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Adverse Cardiovascular Events Arising From Atherosclerotic Lesions With and Without Angiographic Disease Progression

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OBJECTIVES The aim of this study was to use angiography and grayscale and intravascular ultrasound–virtual histology to assess coronary lesions that caused events during a median follow-up period of 3.4 years.

BACKGROUND Vulnerable plaque-related events are assumed to be the result of substantial progression of insignificant lesions.

METHODS In the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, 697 patients with acute coronary syndromes underwent treatment of all culprit lesions followed by 3-vessel imaging to assess the natural history of culprit and untreated nonculprit (NC) lesions. Future adverse cardiovascular events adjudicated to NC lesions were divided into those with versus without substantial lesion progression (SLP) (≥20% angiographic diameter stenosis increase).

RESULTS NC lesion events occurred in 72 patients, 44 (61%) with and 28 (39%) without SLP. Myocardial infarctions (n = 6) occurred only in patients with SLP. Conversely, patients without SLP presented only with unstable or increasing angina requiring rehospitalization. Lesions with versus without SLP occurred later (median time to event 401 vs. 223 days, $p = 0.07$); were less severe at baseline (median diameter stenosis 26.4% vs. 53.8%, $p < 0.0001$) but more severe at the time of the event (mean diameter stenosis 73.8% vs. 56%, $p < 0.0001$); and had comparable baseline median plaque burden (68.7% vs. 70.1%, $p = 0.17$), minimum luminal area (3.7 vs. 4.0 mm^2, $p = 0.60$), and intravascular ultrasound–virtual histology phenotype (83.3% vs. 90.9%, $p = 0.68$; classified as fibroatheromas at baseline).

CONCLUSIONS NC lesions responsible for future cardiovascular events showed angiographic increase during 3.4 years of follow-up, whereas SLP underlay many but not all of them. NC events due to lesions with SLP were angiographically less severe and presented with a delayed time course but were otherwise indistinguishable from NC events that were not associated with SLP. (J Am Coll Cardiol Img 2012;5:S95–105) © 2012 by the American College of Cardiology Foundation

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Most cases of sudden cardiac death and myocardial infarction (MI) are believed to arise from plaque rupture or surface erosion with subsequent thrombotic coronary occlusion of angiographically mild lesions ("vulnerable plaques"). The thin-cap fibroatheroma (TCFA), a metabolically active lesion with a large lipid-rich necrotic core and thin fibrous cap, is regarded as the most common type of rupture-prone and thrombosis-prone plaque (1–7). Angiographically, such lesions frequently undergo rapid progression in stenosis severity after plaque rupture, which may result in a spectrum of syndromes, ranging from sudden coronary occlusion with catastrophic symptoms to asymptomatic plaque progression (8–10).

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ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CSA = cross-sectional area
DS = diameter stenosis
EEM = external elastic membrane
IVUS = intravascular ultrasound
MACE = major adverse cardiac event
MI = myocardial infarction
NC = nonculprit
SLP = substantial lesion progression
TCFA = thin-cap fibroatheroma
VH = virtual histology

The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study investigated the natural history of atherosclerosis using multimodality intravascular imaging in vivo in patients presenting with acute coronary syndrome (ACS) (11–18). After treating all responsible culprit lesions, coronary angiography of the entire coronary tree and grayscale and radiofrequency intravascular ultrasound (IVUS)–virtual histology (VH) imaging of the proximal 6 to 8 cm of all 3 coronary arteries was performed, after which patients were followed for a median of 3.4 years on optimal medical therapy. Angiography was repeated in patients who had events during the follow-up period. Baseline and event-related coronary angiograms were compared to identify lesions responsible for unanticipated future events, which could occur either at the site of original treatment (culprit lesion–related events) or at untreated sites (nonculprit [NC] lesions). No prior study has examined how frequently future adverse cardiovascular events are indeed associated with angiographic substantial lesion progression (SLP) from NC lesions. We therefore sought to assess the frequency and predictors of angiographic SLP (the classic vulnerable plaque as defined by Naghavi et al. [19,20]) leading to NC lesion–related events in the contemporary era after the interventional management of ACS.

METHODS

Study population. In the PROSPECT study, 697 patients with ACS (unstable angina with electrocardiographic changes, non–ST-segment elevation MI, or recent ST-segment elevation MI) were enrolled from 37 sites in the U.S. and Europe. The study was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from all patients. The pre-specified primary end point was the occurrence of major adverse cardiac events (MACEs), the composite of cardiac death, cardiac arrest, MI, or rehospitalization due to unstable or progressive angina. On the basis of follow-up angiography, events were adjudicated as occurring at initially treated sites (culprit lesions) or at previously untreated coronary segments (NC lesions). If follow-up angiography was not performed, the location was classified as indeterminate.

