Effect of Intensive Lipid-Lowering Therapy With Rosuvastatin on Progression of Carotid Intima-Media Thickness in Japanese Patients
– Justification for Atherosclerosis Regression Treatment (JART) Study –

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Background: A recent trial in Western countries has shown that rosuvastatin slows progression of carotid intima-media thickness (IMT) in patients with modest carotid IMT thickening and elevated levels of low-density lipoprotein cholesterol (LDL-C). We conducted a prospective, randomized, open-label, blinded-endpoint trial to determine whether rosuvastatin is more effective than pravastatin in slowing progression of carotid IMT in Japanese patients.

Methods and Results: Adult patients with hypercholesterolemia who had a maximum IMT ≥1.1 mm were randomly assigned to receive rosuvastatin or pravastatin. The primary endpoint was the percent change in the mean-IMT, which was measured by a single observer who was blinded to the treatment assignments. The trial was stopped on April 2011 according to the recommendation by the data and safety monitoring committee. A total of 348 patients (173 rosuvastatin; 175 pravastatin) were enrolled and 314 (159 rosuvastatin; 155 pravastatin) were included in the primary analysis. Mean (SD) percentage changes in the mean-IMT at 12 months were 1.91% (10.9) in the rosuvastatin group and 5.8% (12.0) in the pravastatin group, with a difference of −3.89% (11.5) between the groups (P=0.004). At 12 months, 85 patients (59.4%) in the rosuvastatin group achieved a LDL-C/high-density lipoprotein cholesterol ratio ≤1.5 compared with 24 patients (16.4%) in the pravastatin group (P<0.0001).

Conclusions: Rosuvastatin significantly slowed progression of carotid IMT at 12 months compared with pravastatin.

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Key Words: Carotid intima-media thickness; Dyslipidemia; Randomized controlled trial; Rosuvastatin; Statins

Despite advances in treatment, atherosclerotic vascular disease, such as coronary artery disease (CAD) or ischemic stroke, is a major cause of mortality in Japan. Dyslipidemia is a major risk factor for atherosclerosis, and the results of large-scale clinical trials have shown that lipid-lowering therapy with 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) effectively reduce the risk of cardiovascular events across a wide range of cholesterol levels. Under these circumstances, recent guidelines recommend treatment goals for serum cholesterol levels according to the risk...
category in which an individual patient is classified.6–9

**Editorial p 55**

In addition, recent clinical trials and meta-analyses have shown that intensive lipid-lowering therapy with statins slows the progression or induces regression of atherosclerosis.10–13 These results indicate that progression of coronary plaques can be suppressed by achieving very low levels of low-density lipoprotein cholesterol (LDL-C)10,11 and that regression of atheroma volume can occur when substantial reduction of LDL-C is accompanied by an increase in high-density lipoprotein cholesterol (HDL-C).12,13 Although current guidelines recommend aggressive achievement of LDL-C goals in certain high-risk patients, these recent results suggest that aggressive treatment may also be beneficial in relatively low-risk patients.

Carotid artery intima-media thickness (IMT) is a reasonable marker for cardiovascular risk assessment because a decrease in carotid IMT correlates with a decrease in the risk of cardiovascular events.14,15 In a randomized controlled trial conducted in Western countries, rosuvastatin, one of the strongest statins to date, provided significant reductions in the rate of progression of maximum carotid IMT in middle-aged individuals with modest carotid IMT thickening and elevated LDL-C.16 However, it remains uncertain whether these results are generalizable to Japanese patients. Recently, an open-label study showed that rosuvastatin resulted in significant regression of coronary plaque volume in Japanese patients,17 but this finding has not been confirmed in a randomized controlled trial. On the basis of these findings, we conducted a randomized controlled trial to determine whether intensive therapy with rosuvastatin is more effective than conventional therapy with pravastatin in slowing atherosclerotic progression in Japanese patients by measuring carotid IMT. This trial was stopped according to the recommendation by the data and safety monitoring committee. Here, we report the final results.

