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INTRACORONARY IMAGING AND NONCULPRIT LESION PROGRESSION

Residual Plaque Burden in Patients With Acute Coronary Syndromes After Successful Percutaneous Coronary Intervention

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OBJECTIVES The aim of this study was to characterize and evaluate the clinical impact of untreated atherosclerotic disease after percutaneous coronary intervention (PCI) in patients with acute coronary syndromes (ACS).

BACKGROUND Residual atherosclerotic disease after successful PCI may predispose future major adverse cardiovascular events (MACE). Compared with intravascular ultrasound (IVUS), angiography underestimates the presence and severity of coronary artery disease.

METHODS Following successful PCI of all clinically significant lesions in 697 patients with ACS, 3-vessel grayscale and radiofrequency IVUS was performed. Lesions were prospectively characterized, and patients were followed for a median of 3.4 years. A total of 3,229 untreated lesions (4.89 ± 1.98 lesions/patient) were identified by IVUS, with mean plaque burden (PB) of 49.6 ± 4.2%.

RESULTS By angiography these nonculprit lesions were mild, with mean diameter stenosis of 38.9 ± 15.3%. At least 1 lesion with a PB ≥70% (PB70 lesion) was found in 220 (33%) patients. By multivariable analysis, a history of prior PCI and angiographic 3-vessel disease were independent predictors of PB70 lesions. Patients with PB70 lesions had greater total percent plaque volume, normalized PB, fibroatheromas, thin-cap fibroatheromas, and normalized volumes of necrotic core and dense calcium. Patients with PB70 lesions had greater 3-year rates of MACE due to untreated nonculprit lesions (20.8% vs. 7.7%, $p < 0.0001$). Among imaged nonculprit lesions, the proportion of PB70 lesions causing MACE was significantly greater than non-PB70 lesions (8.7% vs. 1.0%, $p < 0.0001$).

CONCLUSIONS After successful PCI of all angiographically significant lesions, overall untreated atherosclerotic burden remains high, and PB70 lesions are frequently present in the proximal and mid-coronary tree. Patients with PB70 lesions have greater atherosclerosis throughout the coronary tree, have more thin-cap fibroatheromas, and are at increased risk for future cardiovascular events. (PROSPECT: An Imaging Study in Patients With Unstable Atherosclerotic Lesions; NCT00180466) (J Am Coll Cardiol Img 2012;5:S76–85) © 2012 by the American College of Cardiology Foundation

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In patients presenting with acute myocardial infarction or unstable angina with high-risk features, revascularization with percutaneous coronary intervention (PCI) results in improved long-term survival and reduced future major adverse cardiovascular events (MACE) (1,2). However, despite successful revascularization and implementation of secondary prevention strategies, MACE still occurs in approximately one-quarter of patients with acute coronary syndromes (ACS) within 2 to 3 years (3).

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In asymptomatic patients, estimation of overall plaque burden (PB) by coronary calcium scoring is a significant predictor of future MACE and mortality (4,5). However, the prognostic impact of untreated lesions with high PB following ACS is not fully understood. While coronary angiography remains the predominant imaging modality used to guide revascularization and treatment decisions in ACS, it does not characterize the PB and composition of atherosclerotic plaque (6–9). Intravascular ultrasound (IVUS) imaging provides more detailed information regarding the extent and nature of coronary atherosclerosis, including plaque area, vessel remodeling, lesion length, presence of diffuse plaque, and plaque morphology (8,9). Additional characterization of the arterial wall in atherosclerotic plaques can be derived from analysis of the spectral (frequency) backscatter from IVUS (radiofrequency IVUS), which has been correlated to human histologic samples with high sensitivity and specificity (10). The principal results from the PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study, a multicenter, prospective, natural history study of atherosclerosis in which patients with ACS treated successfully with PCI underwent multimodality coronary imaging, have been previously described (11). The aims of the present study are to further: 1) characterize the extent of untreated coronary atherosclerotic disease present following invasive treatment for ACS; 2) determine the prevalence of coronary segments with significant PB following invasive treatment for ACS; and 3) examine the relationship between untreated coronary segments with significant PB and the risk of future MACE in ACS, on both a per-lesion and per-patient basis.

METHODS

Patients and protocol. To study a uniform cohort at high risk for future events, 697 consecutive patients presenting with ACS (ST-segment elevation myocardial infarction, non–ST-segment elevation myocardial infarction, and unstable angina) were enrolled after successful and uncomplicated PCI of all lesions in the coronary tree responsible for the index event, and after PCI of any other angiographically severe lesions. The detailed inclusion and exclusion criteria have been previously reported (11), methodology described (12), and results presented (13–19).

