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Original Scientific Paper

Effect of lipid-lowering therapy with atorvastatin on atherosclerotic aortic plaques: a 2-year follow-up by noninvasive MRI

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Background Using MRI, we reported plaque regression in thoracic aorta and retardation of plaque progression in abdominal aorta by 1-year atorvastatin. However, association between serial plaque changes and LDL-cholesterol levels was not fully elucidated.

Design A prospective, randomized, open-label trial.

Methods We investigated the long-term effect of 20 versus 5-mg atorvastatin on thoracic and abdominal plaques and the association between plaque progression and on-treatment LDL-cholesterol levels in 36 hypercholesterolemic patients. MRI was performed at baseline and 1 and 2 years of treatment. Vessel wall area change was evaluated.

Results The 20-mg dose markedly reduced LDL-cholesterol levels (−47%) versus 5-mg (−35%) dose. After 2 years of treatment, regression of thoracic plaques was found in the 20-mg group (−15% vessel wall area reduction), but not in the 5-mg group (+7%). Although the 20-mg dose induced plaque regression (−14%) from baseline to 1 year, no further regression was seen from 1 to 2 years of treatment (−1%). Regarding abdominal plaques, progression was found in the 5-mg group (+10%), but not in the 20-mg group (+2%). Plaque progression in the 5-mg group was found from baseline to 1 year (+8%), but not from 1 to 2 years (+2%). The degree of thoracic plaque regression correlated with LDL-cholesterol reduction ($r=0.61$), whereas thoracic plaque change from 1 to 2 years correlated with on-treatment LDL-cholesterol levels ($r=0.64$).

Conclusion Twenty milligrams of atorvastatin regressed thoracic plaques. However, maintaining low LDL-cholesterol levels was needed to prevent plaque progression. In abdominal aorta, only retardation of plaque progression was found after 2 years of 20-mg treatment. *Eur J Cardiovasc Prev Rehabil* 16:222–228 © 2009 The European Society of Cardiology

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Keywords: aorta, atherosclerotic plaque, lipid-lowering, MRI

Introduction

Recently, magnetic resonance imaging (MRI) has become a useful tool for the noninvasive evaluation of atherosclerotic plaques in the aorta and carotid arteries [1–4]. A good correlation regarding the aortic plaque extent was found between the MRI findings and histopathology in rabbit models [5]. In humans, the MRI evaluation of the thoracic aorta has been shown to closely correlate with transesophageal echocardiography findings [1]. Using MRI, we [6–9] and others [10] demonstrated the plaque regression in human aortas in response to lipid-lowering therapy. We recently reported the plaque regression in the thoracic aorta and the retardation of plaque progression in the abdominal aorta in response to 1-year intensive LDL-cholesterol (LDL-C) lowering with atorvastatin [8].

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However, the association between serial plaque changes and the on-treatment LDL-C levels has not been fully elucidated. This study therefore extended our previous study by elucidating the long-term effect of 20-mg (the maximal approved dose in Japan) versus 5-mg atorvastatin on aortic plaques and the association between plaque progression and the on-treatment LDL-C levels during a 2-year follow-up in patients with hypercholesterolemia.

Methods

Study patients

Our study was a prospective, randomized, open-label trial to elucidate the effect of 20 versus 5-mg atorvastatin on thoracic and abdominal aortic plaques in asymptomatic patients with hypercholesterolemia [8]. Any patient with a history of atorvastatin treatment was excluded. If patients had been taking other statins, these drugs were discontinued for at least 4 weeks. If patients had a serum LDL-C level of greater than 150 mg/dl, they underwent aortic MRI and were randomized to receive either 20 or 5-mg atorvastatin daily. Our study was approved by the institutional ethics committee. Written informed consent was obtained from all patients. Repeat MRI was scheduled after 1 and 2 years of treatment. Of the 50 patients randomized, 10 withdrew of their own accord, and four had adverse events (one cerebral infarction, one liver dysfunction, one body eruption, and one general fatigue). As a result, 18 patients in the 20-mg group and 18 in the 5-mg group had MRI after 1 and 2 years of treatment. The lipid levels were measured by standard laboratory methods. The plasma high-sensitivity C-reactive protein (hsCRP) levels were measured by a BNII nephelometer (Dade Behring, Germany).

