Comparison of Change in Coronary Atherosclerosis in Patients With Stable Versus Unstable Angina Pectoris Receiving Statin Therapy (from the Treatment With Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology [TRUTH] Study)

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Although statin-induced regression in coronary atherosclerosis seems to be greater in patients with acute coronary syndrome than in those with stable coronary artery disease, no reports have examined this. The purpose of the present study was to compare the changes in coronary atherosclerosis in patients with stable versus unstable angina pectoris (AP). The effects of 8-month statin therapy on coronary atherosclerosis were evaluated using virtual histology intravascular ultrasound, and analyzable intravascular ultrasound data were obtained from 119 patients (83 patients with stable AP and 36 with unstable AP). A significant decrease in plaque volume was observed in patients with unstable AP (−2.2%, $p = 0.02$) but not in patients with stable AP. A significant increase in the necrotic-core component (0.30 mm^3/mm, $p = 0.009$) was observed only in patients with unstable AP. Significant positive correlations were observed between the percentage of change in platelet-activating factor acetylhydrolase and the percentage of change in plaque volume ($r = 0.346$, $p = 0.05$) in patients with unstable AP. No significant correlations were observed in patients with stable AP. Multivariate regression analyses showed that a reduction in platelet-activating factor acetylhydrolase was associated with regression in coronary atherosclerosis, particularly of the fibrous component ($\beta = 0.443$, $p = 0.003$), in patients with unstable AP. In conclusion, regression of the coronary artery plaque volume was greater, although statin therapy did not halt the increases in plaque vulnerability, in patients with unstable AP compared to those with stable AP. A reduction in the serum platelet-activating factor acetylhydrolase level was associated with regression in coronary atherosclerosis, particularly the fibrous plaque volume, in patients with unstable AP. **(Am J Cardiol 2013;111:923−929)**

Recent trials using intravascular ultrasound (IVUS) have shown that statins attenuate the progression or induce regression of coronary artery plaques.[1−4] Although previous studies have suggested that statin-induced regression in coronary atherosclerosis seems to be greater in patients with acute coronary syndrome than in patients with stable coronary artery disease, no reports have examined this issue. Platelet-activating factor acetylhydrolase (PAF-AH), a member of the phospholipase A2 superfamily, hydrolyzes oxidized phospholipids to generate the proinflammatory and proatherogenic products lysophosphatidylcholine and oxidized fatty acids.[5] These products play critical roles in endothelial cell dysfunction and smooth muscle cell apoptosis.[6] Epidemiologic studies have shown that PAF-AH independently predicted the risk of coronary events.[7−9] Furthermore, a recent IVUS study has demonstrated that a decrease in PAF-AH is associated with regression in coronary atherosclerosis in patients with acute coronary syndrome.[10] However, no reports

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have compared the effects of serum PAF-AH on coronary atherosclerosis in patients with acute coronary syndrome versus those with stable coronary artery disease. Therefore, in the present study, we compared the statin-induced changes in coronary atherosclerosis and the correlations between those changes and serum PAF-AH in patients with stable angina pectoris (AP) versus those with unstable AP.

Methods

The present study is a subanalysis of the Treatment With-Statin on Atheroma Regression Evaluated by Intravascular Ultrasound With Virtual Histology (TRUTH) study, a prospective, open-labeled, randomized, multicenter trial performed at 11 Japanese centers that used virtual histology-IVUS to evaluate the effects of 8 months of treatment with pitavastatin versus pravastatin on coronary artery plaque composition.[11] Details of the study design have been previously reported.[12] In brief, 164 patients with AP were randomized to either pitavastatin (4 mg/day, intensive lipid lowering) or pravastatin (20 mg/day, moderate lipid lowering) therapy after successful percutaneous coronary intervention (PCI) under virtual histology-IVUS guidance. None of the participants was taking a statin or another lipid-lowering drug at study enrollment. Follow-up IVUS examinations were performed after 8 months of statin therapy. The patients were included in the present study if they had measurable IVUS-detected lesions at enrollment and at the 8-month follow-up examination. A total of 119 patients (83 with stable AP [39 randomized to pitavastatin and 44 to pravastatin] and 36 with unstable AP [19 randomized to pitavastatin and 17 to pravastatin]) were included in the present subanalysis. We compared the serum lipid markers at baseline and at the 8-month follow-up examination, changes in these markers and the grayscale and virtual histology-IVUS parameters at baseline and the 8-month follow-up examination, and changes in these parameters between patients with stable AP and those with unstable AP.

