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The Effects of Rosuvastatin on Plaque Regression in Patients Who Have a Mild to Moderate Degree of Coronary Stenosis With Vulnerable Plaque

Young Joon Hong, MD, Myung Ho Jeong, MD, Jong Won Chung, MD, Doo Sun Sim, MD, Jung Sun Cho, MD, Nam Sik Yoon, MD, Hyun Ju Yoon, MD, Jae Youn Moon, MD, Kye Hun Kim, MD, Hyung Wook Park, MD, Ju Han Kim, MD, Youngkeun Ahn, MD, Jeong Gwan Cho, MD, Jong Chun Park, MD and Jung Chaee Kang, MD

The Heart Center of Chonnam National University Hospital, Cardiovascular Research Institute of Chonnam National University, Gwangju, Korea

ABSTRACT

Background and Objectives: Intensive lipid-lowering therapy with statins improves the clinical outcomes and patient survival and it reduces the progression of atherosclerosis. Intravascular ultrasound (IVUS) has been used for calculating the plaque volumes to evaluate the mechanisms that may be involved in the progression or regression of coronary artery disease. We used serial IVUS exams to assess the efficacy of rosuvastatin on plaque regression in angina patients who had a mild to moderate degree of vulnerable plaque burden. **Subjects and Methods**: This study was a prospective, randomized, comparative study for lipid lowering therapy with using rosuvastatin 20 mg or atorvastatin 40 mg. IVUS was performed during the baseline coronary angiography and it was repeated after 12 months of treatment. The efficacy parameters included the changes in the atheroma volume and the lipid pool size as determined by IVUS. A total of 45 lesions in 30 patients were analyzed (rosuvastatin: 24 lesions in 16 patients vs. atorvastatin: 21 lesions in 14 patients). **Results**: The low density lipoprotein (LDL)-cholesterol level was reduced from 121±45 mg/dL to 65±25 mg/dL in the rosuvastatin group (a 46% decrease, $p<0.001$), and from 127±37 mg/dL to 72±26 mg/dL in the atorvastatin group (a 43% decrease, $p<0.001$). The total atheroma and vessel volumes were significantly decreased, whereas the lumen volume was significantly increased from baseline to follow-up in both groups (for the rosuvastatin group: the total atheroma volume, 252±80 to 246±79 mm^3, $p<0.001$; the vessel volume, 555±158 to 553±130 mm^3, $p<0.001$; the lumen volume, 303±91 to 307±92 mm^3, $p<0.001$, and for the atorvastatin group: the total atheroma volume, 288±98 to 283±98 mm^3, $p<0.001$; the vessel volume, 607±165 to 604±166 mm^3, $p<0.001$; the lumen volume, 319±71 to 321±73 mm^3, $p<0.001$). The follow-up LDL-cholesterol level was correlated with the change in the total atheroma volume ($r=0.577$, $p<0.001$), the change in the percent atheroma volume ($r=0.558$, $p<0.001$) and the change in the lipid pool size ($r=0.470$, $p=0.001$). **Conclusion**: Both rosuvastatin 20 mg and atorvastatin 40 mg could contribute to the regression of lipid-rich plaque. The follow-up LDL-cholesterol level is related to the regression and stabilization of vulnerable coronary plaque. **(Korean Circ J 2008;38:366-373)**

KEY WORDS: Atherosclerosis; Lipids; Statins, HMG-CoA; Ultrasonics.

Introduction

Statins have been shown to significantly reduce cardiovascular clinical events in a variety of patients, ranging from patients with established cardiovascular disease to those who are at risk for cardiovascular disease.[1-9] Previous studies have demonstrated that the progression of coronary artery atherosclerosis was related to the development of coronary events, and intensive lipid-lowering therapy with statins improved the clinical outcomes and the survival rates and it reduced the progression of atherosclerosis.[1-4]

A ruptured plaque with a superimposed dynamic thrombosis (with or without spasm) seems to underlie the great majority of acute ischemic syndromes: unstable

