Usefulness of Follow-Up Low-Density Lipoprotein Cholesterol Level as an Independent Predictor of Changes of Coronary Atherosclerotic Plaque Size as Determined by Intravascular Ultrasound Analysis After Statin (*Atorvastatin* or *Simvastatin*) Therapy

Myeong-Ki Hong, MD, PhD[a], Cheol Whan Lee, MD, PhD[a], Young-Hak Kim, MD, PhD[a], Duk-Woo Park, MD[a], Se-Whan Lee, MD[a], Chang-Bum Park, MD[a], Jae-Sik Jang, MD[a], Ki-Hoon Han, MD[a], Sang-Sig Cheong, MD, PhD[b], Jae-Joong Kim, MD, PhD[a], Seong-Wook Park, MD, PhD[a], and Seung-Jung Park, MD, PhD[a,*]

Using serial intravascular ultrasound (IVUS), we identified independent predictors of changes in coronary plaque size in relation to serum lipid levels. One hundred three patients with nonstenotic coronary plaques underwent baseline and 12-month follow-up IVUS studies; 54 patients (52%) were treated with statins. Standard IVUS analyses were performed. Baseline IVUS study showed no statistical differences in mean external elastic membrane, lumen, and plaque/media (P&M) area between statin-treated and nonstatin-treated patients. Although there was an increase in mean P&M cross-sectional area in nonstatin-treated patients, mean P&M cross-sectional area decreased in statin-treated patients (0.11 ± 0.24 vs -0.20 ± 0.30 mm^2, $p < 0.001$). There was a positive relation between changes in mean P&M area and follow-up low-density lipoprotein (LDL) cholesterol level ($r = 0.430$, $p < 0.001$), follow-up total cholesterol level ($r = 0.365$, $p < 0.001$), changes in LDL cholesterol level ($r = 0.312$, $p = 0.002$), and changes in total cholesterol level ($r = 0.252$, $p = 0.012$). In multivariate linear regression analysis, the only independent predictor of changes in mean P&M area was follow-up LDL cholesterol level ($r = 0.469$, $p < 0.001$, 95% confidence interval 0.003 to 0.006). The cut-off value of follow-up LDL cholesterol for no change or a decrease in mean P&M area was <100 mg/dl at regression analysis. In conclusion, the present 12-month follow-up IVUS study showed that follow-up LDL cholesterol level was the only independent predictor of changes in coronary plaque size. When patients achieved a follow-up LDL cholesterol level <100 mg/dl, regression or no progression of coronary plaque was expected. Aggressive lipid-lowering treatments with statins to decrease the follow-up LDL cholesterol level to <100 mg/dl are recommended. **(Am J Cardiol 2006;98:866–870)**

Several studies in patients with coronary artery disease have demonstrated clinical benefits of statin therapy in decreasing major adverse cardiac events.[1–3] The beneficial effects of statin therapy on the long-term clinical outcome in those patients may be related to increased endothelial function, anti-inflammatory effects, plaque-modifying effects, antithrombotic effects, and decreased low-density lipoprotein (LDL) cholesterol level.[4] Despite substantially favorable long-term clinical outcomes after statin therapy, previous angiographic studies have shown only minimal changes in angiographic lumen dimension in target lesions in patients who were treated with statins.[5,6] Recently, several intravascular ultrasound (IVUS) studies have demonstrated the benefits of statin therapy to be involved in regression or no progression of coronary plaque size.[7–9] However, independent predictors of regression or no progression of coronary plaque size in relation to serum lipid levels were not sufficiently evaluated. The primary aims of the present study were to identify independent predictors of regression or no progression of coronary plaque size. We also evaluated the beneficial effects of statin therapy on regression or no progression of coronary plaque.

Methods

Study population: From the Asan Medical Center (Seoul, Korea) clinical and IVUS core laboratory database,

The [a]Department of Medicine, University of Ulsan College of Medicine, Asan Medical Center, and [b]GangNeung, Seoul, Korea. Manuscript received January 23, 2006; revised manuscript received and accepted April 18, 2006.

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* Corresponding author: Tel: 82-2-3010-3152; fax: 82-2-475-6898.
E-mail address: sjpark@amc.seoul.kr (S.-J. Park).