**Methods**

**Study Design and Ethical Considerations**

This multicenter, prospective, randomized, open-label, blinded-endpoint (PROBE) trial was conducted between June 2008 and April 2011 in Japan. The trial was conducted in accordance with the Declaration of Helsinki and the ethical principles for clinical studies in Japan. Its protocol was reviewed and approved by the institutional review board of each participating center. All patients provided written informed consent.

**Eligibility Criteria**

The rationale and design of the trial have been reported previously.18 In brief, eligible patients were those with elevated LDL-C (serum level \( \geq 140 \) mg/dl) aged 20 years or older who had a maximum IMT \( \geq 1.1 \) mm measured at the carotid artery. Serum LDL-C levels were measured by using direct homogeneous assay. Otherwise, serum LDL-C levels were calculated using Friedewald’s formula:19

\[
\text{LDL-C} = \text{total cholesterol (TC)} - \text{HDL-C} - \frac{\text{triglyceride (TG)}}{5}
\]

Patients were excluded if they required lipid-lowering agents other than trial treatments and prespecified ones (ie, anion-exchange resin, probucol, or ethyl icosapentate); had received statin therapy within 1 month of starting the trial; had a history of hypersensitivity to statins; had uncontrolled hypertension; had type 1 diabetes mellitus (DM) or uncontrolled type 2 DM; experienced myocardial infarction or stroke within past 3 months; had severe congestive heart failure (New York Heart Association class III–IV); had active hepatic disease, renal disorder (serum creatinine level \( \geq 2 \) mg/dl

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**Figure 1.** Flow chart of the patients enrolled into the trial. RSV, rosuvastatin; PRV, pravastatin; IMT, intima-media thickness.
or creatinine clearance <30 ml·min⁻¹·1.73 m⁻², or elevated creatine kinase level (>500 IU/L); were being treated with cyclosporine; were confirmed or suspected of having a malignant tumor; had hypothyroidism, hereditary muscular disease, a familial history of these diseases, or a history of drug-induced muscular disorders; or had a history of drug abuse or alcoholism. Pregnant women, breast-feeding women, or women who were potentially pregnant or wished to become pregnant during the trial were also excluded.

### Trial Treatments

Patients were randomly assigned to receive rosvastatin 5 mg (intensive therapy) or pravastatin 10 mg (conventional therapy) in a 1:1 ratio (step 1). Both trial treatments were planned to be administered once daily orally for 24 months. Treatment allocation was computer-generated by a central randomization facility using a dynamic allocation method with balancing factors of maximum IMT, serum LDL-C level, presence/absence of DM (including impaired glucose tolerance), and center. If eligibility of the patient was confirmed, the investigator contacted the data center through the interactive web response system and was notified of the allocated treatment. Allocation was concealed to the investigators until they contacted the data center.

In the rosvastatin group, the LDL-C goal was defined as <80 mg/dl for primary prevention and <70 mg/dl for secondary prevention. If the patient did not achieve the LDL-C goal, the daily dose of rosvastatin was increased to 10 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3). In the pravastatin group, the LDL-C goal was defined according to the Japan Atherosclerosis Society (JAS) guideline. In this guideline, the LDL-C goal was defined according to the risk category. In primary prevention, the goal was <160 mg/dl for the low-risk group, <140 mg/dl for the intermediate-risk group, and <120 mg/dl for the high-risk group. For secondary prevention, the goal was <100 mg/dl. If the patient did not achieve these LDL-C goals, the daily dose of pravastatin was increased to 20 mg (step 2), and prespecified lipid-lowering agents were added thereafter (step 3). In both treatment groups, concomitant use of anion-exchange resin, probucol, and ethylicosapentate was allowed during the trial.

