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Effect of Early Statin Treatment in Patients with Cardiogenic Shock Complicating Acute Myocardial Infarction

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Background and Objectives: The benefit of early statin treatment following acute myocardial infarction (MI) complicated with cardiogenic shock (CS) has not been well studied. We sought to assess the effect of early statin therapy in patients with CS complicating acute MI.
Subjects and Methods: We studied 553 statin-naïve patients with acute MI and CS (Killip class IV) who underwent revascularization therapy between November 2005 and January 2008 at 51 hospitals in the Korea Acute Myocardial Infarction Registry. Patients were divided into 2 groups: those who received statins during hospitalization (n=280) and those who did not (n=273). The influence of statin treatment on a 12-month clinical outcome was examined using a matched-pairs analysis (n=200 in each group) based on the propensity for receiving statin therapy during hospitalization.
Results: Before adjustment, patients receiving statin, compared to those not receiving statin, had a more favorable clinical profile, were less likely to suffer procedural complications, and more likely to receive adequate medical therapy. Patients receiving statin had lower unadjusted in-hospital mortality and composite rate of mortality, MI, and repeat revascularization at 12 months, which remained significantly lower after adjustment for patient risk, procedural characteristics, and treatment propensity.
Conclusion: In CS patients with acute MI undergoing revascularization therapy, early statin treatment initiated during hospitalization was associated with lower rates of in-hospital death and 12-month adverse cardiac events. **(Korean Circ J 2013;43:100–109)**

KEY WORDS: Angioplasty; Myocardial infarction; Shock.

Introduction

Early statin therapy has become the standard of care in patients with acute coronary syndrome (ACS).[1-4] However, the great majority of clinical trials have excluded patients with impaired hemodynamics, particularly cardiogenic shock (CS), which is the most com-

mon cause of death following acute myocardial infarction (MI) with high short-term mortality ranging from 42 to 48 percent.[5)6] The present study was conducted to investigate the effect of early statin treatment on a 12-month clinical outcome in CS patients with acute MI undergoing revascularization therapy.

Subjects and Methods

Study population and data collection

The Korea Acute Myocardial Infarction Registry (KAMIR) is the first nationwide, multicenter data collection registry in Korea, designed to track the outcomes of patients presenting with acute MI.[7)8] Since its launch in November 2005, the KAMIR included 51 community and teaching hospitals and contained data on 14870 patients through January 2008.

The study population was derived from patients enrolled in the KAMIR between November 2005 and January 2008. We included 616 patients (18 years of age or older) presenting with acute MI complicated with CS who underwent revascularization therapy either with percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG). From this population, we excluded 53 patients who had been on statin treatment before the onset of acute MI and 10 patients who received non-statin lipid lowering therapy during admission. A total of 553 patients were selected and divided into 2 groups: those who received statin treatment during hospitalization (n=280) and those who did not (n=273). Atorvastatin was used in 41% of the patients (10 mg in 69%, 20 mg in 17%, 40 mg in 14%), pravastatin in 39% (40 mg in 92%, 20 mg in 4%, 10 mg in 4%), rosuvastatin in 9% (10 mg), simvastatin in 6% (20 mg in 75%, 10 mg in 25%), pitavastatin in 4% (2 mg), and fluvastatin in 1% (80 mg), respectively. We defined "early" treatment as statin therapy instituted during hospitalization whether it was before or after revascularization therapy. Statin was started on admission in 60%, within 24 hours in 21%, on day 2 in 9%, on day 3-4 in 6%, and on days 5-12 in 4%, respectively. Statin was administered before PCI or CABG in 52% of the patients.

The diagnosis of acute MI was based on a clinical presentation consistent with acute MI and at least 1 of the following: specific electrocardiographic changes, serial increases in serum cardiac biomarkers of myocardial necrosis, and/or angiographic documentation of coronary artery disease. For the purpose of the present study CS was defined as the presence or development of Killip class IV heart failure.

The present study was conducted according to the Declaration of Helsinki. The institutional review board of all participating centers approved the study protocol. The approval number was 05-49 of Chonnam National University Hospital. Written informed consent was obtained from all participating patients.

