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# Long-term effects of early statin therapy for patients with acute myocardial infarction treated with stent implantation

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## KEYWORDS

Acute myocardial infarction;  
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## Summary

**Objectives:** Statins are widely administered to patients with acute myocardial infarction (AMI), but knowledge of the effects of early statin therapy on the long-term mortality of AMI patients after stent implantation is still limited, especially for beyond low-density lipoprotein cholesterol (LDL-C) lowering effects.

**Methods:** Our 378 consecutive AMI patients who were discharged alive from the hospital with successful stent implantation between 1997 and 2005 were included. We retrospectively evaluated the effects of statin therapy on major adverse cardiovascular events (MACE), including all-cause death, reinfarction, coronary artery bypass grafting, heart failure requiring rehospitalization, and target lesion revascularization.

**Results:** Statins were given to 271 patients according to the physician to achieve a LDL-C level of less than 100 mg/dL. The achieved LDL-C levels in the statin group were 100.7, 95.1, 96.7, and 102.8 mg/dL at discharge, 6 months, 1 year, and 3 years, respectively, whereas those in the non-statin group were 103.2, 107.3, 102.8, and 103.0 mg/dL. These levels were not significantly different between the groups during 3 years. Based on Kaplan–Meier estimates, statin therapy was associated with a reduction of long-term mortality (log-rank test  $P=0.007$ ). Multivariate Cox regression analysis revealed that statin therapy ( $P=0.015$ , hazard ratio: 0.10; 95% confidence interval: 0.01–0.64) was a significant predictor of favorable prognosis. Multivariate analysis revealed that statin treatment had a beneficial effect against MACE over 3 years ( $P=0.008$ ).

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*Conclusions:* Early statin therapy was beneficial for long-term mortality of AMI patients treated with stenting.

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3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) have been proven to reduce long-term cardiac events and mortality in patients with stable coronary artery disease (CAD) [1–3]. Furthermore, early initiation of statins after acute coronary syndrome (ACS) was revealed to be beneficial in randomized controlled trials (RCT) [4–6] and observational studies [7,8]. Stent implantation is the first-line therapy for acute myocardial infarction (AMI); however, in a large-scale RCT such as the Z phase of the A to Z trial, less than half of all patients were treated with percutaneous coronary intervention (PCI) [5]. Statin therapy for stable or unstable CAD following PCI (with stenting 55–56%) has been shown to reduce recurrent cardiac events over 3 to 4 years [9]. Recently, the MUSASHI-AMI trial showed that early statin therapy for Japanese with AMI after PCI (with stenting 81–82%) reduced recurrent cardiovascular events, in particular congestive heart failure, for up to 2 years [6].

Although all these trials concluded that the effects of statins are related to the reduction of low-density lipoprotein cholesterol (LDL-C), statins may possess so-called pleiotropic effects, including plaque stabilization, anti-inflammation, anti-thrombogenicity, enhanced arterial compliance, blood pressure reduction, and modulation of vascular and ventricular functions [10–12]. To clarify the beyond LDL-C lowering effects of statins, it is worthwhile to compare cardiovascular events in patients whose LDL-C levels achieved guideline-based level between groups with and without statins. Therefore we investigated the long-term effects of statin therapy for AMI patients treated with stent implantation, whose LDL-C levels were stabilized at approximately 100 mg/dL.

## Methods

### Study population

We retrospectively analyzed the data of 378 consecutive patients with AMI who were discharged alive from Kishiwada City Hospital with successful stent implantation between January

1997 and December 2005. To confirm AMI status, ischemic symptoms or electrocardiographic changes accompanied by a cardiac troponin T level  $>0.10$  ng/ml were required. On admission, information such as patient's age, gender, risk factors (diabetes mellitus, hypertension, hyperlipidemia, smoking history), previous MI or coronary artery bypass grafting (CABG) and lipid profile (total cholesterol [TC], high-density lipoprotein cholesterol [HDL-C], triglyceride, and LDL-C) was collected. Hyperlipidemia was defined as  $TC \geq 220$  mg/dL,  $HDL-C < 40$  mg/dL,  $TG \geq 150$  mg/dL and/or having received medication. Diabetes mellitus was defined according to World Health Organization criteria, and/or having received medication. Hypertension was defined as systolic blood pressure  $\geq 140$  mmHg, diastolic blood pressure  $\geq 90$  mmHg and/or on medication. During hospitalization, other variables were recorded regarding biochemical markers, echocardiography, quantitative gated single photon emission computed tomography, intervention procedure and major complications. Creatine kinase (CK) was measured immediately after the procedure, every 4 h until the peak.

