Circulation Journal
Official Journal of the Japanese Circulation Society
http://www.j-circ.or.jp

ORIGINAL ARTICLE
Metabolic Disorder

Effect of Long-Term Intensive Lipid-Lowering Therapy With Rosuvastatin on Progression of Carotid Intima-Media Thickness

– Justification for Atherosclerosis Regression Treatment (JART) Extension Study –

Ryuji Nohara, MD; Hiroyuki Daida, MD; Mitsumasa Hata, MD; Kohei Kaku, MD; Ryuzo Kawamori, MD; Junji Kishimoto, PhD; Masahiko Kurabayashi, MD; Izuru Masuda, MD; Ichiro Sakuma, MD; Tsutomu Yamazaki, MD; Hiroyoshi Yokoi, MD; Masayuki Yoshida, MD
for the Justification for Atherosclerosis Regression Treatment (JART) Investigators

Background: Recently, it was reported from the Justification for Atherosclerosis Regression Treatment (JART) Study that intensive therapy with rosuvastatin significantly slowed progression of carotid intima-media thickness (IMT) compared with conventional therapy with pravastatin at 12 months. To assess the long-term efficacy of intensive therapy, the present extension study was conducted.

Methods and Results: Subjects in the intensive therapy group of the JART Study were asked to participate in the extension study and to continue rosuvastatin treatment. A total of 113 subjects were enrolled into the extension study and were included in the analysis. At 24 months, the mean daily dose of rosuvastatin (±SD) was 7.9±2.9 mg. Mean change in mean IMT was –0.005 mm (range, –0.024 to 0.015 mm) at 24 months (P=0.633, compared with baseline). Rosuvastatin lowered low-density lipoprotein cholesterol (mean±SD) by 46.4±13.8% and elevated high-density lipoprotein cholesterol (mean±SD) by 8.9±24.0% at 24 months compared with baseline. Gray scale median was measured in 25 subjects. It increased by 16.93±33.12 (mean±SD) % at 12 months and by 22.50±52.83% at 24 months from baseline (P=0.017, P=0.044, respectively).

Conclusions: Two-year treatment with rosuvastatin inhibited progression of carotid IMT. Rosuvastatin also improved the plaque composition, and this qualitative change occurred relatively early after starting therapy. (*Circ J* 2013; **77:** 1526–1533)

Key Words: Carotid intima-media thickness; Clinical trial; Dyslipidemia; Hydroxymethylglutaryl-CoA reductase inhibitors; Rosuvastatin

Received September 17, 2012; revised manuscript received January 11, 2013; accepted January 30, 2013; released online March 14, 2013 Time for primary review: 38 days

Cardiovascular Center, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, Osaka (R.N.); Department of Cardiology, Juntendo University School of Medicine, Tokyo (H.D.); Department of Cardiovascular Surgery, Nihon University School of Medicine, Tokyo (M.H.); Division of Diabetes, Endocrinology and Metabolism, Department of Medicine, Kawasaki Medical School, Kurashiki (K.K.); Sportology Center, Juntendo University Graduate School of Medicine, supported by High Technology Research Center Grant from the Ministry of Education, Culture, Sports, Science and Technology of Japan, Tokyo (R.K.); Center for Clinical and Translational Research, Kyushu University Hospital, Fukuoka (J.K.); Department of Medicine and Biological Science, Gunma University Graduate School of Medicine, Maebashi (M.K.); Takeda Hospital Medical Examination Center, Kyoto (I.M.); Hokko Memorial Clinic Caress Sapporo, Sapporo (I.S.); Clinical Research Support Center, The University of Tokyo Hospital, Tokyo (T.Y.); Department of Cardiology, Kokura Memorial Hospital, Kitakyushu (H.Y.); and Department of Life Sciences and Bioethics, Graduate School of Medicine, Tokyo Medical and Dental University, Tokyo (M.Y.), Japan

Members are listed in the **Appendix 1**.

Name(s) of grants: Japan Heart Foundation.

Mailing address: Ryuji Nohara, MD, Cardiovascular Center, Kitano Hospital, The Tazuke Kofukai Medical Research Institute, 2-4-20 Ohgimachi, Kita-ku, Osaka 530-8480, Japan. E-mail: noharar@kitano-hp.or.jp

ISSN-1346-9843 doi:10.1253/circj.CJ-12-1149

Continuous accumulation of atherosclerotic plaque is one of the major risk factors for cardiovascular disease. Previous studies using intravascular ultrasound (IVUS) have shown the effects of 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors (statins) on progression of atherosclerosis.[1–6] These imaging studies also enabled quantitative analysis to investigate the relationship between changes in serum lipids and atheroma volume. A recent meta-analysis using data from imaging studies has shown that regression of atheroma volume can occur when the substantial reduction in low-density lipoprotein cholesterol (LDL-C) is accompanied by an increase in high-density lipoprotein cholesterol (HDL-C).[7] These studies, however, generally included patients who required coronary angiography. Therefore, they were mainly secondary prevention patients.

