Clinical Significance of Intensive Lipid-Lowering Therapy Using Statins in Patients With Coronary Artery Disease

– LDL-Cholesterol: The Lower, the Better;
Is It True for Asians? (Pro) –

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Large clinical trials have elucidated that lipid-lowering therapy using statins reduces cardiovascular events in patients with coronary artery disease (CAD). The benefit of statin therapy is proportional to the achieved low-density lipoprotein cholesterol level (LDL-C) up to 70mg/dl. On the basis of this evidence, the American Heart Association and American College of Cardiology offer an optimal LDL-C goal of <70mg/dl for patients with a very high risk of CAD. In addition, with regard to acute coronary syndrome (ACS), which has a high risk for future cardiac events because of the presence of vulnerable plaque, intensive lipid-lowering therapy from the early stage is the standard treatment. On the other hand, the mechanism of inhibition of cardiac events by statins is thought to be predominantly based on stabilization of plaque, but research on the role of plaque regression is also advancing. The clinical significance of intensive lipid-lowering therapy using statins will be discussed from the following standpoints: (1) large-scale clinical trials around the world; (2) the relationship with plaque regression and stabilization; (3) the relationship with the diverse effects of statins; and (4) evidence generated from Japanese patients. (Circ J 2010; 74: 1718–1730)

Key Words: Coronary artery disease; Inflammation; Lipids; Statins

Evidence of Efficacy of Lipid-Lowering Therapy With Statins in Patients With Coronary Artery Disease (CAD)

Once many epidemiological studies had proven an increase in coronary deaths and cardiac events associated with elevated levels of low-density lipoprotein-cholesterol (LDL-C),12 the next clinical question became whether lowering LDL-C by drugs or diet would result in a reduction in cardiac events. This assessment was facilitated by the development of potent cholesterol-lowering drugs such as the 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors (statins). In particular, statin therapy was proposed as a strategy to improve clinical outcomes and accordingly, large clinical trials using statin were started. By 2000, there had been many reports of the results of such large-scale clinical trials3–8 and there was abundant evidence of the significant beneficial effects of lipid-lowering treatment using statin in reducing mortality and cardiovascular morbidity in patients with CAD as shown in Table 1. Interestingly, all the long-term clinical trials demonstrated that the beneficial effects of statin treatment were sustained and cumulative compared with placebo group as shown in Table 1. In the meta-analysis performed by

Table 1. Effect of Statins in Large Clinical Trials

<table>
<thead>
<tr>
<th>Medication</th>
<th>Coronary death (%)</th>
<th>Overall death (%)</th>
<th>MI (%)</th>
<th>Stroke (%)</th>
</tr>
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<tbody>
<tr>
<td>Placebo</td>
<td>8.5</td>
<td>11.5</td>
<td>12.1</td>
<td>4.3</td>
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<tr>
<td>Simvastatin</td>
<td>5.0†</td>
<td>8.2†</td>
<td>7.4**</td>
<td>2.7*</td>
</tr>
<tr>
<td>Placebo</td>
<td>8.3</td>
<td>14.1</td>
<td>10.3</td>
<td>4.5</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>6.4**</td>
<td>11.0†</td>
<td>7.4†</td>
<td>3.7*</td>
</tr>
<tr>
<td>Placebo</td>
<td>5.7</td>
<td>9.4</td>
<td>13.2</td>
<td>3.8</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>4.6</td>
<td>8.7</td>
<td>7.5**</td>
<td>2.6*</td>
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<tr>
<td>Placebo</td>
<td>6.9</td>
<td>14.7</td>
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<td>4.9</td>
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<tr>
<td>Simvastatin</td>
<td>5.7†</td>
<td>12.9†</td>
<td>3.5†</td>
<td>3.6†</td>
</tr>
</tbody>
</table>

*P<0.05; **P<0.01; †P<0.001. MI, myocardial infarction.
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(Pro) Intensive Lipid-Lowering in CAD

the Cholesterol Treatment Trialists Collaborators (CTTC) of 90,056 patients from 14 prospective clinical trials during a mean of 5 years, lowering the LDL-C level by 1 mmol/L (=39 mg/dl) was found to reduce total mortality by 19%, coronary events by 23%, and cardiac events by 21%, except for cerebral hemorrhage (Figure 1A). Thus, in order to reduce cardiac events by 1%, it is necessary to lower the LDL-C level by 1.8 mg/dl (Figure 1B). More importantly, that analysis showed that clinical benefit was linearly related to the absolute reduction in LDL-C.

