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Intensive lipid lowering therapy with titrated rosuvastatin yields greater atherosclerotic aortic plaque regression: Serial magnetic resonance imaging observations from RAPID study

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ABSTRACT

Objective: Although previous randomized clinical trials established a basis for lipid guidelines worldwide, they employed fixed doses of statins throughout trials (fire-and-forget approach). In the real clinical setting, however, statin doses are titrated to achieve target low-density lipoprotein cholesterol (LDL-C) levels (treat-to-target approach). The major objective was to investigate whether intensive lipid-lowering therapy using the treat-to-target approach yielded greater regression of aortic plaques.
Methods: We therefore performed a prospective, randomized trial comparing the effects of standard (achieve LDL-C levels recommended by the Japanese guidelines) and intensive (achieve 30% lower LDL-C levels than standard) rosuvastatin therapy for 1 year in 60 hypercholesterolemic patients with a primary endpoint of aortic atherosclerotic plaques evaluated by non-invasive magnetic resonance imaging (MRI).
Results: Average doses were 2.9 ± 3.1 and 6.5 ± 5.1 mg/day for standard ($n = 29$) and intensive therapy group ($n = 31$), respectively. Although both therapies significantly reduced LDL-C and high-sensitivity C-reactive protein (hsCRP) levels, LDL-C reduction was significantly greater in the intensive group (−46 vs. −34%). MRI study showed that thoracic aortic plaques were significantly regressed in both groups, with greater regression of thoracic plaque in the intensive group (−9.1 vs. −3.2%, $p = 0.01$). Multivariate analyses revealed that thoracic plaque regression was significantly correlated with hsCRP reduction, but not with changes in serum lipids, endothelial function, or doses of rosuvastatin.
Conclusion: Intensive statin therapy with titration targeting lower LDL-C levels resulted in greater thoracic aortic plaque regression compared to standard therapy, which was correlated with hsCRP reduction, suggesting that intensive statin therapy could provide better clinical outcomes.

1. Introduction

It has been clearly established that lipid-lowering therapy using HMG-CoA reductase inhibitors, statins, reduces cardiovascular events in patients with and without a history of coronary artery diseases (CAD) [1]. In the secondary prevention setting, greater reduction in low-density lipoprotein cholesterol (LDL-C) levels has been reported to translate into greater reduction in CAD morbidity [2–4]. Furthermore, compared to standard therapy, intensive therapy using strong statin reportedly brought about greater regression of atherosclerotic plaques detected by intravascular ultrasound (IVUS) [5,6]. This clinical evidence established a basis for dyslipidemia management guidelines worldwide. However, caution should be exercised with regard to a difference in LDL-C lowering approach between these clinical trials and the guidelines based on them. The former involved fixed doses of statins and there was no titration throughout the trials, namely the fire-and-forget approach [7], whereas the latter set targets and

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require the physician to titrate the statin dose accordingly, the treat-to-target approach. However, there is scarce evidence regarding the issue of whether intensive therapy using the treat-to-target approach to achieve lower LDL-C levels than those recommended by a guideline can yield greater regression of atherosclerotic plaques as compared to standard therapy.

Magnetic resonance imaging (MRI) has recently proved to be a useful method for the noninvasive evaluation of human atherosclerotic plaques [8,9] and several studies have shown good correlations between in vivo MRI findings and histopathological findings regarding aortic plaque extent in rabbits [10]. In humans, MRI evaluation of the thoracic aorta was shown to be closely correlated with transesophageal echocardiography findings [8]. In this regard, we previously demonstrated that, intensive LDL-C reduction using high dose atorvastatin, as compared to low dose, yielded greater regression of aortic atherosclerotic plaques evaluated by MRI [11].

To address this issue further, we performed a prospective, randomized trial comparing standard and intensive therapy with rosuvastatin for 1 year, with non-invasive MRI evaluation of aortic plaques as the primary outcome. In this study, rosuvastatin doses were titrated for patients to achieve 2 different LDL-C target levels: standard (LDL-C levels recommended by the Japanese guidelines) and intensive (LDL-C levels 30% lower than the former) levels. We demonstrated, for the first time, that both thoracic and abdominal aortic plaques were significantly regressed in 2 groups in a study using a treat-to-target protocol. Further, intensive therapy achieved greater regression in thoracic plaques as compared to standard therapy. The study also revealed that plaque regression was correlated with reduction in levels of high-sensitivity C-reactive protein (hsCRP), but not of LDL-C.

2. Methods

2.1. Study protocol

Our study was a prospective, randomized, open-label trial to investigate the effects of "Rosuvastatin on Aortic Plaques detected by MRI and compare standard and Intensive lipiD-lowering therapies" (RAPID Study) in this regard. It included a 4-week pre-study observation period followed by a 12-month treatment period. After the observation period, 66 eligible patients (27 women and 39 men, mean age 64 ± 8 years) were randomized to either standard or intensive therapy (standard or intensive group). In standard therapy, attending physicians were instructed to titrate the daily dose of rosuvastatin with a view to achieving the target LDL-C levels recommended by Japan Atherosclerosis Society (JAS) Guidelines for Diagnosis and Treatment of Atherosclerotic Cardiovascular Diseases, whereas in intensive therapy, dose titration was performed with the objective of achieving 30% lower LDL-C levels than those in the JAS guidelines [12].

Subjects aged ≥20 and <75 years who met the criteria for lipid-lowering therapy in the guidelines were recruited. Exclusion criteria included receiving statins or other lipid-lowering drugs, pregnancy, acute coronary syndrome or any cardiovascular diseases needing inpatient-treatment within 6 months, end stage renal disease, hepatic dysfunction (either level of aspartate aminotransaminase or alanine aminotransferase exceeding 3 times normal limits.), malignancies or inflammatory diseases.

