control group	30 d
NAPLES II[21]	668	Statin naive	98% Stable angina/asymptomatic; 2% unstable angina	Atorvastatin	80 mg <24 h before PCI vs no-statin pretreatment	Atorvastatin 20 mg/d	30 d
STATIN STEMI[23]	171	Statin naive	STEMI	Atorvastatin	80 mg in the emergency room vs 10 mg	Atorvastatin 10 mg/d	30 d
Veselka et al[22]	200	Statin naive	Stable angina	Atorvastatin	2-Day pretreatment with 80 mg/d vs no statin pretreatment	NA	In-hospital
Yun et al[19]	445	Statin naive	NSTE-ACS	Rosuvastatin	40 mg 16 h before PCI vs no statin pretreatment	Rosuvastatin 10 to 40 mg/d	30 d
Bozbas et al[24]	93	Statin naive	Stable angina	Pravastatin	7-Day pretreatment with 10 mg/d vs 40 mg/d vs no statin pretreatment	Pravastatin 10 to 40 mg/d	In-hospital
Kinoshita et al[25]	42	Statin naive	Stable angina	Atorvastatin	5-20 mg/d ≥2 wk before PCI to reach LDL-C <70 vs <100 mg/dL	A to rvastatin 5 to 20 mg/d	6 mo
Jia et al[26]	228	Statin naive	29% STEMI; 71% NSTE-ACS	Simvastatin	7-Day pretreatment with 80 mg vs 20 mg	Simvastatin 20 mg/d	In-hospital
Hara et al[27]	37	Statin naive or statin treated	NSTE-ACS	Atorvastatin	20 mg 24 h before PCI vs no statin pretreatment	Atorvastatin 20 mg/d	30 d
Cay et al[28]	299	Statin naive	Stable angina	Rosuvastatin	40 mg 24 h before PCI vs no statin pretreatment	Rosuvastatin 10 to 40 mg/d	In-hospital

PCI indicates percutaneous coronary intervention; ARMYDA, Atorvastatin for Reduction of Myocardial Damage During Angioplasty; ARMYDA-ACS, ARMYDA–Acute Coronary Syndrome; NSTE-ACS, non–ST-segment elevation acute coronary syndrome; ARMYDA-RECAPTURE, ARMYDA Recapture Trial; NAPLES II, Novel Approaches for Preventing or Limiting Events II; STATIN STEMI, Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction; STEMI, ST-segment elevation myocardial infarction; NA, not available; and LDL-C, low-density lipoprotein cholesterol.

*All patients received statin therapy after the intervention, irrespective of the initial randomization assignment.

result shown for MACE that included periprocedural myocardial infarction (Table 3). Complete outcome data at 30 days are reported in Table 3; in particular, 30-day mortality was 0.24% in the high-dose statin group versus 0.56% in the control group (OR, 0.42, 95% CI, 0.11 to 1.64; $P=0.20$), and target-vessel revascularization occurred in 0.32% versus 0.80% (OR, 0.39, 95% CI, 0.12 to 1.26; $P=0.10$). No significant side effects (aspartate transaminase/alanine transaminase or CK elevation >3× ULN) were associated with statin pretreatment in any study.

CRP Data

High-sensitivity CRP levels were measured in 9 studies.[16–21,24,26,27] Periprocedural CRP-level variation (postintervention CRP minus baseline CRP) was lower in patients who received

Table 2. Clinical and Procedural Features in the Overall Population (13 Trials; N=3341)

Characteristics	High-Dose Statin Pretreatment (n=1692)	Controls (n=1649)
Age ≥65 y*	781 (49)	803 (52)
Men	1185 (70)	1231 (75)
Diabetes mellitus	502 (30)	444 (27)
Hypercholesterolemia	699 (41)	606 (37)
Systemic hypertension	1100 (65)	1083 (66)
Active smoker	452 (27)	343 (27)
Previous myocardial infarction	446 (26)	359 (22)
Clinical presentation		
Chronic stable angina	1046 (62)	1009 (61)
ACS	646 (38)	640 (39)
Medical therapy		
β-blockers	904 (53)	857 (52)
ACE inhibitors/sartans	1081 (64)	1033 (631)
Multivessel disease	684 (40)	628 (38)
Multivessel PCI	317 (19)	264 (16)
Treated vessel		
Left main	9 (1)	25 (1.5)
Left anterior descending	887 (52)	884 (54)
Left circumflex	452 (27)	444 (27)
Right coronary	493 (29)	474 (29)
Saphenous vein graft	10 (1)	9 (1)
Lesions B2/C	954 (56)	938 (57)
Antithrombotic therapy		
Unfractionated heparin	1598 (95)	1539 (94)
Bivalirudin	19 (1)	21 (1)
Enoxaparin	75 (4)	89 (5)
Glycoprotein IIb/IIIa inhibitors	296 (17)	306 (19)

ACS indicates acute coronary syndrome (non–ST-segment elevation ACS or ST-segment elevation myocardial infarction); ACE, angiotensin-converting enzyme; and PCI, percutaneous coronary intervention.

Values are reported as n (%).

*Patients enrolled in the study by Veselka et al[22] were excluded.

high-dose statin pretreatment: mean 3.4±10.0 mg/L, median 1.2 mg/L (interquartile range 0.0 to 4.9 mg/L) versus 5.6±16.2 mg/L, median 2.2 mg/L (interquartile range 0.4 to 5.8 mg/L; $P=0.00001$).