### Table 1. Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin (n=159)</th>
<th>Pravastatin (n=155)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, Male</td>
<td>79 (49.7%)</td>
<td>76 (49.0%)</td>
<td>0.908</td>
</tr>
<tr>
<td>Age (mean ± SD) (years)</td>
<td>63.9±8.9</td>
<td>63.3±9.1</td>
<td>0.521</td>
</tr>
<tr>
<td>Elderly (≥65)</td>
<td>83 (52.2%)</td>
<td>73 (47.1%)</td>
<td>0.366</td>
</tr>
<tr>
<td>Blood pressure (mean ± SD) (mmHg)</td>
<td></td>
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<tr>
<td>Systolic</td>
<td>132.4±17.0</td>
<td>131.0±18.0</td>
<td>0.483</td>
</tr>
<tr>
<td>Diastolic</td>
<td>76.7±11.1</td>
<td>74.9±13.5</td>
<td>0.213</td>
</tr>
<tr>
<td>JAS2007 category</td>
<td></td>
<td></td>
<td>0.432</td>
</tr>
<tr>
<td>I</td>
<td>2 (1.3%)</td>
<td>1 (0.6%)</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>52 (32.7%)</td>
<td>59 (38.1%)</td>
<td></td>
</tr>
<tr>
<td>III</td>
<td>79 (49.7%)</td>
<td>72 (46.5%)</td>
<td></td>
</tr>
<tr>
<td>Secondary prevention</td>
<td>26 (16.4%)</td>
<td>23 (14.8%)</td>
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<tr>
<td>CHD risk factors</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Family history of premature CHD</td>
<td>29 (18.2%)</td>
<td>26 (16.8%)</td>
<td>0.733</td>
</tr>
<tr>
<td>Smoking</td>
<td>30 (18.9%)</td>
<td>31 (20.0%)</td>
<td>0.800</td>
</tr>
<tr>
<td>eGFR* (mean ± SD) (ml·min⁻¹·1.73m⁻²)</td>
<td>73.3±15.4</td>
<td>72.8±17.3</td>
<td>0.797</td>
</tr>
<tr>
<td>Medical history</td>
<td></td>
<td></td>
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<tr>
<td>Hypertension</td>
<td>102 (64.2%)</td>
<td>103 (66.5%)</td>
<td>0.669</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>70 (44.0%)</td>
<td>68 (43.9%)</td>
<td>0.978</td>
</tr>
<tr>
<td>Low HDL-C</td>
<td>11 (6.9%)</td>
<td>15 (9.7%)</td>
<td>0.375</td>
</tr>
<tr>
<td>Cerebral infarction</td>
<td>8 (5.0%)</td>
<td>8 (5.2%)</td>
<td>0.958</td>
</tr>
<tr>
<td>Cerebral hemorrhage</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td></td>
</tr>
<tr>
<td>Arteriosclerosis obliterans</td>
<td>4 (2.5%)</td>
<td>2 (1.3%)</td>
<td>0.428</td>
</tr>
<tr>
<td>Coronary disease</td>
<td>26 (16.4%)</td>
<td>23 (14.8%)</td>
<td>0.712</td>
</tr>
<tr>
<td>Other medical treatment</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Antihypertensive drug</td>
<td>88 (55.3%)</td>
<td>87 (56.1%)</td>
<td>0.910</td>
</tr>
<tr>
<td>Antidiabetic drug</td>
<td>37 (23.3%)</td>
<td>39 (25.2%)</td>
<td>0.792</td>
</tr>
<tr>
<td>Aspirin</td>
<td>25 (15.7%)</td>
<td>24 (15.5%)</td>
<td>0.953</td>
</tr>
<tr>
<td>LDL-C (mean ± SD) (mg/dl)</td>
<td>166.9±23.3</td>
<td>166.1±20.8</td>
<td>0.732</td>
</tr>
<tr>
<td>Max-IMT (mean ± SD) (mm)</td>
<td>1.66±0.59</td>
<td>1.61±0.52</td>
<td>0.443</td>
</tr>
</tbody>
</table>

* eGFR=194×Cr⁻¹.094×age⁻⁰.²⁸⁷ (for men) and 194×Cr⁻¹.094×age⁻⁰.²⁸⁷×0.739 (for women). Rosuvastatin group, n=156; pravastatin group, n=154 because of missing measurements.

