Comparison of Effects of Rosuvastatin and Atorvastatin on Plaque Regression in Korean Patients With Untreated Intermediate Coronary Stenosis

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Background: Serial intravascular ultrasound (IVUS) was used to compare the effects of moderate doses of rosuvastatin and atorvastatin on plaque regression in patients with intermediate coronary stenosis.

Methods and Results: This was a prospective, randomized, and comparative study for lipid-lowering therapy with rosuvastatin 20 mg (n=65) and atorvastatin 40 mg (n=63) using serial IVUS (baseline and 11-month follow-up). Efficacy parameters included changes in total atheroma volume (TAV) and percent atheroma volume (PAV) from baseline to follow-up. Changes of TAV (-4.4 ± 7.3 vs. -3.6 ± 6.8 mm³, $P=0.5$) and PAV (-0.73 ± 2.05 vs. $-0.19 \pm 2.00\%$, $P=0.14$) from baseline to follow-up were not significantly different between the 2 groups. Plaque was increased in 15% in the rosuvastatin group and in 30% in the atorvastatin group at follow-up ($P=0.064$). The plaque increase group had higher baseline high-sensitivity C-reactive protein (hs-CRP; 1.28 ± 2.70 mg/dl vs. 0.54 ± 1.16 mg/dl, $P=0.034$) and higher follow-up low-density lipoprotein cholesterol (LDL-C) (78 ± 24 mg/dl vs. 63 ± 21 mg/dl, $P=0.002$) compared with the plaque non-increase group. Follow-up LDL-C (odds ratio [OR]=1.038, 95% confidence interval [CI]=1.003–1.060, $P=0.036$) and baseline hs-CRP (OR=1.025, 95%CI=1.001–1.059, $P=0.046$), not the type of statin, were the independent predictors of plaque increase at follow-up.

Conclusions: Moderate doses of rosuvastatin and atorvastatin could contribute to effective plaque regression. Follow-up LDL-C and baseline hs-CRP are associated with plaque progression in patients with intermediate coronary stenosis. (*Circ J* 2011; **75**: 398–406)

Key Words: Coronary disease; Intravascular ultrasound; Lipid; Plaque

Lipid-lowering therapy with statins improves clinical outcomes,^{1,2} and reduces the progression of atherosclerosis.^{3–5} Previous studies have demonstrated that statin therapy could induce regression of coronary atherosclerosis and that there was a strong linear relationship between achieved low-density lipoprotein cholesterol (LDL-C) levels and the course of atherosclerosis.^{6–8} So far, no study has compared the effects of rosuvastatin and atorvastatin on plaque changes. Our hypothesis was that only moderate doses of statins could contribute to effective LDL-C lowering and plaque regression in Asian patients. Therefore, the primary purpose of the present study was to compare the

effect of a moderate dose of rosuvastatin with that of atorvastatin on plaque regression in untreated intermediate coronary stenosis in Korean patients.

It is not known which factors are associated with plaque progression in patients who use statins. The secondary purpose of the present study was to assess the impact of clinical findings, laboratory findings, and intravascular ultrasound (IVUS) findings on plaque progression in untreated intermediate coronary stenosis in patients who used moderate doses of rosuvastatin or atorvastatin.

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Figure 1. (A) Coronary angiogram and (B) intravascular ultrasound of plaque regression due to statin therapy.

Methods

Patients

This study was a prospective, randomized, and comparative study of lipid-lowering therapy using moderate doses of rosuvastatin and atorvastatin in Korean patients with intermediate coronary stenosis, which was defined as diameter stenosis 30–70% on quantitative coronary angiography (QCA), at Chonnam National University Hospital, Gwangju, Korea. Patients were randomized to take either rosuvastatin 20 mg or atorvastatin 40 mg daily. Statin therapy was started immediately after coronary angiography (CAG) and IVUS in both groups. We excluded the patients with left ventricular dysfunction (ejection fraction <30%), and hepatic or

renal dysfunction (alanine aminotransferase and aspartate aminotransferase >2-fold normal, creatinine >1.5 mg/dl). A total of 128 patients underwent baseline and 11-month follow-up CAG and IVUS (65 patients in the rosuvastatin group vs. 63 patients in the atorvastatin group). The protocol was approved by the institutional review board. Hospital records of patients were reviewed to obtain information on clinical demographics.

