We evaluated the impact of achieved low-density lipoprotein cholesterol (LDL-C) concentrations <70 mg/dL on plaque progression in statin-treated hypertensive angina patients by use of virtual histology-intravascular ultrasound (VH-IVUS). The effects of 10 mg of rosuvastatin on plaque progression were evaluated in 78 patients who achieved LDL-C < 70 mg/dL with statin treatment. The patients were divided into plaque progressors (n=30) and plaque regressors (n=40) on the basis of the baseline minimum lumen area (MLA) site at the 9-month follow-up. The prevalence of chronic kidney disease (CKD) [creatinine clearance (CrCl) < 60 mL/min] and current smoking was higher in progressors than in regressors (90.0% vs. 31.3%, p < 0.001, and 40.0% vs. 12.5%, p=0.005, respectively). Baseline CrCl was significantly lower and baseline apolipoprotein (apo) B/A1 was significantly higher in progressors than in regressors (21±13 mL/min vs. 70±20 mL/min, p < 0.001, and 0.77±0.23 vs. 0.65±0.16, p=0.011, respectively). Absolute and relative fibrotic areas at the MLA site increased in progressors; by contrast, these areas decreased in regressors from baseline to follow-up. CKD [odds ratio (OR): 2.13, 95% confidence interval (CI): 1.77-2.53, p=0.013], smoking (OR: 1.76, 95% CI: 1.23-2.22, p=0.038), and apoB/A1 (OR: 1.25, 95% CI: 1.12-1.40, p=0.023), but not any VH-IVUS parameters, were independent predictors of plaque progression at follow-up. In conclusion, clinical factors including CKD, smoking, and apoB/A1 rather than plaque components detected by VH-IVUS are associated with plaque progression in hypertensive angina patients who achieve very low LDL-C after statin treatment.

Key Words: Coronary disease; Hypertension; Plaque; Lipids; Ultrasonography, Interventional

INTRODUCTION

Hypertension accelerates atherosclerosis and can induce vascular inflammation mediated by various mediators. Plaque progression is associated with the action of angiotensin II and inflammatory and vascular smooth muscle cells, and oxidative stress and endothelial dysfunction, in patients with hypertension.

Intravascular imaging systems, especially intravascular ultrasound (IVUS), have been used to evaluate the mechanisms of plaque progression or regression, and several studies have shown the effects of statins on the course of coronary atherosclerosis and the relationship between concentrations of low-density lipoprotein cholesterol (LDL-C) with statin treatment and plaque progression or regression.

A previous study demonstrated that an increase in systolic blood pressure at follow-up was independently associated with plaque progression in patients with very low achieved LDL-C levels. However, the factors related to
plaque progression are not well understood in statin-treated patients with angina pectoris and hypertension. Therefore, the aim of this study was to evaluate the predictors of plaque progression by use of virtual histology (VH)-IVUS in statin-treated hypertensive angina patients whose achieved LDL-C level was < 70 mg/dL at follow-up.

MATERIALS AND METHODS

1. Patient population

This study was a retrospective, single-center study. A total of 78 statin-treated hypertensive angina patients who achieved an LDL-C level of < 70 mg/dL with statin treatment and who underwent gray-scale and VH-IVUS in non-intervened coronary segments were identified from the Chonnam National University Hospital VH-IVUS registry database. Follow-up angiogram and IVUS examinations were performed in patients with chest pain or a positive finding on a stress test as well as in asymptomatic patients during routine follow-up. All patients received 10 mg/day of rosvastatin from baseline to follow-up.