Coronary angiography was performed after the final PCI, followed by grayscale and radiofrequency IVUS of the left main and proximal 6 to 8 cm of each major epicardial coronary artery using a 20 MHz, 3.2-F sector scanner catheter (intravascular ultrasound–virtual histology [IVUS-VH], Eagle Eye, Volcano Corporation, Rancho Cordova, California). IVUS analysis was performed off-line and not used for procedural guidance. Clinical follow-up was done for at least 3-year follow-up of all patients.

The study was approved by the institutional review board at each participating center, and all patients signed informed, written consent.

ABBREVIATIONS AND ACRONYMS

ACS = acute coronary syndrome(s)
CSA = cross-sectional area
DS = diameter stenosis
EEM = external elastic membrane
IVUS = intravascular ultrasound
IVUS-VH = intravascular ultrasound-virtual histology
MACE = major adverse cardiac events
MLA = minimum lumen area
PB = plaque burden
PCI = percutaneous coronary intervention
TCFA-VH = thin-cap fibroatheroma-virtual histology

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Imaging analysis. All baseline angiograms and IVUS images were prospectively analyzed at independent core laboratories without knowledge of subsequent events. Angiographic qualitative and quantitative measures (quantitative coronary angiography) of the entire length of the coronary tree were made as previously described (11), including each major epicardial coronary artery and every side branch ≥1.5 mm in diameter.

Grayscale and IVUS-VH analysis were performed in the core laboratory analyzing segmental qualitative assessment and quantitative data output. External elastic membrane (EEM) and lumen borders were contoured. Quantitative IVUS measurements, including EEM cross-sectional area (CSA), lumen CSA, plaque and media (EEM minus lumen) CSA, PB (plaque and media divided by EEM CSA) for all recorded frames (each ~0.4 to 0.5 mm in length), and minimal lumen area (MLA) were identified per lesion. Volumetric data were calculated using Simpson's rule and expressed normalized to the length of imaged vessel or lesion.

Lesion analysis. Because physicians reviewing angiograms typically consider discrete mild or intermediate lesions for treatment, we pre-specified lesions visually estimated as having an angiographic percent diameter stenosis (DS) ≥30% for further evaluation. By IVUS analysis, a lesion was defined as a segment with ≥3 consecutive frames with ≥40% PB. By IVUS-VH analysis, lesion phenotype was color-coded and classified as: 1) thin-cap fibroatheroma–virtual histology (TCFA-VH); 2) thick-cap fibroatheroma; 3) pathological intimal thickening; 4) fibrotic plaque; and 5) fibrocalcific plaque using criteria previously described, and reported as CSA and percentages of total plaque area (10). Each grayscale and IVUS-VH frame was coregistered to the angiographic roadmap using fiduciary

Table 1. Characteristics of Patients With and Without PB70 Lesions

	Patients With PB70 Lesions	Patients Without PB70 Lesions	p Value
Age, yrs	58.6 (51.3–68.1)	58.1 (50.5–66.2)	0.24
Male	80.5 (177/220)	75.2 (331/440)	0.13
Diabetes mellitus	20.5 (45/220)	15.6 (68/437)	0.12
White	94.2 (147/156)	92.5 (296/320)	0.49
Height, cm	173.0 (168.0–178.0)	173.0 (165.1–179.0)	0.54
Weight, kg	83.0 (74.4–94.0)	83.0 (73.0–95.3)	0.82
Body mass index, kg/m^2	27.7 (25.4–30.8)	28.1 (25.0–31.4)	0.93
Prior MI	12.8 (47/366)	7.9 (23/290)	0.04
Known CAD, stenosis ≥50%	17.9 (38/212)	11.0 (48/437)	0.01
History of prior PCI	15.1 (33/219)	8.6 (38/440)	0.01
Hypertension	53.0 (115/217)	43.5 (190/437)	0.02
Hypercholesterolemia	51.2 (106/207)	41.6 (164/394)	0.02
Current tobacco use	46.1 (100/217)	48.6 (211/434)	0.54
Clinical presentation			
Recent STEMI (>24 h)	30.5 (67/220)	29.8 (131/440)	0.86
NSTEMI	65.9 (145/220)	66.4 (292/440)	0.91
Unstable angina	3.6 (8/220)	3.9 (17/440)	0.89
Estimated creatinine clearance, ml/min	95.5 (78.0–120.7)	100.3 (76.2–126.9)	0.34
Fasting glucose, mg/dl	102.0 (90.0–121.0)	100.0 (90.0–114.0)	0.26
HbA1c	5.8 (5.4, 6.2)	5.7 (5.3–6.1)	0.14
Metabolic syndrome	53.5 (115/215)	45.6 (193/423)	0.06
More than 1 culprit vessel	30.9 (68/220)	28.0 (123/439)	0.44
HS-CRP	6.50 (2.50–17.00)	8.10 (2.40–19.40)	0.30
Number of diseased epicardial coronary arteries*			
1	20.1 (44/219)	28.7 (123/428)	0.02
2	42.0 (92/219)	44.4 (190/428)	0.56
3	37.9 (83/219)	26.9 (115/428)	0.004
Number of angiographic lesions/patient†	3.00 (1.50–5.00)	2.00 (1.00–3.00)	<0.0001

Values are median (interquartile range) or % (n/N). *Defined as a vessel with any lesion with a visible angiographic diameter stenosis ≥30%. †Lesions with a visible angiographic diameter stenosis ≥30%.