** We used the National Glycohemoglobin Standardization Program value. Rosuvastatin group, n=152; pravastatin group, n=150 because of missing measurements.

JAS, Japan Atherosclerosis Society; CHD, coronary heart disease; eGFR, estimated glomerular filtration rate; HDL, high-density lipoprotein; LDL, low-density lipoprotein; IMT, intima-media thickness; HbA1c, hemoglobin A1c.
The outcome was measured at the far wall of the common carotid artery. Patients were scheduled to undergo ultrasonographic examinations at 0 (within 3 months before enrollment), 12, and 24 months, and B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease. For the measurement of carotid IMT, 2 longitudinal images were obtained in the 3-cm segment proximal to the tip of the flow divider of the right and left common carotid arteries. The outcome was measured at the far wall of the common carotid artery in which the eligibility criterion of maximum IMT ≥1.1 mm was confirmed. A single observer who was blinded to the treatment assignments measured the mean-IMT in the core laboratory using Intimascope® (Media Cross Co Ltd, Tokyo, Japan). It averaged 60 points of IMT values in the segment 2 cm proximal to the dilation of the carotid bulb. In addition, investigators at each institution measured the max-IMT (maximum IMT at the far wall of the common carotid artery), IMT-Cmax (maximum common carotid artery IMT), IMT-Bmax (maximum carotid bulb IMT), and IMT-Imax (maximum internal carotid artery IMT). The primary endpoint defined in the protocol was the percent change in the mean-IMT from baseline to the end of 24 months. The secondary endpoints included the max-IMT, IMT-Cmax, IMT-Bmax, IMT-Imax, serum lipid levels, and LDL-C/HDL-C ratio. For the safety analysis, we classified adverse events under 3 categories in the protocol. We defined an adverse event as “mild” if the patient had signs or symptoms, but could continue the study with no other treatment, “moderate” if the patient had signs or symptoms, but could continue the study with any treatment and “severe” if the patient could not continue the study.