The TRUTH trial was conducted in accordance with the Declaration of Helsinki and with the approval of the ethical committees of the 11 participating institutions. Each patient enrolled in the study provided written informed consent.

Details of the IVUS procedure and examination have been previously reported.[11] In brief, after PCI of the culprit lesion, the IVUS examination was performed for angiographic lesions with <50% lumen narrowing on the distal and proximal sides of the culprit lesion in the PCI vessel. An IVUS catheter (Eagle Eye Gold, Volcano, San Diego, California) was used, and a motorized pullback device withdrew the transducer at 0.5 mm/s. During pullback, a grayscale IVUS was recorded, and raw radiofrequency data were captured at the top of the R wave using a commercially available IVUS console (IVG3, Volcano).[13] After 8 months of statin therapy, the IVUS examination was repeated in the same coronary artery using the same type of IVUS catheter used at baseline.

All baseline and follow-up IVUS core laboratory analyses were performed by an independent and experienced investigator (M.T.) in a blinded manner. Before the IVUS analysis, the baseline and follow-up IVUS images were reviewed side by side on a display, and the distal and proximal ends of the target segment were identified on the basis of the presence of reproducible anatomic landmarks such as the side branch, vein, and stent edge. The target segment of interest had a ≥50% plaque burden according to the IVUS data.[13,14] Plaques close to the PCI site (within 5 mm) were excluded. In patients who underwent multivessel PCI, the vessel with the greatest plaque volume was selected. Manual contour detection of the lumen and external elastic membrane (EEM) was performed for each frame. Quantitative IVUS grayscale analysis was performed according to the guidelines of the American College of Cardiology and European Society of Cardiology.[15] All volumetric data were divided by the lesion length to obtain a volume index. The EEM volume index was calculated as $\Sigma(EEM_{cross\ sectional\ area\ (CSA)})$/lesion length. The lumen volume index was calculated as $\Sigma(LUMEN_{CSA})$/lesion length. The plaque volume index was calculated as $\Sigma(EEM_{CSA} - LUMEN_{CSA})$/lesion length. Virtual histology-IVUS data analysis was determined by grayscale border contour calculation, and the relative and absolute amounts of the different coronary artery plaque components were measured using IVUS Lab, version 2.2 (Volcano).

Blood examinations to measure the lipid levels were performed at baseline and at the 8-month follow-up visit. The serum lipid, apolipoprotein, and high-sensitivity C-reactive protein levels were measured at a central clinical laboratory (SRL, Tokyo, Japan). The serum PAF-AH and high-density lipoprotein−PAF-AH levels were measured at another central clinical laboratory (BML, Tokyo, Japan).

Statistical analyses were performed using StatView, version 5.0 (SAS Institute, Cary, North Carolina). The results are expressed as the mean ± SD or median and range. Differences in continuous variables between the 2 groups were compared using an unpaired Student's *t* test when the variables showed

Table 1
Baseline characteristics

Variable	Stable AP (n = 83)	Unstable AP (n = 36)	p Value
Age (yrs)	67 ± 10	65 ± 11	0.3
Men	68 (82%)	31 (86%)	0.58
Body mass index (kg/m^2)	24.5 ± 3.4	24.3 ± 3.2	0.71
Treatment allocation			0.56
Pitavastatin 4 mg/day	39 (47%)	19 (53%)	
Pravastatin 20 mg/day	44 (53%)	17 (47%)	
Diabetes mellitus	35 (42%)	15 (42%)	0.96
Hypertension	55 (66%)	20 (56%)	0.27
Smoker	31 (37%)	11 (31%)	0.18
Target coronary artery			0.32
Left anterior descending	46 (55%)	21 (58%)	
Left circumflex	5 (6%)	0 (0%)	
Right	32 (39%)	15 (42%)	
Medications			
Aspirin	81 (98%)	36 (100%)	0.35
Thienopyridines	82 (99%)	36 (100%)	0.51
Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	42 (51%)	19 (53%)	0.83
β Blockers	11 (13%)	2 (6%)	0.22
Calcium channel blockers	47 (57%)	13 (36%)	0.04
Follow-up duration (days)	226 ± 37	229 ± 36	0.67

Data are expressed as mean ± SD or n (%).