Blood samples were collected to measure lipid levels and safety parameters (creatinine kinase and liver enzymes) every month during the first 6 months of rosuvastatin treatment, then at 9 and 12 months of treatment. During the first 6 months of the treatments, doses of rosuvastatin were titrated to achieve LDL-C target levels. Throughout the study period, all patients were asked to maintain their habitual diet. Any antihypertensive or antidiabetic drugs or other medications were maintained during the study period.

2.2. Sample size computations

The sample size was calculated based on our previous study [11] comparing the effect of low and high dose atorvastatin on aortic plaques detected by MRI. This study was designed to have a power to demonstrate 27 mm^2 differences in vessel wall area (VWA) between the 2 treatments. A total of 68 plaques in the thoracic aorta were needed for the two-sided t test to demonstrate this with 80% power and an alpha-error of 0.05. Based on our previous study [11] (50 thoracic plaques in 40 subjects), 54 subjects would be needed and we therefore decided to enroll 60 subjects in consideration of dropouts. Sample size calculations were performed using the SAS PROC POWER procedure (SAS Institute Inc., Cary, NC, USA).

2.3. Biochemical analyses of blood samples

Serum total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C) and glucose levels were determined by standard enzymatic methods. Apolipoproteins (apo) levels were determined by immunoturbidimetry. Remnant-like particle cholesterol (RLP-C) levels were measured by the method reported by Miyauchi et al. [13]. Hemoglobin A1c (HbA1c) was determined using high-performance liquid chromatography. Serum hsCRP levels were measured using a BNII nephelometer (Dade Behring, Germany).

2.4. Assessment of endothelial function

Endothelial function was assessed by flow-mediated vasodilation (FMD) of the brachial artery 6 months after randomization. FMD was measured noninvasively using a high-resolution ultrasound apparatus with a 7.5-MHz linear array transducer (Aplio SSA-770A, Toshiba Co Ltd) according to the guidelines of the International Brachial Artery Reactivity Task Force [14]. Detailed protocols of FMD and nitroglycerin-mediated vasodilation (NMD) are described in Supplemental Methods. All measurements were performed in the morning from 9 to 11 am in a temperature-controlled room (25 °C) with the subject in a fasting, resting, and supine state. Electrocardiograms were monitored continuously. The subject's dominant arm (right) was immobilized comfortably in the extended position to allow consistent access to the brachial artery for imaging. The vasodilation responses of the brachial artery were observed using a previously validated technique [15]. For each subject, optimal brachial artery images were obtained between 2 and 10 cm above the antecubital fossa. First, baseline two-dimensional (2-D) images were obtained and after measurement of baseline artery diameter, a narrow-width blood pressure cuff was inflated on the most proximal part of the forearm to an occlusive pressure (200 mmHg) for 5 min to induce hyperemia. The position of the ultrasound transducer was carefully maintained throughout the procedure. The cuff was then deflated rapidly and 2-D images of the artery were obtained for 60–120 s after deflation. Using the same method, we measured endothelium-independent vasodilation due to administering nitroglycerin (NTG, 0.3 mg). The NMD was measured before (baseline) and 5 min after NTG administration. Throughout the study, FMD and NMD were examined by 2 cardiologists who were blinded to the treatment regimen of each subject, using the same ultrasound apparatus and probe set for all measurements. All images were recorded as movie files in a hard disk recorder for later analysis. To measure vasodilator

responses in each patient's artery, movies were played back and a 10–20 mm segment was identified for analysis using anatomic landmarks. To select images reproducibly for the same point in the cardiac cycle, images at peak systole were identified and the diameter of the artery was digitized using a caliper function of the ultrasound apparatus. For each condition (baseline, FMD, baseline before NMD, and after NMD), 3 separate images from 3 different cardiac cycles were digitized and their average segment diameters determined. Both FMD and NMD were expressed as percentage change from baseline. The intra- and inter-observer variability (coefficient of covariance) for repeated diameter measurements at baseline and reactive hyperemia or NMD in the brachial artery were both <3% [15].

2.5. MRI of aortic wall

MRI was performed on the Signa 1.5T Cvi scanner (GE Medical Systems, USA) using a commercially available phased-array body coil. The transverse proton density-weighted (PDW) and T2-weighted (T2W) images of thoracic descending and abdominal aortas were obtained using an ECG-gated, breath-hold, double-inversion-recovery fast spin-echo sequence, as previously reported [8]. Imaging parameters were TR = 2 RR intervals, TE = 10 ms (PDW) and 60 ms (T2W), 20-cm FOV, 4-mm slice thickness, 8-mm interslice gap, 256 × 256 acquisition matrix, and 32 echo-train. At baseline, 9 slices of the thoracic aorta were obtained at 12-mm intervals above the lower corner of the 9th thoracic vertebrae, and 9 slices of the abdominal aorta were obtained at 12-mm intervals above the upper corner of the 4th lumbar vertebrae, which each covered about 10-cm portions of the thoracic aorta below the arch and of the abdominal aorta above the bifurcation of the common iliac artery (Fig. 1). Atherosclerotic plaque was defined as a clearly identified luminal protrusion with focal wall thickening.

Repeat MRI was scheduled at 12 months of treatment, because >6 months of treatment was required to observe plaque regression in the thoracic aorta [16]. Regarding the repeat MRI, special attention was paid to matching the images to those at baseline.

