Impact of Plaque Characteristics Analyzed by Intravascular Ultrasound on Long-Term Clinical Outcomes

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Limited data are available on long-term outcomes for vulnerable plaque analyzed by intravascular ultrasound (IVUS). The aim of this study was to investigate long-term clinical outcomes in 183 patients (79 with stable angina pectoris and 104 with acute coronary syndromes) who underwent preintervention 3-vessel IVUS and single-vessel stent implantation. Critical events, defined as any cause of death and acute coronary syndromes during follow-up, were evaluated. Plaque characteristics were analyzed in the target vessel and nontarget vessels. Vulnerable plaques were arbitrarily defined as plaques with rupture, lipid core, dissection, or thrombus. The mean follow-up period was 50 ± 20 months. Critical events developed in 12 patients (7%; 6 acute coronary syndromes, 6 deaths). The critical event–free rate was not different according to the presence of vulnerable plaques in the target lesion (95% vs 95%, p = 0.86). However, in the nontarget vessels, the long-term critical event–free rate was significantly lower in patients with vulnerable plaques (88% vs 96%, p = 0.04). On multivariate Cox regression analysis, the multiplicity of vulnerable plaques in the nontarget vessels (hazard ratio 2.2, 95% confidence interval 1.4 to 3.4, p = 0.001) was the only independent predictor of long-term critical events. Acute coronary syndromes (odds ratio 5.4, 95% confidence interval 2.1 to 14.3, p = 0.001) and diabetes mellitus (odds ratio 5.2, 95% confidence interval 1.9 to 13.8, p = 0.001) were significantly associated with the multiplicity of vulnerable plaques. In conclusion, the multiplicity of vulnerable plaques in nontarget vessels was the most important predictor of future critical cardiac events in this 3-vessel IVUS study. **(Am J Cardiol 2009;103:1221–1226)**

The concept of vulnerable plaque was developed on the basis of postmortem observations in patients with acute coronary syndromes. These autopsy studies reported that acute coronary syndromes are caused by spontaneous plaque rupture or erosion and subsequent thrombosis.[1,2] The development of imaging techniques can allow the observation of plaque in vivo. Of these, intravascular ultrasound (IVUS) provides detailed, high-quality images of coronary arteries and can detect plaque rupture, and it is easily applicable compared with other invasive imaging techniques, such as optical coherent tomography and angioscopy. We previously reported the prevalent site and difference as clinical presentations of plaque ruptures on 3-vessel IVUS.[3,4] Despite numerous clinical data, it is still insufficient to identify lesions that are at increased risk for thrombosis and subsequent cardiac events. Therefore, we investigated the long-term clinical outcomes of vulnerable plaques detected by 3-vessel IVUS.

Methods

A prospective but nonconsecutive series of 235 patients who were scheduled for coronary intervention underwent preintervention 3-vessel IVUS. Baseline clinical characteristics of patients without IVUS, with 1- or 2-vessel IVUS, and with 3-vessel IVUS have been previously reported.[4] Patients with histories of myocardial infarctions, long lesions (length >30 mm), total occlusions, and severe angulations or calcifications in any major epicardial artery were excluded.[4] Of these 235 patients, 183 patients with single-vessel stent implantation were selected to assess the natural histories of lesions in nonintervened vessels. Most patients were implanted with bare-metal stents (142 of 183). The study population consisted of 79 patients with stable angina pectoris and 104 patients with acute coronary syndromes. The target lesion for stent implantation was determined by the combination of left ventricular wall motion abnormalities, electrocardiographic findings, angiographic lesion morphology, and scintigraphic defects. Serum samples at index intervention were collected just before IVUS, and low-density lipoprotein cholesterol was checked again during follow-up (generally 1 year after the index intervention).

