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Atherosclerosis 191 (2007) 107–114

ATHEROSCLEROSIS

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Serial intravascular ultrasound evidence of both plaque stabilization and lesion progression in patients with ruptured coronary plaques: Effects of statin therapy on ruptured coronary plaque

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Received 10 October 2005; received in revised form 13 December 2005; accepted 18 February 2006
Available online 3 April 2006

Abstract

Using serial intravascular ultrasound (IVUS), we evaluated the natural evolution of non-culprit/non-target lesion ruptured coronary plaques and assessed the impact of statin therapy. Twenty-eight patients with non-stenotic ruptured plaques underwent baseline and 12-month follow-up IVUS studies; half were treated with statins. Standard IVUS analyses were performed. Complete healing of ruptured plaques was observed in four (29%) statin-treated patients and no non-statin-treated patients ($p = 0.049$). Statin-treated patients had an increase in lumen area of $0.4 \pm 0.8\,mm^2$ (versus a decrease in lumen area of $-0.6 \pm 1.0\,mm^2$ in non-statin-treated patients, $p = 0.007$) and no change in plaque area (versus an increase in plaque area of $0.6 \pm 0.9\,mm^2$, $p = 0.051$). During 1-year follow-up, target lesion revascularization was performed in three non-statin-treated patients (21%) and no statin-treated patient ($p = 0.11$). Compared to lesions that did not require revascularization, lesions requiring revascularization had a decrease in lumen area ($-1.7 \pm 1.4\,mm^2$ versus $0.1 \pm 0.8\,mm^2$, $p = 0.001$) as well as an increase in plaque area ($1.6 \pm 1.0\,mm^2$ versus $0.1 \pm 0.7\,mm^2$, $p = 0.002$). In conclusion, the current observational follow-up IVUS study showed beneficial effects of statin treatment on reduction of revascularization rates and stabilization of non-culprit/non-target lesion plaque ruptures without significant stenosis. Conversely, healing of non-statin-treated non-culprit/non-target lesion plaque ruptures can be responsible for lesion progression requiring revascularization.

Keywords: Ultrasonics; Plaque; Coronary artery disease

1. Introduction

Plaque rupture and subsequent thrombus formation is the most important mechanism leading to an acute coronary syndrome (ACS) [1,2]. Recent intravascular ultrasound (IVUS) studies have reported multiple plaque ruptures in ACS as well as in stable angina patients [3–5] indicating that plaque ruptures occurred in non-culprit/non-target lesions as well as in culprit/target lesions. Because culprit/target lesions with ruptured plaque morphologies typically have significant lumen compromise, there is little hesitation to treat with percutaneous revascularization. However, secondary, *non-culprit/non-target lesions* with plaque ruptures are usually not stenotic; and the best treatment (i.e. revascularization versus medical therapy) is controversial, in part because of a lack of natural history data. Several studies in ACS patients have demonstrated clinical benefits of statin therapy in reduc-

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doi:10.1016/j.atherosclerosis.2006.02.040

ing major adverse cardiac events [6,7]. The beneficial effects of statin therapy on the long-term clinical outcome in ACS patients may be related to stabilization of vulnerable plaque [8]. However, there is little in vivo follow-up data concerning the natural evolution of ruptured coronary plaques. One recent IVUS study in 14 ACS patients with 28 non-culprit, non-stenotic plaque ruptures reported that plaque ruptures healed in 50% of cases with medical therapy (statin and antiplatelet agents in all patients) [9]. We previously reported the frequency of primary (target/culprit lesion) and secondary (non-target/non-culprit lesion) ruptured plaques in ACS and stable angina patients [3,10]. In this current observational report we used serial IVUS to evaluate the natural evolution of these secondary ruptured plaques and assessed the impact of statin therapy on the morphologic changes.

2. Methods

2.1. Study population

From the Asan Medical Center clinical and core IVUS laboratory database, we identified 28 patients with non-culprit/non-target plaque ruptures and without significant stenosis in de novo lesions which underwent baseline and 12-month follow-up IVUS studies. The IVUS inclusion criteria for this study was a minimal lumen cross-sectional area (CSA) > 4.0 mm^2 [4,11] and/or a plaque burden < 0.75. Because in Korea, statins were not reimbursed for patients with a total cholesterol <220 mg/dL before this year, statins were only prescribed in 14 of 28 patients (20 mg of atorvastatin in 7 patients and 40 mg of simvastatin in 7 patients). Therefore, we were able to divide the study population into two groups according to statin therapy: statin-treated ($n = 14$) versus non-statin-treated group ($n = 14$). Fibrates (Gemfibrozil 300 mg bid) were given in 7 of 14 non-statin-treated patients and to none of the statin-treated group. Aspirin (indefinitely) and clopidogrel (for 1 month in 17 patients after bare-metal stent implantation and for 6 months in 2 patients after drug-eluting stent implantation) or ticlopidine (for 1 month in 9 patients) were also prescribed.