**Outcome Studies of Intensive Lipid-Lowering Therapy Using Statins**

MIRACL (Myocardial Ischemia Reduction With Aggressive Cholesterol Lowering) was the first outcome study to demonstrate the efficacy of high-dose statin therapy. That study compared high-dose atorvastatin (80 mg) and a placebo administered during the 24- to 96-h period after an episode of unstable angina or non-Q wave myocardial infarction (MI). The combination endpoint of death, non-fatal MI, cardiac
impacted the prognosis of cardiac events (Table 2). In a meta-analysis of 4 large-scale clinical studies (PROVE-IT\textsuperscript{11}, A-to-Z\textsuperscript{12}, TNT\textsuperscript{13} and IDEAL\textsuperscript{14}) that tested statins against each other and compared cardiac events in a standard therapy group with an LDL-C target of 100 mg/dl and an intensive-therapy group with an LDL-C target of 70–80 mg/dl, the analyzed patients numbered 27,548, and the percent reduction in the LDL-C value was 22% in the standard therapy group vs 42% in the intensive therapy group.\textsuperscript{15} For coronary death and MI, the odds ratio in the intensive therapy group vs the standard therapy group was 0.84 (95%CI: 0.77–0.91; P=0.00003), and that for cerebrovascular events was 0.82 (95%CI: 0.71–0.96; P=0.012), with both representing a significant decrease. In addition, in a meta-analysis that included only ACS patients,\textsuperscript{16} high-dose statin therapy that was started early (within 14 days after hospitalization) was shown to be effective in 17,963 patients enrolled in 13 prospective clinical studies. For death and cardiac events occurring within 2 years, the HR was 0.81 with high-dose statin therapy vs standard therapy (P<0.001), and the reduction in mortality started within 4–12 months, with a statistically significant difference observed after 1 year.\textsuperscript{17} In addition, between 1996 and 2006, 6 prospective studies involving 110,271 patients investigated the significance of intensive lipid-lowering therapy in relation to ischemic heart disease, and a meta-analysis\textsuperscript{17} showed that this type of therapy was effective in relation to all events in ACS, including death. Moreover, although no decrease in the mortality rate was observed relative to the stable CAD form of ACS, cardiac events were significantly reduced. In those studies, however, warnings were raised.

Table 2. Meta-Analysis of Strong Statin vs Standard Statin

<table>
<thead>
<tr>
<th>Study</th>
<th>Medication</th>
<th>Trial number patient no.</th>
<th>LDL-C reduction rate</th>
<th>Total events (%)</th>
<th>Event (%)</th>
</tr>
</thead>
<tbody>
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<td>JACC\textsuperscript{15}</td>
<td>Standard</td>
<td>4</td>
<td>22.3</td>
<td>32.3</td>
<td>2.8</td>
</tr>
<tr>
<td></td>
<td>Strong Statin</td>
<td>27,548</td>
<td>42.3</td>
<td>28.8*</td>
<td>2.3**</td>
</tr>
<tr>
<td>Arch Intern Med\textsuperscript{16}</td>
<td>Standard</td>
<td>13</td>
<td>6±12 mg/dl</td>
<td>HR 0.81 (0.77–0.87)\textsuperscript{1}</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Strong Statin</td>
<td>17,963</td>
<td>34±9 mg/dl</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart\textsuperscript{17}</td>
<td>Standard</td>
<td>6</td>
<td>10–25</td>
<td>15.8</td>
<td>3.3</td>
</tr>
<tr>
<td></td>
<td>Strong Statin</td>
<td>110,271</td>
<td>34–46</td>
<td>13.6\textsuperscript{11}</td>
<td>2.4\textsuperscript{1}</td>
</tr>
</tbody>
</table>

\*P<0.05; \**P<0.01; \*P<0.001.

