Aim: In Japan, heart disease and cerebral ischemic disease are major causes of death. A decrease in the level of low-density lipoprotein cholesterol (LDL-C) through intensive treatment with statins positively correlates with a reduction in the volume of plaques in patients with cardiovascular disease. The METEOR trial, evaluating the effect of rosuvastatin on carotid intima-media thickness (IMT), was conducted only in Europe and the US. Here we planned another trial, the Justification for Atherosclerosis Regression Treatment (JART) study, to clarify the efficacy of intensive lipid-lowering therapy with rosuvastatin in Japanese with atherosclerosis.

Methods and Results: Four hundred patients with hypercholesterolemia (LDL-C ≥140 mg/dL) and a maximum IMT of ≥1.1 mm will be treated for 24 months either with intensive lipid-lowering therapy with rosuvastatin (target LDL-C levels: 80 mg/dL for primary prevention, and 70 mg/dL for secondary prevention) or conventional lipid-lowering therapy with pravastatin (target LDL-C level: complying with JASGL2007). The primary endpoint will be the percent change of mean-IMT and the objectives of the study are to compare the two protocols.

Conclusion: The JART trial is a prospective, randomized, open-label, blinded end-point evaluation, multi-center, parallel-group, comparative study to examine the regressive effect of intensive lipid-lowering therapy with statins on atherosclerosis by evaluating IMT in the Japanese population.

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Key words: Atherosclerosis, Carotid intima-media thickness, Lipids, Rosuvastatin

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Introduction

In Japan, heart disease and cerebral ischemic disease are still ranked second and third, respectively, as causes of death. In particular, deaths from heart disease have continued to increase for the past several
years. Atherosclerosis is the major cause of morbidity and mortality in cases of coronary artery disease (CAD) and cerebral ischemic disease. Dyslipidemia has been established as a major pathogenic risk factor for CAD by epidemiologic, genetic, pathogenic, and controlled clinical studies. Large-scale clinical trials have clearly demonstrated that statins effectively reduce the risk of CAD in a wide range of patients.\(^1\)\(^-\)\(^6\)

A growing body of evidence indicates that intensive lipid-lowering therapy with statins, particularly in high-risk patients, slows the rate of atherosclerotic progression compared with moderate therapy. Von Birgelen C et al. found that a decrease in low-density lipoprotein cholesterol (LDL-C) levels positively correlated with a reduction in coronary plaque volume, and that the progression of coronary plaques could be suppressed by decreasing LDL-C levels to 75 mg/dL.\(^7\)

In addition, the Early Statin Treatment in Patients with Acute Coronary Syndromes (ESTABLISH) study, in which intensive lipid-lowering therapy with atorvastatin at 20 mg/day for 6 months was conducted in Japanese patients with acute coronary syndrome, has shown a decrease in LDL-C level of 41.7% and a decrease in coronary plaque volume of 13.1%, demonstrating their correlation.\(^8\) Moreover, the recent ASTEROID trial (A Study To Evaluate the effect of Rosuvastatin On Intravascular ultrasound-Derived coronary atheroma burden), which was conducted in the U.S. and Europe for 2 years using rosuvastatin at 40 mg/day to treat the progression of coronary atherosclerosis, has shown a decrease in LDL-C from 130.4 mg/dL to 60.8 mg/dL with a significant decrease in coronary plaque volume of 6.8%.\(^9\)\(^-\)\(^10\) Thus, intravascular ultrasound demonstrated that a lowering of plasma levels of LDL-C by statins can decrease plaque volume, and an elevation of levels of high-density lipoprotein cholesterol (HDL-C) may partly account for such a decrease. A meta-analysis, including the results of the ASTEROID trial, has shown that the LDL-C/HDL-C ratio is closely related to coronary plaque regression, and a decrease in atheroma volume was observed when the LDL-C/HDL-C ratio decreased to less than 1.5.\(^10\) Two prospective randomized studies evaluating the effects of statins on the volume of plaques in the coronary artery are being conducted in Japan.\(^11\)\(^-\)\(^12\)

Carotid intima-media thickness (IMT) is regarded as a surrogate marker of cardiovascular events in clinical trials of statins, since a decrease in carotid IMT correlates well with a decrease in the risk of cardiovascular events.\(^13\) A study to evaluate the effect of rosuvastatin on carotid IMT was conducted in the U.S. and Europe (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin: the METEOR trial).\(^14\) In that study, LDL-C was decreased from 155 to 78 mg/dL with a decrease in carotid IMT of 0.0014 mm/year after 2 years of treatment with rosuvastatin, demonstrating the suppression of carotid IMT progression by rosuvastatin while the placebo group showed a progression of 0.0131 mm/year.