CAD = coronary artery disease; HS-CRP = high-sensitivity C-reactive protein; MI = myocardial infarction; NSTEMI = non–ST-segment elevation myocardial infarction; PB70 = plaque burden ≥70%; PCI = percutaneous coronary intervention; STEMI = ST-segment elevation myocardial infarction.

branch points to align the imaging modality outputs.

Data, endpoints, and definitions. The primary endpoint of the PROSPECT study was MACE, defined as the composite of cardiac death, cardiac arrest, myocardial infarction, or unstable or progressive angina requiring rehospitalization. On the basis of follow-up angiography, MACE were adjudicated as occurring at the initially treated lesion site(s) responsible for the original ACS (the index "culprit" lesions), or at previously untreated coronary segments ("nonculprit" lesions). Events occurring in patients without follow-up angiography were termed "indeterminate" in location. Events were adjudicated by an independent committee blinded to treatment allocation.

Statistical analysis. Categorical variables were summarized using percentages and counts and compared using chi-square tests or Fisher exact test where appropriate. Continuous variables were summarized as median with interquartile range or mean ± 1 SD and compared using the nonparametric Wilcoxon rank sum test. From those variables in Table 1, the independent predictors of lesions with PB ≥70% (PB70 lesions) were determined using stepwise logistic regression with entry/stay criteria of 0.1/0.1. Event rates were estimated by Kaplan-Meier methods and were compared using log-rank tests. The unadjusted hazard ratios for MACE in patients with versus without PB70 lesions were determined from a Cox proportional hazards model. A p value <0.05 was considered statistically significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, North Carolina).

RESULTS

A total of 697 patients with ACS were enrolled at 37 sites in the United States and Europe following successful PCI of all culprit and angiographically significant lesions. The median age was 58.1 years, 24.0% were women, and 17.1% had diabetes mellitus. Median follow-up was 3.4 years. As previously reported, adherence of patients to prescribed dual antiplatelet therapy, lipid-lowering medications, and beta-blockers was high throughout the follow-up period (11).

Overall disease burden. Angiographic multivessel coronary artery was present in 74.2% of patients, and 30.6% had 3-vessel disease. A mean of 207.1 ± 67.5 mm of the coronary tree was analyzed by IVUS in 660 patients. IVUS imaging identified 3,229 lesions (mean 4.89 ± 1.98 lesions/patient) in the proximal-mid coronary tree. The mean PB was 49.6 ± 4.2%; 288 (8.9%) of the IVUS lesions were PB70 lesions. By angiography these lesions were mild, with mean DS 38.9 ± 15.3%. By IVUS-VH, a total of 1,736 fibroatheromas (mean 2.85 ± 1.91 per patient), including 639 TCFA-VH (mean 1.05 ± 1.37 per patient) and 1,097 thick-cap fibroatheromas (mean 1.79 ± 1.48 per patient), were identified. In the entire cohort, the proportion of total plaque characterized as necrotic core and dense calcium was 13.1% and 6.6%, respectively, while 59.1% was fibrotic tissue and 21.2% was fibrofatty.

Patients with PB70 lesions. At least 1 PB70 lesion was present in 220 patients (33.0%). PB70 lesions were mild by quantitative coronary angiography (mean DS 39.2 ± 14.8%). Characteristics of patients with versus without PB70 lesions are summarized in Table 1. By multivariable analysis, a history of prior PCI and angiographic 3-vessel disease were independent predictors of the occurrence of ≥1 PB70 lesion by IVUS; metabolic syndrome was a borderline predictor (Table 2). By grayscale IVUS analysis, patients with PB70 lesions had a greater number of IVUS lesions, and were more likely to have at least 1 echolucent plaque or ruptured plaque (Table 3). Overall disease burden was greater in patients with PB70 lesions, as measured by overall percentage plaque volume and normalized PB. By IVUS-VH analysis, patients with PB70 lesions had more fibroatheromas, more TCFA-VH, and greater normalized volumes of necrotic core and dense calcium. Even after excluding the individual PB70 lesions from the analysis, the overall percentage PB, and normalized volumes of necrotic core and dense calcium, remained significantly greater in patients with compared with those without PB70 lesions (Table 4).