Coronary angiography. All baseline angiograms were prospectively analyzed without knowledge of subsequent events. Angiographic qualitative and quantitative analysis of the entire coronary tree was performed at the Angiographic Core Laboratory of the Cardiovascular Research Foundation (New York, New York) using proprietary methods modified from Medis CMS software version 7.0 (Medis Medical Imaging Systems, Leiden, the Netherlands). Every 1.5 mm of vessel length, the reference diameter, minimal luminal diameter, and diameter stenosis (DS) were recorded. Analysis of all angiographic lesions with ≥30% visual DS was also pre-specified. NC lesions were divided into those with and those without SLP, prospectively defined as a ≥20% increase in the quantitative coronary angiographic DS between baseline and follow-up.

Grayscale and IVUS-VH imaging and analyses. Grayscale and radiofrequency IVUS of the left main and proximal 6 to 8 cm of each major epicardial coronary artery was performed using a phased-array, 20-MHz, 3.2-F IVUS catheter (Eagle Eye, Volcano Corporation, Rancho Cordova, California) that was placed into the distal coronary artery after intracoronary administration of 0.2 mg nitroglycerin and withdrawn to the aorto-ostial junction using motorized catheter pullback at 0.5 mm/s. During pullback, grayscale IVUS images were recorded, raw radiofrequency data were captured at the top of the R-wave, and reconstruction of the color-coded map by an IVUS-VH data recorder was performed (In-Vision Gold and S5, Volcano Corporation).

Offline grayscale and IVUS-VH analysis were performed by: 1) QCU-CMS software (Medis Medical Imaging Systems) for contouring; 2) pcVH 2.1 software (Volcano Corporation) for contouring

and VH data output; and 3) qVH software (developed within the Cardiovascular Research Foundation) for segmental qualitative assessment and data output.

External elastic membrane (EEM) and luminal borders were contoured for all recorded frames (approximately every 0.5 mm in length depending on the R-R interval). Quantitative IVUS measurements include EEM cross-sectional area (CSA), luminal CSA, plaque and media (defined as EEM CSA minus luminal CSA) CSA, and plaque burden (defined as plaque and media CSA divided by EEM CSA). The proximal and distal reference segments were the most normal looking segments (largest lumen with least plaque) within 5 mm proximal and distal to the lesion but before a major side branch. The remodeling index was defined as lesion EEM CSA divided by mean reference EEM CSA (21).

Radiofrequency IVUS plaque components were color-coded as dense calcium (white), necrotic core (red), fibrofatty (light green), or fibrous tissue (dark green) and reported as CSA and percents of total plaque area (22).

Definitions of lesion types. Data were constructed at 3 levels: lesion level, fibroatheroma level, and slice level. An IVUS lesion was defined as a segment with ≥3 consecutive frames with ≥40% plaque burden. The lesions were considered separate lesions if there was a 5-mm-long normal segment (<40% plaque burden) between them.

Lesions were further classified into 5 main types: 1) VH TCFA; 2) thick-cap fibroatheroma; 3) pathological intimal thickening; 4) fibrotic plaque; and 5) fibrocalcific plaque. Fibroatheromas (VH-TCFA and thick-cap fibroatheroma) had >10% confluent NC lesions (23).

Statistical analysis. Continuous variables are presented as medians and interquartile ranges and were compared using Mann-Whitney *U* tests. Categorical variables are summarized as absolute values and percents and were compared using chi-square or Fisher exact tests. Paired statistical comparisons between groups were performed using Student *t* tests. Time-to-event data are presented as Kaplan-Meier estimates. A p value <0.05 was considered statistically significant. All analyses were performed using SAS version 9.1.3 (SAS Institute Inc., Cary, North Carolina).

RESULTS

Patient characteristics. From the 697 patients examined in the PROSPECT study, 72 (10.3%) experienced major events related to NC lesions during a median follow-up period of 3.4 years. Of them, 44 patients (61%) had events that were attributed to SLP (≥20% quantitative coronary angiographic DS increase), while 28 patients had events attributable to NC lesions without SLP. Baseline patient characteristics and laboratory results are listed in Table 1. Comparing patients with NC lesions with and those without SLP, age, sex, risk factors, baseline lipid and metabolic profile, high-sensitivity C-reactive protein levels, risk score, and number of culprit vessels were similar.

Angiographic analysis. By angiography, all patients with NC events had at least 1 angiographically evident lesion at baseline (≥30% DS by visual estimate) that was treated after the index procedure only with contemporary medical therapy and not with stent implantation or other percutaneous technique. Overall, the 44 patients with SLP causing NC events had 55 NC-related lesions; the 28 patients without SLP causing NC events had 46 NC-related lesions. As shown in Table 2, NC lesions with SLP were less severe at baseline (median DS 26.4% vs. 53.8%, $p < 0.0001$) but more severe at the time of the event (median DS 73.8% vs. 56.0%, $p < 0.0001$) (Fig. 1). The progression in DS from baseline to follow-up was statistically significant, however, in the NC lesion groups both with and without SLP ($p < 0.0001$ in both groups). There were no significant differences regarding lesion location, lesion length, or qualitative morphologies either at baseline or at follow-up between the two groups.