In the subgroup of 1861 patients with normal baseline CRP levels (by trial definition), incidence of periprocedural myocardial infarction was 7.8% in the high-dose statin group versus 10.9% in the control group, whereas in those 734 patients with elevated CRP levels, it was 4.3% versus 12.3%, respectively (Figure 4); the OR for periprocedural myocardial infarction in favor of high-dose statin pretreatment was 0.69 (95% CI, 0.50 to 0.95; $P=0.021$) in patients with normal CRP levels and 0.32 (95% CI, 0.18 to 0.58; $P<0.001$) in those with elevated CRP levels (P for quantitative interaction=0.025, ie, both analyses were in the same direction in favor of high-dose statins, but the effect was greater in the subgroup with elevated CRP).

Outcome According to Various Clinical Features

We pooled data to evaluate the grade of benefit provided by high-dose statin pretreatment according to clinical presentation on admission (Figure 5). In the subgroup with stable angina (n=2293), high-dose statin pretreatment was associated with a lower incidence of periprocedural myocardial infarction (7.5% in the high-dose statin group versus 13.2% in the control group, which corresponds to a 48% relative risk reduction [OR, 0.52, 95% CI, 0.41 to 0.66; $P=0.00001$]). In patients presenting with ACS (n=1032), periprocedural myocardial infarction occurred in 5.9% of patients in the high-dose statin group and 9.0% of those in the control group (OR, 0.64; 95% CI, 0.40 to 1.02; $P=0.06$). The interaction test for clinical presentation was not significant ($P=0.43$).

The ORs for periprocedural myocardial infarction in favor of high-dose statin pretreatment were 0.71 (95% CI, 0.45 to 1.12; $P=0.16$) in patients receiving glycoprotein IIb/IIIa inhibitors (n=603) and 0.49 (95% CI, 0.36 to 0.66; $P=0.00001$) in those not receiving these agents (n=2519; P for interaction=0.18). Patient-level analysis demonstrated that periprocedural myocardial protection by high-dose statin

Table 3. Periprocedural and 30-Day Outcome Data in the 2 Groups

All Trials Pooled	High-Dose Statin Pretreatment*	Controls*	OR (95% CI)	*P*
Periprocedural MI	118 (7.0)	195 (11.9)	0.56 (0.44–0.71)	<0.00001
Periprocedural myocardial injury defined as troponin post-PCI >1×ULN)	572 (35.8)	746 (47.9)	0.57 (0.49–0.67)	<0.00001
Other exploratory definitions of periprocedural myocardial ischemic events				
Post-PCI CK-MB >1×ULN	380 (25.4)	522 (35.9)	0.61 (0.52–0.71)	0.00001
Post-PCI troponin ≥3×ULN	289 (19.3)	428 (29.4)	0.57 (0.48–0.68)	<0.00001
Events at 30 days				
Death	3 (0.24)	7 (0.56)	0.42 (0.11–1.64)	0.20
Spontaneous MI	3 (0.24)	2 (0.16)	1.49 (0.25–8.92)	0.66
TVR	4 (0.32)	10 (0.80)	0.39 (0.12–1.26)	0.10
ST	6 (0.47)	5 (0.40)	1.19 (0.36–3.91)	0.77
MACE (death/all MI/TVR)	125 (7.4)	208 (12.6)	0.56 (0.44–0.71)	<0.00001
MACE (death/all MI/TVR/ST)	126 (7.5)	209 (12.7)	0.56 (0.44–0.71)	<0.00001
MACE (death/spontaneous MI/TVR)	8 (0.6)	18 (1.4)	0.44 (0.19–1.01)	0.05

OR indicates odds ratio; CI, confidence interval; MI, myocardial infarction; PCI, percutaneous coronary intervention; ULN, upper limit of normal; CK-MB, creatine kinase-MB; TVR, target-vessel revascularization; ST, stent thrombosis; and MACE, major adverse cardiac events.

*Reported as n (%).