Laboratory Analysis

Peripheral blood samples were obtained before coronary angiography using direct venipuncture. The blood samples were centrifuged, and serum was removed and stored at -70°C until the assay was performed. The serum levels of total cho-

Table 1. Baseline Characteristics

	Rosuvastatin (n=65)	Atorvastatin (n=63)	P value
Age (years)	59±10	58±10	0.6
Male gender (n)	49 (75)	46 (73)	0.7
Clinical presentation (n)			0.10
Stable angina pectoris	17 (26)	9 (15)	
Unstable angina pectoris	29 (45)	33 (52)	
NSTEMI	5 (8)	16 (26)	
STEMI	14 (22)	5 (8)	
Hypertension (n)	28 (43)	28 (44)	1.0
Diabetes mellitus (n)	12 (19)	18 (29)	0.16
Smoker (n)	24 (37)	18 (29)	0.4
Family history of coronary artery disease (n)	1 (2)	1 (2)	1.0
Ejection fraction (%)	61±10	64±9	0.17
Total cholesterol (mg/dl)	185±42	181±43	0.6
Triglyceride (mg/dl)	125±94	124±117	0.9
LDL-C (mg/dl)	122±37	117±38	0.5
HDL-C (mg/dl)	47±10	48±15	0.7
Apoprotein A1 (mg/dl)	127±16	128±28	0.7
Apoprotein B (mg/dl)	95±24	93±25	0.6
Apoprotein B/A1	0.75±0.18	0.75±0.28	0.9
Lipoprotein (a) (mg/dl)	29±21	26±19	0.4
hs-CRP (mg/dl)	0.50±1.17	0.93±2.03	0.15
NT-pro-BNP (pg/ml)	411±689	315±711	0.5

Data are given as mean±SD or n (%).

NSTEMI, non-ST segment elevation myocardial infarction; STEMI, ST segment elevation myocardial infarction; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; NT-pro-BNP, N-terminal pro-B-type natriuretic peptide.

lesterol, triglyceride, LDL-C, and high-density lipoprotein cholesterol were measured using standard enzymatic methods. High-sensitivity C-reactive protein (hs-CRP) was analyzed turbidimetrically with sheep antibodies against human CRP; this has been validated against the Dade-Behring method.⁹ Serum N-terminal pro-B-type natriuretic peptide was measured using an electrochemiluminescence sandwich immunoassay with an Elecsys 2010 analyzer (Roche Diagnostics, Mannheim, Germany).

Angiography

Coronary angiogram was analyzed with a validated QCA system (Phillips H5000 or Allura DCI program, Philips Medical Systems, Eindhoven, the Netherlands).¹⁰ With the outer diameter of the contrast-filled catheter as the calibration standard, the minimal lumen diameter and reference diameter were measured in diastolic frames from orthogonal projections.

IVUS

IVUS was performed after intra-coronary administration of 300 µg nitroglycerin using a commercially available IVUS system (Boston Scientific/SCIMed, Minneapolis, MN, USA). 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. IVUS data were analyzed by 2 independent observers (H.Y.J. and C.Y.H.). The levels of reproducibility for external elastic membrane (EEM) volume, lumen volume, and total atheroma volume (TAV) using the Spearman rank-order correlation coefficients were 0.95, 0.97, and 0.97, respectively. We

measured diseased segment (normal to normal). The same anatomic image slices were analyzed at baseline and at follow-up. By using the axial landmark (ie, side branch, calcifications, or unusual plaque shapes) and the known pullback speed, identical cross-sectional image slices on serial studies could be identified for comparison. We measured IVUS images spaced precisely 1 mm apart. The leading edges of the EEM and lumen were traced manually using planimetry software (Echoplague 3.0, INDEC Systems, Santa Clara, CA, USA) in accordance with guidelines for IVUS from the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies.¹¹ TAV was calculated by summation of atheroma area from each measured image as: $TAV = \sum (EEM \text{ area} - \text{lumen area})$. The percent atheroma volume (PAV) was determined using the formula: $PAV = 100 \times [\sum (EEM \text{ area} - \text{lumen area}) / \sum (EEM \text{ area})]$. Plaque increase was defined as increase of TAV from baseline to follow-up, and plaque non-increase was defined as decrease of TAV from baseline to follow-up (Figure 1). Soft plaque was less bright compared with the reference adventitia. Fibrotic plaque was as bright as or brighter than the reference adventitia without acoustic shadowing. Calcified plaque was hyperechoic with shadowing. A calcified lesion contained >90° of circumferential lesion calcium. When there was no dominant plaque composition, the plaque was classified as mixed.

