Regression of Luminal Stenosis at the Site of Silent Plaque Disruption in the Era of Optimal Medical Therapy
– Low High-Density Lipoprotein Cholesterol Level Is a Potential Risk of Stenosis Progression –

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Background: Plaque disruption and its healing is thought to be the major mechanism of atherosclerosis, but the contribution of silent plaque disruption to luminal stenosis progression has not been fully clarified. The aim of this study was therefore to examine the change in luminal stenosis at the site of silent plaque disruption.

Methods and Results: Consecutive patients (n=36) who received coronary angiography and angioscopy that identified silent plaque disruption (baseline) and had repeated coronary angiography later (follow-up) were included for analysis. Silent plaque disruption was defined as plaque with thrombus detected in non-culprit segments. Diameter stenosis of the site was angiographically measured at baseline and at follow-up, and their difference was defined as stenosis change. Statin was used in 89% of study patients, and serum low-density lipoprotein cholesterol level was 91±21 mg/dl. The diameter stenosis decreased significantly from baseline to follow-up at 12±4 months (32±14% vs. 27±14%, P<0.001), and the stenosis change was −5.6±7.9%. High-density lipoprotein cholesterol (HDL-C) was significantly associated with stenosis change (r=−0.51, P=0.001) and was the only factor significantly associated with stenosis change.

Conclusions: In the era of optimal medical therapy with statin, the site of silent plaque disruption showed significant regression of luminal stenosis. Nevertheless, serum HDL-C was inversely associated with stenosis change, and its low level remained as a potential risk of luminal stenosis progression at the site of silent plaque disruption. (Circ J 2013; 77: 2573–2577)

Key Words: Angioscopy; High-density lipoprotein cholesterol; Silent plaque disruption; Stenosis; Thrombus

Silent plaque disruption is not a rare finding in the coronary arteries, and a very small percentage of disrupted plaques cause acute myocardial infarction (AMI). Plaque disruption followed by its healing process, however, is thought to be one of the major mechanisms of atherosclerosis progression. Although there is pathological evidence of repeated plaque rupture and healing at the site of significant stenosis, the contribution of silent plaque disruption to the progression of luminal stenosis has not been fully clarified in living patients. Therefore, we examined the change in luminal stenosis at the site of silent plaque disruption and analyzed the factors associated with the change.

Methods

Subjects
Consecutive patients (n=36) who received coronary angiography and angioscopy that identified silent plaque disruption from August 2007 to December 2010 (baseline) and had repeated coronary angiography later for any reason (follow-up) were included for analysis.

Catheterization was performed via a femoral, brachial, or radial artery approach using a 6- or 7-Fr sheath and catheters. Coronary angiogram was recorded with the Innova Cardiovascular imaging system (GE Healthcare Japan, Tokyo, Japan); and quantitative coronary angiographic analysis was performed.
The diameter stenosis of the coronary silent plaque disruption with stenosis change, multivariate stepwise linear regression analysis was performed including age, gender, acute coronary syndrome (ACS), LDL-C, HDL-C, triglyceride, creatinine, C-reactive protein, body mass index, diabetes mellitus, current smoking, and the difference was defined as stenosis change. The site was measured at baseline and at follow-up on the same view; and the difference was defined as stenosis change. The site was marked by recording the position of the angioscopic catheter when the plaque was detected. Intravenous heparin (100 U/kg) was given immediately before catheterization. GPIIb/IIIa inhibitors were not used for any patient because they were not approved in Japan.

The level of optimal medical therapy (OMT) was evaluated using the OMT score defined as the number of criteria fulfilled among the following: (1) systolic blood pressure (SBP) <130 mmHg; (2) diastolic blood pressure (DBP) <80 mmHg; (3) hemoglobin (Hb) A1c <6.9%; (4) low-density lipoprotein cholesterol (LDL-C) <100 mg/dl; (5) triglyceride <150 mg/dl; and (6) high-density lipoprotein cholesterol (HDL-C) ≥40 mg/dl, taking into consideration the Japan Atherosclerosis Society Guidelines for Prevention of Atherosclerotic Cardiovascular Diseases 2012. This study was approved by the Osaka Police Hospital Ethics Committee. Written informed consent was obtained from all the enrolled patients.

