Unstable Coronary Plaque and Its Relation to Coronary Calcium

Axel Schmermund, MD; Raimund Erbel, MD

Abstract—Coronary calcium is intimately associated with coronary atherosclerotic plaque development. The use of electron-beam computed tomography (EBCT) for accurate quantitative measurements has led to an increased interest in understanding the clinical importance of coronary calcium, particularly in terms of the ability to identify unstable coronary plaques that underlie the clinical acute coronary syndromes. Histopathologic studies have demonstrated that calcium is a frequent feature of ruptured plaques, but the presence or absence of calcium does not allow for reliable distinction between unstable versus stable plaques. This issue is complicated by the lack of a prospective definition for “unstable.” Plaque rupture is sometimes found in apparently healthy subjects and in patients with clinically stable disease. Coronary atherosclerosis is a coronary systemic disease process. Imaging of coronary calcium, although unable to identify a localized unstable plaque, potentially can identify the more clinically pertinent “unstable patient.” Almost all patients with a recent acute coronary syndrome have measurable coronary calcium because moderate-to-advanced coronary plaque disease is already present, although obstructive disease frequently is not. Prospective studies have demonstrated that extensive coronary calcium detected by EBCT is associated with a significantly increased incidence of subsequent myocardial infarction, need for revascularization, and coronary death. The incremental prognostic value of coronary calcium compared with that of risk factor assessment remains to be fully defined. The occurrence of an acute coronary syndrome is determined by many factors apart from the extent of atherosclerotic plaque disease. Large prospective trials in the general population are needed to define the subgroups that will benefit most from quantitative assessment of coronary calcium. (Circulation. 2001;104:1682-1687.)

Key Words: calcium ▪ plaque ▪ coronary disease ▪ risk factors ▪ prognosis
core. This layer is composed of preexisting intima in type IV plaques, whereas in type V plaques, the intima has been replaced by pathological fibromuscular tissue.

From a prospective viewpoint, lesion types IV and V can be called vulnerable plaques. In these plaques, an intact tissue layer is covering the lipid core ("cap"). Unfortunately, the nature of necropsy studies does not allow for true prospective studies. Various morphological and cellular characteristics have been associated with the propensity of type IV and V lesions to rupture or cause clinical events.11,12,15,16 Among these characteristics are a large lipid core size, a thin fibrous cap or layer above the lipid core, the loss of smooth muscle cells, the presence of inflammatory cells, and proteolytic activity in this layer. Perhaps with the exception of thickness of the fibrous cap < 65 μm,16 however, threshold values for any one of these characteristics to indicate plaque vulnerability are unknown. Also, it is unclear if one of these characteristics or a combination of them is required to indicate plaque vulnerability, or if some characteristics are more important than others.16

Necropsy studies take a retrospective view. Type VI lesions have been established as representing unstable, complicated plaques. They are characterized by injury to the tissue layer covering the lipid core. The most common type VI lesion is plaque rupture.12,16 Rupture of the layer above the lipid core exposes tissue factor and thrombogenic material to blood components, initiating a cascade of thrombotic changes that can result in sudden occlusion of the vessel lumen. Up to 30% of sudden coronary deaths may be caused by plaque rupture.16,17 The endothelium is absent, exposing the intima and predominantly smooth muscle cells and proteoglycans. Plaque erosion can be diagnosed only in the presence of an overlying thrombus and if serial sectioning fails to detect plaque rupture. Plaque hemorrhage may originate from the luminal surface and, in such cases, represents a subtype of plaque rupture.18 A pivotal complication of the aforementioned lesions is arterial thrombus deposition, which can potentially result in occlusion of the vessel and abrupt reduction of blood flow.

To provide for a clear definition in the setting of this article, we will use the term vulnerable plaque to describe Stary type IV and V lesions that have the potential to develop into type VI (complicated) lesions. To describe type VI lesions, we will use the term complicated plaque. Most complicated plaques are disrupted, but some also show plaque erosion or other pathology as described above. The overall term describing both vulnerable and complicated plaques is unstable plaque.