Grayscale and IVUS-VH analysis. At baseline, IVUS and IVUS-VH analysis was performed in 52 of 101 lesions (51%) causing NC events during follow-up. Nonimaged lesions causing NC events were located in branches or distal vessels, that is, not in the proximal 6 to 8 cm of the 3 major epicardial vessels where grayscale and IVUS-VH imaging was performed. All NC event-related lesions with versus without SLP had a large but comparable plaque burden (median 68.7% vs. 70.1%, $p = 0.17$) and nonsignificantly different minimal luminal area (median 3.7 vs. 4.0 mm^2, $p = 0.60$), and the majority (83.3% vs. 90.9%, $p = 0.68$) were classified as IVUS-VH fibroatheromas at baseline (Fig. 2). There were no differences between the two groups (lesions with vs. without SLP) regarding baseline grayscale IVUS measurements, quantitative IVUS-VH analysis, or IVUS-VH phenotype (Table 3).

NC lesion events. As shown in Table 4, the pattern of events differed significantly between NC lesions with versus without SLP. There were no deaths in either

Table 1. Patient Baseline Clinical Characteristics

	SLP (n = 44)	Non-SLP (n = 28)	p Value
Age (yrs)	58.5 (51.8–67.7)	54.5 (48.4–66)	0.24
Men	33 (75%)	20 (71.4%)	0.74
Body mass index (kg/m^2)	29.7 (26.6–32.7)	28.1 (24.6–33.6)	0.29
Risk factors			
Diabetes mellitus	11 (25%)	7 (25%)	1.00
Insulin dependent	5 (11.4%)	1 (3.6%)	0.39
Hypertension	27/43 (62.8%)	12/26 (46.2%)	0.18
Hypercholesterolemia	3/41 (56.1%)	6/20 (30%)	0.06
Family history of CAD	18/36 (50%)	16/23 (69.6%)	0.14
Current cigarette use	18/43 (41.9%)	17 (60.7%)	0.12
Prior MI	5 (11.4%)	3 (10.7%)	1.00
Prior PCI	9 (20.5%)	3 (10.7%)	0.35
Metabolic syndrome	21 (47.7%)	16/27 (59.3%)	0.35
Framingham risk score	7 (6–9)	7 (5–9.5)	0.66
Clinical presentation			
STEMI >24 h	16 (36.4%)	8 (28.6%)	0.49
NSTEMI	28 (63.6%)	18 (64.3%)	0.96
Unstable angina	0 (0%)	2 (7.1%)	0.15
Laboratory results			
Total cholesterol (mg/dl)	188 (154–208)	163 (146–192.3)	0.18
LDL cholesterol (mg/dl)	106 (83–138.4)	98 (80.6–119)	0.30
HDL cholesterol (mg/dl)	38.8 (33–49)	37.5 (35–41)	0.50
Triglycerides (mg/dl)	128 (88.6–177.1)	117.5 (88.6–165)	0.67
Glycosylated hemoglobin	5.85 (5.4–6.75)	5.7 (5.6–6.2)	0.70
Estimated creatinine clearance (ml/min)	97.2 (75–121.5)	99.9 (86.3–128)	0.42
hs-CRP, day 0 (mg/dl)	8.2 (3.2–28.4)	8.0 (3–12.5)	0.26
hs-CRP, day 30 (mg/dl)	1.7 (0.6–5.1)	1.0 (0.7–2.9)	0.40
hs-CRP, day 180 (mg/dl)	1.8 (0.8–4.7)	1.7 (0.7–4.5)	0.83
Number of culprit vessels			
1	28 (63.6%)	19 (67.9%)	0.71
2	16 (36.4%)	9 (32.1%)	0.71

Values are median (interquartile range), n (%), or n/N (%).
CAD = coronary artery disease; HDL = high density lipoprotein; hs-CRP = high sensitivity C-reactive protein; LDL = low-density lipoprotein; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PCI = percutaneous coronary intervention; SLP = substantial lesion progression; STEMI = ST-segment elevation myocardial infarction.

group. MIs occurred only in patients with SLP. Conversely, patients without SLP presented more commonly with increasing angina leading to rehospitalization.

Table 5 shows the annual cumulative event rates according to lesion progression. NC events attributed to lesions without SLP occurred earlier than those attributed to lesions with SLP (at 1 year, 45.5% vs. 67.9%, p = 0.03; at 2 years, 75% vs. 85.7%, p = 0.05; at 3 years, 97.7% vs. 96.4%, p = 0.15). Time-to-event curves for NC lesion–related MACEs are shown in Figure 3.

