The PROSPECT (Providing Regional Observations to Study Predictors of Events in the Coronary Tree) study was a prospective, observational study in 697 patients undergoing percutaneous coronary intervention for acute coronary syndromes (1). The study was designed to assess the natural history of coronary atherosclerosis using multimodality intravascular imaging to identify those clinical and lesion-related factors that would predict future clinical events. After intervention of the culprit lesion, the 3 epicardial arteries underwent screening of the proximal 6 to 8 cm for “vulnerable plaques” using intravascular ultrasound (IVUS), including compositional (IVUS–virtual histology [VH]) and mechanical (palpography) plaque characterization. Assessed by angiography, most new nonculprit-related events originated from mild lesions. Larger plaque burden (>70%) and smaller minimal luminal area (<4.0 mm²) by IVUS and the presence of a VH-defined thin-cap fibroatheroma (TCFA) were independently associated with an increased risk for subsequent events. Those few lesions that possessed all 3 characteristics had an 18.2% rate of major cardiovascular events during the 3.4-year follow-up period. However, the predictive power of VH-defined TCFA alone was low, mainly because of poor specificity. Of 595 TCFAs identified by VH, only 26 led to coronary events during follow-up.

The data generated offer an important evaluation of the incidence and causes of recurrent events in the setting of current preventive strategies for high-risk patients. Overall, 20.4% of patients had major cardiovascular events, of which 11.6% were related to nonculprit lesions; however, only 1% were myocardial infarctions, while the remaining 10.8% were unstable or progressive angina. In addition, 1.6% of patients had vascular injuries from the imaging procedures. Hence, 1 interpretation of the data is that given the current success in reducing death and myocardial infarction, the increased risk of performing 3-vessel invasive imaging to locate and then prophylactically treat presumed high-risk lesions is not warranted.

The Vulnerable Plaque Concept

Both of us participated in the 1st Vulnerable Plaque Meeting in 2003 on the Greek island of Santorini, which produced a consensus document in which it was proposed to use synonymously the terms “high-risk,” “vulnerable,” and “thrombosis-prone” plaques for plaques at increased risk for subsequent thrombosis and rapid stenosis progression (2). Plaque rupture is by far the most common cause of coronary thrombosis, underlying about 75% of all cases (3). By inference, the most common type of vulnerable plaque is the rupture-prone plaque, also called a TCFA. It is assumed to look like a ruptured plaque, only without surface disruption and thrombosis. The size of the lipid-rich necrotic core, the thickness of the fibrous cap covering the core, and the degree of cap inflammation appear to be the major determinants of subsequent plaque rupture. The remaining coronary thrombi are caused by less well-defined mechanisms, of which “plaque erosion” is the most common type, present in about 25% of patients, generally women (2,3). Erosion-prone vulnerable plaques are heterogeneous and de-
fined only by their fate (thrombosis), as no distinct morphological features other than the absence of endothelial coverage have been identified. The key questions are thus whether vulnerable plaques, in particular TCFA, can be prospectively identified and, if so, prophylactically treated to reduce the lesion-related risk of future coronary events. PROSPECT was designed to answer the first question.

**Prospective Identification of Vulnerable Plaques**

The preceding 3 reports (4–6) present information on the performance of the PROSPECT study and the analysis of its results. Maehara et al. (4) provide insights about definitions and methodology for IVUS (grayscale and VH) and coronary angiography used to identify lesion-related predictors of subsequent coronary events. Performance and analysis of the data were challenging. New approaches, algorithms, and software were developed to permit coregistration of angiographic and IVUS images, and detailed analysis was performed at a level not previously attempted. The required analyses required at least 1 day/patient for angiographic analysis, while grayscale and VH-IVUS results required on average 2.3 days/patient. The size for the entire image set was 2.1 gigabytes/patient. As a result, the study produced an enormous dataset, and the investigators must be congratulated for this outstanding achievement.

On the basis of pre-specified characteristics of necrotic core, dense calcium, and cap thickness, 10 fibroatheroma subtypes were defined and ordered hierarchically based on anticipated risk for subsequent plaque-related events. The investigators are forthright in describing the potential pitfalls of the PROSPECT data acquisition and analysis and important limitations of IVUS-VH for compositional plaque assessment, including insufficient spatial resolution to truly detect a thin fibrous cap or missing endothelium (important for assessment of plaque erosion), artificial VH-defined necrotic core in the shadow behind dense calcium, artificial VH-defined calcium near the lumen, and erroneous tissue coding of thrombus. Thus, the investigators acknowledge that error in the VH assessment of the presence of TCFA may have been introduced. Furthermore, the distinction between fibroatheromas considered unstable (vulnerable) and those considered stable was based on arbitrary cut points for VH-defined necrotic core size (≥10% confluent) and extent of core-to-lumen proximity (>30°). No compelling arguments are provided for the choice of either of these cut points, which differ significantly from the criteria used to define a TCFA at necropsy, in which the sizes of necrotic cores of stable plaques, TCFA, and ruptured plaques averaged 12%, 23%, and 34%, respectively (7). Even given these limitations, the report by Maehara et al. will be of great use, as well as act as a cautionary tale, for those investigators who wish to embark on such a study.

