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Benefit of Early Statin Therapy in Patients With Acute Myocardial Infarction Who Have Extremely Low Low-Density Lipoprotein Cholesterol

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Objectives We investigated whether statin therapy could be beneficial in patients with acute myocardial infarction (AMI) who have baseline low-density lipoprotein cholesterol (LDL-C) levels below 70 mg/dl.

Background Intensive lipid-lowering therapy with a target LDL-C value <70 mg/dl is recommended in patients with very high cardiovascular risk. However, whether to use statin therapy in patients with baseline LDL-C levels below 70 mg/dl is controversial.

Methods We analyzed 1,054 patients with AMI who had baseline LDL-C levels below 70 mg/dl and survived at discharge from the Korean Acute MI Registry between November 2005 and December 2007. They were divided into 2 groups according to the prescribing of statins at discharge (statin group n = 607; nonstatin group n = 447). The primary endpoint was the composite of 1-year major adverse cardiac events, including death, recurrent MI, target vessel revascularization, and coronary artery bypass grafting.

Results Statin therapy significantly reduced the risk of the composite primary endpoint (adjusted hazard ratio [HR]: 0.56; 95% confidence interval [CI]: 0.34 to 0.89; p = 0.015). Statin therapy reduced the risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93; p = 0.031) and coronary revascularization (HR: 0.45, 95% CI: 0.24 to 0.85; p = 0.013). However, there were no differences in the risk of the composite of all-cause death, recurrent MI, and repeated percutaneous coronary intervention rate.

Conclusions Statin therapy in patients with AMI with LDL-C levels below 70 mg/dl was associated with improved clinical outcome. (J Am Coll Cardiol 2011;58:1664–71) © 2011 by the American College of Cardiology Foundation

Lowering of low-density lipoprotein cholesterol (LDL-C) with a 3-hydroxy-3-methylglutaryl–coenzyme A reductase inhibitor (statin) reduces the risk of death and cardiovascular events in both the primary setting and acute coronary syndromes (ACS) (1). Recent trials have supported early intensive statin therapy as the standard therapy for patients with ACS by showing the clinical benefit of intensive lipid reduction to lower LDL-C concentrations (2–4). For very

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high-risk patients, such as those with ACS, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines have set a value of <70 mg/dl as the therapeutic goal for LDL-C (5,6).

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In real clinical practice, physicians often encounter patients with ACS with LDL-C levels below 70 mg/dl. What is the physicians' optimal choice for these patients? A post hoc multivariable analysis of the PROVE IT–TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis In Myocardial Infarction 22) trial revealed no evidence of benefit in patients with baseline LDL-C <66 mg/dl, indicating that further LDL-C reduction may not add any clinical benefit (7). Meanwhile, several studies reported that statin therapy resulted in favorable outcomes regardless of baseline LDL-C levels (8–10). Therefore, the influence of baseline LDL-C on the clinical benefit of lipid-lowering therapy remains controversial. Under these circumstances, we investigated whether statin therapy could be beneficial in patients with acute myocardial infarction (AMI) who have baseline LDL-C levels below 70 mg/dl.

Methods

Study population. A total of 14,885 patients enrolled in the KAMIR (Korea Acute Myocardial Infarction Registry) from November 2005 to December 2007. A total of 1,054 patients with AMI who had serum LDL-C levels below 70 mg/dl comprised the study population. They were divided into 2 groups according to the prescribing of a statin at discharge (statin group n = 607; nonstatin group n = 447). The eligible patients were ≥18 years of age at admission and had suggestive symptoms with or without ST-segment elevation >2 mm in ≥2 precordial leads, ST-segment elevation >1 mm in ≥2 limb leads, or new left bundle branch block on the 12-lead electrocardiogram with concomitant increases in the level of at least one cardiac enzyme. Fasting lipid profiles were obtained within 24 h of admission. Patients who already had a diagnosis of dyslipidemia or had received statin therapy before hospital admission were included in the present study. The criteria for exclusion included concomitant use of fibric acid derivatives, lipid profiles obtained more than 24 h after admission or in a nonfasting state, and estimated life expectancy <12 months.