Carotid artery intima-media thickness (IMT) is a reliable surrogate marker for cardiovascular events.[8–12] O'Leary et al showed that increases in carotid IMT are directly associated with an increased risk of cardiovascular events.[9] It is an intermediate phenotype for early atherosclerosis and can be measured relatively simply and non-invasively on B-mode ultrasound.[10] For these reasons, it has been increasingly used as an endpoint in clinical trials. For example, a recent randomized controlled trial has shown that rosuvastatin slowed progression of maximum carotid IMT in middle-aged individuals with modest carotid IMT thickening.[13] In addition, mean IMT has provided advantages in predicting the risk for cardiovascular events. Mean IMT is obtained by averaging 60 points of IMT at the carotid artery, using Intimascope®. This computer-automated IMT measurement is considered to be more reliable than the established 3-point method.[14]

On the basis of these findings, we designed the Justification for Atherosclerosis Regression Treatment (JART) Study to determine whether intensive lipid-lowering therapy with rosuvastatin is more effective than conventional therapy with pravastatin in slowing atherosclerotic progression by measuring mean IMT.[15] This was a randomized controlled study with a planned follow-up period of 24 months and was stopped according to the recommendation of the data and safety monitoring committee, which reviewed the results of the interim 12-month analysis. It was found that intensive therapy significantly slowed progression of carotid IMT compared with conventional therapy in Japanese subjects,[16] but we could not determine whether intensive therapy further reduces the plaque volume in the longer term because the study was stopped at 12 months.

Accordingly, we conducted the JART Extension Study to assess the long-term effect of intensive lipid-lowering therapy on progression of carotid IMT. The risk of rupture of an atherosclerotic plaque is not only dependent on the plaque size but on the composition of the plaque.[17] Vulnerable plaque is typically characterized by a thin fibrous cap and increased accumulation of lipids and inflammatory cells.[17] This plaque morphology can be assessed as gray scale median (GSM). Thus, we also explored the effects of long-term intensive lipid-lowering therapy on GSM.

Methods

The design and results of the JART Study have been reported previously.[15,16]

Study Design and Ethics Considerations

The JART studies consisted of a prospective, randomized, open-label, blinded-endpoint study and a subsequent open-label extension study. In the randomized study, subjects were assigned to receive rosuvastatin (intensive therapy) or pravastatin (conventional therapy). After the randomized study was stopped, subjects in the intensive therapy group were asked to participate in the extension study and to continue the treatment with rosuvastatin. Patients in the conventional therapy group did not participate in the extension study. Both studies were conducted in accordance with the Declaration of Helsinki and the ethical principles for clinical studies in Japan. Their protocols were reviewed and approved by the institutional review board of each participating center. All subjects provided written informed consent.

Eligibility Criteria

In this study, subjects aged ≥20 years were eligible if they had elevated LDL-C (≥140 mg/dl) and maximum IMT ≥1.1 mm measured at the carotid artery. Serum LDL-C was measured on direct homogeneous assay. Otherwise, serum LDL-C was calculated from the following Friedewald formula.[18]

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

Subjects were excluded if they required lipid-lowering agents other than pre-specified ones (ie, anion-exchange resin, probucol, and ethyl icosapentate); had received statin therapy within 1 month before starting the randomized study; had suspected severe carotid artery stenosis or severe calcification; had familial hypercholesterolemia or secondary hypercholesterolemia; had fasting serum TG ≥400 mg/dl; had a history of hypersensitivity to statins; had uncontrolled hypertension; had type 1 diabetes or uncontrolled type 2 diabetes; experienced myocardial infarction or stroke within 3 months; had severe congestive heart failure, active hepatic disease, renal disorder, or creatine kinase (CK) >500 IU/L. Pregnant women, breast-feeding women, or women who were potentially pregnant during the study were also excluded.

Treatment

In the randomized study, subjects in the intensive therapy group received rosuvastatin 5 mg/day as a starting dose. The daily dose of rosuvastatin was increased to 10 mg if the subject did not achieve the following LDL-C goal: <80 mg/dl for primary prevention and <70 mg/dl for secondary prevention. If the subject did not achieve the LDL-C goal after the dose of rosuvastatin was increased, pre-specified lipid-lowering agents were added thereafter. In the extension study, the dose of rosuvastatin was increased and other agents were added in the same manner.

Outcome Measures

Medical histories were obtained from all subjects before enrollment of the randomized study. Laboratory data including serum lipids were obtained at baseline. Follow-up visits were scheduled at 1, 2, 4, 6, 12, 18, and 24 months throughout the randomized and extension studies. At each visit, serum lipids were measured and treatment compliance was investigated. Laboratory tests were performed at 1, 4, 6, 12, and 24 months. Laboratory data were analyzed at the central laboratory. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) were measured at 0 (baseline), 12, and 24 months.

Subjects were scheduled to undergo ultrasonography at 0 (within 3 months before enrollment), 12, and 24 months. B-mode images were obtained according to the guidelines for ultrasonic assessment of carotid artery disease.[19] 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