DISCUSSION

The major findings of this substudy analysis from PROSPECT are as follows. First, during a median follow-up period of 3.4 years, 61% of NC lesion events were associated with SLP. Second, there were no NC lesion–related deaths, and MIs occurred only in patients with SLP. Conversely, patients without SLP presented only with unstable or increasing angina leading to rehospitalization and revascularization. Third, compared with NC lesions with SLP, lesions without SLP became symptomatic earlier and were more severe at baseline by angiography, suggesting that they were significant at the time of the index event. Fourth, conversely, lesions with SLP became symptomatic later, were less severe at baseline by angiography but not by IVUS, and were more severe angiographically at the time of the event (and with greater angiographic SLP). Last, all lesions causing NC

Table 2. Baseline and Follow-Up Angiographic Variables and Their Changes of NC Lesions

	Baseline			Follow-Up		
	SLP (n = 55)	Non-SLP (n = 46)	p Value	SLP (n = 55)	Non-SLP (n = 46)	p Value
QCA measurements of angiographic NC lesions						
RVD (mm)	2.5 (2–3)	2.3 (2–3.1)	0.62	2.49 (2.02–2.9)	2.3 (2.07–2.93)	0.94
MLD (mm)	1.7 (1.37–2.24)	1.15 (0.8–1.6)	<0.0001	0.69 (0.5–1.1)	1 (0.82–1.40)	0.004
DS (%)	26.4 (13.2–40.2)	53.8 (38–61.6)	<0.0001	73.8 (60.3–80.2)	56 (51.8–66.1)	<0.0001
Lesion length (mm)	9.9 (6.7–15.7)	12.5 (7.7–16.9)	0.38	10.1 (8.2–14.3)	11.1 (7–14.9)	0.82
Thrombus	0 (0%)	0 (0%)	NA	1 (1.8%)	0 (0%)	1.00
Ulceration	0 (0%)	0 (0%)	NA	1 (1.8%)	0 (0%)	1.00
Aneurysm	0 (0%)	0 (0%)	NA	1 (0%)	1 (2.2%)	0.46
Intimal flap	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
Calcification	1 (1.8%)	1 (2.2%)	1.00	1 (1.8%)	1 (2.2%)	1.00
Eccentricity	0 (0%)	0 (0%)	NA	0 (0%)	2 (4.3%)	0.20
Tortuosity	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
Angulation						
Entry angle (°)	14 (9–22)	18 (7–25)	0.71	22 (12–26)	18 (12–25)	0.63
Exit angle (°)	14 (7–19)	13 (5–17)	0.52	15 (9–23)	10 (6–23)	0.31
Maximal angle (°)	20 (13–25)	18 (15–25)	0.76	25 (16–29)	24 (15–31)	0.68
Bifurcation						
Side branch present	7 (12.7%)	7 (15.2%)	0.72	11 (20%)	8 (17.4%)	0.74
DS of side branch (%)	13.1 (6.6–40.5)	22.4 (8.3–53.1)	0.67	38.9 (11.2–80.2)	28.8 (3.7–55)	0.31
Lesion location						
LM	2 (3.6%)	0 (0%)	0.50	2 (3.6%)	0 (0%)	0.50
LAD (or branches)	14 (25.5%)	18 (39.1%)	0.14	14 (25.5%)	18 (39.1%)	0.14
LCX (or branches, including ramus)	16 (29.1%)	16 (34.8%)	0.54	16 (29.1%)	16 (34.8%)	0.54
RCA (or branches)	23 (41.8%)	12 (26.1%)	0.10	23 (41.8%)	12 (26.1%)	0.10
Branches	19 (34.5%)	21 (45.7%)	0.26	19 (34.5%)	21 (45.7%)	0.26

Values are median (interquartile range) or n (%).
DS = diameter stenosis; LAD = left anterior descending coronary artery; LCX = left circumflex coronary artery; LM = left main coronary artery; MLD = minimal luminal diameter; NA = not applicable; NC = nonculprit; QCA = quantitative coronary angiography; RCA = right coronary artery; RVD = reference vessel diameter; SLP = substantial lesion progression.

events had significant plaque burden (>40%) at baseline. However, there were no differences in grayscale or IVUS-VH findings comparing lesions causing NC events whether or not they had SLP.