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Correspondence: Myung Ho Jeong, MD, The Heart Center of Chonnam National University Hospital, Cardiovascular Research Institute of Chonnam National University, 8 Hak-dong, Dong-gu, Gwangju 501-757, Korea
Tel: 82-62-220-6243, Fax: 82-62-228-7174
E-mail: myungho@chollian.net

angina, acute myocardial infarction and sudden death.[10] A vulnerable plaque is defined as the plaque that has a large lipid pool, a thin fibrous cap and macrophage-dense inflammation on or beneath its surface and this type of plaque is responsible for acute coronary events.[11]

Intravascular ultrasound (IVUS) is a valuable adjunct to angiography, and this US modality provides new insights on the diagnosis and therapy for coronary disease.[12] IVUS allows transmural visualization of the coronary arteries and area measurements of the external elastic membrane (EEM), plaque plus media (P & M) and vessel lumen. IVUS with using motorized pullback devices has been used to calculate the volumes to evaluate the mechanisms that may be involved in the progression or regression of coronary artery disease.[13]

However, little data is available about the effects of statins on plaque regression in patients with a mild to moderate degree of a vulnerable plaque burden. Therefore, the purpose of the present study was to assess the efficacy of rosuvastatin 20 mg compared with atorvastatin 40 mg on plaque regression by performing serial IVUS exams in angina patients who had a mild to moderate degree of a vulnerable plaque burden.

Subjects and Methods

Study population

This study was a prospective, randomized and comparative study that focused on lipid lowering therapy with using rosuvastatin or atorvastatin for the angina patients who had mild to moderate degree of coronary stenosis with vulnerable plaque and these patients were seen at Chonnam National University Hospital, Gwangju, Korea.

The patients were randomized to take either rosuvastatin 20 mg or atorvastatin 40 mg daily. Statin therapy was started in both groups immediately after coronary angiography and IVUS. We enrolled a total of 30 patients (45 lesions) who underwent baseline and follow-up coronary angiography and IVUS for the analyses (the rosuvastatin group: 24 lesions in 16 patients vs. the atorvastatin group: 21 lesions in 14 patients). We excluded the patients with myocardial infarction, severe left ventricular dysfunction (an ejection fraction <40%) and hepatic or renal dysfunction (alanine aminotransferase and aspartate aminotransferase >2 times the normal value, creatinine >1.5 mg/dL).

A mild to moderate degree of coronary stenosis was defined as a diameter stenosis of 30% to 60%, as was assessed by performing quantitative coronary angiography (QCA) with using a validated QCA system (Phillips H5000 or Allura DCI program). Vulnerable plaque was defined as plaque with a large lipid core with a thin fibrous cap, and this was observed by IVUS (Fig. 1). After the 12-month treatment period, the patients underwent a repeated cardiac catheterization and IVUS examination of the matched segments under identical conditions. This study's protocol was approved by the institutional review board of Chonnam National University Hospital and informed consent was obtained from all the patients.

Laboratory analysis

For all the patients, serum samples were collected before coronary angiography for measuring the lipid profiles, high sensitivity C-reactive protein (hs-CRP), blood urea nitrogen (BUN), creatinine, aspartate aminotransferase (AST) and alanine aminotransferase (ALT). All the laboratory values were measured after an overnight fast. The serum levels of total cholesterol, low-density lipoprotein (LDL)-cholesterol, high-density lipoprotein (HDL)-cholesterol and triglyceride were measured