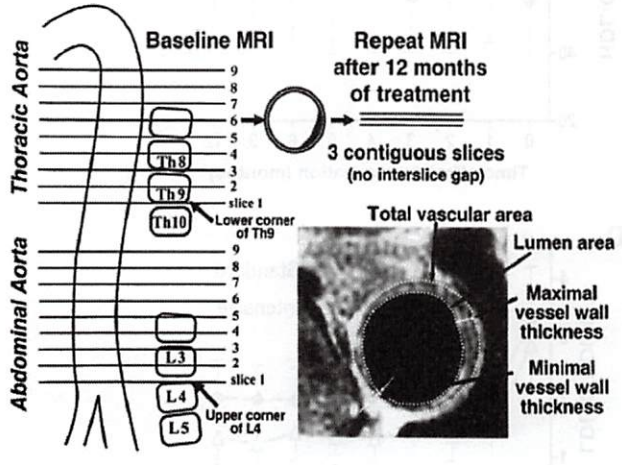

Fig. 1. Magnetic resonance imaging (MRI) slices of aortas and morphometric analysis. At baseline, nine slices of the thoracic aorta were obtained at 12-mm intervals above the lower corner of the ninth thoracic vertebrae (arrow), and nine slices of the abdominal aorta were obtained at 12-mm intervals above the upper corner of the fourth lumbar vertebrae (arrow). After 12 months of treatment, three contiguous slices for each plaque were obtained. The slice most closely matching the one at baseline was selected. The lumen area and total vascular area were calculated from the traced luminal and outer wall boundaries.

Since the aortas were located very close to vertebrae that do not usually move with respiration or bowel movements, these vertebrae (especially the 9th thoracic and 4th lumbar vertebrae) were used as the most important anatomic landmarks (Fig. 1). For each plaque, 3 contiguous slices (no interslice gap) were obtained, and the slice most closely matching the one obtained at baseline was selected using several anatomic landmarks (i.e., vertebrae, intercostal and lumbar arteries, pulmonary arteries and veins, and mesenteric arteries). The matching procedure was carried out by 2 observers blinded to treatment assignment. The interobserver agreement for selection of the slice most closely matching the one at baseline was 96% (120 of 125 plaques), and the discrepancy was resolved by consensus.

2.6. Morphometric analysis and plaque characterization

Maximal and minimal vessel wall thickness (VWT), total vascular area (TVA) and lumen area (LA) in each slice were measured 3 times by manual planimetry using the National Institutes of Health Image software package (Scion Co., USA), and the averages were used for statistical analysis. LA and TVA were calculated from the traced luminal and outer wall boundaries (Fig. 1). VWA was calculated as TVA minus LA. All measurements were performed by Y.M., who was blinded to the treatment assignment and order of images. The accuracy and reproducibility of this method has been previously reported [16–19]. In our study, 10 patients were randomly selected for evaluation of intraobserver variability.

2.7. Statistical analysis

Baseline characteristics were reported as mean ± SD, median with interquartile range, or counts and proportion, as appropriate. Differences between 2 groups were evaluated by the unpaired *t* test for continuous variables and by the chi-square test for categorical variables. Changes in VWT, VWA and LA between baseline and after 12 months within each treatment group and between the 2 treatment groups were evaluated per lesion using a linear mixed model including patient identification number as a random effect. *F* tests were performed for fixed effect covariates. Relationships between changes in VWA and change in each biochemical parameter before and after treatment with rosuvastatin were also evaluated using

Table 1
Baseline characteristics of study subjects.

	Standard (n = 29)	Intensive (n = 31)
Gender, male	16	17
Age, years	63 ± 7	65 ± 9
BMI, kg/m^2	25.8 ± 4.2	24.4 ± 3.1
Smoking, n	8	8
Diabetes mellitus, n	7	11
Hypertension, n	14	15
Coronary artery diseases, n	8	7
TC, mg/dl	257 ± 56	254 ± 45
LDL-C, mg/dl	172 ± 48	164 ± 43
TG, mg/dl	131 [112, 171]	108 [79, 185]
HDL-C, mg/dl	56 ± 17	59 ± 12
hsCRP, mg/l	0.71 [0.37, 1.08]	0.61 [0.27, 1.11]
Medication, n		
Anti-hypertensives	9	11
Aspirin	4	5
Antidiabetic agents	4	5

Abbreviations: BMI, body mass index; TC, total cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein.
Values are mean ± SD except for TG and hsCRP (median [interquartile ranges]).

Table 2
Anthropometric and biochemical parameters and endothelial function before and after rosuvastatin treatments.

	Standard (n = 29)			Intensive (n = 31)			Standard vs. intensive[c]
	Baseline	12 months[a]	p value[b]	Baseline	12 months[a]	p value[b]	
Doses of rosuvastatin at follow-up, mg/day	–	2.9 ± 3.1		–	6.5 ± 5.1		<0.01
Body weight, kg	63.9 ± 9.7	63.4 ± 9.4	NS	59.0 ± 8.0	58.1 ± 8.2	0.026	NS
Waist circumference, cm	86.0 ± 9.8	85.4 ± 9.8	NS	82.8 ± 8.9	81.4 ± 9.2	NS	NS
TC, mg/dl	257 ± 56	202 ± 34	<0.001	254 ± 45	178 ± 29	<0.001	<0.001
LDL-C, mg/dl	172 ± 48	115 ± 29	<0.001	164 ± 43	86 ± 25	<0.001	<0.001
TG, mg/dl	131 [112, 171]	112 [82, 182]	NS	108 [79, 185]	105 [89, 134]	<0.01	NS
HDL-C, mg/dl	56 ± 17	61 ± 17	<0.001	59 ± 12	68 ± 16	<0.001	NS
LDL-C/HDL-C	3.3 ± 0.9	2.0 ± 0.6	<0.001	2.9 ± 0.8	1.3 ± 0.5	<0.001	<0.001
apoA-I, mg/dl	131 ± 29	150 ± 29	<0.001	135 ± 19	160 ± 23	<0.001	NS
apoA-II, mg/dl	27.3 ± 5.3	30.0 ± 3.9	<0.001	26.8 ± 3.4	31.2 ± 5.3	<0.001	NS
apoB. mg/dl	135 ± 28	99 ± 20	<0.001	126 ± 23	81 ± 14	<0.001	<0.01
apoC-II, mg/dl	5.2 ± 2.2	4.7 ± 2.0	<0.01	5.1 ± 2.7	4.3 ± 1.6	0.019	NS
apoC-III, mg/dl	10.4 ± 3.5	10.2 ± 3.6	NS	10.8 ± 4.6	9.9 ± 3.0	NS	NS
apoE, mg/dl	5.0 ± 1.5	4.2 ± 1.0	<0.001	5.2 ± 1.7	4.1 ± 1.1	<0.001	NS
RLP-C, mg/dl	9.5 ± 4.3	6.3 ± 3.4	<0.001	10.6 ± 9.2	4.5 ± 2.3	<0.01	NS
Glucose, mg/dl	100 ± 14	100 ± 20	NS	101 ± 17	107 ± 20	NS	NS
HbA1C, %	5.5 ± 0.5	5.5 ± 0.6	NS	5.6 ± 0.8	5.7 ± 0.9	NS	NS
hsCRP, mg/l	0.71 [0.37, 1.08]	0.48 [0.34, 0.10]	0.020	0.61 [0.27, 1.11]	0.28 [0.17, 0.59]	0.029	NS
FMD, %	5.3 ± 3.2	6.4 ± 3.8	NS	4.3 ± 3.6	6.8 ± 3.6	<0.01	NS
NMD, %	17.1 ± 6.4	16.8 ± 6.8	NS	19.1 ± 6	20.3 ± 6.4	NS	NS