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Table 1
Baseline clinical characteristics

Variable	All (n = 183)	Vulnerable Plaque in Nontarget Vessel		p Value
		No (n = 137)	Yes (n = 46)	
Age (yrs)	58 ± 11	57 ± 11	60 ± 11	0.13
Men	131 (72%)	95 (69%)	36 (78%)	0.25
Acute coronary syndromes	104 (57%)	69 (50%)	35 (76%)	<0.01
Hypertension	81 (45%)	55 (40%)	26 (57%)	0.06
Diabetes mellitus	36 (20%)	21 (15%)	15 (33%)	0.01
Smokers	71 (39%)	53 (39%)	18 (39%)	0.99
Use of statins	92 (51%)	68 (50%)	24 (53%)	0.70
Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers	85 (47%)	59 (43%)	26 (58%)	0.09
C-reactive protein >0.6 mg/dl	37 (21%)	23 (17%)	14 (31%)	0.05
Baseline LDL >100 mg/dl	113 (65%)	90 (69%)	23 (55%)	0.10
Baseline LDL (mg/dl)	112 ± 32	112 ± 31	107 ± 35	0.40
Follow up LDL (mg/dl)	92 ± 30	94 ± 31	88 ± 27	0.27
Change in LDL (mg/dl)	−20 ± 41	−19 ± 41	−22 ± 42	0.70
Critical events	12 (7%)	6 (4%)	6 (13%)	0.04
Major adverse cardiac events	30 (16%)	19 (14%)	11 (24%)	0.11

Data are expressed as mean ± SD or as number (percentage).
LDL = low-density lipoprotein.

Table 2
Quantitative intravascular ultrasound measurements of target lesions

Variable	All (n = 183)	Vulnerable Plaque in Nontarget Vessel		p Value
		No (n = 137)	Yes (n = 46)	
Proximal reference segment				
External elastic membrane cross-sectional area (mm^2)	14.9 ± 3.7	14.7 ± 3.4	15.5 ± 4.4	0.22
Luminal cross-sectional area (mm^2)	9.0 ± 2.3	8.7 ± 2.2	9.3 ± 2.4	0.27
Lesion segment				
External elastic membrane cross-sectional area (mm^2)	14.3 ± 4.0	14.2 ± 3.8	14.8 ± 4.2	0.41
Luminal cross sectional area (mm^2)	2.2 ± 0.4	2.2 ± 0.3	2.2 ± 0.4	0.97
Plaque burden (%)	84 ± 5	84 ± 4	85 ± 4	0.32
Remodeling index	1.03 ± 0.16	1.03 ± 0.17	1.05 ± 0.13	0.51
Positive remodeling	58%	56%	64%	0.30
Arc of calcium (°)	40 ± 66	42 ± 68	34 ± 58	0.50
Calcified plaque	55 (30%)	42 (31%)	13 (28%)	0.74
Distal reference segment				
External elastic membrane cross-sectional area (mm^2)	12.8 ± 3.5	12.8 ± 3.3	12.8 ± 3.8	0.96
Luminal cross sectional area (mm^2)	7.9 ± 2.4	8.0 ± 2.2	7.7 ± 2.5	0.50

Data are expressed as mean ± SD or as number (percentage).

The detailed IVUS analysis method has been previously reported.[4] In brief, IVUS on all 3 major epicardial arteries was performed before any intervention. Vulnerable plaques were arbitrarily considered as plaques containing the following unstable features: rupture, lipid core, dissection, or thrombus. Plaque rupture was defined as a plaque containing a cavity that communicated with the lumen with an overlying residual fibrous cap fragment on IVUS.[5] A dissection was a longitudinal tear in the plaque parallel to the vessel wall. A lipid core was defined as plaque containing an echolucent zone, which was usually shallow in the vessel wall.[6–8] The identification of thrombus required ≥2 of the following: distinct hypoechoic mass, brightly speckled plaque, channeling within the plaque, evacuated plaque cavity, or detached mobile mass.[5] The number of vulnerable plaques was investigated for multiplicity, and patients were arbitrarily classified by the number of vulnerable plaques (0, 1 or 2, and ≥3). Plaques with plaque burden >40% were selected for this study. The qualitative assessment of plaque characteristics required independent review and agreement by 2 interventional cardiologists. Quantitative IVUS analysis was performed using computed planimetry at the target lesion and proximal and distal reference segments. The reference segments were the most normal looking cross sec-