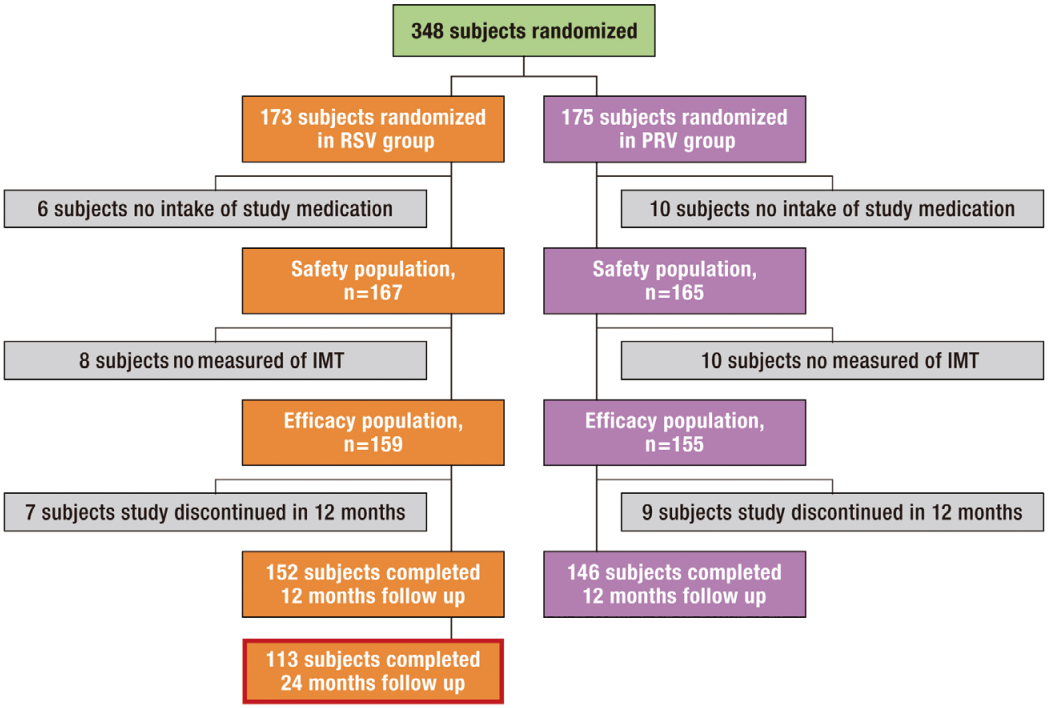

Figure 1. Flow chart of the Justification for Atherosclerosis Regression Treatment and extension studies. IMT, intima-media thickness; PRV, pravastatin; RSV, rosuvastatin.

measured at the far wall of the common carotid artery in which the eligibility criterion of maximum IMT ≥1.1 mm was confirmed. Mean IMT was measured in the core laboratory using Intimascope® (Media Cross, Tokyo, Japan).[14] It averaged 60 points of IMT in the segment 2 cm proximal to the dilation of the carotid bulb. GSM was measured with the method described by Elatrozy et al.[20] For the measurement of GSM, a single experienced technician who was blinded to the subject profile and IMT analyzed the images. GSM was measured in subjects who had baseline mean IMT ≥1.0 mm. The image is obtained under the condition of clear difference between blood area and intima area on the standardization using black. Outlines of an area of plaque, blood, and brightest adventitia at the level of the plaque were drawn in the segment 2 cm proximal to the dilation of the carotid bulb on the B-mode image. The gray scale value of each pixel in the outlined region (0–255; 0, black; 255, white) was used to calculate the GSM. Measurement of GSM was done using Dipp-Image® (DITECT, Tokyo, Japan).

The primary endpoint was the change in mean IMT from baseline to the end of 24 months. The secondary endpoints included GSM, serum lipids, and LDL-C/HDL-C ratio.

Statistical Analysis

The demographic and baseline characteristics are summarized descriptively. In the efficacy analysis, the changes in outcomes from baseline to 12 and 24 months were assessed using paired t-test. In the safety analysis, the frequency and percentage of each adverse drug reaction were summarized descriptively. All data were analyzed using SAS® System Release 9.2 (SAS Institute, Cary, NC, USA). All reported P-values are 2-sided without adjustments for multiple testing.

Results

Trial Profile and Subjects

Figure 1 shows the flow chart of the study. In the rosuvastatin group of the randomized study, 152 subjects completed follow-up during 12 months. Of these, 39 subjects did not participate in the extension study and 113 were included in the final analysis at 24 months.

Table 1 lists the subject demographic and baseline characteristics. Important characteristics were similar to those in the randomized study. Nearly half of the subjects were classified into category III (primary prevention high-risk group) according to the Japan Atherosclerosis Society guidelines.[21] In addition, >60% of subjects had hypertension and nearly half had diabetes (including impaired glucose tolerance [IGT]). At 24 months, the mean daily dose of rosuvastatin (±SD) was 7.9±2.9 mg. A 75% medication adherence rate was achieved in 98.2% (107 subjects) over the study period.

Carotid IMT

Figure 2 shows the changes in mean IMT at 12 and 24 months. The mean IMT (±SD) was 0.916±0.188 mm at baseline (n=113), 0.928±0.190 mm at 12 months and 0.912±0.170 mm at 24 months. Mean change was 0.012±0.082 mm (95% confidence interval [CI]: –0.004 to 0.027 mm) at 12 months and –0.005±0.104 mm (95% CI: –0.024 to 0.015 mm) at 24 months. These changes were not statistically significant as compared with baseline (P=0.141, P=0.633, respectively). The results were unaffected when adjusted for age and gender.

Table 1. Subject Baseline Characteristics

	Rosuvastatin (n=113)
Male	56 (49.6)
Age (years)	63.9±8.1
Elderly (≤65)	58 (51.3)
Blood pressure (mmHg)	
Systolic	133.8±18.2
Diastolic	76.3±11.5
JASGL2007 category	
I	1 (0.9)
II	36 (31.9)
III	56 (49.6)
Secondary prevention	20 (17.7)
CAD risk factors	
Family history of premature CAD	23 (20.4)
Smoking	16 (14.2)
Medical history	
Hypertension	78 (69.0)
Diabetes mellitus	51 (45.1)
Low HDL-C	9 (8.0)
Cerebral infarction	7 (6.2)
Peripheral arterial disease	4 (3.5)
CAD	20 (17.7)
Mean daily dose at 24 months (mg)	7.9±2.9
Other medications	
Anti-hypertensive	68 (60.2)
Anti-diabetic	27 (23.9)
LDL-C (mg/dl)†,‡	164.8±34.1
Max-IMT (mm)	1.48±0.51
HbA_{1c} (NGSP) (%)§	6.27±0.84

Data given as mean±SD or n (%).
†Friedewald formula, LDL-C=total cholesterol–HDL-C–(TG/5). ‡n=111, because of missing measurements. §n=109, because of missing measurements.
CAD, coronary artery disease; HbA_{1c}, hemoglobin A_{1c}; HDL-C, high-density lipoprotein cholesterol; IMT, intima-media thickness; JASGL, Japan Atherosclerosis Society Guidelines; LDL-C, low-density lipoprotein cholesterol; NGSP, National Glycohemoglobin Standardization Program; TG, triglyceride.

