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Early Effect of Lipid-Lowering Therapy With Pitavastatin on Regression of Coronary Atherosclerotic Plaque

—— Comparison With Atorvastatin ——

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Background: Virtual histology intravascular ultrasound (VH-IVUS) is used to diagnose coronary plaques and evaluate statin therapy. However, in most cases, quantitative changes in plaques have been evaluated in the chronic stage. We evaluated the quantitative and qualitative early effects of 2 statins on coronary lesions using VH-IVUS.
Methods and Results: Patients with acute coronary syndrome who underwent emergency percutaneous coronary intervention (PCI) were randomly assigned to receive pitavastatin (n=80; 2 mg/day) or atorvastatin (n=80; 10 mg/day) immediately after PCI. All patients underwent a blood lipid test and VH-IVUS evaluation of non-PCI lesions at admission and after 2–3 weeks of statin administration. After treatment, total cholesterol and low-density lipoprotein-cholesterol (LDL-C) showed significant decreases to similar levels in each group (P<0.001). In the pitavastatin group, the plaque volume index and fibrofatty volume index (FFVI) also decreased significantly. In patients from the pitavastatin group with a dense calcium ratio of ≤10% (n=61), the percentage changes in FFVI and LDL-C were correlated positively (r=0.305, P=0.017), whereas no significant changes were found after treatment in the atorvastatin group.
Conclusions: Fibrofatty composition and plaque volume decreased significantly following treatment with pitavastatin, which suggests that pitavastatin might have a higher affinity for fibrofat compared with atorvastatin. (*Circ J* 2009; **73:** 1466–1472)

Key Words: Atherosclerosis; Intravascular ultrasound; Pitavastatin; Virtual histology

Large-scale clinical studies have recently shown an inhibitory effect on cardiovascular events of lipid-lowering therapy with HMG-CoA reductase inhibitors (statins), indicating the usefulness of this therapy![1–8] The benefit is particularly marked in patients with coronary heart disease (CHD), and the guidelines of the American National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III positively state the utility of lipid-lowering therapy in reducing low-density lipoprotein (LDL)-cholesterol (C) to below 70 mg/dl in patients with coronary artery disease[9] In Japan, the guidelines for prevention of arteriosclerotic diseases specify a target value of LDL-C of less than 100 mg/dl for control of CHD patients in category C![10]

Evaluation of coronary arterial plaques by imaging diagnosis has progressed markedly in recent years. In the REVERSAL study, intravascular ultrasonography (IVUS) was used to compare the effect of lipid-lowering therapy between CHD patients treated with standard and active regimens, with the latter found to inhibit expansion of coronary plaques![11] Size reduction of coronary plaques on IVUS by statin treatment in patients with acute coronary syndrome (ACS) has also been reported in Japan (the ESTABLISH study)![12] Subsequent multicenter studies such as the JAPAN-ACS study have verified the ESTABLISH results through investigation of strong statin-induced volume reduction of coronary plaques![13–15] However, these studies have all evaluated quantitative changes of the plaques, and there have been fewer qualitative evaluations![16]

Spectral analysis of IVUS radiofrequency (RF) data can provide detailed quantitative and qualitative information on coronary plaque composition in vivo![17–21] Nasu et al found that in vivo characterization of coronary plaques by 'virtual histology (VH)' correlated favorably with the results of in vitro histopathological examination of tissue samples obtained by directional coronary atherectomy[22] In this study, we used VH-IVUS to evaluate short-term quantitative and qualitative changes in non-culprit lesions in a comparison of pitavastatin, a new strong statin, with atorvastatin after administration in the early stage (2–3 weeks) after onset of ACS. The follow-up period of 2–3 weeks was chosen to evaluate the inhibition of short-term events within 1 month by early statin administration after ACS onset, and to examine if the statin effect starts to appear in this period.

