Effect of Statin Treatment and Low-Density Lipoprotein-Cholesterol on Short-Term Mortality in Acute Myocardial Infarction Patients Undergoing Primary Percutaneous Coronary Intervention – Multicenter Registry From Tokyo CCU Network Database –

Mizuki Miura, MD; Masao Yamasaki, MD; Yukari Uemura, PhD; Masatomo Yoshikawa, MD; Katsumi Miyauchi, MD; Hiroyuki Tanaka, MD; Hideki Miyachi, MD; Jun Yamashita, MD; Makoto Suzuki, MD; Takeshi Yamamoto, MD; Ken Nagao, MD; Isssei Komuro, MD; Morimasa Takayama, MD

**Background:** Previous trials have found that low low-density lipoprotein-cholesterol (LDL-C) on admission was associated with increased mortality in patients with acute myocardial infarction (AMI). There are few reports, however, on the effect of low LDL-C with or without in-hospital statin treatment on short-term prognosis in AMI patients.

**Methods and Results:** A total of 9,032 AMI patients underwent primary PCI in 68 centers in the Tokyo CCU Network Registry during 2009–2012, in whom LDL-C was measured in 6,486. We divided them into 4 groups: statin-treated/LDL-C <100 mg/dl (n=1,236), statin-treated/LDL-C ≥100 mg/dl (n=3,671), statin-naïve/LDL-C <100 mg/dl (n=662), and statin-naïve/LDL-C ≥100 mg/dl (n=917). We assessed hospital mortality within 30 days. In-hospital all-cause mortality was significantly lower in the statin-treated/LDL-C ≥100-mg/dl group (3.2%, P<0.001). On multivariate Cox regression analysis, adjusted for age, gender, hypertension, diabetes mellitus, dyslipidemia and other clinical factors, the combination of statin treatment and LDL-C ≥100-mg/dl was an independent predictor of lower in-hospital mortality (adjusted HR, 0.211; 95% CI: 0.096–0.462; P<0.001). In the LDL-C <100-mg/dl patients, statin treatment also independently reduced in-hospital mortality (adjusted HR, 0.467; 95% CI: 0.223–0.976; P=0.043). Spontaneously low LDL-C was associated with increased short-term mortality.

**Conclusions:** Statin treatment was associated with better short-term outcome in patients with AMI, even in patients with low LDL-C.

**Key Words:** Acute myocardial infarction; Lipid; Percutaneous coronary intervention; Statin

Low-density lipoprotein-cholesterol (LDL-C) is an important risk factor for coronary artery disease. Statin treatment lowers LDL-C, and significantly reduces cardiovascular mortality and major cardiovascular events, even in healthy subjects without hyperlipidemia. Previous trials have shown that early intensive statin therapy improved long-term clinical outcome of acute coronary syndrome (ACS). Therefore, the ACCF/AHA guidelines, ESC guidelines and JCS guidelines recommend that statins should be given to all patients who have had acute myocardial infarction (AMI), regardless of cholesterol level. In contrast, some studies have found that low LDL-C on admission was associated with increased mortality in ACS patients.

**Editorial p ????**

Some studies have shown that statin-induced low LDL-C on admission was associated not only with long-term mortality reduction but also with reduced short-term mortality in patients with ST-segment elevation myocardial infarction.
Another study, however, did not confirm the efficacy of statin therapy on short-term mortality in ACS patients. The influence of LDL-C on the clinical benefit of statin therapy in the acute phase remains uncertain in ACS patients. We investigated whether statin therapy improves short-term outcome in AMI patients with high and low LDL-C on admission.

