Effect of Statin Treatment in Patients With Acute Myocardial Infarction and Left Ventricular Systolic Dysfunction According to the Level of High-Sensitivity C-Reactive Protein

Hae Chang JEONG,¹ MD, Youngkeun AHN,¹ MD, Keun-Ho PARK,¹ MD, Doo Sun SIM,¹ MD, Young Joon HONG,¹ MD, Ju Han KIM,¹ MD, Myung Ho JEONG,¹ MD, Young Jo KIM,² MD, Shung Chull CHAE,³ MD, Myeong Chan CHO,⁴ MD, Jei Keon CHAE,⁵ MD, Chong Jin KIM,⁶ MD, Seung-Woon RHA,⁷ MD, Yang Soo JANG,⁸ MD, Seok Kyu OH,⁹ MD, In Whan SEONG,¹⁰ MD, and Kwang Soo CHA,¹¹ MD, for the Korea Acute Myocardial Infarction Registry (KAMIR) Investigators

SUMMARY

The effects of statins on the prognosis of patients with left ventricular (LV) systolic dysfunction remain controversial. The aim of this study was to assess the effect of statin treatment on clinical outcomes in acute myocardial infarction (AMI) patients with LV systolic dysfunction. A total of 5,119 AMI patients with LV ejection fraction less than 50% on the initial echocardiogram were analyzed in the Korean Acute Myocardial Infarction Registry. The study population was divided into 4 groups according to the level of high sensitivity C-reactive protein (hs-CRP) and statin treatment: low hs-CRP (hs-CRP $\leq$ 2.0 mg/L) and high hs-CRP (hs-CRP $>$ 2 mg/L) with or without statin therapy. We evaluated the incidence of major adverse cardiac events (MACEs) including cardiac death, reinfarction, target lesion revascularization, and coronary artery bypass grafting during a 12-month period in each group. Statin therapy did not significantly prevent the MACEs in the low hs-CRP groups (with statin: 10.1% versus without statin: 12.0%, $P = 0.249$). In the high hs-CRP groups, however, the incidence of MACEs was significantly decreased with statin treatment (with statin: 11.3%, without statin: 20.8%, $P < 0.001$). These findings were consistently observed in all subgroups of the high-hs CRP group, including the subgroup with an LV ejection fraction less than 40%. In a multivariable logistic regression analysis of the high hs-CRP group, lack of statin therapy was a significant predictor of MACE incidence (odds ratio: 1.573, 95% confidence interval: 1.079-2.293, $P = 0.018$). The statin treatment was associated with better outcome in AMI and LV dysfunction patients with hs-CRP $\geq$ 2 mg/dL. (Int Heart J 2014; 55: 106-112)

Key words: Coronary artery disease, Inflammation, Prognosis

Inflammation is thought to play an important role in the pathophysiology of acute myocardial infarction (AMI) and left ventricular (LV) dysfunction.¹⁻⁴⁾ Ischemic injury promotes myocardial inflammation and pro-inflammatory cytokines stimulate C-reactive protein (CRP) leading to cardiac remodeling with LV dysfunction as its clinical manifestation.^{5,6)} Yet, the mechanisms of LV dysfunction post-AMI remain poorly understood. Indeed, high-sensitivity CRP (hs-CRP) is a marker of inflammation activated early after AMI and is associated with LV dysfunction, and is predictive of worse clinical outcomes.⁷⁾

In addition to reducing cholesterol levels, statins also have an anti-inflammatory action.^{8,9)} How much of the benefit of statins, if any, is due to this anti-inflammatory action in AMI

patients with decreased left ventricular ejection fraction (LVEF) is uncertain.

Conversely, a low level of cholesterol is an independent predictor of a poor prognosis in patients with LV dysfunction.^{10,11)} Therefore, AMI with LV dysfunction is a state characterized by inflammation in which a low level of cholesterol is associated with worse outcome,¹²⁾ in which the usual epidemiological relationship between cholesterol and cardiovascular outcomes is reversed and thus represents an excellent disease model in which to test the statin anti-inflammatory hypothesis.^{13,14)} We therefore investigated whether statin therapy and hs-CRP levels were associated with the long-term clinical outcome in AMI patients with decreased LV systolic function.

