A Randomized Controlled Study to Compare the Effects of Rosuvastatin 2.5 mg and Pravastatin 10 mg on the Plasma Lipid Profile in Japanese Patients with Hypercholesterolemia (ASTRO-1)

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Objective: For new evidence of treatment with statins in Japanese hypercholesterolemic patients, we performed an open-label, randomized, parallel-group comparative study to assess the effect of rosuvastatin 2.5 mg and pravastatin 10 mg on plasma lipids.

Methods: A total of 100 patients in whom the target control levels of LDL-cholesterol (LDL-C) set by the Japan Atherosclerosis Society Guidelines (JASGL2007) had not been achieved were randomly assigned to receive rosuvastatin 2.5 mg / day or pravastatin 10 mg / day for 8 weeks. The primary endpoint was the percent change of LDL-C at week 8.

Results: LDL-C was lowered by -40.3% (from 160.3 to 95.1 mg / dL) in the rosuvastatin group and -22.9% (from 162.9 to 126.0 mg / dL) in the pravastatin group, at week 8 ($P < 0.001$ vs. pravastatin). LDL-C / HDL-C ratio was lowered by -41.3% (from 2.85 to 1.69) and -20.6% (from 2.81 to 2.24), respectively ($P < 0.001$ vs. pravastatin). The rate of achievement of the target LDL-C control level at week 8 was significantly higher in the rosuvastatin group (98.0%) than in the pravastatin group (78.7%) ($P = 0.003$). Both drugs were well tolerated.

Conclusion: Rosuvastatin 2.5 mg produced significantly greater reduction in LDL-C and beneficial effect on other lipid parameters than pravastatin 10 mg, and its safety profile is similar to pravastatin 10 mg.

Key words: Statin, LDL-C, LDL-C / HDL-C ratio, guideline

INTRODUCTION

Based on evidence provided by large-scale clinical studies on patients with dyslipidemia, it has been reported that HMG-CoA reductase inhibitors (statins) possess a potent ability to lower the serum level of LDL-cholesterol (LDL-C), an important risk factor for coronary artery disease, and that this class of drugs is effective in the primary and the secondary prevention of coronary artery disease in patients with dyslipidemia.1-6) Also, the MEGA (Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese) study, a large-scale clinical study conducted in Japanese patients, demonstrated the effectiveness of dietary therapy combined with pravastatin treatment at 10 to 20 mg / day in the primary prevention of coronary artery disease and cerebral infarction in patients with dyslipidemia, which attracted attention.7)

In the United States, the National Cholesterol Education Program (NCEP) Guideline (NCEP Adult Treatment Panel [ATP] III), which was revised based on accumulat-
ed evidence, recommends aggressive reduction of LDL-C level and sets the target control level for LDL-C according to the level of cardiovascular risk. In Japan, the Japan Atherosclerosis Society proposed guidelines for reducing the incidence of coronary artery disease (Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerosis Cardiovascular Diseases [JASGL]), in which patients are classified into categories according to LDL-C level and the number of other major cardiovascular risk factors, and set the target control level of LDL-C for each category.

According to the epidemiological study (Japan Lipid Assessment Program [J-LAP]) on the treatment status of dyslipidemia conducted in Japan in 2003, of the patients treated with lipid-lowering drugs (n = 24,048, 90.4% of whom received the treatment for primary prevention), 91.8% were receiving a statin (87.9% treated with a statin alone; 3.9% treated with a statin in combination with other drugs); however, the target JASGL LDL-C level was achieved in only 63.4% of the treated patients. In respect of the most frequently used statins, the rate of achievement of the target LDL-C level was 57.2% for pravastatin, a drug with moderate LDL-C-lowering activity, but superior safety profile, but only 73.9% even for atorvastatin, which is classified as a strong statin. These results suggest that the lipid control status in patients with dyslipidemia in Japan is not sufficient, and that a novel statin with more potent LDL-C-lowering activity and favorable safety profile is needed.