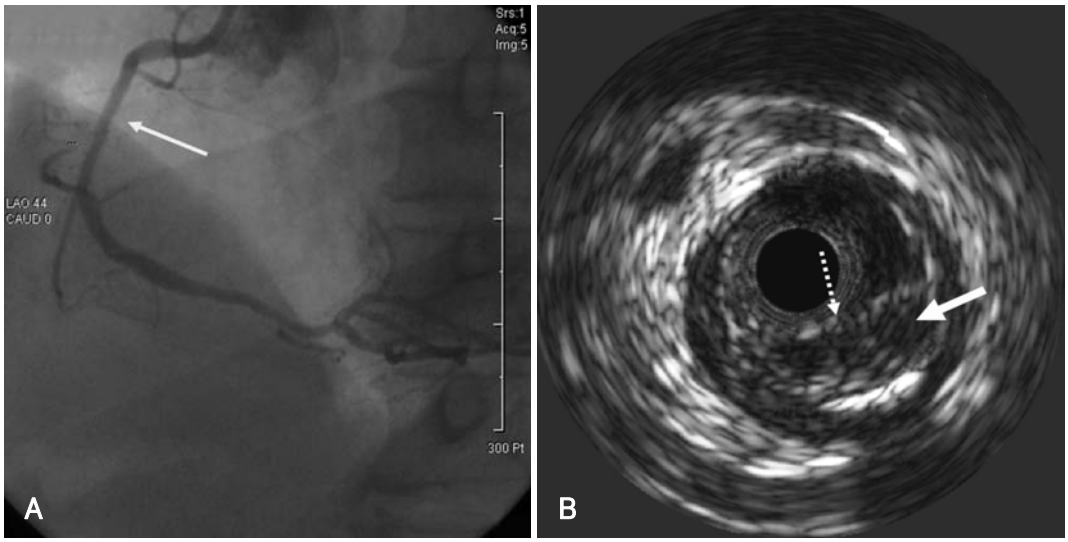

Fig. 1. Example of moderate stenosis with vulnerable plaque. A: the coronary angiography. B: the intravascular ultrasound findings. Note the thin fibrous cap (broken arrow) and large lipid core (solid arrow).

by standard enzymatic methods. hs-CRP was analyzed turbidimetrically with using sheep antibodies against human CRP; this has been validated against the Dade-Behring method.[14]

The serum AST and ALT levels were measured by a kinetic UV test with using an Olympus AU 5431 (AU 5431). The serum BUN levels were assessed by kinetic UV assay and the creatinine levels were analyzed by kinetic colorimetric assay with using an Olympus AU 5431. The serum levels of total cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride, hs-CRP, BUN, creatinine, AST and ALT were measured at baseline and at the 12-month follow-up.

Intravascular ultrasound imaging and analysis

IVUS was performed at baseline and at the 12-month follow-up. The IVUS examinations were performed after intracoronary administration of 200 μg nitroglycerin and with using a commercially available IVUS system (Boston Scientific Corporation/SCIMed, Minneapolis, MN). The IVUS catheter was advanced distal to the target lesion, and imaging was performed retrograde to the aorto-ostial junction at an automatic pullback speed of 0.5 mm/s.

The same anatomic image slices were analyzed at baseline and at follow-up. By using the axial landmark (i.e., side branches, calcifications or unusual plaque shapes) and the known pullback speed, identical cross-sectional image slices on the serial studies could be identified for making comparisons. We measured the IVUS images, which were precisely spaced 1-mm apart. The leading edges of the EEM and lumen were traced manually using planimetry software (Echoplaque 3.0, INDEC Systems Inc., Santa Clara, CA) in accordance with the guidelines for IVUS of the American College of Cardiology Clinical Expert Consensus Document on Standards for the Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies.[12] The total atheroma volume (TAV) was calculated by summation of the atheroma area from each measured image as: TAV=$\sum$ (the EEM area-the lumen area). The percent atheroma volume (PAV) was determined using the formula: PAV =100×[$\sum$ (the EEM area-the lumen area)/$\sum$ (EEM area)] (Fig. 2).

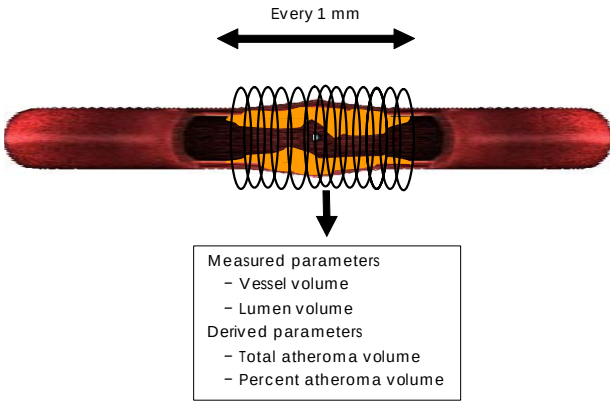

Fig. 2. Volumetric intravascular ultrasound analysis.