Study endpoints and definitions

Twelve-month major adverse cardiac events were defined as the occurrence of major adverse cardiac events, defined as death from any cause, recurrent MI, or repeat revascularization within 12 months after admission. Recurrent MI was defined as the recurrence of symptoms or the presence of electrocardiographic changes in association with a rise in cardiac biomarker levels above the upper limit of normal. Repeat revascularization was defined as any repeat surgical or percutaneous intervention, including revascularization procedures performed to treat segments not treated in the index procedure.

Statistical analysis

Baseline differences between the 2 groups were compared using either the t-test or the Mann-Whitney U test for continuous variables and the chi-square test or Fisher's exact test for categorical variables. Unadjusted hazard ratios (HR) and their 95% confidence intervals (CI) were calculated for outcome variables using Cox regression analysis. Since receiving statin treatment was not randomly assigned in this study population, we used propensity score matching to adjust for potentially confounding factors and selection biases.[9)10] We performed a one-to-one matched analysis without replacement on the basis of the estimated propensity score of each patient. For each patient, a propensity score for the likelihood of receiving statin therapy at admission was calculated by forward logistic regression analysis and included 63 variables of clinical and procedural characteristics, procedural complications, and medical treatment during hospitalization shown in Table 1 and 2. The c-statistic for the propensity score derivation model was 0.84, indicating a strong ability to discriminate between the two groups. Using the estimated logits, we first randomly selected a patient in the group receiving statin and then matched the patient to the closest patient in the group not receiving statin. Patients in the group not receiving statin who had an estimated logit within a standard deviation of 0.6 of the selected patients in the group receiving statin were eligible for matching. We selected 0.6 because this value has been shown to eliminate approximately 90% of the bias in observed confounders.[11] We were successfully able to match 200 patients receiving statin to 200 patients not receiving statin at admission. Differences between matched pairs were evaluated using the paired t-test or the Wilcoxon signed rank test for continuous variables and the McNemer test for categorical variables. The risks of clinical end points in the matched cohort were compared by the use of Cox regression models stratified on matched pairs. To identify independent predictors of the 12-month clinical outcome (composite of death, MI, repeat revascularization), multivariate Cox propor-

tional hazards regression analysis was performed including 14 variables with univariate p<0.01 given the number of events per confounder: age, male gender, smoking, previous stroke, ventricular tachycardia/fibrillation at presentation, smoking, high-sensitivity C-reactive protein, left main culprit lesion, lesion type B2/C, post-PCI Thrombolysis in Myocardial Infarction (TIMI) grade 3, use of aspirin, clopidogrel, beta-blockers, and angiotensin-converting enzyme inhibitors (ACEI) or angiotensin receptor blockers (ARB). The regression analysis was done using backward stepwise selection and variables were removed if p>0.10. A 2-sided p<0.05 was considered statistically significant. Statistical analyses were conducted using Statistical Package for the Social Sciences (SPSS) 17.0 (SPSS Inc., Chicago,

IL, USA) and Stata 11.0 (Stata Corp., College Station, TX, USA).

Results

Baseline characteristics of patients with and without statin treatment during hospitalization are shown in Table 1. Patients who received statin were younger, had chest pain more often, and were less likely to have severe hemodynamic instability and left ventricular (LV) dysfunction. They had higher levels of total and low density lipoprotein-cholesterol and lower levels of glucose at admission. Statin-treated patients were less likely to have left main disease and had a higher rate of post-PCI TIMI 3 flow and a lower rate of peripro-