Mean IMT had decreased in 49 subjects (43.4%) at 12 months and in 54 subjects (47.8%) at 24 months.

GSM

GSM was measured in 25 subjects who had baseline mean IMT ≥1.0 mm. As compared with baseline, GSM (mean±SD) increased by 16.93±33.12% (P=0.017) at 12 months and by 22.50±52.83% (P=0.044) at 24 months, whereas mean IMT decreased by 1.36±9.42% (P=0.478) and by 5.16±10.26% (P=0.019) in the same subjects, respectively. Figure 3 shows the relationship between the changes in GSM and mean IMT in subjects with both measurements. GSM significantly increased at 12 months (P=0.017, compared with baseline) and at 24 months (P=0.044, compared with baseline), but the change in GSM between 12 and 24 months was not statistically significant (P=0.564). In contrast, the change in mean IMT between baseline and 12 months was not statistically significant (P=0.478), whereas a significant decrease in mean IMT occurred at 24 months (P=0.019, compared with baseline).

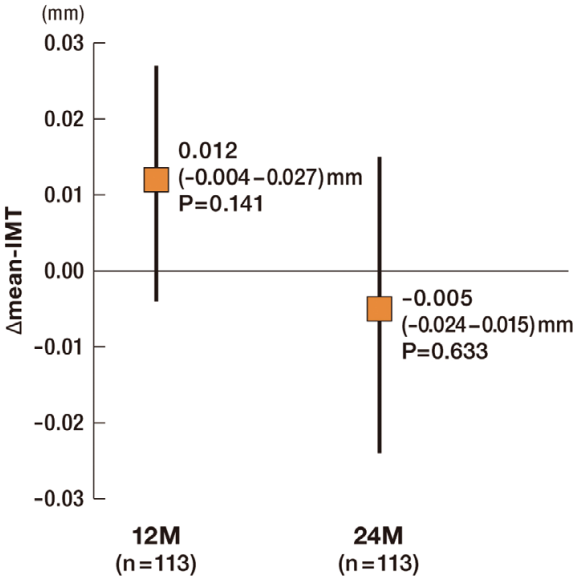

Figure 2. Changes in intima-media thickness (IMT) during treatment with rosuvastatin at 12 and 24 months. Data given as mean (95% confidence interval). P-value was calculated using paired t-test.

Serum Lipids and Other Laboratory Variables

Table 2 lists the changes in serum lipids and LDL-C/HDL-C ratio. Rosuvastatin significantly improved mean serum lipid levels and LDL-C/HDL-C ratio. It lowered LDL-C (mean±SD) by 46.4±13.8%; the mean LDL-C decreased from 164.8±34.1 mg/dl at baseline to 86.5±19.7 mg/dl at 24 months. It also elevated HDL-C (mean±SD) by 8.9±24.0%. According to these favorable changes in LDL-C and HDL-C, the mean LDL-C/HDL-C ratio (±SD) decreased to 1.6±0.5 at 24 months with the percent reduction of 49.3±13.8%. In addition, rosuvastatin improved the lipid management. At 24 months, 104 subjects (92.0%) achieved the LDL-C goal recommended by the Japan Atherosclerosis Society guidelines. At the same time point, 54 subjects (51.4%) achieved LDL-C/HDL-C ratio ≤1.5, whereas 85 subjects (81.0%) achieved LDL-C/HDL-C ratio ≤2.0.

The mean HbA_{1c} (±SD) was 6.3±0.8% at baseline and 6.5±0.9% at 24 months. The mean SBP/DBP (±SD) was 133.8±18.1/76.3±11.5 mmHg and 129.9±15.1/74.2±10.0 mmHg, respectively. Simple linear regression analysis did not show any meaningful relationship between the changes in blood pressures and HbA_{1c}, and mean IMT (data not shown).

Safety

During the follow-up, 1 subject had a cerebrovascular event.

Table 3 lists the adverse drug reactions during follow-up. Adverse drug reactions occurred in 12 subjects (10.6%), but no serious events were reported. Arthralgia, back pain, and myalgia occurred in 3, 1, and 2 subjects, respectively. One subject experienced IGT. The common laboratory changes were those of liver enzymes. Alanine aminotransferase (ALT) increased in 2 subjects, and aspartate aminotransferase (AST) increased in 1 subject. In addition, CK increased in 2 subjects. No subjects discontinued rosuvastatin due to adverse drug reactions (laboratory IGT was defined by each institution, and increases in ALT, AST, and CK were defined as a 3-fold increase of upper limits of normal at each institution).