### Treatment

Stents were placed according to standard protocols. Patients were pretreated before intervention with aspirin 100 mg and cilostazol 50 mg. They received intravenous heparin during the procedure with a target activated clotting time of  $>300$  s. After stenting, all patients received aspirin 100 mg once or twice daily for as long as possible and ticlopidine 100 mg twice daily for at least 1 month. Statins were given within 24 h of hospital admission, according to the physician, to achieve an LDL-C level  $<100$  mg/dL before discharge. More intensive regimen may be appropriate today, however, the goal  $<100$  mg/dL was optimal and, if the baseline LDL-C was  $<100$  mg/dL, further LDL-lowering therapy was not required at the observed period [13]. Statins were not prescribed for those with a low LDL-C level on admission (mean 102.7 mg/dL; non-statin group); however, statins were added for the non-statin group during follow-up, if necessary, from an ethical point of view. Treating physicians

were also allowed to change the dosage of statins and to switch the original statin to another statin during follow-up. Concomitant therapy with beta-adrenergic blocking agents, angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARB), calcium channel blockers, diuretics or nitrates was left to the discretion of the physician.

After discharge, follow-up angiography was performed at around 6 months and the lipid profile was measured at 6 months, 1 year and 3 years. We analyzed major adverse cardiovascular events (MACE), including all-cause death, reinfarction, CABG, heart failure required rehospitalization, and target lesion revascularization (TLR) at 6 months, 1 year and 3 years.

### Statistical analysis

All descriptive data are expressed as the mean  $\pm$  standard deviation (S.D.). StatFlex V5.0 statistical software for Windows (Artek Inc., Osaka, Japan) was used for all statistical analyses. All analyses were performed on an intention-to-treat basis. Comparisons of continuous variables between groups were analyzed by *t* test (2-sided) and comparisons of categorical variables were generated with the chi-square test. Probability values  $<0.05$  were considered statistically significant.

Long-term mortality was estimated using Kaplan–Meier techniques, and the impact of statin therapy as a time-dependent covariate on patient outcome was evaluated with the Cox proportional hazards regression model. Univariate Cox regression analysis was performed to evaluate the influence of variables; age, gender, LVEF, ST elevation, peak CK, anterior myocardial infarction, number of narrowed coronary arteries, LMT  $\geq 50\%$  stenosis, C-reactive protein, TC, HDL-C, triglyceride and LDL-C levels on admission, decrease of LDL-C during hospitalization, statins, ACE inhibitors/ARB, beta blockers, calcium channel blockers, diuretics, nitrates, diabetes mellitus, hypertension, hyperlipidemia, smoking history, number of stents, stent diameter, total length of stents, and PCI for non-IRA. Variables with a  $P \leq 0.20$  on univariate analyses were included in the multivariate model. Univariate analysis of patients with and without MACE over 3 years were performed using the same variables used with univariate Cox regression analysis. Multivariate logistic regression analysis was used to adjust for all variables with a  $P < 0.20$  on univariate analysis associated with MACE over 3 years.

## Results

### Patients

Baseline characteristics and clinical events during follow-up (mean  $\pm$  S.D.,  $1129 \pm 857$  days) were collected. Overall, 271 (72%) patients including 3 familial hypercholesterolemias were given statins within 24 h after admission. Among them, 4 patients had been taking statin before AMI. Pravastatin, atorvastatin, simvastatin and fluvastatin were given to 139 (53%), 89 (33%), 42 (15%) and 1 patients, respectively. Mean doses were 10.5, 11.3, 5.3 and 20 mg, respectively. During follow-up, 36 patients in the non-statin group had an increased LDL-C levels necessitating initiation of statin therapy. Of them, 22 and 27 patients initiated statin therapy, within the first 6 months and 1 year, respectively. Other lipid lowering drugs were added on for 3 patients in the non-statin group. The baseline characteristics of the two groups are shown in Table 1. In the statin group, there were more female and younger patients. More ACE inhibitors or ARB and beta-blockers, and fewer nitrates were prescribed for the statin group. Both groups had similar culprit lesions but the statin group had more PCI in non infarct-related artery (IRA) during hospitalization.