Clinical outcomes. Table 5 summarizes the clinical outcomes in patients with and without PB70 lesions at 3-year follow-up. Overall MACE and MACE

Table 2. Independent Predictors of Lesions With Plaque Burden ≥70%

Variable	OR (95% CI)	p Value
History of PCI	1.79 (1.07–2.99)	0.03
3-vessel disease*	1.77 (1.24–2.52)	0.002
Metabolic syndrome	1.35 (0.96–1.88)	0.08

*Defined as the presence of a lesion with visual angiographic diameter stenosis ≥30% in all 3 major epicardial coronary vessels.
CI = confidence interval; OR = odds ratio; PCI = percutaneous coronary intervention.

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Table 3. Grayscale and IVUS-VH Findings in Patients With Versus Without PB70 Lesions

	Patients With PB70 Lesions	Patients Without PB70 Lesions	p Value
Imaged nonculprit segments, mm	169.52 (136.76–211.04)	174.00 (132.45–216.61)	0.76
IVUS lesions/patient	5.33 ± 1.82 (220)	4.67 ± 2.03 (440)	0.0001
≥1 echolucent plaque	29.5 (65/220)	10.2 (45/440)	<0.0001
≥1 plaque rupture	21.4 (47/220)	10.5 (46/440)	0.0001
Total nonculprit lesion length, mm	91.87 (69.20–121.01)	60.66 (37.24–93.04)	<0.0001
Total plaque volume, %	52.1 (49.7–55.1)	47.9 (45.8–50.1)	<0.0001
Mean EEM CSA, mm^3/mm	16.08 (13.88–18.79)	16.13 (13.86–18.49)	0.83
Mean lumen CSA, mm^3/mm	7.44 (6.54–8.92)	8.35 (7.08–9.62)	<0.0001
Mean plaque + media CSA, mm^3/mm	8.41 (7.10–10.10)	7.78 (6.56–8.99)	<0.0001
≥1 lesion with MLA ≤4.0 mm^2	76.8 (169/220)	44.8 (197/440)	<0.0001
TCFA-VH lesions/patient	1.24 ± 1.42 (202)	0.96 ± 1.34 (407)	0.005
ThCFA lesions/patient	2.04 ± 1.49 (202)	1.67 ± 1.45 (407)	0.002
Fibroatheromas/patient	3.28 ± 1.89 (202)	2.63 ± 1.89 (407)	<0.0001
PIT lesions/patient	1.61 ± 1.72 (202)	1.76 ± 1.69 (407)	0.17
Fibrocalcific lesions/patient	0.06 ± 0.27 (202)	0.05 ± 0.23 (407)	0.50
Patients with ≥1 TCFA	61.4 (124/202)	50.1 (204/407)	0.009
Mean necrotic core CSA, mm^3/mm	0.66 (0.39–1.00)	0.46 (0.26–0.69)	<0.0001
Mean dense calcium CSA, mm^3/mm	0.28 (0.15–0.49)	0.19 (0.10–0.35)	<0.0001
Mean fibrous tissue CSA, mm^3/mm	2.90 (2.21–3.65)	2.40 (1.81–3.05)	<0.0001
Mean fibrofatty CSA, mm^3/mm	0.89 (0.62–1.38)	0.82 (0.50–1.20)	0.03
Necrotic core volume, %	14.1 (8.7–18.2)	11.6 (7.0–17.1)	0.003
Dense calcium volume, %	5.9 (3.3–9.5)	4.7 (2.5–8.6)	0.006
Fibrous tissue volume, %	59.6 (55.3–62.7)	59.9 (55.1–64.4)	0.32
Fibrofatty volume, %	18.4 (13.6–25.1)	20.9 (15.3–27.4)	0.01

Values are median (interquartile range), mean ± SD (n), or % (n/N).
CSA = cross-sectional area; EEM = external elastic membrane; IVUS-VH = intravascular ultrasound-virtual histology; MLA = minimum lumen area; PB70 = plaque burden ≥70%; PIT = pathologic intimal thickening; TCFA-VH = thin-cap fibroatheroma-virtual histology; ThCFA = thick-cap fibroatheroma.

arising from nonculprit lesions were greater in patients with PB70 lesions, primarily due to increased rates of revascularization and rehospitalization for increasing angina (Fig. 1). Patients with only 1 PB70 lesion had similar 3-year MACE rates compared with patients with ≥2 PB70 lesions (26.7% vs. 29.7%, p = 0.68). In the overall cohort, 106 nonculprit lesions were responsible for clinical events during the follow-up period. Of the 54 nonculprit MACE-related lesions in which base-

Table 4. Grayscale and IVUS-VH Findings in Patients With Versus Without PB70 Lesions, Excluding the Lesions With PB70