Table 1. Baseline characteristics before propensity score matching

	Statin (n=280)	No statin (n=273)	p
Age (years)	65±12	68±13	0.021
Male (%)	183 (65.4)	158 (57.9)	0.070
Past medical history (%)			
Smoking	117 (41.8)	103 (37.7)	0.330
Hypertension	149 (53.2)	137 (50.2)	0.476
Diabetes	92 (32.9)	80 (29.3)	0.367
Dyslipidemia	15 (50.6)	9 (3.3)	0.234
Family history	27 (9.6)	23 (8.4)	0.618
Chronic kidney disease	5 (1.8)	3 (1.1)	0.499
Previous coronary artery disease	28 (10.0)	29 (10.6)	0.810
Previous heart failure	10 (3.6)	4 (1.5)	0.115
Previous stroke	25 (8.9)	16 (5.9)	0.169
Presentation data (%)			
Chest pain	215 (76.8)	171 (62.6)	<0.001
Ventricular tachycardia/fibrillation	19 (6.8)	23 (8.4)	0.467
Circulatory arrest	35 (12.5)	55 (20.1)	0.015
Systolic blood pressure (mm Hg)	94±39	77±42	<0.001
Diastolic blood pressure (mm Hg)	59±25	48±28	<0.001
Heart rate (beats/min)	74±34	72±68	0.611
Pre-infarct angina (%)	88 (31.4)	73 (26.7)	0.225
ST-elevation myocardial infarction (%)	238 (85.0)	236 (86.4)	0.627
Left ventricular ejection fraction <40% (%)	152 (54.3)	181 (66.3)	0.004
Laboratory findings			
Total cholesterol (mg/dL)	170±44	157±44	0.001
Low density lipoprotein-cholesterol (mg/dL)	107±37	92±34	<0.001
High density lipoprotein-cholesterol (mg/dL)	42±11	41±13	0.620
Triglycerides (mg/dL)	111±76	108±79	0.668
Serum creatinine (mg/dL)	1.3±1.1	1.5±1.3	0.062
Peak troponin-I (ng/mL)*	32 (6-79)	35 (5-80)	0.781
Glucose at admission (mg/dL)*	187 (138-280)	215 (151-311)	0.012
High-sensitivity C-reactive protein (mg/dL)*	2.0 (0.4-11.6)	1.9 (0.2-8.2)	0.136

*Values are expressed as the median (interquartile range)

cedural complications. Also, they had complex lesions more often, underwent coronary stenting, and received antiplatelet and adequate anti-ischemic medications (Table 2). After propensity score ma-

tching, the major differences in baseline clinical characteristics and proportion of procedures, complications, and medical treatment during hospitalization were minimized or eliminated (Table 3 and 4).

Table 2. Characteristics of procedures, complications, and medical treatment during hospitalization before propensity score matching

	Statin (n=280)	No statin (n=273)	p
Procedures (%)			
Culprit coronary artery			
Left main	14 (5.0)	30 (10.9)	0.017
Left anterior descending artery	114 (40.7)	111 (40.7)	0.991
Left circumflex artery	25 (8.9)	18 (6.6)	0.404
Right coronary artery	127 (45.4)	114 (41.8)	0.352
ACC/AHA type B2/C	209 (74.6)	182 (66.7)	0.039
Multi-vessel disease	170 (60.7)	160 (58.6)	0.614
Fibrinolysis	8 (2.9)	13 (4.8)	0.241
Coronary artery bypass grafting	1 (0.4)	4 (1.5)	0.169
PCI	280 (100)	270 (98.9)	0.120
Time from symptom onset to PCI (hours)*	22.0 (15.0-37.0)	23.0 (16.0-33.2)	0.700
Glycoprotein IIb/IIIa inhibitor	66 (23.6)	66 (24.2)	0.868
Pre-PCI TIMI 3	37 (13.2)	33 (12.1)	0.690
Post-PCI TIMI 3	230 (82.1)	201 (73.6)	0.016
Stenting	265 (94.6)	239 (87.5)	0.003
Drug-eluting stents	239 (85.4)	203 (74.4)	0.001
Multi-vessel PCI	37 (13.2)	49 (17.9)	0.125
Complications (%)			
CPR during PCI	51 (18.2)	84 (30.8)	0.001
Atrial fibrillation	11 (3.9)	7 (2.6)	0.366
Ventricular tachycardia/fibrillation	51 (18.2)	69 (25.3)	0.044
Advanced atrioventricular block	27 (9.6)	32 (11.7)	0.429
Intraaortic balloon counterpulsation	56 (20.0)	101 (37.0)	<0.001
Mechanical ventilation	70 (25.0)	111 (40.7)	<0.001
Temporary cardiac pacing	46 (16.4)	58 (21.2)	0.147
Acute kidney injury	9 (3.2)	13 (4.8)	0.352
Major bleeding	5 (1.8)	5 (1.8)	1.000
Acute stroke	2 (0.7)	9 (3.3)	0.030
Medical treatment during hospitalization (%)			
Unfractionated heparin	166 (59.3)	161 (59.0)	0.941
Low molecular weight heparin	80 (28.6)	79 (28.9)	0.924
Aspirin	277 (98.9)	242 (88.6)	<0.001
Clopidogrel	278 (99.3)	242 (88.6)	<0.001
Cilostazol	79 (28.2)	45 (16.5)	0.001
Beta-blockers	234 (83.6)	195 (71.4)	0.001
ACEI/ARB	208 (74.3)	112 (41.0)	<0.001
Diuretics	87 (31.1)	72 (26.4)	0.222
Long-acting nitrates	166 (59.3)	149 (54.6)	0.264

