



Early Effects of Intensive Lipid-Lowering Treatment on Plaque Characteristics Assessed by Virtual Histology Intravascular Ultrasound

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Purpose: The effects of short-term intensive lipid-lowering treatment on coronary plaque composition have not yet been sufficiently evaluated. We investigated the influence of short-term intensive lipid-lowering treatment on quantitative and qualitative changes in plaque components of non-culprit lesions in patients with acute coronary syndrome.

Materials and Methods: This was a prospective, randomized, open-label, single-center trial. Seventy patients who underwent both baseline and three-month follow-up virtual histology intravascular ultrasound were randomly assigned to either an intensive lipid-lowering treatment group (ezetimibe/simvastatin 10/40 mg, n=34) or a control statin treatment group (pravastatin 20 mg, n=36). Using virtual histology intravascular ultrasound, plaque was characterized as fibrous, fibro-fatty, dense calcium, or necrotic core. Changes in plaque components during the three-month lipid-lowering treatment were compared between the two groups.

Results: Compared with the control statin treatment group, there was a significant reduction in low-density lipoprotein cholesterol in the intensive lipid-lowering treatment group (-20.4±17.1 mg/dL vs. -36.8±17.4 mg/dL, respectively; $p<0.001$). There were no statistically significant differences in baseline, three-month follow-up, or serial changes of gray-scale intravascular ultrasound parameters between the two groups. The absolute volume of fibro-fatty plaque was significantly reduced in the intensive lipid-lowering treatment group compared with the control group (-1.5±3.4 mm³ vs. 0.8±4.7 mm³, respectively; $p=0.024$). A linear correlation was found between changes in low-density lipoprotein cholesterol levels and changes in the absolute volumes of fibro-fatty plaque ($p<0.001$, $R^2=0.209$).

Conclusion: Modification of coronary plaque may be attainable after only three months of intensive lipid-lowering treatment.

Key Words: Coronary artery disease, coronary vessels, ultrasonography, cholesterol, anticholesteremic agents

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INTRODUCTION

Treatment with statin, a 3-hydroxy-3-methylglutaryl-coenzyme reductase inhibitor, has been reported to reduce adverse clinical events in both primary and secondary prevention studies.¹⁻⁶ Studies have also shown that intensive lipid-lowering therapy significantly reduces the risk of coronary events compared with moderate lipid-lowering therapy.^{7,8} Although long-term clinical outcomes have improved following statin therapy, previous angiographic studies have shown only trivial changes in angiographic lumen dimension in statin-treated patients.^{9,10} However, several intravascular ultrasound (IVUS) studies have clearly

demonstrated the benefits of statin treatments, which were significantly associated with regression or no progression of coronary plaque.¹¹⁻¹³

Statin treatments have been recommended for the stabilization of vulnerable plaque and improvements of long-term clinical outcomes in patients with acute coronary syndrome (ACS).^{14,15} Several studies have reported the long-term effects of statin treatments on coronary plaque composition.¹⁶⁻¹⁸ However, studies evaluating the early effects of lipid-lowering treatment on coronary plaque composition are limited.¹⁹ In the present study, using virtual histology (VH)-IVUS, we evaluated and compared short-term (three months) quantitative and qualitative changes in plaque components in ACS patients who received either intensive lipid-lowering or low-dose statin treatment.