Coronary atherosclerotic lesion progression is neither linear nor predictable (10,24). In patients with ACS, angiographic percent DS often increases suddenly because of plaque rupture and thrombus formation (10,24,25). Such plaques have well-defined histopathological characteristics and are usually termed "vulnerable" or "unstable," have a tendency toward acute disruption and increased thrombogenicity, and are also the sites of intense inflammatory activity (6,26). In the present study, NC events associated with SLP occurred in lesions that were relatively mild at baseline (angiographic median DS 26.4%; interquartile range: 13.2% to 40.2%) and, importantly, were responsible for all cases of MI. However, IVUS measurements in these lesions showed a substantial baseline plaque burden of 68.7% (interquartile range: 62.5% to 70.4%), indicating that these were significant plaques but in many cases were not associated with angiographic luminal compromise, because of positive remodeling or the inaccuracies of angiography, which can underestimate lesion severity (27). Therefore, these lesions that appeared mild by angiography were not mild lesions. Previous studies have shown that positive remodeling is a risk factor for plaque vulnerability and major adverse coronary events, is more common in lesions associated with unstable syndromes, and is marker for greater biologic activity (28).

Angiographically, lesions associated with acute coronary events often have "complex" characteristics, consisting of irregular borders, overhanging edges, and intracoronary thrombi (26); these characteristics in patients treated conservatively have been associated with a rapid increase in severity and

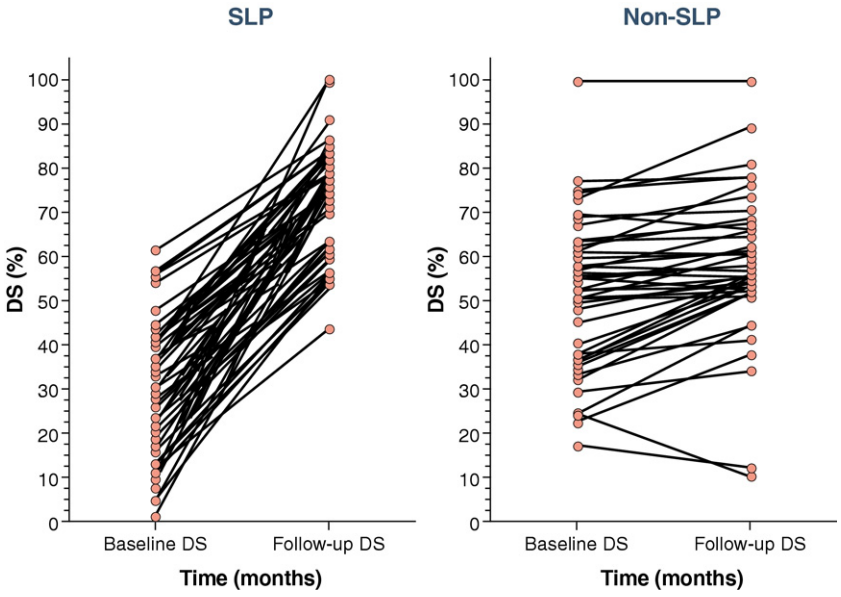

Figure 1. Baseline and Follow-Up Angiography

Angiographic diameter stenosis (DS) percent for each nonculprit event at baseline and follow-up for the substantial lesion progression (SLP) group (left) and the non-SLP group (right).

the development of acute events compared with smooth lesions (29–31). However, these studies were performed before the routine interventional management of lesions causing ACS. In the present study, these complex features were rarely present in NC lesions from which future MACEs arose. Nonetheless, 10.3% of patients developed unanticipated NC lesion–related events within 3 years, usually at the site of an angiographically innocuous appearing mild lesion, 61% of which also met our definition for SLP.

Conversely, NC events without SLP in the present study occurred in the setting of angiographically borderline lesions at baseline, significantly more severe than those with SLP (median DS 53.8% vs. 26.4%, $p < 0.0001$) but still angio-