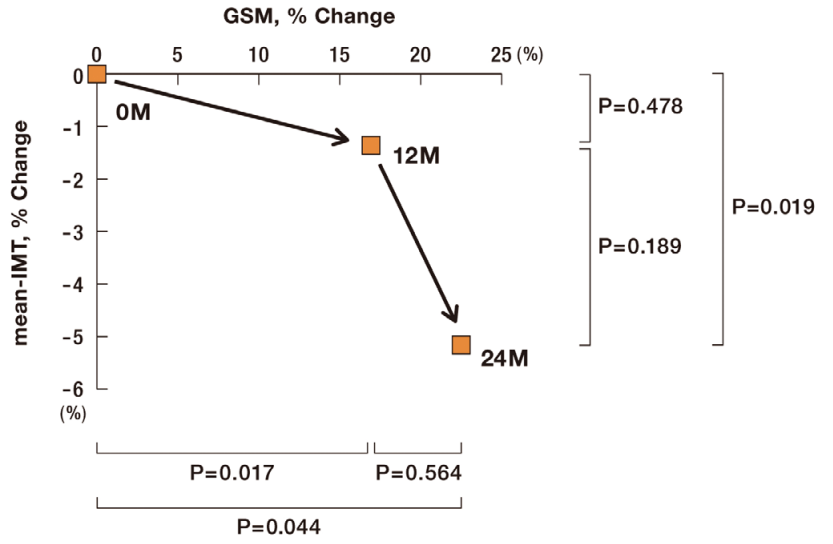

Figure 3. The relationship between the percent changes in gray scale median (GSM) and mean intima-media thickness (IMT) at 12 and 24 months in subjects (n=25) with baseline mean IMT ≥1.0 mm. P-value was calculated using paired t-test.

Table 2. Changes in Serum Lipids at 12, 24 Months

		Change (%)	P-value†
LDL-C‡ (mg/dl)			
Baseline	164.8±34.1 (111)		
12 months	82.7±21.1 (112)	−48.2±16.9 (111)	<0.0001
24 months	86.5±19.7 (105)	−46.4±13.8 (104)	<0.0001
HDL-C (mg/dl)			
Baseline	53.8±11.9 (112)		
12 months	58.2±13.6 (112)	9.3±17.9 (112)	<0.0001
24 months	57.1±14.3 (106)	8.9±24.0 (106)	0.0002
LDL-C‡/HDL-C ratio			
Baseline	3.2±0.9 (111)		
12 months	1.5±0.5 (112)	−51.6±17.2 (111)	<0.0001
24 months	1.6±0.5 (105)	−49.3±13.8 (104)	<0.0001
Non-HDL-C (mg/dl)			
Baseline	194.7±35.0 (112)		
12 months	106.2±22.5 (112)	−44.3±13.7 (112)	<0.0001
24 months	110.4±21.6 (106)	−42.3±13.1 (106)	<0.0001
TG (mg/dl)			
Baseline	153.9±85.8 (112)		
12 months	117.5±54.3 (112)	−13.9±39.4 (112)	0.0003
24 months	122.0±73.6 (106)	−13.4±44.8 (106)	0.0026

Data given as mean±SD (n). †Paired t-test. ‡Friedewald formula, LDL-C=total cholesterol–HDL-C–(TG/5). Abbreviations as in Table 1.

Discussion

We previously reported that 1-year intensive lipid-lowering treatment with rosuvastatin was more effective in slowing progression of carotid IMT than conventional lipid-lowering treatment with pravastatin in the JART Study.[16]

The change in mean IMT in the rosuvastatin group at 12 months was similar to the annual increase of 0.01–0.015 mm in the common carotid artery IMT associated with aging.[19] This indicates that rosuvastatin may halt atherosclerotic progression caused by factors other than aging. In the present study, 2-year treatment with rosuvastatin might induce regression of carotid IMT with regard to progression of carotid IMT with aging. Although not statistically significant, the mean change in mean IMT was <0 mm at 24 months. In addition, the change in mean IMT at 12 months in the extension group (0.012±0.082 mm; 95% CI, −0.004 to 0.027 mm; n=113) was similar to the result in the JART rosuvastatin group at 12 months (0.012±0.093 mm; 95% CI, −0.003 to 0.027 mm; n=145). To consider the clinical meaning of these studies, we summarized the change of mean IMT using the data of the rosuvastatin group in the JART Study at 12 months and the extension group at 24 months. Because carotid IMT is a reliable predictor of cardiovascular events,[8–12] the present finding

supports "the longer, the better" hypothesis, whereas that of the randomized study supports "the lower, the better" hypothesis in Japanese subjects.

Effects of statins on progression of atherosclerosis have been well established. In A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden (ASTEROID), 2-year treatment with rosuvastatin 40 mg resulted in regression of coronary atherosclerosis.[2] 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 at the end of 76-week follow-up.[3] Furthermore, in the Study of Coronary Atheroma by Intravascular Ultrasound: Effect of Rosuvastatin versus Atorvastatin (SATURN), maximum doses of rosuvastatin and atorvastatin resulted in significant regression of coronary atherosclerosis after 2 years of treatment.[22] These studies, however, included secondary prevention patients, who are generally at the highest risk for cardiovascular events. In contrast, the Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin (METEOR) trial included low-risk individuals with mild atherosclerosis and showed that 2-year treatment with rosuvastatin 40 mg did not result in significant regression of atherosclerosis although it significantly slowed progression.[13] The present result suggests that long-term intensive therapy would be expected to induce atherosclerotic regression in Japanese subjects, who are at relatively low risk for cardiovascular events.

The beneficial effect of intensive therapy on plaque volume was mainly derived from modulation of serum lipid levels. In the present study, rosuvastatin lowered mean LDL-C to 86.5 mg/dl at a mean daily dose of 7.9 mg. This indicates that intensive therapy to lower LDL-C to 80 mg/dl is beneficial in Japanese subjects. In addition, rosuvastatin elevated HDL-C by 8.9% and decreased mean LDL-C/HDL-C ratio to 1.6. In a recent meta-analysis, reduction of LDL-C to <87.5 mg/dl provided coronary atherosclerotic regression when accompanied by an approximately 7.5% increase in HDL-C.[7] That meta-analysis has also shown that LDL-C/HDL-C ratio should be managed to <1.5 to decrease atheroma volume. The present results are consistent with those of the meta-analysis and indicate the importance of managing LDL-C/HDL-C ratio in the long term.