MATERIALS AND METHODS

Study design

This trial was a prospective, randomized, open-label, single-center trial to evaluate the early effects of intensive lipid-lowering treatment (ezetimibe/simvastatin 10/40 mg) on plaque characteristics in ACS patients compared with the effects of control statin treatment (pravastatin 20 mg) (ClinicalTrials.gov Identifier: NCT01857843). Patients with the clinical presentation of ACS who underwent a percutaneous coronary intervention of culprit lesions were eligible for the participation in this study. Patients were at least 20 years old at the clinical presentation of ACS, and had *de novo* lesions with diameter stenosis <50% by visual estimation, which were located in non-culprit vessels; reference vessel diameter was >3.0 mm and the segment length of 10–20 mm. Patient exclusion criteria were as follows: 1) failed percutaneous coronary intervention of culprit lesions; 2) is a candidate for coronary artery bypass graft surgery; 3) is in cardiogenic shock; 4) has a history of use of lipid-lowering agents before enrollment; 5) has significant hepatic dysfunction (≥ 3 times the normal reference values); 6) has significant renal dysfunction (serum creatinine >2.0 mg/dL); 7) has significant leukopenia, thrombocytopenia, anemia, or known bleeding diathesis; 8) is pregnant or potentially childbearing; and 9) has saphenous vein graft lesions. We initially estimated that 160 patients were required to undergo randomization. However, because the enrollment of study patients was very slow, this study was prematurely terminated. The main reasons for slow enrollment were a small number of lipid-lowering treatment-naïve patients and the refusal to undergo a three-month follow-up angiography. Subsequently, a total of 70 patients were randomly allocated in a ratio of approximately 1:1 to either the intensive lipid-lowering treatment (ezetimibe 10 mg/simvastatin 40 mg, $n=34$) or control statin treatment (pravastatin 20 mg, $n=36$). All patients were followed at out-patient clinics after the hospital discharge. This study was approved by the Institutional Review Board of our institute and written in-

formed consent was obtained from each patient.

IVUS examination and analysis

Baseline and three-month follow-up gray-scale and VH-IVUS examinations, in the region of interest segments of non-culprit lesions, were performed after an intracoronary administration of 0.2 mg nitroglycerin using a motorized transducer pullback system (0.5 mm/s). The 2.9-Fr IVUS imaging catheter (Eagle Eye, Volcano Corp, Rancho Cordova, CA, USA) with a 20-MHz phased-array transducer was used. Conventional gray-scale quantitative IVUS analyses were performed according to the criteria of the clinical expert consensus document on IVUS to include the external elastic membrane (EEM), lumen, plaque, and media (P&M; P&M=EEM minus lumen) volumes.²⁰ Quantitative and qualitative volumetric VH-IVUS analyses were performed along a 10-mm segment (centered on the segment with minimal lumen area) with the use of an off-line software program (QIVUS[®], Medis Medical Imaging Systems, Leiden, the Netherlands) and a manual contour correction of both the lumen and EEM interface. VH-IVUS analysis classified color-coded tissue as dark-green (fibrous), yellow-green (fibro-fatty), white (dense calcium), or red (necrotic core).²¹⁻²³ VH-IVUS analyses were reported in absolute amounts and as a percentage (relative amounts) of plaque volume. All IVUS images were analyzed at the core laboratory (Cardiovascular Research Center, Seoul, Korea) by analysts who were blinded to the patient and treatment procedure information. Based on reproducible landmarks, such as calcium deposits or side branches, the same segments were identified and analyzed in the baseline and three-month follow-up IVUS examinations.

Statistical analyses

Statistical analyses were performed using SPSS (version 20.0.0, IBM, Armonk, NY, USA). Data are expressed as number (%) or mean \pm standard deviation. Comparisons were made using χ -square statistics, Fisher's exact test, or Student's *t*-tests (paired or unpaired, as appropriate). Pearson's correlation analysis was performed to evaluate the correlation between the changes in low-density lipoprotein cholesterol (LDL-C) levels and changes in the absolute volume of plaque components. A *p*-value of <0.05 was considered to be statistically significant.

RESULTS

Baseline clinical characteristics are summarized in Table 1. No significant differences were found in the baseline clinical characteristics between the two treatment groups. Baseline and three-month follow-up laboratory findings are shown in Table 2. Compared with the control statin treatment group, three-month follow-up total cholesterol and LDL-C levels were significantly lower in the intensive lipid-lowering treatment group. The relative percentages of change in LDL-C from baseline to

three-month follow-up were significantly different between the control statin treatment and intensive lipid-lowering treatment ($-20.4\pm 17.1\%$ vs. $-36.8\pm 17.4\%$, respectively; $p<0.001$) groups.