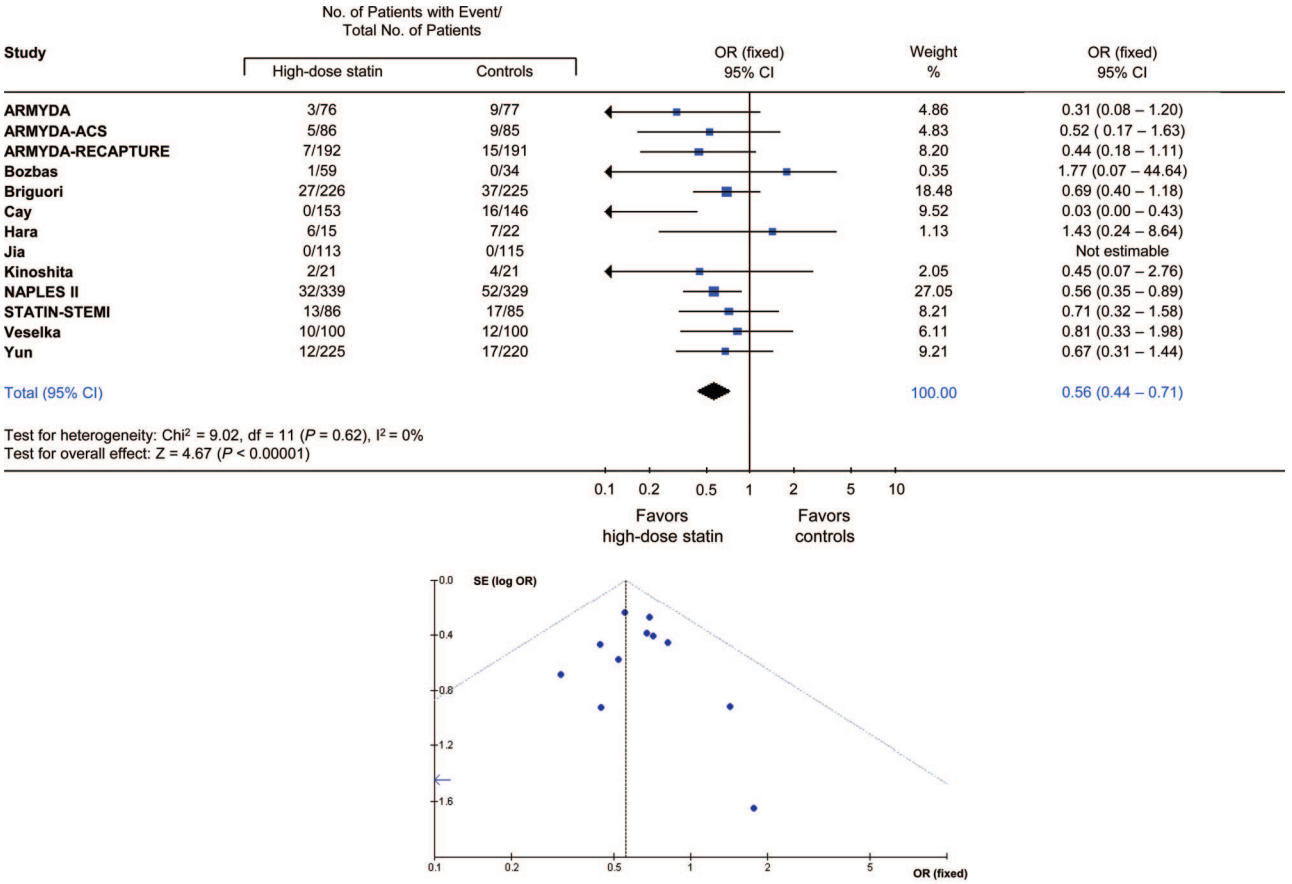

Figure 1. Top, Odds ratios (with 95% confidence interval) of periprocedural myocardial infarction in patients receiving high-dose statin pretreatment vs controls. Bottom, Funnel plot showing no evidence of publication bias. OR indicates odds ratio; CI, confidence interval; ARMYDA, Atorvastatin for Reduction of Myocardial Damage During Angioplasty; ARMYDA-ACS, Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndrome; ARMYDA-RECAPTURE, Atorvastatin for Reduction of Myocardial Damage During Angioplasty–Acute Coronary Syndromes RECAPTURE; NAPLES II, Novel Approaches for Preventing or Limiting Events II; and STATIN STEMI, Efficacy of High-Dose Atorvastatin Loading Before Primary Percutaneous Coronary Intervention in ST-Elevation Myocardial Infarction.

pretreatment was maintained across other subgroups of patients (Figure 5).

Discussion

This collaborative patient-level meta-analysis shows that pretreatment with high-dose statins significantly reduces the risk of adverse cardiac events and periprocedural myocardial infarction in patients undergoing PCI. The finding was robust across all the trials, and was present both in patients who were undergoing PCI after ACS and in those with stable angina. In addition, the benefit was observed in patients receiving dual-antiplatelet therapy (aspirin and a thienopyridine) and in those receiving triple-antiplatelet therapy (also receiving glycoprotein IIb/IIIa inhibitors). High-dose statin therapy reduced high-sensitivity CRP levels over the 24-hour period immediately after PCI, which suggests that the antiinflammatory effect of statins may be a mechanism by which such therapy decreases periprocedural events.

Previous studies have shown that statin therapy, when initiated early after the procedure, improves clinical outcome in patients undergoing PCI.[33] Moreover, data have suggested that patients taking statins at the time of PCI have a lower incidence of periprocedural cardiac ischemic events than those who are statin naive[13–15]; however, those studies were observational and nonrandomized, and included patients with various risk profiles treated with different statins at variable doses and with variable duration of therapy. This is critical, and thus, the meaning of such observational data is questionable and must be considered hypothesis generating. In the last few years, prospective randomized studies have evaluated the issue of whether a statin pretreatment, with fixed doses of a specific agent for a short, definite period, may provide periprocedural cardioprotection in the setting of PCI; the majority of such studies demonstrated a benefit,[16–21,23,25–28] but they did not include large numbers of patients, and 2 studies were not confirmatory.[22,24] Therefore, only pooled analyses that include a large patient population may help to achieve definitive results; a meta-analysis[34] was initially performed on this issue, but it had relevant limitations because it included only 2 prospective trials, which were added into the same analysis as retrospective studies. Three other meta-analyses[35–37] have been published recently that demonstrated the effectiveness of a statin pretreatment in the setting of PCI, but those investigations did not include the newest randomized studies, were conducted at a study level, did not perform time-to-event and subgroup analyses, did not evaluate occurrence of combined and individual MACE, and considered the incidence of periprocedural myocardial infarc-