Statistical Analysis

SPSS for Windows, version 15.0 (SPSS, Chicago, IL, USA) was used for all analyses. Continuous variables are presented

Table 2. Baseline CAG and IVUS

	Rosuvastatin (n=65)	Atorvastatin (n=63)	P value
Target coronary artery (n)			0.10
Left main	3 (5)	5 (8)	
Left anterior descending	37 (57)	35 (55)	
Left circumflex	4 (6)	11 (18)	
Right	21 (32)	12 (19)	
Lesion location (n)			0.5
Proximal	32 (49)	33 (52)	
Middle	21 (32)	20 (32)	
Distal	12 (18)	10 (16)	
RD (mm)	3.29±0.50	3.26±0.48	0.4
MLD (mm)	1.77±0.44	1.79±0.54	0.8
Percent diameter stenosis (%)	46±10	45±9	0.9
IVUS lesion length (mm)	17±10	21±18	0.10
Plaque morphology (n)			0.4
Soft	41 (63)	42 (66)	
Fibrotic	3 (5)	5 (8)	
Calcified	5 (8)	4 (6)	
Mixed	16 (25)	12 (19)	
EEM volume (mm ³)	346±194	385±242	0.3
Lumen volume (mm ³)	180±107	194±126	0.5
TAV (mm ³)	166±93	190±119	0.2
PAV (%)	48.0±6.1	49.9±6.1	0.080

Data are given as mean±SD or n (%).

CAG, coronary angiography; IVUS, intravascular ultrasound; RD, reference diameter; MLD, minimal lumen diameter; EEM, external elastic membrane; TAV, total atheroma volume; PAV, percent atheroma volume.

as mean±1SD; comparisons were done using Student's t-test or the Wilcoxon rank-sum test if normality assumption was violated. Discrete variables are presented as percentages and frequencies; comparisons were done using chi-squared statistics or Fisher's exact test as appropriate. Pearson's correlation coefficient was used to evaluate the associations between follow-up LDL-C vs. change in TAV and PAV and between baseline hs-CRP vs. change in TAV and PAV. Multivariable logistic regression analysis was performed to identify independent predictors of plaque increase at follow-up. $P<0.05$ was considered statistically significant.

Results

Baseline Characteristics

Baseline characteristics are summarized in [Table 1](#). There were no significant differences in age, gender, risk factors for coronary artery disease, ejection fraction, and baseline LDL-C and hs-CRP between rosuvastatin and atorvastatin groups.

CAG and IVUS

Baseline CAG and IVUS findings are summarized in [Table 2](#). There were no significant differences in target lesion, lesion location, minimal lumen diameter on QCA, IVUS lesion length, plaque morphology, TAV, or PAV between the rosuvastatin and atorvastatin groups.

Follow-up Laboratory Tests and IVUS and Changes in Findings

Follow-up laboratory tests and IVUS and changes in findings from baseline to follow-up are summarized in [Table 3](#). There were no significant differences in follow-up LDL-C

and hs-CRP between the rosuvastatin and atorvastatin groups. Follow-up TAV was not significantly different between the rosuvastatin and atorvastatin groups, but follow-up PAV was significantly smaller in the rosuvastatin group compared with the atorvastatin group. Changes of LDL-C and hs-CRP from baseline to follow-up were not significantly different, and changes of TAV and PAV from baseline to follow-up were not significantly different between the rosuvastatin and atorvastatin groups.

Baseline Characteristics vs. Plaque Change

Of 128 patients, plaque was increased in 29 (23%; 15% [10/65] in the rosuvastatin group vs. 30% [19/63] in the atorvastatin group) and was decreased in 99 patients (77%; 85% [55/65] in the rosuvastatin group vs. 70% [44/63] in the atorvastatin group) at 11-month follow-up ($P=0.064$). The baseline characteristics according to plaque increase or non-increase are summarized in [Table 4](#). The patients in the plaque increase group were significantly younger, had lower ejection fraction, higher baseline hs-CRP, and higher follow-up LDL-C compared with those in the plaque non-increase group. There was a trend towards greater plaque regression in patients with acute coronary syndrome compared to those with stable angina pectoris (Δ TAV: -6.0 ± 8.8 mm³ vs. -3.5 ± 6.5 mm³, $P=0.18$; Δ PAV: $-1.03\pm2.32\%$ vs. $-0.29\pm1.89\%$, $P=0.10$, respectively).