Aortic MRI

MRI was performed on a Signa 1.5 T Cvi scanner (GE Medical Systems, Mount Prospect, Illinois, USA) using a phased-array body coil. As we previously reported [8,9], transverse proton density-weighted (PDW) and T2-weighted (T2W) images of the thoracic descending and abdominal aortas were obtained using a double-inversion-recovery fast spin-echo sequence without a fat saturation pulse. Imaging parameters were repetition time=2 RR intervals, echo time=10 (PDW) and 60 ms (T2W), 20-cm field of view, 4-mm slice thickness, 8-mm interslice gap, 256 × 256 matrix, and 32 echo-train. At baseline, nine slices of the thoracic aorta and nine slices of the abdominal aorta were obtained at 12-mm intervals, each of which covered about the 10-cm portions of the thoracic aorta and of the abdominal aorta. Plaque was defined as a clearly identified luminal protrusion with focal wall thickening.

Regarding MRI after 1 and 2 years of treatment, special attention was paid to match the images to those at baseline. As we previously reported [8,9], for each plaque, three contiguous slices (no interslice gap) were obtained, and the slice most closely matching the one at baseline was selected using several anatomical landmarks (i.e. vertebrae, intercostal and lumbar arteries, pulmonary arteries and veins, and mesenteric arteries). The matching procedure was performed by two observers, blinded to the treatment assignment, and all discrepancies were resolved by consensus.

MRI analysis

As we previously reported [8,9], the maximal vessel wall thickness (VWT_{max}), total vascular area (TVA), and lumen area (LA) in the matched slices with plaque at baseline and 1 and 2 years of treatment were measured three times by manual planimetry using an NIH Image software package (Scion Co., Frederick, Maryland, USA) and averages were used for statistical analysis. The vessel wall area (VWA) was calculated as TVA minus LA. All measurements were made by Y.M., blinded to the treatment assignment and the order of images. The intraobserver variability for VWT and VWA measurements were 0.1 mm and 1.3 mm^2, respectively [8].

Plaque characterization was based on the signal intensities of the plaque on PDW and T2W images [1,11]. Lipid components were identified as hyperintense on PDW and hypointense regions on T2W images. Calcium deposits were identified as hypointense regions on both images. As in our previous studies [3,8,9], T1W images were omitted to reduce the examination time.

Statistical analysis

Any differences between two groups were evaluated by the unpaired *t*-test for continuous variables and by the χ^2 test for categorical variables. Any differences among baseline and after 1 and 2 years of treatment were evaluated by repeated-measure analysis of variance with the Bonferroni test for continuous variables. Correlations between the plaque changes and LDL-C levels or other factors were evaluated by Pearson's correlation coefficient. The independent associations between plaque changes and these factors were evaluated using a stepwise multiple linear regression analysis. A P value of less than 0.05 was considered to be statistically significant.

Results

At baseline, age, sex, risk factors, and lipid levels did not differ between the two groups (Table 1). The 20-mg dose markedly reduced LDL-C levels (−47%) in comparison with the 5-mg dose (−33%) ($P < 0.001$). Both the 20 and 5-mg doses also reduced hsCRP levels by −52 and −30%, respectively. However, after a period from 1 year to 2 years of treatment, no change was observed in the lipid or hsCRP levels in either group.