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we identified 103 patients with nonstenotic coronary plaques in de novo lesions who underwent baseline and 12-month follow-up IVUS studies. Fifty-four patients (52%) were treated with statins (20 mg of atorvastatin in 23 patients and 40 mg of simvastatin in 31 patients) for 12 months. Inclusion criteria for these lesions were a minimal lumen cross-sectional area >4.0 mm^2, a plaque burden <0.75, and lesions located in 1 of 3 major epicardial arteries where stent implantation was not performed. When >1 lesion per patient was studied, the lesion with larger plaque burden was selected for this study. Exclusion criteria were severe calcific lesions, failed stenting procedure, cardiogenic shock, recommended coronary artery bypass graft surgery, and previous administration of lipid-lowering agents. During the 1-year follow-up, occurrence of major adverse cardiac events, such as death from any cause, acute myocardial infarction (creatine kinase-MB fraction increase 3 times the upper limit of normal), and target lesion revascularization (percutaneous or surgical intervention of nonstenotic lesions) was evaluated. This study was performed as a part of other studies with patients' written informed consent and approval of the institutional review board. Changes in lipid profiles were calculated as follow-up minus baseline lipid levels.

IVUS imaging and analysis: Baseline and 12-month follow-up IVUS examinations of nonstenotic lesions were performed in the same rigorous manner before any intervention and after intracoronary administration of 0.2 mg of nitroglycerin with a motorized transducer pull-back system (0.5 mm/s) and a commercial scanner (Boston Scientific Corp./SCIMED, Natick, Massachusetts), consisting of a rotating 30- or 40-MHz transducer within a 3.2Fr or 2.6Fr imaging sheath. Quantitative and qualitative analyses were performed according to criteria of the clinical expert consensus document on IVUS.[10]

Quantitative IVUS analysis was performed using computerized planimetry. On playback of the baseline and 12-month follow-up IVUS studies, matching image slices were acquired at 3 different sites of nonstenotic lesions: the segment with the narrowest lumen cross-sectional area and sites 2 mm proximal and distal of the narrowest segment. Quantitative measurements included the external elastic membrane, lumen, and plaque & media (P&M = external elastic membrane − lumen) cross-sectional area. Mean values of IVUS measurements were used in this study. A remodeling index was calculated as the lesion divided by the mean reference external elastic membrane cross-sectional area. Changes (follow-up minus baseline) in IVUS measurements between baseline and 12-month follow-up studies were determined and compared between the statin-treated and nonstatin-treated groups.

Statistical analysis: Statistical analysis was performed with SPSS (SPSS, Inc., Chicago, Illinois). Data are presented as frequencies or mean ± 1 SD. Comparison was performed with chi-square test and unpaired or paired Student's *t* test.

Table 1
Baseline clinical characteristics between statin-treated and nonstatin-treated patients

Variable	Statin Therapy		p Value
	Yes (n = 54)	No (n = 49)	
Age (yrs)	57 ± 9	58 ± 9	0.5
Men	39 (72%)	34 (69%)	0.9
Hypertension	20 (37%)	15 (31%)	0.6
Diabetes mellitus	15 (28%)	11 (22%)	0.7
Cigarette smoker	27 (50%)	22 (45%)	0.8
Total cholesterol ≥220 mg/dl	14 (26%)	10 (20%)	0.7
Baseline C-reactive protein (mg/dl)	0.6 ± 0.8	0.5 ± 0.4	0.8
Lipid profiles at baseline			
Total cholesterol (mg/dl)	190 ± 27	191 ± 35	0.9
LDL cholesterol (mg/dl)	117 ± 23	118 ± 32	0.8
HDL cholesterol (mg/dl)	41 ± 9	42 ± 9	0.7
Triglycerides (mg/dl)	165 ± 73	154 ± 74	0.4
Lipid profiles at 12-mo follow-up			
Total cholesterol (mg/dl)	139 ± 28	188 ± 29	<0.001
LDL cholesterol (mg/dl)	69 ± 26	115 ± 25	<0.001
HDL cholesterol (mg/dl)	49 ± 11	48 ± 11	0.7
Triglycerides (mg/dl)	111 ± 52	124 ± 68	0.3
Changes in lipid profiles			
Total cholesterol (mg/dl)	−50 ± 32	−2 ± 31	<0.001
LDL cholesterol (mg/dl)	−47 ± 29	−2 ± 27	<0.001
HDL cholesterol (mg/dl)	7 ± 8	6 ± 8	0.6
Triglycerides (mg/dl)	−56 ± 56	−30 ± 65	0.044
No. of narrowed coronary arteries			0.9
1	33 (61%)	31 (63%)	
2	13 (24%)	12 (25%)	
3	8 (15%)	6 (12%)	
Clinical presentation			0.9
Stable angina pectoris	17 (32%)	17 (35%)	
Unstable angina pectoris	20 (37%)	17 (35%)	
Acute myocardial infarction	17 (32%)	15 (31%)	
Target coronary artery			0.8
Left anterior descending	26 (48%)	25 (51%)	
Left circumflex	9 (17%)	10 (20%)	
Right	19 (35%)	14 (29%)	
Medications			
Nitrates	50 (93%)	46 (94%)	0.9
Calcium channel blocker	45 (83%)	40 (82%)	1.0
β Blocker	42 (78%)	40 (82%)	0.8
Angiotensin II receptor antagonist	13 (24%)	10 (20%)	0.8
Angiotensin-converting enzyme inhibitor	11 (20%)	9 (18%)	1.0