CAG and IVUS vs. Plaque Change

CAG and IVUS findings according to plaque change are summarized in [Table 5](#). There were no significant differences in the target vessel, lesion location, or QCA data between the plaque increase and non-increase groups. There were no significant differences in baseline IVUS between

Table 3. Follow-up Laboratory Tests and IVUS, and Changes in Findings From Baseline to Follow-up

	Rosuvastatin (n=65)	Atorvastatin (n=63)	P value
Total cholesterol (mg/dl)	124±25	133±32	0.092
Triglyceride (mg/dl)	94±56	103±193	0.7
LDL-C (mg/dl)	62±20	70±24	0.053
HDL-C (mg/dl)	47±12	47±12	0.8
Apoprotein A1 (mg/dl)	130±20	126±22	0.2
Apoprotein B (mg/dl)	59±15	60±19	0.8
Apoprotein B/A1	0.46±0.13	0.50±0.17	0.15
Lipoprotein (a) (mg/dl)	33±30	28±23	0.3
hs-CRP (mg/dl)	0.10±0.14	0.10±0.18	1.0
EEM volume (mm ³)	346±194	385±242	0.4
Lumen volume (mm ³)	182±109	194±126	0.6
TAV (mm ³)	166±93	190±119	0.19
PAV (%)	47.3±6.5	49.7±6.5	0.035
ΔTotal cholesterol (mg/dl)	−61±38	−48±47	0.091
ΔTriglyceride (mg/dl)	−31±79	−19±108	0.5
ΔLDL-C (mg/dl)	−60±33	−47±39	0.057
ΔHDL-C (mg/dl)	−0.5±9.1	−1.1±11.3	0.8
ΔApoprotein A1 (mg/dl)	+3.0±16.1	−2.4±25.8	0.18
ΔApoprotein B (mg/dl)	−36±22	−34±25	0.7
ΔApoprotein B/A1	−0.29±0.11	−0.25±0.10	0.18
ΔLipoprotein (a) (mg/dl)	+5.5±13.8	+2.5±10.5	0.18
Δhs-CRP (mg/dl)	−0.40±1.18	−0.84±2.07	0.16
ΔEEM volume (mm ³)	−3.1±7.9	−5.1±9.5	0.2
Δlumen volume (mm ³)	+1.3±7.1	−1.0±7.3	0.070
ΔTAV (mm ³)	−4.4±7.3	−3.6±6.8	0.5
ΔPAV (%)	−0.73±2.05	−0.19±2.10	0.14

Abbreviations see in Table 1.

the plaque increase and non-increase groups.

Follow-up Laboratory Tests and IVUS and Changes in Findings vs. Plaque Changes

Follow-up laboratory tests and IVUS and changes in findings from baseline to follow-up according to plaque increase or non-increase are summarized in **Table 6**. Follow-up total cholesterol, triglyceride, LDL-C, apoprotein B, and apoprotein B/A1 were significantly higher in the plaque increase group compared with the plaque non-increase group. Changes in total cholesterol, triglyceride, LDL-C, high-density lipoprotein cholesterol, and hs-CRP levels from baseline to follow-up were not significantly different between the plaque increase and non-increase groups. EEM volume increased in the plaque increase group and decreased in the plaque non-increase group from baseline to follow-up.

Plaque Increase vs. Follow-up LDL-C, and Baseline and Follow-up hs-CRP

Plaque was increased in 34% of patients with follow-up LDL-C >70 mg/dl (17/50) and in 15% of patients with follow-up LDL-C ≤70 mg/dl (12/78; $P=0.014$; **Figure 2A**). Plaque was increased in 38% of patients with baseline hs-CRP ≥1.0 mg/dl (6/16) and in 21% of patients with baseline hs-CRP <1.0 mg/dl (23/112; $P=0.020$; **Figure 2B**). Plaque was increased in 37% of patients with follow-up hs-CRP ≥0.1 mg/dl (11/30) and in 18% of patients with follow-up hs-CRP <0.1 mg/dl (18/98; $P=0.045$; **Figure 2C**).

