ORIGINAL ARTICLE

A Prospective Natural-History Study of Coronary Atherosclerosis

Gregg W. Stone, M.D., Akiko Maehara, M.D., Alexandra J. Lansky, M.D., Bernard de Bruyne, M.D., Ecaterina Cristea, M.D., Gary S. Mintz, M.D., Roxana Mehran, M.D., John McPherson, M.D., Naim Farhat, M.D., Steven P. Marso, M.D., Helen Parise, Sc.D., Barry Templin, M.B.A., Roseann White, M.A., Zhen Zhang, Ph.D., and Patrick W. Serruys, M.D., Ph.D., for the PROSPECT Investigators*

ABSTRACT

BACKGROUND

Atherosclerotic plaques that lead to acute coronary syndromes often occur at sites of angiographically mild coronary-artery stenosis. Lesion-related risk factors for such events are poorly understood.

METHODS

In a prospective study, 697 patients with acute coronary syndromes underwent three-vessel coronary angiography and gray-scale and radiofrequency intravascular ultrasonographic imaging after percutaneous coronary intervention. Subsequent major adverse cardiovascular events (death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina) were adjudicated to be related to either originally treated (culprit) lesions or untreated (nonculprit) lesions. The median follow-up period was 3.4 years.

RESULTS

The 3-year cumulative rate of major adverse cardiovascular events was 20.4%. Events were adjudicated to be related to culprit lesions in 12.9% of patients and to nonculprit lesions in 11.6%. Most nonculprit lesions responsible for follow-up events were angiographically mild at baseline (mean [±SD] diameter stenosis, 32.3±20.6%). However, on multivariate analysis, nonculprit lesions associated with recurrent events were more likely than those not associated with recurrent events to be characterized by a plaque burden of 70% or greater (hazard ratio, 5.03; 95% confidence interval [CI], 2.51 to 10.11; P<0.001) or a minimal luminal area of 4.0 mm^2 or less (hazard ratio, 3.21; 95% CI, 1.61 to 6.42; P=0.001) or to be classified on the basis of radiofrequency intravascular ultrasonography as thin-cap fibroatheromas (hazard ratio, 3.35; 95% CI, 1.77 to 6.36; P<0.001).

CONCLUSIONS

In patients who presented with an acute coronary syndrome and underwent percutaneous coronary intervention, major adverse cardiovascular events occurring during follow-up were equally attributable to recurrence at the site of culprit lesions and to nonculprit lesions. Although nonculprit lesions that were responsible for unanticipated events were frequently angiographically mild, most were thin-cap fibroatheromas or were characterized by a large plaque burden, a small luminal area, or some combination of these characteristics, as determined by gray-scale and radiofrequency intravascular ultrasonography. (Funded by Abbott Vascular and Volcano; ClinicalTrials.gov number, NCT00180466.)

From Columbia University Medical Center/New York–Presbyterian Hospital and the Cardiovascular Research Foundation, New York (G.W.S., A.M., A.J.L., E.C., G.S.M., R.M., H.P.); Cardiovascular Center, Onze-Lieve-Vrouwziekenhuis, Aalst, Belgium (B.B.); Vanderbilt University Medical Center, Nashville (J.M.); North Ohio Heart Center/Elyria Memorial Hospital Regional Medical Center, Elyria, OH (N.F.); Mid America Heart Institute, St. Luke's Hospital, Kansas City, MO (S.P.M.); Abbott Vascular, Santa Clara, CA (B.T., R.W., Z.Z.); and Erasmus University, Thoraxcentrum, Rotterdam, the Netherlands (P.W.S.). Address reprint requests to Dr. Stone at the Columbia University Medical Center, Cardiovascular Research Foundation, 111 E. 59th St., 11th Fl., New York, NY 10022, or at gs2184@columbia.edu.

*The investigators, institutions, and research organizations participating in the Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) investigation are listed in the Supplementary Appendix, available at NEJM.org.

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Approximately 1,350,000 Americans annually have an acute coronary syndrome (unstable angina or myocardial infarction with or without ST-segment elevation).[1] Although percutaneous coronary intervention and pharmacologic therapies have improved the prognosis for such patients,[1-4] recurrent major adverse cardiovascular events occur in a substantial proportion of cases.