Gray-scale IVUS analysis showed no statistically significant changes of EEM, lumen, and P&M volume from baseline to the three-month follow-up in both groups. There were no signifi-

Table 1. Baseline Clinical Characteristics*

Variables	Control statin treatment (n=36)	Intensive lipid-lowering treatment (n=34)	p value
Age (yrs)	59.3±10.7	60.9±10.9	0.522
Male	27 (75.0)	27 (79.4)	0.660
Diabetes mellitus	9 (25.0)	11 (32.4)	0.496
Hypertension	21 (58.3)	17 (50.0)	0.484
Current smoker	18 (50.0)	15 (44.1)	0.622
Lesion location			0.243
Left anterior descending artery	13 (36.1)	18 (52.9)	
Left circumflex artery	14 (38.9)	12 (35.3)	
Right coronary artery	9 (25.0)	4 (11.8)	
Clinical presentation			0.905
Non-ST elevation myocardial infarction	7 (19.4)	7 (20.6)	
ST elevation myocardial infarction	29 (80.6)	27 (79.4)	
Medications			
Aspirin	36 (100.0)	34 (100.0)	1.0
Clopidogrel	36 (100.0)	34 (100.0)	1.0
Statin	36 (100.0)	34 (100.0)	1.0
Beta-blocker	32 (88.9)	31 (91.2)	0.750
ACEI or ARB	33 (91.7)	30 (88.2)	0.632
Calcium-channel blocker	5 (15.2)	1 (3.2)	0.102

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker.

*Values are n (%) or mean±SD.

Table 2. Laboratory Findings*

Variables	Control statin treatment (n=36)	Intensive lipid-lowering treatment (n=34)	p value
Total cholesterol (mg/dL)			
Baseline	196.8±38.4	190.8±24.7	0.442
Three-month follow-up	153.3±38.5 [†]	129.7±30.3 [†]	0.006
ΔTotal cholesterol	-43.6±37.3	-61.1±42.1	0.070
LDL cholesterol (mg/dL)			
Baseline	119.1±29.9	111.4±22.0	0.230
Three-month follow-up	92.2±21.8 [†]	68.1±15.3 [†]	<0.001
ΔLDL cholesterol	-26.9±20.4	-43.4±24.1	0.003
HDL cholesterol (mg/dL)			
Baseline	39.4±6.3	36.0±8.9	0.072
Three-month follow-up	40.7±8.8	37.8±8.7	0.173
ΔHDL cholesterol	1.3±8.8	1.8±7.5	0.793
Triglyceride (mg/dL)			
Baseline	136.8±80.9	120.6±90.4	0.435
Three-month follow-up	131.1±64.9	127.6±76.3	0.836
ΔTriglycerides	-1.8±94.4	7.1±56.9	0.637
hsCRP (mg/L)			
Baseline	7.6±17.0	5.2±8.3	0.474
Three-month follow-up	2.1±2.5	3.8±7.2	0.201
ΔhsCRP	-5.5±17.4	-1.3±10.9	0.250

LDL, low-density lipoprotein; HDL, high-density lipoprotein; hsCRP, high-sensitive C-reactive protein.

Δ indicates changes from baseline to three-month follow-up.

*Values are mean±SD, [†] $p<0.05$ for comparison between baseline and three-month follow-up levels.

Table 3. Intravascular Ultrasound Analysis between Intensive Lipid-Lowering Treatment and Control Statin Treatment*