### Lipid profile

At the time of admission, serum lipid levels were significantly different between the two groups (Table 1). The mean LDL-C levels in statin group strikingly decreased to 100.7 mg/dL during hospitalization and achieved the goal,  $<100$  mg/dL, after 6 months and 1 year, but increased slightly after 3 years. In contrast, those in the non-statin group were all between 100 and 110 mg/dL, as shown in Fig. 1. The difference of LDL-C levels between the two groups during the 3 years after admission was not significant with two-factor mixed design with repeated measures in one-factor analysis. The achieved HDL-C levels in statin group were 41.7, 52.1, 51.1, and 51.0 mg/dL at discharge, 6 months, 1 year, and 3 years, respectively, whereas those in the non-statin group were 42.4, 49.9, 48.9, and 48.5 mg/dL. The difference of HDL-C levels between the two groups during 3 years was not significant.

### Long-term mortality and MACE

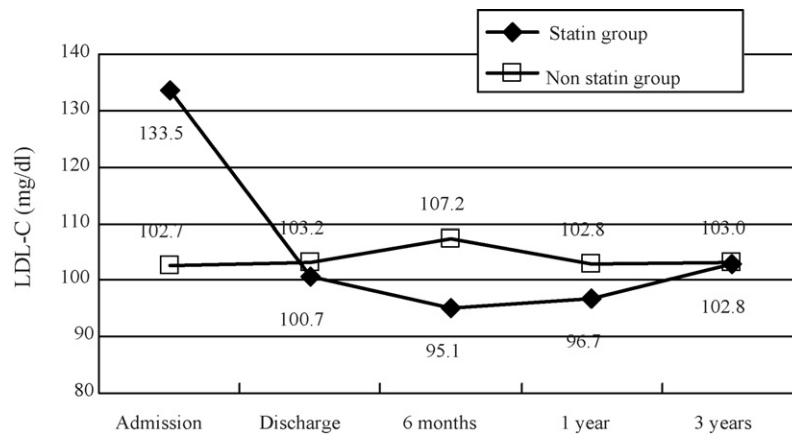
Kaplan–Meier curves in the two groups are shown in Fig. 2, and the log-rank test revealed that statin therapy was associated with the reduction

**Table 1** Baseline characteristics of patients

	Statin group	Non-statin group	P-value
N	271	107	
Male, no. (%)	184 (68)	86 (81)	0.016
Age (y)	65.6 ± 11.6	69.0 ± 11.5	0.009
LVEF (%)	57.3 ± 14.0	59.1 ± 14.7	0.30
<40%, no. (%)	26 (10)	10 (9)	0.84
ST elevated MI, no. (%)	204 (75)	79 (74)	0.77
Peak creatine kinase (IU/L)	2532.9 ± 2359.4	2107.1 ± 2159.0	0.11
Prior MI, no. (%)	19 (7)	9 (8)	0.64
Prior CABG, no. (%)	1 (0)	2 (2)	0.14
Culprit location, no. (%)			0.79
Anterior	129 (48)	52 (49)	
Inferior	110 (41)	45 (42)	
Lateral	32 (12)	10 (9)	
No. of narrowed coronary arteries	2.0 ± 0.8	1.9 ± 0.8	0.24
Single, no. (%)	82 (30)	37 (35)	
Double, no. (%)	101 (37)	44 (41)	
Triple, no. (%)	88 (32)	26 (24)	
LMT ≥50% stenosis, no. (%)	26 (10)	8 (7)	0.52
Lipid profile on admission			
Total cholesterol (mg/dL)	212.2 ± 39.7	168.6 ± 34.2	<0.0001
HDL-C (mg/dL)	49.3 ± 14.1	45.4 ± 12.2	0.023
Triglyceride (mg/dL)	145.4 ± 134.8	106.1 ± 63.6	0.004
LDL-C (mg/dL)	133.5 ± 38.3	102.7 ± 31.9	<0.0001
C-reactive protein (mg/dL)			
On admission	0.46 ± 1.86	1.49 ± 4.11	0.006
After 6 months	0.10 ± 0.54	0.25 ± 0.97	0.11
Risk factor, no. (%)			
Diabetes mellitus	90 (33)	26 (24)	0.091
Hypertension	136 (50)	49 (46)	0.44
Hyperlipidemia	224 (83)	35 (32)	<0.0001
Smoking history	129 (48)	56 (52)	0.36
Concomitant drugs, no. (%)			
ACE inhibitors/ARB	223 (82)	76 (71)	0.015
Beta-blockers	181 (67)	54 (50)	0.003
Calcium channel blockers	37 (14)	18 (17)	0.43
Diuretics	42 (15)	20 (19)	0.45
Nitrates	119 (44)	65 (61)	0.003
Stent profile			
Diameter (mm)	3.11 ± 0.46	3.14 ± 0.41	0.55
<3.0 mm, no. (%)	50 (18)	15 (14)	0.30
No. of stents	1.2 ± 0.5	1.2 ± 0.6	0.92
One, no. (%)	217 (80)	89 (83)	
Two, no. (%)	46 (17)	13 (12)	
More than two, no. (%)	8 (3)	5 (5)	
Total length (mm)	20.4 ± 8.3	18.7 ± 8.1	0.11
Type, no. (%)			0.014
Multilink	95 (35)	49 (46)	
S660,670	68 (25)	27 (25)	
Driver	65 (24)	8 (7)	
Nir	13 (5)	10 (9)	
Cypher	8 (3)	2 (2)	
Others*	22	11	
PCI for non-IRA, no. (%)	77 (28)	13 (12)	0.001