Definitions of myocardial infarction and stable angina, and identification of culprit/target lesions have been described previously [3]. During the 1-year follow-up, we tabulated the occurrence of major adverse cardiac events including death of any causes, myocardial infarction (elevation of the CK-MB fraction to a value three times the upper limit of normal), and target lesion revascularization (TLR = percutaneous or surgical intervention of the non-culprit/non-target plaque rupture). All patients provided written informed consent, and approval of the Ethics Committee was obtained.

2.2. IVUS imaging and analysis

Baseline and 12-month follow-up IVUS examinations of non-culprit/non-target lesion plaque ruptures were performed in the same rigorous manner, before any intervention, and after intracoronary administration of 0.2 mg nitroglycerin

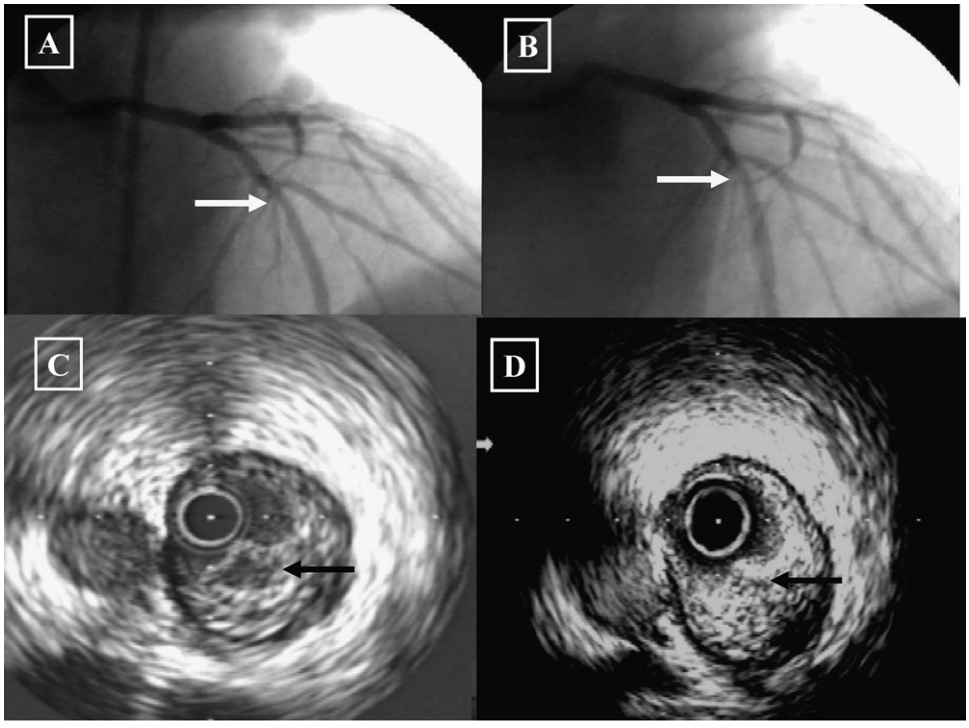

Fig. 1. Typical example of healing of a ruptured plaque is shown. Panels A and B are the baseline and 12-month follow-up angiograms, respectively. (The white arrows show the lesion.) Panels C and D are the corresponding IVUS images. (The black arrows show the rupture cavity at baseline that is almost entirely gone at follow-up.).

using motorized transducer pullback system (0.5 mm/s) and a commercial scanner (Boston Scientific Corp./SCIMED) consisting of a rotating 30 MHz transducer within a 3.2 Fr imaging sheath. Qualitative and quantitative analyses were performed according to criteria of the clinical expert consensus document on IVUS [12].

The IVUS diagnosis of plaque rupture required a plaque containing a cavity that communicated with the lumen with an overlying residual fibrous cap fragment [13]. The diagnosis of plaque rupture required independent review and agreement by two authors (M-KH and Y-HK). IVUS evidence of complete plaque rupture healing was the disappearance of the intraplaque cavity, complete continuation of the intimal layer [9], and no reduction of lumen CSA (Fig. 1). Incomplete healing of plaque rupture was defined as >50% decrease in plaque cavity CSA without a reduction of lumen CSA.

Quantitative IVUS analysis was performed using computerized planimetry at the maximum plaque rupture site and the proximal and distal reference segments. The reference segments were the most normal looking cross-sections within 5 mm proximal and distal to the lesion, but before any side branch. Quantitative measurements included external elastic membrane (EEM), lumen, and plaque and media (P&M = EEM minus lumen minus ruptured cavity) CSA, and plaque burden (P&M & ruptured cavity CSA divided by EEM CSA). A significant stenosis was defined as minimal lumen CSA $\leq 4.0\,mm^2$ [9]. A remodeling index was calculated as the lesion divided by the mean reference EEM CSA. The intraplaque cavity was measured and extrapolated to the ruptured capsular area [3,4]. Changes in IVUS measurements between baseline and 12-month follow-up studies were determined and compared between the statin-treated versus non-statin-treated groups.

