Circ J 2009; **73:** 2110–2117

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) ——

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Background: It has been suggested that intensive lipid-lowering therapy using statins significantly decreases atheromatous plaque volume. The effect of rosuvastatin on plaque volume in patients with stable coronary artery disease (CAD), including those receiving prior lipid-lowering therapy, was examined in the present study.
Methods and Results: A 76-week open-label trial was performed at 37 centers in Japan. Eligible patients began treatment with rosuvastatin 2.5 mg/day, which could be increased at 4-week intervals to ≤20 mg/day. A total of 214 patients underwent intravascular ultrasound (IVUS) at baseline; 126 patients had analyzable IVUS images at the end of the study. The change in the serum low-density lipoprotein-cholesterol level from baseline to end of follow-up was –38.6±16.9%, whereas that of high-density lipoprotein-cholesterol was +19.8±22.9% (both P< 0.0001). Percent change of plaque volume, the primary endpoint, was –5.1±14.1% (P<0.0001).
Conclusions: Rosuvastatin exerted significant regression of coronary plaque volume in Japanese patients with stable CAD, including those who had previously used other lipid-lowering drugs. Rosuvastatin might be useful in the setting of secondary prevention in patients with stable CAD. (*Circ J* 2009; **73:** 2110–2117)

Key Words: Atherosclerosis; Coronary artery disease (CAD); Intravascular ultrasound (IVUS); Lipid-lowering therapy; Rosuvastatin

Several previous studies have suggested that cardiovascular morbidity and mortality in patients with hypercholesterolemia with or without coronary artery disease (CAD) can be significantly reduced by lipid-lowering therapy with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins).[1–5] Although statins may induce plaque regression and stabilization and improve endothelial function, the exact mechanism of these drugs' effects on ameliorating CAD remains uncertain. Various studies using intravascular ultrasound (IVUS) have suggested that changes in plaque volume might be related to clinical outcome in patients with CAD.[6–15] In other words, regression or attenuation of the progression of coronary plaque volume might be associated with beneficial outcome in terms of cardiovascular events. Therefore, serial observation of plaque volume would be a reasonable approach to evaluate the efficacy of the medical interventions that are used to prevent cardiovascular events.

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To date, although successful regression of plaque volume by lipid-lowering therapy using statins has been demonstrated in statin-naïve Japanese patients with acute coronary syndromes (ACS),[16] no trial has evaluated the effect of these drugs on coronary plaque volume in Japanese individuals with stable CAD.

Among the statin class of medications, rosuvastatin is considered to have robust effects, including highly effective low-density lipoprotein-cholesterol (LDL-C) lowering, significantly raising high-density lipoprotein-cholesterol (HDL-C), lowering high-sensitivity C-reactive protein (hs-CRP), and stabilizing risk factors and biomarkers of atherosclerosis in experimental animal models, as well as clinically.[17,18] However, although this drug has undergone several multicenter clinical trials worldwide,[19–21] empirical evidence for its efficacy in Japanese patients is relatively

Received May 26, 2009; revised manuscript received July 20, 2009; accepted July 31, 2009; released online October 5, 2009
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Trial Registration: ClinicalTrials.gov Identifier: NCT-00329160. http://clinicaltrials.gov/ct2/show/NCT-00329160
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limited.

The purpose of this multicenter study was to investigate the effect of rosuvastatin on plaque regression using IVUS imaging in Japanese hypercholesterolemic patients with stable CAD. This trial included not only patients with de novo use of statin, but also those in whom prior use of other statins did not exert sufficient lowering of LDL-C; these criteria are believed useful because the target population is representative of patients seen in actual clinical practice.

Methods

Study Design

The Coronary Atherosclerosis Study Measuring Effects of Rosuvastatin Using Intravascular Ultrasound in Japanese Subjects (COSMOS) was a 76-week, open-label, multicenter study to evaluate the effect of rosuvastatin on coronary artery atheroma volume as measured by IVUS in Japanese patients with stable CAD. The aims and design of this study are reported elsewhere.[22] Eligible patients started treatment with rosuvastatin 2.5 mg once daily; in those whose LDL-C remained >80 mg/dl after 4 weeks of treatment, the dosage could be titrated up to a maximum of 20 mg/day, which is the highest approved regimen by the Ministry of Health, Labor and Welfare of Japan.