	Baseline	Three-month follow-up	p value	Change in three months	p value [†]
Gray-scale intravascular ultrasound analysis					
External elastic membrane volume (mm ³)					0.730
All patients (n=70)	154.1±57.9	150.9±63.6	0.758	-3.2±23.8	
Control statin treatment (n=36)	163.5±60.9	161.3±71.2	0.886	-2.2±30.2	
Intensive lipid-lowering treatment (n=34)	144.1±53.6	140.0±53.2	0.750	-4.2±14.6	
Lumen volume (mm ³)					0.598
All patients	71.6±32.2	70.2±34.1	0.793	-1.4±16.3	
Control statin treatment	77.0±32.8	74.6±36.0	0.762	-2.4±20.3	
Intensive lipid-lowering treatment	65.9±31.1	65.5±31.9	0.957	-0.4±10.8	
Absolute total plaque volume (mm ³)					0.231
All patients	82.5±32.3	80.8±35.9	0.773	-1.7±13.7	
Control statin treatment	86.5±34.7	86.7±41.9	0.981	0.3±17.0	
Intensive lipid-lowering treatment	78.3±29.5	74.5±27.4	0.596	-3.7±9.0	
Virtual histology intravascular ultrasound analysis					
Absolute volume of fibro-fatty plaque (mm ³)					0.024
All patients	5.6±3.9	5.2±4.8	0.575	-0.3±4.3	
Control statin treatment	6.0±3.8	6.7±5.8	0.568	0.8±4.7	
Intensive lipid-lowering treatment	5.2±4.0	3.7±2.6	0.063	-1.5±3.4	
Absolute volume of fibrous plaque (mm ³)					0.229
All patients	30.6±14.6	29.3±15.7	0.600	-1.3±9.5	
Control statin treatment	31.2±14.4	31.2±17.7	0.999	-0.1±11.6	
Intensive lipid-lowering treatment	30.1±14.9	27.3±13.1	0.420	-2.8±6.5	
Absolute volume of necrotic core (mm ³)					0.415
All patients	12.3±8.9	12.9±11.4	0.704	0.6±5.6	
Control statin treatment	13.6±10.0	13.7±13.7	0.977	0.1±6.4	
Intensive lipid-lowering treatment	10.9±7.5	12.2±8.5	0.516	1.2±4.6	
Absolute volume of dense calcium (mm ³)					0.746
All patients	5.1±6.8	5.1±8.0	0.982	0.0±4.0	
Control statin treatment	6.5±8.4	6.4±10.2	0.960	-0.2±5.4	
Intensive lipid-lowering treatment	3.7±4.4	3.7±4.6	0.957	0.1±1.8	
Percentage of fibro-fatty plaque volume (%)					0.235
All patients	10.9±6.3	10.3±8.1	0.625	-0.5±7.4	
Control statin treatment	11.4±7.6	11.8±10.2	0.865	0.5±8.9	
Intensive lipid-lowering treatment	10.4±4.8	8.8±4.6	0.161	-1.6±5.3	
Percentage of fibrous plaque volume (%)					0.200
All patients	59.4±11.0	59.7±15.6	0.896	0.3±13.1	
Control statin treatment	57.4±11.5	59.6±19.3	0.545	2.3±16.6	
Intensive lipid-lowering treatment	61.6±10.2	59.8±10.7	0.481	-1.7±7.7	
Percentage of necrotic core volume (%)					0.208
All patients	20.6±8.2	21.4±9.6	0.584	0.8±8.8	
Control statin treatment	20.7±8.3	20.2±10.4	0.832	-0.5±9.1	
Intensive lipid-lowering treatment	20.4±8.2	22.7±8.7	0.285	2.1±8.3	
Percentage of dense calcium volume (%)					0.866
All patients	8.3±7.5	7.8±7.5	0.529	-0.5±6.4	
Control statin treatment	9.3±9.1	8.8±9.0	0.806	-0.5±8.3	
Intensive lipid-lowering treatment	7.3±5.1	6.7±5.3	0.677	-0.3±3.8	

*Values are mean±SD, †p value for comparison of changes in intravascular ultrasound variables from baseline to three-month follow-up between intensive lipid-lowering treatment and control statin treatment.

cant differences found for serial changes of EEM, lumen, and P&M volume between the two groups (Table 3).

The findings from VH-IVUS analysis are shown in Table 3. While there appeared to be a tendency of reduced absolute fibro-fatty plaque volume in the intensive lipid-lowering treatment group (from $5.2 \pm 4.0 \text{ mm}^3$ at baseline to $3.7 \pm 2.6 \text{ mm}^3$ at the three-month follow-up, $p=0.063$), there were no significant changes in absolute fibro-fatty plaque volume in the control statin treatment group. The reduction of absolute fibro-fatty plaque volume from baseline to the three-month follow-up was greater in the intensive lipid-lowering treatment group compared with the control statin treatment group ($-1.5 \pm 3.4 \text{ mm}^3$ vs. $0.8 \pm 4.7 \text{ mm}^3$, $p=0.024$) (Table 3, Fig. 1). However, there were no statistically significant changes in fibrous, necrotic core, and dense calcium volume from baseline to the three-month follow-up between the two groups.