Recurrent cardiac ischemic events can be due to recurrence at the original treatment site, the presence of untreated lesions elsewhere, or progressive lesions. However, prospective, systematic data on the origin of recurrent events are lacking. Moreover, retrospective studies have shown that most atherosclerotic plaques responsible for future acute coronary syndromes are angiographically mild,[5,6] and the lesion-related risk factors for major adverse cardiovascular events are poorly understood. Pathological studies have shown that thrombotic coronary occlusion after rupture of a lipid-rich atheroma with only a thin fibrous layer of intimal tissue covering the necrotic core (a thin-cap fibroatheroma) is the most common cause of myocardial infarction and death from cardiac causes.[7-9] However, the prospective identification of thin-cap fibroatheromas has not been achieved, in part because the imaging tools to identify them in vivo did not exist until recently.

We therefore performed a prospective, multicenter study of the natural history of coronary atherosclerosis, using multimodality intravascular imaging to identify the clinical and lesion-related factors that place patients at risk for adverse cardiac events.

Methods

Study Design

The Providing Regional Observations to Study Predictors of Events in the Coronary Tree (PROSPECT) study was conducted at 37 sites in the United States and Europe. The study was designed by the principal investigator and the sponsor, Abbott Vascular, and was funded by Abbott Vascular and Volcano. The sponsor participated in site selection and management and in data collection and analysis (see the Supplementary Appendix, available with the full text of this article at NEJM.org). The principal investigator had unrestricted access to the data, maintained the database, prepared all drafts of the manuscript, made the decision to submit the manuscript for publication, and vouches for the integrity of the study. The study was approved by the institutional review board at each participating center.

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Study Patients and Protocol

Patients with acute coronary syndromes were enrolled after undergoing successful and uncomplicated percutaneous coronary intervention for the treatment of all coronary lesions believed to be responsible for the index event and after the completion of any other planned interventions. Detailed inclusion and exclusion criteria are listed in Table 1 in the Supplementary Appendix. All patients provided written informed consent. The study was conducted in accordance with the protocol, which is available at NEJM.org.

Angiography was performed, followed by both gray-scale and radiofrequency intravascular ultrasonography of the left main coronary artery and the proximal 6 to 8 cm of each of the major epicardial coronary arteries, with the use of a synthetic-aperture-array, 20-MHz, 3.2-French catheter (Eagle Eye, In-Vision Gold, Volcano) with motorized catheter pullback (0.5 mm per second). In contrast to conventional gray-scale intravascular ultrasonography, radiofrequency intravascular ultrasonography uses spectral (frequency) analysis as well as amplitude data from the intravascular ultrasonographic signal, providing information about tissue composition that has been correlated with data from histologic samples.[10,11] The analysis was performed offline and was not used for procedural guidance. Levels of serum creatinine, fasting lipids, glucose, glycated hemoglobin, and high-sensitivity C-reactive protein were measured at baseline. Medication use after discharge was according to local standards. Clinical follow-up occurred at 30 days, at 6 months, and then yearly for at least 2 years.

Imaging Analysis

All baseline angiograms and intravascular ultrasonographic images were prospectively analyzed at independent core laboratories by means of prespecified methods,[12,13] without knowledge of subsequent events. Angiographic qualitative and quantitative measurements[12] were obtained for the entire length of the coronary tree, including each epicardial vessel and side branch that was at least 1.5 mm in diameter, with the use of proprietary methods modified from Medis CMS software, version 7.0 (Leiden, the Netherlands), which were

validated in 78 randomly selected coronary segments. For each 1.5 mm of vessel, we recorded the reference diameter, minimal luminal diameter, and diameter stenosis (the percentage of cross-sectional diameter lost to stenosis). Analysis of all angiographic lesions with at least 30% visible diameter stenosis was also prespecified.