Methods

Subjects
The subjects were from the Tokyo CCU Network registered cohort. The Tokyo CCU Network Scientific Committee operates through 68 cardiovascular centers, in which patients with AMI can be given emergency percutaneous coronary intervention (PCI) with the help of ambulance units coordinated from the control room of the Tokyo Fire Department. A total of 10,842 patients with AMI were enrolled in the Tokyo CCU Network registry between January 2009 and December 2012. AMI cases were identified using a principal discharge diagnosis of AMI based on the International Classification of Diseases version 9 or 10. We identified 6,486 patients with AMI undergoing primary PCI who had been checked for serum LDL-C on admission. They were divided into 4 groups according to statin therapy given during the acute phase and LDL-C on admission: statin-treated/LDL-C <100 mg/dl (n=1,236); statin-treated/LDL-C ≥100 mg/dl (n=3,671); statin-naive/LDL-C <100 mg/dl (n=662); statin-naive/LDL-C ≥100 mg/dl (n=917; Figure 1). The study included patients with a diagnosis of hyperlipidemia and receiving statin therapy. The therapeutic strategies of STEMI and non-STEMI (NSTEMI) depended on each institute and the individual cardiologist, but all patients were treated according to the Japanese Circulation Society, ESC and ACCF/AHA guidelines for the diagnosis and treatment of AMI.

Data Collection and Endpoints
From the hospital records of eligible patients, we extracted information on demographics, medical history, clinical data, emergency medical services, and the use of therapeutic intervention such as PCI, surgery, and medical circulatory support. The primary endpoint was all-cause hospital mortality within 30 days, beginning from the first day of hospitalization.

Statistical Analysis
Continuous variables are presented as mean±SD. Differences between the groups in demographic and clinical characteristics and in therapeutic interventions and laboratory data were analyzed using chi-squared test. Cumulative mortality during the first 30 days after admission was evaluated using Kaplan-Meier curves, and log-rank test for comparisons between the groups. All available variables considered potentially relevant were included, namely age, gender, hypertension, dyslipidemia, diabetes mellitus, smoking habit, hyperuricemia, medical history (previous history of MI, PCI, coronary artery bypass grafting [CABG] or stroke), medication, door-to-balloon time, Killip class on presentation, initial vital signs, ST-segment elevation, MI location, location of the culprit lesion, multivessel disease, pre- and post-Thrombolysis in Myocardial Infarction (TIMI) flow grade and mechanical support. To assess the efficacy of statin treatment on short-term mortality in both high and low LDL-C AMI patients, we performed multivariate Cox regression analysis with 2 models. Model 1 was adjusted for general coronary artery disease risk factors: age, gender, hypertension, diabetes mellitus, dyslipidemia, history of smoking, and hemodialysis. Model 2 was adjusted for general coronary artery disease risk factors and other clinical factors related to the prognosis of AMI: hyperuricemia, history of PCI and CABG, in-hospital medication (aspirin, clopidogrel, β-blocker, angiotensin-converting enzyme inhibitor [ACEI], angiotensin receptor blocker [ARB]), door-to-balloon time, Killip class ≥3, C-reactive protein on admission, peak creatine kinase, ST-segment elevation/non-ST-segment elevation, first MI, MI location (anterior, other), multivessel disease, pre-procedural TIMI flow grade ≥2, post-procedural TIMI flow grade ≥2, use of drug-eluting stent, use of bare metal stent (BMS), thrombus aspiration, distal protection, institution and calendar year. Cox proportional hazards regression was used to calculate hazard ratios (HR). All analyses were 2-tailed with clinical significance defined as P<0.05. Human subject
Table 1. Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Statin-treated</th>
<th>Statin-naïve</th>
<th>P-value</th>
<th>Statin-treated</th>
<th>Statin-naïve</th>
<th>P-value</th>
<th>P-value among 4 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>1,236 (91.1)</td>
<td>3,671 (56.6)</td>
<td>&lt;0.001</td>
<td>71.6±12.4</td>
<td>68.7±13.0</td>
<td>0.114</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Male</td>
<td>69.4±11.6</td>
<td>65.1±12.7</td>
<td>0.844</td>
<td>509 (76.9)</td>
<td>679 (74.0)</td>
<td>0.099</td>
<td>0.177</td>
</tr>
</tbody>
</table>

**Medical history**

- **Hypertension**: 819 (66.3) vs. 2,160 (58.8), <0.001.
- **Dyslipidemia**: 558 (45.1) vs. 1,972 (53.7), <0.001.
- **DM**: 483 (39.1) vs. 1,096 (29.8), <0.001.
- **Smoking**: 446 (36.1) vs. 1,474 (40.1), <0.012.
- **Hyperuricemia**: 75 (6.1) vs. 179 (4.9), 0.103.
- **Old MI**: 224 (19.3) vs. 450 (12.9), <0.001.
- **Previous PCI**: 208 (16.8) vs. 226 (6.2), <0.001.
- **Previous CABG**: 27 (2.2) vs. 30 (0.8), <0.001.
- **Previous CVA**: 74 (6.0) vs. 155 (4.2), 0.013.