Recently, Lorenz et al reported a meta-analysis on the association between cardiovascular risk and change of carotid IMT.[23] They considered, however, only the quantity of plaque; it may be important to take into account the quality in addition to the quantity. Soeda et al reported that lipid-lowering therapy with statins may reduce plaque volume and stabilize vulnerable plaque.[24] We also explored the relationship between changes in composition and volume of plaque. We found that a significant increase in GSM occurred at 12 months followed by a significant decrease in mean IMT at 24 months. Echogenic plaque has a more stable phenotype and is associated with lower risk for cardiovascular events, whereas echolucent plaque contains more lipid and less fibrous tissue.[25–27] Thus, the present results suggest that a qualitative change in plaque may occur relatively early after starting intensive therapy, followed by a quantitative change. A previous study using angioscopy and IVUS has shown similar results.[28] In that study, subjects with coronary artery disease were treated with atorvastatin, and serial analysis showed early loss of yellow color in plaque and subsequent plaque regression. Because the reduction in yellow color intensity is attributable to a change in the thickness of the fibrous cap, these changes suggested that the improvement in plaque characteristics occurs early, whereas the reduction in atheroma volume occurs over a prolonged period.[28] The beneficial effect of statin on the thickness of the fibrous cap was also reported in a study using intravascular optical coherence tomography.[29]

Rosuvastatin was well-tolerated during the 2-year follow-up. No serious adverse drug reaction was reported. Relatively few patients experienced myopathy or hepatotoxicity – the most clinically important adverse reactions of statins – such as muscle symptoms, and increases in CK, ALT, or AST. In the analysis of other laboratory variables, mean HbA_{1c} increased and mean SBP and DBP decreased during treatment, but these changes were thought not to be clinically meaningful. Although IGT occurred in only 1 subject, the changes in HbA_{1c}, SBP and DBP did not affect progression of carotid IMT.

Table 3. Adverse Drug Reactions During Follow-up

	Rosuvastatin (n=113)
Serious	0 (0)
Not serious	12 (10.6)
Infections and infestations	
Cystitis	1 (0.9)
Metabolism and nutrition	
IGT†	1 (0.9)
Nerve	
Headache	1 (0.9)
Gastrointestinal	
Abdominal discomfort	2 (1.8)
Nausea	1 (0.9)
Hepatobiliary	
Liver function abnormality	1 (0.9)
Skin and subcutaneous tissue	
Eczema	1 (0.9)
Generalized rash	1 (0.9)
Pruritic rash	1 (0.9)
Musculoskeletal and connective tissue	
Arthralgia	3 (2.7)
Back pain	1 (0.9)
Myalgia	2 (1.8)
Heaviness	2 (1.8)
Musculoskeletal stiffness	1 (0.9)
Kidney	
Hematuria	1 (0.9)
General disorders and injection site conditions	
Ineffectiveness	2 (1.8)
Discomfort	1 (0.9)
Malaise	2 (1.8)
Peripheral edema	1 (0.9)
Laboratory tests	
ALT increased‡	2 (1.8)
AST increased‡	1 (0.9)
CK increased‡	2 (1.8)
GGT increased	1 (0.9)

Data given as n (%).
†As defined by each institution. ‡Defined as 3-fold increase of upper limits of normal in each institution.
ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; GGT, γ-glutamyltransferase; IGT, impaired glucose tolerance.

Study Limitations

Some limitations should be mentioned. First, we adopted an open-label design, which might induce bias in assessing the outcomes. Although mean IMT was measured using computer software, the observer knew whether the datum was obtained at baseline or follow-up. Second, we did not enroll subjects in the conventional therapy group of the JART Study. Thus, the sample size was too small to obtain statistically significant changes in the primary endpoint. The JART Study was initially planned to continue for 24 months, but was stopped at 12 months on the recommendation of the safety and monitoring committee. The JART Extension Study was then conducted to assess the long-term efficacy of intensive lipid-lowering therapy in the rosuvastatin group in the JART Study. This placed an inherent limitation on the sample size, but although this sample size does not provide sufficient power for statistical significance, we feel that the trend identified in this study will be of interest because of the large number of patients potentially affected. Third, GSM was evaluated in a limited number of subjects. This led to a reduction of statistical power to detect the treatment effect on GSM.

Conclusions

First, long-term intensive lipid-lowering therapy with rosuvastatin inhibited progression of carotid IMT and improved the plaque composition in Japanese subjects. Second, qualitative change in plaque may occur relatively early after starting intensive therapy. We also found that long-term intensive therapy was well-tolerated. Further study is warranted to confirm the effects of long-term intensive therapy on the quality and quantity of atherosclerotic plaque in Japanese subjects.

Acknowledgments

A Japan Heart Foundation Research Grant supported this study registered to the University hospital Medical Information Network (UMIN) as ID UMIN000005774.

Disclosures

Ryuji Nohara, MD, received lecture fees from AstraZeneca K.K. and Daiichi Sankyo Co, Ltd, and scholarship funds from AstraZeneca K.K.. Hiroyuki Daida, MD, received lecture fees from AstraZeneca K.K., Shionogi & Co, Ltd and Daiichi Sankyo Co, Ltd, and scholarship funds from AstraZeneca K.K., Shionogi & Co, Ltd and Daiichi Sankyo Co, Ltd. Mitsumasa Hata, MD, received lecture fees from AstraZeneca K.K. and Shionogi & Co, Ltd, and scholarship funds from AstraZeneca K.K.. Kohei Kaku, MD, received scholarship funds from Daiichi Sankyo Co, Ltd. Ryuzo Kawamori, MD, and Tsutomu Yamazaki, MD, received lecture fees from AstraZeneca K.K. and Shionogi & Co, Ltd. Ichiro Sakuma, MD, received consultancy fees from AstraZeneca K.K., and lecture fees from AstraZeneca K.K. and Shionogi & Co, Ltd. Hiroyoshi Yokoi, MD, received lecture fees from AstraZeneca K.K. and Daiichi Sankyo Co, Ltd. Masayuki Yoshida, MD, received lecture fees from AstraZeneca K.K. and Shionogi & Co, Ltd, and scholarship funds from AstraZeneca K.K. and Shionogi & Co, Ltd.