Offline gray-scale and radiofrequency intravascular ultrasonographic analyses were performed in the core laboratory with the use of QCU-CMS software (Medis) for contouring, pcVH 2.1 software (Volcano) for contouring and data output, and proprietary qVH software (Cardiovascular Research Foundation) for segmental qualitative assessment and quantitative data output. External-elastic-membrane and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). Quantitative intravascular ultrasonographic measurements included the cross-sectional areas of the external elastic membrane, the lumen, and the plaque and media (cross-sectional area of the external elastic membrane minus that of the lumen), plaque burden (plaque-and-media cross-sectional area divided by external-elastic-membrane cross-sectional area), and minimal luminal area. On the basis of radiofrequency intravascular ultrasonography, plaque components were identified as dense calcium, necrotic core, fibrofatty tissue, or fibrous tissue, with the cross-sectional area and percentage of total plaque area reported for each component.[10]

A lesion on intravascular ultrasonographic imaging was defined as at least three consecutive frames with a plaque burden of at least 40%. Such lesions were classified by means of radiofrequency analysis as one of the following: thin-cap fibroatheroma, thick-cap fibroatheroma, pathologic intimal thickening, fibrotic plaque, or fibrocalcific plaque (Fig. 1 in the Supplementary Appendix).[13] Each gray-scale and radiofrequency intravascular ultrasonographic frame was coregistered with the corresponding frame from the angiographic roadmap with the use of side branches for alignment.

DATA, END POINTS, AND DEFINITIONS

Independent study monitors verified all data on case-report forms. The prespecified primary end point was the incidence of major adverse cardiovascular events (the composite of death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization due to unstable or progressive angina according to the Braunwald Unstable Angina Classification and the Canadian Cardiovascular Society Angina Classification). The primary end point was adjudicated by a clinical events committee that had no knowledge of other patient data and that used original source documents. On the basis of follow-up angiography, major adverse cardiovascular events were further adjudicated as occurring at initially treated sites (culprit lesions) or at previously untreated coronary segments (nonculprit lesions). If follow-up angiography was not performed, the site associated with the event was classified as indeterminate. An example of plaque characterization from an event related to a nonculprit lesion is shown in Figure 2 in the Supplementary Appendix.

STATISTICAL ANALYSIS

Sample size was calculated to provide adequate power to identify variables associated with nonculprit-lesion–related major adverse cardiovascular events on the basis of a range of assumptions about the frequency of high-risk characteristics, their predictive accuracy, the overall rate of such events, and the hazard ratio for the risk factor. For example, if 71% of patients had a high-risk variable with 85% sensitivity and 85% specificity, 700 patients would be needed to provide 83% and 99% power to detect a hazard ratio of 3.0 for nonculprit-lesion–related rates of major adverse cardiovascular events of 5% and 10%, respectively, with a one-sided alpha of 0.025.

Time-to-event data are presented as Kaplan–Meier estimates. Baseline variables that were considered clinically relevant or that showed a univariate relationship with outcome were entered into multivariate Cox proportional-hazards regression models. Variables for inclusion were carefully chosen, given the number of events available, to ensure parsimony of the final models.[14] Lesion-level multivariate models were adjusted for patient effects by means of the marginal Cox model,[15] and nonsignificant variables were dropped by means of backward selection. Statistical analyses were performed with the use of SAS software, version 9.1.3 (SAS Institute).

RESULTS

PATIENTS

Between October 29, 2004, and June 8, 2006, a total of 697 patients with acute coronary syn-

dromes were enrolled after they had undergone successful percutaneous coronary intervention (Table 1). The median age was 58.1 years, 24.0% were women, and 17.1% had diabetes mellitus. The median follow-up was 3.4 years. The rate of use of antiplatelet, lipid-lowering, and other medications was high throughout the follow-up period (Table 2 in the Supplementary Appendix).

BASELINE IMAGING

Angiographic images, gray-scale intravascular ultrasonographic images, and radiofrequency intravascular ultrasonographic images from the index procedures could be evaluated in 697 (100%), 673 (96.6%), and 623 (89.4%) of the patients, respectively. Intravascular ultrasonographic imaging was restricted to the proximal and middle portions of the coronary arteries, where the vessel diameter was sufficient to accommodate the imaging catheters (Table 3 in the Supplementary Appendix).

The frequency of residual disease after percutaneous coronary intervention varied substantially depending on the imaging technique. On angiography, 1814 untreated lesions (i.e., those with a visually ascertained diameter stenosis of at least 30%) were identified in the entire coronary vasculature, including 110 with a diameter stenosis of at least 50% and 12 with a diameter stenosis of at least 70%. Gray-scale intravascular ultrasonography identified 3160 lesions in the proximal-to-middle segments of the three major epicardial coronary arteries in 673 patients, including 620 lesions with a minimal luminal area of 4.0 mm^2 or less and 283 lesions with a plaque burden of at least 70%. On the basis of radiofrequency intravascular ultrasonography, most lesions were classified as pathologic intimal thickening or fibroatheromas (Table 4 in the Supplementary Appendix); 596 thin-cap fibroatheromas were identified in 313 of 623 patients.

