Original Article

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Differential Benefit of Statin in Secondary Prevention of Acute Myocardial Infarction according to the Level of Triglyceride and High Density Lipoprotein Cholesterol

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Background and Objectives: The differential benefit of statin according to the state of dyslipidemia has been sparsely investigated. We sought to address the efficacy of statin in secondary prevention of myocardial infarction (MI) according to the level of triglyceride and high density lipoprotein cholesterol (HDL-C) on admission.

Subjects and Methods: Acute MI patients (24653) were enrolled and the total patients were divided according to level of triglyceride and HDL-C on admission: group A (HDL-C≥40 mg/dL and triglyceride<150 mg/dL; n=11819), group B (HDL-C≥40 mg/dL and triglyceride≥150 mg/dL; n=3329), group C (HDL-C<40 mg/dL and triglyceride<150 mg/dL; n=6062), and group D (HDL-C<40 mg/dL & triglyceride≥150 mg/dL; n=3443). We evaluated the differential efficacy of statin according to the presence or absence of component of dyslipidemia. The primary end points were major adverse cardiac events (MACE) for 2 years.

Results: Statin therapy significantly reduced the risk of MACE in group A (hazard ratio =0.676; 95% confidence interval: 0.582-0.785; p<0.001). However, the efficacy of statin was not prominent in groups B, C, or D. In a propensity-matched population, the result was similar. In particular, the benefit of statin in group A was different compared with group D (interaction p=0.042)

Conclusion: The benefit of statin in patients with MI was different according to the presence or absence of dyslipidemia. In particular, because of the insufficient benefit of statin in patients with MI and dyslipidemia, a different lipid-lowering strategy is necessary in these patients. **(Korean Circ J 2016;46(3):324-334)**

KEY WORDS: Statin; Acute myocardial infarction; Triglyceride; High-density lipoprotein cholesterol; Prognosis.

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Introduction

The efficacy of statins in the secondary prevention of acute myocardial infarction (MI) have been well established and statin therapy has been regarded as essential part of medical therapy in all patients with acute MI.[1-3] The benefit of statin was demonstrated, irrespective of plasma level of low density lipoprotein cholesterol (LDL-C). The Cholesterol and Recurrent Event (CARE) trial revealed that cholesterol lowering with statin improved clinical outcome in patients with coronary artery disease who have average cholesterol level.[4] Another study reported that statin therapy is also beneficial, even in acute coronary syndrome patients with extremely low baseline LDL-C level (<70 mg/dL).[5]

Although the statin is a most powerful drug for lowering LDL-C, the effect of statin on increasing HDL-C and lowering triglyceride

are modest or suboptimal. However, there have been few trials that evaluated the benefit of statin in acute MI patients with low HDL-C and high triglyceride. The subgroup analysis of Justification for the Use of Statin in Primary Prevention; An Intervention Trial Evaluating Rosuvastatin trial revealed that the efficacy of statin was less prominent in patients with metabolic syndrome.[6] However, this trial evaluated healthy men and women with elevated C-reactive protein.

In real clinical practice, the number of MI patients with lipid profiles of dyslipidemia is substantial, especially in Asian communities.[7] Therefore, it is necessary to evaluate the benefit of statin in this group of acute MI. We investigated the differential effect of statin according to the baseline level of HDL-C and triglyceride.

Subjects and Methods

Study population

This study enrolled 36580 patients, diagnosed as acute MI consecutively from November 2005 to January 2012, and analyzed retrospectively. This data was collected from the Korea Acute Myocardial Infarction Registry (KAMIR), which is a multi-centered and ongoing observational trial designed to evaluate demographic, angiographic, and clinical data about acute myocardial infarction patients. The KAMIR was supported by a research grant from the Korean Society of Cardiology and the study protocol was evaluated and approved by the ethics committee at each institution.

Among total enrolled patients, 20703 patients were diagnosed as ST-segment elevation myocardial infarction (STEMI) and 15877 patients were diagnosed as non-ST-segment elevation myocardial infarction. The diagnostic criteria for acute myocardial infarction was defined as a typical rise and fall of cardiac biomarker values and at least one of following: 1) symptoms of ischemia, 2) development of pathologic Q wave in the electrocardiogram, 3) new significant ST-segment or T wave change or new-onset left bundle branch block, or 4) identification of intracoronary lesion by angiography.[8] All eligible patients were diagnosed as acute MI and >18 years of age at admission. Fasting lipid profiles were evaluated within 24 hours after admission. The patients who had been treated by statin before the episode of acute myocardial infarction were also included in this study. There was no limitation of enrollment according to the strategy of therapy. The procedure of percutaneous coronary intervention (PCI) was done according to local standard protocol. The administration of glycoprotein IIb/IIIa inhibitor and selection between unfractionated or low molecular weight heparin were left to the discretion of the individual clinician. In the case of STEMI, PCI was performed with the intention of restoring blood flow in the infarct-related coronary artery as soon as possible. The use of other medications (e.g., aspirin, clopidogrel, beta-blocker, and renin-angiotensin system blocker) was decided based on the clinical state of an individual patient.

The exclusion criteria in this study were following: 1) patients with normal coronary artery on angiography, 2) MI because of coronary artery spasm, 3) patients who died in a hospital, or 4) patients with missing records about the use of statin. After excluding these patients, 24653 patients were divided into 4 groups, according to the baseline level of HDL-C and triglyceride, and analyzed: group A (HDL-C≥40 mg/dL and triglyceride<150 mg/dL; n=11819), group B (HDL-C≥40 mg/dL and triglyceride≥150 mg/dL; n=3329), group C (HDL-C<40 mg/dL and triglyceride<150 mg/dL; n=6062), and group D (HDL-C<40 mg/dL and triglyceride≥150 mg/dL; n=3443).