The effects of 9 months of rosuvastatin therapy on coronary plaque progression were evaluated by using VH-IVUS. The included patients were divided into plaque progressors (n=30) and plaque regressors (n=40) according to the American College of Cardiology Clinical Expert Consensus Document on Standards for Acquisition, Measurement and Reporting of Intravascular Ultrasound Studies. Measurements were made at every 1-mm interval for the region of interest, which was defined as the segment between distal and proximal reference sites. Volumetric data were generated by the software by using Simpson’s method. The external elastic membrane (EEM) and lumen cross-sectional areas (CSAs) were measured. Plaque plus media (P&M) CSA was calculated as EEM minus lumen CSA, and plaque burden was calculated as P&M divided by EEM CSA. Total atheroma volume (TAV) was determined by summation of the plaque area, which was defined as the difference between EEM and lumen area, for all evaluable images as TAV=∑(EEM area – lumen area). The percent atheroma volume (PAV) was calculated as the percentage of the sum of EEM areas occupied by TAV: PAV=100 × ∑(EEM area - lumen area)/∑(EEM area). 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. Atheromas have been classified in four categories by gray-scale IVUS: (1) soft plaque (lesion echogenicity less than the surrounding adventitia), (2) fibrous plaque (intermediate echogenicity between soft (echolucent) atheromas and highly echogenic calcified plaques), (3) calcified plaque (echogenicity higher than the adventitia with acoustic shadowing), and (4) mixed plaques (no single acoustical subtype represents > 80% of the plaques). VH-IVUS analysis classified the color-coded tissue into four major components: (1) dark green (FT), (2) light green (FF), (3) red (NC), and (4) white (DC). Two experienced, independent IVUS analysts defined thin-cap fibroatheroma as a lesion fulfilling the following criteria in at least three consecutive frames: NC > 10% without evident over-
Very Low LDL-C and Plaque Progression

Fig. 1. Representative case of plaque progression from baseline to the 9-month follow-up in a patient with hypertension who presented with unstable angina and whose achieved low-density lipoprotein cholesterol level was 58 mg/dL: (A) baseline coronary angiography, (B) follow-up coronary angiography, (C) baseline virtual histology-intravascular ultrasound, (D) follow-up virtual histology-intravascular ultrasound.

lying fibrous tissue and PAV ≥40%. VH-IVUS analysis was reported in absolute amounts and as a percentage of plaque area or volume.

5. Statistical analysis

The Statistical Package for the Social Sciences (SPSS) for Windows, version 15.0 (Chicago, IL, USA), was used for all analyses. Continuous variables were presented as the mean value ± 1 SD; comparisons were conducted by Student’s t-test or nonparametric Wilcoxon test if the normality assumption was violated. Discrete variables were presented as percentages and relative frequencies; comparisons were conducted by chi-square statistics or Fisher’s exact test as appropriate. Multivariate analysis was used to identify the independent predictors of plaque progression at the baseline MLA site from baseline to follow-up. All variables with a p value < 0.10 in the univariate analysis were tested. A p value < 0.05 was considered statistically significant.

RESULTS

The baseline characteristics of the patients and their coronary angiographic findings are summarized in Table 1. The prevalence of unstable angina (vs. stable angina), current smoking, and CKD was higher in progressors than in regressors. Prior percutaneous coronary intervention had been performed more frequently in progressors than in regressors. Baseline creatinine was significantly higher and CrCl was significantly lower in progressors than in regressors. Baseline apoB and apoB/A1 were significantly higher in progressors than in regressors. No significant difference was observed in the use of RAS blocker between the groups. The target lesion was located in the right coronary artery more frequently in progressors than in regressors.

Baseline gray-scale and VH-IVUS findings are summarized in Table 2. There were no significant differences in baseline gray-scale or VH-IVUS findings between progressors and regressors.

Follow-up clinical, laboratory, gray-scale, and VH-IVUS data are summarized in Table 3. The mean follow-up duration from baseline to follow-up IVUS examinations was 9.2 ± 2.5 months in progressors and 9.0 ± 1.8 months in regressors. No significant difference was observed in the use of RAS blocker between the groups. Follow-up plaque burden at the MLA site was significantly greater in progressors than in regressors. Absolute and relative FT areas at the MLA site were significantly greater in progressors than in regressors.