ADVERSE EVENTS

Eleven patients (1.6%) had complications that were attributed to the three-vessel imaging procedure (10 dissections and 1 perforation). These complications resulted in 3 nonfatal myocardial infarctions (in 0.4% of patients).

During a median follow-up period of 3.4 years, 149 major adverse cardiovascular events occurred in 135 patients (3-year cumulative rate, 20.4%) (Fig. 1). Most events were rehospitalizations for unstable or progressive angina; cardiovascular events (death from cardiac causes, cardiac arrest, or myocardial infarction) occurred in only 31 patients (3-year cumulative rate, 4.9%) within 3 years (Table 2). The 3-year cumulative rate of major adverse cardiovascular events that were judged to be recurrent disease at originally treated culprit lesions was 12.9% (118 lesions in 83 patients). The 3-year cumulative event rate judged to be related to nonculprit lesions was 11.6% (104 lesions in 74 patients). The origin of 18 events in 17 patients (2.7%) was indeterminate.

CORRELATES OF EVENTS RELATED TO NONCULPRIT LESIONS

The mean angiographic diameter stenosis of the 106 nonculprit lesions subsequently responsible for major adverse cardiovascular events was 32.3±20.6% at baseline and 65.4±16.3% at follow-up ($P<0.001$). At baseline, 32 of these lesions (30.2%) were angiographically inconspicuous (less than 30% stenosis on the basis of visual assessment). On quantitative angiography, 30 (28.3%) of these 106 lesions were at least 50% stenotic but less than 70% stenotic, and 5 (4.7%) were at least 70% stenotic. Among these 106 nonculprit lesions, 55 were imaged by intravascular ultrasonography, and all were found to have a baseline plaque burden of at least 40%.

The baseline patient-level and lesion-level correlates of nonculprit-lesion–related major adverse cardiovascular events are given in Table 3, and Tables 5 and 6 in the Supplementary Appendix. The strongest patient-level predictor of nonculprit-lesion–related major adverse cardiovascular events at follow-up was insulin-requiring diabetes, whereas a baseline plaque burden of at least 70%, a minimal luminal area of 4.0 mm^2 or less, and the presence of thin-cap fibroatheromas were independent predictors of subsequent nonculprit-lesion–related major adverse cardiovascular events. During follow-up, major adverse cardiovascular events originated from lesions that included 0, 1, 2, or all 3 of these variables in 0.3%, 4.8%, 10.5%, and 18.2% of lesions, respectively. Of 51 nonculprit lesions that were evaluated and classified based on radiofrequency intravascular ultrasonographic imaging and that resulted in major adverse cardiovascular events, 26 (51.0%) were thin-cap fibroatheromas, 8 (30.8%) of which had a minimal luminal area greater than 4.0 mm^2 and a plaque burden of less than 70% (i.e., thin-cap fibroatheroma was the only independent

risk factor for subsequent major adverse cardiovascular events). Nonculprit-lesion–related major adverse cardiovascular events arose more frequently from thin-cap fibroatheromas with a large plaque burden, a small minimal luminal area, or both (Fig. 2). In contrast, follow-up events rarely originated from nonfibroatheromas, regardless of lesion severity (Fig. 3 in the Supplementary Appendix).

DISCUSSION

We used gray-scale and radiofrequency intravascular ultrasonographic imaging prospectively to characterize coronary atherosclerosis before longitudinal follow-up. We found that approximately one in five patients with acute coronary syndromes who were successfully treated with percutaneous coronary intervention and contem-