Statistical analysis

The Statistical Package for Social Sciences (SPSS) for Windows, version 15.0 (Chicago, Illinois) was used for all the analyses. The continuous variables are presented as mean values±SDs (standard deviations) and they were compared using paired or unpaired student's t-tests or the nonparametric Wilcoxon test if the normality assumption was violated. The discrete variables are presented as percentages and relative frequencies. Linear regression analysis was used to evaluate the associations between the follow-up LDL-cholesterol level vs. the ΔTAV, ΔPAV, Δlumen volume, Δvessel volume and Δlipid pool size. A $p<0.05$ was considered statistically significant.

Results

Baseline clinical characteristics

The baseline clinical characteristics are summarized in Table 1. Although there was a trend that the rosuvastatin group had more male patients compared with the atorvastatin group, no significant differences were seen for the patient demographics and other medications.

Table 1. Baseline clinical characteristics

	Rosuvastatin (n=16)	Atorvastatin (n=14)	p
Age (years)	60±8	62±9	0.8
Male gender, n (%)	12 (75)	6 (43)	0.073
Clinical presentation, n (%)			0.4
Stable angina	5 (31)	6 (43)	
Unstable angina	11 (69)	8 (57)	
Diabetes mellitus, n (%)	4 (25)	2 (14)	0.6
Hypertension, n (%)	7 (44)	8 (57)	0.4
Smoking, n (%)	3 (19)	2 (14)	0.7
Family history of coronary disease, n (%)	1 (6)	2 (14)	0.5
Prior MI, n (%)	1 (6)	2 (14)	0.5
Prior PCI, n (%)	3 (19)	3 (21)	0.9
Ejection fraction (%)	67±9	63±13	0.4
Medications, n (%)			
Aspirin	15 (94)	13 (93)	0.9
Clopidogrel	6 (38)	6 (43)	0.8
ACE inhibitor	7 (44)	6 (43)	1.0
ARB	8 (50)	7 (50)	1.0
β-blocker	14 (88)	12 (86)	0.9
Calcium channel blocker	12 (75)	10 (71)	0.8

MI: myocardial infarction, PCI: percutaneous coronary intervention, ACE: angiotensin converting enzyme, ARB: angiotensin receptor blocker

Changes in the laboratory findings

The baseline and follow-up laboratory findings are summarized in Table 2. The total cholesterol, triglyceride and LDL-cholesterol levels were decreased and the HDL-cholesterol level was increased from baseline to follow-up in both groups. The LDL-cholesterol level at follow-up was decreased by 46% compared with the baseline level in the rosuvastatin group ($p<0.001$) and the LDL-cholesterol level at follow-up was decreased by 43% compared with the baseline level in the atorvastatin group ($p<0.001$) (Δ=-56±46 mg/dL in the rosuvastatin group vs. Δ=-55±32 mg/dL in the atorvastatin group, $p=0.9$) (Fig. 3). The HDL-cholesterol level in the rosuvastatin group at follow-up was increased by 8% compared with the baseline level ($p<0.001$) and the HDL-cholesterol level in the atorvastatin group was decreased by 7% compared with the baseline level (Δ=+4.0±11.8 mg/dL in the rosuvastatin group vs. Δ=+2.4±9.1 mg/dL in the atorvastatin group, $p=0.7$) (Fig. 3). The hs-CRP level at follow-up was decreased in both groups, but there was no significant difference between both groups ($p=0.9$). There were no significant differences in the baseline and follow-up levels of serum BUN, creatinine, AST and ALT between both groups.

Table 2. Baseline and follow-up laboratory findings

	Rosuvastatin (n=16)	Atorvastatin (n=14)	p
Baseline			
Total cholesterol (mg/dL)	180±52	182±45	0.9
Triglyceride (mg/dL)	95±43	84±54	0.5
LDL-cholesterol (mg/dL)	121±45	127±37	0.7
HDL-cholesterol (mg/dL)	52±7	46±12	0.11
Lp (a) (mg/dL)	27±21	27±20	1.0
hs-CRP (mg/dL)	1.24±0.19	1.30±2.20	0.6
BUN (mg/dL)	15±5	14±5	0.6
Creatinine (mg/dL)	0.9±0.2	0.9±0.2	1.0
AST (U/L)	27±11	30±11	0.5
ALT (U/L)	29±19	32±17	0.6
Follow-up			
Total cholesterol (mg/dL)	128±27	129±30	0.9
Triglyceride (mg/dL)	72±47	59±11	0.3
LDL-cholesterol (mg/dL)	65±25	72±26	0.5
HDL-cholesterol (mg/dL)	56±13	49±12	0.12
Lp (a) (mg/dL)	27±24	25±22	0.8
hs-CRP (mg/dL)	0.07±0.19	0.08±0.10	0.9
BUN (mg/dL)	17±5	15±6	0.6
Creatinine (mg/dL)	0.9±0.2	0.9±0.3	1.0
AST (U/L)	32±13	37±29	0.5
ALT (U/L)	32±19	40±45	0.4