The other authors have no conflicts of interest.

References

1. Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. *JAMA* 2004; **291:** 1071–1080.
2. Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006; **295:** 1556–1565.
3. Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: Multicenter Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS). *Circ J* 2009; **73:** 2110–2117.
4. Okazaki S, Yokoyama T, Miyauchi K, Shimada K, Kurata T, Sato H, et al. Early statin treatment in patients with acute coronary syndrome: Demonstration of the beneficial effect on atherosclerotic lesions by serial volumetric intravascular ultrasound analysis during half a year after coronary event: The ESTABLISH Study. *Circulation* 2004; **110:** 1061–1068.
5. Otagiri K, Tsutsui H, Kumazaki S, Miyashita Y, Aizawa K, Koshikawa M, et al. Early intervention with rosuvastatin decreases the lipid components of the plaque in acute coronary syndrome: Analysis using integrated backscatter IVUS (ELAN study). *Circ J* 2011; **75:** 633–641.
6. Hong YJ, Jeong MH, Hachinohe D, Ahmed K, Choi YH, Cho SH, et al. Comparison of effects of rosuvastatin and atorvastatin on plaque regression in Korean patients with untreated intermediate coronary stenosis. *Circ J* 2011; **75:** 398–406.
7. Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007; **297:** 499–508.
8. Espeland MA, O'Leary DH, Terry JG, Morgan T, Evans G, Mudra H. Carotid intimal-media thickness as a surrogate for cardiovascular disease events in trials of HMG-CoA reductase inhibitors. *Curr Control Trials Cardiovasc Med* 2005; **6:** 3.
9. O'Leary DH, Polak JF, Kronmal RA, Manolio TA, Burke GL, Wolfson SK Jr; for the Cardiovascular Health Study Collaborative Research Group. Carotid-artery intima and media thickness as a risk factor for myocardial infarction and stroke in older adults. *N Engl J Med* 1999; **340:** 14–22.
10. Lorenz MW, Markus HS, Bots ML, Rosvall M, Sitzer M. Prediction of clinical cardiovascular events with carotid intima-media thickness: A systematic review and meta-analysis. *Circulation* 2007; **115:** 459–467.
11. Kitagawa K, Hougaku H, Yamagami H, Hashimoto H, Itoh T, Shimizu Y, et al. Carotid intima-media thickness and risk of cardiovascular events in high-risk patients: Results of the Osaka Follow-Up Study for Carotid Atherosclerosis 2 (OSACA2 Study). *Cerebrovasc Dis* 2007; **24:** 35–42.
12. Greenland P, Alpert JS, Beller GA, Benjamin EJ, Budoff MJ, Fayad ZA, et al. 2010 ACCF/AHA guideline for assessment of cardiovascular risk in asymptomatic adults: A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation* 2010; **122:** e584–e636.
13. Crouse JR 3rd, Raichlen JS, Riley WA, Evans GW, Palmer MK, O'Leary DH, et al. Effect of rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: The METEOR Trial. *JAMA* 2007; **297:** 1344–1353.
14. Yanase T, Nasu S, Mukuta Y, Shimizu Y, Nishihara T, Okabe T, et al. Evaluation of a new carotid intima-media thickness measurement by B-mode ultrasonography using an innovative measurement software, Intimascope. *Am J Hypertens* 2006; **19:** 1206–1212.
15. Kurabayashi M, Sakuma I, Kawamori R, Daida H, Yamazaki T, Yoshida M, et al. Can intensive lipid-lowering therapy with statins ameliorate atherosclerosis in Japanese patients? Rationale and design of the JART study. *J Atheroscler Thromb* 2010; **17:** 416–422.
16. Nohara R, Daida H, Hata M, Kaku K, Kawamori R, Kishimoto J, et al. 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. *Circ J* 2012; **76:** 221–229.
17. Ostling G, Gonçalves I, Wikstrand J, Berglund G, Nilsson J, Hedblad B. Long-term treatment with low-dose metoprolol CR/XL is associated with increased plaque echogenicity: The Beta-blocker Cholesterol-lowering Asymptomatic Plaque Study (BCAPS). *Atherosclerosis* 2011; **215:** 440–445.
18. Friedewald WT, Levy RI, Fredrickson DS. Estimation of the concentration of low-density lipoprotein cholesterol in plasma, without use of the preparative ultracentrifuge. *Clin Chem* 1972; **18:** 499–502.
19. Joint committee with the guidelines subcommittee of the Japan Academy of Neurosonology for ultrasonic assessment of carotid artery disease and the subcommittee for research into methods of screening atherosclerotic lesions. Guidelines for ultrasonic assessment of carotid artery disease: Preliminary report. *Neurosonology* 2002; **15:** 20–33.
20. Elatrozy T, Nicolaides A, Tegos T, Zarka AZ, Griffin M, Sabetai M. The effect of B-mode ultrasonic image standardisation on the echodensity of symptomatic and asymptomatic carotid bifurcation plaques. *Int Angiol* 1998; **17:** 179–186.
21. Teramoto T, Sasaki J, Ueshima H, Egusa G, Kinoshita M, Shimamoto K, et al. Executive summary of Japan Atherosclerosis Society (JAS) guideline for diagnosis and prevention of atherosclerotic cardiovascular diseases for Japanese. *J Atheroscler Thromb* 2007; **14:** 45–50.