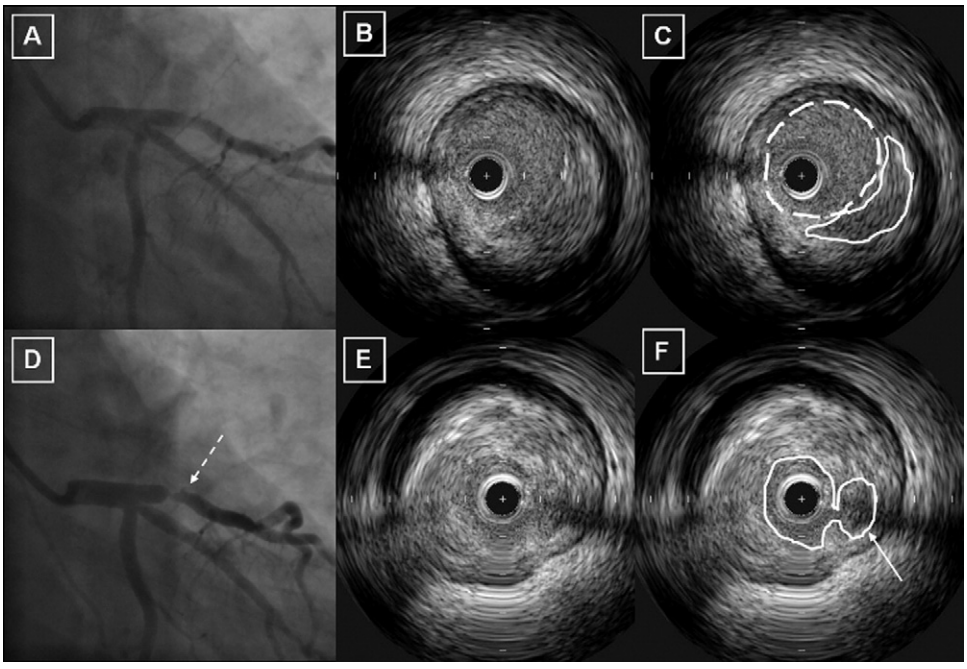

Figure 1. Representative images showing a critical event in a nontarget vessel. The patient was treated with single-stent implantation in the right coronary artery, and his left anterior descending coronary artery showed intermediate stenosis on angiography *(A)*. IVUS showed a large lipid pool (*B* and *C* are identical images; the *solid circle* is suggestive of a lipid core and the *dashed circle* is the lumen). Six months later, acute myocardial infarction developed from the left anterior descending coronary artery, which showed tight stenosis with ruptured plaque (*dashed arrow* in *D* and *solid arrow* in *F*; *E* and *F* are identical images).

tions within 5 mm proximal and distal to the lesion but before any side branch. Quantitative measurements included external elastic membrane, lumen, plaque cross-sectional area, and the arc of calcium. Calcified plaque was considered as plaque that appeared as bright echoes that obstructed the penetration of ultrasound.[9] A remodeling index was calculated as the lesion external elastic membrane area divided by the mean reference external elastic membrane area. Positive remodeling was defined as a remodeling index ≥ 1.0.[9]

The primary end points were the composite of acute coronary syndromes and death from any cause, and these were considered critical events. All events were based on clinical diagnoses. Medical records were reviewed to obtain information on clinical demographics and medical history. To validate follow-up data, information about death was obtained from the registry of the National Health Insurance Corporation, with the use of a unique personal identification number. Acute coronary syndromes included clinical presentation of acute myocardial infarction and unstable angina pectoris. Acute myocardial infarction was defined as continuous chest pain at rest with abnormal levels of cardiac enzymes (creatinine kinase-MB or troponin T), as previously reported.[4] Major adverse cardiovascular events were assessed as a secondary outcome and defined as the composite of death, acute coronary syndromes, any revascularization by percutaneous coronary intervention or bypass graft, and stroke.