There were positive correlations between follow-up LDL-

C and ΔTAV ($r=0.274$, $P=0.003$), and follow-up LDL-C and ΔPAV ($r=0.225$, $P=0.014$). There were positive correlations between baseline hs-CRP and ΔTAV ($r=0.234$, $P=0.011$), and baseline hs-CRP and ΔPAV ($r=0.212$, $P=0.021$).

Independent Predictors of Plaque Increase

The following variables were tested to determine the independent predictors of plaque increase at follow-up (variables with $P<0.1$ in univariate analysis): type of statin, age, ejection fraction, baseline hs-CRP, baseline apoprotein B/A1, baseline TAV, and follow-up LDL-C. Follow-up LDL-C (odds ratio [OR]=1.038, 95% confidence interval [CI]=1.003–1.060, $P=0.036$) and baseline hs-CRP (OR=1.025, 95% CI=1.001–1.059, $P=0.046$), but not type of statin, were the independent predictors of plaque increase at follow-up.

Discussion

The present serial IVUS study has demonstrated that (1) changes in LDL-C and hs-CRP from baseline to follow-up were not significantly different, and changes of TAV and PAV from baseline to follow-up were not significantly different between rosuvastatin and atorvastatin groups; (2) plaque was decreased in 85% of patients in the rosuvastatin group and in 70% of patients in the atorvastatin group at 11-month follow-up; and (3) follow-up LDL-C and baseline hs-CRP, but not type of statin, were the independent predictors of plaque increase at follow-up. Moderate doses of rosuvastatin and atorvastatin could contribute to effective plaque

Table 4. Baseline Characteristics vs. Plaque Change

	Plaque increase (n=29)	Plaque non-increase (n=99)	P value
Type of statin (n)			0.064
Rosuvastatin	10 (15)	55 (85)	
Atorvastatin	19 (30)	44 (70)	
Age (years)	54±10	59±10	0.011
Male gender (n)	20 (69)	75 (76)	0.5
Clinical presentation (n)			0.6
Stable angina pectoris	6 (21)	20 (20)	
Unstable angina pectoris	11 (38)	50 (51)	
NSTEMI	6 (21)	15 (15)	
STEMI	6 (21)	14 (14)	
Hypertension (n)	11 (38)	45 (46)	0.5
Diabetes mellitus (n)	6 (21)	24 (24)	0.7
Smoker (n)	11 (38)	32 (32)	0.7
Family history of coronary artery disease (n)	2 (7)	0 (0)	0.2
Ejection fraction (%)	58±12	64±9	0.038
Total cholesterol (mg/dl)	193±50	182±41	0.2
Triglyceride (mg/dl)	145±161	118±81	0.2
LDL-C (mg/dl)	126±40	118±37	0.3
HDL-C (mg/dl)	50±19	47±10	0.5
Apoprotein A1 (mg/dl)	128±30	127±19	0.9
Apoprotein B (mg/dl)	101±26	92±24	0.085
Apoprotein B/A1	0.83±0.27	0.73±0.22	0.060
Lipoprotein (a) (mg/dl)	28±18	27±20	0.8
hs-CRP (mg/dl)	1.28±2.70	0.54±1.16	0.034
NT-pro-BNP (pg/ml)	561±965	310±585	0.2
Medications at discharge (n)			
Aspirin	27 (93)	94 (95)	0.8
Clopidogrel	12 (41)	38 (38)	0.7
ACEI/ARB	11 (38)	45 (46)	0.5
β -blockers	11 (38)	32 (32)	0.7
Calcium-channel blockers	20 (69)	64 (64)	0.5

Data are given as mean $\pm$ SD or n (%).

ACEI/ARB, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker. Other abbreviations see in Tables 1, 2.

regression, and follow-up LDL-C and baseline hs-CRP are associated with plaque progression in Korean patients with untreated intermediate coronary stenosis. This therefore suggests that different types of statins with similar efficacy in LDL-C and hs-CRP reduction have similar effects on plaque regression at follow-up.