A total of 19 scheduled visits were planned during the course of the study. Subjects attended follow-up visits every 4 weeks over 76 weeks after starting treatment with rosuvastatin. IVUS and coronary angiography (CAG) were performed at baseline and week 76. Prior to any study-related activities, all subjects signed an informed consent form. The study was approved by the institutional review board or independent ethics committee of all participating centers.

Patient Population

Included in the study were patients aged 20–75 years who were undergoing elective (not emergency) CAG or scheduled percutaneous coronary intervention (PCI) with ≥1 significant stenosis ≥75% and ≥1 untouched nonculprit target lesion of ≤50% stenosis that could be imaged by IVUS, and either LDL-C ≥140 mg/dl or total cholesterol (TC) ≥220 mg/dl in untreated patients or LDL-C ≥100 mg/dl or TC ≥180 mg/dl in those previously treated for hyperlipidemia. Patients with acute myocardial infarction within 72 h of study onset, heart failure (New York Heart Association class Ⅲ or Ⅳ), secondary hyperlipidemia, left main CAD of >50% stenosis, uncontrolled hypertension, uncontrolled diabetes, liver or kidney dysfunction, and short plaque lesions (<6 mm) were excluded, as were those currently receiving cyclosporine or hemodialysis and patients with lesions requiring intervention. However, patients already taking lipid-lowering drugs at time of study entry were allowed to enter in order to make the patient population similar to that seen in actual clinical practice. Patients who did not receive lipid-lowering drugs during 3 months before receiving study drugs were defined as "patients without prior use of lipid-lowering drugs".

IVUS Procedure

IVUS was used to examine plaque volume, lumen volume, and vessel volume at baseline and after 76 weeks of treatment. Upon intracoronary administration of nitroglycerin 100–300 μg, a catheter was advanced into the target vessel and the transducer positioned as distal as possible to the target lesion. The transducer was withdrawn by motor at a speed of 0.5 mm/s. Investigators were required to use the same imaging system with the same type of IVUS catheter for both the baseline and follow-up examinations: Clearview®, Galaxy™, or Galaxy2™ ultrasound system with Atlantis™ SR Pro 2 40 MHz imaging catheter (Boston Scientific, MA, USA). Images were optimized under visual inspection by manipulating the system settings. IVUS images were recorded on S-VHS videotapes or DVD+RW disk. The images were logged and analyzed by 2 experienced technicians who were unaware of the patient's profile, imaging date, and baseline/follow-up labels.

IVUS Imaging

Plaque volume was assessed by volumetric analysis using the echoPlaque2 system (Indec Systems, CA, USA). Baseline and follow-up IVUS images were reviewed side by side on a display, and the target segment selected. The target segment to be monitored was determined in a non-PCI site (>5 mm proximal or distal to the PCI site) with a reproducible index such as a side branch and its bifurcation, calcifications, or stent edges. A series of cross-sectional images every 0.09 mm apart was measured by manual onscreen planimetry. IVUS tracing was performed in accordance with standards of the American College of Cardiology and European Society of Cardiology.[23] Manual planimetry was used to trace the leading edges of the luminal and external elastic membrane borders. The accuracy and reproducibility of this method have been established.[24]

IVUS Measurements and Endpoints

The primary endpoint was the percent change in total atheroma volume (TAV) from baseline to week 76 ("follow-up"). Secondary endpoints were actual volume changes and percent changes in plaque area from baseline to follow-up at the same preselected coronary artery cross-section.

Clinic Visits and Laboratory Tests

During this trial, clinic visits were scheduled every 4 weeks over 1.5 years. Percent changes in lipids profiles (TC, LDL-C, HDL-C, remnant-like particle-cholesterol, apolipoprotein (Apo) A-I, ApoA-Ⅱ, and ApoB) from baseline to follow-up were calculated for each patient. Change in the hs-CRP level was also measured. All laboratory measurements were performed at a central clinical laboratory (SRL, Tokyo, Japan).

Safety

Adverse events, subjective symptoms/objective findings, body weight, resting 12-lead ECG, chest X-ray, general blood tests (hematology, renal and liver function, glucose metabolism), urinalysis, and vital signs (blood pressure, pulse rate) were recorded throughout the trial, which conformed to Good Clinical Practice (GCP), Good Post-Marketing Study Practice (GPSP), and Good Vigilance Practice (GVP) as established by the Ministry of Health, Labor and Welfare of Japan.