\*Total events: coronary death, MI, stroke, unstable angina pectoris, revascularization; OR 0.84, 95% CI 0.80–0.89, P=0.0001.

**Stroke: OR 0.82, 95% CI 0.71–0.96, P=0.012.

\*\*Event: cardiovascular death, ACS, revascularization; P<0.0001.

\*\*\*Event: cardiovascular death, ACS, stroke; OR 0.84, 95% CI 0.77–0.91, P<0.0001.

\*\*\*\*CHF; OR 0.72, 95% CI 0.62–0.83, P<0.0001.

LDL-C, low-density lipoprotein cholesterol; CAD, coronary artery disease; ACS, acute coronary syndrome; OR, odds ratio; CI, confidence interval. Other abbreviation see in Table 1.

PCI, percutaneous coronary intervention. Other abbreviations see in Tables 1,2.
with regard to hepatic dysfunction and significant elevation of creatine phosphokinase with high-dose statin therapy. However, the positive association between absolute reduction of LDL-C and major cardiovascular events suggests that a large reduction in LDL-C produces a greater reduction in adverse events. Therefore, the optimal goal of less than 70 mg/dl has become the standard not only for patients at very high risk, but for patients with CAD in Europe and the United States.

Figure 2. (A) Intravascular ultrasound images before and after 6 months' treatment in the ESTABLISH trial. (Left) Atorvastatin has significantly reduced plaque area whereas no change in the plaque area can be seen in control (Right). (B) Low-density lipoprotein (LDL) cholesterol significantly decreased from 125 mg/dl to 70 mg/dl in the statin group. A significant reduction of the volume of coronary plaque was noted in atorvastatin group (8.3%), but not in control group. Reference 20.
Do Statins Cause Regression of Coronary Plaque?

The clinical issue arose of whether LDL-C reduction through statin therapy retarded progression of coronary artery plaque. The development of intravascular ultrasound (IVUS) enabled measurement of the volume of coronary artery plaque, allowing us to determine the percent change in this parameter before and after medical intervention. The REVERSAL (Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial was a landmark statin intervention trial that investigated whether the reduction of LDL-C by statins attenuated the progression of coronary artery plaque in patients with CAD. A total of 654 patients were randomized into 2 groups, administered either atorvastatin 80 mg (LDL-C ≤ 79 mg/dl) or pravastatin 40 mg (LDL-C ≤ 100 mg/dl), and the change in coronary plaque volume on IVUS after 18 months of treatment was compared between the groups. Although an increase in plaque volume was observed in the pravastatin group, the atorvastatin group halted plaque progression (% change in plaque volume: 2.7% vs −0.4%). This finding thus demonstrated that intensive lipid-lowering therapy using atorvastatin attenuated plaque progression.

In addition, the ASTEROID (A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) study first demonstrated that rosuvastatin 40 mg treatment for 24 months to average LDL-C levels well below 70 mg/dl produced plaque regression by 15% in CAD patients. That was a single-arm study, but the it unexpectedly found a remarkable reduction of LDL-C and an increase in the high-density lipoprotein-cholesterol (HDL-C) level. Therefore, ASTEROID demonstrated that atorvastatin 80 mg halted plaque progression, but there was not regression, whereas there was actual regression at least on average in ASTEROID.