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CABG, coronary artery bypass grafting; HDL-C, high-density lipoprotein cholesterol; IRA, infarct-related artery; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; MI, myocardial infarction; PCI, percutaneous coronary intervention.

\* Others included Palmaz, Tsunami, GFX, TERUMO, and, Express.



**Figure 1** The difference of low-density lipoprotein cholesterol (LDL-C) levels between statin and non-statin groups during the 3 years was not significant using a two-factor mixed design with repeated measures on one-factor analysis.

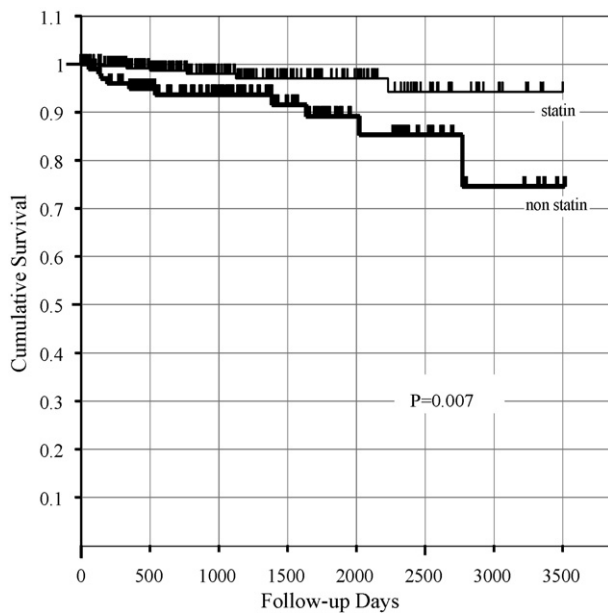
of long-term mortality significantly ( $P=0.007$ ). During follow-up, 16 patients died, including 4 cardiac deaths. Age ( $P=0.025$ ), LVEF ( $P=0.009$ ), peak CK ( $P=0.020$ ) and statin use ( $P=0.012$ , hazard ratio [HR]: 0.27, 95% confidence interval [CI]: 0.09–0.75)

significantly influence prognosis with univariate Cox regression analysis (Table 2). A multivariate Cox proportional hazards regression model including age, LVEF, peak CK, TC and LDL-C levels on admission, hypertension, hyperlipidemia, statin,

**Table 2** Predictors of long-term mortality in univariate Cox regression analysis

Variable	Hazard ratio	95%CI	P-value
Male	2.54	0.57–11.2	0.22
Age (y)	1.74 (+10)	1.07–2.81	0.025
LVEF (%)	1.69 (–10)	1.14–2.51	0.009
ST elevation	2.53	0.57–11.1	0.22
Peak creatine kinase (IU/L)	1.19 (+1000)	1.03–1.37	0.020
Anterior myocardial infarction	1.83	0.66–5.05	0.24
No. of narrowed coronary arteries	1.16	0.60–2.25	0.65
LMT >50% stenosis	1.55	0.35–6.83	0.56
C-reactive protein on admission (mg/dL)	0.99 (+1.0)	0.82–1.19	0.93
Total cholesterol on admission (mg/dL)	0.90 (+10)	0.80–1.01	0.061
HDL-C on admission (mg/dL)	0.86 (+10)	0.52–1.42	0.55
Triglyceride on admission (mg/dL)	0.98 (+10)	0.92–1.05	0.53
LDL-C on admission (mg/dL)	0.90 (+10)	0.77–1.04	0.16
Decrease of LDL-C during hospitalization (mg/dL)	0.95 (+10)	0.81–1.10	0.46
Diabetes mellitus	1.47	0.53–4.06	0.46
Hypertension	2.33	0.81–6.72	0.12
Hyperlipidemia	0.47	0.17–1.24	0.12
Smoking history	1.33	0.47–3.76	0.59
Statins	0.27	0.09–0.75	0.012
ACE inhibitors/ARB	0.86	0.28–2.66	0.79
Beta blockers	0.80	0.30–2.16	0.66
Calcium channel blockers	1.37	0.39–4.84	0.62
Diuretics	2.74	0.95–7.90	0.063
Nitrates	0.60	0.19–1.72	0.32
Stent diameter (mm)	1.32 (–0.5)	0.86–2.00	0.20
No. of stents	1.10	0.50–2.45	0.81
Total length of stents (mm)	1.12 (+5)	0.83–1.50	0.45
PCI for non-IRA	0.24	0.03–1.85	0.17

