Impact of Statins Therapy for Ischemic Heart Disease Patients with Low-Density Lipoprotein Cholesterol Levels Less Than 100 mg/dL

Masanori Kuwabara, Fumiaki Kondo, Tomoyuki Hamada, Jun-ichi Takahashi, Nanae Takenaka and Takashi Furuno

Background: The objective of this study was to determine whether the use of statins prevents the progression of ischemic heart disease (IHD) in patients with low levels of low-density lipoprotein cholesterol (LDL-C).

Methods: We reviewed data obtained from IHD patients who underwent first percutaneous coronary intervention (PCI). Patients underwent follow-up coronary angiography (re-CAG) after PCI. However, only patients with LDL-C levels less than 100 mg/dL at PCI were included in this study. Ultimately, 92 patients were enrolled. All patients were divided into two groups: 1) patients who were treated with statins (n = 69), and 2) patients who were not treated with statins (n = 23).

Results: The two groups had similar LDL-C levels at PCI. At re-CAG, the ratio of patients who underwent PCI for de novo lesion in the statin group was lower than that in the non-statin group (12% vs. 48%) (p < 0.001). In multiple regression analysis, statin usage and LDL-C level at PCI were independent predictors of the ratio of patients undergoing PCI for de novo lesion.

Conclusions: Statins therapy for patients whose LDL-C levels are less than 100 mg/dL has a beneficial effect on secondary prevention of IHD.

Key Words: Ischemic heart disease • Low-density lipoprotein cholesterol • Secondary prevention • Statins

INTRODUCTION

Lowering levels of low-density lipoprotein cholesterol (LDL-C) with statins reduces the risk of death and cardiovascular events for both primary and secondary prevention. For patients with acute coronary syndrome (ACS), intensive lipid-lowering therapy reduces adverse clinical events, including death and myocardial infarction (MI), compared with the effect of moderate-dose therapy. While the preponderance of evidence suggests that a lower serum concentration of LDL-C is associated with improved outcomes, the benefits of intensive lipid-lowering therapy with statins may extend beyond those directly attributable to their lipid-lowering effects, i.e., benefits attributable to their so-called pleiotropic effects. Target LDL-C levels have been established in Japanese guidelines, according to different risk categories which consisted of the number of risk factors except LDL-C. For ischemic heart disease (IHD) patients, the recommended target LDL-C level is less than 100 mg/dL. However, for very high-risk patients, the American College of Cardiology/American Heart Association (ACC/AHA) guidelines have set a value of less than 70 mg/dL as the therapeutic goal for LDL-C.

A post hoc multivariate analysis of the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) trial revealed no evidence of benefit in patients with...
baseline LDL-C less than 66 mg/dL, indicating that further LDL-C reduction may not provide any clinical benefit.\textsuperscript{10} Meanwhile, several studies have shown that statin therapy resulted in favorable outcomes regardless of baseline LDL-C levels.\textsuperscript{11,12} Therefore, the influence of baseline LDL-C on the clinical benefit of lipid-lowering therapy remains controversial. Particularly for Japanese patients, there has been little information on this matter.

In this study, we investigated whether statin therapy is beneficial in Japanese patients with IHD who had baseline LDL-C levels less than 100 mg/dL.

**METHODS**

**Subjects**

We retrospectively reviewed data obtained from consecutive IHD patients who underwent first percutaneous coronary intervention (PCI) for angina pectoris (AP) or ACS from January 2008 to March 2011 in Kochi Red Cross Hospital, Kochi Prefecture, Japan. Only patients whose LDL-C levels were less than 100 mg/dL at PCI were included, and subjects undergoing hemodialysis were excluded. A total of 92 consecutive patients, including 56 patients who underwent PCI for AP and 36 patients who underwent PCI for ACS, were enrolled in this study. All of those patients underwent coronary angiography (re-CAG) at approximately 8 months after PCI.

Coronary angiography and PCI were performed according to standard practices. Usage of bare metal stent or drug-eluting stent was determined at the operator’s discretion.

We performed PCI for lesions that were angiographically in excess of 75% stenosis at first PCI and re-CAG. At re-CAG, additional PCI was performed not only for de novo lesion but also for in-stent restenosis; the stenosis lesions for which PCI was performed were not significant stenosis lesions (0-50% stenosis) at first PCI.

**Clinical evaluation**

The patients were divided into two groups: a group of patients who were treated with statins (statin group, n = 69), and a group of patients who were not treated with statins (non-statin group, n = 23). Use of statins was determined by the patient’s primary physician. Furthermore, the statin group was divided into two groups: one group of patients who had already been treated with a statin before PCI (statin group A, n = 46), and another group of patients who commenced treatment after PCI (statin group B, n = 23). In the statin group, the bare metal stent and drug-eluting stent was delivered for 28 patients (41%) and for 41 patients (59%), respectively. In the non-statin group, the bare metal stent and drug-eluting stent was delivered for 12 patients (52%) and for 11 patients (48%), respectively. The agents used, numbers of patients, and daily doses were as follows: atorvastatin, 29 patients, 10 mg; rosuvastatin, 10 patients, 2.5 mg; rosuvastatin, 9 patients, 5 mg; and pravastatin, 21 patients, 10 mg.