The published data regarding the correlation between lipid-lowering therapy and plaque regression in Japan is summarized in Table 3. An IVUS assessment for patients with ACS was conducted in the ESTABLISH (Early Statin Treatment in Patients with Acute Coronary Syndrome) study, which was the first to demonstrate that intensive lipid-lowering therapy with atorvastatin led to a significant plaque regression in Japanese ACS patients. Briefly, 70 ACS patients who had undergone successful percutaneous coronary intervention (PCI) were randomized into an intensive lipid-lowering therapy group (atorvastatin 20 mg/day) and a control group. IVUS was performed at baseline and after 6 months of treatment, and the plaque volume was measured in the non-PCI site. Figure 2 presents the results: the reduction in LDL-C was 41.7% in the atorvastatin group and plaque volume was reduced by 13%, whereas in the control group plaque volume increased by 8%. The percent change in plaque volume correlated positively with the percent decrease in LDL-C, and it was demonstrated that the greater the decrease in LDL-C, the greater the plaque regression. This tendency was observed regardless of the baseline LDL-C level, and it was thus surmised that plaque regression by aggressive LDL-C lowering could be attributed to the acute effect of statins in ACS, independent of the baseline LDL-C level. The limitations of the ESTABLISH trial were that it was a relatively small trial conducted at a single center. Therefore, the JAPAN-ACS (Japan Assessment of Pitavastatin and Atorvastatin in Acute Coronary Syndrome) study was designed as a large-scale, multicenter trial to overcome those flaws. The JAPAN-ACS study was the world’s first head-to-head trial between pitavastatin 4 mg and atorvastatin 20 mg. The results showed no differences between the 2 groups in either the percent decrease in LDL-C (36.2% vs 35.8%) or the percent plaque regression (17% vs 18%) over the 10-month observation period, and it was demonstrated that both statins showed
equivalent plaque-regression effects. At the same time, it was confirmed that the marked efficacy of high-dose statin therapy in bringing about plaque regression was also seen in Japanese patients. However, this study did not find any correlation between LDL-C reduction and plaque regression, and it differed from the ESTABLISH study, which included a control group (Figure 3). However, this was not surprising because JAPAN-ACS did not have a placebo arm that was no lipid-lowering therapy. The scattergrams were obtained from the cluster with groups exclusively on intensive statin therapy. It was considered that other factors were also responsible for the plaque regression. The impressive result was that the administration of the statins used over 10 months caused a net reduction of plaque volume in 88% of patients with ACS, even at a mean LDL-C level of 82.6 mg/dl. This suggested that pitavastatin, as well as atorvastatin itself, might play a specific role in the regression of atherosclerosis in patients with ACS, not only by a reduction of the LDL-C level. The COSMOS (Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects) study demonstrated that rosuvastatin shows plaque-regression effects in stable CAD patients in Japan. In that study, rosuvastatin was not administered in a fixed dose: the protocol called for dose escalation if the LDL-C level reached 80 mg/dl, and the final mean dose of rosuvastatin was 17 mg/day. The COSMOS study was a single-arm study, with no control group and only a single statin group. The LDL-C level was reduced by 39% from 140.2 mg/dl to 82.9 mg/dl, and IVUS performed after an 18-month observation period showed that the plaque regression rate was 5%, which was statistically significant.

When all of the different IVUS studies were examined by plotting LDL-C values against the change in atheroma volume, a relationship between mean LDL-C level and median change in percent atheroma volume was observed (Figure 4). Linear regression analysis showed that the mean plaque progression rate correlated with the mean LDL-C level, despite the known limitations of cross-trial comparisons. When viewed in this context, there exists no apparent threshold LDL-C level beyond which the benefits of statin therapy are no longer evident. If regression of the disease is the desired outcome, then lower LDL-C is better.

Several clinical trials have investigated by IVUS the beneficial effect of statin treatment on plaque regression; however, the impact of plaque regression on clinical outcomes in patients with CAD has not been defined. Nicholls et al reported that coronary plaque progression was evaluated in 4,137 patients in 6 clinical trials that used serial IVUS to clarify the relationship between the extent and progression of coronary atherosclerosis and the subsequent risk for adverse cardiovascular outcomes. In their meta-analysis, plaque volume increased by 0.3%, and 19.9% of subjects experienced major adverse cardiovascular event (MACE: death, MI, revascularization). Each standard deviation increase in plaque volume was associated with a 1.32-fold (95%CI: 1.22–1.42; P<0.001) greater likelihood of experiencing MACE. During follow-up (21.1±3.7 months), greater increases in plaque volume were observed in subjects who experienced MACE compared with those who did not (0.95±0.19% vs 0.46±0.16%; P<0.001). Thus, plaque regression may be sufficient to produce a clinical benefit, even though the absolute amount of regression achieved is small. These findings imply that plaque regression could be a realistic goal, because plaque regression on volumetric IVUS is associated with better long-term clinical outcomes.
Can Intensive Lipid-Lowering Therapy Using Statins Bring About Qualitative Changes in Plaque?