Categorical variables were compared using the chi-square test for equality of proportions and are presented as raw numbers and percentages. Continuous variables were compared using Student's *t* test and are presented as mean $\pm$ SD. Kaplan-Meier analysis was used to determine the event-free survival rate, and differences between groups were analyzed using the log-rank test. Predictors of the time to an event were investigated by means of univariate and multivariate Cox regression. In addition, multivariate logistic regression analysis was performed to assess independent risk factors for the multiplicity of vulnerable plaques. A p value <0.05 was considered statistically significant. Stata SE version 10.0 for Windows (StataCorp LP, College Station, Texas) was used for analysis.

Results

Baseline clinical characteristics and quantitative IVUS measurements are listed according to the presence of vulnerable plaques in the nontarget vessels in Tables 1 and 2. The patients with vulnerable plaques in nontarget vessels were more likely to present with acute coronary syndromes (76% vs 50%, $p = 0.002$) and had a higher prevalence of diabetes mellitus (33% vs 15%, $p = 0.01$). Critical events, including acute coronary syndromes and deaths, occurred in more patients with vulnerable plaques in nontarget vessels than those without vulnerable plaques in nontarget vessels (13% vs 4%, $p = 0.04$). In qualitative IVUS analysis, a total of 216 vulnerable plaques were found in 134 of 183 patients, and 1.2 ± 1.1 (range 0 to 5) vulnerable plaques were found in each patient. In the target vessel, 148 vulnerable plaques were found in 133 patients, and 0.8 ± 0.6 (range 0 to 3) vulnerable plaques were found in each patient. In nontarget vessels, 68 vulnerable plaques were found in 46 patients, and 0.4 ± 0.8 (range 0 to 4) vulnerable plaques were found in each patient. According to the initial clinical presentation, 11 of 79 patients (14%) with stable angina

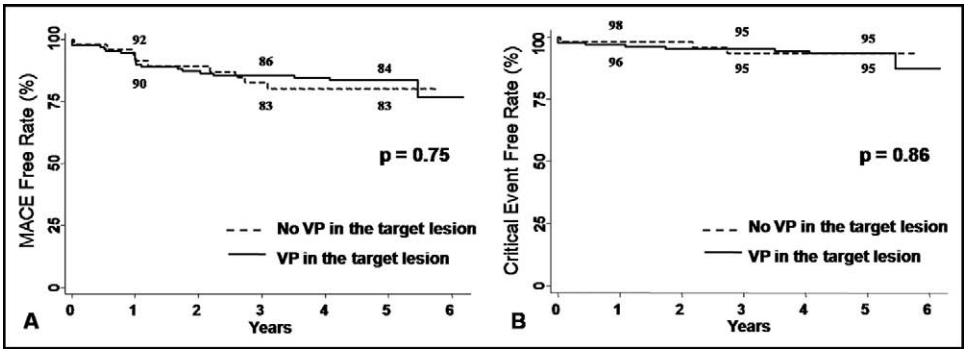

Figure 2. Kaplan-Meier curves for major adverse cardiovascular events (MACE) *(A)*, composed of death, acute coronary syndromes, any revascularizations, and stroke and critical events *(B)* according to the presence of vulnerable plaque (VP) in the target lesion.