LDL-cholesterol: low-density lipoprotein-cholesterol, HDL-cholesterol: high-density lipoprotein-cholesterol, Lp(a): lipoprotein A, hs-CRP: high-sensitivity C-reactive protein, BUN: blood urea nitrogen, AST: aspartate aminotransferase, ALT: alanine aminotransferase

Intravascular ultrasound results

The baseline IVUS results are summarized in Table 3. No significant differences were seen in the baseline IVUS findings for both groups. The volumetric IVUS results are summarized in Table 4. The TAV, PAV and vessel volume were significantly decreased and the lumen volume was significantly increased from baseline to the follow-up in both groups (ΔTAV=-5.62±7.71 mm^3, ΔPAV=-0.80±1.27%, Δvessel volume=-1.96±5.23 mm^3 and Δlumen volume=+3.68±5.86 mm^3 in

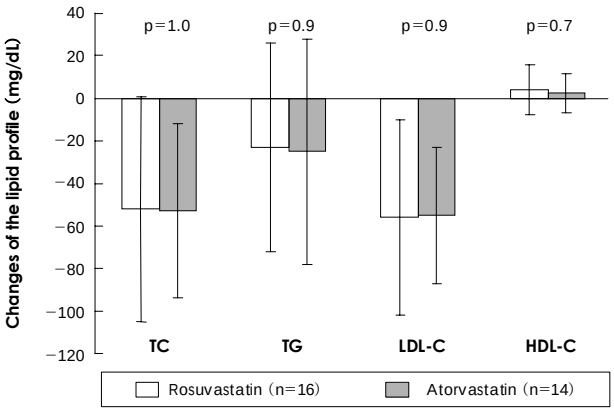

Fig. 3. The changes of the lipid profiles from baseline to follow-up. TC: total cholesterol, TG: triglyceride, LDL-C: low-density lipoprotein-cholesterol, HDL-C: high-density lipoprotein-cholesterol.

Table 3. Baseline coronary angiographic and IVUS findings

	Rosuvastatin (lesions, n=24)	Atorvastatin (lesions, n=21)	p
Target artery (%)			0.1
Left anterior descending artery	21 (87)	18 (86)	
Left circumflex artery	0 (0)	3 (14)	
Right coronary artery	3 (13)	0 (0)	
Lesion location (%)			0.7
Proximal	11 (46)	8 (38)	
Middle	13 (54)	13 (62)	
Distal	0 (0)	0 (0)	
Baseline TIMI grade 3 flow (%)	24 (100)	21 (100)	1.0
IVUS data			
Reference			
EEM CSA (mm^2)	14.7±5.9	14.5±4.9	0.9
Lumen CSA (mm^2)	10.1±4.8	10.0±1.2	1.0
P&M CSA (mm^2)	4.6±3.4	4.5±0.2	0.9
Plaque burden (%)	31±14	31±15	1.0
Minimum lumen site			
EEM CSA (mm^2)	14.2±3.6	14.3±3.4	0.9
Lumen CSA (mm^2)	7.0±2.4	6.9±2.5	0.9
P&M CSA (mm^2)	7.2±2.3	7.4±2.4	0.6
Plaque burden (%)	51±13	52±12	0.9
Largest lipid pool size (mm^2)	1.01±0.46	0.92±0.24	0.4

IVUS: intravascular ultrasound, TIMI: Thrombolysis In Myocardial Infarction, EEM: external elastic membrane, CSA: cross-sectional area, P&M: plaque plus media

the rosuvastatin group vs. ΔTAV=-4.74±8.51 mm^3, ΔPAV=-0.57±1.15%, Δvessel volume=-2.78±8.24 mm^3 and Δlumen volume=+2.00±6.61 mm^3 in the atorvastatin group) (Fig. 4). The lipid pool size was significantly decreased in both groups (Δ=-0.76±0.37 mm^2 in the rosuvastatin group vs. Δ=-0.61±0.28 mm^2 in the atorvastatin group, p=0.13) (Fig. 5).