2.3. Angiographic analysis

Using the guiding catheter for magnification-calibration and an on-line system (ANCOR V2.0, Siemens, Germany), quantitative measurements of minimal luminal diameter of the ruptured plaque segment and of the reference vessel were performed at baseline and 12-month follow-up. Qualitative angiographic lesion appearance was assessed as normal, lumen irregularity, intimal flap, thrombus, aneurysm, and/or ulceration [5]

2.4. Statistical analysis

Statistical analysis was performed with SPSS. Data are presented as frequencies or mean ± 1S.D. Comparison was performed with Fisher's exact test and unpaired or paired Student's *t*-test. Linear and logistic regression analysis was performed to determine the predictor of changes of ruptured cavity CSA (a continuous measure of healing) and complete healing of plaque rupture, respectively. A *p*-value <0.05 was considered statistically significant.

3. Results

Clinical characteristics of the 28 patients are shown in Table 1, and baseline and follow-up angiography are shown in Table 2. The interval between baseline and follow-up studies was 11.9 ± 1.3 months. Overall, 4 lesions healed completely without stenosis progression, 1 lesion healed incompletely without stenosis progression, 20 lesions did not heal and did not result in stenosis, and 3 lesions progressed to a focal stenosis requiring intervention. Overall, there was essentially no change in IVUS plaque dimensions: lesion site EEM CSA ($20.0 \pm 6.8\,mm^2$ at baseline and $19.7 \pm 6.8\,mm^2$ at follow-up, $p = 0.16$), P&M CSA ($10.5 \pm 4.3\,mm^2$ at base-

Table 1
Baseline clinical characteristics of patients with ruptured plaques between statin-treated vs. no-statin group (%)

	Overall	Statin treatment	No-statin	*P*
Number of patients	28	14	14	
Age (years)	56 ± 9	56 ± 10	55 ± 8	0.3
Male gender	25 (89)	12 (86)	13 (93)	0.5
Hypertension	12 (43)	5 (36)	7 (50)	0.4
Diabetes mellitus	7 (25)	3 (21)	4 (29)	0.5
Cigarette smoking	16 (57)	9 (64)	7 (50)	0.4
Hypercholesterolemia (total cholesterol ≥ 220 mg/dL)	7 (25)	5 (36)	2 (14)	0.19
Lipid profiles at baseline				
Total cholesterol (mg/dL)	188 ± 32	198 ± 27	177 ± 35	0.077
LDL cholesterol (mg/dL)	112 ± 32	121 ± 29	103 ± 34	0.15
HDL cholesterol (mg/dL)	40 ± 8	38 ± 9	42 ± 7	0.2
Triglycerides (mg/dL)	182 ± 80	197 ± 78	166 ± 82	0.3
Lipid profiles at 12-month follow-up				
Total cholesterol (mg/dL)	153 ± 36	149 ± 32	158 ± 41	0.5
LDL cholesterol (mg/dL)	84 ± 33	75 ± 30	94 ± 34	0.14
HDL cholesterol (mg/dL)	42 ± 10	42 ± 10	42 ± 9	0.8
Triglycerides (mg/dL)	138 ± 67	158 ± 71	116 ± 57	0.11
Number of diseased vessels				0.9
1	15 (54)	8 (57)	7 (50)	
2	7 (25)	3 (21)	4 (29)	
3	6 (21)	3 (21)	3 (21)	
Clinical diagnosis				0.6
Stable angina	6 (21)	2 (14)	4 (29)	
Unstable angina, class IIIB	8 (29)	4 (29)	4 (29)	
Acute myocardial infarction	14 (50)	8 (57)	6 (43)	
Ruptured plaque location				0.9
Left anterior descending artery	10 (36)	5 (36)	5 (36)	
Left circumflex artery	5 (18)	2 (14)	3 (21)	
Right coronary artery	13 (46)	7 (50)	6 (43)	
Medications				
Nitrates	25 (89)	12 (86)	13 (93)	0.5
Calcium channel blocker	20 (71)	10 (71)	10 (71)	0.7
Beta-blocker	18 (64)	10 (71)	8 (57)	0.4
Angiotensin II receptor antagonist	7 (25)	3 (21)	4 (29)	0.5
Angiotensin-converting enzyme inhibitor	8 (29)	4 (29)	4 (29)	0.7

Table 2
Angiographic analysis of ruptured plaques at baseline and 1-year follow-up