**Data analysis**

All data were expressed as mean ± standard deviation (SD) or frequencies (percentage), and the differences in continuous variables were assessed using Student’s \( t \) test. Pearson’s chi-square test was used for comparisons between non-continuous variables, and Fisher’s exact test was used when expected frequency was lower than 5. Statistical significance was defined by \( p \leq 0.05 \). Statistical analysis was performed using SPSS (version 14.0J) statistical software (SPSS Inc., Chicago, Illinois, USA).

**RESULTS**

**Study population**

A total of 92 patients (72 men and 20 women) were enrolled in this study. The mean age of the patients was 70 ± 10 years, and 36 patients (39%) had ACS. The statin and non-statin groups were similar in age, gender, follow-up period and prevalence of hypertension, diabetes mellitus, chronic kidney disease, and ACS. Clinical characteristics of the patients are shown in Table 1. There were no significant differences between the two groups in prescriptions of antihypertensive medicines, including angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers, calcium channel blockers, \( \beta \) blockers, aspirin, clopidogrel, nitrate, nicorandil and anti-hyperlipidemic drugs such as ezetimibe, icosapentate and fibrate. The two groups were similar in LDL-C levels.
at PCI, however, LDL-C level in the statin group was significantly lower than that in the non-statin group at re-CAG. There was no significant difference in triglyceride and HDL-C levels between the two groups.

**PCI at re-CAG**

The ratio of patients who underwent PCI for de novo lesion in the statin group was lower than that in the non-statin group (12% vs. 48%) (p < 0.001), however, the ratios of patients who underwent PCI for in-stent lesion were not significantly different between the two groups (15% vs. 26%) (p = n.s.).

As shown in Figure 1, LDL-C level at re-CAG (66 ± 14 mg/dL) was significantly lower than that at PCI (88 ± 10 mg/dL) (p < 0.001) in group B. LDL-C level at re-CAG in group B, and was also significantly lower than that at re-CAG (87 ± 14 mg/dL) (p < 0.001) in group A. LDL-C levels at re-CAG were increased in both the non-statin group and statin group A (p = 0.07 and p < 0.001, respectively). There was no significant difference between statin groups A and B in the ratio of patients who underwent PCI for de novo (9% vs. 17%) (p = n.s.) or in-stent lesion (11% vs. 22%) (p = n.s.).

**Multiple regression analysis**

In multiple regression analysis, statin usage and LDL-C level at PCI were independent predictors of the ratio of patients undergoing PCI for de novo lesion (Table 2).

**DISCUSSION**

Current Japanese guidelines provide recommendations for initiating statin therapy with targeting the optimal therapeutic goal of LDL-C less than 100 mg/dL in IHD patients; however, in ACC/AHA guidelines, LDL-C less than 70 mg/dL is recommended for patients at high risk of cardiovascular events.

Tsai et al. examined the relationship between statin therapy at discharge and clinical outcomes in 155 patients with ACS whose baseline LDL-C levels were less

**Table 1.** Clinical characteristics

<table>
<thead>
<tr>
<th></th>
<th>Statin group (n = 69)</th>
<th>Non-statin group (n = 23)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>71 ± 11</td>
<td>70 ± 9</td>
<td>0.711</td>
</tr>
<tr>
<td>Sex: male, n (%)</td>
<td>56 (81%)</td>
<td>16 (70%)</td>
<td>0.248</td>
</tr>
<tr>
<td>Follow-up interval, months</td>
<td>7.8 ± 2.4</td>
<td>8.3 ± 2.9</td>
<td>0.361</td>
</tr>
<tr>
<td>LDL-C at PCI, mg/dL</td>
<td>81 ± 13</td>
<td>81 ± 14</td>
<td>0.927</td>
</tr>
<tr>
<td>LDL-C at re-CAG, mg/dL</td>
<td>80 ± 17</td>
<td>89 ± 19</td>
<td>0.025</td>
</tr>
<tr>
<td>Triglyceride at PCI, mg/dL</td>
<td>127 ± 123</td>
<td>103 ± 102</td>
<td>0.389</td>
</tr>
<tr>
<td>Triglyceride at re-CAG, mg/dL</td>
<td>130 ± 89</td>
<td>121 ± 72</td>
<td>0.639</td>
</tr>
<tr>
<td>HDL-C at PCI, mg/dL</td>
<td>46 ± 12</td>
<td>45 ± 11</td>
<td>0.806</td>
</tr>
<tr>
<td>HDL-C at re-CAG, mg/dL</td>
<td>48 ± 11</td>
<td>49 ± 13</td>
<td>0.66</td>
</tr>
<tr>
<td>Acute coronary syndrome, n (%)</td>
<td>24 (35%)</td>
<td>12 (52%)</td>
<td>0.142</td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>37 (54%)</td>
<td>13 (57%)</td>
<td>0.812</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>30 (44%)</td>
<td>6 (26%)</td>
<td>0.142</td>
</tr>
<tr>
<td>Chronic kidney disease, n (%)</td>
<td>23 (35%)</td>
<td>9 (39%)</td>
<td>0.716</td>
</tr>
<tr>
<td>Bare metal stent at PCI, n (%)</td>
<td>28 (41%)</td>
<td>12 (52%)</td>
<td>0.232</td>
</tr>
<tr>
<td>Drug eluting stent at PCI, n (%)</td>
<td>41 (59%)</td>
<td>11 (48%)</td>
<td>0.354</td>
</tr>
</tbody>
</table>