### Angioscopy and Evaluation

The angioscope RX-3310A and MV-5010A (Machida, Tokyo, Japan) and optic fiber DAG-2218LN (Machida, Tokyo, Japan) were used. Angioscopic observation was done while blood was cleared away from view by the injection of 3% dextran-40 as we have previously reported.9 Thrombus was defined as white or red material that had cotton-like or ragged appearance or that presented fragmentation with or without protrusion into the lumen or adherent to the luminal surface. The plaques with thrombus were defined as disrupted plaques. The disrupted plaques in the non-culprit segments were defined as silent plaque disruption. When silent plaque disruption was detected on angioscopy, the site was marked on the angiogram by recording the position of the angioscopic catheter. The yellow color grade at silent plaque disruption was determined (0, white; 1, slight yellow; 2, yellow; 3, intensive yellow) by comparison with standard colors as we have previously reported.10,11 Two specialists of angioscopy evaluated the angioscopic images blinded to patient characteristics. In the case of disagreement, a third reviewer served as an arbitrator. The inter- and intra-observer reproducibility for the interpretation of angioscopic images was 85% and 95% for plaque color, and 90% and 100% for thrombus, respectively.

### Table 1. Patient Characteristics

| Risk factors                  | n | Male gender (%) | Age (years) | Acute coronary syndrome |
|-------------------------------|---|-----------------|-------------|-------------------------|
| Diabetes mellitus             | 14 (39) |
| Hypertension                  | 25 (69) |
| Hypercholesterolemia          | 31 (86) |
| Current smoking               | 5 (14) |
| BMI                           | 25±4        |

#### Lipid profile (mg/dl)

- Total cholesterol: 197±36
- HDL-C: 45±10
- Triglyceride: 190±144
- LDL-C: 116±32

#### Medications

- Statin: 20 (56)
- Aspirin: 26 (72)
- Clopidogrel/Ticlopidine: 22 (61)
- ARB/ACEI: 12 (33)
- β-blocker: 14 (39)

#### Follow-up

- Diabetes mellitus: 17 (47)
- Hypertension: 30 (83)†
- Hypercholesterolemia: 35 (97)‡
- Current smoking: 0 (0)†
- BMI: 25±3
- Total cholesterol: 167±27†
- HDL-C: 46±12
- Triglyceride: 147±77
- LDL-C: 91±21†
- HbA1c (%): 5.9±0.8
- Creatinine (mg/dl): 0.9±0.2
- CRP (mg/dl): 0.4±1.0

#### Medications

- Statin: 32 (89)‡
- Aspirin: 36 (100)†
- Clopidogrel/Ticlopidine: 29 (81)
- ARB/ACEI: 24 (67)‡
- β-blocker: 22 (61)‡

Data given as n (%) or mean±SD. †P<0.05 vs. baseline. HbA1c data given as Japan Diabetes Society (JDS). National Glycohemoglobin Standardization Program (NGSP) hemoglobin can be calculated as [JDS]+0.4. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; CRP, C-reactive protein; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol.

### Table 2. Characteristics of Silent Plaque Disruption Sites

| Coronary vessel                  | Baseline | Follow-up | Change  |
|----------------------------------|----------|-----------|---------|
| Left anterior descending coronary artery | 8 (22)   | 3 (8)     | -5.0±7.9 |
| Left circumflex coronary artery   | 25 (70)  | 27±14     |         |
| Right coronary artery            | 25 (70)  | 27±14     |         |

#### Characteristic of Silent Plaque Disruption Sites

- Yellow color grade: 2.5±0.7

Data given as n (%) or mean±SD.
Stenosis Change at Disrupted Silent Plaque

Stenosis change was not different between the patients with and without statin treatment (−5.8±7.8% vs. −4.0±9.3%, P=0.67). There was no correlation between stenosis change and the percent change of LDL-C from baseline to follow-up (R=−0.002, P=0.99). The stenosis change was not different between the patients with and without ACS (−3.1±8.5% vs. −6.3±7.7%, P=0.32).

Discussion

According to the present results, luminal stenosis at the site of silent plaque disruption decreased significantly during follow-up in the era of optimal medical therapy, with statin used in 89% of patients achieving a mean serum LDL-C level of 91 mg/dl. Furthermore, the stenosis change was significantly and inversely associated with serum HDL-C level.