### Table 2. Changes in the Primary and Secondary Endpoints

<table>
<thead>
<tr>
<th></th>
<th>Rosuvastatin</th>
<th>Pravastatin</th>
<th>Change (mm)</th>
<th>Change (%)</th>
<th>Difference</th>
<th>P value</th>
<th>Change (mm)</th>
<th>Change (%)</th>
<th>Difference</th>
<th>P value</th>
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<tbody>
<tr>
<td><strong>Primary</strong></td>
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<td>Mean-IMT (mm)</td>
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<tr>
<td>Baseline</td>
<td>0.919±0.223</td>
<td>0.868±0.194</td>
<td>(157)</td>
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<tr>
<td>12 months</td>
<td>0.923±0.186</td>
<td>0.904±0.191</td>
<td>(146)</td>
<td>1.91±10.9</td>
<td>(145)</td>
<td>0.042±0.094</td>
<td>(144)</td>
<td>5.80±12.0</td>
<td>(144)</td>
<td>-0.030±0.094</td>
</tr>
<tr>
<td>24 months*</td>
<td>0.906±0.169</td>
<td>0.916±0.215</td>
<td>(67)</td>
<td>-0.030±0.094</td>
<td>0.007</td>
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<td><strong>Secondary</strong></td>
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<td>Max-IMT (mm)</td>
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<tr>
<td>Baseline</td>
<td>1.55±0.60</td>
<td>1.53±0.51</td>
<td>(159)</td>
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<tr>
<td>12 months</td>
<td>1.51±0.57</td>
<td>1.52±0.54</td>
<td>(147)</td>
<td>-0.01±0.31</td>
<td>(147)</td>
<td>0.01±0.24</td>
<td>(149)</td>
<td>1.10±17.7</td>
<td>(149)</td>
<td>-0.02±0.27</td>
</tr>
<tr>
<td>24 months*</td>
<td>1.50±0.55</td>
<td>1.50±0.55</td>
<td>(72)</td>
<td>0.02±0.35</td>
<td>(72)</td>
<td>0.030±0.32</td>
<td>(76)</td>
<td>2.49±22.5</td>
<td>(76)</td>
<td>-0.02±0.34</td>
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<tr>
<td><strong>Mean-IMT (mm)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.34±0.51</td>
<td>1.29±0.46</td>
<td>(154)</td>
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<tr>
<td>12 months</td>
<td>1.28±0.42</td>
<td>1.30±0.49</td>
<td>(143)</td>
<td>-0.02±0.29</td>
<td>(142)</td>
<td>0.02±0.22</td>
<td>(147)</td>
<td>2.54±18.4</td>
<td>(147)</td>
<td>-0.03±0.26</td>
</tr>
<tr>
<td>24 months*</td>
<td>1.24±0.36</td>
<td>1.30±0.56</td>
<td>(71)</td>
<td>-0.06±0.40</td>
<td>(70)</td>
<td>0.08±0.33</td>
<td>(77)</td>
<td>5.90±26.7</td>
<td>(77)</td>
<td>-0.14±0.37</td>
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<td><strong>Bmax (mm)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.62±0.68</td>
<td>1.61±0.58</td>
<td>(151)</td>
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<tr>
<td>12 months</td>
<td>1.72±0.68</td>
<td>1.75±0.63</td>
<td>(137)</td>
<td>0.12±0.42</td>
<td>(135)</td>
<td>0.14±0.42</td>
<td>(144)</td>
<td>12.0±35.8</td>
<td>(144)</td>
<td>-0.02±0.42</td>
</tr>
<tr>
<td>24 months*</td>
<td>1.81±0.67</td>
<td>1.67±0.62</td>
<td>(70)</td>
<td>0.25±0.45</td>
<td>(69)</td>
<td>0.13±0.57</td>
<td>(75)</td>
<td>16.0±51.9</td>
<td>(75)</td>
<td>0.12±0.51</td>
</tr>
<tr>
<td><strong>Imax (mm)</strong></td>
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<tr>
<td>Baseline</td>
<td>1.26±0.65</td>
<td>1.18±0.58</td>
<td>(146)</td>
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</tr>
<tr>
<td>12 months</td>
<td>1.29±0.72</td>
<td>1.23±0.57</td>
<td>(134)</td>
<td>0.05±0.48</td>
<td>(133)</td>
<td>0.06±0.31</td>
<td>(139)</td>
<td>10.1±35.7</td>
<td>(139)</td>
<td>-0.01±0.40</td>
</tr>
<tr>
<td>24 months*</td>
<td>1.41±0.70</td>
<td>1.21±0.57</td>
<td>(68)</td>
<td>0.20±0.66</td>
<td>(65)</td>
<td>0.11±0.40</td>
<td>(69)</td>
<td>15.2±43.3</td>
<td>(69)</td>
<td>0.08±0.54</td>
</tr>
</tbody>
</table>

*Data of patients who had completed 24 months follow-up at study discontinuation. Data are mean±SD, ( ) = n. IMT, intima-media thickness.
**Statistical Analysis**

A sample size of 200 patients in each group was determined to detect a 0.35% difference (SD 1%) in the percent change in the mean-IMT between the rosvastatin group (assumed to have a percent change of 0.35%) and the pravastatin group (assumed to have a percent change of 0%) with a power of 0.90 and a 2-sided type-I error level of 0.05. These assumptions were obtained from the results of a previous trial.16

In the efficacy analysis, the full analysis set (FAS) was defined as the primary analysis set. The FAS included all randomized patients who met major eligibility criteria and received at least one dose of trial treatment and had at least one assessment for carotid IMT according to the guideline.22 The safety analysis included all patients who received at least one dose of trial treatment and had at least one safety assessment. Between-group comparisons at baseline were performed using the chi-square test. In the primary analysis, the percent change in the mean-IMT was compared between the treatment groups using a t-test. In the secondary analyses, the changes in continuous variables were compared using a t-test and the percent changes of categorical variables were compared using Fisher’s exact test. All data were analyzed by using SAS® System Release 9.2 (SAS Institute, Cary, NC, USA). All reported P values are 2-sided.

