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Vulnerable atherosclerotic plaques of coronary arteries in patients with stable coronary artery disease: 12-months follow-up

Relevance	A key objective of modern cardiology is the assessment of acute coronary syndrome (ACS) risk in patients with coronary artery disease (CAD) to develop preventive measures and choose optimal treatment strategies.
Objective	Detect vulnerable plaques of non-target coronary arteries in patients with stable CAD during routine percutaneous coronary intervention using virtual-histology intravascular ultrasound (VH-IVUS) and view their morphology over time.
Materials and Methods	The prospective observational cohort study included 58 patients with stable CAD. After stenting of a target vessel, VH-IVUS was carried out in proximal and middle segments (6–8 cm) of a non-target coronary artery with no significant stenosis according to coronary angiography. Twelve months later, all patients underwent coronary angiography with re-IVUS of previously detected lesions. Death, myocardial infarction, rehospitalization, and unplanned myocardial revascularization due to vulnerable plaques were the endpoints of the study.
Results	IVUS with virtual histology revealed 58 lesions of non-target coronary arteries in 56 (96.5%) patients. Two patients had no lesions in non-target coronary arteries. A large necrotic core with thin cap (thin-cap fibroatheroma) was detected in 12 (20.7%) plaques, six of which had additional ACS risk criteria (stenosis area >70% and/or lumen area <4 mm^2). Within the 12-month follow-up period, three patients (one with a vulnerable plaque in IVUS) were hospitalized with a clinical picture of ACS. One cardiac death was registered in a patient with the IVUS vulnerable plaque. 7 of 12 vulnerable plaques stabilized in 12 months.
Conclusion	1) The data presented indicate a high rate (20.7%) of vulnerable plaques of non-target coronary arteries in patients with stable CAD who underwent stenting; 2) Two (16.6%) patients with vulnerable plaques reached endpoints (death and rehospitalization) within the 12-month follow-up period; 3) An analysis of atherosclerotic plaques in non-target coronary arteries over time showed that vulnerable plaques stabilized and did not cause ACS in more than half of cases (7 of 12); 4) Plaques that were not vulnerable according to IVUS were not likely to destabilize within the 12-month follow-up period.

Keywords	IVUS; vulnerable plaque; thin-cap fibroatheroma
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Introduction

Acute coronary syndrome (ACS) is a major cause of lethal outcomes [1]. The pathogenesis of ACS is, in most cases, due to rupture of a coronary arterial plaque [2].

Important tasks of applied cardiology is development of methods for timely detection of these plaques, deciding on optimal treatment strategies, and scheduling of revascularization procedures [3]. However, these vulnerable plaques cannot be detected with coronary angiography [4].

Virtual-histology intravascular ultrasound (VH-IVUS) provides an image of the atherosclerotic plaque morphology [5]. The presence of a large necrotic core with a thin cap is predictive of plaque rupture with subsequent development of ACS [6].

Three prospective studies have shown that vulnerable plaques detected by VH-IVUS cause

adverse cardiac events (PROSPECT [6], VIVA [7], and ATHEROREMO-IVUS [8]). These studies proved that having plaques with a combination of three IVUS signs, 1) thin-cap fibroatheroma (TCFA), 2) stenosis area >70%, 3) minimum lumen area at the stenosis site <4 mm^2 [6–8], have the greatest prognostic power for the risk of acute coronary events. At the same time, an extremely low occurrence (6%) of such plaques was demonstrated by IVUS [8].

The studies mentioned above have several limitations. The PROSPECT study included only patients with ACS. VIVA and ATHEROREMO-IVUS included patients with both ACS and stable angina, which made it impossible to fully extrapolate their findings to the patients with chronic coronary artery disease (CAD). The incidence of vulnerable plaques (22% in PROSPECT, 60.2% in VIVA) did not agree with the risk of adverse events (4.9% in PROSPECT, 2.9% in VIVA) [9]. In the PROSPECT study, the endpoints were rehospitalization, indications for which could not always be defined objectively. In the VIVA study, myocardial revascularization prevailed over the combined endpoint, although, it might have been associated with a prior procedure [8, 9]. Not all lesions causing adverse events were vulnerable, according to virtual-histology IVUS (49% in PROSPECT, 38.5% in VIVA). A follow-up VH-IVUS was not performed. There is a chance that many initially stable plaques could destabilize over time [8, 9].