Rosuvastatin, the sixth statin to be approved in Japan, is classified as a hydrophilic statin, like pravastatin. In foreign countries, the drug has been demonstrated to be safe and effective, and already been prescribed widely in clinical settings. However, there are few data on the efficacy and safety of rosuvastatin in Japanese patients because the application for approval of the drug was based on overseas data extrapolated to Japan. A pharmacokinetic study conducted in Japan showed that the blood concentration of the rosuvastatin in Japanese patients was almost twice that in Caucasians, based on which the initial dose for Japanese patients was set at 2.5 mg / day, half of the dose used in the United States. In Japan, the efficacy and safety of low-dose rosuvastatin, i.e., 2.5 mg, was confirmed from the results of a post-marketing surveillance of the drug published in 2007, which suggested that rosuvastatin 2.5 mg was more effective than pravastatin 10 mg and that the drug also posed no safety problem. However, there are few data based on direct comparison of the efficacy and safety of rosuvastatin 2.5 mg and pravastatin 10 mg.

The present study was conducted to compare the efficacy and safety of rosuvastatin 2.5 mg and pravastatin 10 mg in patients with hypercholesterolemia, in whom the statin treatment was administered for primary prevention of coronary artery disease (ASTRO-I: A Study to verify the efficacy of rosuvastatin 2.5 mg as aggressive lipid-lowering therapy for hypercholesterolemia).

**PATIENTS AND METHODS**

The study was designed as an open-label, randomized, parallel-group comparative study; it was conducted from December 2007 through April 2008 at 9 medical institutions in Japan, with the approval of the institutional review board of each of these institutions, in accordance with the ethical principles proposed in the Declaration of Helsinki. Written consent was obtained from the study patients prior to their participation in the study.

Eligible patients were hypercholesterolemic patients in whom the target LDL-C level set by JASGL2007 had not been achieved, who were 20 years or older, had no history of coronary artery disease, had LDL-C level of less than 180 mg / dL, and had not received a statin within the previous 2 months. Patients with any of the following conditions were excluded from the study: severe hypertension, type 1 diabetes mellitus, familial hypercholesterolemia, cerebrovascular disorder within 3 months prior to the start of the study, active hepatic disease (ALT or AST > 100 IU / L, or total bilirubin > 2.5 mg / dL), renal dysfunction (serum creatinine ≥ 2.0 mg / dL or creatinine clearance < 30 ml / min / 1.73 m²), serum CK > 1000 IU / L, pregnancy or possible pregnancy, hypothyroidism, hereditary muscular disease (e.g., muscular dystrophy) or family history of the disease, past history of drug-induced muscular disorder, drug abuse, and alcohol addiction.

After confirmation of eligibility, the eligible patients were registered in the central data center and randomly assigned to receive either rosuvastatin 2.5 mg / day (rosuvastatin 2.5 mg group) or pravastatin 10 mg / day (pravastatin 10 mg group) (Fig. 1). The allocation was performed by a biased coin method, taking into account a balance between the treatment groups and LDL-C level at registration, an adjustment factor for the allocation.

The duration of administration of the study drug was 8 weeks. Compliance with the treatment was checked at each visit. During the study period, concomitant use of other lipid-lowering agents (statins, fibrates, anion exchangers, cholesterol transporter inhibitors, probucol,
nicotinates, phytosterols, etc.) and cyclosporin were prohibited, because these drugs might potentially affect the efficacy and safety evaluation of the study drugs.

Clinical laboratory tests to determine the serum lipid profile (LDL-C, HDL-C and TG: these were measured directly by enzyme assay, ApoB and ApoA-1: by turbidimetric immunoassay) and other blood chemistry parameters (CK, AST, ALT, total bilirubin, urea nitrogen, creatinine) were performed at weeks 0, 4, and 8, and qualitative urinalysis (protein, sugar, occult blood) was performed at weeks 0 and 8. All the blood samples were collected under the fasting condition. The laboratory tests were performed centrally at SRL Medisearch, Inc. (Tokyo, Japan).