Methods

Study Design and Patient Population

The study was performed as a prospective, randomized, single-center trial to assess the effect of 2- to 3-weeks of

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Table 1. Baseline Clinical Characteristics

	Total (n=160)	Pitavastatin (n=80)	Atorvastatin (n=80)	P value
Age (years)	62.0±10.6	62.3±10.7	61.7±10.7	0.73
Men, n (%)	121 (75.6)	64 (80.0)	57 (71.3)	0.20
Body mass index (kg/m^2)	24.2±5.9	24.3±5.4	24.2±6.4	0.40
Hypertension, n (%)	65 (40.6)	33 (41.3)	32 (40.0)	0.87
Hyperlipidemia, n (%)	137 (85.6)	69 (86.2)	68 (85.0)	0.82
Diabetes, n (%)	85 (53.1)	41 (51.3)	44 (55.0)	0.63
Smoker, n (%)	53 (33.1)	28 (35.0)	25 (31.3)	0.61
Familial history of coronary artery disease, n (%)	23 (14.4)	11 (13.8)	12 (15.0)	0.83
Target coronary artery				0.38
Left assending artery, n (%)	63 (39.4)	34 (42.5)	29 (36.3)	
Left circumflex artery, n (%)	46 (28.8)	18 (22.5)	28 (35.0)	
Right coronary artery, n (%)	37 (23.1)	20 (25.0)	17 (21.3)	
Left main coronary artery, n (%)	14 (18.8)	8 (10.0)	6 (7.5)	
Medication				
Angiotensin II receptor blockers, n (%)	121 (75.6)	63 (78.8)	58 (72.5)	0.36
Angiotensin-converting enzyme inhibitors, n (%)	16 (10.0)	8 (10.0)	8 (10.0)	1.00
β-blockers, n (%)	61 (38.1)	36 (45.0)	25 (31.3)	0.07
Calcium-channel blockers, n (%)	72 (45.0)	38 (47.5)	34 (42.5)	0.53
Time of follow up (days)	17.5±4.1	17.8±5.0	17.2±2.8	0.18

Values are mean±SD.

treatment with 2 strong statins, pitavastatin and atorvastatin, based on serial IVUS analysis of quantitative or qualitative changes in atherosclerosis at non-percutaneous coronary intervention (PCI) sites. Patients with ACS with significant stenosis on initial coronary angiography who received PCI were eligible for the study, and 160 such patients were enrolled between February 2006 and June 2008. ACS was defined as unstable angina of Braunwald's class IIIB (angina at rest without increased creatine kinase (CK)-MB activity within 24 h before coronary angiography), non-ST-elevated myocardial infarction (MI) or ST-elevated MI. MI was diagnosed by the rise (>2 times) in serum creatine phosphokinase and positivity for troponin I. Exclusion criteria were failed PCI, recommended coronary artery bypass grafting (CABG), cardiogenic shock, administration of lipid-lowering drugs before enrollment, and renal or hepatic dysfunction. The patients were randomly divided into 2 groups (the pitavastatin and atorvastatin groups) immediately after coronary angiography and IVUS on admission, and oral administration of pitavastatin (2 mg/day; n=80) or atorvastatin (10 mg/day; n=80) was initiated. All other medications were chosen by the attending physicians. IVUS was performed again before discharge (after 2–3 weeks) and changes in serum lipid levels and IVUS data before and after treatment were evaluated. The study was approved by the local medical ethics committee (No. 1728) and informed consent was obtained from each patient.

Clinical Data and Coronary Risk Factors

Patient demographics, coronary risk factors (hypertension, diabetes mellitus, and history of smoking) and laboratory data were recorded for all the patients. Laboratory tests were performed at baseline and in follow up as routine clinical practice and were analyzed at the Dokkyo University School of Medicine.

Target Vessel Criteria

The 5 criteria for the target vessel were as follows: de novo and no significant plaque (angiographic lumen diameter stenosis <50%); calcification not limiting quantitative assessment of the cross-sectional area; angiographic reference diameter >3.0 mm and segment length of 5–15 mm; distance from the PCI site >5.0 mm; and serial high-quality IVUS studies of the entire segment.