From the ¹ Chonnam National University Hospital, Gwangju, ² Yeongnam University Hospital, ³ Kyungpook National University Hospital, Daegu, ⁴ Chungbuk National University Hospital, Cheongju, ⁵ Chonbuk National University Hospital, Jeonju, ⁶ Kyung Hee University Hospital, ⁷ Korea University Guro Hospital, ⁸ Yonsei University Severans Hospital, Seoul, ⁹ Wonkwang University Hospital, Iksan, ¹⁰ Chungnam Nat University Hospital, Daejeon, and ¹¹ Pusan National University Hospital, Busan, Korea.

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Address for correspondence: Youngkeun Ahn, MD, Department of Cardiology, Cardiovascular Center, Chonnam National University Hospital, 671 Jebongro, Donggu, Gwangju 501-757, Korea. E-mail: cecilyk@hanmail.net

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Figure 1. Study flow chart. 16,526 AMI patients who underwent 2-dimensional echocardiogram. AMI indicates acute myocardial infarction; hs-CRP, high-sensitivity C-reactive protein; KAMIR, Korea Acute Myocardial Infarction Registry; and PCI, percutaneous coronary intervention.

METHODS

Korea Acute Myocardial Infarction Registry (KAMIR): The Korea AMI Registry (KAMIR) is a Korean prospective, multicenter, and observational online registry started in November 2005 that was designed to reflect “real-world” practice in Korean AMI patients with support from the Korean Circulation Society. The general characteristics of KAMIR have been described elsewhere.¹⁵⁾ The study protocol was approved by the ethics committee at each participating institution, and all patients were informed about their participation in the registry.

Study population: For the present study, we enrolled 18,724 patients from November 2005 to June 2011. Patients were eligible for enrollment if they presented with AMI within 12 hours after symptom onset, if they were successfully treated by percutaneous coronary intervention (PCI) with or without stent implantation, and if they survived the hospitalization period and had completed a one-year clinical follow-up period. The following patients were excluded sequentially: patients with LVEF greater than 50%, patients lacking information on hs-CRP levels and statin administration, and patients with hs-CRP greater than 10 mg/L and with active infections, tumors, or inflammatory disease. A total of 5,119 patients were included in the study. We divided the population using a hs-CRP value of 2.0 mg/L as the cutoff point. Thus, the low hs-CRP group consisted of patients with hs-CRP ≤ 2.0 mg/L ($n = 2,028$) and the high hs-CRP group consisted of patients with hs-CRP > 2 mg/L ($n = 3,091$). Both hs-CRP groups were then broken into subgroups according to the statin treatment: a low hs-CRP without statin group ($n = 440$), low hs-CRP with statin group ($n = 1,588$), high hs-CRP without statin group ($n = 847$), and high hs-CRP with statin group ($n = 2,244$) (Figure 1). The statins were started before or immediately after PCI and continued in the hospital period, at discharge, and throughout the follow-up period. The 29 patients in whom statin treatment was discon-

tinued during the study period were excluded from the analysis. Statin treatment before the AMI did not have an effect on assignment to the groups. The choice of type and dose of statin was left to the doctor’s discretion. The statins prescribed were simvastatin (20, 40, 80 mg), rosuvastatin (5, 10, 20 mg), pravastatin (5, 10, 20, 40 mg), pitavastatin (2 mg), lovastatin (20 mg), atorvastatin (10, 20, 40, 80 mg), and fluvastatin (20, 40, 80 mg).