Stabilization of plaque is considered the major contributor to reducing cardiovascular events, and identification of vulnerable plaque has great clinical implication. Imaging techniques to detect qualitative changes in coronary artery walls, including coronary angioscopy (CAS), optical coherence tomography (OCT) using infrared rays, magnetic resonance imaging (MRI), and IVUS, have significantly developed and advanced in recent years. These tools offer the potential for quantitative tissue characterization of the coronary arterial wall. Application of these imaging techniques also allows us to monitor qualitative improvements in response to pharmacological interventions.

In the CPLASS (Coronary PLAque stabilization by Statin Study), the integrated backscatter (IB) value of IB-IVUS was used as the endpoint to compare an atorvastatin 10 mg group and a control group over a 6-month period. The results showed that the IB value increased depending on the percent decrease in LDL-C; that is, the plaque stabilized. In particular, significant plaque stabilization occurred when LDL-C was decreased by 50% or more. Takano et al evaluated plaque quality using OCT after atorvastatin intervention in 31 stable CAD patients who were randomized into an atorvastatin group and a control group and followed for 12 months. Angioscopy was used to evaluate 145 sites on the basis of 4 grades of plaque color (yellow to white), and in the statin group LDL-C was reduced by 45%, the plaque color score changed from 2.03 to 1.13 (ie, from yellow to white), and the plaque color score decreased according to the reduction in the LDL-C concentration. Takarada et al carried out research using OCT during statin intervention for 9 months after ST elevation MI (STEMI). The fibrous-cap thickness was compared between a 23-patient statin group that was administered a statin and 17 control patients. LDL-C was reduced in the statin group from 144 to 91 mg/dl, and the fibrous-cap thickness was significantly increased at 188% compared with 117% in the control group, thus indicating plaque stabilization. Toi et al used virtual histology (VH) IVUS to evaluate the short-term effect of high-dose statin therapy on plaque properties in the acute stage of ACS in 160 patients. When pitavastatin 2 mg and atorvastatin 10 mg were administered for 2–3 weeks, the plaque volume decreased significantly by 2.6% in the pitavastatin group accompanied by a significant decrease in the fibrofatty component. On the other hand, in the atorvastatin group, there were no changes in either the plaque volume or the tissue characteristics. No consensus has yet been reached regarding the evaluation of plaque properties by VH-IVUS, but this technique has indicated the possibility of differences in the short-term effects of different drugs on plaque properties. The statin-intervention studies noted thus far have demonstrated that statin administration has various favorable effects, including plaque stabilization and especially reduction of the lipid pool and an increase in the thin fibrous cap. These plaque stabilization studies were summarized in Table 4.

In addition, Hirayama et al carried out clinical research aimed at elucidating the processes by which statins beneficially alter the volume and quality of plaque. Their study design consisted of administering atorvastatin 10–20 mg to stable CAD patients and then observing the plaque quality and volume over time. Both IVUS and CAS were performed after 6 and 18 months of treatment, and the plaque quality and volume were assessed. Angioscopy showed that the plaque color had already changed from yellow to white at the 6-month point, indicating stabilization, and this remained unchanged after 18 months. However, the plaque volume continually decreased during the period from 6 to 18 months. Accordingly, this research demonstrated that statin therapy leads to qualitative improvement in plaque during the early stage of medication and that quantitative improvement continues during the long-term.

Pleiotropic and Anti-Inflammatory Effects of Statins

Many clinical studies have demonstrated that statins reduce hs-C-reactive protein (hs-CRP). The REVERSAL trial showed that high-dose statin therapy lowers hs-CRP even more than standard statin therapy. Moreover, it has also been demonstrated that there is an increase in cardiac events, regardless of primary or secondary prevention, when the hs-CRP level is high, and that lowering the hs-CRP concentration by statin therapy reduces the number of cardiac events. In light of those results, it was realized that hs-CRP is also an important clinical marker, and at the same time attention was drawn to the role of inflammation in the mechanism by which statins reduce clinical events.