IVUS Volume or RF Data Acquisition and Analysis

IVUS RF data were acquired using a 20-MHz 2.9 Fr phased-array IVUS catheter (Eagle Eye Gold, Volcano Corp, Rancho Cordova, CA, USA) and a dedicated console (IVG3, Volcano Corp). Automated continuous pullback (0.5 mm/s) was performed after intracoronary administration of isosorbide dinitrate (2.5 mg). The IVUS RF data were stored on a hard disk for off-line analysis. Manual contour detection of both the lumen and the media-adventitia interface was performed for the target segment. Quantitative and qualitative analysis of target segments was performed with VH software (IVUS VH1.3j, Volcano Corp). VH uses IVUS RF data to classify a plaque into 4 components: fibrous (FI), fibrofatty (FF), dense calcium (DC), and necrotic core (NC). These components are assigned color codes of green, greenish-yellow, white and red, respectively, and color-coded tissue maps are constructed. The components can be identified within the plaque, as previously validated by preliminary in vitro and in vivo studies[21,22] The IVUS volume analysis included the external elastic membrane volume (EEMV), lumen volume (LV), plaque volume (PV) and segment length. Each volume index (VI) was defined as the volume divided by the segment length[23,24] The change in each VI was calculated as [follow up VI−baseline VI] and the percentage change in VI as [(change in VI/baseline VI)×100]. All 160 cases or 119 cases with a DC ratio in the plaque of <10% in the IVUS baseline data were used in qualitative and quantitative evaluations by IVUS and the results were compared between the 2 groups. Based on reproducible landmarks (eg, a calcium deposit or side branch), the same segment was identified in the IVUS run at baseline and in follow up. IVUS analysis was performed once at baseline and at follow up by the same independent, experienced investigator who was blinded to the patient groups.

Sequential investigation of the data with exclusion of cases with a higher DC ratio showed a significant correlation between the % changes of LDL and FFVI in patients

Table 2. Lipid Profile at Baseline and Follow up

	Total (n=160)	Pitavastatin (n=80)	Atrvastatin (n=80)	P value
TC				
Baseline (mg/dl)	185.1±43.1	178.0±44.0	191.1±42.1	0.11
Follow up (mg/dl)	139.6±27.8***	133.1±26.6***	146.5±29.0***	0.01
Change in TC (%)	–22.2±14.6	–22.5±17.3	–22.0±11.8	0.87
Triglyceride				
Baseline (mg/dl)	103.1±57.1	86.2±55.2	120.3±59.0	0.01
Follow up (mg/dl)	78.6±30.6***	65.8±35.5**	91.4±25.7**	0.03
Change in TG (%)	–3.6±9.3	–8.0±8.4	0.8±10.1	0.61
HDL-C				
Baseline (mg/dl)	45.5±10.3	45.5±11.1	45.5±9.4	0.99
Follow up (mg/dl)	42.7±10.0	42.8±12.1	42.6±7.9	0.91
Change in HDL-C (%)	–3.8±2.8	–2.6±2.5	–5.1±3.0	0.60
LDL-C				
Baseline (mg/dl)	117.0±38.1	114.7±36.7	122.0±40.7	0.29
Follow up (mg/dl)	80.1±24.3***	74.8±20.6***	85.3±28.0***	0.02
Change in LDL-C (%)	–29.5±18.3	–31.0±20.1	–27.9±16.4	0.39

Values are mean±SD. **P<0.01 or ***P<0.001 vs baseline using a paired t-test.
TC, total cholesterol; HDL-C, high-density lipoprotein-cholesterol; LDL-C, low-density lipoprotein-cholesterol.