In the present study, by evaluating changes in carotid IMT as the endpoint, we aim to compare intensive treatment with conventional treatment: in the former, lipid management will be conducted in reference to the target LDL-C level specified by the National Cholesterol Education Program-Adult Treatment Panel III (NCEP ATP III) with the objective of decreasing the incidence of coronary artery disease; and in the latter, the target level specified in the “Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases (2007)” recommended by the Japan Atherosclerosis Society (JASGL2007) will be adopted.

**Methods**

**Study Design**

A prospective, randomized, open-label, blinded end-point evaluation, multi-center, parallel-group, comparative study.

**Study Population**

Patients who have hypercholesterolemia and a maximum IMT ≥1.1 mm as measured with B-mode ultrasound at the posterior wall of the common carotid artery.

**Inclusion Criteria**

1. Patients giving written consent after being provided with sufficient explanation about participation in this clinical trial.
2. Patients aged 20 years or older at the time of giving consent (no limitation on gender or hospitalization status).
3. Patients with a serum LDL-C level ≥140 mg/dL (according to the diagnostic criteria in JASGL2007).
   
   LDL-C levels: measured directly or calculated with the Friedewald equation in the case of triglyceride (TG) < 400 mg/dL.
   
   \[(\text{LDL-C}) = (\text{Total cholesterol}) - (\text{HDL-C}) - \frac{\text{TG}}{5}\]
4. Patients with hypercholesterolemia and a maximum IMT ≥1.1 mm as measured by ultrasound (according to the diagnostic criteria for atherosclerosis in the Guidelines for Ultrasonic Assessment of Carotid Artery Disease).

...
Exclusion Criteria
(1) Patients that require lipid-lowering therapy other than with the study drug or specified lipid-lowering drugs (anion-exchange resin, probucol, and ethyl icosapentate (EPA)).
(2) Patients who have taken statins within 1 month of the start of the clinical trial.
(3) Patients suspected of having serious carotid artery stenosis (≥80%) or having serious calcification.
(4) Patients with familial hypercholesterolemia or secondary hypercholesterolemia.
(5) Patients with a fasting serum TG level ≥400 mg/dL.
(6) Patients with a history of sensitivity to statins.
(7) Patients with uncontrolled hypertension.
(8) Patients with Type 2 diabetes or uncontrolled Type II diabetes.
(9) Patients who have experienced myocardial infarction or a cerebral stroke within 3 months or patients with serious heart failure (New York Heart Association class III to IV).
(10) Patients with active hepatic disease.
(11) Patients with renal disorder [serum creatinine (Cr) level ≥2.0 mg/dL or creatinine clearance (Ccr) < 30 mL/min/1.73 m²].
(12) Patients with creatinine kinase (CK) level > 500 IU/L.
(13) Patients currently being treated with cyclosporine.
(14) Patients that are pregnant or potentially pregnant, patients breast-feeding, or patients aiming to become pregnant during the clinical trial.
(15) Patients with or suspected of having a malignant tumor, or patients with a history of malignant tumors except those in whom recurrences have not been confirmed by routine observation after treatment.
(16) Patients with hypothyroidism, hereditary muscular diseases (muscular dystrophy, etc.) or a familial history of these diseases. Patients with a history of drug-related muscular disorders.
(17) Patients with a history of drug abuse or alcoholism.
(18) Patients who are ineligible in the opinion of the investigator.

In advance of the initiation of the clinical trial, the protocol was approved by the appropriate institutional review board or an independent ethics committee at each site.

Medications and Treatment Period
The eligible patients will be randomly assigned to receive either intensive lipid-lowering treatment with rosuvastatin or conventional lipid-lowering treatment with pravastatin under the instructions of the registration center. For equalization between the arms, patients will be dynamically assigned based on i) maximum IMT, ii) serum LDL-C, iii) anamnestic diabetes (including abnormal glucose tolerance), and iv) institution. The patients will be administered rosuvastatin for 24 months at an initial dose of 5mg once daily or pravastatin at 10 mg once daily. If the initial treatment fails to reduce the target LDL-C level, the dose can be increased to 10 mg/day for rosuvastatin or 20 mg/day for pravastatin (Fig. 1). Furthermore, the investigator-in-charge is allowed to administer combination therapy with anion-exchange resin, probucol or EPA, if the increased dose of each test drug fails to reduce the target LDL-C level.

Sample Size
In the protocol, the assumptions used for power calculations require a sample size of 173 patients to provide 90% power (assuming a SD of 1.0%) and an alpha level of 0.05% for a two-sided test. It is there-
fore determined that the enrollment of 200 patients per treatment will provide an adequate number of patients considering possible discontinuations and dropouts.