Data for changes in laboratory, gray-scale, and VH-IVUS findings from baseline to follow-up are summarized in Table 4. EEM CSA, P&M CSA, and plaque burden at the MLA site increased in progressors but decreased in regressors from baseline to follow-up. Absolute and relative FT areas at the MLA site increased in progressors but de-
TABLE 1. Baseline characteristics and coronary angiographic findings

|                      | Progressor (n=30) | Regressor (n=47) | p value |
|----------------------|-------------------|------------------|---------|
| Age (yrs)            | 67±8              | 65±7             | 0.274   |
| Male gender          | 21 (70.0%)        | 27 (56.3%)       | 0.225   |
| Clinical presentation|                   |                  |         |
| Stable angina pectoris| 6 (20.0%)        | 21 (43.8%)       | 0.032   |
| Unstable angina pectoris| 24 (80.0%)      | 27 (56.3%)       |         |
| Diabetes mellitus    | 6 (20.0%)         | 15 (31.3%)       | 0.276   |
| Smoker               | 12 (40.0%)        | 6 (12.5%)        | 0.005   |
| Chronic kidney disease| 27 (90.0%)       | 15 (31.3%)       | <0.001  |
| Prior PCI            | 6 (20.0%)         | 0 (0.0%)         | 0.001   |
| Systolic blood pressure (mmHg) | 154±34          | 148±32           | 0.078   |
| Diastolic blood pressure (mmHg) | 99±22           | 94±16            | 0.095   |
| Ejection fraction (%)| 65±6              | 68±7             | 0.109   |
| White blood cells (10³/mm³) | 6.9±1.9         | 6.7±1.8          | 0.821   |
| Hemoglobin (g/dL)    | 13.8±1.3          | 13.4±1.6         | 0.262   |
| Platelet count (10³/mm³) | 222±38          | 226±39           | 0.802   |
| Glucose (mg/dL)      | 130±32            | 133±50           | 0.586   |
| Creatinine (mg/dL)   | 4.6±1.8           | 4.0±0.4          | <0.001  |
| Creatinine clearance (mL/min) | 21±13           | 70±20            | <0.001  |
| Total cholesterol (mg/dL) | 177±30          | 169±34           | 0.288   |
| Triglyceride (mg/dL) | 126±43            | 114±45           | 0.236   |
| LDL cholesterol (mg/dL) | 113±29          | 110±27           | 0.713   |
| HDL cholesterol (mg/dL) | 44±9            | 47±11            | 0.273   |
| Apolipoprotein A1 (mg/dL) | 121±13          | 127±16           | 0.077   |
| Apolipoprotein B (mg/dL) | 93±22           | 83±19            | 0.041   |
| Apolipoprotein B/A1  | 0.77±0.23        | 0.65±0.16        | 0.011   |
| hs-CRP (mg/dL)       | 0.29±0.64        | 0.14±0.16        | 0.210   |
| NT-pro-BNP (pg/mL)   | 119±164          | 109±128          | 0.778   |
| Lipoprotein (a) (mg/dL) | 19±13           | 18±9             | 0.692   |
| Use of RAS blocker   | 18 (60.0%)       | 30 (62.5%)       | 0.854   |
| Target coronary artery|                  |                  | 0.008   |
| Left anterior descending | 12 (40.0%)     | 24 (50.0%)       |         |
| Left circumflex      | 0 (0.0%)         | 9 (18.8%)        |         |
| Right                | 18 (60.0%)       | 15 (31.3%)       |         |
| Lesion location      |                   |                  | 0.153   |
| Proximal             | 12 (40.0%)       | 30 (62.5%)       |         |
| Middle               | 15 (50.0%)       | 15 (31.3%)       |         |
| Distal               | 3 (10.0%)        | 3 (6.3%)         |         |
| Reference diameter (mm) | 3.32±0.33       | 3.38±0.40        | 0.510   |
| Pre-minimal luminal diameter (mm) | 1.78±0.48 | 1.76±0.44 | 0.882 |
| Percent diameter stenosis (%) | 47±11          | 48±9             | 0.586   |

PCI: percutaneous coronary intervention, LDL: low-density lipoprotein, HDL: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, NT-pro-BNP: N-terminal pro-B type natriuretic peptide, RAS: renin-angiotensin system.