Study protocols

Each of the four groups was divided into two subgroups according to the prescription of statin at discharge after an episode of acute MI. We compared the clinical outcome between a statin user and non-user in each of the 4 groups.

The primary end points were cumulative incidence of major adverse cardiac events (MACE). MACE was defined as the composite of cardiac death, recurrence of non-fatal MI, target vessel revascularization (TVR), and coronary artery bypass surgery. Cardiac death was defined as all-cause mortality without a definite non-cardiac cause and recurrent MI was defined as recurrent symptoms with a new electrocardiographic deviation or abnormal elevation of cardiac marker at least twice the upper limit of the reference range. TVR was defined as any repeated intervention in the treated vessel within and beyond the target lesion. The secondary end points were cardiac death, non-fatal MI, TVR, and target-lesion revascularization (TLR), respectively. TVR was defined as repeated intervention that is limited within the previous target lesion. Clinical follow up was performed during 2 years and the cumulative incidence of the primary and secondary endpoints was compared between the statin and non-statin group in each group A and group B.

To adjust the selection bias that inevitably occurs in the analysis of registry data, we adopted propensity score matching. We compared baseline characteristics and clinical outcome and after propensity score matching. To adjust compounding variables more accurately, we also performed multivariate analysis after propensity score matching. Additionally, the benefit of statin in groups B, C, or D was compared with the benefit in group A.

Statistical analysis

All analyses were performed using SPSS Version 21 (SPSS Inc., Chicago, IL, USA). Categorical baseline variables are presented as

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counts and percentages and continuous variables are expressed as mean±standard deviation. Differences in baseline characteristics were compared by the Student t-test for continuous variables and the Pearson chi-square test for categorical variables. Cumulative cardiac event-free survivals were evaluated by the Kaplan-Meier method and compared by the log-rank test between the statin user and non-user. Because the baseline characteristics were significantly different between these two groups, we performed propensity score matching.

Propensity score matching is a statistical matching technique that attempts to estimate the effect of statin therapy in this statistical analysis of observational data. Propensity scores were estimated using a non-parsimonious multivariable logistic regression model, with the dependent variable was the use of statin, and the 13 baseline characteristics were entered as covariates. Matching was performed using R-macro (1-to-1 with a replacement) and a caliper width of 0.25 of the standard deviation. In the propensity score-matched analysis, many patients remained unmatched and were thus excluded from this analysis. The comparison of baseline characteristics and survival analyses was also done after propensity matching. To evaluate the clinical benefit of statin more accurately, we used multivariate Cox regression analysis. The covariates for this analyses were age over 65 years, hypertension, diabetes mellitus, left ventricular ejection fraction, Killip classification, post-thrombolysis in myocardial infarction (TIMI) flow, and the use of aspirin, clopidogrel, beta-blocker, and renin-angiotensin system blocker. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated and all tests were two-tailed: the $p<0.05$ was considered significant.

Results

Baseline characteristics

Before propensity matching, many clinical baseline characteristics were different between the statin user and non-user in each of the 4 groups. Therefore, we adjusted these differences with propensity score matching. But despite propensity matching, the rate of use of unfractionated heparin or low-molecular weight heparin was significantly different in group A and group C. The average age was different between that in user and non-user in group D. Furthermore, the systolic and diastolic blood pressures were not adjusted appropriately in group C. However, most of other differences of the baseline clinical and procedural characteristics were adjusted appropriately after matching (Tables 1 and 2).

The angiographic and procedural characteristics were also adjusted by propensity score matching. After adjustment, there was no significant difference between the statin and non-statin groups in groups A, B, and D. However, the pre-TIMI and post-TIMI flows were significantly different between the statin and non-statin groups in group C (Tables 3 and 4).

Clinical outcome before propensity matching

This lipid-lowering therapy with statin significantly reduces the cumulative incidence of MACE in group A (HR=0.676; 95% CI: 0.582-0.785; $p<0.001$) and group C (HR=0.798, 95% CI: 0.649-0.980, $p=0.031$). Although statistically insignificant, statin therapy had a tendency to reduce the rate of MACE in group B. However, the benefit of statin was not prominent in group D before propensity-score matching (Fig. 1). The benefit of statin in group A was significantly different from group D (interaction $p=0.042$) (Fig. 1).

Clinical outcome after propensity matching

In a propensity-matched population, statin therapy significantly reduces the cumulative incidence of MACE in group A (HR=0.752, CI: 0.609-0.929, $p=0.008$). However, this benefit of statin therapy was not prominent in groups B, C, or D (Fig. 1). In particular, the benefit of statin in group D was significantly different from group A (interaction $p=0.043$) (Fig. 1).

To evaluate the impact of statin therapy on clinical outcome more accurately, we performed multivariate Cox regression analysis. This analysis demonstrated that the benefit of statin therapy was significant in group A (HR=0.692, CI: 0.543-0.882, $p=0.003$). However, this benefit was not prominent in groups B, C, or D (Table 5).

The comparison of the incidence of a secondary end point was performed after propensity matching. Statin therapy significantly reduced cardiac death in group A (HR=0.628, CI: -0.938, $p=0.023$) (Fig. 2). However, the impact of statin on recurrence of non-fatal MI, TVR, or TLR was not prominent in group A. In groups B, C, or D, the benefit of statin on the secondary end point was not significant (Fig. 2).