**Observation Items and Schedule**

The observation items and schedule are shown in **Table 1**.

**Efficacy Evaluation**

**Primary Endpoint**

The percent changes from baseline in mean-IMT at the end of 24 months. The mean IMT is the average of the maximum IMTs before and after treatment.

**Secondary Endpoint**

The following 12 endpoints will be evaluated.

1. Time to percent change in mean-IMT.
2. Time to percent change in max-IMT of the distal wall of the common carotid artery (IMT-Cmax-distal wall).
3. Time to percent change in IMT-Cmax of the common carotid artery, IMT-Bmax of the carotid sinus, and IMT-Imax of the internal carotid artery.
4. Percentage of cases in which mean-IMT decreased at the end of 12 months and 24 months.
5. Time to percent change in the LDL-C/HDL-C ratio.
6. Percentage of cases in which the LDL-C/HDL-C ratio was ≤1.5 at the end of 12 months and 24 months.
7. Percentage of cases in which the LDL-C/HDL-C ratio was ≤2.0 at the end of 12 months and 24 months.
8. Correlation between the LDL-C/HDL-C ratio and max-IMT.
9. Correlation between the LDL-C/HDL-C ratio and mean-IMT.
10. Time to percent change of serum lipids (LDL-C, HDL-C, and TG), glycosylated hemoglobin (HbA1c), systolic blood pressure, and diastolic blood pressure.
11. JASGL2007 achievement ratio according to the management target level of LDL-C.
12. Cumulative incidence and content of cardiovascular and cerebrovascular events.

Cardiac events: myocardial infarction, angina pectoris, congestive heart failure, and coronary artery bypass graft

Cerebrovascular events: cerebral hemorrhage, cerebral infarction, subarachnoid hemorrhage, and transient ischemic attack

**Safety Evaluation**

Details and incidence of adverse events.

**Analysis Population**

Full Analysis Set (FAS): All allocated patients

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**Table 1. Items and schedule**

<table>
<thead>
<tr>
<th>Schedule</th>
<th>Registration</th>
<th>Treatment period</th>
</tr>
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<tbody>
<tr>
<td>VISIT 1</td>
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<td>VISIT 3</td>
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<td>VISIT 5</td>
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<td>18</td>
<td>24</td>
</tr>
<tr>
<td>(Completion)</td>
<td>Discontinue</td>
<td></td>
</tr>
</tbody>
</table>

**Items**

- Patients characteristics
- Blood pressure (Systolic, Diastolic)
- Carotid IMT measurement
- Blood chemistry
  - Other parameters except HbA1c
  - HbA1c
- Serum lipids
- Adverse events

Carotid IMT measurement: max-IMT, maximal carotid IMT, maximal carotid sinus IMT and maximal internal carotid artery IMT will be measured with a B-mode ultrasound at each study site. Mean-IMT will be determined in the laboratory. Carotid IMT measurements at VISIT 1 and VISIT 2 are for considering eligibility at each study site and obtaining baseline values for treatment in the laboratory, respectively.

Blood chemistry tests: aspartate aminotransferase, alanine aminotransferase, γ-glutamyl transpeptidase, blood urea nitrogen, creatinine, creatine kinase and HbA1c.

Serum lipids: total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol and triglycerides

IMT: intima-media thickness, HbA1c: glycosylated hemoglobin
except those who did not receive the test drug at all during the treatment period, patients whose IMTs were not measured at all during the observation and treatment periods, or patients for which the results of the efficacy evaluation were insufficient for analysis.

Per Protocol Set (PPS): The FAS population except patients who did not meet the inclusion and exclusion criteria, patients whose compliance with the therapy was less than 75%, patients who were administered a prohibited drug in the study protocol, or patients who had insufficient IMT data at the start and completion of the study.

Safety Population (SP): All allocated patients except those who did not receive the test drug at all during the treatment period, or patients who had no observation record after allocation of the study.

Statistical Analysis

Evaluation of Efficacy: In the FAS and PPS, the mean-IMT value at the start of the study will be used as a baseline for calculating the percent change in Month 24, as well as the two-sided 95% confidence interval. The two-sided level of significance will be set at \( p < 0.05 \).

Safety Evaluation: In the SP, the incidence of each adverse event will be calculated for each group. The basal analytical amount and incidence of abnormality for each parameter of laboratory tests will be calculated for each group.

Compliance with the Ethical Principles in Clinical Studies and the Declaration of Helsinki

The study is to be conducted in accordance with the Ethical Principles in Clinical Studies published by the Ministry of Health, Labor and Welfare of Japan and the ethical principles originating in the Declaration of Helsinki.