Mechanisms of Stenosis Change

The processes of plaque disruption and of healing should be discussed separately. The process of plaque disruption includes disruption of plaque (rupture or erosion) with the exposure of thrombogenic material to blood, protrusion of necrotic core in the case of plaque rupture, and thrombogenesis. The healing process of disrupted plaque includes lysis of thrombus, organization of thrombus, smooth muscle cell proliferation, matrix production, the replacement of matrix by collagen fibers, and positive/negative vessel remodeling. Both steps can contribute to the progression of luminal stenosis. An abrupt increase of luminal stenosis is often observed in the case of...
minal stenosis. In the present study, we examined the changes in luminal stenosis in this healing process of disrupted plaque. Therefore, we have no data on its change in the process of plaque disruption.

The process of plaque healing is in part similar to the process of post-percutaneous coronary intervention vessel response, which includes various mechanisms mentioned here and are influenced by various factors. The strength of injury to the vessel wall has been shown to be associated with the thickness of the neointima. Some medications, including statins, are known to have anti-proliferative effect on smooth muscle cells, although they are not strong enough to prevent in-stent restenosis effectively via oral treatment.

We have shown in the present study that luminal stenosis decreases significantly under optimal medical therapy and that low serum HDL-C level still remains as a potential risk of luminal stenosis progression. Although the progression of luminal stenosis at the site of silent plaque disruption has been previously reported in 2005, only 70% of those subjects had statin and had higher LDL-C level both at baseline and at AMI or unstable angina, which would be caused by protrusion of necrotic core with thrombus formation or intra-plaque hemorrhage. The healing process of disrupted plaque, however, may increase or decrease the luminal stenosis. The lysis of thrombus, washout of protruded necrotic core, replacement of matrix by collagen fibers, and positive vessel remodeling may decrease luminal stenosis, but the proliferation of smooth muscle cell and negative vessel remodeling may increase luminal stenosis. In the present study, we examined the changes in luminal stenosis in this healing process of disrupted plaque. Therefore, we have no data on its change in the process of plaque disruption.

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follow-up compared to the present study. Baseline stenosis at the site of silent plaque disruption was relatively less severe (12.3%) in the previous report compared to the present study. Data on HDL-C level were not available in the previous report, but the less aggressive statin treatment with the higher LDL-C level in the previous report, might have caused the progression of stenosis, while the more aggressive statin treatment with the lower LDL-C level in the present study might have caused the regression of stenosis. The stronger effect of statin as shown by plaque stabilization has been shown for the more vulnerable plaques and in the patients who achieved lower LDL-C level. Although we could not detect a favorable effect of statin or of lowering LDL-C in the present study in which patients were commonly treated aggressively by statins, the comparison of the 2 studies suggests the importance of aggressive statin therapy.

A diagnosis of ACS did not influence stenosis change at the non-culprit segments where plaque disruption with thrombus formation was present, suggesting that the local condition of plaque disruption has a stronger influence than the systemic condition of ACS on stenosis change.

If this healing process of silent plaque disruption is part of the natural process of atherosclerosis progression, then low serum HDL-C would be an important risk factor of atherosclerosis progression, supporting the idea that increasing serum HDL-C level is another target of optimal medical therapy.

**Study Limitations**

This study included a small number of patients with follow-up angiography and might have a selection bias. The reasons however, for performing or not performing follow-up angiography had nothing to do with the lesions with silent plaque disruption, and therefore, the bias should be limited. We could not detect the influence of LDL-C level or of statin use on the stenosis change, probably because the present patients were commonly taking statin with the exception of only a few patients. Although luminal stenosis was evaluated on IVUS or OCT. Although we have demonstrated the significant regression of luminal stenosis at the site of silent plaque disruption from the time of its detection to follow-up, the whole process of silent plaque disruption from the time before its occurrence to follow-up may contribute to the progression of luminal stenosis, which has not been clarified in the present study.

**Conclusions**

In the era of optimal medical therapy with statin and low serum LDL-C, the site of silent plaque disruption showed significant regression of luminal stenosis. Nevertheless, serum HDL-C level was inversely associated with stenosis change, and its low level remained as a potential risk of luminal stenosis progression at the site of silent plaque disruption.

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**Supplementary Files**

**Supplementary File 1**

**Movie S1.** The angioscopic image at the site of silent plaque disruption shows the presence of fresh white thrombus on the yellow plaque. The fragmentation of thrombus is observed.

Please find supplementary file(s);
http://dx.doi.org/10.1253/circbj.13-0299