The importance of inhibition of inflammation in tissues is clear from the fact that inflammation is involved in vulnerable plaque, and it was surmised that the possibility that statins

<table>
<thead>
<tr>
<th>Table 4. Plaque Stabilization Trials in Japan</th>
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<td><strong>Imaging device</strong></td>
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<tr>
<td>---------------------</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>n</td>
</tr>
<tr>
<td>Duration (months)</td>
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<tr>
<td>LDL pre</td>
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<td>Pre</td>
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<tr>
<td>Post</td>
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<tr>
<td>P value</td>
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IB, integrated backscatter; IVUS, intravascular ultrasound; OCT, optical coherence tomography; VH, virtual histology; LDL, low-density lipoprotein.
Figure 5. (A) Design of this study. (B) Representative sections show immunoreactivity for macrophages. Immunohistochemical analysis of the aneurysm walls of control and atorvastatin-treated tissue. The number of positive cells in the atorvastatin group was less than that in the control. (C) In the quantitative analysis, the number of dendritic cells, macrophages, and T cells in the aneurysm wall was significantly lower in the atorvastatin group than in the control group. AAA, abdominal aortic aneurysm. Reference 34.
inhibit inflammation in tissues is also clinically important. In that context, we carried out a clinical study aimed at confirming the anti-inflammatory effect of a statin in the tissues of patients with an abdominal aortic aneurysm (AAA). This was a prospective clinical study conducted in 20 AAA patients scheduled to undergo surgery, who were randomized into a group orally administered atorvastatin 20 mg and a control group, consisting of 10 patients each. Tissue specimens were obtained from each patient at the time of surgery, and the inflammatory tissue findings were compared between the groups. The time interval between initiation of atorvastatin administration and surgery was approximately 1 month. Figure 5 compares the findings in the 2 groups: the numbers of inflammatory cells, macrophages, dendritic cells, and T cells were all reduced in the atorvastatin group compared with the control group. Quantitatively, as well, the inhibitory effect was approximately 50% and statistically significant. Accordingly, these results demonstrate that even short-term administration of a statin can inhibit tissue inflammation. In addition, the anti-inflammatory effect of statins was
studied in a porcine coronary artery stent model with the objective of proving the hypothesis that increasing the statin concentration can more potently inhibit tissue inflammation. Thus, the tissue concentration of a statin was elevated locally by insertion of a statin-eluting stent, and inflammatory cell adhesion in the tissue was used as the endpoint and evaluated for correlation with the statin tissue concentration. On the 3rd day after bare-metal stent implantation in the porcine coronary artery, monocyte adhesion to the stent surface was observed by electron microscopy. Figure 6 shows that cell adhesion was significantly inhibited by local statin administration compared with systemic dosing. Accordingly, this study proved that the anti-inflammatory effect of a statin is further increased when the local statin concentration is elevated. Furthermore, we evaluated neointimal hyperplasia 28 days after stenting. In our results, large reductions in the early inflammatory response produce greater inhibition of late neointima as shown in Figure 6B. Thus, clinical and experimental data suggest the importance of the anti-inflammatory effect by statins as a contributor to plaque stabilization, plaque regression, and reduction in clinical events.

Inhibition of inflammation in tissues is important, but serious limitations exist regarding the evaluation methods because our ability to examine inflammation is currently restricted to using tissue sections, not in vivo clinical imaging. However, in recent years, progress in molecular imaging techniques has enabled us to assess the extent of inflammation in vivo by means of MRI. Furthermore, fluorodeoxyglucose (FDG) with positron emission tomography (PET) is a molecular imaging technique that is highly sensitive to metabolically active processes using glucose as a fuel. Recently, arterial FDG PET imaging has been suggested as a biomarker for reporting on the metabolic activity of atherosclerosis. It is thus anticipated that, in the future, imaging diagnosis will have a role in monitoring the response of atherosclerosis, especially vulnerable plaque stabilization, to statin therapy.