Privacy Protection of Study Patients

The study is to be conducted in compliance with the following points to protect the privacy of the study patients. The confidentiality of each patient’s information should be strictly maintained.

1. Attention to the treatment of medical records related to the study (including IMT image information, Informed Consent Form, etc.
2. Some patient information should not be inputted into the support system of the clinical study.
3. Patient anonymity must be maintained when the results of the study are published.
4. Data obtained from the study should not be used for any other purpose except the study objectives.
5. In the case where clinical samples are measured in other laboratories, the samples should be treated in accordance with the ethical guidelines of the clinical trial (assumed name, storage and disposal of the test drugs, limitation of access to data, etc).

Study Organization

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**Discussion**

Recent randomized clinical trials have confirmed that intensive LDL-C lowering therapy reduces the incidence of CAD in both primary and secondary prevention, and a meta-analysis of major statin trials revealed that the greater the reduction in LDL-C, the greater the reduction in risk for CAD\(^{15, 16}\). However, questions remain regarding the specific level of LDL-C needed to achieve the regression of carotid IMT.

In the METEOR trial, LDL-C was decreased to 78 mg/dL and carotid IMT was decreased by 0.0014 mm/year in the rosuvastatin (40 mg/day) group whereas the group given a placebo showed a progression of IMT after 2 years of follow-up\(^{14}\). However, the effect of rosuvastatin on IMT in Japanese patients has not yet been investigated. The present study was designed to evaluate this effect.

Carotid IMT is a highly reproducible and reliable measure\(^{17}\). A cardiovascular Health Study showed that asymptomatic persons without clinical symptoms or signs of cardiovascular disease 65 years of age or older had a higher risk of myocardial infarction or stroke, when their maximum IMT was 1.18 mm or more in the common and internal carotid artery\(^{18}\). In a nested case-control study in subjects selected from participants in the Rotterdam study, IMT of the common carotid was significantly increased in subjects with myocardial infarction compared to controls (1.17 mm vs 1.02 mm, \(p<0.05\))\(^{19}\). It has also been reported that increased carotid IMT relates to an increase in the risk of cardiovascular disease even in asymptomatic individuals including young populations\(^{20, 21}\), and carotid IMT is useful as a surrogate marker for cardiovascular events in intervention studies\(^{22}\). Particularly in studies of statins, carotid IMT has proved a highly reliable surrogate marker; a decrease in carotid IMT correlates well with a decrease in the risk of cardiovascular events\(^{13}\). B-mode ultrasound is widely used in clinical practice to measure carotid IMT non-invasively. However, this technique is likely to cause inter-institutional variation in measurements due to differences in the device used, and non-uniformity of the protocol involved etc. In the present study, the endpoint, changes of carotid IMT, will be evaluated in the IMT Core Laboratory in a blinded manner, to adequately maintain objectivity, scientific credibility, and ethics. This study will be conducted as a multi-center, prospective, randomized, open-label, evaluator-blinded, parallel-group, comparative study that incorporates a safety evaluation committee and statistical experts, to evaluate the effect of rosuvastatin on carotid IMT.

In a high-resolution magnetic resonance imaging trial to evaluate the effect of rosuvastatin therapy on the morphology and composition of carotid plaques in moderately hypercholesterolemic patients (the ORION trial), treatment with rosuvastatin at 5 mg/day and 40 mg/day for 2 years decreased LDL-C levels from 153.6 mg/dL to 95.0 mg/dL and from 145.0 mg/dL to 57.7 mg/dL, respectively, leading to a 41.4% decrease from baseline in the lipid-rich necrotic core\(^{23}\). In the METEOR trial, significant suppression of carotid IMT was observed when the LDL-C level was decreased to 78 mg/dL by treatment with rosuvastatin at 40 mg/day for 2 years\(^{44}\). Also in the ASTEROID trial, a significant decrease in coronary plaque volume was observed when the LDL-C level was decreased to 60.8 mg/dL by intensive treatment with rosuvastatin at 40 mg/day for 2 years\(^{29}\).

Based on the results of these studies, we decided to compare changes in carotid IMT between an intensive treatment group and a conventional treatment group: in the former group, lipid management will be conducted with reference to the target LDL-C level specified by NCEP ATP III with the objective of decreasing the incidence of coronary artery disease; and in the latter group, the target level specified in the JASGL2007 will be adopted. If carotid IMT regression is not evident in the conventional group but is observed in the intensive treatment group, this study will provide new insight and guidance for the target level of LDL-C in order to induce regression of atherosclerosis in the Japanese population.

**Acknowledgments**

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