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CI, confidence interval; HDL-C, high-density lipoprotein cholesterol; IRA, infarct-related artery; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.



**Figure 2** Cumulative survival curves revealed that statin therapy was associated with the reduction of the long-term mortality significantly ( $P=0.007$ ).

diuretics, stent diameter, and PCI for non-IRA revealed that statin therapy ( $P=0.015$ , HR: 0.010, 95%CI: 0.01–0.64), age ( $P=0.022$ , HR: 2.55 for a 10 year increment, 95%CI: 1.14–5.65) and peak CK ( $P=0.032$ , HR: 1.30 for a 1000 IU/L increment, 95%CI: 1.02–1.66) were significant predictors of prognosis (Table 3).

The incidences of MACE in both groups were not significantly different at 6 months, and at 1 year, however, they were almost different at 3 years ( $P=0.053$ ). Between patients treated with pravastatin and those with atorvastatin, there were no significant differences in MACE. Univariate analyses showed that patients with MACE over 3 years

tended to have low LVEF, more diabetes, had received fewer statins, more diuretics and smaller stents. Multiple logistic regression analysis including LVEF, diabetes mellitus, anterior MI, statin, ACE inhibitors/ARB, diuretics, and stent diameter showed that statin usage ( $P=0.008$ , odds ratio: 0.36, 95%CI: 0.19–0.84) and LVEF ( $P=0.037$ , odds ratio: 1.40 for a 10% reduction, 95%CI: 1.01–1.91) were independent predictors of MACE over 3 years (Table 4). Those who were added statins during follow-up in non-statin group did not have a higher event rate (15/36) than the others (25/71).

### Safety and tolerability

Nine patients discontinued statin treatment due to liver dysfunction (5/271), skin rash (1/271), change to fibrates (1/271), and excess lowering of the LDL-C level (2/271). No patient developed myopathy.

### Discussion

Among AMI patients treated with stent implantation and whose LDL-C levels were stabilized at around 100 mg/dL, the early initiation of statin treatment was associated with the significant reduction of long-term mortality and the rate of MACE over 3 years, when compared with non-statin treatment. Although, low-dose statins were administered, the long-term effects were beneficial. Despite the striking decrease of LDL-C levels following treatment, the multivariate Cox regression analysis showed that statin therapy was the significant predictor of long-term mortality above the LDL-C reduction or lipid profiles; therefore the benefit of statin therapy may be related to beyond LDL-C lowering effects.

**Table 3** Multivariate Cox proportional hazards regression model of long-term mortality

Variable	Hazard ratio	95%CI	P-value
Statins	0.10	0.01–0.64	0.015
Age (y)	2.55 (+10)	1.14–5.65	0.022
Peak creatine kinase (IU/L)	1.30 (+1000)	1.02–1.66	0.032
Hyperlipidemia	3.82	0.62–23.52	0.15
Stent diameter (mm)	1.58 (–0.5)	0.84–2.96	0.15
Total cholesterol on admission (mg/dL)	1.19 (+10)	0.84–1.69	0.32
LVEF (%)	1.26 (–10)	0.72–2.19	0.42
LDL-C on admission (mg/dL)	0.87 (+10)	0.61–1.23	0.42
Diuretics	0.45	0.05–3.90	0.47
Hypertension	1.65	0.38–6.99	0.50
PCI for non-IRA	0.61	0.06–5.56	0.66

CI, confidence interval; IRA, infarct-related artery; LDL-C, low-density lipoprotein cholesterol; LMT, left main trunk; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention.