Abbreviations: TC, total cholesterol, LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; apo, apolipoprotein; RLP-C, remnant-like particle-cholesterol; HbA1c, hemoglobin A1c; hsCRP, high sensitive C-reactive protein; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation; RLP-C, remnant-like particle-cholesterol; HbA1c, hemoglobin A1c; hsCRP, high sensitive C-reactive protein; FMD, flow-mediated dilatation; NMD, nitroglycerin-mediated dilatation.

Values are mean ± SD except for statin doses, TG and hsCRP (median [interquartile ranges]). NS, not significant.

[a] FMD/NMD were determined 6 months after randomization.

[b] The values of TG/hsCRP were analyzed after logarithmic transformation.

[c] The percent changes from baseline were compared.

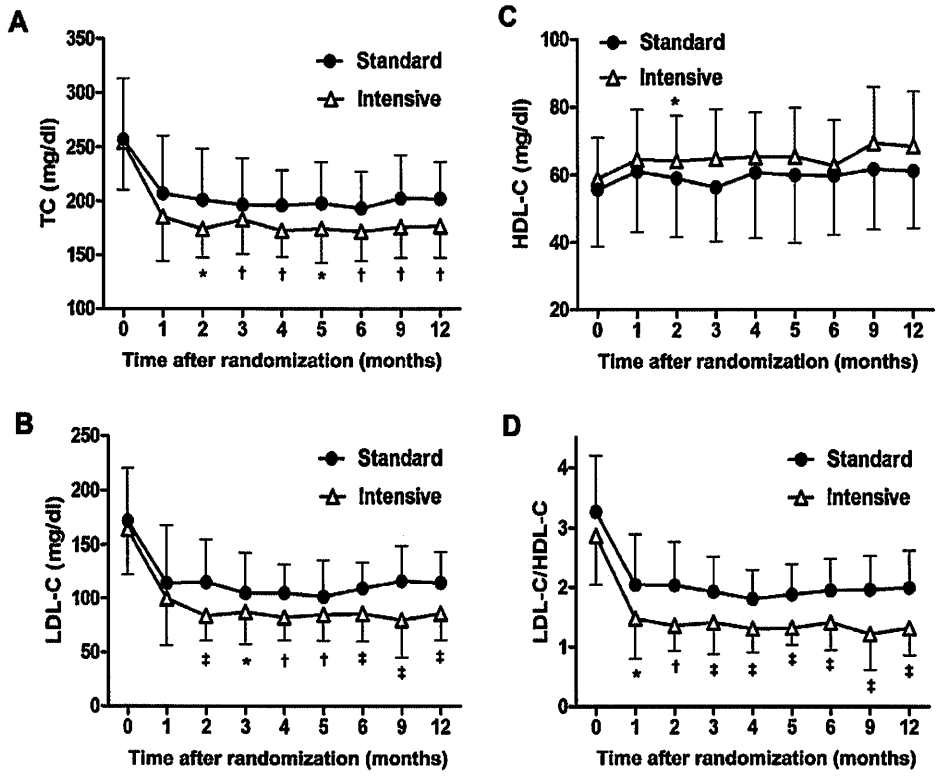

Fig. 2. Changes in serum TC (A), LDL-C (B), HDL-C (C) levels and ratios of LDL-C/HDL-C (D) levels during the study period. *$p < 0.05$, †$p < 0.01$, ‡$p < 0.001$ standard vs. intensive group.

Table 3
Changes in vessel wall thickness, vessel wall area and lumen area after 12 months of rosuvastatin treatments.