The primary efficacy endpoint was the percent change of LDL-C at week 8, and the secondary efficacy endpoints were the percent change of the serum lipid levels (LDL-C, HDL-C, TG, ApoB, ApoA-1, LDL-C / HDL-C ratio, ApoB / ApoA-1 ratio) at week 4, the percent change of the serum lipid levels (HDL-C, TG, ApoB, ApoA-1, LDL-C / HDL-C ratio, ApoB / ApoA-1 ratio) at week 8, the rate of achievement of the JASGL2007 target LDL-C control level at week 8, and the rate of achievement of LDL-C / HDL-C ratio of 1.5 and that of 2.0 at week 8. The safety endpoints were the types and frequency of adverse events in each treatment group.

The rationale for the sample size was as follows. On the basis of the results of an overseas study,\textsuperscript{13} the percent change of LDL-C at week 8 was assumed to be 35% and 24% for rosuvastatin 2.5 mg and pravastatin 10 mg, respectively, with a standard deviation of 15%. Based on these assumptions, the number of patients required to verify the superiority of rosuvastatin 2.5 mg over pravastatin 10 mg from the difference in the mean of percent change with a 2-sided significance level ($\alpha$) of 0.05 and statistical power (1-$\beta$) of 0.9 was 41 for each group. Therefore, the number for patients per group was set at 50 to allow for possible dropouts and treatment discontinuations. In the comparison between the treatment groups, the metric data were analyzed by 2-sample $t$-test, the ordinal data by Wilcoxon's 2-sample test, and the ratios by Fisher's exact test. All statistical tests were 2-sided and conducted at a significance level of 5%.

**RESULTS**

A total of 100 patients were enrolled in this study after they were confirmed to be eligible, and 50 each of these patients were randomly assigned to receive 2.5 mg / day of rosuvastatin or 10 mg / day of pravastatin. Of these patients, the study drug administration for 8 weeks could be completed in 49 and 47 patients, respectively, of the rosuvastatin and pravastatin groups. One patient of the rosuvastatin 2.5 mg group (lost to follow-up) and 3 patients of the pravastatin 10 mg group (one each of occurrence of an adverse event [cervical spondylosis], physician's judgment, and LDL-C < 100 mg / dL requiring no treatment with the study drug at week 0) discontinued the study (Fig. 2).

The lost to follow-up patient from the rosuvastatin 2.5 mg group was completely excluded from the analyses, because of the lack of availability of any data after the start of treatment. Thus, 49 patients from the rosuvastatin 2.5 mg group and 50 patients from the pravastatin 10 mg group were included for the final analysis of the efficacy and safety. In regard to the background characteristics of the patients eligible for the analysis set, the mean age was higher in the rosuvastatin 2.5 mg group, and the number of patients with a family history of coronary artery disease tended to be higher in the pravastatin 10 mg group. No differences in other background characteristics were observed between the two groups (Table 1). A compli-
Efficacy

The percent change of LDL-C at week 8, the primary endpoint, was -40.3% (from 160.3 to 95.1 mg/dL) in the rosuvastatin 2.5 mg group and -22.9% (from 162.9 to 126.0 mg/dL) in the pravastatin 10 mg group, with a significant difference between the two groups ($P < 0.001$) (Fig. 3). The percent change of LDL-C at week 4 was significantly lowered in the rosuvastatin 2.5 mg group than the pravastatin 10 mg group ($P < 0.001$) (Table 2).

Rosuvastatin 2.5 mg group showed significant reduction of LDL-C / HDL-C than the pravastatin 10 mg group at both week 4 and 8 ($P < 0.001$ for both vs. pravastatin). Rosuvastatin 2.5 mg group also showed significant improvement of ApoB and ApoB / ApoA-1 ratio than the pravastatin 10 mg group at both week 4 and 8 ($P < 0.001$ for all vs. pravastatin), and ApoA-1 at week 8 ($P = 0.011$ for all vs. pravastatin) (Table 2, Fig. 4).