Table 3. Quantitative IVUS Data in All Cases for Each Group

	Total (n=160)	Pitavastatin (n=80)	Atorvastatin (n=80)	P value
Average Length (mm)	7.7±2.1	7.6±2.3	7.8±1.8	0.414
EEMI				
Baseline (mm^3/mm)	16.0±4.2	16.0±5.0	16.0±3.5	0.916
Follow up (mm^3/mm)	15.8±4.3	15.7±5.1	16.0±3.6	0.745
Percent change in volume (%)	–1.1±6.1	–1.6±6.3	–0.5±6.0	0.346
LVI				
Baseline (mm^3/mm)	6.0±2.0	6.0±2.2	6.0±1.8	0.858
Follow up (mm^3/mm)	6.0±2.1	6.0±2.5	5.9±1.7	0.878
Percent change in volume (%)	–0.1±13.7	0.1±11.4	–0.4±15.9	0.829
PVI				
Baseline (mm^3/mm)	10.0±2.8	10.0±3.3	10.0±2.3	0.977
Follow up (mm^3/mm)	9.9±2.8	9.7±3.2*	10.0±2.5	0.527
Percent change in volume (%)	–1.2±9.1	–2.6±9.3	0.2±8.9	0.107

Values are mean±SD. *P<0.05 vs baseline by using a paired t-test.
IVUS, intravascular ultrasound; EEMI, external elastic membrane index; LVI, lipid volume index; PVI, plaque volume index.

with a DC ratio of less than 10%. Data from this group are presented below.

Statistical Analysis

Statistical analysis was performed with Stat View 5.0 (SAS Institute, Cary, NC, USA). Quantitative data are presented as mean±standard deviation. Differences between the 2 groups were assessed with a chi-square test for categorical variables and with an unpaired Student's t-test for continuous variables. Differences in continuous variables between baseline and follow up were assessed with a paired Student's t-test. Percentage changes from baseline for all lipid parameters and VI values were tested using a 1-sample t-test. Correlations between the percentage change in each VI and lipid parameters were analyzed by linear regression analysis and a correlation coefficient was calculated. In addition, multiple regression analysis was performed using the baseline IVUS data, baseline and follow-up data for total cholesterol (TC), triglyceride (TG), high-density lipoprotein (HDL) and LDL, and statin types as predictor variables, and the % changes of PVI and FFVI as outcome variables. A value of P<0.05 was considered to be statistically significant in all analyses.

Results

Baseline Characteristics

Coronary risk factors and clinical characteristics did not differ significantly between the pitavastatin and atorvastatin groups (**Table 1**), and there were no serious cardiovascular events, including myocardial infarction, unstable angina or death, in either group.

Lipid Profile

Oral administration of each statin was continued throughout the study period with no adverse effects. The levels of TC and LDL-C were significantly reduced after drug administration in both groups (P<0.001 in each). Both baseline and follow-up TC and LDL-C were lower in the pitavastatin group, but the percentage changes did not differ significantly between the 2 groups. TG was also lower in the pitavastatin group at baseline and follow up, but there was also no significant difference in the percentage change between the 2 groups. HDL-C did not change significantly after treatment in either group, and there was no significant difference between the 2 groups at baseline, in follow up, or in the percentage change of HDL-C (**Table 2**).

Quantitative IVUS Data

There was no significant difference in the average target

Table 4. Quantitative IVUS Data in Cases of Dense Calcium Plaque Ratios of <10% for Each Group

	Total (n=119)	Pitavastatin (n=61)	Atorvastatin (n=58)	P value
Average Length (mm)	7.1±5.2	6.9±4.4	7.3±6.1	0.706
EEMI				
Baseline (mm^3/mm)	16.7±4.1	16.6±5.0	16.7±3.3	0.989
Follow up (mm^3/mm)	16.5±4.2	16.3±5.1	16.7±3.3	0.735
Percent change in volume (%)	–0.8±6.5	–1.8±7.0	0.2±6.0	0.150
LVI				
Baseline (mm^3/mm)	6.2±2.0	6.2±2.2	6.3±1.8	0.914
Follow up (mm^3/mm)	6.2±2.1	6.2±2.5	6.1±1.7	0.823
Percent change in volume (%)	0.1±14.8	0.57±12.6	–0.2±16.9	0.816
PVI				
Baseline (mm^3/mm)	10.4±2.8	10.4±3.3	10.4±2.3	0.977
Follow up (mm^3/mm)	10.3±2.8	10.1±3.3*	10.5±2.4	0.494
Percent change in volume (%)	–1.9±9.6	–3.2±10.4	1.2±8.8	0.034