Increased in regressors from baseline to follow-up. EEM volume and TAV increased in progressors; by contrast, EEM volume, TAV, and PAV decreased in regressors from baseline to follow-up. Absolute FT volume increased in progressors but decreased in regressors from baseline to follow-up.

Independent predictors of plaque progression at the MLA site are shown in Table 5. The following variables were tested to determine the independent predictors of plaque progression at the baseline MLA site (variables with p < 0.10 in the univariable analysis: CKD, baseline apoB/A1, smoking, right coronary artery lesion, systolic blood pressure, ∆EEM CSA at MLA site, and ∆relative FT area at MLA site). CKD [odds ratio (OR): 2.13, 95% confidence interval (CI): 1.77-2.53, p=0.013], apoB/A1 (OR: 1.25, 95% CI: 1.12-1.40, p=0.023), and smoking (OR: 1.76, 95% CI: 1.23-2.22, p=0.038) were independent predictors of plaque progression at follow-up.

DISCUSSION

The present study demonstrated that 1) there was a higher prevalence of current smoking and CKD and a higher baseline level of apoB/A1 in progressors than in re-
TABLE 2. Baseline gray-scale and virtual histology intravascular ultrasound findings

|                                | Progressor (n=30) | Regressor (n=47) | p value |
|--------------------------------|------------------|------------------|---------|
| **IVUS lesion length (mm)**    | 17±6             | 18±8             | 0.458   |
| **Plaque morphology at MLA site** |                  |                  |         |
| Soft                           | 15 (50.0%)       | 15 (31.3%)       | 0.134   |
| Fibrotic                       | 0 (0.0%)         | 3 (6.3%)         |         |
| Calcified                      | 0 (0.0%)         | 3 (6.3%)         |         |
| Mixed                          | 15 (50.0%)       | 27 (56.3%)       |         |
| **Minimum lumen area site**    |                  |                  |         |
| EEM CSA (mm³)                  | 14.6±4.8         | 15.2±3.2         | 0.533   |
| Lumen CSA (mm³)                | 6.1±2.9          | 6.2±1.6          | 0.857   |
| P&M CSA (mm³)                  | 8.4±2.5          | 9.0±2.2          | 0.349   |
| Plaque burden (%)              | 59±8             | 59±7             | 0.933   |
| **Absolute plaque area**       |                  |                  |         |
| Fibrotic area (mm³)            | 2.57±1.14        | 3.04±1.30        | 0.110   |
| Fibro-fatty area (mm³)         | 0.39±0.21        | 0.51±0.43        | 0.097   |
| Dense calcium area (mm³)       | 0.77±0.99        | 0.78±0.47        | 0.954   |
| Necrotic core area (mm³)       | 1.24±0.89        | 1.24±0.74        | 0.984   |
| **Relative plaque area**       |                  |                  |         |
| Fibrotic area (%)              | 52.3±15.4        | 54.1±12.2        | 0.576   |
| Fibro-fatty area (%)           | 9.2±6.3          | 8.5±5.6          | 0.612   |
| Dense calcium area (%)         | 14.9±11.3        | 15.4±10.8        | 0.853   |
| Necrotic core area (%)         | 23.5±9.8         | 22.0±7.1         | 0.471   |
| **Volumetric analysis**        |                  |                  |         |
| EEM volume (mm³)               | 263±144          | 284±150          | 0.534   |
| Lumen volume (mm³)             | 139±70           | 144±77           | 0.753   |
| Total atheroma volume (mm³)    | 124±76           | 140±76           | 0.375   |
| Percent atheroma volume (%)    | 47±6             | 48±4             | 0.361   |
| **Absolute plaque components** |                  |                  |         |
| Fibrotic volume (mm³)          | 35.9±26.8        | 43.8±28.0        | 0.223   |
| Fibro-fatty volume (mm³)       | 6.3±4.8          | 7.9±7.1          | 0.282   |
| Dense calcium volume (mm³)     | 10.2±13.9        | 9.7±7.1          | 0.835   |
| Necrotic core volume (mm³)     | 12.5±12.4        | 14.2±8.9         | 0.477   |
| **Relative plaque components** |                  |                  |         |
| Fibrotic volume (%)            | 57.9±11.9        | 57.1±9.1         | 0.744   |
| Fibro-fatty volume (%)         | 11.5±8.2         | 9.5±4.5          | 0.229   |
| Dense calcium volume (%)       | 12.7±9.6         | 13.6±7.3         | 0.676   |
| Necrotic core volume (%)       | 18.1±8.3         | 20.1±6.5         | 0.249   |
| **Thin-cap fibroatheroma**     | 6 (20.0%)        | 9 (18.8%)        | 0.892   |