The KAMIR, launched in November 2005, was a Korean prospective, multicenter data collection registry reflecting real world treatment practices and outcomes in Asian patients diagnosed with AMI. The registry included 50 community and teaching hospitals with facilities for primary percutaneous coronary intervention (PCI) and on-site cardiac surgery. The KAMIR was supported by a research grant from the Korean Circulation Society in commemoration of its 50th anniversary. Data were collected by a trained study coordinator using a standardized case report form and protocol. The study protocol was approved by the ethics committee at each participating institution.

Abbreviations and Acronyms

ACS = acute coronary syndrome
AMI = acute myocardial infarction
CABG = coronary artery bypass grafting
hs-CRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein cholesterol
MACE = major adverse cardiac event(s)
PCI = percutaneous coronary intervention
TVR = target vessel revascularization

Medical treatment and PCI procedure. All patients received a 300-mg loading dose of aspirin, 300- to 600-mg loading dose of clopidogrel, and heparin. The maintenance dose was 100 mg/day for aspirin and 75 mg/day for clopidogrel. Aspirin and clopidogrel were administered to all patients for ≥6 months as per existing guidelines. Statins were administered for at least 1 month after discharge to the statin group. After 1 month, the use of statins was left to the discretion of physicians. The post-intervention medication included aspirin, clopidogrel, beta-blockers, angiotensin-converting enzyme inhibitors, and angiotensin II receptor blockers. After discharge, the patients continued receiving the same medications that they received during hospitalization, except for some intravenous or temporary medications. Coronary artery stenting was performed using standard techniques. The decisions for pre-dilation, direct stenting, post-adjunctive balloon inflation, and administration of glycoprotein IIb/IIIa receptor blockers were left to the discretion of individual physicians. Clinical follow-up was performed at 1, 6, and 12 months and when angina-like symptoms occurred.

Study definition and endpoints. AMI was diagnosed by the presence of characteristic clinical presentation, serial changes on electrocardiogram suggesting infarction, and increases in cardiac enzyme levels. Dyslipidemia was defined as a diagnosis previously made by a physician or treatment with lipid-lowering medications. The primary endpoint was the composite of major adverse cardiac events (MACE) during the 12 months of clinical follow-up. MACE was defined as the composite of all-cause death, MI, and repeated PCI or coronary artery bypass grafting (CABG). All-cause deaths were considered cardiac deaths unless a noncardiac death could be defined clearly. Recurrent MI was defined as recurrent symptoms with new electrocardiographic changes compatible with MI or cardiac markers at least twice the upper limit of normal. Target vessel revascularization (TVR) was defined as any repeated intervention driven by the lesions located in the treated vessel within and beyond the target limits. The secondary endpoints were individual components of the primary endpoint, including cardiac death, all-cause death, recurrent MI, and coronary revascularization procedures.

Statistical analysis. All statistical analyses were conducted with SPSS version 16.0 (SPSS Inc., Chicago,

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Illinois). For continuous variables, differences between groups were evaluated by an unpaired *t* test or Mann-Whitney rank-sum test. For discrete variables, differences were expressed as counts and percentages and were analyzed with a chi-square or Fisher exact test between groups as appropriate. We constructed Kaplan-Meier curves for patients in the statin or nonstatin therapy group to the composite of the primary endpoint, and difference between the groups was assessed by log-rank test. A propensity score analysis was performed to adjust potential confounders using a logistic regression model. All available variables considered potentially relevant were included: age, sex, hypertension, diabetes mellitus, dyslipidemia, smoking, previous history of MI, Killip class on presentation, left ventricular ejection fraction, lipid profiles, use of glycoprotein IIb/IIIa inhibitors, medications, success rate of PCI, involvement of left main coronary artery, multivessel disease, lesion complexity, and pre- and post-procedural Thrombolysis In Myocardial Infarction (TIMI) flow grade. The predicted accuracy of the logistic model was assessed using the area under the receiver-operating characteristic curve (C statistic), which was 0.760. Cox proportional hazards regression was used to compute hazard ratios (HRs) as