Table 1. Demographic, Clinical, and Procedural Characteristics of the Patients.*

Characteristic	Value
Age — yr	
Median	58.1
Interquartile range	50.5–66.6
Female sex — no. of patients/total no. (%)	167/697 (24.0)
Diabetes mellitus — no. of patients/total no. (%)	119/694 (17.1)
Diabetes requiring insulin — no. of patients/total no. (%)	21/694 (3.0)
Metabolic syndrome — no. of patients/total no. (%)	327/673 (48.6)
Current cigarette use — no. of patients/total no. (%)	328/687 (47.7)
Hypertension — no. of patients/total no. (%)	320/691 (46.3)
Hyperlipidemia — no. of patients/total no. (%)	279/632 (44.1)
Previous myocardial infarction — no. of patients/total no. (%)	73/693 (10.5)
Family history of coronary artery disease — no. of patients/total no. (%)	276/616 (44.8)
Framingham risk score†	
Median	7.0
Interquartile range	5.0–9.0
Previous PCI — no. of patients/total no. (%)	77/696 (11.1)
Clinical presentation — no. of patients/total no. (%)	
ST-segment elevation myocardial infarction	211/697 (30.3)
Non–ST-segment elevation myocardial infarction	457/697 (65.6)
Unstable angina with ECG changes	29/697 (4.2)
Body-mass index‡	
Median	27.9
Interquartile range	25.1–31.2
Cholesterol — mg/dl§	
Total	
Median	170.0
Interquartile range	149.0–198.0
LDL	
Median	93.6
Interquartile range	62.6–121.4
HDL	
Median	38.6
Interquartile range	33.0–45.0

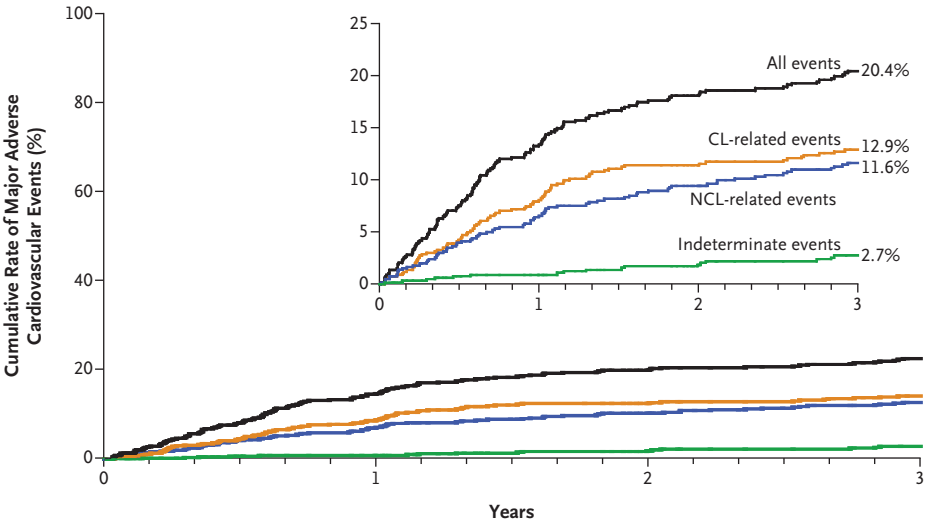
Table 1. (Continued.)

Characteristic	Value
Triglycerides — mg/dl¶	
Median	124.0
Interquartile range	88.6–177.1
Glycated hemoglobin — %	
Median	5.8
Interquartile range	5.3–6.2
Estimated creatinine clearance — ml/min	
Median	97.8
Interquartile range	76.4–123.6
High-sensitivity C-reactive protein — mg/dl	
Median	7.2
Interquartile range	2.5–18.9
No. of diseased epicardial coronary arteries — no. of patients/total no. (%)‖	
One	149/697 (21.4)
Two	283/697 (40.6)
Three	265/697 (38.0)
Intervention — no. of patients/total no. (%)	
One-vessel PCI	507/697 (72.7)
Two-vessel PCI	190/697 (27.3)
Stent implanted in PCI-identified culprit lesions	891/928 (96.0)
Drug-eluting stent implanted, among stented lesions	589/891 (66.1)

* ECG denotes electrocardiogram, HDL high-density lipoprotein, LDL low-density lipoprotein, and PCI percutaneous coronary intervention.
† The Framingham risk score ranges from 0 to 40, with higher scores indicating a greater likelihood of first-time overt or recurrent coronary heart disease.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ To convert the values for cholesterol to millimoles per liter, multiply by 0.02586.
¶ To convert the values for triglycerides to millimoles per liter, multiply by 0.01129.
‖ This category refers to any lesion with a stenosis ≥30% of vessel diameter.