A total of 45 thoracic aortic plaques (25 in the 20-mg group and 20 in the 5-mg group) and 63 abdominal

Table 1 Demographic and laboratory data at baseline and after 1 and 2 years of treatment

	20-mg dose ($n=18$)							5-mg dose ($n=18$)							
	Baseline	Baseline versus 1 year	1 year	1 year versus 2 years	2 years	Change from baseline to 2 years (%)	*P* value	Baseline	Baseline versus 1 year	1 year	1 year versus 2 years	2 years	Change from baseline to 2 years (%)	*P* value	20-mg versus 5-mg
Age (years)	59±7							60±6							NS
Sex (male) (%)	7 (39)							6 (33)							NS
Smoking (%)	1 (6)							2 (11)							NS
Diabetes (%)	3 (17)							2 (11)							NS
Hypertension (%)	6 (33)							6 (33)							NS
Prior stain use (%)	7 (39)							7 (39)							NS
SBP (mmHg)	126±14	NS	127±12	NS	125±12	−1	NS	126±11	NS	124±11	NS	126±9	0	NS	NS
LDL-C (mm/dl)	200±47	<0.001	107±34	NS	106±36	−47	<0.001	195±35	<0.001	129±32	NS	130±33	−33	<0.001	<0.001
TG (mg/dl)	162±50	<0.001	113±37	NS	113±35	−26	<0.001	160±85	NS	141±85	NS	125±59	−22	<0.01	NS
HDL-C (mg/dl)	62±15	NS	64±16	NS	65±15	+5	NS	63±14	NS	64±11	NS	65±12	+3	NS	NS
hsCRP (mg/l)	0.71	<0.001	0.38	NS	0.34	−52	<0.001	0.60	<0.02	0.38	NS	0.42	−30	<0.05	NS

P value compared with the baseline. Data are presented as mean ± SD or number (%) of patients, except for hsCRP that is presented as the median value. Diabetes was defined as fasting plasma glucose level of ≥ 126 mg/dl or treated with insulin or hypoglycemic drugs. Hypertension was defined as blood pressures of ≥ 140/90 mmHg or treated with medication. HDL-C, HDL-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; TG, triglyceride.

plaques (31 in the 20-mg group and 32 in the 5-mg group) were followed up for 2 years. At baseline, there was no difference in VWT_{max} or VWA between the two groups. Calcification was found in 12% of thoracic and 16% of abdominal plaques in the 20-mg group versus 10% of thoracic and 19% of abdominal plaques in the 5-mg group (P = NS). Only one thoracic plaque was identified as a plaque with a lipid-rich core, as we previously reported [8].

After 2 years of treatment, a significant regression of thoracic plaques was found in the 20-mg group (−15% VWA reduction, $P < 0.001$) but not in the 5-mg group (+7%) (Fig. 1). Although the 20-mg dose induced plaque regression (−14%) from baseline to 1 year of treatment, no further regression was observed after a period from 1 year to 2 years of treatment (−1%). Regarding abdominal plaques, progression was found in the 5-mg group (+10%, $P < 0.002$), but not in the 20-mg group (+2%). However, a significant progression in the 5-mg group was observed from baseline to 1 year (+8%), but not from 1 to 2 years of treatment (+2%).