Table 1 Baseline Clinical Characteristics

	Statin Group (n = 607)	Nonstatin Group (n = 447)	p Value
Male*	437 (72.0)	314 (70.4)	0.573
Age, yrs†	71.0 (60.0–78.0)	71.0 (62.0–80.0)	0.809
Medical history*			
Hypertension	330 (54.4)	225 (50.3)	0.195
Diabetes mellitus	209 (34.4)	154 (34.5)	0.995
Dyslipidemia	81 (13.3)	42 (9.4)	0.048
Smoking	331 (54.5)	243 (54.4)	0.957
Previous history of MI	51 (8.4)	16 (3.6)	0.002
Previous history of PCI	78 (12.9)	37 (8.3)	0.019
Previous CABG	7 (1.2)	3 (0.7)	0.531
Previous history of CVA	51 (8.4)	91 (9.2)	0.661
Previous history of PVD	11 (1.8)	6 (1.3)	0.550
Previous history of HF	19 (3.1)	18 (4.0)	0.434
Killip class ≥III on presentation*	128 (21.1)	103 (23.0)	0.448
LVEF, %‡	50.6 ± 12.2	50.6 ± 12.9	0.980
Laboratory findings†			
Total cholesterol, mg/dl	123.0 (108.0–123.0)	122.0 (108.0–136.0)	0.453
HDL-C, mg/dl	40.0 (33.0–48.0)	41.0 (32.0–50.0)	0.929
LDL-C, mg/dl	58.0 (48.0–65.0)	59.0 (48.0–65.0)	0.709
Triglycerides, mg/dl	84.0 (56.0–126.5)	77.0 (54.0–115.0)	0.083
Peak creatine kinase-MB, ng/ml	46.3 (13.2–149.1)	36.5 (11.0–148.4)	0.331
Peak troponin I, ng/ml	13.0 (2.1–42.7)	12.5 (2.5–49.5)	0.834
Serum creatinine, mg/dl	1.0 (0.9–1.3)	1.1 (0.9–1.3)	0.852
hs-CRP, mg/dl	1.4 (0.2–8.5)	1.3 (0.2–7.0)	0.525
NT-proBNP, pg/ml	568.5 (144.0–2,600.0)	659.5 (169.8–2,688.0)	0.386
Indication for PCI*			0.205
ST-segment elevation MI	329 (54.3)	224 (50.3)	
Non–ST-segment elevation MI	277 (45.7)	221 (49.7)	
Medications*			
Aspirin	595 (98.0)	430 (96.2)	0.073
Clopidogrel	581 (95.7)	418 (93.5)	0.112
Beta-blocker	480 (79.1)	311 (69.6)	<0.001
Angiotensin-converting enzyme inhibitor	453 (74.6)	312 (69.8)	0.082
Angiotensin receptor blocker	146 (24.1)	100 (22.4)	0.524
Glycoprotein IIb/IIIa inhibitors	58 (9.6)	40 (8.9)	0.737
Unfractionated heparin	364 (60.0)	240 (53.7)	0.042
Low-molecular-weight heparin	188 (31.0)	159 (35.6)	0.116
Heparin§	459 (75.6)	330 (73.8)	0.507

Values are n (%), median (25 to 75 percentile), or mean ± SD. *Comparison made using the chi-square test. †Comparison made using the Mann-Whitney test. ‡Comparison made using the *t* test. §Sum of low-molecular-weight heparin and unfractionated heparin.

CABG = coronary artery bypass grafting; CVA = cerebrovascular accidents; HDL-C = high-density lipoprotein cholesterol; HF = heart failure; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein cholesterol; LVEF = left ventricular ejection fraction; MI = myocardial infarction; NT-proBNP = N-terminal pro–B-type natriuretic peptide; PCI = percutaneous coronary intervention; PVD = peripheral vascular disease.