	Patients with PB70 lesions	Patients without PB70 lesions	p Value
Total plaque volume, %	48.3 (44.9–52.0)	46.6 (43.5–50.3)	<0.0001
Mean EEM CSA, mm^3/mm	15.08 (11.29–19.01)	15.47 (11.84–19.86)	0.02
Mean lumen CSA, mm^3/mm	7.69 (5.75–9.83)	8.02 (6.21–10.60)	0.0001
Mean plaque + media CSA, mm^3/mm	7.24 (5.46–9.36)	7.26 (5.44–9.39)	0.72
Mean necrotic core CSA, mm^3/mm	0.42 (0.21–0.77)	0.36 (0.18–0.68)	0.002
Mean dense calcium CSA, mm^3/mm	0.18 (0.07–0.38)	0.14 (0.05–0.31)	0.0004
Mean fibrous tissue CSA, mm^3/mm	2.21 (1.45–3.42)	2.23 (1.39–3.25)	0.44
Mean fibrofatty CSA, mm^3/mm	0.70 (0.36–1.28)	0.73 (0.34–1.30)	0.83
% Necrotic core volume	12.0 (6.4–19.3)	10.9 (5.4–17.6)	0.004
% Dense calcium volume	4.9 (2.0–9.5)	4.0 (1.7–8.3)	0.002
% Fibrous tissue volume	59.8 (53.8–65.4)	60.6 (54.1–66.1)	0.05
% Fibrofatty volume	18.3 (11.9–27.1)	19.5 (12.4–28.6)	0.04

Values are median (interquartile range).
IVUS-VH = intravascular ultrasound–virtual histology; other abbreviations as in Table 3.

Table 5. Three-Year Clinical Outcomes of Patients With Versus Without PB70 Lesions

	Patients With PB70 Lesions	Patients Without PB70 Lesions	HR (95% CI)	p Value
Composite MACE	29.1 (60)	16.7 (68)	1.87 (1.32–2.65)	0.0003
Death	2.4 (5)	3.7 (15)	0.66 (0.24–1.82)	0.42
Cardiac death	1.9 (4)	1.5 (6)	1.33 (0.38–4.71)	0.66
Cardiac arrest	1.0 (2)	0.2 (1)	3.99 (0.36–43.99)	0.22
Myocardial infarction	4.5 (9)	3.0 (12)	1.50 (0.63–3.55)	0.36
Rehospitalization	26.5 (54)	14.0 (57)	2.00 (1.38–2.91)	0.0002
For unstable angina	11.0 (22)	6.9 (28)	1.57 (0.90–2.74)	0.11
For progressive angina	23.6 (48)	10.6 (43)	2.38 (1.58–3.59)	<0.0001
Revascularization	26.0 (53)	13.8 (56)	1.99 (1.37–2.90)	0.0002
Stent thrombosis (ARC definite/probable)	4.3 (9)	2.5 (10)	1.80 (0.73–4.44)	0.19
Nonculprit lesion–related MACE	20.8 (42)	7.7 (31)	2.85 (1.79–4.53)	<0.0001
Death	0.0 (0)	0.0 (0)	N/A	N/A
Cardiac arrest	0.0 (0)	0.0 (0)	N/A	N/A
Myocardial infarction	1.6 (3)	0.8 (3)	1.96 (0.40–9.73)	0.40
Rehospitalization	19.3 (39)	7.2 (29)	2.81 (1.74–4.54)	<0.0001
For unstable angina	3.5 (7)	3.5 (14)	0.98 (0.40–2.44)	0.97
For progressive angina	17.8 (36)	4.2 (17)	4.49 (2.52–7.99)	<0.0001
Revascularization	18.8 (38)	7.2 (29)	2.74 (1.69–4.44)	<0.0001

Values are % (n).
ARC = Academic Research Consortium; CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac events; N/A = not applicable; PB70 = plaque burden ≥70%.

line IVUS imaging data were available, 25 (46%) were PB70 lesions, and the proportion of PB70 lesions causing subsequent MACE was significantly greater than the proportion of non-PB70 lesions responsible for MACE (8.7% vs. 1.0%, $p < 0.0001$).