*Values are expressed as the median (interquartile range). ACC/AHA: American College of Cardiology/American Heart Association, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CPR: cardiopulmonary resuscitation, PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction

Unadjusted and adjusted clinical outcomes within 12 months after admission are summarized in Table 5 and 6. Among the 273 patients without statin treatment, the unadjusted in-hospital mortality was 43.2% compared to 12.9% among the 280 patients with statin treatment (p<0.001). After propensity score matching, patients who did not receive statin still exhibited higher in-hospital

Table 3. Baseline characteristics after propensity score matching

	Statin (n=200)	No statin (n=200)	p
Age (years)	66±12	66±13	0.894
Male (%)	126 (63.0)	123 (61.5)	0.813
Past medical history (%)			
Smoking	79 (39.5)	76 (38.0)	0.834
Hypertension	110 (55.0)	106 (53.0)	0.777
Diabetes	60 (30.0)	52 (26.0)	0.461
Dyslipidemia	9 (4.5)	7 (3.5)	0.791
Family history	17 (8.5)	19 (9.5)	0.868
Chronic kidney disease	3 (1.5)	3 (1.5)	1.000
Previous coronary artery disease	22 (11.0)	23 (11.5)	1.000
Previous heart failure	7 (3.5)	4 (2.0)	0.549
Previous stroke	17 (8.5)	13 (6.5)	0.557
Presentation data			
Chest pain (%)	136 (68.0)	135 (67.5)	1.000
Ventricular tachycardia/fibrillation (%)	14 (7.0)	14 (7.0)	1.000
Circulatory arrest (%)	30 (15.0)	37 (18.5)	0.419
Systolic blood pressure (mm Hg)	89±41	90±35	0.286
Diastolic blood pressure (mm Hg)	56±25	53±26	0.996
Heart rate (beats/min)	77±38	78±37	0.329
Pre-infarct angina (%)	58 (29.0)	54 (27.0)	0.720
ST-elevation myocardial infarction (%)	166 (83.0)	169 (84.5)	0.791
Left ventricular ejection fraction <40% (%)	111 (55.5)	115 (57.5)	0.760
Laboratory findings			
Total cholesterol (mg/dL)	166±41	166±43	0.922
Low-density lipoprotein cholesterol (mg/dL)	99±33	97±32	0.837
High-density lipoprotein cholesterol (mg/dL)	41±11	42±13	0.609
Triglycerides (mg/dL)	109±74	108±83	0.873
Serum creatinine (mg/dL)	1.4±1.3	1.4±0.5	0.896
Peak troponin-I (ng/mL)*	25 (4-50)	27 (5-71)	0.628
Glucose at admission (mg/dL)*	189 (141-285)	194 (140-279)	0.852
High-sensitivity C-reactive protein (mg/dL)*	1.3 (0.2-5.0)	1.4 (0.2-6.5)	0.779