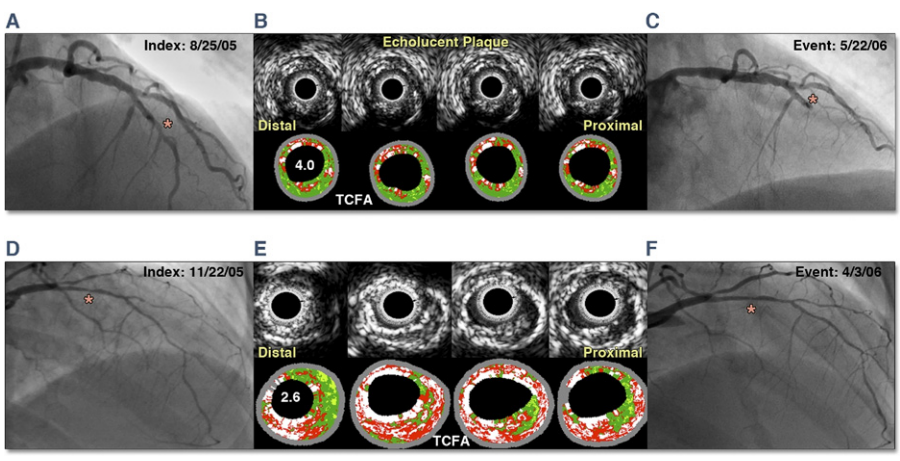

Figure 2. 2 Patients With NC Events: 1 With and 1 Without SLP

Middle left anterior descending coronary artery (LAD) lesion **(*) (A)** with substantial lesion progression (SLP), which caused a nonculprit (NC) event **(C)**. The baseline minimal luminal area (MLA) was 4.0 mm^2, and the lesion was classified as a thin-cap fibroatheroma (TCFA) **(B)**. Proximal LAD lesion (asterisk) **(D)** without SLP, which caused an NC event **(F)**. The baseline MLA was 2.6 mm^2, and the lesion was classified as a TCFA **(E)**. The **asterisk** represents the lesion.

Table 3. Baseline Grayscale IVUS and IVUS-VH Variables

	SLP (n = 30)	Non-SLP (n = 22)	p Value
Lesion length (mm)	19.2 (13.2–36.2)	27.3 (22–40.5)	0.17
VH phenotype			
Any FA (TCFA or ThCFA)	25 (83.3%)	20 (90.9%)	0.68
TCFA	15 (50%)	11 (50%)	1.00
ThCFA	10 (33.3%)	9 (40.9%)	0.58
PIT	4 (13.3%)	2 (9.1%)	1.00
Fibrotic plaque	0 (0%)	0 (0%)	NA
Fibrocalcific plaque	1 (3.3%)	0 (0%)	1.00
MLA site			
Distance from ostium to lesion MLA site (mm)	26.8 (12.9–40.5)	29.6 (16.5–52.6)	0.60
EEM area (mm^2)	12.9 (8.7–15.9)	12.5 (10.87–16.11)	0.39
Luminal area (mm^2)	3.7 (3.3–4.5)	4.0 (3.24–5.17)	0.60
P&M area (mm^2)	8.4 (5.6–10.8)	9.0 (7.1–12.1)	0.30
Plaque burden (%)	68.7 (62.5–70.4)	70.1 (65–74.7)	0.17
Remodeling index	0.9 (0.8–1.0)	0.9 (0.8–1.0)	0.69
Necrotic core (%)	15 (9.7–26.1)	12.8 (7.1–24.5)	0.53
DC (%)	4.9 (2.2–11.4)	3.4 (2.0–6.4)	0.58
FF (%)	10.4 (7.4–19.5)	16.7 (6.7–25.2)	0.51
FT (%)	61 (52.8–69.4)	61 (58–66.8)	0.95
Volumetric analysis (%)			
Necrotic core	15.3 (9.1–21.5)	14.1 (8.8–23.4)	0.89
DC	5.9 (2.5–13.5)	6.5 (2.7–9.2)	0.83
FF	14.3 (8.9–21.5)	17.8 (10.9–24.3)	0.46
FT	58.8 (54.0–67.5)	59.8 (54.9–65.4)	0.93

Values are median (interquartile range) or n (%).
DC = dense calcium; EEM = external elastic membrane; FA = fibroatheroma; FF = fibrofatty; FT = fibrotic; IVUS = intravascular ultrasound; MLA = minimal luminal area; NA = not applicable; P&M = plaque and media; PIT = pathologic intimal thickening; SLP = substantial lesion progression; TCFA = thin-cap fibroatheroma; ThCFA = thick-cap fibroatheroma; VH = virtual histology.

graphically intermediate in severity despite a median plaque burden by IVUS of 70.1% (interquartile range: 65% to 74.7%). Thus, these lesions were more severe at baseline than suggested by angiography. This contention is supported by the shorter time to NC events in the setting of non-SLP compared with SLP. Physiologic lesion assessment may be a superior technique to assess ischemia-producing lesions requiring revascularization than IVUS. Although previous studies have focused on the use of physiologic lesion assessment to defer interventions in nonischemia-producing lesions that would otherwise be treated (32,33), the present data suggest a potentially equally important role in identifying ischemia caused by anatomically intermediate lesions for which intervention would otherwise be deferred. Of note, however, even in the NC lesions we classified as not having SLP, there was significant disease progression from baseline to the time of event, suggesting that it was not merely the severity of the initial stenosis that resulted in the NC event.

In earlier long-term follow-up studies, risk factors and local coronary anatomy were predictors of stenosis progression (34,35). In a study from the National Heart, Lung, and Blood Institute in which IVUS parameters were not assessed, younger patient age, unstable clinical presentation, and overall severity of angiographic coronary artery disease were proposed as predictors of substantial coronary stenosis progression (36). In addition, newer studies suggest a correlation between temporal changes in plaque composition and circulating biomarkers (37,38). However, in the present larger study, there were no differences between the plaques with versus without SLP regarding patient age, risk factors, and serologic predictors including, high-sensitivity C-reactive protein levels.