Discussion

Our study evaluated the differential benefit of statin according to the baseline level of HDL-C and triglyceride and revealed that the impact of statin on clinical outcome was not significant in acute MI patients with lipid profiles of dyslipidemia (HDL-C<40 mg/dL and triglyceride≥150 mg/dL). On contrary, the benefit of statin was prominent in patients without lipid components of dyslipidemia (HDL-C≥40 mg/dL and triglyceride<150 mg/dL). The benefit of statin was significantly different in these two groups.

Although the current guidelines recommend that statin therapy

Table 1. Comparison of clinical baseline characteristics after propensity score matching in group A (HDL-C≥40 mg/dL and TG<150 mg/dL) and group B (HDL-C≥40 mg/dL and TG≥150 mg/dL)

	Group A			Group B		
	Statin group (n=2488)	Non-statin group (n=2563)	p	Statin group (n=544)	Non-statin group (n=583)	p
Age	67.2±12.2	67.0±12.7	0.551	59.4±12.0	59.8±12.7	0.593
Gender (male)	1956 (64.5)	2009 (66.1)	0.194	503 (72.7)	513 (74.2)	0.513
BMI (kg/m^2)	23.5±3.4	23.2±3.5	0.005	25.0±3.0	24.7±2.9	0.063
SBP (mmHg)	130.6±27.7	129.2±28.0	0.050	134.8±28.0	134.5±26.5	0.859
DBP (mmHg)	79.1±16.2	78.4±16.4	0.134	82.1±17.2	82.3±15.9	0.850
HR (/min)	78.0±19.9	77.8±19.7	0.670	78.9±19.9	78.2±17.8	0.488
IHD Hx.	446 (14.8)	465 (15.4)	0.488	87 (12.7)	95 (13.8)	0.566
HTN Hx.	1531 (50.7)	1525 (50.5)	0.896	363 (53.0)	330 (47.8)	0.055
DM Hx.	681 (22.5)	736 (24.4)	0.087	169 (24.6)	193 (27.9)	0.160
HL Hx.	321 (10.6)	277 (9.1)	0.104	119 (17.2)	110 (15.9)	0.784
MI type STEMI	1707 (56.5)	1687 (55.3)		399 (57.7)	375 (54.3)	0.204
NSTEMI	1316 (43.5)	1355 (44.7)		293 (42.3)	316 (45.7)	
STEMI Tx. (primary PCI)	848 (91.6)	765 (90.7)	0.817	198 (89.6)	172 (93.0)	0.258
NSTEMI Tx. (early invasive Tx.)	570 (76.2)	541 (743)	0.400	139 (84.2)	122 (81.8)	0.276
LVEF (%)	51.6±13.6	51.3±17.1	0.501	53.6±11.4	53.5±11.3	0.966
Killip class≥II	845 (27.8)	855 (28.2)	0.929	142 (20.5)	148 (21.3)	0.860
Peak CK-MB (ng/mL)	130.2±240.3	132.9±280.0	0.687	128.3±195.3	121.5±161.7	0.485
Peak Tro-I (ng/mL)	43.9±181.6	41.4±87.4	0.525	37.6±67.0	37.7±6.8	0.988
Total cholesterol (mg/dL)	186.6±40.6	182.0±38.9	0.069	213.0±42.1	209.4±44.1	0.184
Triglyceride (mg/dL)	84.5±31.4	82.9±31.2	0.049	234.0±137.5	234.5±119.7	0.948
HDL-C (mg/dL)	52.2±22.3	51.9±15.1	0.587	50.5±17.3	50.8±24.4	0.813
LDL-C (mg/dL)	108.6±39.6	107.3±38.2	0.398	130.1±42.4	127.5±39.7	0.387
Hs CRP (mg/L)	9.5±46.0	9.1±33.0	0.669	12.3±60.5	11.6±58.9	0.853
NT pro BNP (pg/mL)	2556±5752	2963±6540	0.043	1486±4329	1318±3627	0.553
HbA1c (%)	6.5±2.1	6.5±2.3	0.628	6.6±1.6	6.9±3.6	0.187
Glucose (mg/dL)	163.5±73.9	165.2±78.1	0.393	174.4±83.9	174.2±79.5	0.970
Creatinine (mg/dL)	1.0±0.9	1.1±1.0	0.003	1.0±1.0	1.0±0.8	0.838
Unfractionated heparin	1885 (63.1)	1751 (58.3)	<0.001	391 (57.4)	367 (53.3)	0.130
LMWH	782 (26.2)	882 (29.4)	0.006	220 (32.3)	252 (36.6)	0.092
Glycoprotein IIb/IIIa inhibitor	340 (18.0)	288 (15.9)	0.038	77 (17.3)	56 (14.0)	0.183
Aspirin	2910 (95.9)	2911 (95.9)	0.948	661 (95.2)	661 (95.2)	1.000
Clopidogrel	2692 (88.7)	2668 (879)	0.338	605 (87.2)	609 (87.8)	0.746
Calcium channel blocker	371 (12.7)	385 (13.0)	0.696	101 (15.1)	100 (15.0)	0.939
Beta blocker	2216 (73.0)	2166 (71.4)	0.152	540 (77.8)	517 (74.5)	0.147
RAAS blocker	2336 (77.0)	2292 (75.5)	0.185	567 (81.7)	547 (78.8)	0.177
Spironolacton	144 (4.9)	129 (4.4)	0.299	21 (3.2)	17 (2.6)	0.495

Values are n (%) or mean±standard deviation. HDL-C: high density lipoprotein cholesterol, TG: triglyceride, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, IHD Hx.: ischemic heart disease history, HTN Hx.: hypertension history, DM: diabetes mellitus, HL Hx.: hyperlipidemia history, MI: myocardial infarction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, PCI: percutaneous coronary intervention, LVEF: left ventricular ejection fraction, CK-MB: creatine kinase-MB, LDL-C: low density lipoprotein cholesterol, Hs CRP: high sensitivity C-reactive protein, NT pro BNP: N-terminal pro-brain natriuretic peptide, HbA1c: hemoglobin A1C, LMWH: low molecular weight heparin, RAAS: rennin angiotensin aldosterone system