Sample Size

In the protocol, the assumptions used for power calculations required a sample size of 126 patients to provide 80% power (assuming a standard deviation (SD) of 25%) to detect a 6.3% difference in the primary endpoint with 2.5% type I error rate for a 1-sided test. This calculation was made based on data from previous trials.[10,25] It was there-

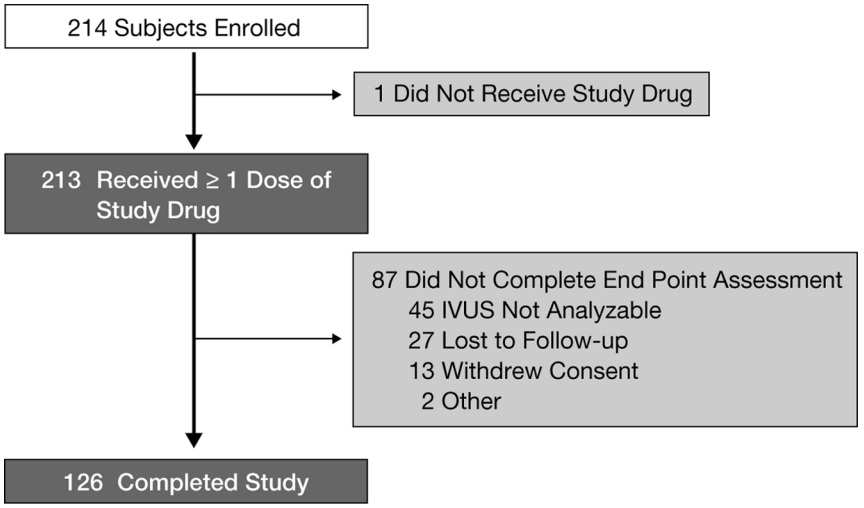

Figure 1. Flow of patients through the trial.

Table 1. Baseline Patient Characteristics and Analyzed Coronary Artery

Parameter	Completed the study Mean±SD (n=126)	Received ≥1 dose of study drug Mean±SD (n=213)
Age (years)	62.6±7.7	62.8±8.1
Male (%)	76.2	77.5
BMI (kg/m^2)	25.0±3.3	25.0±3.1
Hypertension (%)	76.2	77.5
Smoking (%)	28.6	29.6
Diabetes (%)	37.3	41.8
Family history of CAD (%)	20.6	23.0
Low HDL-C (%)	25.4	27.2
Unstable angina (%)	7.9	6.6
Prior use of lipid-lowering drugs (%)	73.0	72.8
Dosage at follow-up IVUS (mg/day)	16.9±5.3	
Analyzed coronary artery: vessel (%)		
RCA	40.5	
LAD	30.2	
LCX	28.6	
LMT	0.7	
Analyzed coronary artery: segment (%)		
Proximal to treated site	26.2	
Distal to treated site	31.7	
Untreated vessel lesions and others	42.1	
Lesion length (mm)	10.8±3.5	

SD, standard deviation; BMI, body mass index; CAD, coronary artery disease; HDL-C, high-density lipoprotein-cholesterol; IVUS, intravascular ultrasound; RCA, right coronary artery; LAD, left anterior descending artery; LCX, left circumflex artery; LMT, left main trunk.

fore determined that enrollment of 200 individuals would provide an adequate number of patients with evaluable endpoints during the study period.

Statistical Analysis

Statistical analyses were performed using SAS software, version 9.1.3 (SAS Institute Inc, NC, USA). Efficacy results are reported as mean with SD and median with interquartile range (IQR) from baseline to follow-up. Student's t-test was used to validate significant difference of percent change in each endpoint parameter. Two-sample t-test was used to compare subgroups, and 1-sample t-test for changes within each subgroup at follow-up vs baseline. Safety analyses were performed in all patients who received ≥1 dose of study drug.

Results

Patient Population

We enrolled 214 eligible patients between October 2005 and October 2008. One patient did not receive the study drug, 45 did not have analyzable IVUS images at follow-up, 27 withdrew because of adverse events, 13 withdrew consent, and 2 were withdrawn for protocol violations, a total of 126 patients completed the trial (**Figure 1**). The mean (±SD) age was 62.6±7.7 years; 76.2% were male (n=96). With regard to associated pathological conditions, 47 patients (37.3%) had diabetes, 96 (76.2%) had hypertension, and 7.9% had unstable angina; 92 patients (73.0%) had been previously treated with lipid-lowering drugs. The mean dosage of rosuvastatin at follow-up IVUS was 16.9±5.3 mg/day. Among the 126 patients who completed the trial, 92 (72.2%) received the maximum dosage (20 mg/day) (**Table 1**).