**Laboratory findings**

- **Total cholesterol (mg/dl)**: 150 (135–169) vs. 212.2±41.4, <0.001.
- **LDL-C (mg/dl)**: 78.4±17.1 vs. 139.1±36.0, <0.001.
- **Triglycerides (mg/dl)**: 113.7±120.1 vs. 135.2±102.1, 0.748 vs. 97.0±119.0, 120.0±98.7, 0.289 vs. 0.001.
- **Serum creatinine (mg/dl)**: 1.4±1.8 vs. 1.1±0.9, <0.001 vs. 1.8±2.1, 1.3±1.4, <0.001.
- **CRP (mg/dl)**: 0.3 (0.1–1.0) vs. 0.2 (0.1–0.5), 0.032 vs. 0.4 (0.1–2.8), 0.3 (0.1–0.8), 0.043 vs. <0.001.
- **Peak creatine kinase (IU/L)**: 2,543 (3,578.3) vs. 2,491.4±2,471.4, <0.001 vs. 2,956.8±5,100.6, 2,874.0±3,464.5, 0.008 vs. <0.001.

**Medications**

- **Aspirin**: 1,212 (98.1) vs. 3,600 (98.0), 1.00 vs. 577 (87.3), 786 (85.7), 0.373 vs. <0.001.
- **Clopidogrel**: 1,070 (86.6) vs. 3,049 (83.0), 0.003 vs. 476 (72.0), 603 (65.8), 0.008 vs. <0.001.
- **β-blocker**: 701 (56.7) vs. 2,074 (56.5), 0.894 vs. 257 (38.9), 266 (29.0), <0.001 vs. <0.001.
- **ACEI**: 395 (32.0) vs. 1,297 (35.3), 0.032 vs. 144 (21.8), 151 (16.5), 0.009 vs. <0.001.
- **ARB**: 492 (39.8) vs. 1,493 (40.7), 0.615 vs. 162 (24.5), 195 (21.3), 0.143 vs. <0.001.

Data given as n (%), mean±SD, or median (IQR). ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CABG, coronary artery bypass grafting; CRP, C-reactive protein; CVA, cerebrovascular accidents; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Results

Baseline Clinical Characteristics

A total of 9,032 patients with AMI undergoing primary PCI were included in the study, 6,486 of whom (mean age, 67.1 years, 4,986 male) had LDL-C measured on admission. We divided the 6,486 patients into 4 groups: statin-treated/LDL-C<100 mg/dl (n=1,236); statin-treated/LDL-C≥100 mg/dl (n=3,671); statin-naïve/LDL-C<100 mg/dl (n=662); and statin-naïve/LDL-C≥100 mg/dl (n=917). We were able to follow up 5,519 patients (85.1%). A total of 4,907 patients (75.7%) were on statin therapy in the acute phase, defined as within 30 days of admission, of whom 1,190 (24.3%) were taking rosuvastatin, 12.4% atorvastatin (n=609), 14.7% pitavastatin (n=721), and 0.7% fluvastatin (n=35). The status of the others was unclear. None of the statin-naïve group received statins during hospital admission. There were no significant differences in gender between the groups. The statin-treated/LDL-C<100 mg/dl group had higher incidences of hypertension, diabetes mellitus, old MI and previous PCI. Dyslipidemia and high body mass index (BMI) were significantly more common in
the statin-treated/LDL-C ≥100-mg/dl group, and prior stroke was more common in the statin-naïve/LDL-C <100-mg/dl group. Regardless of LDL-C, the statin-treated groups had more Killip I patients. The statin-naïve/LDL-C <100-mg/dl group had more Killip IV patients. Door-to-balloon time was similar in all 4 groups. ST-segment elevation was more common in the statin-naïve/LDL-C <100-mg/dl group, and prior stroke in 75 patients in the statin-naïve/LDL-C ≥100-mg/dl group.