Values are mean±SD. *P<0.05 vs baseline by using a paired t-test.
Abbreviations see in Table 3.

Table 5. Composition Data of IVUS in All Cases for Each Group

	Total (n=160)	Pitavastatin (n=80)	Atorvastatin (n=80)	P value
FIVI				
Baseline (mm^3/mm)	6.2±2.2	6.1±2.6	6.2±1.8	0.872
Follow up (mm^3/mm)	6.1±2.3	5.9±2.6	6.3±2.0	0.423
Percent change in volume (%)	–0.1±20.3	–1.8±22.2	1.6±18.4	0.401
FFVI				
Baseline (mm^3/mm)	1.5±1.0	1.2±0.9	1.8±1.0	0.002
Follow up (mm^3/mm)	1.4±1.0	1.0±0.8*	1.9±1.2	<0.001
Percent change in volume (%)	5.5±57.0	4.0±77.4	7.0±36.8	0.815
DCVI				
Baseline (mm^3/mm)	0.7±0.6	0.8±0.6	0.6±0.5	0.052
Follow up (mm^3/mm)	0.7±0.6	0.8±0.6	0.7±0.5	0.143
Percent change in volume (%)	22.5±68.9	15.5±76.6	29.4±61.2	0.268
NCVI				
Baseline (mm^3/mm)	1.6±1.0	1.9±1.1	1.4±0.8	0.015
Follow up (mm^3/mm)	1.6±1.0	1.9±1.1	1.3±0.8	0.001
Percent change in volume (%)	28.7±216.9	24.3±262.3	33.1±171.5	0.357

Values are mean±SD. *P<0.05 vs baseline by using a paired t-test.
FIVI, fibrous volume index; FFVI, fibro-fatty volume index; DCVI, dense calcium volume index; NCVI, necrotic core volume index. Other abbreviation see in Table 3.

Table 6. Composition Data of IVUS in Cases of Dense Calcium Plaque Ratios of <10% for Each Group

	Total (n=119)	Pitavastatin (n=61)	Atrvastatin (n=58)	P value
FIVI				
Baseline (mm^3/mm)	6.8±2.2	6.8±2.5	6.8±2.0	0.943
Follow up (mm^3/mm)	6.7±2.3	6.7±2.5	6.8±2.1	0.755
Percent change in volume (%)	0.3±21.1	–0.2±22.9	0.8±19.3	0.819
FFVI				
Baseline (mm^3/mm)	1.8±1.0	1.4±1.0	2.1±1.0	0.001
Follow up (mm^3/mm)	1.7±1.0	1.2±0.8*	2.1±1.2	<0.001
Percent change in volume (%)	0.1±45.4	–3.6±54.9	3.7±35.9	0.469
DCVI				
Baseline (mm^3/mm)	0.5±0.3	0.5±0.3	0.4±0.3	0.281
Follow up (mm^3/mm)	0.5±0.4	0.5±0.4	0.5±0.4	0.719
Percent change in volume (%)	26.1±75.2	17.1±88.2	35.2±62.3	0.276
NCVI				
Baseline (mm^3/mm)	1.4±1.1	1.8±1.2	1.1±0.9	0.005
Follow up (mm^3/mm)	1.4±1.0	1.7±1.1	1.1±0.8	0.001
Percent change in volume (%)	28.7±216.9	24.3±262.3	33.1±171.5	0.949