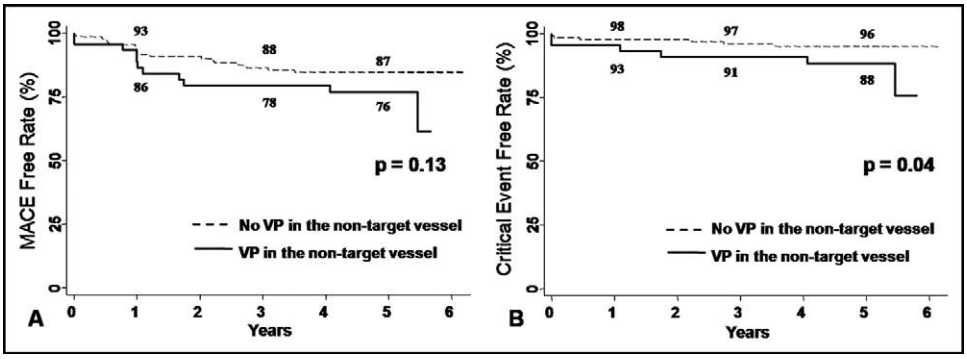

Figure 3. Kaplan-Meier curves for major adverse cardiovascular events (MACE) *(A)*, composed of death, acute coronary syndromes, any revascularizations, and stroke and critical events *(B)* according to the presence of vulnerable plaque (VP) in the nontarget vessels.

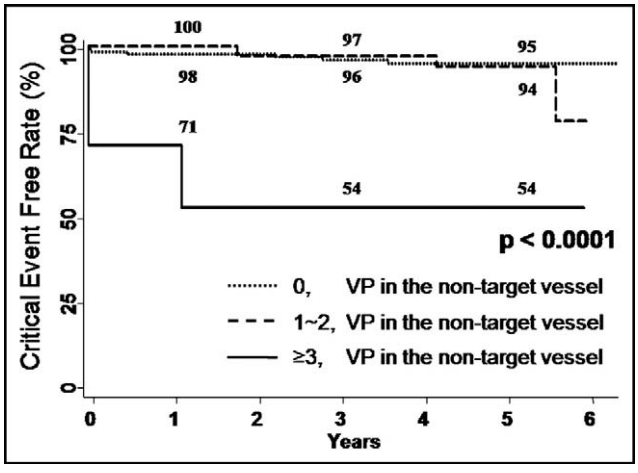

Figure 4. Kaplan-Meier curves for critical events according to the multiplicity of vulnerable plaque (VP) in the nontarget vessels.

pectoris and 35 of 104 patients (34%) with acute coronary syndromes had vulnerable plaques in the nontarget vessels ($p = 0.002$). The frequency of calcified plaque in the target lesion was not significantly different between acute coronary syndromes and stable angina pectoris as an initial presentation (28% vs 33%, $p = 0.4$).

Of 68 vulnerable plaques in the nontarget vessels, the number of ruptures, lipid cores, dissections, and thrombi were 17, 39, 2, and 10, respectively. Critical events developed in 12 patients (7%; 2 acute stent thromboses, 1 subacute stent thrombosis, 2 acute myocardial infarctions in nontarget vessels, 1 unstable angina pectoris in a nontarget vessel, and 6 deaths that could not be specified as target or nontarget vessel), and all patients were treated with bare-metal stents in the initial procedures. A case of a critical event in a nontarget vessel is shown in Figure 1. The presence of vulnerable plaques in the target lesion did not significantly influence critical events or major adverse cardiovascular events (Figure 2). However, the long-term critical event–free rate was significantly lower in patients with vulnerable plaques in nontarget vessels (88% vs 96%, $p = 0.04$; Figure 3). There was a lower tendency toward major adverse cardiovascular event–free rate in the same subjects, but statistical significance was not reached (76% vs 87%, $p = 0.13$; Figure 3). According to the number of vulnerable plaques in nontarget vessels, the patients were classified as follows: 0 (in 137 patients), 1 or 2 (in 39 patients), and ≥3 (in 7 patients). For the multiplicity of vulnerable plaques, the critical event–free rate was also significantly different, and the multiplicity of vulnerable plaques resulted in poor outcomes (95% vs 94% vs 54%, respectively, $p < 0.0001$; Figure 4). Multivariate Cox regression analysis showed that the multiplicity of vulnerable plaque in the nontarget vessels was the only independent risk factor for long-term critical events (hazard ratio 2.2, 95% confidence interval 1.4 to 3.4, $p = 0.001$). In the multivariate logistic regression analysis, presentation with acute coronary syndromes (odds ratio 5.4, 95% confidence interval 2.1 to 14.3, $p = 0.001$), and diabetes mellitus (odds ratio 5.2, 95% confidence interval 1.9

to 13.8, p = 0.001) remained as independent risk factors for the multiplicity of vulnerable plaques in nontarget vessels.