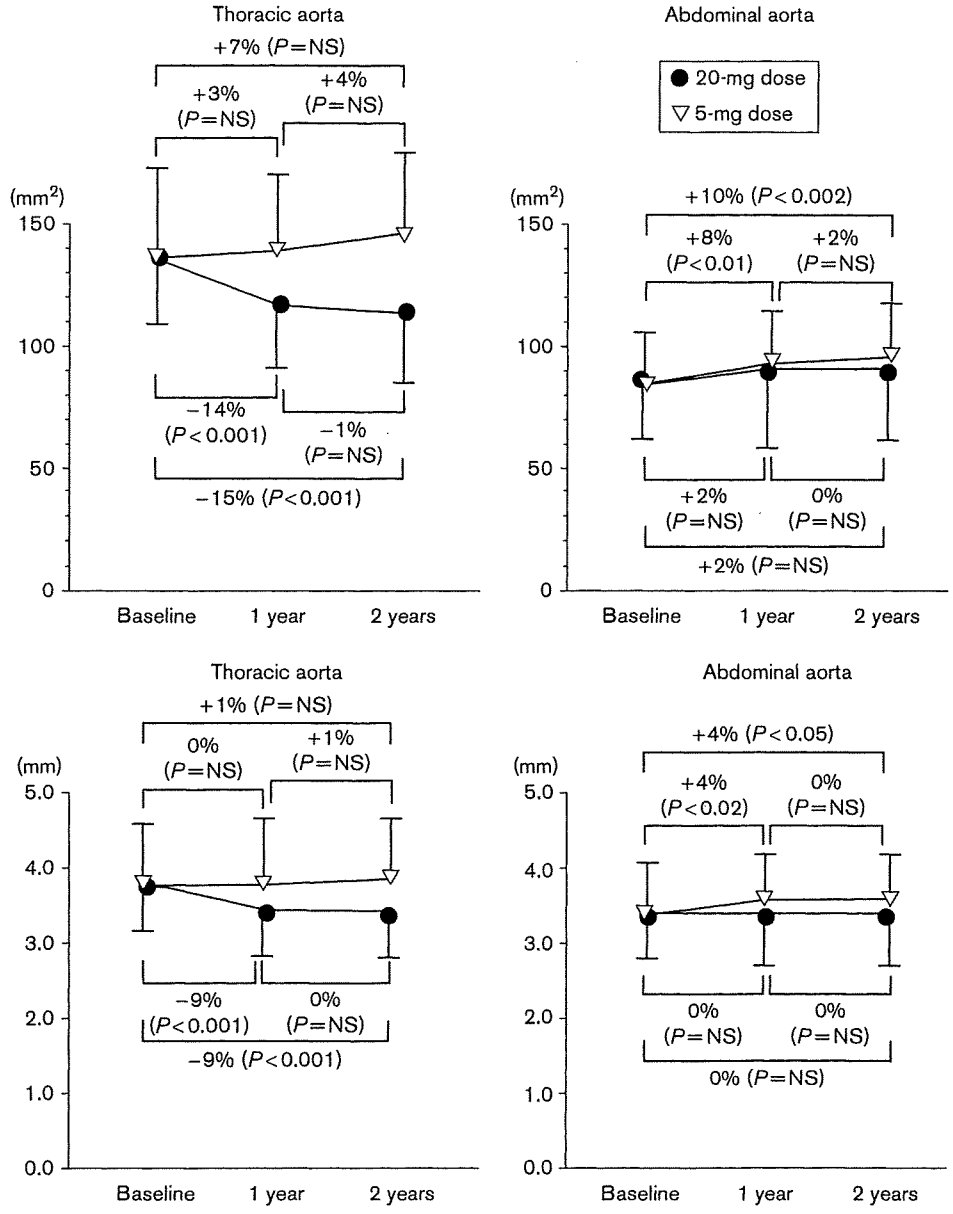
From baseline to 1 year, the VWA change in thoracic plaques correlated well with the degree of LDL-C reduction ($r = 0.61$), but there was only a weak correlation in abdominal plaques ($r = 0.30$) (Table 2). After a period from 1 year to 2 years of treatment, no significant plaque changes were found in either group (Fig. 1). However, the VWA change in thoracic plaques correlated with the LDL-C level after treatment (on-treatment LDL-C level), the degree of LDL-C reduction, and the on-treatment HDL-C level (Table 2). As shown in Fig. 2, the VWA change in thoracic plaques from 1 to 2 years of treatment correlated well with the on-treatment LDL-C level (r=0.64). No such correlations were found in abdominal plaques. In the multiple linear regression analysis (Table 3), the VWA changes from baseline to 1 year in both thoracic and abdominal plaques were related to the degree of LDL-C reduction. However, from 1 to 2 years of treatment, the VWA change in thoracic plaques was found to be related only to the on-treatment LDL-C level. Examples of plaque regression or progression are shown in Fig. 3.