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Table 2. Comparison of clinical baseline characteristics after propensity score matching in group C (HDL-C<40 mg/dL and TG<150 mg/dL) and group D (HDL-C<40 mg/dL and TG≥150 mg/dL)

	Group C			Group D		
	Statin group (n=1305)	Non-statin group (n=1326)	p	Statin group (n=610)	Non-statin group (n=632)	p
Age	67.0±12.3	66.9±12.6	0.775	59.6±12.8	61.3±12.6	0.012
Gender (male)	1169 (74.2)	1180 (74.9)	0.653	580 (79.1)	575 (78.4)	0.794
BMI (kg/m^2)	23.9±3.1	23.6±3.3	0.022	25.2±2.9	24.9±3.5	0.090
SBP (mmHg)	126.1±27.5	123.3±28.8	0.006	131.2±28.4	129.0±26.6	0.124
DBP (mmHg)	76.7±15.8	75.1±16.8	0.006	79.8±17.6	79.0±16.4	0.401
HR (/min)	77.7±20.2	78.3±21.4	0.431	77.6±18.4	75.9±16.4	0.074
IHD Hx.	248 (15.8)	264 (16.9)	0.394	100 (13.7)	126 (17.3)	0.060
HTN Hx.	775 (49.2)	803 (51.3)	0.238	379 (51.9)	374 (51.1)	0.752
DM Hx.	483 (30.8)	523 (33.4)	0.109	245 (33.5)	270 (36.9)	0.177
HL Hx.	145 (9.2)	117 (7.4)	0.114	113 (15.4)	97 (13.2)	0.180
MI type STEMI	881 (55.9)	833 (52.9)	0.093	395 (53.9)	385 (52.7)	0.660
NSTEMI	696 (44.1)	742 (47.1)		338 (46.1)	345 (47.3)	
STEMI Tx. (primary PCI)	455 (90.6)	416 (89.1)	0.210	228 (92.3)	228 (93.4)	0.916
NSTEMI Tx. (early invasive Tx.)	347 (80.5)	301 (73.0)	0.018	165 (77.8)	141 (79.2)	0.741
LVEF (%)	51.5±20.7	50.3±21.7	0.139	54.1±11.2	53.4±11.9	0.280
Killip class≥II	477 (30.2)	516 (32.7)	0.258	163 (22.2)	171 (23.3)	0.729
Peak CK-MB (ng/mL)	116.8±251.3	112.2±217.3	0.582	115.4±182.4	116.7±181.7	0.895
Peak Tro-I (ng/mL)	39.0±79.9	37.7±106.2	0.730	37.2±67.7	37.8±70.4	0.785
Total cholesterol (mg/dL)	160.8±38.6	153.4±40.2	<0.001	193.5±46.6	188.5±46.9	0.068
Triglyceride (mg/dL)	93.3±30.8	92.2±31.2	0.287	251.6±148.7	252.3±146.3	0.935
HDL-C (mg/dL)	33.1±5.2	32.7±5.6	0.043	33.1±4.7	32.8±5.2	0.279
LDL-C (mg/dL)	106.0±35.2	98.9±37.9	<0.001	116.2±40.9	112.8±38.9	0.059
Hs CRP (mg/L)	12.5±55.6	11.0±37.4	0.185	9.5±48.7	7.9±20.6	0.392
NT pro BNP (pg/mL)	3273±6789	3664±8660	0.038	1792±4989	1966±5295	0.610
HbA1c (%)	6.7±2.6	6.7±2.6	0.936	7.0±1.9	6.8±1.5	0.109
Glucose (mg/dL)	165.2±78.7	172.5±87.7	0.015	177.1±85.7	179.8±86.4	0.545
Creatinine (mg/dL)	1.2±1.1	1.3±1.8	0.001	1.2±1.2	1.3±1.4	0.266
Unfractionated heparin	976 (62.8)	930 (59.7)	0.071	347 (54.9)	375 (51.9)	0.256
LMWH	428 (27.6)	437 (28.0)	0.761	207 (28.7)	250 (34.6)	0.016
Glycoprotein IIb/IIIa inhibitor	180 (17.6)	149 (15.9)	0.302	94 (18.7)	75 (15.0)	0.126
Aspirin	1520 (96.3)	1524 (96.5)	0.703	709 (96.7)	707 (96.5)	0.774
Clopidogrel	1415 (89.6)	1395 (88.3)	0.256	674 (92.0)	668 (91.1)	0.573
Calcium channel blocker	187 (12.3)	195 (12.8)	0.627	84 (11.8)	86 (12.2)	0.809
Beta blocker	1157 (73.3)	1125 (71.2)	0.203	593 (80.9)	593 (80.9)	1.000
RAAS blocker	1178 (74.6)	1185 (75.0)	0.774	610 (83.2)	585 (79.8)	0.069
Spironolacton	94 (6.2)	77 (5.1)	0.165	29 (4.1)	33 (4.7)	0.576