*Values are expressed as the median (interquartile range). Propensity score for the likelihood of receiving statin therapy was calculated by forward logistic regression analysis including 63 variables of clinical and procedural characteristics, procedural complications, and medical treatment during hospitalization shown in Table 1 and 2: age, gender, smoking, hypertension, diabetes, dyslipidemia, family history, chronic kidney disease, previous coronary artery disease, previous heart failure, previous stroke, presentation with chest pain, ventricular tachycardia/fibrillation, circulatory arrest, systolic blood pressure, diastolic blood pressure, heart rate, pre-infarct angina, ST-elevation myocardial infarction, left ventricular ejection fraction <40%, total cholesterol, low density lipo-protein-cholesterol, high density lipoprotein-cholesterol, triglyceride, serum creatinine, peak troponin-I, glucose at admission, high-sensitivity C-reactive protein, culprit coronary artery (left main, left anterior descending artery, left circumflex artery), right coronary artery, lesion type B2/C, multi-vessel disease, fibrinolysis, coronary artery bypass grafting, PCI, time from symptom onset to PCI, glycoprotein IIb/IIIa inhibitor, pre-PCI TIMI 3, post-PCI TIMI 3, stenting, drug-eluting stents, multi-vessel PCI, in-hospital complications CPR during PCI, atrial fibrillation, ventricular tachycardia/fibrillation, advanced atrioventricular block, intraaortic balloon counterpulsation, mechanical ventilation, temporary cardiac pacing, acute kidney injury, major bleeding, acute stroke, medical treatment during hospitalization (unfractionated heparin, low molecular weight heparin, aspirin, clopidogrel, cilostazol, beta-blockers, ACEI/ARB, diuretics, long-acting nitrates). PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction, CPR: cardiopulmonary resuscitation, ACEI/ARB: angiotensin-converting enzyme inhibitors/angiotensin receptor blocker

mortality than those who received statin (17.0% vs. 29.5%, p= 0.002). The unadjusted 12-month mortality and composite major adverse cardiac events were significantly higher in patients with-

out statin treatment (45.4% vs. 18.9%, p<0.001 and 50.9% vs. 24.6%, p<0.001, respectively). In the propensity score-matched cohort, Cox regression analysis stratified on matched pairs showed

Table 4. Characteristics of procedures, complications, and medical treatment during hospitalization after propensity score matching

	Statin (n=200)	No statin (n=200)	p
Procedures (%)			
Culprit coronary artery			
Left main	12 (6.0)	18 (9.0)	0.307
Left anterior descending artery	81 (40.5)	86 (43)	0.731
Left circumflex artery	20 (10.0)	12 (6.0)	0.230
Right coronary artery	87 (43.5)	84 (42.0)	0.905
ACC/AHA type B2/C	132 (66.0)	134 (67.0)	0.851
Multi-vessel disease	127 (63.5)	120 (60.0)	0.505
Fibrinolysis	8 (4.0)	10 (5.0)	0.815
Coronary artery bypass grafting	1 (0.5)	1 (0.5)	1.000
PCI	200 (100)	200 (100)	1.000
Time from symptom onset to PCI (hours)*	22.5 (17.3-45.1)	21.8 (16.0-33.8)	0.812
Glycoprotein IIb/IIIa inhibitor	46 (23.0)	47 (23.5)	1.000
Pre-PCI TIMI 3	31 (15.5)	29 (14.5)	0.880
Post-PCI TIMI 3	158 (79.0)	162 (81.0)	0.716
Stenting	187 (93.5)	186 (93.0)	1.000
Drug-eluting stents	166 (83.0)	160 (80.0)	0.519
Multi-vessel PCI	29 (14.5)	30 (15.0)	1.000
Complications (%)			
CPR during PCI	47 (23.5)	43 (21.5)	0.344
Atrial fibrillation	9 (4.5)	6 (3.0)	0.581
Ventricular tachycardia/fibrillation	37 (18.5)	42 (21.0)	0.635
Advanced atrioventricular block	20 (10.0)	22 (11.0)	0.875
Intraaortic balloon counterpulsation	37 (18.5)	44 (22.0)	0.326
Mechanical ventilation	64 (32.0)	66 (33.0)	0.901
Temporary cardiac pacing	35 (17.5)	39 (19.5)	0.704
Acute kidney injury	8 (4.0)	11 (5.5)	0.648
Major bleeding	4 (2.0)	3 (1.5)	1.000
Acute stroke	2 (1.0)	4 (2.0)	0.687
Medical treatment during hospitalization (%)			
Unfractionated heparin	119 (59.5)	120 (60.0)	1.000
Low molecular weight heparin	57 (28.5)	65 (32.5)	0.505
Aspirin	198 (99.0)	196 (98.0)	0.687
Clopidogrel	198 (99.0)	196 (98.0)	0.687
Cilostazol	41 (20.5)	41 (20.5)	1.000
Beta-blockers	160 (80.0)	153 (76.5)	0.504
ACEI/ARB	111 (55.5)	110 (55.0)	1.000
Diuretics	56 (28.0)	56 (28.0)	1.000
Long-acting nitrates	117 (58.5)	117 (58.5)	1.000