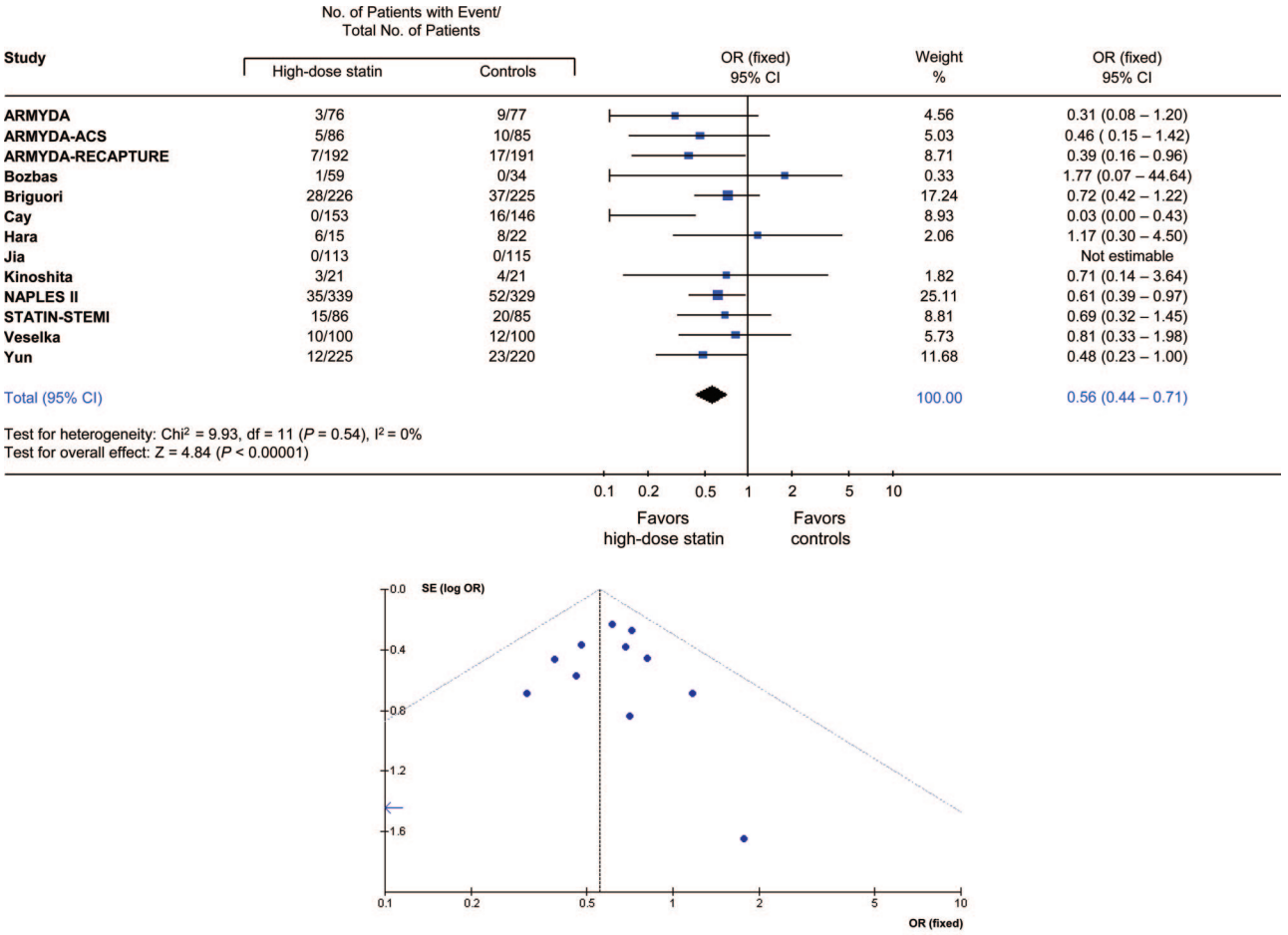

Figure 2. Top, Odds ratios (with 95% confidence interval) of major adverse cardiac events at 30 days in patients receiving high-dose statin pretreatment vs controls. Bottom, Funnel plot showing no evidence of publication bias. Abbreviations as in Figure 1.

tion only according to the per trial definition. The present meta-analysis, which included 3341 patients and was performed at a patient level by a fixed-effects model, owing to the lack of heterogeneity, indicates that a short-term, high-dose statin pretreatment significantly reduces the incidence of periprocedural myocardial infarction in patients undergoing PCI when a universal, contemporary definition of such a complication[31] is used; in particular, use of high-dose statins was associated with a 44% risk reduction for periprocedural infarction, and 20 patients would need to be treated to avoid 1 event. High-dose statin pretreatment decreased the rate of periprocedural myocardial infarction even when a per trial definition was applied (60% risk reduction), and it decreased the rate of periprocedural myocardial injury defined by any troponin elevation (43% risk reduction). Occurrence of periprocedural myocardial infarction by cardiac marker elevation, even if clinically silent, may affect cardiovascular outcome and overall survival in patients treated with PCI[5]; of note, the relative increase in mortality at 6 months associated with each elevation of CK-MB values has been demonstrated

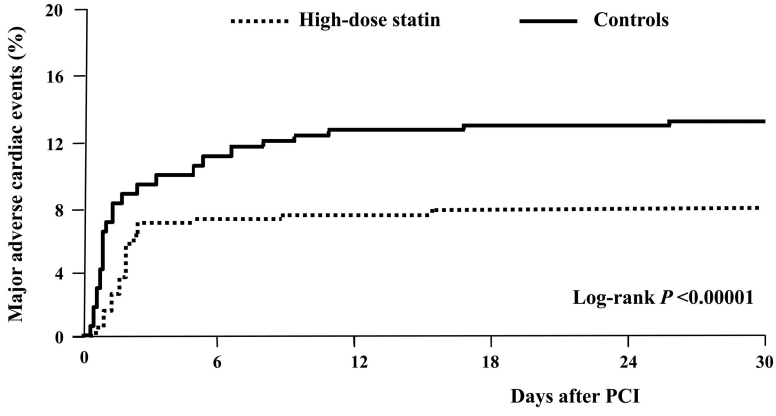

Figure 3. Major adverse cardiac events curves at 30 days in high-dose statin vs control arms. PCI indicates percutaneous coronary intervention.