Table 2. Baseline and Follow-up Laboratory Results (n=126)

	Baseline		Follow-up		% change	P value*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)		
Lipids (mg/dl)						
TC	213.6±34.7	210.0 (188.0, 236.0)	157.8±24.1	157.0 (142.0, 170.0)	–24.7±14.2	<0.0001
TG	147.8±85.7	128.5 (96.0, 160.0)	130.3±64.6	114.0 (85.0, 165.0)	–4.8±38.4	0.1639
HDL-C	47.1±10.8	45.0 (40.0, 53.0)	55.2±11.7	55.5 (47.0, 61.0)	19.8±22.9	<0.0001
LDL-C	140.2±31.5	138.5 (118.0, 155.0)	82.9±18.7	78.5 (70.0, 91.0)	–38.6±16.9	<0.0001
VLDL-C	25.8±16.7	23.2 (15.6, 30.6)	21.8±12.4	19.3 (13.4, 28.0)	2.9±67.5	0.6264
Non-HDL-C	166.5±33.5	163.5 (145.0, 186.0)	102.5±21.5	98.0 (88.0, 114.0)	–36.7±15.0	<0.0001
ApoA-1	123.9±22.0	121.5 (110.0, 136.0)	143.3±24.1	141.0 (130.0, 157.0)	17.0±17.5	<0.0001
ApoA-2	26.8±5.3	26.2 (23.3, 29.2)	29.0±4.1	28.8 (26.3, 31.3)	10.9±17.6	<0.0001
ApoB	115.4±23.0	113.5 (99.0, 128.0)	77.2±15.0	74.0 (68.0, 86.0)	–31.3±16.1	<0.0001
Lp(a)	30.0±34.5	19.0 (8.0, 34.0)	31.0±41.7	15.0 (6.5, 36.0)	–1.7±38.4	0.6185
sdLDL	0.36±0.04	0.36 (0.34, 0.37)	0.35±0.03	0.35 (0.33, 0.36)	–2.4±11.0	0.003
ApoB/A-I ratio	0.96±0.28	0.92 (0.77, 1.12)	0.55±0.13	0.53 (0.47, 0.61)	–40.2±16.0	<0.0001
Non-HDL-C/HDL-C ratio	3.72±1.14	3.57 (2.93, 4.37)	1.94±0.57	1.84 (1.54, 2.15)	–47.33±15.82	<0.0001
LDL-C/HDL-C ratio	3.12±0.95	3.03 (2.46, 3.66)	1.56±0.45	1.47 (1.27, 1.78)	–47.54±15.09	<0.0001
HbA_{1c} (%)†	5.92±0.98	5.60 (5.30, 6.50)	6.25±1.00	6.00 (5.50, 7.00)	1.15±9.94	0.3205
hs-CRP (ng/ml)	3,362±7,823	911 (353, 3,210)	933±1,549	484 (260, 995)	18.1±291.3	0.4868

*One-sample t-test. †HbA_{1c} was assessed in 83 patients.
IQR, interquartile range; TC, total cholesterol; TG, triglycerides; LDL-C, low-density lipoprotein-cholesterol; VLDL-C, very low-density lipoprotein-cholesterol; sdLDL, small dense LDL; hs-CRP, high-sensitivity C-reactive protein. Other abbreviations: see Table 1.

Table 3. Baseline and Follow-up IVUS Results (n=126)

	Baseline		Follow-up		Percent change (%)		95%CI	P value*
	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)	Mean±SD	Median (IQR)		
Volume, mm^3								
Plaque	72.1±38.1	63.2 (41.9, 101.4)	66.8±34.0	60.3 (40.7, 91.5)	–5.1±14.1	–6.5 (–15.5, 4.5)	–7.6, –2.6	<0.0001
Lumen	78.3±40.2	69.9 (47.4, 105.8)	81.6±39.3	73.5 (52.9, 110.4)	7.3±15.6	5.9 (–1.7, 16.2)	4.5, 10.0	<0.0001
Vessel	150.4±72.4	136.0 (93.4, 204.4)	148.5±67.4	133.0 (98.9, 207.6)	0.8±11.7	–1.0 (–7.3, 8.6)	–1.3, 2.8	0.4673
Area, mm^2								
Plaque	8.9±3.6	8.8 (6.4, 10.8)	6.9±3.1	6.8 (4.6, 8.6)	–21.9±20.0	–23.4 (–34.2, –8.3)	–25.4, –18.3	<0.0001
Lumen	6.1±2.7	5.8 (3.7, 7.8)	7.1±3.1	6.5 (4.7, 9.1)	20.7±28.5	17.8 (0.8, 35.5)	15.7, 25.7	<0.0001
Vessel	15.0±5.4	14.7 (12.0, 18.3)	14.0±5.1	14.3 (10.1, 17.0)	–5.8±14.6	–6.4 (–15.4, 2.5)	–8.4, –3.3	<0.0001