The rate of achievement of the JASGL2007 target LDL-C level at week 8 was 98.0% (48 / 49) in the rosuvastatin 2.5 mg group and 78.7% (37 / 47) in the pravastatin 10 mg group, the rate being significantly higher in the rosuvastatin 2.5 mg group ($P = 0.003$) (Fig. 5). The rate of achievement of LDL-C / HDL-C ratio of 2.0 at week 8 was 73.5% (36 / 49) in the rosuvastatin 2.5 mg group and 40.4% (19 / 47) in the pravastatin 10 mg group, and that of 1.5 was 49.0% (24 / 49) and 14.9% (7 / 47), respectively, in the two groups, with both the rates being significantly higher in the rosuvastatin 2.5 mg group ($P = 0.002$ and $P$)
Safety

No serious adverse events were observed in either treatment group. The adverse events that were judged to be possibly related to the study drug by the investigators were CK increased in 2 patients from the rosuvastatin 2.5 mg group and CK increased in 1 patient and dizziness in 1 patient from the pravastatin 10 mg group (Table 3). No significant changes of the blood chemistry parameters and qualitative urinalysis were observed in either treatment group.

Thus, the results showed favorable safety profiles of both rosuvastatin 2.5 mg and pravastatin 10 mg, indicating that both the drugs were well tolerated.

**DISCUSSION**

Many large-scale overseas and domestic clinical studies of statins have demonstrated the effectiveness of LDL-C lowering therapy in the primary prevention of cardiovascular diseases and cerebrovascular stroke, con-
## Table 2  Changes in serum lipid levels over time