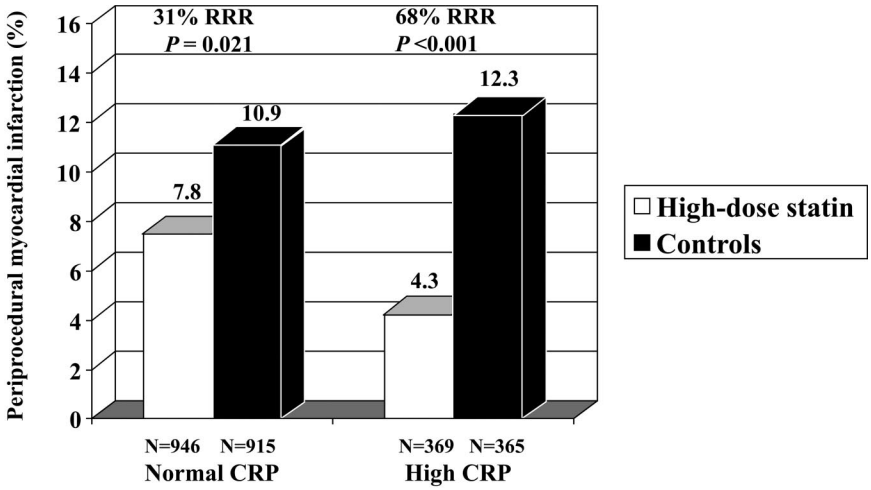

Figure 4. Incidence of periprocedural myocardial infarction in the 2 groups (high-dose statin pretreatment vs controls) according to baseline high-sensitivity C-reactive protein (CRP) levels. RRR indicates relative risk reduction.

to be similar for both spontaneous and PCI-related myocardial necrosis.[38] Furthermore, previous studies demonstrated a correlation between the degree of postprocedural CK-MB increase and mortality risk during follow-up[2–4]; in particular, a meta-analysis that pooled data from 23 230 patients[5] showed that the excess mortality at 1 year was 1.7%, 2.8%, and 7.4% for patients with postintervention CK-MB elevation of 1 to 3 times ULN, 3 to 5 times ULN, and >5 times ULN, respectively. Thus, therapeutic strategies able to reduce the incidence of periprocedural myocardial injury may favorably influence clinical outcome after PCI. Although there is irrefutable evidence that periprocedural myocardial injury results in higher mortality rates during long-term follow-up, a meta-analysis assessing the long-term benefit of high-dose statin pretreatment before PCI might add even more substantial evidence for this particular treatment modality.

In the present meta-analysis, patients pretreated with high-dose statins also had a 44% reduction in risk of 30-day MACE after intervention (number needed to treat=19). Although the incidence of MACE may have been statistically accounted for in part by periprocedural myocardial infarction, other individual outcome measures, including spontaneous myocardial infarction, 30-day mortality, and target-vessel revascularization, were all considerably lower in the high-dose statin arm, although these were not significant owing to the small number of end points attained in these subgroup analyses; future studies may well provide results for a larger number of patients, thereby allowing a much more informative review of these potential benefits.

The incidence of MACE that did not include periprocedural myocardial infarction was lower in the high-dose statin group (0.8% absolute reduction, 56% relative reduction), which was of borderline significance because of the low event rate but was similar to the overall finding for MACE that included periprocedural myocardial infarction; importantly, this occurred despite the fact that all patients continued statin treatment after intervention irrespective of initial randomization assignment and that in the control arm, statin therapy was initiated early after PCI. No evidence of publication bias was found in the results of the present meta-anal-

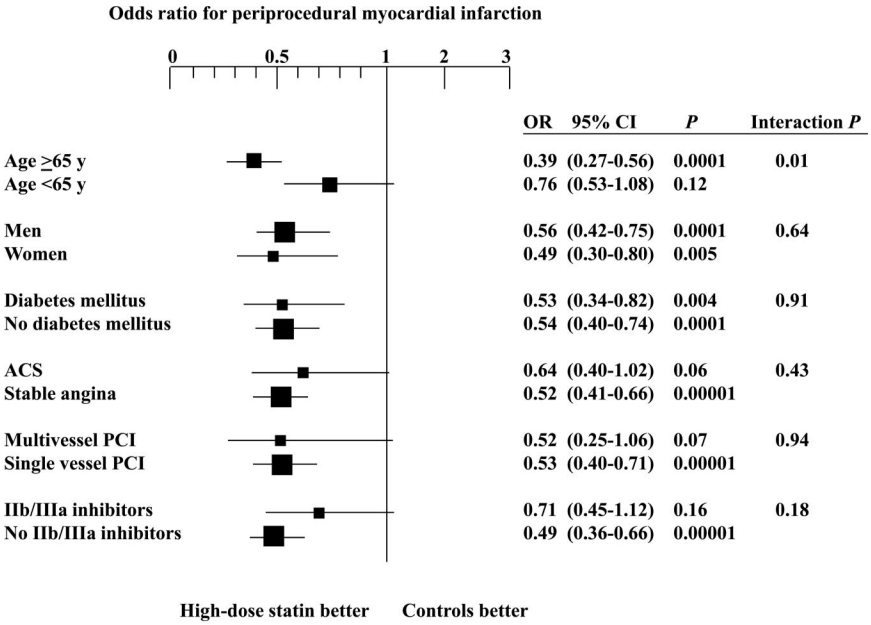

Figure 5. Periprocedural myocardial protection by high-dose statin across various subgroups of patients. ACS indicates acute coronary syndrome; PCI, percutaneous coronary intervention; OR, odds ratio; and CI, confidence interval.