	Standard	Intensive
Thoracic aorta	(n = 53 lesions)	(n = 55 lesions)
Vessel wall area		
Baseline, mm^2	164 ± 44	156 ± 39
12 months, mm^2	158 ± 45	142 ± 41
Nominal change, mm^2	−5.6 ± 16.2	−14.3 ± 20.8*
Percent change, %	−3.2 ± 9.9	−9.1 ± 13.3*
p value (compared with baseline)	0.057	0.0003
Lumen area		
Baseline, mm^2	385 ± 93	353 ± 82
12 months, mm^2	404 ± 98	366 ± 85
Nominal change, mm^2	18.0 ± 34.6	12.9 ± 24.9
Percent change, %	5.4 ± 9.6	3.8 ± 6.5
p value (compared with baseline)	0.0032	0.004
Maximal vessel wall thickness		
Baseline, mm	3.8 ± 0.9	3.6 ± 0.8
12 months, mm	3.4 ± 0.8	3.3 ± 0.8
Nominal change, mm	−0.34 ± 0.49	−0.28 ± 0.59
Percent change, %	−9.0 ± 11.8	−6.8 ± 17.4
p value (compared with baseline)	0.001	0.0064
Abdominal aorta	(n = 71 lesions)	(n = 86 lesions)
Vessel wall area		
Baseline, mm^2	110 ± 37	107 ± 42
12 months, mm^2	103 ± 39	102 ± 47
Nominal change, mm^2	−6.6 ± 15.8	−5.0 ± 16.0
Percent change, %	−5.8 ± 14.7	−5.4 ± 14.8
p value (compared with baseline)	0.021	0.0803
Lumen area		
Baseline, mm^2	185 ± 59	177 ± 50
12 months, mm^2	192 ± 60	181 ± 52
Nominal change, mm^2	6.7 ± 15.0	4.4 ± 12.2
Percent change, %	4.8 ± 10.4	2.7 ± 7.2
p value (compared with baseline)	0.2318	0.1821
Maximal vessel wall thickness		
Baseline, mm	3.6 ± 0.9	3.7 ± 1.1
12 months, mm	3.6 ± 1.0	3.7 ± 1.1
Nominal change, mm	−0.05 ± 0.64	−0.02 ± 0.63
Percent change, %	−0.7 ± 16.8	0.3 ± 16.7
p value (compared with baseline)	0.6297	0.8377

Changes in vessel wall thickness, vessel wall area and lumen area between baseline and after 12 months of treatment were evaluated per lesion using a linear mixed model including patient number as a random effect.
Values are mean ± SD. NS, not significant. *$p < 0.05$, standard vs. intensive.

the linear mixed model. Multiple linear mixed model analysis including the changes in LDL-C, TG, HDL-C, hsCRP, FMD, and doses at follow-up was also performed. Correlations between changes in VWA and those in hsCRP levels were evaluated by Pearson' correlation coefficient. A p value of <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.3 (SAS Institute Inc., Cary, NC, USA).

3. Results

3.1. Patient characteristics

Among 66 randomized subjects, 6 discontinued the study because of myalgia (1 from standard, 1 from intensive) or ceasing hospital visits for unknown reasons (3 from standard, 1 from intensive). As a result, 60 patients (29 in standard group and 31 in intensive group) underwent repeat MRI after 12 months of treatment (Table 1). There were 8 and 7 patients with CAD in the standard and intensive group, respectively. There were no differences in age, gender, smoking status, number of subjects with diabetes/hypertension, or in lipid and hsCRP levels at baseline between the 2 groups. None of the patients had a history of statins or other prior lipid-lowering drugs.

3.2. Anthropometric and laboratory findings and endothelial function

Table 2 shows mean doses of rosuvastatin after the 12-month treatment periods: 2.9 ± 3.1 vs. 6.5 ± 5.1 mg/day, for standard and intensive, respectively. Body weight and waist circumference were unchanged during the study. Although both therapies reduced total cholesterol (TC) and LDL-C levels, intensive therapy brought about a significantly greater reduction in TC and LDL-C levels throughout the study as compared to standard therapy, as shown in Fig. 2A and B. Mean LDL-C levels during follow-up were 111 and 87 mg/dL and mean percentages of LDL-C reduction were −34 and −46% in the standard and intensive groups, respectively. After 12 months of the treatments, 24 patients (83%) in the standard group and 24 patients (78%) in the intensive group had achieved the respective target LDL-C levels. Rosuvastatin also raised HDL-C levels though there were no differences between the 2 groups, except for at 2 months of treatment when HDL-C levels in the intensive group were significantly higher than those in the standard group (Fig. 2C). These changes in LDL-C and HDL-C levels resulted in a marked difference in LDL-C/HDL-C ratios. The ratios in the intensive group stayed below 1.5 throughout the study period as shown in Fig. 2D. Only intensive therapy resulted in a significant reduction in TG levels. Mirroring the changes in lipid levels, apolipoprotein (apo) B, apoC-II, apoE, and remnant-like particle cholesterol (RLP-C) levels were reduced and apoA-I and apoA-II levels increased after both treatments. Diabetic parameters were unchanged and hsCRP levels were significantly decreased in both groups. Endothelial function as represented by FMD was significantly increased in the intensive but not the standard therapy group. However, NMD was not affected during the study in either group.

3.3. MRI results

A total of 108 thoracic and 157 abdominal aortic plaques were detected by MRI and these atherosclerotic lesions were followed up. At baseline, there were no differences in VWA, LA and maximal VWT (maxVWT), between the groups (Table 3). After 12 months of the treatments, repeat MRI studies revealed that thoracic plaques were significantly regressed in both groups, and abdominal plaques were reduced only in the standard, but not in the intensive group. In contrast to the abdominal aorta, in which there was no difference in reduction in VWA between the groups (−5.8 vs. −5.4%; standard vs. intensive, respectively), intensive therapy brought about significantly greater regression in the VWA of the thoracic aorta as compared to standard therapy (−3.2 vs. −9.1%; standard vs. intensive, respectively). Both therapies resulted in a significant increase in LA both in the thoracic (5.4 vs. 3.8%; standard vs. intensive, respectively), but not in abdominal aorta (4.8 vs. 2.7%; standard vs. intensive, respectively). In contrast to its effects on VWA, rosuvastatin therapy reduced maxVWT in the thoracic (−9.0 vs. −6.8%; standard vs. intensive, respectively), but not in the abdominal aorta (−0.7 vs. 0.3%; standard vs. intensive, respectively). Representative cases of plaque regression or progression are shown in Fig. 3. Also, the subject-based analysis in Supplemental Table confirms that the 2 therapies resulted in plaque regression both in the thoracic and abdominal aorta, though a significant difference between the treatments was not detected.