	Baseline	1-Year follow-up	P
Overall ($n=28$)			
Proximal reference vessel size	3.7 ± 0.7	3.6 ± 0.7	0.2
Minimal lumen diameter	2.3 ± 0.7	2.2 ± 0.7	0.5
Distal reference vessel size	3.4 ± 0.7	3.4 ± 0.6	0.8
Angiographic appearance (%)			0.7
Normal	15 (54)	18 (64)	
Lumen irregularity	7 (25)	6 (21)	
Ulceration	6 (21)	4 (14)	
No-statin group ($n=14$)			
Proximal reference vessel size	3.7 ± 0.7	3.6 ± 0.7	0.3
Minimal lumen diameter	2.2 ± 0.8	2.1 ± 0.8	0.4
Distal reference vessel size	3.3 ± 0.8	3.3 ± 0.7	0.5
Angiographic appearance (%)			0.7
Normal	7 (50)	6 (43)	
Lumen irregularity	4 (29)	6 (43)	
Ulceration	3 (21)	2 (14)	
Statin treatment ($n=14$)			
Proximal reference vessel size	3.7 ± 0.6	3.6 ± 0.5	0.4
Minimal lumen diameter	2.4 ± 0.6	2.4 ± 0.7	1.0
Distal reference vessel size	3.4 ± 0.6	3.4 ± 0.6	0.5
Angiographic appearance (%)			0.14
Normal	8 (57)	12 (86)	
Lumen irregularity	3 (21)		
Ulceration	3 (21)	2 (14)	

line and 10.7 ± 4.2 mm^2 at follow-up, $p=0.18$), and lumen CSA (6.8 ± 3.4 mm^2 at baseline and 6.8 ± 3.9 mm^2 at follow-up, $p=0.7$).

The statin-treated group had a tendency for an increased frequency of hypercholesterolemia (Table 1). However, there were no differences in baseline angiography (Table 2), baseline IVUS (Table 3), or interval between studies (11.9 ± 1.3 months in the statin-treated group versus 11.9 ± 1.4 months in the no-statin group, $p=1.0$).

3.1. No-statin group

The 14 no-statin treated patients had no overall serial change in qualitative or quantitative *angiographic* variables (Table 2). However, there was an increase in P&M CSA and a tendency toward a decrease in lumen CSA and ruptured cavity CSA (Table 3). None of the lesions in these patients healed completely; however, 1 lesion in fibrate-treated patient healed partially, 10 lesions showed no change, and three lesions in 1 fibrate-treated patient and 2 no-fibrate treated patients progressed to a significant stenosis requiring revascularization.

3.2. Statin-treated group

No patient had a prior history of statin treatment; statins were started after the baseline IVUS study and were continued for at least 1 year in 14 patients. The 14 statin-treated patients had no overall serial changes in quantitative angiographic variables although there was a tendency for improvement in qualitative morphologies (Table 2). In 4 patients with complete healing of plaque ruptures, the angiographic appearance at 1-year follow-up had normalized, and IVUS appearance showed the replacement of the ruptured cavity with fibrotic plaque. In the other 10 patients there were no definite changes in plaque echogenicity. In overall 14 statin-treated patients, IVUS showed a decrease in ruptured cavity CSA and a tendency for an increase in lumen CSA, but no changes in EEM and P&M CSA (Table 3).

Table 3
IVUS analysis of ruptured plaques at baseline and 1-year follow-up

	Baseline	1-Year follow-up	P
No-statin group			
Proximal reference segment			
External elastic membrane CSA (mm^2)	20.7 ± 7.6	20.6 ± 7.7	0.6
Lumen CSA (mm^2)	11.6 ± 5.6	11.7 ± 5.6	0.5
Ruptured plaque segment			
External elastic membrane CSA (mm^2)	19.9 ± 7.0	19.6 ± 7.0	0.13
Lumen CSA (mm^2)	6.5 ± 2.9	5.9 ± 3.2	0.060
Plaque and media and ruptured cavity CSA (mm^2)	13.5 ± 5.5	13.7 ± 5.4	0.16
Plaque and media CSA (mm^2)	10.5 ± 4.7	11.0 ± 4.7	0.026
Ruptured cavity CSA (mm^2)	3.0 ± 1.6	2.7 ± 1.9	0.073
Remodeling index	1.0 ± 0.0	1.0 ± 0.1	0.3
Calcium arc (°)	23 ± 46	23 ± 45	0.3
Distal reference segment			
External elastic membrane CSA (mm^2)	18.6 ± 6.7	18.6 ± 6.6	0.4
Lumen CSA (mm^2)	10.6 ± 5.4	10.5 ± 5.5	0.5
Statin treatment			
Proximal reference segment			
External elastic membrane CSA (mm^2)	21.1 ± 6.6	21.1 ± 6.6	0.7
Lumen CSA (mm^2)	12.0 ± 4.1	12.0 ± 4.1	0.2
Ruptured plaque segment			
External elastic membrane CSA (mm^2)	20.0 ± 6.8	19.8 ± 6.8	0.2
Lumen CSA (mm^2)	7.2 ± 3.9	7.6 ± 4.3	0.057
Plaque and media and ruptured cavity CSA (mm^2)	12.8 ± 4.3	12.2 ± 4.3	0.015
Plaque and media CSA (mm^2)	10.5 ± 4.1	10.4 ± 3.8	0.9
Ruptured cavity CSA (mm^2)	2.3 ± 0.8	1.8 ± 1.4	0.011
Remodeling index	1.0 ± 0.1	1.0 ± 0.1	0.4
Calcium arc (°)	33 ± 55	32 ± 54	0.3
Distal reference segment			
External elastic membrane CSA (mm^2)	19.1 ± 7.0	19.1 ± 7.0	0.2
Lumen CSA (mm^2)	10.5 ± 4.5	10.6 ± 4.5	0.3