Study definitions and outcome measurement: Blood samples for baseline laboratory tests including hs-CRP were obtained in the emergency room before PCI. Levels of hs-CRP were analyzed by immunoturbidimetric analysis (Tina-quant hs-CRP latex assay, Roche/Hitachi, Cobas, Mannheim, Germany). Twelve-hour fasting serum levels of total cholesterol, triglycerides, and low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were measured by standard enzymatic methods. Echocardiograms were performed before or after PCI within 24 hours. Conventional echocardiographic studies including Doppler tissue imaging was performed according to the recommendations of the American Society of Echocardiography. Left ventricular end-systolic and end-diastolic dimensions, interventricular septal and posterior wall thicknesses, and left atrial anteroposterior diameter were determined from 2-dimensional imaging. Ejection fraction was calculated using the biplane Simpson method. We tried to obtain high-frame rate images, and gain settings were adjusted to avoid background noise and to obtain clear Doppler tissue image tracings.

Angiographic procedure and postintervention management: Coronary angiography was performed through either the radial or the femoral artery by a standard technique. Interventional strategies such as the preprocedural utilization of glycoprotein IIb/IIIa inhibitors and the use of thrombectomy devices and the performance of postdilatation, intravascular ultrasound, or multivessel stenting were left to the discretion of the individual operator. Bare metal stents (BMS) and drug-eluting stents (DES) were used at the discretion of the individual operator. Successful PCI was defined as TIMI grade 3 flow with residual stenosis ≤ 50% in the infarct-related artery. During the in-hospital period, patients received essential medical treatment that included β -blockers, angiotensin-converting enzyme inhibitors, or angiotensin II receptor blockers. After discharge, the patients continued to receive the same optimal medications that they had received in the hospital. Patients were required to visit the outpatient clinic of the cardiology department at the end of the first month, every 6 months after the PCI procedure, and when angina-like symptoms occurred. Therefore, in the present study, we collected clinical follow-up data at one month, 6 months, and 12 months. In our study, the primary end point was composite major adverse cardiac events (MACEs) during a 12-month period. MACEs were defined as the composite of cardiac death, recurrent MI, and target lesion revascularization or coronary artery bypass grafting. Recurrent MI was defined as recurrent symptoms with new ST-segment elevation or re-elevation of cardiac markers at least twice the upper limit of normal. Target lesion revascularization was defined as ischemia-induced PCI of the target lesion resulting from restenosis or re-occlusion within the stent or at the adjacent 5 mm of the distal or proximal segment.

Statistical analysis: All analyses were performed with SPSS for Windows, version 18.0 (SPSS, Inc., Chicago, IL, USA).

Table I. Baseline Clinical Characteristics of the Patients According to the Level of Hs-CRP and Statin Therapy