The classic vulnerable plaque has most frequently been pathologically characterized as a TCFA (7). However, in the present IVUS-VH study, half of the lesions responsible for NC events with or without SLP were not characterized by IVUS-VH as VH TCFAs. There are a number of

Table 4. Overall Number and Types of Events During a Median Follow-Up Period of 3.4 Years

	SLP (n = 44)	Non-SLP (n = 28)	p Value
NC lesion MACEs			
Composite MACEs	44 (100%)	28 (100%)	0.15
Cardiac death, cardiac arrest, or MI	6 (14.1%)	0 (0%)	0.053
Cardiac death	0 (0%)	0 (0%)	NA
Cardiac arrest	0 (0%)	0 (0%)	NA
MI	6 (14.1%)	0 (0%)	0.053
Q-wave MI	2 (4.8%)	0 (0%)	0.29
Non–Q-wave MI	4 (9.2%)	0 (0%)	0.11
Rehospitalization	39 (93.2%)	28 (100%)	0.009
Due to unstable angina	15 (45.8%)	6 (23.6%)	0.30
Due to increasing angina	28 (63.6%)	24 (100%)	0.004
Other NC lesion events			
Revascularization (PCI or CABG)	44 (100%)	23 (100%)	0.59
Due to MI	6 (14.1%)	0 (0%)	0.053
Due to unstable angina	14 (44%)	5 (19.6%)	0.23
Due to increasing angina	28 (63.6%)	19 (100%)	0.24
Stent thrombosis	0 (0%)	0 (0%)	NA
Death	0 (0%)	0 (0%)	NA

Values are n (%).
CABG = coronary artery bypass graft; MACE = major adverse cardiac event; MI = myocardial infarction; NA = not applicable; NC = nonculprit; PCI = percutaneous coronary intervention; SLP = substantial lesion progression.

potential explanations. First, recent studies have shown that coronary artery lesion phenotype is highly dynamic. New VH TCFAs can develop from pathological intima thickening or thick-cap fibroatheroma, indicating that the original phenotype at baseline may evolve (39). This is likely given that thick-cap fibroatheromas were intermediate in risk between TCFAs and nonfibro-

Table 5. Event Rates Over Time According to Lesion Progression

	MACEs at 1 Yr			MACEs at 2 Yrs			MACEs at 3 Yrs		
	SLP (n = 20)	Non-SLP (n = 19)	p Value	SLP (n = 33)	Non-SLP (n = 24)	p Value	SLP (n = 43)	Non-SLP (n = 27)	p Value
NC lesion MACEs									
Composite MACEs	20 (45.5%)	19 (67.9%)	0.03	33 (75%)	24 (85.7%)	0.053	43 (97.7%)	27 (96.4%)	0.15
Cardiac death, cardiac arrest, or MI	2 (4.5%)	0 (0%)	0.26	3 (6.9%)	0 (0%)	0.17	6 (14.1%)	0 (0%)	0.053
Cardiac death	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
Cardiac arrest	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
MI	2 (4.5%)	0 (0%)	0.26	3 (6.9%)	0 (0%)	0.17	6 (14.1%)	0 (0%)	0.053
Q-wave MI	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA	2 (4.8%)	0 (0%)	0.29
Non–Q-wave MI	2 (4.5%)	0 (0%)	0.26	3 (6.9%)	0 (0%)	0.17	4 (9.2%)	0 (0%)	0.11
Rehospitalization	18 (40.9%)	19 (67.9%)	0.01	30 (68.2%)	24 (85.7%)	0.02	38 (86.4%)	27 (96.4%)	0.01
Due to unstable angina	6 (13.6%)	4 (14.3%)	0.94	11 (25.3%)	5 (18.2%)	0.53	14 (32.3%)	6 (23.6%)	0.42
Due to increasing angina	12 (27.3%)	16 (57.1%)	0.007	21 (47.7%)	21 (76.2%)	0.005	28 (63.6%)	23 (84.1%)	0.007
Other culprit lesion events									
Revascularization (PCI or CABG)	20 (45.5%)	16 (57.1%)	0.20	22 (75.0%)	20 (71.4%)	0.60	43 (97.7%)	22 (80.4%)	0.50
Due to MI	2 (4.5%)	0 (0%)	0.26	3 (6.9%)	0 (0%)	0.17	6 (14.1%)	0 (0%)	0.053
Due to unstable angina	6 (13.6%)	4 (14.3%)	0.94	11 (25.3%)	4 (14.3%)	0.33	13 (30%)	5 (19.6%)	0.34
Due to increasing angina	12 (27.3%)	13 (46.4%)	0.07	21 (47.7%)	17 (61.3%)	0.14	28 (63.6%)	18 (65.6%)	0.35
Stent thrombosis	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA
Death	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA	0 (0%)	0 (0%)	NA

Values are n (%).
Abbreviations as in Table 4.