3.3. Comparison of statin-treated versus no-statin patients

Complete healing of ruptured plaques was observed in 4 statin-treated patients (29%, simvastatin in two patients

Table 4
Changes in IVUS ruptured plaque segment analysis between statin-treated and non-statin-treated lesions

	Statin treatment	No-statin	*P*
Number of lesions	14	14	
ΔExternal elastic membrane CSA (mm^2)	-0.1 ± 0.1	-0.3 ± 0.7	0.4
ΔLumen CSA (mm^2)	0.4 ± 0.8	-0.6 ± 1.0	0.007
ΔPlaque and media and ruptured cavity CSA (mm^2)	-0.6 ± 0.8	0.3 ± 0.7	0.005
ΔPlaque and media CSA (mm^2)	0.0 ± 0.7	0.6 ± 0.9	0.051
ΔRuptured cavity CSA (mm^2)	-0.5 ± 0.7	-0.3 ± 0.6	0.4

Table 5
Changes in IVUS ruptured plaque segment analysis between statin-treated and no-statin, no-fibrate treated lesions

	Statin treatment	No-statin, No-fibrate	*P*
Number of lesions	14	7	
ΔExternal elastic membrane CSA (mm^2)	-0.1 ± 0.1	-0.4 ± 0.8	0.4
ΔLumen CSA (mm^2)	0.4 ± 0.8	-0.5 ± 1.1	0.037
ΔPlaque and media and ruptured cavity CSA (mm^2)	-0.6 ± 0.8	0.1 ± 0.2	0.038
ΔPlaque and media CSA (mm^2)	0.0 ± 0.7	0.7 ± 0.9	0.046
ΔRuptured cavity CSA (mm^2)	-0.5 ± 0.7	-0.6 ± 0.7	0.8

and atorvastatin in two patients) and none of no-statin group ($p = 0.049$). There were no significant changes in remodeling index between baseline and 1-year follow-up in either group (Table 3). Table 4 compares the changes in cross-sectional measurements between the two groups. There was an increase in lumen CSA in statin-treated patients (compared to a decrease in lumen CSA in no-statin patients); and there was no change in P&M CSA in statin-treated patients (compared to an increase in no-statin patients). Changes in EEM CSA and ruptured cavity CSA were similar. During the follow-up period, revascularization was performed in three non-statin-treated patients (21%) and no statin-treated patient ($p = 0.11$). Comparisons of the changes in cross-sectional measurements between statin-treated ($n = 14$) versus no-statin, no-fibrate patients ($n = 7$) are shown in Table 5.

3.4. Lesions that progressed to require revascularization (Fig. 2)

Serial changes comparing IVUS findings of lesions requiring revascularization within 1 year ($n = 3$) versus non-revascularization lesions ($n = 25$) are shown in Table 6. Although the numbers are small, lesions requiring revascularization all had a larger decrease in lumen CSA as well as a larger increase in P&M CSA compared to lesions that did not require revascularization. In these three lesions lumen CSA