Correlations between the follow-up low-density lipoprotein-cholesterol levels vs. the volumetric intravascular ultrasound data

There were linear relations between the ΔTAV (r=0.577, p<0.001) and the ΔPAV (r=-0.558, p<0.001) vs. the follow-up LDL-cholesterol levels. Using regression analysis, the cut-off value of the follow-up LDL-cholesterol level for the patients with no TAV and PAV increases was around 100 mg/dL (Fig. 6A and B). There were linear relations between the Δlumen volume (r=-0.371, p=0.012, Fig. 6C), the Δvessel volume (r=0.344, p=0.021, Fig. 6D) and the Δlipid pool size (r=0.470, p=0.001, Fig. 6E) vs. the follow-up LDL-cholesterol level.

Side effects

There were no serious side effects like rhabdomyolysis, cognitive loss, gastrointestinal and neurological effects, psychiatric problems, immune effects (e.g., lupus-like syndrome), erectile dysfunction and gynecomastia during the 12-months of treatment in both groups.

Table 4. The baseline and follow-up volumetric intravascular ultrasound data

	Rosuvastatin (lesions, n=24)	Atorvastatin (lesions, n=21)	p
Baseline			
Vessel volume (mm^3)	555±158	607±165	0.3
Lumen volume (mm^3)	303±91	319±71	0.5
Total atheroma volume (mm^3)	252±80	288±98	0.19
Percent atheroma volume (%)	45.5±6.1	46.9±4.0	0.4
Follow-up			
Vessel volume (mm^3)	553±158	604±166	0.3
Lumen volume (mm^3)	307±92	321±73	0.6
Total atheroma volume (mm^3)	246±79	283±98	0.17
Percent atheroma volume (%)	44.7±6.0	46.3±4.6	0.3

Discussion

This study demonstrated that lipid lowering therapy with using either rosuvastatin 20 mg or atorvastatin 40 mg induced significant plaque regression and stabilization in angina patients who had a mild to moderate degree of coronary stenosis with vulnerable plaque. The follow-up LDL-cholesterol level was related to the regression and stabilization of vulnerable plaque.

Multiple studies have shown that statins lower the mortality and morbidity of patients with coronary artery disease and other atherosclerotic vascular diseases.[1-9] Statins effectively inhibit mevalonate synthesis and they lower the LDL-cholesterol. Beyond lowering the blood lipoprotein level, statins have favorable effects on vascular inflammation,[15-17] endothelial function,[18][19] platelet adhesion and thrombosis.[20] Kim et al.[21] reported that rosuvastatin blocked the activation of c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-kappa B), resulting in a decrease of tumor necrosis factor-alpha and interleukin-6.

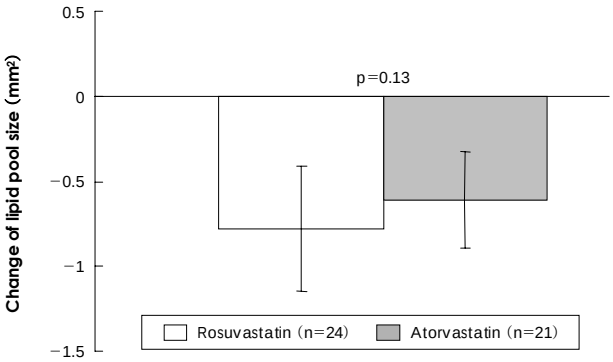

Fig. 5. The change of the lipid pool size from baseline to follow-up.