Correlates and influence of the degree of plaque burden. To further characterize the features and prognostic impact of individual lesions according to PB, we grouped the 3,229 nonculprit lesions prospectively identified by IVUS into 4 groups according to their maximum percent PB; those with maximum PB

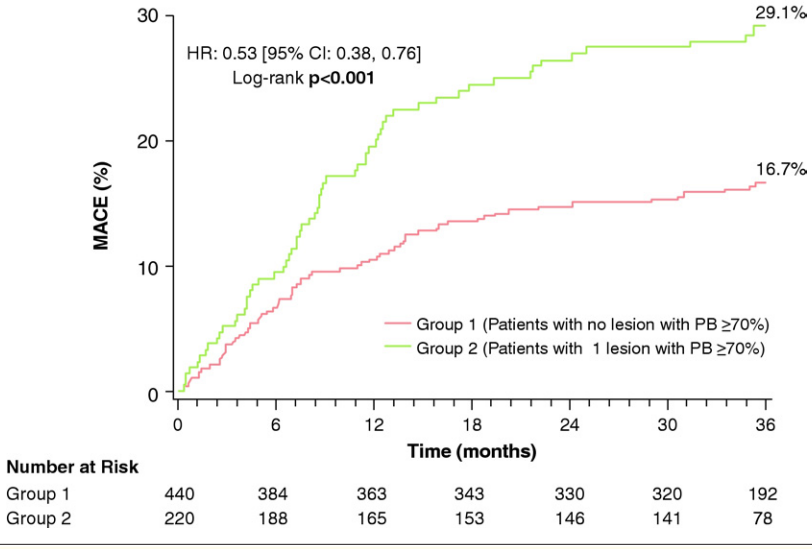

Figure 1. MACE During Follow-Up

Major adverse cardiac events (MACE) in patients with lesions with plaque burden (PB) ≥70% compared with those without lesions with PB ≥70%. CI = confidence interval; HR = hazard ratio.

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≤50% (median average PB over the nonculprit lesion 42.9%, n = 904), maximum PB of 50% to 60% (median average PB 47.5%, n = 1,239), maximum PB of 60% to 70% (median average PB 52.3%, n = 798), and maximum PB ≥70% (median average PB 57.4%, n = 288). Lesions with greater maximum PB were significantly longer, had greater total plaque volume, smaller MLA, were more likely echolucent and/or ruptured plaques, had greater amounts of necrotic core, and were more likely to be fibroatheromas (Table 6). As seen in Figure 2, the per-lesion event rate during the median 3.4-year follow-up period increased exponentially with increasing maximum PB.

DISCUSSION

The PROSPECT study is the first prospective, natural history study of atherosclerosis using multimodality intracoronary imaging to characterize the coronary tree following high-risk ACS (11). In this analysis, IVUS imaging demonstrated that despite treating all lesions believed to be angiographically significant with PCI, the overall remaining untreated atherosclerotic burden was significant, with an average of nearly 5 lesions per patient identified in the proximal mid coronary tree alone. Mean plaque volume of these lesions was nearly 50% of the EEM volume, with a significant proportion of the plaque characterized by IVUS-VH as necrotic core or dense calcium. At least 1 PB70 lesion was found in one-third of all patients. On a per-lesion basis, lesions with greater PB also had other numerous high-risk characteristics, including longer length and smaller MLA, were more likely to contain angiographically silent greater plaque ruptures, and had greater amounts of necrotic core. Patients with a history of prior PCI or visible angiographic lesions in all 3 coronary vessels, factors reflecting more exten-

Table 6. Grayscale and IVUS-VH Findings in 3,229 Individual Lesions According to the Maximum Severity of PB