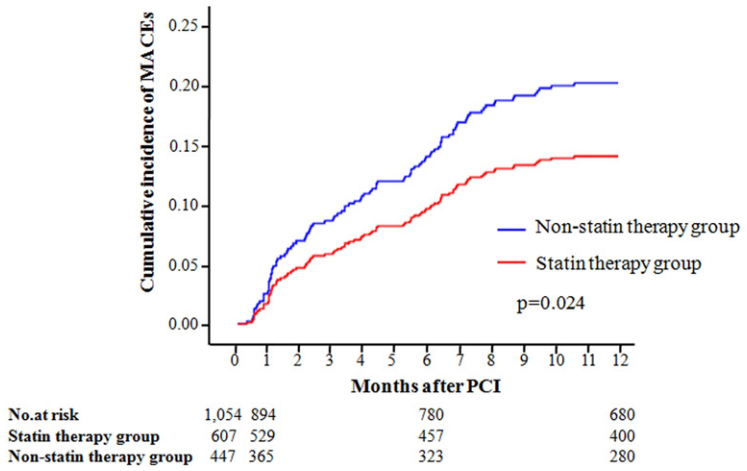

Figure 1 **Estimates of the Rate of the Primary Endpoint Events**

The primary endpoint was the composite of death, recurrent myocardial infarction, and coronary revascularization. MACE = major adverse cardiac event(s); PCI = percutaneous coronary intervention.

estimates for each endpoint. The HRs were adjusted for propensity score and important risk covariables that had significant effects ($p < 0.1$) in the univariate analysis for clinical outcomes. All analyses were 2-tailed, with clinical significance defined as $p < 0.05$.

Results

Baseline clinical characteristics. A total of 1,054 patients with AMI were included in the present study. They were divided into 2 groups according to the prescribing of statins at discharge (statin group n = 607; nonstatin group n = 447). In the statin group, 541 patients (89.1%) received statins during hospital admission, whereas 66 patients (10.9%) did not. None of the nonstatin group received statins during hospital admission. No significant differences in the baseline characteristics were found between the groups, except that the statin group had a higher incidence of prior dyslipidemia and MI. Laboratory findings were also comparable between the groups. No significant differences in the in-hospital and discharge medical treatment were found between the groups, except that the statin group more commonly received beta-blockers (Table 1).

Procedural characteristics. A total of 809 patients (76.8%) underwent PCI, with 83.6% undergoing stent implantation. The success rate of PCI was comparable in both groups (96.2% in the statin group vs. 95.4% in the nonstatin group; p = 0.583). Analysis of angiographic findings showed no differences in location of culprit lesions, prevalence of multivessel disease, ACC/AHA lesion type, distribution of pre- and post-procedural TIMI flow grade, stent type and length, and stent diameter (Table 2).

Clinical outcomes. During the 12-month follow-up period, a primary endpoint event occurred in 58 patients (14.5%) in the statin group and 57 patients (20.4%) in the nonstatin group (log-rank p = 0.024) (Fig. 1). Statin therapy significantly reduced the risk of the composite primary endpoint (adjusted HR: 0.56; 95% confidence interval [CI]: 0.34 to 0.89; p = 0.015) (Table 4). Outcomes for the selected secondary endpoints are shown in Table 4. Cardiac death occurred in 16 patients (4.0%) in the statin group and 21 patients (7.5%) in the nonstatin group. Statin therapy reduced the risk of cardiac death (HR: 0.47; 95% CI: 0.23 to 0.93; p = 0.031). Coronary revascularization occurred in 27 patients (6.8%) in the statin group and 28 patients (10.0%) in the nonstatin group. Statin therapy reduced the risk of coronary revascularization (HR: 0.45; 95% CI: 0.24 to 0.85; p = 0.013). Although statin therapy reduced the risk of cardiac death and coronary revascularization, there were no differences in the risk of the composite of all-cause death, recurrent MI, and repeated PCI rate.

Outcomes for each component of the secondary endpoints at the follow-up of 6 months and 12 months are summarized in Table 3. At 6 months, statin therapy significantly decreased cardiac death (3.1% vs. 5.9%; p = 0.031), CABG (1.8% vs. 2.8%; p = 0.012), and the composite of MACE (10.9% vs. 13.9%; p = 0.048), with no differences in all-cause death, MI, re-PCI, and TVR. Likewise, at 12 months, statin therapy significantly decreased cardiac death (4.0% vs. 7.5%; p = 0.048), CABG (2.0% vs. 3.9%; p = 0.003), and the composite of MACE (14.5% vs. 20.4%; p = 0.014), with no differences in all-cause death, MI, re-PCI, and TVR.