*One-sample t-test.
CI, confidence interval. Other abbreviations: see Tables 1 and 2.

Lipid Profiles

The mean LDL-C at follow-up was 82.9±18.7 mg/dl, representing 38.6% reduction from baseline (P<0.0001). On the other hand, HDL-C at follow-up was 55.2±11.7 mg/dl, which corresponded to 19.8% increase from baseline (P<0.0001). The LDL-C/HDL-C ratio was significantly reduced from 3.1±1.0 to 1.6±0.5 (P<0.0001). Other lipid parameters were also significantly improved (**Table 2**).

Reduction of Plaque Volume

Significant regression of plaque volume was observed from baseline to follow-up. At final assessment, the mean percent change in TAV was –5.1±14.1% (median –6.5%, P<0.0001). Plaque volume was significantly reduced regardless of prior use of lipid-lowering drugs (P<0.02). Among all patients enrolled, 60% had net plaque regression. Although lumen volume significantly increased, vessel volume did not change (mean percent change in lumen volume +7.3±15.6% (P<0.0001); that of vessel volume was +0.8±11.7% (P=0.4673); **Table 3**). **Figure 2** is a representative example of significant regression of plaque volume.

Results for the primary endpoint for prespecified subgroups are shown in **Table 4**. Although significant differences in plaque regression were observed in patients stratified by median evaluated plaque length (P=0.0236), no difference was observed among subgroups classified by gender, age, BMI, LDL-C at baseline, HDL-C at baseline, prior use of lipid-lowering drugs, hypertension, smoking status, diabetes, unstable angina, and family history of cardiovascular events. Among patients stratified according to whether they had previously used lipid-lowering drugs, statistically significant differences were noted regarding some lipids parameters: percent change in LDL-C was significantly different (in those with prior use, –33.5±16.1%; without, –52.5±9.6%; P<0.0001), whereas that of HDL-C was comparable between the 2 subgroups (+20.3±23.9% vs +18.3±20.3%).

Figure 3 shows the relationship between the change in HDL-C or the LDL-C/HDL-C ratio and TAV. There was a weak but significant correlation between the percent change in TAV and HDL-C (r=–0.202; P=0.0234), as well as with the LDL-C/HDL-C ratio (r=0.193; P=0.0301). However, no significant relationship was observed between the percent change of TAV and other laboratory data.

Adverse Events

No major adverse events, including death, myocardial infarction, stroke, and rhabdomyolysis, were noted during this study. Three patients required prolonged hospitalization because of anemia, neutropenia, liver dysfunction, and an increase in the CRP level. **Table 5** shows the adverse events recorded during the observation period.