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Treatment group</th>
<th>Week 0</th>
<th>Week 4</th>
<th>Week 8</th>
<th>% change at week 4</th>
<th>% change at week 8</th>
<th>Between-group comparison§</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>RSV group</td>
<td>PRV group</td>
<td>RSV group</td>
<td>PRV group</td>
<td>RSV group</td>
<td>PRV group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL-C (mg/dL)</td>
<td>RSV group</td>
<td>160.3 ± 21.8</td>
<td>93.2 ± 15.1</td>
<td>95.1 ± 18.3</td>
<td>-41.5 ± 9.1</td>
<td>&lt; 0.001 ***</td>
<td>-40.3 ± 11.2</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>162.9 ± 21.6</td>
<td>129.3 ± 20.2</td>
<td>126.0 ± 19.5</td>
<td>-20.3 ± 9.7</td>
<td></td>
<td>-22.9 ± 11.6</td>
<td></td>
</tr>
<tr>
<td>HDL-C (mg/dL)</td>
<td>RSV group</td>
<td>58.7 ± 13.1</td>
<td>59.0 ± 13.5</td>
<td>59.7 ± 13.0</td>
<td>1.1 ± 10.4</td>
<td>0.770</td>
<td>2.4 ± 10.4</td>
<td>0.031 *</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>61.5 ± 17.0</td>
<td>61.4 ± 16.7</td>
<td>59.9 ± 17.0</td>
<td>0.5 ± 9.9</td>
<td></td>
<td>-2.4 ± 11.0</td>
<td></td>
</tr>
<tr>
<td>TG (mg/dL)</td>
<td>RSV group</td>
<td>129.5 ± 68.6</td>
<td>110.5 ± 62.1</td>
<td>107.9 ± 50.2</td>
<td>-11.0 ± 26.7</td>
<td>0.045 *</td>
<td>-11.2 ± 27.4</td>
<td>0.099</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>126.9 ± 63.2</td>
<td>122.0 ± 65.0</td>
<td>120.6 ± 55.0</td>
<td>4.9 ± 47.9</td>
<td></td>
<td>0.8 ± 41.7</td>
<td></td>
</tr>
<tr>
<td>ApoB (mg/dL)</td>
<td>RSV group</td>
<td>122.8 ± 17.5</td>
<td>77.4 ± 12.4</td>
<td>80.9 ± 16.1</td>
<td>-36.7 ± 8.4</td>
<td>&lt; 0.001 ***</td>
<td>-33.8 ± 10.8</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>123.4 ± 15.5</td>
<td>100.4 ± 14.8</td>
<td>101.7 ± 14.9</td>
<td>-18.4 ± 9.1</td>
<td></td>
<td>-18.2 ± 10.8</td>
<td></td>
</tr>
<tr>
<td>ApoA-1 (mg/dL)</td>
<td>RSV group</td>
<td>145.0 ± 22.3</td>
<td>146.2 ± 22.7</td>
<td>148.4 ± 23.8</td>
<td>1.1 ± 8.7</td>
<td>0.585</td>
<td>2.6 ± 9.3</td>
<td>0.011 *</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>152.1 ± 27.7</td>
<td>151.8 ± 27.8</td>
<td>148.1 ± 24.9</td>
<td>0.1 ± 9.2</td>
<td></td>
<td>-2.3 ± 9.3</td>
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</tr>
<tr>
<td>LDL-C / HDL-C ratio</td>
<td>RSV group</td>
<td>2.85 ± 0.67</td>
<td>1.69 ± 0.58</td>
<td>1.69 ± 0.58</td>
<td>-41.6 ± 10.1</td>
<td>&lt; 0.001 ***</td>
<td>-41.3 ± 10.9</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>2.81 ± 0.70</td>
<td>2.24 ± 0.63</td>
<td>2.24 ± 0.61</td>
<td>-20.2 ± 11.4</td>
<td></td>
<td>-20.6 ± 11.3</td>
<td></td>
</tr>
<tr>
<td>ApoB / ApoA-1 ratio</td>
<td>RSV group</td>
<td>0.87 ± 0.18</td>
<td>0.55 ± 0.15</td>
<td>0.56 ± 0.16</td>
<td>-37.0 ± 9.2</td>
<td>&lt; 0.001 ***</td>
<td>-35.2 ± 10.6</td>
<td>&lt; 0.001 ***</td>
</tr>
<tr>
<td></td>
<td>PRV group</td>
<td>0.84 ± 0.18</td>
<td>0.68 ± 0.16</td>
<td>0.70 ± 0.15</td>
<td>-18.0 ± 10.6</td>
<td></td>
<td>-16.0 ± 9.4</td>
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</tr>
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</table>

RSV group: rosuvastatin 2.5 mg group, PRV group: pravastatin 10 mg group, SD: standard deviation
Percent change at week 4 (week 8) (%) = ([value at week 4 (week 8)] - [value at week 0]) / [value at week 0] × 100
§: 2-sample t-test; ***: P < 0.001, *: P < 0.05
Fig. 4 Changes over time in LDL-C, LDL-C / HDL-C ratio, ApoB, and ApoB / ApoA-1 ratio.
RSV group: rosuvastatin 2.5mg group, PRV group: pravastatin 10 mg group
The circles indicate the means, the bars indicate the 95%CI.
2 sample t-test for comparison of percent change from week 0 of RSV group with that of PRV group; ***: $p < 0.001$