HDL = high-density lipoprotein.

Stepwise multivariate linear regression analysis was performed to determine the independent predictors of change in mean P&M cross-sectional area. A p value <0.05 was considered statistically significant.

Results

Baseline clinical characteristics of the 103 patients are listed in Table 1. There were no significant differences in baseline clinical characteristics and lipid profiles between statin-treated and nonstatin-treated patients. Statin therapy was started during the initial hospitalization period. LDL cholesterol level at 1 month after discharge was similar to that

Table 2
Intravascular ultrasound analysis at baseline and one-year follow-up

	Baseline	1-Year Follow-up	p Value
Overall			
Mean EEM CSA (mm^2)	16.98 ± 4.13	16.81 ± 4.16	<0.001
Mean lumen CSA (mm^2)	7.66 ± 2.20	7.54 ± 2.20	<0.001
Mean P&M CSA (mm^2)	9.32 ± 2.71	9.27 ± 2.77	0.101
Nonstatin group			
Mean EEM CSA (mm^2)	17.01 ± 4.07	16.90 ± 4.10	<0.001
Mean lumen CSA (mm^2)	7.74 ± 2.13	7.52 ± 2.16	<0.001
Mean P&M CSA (mm^2)	9.27 ± 2.77	9.38 ± 2.88	0.002
Statin group			
Mean EEM CSA (mm^2)	16.95 ± 4.23	16.72 ± 4.25	<0.001
Mean lumen CSA (mm^2)	7.58 ± 2.28	7.56 ± 2.24	0.521
Mean P&M CSA (mm^2)	9.37 ± 2.67	9.17 ± 2.69	<0.001

CSA = cross-sectional area; EEM = external elastic membrane.

Table 3
Intravascular ultrasound analysis between statin-treated and nonstatin-treated lesions

	Statin Therapy		p Value
	Yes	No	
Baseline			
Mean EEM CSA (mm^2)	16.95 ± 4.23	17.01 ± 4.07	0.9
Mean lumen CSA (mm^2)	7.58 ± 2.28	7.74 ± 2.13	0.7
Mean P&M CSA (mm^2)	9.37 ± 2.67	9.27 ± 2.77	0.9
Types of plaques			1.0
Soft	39 (72%)	36 (74%)	
Fibrotic	8 (15%)	7 (14%)	
Fibrocalcific	7 (13%)	6 (12%)	
Total arc of calcium (degrees)	60 ± 22	58 ± 28	0.5
Remodeling index	1.0 ± 0.1	1.0 ± 0.0	0.2
1-Yr follow-up			
Mean EEM CSA (mm^2)	16.72 ± 4.25	16.90 ± 4.10	0.8
Mean lumen CSA (mm^2)	7.56 ± 2.24	7.52 ± 2.16	0.9
Mean P&M CSA (mm^2)	9.17 ± 2.60	9.38 ± 2.88	0.7
Remodeling index	1.0 ± 0.1	1.0 ± 0.1	0.4
Changes			
Mean EEM CSA (mm^2)	−0.23 ± 0.21	−0.11 ± 0.16	0.002
Mean lumen CSA (mm^2)	−0.03 ± 0.29	−0.22 ± 0.27	0.001
Mean P&M CSA (mm^2)	−0.20 ± 0.30	0.11 ± 0.24	<0.001

Abbreviations as in Table 2.

at 12-month follow-up and remained stable during the 12-month follow-up. An increased dose of statin to decrease LDL cholesterol level was not needed in any patient in the statin-treated group. Intervals between baseline and follow-up studies were 11.8 ± 2.1 and 11.9 ± 2.3 months, respectively (p = 0.7). One-year follow-up total and LDL cholesterol levels were significantly lower in statin-treated patients. During 1-year follow-up, major adverse cardiac events, such as death, acute myocardial infarction, and revascularization in nonstenotic target lesions did not occur in either group.