ysis, and no heterogeneity among the trials was found, despite differences in the study designs. Moreover, when individual data were pooled, subgroup analysis revealed that the clinical benefit of high-dose statin pretreatment was significant irrespective of clinical presentation (48% reduction in risk of periprocedural infarction in stable angina and 36% in ACS). Because the absolute number of patients with ACS was relatively low, a need remains for a large randomized, controlled trial to focus on the relevant MACE and periprocedural myocardial infarction reduction observed in the present meta-analysis in this subset. Patients with severe renal failure or with liver or muscle disease were excluded from all trials by protocol, and this precluded assessment of a benefit of high-dose statin in those subgroups of patients.

The possible mechanisms underlying the early protective action of statins are unclear, but are not likely due to cholesterol-lowering effects, because all trials included in the analysis used a short-term pretreatment with high-dose statin (median 0.5 days), which did not produce significant effects on cholesterol levels. Various studies demonstrated early lipid-independent (ie, pleiotropic) effects of statins, including antithrombotic action,[39] improvement of coronary flow velocity reserve by vasodilation of coronary microvessels,[40] and rapid (<12 hours after a single dose of atorvastatin) improvement of endothelial function[41]; in particular, a planned subanalysis of the ARMYDA trial[42] showed that myocardial protection conferred by atorvastatin is paralleled by attenuation of procedural endothelial activation, with significant reduction of adhesion molecules to peak levels after intervention. Furthermore, in STATIN STEMI,[23] pretreatment with high-dose atorvastatin before primary PCI improved microvascular coronary perfusion and ST-segment resolution rates compared with low-dose atorvastatin. A higher inflammatory status in patients undergoing PCI is associated with enhanced risk of periprocedural complications and cardiac events during follow-up.[43,44] Statins have anti-inflammatory effects both in vitro and in vivo.[45,46] In the present meta-analysis, high-dose statin pretreatment was associated with a lower post-PCI increase in CRP levels and provided periprocedural cardioprotection mainly in the subgroup with elevated baseline CRP values; because 4 studies did not perform measurement of CRP levels, the study groups without CRP determination might have differed in some way. The present meta-analysis provides additional evidence to support the subclinical inflammatory hypothesis of atherosclerosis and a likely mechanism by which high-dose statins are beneficial as pretreatment for PCI. However, patients with normal levels of high-sensitivity CRP have a greatly reduced OR when treated with high-dose statins compared with control subjects; this suggests that other mechanisms may be at play that may ultimately influence outcome during or after PCI. All of the aforementioned pleiotropic effects of statins might contribute to decrease myocardial necrosis due to procedural microembolization in the setting of PCI. In particular, patients with ACS and high inflammatory status, in whom there is a complex interaction between endothelial dysfunction/activation, inflammation, and thrombosis, may derive a relevant benefit from early high-dose statin therapy before an invasive strategy.

Experimental data in mice have demonstrated that acute administration of a statin can reduce infarct size after ligation of the left anterior descending artery and subsequent reperfusion[11,12,47]; this animal model has enabled in-depth experiments on the molecular mechanisms of this cardioprotection. In particular, the beneficial effect of atorvastatin may share the same molecular mechanisms as ischemic preconditioning, ie, activation of nitric oxide synthase and promotion of cyclooxygenase-2 and prostaglandin I2.[47,48] Atorvastatin induces rapid (within 5 minutes) activation of the phosphatidylinositol 3-kinase and serine/threonine kinase (Akt) signaling cascades, which in turn causes phosphorylation and activation of nitric oxide synthase.[12] The beneficial effect of atorvastatin on infarct size is absent in nitric oxide synthase knockout mice and may be reversed by administration of specific inhibitors of phosphatidylinositol 3-kinase or nitric oxide synthase.[12,47] Interestingly, the acute protective effect of atorvastatin on myocardial injury in the animal model may wane with a longer treatment, but this effect can be recaptured by a "reloading" given immediately before ischemia/reperfusion.[48] In the ARMYDA-RECAPTURE trial,[20] short-term pretreatment with a high-dose atorvastatin load before PCI was associated with improved periprocedural outcome even in patients undergoing chronic statin therapy, who represent a relevant proportion of those patients receiving percutaneous revascularization.

Although results of retrospective studies (which included patients receiving a multitude of statins) may suggest the presence of a class effect, the large majority of prospective randomized trials demonstrating periprocedural cardioprotection by statins in patients undergoing PCI used a short-term pretreatment with high doses of a potent statin (atorvastatin or rosuvastatin). In particular, studies using atorvastatin 80 mg and rosuvastatin 40 mg before PCI represented 54% and 19%, respectively, of the overall weight in the present meta-analysis. Thus, when a strategy of short-term pretreatment with statins before PCI is adopted, it would be appropriate to use potent statins at high doses (ie, atorvastatin 80 mg or rosuvastatin 40 mg).