Angiographic and Procedural Characteristics

Myocardial infarction location was similar among the groups except for anterior and inferior MI. The LDL-C ≥100-mg/dl profile had more left anterior descending artery lesions and more multivessel diseases than the LDL-C <100-mg/dl profile. On angiography, pre-procedural TIMI flow grades were similar except for TIMI 0 flow. The statin-naïve groups had more BMS and more commonly received mechanical support. Use of thrombus aspiration device and of distal protection device was similar. Post-procedural angiography was more often TIMI 3 flow in the statin-treated profiles (Table 2).

Clinical Outcome

During the 30-day follow-up period, all-cause mortality occurred in 50 patients in the statin-treated/LDL-C <100-mg/dl group, in 89 patients in the statin-naïve/LDL-C <100-mg/dl group, in 42 patients in the statin-treated/LDL-C ≥100-mg/dl group, and in 75 patients in the statin-naïve/LDL-C ≥100-mg/dl group. In-hospital 30-day mortality was significantly higher in the LDL-C <100-mg/dl group than in the LDL-C ≥100-mg/dl group, independent of statin treatment (13.0% vs 6.8%, P<0.001). Moreover, all-cause mortality was significantly higher in the statin-naïve/LDL-C <100-mg/dl group within 30 days of hospitalization (P<0.001). On Kaplan-Meier analysis the 4 groups had significantly different survival curves (P<0.001; Figure 2A), including for cardiac and non-cardiac death (both P<0.001; Figures 2B, C). The statin-treated profile and the LDL-C ≥100-mg/dl profile tended to have lower mortality compared with the statin-naïve profile and the LDL-C <100-mg/dl profile.