A significant linear correlation was found between the changes in LDL-C from baseline to the three-month follow-up and that of absolute fibro-fatty plaque volume ($p < 0.001$, $R^2 = 0.209$) and fibrous plaque volume ($p = 0.026$, $R^2 = 0.071$) (Fig. 2). In the multivariate analyses including statin groups, changes in LDL-C were still the independent predictor of changes in fibro-fatty plaque volume ($p < 0.001$) while not for fibrous plaque volume ($p = 0.055$). Treatment group itself was not an independent predictor for changes in fibro-fatty ($p = 0.289$) and fibrous plaque volume ($p = 0.652$).

No major adverse cardiovascular events, such as cardiovascular mortality, myocardial infarction, or stroke occurred during the study period for patients in either of the two groups. As for the adverse effects of drugs, 3 episodes of myalgia and/or general weakness were reported, 2 in the control and 1 in the intensive lipid lowering group.

DISCUSSION

This randomized study showed that significant changes in coronary plaque components (i.e., reduction of absolute volume of fibro-fatty plaque) as well as decreases in LDL-C levels were observed early (at three-month follow-up) in ACS patients who were given an intensive lipid-lowering treatment. There was a significant linear correlation between the changes in LDL-C levels and changes in absolute volume of fibro-fatty plaque.

Statins have several beneficial properties beyond their lipid-lowering effect, including atherosclerotic plaque stabilization, oxidative stress reduction, enhancement of endothelial function, a decrease in vascular inflammation, and improvements of vascular healing after stent implantation.^{24,25} Previous gray-scale IVUS studies showed that statin treatment was associated with regression or no progression of coronary artery atherosclerotic plaque.¹¹⁻¹³ Ezetimibe is a member of a class of non-statin agents that inhibit the absorption of cholesterol from the intestine by blocking the Niemann-Pick-like 1 receptor and reduce the absorption of both dietary and biliary cholesterol by 54% to 65%.^{26,27} The combination treatment of ezetimibe and statin inhibits both the cholesterol synthesis and intestinal cholesterol absorption, resulting in approximately 18% greater reduction in LDL-C levels than the treatment with statin alone.^{28,29} A recent randomized study showed that an additional decrease in LDL-C levels after the addition of ezetimibe to statin therapy was associated with a reduction of cardiovascular events compared with statin mono-therapy in stabilized ACS patients.³⁰

Several VH-IVUS studies evaluated the effect of statin treatment on coronary plaque components with respect to different types or dosages of statins and the duration of statin treatment.¹⁶⁻¹⁹ In a recent study, 24-month maximally-intensive statin treatment in 36 rosuvastatin (40 mg)- and 35 atorvastatin (80 mg)-treated patients resulted in a coronary atheroma regression and a reduction in fibro-fatty components.¹⁸ In another study,