Overall, there were significant decreases in mean external elastic membrane and lumen cross-sectional area, with a tendency for a decrease in mean P&M cross-sectional area.

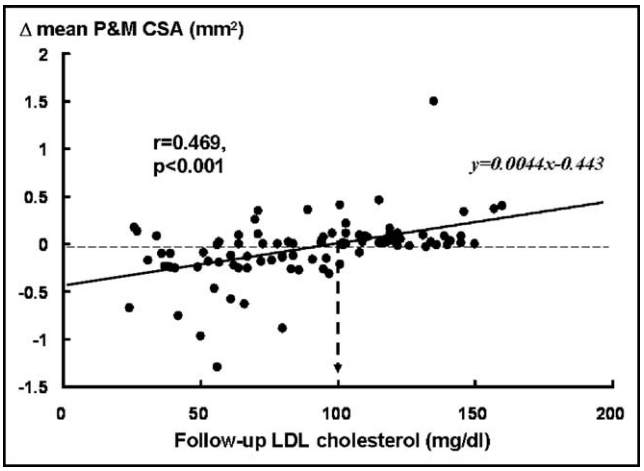

Figure 1. Relation between change (Δ) in mean P&M cross-sectional area (CSA) and follow-up LDL cholesterol level is shown (r = 0.469, p <0.001). The cut-off value of follow-up LDL cholesterol for no change or a decrease in mean P&M cross-sectional area was <100 mg/dl at this regression analysis.

In nonstatin-treated patients, IVUS study showed significant decreases in mean external elastic membrane and lumen cross-sectional area and a significant increase in mean P&M cross-sectional area. In statin-treated patients, mean external elastic membrane and P&M cross-sectional area significantly decreased without changes in mean lumen cross-sectional area (Table 2).

Baseline and 12-month follow-up IVUS studies showed no statistical differences in mean external elastic membrane and luminal and P&M cross-sectional areas between statin-treated and nonstatin-treated patients. However, although there was an increase in mean P&M cross-sectional area in nonstatin-treated patients, there was a decrease in mean P&M cross-sectional area in statin-treated patients (0.11 ± 0.24 vs −0.20 ± 0.30 mm^2, respectively, p <0.001). The decrease in mean external elastic membrane cross-sectional area in statin-treated patients and the decrease in mean lumen cross-sectional area in nonstatin-treated patients were significantly larger (Table 3).

Predictors of change in mean P&M cross-sectional area: There was no significant correlation between change in mean P&M cross-sectional area versus baseline total cholesterol level (r = 0.108, p = 0.3), baseline LDL cholesterol level (r = 0.118, p = 0.24), baseline high-density lipoprotein cholesterol level (r = 0.064, p = 0.5), baseline C-reactive protein level (r = 0.037, p = 0.7), follow-up high-density lipoprotein cholesterol level (r = 0.114, p = 0.3), and change in high-density lipoprotein cholesterol level (r = 0.057, p = 0.6). Univariate predictors of change in mean P&M cross-sectional area were entered into the multivariate model: follow-up LDL cholesterol level (r = 0.430, p <0.001), follow-up total cholesterol level (r = 0.365, p <0.001), change in LDL cholesterol level (r = 0.312, p = 0.002), and change in total cholesterol level (r = 0.252, p = 0.012). In stepwise multivariate linear regression analysis, the only independent

predictor of change in mean P&M cross-sectional area was follow-up LDL cholesterol level ($r = 0.469$, $p < 0.001$, 95% confidence interval 0.003 to 0.006). When the cut-off value of follow-up LDL cholesterol was <100 mg/dl at regression analysis, no change or a decrease in mean P&M cross-sectional area occurred. This relation is shown in Figure 1.