Subgroup analysis showed that the beneficial effects of statin therapy appeared to be prominent in men, the elderly, those without diabetes mellitus, those without hypertension, those without prior dyslipidemia, smokers or ex-smokers, those with an initial diagnosis of ST-segment elevation myocardial infarction (STEMI), and those with higher

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Table 2 Procedural Characteristics

	Statin Group (n = 607)	Nonstatin Group (n = 447)	p Value
Location of culprit lesion			
Left anterior descending artery	229 (44.0)	157 (47.6)	0.301
Left circumflex artery	64 (12.3)	50 (15.2)	0.231
Right coronary artery	216 (41.5)	116 (35.2)	0.066
Left main coronary artery	12 (2.3)	7 (2.1)	0.861
Multivessel disease	277 (53.1)	187 (56.2)	0.376
ACC/AHA lesion types			
A	28 (5.7)	14 (4.8)	0.584
B1	89 (18.2)	48 (16.5)	0.545
B2	147 (30.1)	84 (28.9)	0.724
C	225 (46.0)	145 (49.8)	0.302
B2/C	372 (76.1)	229 (78.7)	0.400
Pre-procedural TIMI flow grade			
0	217 (43.9)	117 (38.0)	0.097
1	55 (11.1)	39 (12.7)	0.513
2	70 (14.2)	52 (16.9)	0.298
3	152 (30.8)	100 (32.5)	0.614
Stent type			0.182
Bare-metal stent	35 (8.5)	31 (11.7)	
Drug-eluting stent	375 (91.5)	235 (88.3)	
Stent length, mm*	25.4 ± 7.2	24.9 ± 5.9	0.296
Stent diameter, mm*	3.2 ± 0.4	3.1 ± 0.4	0.188
No. of stents*	1.5 ± 0.8	1.5 ± 0.8	0.358
Post-procedural TIMI flow grade			
0	16 (3.5)	7 (2.4)	0.389
1	7 (1.5)	1 (0.3)	0.159
2	18 (3.9)	17 (5.8)	0.238
3	419 (91.1)	270 (91.5)	0.835

Values are n (%) or mean ± SD.
ACC/AHA = American College of Cardiology/American Heart Association; TIMI = Thrombolysis In Myocardial Infarction.

serum levels of high-sensitivity C-reactive protein (hs-CRP). However, the p value for homogeneity was not significant in all subgroup analyses. Stratified Cox analyses for the primary endpoint favored statin therapy in all subgroup analyses (Fig. 2).

Discussion

Current guidelines provide recommendations for initiating statin therapy for targeting the optional therapeutic goal of LDL-C <70 mg/dl in patients at high risk of cardiovascular events (5,6). Although physicians follow the guidelines, the decision to treat very high-risk patients with statins who already have baseline LDL-C levels below 70 mg/dl remains controversial in regard to benefit, risk, and cost. In patients with ACS with LDL-C levels below 70 mg/dl, the present study showed that statin therapy significantly reduced the risk of the endpoints defined as the composite of all-cause death, MI, and coronary revascularization.

Until now, no trials have been randomized with regard to the degree of baseline LDL-C levels. Some observational studies and post-hoc analyses of randomized clinical trials (RCTs) have reported the influence of baseline LDL-C levels on the clinical benefit of lipid-lowering therapy (7–12). Tsai et al. (12) examined the relationship between statin therapy at discharge and clinical outcomes in 155 patients with ACS with baseline LDL-C levels ≤80 mg/dl. Statin-treated patients had a lower incidence of death, re-infarction, or stroke at 6 months compared