Values are n (%) or mean±standard deviation. HDL-C: high density lipoprotein cholesterol, TG: triglyceride, BMI: body mass index, SBP: systolic blood pressure, DBP: diastolic blood pressure, HR: hazard ratio, IHD Hx.: ischemic heart disease history, HTN: hypertension, DM: diabetes mellitus, HL: hyperlipidemia, MI: myocardial infarction, STEMI: ST-segment elevation myocardial infarction, NSTEMI: non-ST segment elevation myocardial infarction, PCI: percutaneous coronary intervention, LVEF: left ventricular ejection fraction, CK-MB: creatine kinase-MB, LDL-C: low density lipoprotein cholesterol, Hs CRP: high sensitivity C-reactive protein, NT pro BNP: N-terminal pro-brain natriuretic peptide, HbA1c: hemoglobin A1C, LMWH: low molecular weight heparin, RAAS: rennin angiotensin aldosterone system

Table 3. Comparison of coronary angiographic and procedural characteristics after propensity score matching in group A (HDL-C≥40 mg/dL and TG<150 mg/dL) and group B (HDL-C≥40 mg/dL and TG≥150 mg/dL)

		Group A			Group B		
		Statin group (n=2488)	Non-statin group (n=2563)	p	Statin group (n=544)	Non-statin group (n=583)	p
Type of culprit lesion	A	92 (3.8)	94 (4.1)	0.459	26 (4.6)	30 (5.9)	0.262
	B1	433 (17.8)	445 (19.2)		109 (19.3)	118 (23.1)	
	B2	773 (31.7)	737 (31.9)		172 (30.5)	153 (30.0)	
	C	1138 (46.7)	1036 (44.8)		257 (45.6)	209 (41.0)	
Location of culprit lesion	LM	44 (1.7)	58 (2.2)	0.414	7 (1.1)	5 (0.8)	0.258
	LAD	1370 (51.5)	1333 (51.7)		284 (46.6)	305 (50.3)	
	LCX	427 (16.0)	419 (16.2)		106 (17.4)	115 (19.0)	
	RCA	820 (30.8)	769 (29.8)		213 (34.9)	181 (29.9)	
PreTIMI flow	0	1171 (46.7)	1059 (43.4)	0.121	273 (47.2)	260 (46.1)	0.753
	I	300 (12.0)	323 (13.2)		78 (13.5)	67 (11.9)	
	II	382 (15.2)	392 (16.1)		80 (13.8)	86 (15.2)	
	III	653 (26.1)	665 (27.3)		148 (25.6)	151 (26.8)	
PostTIMI flow	0	40 (1.6)	27 (1.2)	0.329	7 (1.3)	8 (1.5)	0.118
	I	24 (1.0)	31 (1.3)		1 (0.2)	8 (1.5)	
	II	110 (4.5)	99 (4.3)		30 (5.4)	26 (4.8)	
	III	2255 (92.8)	2170 (93.3)		515 (93.1)	503 (92.3)	
Type of stent	BMS	180 (8.1)	168 (8.0)	0.891	37 (7.1)	31 (6.1)	0.794
	DES	2037 (91.9)	2022 (92.0)		481 (92.9)	474 (93.9)	
Stent size		23.9±7.2	24.0±6.7	0.746	24.7±7.1	24.3±6.7	0.449
Stent diameter		3.1±0.4	3.1±0.4	0.488	3.1±0.5	3.2±0.5	0.659
Reference diameter		3.0±0.5	3.1±0.5	0.754	3.1±0.6	3.1±0.5	0.689
Lesion length		23.5±12.0	22.6±10.5	0.130	22.7±11.9	23.9±10.4	0.356

Values are n (%) or mean±standard deviation. HDL-C: high density lipoprotein cholesterol, TG: triglyceride, TIMI: thromboysis in myocardial infarction, LM: left main, LAD: left anterior descending artery, LCX: left circumflex artery, RCA: right coronary artery, BMS: bare metal stent, DES: drug-eluting stent

should be initiated and continued in all acute MI patients without contraindications to its use, a trial evaluated the impact of baseline LDL-C on the efficacy of statin and reported that the benefit of high-intensity statin declines as a function of decreasing baseline LDL-C level.[9][10] However, there was no large-scaled study that evaluated the impact of baseline HDL-C and triglyceride on the benefit of statin in secondary prevention of acute MI.

Although a causal relationship was not established, the level of HDL-C is inversely related to the development and prevalence of coronary heart disease.[11] Moreover, two randomized-controlled trials reported that increasing HDL-C level improve the clinical cardiovascular outcome.[12][13] Additionally, most patients with low HDL-C have increased blood level of triglyceride and hypertriglyceridemia also appears to increase cardiovascular risk.[14] However, the impact of dyslipidemia on the benefit of statin has been sparsely investigated.

There was a slight discrepancy between the results of our study and the subgroup analysis of CARE trial. The subgroup study of CARE trial revealed that the benefit of statin was significant in MI with low HDL-C (<37 mg/dL) (HR=0.079, p=0.008). The statin therapy also revealed the tendency to reduce cardiovascular risk (HR=0.085, p=0.07) in acute MI patients with a high level of triglyceride (≥144 mg/dL), although it is not statistically significant.[4] However, this study did not evaluate the benefit of statin in acute MI patients with both components of lipid profiles of metabolic syndrome. The magnitude of risk reduction was smaller in patients with low HDL-C or high triglyceride, when compared with patients with high HDL-C (≥37 mg/dL) or low triglyceride (<144 mg/dL) in the CARE trial. This trend was more prominent in our study. The cause of this discrepancy may be explained by difference in the ethnicity of the enrolled patients, as well as the diversity of types and doses of used statin.