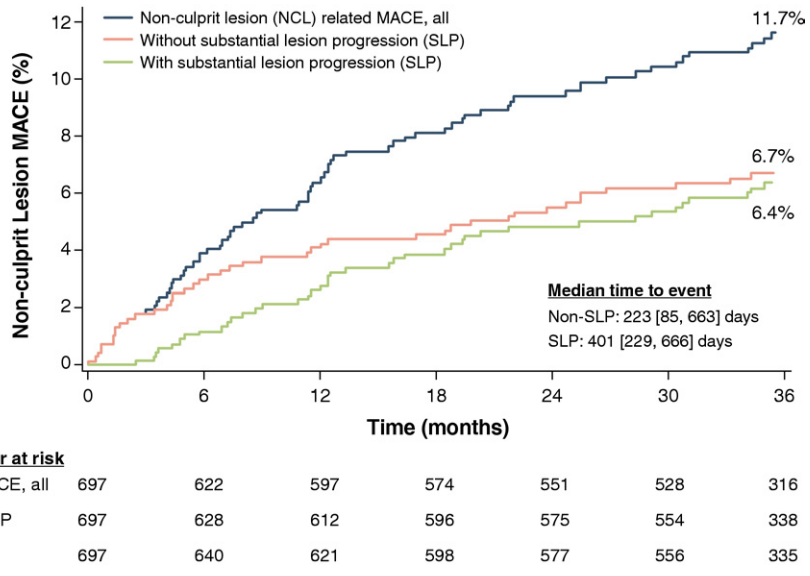

Figure 3. Time-to-Event Curves for NC Lesion–Related MACEs in 697 Patients With Acute Coronary Syndromes

Major adverse cardiac events (MACEs) included cardiac death, cardiac arrest, myocardial infarction, or rehospitalization for unstable or progressive angina. The 3-year cumulative MACE rates are shown (Kaplan-Meier estimates). The 3-year rates were 11.7% for all nonculprit (NC) lesion–related events, 6.4% with substantial lesion progression (SLP), and 6.7% without SLP.

atheromas (40). Second, in the present study, the time to SLP events was longer than the time to non-SLP events, presumably indicating more time for phenotype evolution into a TCFA that most likely then ruptured and thrombosed, causing SLP. Third, in contrast, not all TCFAs lead to events or are even associated with SLP. TCFAs can rupture silently or heal spontaneously without causing events. Finally, not all TCFAs rupture. There are other lesion types responsible for events, such as surface erosions in the absence of cap disruption or unruptured TCFAs with superimposed thrombosis (41).

Study limitations. First, there was no control group of lesions that progressed without causing clinical events. Angiographic follow-up was not performed in asymptomatic patients in PROSPECT, so as not to disturb the natural history of the disease, as has happened in restenosis studies.

Second, the axial resolution of IVUS used in this study was approximately 150 μm, whereas the pathologic definition of TCFA requires a cap thickness $<$65 μm. Nonetheless, the identification of a VH TCFA by radiofrequency IVUS has prognostic value for the site-specific identification of lesions likely to cause future MACEs (11).

Third, IVUS was performed per protocol in the proximal 6 to 8 cm of the coronary tree but infrequently in distal vessels and branches. All 101 angiographic NC MACE-related lesions had baseline angiography, but only 52 arose from lesions in the left main, proximal, or mid left anterior descending or circumflex coronary artery, or proximal to distal right coronary arteries that were imaged at baseline by grayscale IVUS and IVUS-VH.

Fourth, the IVUS catheter may at times have been tightly wedged within the atherosclerotic lesion, precluding accurate assessment of plaque burden or luminal area; this may in part explain the discrepancy between angiographic and IVUS lesion severity. It is unlikely that this would have affected VH phenotype classification, however.

Fifth, there were relatively few MIs, and all deaths were classified as indeterminate given the absence of follow-up angiography. Nonetheless, many of the patients with unstable or progressive angina had clear evidence of angiographic plaque rupture, with the vessel likely remaining patent because of their intense pharmacologic treatment and close clinical follow-up with early treatment.

Sixth, classification of these 2 types of NC lesions occurred only at the end point; the 2 types of NC lesions do not represent types of disease that were identified at baseline.

Finally, IVUS-VH was not routinely performed at follow-up, which might have provided additional insights into plaque compositional evolution.

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CONCLUSIONS

The present study confirms the unpredictable character of disease progression in NC lesions, demonstrating implications related to the type of progression. Approximately 60% of NC events exemplified the classic notion of vulnerable plaque (SLP of angiographically mild lesions), while 40% were at least in part attributable to unrecognized and untreated significant disease with significant but less change in angiographic severity over time. NC lesions that progressed rapidly were more likely to result in severe cardiovascular events, including MI.

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