*Values are expressed as the median (interquartile range). ACC/AHA: American College of Cardiology/American Heart Association, ACEI: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, CPR: cardiopulmonary resuscitation, PCI: percutaneous coronary intervention, TIMI: Thrombolysis in Myocardial Infarction

Table 5. Unadjusted clinical outcomes before propensity score matching

	Statin (n=280)	No statin (n=273)	Hazard ratio (95% CI)	p
In-hospital (%)				
Death	36 (12.9)	118 (43.2)	0.19 (0.13-0.29)	<0.001
30-day outcomes (%)				
Death	43 (15.4)	122 (44.7)	0.28 (0.20-0.40)	<0.001
MI	3 (1.1)	1 (0.4)	2.07 (0.21-20.12)	0.529
Repeat revascularization	0	3 (1.1)	-	-
Death/MI	46 (16.4)	123 (45.1)	0.30 (0.21-0.42)	<0.001
Death/MI/repeat revascularization	46 (16.4)	126 (46.2)	0.29 (0.21-0.41)	<0.001
6-month outcomes (%)				
Death	49 (17.5)	123 (45.1)	0.31 (0.22-0.43)	<0.001
MI	6 (2.1)	2 (0.7)	2.604 (0.52-13.01)	0.244
Repeat revascularization	6 (2.1)	13 (4.8)	0.33 (0.12-0.87)	0.025
Death/MI	55 (19.6)	125 (45.8)	0.34 (0.25-0.47)	<0.001
Death/MI/repeat revascularization	61 (21.8)	138 (50.5)	0.33 (0.24-0.45)	<0.001
12-month outcomes (%)				
Death	53 (18.9)	124 (45.4)	0.33 (0.24-0.46)	<0.001
MI	6 (2.1)	2 (0.7)	2.96 (0.60-14.67)	0.184
Repeat revascularization	10 (3.6)	13 (4.8)	0.76 (0.33-1.74)	0.517
Death/MI	58 (20.7)	126 (46.2)	0.35 (0.26-0.48)	<0.001
Death/MI/repeat revascularization	69 (24.6)	139 (50.9)	0.37 (0.28-0.49)	<0.001

CI: confidence interval, MI: myocardial infarction

that statin treatment during hospitalization was significantly associated with a reduction in 12-month mortality (23.0% vs. 32.5%; HR, 0.53; 95% CI, 0.35-0.82; p=0.004) and composite major adverse cardiac events (25.5% vs. 40.0%; HR, 0.44; 95% CI, 0.29-0.66; p< 0.001) (Figs. 1 and 2). On multivariate analysis, factors associated with a reduction in 12-month death/MI/repeat revascularization were post-PCI TIMI flow 3 (HR, 0.53; 95% CI, 0.37-0.77; p=0.001), use of statin (HR, 0.53; 95% CI, 0.38-0.74; p<0.001), ACEI/ARB (HR, 0.50; 95% CI, 0.35-0.74; p<0.001), and beta blockers (HR, 0.51; 95% CI, 0.35-0.74, p<0.001). Factors associated with an increase in 12-month death/MI/repeat revascularization were left main disease (HR, 2.09; 95% CI, 1.11-3.92; p=0.022), previous stroke (HR, 2.06; 95% CI, 1.23-3.44; p=0.006), and older age (>65 years) (HR, 1.10; 95% CI, 1.004-1.033, p=0.013).