Table 3 Clinical Outcomes at 6 and 12 Months According to Statin Medication

	Statin Group (n = 607)	Nonstatin Group (n = 447)	p Value
6-month outcomes			
Cardiac death	14 (3.1)	19 (5.9)	0.031
Total death	19 (4.2)	22 (6.8)	0.071
MI	9 (2.0)	2 (0.6)	0.386
Repeated PCI	14 (3.1)	13 (4.0)	0.336
TVR	5 (1.1)	8 (2.5)	0.081
CABG	8 (1.8)	9 (2.8)	0.012
MACE	50 (10.9)	45 (13.9)	0.048
12-month outcomes			
Cardiac death	16 (4.0)	21 (7.5)	0.048
Total death	23 (5.8)	26 (9.3)	0.101
MI	9 (2.3)	5 (1.8)	0.644
Repeated PCI	19 (4.8)	17 (6.1)	0.232
TVR	8 (2.0)	10 (3.6)	0.209
CABG	8 (2.0)	11 (3.9)	0.003
MACE	58 (14.5)	57 (20.4)	0.014

Values are n (%). All comparisons were made using the chi-square test.
MACE = major adverse cardiac event(s); TVR = target vessel revascularization; other abbreviations as in Table 1.

Table 4 Cumulative Secondary Endpoints at 12 Months According to Statin Medication

	Unadjusted HR (95% CI)	p Value	Adjusted HR (95% CI)	p Value
Death	0.62 (0.35–1.09)	0.092	0.56 (0.26–1.20)	0.133
Cardiac death	0.54 (0.28–0.90)	0.036	0.47 (0.23–0.93)	0.031
Noncardiac death	0.98 (0.31–3.07)	0.966	0.89 (0.20–4.09)	0.885
MI	1.27 (0.43–3.78)	0.671	1.38 (0.45–4.19)	0.570
Coronary revascularization	0.57 (0.33–0.98)	0.044	0.45 (0.24–0.85)	0.013
Repeated PCI	0.77 (0.40–1.48)	0.435	0.63 (0.29–1.35)	0.232
TVR	0.55 (0.22–1.40)	0.202	0.51 (0.19–1.40)	0.191
CABG	0.25 (0.08–0.79)	0.018	0.15 (0.04–0.55)	0.004
MACE	0.66 (0.45–0.95)	0.026	0.56 (0.34–0.89)	0.015

CI = confidence interval; HR = hazard ratio; other abbreviations as in Tables 1 and 3.