IVUS is a useful tool for assessing the effect of therapies on the vascular wall, providing a precise and continuous measure of disease progression.¹² The recent REVERSAL of Atherosclerosis with Lipitor (REVERSAL) study showed that plaque volume progression was smaller with aggressive statin treatment with atorvastatin 80 mg daily than moderate statin treatment with pravastatin 40 mg daily.⁶ And the 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.⁷ Previous studies have shown that there is a very strong linear relationship between achieved LDL-C levels and the course of atherosclerosis.^{3–8} In the present study, 20 mg of rosuvastatin lowered LDL-C to 62 mg/dl (49% decrease, $P < 0.001$) and 40 mg of atorvastatin lowered LDL-C to 70 mg/dl (40% decrease, $P < 0.001$), and moderate doses of both statins

could regress plaque effectively, and plaque was increased in 34% of patients with follow-up LDL-C > 70 mg/dl and in 15% of patients with follow-up LDL-C ≤ 70 mg/dl, and follow-up LDL-C was the independent predictor of plaque increase, as in previous studies. In the present study, changes of TAV and PAV from baseline to follow-up were not significantly different between the rosuvastatin and atorvastatin groups. The present results suggest that effective LDL-C lowering and plaque regression can be achieved using only moderate doses of statins, and that different types of statins with similar LDL-C-lowering effects have similar effects on plaque regression in Korean patients with intermediate coronary stenosis.

CRP has emerged as a simple tool for detecting systemic inflammation.^{13,14} A previous study demonstrated that CRP was strongly associated with atherosclerosis measured at various sites in the arterial tree.¹⁵ Several mechanisms have been described by which CRP and other inflammatory mediators may be actively involved in atherogenesis.¹⁶ CRP is produced by smooth muscle cells of atherosclerotic lesions,¹⁷ and the locally produced CRP could directly participate in atherogenesis and the development of cardiovascular complications. In the present study, plaque was increased in 38% of patients

	Plaque increase (n=29)	Plaque non-increase (n=99)	P value
Target coronary artery (n)			0.3
Left main	3 (10)	5 (5)	
Left anterior descending	16 (55)	55 (56)	
Left circumflex	1 (3)	14 (14)	
Right	9 (31)	25 (25)	
Lesion location (n)			0.5
Proximal	16 (55)	49 (49)	
Middle	9 (31)	32 (32)	
Distal	4 (14)	18 (18)	
RD (mm)	3.32±0.58	3.25±0.48	0.2
MLD (mm)	1.75±0.54	1.80±0.44	0.18
Percent diameter stenosis (%)	47±13	45±10	0.6
IVUS lesion length (mm)	17±15	20±15	0.7
Plaque morphology (n)			0.3
Soft	19 (66)	64 (65)	
Fibrotic	4 (14)	4 (4)	
Calcified	2 (7)	7 (7)	
Mixed	4 (14)	24 (24)	
EEM volume (mm ³)	304±202	385±221	0.076
Lumen volume (mm ³)	157±111	198±118	0.095
TAV (mm ³)	147±95	187±108	0.074
PAV (%)	49±7	49±6	1.0

Data are given as mean±SD or n (%).

Abbreviations see in Table 2.

	Plaque increase (n=29)	Plaque non-increase (n=99)	P value
Total cholesterol (mg/dl)	146±35	123±25	<0.001
Triglyceride (mg/dl)	144±280	85±44	0.046
LDL-C (mg/dl)	78±24	63±21	0.002
HDL-C (mg/dl)	49±14	47±12	0.4
Apoprotein A1 (mg/dl)	128±23	128±20	0.9
Apoprotein B (mg/dl)	70±16	57±16	<0.001
Apoprotein B/A1	0.56±0.16	0.45±0.14	0.001
Lipoprotein (a) (mg/dl)	30±19	31±29	0.9
hs-CRP (mg/dl)	0.16±0.43	0.12±0.31	0.7
EEM volume (mm ³)	305±201	380±221	0.10
Lumen volume (mm ³)	154±111	199±120	0.074
TAV (mm ³)	151±95	180±105	0.17
PAV (%)	50±7	48±7	0.10
ΔTotal cholesterol (mg/dl)	-46±48	-58±41	0.18
ΔTriglyceride (mg/dl)	-1±146	-33±71	0.11
ΔLDL-C (mg/dl)	-49±36	-55±38	0.4
ΔHDL-C (mg/dl)	-1.0±10.3	-0.8±10.2	0.9
ΔApoprotein A1 (mg/dl)	+0.5±22.0	+0.5±21.3	1.0
ΔApoprotein B (mg/dl)	-31±22	-37±24	0.3
ΔLipoprotein (a) (mg/dl)	+2.2±10.4	+4.8±12.9	0.3
Δhs-CRP (mg/dl)	-1.27±2.80	-0.43±1.18	0.2
ΔEEM volume (mm ³)	+1.3±5.6	-5.6±8.9	<0.001
ΔLumen volume (mm ³)	-2.6±5.7	+1.0±7.5	0.021
ΔTAV (mm ³)	+3.8±2.9	-6.3±6.2	<0.001
ΔPAV (%)	+1.4±1.7	-1.0±1.9	<0.001