	PB ≤50% (n = 904)	PB 50%–60% (n = 1,239)	PB 60%–70% (n = 798)	PB ≥70% (n = 288)	p Value Trend
Grayscale lesion length and volumetric data					
Lesion length, mm	6.01 (3.52–10.95)	10.87 (6.05–18.55)	16.73 (9.72–28.81)	26.98 (17.26–39.62)	<0.0001
Total EEM volume, mm^3	90.87 (48.38–172.29)	159.87 (83.95–313.52)	251.94 (136.86–454.61)	450.46 (258.48–692.57)	<0.0001
Total plaque + media volume, mm^3	38.74 (20.83–73.66)	76.08 (39.50–150.00)	133.45 (71.32–238.67)	261.32 (149.28–394.08)	<0.0001
Mean plaque volume, %	42.9 (41.3–44.7)	47.5 (45.3–49.9)	52.3 (49.6–55.1)	57.4 (53.4–60.7)	<0.0001
Mean EEM CSA, mm^3/mm	15.62 (11.20–19.91)	15.12 (11.41–19.86)	15.54 (12.29–19.01)	16.53 (13.51–20.42)	0.0004
Mean lumen CSA, mm^3/mm	8.81 (6.43–11.34)	7.84 (5.89–10.50)	7.33 (5.81–9.07)	6.95 (5.88–8.70)	<0.0001
Mean plaque + media CSA, mm^3/mm	6.64 (4.81–8.56)	7.17 (5.46–9.37)	8.18 (6.27–10.25)	9.51 (7.40–11.96)	<0.0001
MLA site data					
MLA, mm^2	7.57 (5.48–10.05)	6.14 (4.39–8.23)	5.01 (3.91–6.28)	4.14 (3.32–5.05)	<0.0001
Plaque burden, %	46.0 (43.6–48.1)	54.8 (52.4–57.4)	64.1 (62.1–66.6)	73.2 (71.2–75.4)	<0.0001
MLA site data					
Echolucent plaque	0.3 (3/904)	2.0 (25/1,239)	6.6 (53/798)	18.1 (52/288)	<0.0001
Plaque rupture	0.2 (2/904)	2.3 (28/1,239)	4.6 (37/798)	13.2 (38/288)	<0.0001
Remodeling index	0.94 (0.86–0.98)	0.93 (0.84–1.00)	0.93 (0.83–1.01)	0.96 (0.85–1.07)	<0.0001
Volumetric IVUS-VH data, %					
Mean necrotic core volume	9.9 (5.0–16.1)	11.4 (5.7–18.5)	13.0 (7.3–20.1)	13.6 (8.5–20.2)	<0.0001
Mean dense calcium volume	3.4 (1.1–7.2)	4.2 (1.8–8.5)	5.6 (2.4–9.9)	6.0 (2.9–10.0)	<0.0001
Mean fibrous tissue volume	61.4 (54.3–67.0)	60.6 (54.2–65.9)	59.1 (53.6–64.4)	59.2 (53.6–64.4)	<0.0001
Mean fibrofatty volume	20.5 (13.0–30.1)	18.7 (11.9–28.1)	18.1 (11.9–26.6)	17.5 (11.4–24.9)	0.0002
VH lesion classification					
Fibroatheroma	43.0 (348/810)	58.7 (656/1117)	74.1 (519/700)	83.0 (210/253)	<0.0001
Thin cap	15.7 (127/810)	20.1 (224/1117)	30.9 (216/700)	29.6 (75/253)	<0.0001
Thick cap	27.3 (221/810)	38.7 (432/1117)	43.3 (303/700)	53.4 (135/253)	<0.0001
PIT	52.1 (422/810)	37.3 (417/1117)	23.4 (164/700)	15.4 (39/253)	<0.0001
Fibrotic	3.3 (27/810)	3.0 (34/1117)	1.1 (8/700)	1.2 (3/253)	0.01
Fibrocalcific	1.6 (13/810)	0.9 (10/1117)	1.3 (9/700)	0.4 (1/253)	0.32

Values are median (interquartile range) or % (n/N).
CSA = cross sectional area; EEM = external elastic membrane; MLA = minimum lumen area; PB70 = plaque burden; PIT = pathologic intimal thickening; TCFA-VH = thin-cap fibroatheroma-virtual histology; ThCFA = thick-cap fibroatheroma.

sive coronary artery disease, were more likely to have PB70 lesions. Patients with compared with those without PB70 lesions had greater overall atherosclerosis and necrotic core, both in the PB70 lesions themselves and at other sites in the coronary tree.

On a per-lesion level, the MACE rate during median follow-up of 3.4 years rose exponentially with increasing PB. On a patient level, patients with PB70 lesions had nearly a 2-fold increase in 3-year MACE compared with patients without PB70 lesions, primarily driven by increased rates of rehospitalization and revascularization events arising from nonculprit lesions. More than two-thirds of future clinical events in patients with PB70 lesions arose from nonculprit lesions, compared with less than one-half of the events in patients without a PB70 lesion (in whom a greater proportion of events arose from recurrent disease at originally treated culprit lesions). This observation is consistent with the imaging findings of increased atherosclerosis and greater necrotic core in patients with PB70 lesions (as well as in the PB70 lesions themselves). Interestingly, the presence of only 1 PB70 lesion conferred a similar increased risk of adverse events as when multiple PB70 lesions per patient were present. Moreover, a high proportion of clinical events at follow-up attributed to imaged nonculprit lesions were caused by PB70 lesions, consistent with their increased lesion-specific risk. However, even when the 25 events arising from imaged PB70 lesions were excluded, the rate of nonculprit MACE remained numerically greater in patients with compared to those without PB70 lesions, reflecting the increased patient-level risk. Moreover, while the concomitant presence of smaller MLA and greater necrotic core no doubt contributed to the increased lesion-specific risk in PB70 lesions, the percent PB was found to be the strongest multivariable predictor of future lesion-specific MACE (11).

As previously reported, most of the events at follow-up were rehospitalizations for unstable or progressive angina (11). Because fractional flow reserve was not routinely performed during the PROSPECT study, it is unknown what proportion of PB70 lesions were ischemia-producing at the time of initial imaging. However, <50% of the PB70 lesions had an MLA <4.0 mm^2, and only 4.9% had an MLA ≤2.4 mm^2. In this regard initial studies that associated a MLA <4.0 mm^2 with ischemia (20,21) have come into question given poor specificity of this measure. Recently, Kang et al. reported that an MLA ≥2.4 mm^2 has high accuracy for excluding angiographically intermediate lesions with ischemic potential (22). Given the greater presence of necrotic core in PB70 lesions, it is possible that they may be more likely to rapidly progress and rupture (23), regardless of their ischemic potential at the time of the initial imaging.