Study Limitations

Of the trials identified, the sole investigators who declined to participate in the patient-level analysis were Veselka et al,[22] ie, the authors of 1 of the 2 studies in which a significant clinical benefit by statin pretreatment was not demonstrated. Although their data were entered in the trial-level analysis and did not affect the overall results, lack of inclusion in the patient-level analysis may represent a study limitation. Another limitation is that the included studies used different dosing strategies of statins, and the time points at which cardiac markers were measured after PCI were variable. Moreover, 4 of the 13 studies[22,24,26,28] did not collect 30-day data, and the MACE for those 4 studies only included periprocedural myocardial infarction. Finally, because the antithrombotic treatments used in the various trials appear to be different, the robustness of meta-driven conclusions may be limited and the clinical benefit of high-dose statins observed in the present meta-analysis may be affected; a

standardized approach to antithrombotic therapies in a larger randomized trial would help eliminate this confounder.

Conclusions

Cost-effectiveness analysis of the initiation of statin therapy before PCI would likely be very favorable, because there was no risk excess associated with high-dose loading with statins before the procedure (none of the trials reported significant side effects), and the cost of a few doses of statin is negligible. The consistency across the trials and the strength of the effect observed in the present meta-analysis suggest that a strategy of high-dose statin pretreatment should be used routinely in patients undergoing PCI, irrespective of clinical presentation and chronic statin therapy; guideline committees should consider updates to incorporate this novel strategy for peri-PCI prevention of ischemic events.

Acknowledgments

Drs Di Sciascio and Patti had full access to all the data, and had final responsibility for the decision to submit for publication. Drs Patti, Cannon, and Di Sciascio developed the original idea for this work. Dr Mega undertook the literature search. S. Murphy and Dr Patti performed the statistical analyses. Drs Patti, Pasceri, Briguori, Yun, Jeong, Colombo, Kim, Choi, Bozbas, Kinoshita, Fukuda, Jia, Hara, and Cay provided the original trial data. All authors contributed to the interpretation of results. Dr Patti wrote the draft; all authors contributed to critical revision of the paper for important intellectual content.

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There was no funding source for this study. Four of the studies included in this meta-analysis were funded.[19,22,23,27]

Disclosures

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CLINICAL PERSPECTIVE

In this collaborative patient-level meta-analysis of 13 randomized, controlled trials (n=3341 patients), we demonstrated that short-term pretreatment with high-dose statins reduces the incidence of periprocedural myocardial infarction and early major adverse cardiac events in patients undergoing percutaneous coronary intervention. This outcome improvement was irrespective of clinical presentation, chronic statin therapy, or antithrombotic treatment, and was more pronounced in patients with high baseline inflammatory status. Our results strengthen the concept that the clinical benefit provided in the short-term by high-dose statins is due to pleiotropic effects. These data suggest that a strategy of early initiation of high-dose statins should be implemented routinely in patients who are candidates for percutaneous coronary intervention, and guideline committees should consider updates to incorporate this novel strategy for periprocedural percutaneous coronary intervention prevention of ischemic events.

PCI 직전 고용량 스타틴 투여는 단기 예후 개선에 효과가 있다: 13개 연구 메타분석

김 상 현 교수 서울대학교 보라매병원 순환기내과

Summary

배경

최근 여러 연구에서 경피적 관상동맥 중재술(percutaneous coronary intervention, PCI) 전에 스타틴을 투여하는 것이 심혈관 사건 발생을 감소시킨다는 결과가 발표되었다. 하지만 대부분의 연구가 관찰 연구들이었고, 전향적 연구들의 경우 환자 수가 많지 않은 소규모 연구였으며 대상 환자군에 차이가 있었다. 이에 PCI 직전 고용량 스타틴 투여가 필요한지 메타분석을 실시하였다.

방법 및 결과

13개의 무작위 연구들의 자료를 이용하여 메타분석을 실시하였다. 고용량 스타틴 투여군 1,692명과 저용량 스타틴 혹은 투여받지 않은 군 1,649명 등을 포함하여 3,341명의 자료를 분석하였고, PCI 후에는 모든 환자에서 스타틴 투여가 시행되었다. 시술 후 심근경색은 creatine kinase-MB(CK-MB)가 정상 상한치의 3배 이상 증가한 경우로 정의하였고, 30일 주요 심장사건은 사망, 심근경색, 혈관 재개통술 여부로 정의하였다.

시술 후 심근경색의 발생률은 고용량 스타틴 투여군은 7.0%, 대조군은 11.9%로서 고용량 스타틴 투여군에서 44% 낮았다(OR, 0.56; 95% CI, 0.44-0.71, *P*<0.00001). 30일 주요 심장사건 발생은 고용량 스타틴 투여군은 7.4%, 대조군은 12.6%로서 역시 고용량 스타틴 투여군에서 44% 낮았다. 시술 직후 사건을 제외한 30일 주요 심장사건 발생은 고용량 스타틴 투여군에서 0.6%, 대조군에서 1.4%였다(*P*=0.05). 임상 유형별로 분류한 소그룹 분석에서도 고용량 스타틴 투여는 모든 소그룹에서 효과가 있었다. 그러나 특히 기저 CRP(C-reactive protein) 수치가 높았던 군 734명에서 시술 후 심근경색 위험도의 68% 감소 결과를 보여, CRP가 높지 않았던 1,861명 군에서의 31% 위험도 감소보다 큰 효과를 보였다(*P*=0.025).