**Results**

**Trial Profile and Patient Population**

The trial was stopped on April 2011, according to the recommendation of the safety monitoring committee. The finding of superiority of rosvastatin led to the decision to terminate the trial. Therefore, we report the analysis of data at 12 months as the final results. Figure 1 is a flow diagram of the trial. A total of 348 patients (173 rosvastatin group; 175 pravastatin group) were enrolled into the study. Of these, 332 (167 rosvastatin group; 165 pravastatin group) were included in the safety analysis and 314 (159 rosvastatin group; 155 pravastatin group) were included in the FAS.

The demographic and baseline characteristics were well balanced between the treatment groups (Table 1). Approximately half of the patients were men. In both treatment groups, nearly half of the patients were classified into category III (primary prevention high-risk group) according to the JAS guideline.9 In addition, more than 60% of patients had hypertension and nearly half patients had DM (including impaired glucose tolerance). At 12 months, mean (SD) daily dose was 7.7 (2.8) mg for rosvastatin and 14.5 (5.0) mg for pravastatin.

**Carotid IMT**

Compared with pravastatin, rosvastatin significantly slowed progression of the mean-IMT (Table 2). Mean (SD) percent change in the mean-IMT at 12 months was 1.91% (10.9%) in the rosvastatin group and 5.80% (12.0%) in the pravastatin group, with a difference of −3.89% (11.5%) between the treatment groups (P=0.004). Similar results were obtained after adjusting for the mean-IMT at baseline (P=0.021). The mean percent change in the mean-IMT between the treatment groups (P=0.003) was smaller in the rosvastatin group, but the difference was not statistically significant (Table 2). Percent changes in the max-IMT, IMT-Bmax, and IMT-Imax were similar between the treatment groups.

**Serum Lipid Levels and Other Parameters**

As secondary endpoints, we analyzed the correlations between LDL-C/HDL-C and the mean-IMT, and the max-IMT, but neither of them was statistically significant.

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Compared with pravastatin, rosvastatin significantly lowered mean serum levels of LDL-C, TG, the LDL-C/HDL-C ratio, and non-HDL cholesterol (Table 3). The significant reduction in lipid parameters in both groups maximized at 2 months and continued during the study period. Rosuvastatin lowered the LDL-C level by 47.9%; mean (SD) serum level decreased from 163.8 (30.9) mg/dl at baseline to 83.7 (23.9) mg/dl at 12 months.

Both treatments improved lipid management. At 12 months, 145 patients (91.2%) in the rosvastatin group and 95 (61.3%) in the pravastatin group achieved the LDL-C goal recommended by the JAS guideline. In addition, rosvastatin significantly improved the LDL-C/HDL-C ratio. At 12 months, 85 patients (59.4%) in the rosvastatin group and 24 (16.4%) in the pravastatin group achieved LDL-C/HDL-C ≤1.5 (P<0.0001), while 124 (86.7%) and 64 (43.8%) achieved LDL-C/HDL-C ≤2.0, respectively (P<0.0001).

SBP and DBP (SD) were, respectively, 132.4/76.6 (17.0/11.1) mmHg at baseline, 128.9/73.0 (12.7/8.8) mmHg at 12 months and 130.1/75.3 (14.3/10.3) mmHg at 24 months in the rosvastatin group. Compared with baseline, SBP at 12 and 24 months and DBP at 12 months were significantly lowered (P=0.003, P=0.0002, P=0.016; respectively) in the rosvastatin group. In the pravastatin group, SBP/DBP (SD) were 131.0/74.9 (18.0/13.5) mmHg at baseline, 128.0/73.1 (13.5/10.3) mmHg...
at 12 months and 128.5/73.0 (13.5/7.7) mmHg at 24 months. There was no significant change during the study period in the pravastatin group. Between the treatment groups, both SBP and DBP showed no significant difference at 12 and 24 months.