IVUS: intravascular ultrasound, MLA: minimum lumen area, EEM: external elastic membrane, CSA: cross-sectional area, P&M: plaque plus media.

Hypertension is associated with progression of atherosclerosis by the action of angiotensin II, vascular smooth muscle cells, and oxidative stress and endothelial dysfunction. Reductions in LDL-C levels produced by statins are associated with coronary plaque regression. Lee et al. reported that statin therapy significantly reduces the risk of the composite of 1-year major adverse cardiac events including death, recurrent myocardial infarction, target vessel revascularization, and coronary artery bypass grafting in patients with acute myocardial infarction who have baseline LDL-C levels < 70 mg/dL. Bayturan et al. reported that an increase in systolic blood pressure at follow-up is one of the risk factors for plaque progression despite the achievement of very low levels of LDL-C. However, the predictors of plaque progression in statin-treated hypertensive angina patients who achieve LDL-C levels < 70 mg/dL are not well known.

In the present study, CKD was shown to be an independent predictor of plaque progression in patients with angina pectoris and hypertension who achieved very low LDL-C levels after moderate-intensity rosuvastatin treatment.
|                          | Progressor (n=30) | Regressor (n=47) | p value |
|--------------------------|-------------------|------------------|---------|
| Follow-up durations (months) | 9.2±2.5           | 9.0±1.8          | 0.785   |
| Systolic blood pressure (mmHg)    | 146±32           | 141±26           | 0.176   |
| Diastolic blood pressure (mmHg)    | 96±21            | 92±16            | 0.368   |
| Rosuvastatin 10 mg use | 30 (100%)         | 47 (100%)        | 1.000   |
| Use of RAS blocker         | 21 (70.0%)        | 35 (74.5%)       | 0.554   |
| Total cholesterol (mg/dL)  | 120±14           | 121±18           | 0.773   |
| Triglyceride (mg/dL)       | 86±38            | 78±31            | 0.319   |
| LDL cholesterol (mg/dL)    | 58±9             | 58±13            | 0.610   |
| HDL cholesterol (mg/dL)    | 50±11            | 50±10            | 0.733   |
| Apolipoprotein A1 (mg/dL)  | 124±39           | 132±33           | 0.347   |
| Apolipoprotein B (mg/dL)   | 58±12            | 54±10            | 0.456   |
| hs-CRP (mg/dL)             | 0.47±0.08        | 0.41±0.06        | 0.118   |
| MLA site                   |                  |                  |         |
| EEM CSA (mm²)              | 15.1±5.4         | 14.6±3.0         | 0.655   |
| Lumen CSA (mm²)            | 6.1±3.1          | 6.3±1.5          | 0.739   |
| P&M CSA (mm²)              | 8.9±2.8          | 8.2±2.0          | 0.203   |
| Plaque burden (%)          | 61±8             | 57±6             | 0.010   |
| Absolute plaque area       |                  |                  |         |
| Fibrotic area (mm²)        | 3.4±1.44         | 2.5±1.47         | 0.019   |
| Fibro-fatty area (mm²)     | 0.46±0.37        | 0.46±0.50        | 0.981   |
| Dense calcium area (mm²)   | 0.72±0.41        | 0.79±0.46        | 0.510   |
| Necrotic core area (mm²)   | 1.13±0.68        | 1.05±0.46        | 0.571   |
| Relative plaque area       |                  |                  |         |
| Fibrotic area (%)          | 59.5±11.0        | 50.7±15.4        | 0.004   |