Variable	Low hs-CRP group (hs-CRP $\leq$ 2.0 mg/L, $n = 2,028$)			High hs-CRP group (hs-CRP $>$ 2.0 mg/L, $n = 3,091$)		
	Without statin ($n = 440$)	With statin ($n = 1,588$)	<i>P</i>	Without statin ($n = 847$)	With statin ($n = 2,244$)	<i>P</i>
Age, years	63.7 $\pm$ 12.9	63.9 $\pm$ 12.5	0.841	65.2 $\pm$ 13.0	65.7 $\pm$ 12.3	0.572
Male	321 (73.3)	1,183 (74.6)	0.581	611 (72.2)	1,565 (69.8)	0.189
Body mass index, kg/m ²	23.8 $\pm$ 3.2	23.9 $\pm$ 3.3	0.572	23.5 $\pm$ 3.3	23.9 $\pm$ 3.2	0.061
Killip class III-IV	75 (18.1)	203 (13.5)	0.027	197 (24.0)	389 (17.9)	$<$ 0.001
Medical history						
Hypertension	211 (48.7)	712 (45.1)	0.178	411 (48.9)	1,124 (50.4)	0.449
Diabetes mellitus	111 (25.7)	409 (25.9)	0.919	262 (31.1)	687 (30.9)	0.913
Smoking	248 (57.7)	977 (62.4)	0.073	476 (56.6)	1,304 (58.7)	0.302
Hyperlipidemia	44 (10.2)	229 (14.5)	0.021	51 (6.1)	224 (10.1)	0.001
Diagnosis			0.124			0.703
STEMI	319 (72.8)	1,094 (69.0)		588 (69.4)	1,553 (69.2)	
NSTEMI	121 (27.2)	494 (31.0)		259 (30.6)	691 (30.8)	
Echocardiographic finding						
Left ventricular ejection fraction, %	41.9 $\pm$ 7.6	42.3 $\pm$ 7.1	0.306	41.5 $\pm$ 8.1	41.5 $\pm$ 7.5	0.781
Laboratory findings						
Maximum troponin I, ng/mL	5.3 $\pm$ 9.6	6.1 $\pm$ 12.2	0.228	6.3 $\pm$ 10.1	6.4 $\pm$ 11.8	0.807
Total cholesterol, mg/dL	178.9 $\pm$ 45.3	189.1 $\pm$ 43.7	$<$ 0.001	173.6 $\pm$ 42.7	183.3 $\pm$ 44.9	$<$ 0.001
Triglyceride, mg/dL	124.9 $\pm$ 91.6	130.0 $\pm$ 102.4	0.325	110.1 $\pm$ 67.2	122.6 $\pm$ 96.6	$<$ 0.001
Low-density lipoprotein cholesterol, mg/dL	112.9 $\pm$ 38.9	121.0 $\pm$ 39.7	$<$ 0.001	109.5 $\pm$ 45.7	119.2 $\pm$ 40.1	$<$ 0.001
High-density lipoprotein cholesterol, mg/dL	46.2 $\pm$ 19.8	45.4 $\pm$ 22.8	0.499	43.9 $\pm$ 18.4	43.4 $\pm$ 14.1	0.528
Hs-CRP, mg/L	0.7 $\pm$ 0.5	0.7 $\pm$ 0.5	0.534	4.2 $\pm$ 2.3	4.0 $\pm$ 2.2	0.250
Medical therapy during hospitalization						
β -Blocker	360 (81.8)	1,286 (81.0)	0.711	669 (79.0)	1,838 (82.0)	0.069
Angiotensin-converting enzyme inhibitor	299 (68.0)	1,117 (70.3)	0.214	627 (74.0)	1,672 (74.6)	0.214
Angiotensin receptor blocker	73 (16.7)	294 (18.5)	0.385	148 (17.5)	459 (20.5)	0.063

Values are presented as the n (%) of patients or mean $\pm$ SD. Hs-CRP indicates high-sensitivity C-reactive protein; NSTEMI, Non-ST-segment elevation myocardial infarction; and STEMI, ST-segment elevation myocardial infarction.

Continuous variables are presented as the mean $\pm$ standard deviation and were compared using the unpaired Student t test. Discrete variables are expressed as percentages and frequencies and were compared by chi-square statistics. All statistical tests were 2-tailed with statistical significance defined as a $P \leq 0.05$. Univariate analyses using Pearson's chi-square test or Student's t test were performed to evaluate the prognostic significance of demographic and clinical variables for the incidence of MACEs. In addition, the adjusted cumulative incidences of MACEs at 12 months among the groups were analyzed by multivariable Cox regression analysis. The results are presented as adjusted hazard ratios (HRs) with 95% confidence intervals (CIs) and P values. We further evaluated the effects of the statin therapies on the incidence of MACEs in the different subgroups of patients by Cox regression analysis. Multivariable logistic regression analysis was used to determine independent predictors of 12-month MACEs.

RESULTS

Baseline clinical characteristics and coronary angiographic and procedural findings: As shown in Table I, the baseline clinical characteristics of the patients were similar among the groups. However, more patients in the low and high hs-CRP without statin groups than with statin groups had a higher Killip class (III to IV). By contrast the low and high hs-CRP with statin groups had more hyperlipidemia patients, and the levels of total cholesterol and LDL cholesterol were higher in the same group. The use of in-hospital medication other than statins was

similar among the groups. The most common infarct-related artery was the left anterior descending artery in all groups. There were no significant differences in lesion type according to ACC/AHA classification or initial TIMI flow among the groups. Other coronary angiographic and procedural findings are presented in Table II.