Discussion

Early statin therapy has become recommended as a standard treatment in patients with ACS,[1-4] and a number of clinical trials have supported the initiation of statin therapy before discharge after ACS.[12-17] However, most clinical trials have excluded CS patients, and little data is available on the benefit of statin in patients with CS complicating acute MI. The present study suggested that early statin

treatment during hospitalization improved in-hospital survival as well as the 12-month clinical outcome in CS patients with acute MI undergoing revascularization therapy. One finding of note in our study is that statin therapy was associated with reduced in-hospital mortality. There have only been a few studies on the survival benefit of statin therapy very early in the course of ACS. Two series of observational studies from the National Registry of Myocardial Infarction 4 (n=174635; 2270 CS patients)[14] and the Global Registry of Acute Coronary Events (n=15481; 186 CS patients)[18] revealed that the use of statin therapy during hospitalization for ACS was associated with a significantly lower rate of in-hospital mortality: 3.9% vs. 8.6%, p<0.001 and 2.1% vs. 9.9%, p<0.001, respectively. Garot et al.[19] investigated the early beneficial effect of statin therapy in patients undergoing PCI for acute ST-elevation MI complicated by CS. Patients undergoing statin therapy at the time of PCI (n=30) had significantly lower in-hospital mortality than those without statin therapy (n=81) {46.7% vs. 70.4%; odds ratio (OR), 0.35; 95% CI, 0.15-0.88; p=0.026}. Schmidt et al.[20] observed that patients suffering multiple organ dysfunction syndrome (MODS) treated with statin (n=40, cardiovascular causes 93%) had significantly lower in-hospital mortality than age- and sex-matched MODS patients not treated with statin (n=80) (35% vs. 72%, p<0.0001). Suggested mechanisms by which statin therapy may influence early mortality in

Table 6. Adjusted clinical outcomes after propensity score matching

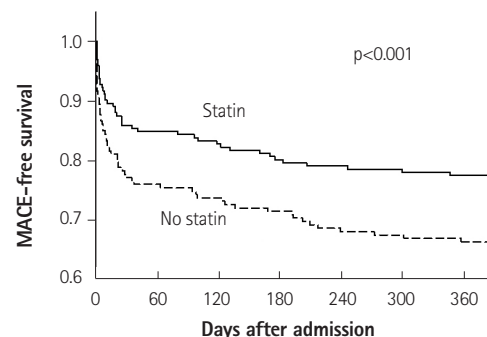|	Statin (n=200)	No statin (n=200)	Hazard ratio (95% CI)	p
In-hospital (%)				
Death	34 (17.0)	59 (29.5)	0.48 (0.30-0.78)	0.002
30-day outcomes (%)				
Death	39 (19.5)	63 (31.5)	0.43 (0.27-0.69)	<0.001
MI	0	1 (0.5)	-	-
Repeat revascularization	0	3 (1.5)	-	-
Death/MI	39 (19.5)	64 (32.0)	0.43 (0.27-0.69)	<0.001
Death/MI/repeat revascularization	39 (19.5)	67 (33.5)	0.41 (0.26-0.65)	<0.001
6-month outcomes (%)				
Death	45 (22.5)	64 (32.0)	0.52 (0.34-0.79)	0.003
MI	1 (0.5)	2 (1.0)	0.50 (0.05-5.51)	0.571
Repeat revascularization	3 (1.5)	13 (6.5)	0.11 (0.01-0.88)	0.037
Death/MI	46 (23.0)	66 (33.0)	0.51 (0.33-0.78)	0.002
Death/MI/repeat revascularization	49 (24.5)	79 (39.5)	0.43 (0.28-0.66)	<0.001
12-month outcomes (%)				
Death	46 (23.0)	65 (32.5)	0.53 (0.35-0.82)	0.004
MI	1 (0.5)	2 (1.0)	0.50 (0.05-5.51)	0.571
Repeat revascularization	4 (2.0)	13 (6.5)	0.23 (0.07-0.81)	0.022
Death/MI	47 (23.5)	67 (33.5)	0.50 (0.33-0.77)	0.002
Death/MI/repeat revascularization	51 (25.5)	80 (40.0)	0.44 (0.29-0.66)	<0.001