The above sets out some of the pending issues of the dynamical assessment of vulnerable lesions of coronary arteries and of the identification of predictors of acute adverse events caused by vulnerable plaques. Thus, the objective of our study was to identify and assess with repeated VH-IVUS the morphology of vulnerable plaques of non-target coronary arteries in patients with stable CAD during routine percutaneous coronary intervention.

Materials and Methods

A prospective, observational, cohort study of patients with stable CAD was performed. The study excluded patients with ACS. All patients underwent stenting of a target lesion followed by VH-IVUS of proximal and middle segments (6–8 cm) of a non-target coronary artery having no significant stenosis according to coronary angiography. If the artery had no IVUS stenosis changes, an intravascular examination was made on another non-target vessel. All intravascular ultrasound examinations were performed using the iLab imaging system (Boston Scientific, USA) and the iMap virtual histology software. The catheter was threaded automatically at a standard rate of 0.5 mm/sec. The local ethical committee approved the protocol of this study. All patients signed informed written consent.

Virtual histology was performed on lesions with lumen stenosis of 40% or more. The minimum lumen area, atherosclerotic plaque area with respect to the vessel lumen, plaque morphology, and cap thickness were assessed. Virtual histology identified four components in the structure of atherosclerotic plaques: fibrosis, lipids, necrotic core, and calcinosis. An atherosclerotic plaque with a large necrotic core >40% adjacent to the coronary artery lumen and with a TCFA was considered as vulnerable. An additional criteria for risk of adverse coronary events was a minimal residual lumen <4 mm^2 and plaque area >70% of the vessel lumen.

Death, myocardial infarction, rehospitalization, and repeated, unplanned myocardial revascularization due to vulnerable plaques were the endpoints of the study. Twelve months later, all patients underwent follow-up coronary angiography with repeated VH-IVUS of the previously identified lesions in the non-target coronary artery.

A similar analysis of the study cohort and an index of interventions has been published earlier [10]. Fifty-eight patients were enrolled in the study. The clinical, anamnestic, and angiographic characteristics of the study sample are presented in Table 1. During the follow-up period, all patients took antiplatelet drugs, statins, beta-blockers, and angiotensin-converting enzyme inhibitors.

The findings were processed using the STATISTICA 8.0 software package (StatSoft, Inc.). Both parametric (with a normal distribution) and nonparametric (with a non-normal distribution) criteria were used. The normality of distribution was determined using the Kolmogorov-Smirnov criterion. Means and standard deviations were calculated (M±SD).

Results

IVUS was performed on 64 non-target coronary arteries in 58 patients. Fifty-eight stenosis lesions were detected in 56 coronary arteries of 56 (96.5%) patients. Two (3.5%) patients had no IVUS lesions in non-target coronary arteries. Two patients had two lesions in one non-target coronary artery. Twelve (20.7%) lesions had a large necrotic core and a TCFA. Five (8.6%) lesions constricted the vessel lumen area by more than 70% (including 4 cases of the stenosis area >70% combined with the residual lumen area <4 mm^2), 10 (17.2%) lesions had a minimum lumen area <4 mm^2.