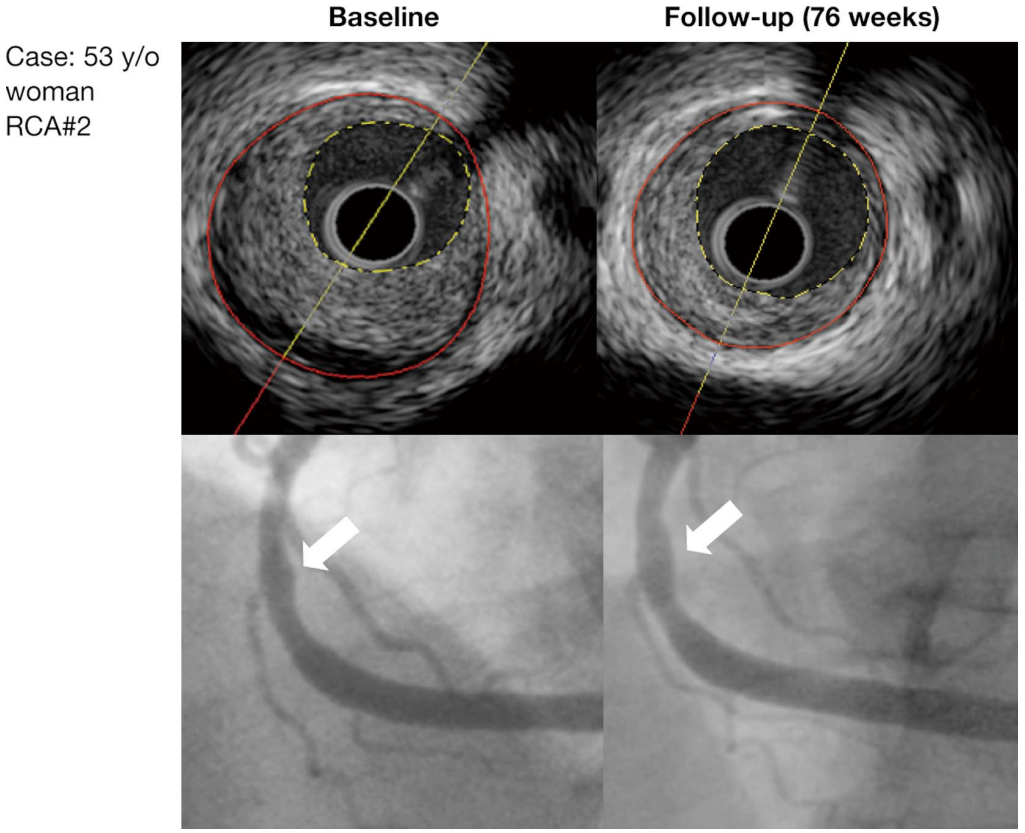

Figure 2. Example of plaque regression in a patient. (**Top Left**) Single cross-section at baseline intravascular ultrasound (IVUS) examination. (**Top Right**) Same cross-section after 76 weeks of treatment. (**Bottom**) Coronary angiograms of evaluated vessels. Arrows indicate where the cross-sectional IVUS images shown in the top panels were taken. RCA, right coronary artery.

Table 4. Primary Endpoint in Prespecified Subgroups

Subgroup	Category	No. patients	% change in plaque volume		P value
			Mean±SD	Median (IQR)	
Gender	Male	96	–5.5±13.5	–6.8 (–15.5, 2.8)	0.5043*
	Female	30	–3.6±15.9	–2.4 (–15.6, 5.1)	
Age (years)‡	<64	68	–5.9±14.0	–5.9 (–16.5, 2.8)	0.4981*
	≥64	58	–4.1±14.2	–7.0 (–14.9, 5.0)	
BMI (kg/m^2)	<25	69	–6.1±13.5	–6.8 (–16.0, 4.0)	0.3682*
	≥25	57	–3.8±14.7	–5.8 (–14.1, 4.6)	
LDL-C at baseline (mg/dl)	<100	12	–2.6±13.3	–2.4 (–14.8, 7.0)	0.9819†
	100–<120	21	–5.0±13.4	–4.9 (–13.6, 5.4)	
	120–<140	32	–5.4±15.6	–4.7 (–17.0, 5.7)	
	140–<160	32	–5.5±15.8	–8.1 (–16.2, 0.7)	
	≥160	29	–5.5±11.6	–6.7 (–14.9, 1.1)	
HDL-C at baseline (mg/dl)	<40	31	–8.0±14.4	–6.8 (–17.2, 1.2)	0.1771*
	≥40	95	–4.1±13.9	–6.4 (–14.9, 5.1)	
Plaque length (mm)‡	<10.7	63	–2.2±15.2	–1.1 (–15.5, 7.8)	0.0236*
	≥10.7	63	–7.9±12.3	–7.9 (–16.0, –1.3)	
Prior lipid-lowering drugs	Yes	92	–4.0±14.7	–5.2 (–15.3, 6.4)	0.1770*
	No	34	–7.9±12.0	–7.9 (–16.6, –1.3)	
Hypertension	Yes	96	–5.5±14.8	–7.0 (–15.9, 4.2)	0.5068*
	No	30	–3.6±11.6	–4.4 (–14.1, 4.6)	
Smoking	Yes	36	–6.5±13.6	–8.6 (–16.1, 1.3)	0.4748*
	No	90	–4.5±14.3	–5.2 (–14.9, 5.1)	
Diabetes	Yes	47	–2.8±14.6	–4.9 (–13.6, 7.8)	0.1618*
	No	79	–6.4±13.6	–7.0 (–16.0, 1.4)	
Unstable angina	Yes	10	–12.4±5.2	–12.7 (–16.5, –7.4)	0.0860*
	No	116	–4.4±14.4	–5.2 (–15.0, 5.0)	
Family history of CV events	Yes	26	–7.7±10.2	–6.9 (–15.6, –3.8)	0.2783*
	No	100	–4.4±14.9	–5.7 (–14.5, 5.0)	