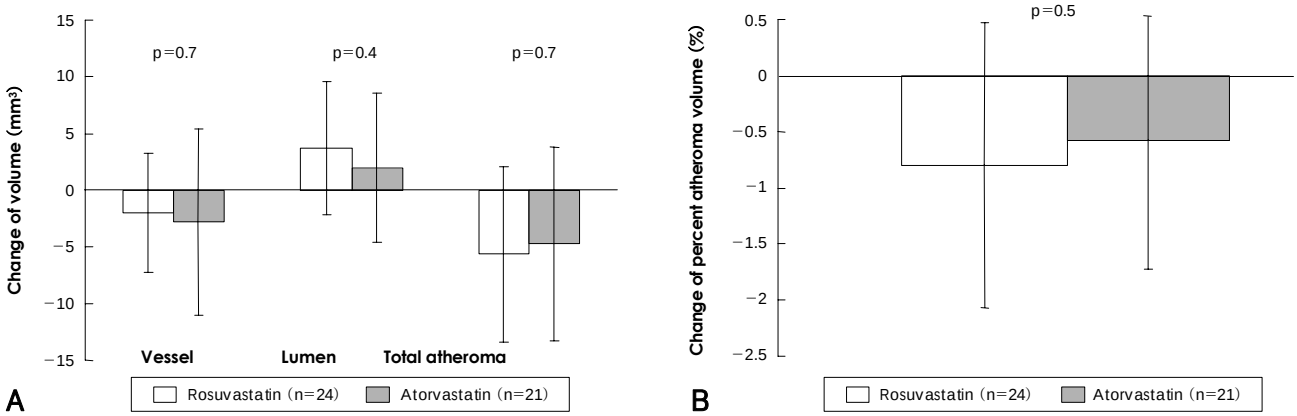

Fig. 4. The changes of the volumetric intravascular ultrasound parameters (A) and the percent atheroma volume (B) from baseline to follow-up.