Abbreviations see in Tables 1,2.

with baseline hs-CRP ≥ 1.0 mg/dl and in 21% of patients with baseline hs-CRP < 1.0 mg/dl, and plaque was increased in 37% of patients with follow-up hs-CRP ≥ 0.1 mg/dl and in 18% of patients with follow-up hs-CRP < 0.1 mg/dl, and baseline hs-CRP was associated with plaque increase at follow-up, and the reduction of hs-CRP and plaque decrease from baseline to follow-up were similar in the rosuvastatin and atorvastatin groups. A previous experimental study has demonstrated that CRP accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice.¹⁸ CRP is related to the progression of coronary atherosclerosis^{19,20} and to peripheral atherosclerosis.^{21–24} The present results have demonstrated a relationship between levels of circulating inflammatory markers and risk of progressive atherosclerosis in Korean patients with intermediate coronary stenosis. Moderate doses of statins might be sufficient to reduce LDL-C and hs-CRP and to regress plaque more effectively in Asian patients compared with Caucasian patients.

Study Limitations

First, this was a single-center study and was based on a small sample, thus raising the possibility of selection bias. Second, serial follow-up of serum hs-CRP level was not done. Therefore, we did not demonstrate the impact of sequential change of hs-CRP level on plaque progression or regression. Third, plaque morphology was assessed visually using grayscale IVUS, which has significant limitations in assessing plaque composition. At present, radiofrequency analysis has become available for further plaque characterization. Fourth, the mean follow-up period was only 11 months, longer-term IVUS follow-up data were not collected.

Conclusions

Moderate doses of rosuvastatin and atorvastatin could contribute to plaque regression. Follow-up LDL-C and baseline hs-CRP are associated with plaque progression in Korean patients with intermediate coronary stenosis. Different types of statins with similar efficacy in LDL-C and hs-CRP reduction have similar effects on plaque regression at follow-up.

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Disclosures

There are no potential conflicts to declare.