Values are mean±SD. *P<0.05 vs baseline by using a paired t-test.
Abbreviations see in Tables 3,5.

vessel length between the 2 groups (**Table 3**), and EEMVI, LVI and PVI did not differ between the groups at baseline, in follow up, or in the percentage changes. There was no significant change in EEMVI or LVI in either group, but PVI was significantly reduced in the pitavastatin group (–2.61±9.34%, P=0.011), but not in the atorvastatin group. In cases where DC was <10% in plaques in the quantitative IVUS data (pitavastatin group, n=61; atorvastatin group, n=58) (**Table 4**), there was no significant difference in the average target vessel length or in EEMVI or LVI at base-

Table 7. Correlation Between Each Composition Volume Index at Baseline (n=160)

Composition	Regression coefficient	P value
FIVI and FFVI	0.219	0.001
FIVI and NCVI	–0.766	<0.001
FIVI and DCVI	–0.703	<0.001
FFVI and NCVI	–0.644	<0.001
FFVI and DCVI	–0.528	<0.001
NCVI and DCVI	0.517	<0.001

Abbreviations see in Table 5.

line, in follow up, or in the percentage change between the sub-groups. There was also no significant change in EEMVI or LVI in either sub-group. There was no difference in PVI at baseline or in follow up between the sub-groups, but PVI was significantly reduced after administration in the pitavastatin sub-group (P=0.029). The percentage change in PVI in the pitavastatin sub-group was significantly smaller than that in the atorvastatin sub-group (–3.21±10.40% vs 1.19±8.78%, P=0.034).

Compositional IVUS Data

In the compositional IVUS data, neither the FIVI nor the DCVI differed at baseline, in follow up, or in the percentage change between the groups, and showed no significant changes in either group (**Table 5**). The baseline and follow-up values of the FFVI were significantly lower in the atorvastatin group (P=0.002 and P<0.001, respectively) and a comparison of these values showed a significant reduction after treatment only in the pitavastatin group (P=0.035). The NCVI was significantly greater at baseline and in follow up in the atorvastatin group (P=0.015 and P=0.001, respectively), but the change after treatment was not significant in either group. Similar baseline and follow-up values and percentage changes to those shown in **Table 5** were found in both groups for cases with a plaque DC ratio at baseline of less than 10% (**Table 6**).