### Table 2. Angiographic and Procedural Characteristics

<table>
<thead>
<tr>
<th>MI location</th>
<th>Statin-treated LDL-C &lt;100 mg/dl</th>
<th>Statin-naive LDL-C &lt;100 mg/dl</th>
<th>Statin-treated LDL-C ≥100 mg/dl</th>
<th>Statin-naive LDL-C ≥100 mg/dl</th>
<th>P-value</th>
<th>P-value among the 4 groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anterior</td>
<td>543 (45.7)</td>
<td>1,739 (49.7)</td>
<td>319 (50.7)</td>
<td>416 (47.7)</td>
<td>0.017</td>
<td>0.250 0.021</td>
</tr>
<tr>
<td>Inferior</td>
<td>512 (43.1)</td>
<td>1,326 (37.9)</td>
<td>275 (43.7)</td>
<td>345 (39.5)</td>
<td>0.002</td>
<td>0.111 0.002</td>
</tr>
<tr>
<td>Posterior</td>
<td>117 (8.8)</td>
<td>331 (9.5)</td>
<td>71 (11.3)</td>
<td>82 (9.4)</td>
<td>0.690</td>
<td>0.261 0.545</td>
</tr>
<tr>
<td>Lateral</td>
<td>137 (11.5)</td>
<td>421 (12.0)</td>
<td>69 (11.0)</td>
<td>98 (11.2)</td>
<td>0.678</td>
<td>0.934 0.819</td>
</tr>
<tr>
<td>Pre-procedural TIMI flow grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>634 (56.8)</td>
<td>1,939 (60.6)</td>
<td>319 (54.2)</td>
<td>479 (58.7)</td>
<td>0.028</td>
<td>0.091 0.111</td>
</tr>
<tr>
<td>1</td>
<td>99 (8.9)</td>
<td>280 (8.8)</td>
<td>72 (12.2)</td>
<td>91 (11.2)</td>
<td>0.902</td>
<td>0.555 0.016</td>
</tr>
<tr>
<td>2</td>
<td>202 (18.1)</td>
<td>519 (16.2)</td>
<td>114 (19.4)</td>
<td>132 (16.2)</td>
<td>0.149</td>
<td>0.135 0.032</td>
</tr>
<tr>
<td>3</td>
<td>181 (16.2)</td>
<td>461 (14.4)</td>
<td>84 (14.3)</td>
<td>114 (14.0)</td>
<td>0.143</td>
<td>0.877 0.076</td>
</tr>
<tr>
<td>Location of culprit lesion</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LMC</td>
<td>29 (2.4)</td>
<td>31 (0.9)</td>
<td>29 (4.5)</td>
<td>27 (3.0)</td>
<td>&lt;0.001 1.30 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>499 (41.3)</td>
<td>1,777 (49.3)</td>
<td>270 (42.2)</td>
<td>424 (47.6)</td>
<td>&lt;0.001 0.042 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>LCX</td>
<td>186 (15.4)</td>
<td>547 (15.2)</td>
<td>90 (14.1)</td>
<td>128 (14.4)</td>
<td>0.853</td>
<td>0.941 0.815</td>
</tr>
<tr>
<td>RCA</td>
<td>491 (40.6)</td>
<td>1,243 (34.5)</td>
<td>248 (38.8)</td>
<td>309 (34.7)</td>
<td>&lt;0.001 0.106 0.001</td>
<td></td>
</tr>
<tr>
<td>Multivessel disease</td>
<td>587 (48.4)</td>
<td>1,443 (40.3)</td>
<td>333 (51.4)</td>
<td>356 (39.8)</td>
<td>&lt;0.001 0.106 0.001</td>
<td></td>
</tr>
<tr>
<td>Mechanical support</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Assisted circulation†</td>
<td>243 (19.9)</td>
<td>477 (13.1)</td>
<td>202 (31.4)</td>
<td>214 (24.9)</td>
<td>&lt;0.001 0.005 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Artificial respiration</td>
<td>163 (13.4)</td>
<td>228 (6.4)</td>
<td>182 (28.7)</td>
<td>152 (17.9)</td>
<td>&lt;0.001 0.149 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Blood purification therapy</td>
<td>84 (7.0)</td>
<td>71 (2.0)</td>
<td>102 (16.1)</td>
<td>52 (6.1)</td>
<td>&lt;0.001 0.005 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Temporary pacing</td>
<td>164 (14.1)</td>
<td>276 (8.3)</td>
<td>101 (16.6)</td>
<td>106 (13.5)</td>
<td>&lt;0.001 0.111 &lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Post-procedural TIMI flow grade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>26 (2.3)</td>
<td>45 (1.4)</td>
<td>20 (3.3)</td>
<td>30 (3.8)</td>
<td>0.040</td>
<td>0.665 &lt;0.001</td>
</tr>
<tr>
<td>1</td>
<td>8 (0.7)</td>
<td>20 (0.6)</td>
<td>7 (1.2)</td>
<td>15 (1.9)</td>
<td>0.828</td>
<td>0.386 0.004</td>
</tr>
<tr>
<td>2</td>
<td>43 (3.8)</td>
<td>162 (5.0)</td>
<td>36 (6.0)</td>
<td>42 (5.4)</td>
<td>0.120</td>
<td>0.639 0.170</td>
</tr>
<tr>
<td>3</td>
<td>1,060 (93.2)</td>
<td>3,040 (93.1)</td>
<td>536 (89.5)</td>
<td>697 (88.9)</td>
<td>0.892</td>
<td>0.794 &lt;0.001</td>
</tr>
</tbody>
</table>

Data given as n (%). †Intra-aortic balloon pumping and percutaneous cardio pulmonary support device. LAD, left anterior descending artery; LCX, left circumflex artery; LMC, left main coronary trunk; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction. Other abbreviations as in Table 1.
Figure 2. Kaplan-Meier curves for 30-day incidence of clinical outcome in patients with acute myocardial infarction (AMI) undergoing primary percutaneous coronary intervention (PCI) stratified according to presence or absence of statin treatment in the acute phase, and low-density lipoprotein-cholesterol (LDL-C) on admission ≥ or <100 mg/dl. (A) all cause mortality; (B) cardiac death; (C) non-cardiac death. (1) Statin-treated and LDL-C ≥100 mg/dl, (2) statin-treated and LDL-C <100 mg/dl, (3) statin-naïve and LDL-C ≥100 mg/dl, (4) statin-naïve and LDL-C <100 mg/dl.
The most important result of the present study is that statin therapy was associated with better short-term outcome in AMI patients undergoing primary PCI regardless of LDL-C level on admission. This large observational study strengthens the existing evidence for the benefit of statin therapy during the acute phase in AMI patients.