**Table 4** Multiple logistic regression analysis of major adverse cardiovascular events in 3 years

Variable	Odds ratio	95%CI	P-value
Statins	0.36	0.16–0.77	0.008
LVEF (%)	1.40 (–10)	1.01–1.91	0.038
Diabetes mellitus	2.13	0.97–4.66	0.059
ACE inhibitors/ARB	2.71	0.92–7.99	0.071
Stent diameter (mm)	1.35 (–0.5)	0.91–2.00	0.14
Diuretics	1.59	0.50–5.05	0.43
Anterior myocardial infarction	0.97	0.43–2.14	0.93

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blockers; CI, confidence interval; LVEF, left ventricular ejection fraction.

In the MIRACL [4] and PROVE IT-TIMI 22 trials [14], beneficial effects of statins were observed in a short period, such as 4 months. In contrast, in patients with stable CAD, Kaplan–Meier curves show little detectable difference in the first [1,3] or second years [2]. Our results showed that the benefits of statins were not statistically significant during the first 6 months and 1 year. Two recent meta-analyses also suggested that the benefit of early statin initiation for ACS took more than 4 months to become apparent [10,15]. The time-course difference of statin effects between the MIRACL and PROVE IT-TIMI 22 trials and our study may be explained by the specific atorvastatin use of these trials, however, the majority of our study used pravastatin and there were no significant differences in MACE between pravastatin and atorvastatin. The difference of stent implantation may also explain the early inconsistent response; in our study, all patients received stents but in the other trials, the rate of PCI was 0% and 69%, respectively.

The MUSASHI-AMI trial revealed that the early initiation of statin treatment reduced recurrent cardiovascular events, in particular, congestive heart failure for Japanese AMI patients treated with PCI [6]. Both the MUSASHI-AMI trial and our study included AMI patients treated with stent implantation, which may reflect the most common situation encountered in clinical practice. However, previous studies including MUSASHI-AMI could not differentiate statin's beneficial effects of LDL-C lowering or beyond LDL-C lowering, because the achieved LDL-C levels were significantly different between groups with and without statins. In the present study, the achieved LDL-C levels were not significantly different; thus, statin therapy would show beyond LDL-C lowering effects. HDL-C levels also could not explain the difference in mortality.

Meta-analysis of early statin initiation for ACS did not show any significant relation between the reduction in LDL-C level and event-risk reduction [10]. These results also revealed that statins should

have beyond LDL-C lowering effects; pleiotropic effects. Data from PROVE IT-TIMI 22 demonstrate clearly that the decrease in C-reactive protein can be modulated by the dose of statin therapy [14]. In our data, there was no significant difference of the C-reactive protein level over 6 months between the statin group and non-statin group. The mechanism by which statin therapy improves survival in AMI patient after stenting is unclear, but some unmeasurable factors, in addition to plaque stabilization and prevention of atheroma development, may be responsible for the present findings.

Although, the lack of placebo-controlled, randomized design could be regarded as a limitation of the present study, a placebo-controlled design may be difficult to justify on ethical grounds given the well-established effects of statins on secondary prevention. During follow-up, about 34% of patients in the non-statin group were necessitated to treat with statins because the LDL-C levels were elevated. This is also a limitation on ethical point of view, however, the effects of statins may be different for the patients who treated after the acute phase immediately. Moreover, because statin treatment was initiated only for patients with elevated LDL-C levels, the data do not allow us to determine how aggressively the LDL-C level should be lowered. The guideline was updated, as an option, to an LDL-C goal <70 mg/dL when the risk is very high, as in ACS [16], however, it was appropriate at the beginning period, 1997, to refer to an LDL-C level of 100 mg/dL as "low". Ethnic differences could have also made different responses to statin therapy. The subanalysis of MUSASHI-AMI trial recently reported that pravastatin was superior to lipophilic statin including atorvastatin at presenting new Q-wave appearance and reducing cardiovascular events, even though the achieved LDL-C level was significantly higher (107 mg/dL vs 90 mg/dL) [17]. There was no significant association between the reduction of mortality or MACE and an LDL-C level <70 mg/dL in our study (data were not shown); therefore, further research is required to deter-

mine whether the updated goal could apply just as much to Japanese.

In conclusion, our results suggest that early statin initiation for AMI with stent implantation was associated with a great benefit for long-term mortality. Further clinical studies are needed to confirm beyond LDL-C lowering effects of statins.

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