The main mechanisms, by which statin improves cardiovascular

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outcomes, are lowering LDL-C level and decreasing systemic inflammation.[4)6)] The effect of statin on increasing HDL-C and decreasing triglyceride is not substantial or optimal. This study revealed that the magnitude of reduction of LDL-C and high-sensitivity C-reactive protein were similar between group A and group D after statin therapy for 1 year (Fig. 3). This result suggested that the low density lipoprotein (LDL) lowering and anti-inflammatory effect of statin were not different according to the baseline level of HDL-cholesterol and triglyceride. However, the difference of baseline characteristics were not adjusted when we compared the LDL-lowering and anti-inflammatory effect of statin between groups A and D. This is a limitation of this study. Although there were a decrease of triglyceride and increase of HDL-C after statin therapy, the level of triglyceride and HDL-C did not achieve normal range in a group with both components of the lipid profile of the metabolic syndrome.

Therefore, a different strategy may be necessary for the secondary prevention of MI in patients with lipid components of the metabolic syndrome. The medications, which target low HDL-C and high triglyceride, were evaluated in several clinical trials. The long-term use of fenofibrate, the most potent type of fibrate, failed to reduce cardiovascular event in the Fenofibrate Intervention and Event Lowering in Diabetes trial.[15)] Another trial revealed that the combination of fenofibrate and simvastatin did not reduce the rate of fatal cardiovascular events, non-fatal MI or non-fatal stroke, when compared with simvastatin alone.[16)] Several studies revealed that a combined HDL-C-raising with nicotinic acid and LDL-C lowering with statin regimen significantly reduced the risk of a composite of death, MI, stroke, and revascularization.[17-19)] The magnitude of risk reduction with this combination therapy was greater than that typically observed in studies that evaluated statin alone. These results suggested that the combination of

Table 4. Comparison of angiographic and procedural characteristics after propensity score matching in group C (HDL-C<40 mg/dL and TG<150 mg/dL) and group D (HDL-C<40 mg/dL and TG≥150 mg/dL)

		Group C			Group D		
		Statin group (n=1305)	Non-statin group (n=1326)	p	Statin group (n=610)	Non-statin group (n=632)	p
Type of culprit lesion	A	52 (4.1)	43 (3.6)	0.743	19 (3.1)	30 (5.2)	0.086
	B1	185 (14.5)	180 (14.9)		116 (18.9)	134 (23.3)	
	B2	402 (31.5)	398 (33.0)		208 (33.9)	170 (29.6)	
	C	638 (50.0)	584 (48.5)		270 (44.0)	241 (41.9)	
Location of culprit lesion	LM	35 (2.5)	33 (2.5)	0.871	16 (2.4)	20 (3.0)	0.496
	LAD	624 (44.0)	602 (45.0)		270 (40.1)	272 (41.1)	
	LCX	209 (14.7)	205 (15.3)		118 (17.5)	129 (19.5)	
	RCA	550 (38.8)	499 (37.3)		269 (40.0)	241 (36.4)	
PreTIMI flow	0	648 (48.5)	568 (45.1)	0.022	298 (47.4)	286 (46.1)	0.957
	I	139 (10.4)	179 (14.2)		72 (11.4)	71 (11.4)	
	II	199 (14.9)	194 (15.4)		93 (14.8)	92 (14.8)	
	III	349 (26.1)	318 (25.3)		166 (26.4)	172 (27.7)	
PostTIMI flow	0	22 (1.7)	33 (2.7)	0.015	7 (1.1)	10 (1.7)	0.507
	I	12 (0.9)	15 (1.2)		9 (1.5)	6 (1.0)	
	II	52 (4.1)	77 (6.4)		29 (4.8)	21 (3.5)	
	III	1182 (93.2)	1078 (89.6)		565 (92.6)	563 (93.8)	
Type of stent	BMS	104 (8.9)	89 (8.3)	0.286	47 (8.2)	37 (6.8)	0.055
	DES	1068 (91.1)	978 (91.7)		524 (91.8)	508 (93.2)	
Stent length (mm)		24.7±7.3	24.6±6.7	0.590	24.3±7.2	23.7±6.9	0.139
Stent diameter (mm)		3.1±0.4	3.1±0.4	0.826	3.1±0.4	3.1±0.4	0.267
Reference diameter (mm)		3.0±0.8	3.0±0.6	0.124	3.1±0.6	3.1±0.5	0.894
Lesion length (mm)		24.1±11.6	24.3±11.6	0.816	23.4±10.1	24.5±12.6	0.348

Values are n (%) or mean±standard deviation. HDL-C: high density lipoprotein cholesterol, TG: triglyceride, TIMI: thrombolysis in myocardial infarction, LM: left main, LAD: left anterior descending, LCX: left circumflex, RCA: right coronary artery, BMS: bare-metal stent, DES: drug-eluting stent