In Vivo Studies Using Intravascular Ultrasound

Intravascular ultrasound (IVUS), unlike coronary angiography, allows for visualization of changes of the vessel wall, the site of development of atherosclerotic plaques. The above-mentioned classification of coronary lesions suggested by the AHA can be reproduced using IVUS (Figure 3).19 Indeed, clinical symptoms—stable or unstable angina—are related to plaque morphology described by IVUS in analogy to the AHA classification rather than to angiographic stenosis severity.19 In particular, IVUS enables the detection of plaque rupture.19–21 The changes in plaque morphology can be examined over time.21 Unfortunately, such studies are limited to symptomatic patients undergoing coronary angiography. Acute coronary syndromes often are not preceded by typical symptoms of CAD.22

Complicated Plaques in Symptomatic and Asymptomatic Subjects

Histopathologic studies have established plaque rupture (AHA lesion type VIa) as the most common cause of acute coronary syndromes,11,12,16–18 and this has been confirmed by in vivo studies using IVUS.20 However, a number of observations indicate that the detection of plaque rupture is neither sensitive nor specific for distinguishing patients with acute coronary syndromes from those without. An obvious explanation is provided by plaque erosion, which frequently causes intraluminal thrombus deposition (AHA lesion type VIc).16,17 Plaque rupture, however, is also observed in ≤25% of patients with stable angina pectoris.11,20 It is detected in ≤20% of patients dying of noncardiac, but atherosclerosis-related, causes.23 Furthermore, and perhaps most surprisingly, ≤10% of apparently healthy individuals with traumatic death show plaque rupture.23,24 Also, >1 plaque rupture often is observed in individuals with SCD.11,25 Such individuals frequently show evidence of previous healed plaque ruptures which are calcified. Conversely, SCD and other acute coro-
Coronary Calcium in Complicated Plaques

In a series of 50 patients with a mean age of 49 years, Farb et al.\(^\text{17}\) reported that calcium is a frequent feature (in \(\approx 70\%\) of subjects) of plaque rupture. Calcium was associated less frequently with plaque erosion.\(^\text{17}\) Burke et al.\(^\text{27}\) classified culprit plaques in 108 victims of SCD with a mean age of 50 years as “stable” (n=20), “erosion” (n=33), “acute rupture” (n=37), and “healed rupture” (n=18). The most frequently calcified plaques were acute ruptures (80%). The most extensively calcified plaques were healed ruptures. Eroded plaques displayed the lowest frequency and extent of calcium. Taylor et al.\(^\text{28}\) reported similar results. Figure 4 illustrates these findings schematically.

There are also histopathologic reports suggesting that ruptured plaques are less likely to be calcified.\(^\text{29,30}\) Gertz and Roberts,\(^\text{29}\) in a series of 17 patients with plaque rupture and fatal acute myocardial infarction (AMI), observed less extensive calcium in ruptured than in nonruptured coronary segments. Cheng et al.\(^\text{30}\) comparing 12 lesions that presumably caused fatal AMI with 12 stable lesions, also observed less extensive calcium in the former lesions. Although these studies included relatively few patients, IVUS studies in much larger patient populations also found unstable clinical symptoms associated with less calcium.\(^\text{31,32}\)

The disparate results of the above-named studies can be explained in part by differences in methodology and patient age and selection, as well as methods of preservation. The observation remains that calcium is frequently present in complicated plaques and that it can be quite extensive in these plaques. Because there is considerable overlap between all types of plaques, calcium is a marker for neither unstable nor stable plaques.

Coronary Calcium in Acute Coronary Syndromes

We performed EBCT in 118 consecutive patients (mean age, 57\(\pm\)11 years) with previous AMI (n=101) or unstable angina (n=17) as the first manifestation of CAD.\(^\text{33}\) The vast majority of patients with at least moderate angiographic disease (105 of 110; 96%) had measurable calcium by EBCT. Those patients with a negative EBCT had minimal or no atherosclerotic plaque formation (confirmed by IVUS). They were younger and tended to be active cigarette smokers.

Raggi et al.\(^\text{8}\) recently confirmed these findings in 172 patients with a first AMI (mean age, 53\(\pm\)8 years). The angiographic status of these patients was not reported. Overall, 165 (96%) patients showed coronary calcium by EBCT. In 87% of the 172 patients, the extent of calcium was greater than would have been expected with regard to their age and sex. These data suggest that even in patients with an acute coronary syndrome as the first manifestation of CAD, coronary calcium is almost always present and usually exceeds the amount observed in asymptomatic subjects or patients with atypical symptoms.

Acute coronary syndromes generally result from extensive coronary atherosclerosis.\(^\text{34}\) This explains why extensive calcium is frequently observed in patients with acute coronary syndromes, although calcium cannot be used to identify unstable plaques. The extent of coronary calcium is closely related to the extent of coronary atherosclerosis (Figure 5).\(^\text{35–38}\) Patients with a negative EBCT rarely have angiographic CAD, and multivessel CAD is almost never observed.\(^\text{1,2}\) More importantly, nonobstructive plaques are re-
vealed by EBCT.35,38 These plaques often show advanced stages of development in terms of the Stary classification and are important determinants of the clinical course of the disease, especially regarding AMI.39

The mechanisms that influence atherosclerotic plaque development—and progression of calcification40—at least in part affect the coronary tree in a systemic fashion. In a clinical study, the term “multifocal plaque instability” has been coined.41 Thus, the importance of identifying localized vulnerable or complicated plaques needs to be weighed against assessing the extent of atherosclerotic plaque disease as the underlying substrate of instability.