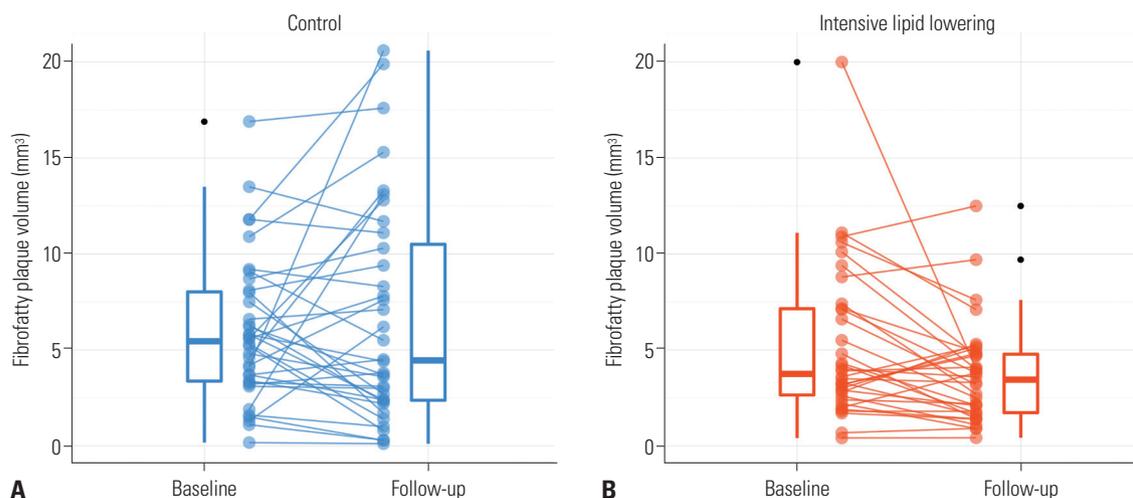


Fig. 1. Changes in absolute volume of fibro-fatty plaque. (A) The absolute volume of fibro-fatty plaque changed from $6.0 \pm 3.8 \text{ mm}^3$ at baseline to $6.7 \pm 5.8 \text{ mm}^3$ at three-month follow-up after control statin treatment (pravastatin 20 mg). (B) The absolute volume of fibro-fatty plaque decreased from $5.2 \pm 4.0 \text{ mm}^3$ at baseline to $3.7 \pm 2.6 \text{ mm}^3$ at three-month follow-up after intensive lipid-lowering treatment (ezetimibe/simvastatin, 10/40 mg).

12-month treatment with fluvastatin (60 mg/day, n=40) resulted in a significant regression of plaque volume and significant reduction of fibro-fatty volume compared with a control group (n=40).¹⁶ The results from a randomized study that evaluated six-months of statin treatment showed that there were higher percentages of plaque volume regression and lower percentages of necrotic core expansion in higher-dose atorvastatin (40 mg)-treated (n=20) than in lower-dose atorvastatin (10 mg)-treated patients (n=20),¹⁷ and a randomized study involving only two to three weeks of statin treatment showed significant plaque regression and reduction of fibro-fatty components in pitavastatin (2 mg)-treated (n=80), but not in atorvastatin (10 mg)-treated patients (n=80).¹⁹

In the present study, three-month intensive lipid-lowering

treatment resulted in a significant reduction in fibro-fatty plaque volume, which is in accordance with previous studies.^{16,18,19} Plaque regression was not significantly different between the control statin and intensive lipid-lowering treatment groups ($0.3 \pm 17.0 \text{ mm}^3$ vs. $-3.7 \pm 9.0 \text{ mm}^3$, respectively; $p=0.231$). For the evaluation of early effects of lipid-lowering treatment on coronary plaque components, a statin versus statin comparison was performed in the above-mentioned previous study,¹⁹ while the present study compared statin mono-therapy with the addition of ezetimibe to statin therapy.

Although this study is not without some limitations, it demonstrates the early positive effects of intensive lipid-lowering treatment. Small sample size, due to the single study site, may have a potential for selection bias. Also, most of the VH-IVUS