To determine which factors influenced plaque regression in the aorta in detail, we performed a linear mixed model analysis to assess relationships between changes in VWA and those in each biochemical parameter and FMD before and after treatments. As shown in Table 4, there was no significant correlation between thoracic and abdominal plaque regression and the doses of rosuvastatin after 12 months of the treatments and the changes

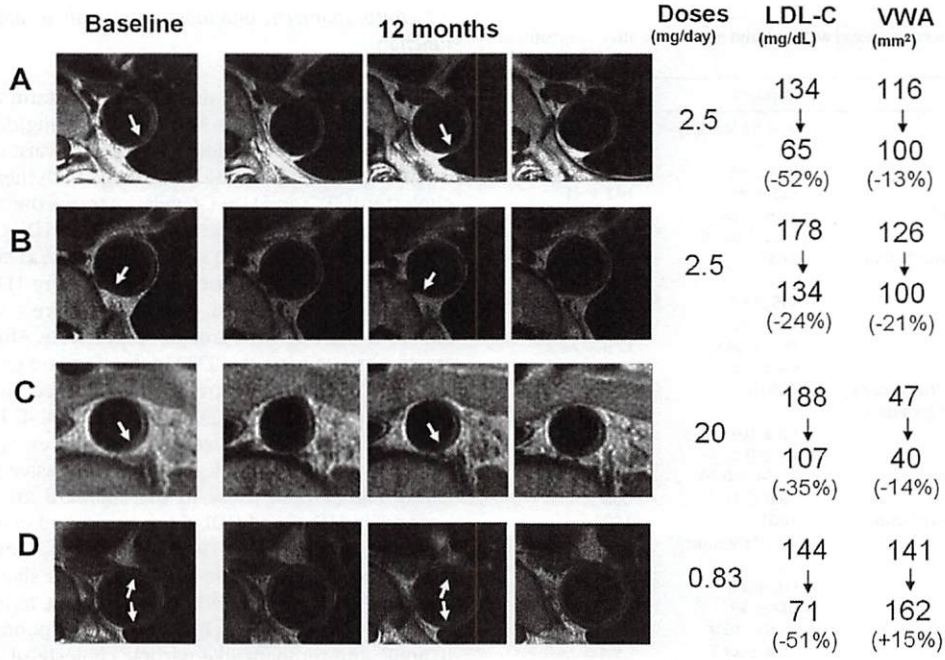

Fig. 3. Images at baseline and after 12 months of treatment. After 12 months, 3 contiguous slices (no interslice gap) for each plaque were obtained, and the slice most closely matching the one at baseline was selected. In the selected slices, arrows indicate plaques. (A) Thoracic aortic plaque that showed regression (13% vessel wall area (VWA) reduction) with 52% low-density lipoprotein-cholesterol (LDL-C) reduction due to 2.5-mg rosuvastatin; (B) thoracic plaque that showed regression (21%) with 24% LDL-C reduction due to 2.5 mg; (C) abdominal plaque that showed regression (14%) with 35% LDL-C reduction due to 20 mg; and (D) thoracic aortic plaque that showed progression (15%) despite 51% LDL-C reduction due to 20 mg.

(percent and nominal) in LDL-C, TG, HDL-C, LDL-C/HDL-C, apoB and %FMD. In sharp contrast to these parameters, thoracic plaque regression was significantly correlated with reductions in hsCRP (nominal changes, $p = 0.007$, percent changes, $p = 0.003$). However, we did not observe such an association in the abdominal aorta. Fig. 4 shows the results of a simple correlation analysis between changes in VWA and hsCRP levels evaluated by Pearson's correlation coefficient, which confirmed that there was a significant positive correlation among these changes in the thoracic, but not in the abdominal aorta. Although no subject complained of anything and there were no objective findings, 4 (1 intensive; 3 standard) subjects had hsCRP levels of 3.0 mg/L or greater indicating acute inflammatory illness so we did not include these subjects in the analysis. The results confirmed the finding for the subjects overall; reduction in hsCRP levels was significantly correlated with plaque regression in the thoracic aorta (Fig. 4B), but not the abdominal aorta (Fig. 4D).

Table 4
P values for changes in serum lipids, high-sensitive C-reactive protein levels and endothelial function as fixed-effect covariates in the linear mixed model of changes in vessel wall area in thoracic aorta.

	Changes in vessel wall area in thoracic aorta	
	Nominal change (mm^2)	Percent change (%)
	p value	*p* value
Thoracic aorta (91 lesions)		
LDL-C	0.387	0.393
TG	0.819	0.969
HDL-C	0.554	0.251
LDL-C/HDL-C	0.734	0.614
apoB	0.219	0.134
hsCRP	0.007	0.003
%FMD	0.895	0.719
Doses at follow-up	0.194	0.169
Abdominal aorta (149 lesions)		
LDL-C	0.442	0.409
TG	0.988	0.598
HDL-C	0.993	0.820
LDL-C/HDL-C	0.905	0.927
apoB	0.852	0.656
hsCRP	0.244	0.320
%FMD	0.712	0.605
Doses at follow-up	0.729	0.971

Relationship between changes in each biochemical parameter and changes in vessel wall area were evaluated per lesion using a linear mixed model including patient number as a random effect.
Abbreviations: BMI, body mass index; TC, total cholesterol, LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; apoB, apolipoprotein B; hsCRP, high sensitive C-reactive protein; FMD, flow-mediated dilatation.