Noninvasive assessment using coronary calcium scoring and computed tomographic coronary angiography has shown a consistent association with

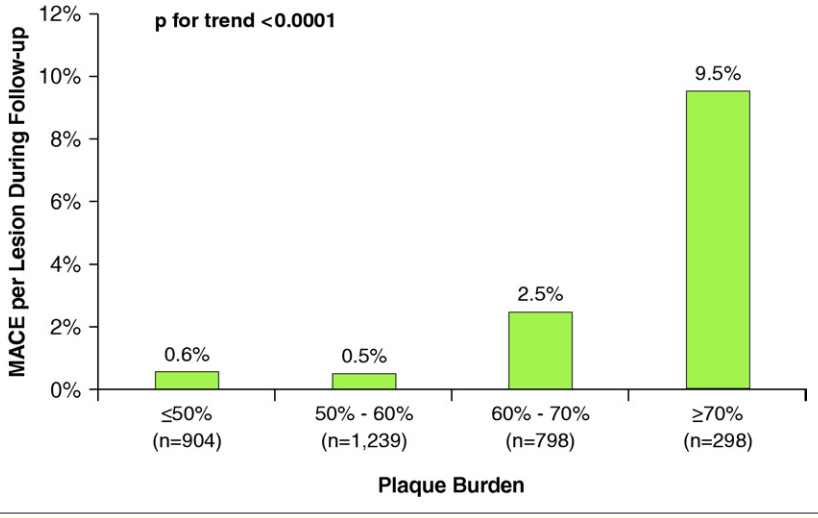

Figure 2. MACE per Lesion During Follow-Up

Major adverse cardiac events (MACE) per lesion during a median follow-up of 3.4 years according to the maximum degree of plaque burden.

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overall disease burden and the risk of future cardiovascular events (4,5,24,25). These studies generally measured disease burden by calcium scores (4,5) or by the number of epicardial vessels with obstructive lesions (24,25). The present study extends this evidence by correlating clinical outcomes with detailed measurements of overall coronary atherosclerosis and plaque characteristics using IVUS analysis. On the basis of these data, patients with substantial residual atherosclerosis found on invasive imaging after PCI should be considered at particularly high risk for future events (especially when PB70 lesions are present).

Study limitations. As post-hoc analysis, the results of the present study should be considered exploratory and hypothesis-generating. A requirement for study enrollment was the ability to perform IVUS imaging of the proximal 6 to 8 cm of all major epicardial vessels. Thus, patients with chronically occluded or diffusely diseased vessels were not included in this analysis. Angiographic follow-up was performed only in patients with clinical events necessitating repeat angiography; thus, data regarding progression of atherosclerotic disease were limited to these patients. Approximately one-half of nonculprit lesion–related MACE arose from lesions distal in the coronary tree that were not imaged by IVUS-VH. Most of these lesions supply a smaller amount of myocardium, however, and thus are likely to be of less clinical relevance than the lesions successfully imaged. Nonetheless, IVUS-VH data were available at baseline from only approximately one-half of the nonculprit lesions from which unanticipated future events arose, and the findings from the present report therefore apply principally to the proximal and mid coronary tree. The accuracy of coregistering the angiographic and IVUS frames using fiduciary side branches has inherent limitations given angiographic foreshortening, nonconstant IVUS pullback speed, and different image slice widths. Nonetheless, the technique as applied in the PROSPECT study appears to provide clinical utility. Finally, while the nature of the underlying atherosclerosis in patients with PB70 lesions is consistent with the role of systemic inflammation in the pathogenesis and progression of coronary artery disease, the present study did not specifically assess measures of inflammation, such as serum biomarkers or local evidence of macrophage or T-cell infiltration.

CONCLUSIONS

A large amount of untreated coronary atherosclerosis remains in patients following successful PCI for high-risk ACS. Untreated lesions are characterized by a large overall plaque volume, significant amounts of necrotic core and dense calcium, and a high proportion of fibroatheromas. Patients with at least 1 PB70 lesion are at especially high risk of future MACE arising not only from these severe lesions, but also at sites of lesser PB, possibly reflecting the systemic inflammatory nature of ACS. The high rate of future events in these patients was evident despite close clinical monitoring and adherence to evidence-based medical therapies. Further studies are warranted to determine the appropriate management strategies for patients with severe residual atherosclerosis after successful PCI in ACS.

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