Discussion

Intensive LDL-C lowering with 20-mg atorvastatin induced plaque regression in thoracic aorta. Plaque regression was found from baseline to 1 year, but no further regression was found after a period from 1 year to 2 years of treatment. From baseline to 1 year, the degree of plaque regression was related to the degree of LDL-C reduction, whereas the plaque change from 1 to 2 years of treatment was closely related to the on-treatment LDL-C levels. In the abdominal aorta, even 2-year treatment with 20-mg atorvastatin could not induce plaque regression.

Using MRI, the previous study, looking at the effect of 80-mg versus 20-mg simvastatin on thoracic aortic plaques, showed that greater LDL-C reduction was associated with a larger and faster regression [7]. Simvastatin reduced LDL-C levels by −38% and VWA in thoracic plaques by −11% at 1 year, and a further regression (−5%) was found from 1 to 2 years [6]. This study showed that 20-mg atorvastatin induced marked LDL-C reduction (−47%) and VWA reduction in thoracic plaques (−14%) after 1 year of treatment. However, no further regression (−1%) was found after a period from 1 year to 2 years of treatment. Using ultrasound, the Atorvastatin versus Simvastatin on Atherosclerosis Progression Trial reported 80-mg atorvastatin to induce marked LDL-C reduction (−50%) and a regression of carotid intima-media thickness during 2 years of treatment, but most of the regression was found at 1 year [12]. Therefore,

Fig. 1



Changes in vessel wall area (VWA) and maximal vessel wall thickness after 1 and 2 years of treatment. After 2 years of treatment, a regression of thoracic plaques was found in the 20-mg group (−15% VWA reduction) but not in the 5-mg group (+7%). The 20-mg dose induced plaque regression (−14%) from baseline to 1 year, but no further regression was observed after a period from 1 to 2 years (−1%). In abdominal plaques, progression was found in the 5-mg group (+10%), but not in the 20-mg group (+2%). However, progression in the 5-mg group was found from baseline to 1 year (+8%), but not from 1 to 2 years of treatment (+2%).

greater LDL-C reduction would cause a larger and faster plaque regression, and such plaque regression would occur within 1 year of intensive LDL-C lowering therapy. Lima *et al.* [10] reported plaque regression in the thoracic aorta to be strongly associated with LDL-C reduction. This study also showed the degree of plaque regression in the thoracic aorta to closely correlate with LDL-C reduction ($r = 0.61$). The degree of LDL-C reduction appeared to be an important factor for plaque regression in the thoracic aorta.

From 1 to 2 years of treatment, the change in thoracic plaques closely correlated with the LDL-C level achieved after treatment ($r = 0.64$). This on-treatment LDL-C level was an independent factor for plaque progression in the thoracic aorta after a period from 1 to 2 years of treatment. Therefore, maintaining low LDL-C levels appeared to be an important factor for the prevention of plaque progression in the thoracic aorta. At least, maintaining LDL-C levels lesser than 110 mg/dl may be needed to prevent plaque progression in the thoracic

aorta (Fig. 2). For coronary plaques, Birgelen *et al.* [13] reported plaque area changes by intravascular ultrasound to correlate with LDL-C levels ($r = 0.41$) and an LDL-C level of less than 75 mg/dl to predict no plaque progression. Hong *et al.* [14] also reported LDL-C levels to be related to coronary plaque changes ($r = 0.47$) and an LDL-C level of less than 100 mg/dl to predict no progression. Hence, maintaining much lower LDL-C levels may therefore be needed to prevent plaque progression in the coronary arteries than in the thoracic aorta.