22. Nicholls SJ, Ballantyne CM, Barter PJ, Chapman MJ, Erbel RM, Libby P, et al. Effect of two intensive statin regimens on progression of coronary disease. *N Engl J Med* 2011; **365:** 2078–2087.
23. Lorenz MW, Polak JF, Kavousi M, Mathiesen EB, Völzke H, Tuomainen TP, et al. Carotid intima-media thickness progression to predict cardiovascular events in the general population (the PROG-IMT collaborative project): A meta-analysis of individual participant data. *Lancet* 2012; **379:** 2053–2062.
24. Soeda T, Uemura S, Okayama S, Kawakami R, Sugawara Y, Nakagawa H, et al. Intensive lipid-lowering therapy with rosuvastatin stabilizes lipid-rich coronary plaques: Evaluation using dual-source computed tomography. *Circ J* 2011; **75:** 2621–2627.
25. Grønholdt ML, Nordestgaard BG, Schroeder TV, Vorstrup S, Sillesen H. Ultrasonic echolucent carotid plaques predict future strokes. *Circulation* 2001; **104:** 68–73.
26. Mathiesen EB, Bønaa KH, Joakimsen O. Echolucent plaques are associated with high risk of ischemic cerebrovascular events in carotid stenosis: The Tromsø study. *Circulation* 2001; **103:** 2171–2175.
27. Grønholdt ML, Wiebe BM, Laursen H, Nielsen TG, Schroeder TV, Sillesen H. Lipid-rich carotid artery plaques appear echolucent on ultrasound B-mode images and may be associated with intraplaque haemorrhage. *Eur J Vasc Endovasc Surg* 1997; **14:** 439–445.
28. Hirayama A, Saito S, Ueda Y, Takayama T, Honye J, Komatsu S, et al. Qualitative and quantitative changes in coronary plaque associated with atorvastatin therapy. *Circ J* 2009; **73:** 718–725.
29. Takarada S, Imanishi T, Kubo T, Tanimoto T, Kitabata H, Nakamura N, et al. Effect of statin therapy on coronary fibrous-cap thickness in patients with acute coronary syndrome: Assessment by optical coherence tomography study. *Atherosclerosis* 2009; **202:** 491–497.

Appendix 1

The following persons participated in this trial.

Steering Committee: Ryuji Nohara (principal investigator and trial chair), Hiroyuki Daida, Mitsumasa Hata, Kohei Kaku, Ryuzo Kawamori, Masahiko Kurabayashi, Izuru Masuda, Ichiro Sakuma, Tsutomu Yamazaki, Hiroyoshi Yokoi, Masayuki Yoshida.

Statistical Analysis: Junji Kishimoto.

Data and Safety Monitoring Committee: Tadatoshi Takayama (chair) (Nihon University), Yoshiyuki Rikitake (Kobe University).

Investigators: Kohichiro Aihara, Kenichi Aizawa, Kenji Ando, Masashi Arai, Kohsei Eguchi, Yoshio Fujitani, Katsuhito Fujiu, Yoshiko Furukawa, Kosaku Goto, Masahiko Goya, Sumiko Hamamoto, Mitsuru Hashiramoto, Mitsumasa Hata, Makoto Hiki, Yukio Hiroi, Takahisa Hirose, Hidenori Hirukawa, Yumiko Hosoya, Fuki Ikeda, Yasushi Imai, Moriaki Inoko, Yoshinori Inoue, Hideto Ishii, Nobukazu Ishizaka, Tatsuya Iso, Masashi Iwabuchi, Arata Iwasaki, Masatoshi Jibiki, Kohei Kaku, Akio Kanazawa, Yukiko Kanda, Satoshi Kaneko, Hideaki Kaneto, Ryuichi Kasami, Fumiko Kawasaki, Tomohiko Kimura, Noriyuki Kinoshita, Mineo Kodama, Takahide Kohro, Katsuhiro Kondo, Hakuoh Konishi, Masahiko Kurabayashi, Ichiro Manabe, Izuru Masuda, Munehide Matsuhisa, Michihiro Matsuki, Sahohime Matsumoto, Eriko Matsunaga, Takaaki Matsuoka, Hiroyuki Matsushima, Kohshiro Monzen, Hiroyuki Morita, Tomoatsu Mune, Takehiro Nakahara, Akihiko Nakano, Go Nishimura, Kazuyoshi Nishino, Ryuji Nohara, Chie Ohmura, Hirotoshi Ohmura, Teruo Okabe, Seizo Okauchi, Akihiko Ozaki, Tetsuya Saito, Yuichiro Saito, Koyu Sakai, Ichiro Sakuma, Yasukazu Sato, Satoshi Satoi, Daigo Sawaki, Hisakuni Sekino, Yoshiko Sewake, Tomoaki Shimizu, Masashi Shimoda, Kentaro Shimokado, Shinichi Shirai, Yoshimitsu Soga, Norihide Sugano, Shinya Suzuki, Tohru Suzuki, Makio Takahashi, Norihide Takaya, Yoshifumi Tamura, Satsuki Tanaka, Fuminori Tatsumi, Kazuhito Tawaramoto, Tomoyuki Tomita, Hiroto Tsuchiya, Kensuke Tsushima, Tomoko Urakawa, Hirotaka Watada, Masafumi Watanabe, Yoshihiko Yamada, Hiroyoshi Yokoi, Masayuki Yoshida, Takeshi Yoshihiro, Hiroshi Yoshioka.