Clinical outcomes at 12 months: The incidence of MACEs was significantly reduced by statin treatment in the total study population, regardless of the level of hs-CRP (without statin group: 17.8% versus with statin group: 10.8%, $P < 0.001$). However, in the low hs-CRP group, the incidence of MACEs did not differ significantly according to statin treatment (without statin group: 12.0% versus with statin group: 10.1%, $P = 0.249$). Meanwhile, the incidence of MACEs was significantly lower in the group treated with statins (without statin group: 20.8% versus with statin group: 11.3%, $P < 0.001$), which was mainly due to the decreased cardiac death rate (9.8% versus 6.6%, $P = 0.003$) (Table III).

The adjusted cumulative incidences of MACEs during the 12 months among the groups according to multivariable Cox regression analysis are presented in Figure 2. The incidences of MACEs at 12 months were not significantly different between the low hs-CRP with statin group and the low hs-CRP without statin group (Figure 2A). However, the incidences of MACEs were reduced by statin treatment in the high hs-CRP group (Figure 2B). This trend was also found in patients with an LVEF less than 40% (Figure 3A, B).

In another subgroup analysis, in the high hs-CRP group, statin treatment significantly reduced the incidence of MACEs in all subgroups, while in the low hs-CRP group, statin treat-

Table II. Baseline Coronary Angiographic and Procedural Characteristics of the Patients According to the Level of Hs-CRP and Statin Therapy

Parameter	Low hs-CRP group (hs-CRP $\leq$ 2.0 mg/L, $n = 2,028$)			High hs-CRP group (hs-CRP $>$ 2.0 mg/L, $n = 3,091$)		
	Without statin ($n = 440$)	With statin ($n = 1,588$)	P	Without statin ($n = 847$)	With statin ($n = 2,244$)	P
Infarct-related coronary artery			0.302			0.536
Left anterior descending artery	254 (57.7)	924 (58.2)		491 (58.0)	1,310 (47.4)	
Right coronary artery	124 (28.2)	398 (25.1)		232 (27.4)	568 (25.3)	
Left circumflex artery	57 (13.0)	234 (14.7)		106 (12.5)	316 (14.1)	
Left main	5 (1.1)	32 (2.0)		18 (2.1)	50 (2.2)	
Multivessel coronary disease	232 (52.7)	856 (53.9)	0.661	506 (59.7)	1,312 (58.5)	0.521
Lesion type B ₂ -C	291 (66.1)	1,062 (66.9)	0.701	625 (73.8)	1,702 (75.8)	0.209
Initial TIMI flow grade 0	208 (51.0)	774 (52.7)	0.138	393 (26.3)	1,104 (51.2)	0.230
Stent						
Drug-eluting stent	387 (87.9)	1,353 (85.2)	0.334	680 (80.3)	1,877 (83.6)	0.119
Stent size, mm	23.4 $\pm$ 7.1	23.5 $\pm$ 7.9	0.773	24.8 $\pm$ 6.6	25.0 $\pm$ 6.6	0.370
Stent diameter, mm	3.2 $\pm$ 0.4	3.2 $\pm$ 0.4	0.793	3.2 $\pm$ 0.4	3.1 $\pm$ 0.4	0.123
Number of stents	1.4 $\pm$ 0.8	1.5 $\pm$ 0.8	0.063	1.6 $\pm$ 0.8	1.6 $\pm$ 0.9	0.293
GP IIb/IIIa inhibitor use during PCI	58 (13.2)	251 (15.8)	0.175	111 (13.1)	308 (13.7)	0.653

GP indicates glycoprotein; hs-CRP, high sensitivity C-reactive protein; PCI, percutaneous coronary intervention; and TIMI, Thrombolysis in Myocardial Infarction.