porary medical therapy had recurrent major adverse cardiovascular events within 3 years. Events were nearly equally divided between those related to initially treated lesions and those related to previously untreated lesions. Most events were rehospitalizations for unstable or progressive angina; death from cardiac causes, cardiac arrest, and myocardial infarction were less common. Although the nonculprit lesions that led to major adverse cardiovascular events were frequently mild on angiographic assessment, most were characterized by a large plaque burden, a small luminal area, or both, as seen on gray-scale intravascular ultrasonography but not on angiography; no major adverse cardiovascular events arose from untreated segments with a plaque burden resulting in less than 40% loss of cross-sectional luminal area. The prospective identification of nonculprit lesions associated with major adverse cardiovascular events was further enhanced by the use of radiofrequency intravascular ultrasonography to characterize the morphologic features of plaques, with thin-cap fibroatheromas representing the highest-risk phenotype. Conversely, major adverse cardiovascular events related to nonculprit lesions rarely developed from nonfibroatheromas, regardless of the plaque burden or minimal luminal area.

The primary purpose of this natural-history study was to provide prospective in vivo confir-



No. at Risk				
All patients	697	557	506	480
Patients with CL-related events	697	590	543	518
Patients with NCL-related events	697	595	553	521
Patients with indeterminate events	697	634	604	583

Figure 1. Time-to-Event Curves for Major Adverse Cardiovascular Events after Successful, Uncomplicated Percutaneous Coronary Intervention in 697 Patients with Acute Coronary Syndromes.

The 3-year cumulative rates of major adverse cardiovascular events are shown (Kaplan–Meier estimates). The 1-year rates were 13.2% for all such events, 7.9% for events related to culprit lesions (CL), 6.4% for events related to nonculprit lesions (NCL), and 0.9% for events of indeterminate origin. CL-related events were those adjudicated to be recurrent disease at the sites of originally treated culprit lesions, NCL-related events were adjudicated to be at sites of nonculprit lesions. Some patients had both CL-related and NCL-related events, and some patients had multiple CL-related events, multiple NCL-related events, or both at different times (in which case the first event is represented in the time-to-event curve). Major adverse cardiovascular events were defined as death from cardiac causes, cardiac arrest, myocardial infarction, and rehospitalization for unstable or progressive angina.

Table 2. Kaplan–Meier Estimates for Cumulative Rates of Major Adverse Cardiovascular Events at 3 Years.*

Event	Events Related to Culprit Lesions	Events Related to Nonculprit Lesions	Indeterminate Events	All Events
	percent (number of patients)			
Composite cardiac events†	12.9 (83)‡	11.6 (74)	2.7 (17)	20.4 (132)
Death from cardiac causes, cardiac arrest, or myocardial infarction	2.2 (14)	1.0 (6)	1.9 (12)	4.9 (31)
Death from cardiac causes	0.2 (1)	0	1.8 (11)	1.9 (12)
Cardiac arrest	0.3 (2)	0	0.2 (1)	0.5 (3)
Myocardial infarction	2.0 (13)	1.0 (6)§	0.3 (2)	3.3 (21)
Rehospitalization for unstable or progressive angina	11.5 (74)	10.8 (69)	0.8 (5)	17.5 (113)
Other events				
Revascularization	10.9 (70)	10.5 (67)	0	17.1 (110)
Stent thrombosis¶	2.0 (13)	0	1.3 (8)	3.3 (21)

* Rates shown are Kaplan–Meier estimates at 3 years. Events occurred in three patients after the 3-year data presented here had been collected.
† Composite cardiac events were death from cardiac causes, cardiac arrest, myocardial infarction, or rehospitalization for unstable or progressive angina.
‡ Events related to culprit lesions were due to stent thrombosis (in 13 patients), restenosis (in 107 patients), and new stent-related side-branch lesions (in 5 patients).
§ All six myocardial infarctions were spontaneous infarctions; none were related to revascularization procedures.
¶ This category includes definite and probable stent thrombosis according to the Academic Research Consortium criteria.

mation of the hypothesis that acute coronary syndromes arise from atheromas with certain histopathological characteristics, and that these characteristics are not necessarily dependent on the degree of angiographic stenosis at that site. Although most of the lesions responsible for major adverse cardiovascular events during follow-up were angiographically mild, intravascular ultrasonography showed that most had either a small luminal area, a large plaque burden, or both — findings that are consistent with the results of pathological studies.[7-9] Moreover, although actual histologic assessment of the coronary arteries in vivo is not feasible, the development of radiofrequency intravascular ultrasonography makes it possible to characterize the vessel wall with the use of an imaging technique that has been shown to correlate reasonably well with histologic findings. Events related to nonculprit lesions typically occurred at sites that were classified as thin-cap fibroatheromas on the basis of radiofrequency intravascular ultrasonography, a finding that is consistent with the established concept of vulnerable plaque.[7-9]