**Cardiovascular and Cerebrovascular Events as a Secondary Endpoint for the Efficacy Evaluation**

At 12 months of treatment, a cardiovascular event occurred in one of the 159 patients in the rosuvastatin group and a cerebrovascular event occurred in one of the 155 patients in the pravastatin group and a cerebrovascular event occurred in one of the 155 patients in the pravastatin group. Among the patients with events, 22.2% and 39 events, 23.6%, respectively.

**Safety**

During the follow-up, 1 patient in the pravastatin group died (Table 4). The most common adverse event was myalgia (3.5% in the rosuvastatin group, 0% in the pravastatin group). Further, 5 patients (2.9%) in the rosuvastatin group and 1 (0.6%) in the pravastatin group reported arthralgia. Back pain occurred in 2 (1.2%) and 1 patient (0.6%) in the rosuvastatin and pravastatin groups, respectively. The most common laboratory changes were those of liver enzymes. In the rosuvastatin and pravastatin groups, respectively. The most common laboratory changes were those of liver enzymes. In the rosuvastatin and pravastatin groups, respectively. The most common laboratory changes were those of liver enzymes. In the rosuvastatin and pravastatin groups, respectively. The most common laboratory changes were those of liver enzymes. In the rosuvastatin and pravastatin groups, respectively.

Although “mild” adverse events that needed no treatment were imbalanced between the rosuvastatin (58 events, 34.7%) and pravastatin groups (24 events, 14.5%), there was no clinical meaningful difference in adverse events that needed any treatment (“moderate” plus “severe”) between the groups (37 events, 22.2% and 39 events, 23.6%, respectively).

**Discussion**

Our results have shown that intensive lipid-lowering therapy with rosvastatin slowed progression of the mean-IMT more effectively than conventional therapy with pravastatin in Japanese patients within a relatively short treatment period. At 12 months, the percent change in the mean-IMT was significantly lower in the rosuvastatin group. The mean-IMT was obtained by averaging 60 points of IMT at the far wall of the common carotid artery using Intimascope®. IMT at the far wall of the common carotid artery is a reliable marker for atherosclerosis, and the computer-automated IMT measurements with higher axial resolution are considered to be more reliable than the manual 3-point method. These factors support the reliability and precision of our results. The data of the max-IMT, IMT-Cmax, IMT-Bmax and IMT-Imax were less objective and reproducible than the data of the mean-IMT, because they were measured in each institution. This may be a reason why significant differences in the percent change between treatment groups were not observed.

This treatment effect on atherosclerotic progression was consistent with reports from recent studies. A prospective cross-sectional study of patients with asymptomatic CAD showed regression of the carotid IMT following 16 weeks of...
Effect of Rosuvastatin on IMT

In the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial, a 40-mg dose of rosuvastatin significantly slowed progression of the maximum IMT over the 12 carotid artery sites, including the common carotid, carotid bulb, and internal carotid, in middle-aged individuals.16 In the Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese subjects (COSMOS), a mean daily dose of 16.9 mg rosuvastatin induced regression of coronary plaque volume in patients with stable CAD.17 We consider this consistency, irrespective of ethnicity, indicates the beneficial effects of intensive therapy on atherosclerosis. Furthermore, in our trial the change in the mean-IMT in the rosuvastatin group, +0.012 mm, was similar to the annual increase of 0.01–0.015 mm in the common carotid artery ITM associated with aging in healthy Japanese.20 This result suggests that rosuvastatin may halt atherosclerosis progression caused by factors other than aging. Although we could not fully assess the treatment effects at 24 months because of the trial’s termination, rosuvastatin may further slow progression of atherosclerosis in the longer term, considering the results of the METEOR trial over 2 years.16