*Two-sample t-test. †One-way analysis of variance. ‡Data dichotomized according to the median value.
CV, cardiovascular. Other abbreviations: see Tables 1 and 2.

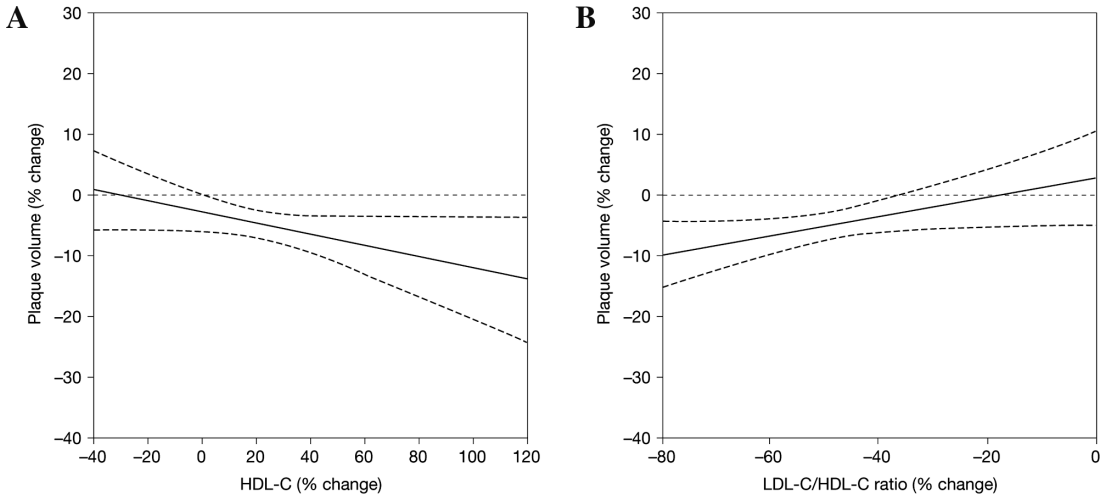

Figure 3. Correlation between change in (**A**) HDL-C and (**B**) LDL-C/HDL-C ratio and change of plaque volume. Relationship between change in HDL-C level or LDL-C/HDL-C ratio and change in plaque volume (Solid line). Upper and lower limits for 95% confidence interval of mean values (Dotted lines). HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 5. Adverse Events in 213 Patients During the Observation Period (76 Weeks)

Preferred term	Patients (n)	Events (n)	Incidence (%)
Death	0	0	0.0
Myocardial infarction	0	0	0.0
Stroke	0	0	0.0
Rhabdomyolysis	0	0	0.0
Discontinuation/dose reduction of study drug*	16	26	7.5
Adverse events*	74	166	34.7
Laboratory abnormality	54	113	25.4
Others	33	53	15.5

*Causal relationship to study drug could not be excluded.

Discussion

Intensive lipid-lowering therapy with rosuvastatin accomplished significant regression of coronary plaque volume in a considerable number of patients with stable CAD in the present study. Although the relatively small number of patients might have had some effect on the results, the difference in the percent change in plaque volume between patients with and without prior use of lipid-lowering drugs was not statistically significant. It should be stressed that this beneficial effect of rosuvastatin was observed even in patients with prior use of lipid-lowering drugs, which suggests that further reduction of LDL-C with rosuvastatin could induce significant atheroma regression, supporting "the lower the better" hypothesis in secondary prevention, at least from the aspect of IVUS plaque imaging. Our data may be extrapolated to actual clinical settings in which patients undergoing cardiac catheterization or PCI often receive lipid-lowering therapy before admission.