The efficacy of statins during the acute phase in AMI patients has previously been described, but one study did not confirm their efficacy on short-term mortality in ACS patients. The Pravastatin or Atorvastatin Evaluation and Infection 22 (PROVE IT-TIMI 22) trial showed that intensive lipid lowering, and also for cardiac and non-cardiac death.

On Cox regression analysis to identify the effect of statin therapy for low LDL-C profile on short-term mortality, the combination of statin treatment and LDL-C \( \geq 100 \text{ mg/dl} \) was an independent predictor for lower in-hospital mortality, both in the unadjusted and the adjusted models. In the group of patients with LDL-C <100 mg/dl, statin treatment also independently reduced in-hospital mortality (Table 3).

Stratified Cox analysis showed that statin therapy improved short-term mortality in almost all subgroups. P-value for interaction was not significant in the subgroup analyses except for age, hypertension, dyslipidemia and initial diagnosis. There were no qualitative interactions (Figure 3).

### Table 3. Mortality Risk vs. Statin Treatment and LDL-C

<table>
<thead>
<tr>
<th>Statin-treated/LDL-C &lt;100 mg/dl</th>
<th>Unadjusted HR (95% CI)</th>
<th>P-value</th>
<th>Model 1 HR (95% CI)</th>
<th>P-value</th>
<th>Model 2 HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin-treated/LDL-C ≥100 mg/dl</td>
<td>0.098 (0.068–0.142)</td>
<td>&lt;0.001</td>
<td>0.134 (0.090–0.201)</td>
<td>&lt;0.001</td>
<td>0.211 (0.096–0.462)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Statin-naïve/LDL-C &lt;100 mg/dl</td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Statin-naïve/LDL-C ≥100 mg/dl</td>
<td>0.702 (0.516–0.956)</td>
<td>0.025</td>
<td>0.783 (0.569–1.077)</td>
<td>0.132</td>
<td>1.274 (0.662–2.450)</td>
<td>0.469</td>
</tr>
</tbody>
</table>

Model 1, adjusted for age, gender, hypertension, DM, dyslipidemia, history of smoking and hemodialysis; model 2, adjusted for age, gender, hypertension, DM, dyslipidemia, history of smoking, hemodialysis, history of previous PCI and CABG, in-hospital medication (aspirin, clopidogrel, \( \beta \)-blocker, ACEI, ARB), door-to-balloon time, Killip class \( \geq 3 \), CRP on admission, peak creatine kinase, ST-segment elevation/non-ST-segment elevation, first MI, MI location (anterior, other), multivessel disease, pre-procedural TIMI flow grade \( \geq 2 \), post-procedural TIMI flow grade \( \geq 2 \), use of drug-eluting stent, use of bare metal stent, thrombus aspiration, distal protection, institution and calendar year. Abbreviations as in Tables 1, 2.

**Discussion**

The most important result of the present study is that statin therapy was associated with better short-term outcome in AMI patients undergoing primary PCI regardless of LDL-C level on admission. This large observational study strengthens the existing evidence for the benefit of statin therapy during the acute phase in AMI patients.

The efficacy of statins during the acute phase in AMI patients has previously been described, but one study did not confirm their efficacy on short-term mortality in ACS patients. The Pravastatin or Atorvastatin Evaluation and Infection 22 (PROVE IT-TIMI 22) trial showed that intensive lipid lower-
ing with 80-mg atorvastatin, as compared with moderate lipid lowering with 40-mg pravastatin, reduced the HR for death from any cause or major cardiovascular event at 30 days by 17%.