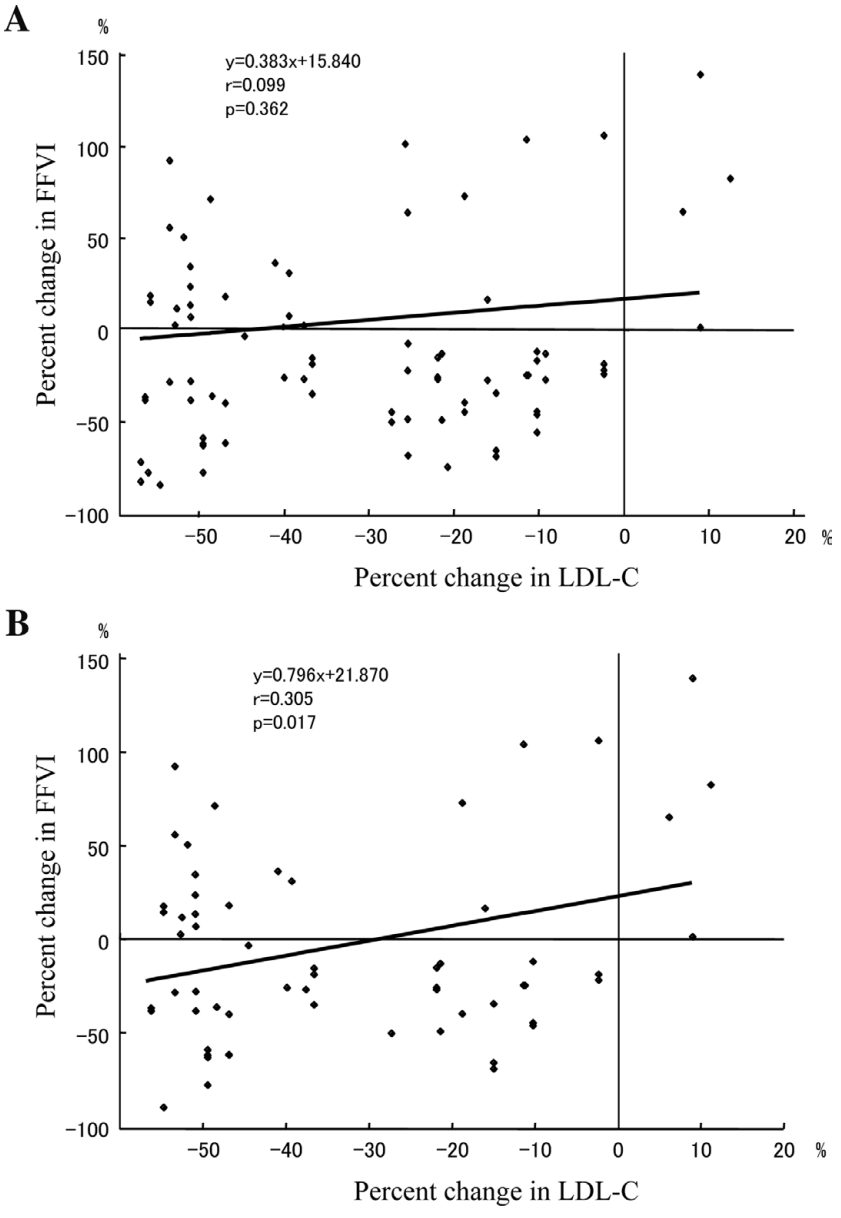

Figure. Correlation between the percentage change in low-density lipoprotein-cholesterol (LDL-C) and the percentage change in fibrofatty volume index (FFVI). In all patients in the pitavastatin group, there was no correlation between the percentage change in LDL-C and the percentage change in FFVI with pitavastatin (n=80; **A**), but these parameters showed a positive correlation in cases with a dense calcium plaque ratio at baseline of less than 10% with pitavastatin (n=61, r=0.305, P=0.017; **B**).

Correlations Between Each Compositional VI at Baseline
Correlations among compositional VI items at baseline in the 160 patients are shown in **Table 7**. Positive correlations were found between FI and FF and between FI and DC, whereas FI and NC, FI and DC, FF and NC, and FF and DC showed negative correlations.

Relationship Between Cholesterol and Serial IVUS Data
In the pitavastatin group, the percentage change in LDL was not significantly correlated with EEMVI, LVI or PVI from the quantitative IVUS data or the percentage changes in FIVI, NCVI or DCVI from the compositional IVUS data ($P>0.05$). The percentage change in LDL-C was not correlated with the percentage change in FFVI in all patients in the pitavastatin group (**Figure A**), but these parameters showed a positive correlation in cases with a plaque DC ratio at baseline of less than 10% ($r=0.305$, $P=0.017$; **Figure B**).

Multiple Regression Analysis
Multiple regression analysis was performed using the baseline IVUS data, baseline and follow-up data of TC, TG, HDL, and LDL, and statin types as predictor variables, and the % changes of PVI and FFVI as outcome variables. A mild correlation with a correlation coefficient of 0.213 was found between pitavastatin and % change of PVI ($P<0.001$).

Discussion

Pitavastatin or atorvastatin was administered to patients with ACS immediately after PCI, and short-term changes in lipids and IVUS findings were examined. Regarding the changes in lipids (**Table 1**), TC, TG and LDL-C showed similar significant decreases after administration of either statin, suggesting that pitavastatin and atorvastatin had an equivalent effect on blood lipids during the short observation period. In the quantitative IVUS data, PVI ranged from 2.6–3.2% in patients in the pitavastatin group and decreased significantly in patients with a DC of <10% compared to similar patients in the atorvastatin group. The lower PVI value compared to the value of 10.6% reported by Takashima et al[14] might have been due to the shorter observation period.