Brugaletta et al. (5) report a subanalysis from the PROSPECT study in which 114 patients underwent simultaneous IVUS-VH–based plaque evaluation and palpography. In this subgroup, there were 16 clinical events and 488 VH-defined fibroatheromas identified, of which 111 were VH TCFA. Compared with the overall PROSPECT population, the expected number of VH TCFA (111 of 114 ∼ 1 per patient) is similar but about twice the expected number of thick-cap fibroatheromas (377 of 114 = 3.3 per patient vs. 1,018 of 623 = 1.6 per patient in PROSPECT [1]). The reason for this discrepancy is not commented on, but a possible explanation could be that necrotic core–rich plaques containing <10% confluent necrotic core were defined as fibroatheromas in this subanalysis but not in the entire PROSPECT study. The investigators also do not explain why one of the most common lesion types, pathological intimal thickening, was excluded from the analysis. Indeed, Figure 2 of Brugaletta et al. (5) may show that necrotic core–containing pathological intimal thickenings were reclassified as fibroatheroma for the purpose of this substudy. Nonetheless, palpography was unable to distinguish between different subtypes of VH–defined fibroatheromas and did not provide prognostic information of clinical value in this population.

These results are disappointing. Palpography had previously been shown to identify vulnerable plaques in human necropsy samples (8) and to correlate with clinical presentation while reflecting compositional change resulting from medical therapy (9). The current results call into question any potential role of palpography in the detection of high-risk lesions and the discrepancy with previous studies.

In the second PROSPECT substudy, Wykrzykowska et al. (6) examined the longitudinal distribution of atherosclerotic plaque burden, IVUS-VH necrotic core content, and TCFA plaque phenotype in nonculprit lesions. This descriptive analysis of patients confirms previous data obtained at necropsy, or with angiography, IVUS, or multislice computed tomographic angiography, namely, that high-risk lesions tend to be located more proximally within the left coronary artery. The left main coronary artery appears to be the exception, as the plaque burden is less and the proportion of the lesion taken up by
VH-defined necrotic core is relatively smaller than in the proximal segments of the other epicardial arteries. This finding may reflect selection bias, as patients with smaller left main coronary artery diameters by angiography may not have been enrolled in the study. The right coronary artery also demonstrates less of a gradient from the proximal to distal vessel.

In this substudy, the percent necrotic core volume determined by VH was similar in the proximal and mid segments and only slightly greater than in the distal segments. This finding is in variance with a previous study in which the predominant site of plaque rupture was noted to be in the proximal segment of the left anterior descending coronary artery, the entire left circumflex artery, and the proximal and distal segments of the right coronary artery (10). It would seem logical that the site of the highest necrotic core volume would be the site of the greatest risk for plaque rupture leading to clinical ischemic events, unless plaque morphology and composition are more dynamic than previous thought.

What Have We Learned Since the First Vulnerable Plaque Meeting in 2003?

Studies using clinical events as outcomes and those evaluating diagnostic approaches to determine the presence of high-risk lesions have shown varying results. In the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial, stable patients with coronary artery disease treated aggressively with pharmacologic therapies and lifestyle modification had an 18.5% risk for death or nonfatal myocardial infarction over a median 4.6-year follow-up (11), while the 3.4-year event rate of nonculprit lesions in PROSPECT was 11.6%, and these events were generally progressive angina (1). Therefore, the question arises whether we are evaluating the wrong patient group, and if so, how to better focus our attention on truly high-risk patients.

This is important for several reasons. First, given the difficulty in assessing and properly analyzing lesions evaluated by angiography, IVUS, and IVUS-VH, as shown by Maehara et al. (4), it behooves us to ensure that the evaluated patients are at high risk for death and myocardial infarction. If we are generally identifying those lesions that will subsequently cause angina, we can simply wait for the event to happen and then perform the necessary intervention, thereby reducing the evaluated number of patients and the effort necessary to identify the presence of such lesions. Second, it is clear that invasive imaging of the 3 coronary arteries is associated with a small but present risk for vascular damage, which may represent a barrier too high to overcome when determining the risk/benefit ratio of prophylactic treatment for such lesions. Finally, the cost and organization necessary to make such invasive evaluations on a large number of patients will make private and/or governmental payers leery.

The development and regression of high-risk lesions may be more dynamic than hitherto thought. Kubo et al. (12) demonstrated that most VH TCFAs healed during a 1-year follow-up period, while new VH TCFAs developed. Hence, a 1-time assessment of the coronary tree may be inadequate, and serial evaluations are necessary to determine the future risk for plaque instability. This may be the reason that of the 51 nonculprit lesion-related recurrent events observed in PROSPECT, only 26 occurred at sites of VH-defined TCFAs. Another explanation could be insufficient diagnostic performance of IVUS-VH in detecting TCFAs (13). Thus, perhaps after the identification of a TCFA, intensive pharmacologic treatment should be initiated, along with serial imaging (preferably noninvasive), and only if the TCFA persists should a prophylactic intervention be performed. Indeed, an evaluation of TCFA behavior after intensive pharmacologic treatment would be helpful in this regard.

Finally, the data suggest that determining the presence of a VH-defined TCFA may not be enough. Insofar as about 25% of lesions causing coronary thrombosis are not TCFAs (3), simply focusing on TCFAs will result in a false sense of security if imaging shows no TCFAs and cannot identify lesions prone to plaque erosion. IVUS-VH cannot detect those lesions, or at least the data have not been shown, and so it may fall to other imaging protocols to determine this important subset of lesions.

PROSPECT was an important, some say landmark, study which has led to valuable insights into the natural history of atherosclerosis. The present supplement is evidence of the wealth of data that have been gleaned from this study. It is our hope that studies will be performed to evaluate other novel imaging protocols, both invasive and noninvasive, to further define the natural history of high-risk lesions and the effect of treatment.
REFERENCES


Key Words: acute coronary syndrome ▪ IVUS ▪ myocardial infarction ▪ plaque erosion ▪ plaque rupture ▪ thin cap fibroatheroma.