To further assess the role of hsCRP levels in plaque regression during rosuvastatin treatment, we performed a multivariate analysis using a linear mixed model on the factors used in Table 4 and the changes in thoracic VWA/maxVWT. Table 5 shows that, even after adjustment for serum lipids, FMD and doses at follow-up, the negative associations of nominal and percent changes in thoracic VWA/maxVWT with those in hsCRP levels still remained significant.

4. Discussion

Although previous randomized clinical trials undoubtedly established a basis for guidelines to treat dyslipidemia worldwide, the protocol employed in these trials was the so-called "fire-and-forget" approach using fixed doses of statins without titration. Obviously, it does not represent the real clinical setting where we use the "treat-to-target" approach in which statin doses are titrated to achieve target LDL-C levels in guidelines. Therefore the present study, which was designed to assess the effects of standard and intensive therapies on atherosclerotic plaque regression, adopted the treat-to-target approach. One year of

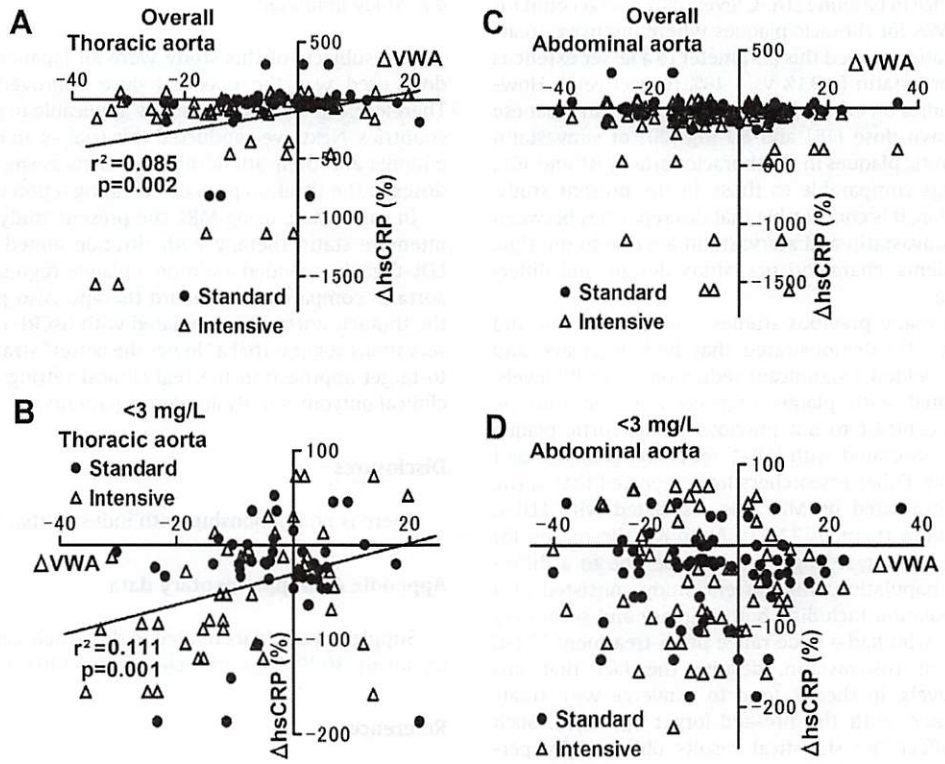

Fig. 4. Associations between percent changes in aortic plaques (A and B, thoracic; C and D, abdominal aorta) and those in serum hsCRP levels in subjects overall (A, C) and subjects with 3 mg/L of hsCRP or less (B, D). Correlations were evaluated by Pearson's correlation coefficient.

intensive therapy with rosuvastatin resulted in greater regression of plaques in the thoracic aorta compared to standard therapy. In contrast, regressions in abdominal aortic plaques were no different between the therapies. In the intensive group, despite greater reductions in LDL-C levels and LDL-C/HDL-C ratios, these changes were not associated with aortic plaque regression. Only hsCRP reduction was significantly correlated with thoracic aorta plaque regression.

Table 5
Relationship between changes in vessel wall area of thoracic and changes in biochemical parameters after 12 months treatment.

		p for VWA	*p* for maxVWT
Nominal changes			
LDL-C, mg/dl	−70.3 ± 36.4	0.710	0.496
TG, mg/dl	−12 [−45, 7]	0.944	0.987
HDL-C, mg/dl	7.99 ± 6.82	0.756	0.187
hsCRP, mg/l	−0.179 [−0.450, −0.007]	0.018	0.060
FMD, %	1.30 ± 4.57	0.979	0.731
Doses at follow-up	–	0.287	0.777
Percent changes			
LDL-C, %	−40.5 ± 14.4	0.266	0.633
TG, %	−11.0 [−33.9, 5.1]	0.725	0.496
HDL-C, %	15.0 ± 12.0	0.559	0.052
hsCRP, %	−24.1 [−47.0, −4.2]	0.007	0.024
FMD, %	−13.1 ± 64.8	0.362	0.152
Doses at follow-up	–	0.066	0.773

A multivariate analysis was performed by using a linear mixed model.
Abbreviations: LDL-C, low-density lipoprotein cholesterol; TG, triglycerides; HDL-C, high-density lipoprotein cholesterol; hsCRP, high sensitive C-reactive protein; FMD, flow-mediated dilatation; VWA, vessel wall area; maxVWT, maximal vessel wall thickness.
Values are mean ± SD except for TG and hsCRP (median [interquartile ranges]).

We previously compared the effects of intensive LDL-C lowering therapy using 20 mg/day atorvastatin with 5 mg/day on aortic plaques detected by MRI in hypercholesterolemic patients, which respectively achieved reductions in LDL-C levels of −47 and −34% [11]. The differences in LDL-C reduction were accompanied by distinct responses in thoracic aorta plaque areas due to high dose (−18%) and low dose (+4%) atorvastatin, indicating that greater LDL-C reduction resulted in greater plaque regression. Although atorvastatin therapy was less effective on abdominal aortic plaques than thoracic ones, an advantage of high dose atorvastatin was still observed (+3% vs. +12%, 20 mg vs. 5 mg).