Discussion

In the analysis of 103 patients who underwent serial IVUS examinations, we found that the only independent predictor of changes in coronary plaque size was follow-up LDL cholesterol level. When a follow-up LDL cholesterol level <100 mg/dl is achieved with aggressive statin treatments, regression or no progression of coronary plaque may be expected. In statin-treated patients, there was no significant change in mean lumen cross-sectional area; a decrease in mean P&M cross-sectional area contributed to a decrease in mean external elastic membrane cross-sectional area. In nonstatin-treated patients, there was a significant decrease in mean lumen cross-sectional area, a decrease in mean external elastic membrane cross-sectional area, and an increase in mean P&M cross-sectional area contributed equally to the decrease in mean lumen cross-sectional area.

Previous angiographic studies have shown that lipid-lowering therapy may be related to a delay in progression of coronary atherosclerosis.[5,6] Compared with IVUS, which can directly visualize and measure atherosclerotic plaque in the vessel wall, angiographic study could visualize only the lumen dimension and might indirectly estimate the severity of atherosclerotic plaque. Therefore, extent of angiographically minimal changes in the lumen diameter of the target vessel did not correlate well with the substantial clinical benefits in patients who were treated with statins. A previous IVUS study in patients who were treated with 10 mg of pravastatin showed the efficacy of statin treatment for the prevention of further progression of coronary atherosclerosis.[11] However, regression of coronary plaque was not demonstrated in that IVUS study.[11] For a lower LDL cholesterol level and better long-term clinical outcomes, intensive lipid-lowering therapy with higher doses and different kinds of statin was recommended. A qualitative analysis of 1 IVUS study in patients who were treated with up to 80 mg of atorvastatin showed an increase in plaque hyperechogenicity that resulted from a change in plaque composition.[12] Quantitative analyses in recent IVUS studies showed that significant plaque regression occurred after statin treatment in patients with acute coronary syndrome who used 20 mg of atorvastatin for 6 months[7] and in patients with stable coronary artery disease who used 40 mg of simvastatin for 12 months.[8] In the present study, 20 mg of atorvastatin or 40 mg of simvastatin was used, and there was a statistical difference in change in mean P&M cross-sectional area between nonstatin-treated and statin-treated patients. These findings are consistent with those of the previous studies.[7,8] When the potency between different kinds and doses of statins on progression of coronary atherosclerosis was compared, a randomized Reversal of Atherosclerosis With Aggressive Lipid Lowering (REVERSAL) trial showed no change in atheroma burden in intensive lipid-lowering treatments with 80 mg of atorvastatin, whereas progression of coronary atherosclerosis occurred in moderate lipid-lowering treatment with 40 mg of pravastatin.[9]

Von Birgelen et al[13] reported that baseline LDL cholesterol level had a positive relation with annual changes in plaque size in a serial IVUS study with 60 left main coronary arteries. There was an inverse relation between baseline high-density lipoprotein cholesterol level and annual changes in plaque size.[13] In a randomized study, Okazaki et al[7] found that early aggressive lipid-lowering therapy with 20 mg of atorvastatin resulted in a decrease in coronary plaque in patients with acute coronary syndrome. They reported that follow-up and percent decrease in LDL cholesterol level, and not a baseline LDL cholesterol level, had a significant positive correlation with percent changes in plaque volume.[7] In the present study, follow-up LDL cholesterol level and change in LDL cholesterol level were predictors of change in mean P&M cross-sectional area in univariate analysis. Follow-up LDL cholesterol level was the only independent predictor for change in mean P&M cross-sectional area in multivariate analysis. Although the relative parameter (i.e., percent changes in plaque volume) was used in a previous study[7] and the absolute parameter (i.e., change in mean P&M cross-sectional area) was used in the present study, the present findings were similar to those of the previous study.[7] The previous IVUS study suggested that using a baseline LDL cholesterol value of 75 mg/dl as the cutoff at regression analysis predicted no annual increase in plaque size.[13] The cut-off value for no change or a decrease in mean P&M cross-sectional area was a follow-up LDL cholesterol level <100 mg/dl at regression analysis in the present study. The differences between the 2 studies might be explained by different target lesions, different study populations (white vs Korean patients), and different percentages of the study population who were treated with statins. The follow-up LDL cholesterol value of 100 mg/dl at regression analysis for regression or no progression of coronary plaque in the present study is the same LDL cholesterol level that has been recommended for patients with coronary artery disease in current United States and European guidelines.[14,15] This study was a single-center, retrospective, nonrandomized study. Data about C-reactive protein level were not obtained at follow-up.

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