Table III. Clinical Outcomes at 12-months

Outcomes	Low hs-CRP group (hs-CRP $\leq$ 2.0 mg/L, $n = 2,028$)			High hs-CRP group (hs-CRP $>$ 2.0 mg/L, $n = 3,091$)		
	Without statin ($n = 440$)	With statin ($n = 1,588$)	P	Without statin ($n = 847$)	With statin ($n = 2,244$)	P
Composite	53 (12.0)	161 (10.1)	0.249	176 (20.8)	253 (11.3)	< 0.001
Cardiac death	21 (4.8)	68 (4.3)	0.657	83 (9.8)	148 (6.6)	0.003
Re-myocardial infarction	6 (1.4)	21 (1.3)	0.947	17 (2.0)	30 (1.3)	0.174
Target lesion revascularization	34 (7.7)	97 (6.1)	0.222	72 (8.5)	152 (6.8)	0.099
Coronary artery bypass graft	2 (0.5)	6 (0.4)	0.820	5 (0.6)	3 (0.1)	0.026

Hs-CRP indicates high-sensitivity C-reactive protein.

Figure 2. Adjusted cumulative incidences of major adverse cardiac events (MACEs) at 12 months in the low hs-CRP group (A) and the high hs-CRP group (B). Variables in the multivariable Cox regression analysis. hs-CRP indicates high-sensitivity C-reactive protein and HR, hazard ratio.

ment did not significantly influence the incidence of MACEs in any subgroup (Figure 4).

Multivariate logistic regression analysis was performed to identify the predictors of MACEs. In the low hs-CRP group, Killip class III to IV, hypertension, and age $\geq$ 65 years were independent predictors of MACEs after adjustment for the clinical characteristics in model 1. In model 2, Killip class III to IV, hypertension, and multivessel disease were independent pre-

dictors of MACEs after adjustment for angiographic and procedural data in addition to clinical characteristics. In the high hs-CRP group, lack of statin treatment, Killip class III to IV, age $\geq$ 65 years, and lack of beta-blocker treatment were independent predictors of MACEs in model 1, whereas lack of statin treatment, Killip class III to IV, and age $\geq$ 65 years were independent predictors of MACEs in model 2 (Table IV).

Figure 3. Adjusted cumulative incidences of major adverse cardiac events (MACEs) at 12 months in the subgroup of patients with left ventricular ejection fraction less than 40%. (A) Low high-sensitivity C-reactive protein (hs-CRP) group; (B) high hs-CRP group.

Figure 4. Subgroup analysis. Adjusted odds ratios (ORs) for the incidence of major adverse cardiac events (MACEs) associated with statin therapy in the entire study population and in various subgroups of patients according to age, diabetes mellitus, Killip class, level of low-density lipoprotein (LDL) cholesterol, and final diagnosis. STEMI indicates ST-segment elevation myocardial infarction and NSTEMI, non-ST-segment elevation myocardial infarction.

DISCUSSION

In the current study, we investigated the effects of statins on long-term clinical outcomes in AMI patients with decreased LV systolic function. The major finding of our study was that statin therapy significantly reduced the incidence of MACEs, including cardiac death, in AMI patients with elevated levels of hs-CRP, but not in AMI patients with low levels of hs-CRP.

Clinical implications of the study: The pleiotropic effects of statins, independent of their lipid-lowering effect, have been described to reduce plaque thrombogenicity, improve endothelial function, and inhibit free-radical production in the vascular wall.¹⁶⁾ Moreover, statins have potent anti-inflammatory effects on myocardium as well as beneficial effects in AMI and LV

dysfunction patients, such as improvements in symptom severity, B natriuretic peptide (BNP) levels, and endothelial function.^{17,18)} Nevertheless, the effect of statins on the clinical prognosis of LV dysfunction patients remains equivocal. The first important randomized clinical trial on statins in LV dysfunction patients was The Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA) study.¹⁹⁾ A total of 5,091 patients with ischemic systolic heart failure (NYHA class II-IV) were randomized to receive rosuvastatin (10 mg/day) or placebo and were followed-up prospectively for a median of 2.7 years. Despite significantly decreasing LDL cholesterol and CRP levels and reducing cardiovascular hospitalizations, rosuvastatin failed to reduce the primary outcome (death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal

Table IV. Multivariate Logistic Regression Analysis for Predicting Major Adverse Cardiac Events

Variable	Unadjusted Model		Model 1*		Model 2**	
	HR (95% CI)	P	HR (95% CI)	P	HR (95% CI)	P
Low hs-CRP group						
Killip class III-IV	6.253 (3.718-10.515)	< 0.001	2.797 (1.704-4.591)	< 0.001	3.591 (2.075-6.213)	< 0.001
Hypertension	2.140 (1.259-3.636)	0.004	2.100 (1.305-3.379)	0.002	2.508 (1.460-4.307)	0.001
Multivessel disease	1.801 (1.048-3.097)	0.031			1.797 (1.044-3.095)	0.034
Age ≥ 65 years	3.865 (2.081-7.179)	< 0.001	1.503 (1.075-2.102)	0.017	1.336 (0.775-2.410)	0.281
Lack of beta-blocker treatment	2.915 (1.733-4.902)	< 0.001	1.041 (0.601-1.804)	0.961	1.099 (0.591-2.044)	0.765
Lack of statin treatment	1.214 (0.873-1.689)	0.294	1.089 (0.635-1.869)	0.756	1.306 (0.559-1.920)	0.911
High hs-CRP group						
Lack of statin treatment	1.733 (1.263-2.375)	< 0.001	1.651 (1.168-2.333)	0.004	1.573 (1.079-2.293)	0.018
Killip class III-IV	2.922 (2.121-4.025)	< 0.001	1.722 (1.188-2.497)	0.004	1.615 (1.077-2.421)	0.020
Age ≥ 65 years	4.144 (2.731-6.288)	< 0.001	1.567 (1.047-2.346)	0.029	1.688 (1.087-2.623)	0.020
Lack of beta-blocker treatment	2.136 (1.546-2.949)	< 0.001	1.521 (1.014-2.282)	0.043	1.478 (0.943-2.315)	0.088
STEMI	1.336 (0.975-1.832)	0.071	1.432 (1.006-2.040)	0.046	1.393 (0.928-2.090)	0.109
Multivessel disease	1.775 (1.267-2.486)	0.001			1.149 (0.782-1.690)	0.479

* Model 1 was adjusted for clinical characteristics ** Model 2 was adjusted for clinical characteristics, angiographic findings, and procedural data. CI indicates confidence interval; hs-CRP, high-sensitivity C-reactive protein; and HR, hazard ratio.

stroke) or the number of deaths from any other cause. The GISSI-HF (Gruppo Italiano per lo Studio della Sopravvivenza nell'Insufficienza Cardiaca) study was another placebo-controlled randomized clinical trial in 4,574 heart failure patients that yielded similar results.²⁰⁾ In this trial, which also included patients with nonischemic and/or diastolic heart failure (NYHA class II-IV), rosuvastatin (10 mg/day) failed to improve cardiovascular outcomes after a median of 3.9 years. Notably, statin administration could also have adverse effects in LV dysfunction patients given the association between low cholesterol levels and poor outcome in advanced LV dysfunction. Other considerations contraindicating statin use in LV dysfunction include their adverse effects on coenzyme Q10 (ubiquinone) and selenoproteins that are important for myocardium biology.²¹⁻²³⁾ However, McMurray, *et al* retrospectively analyzed the CORONA study to examine outcomes in patients with heart failure in relation to hs-CRP concentrations and the effect of statin therapy.¹²⁾ They compared 10 mg rosuvastatin daily with placebo in 4,961 patients with ischemic systolic LV dysfunction according to a baseline hs-CRP < 2.0 mg/L or ≥ 2.0 mg/L. The result was that more placebo-treated patients had a primary end point in the high hs-CRP group and in the low hs-CRP group, however, the incidence of primary end point was not significantly different between the placebo and rosuvastatin groups. To the best of our knowledge, this is the only study that has described an interaction between hs-CRP and the effect of statins. The effect of statins in AMI patients with left ventricular dysfunction according to the level of hs-CRP has not been reported.²⁴⁾