In the compositional IVUS data, FFVI was significantly reduced only in the pitavastatin group, suggesting that PVI reduction by pitavastatin contributed to the FFVI reduction. Interestingly, in 61 patients with a DC of less than 10%, only the percentage changes in FFVI and LDL-C were positively correlated ($r=0.305$, $P=0.017$; **Figure A**). In addition, as shown in **Table 7**, correlations between FI and FF and between NC and DC were present in the baseline plaque composition. In compositional IVUS, the FI and FF categories (consisting of FI components and lipids) might reflect relatively 'young' plaques, while the NC and DC categories might be due to 'older' plaques that mainly consist of necrotic substances and calcium, suggesting that pitavastatin affects young plaques, which can easily change, in the early stage. Recent clinical studies of pitavastatin in patients with ACS have reported a size reduction of coronary plaques[14] and early stabilization of carotid arterial plaques within 1 month[25]

The differences between pitavastatin and atorvastatin treatment in IVUS in the early stage might occur for the following 3 reasons. First, the main action of statins is enhancement of LDL receptor expression in the liver to decrease the blood LDL-C level. In addition to the antiarteriosclerotic effect, involvement of "pleiotropic effects" has been reported, such as direct action on blood vessels, promotion of smooth muscle cell proliferation, inhibition of migration of these cells, and an anti-inflammatory effect[26] Pitavastatin has also been reported to improve vascular endothelial function more rapidly than atorvastatin[27] suggesting that the pleiotropic effects of pitavastatin are stronger than those of atorvastatin. Second, transfer of the drug to blood vessels at a pharmacologically sufficient concentration is important for stabilization and size reduction of plaques. The maximum blood concentration (C_{max}) of atorvastatin at a dose of 10 mg is 3 nmol/L[28] whereas that of pitavastatin at a dose of 2 mg is 82.5 nmol/L (36.3 ng/ml)[29] showing that the C_{max} of pitavastatin is higher than that of atorvastatin. Third, the concentration of atorvastatin required to promote vascular smooth muscle growth or inhibit migration in vitro is 1,000 nmol/L[28] while that of pitavastatin is as low as 10 nmol/L.[30] These findings suggest that the direct pleiotropic effect of pitavastatin on vascular wall plaques is stronger than that of atorvastatin and that transfer of pitavastatin to blood vessels is more efficient. Therefore, a sufficient concentration of pitavastatin might be present to maintain the pleiotropic effect, leading to rapid manifestation of the pharmacological activity of pitavastatin.

Study Limitations
The small number of controls for the baseline and follow-up lipid profile data and IVUS data for TG, LDL, FFVI, and NCVI might have affected the results and this requires further investigation using an increased number of cases. As described in many reports, it is possible that thrombus was present in the observation of regression of the PV in the acute phase because their discrimination is difficult on IVUS, and this might also have influenced the results. Moreover, the accuracy and reproducibility of identification of tissue properties on VH-IVUS might be uncertain[31] and this also requires further study. The study focused on the effects of statins over a short period, but long-term observation is necessary to judge the clinical efficacy. In addition, drug potency was judged to be equivalent based on similar changes in the blood lipid levels, but a dose-setting study might be necessary to establish the equivalence of potency with certainty. Within these limitations, the results are significant from an academic perspective because they show that the plaque regression course can be observed using VH-IVUS. Clinically, the study shows that statin treatment can be used to inhibit short-term events following PCI.

Conclusion

Blood lipid levels were significantly lowered from pretreatment levels by both statins. Qualitative evaluation by IVUS showed that the FF composition was significantly reduced and PV was also reduced by pitavastatin compared to the respective values found with atorvastatin, suggesting that fibrofat is more sensitive to pitavastatin than to atorvastatin in the early stage.

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