| Fibro-fatty area (%)       | 7.5±4.2          | 8.7±7.8          | 0.386   |
| Dense calcium area (%)     | 13.8±8.0         | 17.8±12.0        | 0.110   |
| Necrotic core area (%)     | 19.1±7.2         | 22.7±10.2        | 0.073   |
| Volumetric analysis        |                  |                  |         |
| EEM volume (mm³)           | 265±153          | 274±147          | 0.783   |
| Lumen volume (mm³)         | 140±75           | 145±77           | 0.774   |
| Total atheroma volume (mm³)| 125±80           | 130±71           | 0.796   |
| Percent atheroma volume (%)| 47±5             | 46±4             | 0.431   |
| Absolute plaque components |                  |                  |         |
| Fibrotic volume (mm³)      | 38.0±31.9        | 37.7±30.0        | 0.957   |
| Fibro-fatty volume (mm³)   | 6.7±10.1         | 6.6±7.0          | 0.939   |
| Dense calcium volume (mm³) | 8.5±8.3          | 10.0±6.9         | 0.413   |
| Necrotic core volume (mm³) | 13.1±10.2        | 12.3±7.4         | 0.686   |
| Relative plaque components |                  |                  |         |
| Fibrotic volume (%)        | 57.9±12.4        | 54.8±11.3        | 0.260   |
| Fibro-fatty volume (%)     | 8.1±3.2          | 8.9±6.1          | 0.469   |
| Dense calcium volume (%)   | 13.2±7.7         | 16.1±8.2         | 0.122   |
| Necrotic core volume (%)   | 20.8±7.7         | 20.1±8.1         | 0.692   |

CKD is associated with poor clinical outcomes, increased prevalence of coronary artery disease, and accelerated atherosclerosis. Renal dysfunction is associated with atheroma progression and an unstable plaque phenotype, which provides novel insight into the mechanisms of poor clinical outcome in CKD patients. The exact mechanisms of plaque progression and formation of vulnerable plaque in CKD patients are not well known, but several mechanisms have been postulated. CKD patients have elevated serum matrix metalloproteinases that are associated with plaque growth and fibrous cap disruption. Matrix metalloproteinases are related to endothelial dysfunction, vascular remodeling, and arterial stiffening in CKD patients. CKD potentiates foam cell formation, which enhances macrophage infiltration into the vascular wall and inhibits cholesterol efflux. Therefore, aggressive statin therapy is...
TABLE 4. Changes of laboratory, gray-scale and virtual histology intravascular ultrasound findings from baseline to follow-up

|                         | Progressor (n=30) | Regressor (n=47) | p value |
|-------------------------|-------------------|------------------|---------|
| Total cholesterol (mg/dL)| −58±31            | −49±30           | 0.203   |
| Triglyceride (mg/dL)     | −40±35            | −36±30           | 0.586   |
| LDL cholesterol (mg/dL)  | −53±26            | −52±26           | 0.872   |
| HDL cholesterol (mg/dL)  | +6±13             | +3±10            | 0.179   |
| Apolipoprotein A1 (mg/dL)|  3±47             |  5±37            | 0.870   |
| Apolipoprotein B (mg/dL) | −35±21            | −29±16           | 0.105   |
| Apolipoprotein B/A1      | −0.30±0.18        | −0.24±0.15       | 0.112   |
| Lipoprotein (a) (mg/dL)  | +2±11             | +5±10            | 0.199   |
| hs-CRP (mg/dL)           | +0.02±0.91        | +0.12±0.48       | 0.536   |