**Issues Associated With Statin Therapy**

Even in routine medical clinical practice, we encounter ACS patients with a low LDL level of less than 80 mg/dl, and we are concerned about whether we should prescribe statins to these patients. The large-scale clinical trials that have been carried out to date have not clarified the pluses and minuses of administering lipid-lowering statin therapy to low-LDL patients because none of these trials have taken into account the pretreatment LDL level. However, an observational study of ACS patients compared the prognosis (mortality, re-infarction, and stroke) over a 6-month period in patients with an LDL level of less than 80 mg/dl based on whether or not a statin was administered at the time of discharge from hospital. The incidence of events in the statin-treated group was 9.5%, which was significantly lower than the 29% incidence reported for the untreated group. Furthermore, a meta-ana-
sis has provided useful insights into the issues of threshold and target levels by documenting the multivariate relationship of clinical outcome to baseline LDL and magnitude of LDL reduction. That study showed a graded relationship of treatment benefit according to tertiles of baseline LDL (from <70 to >100 mg/dl) and quartiles of percent LDL lowering (from <10% to >30%), which analysis demonstrated there is great clinical benefit to lowering the LDL level in patients with a high LDL-C level prior to intervention, although it has become increasingly clear that this benefit is also seen in patients with a low LDL level.

For the very-high-risk group of patients, such as those with ACS, the ACC/AHA guidelines have set a value of less than 70 mg/dl as the therapeutic target for LDL-C, but that does not mean that all issues have been resolved. In each of the clinical trials that studied ACS patients, including the PROVE-IT and A-to-Z trials, the statin dosage was fixed, and the design did not provide for adjustment of the administered dose toward the therapeutic target for LDL-C. In other words, rather than the LDL-C value, the statin dose or type becomes important. In particular, in studies that compare statins, there is a possibility that differences in the pleiotropic effects of statins (eg, anti-inflammatory activity, improvement in endothelial function, reduction of oxidative stress, and antithrombotic activity) come into play. In consideration of this background, European Society of Cardiology guideline the administration criteria for statins in the treatment of ACS recommended are within the early (1–4 day) period after onset, with an LDL target of less than 100 mg/dl (Class I, Evidence Level B), and intensive statin lipid-lowering therapy with an LDL target of less than 70 mg/dl (Class IIa, Evidence Level B) within 10 days of hospitalization.

Evidence and Issues Associated With Secondary Prevention Using Statins in Japanese

As an observational study performed to date, our ESTABLISH study was increased to a patient total of 180 and reported as the Extended-ESTABLISH study (Figure 7A). This study followed the atorvastatin group and control group for 6 months, after which a statin was administered to all of the patients and subsequent events, including death, ACS, and stroke, were evaluated. Evaluation was performed regarding whether early administration of a statin influenced subsequent events, and it was found that the prognosis was significantly improved in the early statin administration group (Figure 7B). In addition, efficacy of statins in stable disease was reported in the observational CREDO-KYOTO (Coronary REvascularization Demonstrating Outcome Study in Kyoto) study, in which prognosis was significantly improved in the statin administration group. The MUSASHI (Multicenter Study for Aggressive Lipid-Lowering Strategy by HMG-CoA Reductase Inhibitors in Patients With Acute Myocardial Infarction) study is the only prospective clinical study that investigated ACS and their results showed that reduction of the LDL-C level to at least 100 mg/dl by a statin reduced the number of cardiac events.

However, we do not have a prospective clinical trial to test whether intensification of statin therapy based on achieving LDL-C levels would improve clinical outcomes in Japan similar to those in Europe and the United States. At present there have not even been any studies in Japan that have provided a rationale for a value such as 100 mg/dl for the LDL-C concentration and the beneficial effects occur regardless of the baseline LDL-C level and risk factors. The REAL-CAD (Randomized Evaluation of Aggressive or Moderate Lipid Lowering Therapy with Pitavastatin in Coronary Artery Disease multicenter, prospective, large-scale clinical study) (NCT01042730, UMIN000002680) is being carried out in an attempt to answer these issues in Japan (Figure 8). Stable CAD patients are randomized into pitavastatin 1 mg and 4 mg groups and then followed-up for 3 years in regard to primary endpoints consisting of cardiovascular death, non-fatal MI, non-fatal cerebral infarction, and unstable angina pectoris.
requiring emergency hospitalization. It was estimated that a difference of 20mg/dl in the LDL-C level between the 2 dosage groups during follow-up would represent an approximately 16% reduction in the relative risk, and that the annual incidence of events in Japan will be approximately 2.5%. It was then calculated that 12,600 patients will be needed for the analyses. When the study results are reported after 5 years, we will have categorical evidence regarding the effects of statins in Japan. The optimal statin dose, as well as the target LDL-C concentration for secondary prevention in Japanese patients, will have been clarified. It can be surmised that these results will effect future Japanese treatment guidelines.