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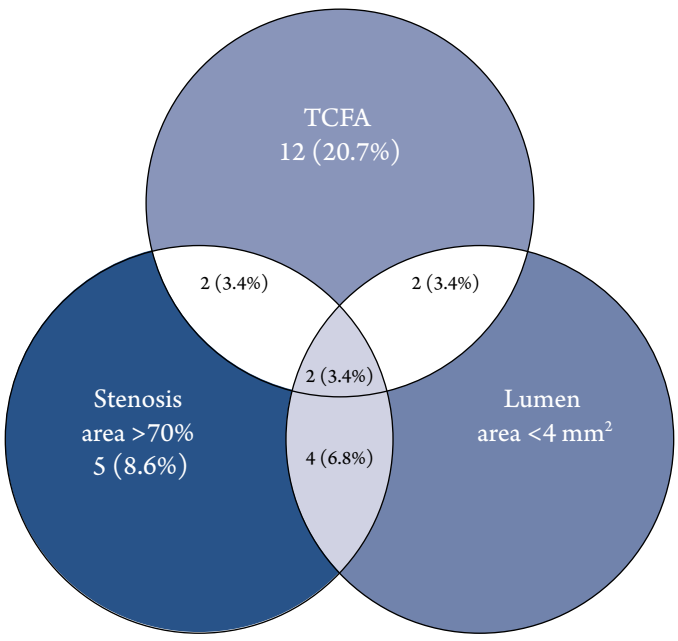
Table 1. Characteristics of the study cohort

Parameter	n=58	
	Abs.	%
Age, years	60.4±6.6	–
Male	38	65.5
Overweight	53	91.4
Smoking	11	18.9
Hypercholesterolaemia	37	63.8
Left ventricular ejection fraction, %	61.4±11.5	–
Hypertensive heart disease	58	100
Type 2 diabetes	16	27.6
History of myocardial infarction	27	46.5
History of stroke	3	5.2
Angina pectoris:		
• FC I	11	19.0
• FC II	35	60.3
• FC III	12	20.7
IVUS-lesions of the coronary arteries		
• LAD	21	36,2
• LCX	13	22.4
• RCA	24	41.4
Successful outcome of the index intervention	56	96.5
In-hospital complications of stenting	0	0

IVUS, intravascular ultrasound; FC, functional class; LAD, left anterior descending artery; LCX, left circumflex artery; RCA, right coronary artery.

Figure 1. Results of VH-IVUS



TCFA, thin-cap fibroatheroma.

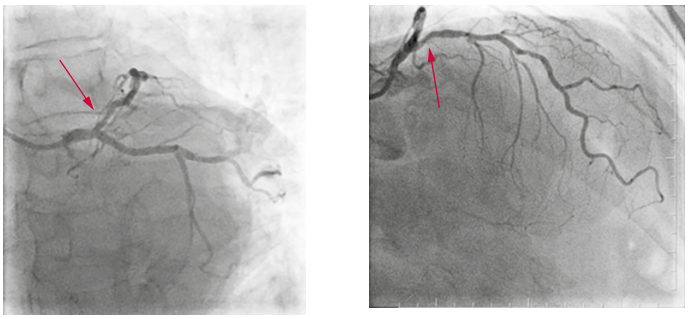
Of 12 vulnerable plaques, two (3.4%) lesions obstructed the artery area by >70%, two (3.4%) lesions were combined with the minimum lumen area <4 mm², two (3.4%) lesions had all three risk criteria for adverse coronary events: TCFA, stenosis area >70%, minimum lumen area <4 mm² (Figure 1). Patients with vulnerable plaques, unlike patients without such abnormalities, did not have statistically significant differences in cardiovascular risk factors [10].

During the 12-month follow-up period, three patients were hospitalized with clinical presentation of ACS. Only one of them had a previously identified TCFA with minimum lumen area 3.91 mm² and stenosis 65%. The follow-up coronary angiography did not identify any significant lesions in this patient. A previously implanted stent had no signs of thrombosis or restenosis. Thus, no intervention was made. In two other cases, ACS was due to the progression of initially stable lesions of interest previously detected by IVUS in non-target coronary arteries. This shows that destabilization of previously stable plaques could cause ACS. Both patients underwent re-stenting of the symptom-associated vessels. Thus, only one hospitalization due to ACS was associated with the initial presence of a vulnerable plaque.