**MLA site**

|                          | Progressor (%) | Regressor (%) | p value |
|--------------------------|----------------|---------------|---------|
| ∆EEM CSA (mm²)           | +0.48±0.73     | −0.63±0.67    | <0.001  |
| ∆Lumen CSA (mm²)         |  0.00±0.39     | +0.10±0.35    | 0.239   |
| ∆P&M CSA (mm²)           | +0.49±0.40     | −0.71±0.63    | <0.001  |
| ∆Plaque burden (%)       | +1.8±1.8       | −2.4±2.7      | <0.001  |
| ∆Fibrotic area (mm²)     | +0.84±0.77     | −0.44±0.75    | <0.001  |
| ∆Fibro-fatty area (mm²)  | +0.07±0.37     | −0.05±0.37    | 0.165   |
| ∆Dense calcium area (mm²)| −0.05±0.74     | +0.01±0.35    | 0.699   |
| ∆Necrotic core area (mm²)| −0.11±0.71     | −0.19±0.66    | 0.599   |
| ∆Fibrotic area (%)       | +7.2±10.5      | −3.4±15.3     | 0.001   |
| ∆Fibro-fatty area (%)    | −1.7±5.5       | +0.2±7.2      | 0.223   |
| ∆Dense calcium area (%)  | −1.1±8.9       | +2.4±9.3      | 0.101   |
| ∆Necrotic core area (%)  | −4.4±10.0      | +0.7±12.7     | 0.053   |

**Volumetric analysis**

|                          | Progressor (%) | Regressor (%) | p value |
|--------------------------|----------------|---------------|---------|
| ∆EEM volume (mm³)        | +2.1±21.8      | −9.0±11.1     | 0.010   |
| ∆Lumen volume (mm³)      | +1.2±11.7      | +0.8±6.6      | 0.879   |
| ∆Total atheroma volume (mm³)| +0.9±11.1   | −10.4±9.9    | <0.001  |
| ∆Percent atheroma volume (%)| 0.0±2.2      | −2.1±2.2      | <0.001  |

**Absolute plaque components**

|                          | Progressor (%) | Regressor (%) | p value |
|--------------------------|----------------|---------------|---------|
| ∆Fibrotic volume (mm³)   | +2.1±10.2      | −6.1±8.1      | <0.001  |
| ∆Fibro-fatty volume (mm³)| +0.4±7.8       | −1.4±4.3      | 0.209   |
| ∆Dense calcium volume (mm³)| −1.6±5.8    | +0.3±3.4      | 0.068   |
| ∆Necrotic core volume (mm³)| +0.6±4.8     | −2.1±6.4      | 0.066   |

**Relative plaque components**

|                          | Progressor (%) | Regressor (%) | p value |
|--------------------------|----------------|---------------|---------|
| ∆Fibrotic volume (%)     |  0.0±9.7       | −2.3±12.0     | 0.391   |
| ∆Fibro-fatty volume (%)  | −3.4±7.8       | −0.6±7.2      | 0.112   |
| ∆Dense calcium volume (%)| +0.5±4.8       | +2.6±7.9      | 0.153   |
| ∆Necrotic core volume (%)| +2.7±7.8       |  0.0±10.8     | 0.240   |

LDL: low-density lipoprotein, HDL: high-density lipoprotein, hs-CRP: high-sensitivity C-reactive protein, MLA: minimum lumen area, EEM: external elastic membrane, CSA: cross-sectional area, P&M: plaque plus media.