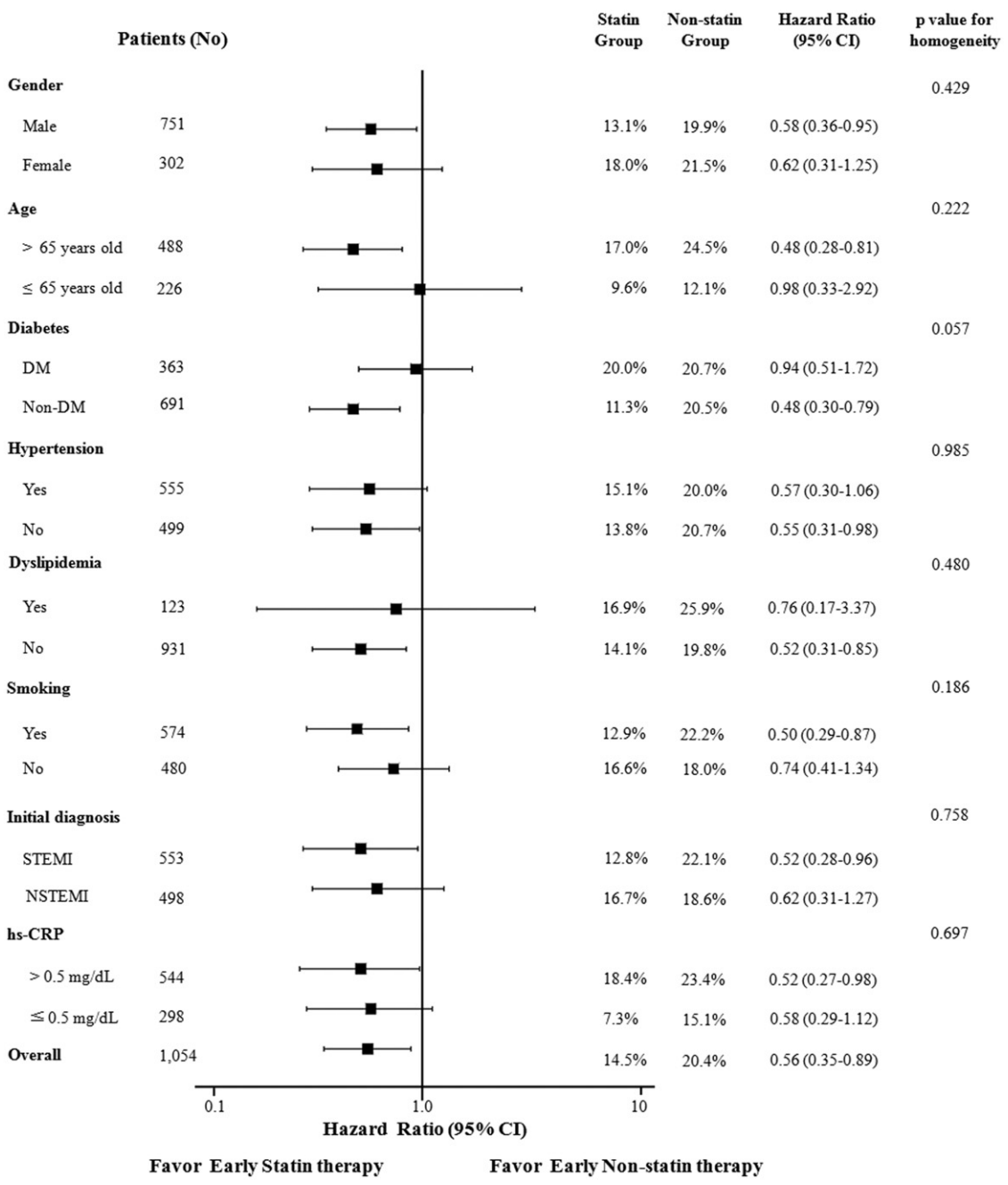

Figure 2 Estimates of Hazard Ratios for the Primary Endpoint in Selected Subgroups

Hazard ratios are shown on a logarithmic scale. CI = confidence interval; hs-CRP = high-sensitivity C-reactive protein; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction.

with non–statin-treated patients (29.0% vs. 9.5%; p = 0.005). Leeper et al. (10) also reported improved survival (HR: 0.65; 95% CI: 0.53 to 0.80) with statin therapy in patients with LDL-C levels below 60 mg/dl. Meanwhile, a post hoc multivariable analysis of the PROVE IT–TIMI 22 trial revealed no evidence of benefit in patients with baseline LDL-C <66 mg/dl (7). Considering these inconsistent results, the present study added evidence to the effect of statin therapy for patients with ACS who have baseline LDL-C levels below 70 mg/dl.

In the present study, statin therapy significantly reduced the risk of the composite primary endpoint, mainly driven by the risk reduction of cardiac death and coronary revascularization. These results are consistent with many RCTs, such as the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial (13), A to Z

(Aggrastat to Zocor) trial (14), and PROVE IT-TIMI trial (4). However, differences are found between the present study and these RCTs in which component of the primary endpoint led the composite risk reduction. The component was cardiovascular death in the A to Z trial and coronary revascularization in the PROVE IT-TIMI trial. None of these trials showed a risk reduction in all-cause death and recurrent MI. In a pooled analysis of 7 RCTs of statin therapy in patients with ACS, statin therapy reduced the risk of death (HR: 0.75; 95% CI: 0.61 to 0.93) and revascularization (HR: 0.86; 95% CI: 0.78 to 0.96), with no differences in recurrent MI and stroke (15). Compared with these RCTs and meta-analyses, the present study showed a similar trend of risk reduction related to each component of the primary endpoint and potentially extended the results of these trials to patients with ACS with very low LDL-C levels.