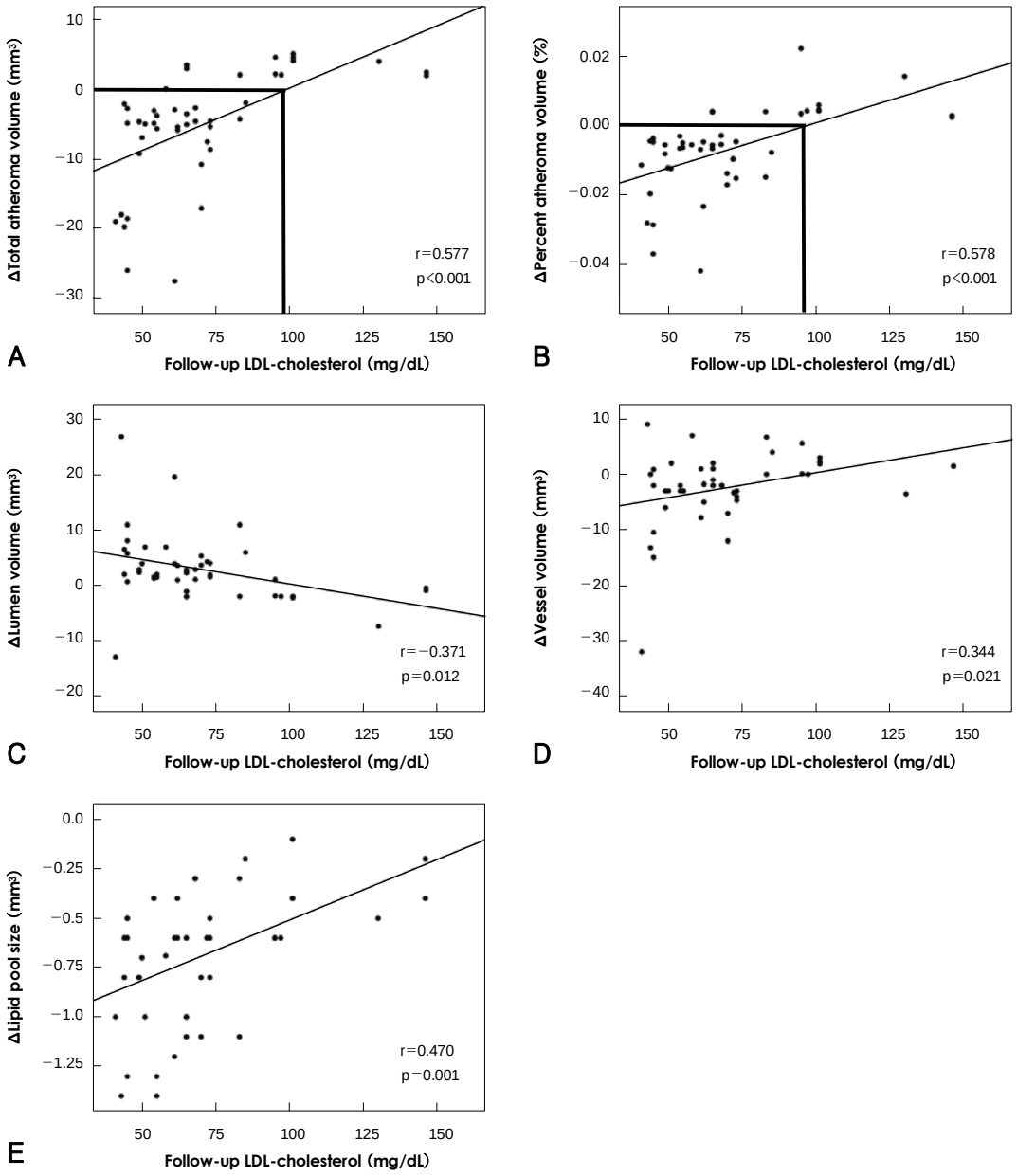

Fig. 6. The correlations between the follow-up low-density lipoprotein (LDL)-cholesterol and the Δtotal atheroma volume (A), the Δpercent atheroma volume (B), the Δlumen volume (C), the Δvessel volume (D) and the Δlipid pool size (E).

A recent study of The REVERSal of Atherosclerosis with Lipitor (REVERSAL) showed that the progression of the atheroma plaque volume was less with an aggressive dose of statin dosage than that with a moderate dose of statin.[22] Another study of A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-derived Coronary Atheroma Burden (ASTEROID) trial demonstrated that intensive statin therapy with rosuvastatin 40 mg daily could induce regression of coronary atherosclerosis and there was a very strong linear relationship between the achieved LDL-cholesterol levels and the course of atherosclerosis.[23][24]

Previous IVUS studies have shown that the follow-up LDL-cholesterol level was the independent predictor of the changes in the size of coronary plaque. Hong et al.[25] reported that when patients achieved a follow-up LDL-cholesterol level <100 mg/dL, regression or no progression of coronary plaque was expected. Nicholls et al.[26] reported that statin therapy was associated with regression of coronary atherosclerosis when the LDL-cholesterol level was substantially reduced and the HDL-cholesterol level was increased by more than 7.5%. Nissen et al.[27] reported that the reduced rate of progression of atherosclerosis that was associated with intensive statin treatment (80 mg of atorvastatin orally per day), as compared with moderate statin treatment (40 mg of pravastatin orally per day), was significantly related to greater reductions in the levels of both atherogenic

lipoproteins and CRP in patients with coronary artery disease at 18-months of follow-up. In the present study, we demonstrated that plaque regression was correlated with the reduction of the LDL-cholesterol level by performing volumetric IVUS analyses. According to the IVUS analyses, both rosuvastatin 20 mg and atorvastatin 40 mg, which were relatively lower dosages as compared to those used in the previous studies, effectively reduced the atheroma volume and increased the lumen volume. Both rosuvastatin 20 mg and atorvastatin 40 mg effectively reduced the LDL-cholesterol level (follow-up LDL-cholesterol level: 65±25 mg/dL by rosuvastatin 20 mg and 72±26 mg/dL by atorvastatin 40 mg) and it changed the plaque contents such as removal of the lipid from vulnerable plaque. With a more intensive dose of statin, plaque regression and stabilization probably could be more rapidly achieved.

There are several study limitations to be mentioned. First, the present study is a retrospective single-center study, so it is subject to the limitations inherent in this type of clinical investigation. Second, the number of patients was small. Thus, some selection bias cannot be entirely excluded. We are now continuing to enroll patients into this study. Third, the follow-up duration of this study was relatively short. We conclude that both rosuvastatin 20 mg and atorvastatin 40 mg could contribute to the regression and stabilization of lipid-rich coronary plaque. The follow-up LDL-cholesterol level is an important factor for the regression and stabilization of vulnerable plaque.

Acknowledgments

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