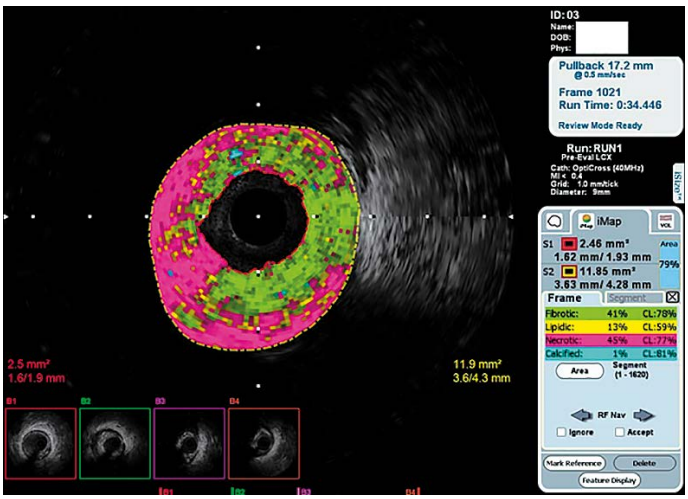
During the 12-month follow-up period, only one cardiac death was registered. This patient had a vulnerable plaque in the anterior descending artery with three risk factors for acute coronary events, TCFA, minimum lumen area 2.46 mm², and stenosis area 79% (Figure 2). The post-mortem examination revealed transmural myocardial infarction of the front left ventricular wall caused by thrombosis of the proximal anterior descending artery. No thrombosis of the stent implanted at the first intervention in the right coronary artery was identified. All 12-month follow-up endpoints are presented in Table 2.

Twelve months later, all surviving patients underwent follow-up coronary angiography with repeated VH-IVUS of the previously identified lesions in the non-target coronary artery. Atherosclerotic plaques stabilized overtime in seven patients with TCFA (58.3% of all patients with vulnerable plaques) due to fibrous cap thickening (Figure 3). The five remaining vulnerable plaques did not change significantly in 12 months. No patients with initially stable lesions had destabilization of these coronary plaques at the follow-up IVUS. Two patients with stable plaques had new risk criteria for ACS, stenosis area >70% in one case and lumen area <4 mm² in another. At twelve months, the follow-up VH-IVUS mostly did

Figure 2. Vulnerable plaque in a deceased patient



Insignificant stenosis of the proximal anterior descending artery according to angiography (arrow).



IVUS thin-cap fibroatheroma.

not reveal any significant changes in the morphology of stable plaques (Table 3).

Discussion

This study was performed to identify vulnerable plaques in the non-target coronary arteries using VH-IVUS in patients with stable CAD, to assess plaque morphology after 12 months, and to analyze their effect on the incidence of acute coronary events. The role of vulnerable plaques in the development of atherothrombosis and on the pathogenesis of acute coronary accidents is clear. At the same time, it is evident that there is not enough information on the behavior of vulnerable plaques over time and on their direct effect on the development of ACS. As a result of more effective management of patients with ACS, more significant efforts are focused on the development of methods of risk stratification for an adverse course of CAD. Promising approaches are 1) identification of hemodynamically insignificant plaques with signs of vulnerability and subsequent prospective monitoring of these patients, 2) registration of adverse cardiovascular events, and 3) determination of independent contributions of various clinical and laboratory factors.

Table 2. Endpoints at the end of the 12-month follow-up period

Endpoints	n=12
Death, n (%)	1 (8.3)
Hospitalization with ACS, n (%)	1 (8.3)
Myocardial infarction, n (%)	0
Repeat revascularization, n (%)	0