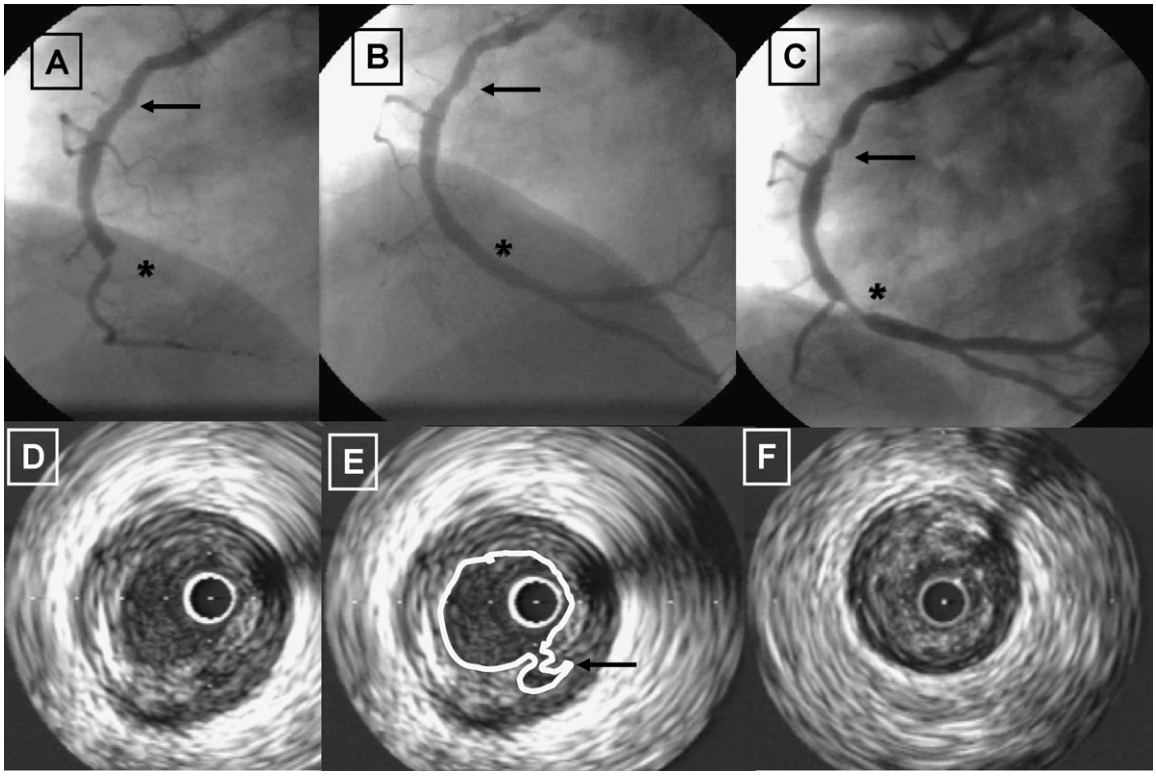

Fig. 2. Panels A–C are pre-intervention, post-stenting of the distal culprit lesion (black asterisks), and 12-month follow-up angiograms with in-stent restenosis, respectively. Panels D and E are identical IVUS images of a secondary proximal plaque rupture with the exception of the labels in Panel E. Panel F is the corresponding IVUS image at 12-month follow-up showing progressive decrease in lumen cross-sectional area. Arrows indicate the ruptured plaque segment.

Table 6
Serial IVUS changes in lesion that progressed to require revascularization compared to lesions that did not progress

	TLR ($n=3$)	Non-TLR ($n=25$)	P
ΔExternal elastic membrane CSA (mm^2)	−0.6 ± 1.4	−0.2 ± 0.3	0.6
ΔLumen CSA (mm^2)	−1.7 ± 1.4	0.1 ± 0.8	0.001
ΔPlaque and media and ruptured cavity CSA (mm^2)	1.1 ± 1.0	−0.3 ± 0.7	0.04
ΔPlaque and media CSA (mm^2)	1.6 ± 1.0	0.1 ± 0.7	0.002
ΔRuptured cavity CSA (mm^2)	−0.5 ± 0.7	−0.4 ± 0.7	0.8

TLR: target lesion revascularization.

decreased from 5.0 ± 0.9 to 3.3 ± 1.2 mm^2 and P&M CSA increased from 10.5 ± 0.9 to 12.1 ± 1.0 mm^2.

3.5. Predictors of healing

Fig. 3 shows the serial changes in ruptured cavity CSA between baseline and 12-month follow-up in the two groups. The Δruptured cavity CSA was correlated with ΔP&M CSA: overall ($r=0.412$, $p=0.029$, 95% CI = −0.614 to −0.035); in statin-treated patients ($r=0.387$, $p=0.172$, 95% CI = −0.973 to 0.194); and in no-statin patients ($r=0.646$, $p=0.017$, 95% CI = −0.821 to −0.100). This relationship is shown in Fig. 4. Univariate predictors of changes in ruptured cavity CSA were entered into the multivariate model: initial ruptured cavity CSA ($r=0.346$, $p=0.077$, 95% CI = −0.020 to 0.371), baseline total cholesterol level ($r=0.356$, $p=0.048$, 95% CI = −0.006 to 0.000), and baseline LDL cholesterol level ($r=0.219$, $p=0.272$, 95% CI = −0.013 to 0.004). Follow-up total cholesterol and LDL levels and their changes and statin versus non-statin treatment were forced into the model. In multivariate linear regression analysis of the entire cohort of 28 patients, the only independent predictor of Δruptured cavity CSA was the baseline total cholesterol level ($r=0.411$, $p=0.033$, 95% CI = −0.016 to −0.001). In a multivariate logistic regression model, there were no predictors for complete healing of plaque rupture.