References

- Cannon CP, Braunwald E, McCabe CH, Rader DJ, Rouleau JL, Belder R, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 Investigators: Intensive versus moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med* 2004; **350**: 1495–1504.
- Kasai T, Miyauchi K, Kajimoto K, Kubota N, Kurata T, Amano A, et al. The impact of pravastatin therapy on long-term outcome in patients with metabolic syndrome undergoing complete coronary revascularization. *Circ J* 2009; **73**: 2104–2019.
- Nissen SE, Tuzcu EM, Schoenhagen P, Brown BG, Ganz P, Vogel RA, et al; REVERSAL Investigators. Effect of intensive compared with moderate lipid-lowering therapy on progression of coronary atherosclerosis: A randomized controlled trial. *JAMA* 2004; **291**: 1071–1080.
- Takayama T, Hiro T, Yamagishi M, Daida H, Hirayama A, Saito S, et al; COSMOS Investigators. Effect of rosuvastatin on coronary atheroma in stable coronary artery disease: Multicenter coronary atherosclerosis study measuring effects of rosuvastatin using intravascular ultrasound in Japanese subjects (COSMOS). *Circ J* 2009; **73**: 2110–2117.
- Toi T, Taguchi I, Yoneda S, Kageyama M, Kikuchi A, Tokura M, et al. Early effect of lipid-lowering therapy with pitavastatin on regression of coronary atherosclerotic plaque: Comparison with atorvastatin. *Circ J* 2009; **73**: 1466–1472.
- Nissen SE, Tuzcu EM, Schoenhagen P, Crowe T, Sasiela WJ, Tsai J, et al. Reversal of Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) Investigators: Statin therapy, LDL cholesterol, C-reactive protein, and coronary artery disease. *N Engl J Med* 2005; **352**: 29–38.
- Nissen SE, Nicholls SJ, Sipahi I, Libby P, Raichlen JS, Ballantyne CM, et al; ASTEROID Investigators. Effect of very high-intensity statin therapy on regression of coronary atherosclerosis: The ASTEROID trial. *JAMA* 2006; **295**: 1556–1565.
- Nicholls SJ, Tuzcu EM, Sipahi I, Grasso AW, Schoenhagen P, Hu T, et al. Statins, high-density lipoprotein cholesterol, and regression of coronary atherosclerosis. *JAMA* 2007; **297**: 499–508.
- Roberts WL, Moulton L, Law TC, Farrow G, Cooper-Anderson M, Savory J, et al. Evaluation of nine automated high-sensitivity C-reactive protein methods: Implications for clinical and epidemiological applications. Part 2. *Clin Chem* 2001; **47**: 418–425.
- Reiber JH, van der Zwet PM, Koning G, von Land CD, van Meurs B, Gerbrands JJ, et al. Accuracy and precision of quantitative digital coronary arteriography: Observer-, short-, and medium-term variabilities. *Catheter Cardiovasc Diagn* 1993; **28**: 187–198.
- Mintz GS, Nissen SE, Anderson WD, Bailey SR, Erbel R, Fitzgerald PJ, et al. American College of Cardiology clinical expert consensus document on standards for acquisition, measurement and reporting of intravascular ultrasound studies (IVUS): A report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. *J Am Coll Cardiol* 2001; **37**: 1478–1492.
- Nissen SE, Yock P. Intravascular ultrasound: Novel pathophysiological insights and current clinical applications. *Circulation* 2001; **103**: 604–616.
- Ridker PM, Cannon CP, Morrow D, Rifai N, Rose LM, McCabe CH, et al. Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction 22 (PROVE IT-TIMI 22) Investigators: C-reactive protein levels and outcomes after statin therapy. *N Engl J Med* 2005; **352**: 20–28.
- Morrow DA, Braunwald E. Future of biomarkers in acute coronary syndromes: Moving toward a multimarker strategy. *Circulation* 2003; **108**: 250–252.
- van der Meer IM, de Maat MP, Bots ML, Breteler MM, Meijer J, Kiliaan AJ, et al. Inflammatory mediators and cell adhesion molecules as indicators of severity of atherosclerosis: The Rotterdam Study. *Arterioscler Thromb Vasc Biol* 2002; **22**: 838–842.
- Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. *Circulation* 2002; **105**: 1135–1143.
- Jabs WJ, Theissing E, Nitschke M, Bechtel JF, Duchrow M, Mohamed S, et al. Local generation of C-reactive protein in diseased coronary artery venous bypass grafts and normal vascular tissue. *Circulation* 2003; **108**: 1428–1431.
- Paul A, Ko KW, Li L, Yechoor V, McCrory MA, Szalai AJ, et al. C-reactive protein accelerates the progression of atherosclerosis in apolipoprotein E-deficient mice. *Circulation* 2004; **109**: 647–655.
- Nakachi T, Kosuge M, Hibi K, Ebina T, Hashiba K, Mitsuhashi T, et al. C-reactive protein elevation and rapid angiographic progression of nonculprit lesion in patients with non-ST-segment elevation acute coronary syndrome. *Circ J* 2008; **72**: 1953–1959.
- Imai K, Okura H, Kume T, Yamada R, Miyamoto Y, Kawamoto T, et al. C-reactive protein predicts non-target lesion revascularization and cardiac events following percutaneous coronary intervention in patients with angina pectoris. *J Cardiol* 2009; **53**: 388–395.
- Elias-Smale SE, Kardys I, Oudkerk M, Hofman A, Witteman JC. C-reactive protein is related to extent and progression of coronary and extra-coronary atherosclerosis: results from the Rotterdam study. *Atherosclerosis* 2007; **195**: e195–e202.
- Arenillas JF, Alvarez-Sabin J, Molina CA, Chacón P, Fernández-Cadenas I, Ribó M, et al. Progression of symptomatic intracranial large artery atherosclerosis is associated with a proinflammatory state and impaired fibrinolysis. *Stroke* 2008; **39**: 1456–1463.
- Tzoulaki I, Murray GD, Lee AJ, Rumley A, Lowe GD, Fowkes FG. C-reactive protein, interleukin-6, and soluble adhesion molecules as predictors of progressive peripheral atherosclerosis in the general population: Edinburgh Artery Study. *Circulation* 2005; **112**: 976–983.
- Hashimoto H, Kitagawa K, Hougaku H, Etani H, Hori M. Relationship between C-reactive protein and progression of early carotid atherosclerosis in hypertensive subjects. *Stroke* 2004; **35**: 1625–1630.