The ESTABLISH trial demonstrated a significant 13% regression of plaque volume by atorvastatin,[16] which is somewhat greater than that exerted by rosuvastatin in the present study. However, the ESTABLISH study examined statin-naïve Japanese patients with ACS, in whom there were more lipid-rich plaques than in the present patients with stable CAD. Hirayama's group[26] also detected using IVUS significant 17.8% regression of plaque volume in patients with stable CAD who received atorvastatin for 80 weeks. However, the grade of yellow plaque in that study was markedly improved, as evidenced by angiography, suggesting that the plaques they observed were relatively vulnerable compared with those in our study. Takashima et al[15] reported that plaque volume was reduced and lumen volume was increased by treatment with pitavastatin. Although ACS patients accounted for 56.1% of the pitavastatin group in their study, the changes in plaque volume and lumen volume showed a similar tendency to those observed in the present study. Changes in plaque volume and lumen volume achieved by statin treatment are greatly influenced by baseline vascular conditions, such as the proportion of plaque volume relative to the total vessel volume, severity of arteriosclerosis, and progression of remodeling. Therefore, the noted difference in the degree and pattern of regression exerted by various statins could be attributed to differences in plaque tissue characteristics and the patient's treatment history.

Our data might be more fruitfully compared with those obtained in previous similar trials such as ASTEROID.[27] In that study of Western patients, a –53.2% reduction in LDL-C (to 60.8±20.0 mg/dl) elicited by very high-intensity rosuvastatin therapy (40 mg/day) was accompanied by a reduction in plaque volume of –6.7±11.1%. In our study, the results were –38.6% (to 82.9±18.7 mg/dl) and –5.1±14.1%, respectively, suggesting that our Japanese patient population, who received much lower doses, showed comparable regression of plaque volume with less reduction of LDL-C.

Unlike in previous studies,[6,16,23–25] the correlation between the reduction in LDL-C and regression of TAV was not significant in the present study. One reason for this could be that we did not have a placebo control arm. It is interesting, however, that the percent change in TAV correlated significantly, albeit weakly, with HDL-C (r=–0.202; P=0.0234) and the LDL-C/HDL-C ratio (r=0.193; P=0.0301). It should be stressed that plaque regression was observed in three fifths of the present patients, regardless of the level of LDL-C reduction. This suggests that the regressive effect of rosuvastatin on plaque volume is mediated not simply by LDL-C reduction, but by multiple mechanisms.

We observed that the increase in HDL-C exerted by rosuvastatin was comparable between patients with and without prior use of lipid-lowering drugs (approximately 20% in both subgroups). This finding could explain the difference between our data and those of the ASTEROID Study.[27] We previously demonstrated that regression of plaque volume was associated with an increase in HDL-C,[28] which in part supports the present data. In addition, the LDL-C/HDL-C ratio improved from 3.12 to 1.56 in this study, which might also influence plaque regression.[29]

Another possible reason for the difference in the degree of plaque regression between this study and previous studies is differences in IVUS methodology. In ASTEROID,[27] IVUS measurement was performed on cross-sectional images obtained at 1.0-mm intervals, whereas in our study the separation between cross-sectional images was <0.1 mm. Therefore, the previous study showed the general effect of statin on longer coronary segments, whereas we evaluated more specific effects on local plaque segment.

It should also be stressed that administration of rosuvastatin over 76 weeks led to significant regression of coronary plaque volume with acceptable safety and tolerability, even though 72% of patients were finally treated with the highest approved dosage (20 mg/day).

Study Limitations

Because there was no placebo arm, the net effect of rosuvastatin was not clarified. Also, we examined only single measurable plaques, which may not represent the pan-coronary nature of plaque. In this study, thorough IVUS examination of all 3 coronary branches was not possible for ethical reasons.

Conclusions

This study demonstrated that 76-week administration of rosuvastatin resulted in significant coronary plaque regression in Japanese patients with stable CAD, together with potent LDL-C lowering as well as a significant increase of HDL-C and improvement of the LDL-C/HDL-C ratio. The present results suggest that rosuvastatin may be useful for secondary prevention in stable CAD patients, including those switched from other lipid-lowering drugs.

Acknowledgments

This study was supported by AstraZeneca and Shionogi Co Ltd. This study was reported to the Ministry of Health, Labor and Welfare of Japan and conformed to Good Clinical Practice (GCP), Good Post-Marketing Study Practice (GPSP), and Good Vigilance Practice (GVP).

Trial Registration

Clinical Trials government identifier: NCT-00329160.

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