To our knowledge, the present study is the first to show that statin therapy can improve the long-term clinical outcomes in AMI patients with LV systolic dysfunction who were prone to high inflammatory status. The findings suggest that statin therapy was beneficial in the group of patients with baseline hs-CRP levels ≥ 2.0 mg/L. No such benefit was observed in the group of patients with hs-CRP < 2.0 mg/L. One cause of this controversy is presumed to be that the clinical trials described above did not consider the concept of inflammation. It is well known that local and systemic inflammation plays a pivotal role in the pathogenesis of AMI and LV dysfunction. Hs-CRP, an inflammatory biomarker that independently predicts future

vascular events, improves global classification of risk.²⁵⁾ These findings indicate that there is a group of heart failure patients that may indeed benefit from statin treatment. An explanation for these findings is that statins might exert beneficial effects only in the early stages of the CVD continuum, as in low risk subjects without CVD and early stage heart failure patients, and in high risk patients with end-stage heart failure. Thus, we believe that early prescription of statin therapy in the present study might have played an additional role in the protection of AMI patients with decreased LV systolic function who have high levels of hs-CRP, and thereby decreased the prevalence of MACEs. Also, hs-CRP level is particularly helpful in detecting those heart failure patients more likely to benefit from statin treatment.

Some aspects of the methodology of our study should be compared with previous studies. First, we applied a 2 mg/L cutoff value of hs-CRP. A potential clinical hs-CRP cutoff value of 2 mg/L is supported by studies in the Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin (JUPITER) and Atherosclerosis Risk in Communities (ARIC) populations.²⁶⁻²⁹⁾ Second, according to the low-grade inflammation concept, we excluded 430 patients with levels ≥ 10 mg/L because infections, trauma, and acute illness have been associated with increases in hs-CRP levels.³⁰⁾ We therefore believe that measured hs-CRP levels largely correspond to a patient's baseline grade of inflammation, but we cannot exclude the possibility that some patients experienced slight increases in hs-CRP levels < 10 mg/L because of acute disease.

Study limitations: First, although our study included a large number of subjects, because of the nonrandomized nature of the registry study, there were baseline differences in several important prognostic factors between our primary comparison groups. Although we included most confounders in the multivariable Cox regression model to control for the baseline biases, it is possible that some potential confounders may have crept in. For example, those taking statins are less severely compromised (lower proportion of Killip III-IV, less anterior descending coronary artery as culprit vessel) and might have a better outcome. However, this multicenter registry may help complete the picture gained from randomized trials, which

usually have highly selected patients treated in a nonroutine setting. Therefore, our study is of value because it used registry data, which reflects the real world. Second, our study did not present the exact criteria for statin therapy, and did not provide a clear rationale for the patients not treated with statins. Total cholesterol and LDL levels were significantly higher in the statin treatment group, irrespective of hs-CRP levels. Statins might have been prescribed based on the medical insurance of our country. Third, the type and dose of statins were not controlled in our study and the changes were not evaluated. Fourth, other medications which can affect hs-CRP levels, such as non-steroidal anti-inflammatory drugs, were not evaluated. Finally, the follow-up hs-CRP and cholesterol levels were not evaluated. Therefore, a prospective randomized controlled trial is required to confirm this apparent therapeutic effect of statins in AMI patients with LV systolic dysfunction.

Conclusions: In conclusion, the present study showed that statin treatment had an effect on long-term clinical outcomes in AMI patients with decreased LV systolic function who had high levels of hs-CRP. Therefore, these results indicate that the hs-CRP level is particularly helpful in detecting AMI patients with LV dysfunction who are more likely to benefit from statin treatment.

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