Discussion

In this 3-vessel IVUS study with a mean follow-up period of 50 ± 20 months, the presence of vulnerable plaques in the target lesions did not significantly influence long-term clinical outcomes. However, the multiplicity of vulnerable plaques in nontarget vessels was the only independent predictor of long-term critical outcomes such as death and acute coronary syndromes. The multiplicity of vulnerable plaques was significantly prevalent in patients with acute coronary syndromes or diabetes mellitus.

To date, it is still insufficient to identify lesions with morphologic characteristics of vulnerable plaque in daily clinical practice.[10] Although plaque rupture has been known to precede lesions, acute coronary syndromes can unexpectedly occur without plaque rupture,[2] and plaque rupture can be even found in patients with stable angina pectoris.[4] Although several morphologic characteristics of plaques by IVUS have been suggested to identify possible candidates for vulnerable plaque, including dissection, thrombus, and lipid core,[5,8,11] there have been no long-term follow-up data about them. Therefore, such characteristics as well as rupture were investigated in the present study, and vulnerable plaque defined as such characteristics predicted poor outcomes. Another follow-up study has been reported, showing that no clinical event–related ruptured plaque in nontarget vessels occurred, and half of ruptured plaques had even healed during about 2 years of follow-up.[12] Although this was a prospective and serial follow-up IVUS study, small size (only 14 patients) and a short follow-up period mainly contributed to the results, which are discordant with the results of our study. Also, the different definition of vulnerable plaque might have caused this discordance.

In addition, most studies have focused on the impact of vulnerable plaque, especially ruptured plaque, in the target lesion, which would be usually treated by percutaneous coronary intervention.[4,13] However, many adverse cardiac events occur from the nontarget vessels after percutaneous coronary intervention, 3 or 5 times after 2 years compared with events from the target lesion.[14] Vulnerable plaque in the nontarget vessels was reported as a predictor for adverse cardiac events, compared with vulnerable plaque in the target lesion, although it was on angiographic evaluation.[15] Vulnerable plaque in the target lesion would be treated on site, and acute coronary syndromes are associated with the widespread inflammation of the coronary vasculature, so-called pancoronaritis.[16,17] Glaser et al[18] reported that the multiplicity of diseased vessels was a major predictor of plaque progression (adjusted odds ratio 1.7 for 2-vessel disease, adjusted odds ratio 3.3 for 3-vessel disease). These results support the idea that future cardiac events are affected by the entire coronary disease burden rather than the vulnerability of the local culprit lesion. Therefore, it is reasonable to accept our result that the multiplicity of vulnerable plaques in the nontarget vessels was more predictive of future adverse events, especially death and acute coronary syndromes, than vulnerable plaque in the target lesion.

Although our results provide profound understanding of the long-term fate of vulnerable plaque, it is difficult to perform 3-vessel IVUS in all patients with coronary disease in daily clinical practice. Thus, it is clinically useful to find risk factors for the multiplicity of vulnerable plaque. Initial presentation with acute coronary syndromes and diabetes mellitus were found to be risk factors in the present study.

Clinical outcomes were assessed retrospectively in the present study, although it was based on a prospective cohort. Thus, we could not exactly differentiate the causes of death for some patients. In the study population, subjects who underwent only single-vessel stent implantation were investigated to assess the natural clinical outcomes of nonintervened vessels. Therefore, our study population might be a lower risk group than the general population of patients who undergo percutaneous coronary intervention.

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