Fig. 5 Achievement of JASGL2007 target LDL-C control level at week 8.
RSV group: rosuvastatin 2.5mg group, PRV group: pravastatin 10 mg group
Fisher's exact test
The JASGL2007 target LDL-C control level was set according to the number of concurrent major risk factors other than LDL-C ([male ≥ 45 years, female ≥ 55 years), hypertension, diabetes mellitus (including impaired glucose tolerance), smoking, family history of coronary artery disease, low HDL cholesterol (< 40 mg / dL)]: Category I without major risk factor: < 160 mg / dL, Category II with 1 or 2 major risk factors: < 140 mg / dL, Category III with 3 or more major risk factors, or complicated by diabetes mellitus, cerebral infarction or arteriosclerosis obliterans: < 120 mg / dL.
firming that LDL-C is an important risk factor for these diseases. These studies include those on aggressive lipid-lowering therapy in patients classified as high-risk for atherosclerotic diseases despite not so high level of LDL-C at baseline. In the ASCOT-LLA (Anglo-Scandinavian Cardiac Outcomes Trial - Lipid Lowering Arm) study, a higher efficacy was observed in the concomitant atorvastatin 10 mg group as compared with that in the placebo group in terms of the primary prevention of cardiovascular disease and cerebrovascular stroke in hypertensive patients with 3 or more cardiovascular risk factors (LDL-C before treatment, 131 mg / dL; LDL-C after treatment, 90 mg / dL; percent change, -31%). In the CARDS (the Collaborative Atorvastatin Diabetes Study) also, a higher efficacy of atorvastatin 10 mg as compared with placebo was observed in the primary prevention of cardiovascular disease and cerebrovascular stroke in patients with type 2 diabetes mellitus (LDL-C before treatment, 118 mg / dL; LDL-C after treatment, 81 mg / dL; percent change, -31%). The ASTEROID trial demonstrated that rosuvastatin 40 mg / day as aggressive lipid-lowering therapy in patients with coronary atherosclero-

<table>
<thead>
<tr>
<th>Table 3</th>
<th>Adverse events</th>
<th>RSV group</th>
<th>PRV group</th>
</tr>
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<tbody>
<tr>
<td>Adverse events</td>
<td>n=49</td>
<td>n=50</td>
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</tr>
<tr>
<td>All adverse events</td>
<td>13 (2)</td>
<td>18 (2)</td>
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<tr>
<td>Common cold</td>
<td>5 (0)</td>
<td>5 (0)</td>
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<tr>
<td>Gastrointestinal disorders (diarrhea, colitis)</td>
<td>0 (0)</td>
<td>4 (0)</td>
<td></td>
</tr>
<tr>
<td>CK increased</td>
<td>2 (2)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Pollinosis</td>
<td>1 (0)</td>
<td>2 (0)</td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>0 (0)</td>
<td>1 (1)</td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>5¶(0)</td>
<td>5§(0)</td>
<td></td>
</tr>
</tbody>
</table>

†: knee pain, myalgia, tinea, insomnia, sleepiness
§: headache, contusion of breast, cervical spondylosis, hordeolum, numbness of left leg
sis, regressed the atherosclerotic lesions of the coronary arteries.39 These reports suggest the importance of aggressive lowering of LDL-C in the prevention of atherosclerotic diseases.

In the present study, the rate of achievement of the JASGL2007 target LDL-C control level was 98.0% in the rosuvastatin 2.5 mg group and 78.7% in the pravastatin 10 mg group, the rate being significantly higher \( P = 0.003 \) and highly satisfactory (close to 100%) in the rosuvastatin 2.5 mg group. This study targeted patients with no history of cardiovascular disease and patient population contained those who classified into category I and Category II (target LDL-C level: < 160 mg / dL, 140 mg / dL, respectively) by 80%. Therefore, it was thought that the rate of achievement in pravastatin 10 mg group was higher than those in previous studies (e.g. 57.2% in J-LAP, an epidemiological study in Japan10). The LDL-C level at week 8 was 95.1 mg / dL in the rosuvastatin 2.5 mg group and 126.0 mg / dL in the pravastatin 10 mg group, and the percent change of LDL-C was -40.3% and -22.9% in the rosuvastatin and pravastatin groups, respectively, the percent change being significantly higher in the rosuvastatin 2.5 mg group. We consequently found the imbalance of age which had not been included as adjustment factor for the allocation, but we confirmed that the baseline imbalance on age did not affect the results with analysis adjusting for age. There is few report about influence of age on LDL-C reduction in statin treatment. However, JASGL2007 which prepared for the adults aged less than 64 years can be applied those aged 65-74 years for clinical management.20 These results suggest that rosuvastatin is an excellent statin that may be used as monotherapy in hypercholesterolemic patients who are candidates for the primary prevention of coronary artery disease. Because of the non-feasibility of using the true endpoint, the present study was performed using a surrogate endpoint. It is expected that rosuvastin will also be demonstrated to be effective in preventing the cardio / cerebrovascular events, the true endpoint, in future studies.