However, the mechanism by which the risk of cardiovascular death and coronary revascularization is reduced is not fully understood. It can be partly explained by the fact that statins exhibit a number of biological effects, besides lowering serum levels of LDL-C, that may be relevant in the setting of acute ischemic events. Statins improve vascular endothelial function, attenuate vascular inflammation, stabilize plaques, correct prothrombotic tendencies, and influence myocardial protection and remodeling (16–19). Usually patients with very low LDL-C levels are older and more likely to have histories of other important comorbidities, such as diabetes mellitus and hypertension, than patients with higher LDL-C levels. Considering this, patients with very low LDL-C levels might benefit as much or more from statin therapy as patients with higher LDL-C levels. Thus, it is not necessarily surprising that the beneficial effects of statins in these high-risk patients became more potent after controlling for the propensity score and covariates. However, we should be cautious about interpreting the mentioned pleiotropic effects of statins because those effects take several months to occur. The present study showed that the beneficial effect of statins was also apparent after 6 months. We also analyzed the clinical outcome at 1 month, and there were no significant differences in the primary endpoint between the groups. This is consistent with and expands on 2 meta-analyses (20,21), both of which also showed that beneficial effects of statins were apparent only after more than 4 months.

In subgroup analyses, although differences were statistically significant in some groups and not in others, mainly because of sample size, the beneficial effects of statin therapy appeared to be prominent in men, the elderly, those without diabetes mellitus, those without hypertension, those without prior dyslipidemia, smokers or ex-smokers, those with initial diagnoses of STEMI, and those with higher serum levels of hs-CRP. This finding indicates that statin therapy might be considered in patients with ACS who do not have a history of diabetes mellitus, hypertension, or dyslipidemia. They are often regarded as low-risk patients and are less likely to be prescribed statins. Statin therapy was also favored in patients with higher serum levels of hs-CRP. The JUPITER (Justification for the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) trial demonstrated that statin therapy reduces vascular events in apparently healthy men and women with low levels of LDL-C who are at higher risk because of elevated hs-CRP levels (22). Likewise, our study showed more prominent beneficial effects in patients with ACS with very low LDL-C levels and elevated hs-CRP levels.

The results of the present study cannot be extrapolated to a clinical population presenting under more routine circumstances. The present study only included acute events of AMI. Early studies have indicated that cholesterol levels decrease significantly after ACS (23). Therefore, further study is needed to evaluate the effect of statins in patients with stable coronary artery disease and LDL-C <70 mg/dl.

Study limitations. First, the study lacked data on specific statins and doses. Therefore, we could not evaluate differences between intensive versus moderate statin therapy. Second, we could only exclude the use of fibric acid derivatives, leaving the use of bile acid sequestration agents unknown. Fortunately, bile acid sequestration agents are not commonly prescribed in Korea compared with statins or fibric acid derivatives. Third, the present study was designed to administer statins for at least 1 month after discharge for the statin group. After 1 month, the use of statins was left at the discretion of physicians. Therefore, the beneficial effects of statins in the present study are only attributable to the time period of 1 month after discharge. Fourth, the present study was analyzed retrospectively. The nonrandomized nature of the registry data could have resulted in selection bias. Although most confounders were included in the multivariate regression analysis, it is possible that some potential bias were included. Large-scale, prospective RCTs are needed to clarify the effects of statins in patients with ACS with varying degrees of baseline LDL-C levels. Nonetheless, the present study has strengths in that the nonrandomized design of the study included many patients who would not have been enrolled in randomized trials, including the elderly and those with severe comorbidities. Also, the present study only included patients with ACS, especially AMI; had a relatively large sample size compared with other observational studies and the PROVE IT–TIMI 22 trial (all enrolled patients, n = 2,986; patients with LDL-C ≤92 mg/dl, n = 749); and had relative homogeneity of the study population between the groups, despite the nonrandomized design.

Conclusions

The present study showed that statin therapy in patients with AMI with LDL-C levels below 70 mg/dl was associated with improved clinical outcome. Statin therapy significantly reduced the risk of the composite of the MACE,

mainly driven by the risk reduction in cardiac death and coronary revascularization. However, further randomized trials are needed based on the pre-treatment LDL-C levels in patients with ACS, as well as in stable coronary artery disease.

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Key Words: low-density lipoprotein cholesterol ■ myocardial infarction ■ statin.

APPENDIX

For a complete list of KAMIR investigators, please see the online version of this article.