Oðuncu et al reported that statin-pretreated individuals with STEMI undergoing PCI had lower in-hospital mortality and less frequent development of heart failure regardless of LDL-C on admission. In contrast, some studies found that low LDL-C on admission was associated with increased mortality in ACS patients. Considering these inconsistent results, the present study provides further evidence for the beneficial effect of statin therapy on short-term mortality in AMI patients regardless of LDL-C level on admission.

In the present study, statin therapy significantly reduced in-hospital all-cause death in AMI patients undergoing primary PCI. These results are consistent with some previous studies, but there are also differences between the present study and some studies. The PROVE IT-TIMI 22 trial demonstrated the efficacy of statin therapy for a composite endpoint of death from any cause, MI, documented unstable angina requiring rehospitalization, revascularization and stroke, but it did not find a risk reduction in all-cause death.

Therefore, further work is needed to evaluate the efficacy of statins in patients with CKD and hemodialysis.

Some trials in Western countries proved that an aggressive lipid-lowering strategy with high-dose statin reduced major cardiovascular events in patients with ACS and chronic ischemic heart disease. In Asia, in the MUSASHI-PCI patient cohort, those patients whose LDL-C at 6 months after statin treatment was <75 mg/dl had fewer cardiovascular events as compared with the 75–125- or >125-mg/dl groups. Therefore, the concept of “the lower, the better” could be important for patients with very high cardiovascular risk not only in Western countries but also in Asian countries. The present study showed that statin treatment was significantly associated with better short-term outcome in AMI patients undergoing primary PCI, even in patients with low LDL-C. This is compatible with previous results. In the present registry, frequency of statin use was 75.7% in the acute phase in AMI patients. Prevalence of statin use was lower in the LDL-C <100-mg/dl group compared with the LDL-C ≥100-mg/dl group (65.1% vs. 80.0%). It is important for all AMI patients to receive statin intensively regardless of LDL-C level.

In contrast, some studies found that low LDL-C on admission was associated with increased mortality in ACS patients. In the present study, statin-naïve/LDL-C <100-mg/dl AMI patients had increased short-term mortality. The mechanism of this paradox is not clear. This may be because the low LDL-C profile is associated with a higher incidence of comorbidity and cachexia. In the present study, the LDL-C <100-mg/dl profile was associated with a higher rate of previous PCI and previous CABG, higher serum creatinine and higher CRP than the LDL ≥100-mg/dl profile, regardless of statin treatment. In the statin treatment groups, the LDL-C <100-mg/dl profile was associated with a higher prevalence of advanced age and lower BMI than the LDL ≥100-mg/dl profile. To put it plainly, it is important to lower LDL-C for primary and secondary AMI prevention, but AMI patients with low LDL-C on admission have increased mortality (cholesterol paradox).

The present study has not clarified the mechanism by which statins reduce short-term mortality in AMI patients. In addition to their LDL-lowering effect, statins have been reported to have anti-inflammatory activity, to improve endothelial function, and to have antiplatelet and antioxidant activities. In a clinical study, Nocihka et al showed that statin is effective for patients with heart failure and preserved ejection fraction to reduce infection deaths.

Another study has shown that early statin treatment in patients with ACS improves biomarkers of inflammation. It is not known, however, as to what extent these activities contribute to the reduction of in-hospital mortality in AMI patients. Therefore, further work is needed to evaluate the effect of statins on the acute phase in AMI patients.

Study Limitations
First, the study lacked data on the type of statin and dose in many cases. Second, the timing of initiation of statin therapy was not clear. We knew only whether AMI patients took a statin during the acute phase or not. Third, the study was not randomized. The registry data might have a selection bias. Fourth, the study was limited to a specific geographic area.

Conclusions
Statin treatment was significantly associated with better short-term outcome in AMI patients undergoing primary PCI regardless of LDL-C level. Spontaneously low LDL-C on admission, however, was associated with increased short-term mortality. Randomized clinical trials are needed to evaluate the relationship between statin therapy and short-term mortality in AMI patients.

Acknowledgments
The authors thank all members of the Tokyo CCU Network Scientific Committee, Tokyo Fire Department, Tokyo Medical Association, and Tokyo Metropolitan Government.

Disclosures
None.

Conflict of Interest
None.

References