Since the progression of coronary atherosclerosis is a contributory factor to coronary artery disease, suppression of these processes may contribute to the prevention of coronary artery disease, although there is currently no supporting evidence for this contention. In regard to the relationship between the serum lipid levels and the atheroma volume, the results of a meta-analysis of four large-scale clinical studies that evaluated the atheroma volume by IVUS (intravascular ultrasound)21 showed that the patient group that exhibited regression of the atheroma volume also showed significantly greater reduction of LDL-C, LDL-C / HDL-C ratio, ApoB and ApoB / ApoA-1 ratio, and increase of HDL-C and ApoA-1 than the group that did not. In the present study, the above 6 parameters were significantly improved in the rosuvastatin 2.5 mg group than in the pravastatin 10 mg group at both week 4 and 8. The results of the above meta-analysis also indicated that progression of coronary atherosclerosis was observed in patients with LDL-C / HDL-C ratio exceeding 2.0, whereas mild regression was observed in patients with the ratio of 1.5 to 2.0, and distinct regression was observed in those with the ratio of below 1.5.21 Though there is no similar study to evaluate the regression of atheroma for Japanese patient, Noike et al. suggested that LDL-C / HDL-C ratio should be managed at < 2.5 in Japanese hypercholesterolemic patients with coronary risk factors based on the evaluation of the relationship between plaque formation in the coronary artery by IVUS and lipid levels.22 In the present study, the rates of achievement of LDL-C / HDL-C ratio of both ≤ 1.5 and ≤ 2.0 were significantly higher in the rosuvastatin 2.5 mg group than in the pravastatin 10 mg group, suggesting that rosuvastatin was more potent than pravastatin in regression of coronary atherosclerosis.

As is evident from the results of large-scale clinical studies,2,3,7 pravastatin is a statin with an excellent safety profile. In the present study, hepatic dysfunction or myopathy-like symptoms, both significant adverse reactions to statins, were not observed in either treatment group. Although serum CK increased was observed in 2 patients of the rosuvastatin 2.5 mg group and 1 patient of the pravastatin 10 mg group, the adverse events were mild and did not pose any clinically significant problem. No adverse events that would pose a safety concern were observed in either treatment group. These results suggest that rosuvastatin is a well-tolerated and highly safe statin, similar to pravastatin.

We have compared the effect of rosuvastatin 5 mg and atorvastatin 10 mg in hypercholesterolemic patients including those who categorized as secondary prevention, and obtained results suggesting that rosuvastatin 5 mg is safe and effective in improving the LDL-C and other lipid abnormality, as in the present study (ASTRO-2 study). Although statins are used as the drugs of first choice for pharmacologic therapy of hypercholesterolemia, consideration has to be given in many of cases according to the degree of risk for coronary artery disease of the patients, while making a choice of the statins to be used. The ASTRO-2 study and the present study suggested that rosu-
vastatin provides an optimal monotherapy for Japanese hypercholesterolemic patients with a variety of risk factors for coronary artery disease.

**CONCLUSION**

Rosuvastatin 2.5 mg and pravastatin 10 mg were compared in terms of their effects in improving the serum lipid parameters and their safety in Japanese patients with hypercholesterolemia in whom the target LDL-C level had not been achieved. Rosuvastatin 2.5 mg produced significantly greater reduction in LDL-C and beneficial effect on other lipid parameters than pravastatin 10 mg, and its safety profile is similar to pravastatin 10 mg.

**STUDY ORGANIZATION**

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**APPENDIX**

We would like to thank the following investigators:

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