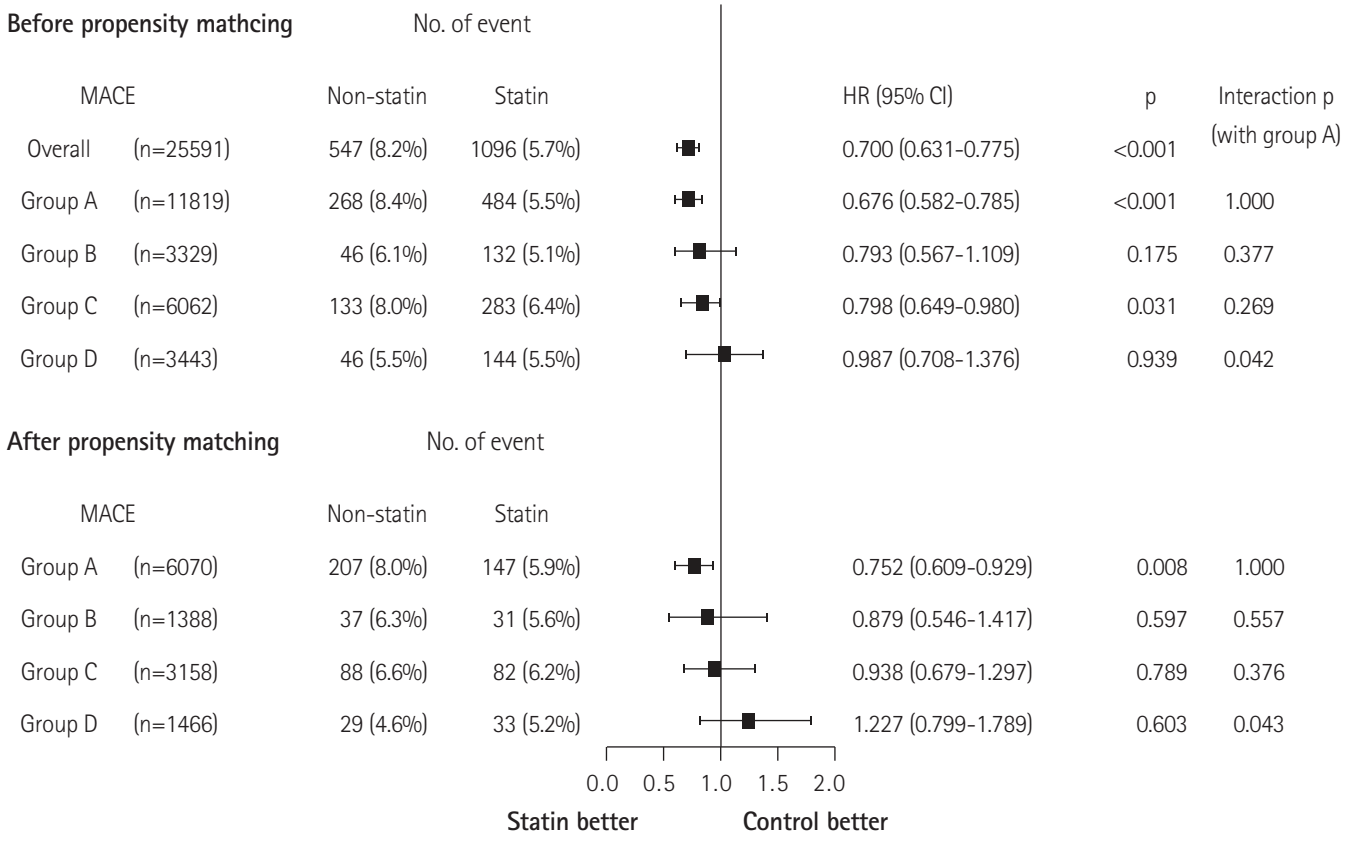

Fig. 1. The benefit of statin on MACE before and after propensity matching in each of the 4 groups, which were divided according to the baseline level of high density lipoprotein cholesterol and triglyceride. Group A (HDL-C≥40 mg/dL and triglyceride<150 mg/dL; n=11819), group B (HDL-C≥40 mg/dL and triglyceride≥150 mg/dL; n=3329), group C (HDL-C<40 mg/dL and triglyceride<150 mg/dL; n=6062) and group D (HDL-C<40 mg/dL and triglyceride≥150 mg/dL; n=3443). MACE: major adverse cardiac event, HDL-C: high density lipoprotein cholesterol, HR: hazard ratio, CI: confidence interval.

Table 5. The impact of statin therapy on primary end point after propensity score matching

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	p	HR (95% CI)	p
Group A (n=5051)	0.752 (0.609-0.929)	0.008	0.692 (0.543-0.882)	0.003
Group B (n=1227)	0.879 (0.546-1.417)	0.597	0.912 (0.628-1.489)	0.651
Group C (n=2631)	0.938 (0.679-1.297)	0.789	0.952 (0.691-1.318)	0.839
Group D (n=1242)	1.227 (0.799-1.789)	0.603	1.257 (0.734-2.154)	0.404

The covariates in this multivariate analysis were age over 65 years, hypertension, diabetes mellitus, left ventricular ejection fraction, Killip classification, post-TIMI flow, and the use of aspirin, clopidogrel, beta-blocker, and renin-angiotensin system blocker. TIMI: thrombolysis in myocardial infaction, HR: hazard ratio, CI: confidence interval

nicotinic acid and statin provides additional benefit beyond that attributable to simply lowering LDL-C by statin. However, because the population of these studies was relatively small, larger randomized-controlled trials are necessary to demonstrate the additive benefit of nicotinic acid on cardiovascular outcome. Another type of HDL-C-raising medication, cholesterol ester transfer protein inhibitor, is also under investigation.[20][21]

Our study has several limitations. First, the reason for not using statin was omitted in this registry. The total of enrolled patients not treated by statin was 29.5% and this percentage is similar with another study.[22] The second limitation is that the enrolled patients were treated by various types and dosages of statin. Therefore, we cannot evaluate the effect of a specific type or dosage of statin. Third, we did not analyze the differential benefit of other current studies. Fourth, the level of TG was not adjusted when we analyzed the change of HDL-C and TG. Moreover, because this study was retrospective, a randomized controlled study is necessary to demonstrate the differential benefit of statin more accurately, according to the levels of HDL-C and triglyceride.