결론

PCI 직전 고용량 스타틴 투여는 시술 후 심근경색과 30일 주요 심장사건의 발생을 유의하게 감소시켰다. PCI 직전 모든 환자에서 고용량 스타틴 투여가 고려되어야 한다.

Commentary

이 연구는 ARMYDA, ARMYDA-ACS, ARMYDA-RECAPURE, NAPLES II, STATIN STEMI 등 13개 연구의 3,341명 결과를 메타분석하여 PCI 전 고용량 스타틴 사용이 임상적으로 효과가 있는가를 분석하였다. 결과는 CK-MB가 정상 상한치의 3배 이상 증가로 정의되는 시술 후 심근경색과 30일 주요 심장사건이 각각 44% 유의하게 감소되었고, 특히 기저 CRP 수치가 높았던 환자군에서 더 좋은 효과를 보였다.

이번 연구에 포함된 각각의 연구들을 살펴보면 대상 환자는 37-668명으로 환자수 규모는 작은 편이고, 임상 양상도 안정형 협심증에서부터 NSTEMI-ACS, STEMI까지 다양하였으며, 투여한 스타틴 종류와 용량 그리고 시술 전 투여 시각이나 기간도 매우 다양하였다. PCI 전 스타틴 투여에 의한 시술 후 심근경색의 감소와 30일 주요 심장사건 감소 효과는 스타틴의 지질 수치 개선 효과보다는 PI-3K/Akt 경로를 통한 nitric oxide 생산 증가 등으로 인한 항염증 효과, 항산화 효과, 항혈전 효과 등의 다면성 효과에 의한 것으로 추측되고 있다. 그렇다면 모든 환자에서 PCI 전 고용량 스타틴 투여를 해야 하는가? 여기에 대해서는 상반된 견해가 존재할 수 있기에, 이에 관한 내용을 찬성과 반대 입장에서 분석하고 기술해보았다.

우선, PCI 전 고용량 스타틴 투여를 고려하게 되는 이유는 다음과 같다. 첫째, 이 연구에서 1년 예후에 관한 결과가 없는 것이 아쉬운 점이다. 하지만, 과거 타 메타분석 연구 결과에서 시술 후 CK-MB 상승이 정상 상한치의 1-3배, 3-5배, 5배 이상의 군에서 1년째 사망률이 각각 1.7%, 2.8%, 7.4%로서, 시술 후 CK-MB 수치가 1년 사망률과 연관성이 있었기에 이 연구 결과가 시사하는 바가 크다. PCI 전 고용량 스타틴 투여가 시술 후 심근경색 발생을 감소시키는 단기 효과는 1년 사망률과 연관될 가능성이 높은 것이다. 물론 이는 추측일 뿐이며, 연구를 통해 증명되어야 할 필요성이 있다. 둘째, PCI 시술 전 1회의 고용량 스타틴 투여는 안전성에 큰 문제가 없고 비용도 크지 않다는 주장도 설득력이 있다. 이를 통해서 단기간 예후 개선을 얻을 수 있다면 모든 환자에서 시행하지 않을 이유가 없다는 것이다.

반대로 모든 환자에서 PCI 전 고용량 스타틴 투여는 무리라는 이유는 다음과 같다. 첫째, 30일 주요 심장사건을 보면, 사망이 각각 3명과 7명, 심근경색이 3명 vs. 2 명, 혈관재개통술 필요가 4명 vs. 10명으로서 사건 발생률이 매우 낮기에 이들의 합인 주요 심장사건이 통계적으로 유의한 차이를 보인다고, 이를 그대로 임상에 적용할 수 있을 것인가 하는 의문이다. 둘째, 시술 후 심근경색을 제외한 30일 주요 심장사건의 양 군 간의 차이는 통계적으로 유의하지도 않았다. 시술 전 고용량 스타틴 투여로 확실히 증명된 것은 시술 직후 심근경색 발생를 감소일 뿐이고, 이를 제외한 30일 주요 심장사건이나 장기 예후에 대해서는 근거가 없다는 것이다. 셋째, 각각의 연구들의 스타틴 투여 기간이 달라서 PCI 전 2일, 3일, 7일 혹은 24시간, 16시간 전 투여 등으로 다양하였고, 임상 양상도 다양하였으며, 연구 결과들도 유의한 효과를 보였거나 보이지 못했던 연구 결과들이 섞여 있다. 이 연구 결과를 통해, 시술 바로 직전 1회 투여 만으로, 또는 염증반응이 심하지 않은 안정형 협심증에서도 효과가 있는가에 대한 결론을 얻기에는 무리이다. 또한, 저자들이 기술하였듯이 4개의 연구에서만 30일 주요 심장사건 자료가 있었을 뿐이기에 연구 결과의 대표성에도 의문이 있다.

결론적으로, PCI 전 고용량 스타틴 투여는 시술 관련 심근경색의 발생을 감소시키고 이에 대한 효과로 인해 30일 주요 심장사건을 감소시켰으나, 시술 관련 심근경색을 제외한 순수한 30일 주요 심장사건의 감소 경향은 있지만 유의한 차이를 보이지는 않았다. 따라서 모든 PCI 환자에서 고용량 스타틴 투여를 권유하기 위해서는 추가적인 전향적 무작위 연구를 통한 근거 확인이 필요하다고 판단되며, 특히 NSTEMI-ACS, STEMI와 안정형 협심증을 따로 나누어서 일정한 투여 시점을 정한 디자인으로 연구하는 것이 필요하다.

References

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