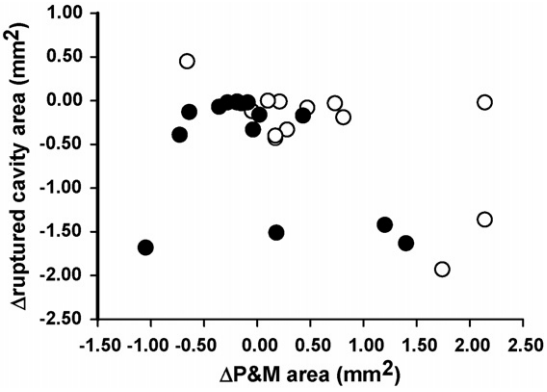

Fig. 4. The relationship between changes of ruptured cavity area and changes of plaque and media (P&M) area are shown: overall ($r=0.412$, $p=0.029$), no-statin group ($r=0.646$, $p=0.017$), and statin-treated group ($r=0.387$, $p=0.172$). Black circle: statin-treated patients and white circle: non-statin-treated patients.

4. Discussion

In the analysis of 28 patients who underwent serial IVUS examination, we found that most (25 of 28 lesions) non-culprit/non-target lesion plaque ruptures remained stable without the need for revascularization for up to 1 year even if the ruptured cavities did not entirely heal. Overall, 20 non-culprit/non-target lesion plaque ruptures did not change, five healed completely or partially, and three progressed to stenosis. Lesions that healed showed a resolution of complex angiographic morphology. Lesions that progressed to require revascularization showed an increase in P&M CSA to account for the decrease in lumen CSA. Statin treatment was associated with inhibition of plaque progression and lumen reduction, promotion of plaque rupture healing (apparently,

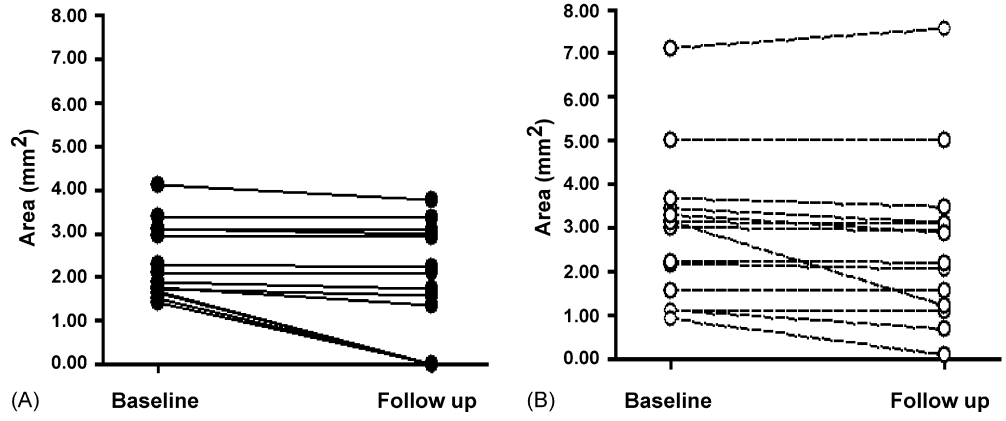

Fig. 3. Serial changes of ruptured cavity area between baseline and 12-month follow-up are shown in the statin-treated group (A) and the no-statin group (B).

independent of stabilization of P&M CSA) and improved 1-year clinical outcomes.

4.1. Natural evolution of secondary (subclinical) plaque ruptures

Previous pathologic studies have reported that coronary lesions with subclinical plaque rupture commonly heal and that healing may be related to stenosis progression [14,15]. Similarly, in the pre-statin era, angiographic follow-up studies of non-culprit lesions with complex morphology have shown lesion progression [16,17]. In the current report serial IVUS study showed an increase in P&M CSA and a decrease in lumen CSA in the non-statin treated group. Importantly, there were three non-statin-treated lesions that progressed to a significant stenosis requiring revascularization. These findings confirmed previous pathologic studies suggesting that plaque rupture healing was one of the mechanisms of stenosis progression [14,15]. One pathologic study suggested a relation between chronic, rather acute ulcerated plaques and ACS [18].