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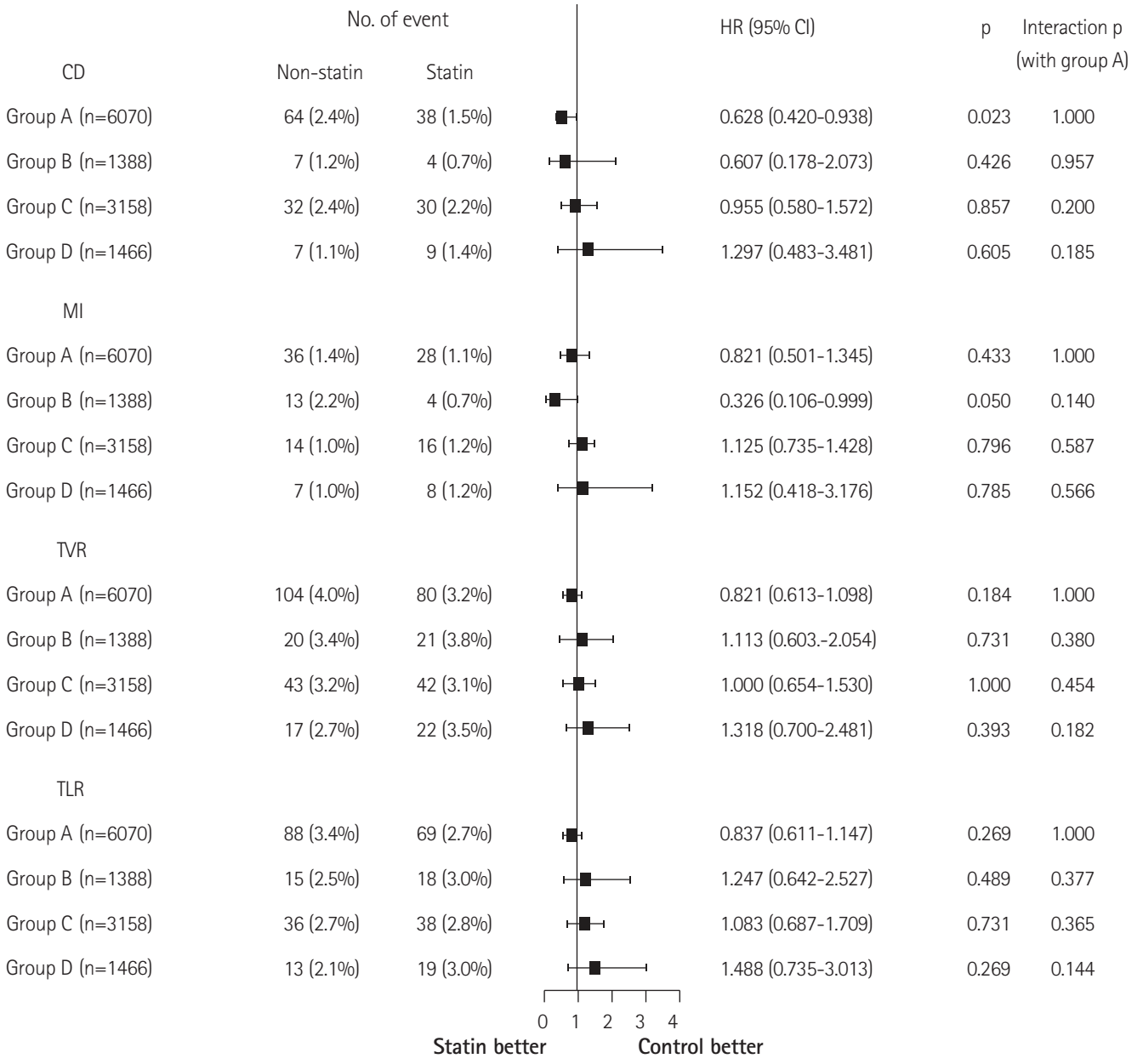

Fig. 2. The benefit of statin on the secondary end point in each of the 4 groups. Group A (HDL-C≥40 mg/dL and triglyceride<150 mg/dL; n=11819), group B (HDL-C≥ 40 mg/dL and triglyceride≥150 mg/dL; n=3329), group C (HDL-C<40 mg/dL and triglyceride<150 mg/dL; n=6062), and group D (HDL-C<40 mg/dL and triglyceride≥150 mg/dL; n=3443). HDL-C: high density lipoprotein cholesterol, CD: cardiac death, MI: myocardial infarction, TVR: target vessel revascularization, TLR: target lesion revascularization, HR: hazard ratio, CI: confidence interval.

Conclusion

The benefit of statin in secondary prevention was significant in acute MI patients with low triglyceride and high HDL-C. However, the benefit was not prominent in patients with high triglyceride and low HDL-C.

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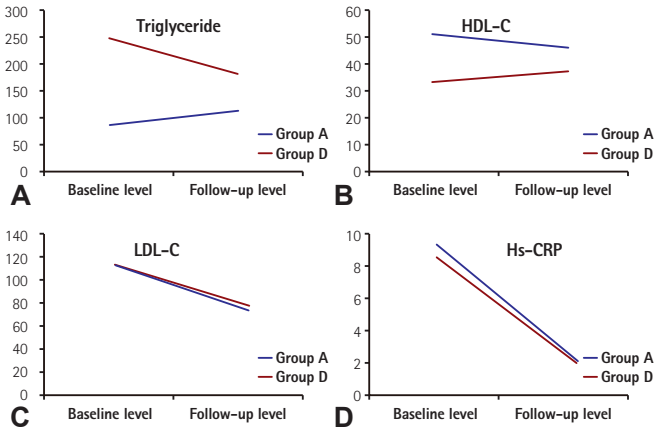

Fig. 3. Comparison of changes of the levels of triglyceride (A), HDL-C (B), LDL-C (C), and hs-CRP (D) after statin therapy between group A and group D. HDL-C: high density lipoprotein cholesterol, LDL-C: low density lipoprotein cholesterol, hs-CRP: high sensitivity C-reactive protein.

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