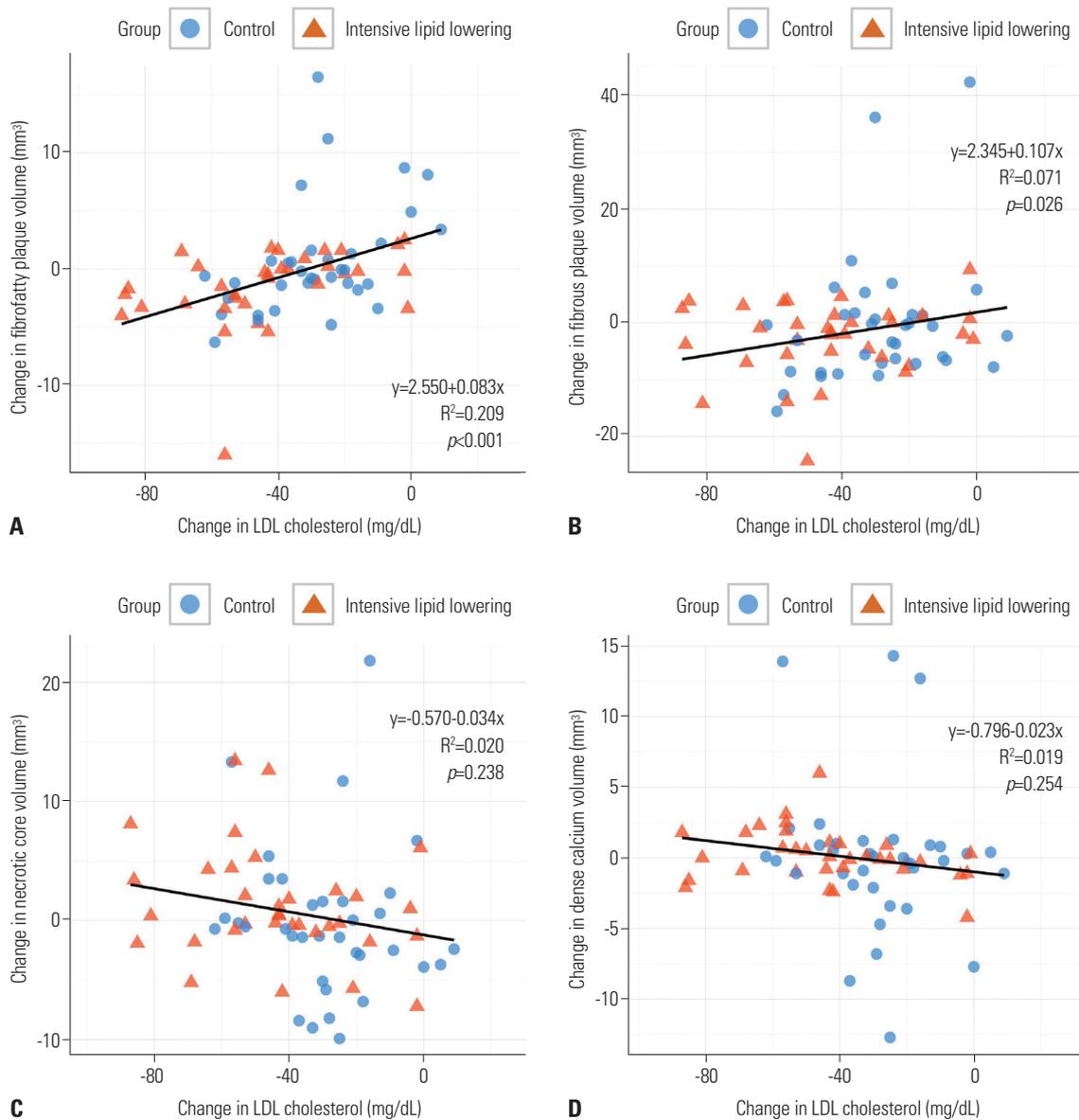


Fig. 2. Correlation between change in low-density lipoprotein (LDL)-cholesterol and change in absolute volume of each plaque component. (A) Fibro-fatty plaque, (B) fibrous plaque, (C) necrotic core, and (D) dense calcium. Blue circles denote control group, and red triangles are for intensive lipid-lowering group.

parameters studied were not found to be different at the levels of statistical significance between the two groups, with the exception of the absolute volume of fibro-fatty plaque. Considering that the purpose of the present study was to evaluate the early effects of intensive lipid-lowering treatment on changes in coronary plaque components, these results suggest that the absolute volume of fibro-fatty plaque may be the most sensitive parameter affected by the intensive lipid-lowering treatment. Furthermore, changes in the absolute volume of fibro-fatty plaque may be a potential early indicator of efficacy in intensive lipid-lowering treatment regimens.

In conclusion, the most significant effects of intensive lipid-lowering treatment, such as the addition of ezetimibe to statin therapy, on coronary plaque modification may appear early during treatment. Therefore, it may be necessary to consider early aggressive LDL-C control by intensive lipid-lowering for the initiation of rapid and effective plaque modification in ACS patients.

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