Our 2 studies are consistent in that high-dose statin yielded greater plaque regression in the thoracic aorta, whose plaque is more susceptible to regression than that in the abdominal aorta. Although the 2 studies are not directly comparable, rosuvastatin significantly (in intensive group, nearly significant) reduced plaque areas in the abdominal aorta (Table 3), whereas high dose atorvastatin did not, and low dose atorvastatin increased it. Moreover, dose responses in abdominal aortic plaques were observed in atorvastatin, but not in rosuvastatin therapy. Although the precise reasons for these observations are unclear, the following differences might account for the discrepancies: 1) prior statin use (0% vs. 40%), 2) VWA at baseline (160 vs. 135 mm^2, thoracic; 108 vs. 83 mm^2, abdominal), 3) LDL-C levels at baseline (164 vs. 200 mg/dL), 4) follow-up LDL-C levels (115/86 vs. 132/108 mg/dL, standard/intensive), 5) age (64 vs. 59), 6) current smokers (27% vs. 8%), 7) coronary artery diseases (25% vs. 0%), 8) type 2 diabetes (30% vs. 18%). Greater regression in abdominal aortic plaques due to rosuvastatin as compared to atorvastatin might be attributable, in particular, to the difference in prior statin use and follow-up LDL-C levels. However, in the case of the thoracic aorta, these interpretations cannot be

applied. The difference in baseline LDL-C levels may also account for the difference in VWA for thoracic plaques where intensive treatment with rosuvastatin reduced this parameter to a lesser extent as compared with atorvastatin (−9.1% vs. −18% respectively). However, there are 2 studies on ethnic populations other than Japanese in which an unknown dose [16] and 80 mg [20] of simvastatin reduced atherosclerotic plaques in the thoracic aorta by 8% and 10%, respectively, findings comparable to those in the present study. Overall, in our opinion, it is conceivable that discrepancies between the studies with rosuvastatin and atorvastatin are due to multiple factors such as patients' characteristics, study design, and difference in drugs per se.

Consistent with many previous studies [21], the present and our previous study [11] demonstrated that both intensive and standard therapies yielded a significant reduction in hsCRP levels, which was correlated with plaque regression in the thoracic aorta. However, in contrast to our previous study, aortic plaque regression was not associated with LDL-C reduction (Tables 4 and 5) in the present one. Other researchers have reported that aortic plaque regression evaluated by MRI was associated with LDL-C reduction due to statin therapy [22,23]. Although the reason for this discrepancy is unclear, it might possibly be due to a difference in the study population. The current study consisted of a heterogeneous population including both primary and secondary prevention patients who had a wide range of on-treatment LDL-C levels and doses of rosuvastatin, despite the fact that on-treatment LDL-C levels, in theory, tend to converge with treat-to-target as compared with the fire-and-forget approach. Such variations might affect the statistical results obtained by performing simple correlation (Table 4) and linear model (Table 5) analyses.

On the other hand, these observations highlighted the importance of the response in hsCRP levels in thoracic, but not abdominal, plaque regression due to rosuvastatin therapy (Tables 4 and 5). In agreement with our present and previous [11] findings, serial IVUS observations in the REVERSAL trial [6] demonstrated that reduction in hsCRP levels was the next most powerful predictor to LDL-C levels. Furthermore, Saam et al. [24] observed that, during follow-up of asymptomatic subjects including statin-users (69%), serial MRI imaging of carotid artery revealed a positive association of plaque progression with baseline CRP levels, but not with lipid levels. These findings suggest that statin therapy reduces atherosclerotic plaques not only by lowering LDL-C levels, but also by decreasing hsCRP levels, which is supported by several basic studies reporting a direct influence of CRP in atherogenesis [25,26]. Backing up this concept, the PROVE-IT TIMI-22 study [2] demonstrated that greater reduction in hsCRP levels due to statin also resulted in better clinical outcomes.

Whether greater regression of atherosclerotic plaques is directly correlated with clinical outcomes is a relevant and important question and to our knowledge, no one has yet addressed it. In most studies evaluating plaque regression, the sample sizes had been too small and the observation periods too short to detect differences in incidence of clinical events. However, the PROVE-IT TIMI-22 study [2] reported a greater reduction in cardiovascular events with intensive lipid lowering using atorvastatin 80 mg/day as compared to standard therapy using pravastatin 40 mg/day. Interestingly, the REVERSAL study [6], which used the same drugs and doses, demonstrated that intensive therapy yielded greater plaque regression using IVUS. Therefore, IVUS findings at least indicate a direct relationship between the burden of coronary atherosclerosis and adverse cardiovascular events [27]. Although these observations suggest that the answer to the above question is "yes", further studies are needed to provide direct evidence.

4.1. Study limitations

The subjects of this study were all Japanese and the maximal dose used was the maximal dose approved in Japan, 20 mg. Therefore, our results may not be applicable to populations in other countries. Next, we conducted this trial as an open label one with patients and their attending physicians aware of the rosuvastatin doses in the titration protocol, creating a potential bias.

In conclusion, using MRI, the present study demonstrated that intensive statin therapy with titration aimed at achieving lower LDL-C goals provided additional plaque regression in the thoracic aorta as compared to standard therapy. Also plaque regression in the thoracic aorta was correlated with hsCRP reduction. These observations suggest that a "lower the better" strategy using the treat-to-target approach in the real clinical setting may provide better clinical outcomes in dyslipidemic patients.

Disclosures

There is no relationship with industry that I should disclose.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.atherosclerosis.2013.10.007.

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