Table 2 Correlations between changes in vessel wall area and lipid levels: simple linear correlation coefficient

	Percent changes in VWA of thoracic aorta			
	From baseline to 1 year		From 1 to 2 years	
	r	*P* value	*r*	*P* value
On-treatment LDL-C level (mg/dl)	0.47	<0.001	0.64	<0.001
Percent change in LDL-C (%)	0.61	<0.001	0.44	<0.002
On-treatment HDL-C level (mg/dl)	−0.12	NS	−0.26	<0.05
Percent change in HDL-C (%)	0.03	NS	0.12	NS
Percent change in hsCRP (%)	0.50	<0.001	−0.20	NS
Age at baseline (years)	0.01	NS	0.14	NS
Systolic BP (mmHg)	−0.06	NS	−0.02	NS
VWA at baseline (mm^2)	−0.07	NS	−0.04	NS
	Percent changes in VWA of abdominal aorta			
On-treatment LDL-C level (mg/dl)	0.32	<0.01	0.16	NS
Percent change in LDL-C (%)	0.30	<0.01	0.17	NS
On-treatment HDL-C level (mg/dl)	−0.30	<0.01	−0.16	NS
Percent change in HDL-C (%)	−0.10	NS	−0.07	NS
Percent change in hsCRP (%)	−0.02	NS	−0.17	NS
Age at baseline (years)	0.30	<0.01	0.11	NS
Systolic BP (mmHg)	0.04	NS	−0.01	NS
VWA at baseline (mm^2)	−0.08	NS	−0.01	NS

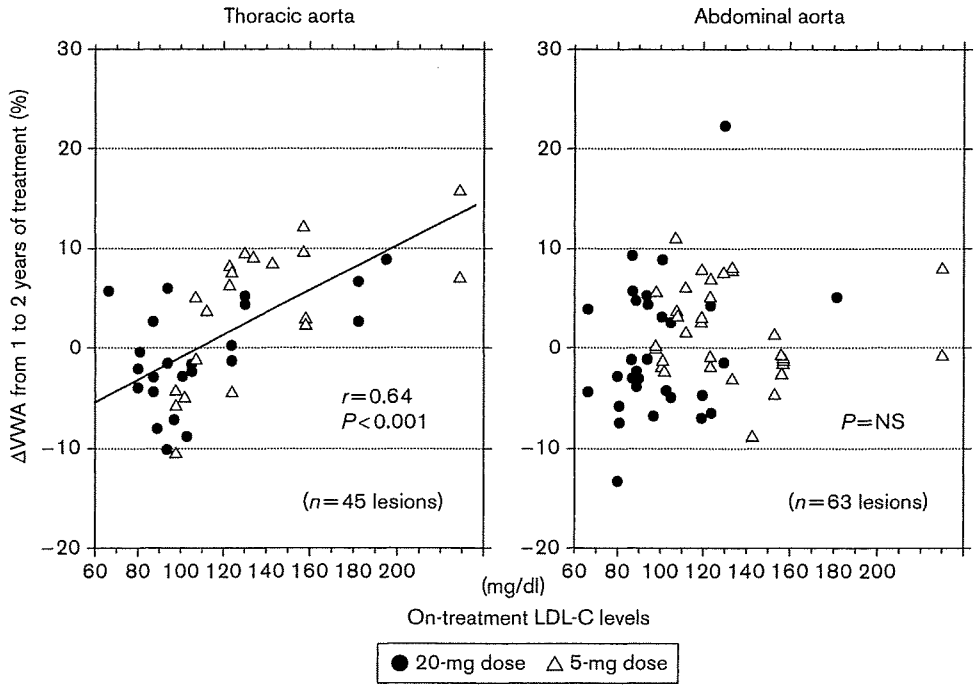
BP, blood pressure; HDL-C, HDL-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, LDL-cholesterol; SBP, systolic blood pressure; VWA, vessel wall area.