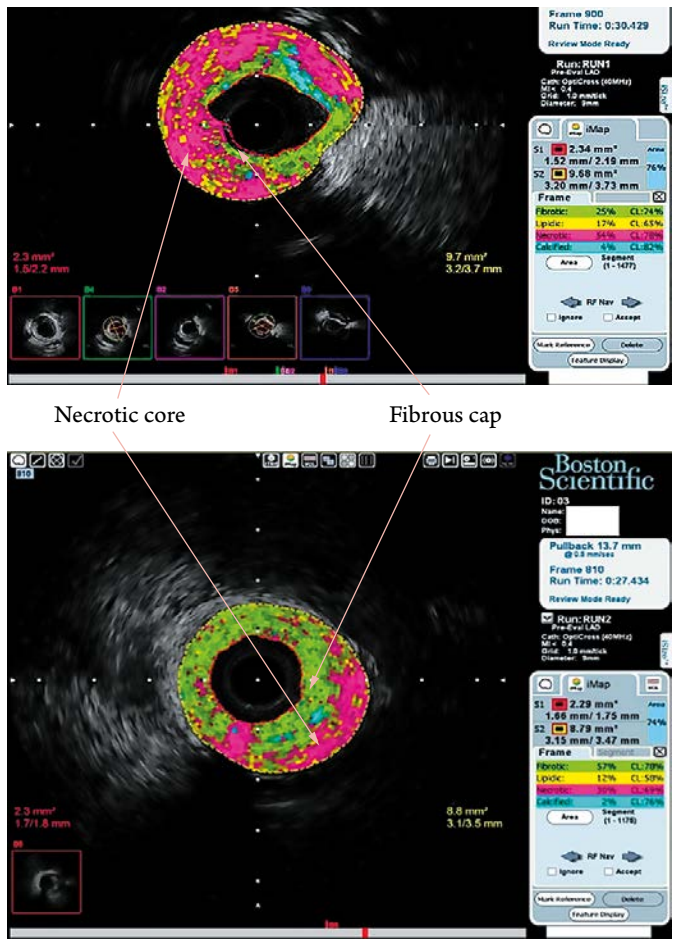
ACS, acute coronary syndrome.

Table 3. Dynamic IVUS of plaques

Criterion	Baseline	12 months
TCFA, n	12	5
Stenosis area >70%, n	9	10
Lumen area <4 mm², n	18	19
Stable plaques, n	46	51*

* – two patients had plaques of interest stented during rehospitalization due to ACS. TCFA, thin-cap fibroatheroma; ACS, acute coronary syndrome

Figure 3. Stabilization of the atherosclerotic plaque



At the top, thin-cap fibroatheroma (baseline); at the bottom, stabilization of the plaque due to the involution of the necrotic core and thickening of the fibrous cap (control examination in 12 months).

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The ATHEROREMO IVUS study demonstrated that virtual histology of only one symptom-unassociated coronary artery predicts the risk of adverse cardiovascular events within 12 months [8]. In the study cohort, each fifth (20.7%) patient had TCFA in a non-target coronary artery. This was less than in previous studies. i.e., 22% in PROSPECT [6] and 60.2% in VIVA [7]. This difference is due to the exclusion from the study of patients with ACS, which is known to destabilize symptom-unassociated lesions [11]. Moreover, half of the identified vulnerable plaques had additional risk criteria for the adverse coronary events, i.e., stenosis area >70% and/or minimum lumen are <4 mm^2.

In this study, only in two patients with vulnerable atherosclerotic plaques reached endpoints of death and/or hospitalization due to ACS. The results confirm findings of other studies [6, 7] that the presence of vulnerable plaques is inconsistent with the occurrence of adverse coronary events (20.7% vs. 3.3%, respectively).

Dynamic analysis of the morphology of the coronary lesions showed that initially stable plaques are not likely to destabilize. Despite this, two patients with initially stable plaques were rehospitalized with ACS. Coronary angiography identified progression of the lesions of interest. VH-IVUS of the symptom-associated lesions was not performed before stenting. Therefore, destabilization of the plaques of interest cannot be ruled out as the cause of ACS. Vulnerable plaques are, by contrast, likely to stabilize and not lead to acute coronary events. The causes of the stabilization of vulnerable plaques or the absence of ACS require further research. This favorable IVUS pattern over time might be due to the optimal drug therapy administered to the subjects.

Conclusion

1. There was a high rate (20.7%) of vulnerable plaques of non-target coronary arteries in patients with stable CAD who underwent stenting.
2. Two (16.6%) patients with vulnerable plaques reached endpoints (death and/or rehospitalization) within the 12-month follow-up period.
3. The dynamic analysis of atherosclerotic plaques in non-target coronary arteries showed that, in more than half of cases (7 of 12), vulnerable plaques stabilize and do not cause ACS.
4. Plaques that are not vulnerable, according to IVUS, were not likely to destabilize within the 12-month follow-up period.

This paper is a part of the research «Rationale for intravascular diagnostic techniques for coronary arteries in patients with CAD»

No conflict of interest is reported.

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