In contrast, in the statin-treatment era, angiographic follow-up studies of non-culprit lesions with complex morphology showed no significant changes [19] or reduction [9] of diameter stenosis. In a recent study Rioufol et al. performed 2-year follow-up IVUS analysis in 14 ACS patients with 28 non-culprit lesion plaque ruptures [9]. Statins (40 mg of pravastatin in 9 patients and 40 mg of simvastatin in 5) and dual anti-platelet therapy for more than 9 months were given to all patients; therefore, there was no non-statin-treated group. There were no clinical events, and half of the lesions had healed (defined as disappearance of the plaque cavity with complete intimal continuity) [9]. The frequency of healing was less in the current study; however, the duration of follow-up was 1-year versus 2-year in the study by Rioufol et al. [9]. The discrepancy of different healing rate between the current study and the previous study [9] might be explained by the findings of a recent angioscopic study [20]. They reported that the healing rate of ruptured plaque increased significantly according to the angioscopic follow-up period (23% at less than 12 months versus 55% at more than 12 months, $p < 0.05$) [20].

In the current study we were able to compare statin therapy (20 mg atorvastatin in seven patients and 40 mg simvastatin in seven) versus no-statins. In the current study major adverse cardiac events occurred less frequently in the statin treatment group compared to the no-statin group (0% versus 21%); and there were significant differences in complete healing of ruptured plaques (29% in statin treatments group versus none in no-statin group, $p = 0.049$).

4.2. Statin therapy for ruptured plaque stabilization and inhibition of plaque progression

Recent clinical studies have demonstrated the clinical benefits of statin treatment in ACS patients [6]. In PROVE IT-TIMI 22, compared with moderate lipid lowering regimen, an intensive lipid lowering statin regimen provided greater protection against death or major cardiovascular events in ACS patients [7]. A recent angioscopic study showed that lower C-reactive protein level at follow-up and statin treatment might be associated with healing of plaque rupture [20]. Compared with a control group, administration of statins to ACS patients showed beneficial effects on non-culprit lesions with a reduced plaque volume assessed by serial IVUS [21].

In patients with stable atherosclerosis, several studies using IVUS and magnetic resonance imaging have suggested that intensive lipid lowering treatment with statins is associated with regression of carotid or coronary atherosclerotic lesions [22–24]. In ACS patients, early aggressive lipid lowering therapy with atorvastatin 20 mg for 6 months was associated with plaque regression in non-culprit lesions [21]. In the current study highly selected plaque ruptures were chosen rather than non-selected lesions with/without plaque rupture. There was no change in plaque area ($0.0 \pm 0.7\ mm^2$) in the statin treatment group versus plaque progression ($0.6 \pm 0.9\ mm^2$) in the no-statin group. This finding suggests that statin may be associated with inhibition of plaque progression in ruptured plaque lesions that have a high potential of plaque progression.

In the study by Rioufol et al, there were no predictive factors for plaque rupture healing [9]; however, a dichotomous definition of plaque rupture healing was used. Similarly, using a dichotomous definition of plaque rupture healing, we were also unable to find predictive factors for plaque healing. However, using the change in plaque rupture cavity CSA as a continuous measure of plaque rupture healing, the baseline total cholesterol level was the only predictor of the change in plaque rupture cavity CSA.

We found that changes in P&M CSA predicted plaque rupture healing in the no-statin group ($r = 0.646$, $p = 0.017$); this was influenced mostly by the three lesions that progressed to a significant stenosis associated with P&M progression and plaque cavity regression. However, *this relationship was not apparent in the statin-treated group* suggesting that statins may induce healing *independent* of their effect on quantitative plaque measurements. This independent effect of statins on plaque stabilization has been suggested by other studies [25,26].

4.3. Limitations

This study was a single center, retrospective and non-randomized study (with regards to statin versus no-statin assignment) with a small number of patients. Similarly, there was no consideration given to the specific type or dosing of statin. The study population is heterogeneous; 21% in stable angina patients and 79% in acute coronary syndrome patients. The follow-up duration was 12 months. Data about C-reactive protein level were not obtained at follow-up; therefore, relationship between the changes of C-reactive protein

level and healing of plaque ruptures could not be evaluated in this study. It is likely that not all plaque ruptures will be detectable by IVUS because of confounding IVUS morphology (i.e., thrombus may obscure the ruptures).

5. Conclusions

The current 12-month follow-up IVUS study showed beneficial effects of statin treatment on reduction of TLR rates and visual stabilization of non-culprit/non-target lesion plaque ruptures without significant stenosis. Thus, non-lumen compromising plaque ruptures may not require revascularization as long as patients receive optimum medical therapy. Conversely, the current 12-month follow-up IVUS study documents that healing of non-culprit/non-target lesion plaque ruptures can be responsible for lesion progression; although the number was small, this later phenomenon was seen only in non-statin-treated patients.

Acknowledgments

This study was supported in part by the Cardiovascular Research Foundation, Seoul, Korea and a grant of the Korea Health 21 R&D Project, Ministry of Health and Welfare, Korea (0412-CR02-0704-0001).

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