Table 3 Correlations between changes in vessel wall area and lipid levels: stepwise multiple linear regression analysis

	Percent changes in VWA of thoracic aorta			
	From baseline to 1 year		From 1 to 2 years	
	β	*P* value	β	*P* value
On-treatment LDL-C level (mg/dl)	0.29	NS	0.60	<0.002
Percent change in LDL-C (%)	0.53	<0.001	0.10	NS
On-treatment HDL-C level (mg/dl)	0.02	NS	−0.02	NS
Percent change in hsCRP (%)	0.37	<0.005	−0.21	NS
Age at baseline (years)	0.08	NS	0.18	NS
	Percent changes in VWA of abdominal aorta			
On-treatment LDL-C level (mg/dl)	0.08	NS	0.03	NS
Percent change in LDL-C (%)	0.36	<0.02	0.13	NS
On-treatment HDL-C level (mg/dl)	−0.16	NS	−0.03	NS
Percent change in hsCRP (%)	−0.08	NS	−0.11	NS
Age at baseline (years)	0.23	NS	−0.02	NS

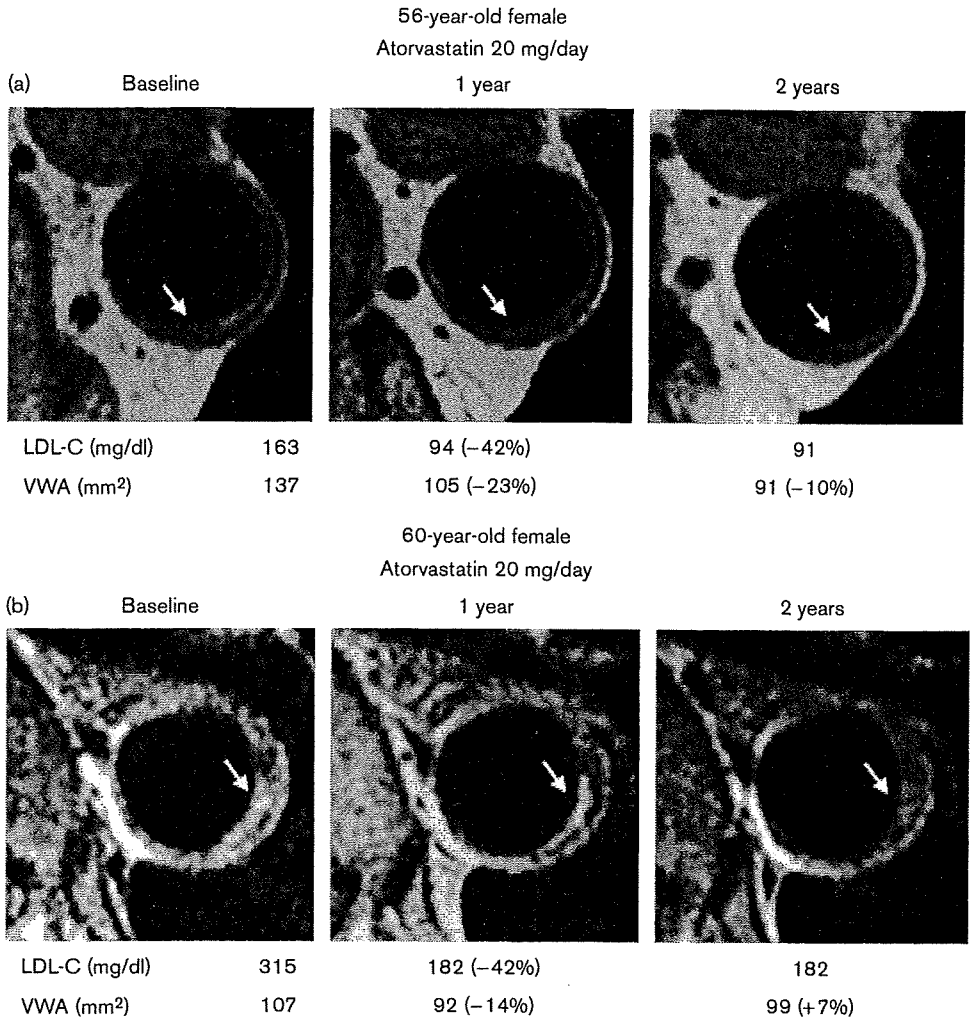
β, regression coefficient; HDL-C, HDL-cholesterol; hsCRP, high-sensitivity C-reactive protein; LDL-C, LDL-cholesterol; VWA, vessel wall area.