Of 51 nonculprit-lesion–related recurrent events occurring in the imaged segments, 26 (51%) occurred at sites with thin-cap fibroatheromas. There may be several explanations for why adverse events were also associated with other plaque types (most commonly thick-cap fibroatheromas). First, some thin-cap fibroatheromas may not have been identified during the study because of equipment limitations. Second, because intravascular ultrasonography was performed only at baseline, it is possible (indeed likely) that some atheromas evolved over time — that is, thick-cap fibroatheromas developed into thin-cap fibroatheromas.[18] This concept is supported by the observation that thick-cap fibroatheromas were associated with an intermediate risk of cardiac events — higher than the risk associated with plaques that were not fibroatheromas and lower than the risk associated with thin-cap fibroatheromas. Such a model is consistent with the construct of Virmani et al., whereby the atherosclerotic lesion progresses from a low-risk to a high-risk phenotype before plaque rupture.[19]

A second objective of this study was to determine prospectively and systematically how often recurrent events occur at the sites of nonculprit lesions as opposed to the sites of previously treated lesions. Of 157 recurrent events for which the lesion location could be determined, 74 (47%) were related to original nonculprit lesions. Despite undergoing successful percutaneous coronary intervention for all coronary stenoses believed to require revascularization, within 3 years after treatment 11.6% of patients had unanticipated major adverse cardiovascular events associated with untreated coronary segments. Most of these sites showed no evidence of severe stenosis on conventional angiography, but we were able to identify three characteristics of lesions that were significant predictors of subsequent events: a small luminal area, a large plaque burden, and the presence of a thin-cap fibroatheroma.

Although the in vivo detection of potentially vulnerable plaque is of considerable mechanistic interest, there are several reasons why the methods we have used are not currently suitable for clinical application as a means of identifying sites in the coronary vasculature for potential intervention. First, the specificity of our methods is insufficient for such a purpose. Of 595

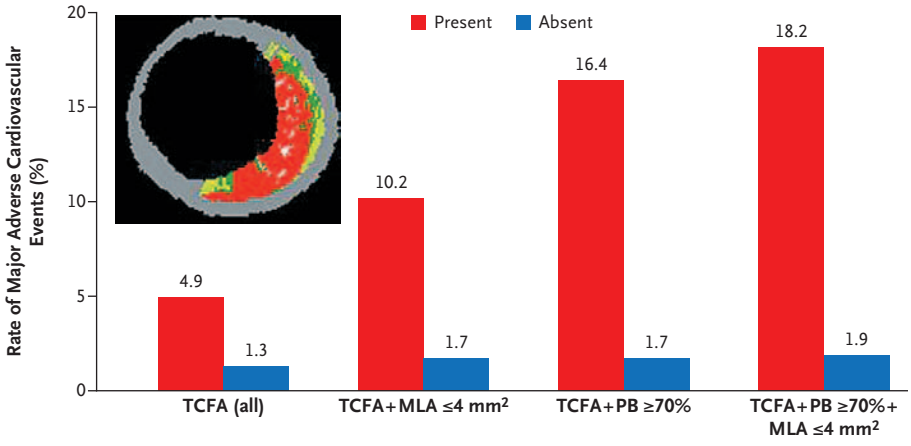
Table 3. Independent Correlates of Major Adverse Cardiovascular Events Related to Nonculprit Lesions during Follow-up.*

Correlates	Hazard Ratio (95% CI)	P Value
Predictors of patient-level events†		
Insulin-requiring diabetes	3.32 (1.43–7.72)	0.005
Previous percutaneous coronary intervention	2.03 (1.15–3.59)	0.02
Predictors of events at individual lesion sites‡		
Plaque burden ≥70%	5.03 (2.51–10.11)	<0.001
Thin-cap fibroatheroma	3.35 (1.77–6.36)	<0.001
MLA ≤4.0 mm^2	3.21 (1.61–6.42)	0.001

* Major adverse cardiovascular events comprised death from cardiac causes, cardiac arrest, myocardial infarction, and rehospitalization for unstable or progressive angina. MLA denotes minimal luminal area.