TABLE 5. Independent predictors of plaque progression at minimum lumen area site

|                                | Odds ratio | 95% confidence interval | p value |
|--------------------------------|------------|--------------------------|---------|
| Chronic kidney disease (creatinine clearance < 60 mL/min) |  2.13      |  1.77-2.53               | 0.013   |
| Apolipoprotein B/A1            |  1.25      |  1.12-1.40               | 0.023   |
| Smoking                        |  1.76      |  1.23-2.22               | 0.038   |
| Right coronary artery lesion   |  2.01      |  0.98-3.13               | 0.213   |
| Systolic blood pressure (mmHg) |  1.12      |  0.37-2.12               | 0.624   |
| ∆EEM CSA at MLA site (mm²)     |  1.05      |  0.84-1.32               | 0.648   |
| ∆Relative fibrotic area at MLA site (%) |  1.42  |  0.87-2.31               | 0.188   |

EEM: external elastic membrane, CSA: cross-sectional area, MLA: minimum lumen area.
needed to regress and stabilize coronary plaque in CKD patients.

In the present study, smoking was also shown to be independently associated with plaque progression in patients with angina pectoris and hypertension who achieved very low LDL-C levels after statin treatment. Lehman et al.22 reported that smoking was associated with plaque progression in patients who presented to the emergency department with acute chest pain but who initially showed no evidence of acute coronary syndromes by contrast-enhanced 64-slice computed tomography. Epidemiological studies of diverse populations have shown that smoking is a risk factor for the development of coronary and peripheral vascular disease.23 Therefore, smoking cessation is needed to improve the lipid profile and reverse the atherogenic effects of smoking.

Last, the baseline apoB/A1 concentration was an independent predictor of plaque progression at follow-up in statin-treated patients with angina pectoris and hypertension in the present study. Juonala et al.24 reported that apoB and apoA1 are directly related to adulthood carotid artery intima-media thickness and that apoB/A1 is superior to the ratio of LDL-C to high-density lipoprotein-cholesterol (HDL-C) in predicting increased carotid artery intima-media thickness in adulthood. ApoB-containing lipoproteins carry lipids from the liver to intestine to the sites of use, whereas apoA1-containing particles mediate the reverse cholesterol transport and bring excess cholesterol from peripheral tissues to the liver.25 Concentrations of apoB and apoA1 reflect the particle numbers of their respective lipoprotein classes and thus the opposite aspects of the risk. A high apoB/A1 indicates the number of atherogenic lipoprotein particles that are likely to be deposited in the arterial wall.26 ApoB/A1 is associated with plaque progression even if very low levels of LDL-C are achieved after statin treatment.

There are several limitations to mention. First, the analyses were retrospective and are subject to the limitations inherent in this type of clinical investigation. Second, the results of this study are only applicable to selected hypertensive angina patients. So, the results in the present study might not be generalizable in all patients with coronary artery disease such as acute myocardial infarction. Third, the prevalence of unstable angina (vs. stable angina) was significantly higher in progressors than in regressors. However, the plaque characteristics were not significantly different between progressors and regressors and unstable angina itself was not an independent predictor of plaque progression at follow-up. Fourth, the prevalence of CKD was significantly higher in progressors than in regressors. Because it is possible for CKD patients to have a large amount of calcium compared with non-CKD patients, they might be resistant to regression by statin therapy. Fifth, we defined decreased renal function on the basis of estimated creatinine clearance rather than direct measurements of the glomerular filtration rate. Sixth, we did not have information about the duration of exposure and the amount of smoking. Seventh, there is a possibility of overestimation of the NC component in lesions with heavily calcified plaques by VH-IVUS.

Clinical factors including CKD, smoking, and apoB/A1 rather than plaque components detected by VH-IVUS are associated with plaque progression in hypertensive angina patients who achieve very low LDL-C after statin treatment.

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CONFLICT OF INTEREST STATEMENT

None declared.

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