Values are expressed as the mean value ± SD.

**Table 2.** Multiple regression analysis; PCI for de novo lesion at re-CAG

<table>
<thead>
<tr>
<th></th>
<th>Coefficient</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin usage</td>
<td>-0.407</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Age</td>
<td>-0.047</td>
<td>0.616</td>
</tr>
<tr>
<td>LDL-C at PCI</td>
<td>0.328</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>LDL-C at re-CAG</td>
<td>-0.11</td>
<td>0.255</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>-0.407</td>
<td>0.582</td>
</tr>
</tbody>
</table>

Abbreviations are in Table 1.
than 80 mg/dL. Statin-treated patients had lower incidences of death, re-infarction, and stroke at 6 months than patients who were not treated with statin.\textsuperscript{13}

In Japanese IHD patients with LDL-C levels less than 100 mg/dL, the present study showed that the customary Japanese dose of statin significantly reduced the ratio of patients who underwent PCI for de novo lesion. However, the mechanism by which the ratio of patients who underwent PCI for de novo lesion was decreased in the present study is not fully understood. It can be partly explained by the fact that statins exhibit a number of biological effects, besides lowering serum levels of LDL-C. Statins improve vascular endothelial function, attenuate vascular inflammation, stabilize plaques, correct prothrombotic tendencies, and influence myocardial protection and remodeling.\textsuperscript{14-17}

Lee et al.\textsuperscript{18} investigated whether statin therapy could be beneficial for patients with acute myocardial infarction who have baseline LDL-C levels less than 70 mg/dL. They reported that statin therapy reduced the risk of cardiac death and coronary revascularization and suggested that these beneficial effects were derived from the pleiotropic effects of statin.

In the present study, there was no significant difference between statin groups A and B in the ratio of patients who underwent PCI for de novo lesion, although LDL-C level at re-CAG in statin group B was significantly lower than that at re-CAG in statin group A. Furthermore, not LDL-C level at re-CAG but statin usage itself remained an independent predictor of the ratio of patients undergoing PCI for de novo lesion. From these findings, we speculate that the lower ratio of patients who underwent PCI for de novo lesion was caused, at least partly, by the pleiotropic effects of statins such as stabilizing plaque and attenuating vascular inflammation. Although the differences of pleiotropic effects among statins were previously reported,\textsuperscript{6} we did not compare those among types of statins in the present study by the limited number of patients.

Surprisingly, LDL-C levels not at re-CAG but at PCI was a predictor of the ratio of patients undergoing PCI for de novo lesion at re-CAG. Although LDL-C levels at re-CAG in statin group A was significantly higher than that in statin group B. The ratio of patients who underwent PCI for de novo lesion in statin group A was smaller than that in statin group B (9% vs. 17%) (p = n.s.). This difference was not statistically significant. Possibly because of the sample size, and speculate the long-term statin therapy may led to more effective pleiotropic action in group A.

We have sometimes observed that LDL-C levels in patients with ACS become lower than those in the daily situations of those patients.\textsuperscript{19} In the present study, LDL-C levels actually increased in the non-statin group and statin group A, possibly due to 39% of our patients had ACS. It might be better to initiate statin treatment at PCI for ACS even in patients with low levels of LDL-C.

In our study, the prevalence of in-stent restenosis which was 15% of patients in statin group and 26% in the non-statin group, higher than that in previous studies. Because of the clinical setting, such as ACS, the bare metal stent was selected for 52% of patients in non-statin group, which might lead to those relatively higher adverse outcomes.

There were several limitations in the present study. First, this was a single center study and not prospective. Accordingly, the ratio of patients who underwent PCI at re-CAG might be influenced by the discretion of the operator at re-CAG and we did not show that the de novo lesion has ischemia by stress myocardial scintigraphy. Consequently, there may be some bias for the indication of repeat PCI even in patients whose LDL-C was less than 100 mg/dl. We did not measure high-sensitive C-reactive protein or oxidized LDL-C level. Furthermore, we could not further evaluate in-stent restenosis because of its association with multiple factors such as type of stent, stent length, and vessel diameter.

**CONCLUSIONS**

Statin therapy for Japanese patients whose LDL-C levels are even less than 100 mg/dL at their first PCI has a beneficial effect on secondary prevention of IHD.

**REFERENCES**

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