† Demographic, clinical, and laboratory-based variables were considered for entry into the patient-level multivariate regression model. The final variables entered were age, sex, hypertension, insulin-requiring diabetes, previous percutaneous coronary intervention, baseline C-reactive protein level, and family history of premature coronary artery disease.

‡ Angiographic and ultrasonographic variables, as well as the significant patient-level predictors, were considered for entry into the lesion-level multivariate regression model. The final variables entered were MLA, plaque burden at the MLA, external elastic membrane at the MLA, lesion length, distance from the coronary ostium to the MLA, remodeling index, thin-cap fibroatheroma, insulin-requiring diabetes, and previous percutaneous coronary intervention. An MLA of 4.0 mm^2 or less and a plaque burden of 70% or more were prespecified for use in this model, since they have been used frequently in previous studies.[16,17] However, the same variables (plaque burden, MLA, and thin-cap fibroatheroma) were identified as the three independent determinants of future cardiac events associated with specific nonculprit lesions in post hoc multivariate models that incorporated MLA and plaque burden as continuous data or with cutoff points selected on the basis of receiver-operating-characteristic curves (Table 7 in the Supplementary Appendix).



	TCFA (all)	TCFA+MLA ≤4 mm²	TCFA+PB ≥70%	TCFA+PB ≥70%+ MLA ≤4 mm²
Lesion hazard ratio (95% CI)	3.90 (2.25–6.76)	6.55 (3.43–12.51)	10.83 (5.55–21.10)	11.05 (4.39–27.82)
P value	<0.001	<0.001	<0.001	<0.001
Prevalence (%)	46.7	15.9	10.1	4.2

Figure 2. Event Rates for Lesions That Were and Those That Were Not Thin-Cap Fibroatheromas, at a Median Follow-up of 3.4 Years.

Event rates associated with 595 nonculprit lesions that were characterized as thin-cap fibroatheromas (TCFA) and 2114 that were not by means of radiofrequency intravascular ultrasonographic imaging are shown according to minimal luminal area (MLA) and plaque burden (PB) as detected on gray-scale intravascular ultrasonography. The inset shows an example of a thin-cap fibroatheroma imaged by radiofrequency ultrasonography. Data on prevalence are for one or more such lesions per patient. Lesions in patients with indeterminate events were excluded. (For additional details, see Table 6 in the Supplementary Appendix.) CI denotes confidence interval.

thin-cap fibroatheromas identified on radiofrequency intravascular ultrasonography, only 26 were sites of recurrent events at a median follow-up of 3.4 years (estimated Kaplan–Meier event rate, 4.9%). Specificity was similarly limited for a plaque burden of at least 70% (event rate, 9.6%) and a minimal luminal area of 4.0 mm² or less (event rate, 5.3%). Even when all three predictive variables were present, the event rate rose to only 18.2%. These figures suggest that although such lesion characteristics are conducive to the occurrence of a subsequent event, they are not sufficient to predict which atheromas will undergo plaque progression in the intermediate term. Second, the intravascular ultrasonographic catheters used in this study cannot be used to evaluate the distal portions of the coronary arteries; in our protocol, we examined only the proximal 6 to 8 cm of the coronary tree. All 106 nonculprit lesions associated with recurrent events were evaluated with the use of baseline angiography, but only 55 of these lesions were seen on gray-scale ultrasonography and only 51 were seen on radiofrequency intravascular ultrasonography. Third, the use of intravascular ultrasonography was associated with serious adverse events in 11 patients, including 10 coronary dissections and 1 perforation, indicating that these procedures are not without risk. Finally, it is unclear what therapeutic approaches might be effective in mitigating the risk associated with specific lesion features.

In summary, we used conventional coronary angiography, gray-scale intravascular ultrasonography, and radiofrequency intravascular ultrasonography to assess the coronary vasculature in patients who had undergone successful percutaneous coronary intervention for an acute coronary syndrome. At 3 years, the rate of recurrent major adverse cardiovascular events was 20.4%; nearly half these events were associated with nonculprit lesions, most of which appeared by angiography to be mild. Lesion characteristics that were predictive of events associated with nonculprit lesions included a large plaque burden, a small luminal area, and thin-cap fibroatheromas.

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