Conclusions

Large-scale clinical trials and meta-analyses have clarified that intensive lipid-lowering therapy using statins is useful for bringing about stabilization and regression of plaque, as well as inhibiting adverse cardiovascular events. As a result, the American College of Cardiology has established an LDL-C target value of 70 mg/dl for secondary prevention. Still, various issues remain, including when statin therapy should be initiated, which statin should be administered, what the appropriate statin dosage is, and how long medication should be continued. In Japan, we still lack evidence that, as secondary prevention, events are decreased by intensive lipid-lowering with statins. We are very hopeful that the results of the large-scale clinical trials that are currently in progress in Japan will resolve this issue.

References


Authors’ Comments on the Con-Side Authors

We agreed with Dr Sakamoto’s opinion that “lower is better” is not applicable for all patients.43 Certainly, the decision whether to start intensive-lipid lowering therapy should be done on a patient-specific basis, and intensive-lipid lowering therapy may not be indicated in those patients who are unlikely to benefit if their risk from other competing comorbidity exceeds their cardiovascular risk. However, a significant risk for subsequent adverse cardiovascular events remains a clinical problem in patients with CAD. Dr Sakamoto mentioned low adverse events rates in Japanese patients compared with Caucasians. However, the annual event rate in the Extended-ESTABLISH trial was 24.7% in the control group during 4.2 years follow-up. This rate is not low in Japanese patients,40 as we expected. The cause of increased events is the composite of disease progression, especially in the culprit artery, but it also involves non-culprit lesions that appear to have a variable risk of progression. We can not expect future adverse cardiovascular events because plaque rupture and thrombus formation accidentally happened. So, the important issue we have to do is risk reduction for each patient. Fortunately, cardiovascular events, including death have been reduced significantly with enhanced management of intensive lipid lowering therapy with statin. It is also important that statin treatment, can alter plaque composition and reduce plaque volume, resulting in parallel reduction in the risk of adverse clinical outcomes. In addition, the positive relationship between LDL-C reduction and adverse events, plaque volume, and plaque stabilization suggests that larger reduction in LDL-C provides clinical benefits in patients with CAD. We should be concerned about the cut point selected according to the clinical trial. Furthermore, American and European meta-analysis data demonstrate that intensive statin treatment increases hepatic dysfunction and muscle injury compared with moderate statin treatment,12 as Dr Sakamoto pointed out. However, doses of atorvastatin (20 mg) or rosuvastatin (10 mg) as intensive lipid-lowering therapy in Japan are much lower than that of intensive doses (80 mg and 40 mg, respectively) in USA. In fact, increases in enzyme levels were not frequent in the statin group (atorvastatin 20 mg or pitavastatin 4 mg) of the ESTABLISH20 and JAPAN-ACS21 trials. In view of the highly beneficial risk profile of the intensive lipid-lowering strategy with statins in Japanese, physicians should emphasize to patients the benefits of taking their prescribed drug.

We know the limitations to interpretation. For example, we have no prospective clinical trial to test whether intensification of statin therapy based on achieving LDL-C levels will improve clinical outcomes in Japan. In addition, we only have a surrogate marker trial in Japan evaluating plaque volume and quality. Based on these trials, the more beneficial effect was achieved with higher statins doses than with standard doses. However, it is not possible to claim with certainly that intensive lipid-lowering therapy with higher doses of statins will provide incremental benefit over standard lower doses in all Japanese patients. Several ongoing trials are certain to resolve this issue.