Fig. 2



Correlations between the on-treatment LDL-C level and the percent change in VWA (ΔVWA) from 1 to 2 years of treatment. In thoracic plaques, the VWA change after a period from 1 to 2 years of treatment correlated well with the on-treatment LDL-C level ($r = 0.64$). No such correlation was found in abdominal plaques.

Fig. 3



Images at baseline and after 1 and 2 years of treatment. (a) A thoracic plaque that showed a regression (−23% VWA reduction) after 1 year, by 42% LDL-C reduction with 20-mg atorvastatin. After a period from 1 to 2 years, a further regression (−10%) was found with an LDL-C level of 91 mg/dl; (b) a thoracic plaque that showed a regression (−14%) after 1 year, by 42% LDL-C reduction. However, after a period from 1 to 2 years, a progression (+7%) was observed with an LDL-C level of 182 mg/dl. Arrows indicate plaques.

Regarding abdominal plaque, even 2-year 20-mg atorvastatin could not cause regression. In rabbits fed with a cholesterol diet, the thoracic aorta showed more severe atheroma than the abdominal aorta [15]. Using ultrasonography, Tribouilloy *et al.* [16] reported an association between LDL-C levels and thoracic plaques, whereas Giral *et al.* [17] found no association between LDL-C and abdominal plaques. Using MRI, we previously reported LDL-C levels to correlate with the plaque extent in the thoracic aorta but not in the abdominal aorta [2]. Plaque formation in the thoracic aorta may thus be more closely related to LDL-C levels than in the abdominal aorta. Therefore, LDL-C lowering is more likely to be effective for plaque regression in the thoracic aorta.

Our study has several limitations. First, our study was performed on a small number of Japanese patients. The 20-mg dose was used as the higher dose of atorvastatin, because it is the maximal approved dose in Japan. The 20-mg dose is less than the dose (80 mg) in trials in Western countries [12,18]. Therefore, our results may not be applicable to other ethnic groups, but the degree of LDL-C reduction (−47%) by 20 mg in this study was similar to that with 80 mg in the Atorvastatin versus Simvastatin on Atherosclerosis Progression Trial (−50%) [12]. Second, of the 50 patients randomized, only 36 had MRI after 1 and 2 years of treatment. This may have caused some selection bias and have confounded the results. Third, all images were obtained without fat

saturation pulse, thereby causing some water–fat shift artifacts. In future studies, images should be obtained with fat saturation pulse. Finally, because TVA and VWT were measured by one observer, no interobserver variability was evaluated in our study. Therefore, the method of measurement may not be applicable to other laboratories, and further study will be needed.

In conclusion, 20-mg atorvastatin treatment induced plaque regression in the thoracic aorta. Plaque regression was, however, found from baseline to 1 year, but no further regression was found after a period from 1 to 2 years of treatment. The degree of plaque regression was related to the degree of LDL-C reduction, whereas the plaque change from 1 to 2 years of treatment was closely related to the on-treatment LDL-C levels. Maintaining low LDL-C levels thus appeared to be an important factor for preventing plaque progression. In the abdominal aorta, only the retardation of plaque progression was found, even after 2 years of 20-mg treatment. Between the thoracic and abdominal plaques, there may be some difference in the susceptibilities to LDL-C lowering and on-treatment LDL-C levels.

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