CI: confidence interval, MI: myocardial infarction
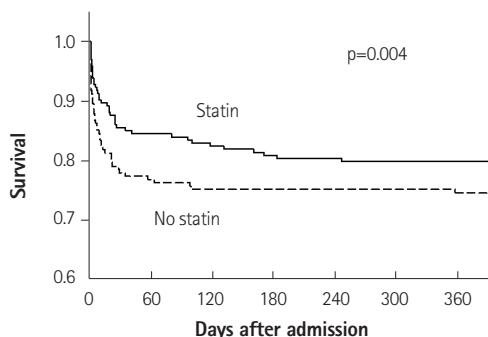
Statin							
No. at risk	200	161	158	155	155	154	140
Cumulative no. of events (%)	1	39	42	45	45	46	46
Cumulative incidence (%)	0.5	19.5	21	22.5	22.5	23	23
No statin							
No. at risk	200	137	136	136	135	135	122
Cumulative no. of events (%)	1	63	64	64	64	64	65
Cumulative incidence (%)	0.5	31.5	32	32	32	32	32.5

Fig. 1. Twelve-month survival in propensity-matched patients with cardiogenic shock complicating acute myocardial infarction according to use of statin.

Statin							
No. at risk	200	158	155	151	149	147	133
Cumulative no. of events (%)	1	39	42	46	48	49	51
Cumulative incidence (%)	0.5	19.5	21	23	24	24.5	25.5
No statin							
No. at risk	200	130	127	125	118	117	104
Cumulative no. of events (%)	1	67	70	72	78	79	80
Cumulative incidence (%)	0.5	33.5	35	36	39	39	40

Fig. 2. Twelve-month event-free survival from major adverse cardiac events (MACE) in propensity-matched patients with cardiogenic shock complicating acute myocardial infarction according to use of statin.

patients with MODS included modulation of inflammatory responses through enhanced expression of endothelial nitric oxide synthase and reduced polymorphonuclear leukocyte-endothelium interactions,[21] and an increase in vagal activity, which prevents a spillover

of proinflammatory products into the circulation.[22-24] Merx et al.[25][26] reported that statin treatment improved survival in a murine model of sepsis-induced hemodynamic alterations. As with pretreatment with simvastatin,[25] mice treated 6 hours after onset of sepsis with

atorvastatin, pravastatin, or simvastatin demonstrated preservation of cardiac function and hemodynamic stability.[26] Improved susceptibility to endothelial nitric oxide synthase stimulation and reduced endothelial adhesion of leukocytes were proposed as underlying mechanisms. In an observational study by Almog et al.[27] on 361 patients with acute bacterial infection, prior statin therapy was associated with a reduced rate of severe sepsis (OR, 0.07; 95% CI, 0.01-0.51; p=0.01). More recently, Hackama et al.[28] also showed in a matched-pair analysis on 141487 patients with cardiovascular disease that statin therapy at both high and low doses was associated with a considerably lower rate of fatal sepsis (OR, 0.75; 95% CI, 0.61-0.93). In a similar manner, in patients with CS complicating acute MI, the use of statins combined with timely revascularization may provide a potential survival benefit through modification of the heightened systemic inflammation, which may primarily manifest as an increase in early mortality frequently in association with severe myocardial ischemic insult, refractory heart failure, and malignant ventricular arrhythmia. This mortality-reducing cardioprotective effect of statins needs to be confirmed in appropriately powered randomized clinical trials.

Our analysis has several limitations. First, although these results come from a large cohort and adjustment was performed using propensity score analysis for a large number of confounding variables, unmeasurable factors may still exist. Second, the distinction between CS caused by LV failure and other etiologies such as predominant right ventricular shock or mechanical complications was not possible. Finally, we could not assess the effect of specific types of statins, dosages, or timing of statin treatment (i.e., before or after PCI or CABG) on observed outcomes.

In conclusion, in statin-naïve CS patients with acute MI undergoing revascularization therapy, early statin treatment initiated during hospitalization was associated with lower in-hospital mortality and a reduction in major adverse cardiac events at a 12-month follow-up. Additional research is warranted to elucidate the pathophysiologic mechanisms for the benefit of early statin use in this highest risk subset of patients with acute MI.

Acknowledgments

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