This beneficial effect on atherosclerosis seems to be mainly derived from the reduction in LDL-C levels. Japanese studies have reported that rosuvastatin has a strong LDL-C lowering effect and clinical benefit.24,25 In our trial, rosuvastatin lowered the mean LDL-C level to 83.7 mg/dl at 12 months (mean reduction, 47.9%), with a mean daily dose of 7.7 mg. In the METEOR trial and COSMOS, rosuvastatin also lowered the serum LDL-C level to approximately 80 mg/dl and this lipid-lowering effect led to slowing of progression or induction of regression of atherosclerosis.16,17 Another Japanese study has also shown that the incidence of cardiovascular events in increased when LDL-C levels were >80 mg/dl.26 Although the current JAS guideline recommends lowering the LDL-C level to 100–160 mg/dl according to the risk category of the patient,9 the findings indicate that intensive therapy to lower LDL-C to 80 mg/dl is beneficial in Japanese patients as well as Westerners. Though HbA1c increased 0.12% at 12 months from baseline in the rosuvastatin group (P=0.003) in this study, considering the total balance between benefit and safety, our results suggest that intensive lipid-lowering therapy with rosuvastatin is effective.

With regard to atherosclerosis regression, the serum HDL-
C level plays an important role. In a meta-analysis that combined raw data from 4 randomized trials, reduction of LDL-C to <87.5 mg/dl provided coronary atherosclerotic regression when accompanied by an approximately 7.5% increase in HDL-C. In that meta-analysis, the relationship between the change in percent atheroma volume and the LDL-C/HDL-C ratio was calculated, and the result was that the LDL-C/HDL-C ratio should be managed to <1.5 to decrease atheroma volume. In our trial, more than half of the patients achieved LDL-C/HDL-C ≤1.5 with the use of rosuvastatin. Although further study with a longer term is needed, our results indicate the favorable effect of rosuvastatin on the LDL-C/HDL-C ratio. Carotid IMT is associated with future risk of atherosclerotic vascular events. The Atherosclerosis Risk in Communities (ARIC) study has shown that for every 0.19-mm increment in carotid IMT, risk of death or myocardial infarction increased by 36% in middle-aged patients. In another study, patients with a mean-IMT >1.15 mm had a 94% likelihood of CAD. This predictive value of the carotid IMT has not yet been confirmed in Japanese patients, who have cardiovascular events less frequently than those in Western countries. However, even low-risk patients may benefit from intensive therapy. For example, the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER) trial included healthy persons without hyperlipidemia but with elevated levels of high-sensitivity C-reactive protein, and revealed that rosuvastatin significantly reduced the incidence of major cardiovascular events. That result suggests the possibility that favorable treatment effects may lead to a reduction in atherosclerotic events even in low-risk patients.

Study Limitations
Some limitations should be mentioned. First, we adopted the PROBE design, which might have induced bias in the assessment of the outcomes. Although the mean-IMT, the primary endpoint, was measured by a single observer who was blinded to the treatment assignments, the secondary endpoints were measured by investigators who were aware of the allocated treatments. Thus, open-label treatments might affect the investigators’ measurements. Second, we could not fully acquire data at 24 months because of early termination of the trial. Third, early termination also led to a reduction in statistical power to detect treatment effects on the secondary endpoints. Treatment effects of longer term treatment, including secondary endpoints, should be assessed in a future clinical trial.

Conclusions
Intensive lipid-lowering therapy with rosuvastatin slows progression of the mean-IMT within 12 months. To our knowledge, this is the first randomized controlled trial in Japan to assess the effects of lipid-lowering therapy on carotid IMT, and we have found that Japanese patients benefit from intensive therapy as well as those in Western countries. In addition, intensive therapy may reduce the risk of atherosclerotic vascular events. Further study is warranted to confirm the effects of rosuvastatin in the longer term. Currently, we are conducting an extension study and the results will be reported in the near future.

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**Appendix**

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