The concern remains that it may be impossible to separate patients who will develop an acute coronary syndrome from patients who will develop stable angina pectoris on the basis of coronary calcium.42 This may not necessarily be problematic because stable angina can be identified and treated. The challenge is to determine who with the same atherosclerotic plaque burden will have a clinical acute coronary syndrome and who will have no clinical manifestation of the disease. In individual subjects, comparable amounts of atherosclerotic plaque disease can have vastly different functional consequences, which are determined by numerous factors that are only partly understood. On the basis of EBCT, how important is the extent of coronary atherosclerosis as a prognostic factor in its own right?

Short- and Long-Term Prospective Studies

In patients presenting to the emergency room with chest pain and no initial objective signs of myocardial ischemia, a negative EBCT indicated an excellent prognosis with regard to major cardiac events over the subsequent 1 to 4 months.33,44 EBCT yielded negative predictive values in the range of 98% to 100%. In symptomatic patients undergoing coronary angiography, increased amounts of coronary calcium detected by EBCT were highly predictive of subsequent events over 30 months.45 In direct comparison, EBCT performed better than coronary angiography (that is, number of stenotic major coronary arteries) in this respect.

There are currently 3 published studies reporting on EBCT-derived prospective prediction of hard events (ie, AMI and cardiac death) in asymptomatic subjects (Table).6,8,9 Arad et al9 observed a tendency for higher scores in subjects with hard events than in subjects who underwent revascularization. The prespecified calcium score cut points of 80 and 160 both were associated with odds ratios of approximately 22 for suffering coronary death or AMI, with wide confidence intervals (95% CI, 5.1 to 97.4 and 6.4 to 77.4, respectively). The status of established risk factors was determined by questionnaire. In a multivariate analysis in a subgroup of patients with all information available (n = 787), the calcium score cut points were associated with odds ratios for suffering any event in the range of 14 to 20 and the risk factors, including age, with odds ratios in the range of 3 to 6.

Raggi et al8 (Table) found that subjects with calcium scores in the highest quartile had an odds ratio of 21.5 (95% CI, 2.8 to 162.4) for suffering AMI or cardiac death. Risk factor data were obtained by questionnaire. Subjects in the highest

Demographic and Design Characteristics of the Published Reports on the Predictive Value of EBCT for Myocardial Infarction and Cardiac Death in Subjects With No Clinical CAD

<table>
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<tr>
<th>Arad et al9</th>
<th>Raggi et al8</th>
<th>Detrano et al6</th>
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<tr>
<td>Participants, n</td>
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<td>672</td>
</tr>
<tr>
<td>Sex, % male</td>
<td>71</td>
<td>50</td>
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<tr>
<td>Age, y (mean±SD)</td>
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<td>52±8</td>
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<td>Scanning protocol</td>
<td>3-mm slices lesion ≥0.93 mm²</td>
<td>3-mm slices lesion ≥1.37 mm²</td>
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<tr>
<td>Median calcium score</td>
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<td>3</td>
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<tr>
<td>Mean follow-up, y</td>
<td>3.6</td>
<td>2.8</td>
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<tr>
<td>Follow-up completed, %</td>
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<td>100</td>
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<td>Hard events, n</td>
<td>18</td>
<td>27</td>
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<td>Comment</td>
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<td>Standard EBCT scanning protocol Participants referred by primary care physicians for assessment of cardiovascular risk</td>
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quartile of cardiovascular risk distribution had an odds ratio of 7.0 (95% CI, 1.6 to 31.5).

Detrano et al. reported an odds ratio of 2.7 associated with a calcium score above the median. Receiver operating characteristic curve analysis of calcium scores for separating subjects with from those without AMI or coronary death yielded an area under the curve (± SEM) of 0.64±0.05. For comparison, this value was 0.86±0.07 in the study by Arad et al. Risk factors were assessed by questionnaire and direct measurements of laboratory values. An ECG was recorded in all subjects. The combined analysis of risk factors and ECG yielded an area under the curve of 0.69±0.05, so that for predicting hard events, EBCT was not superior in this report.

The 3 studies discussed above all have some limitations, including the mode of referral (Table). In 2 studies, the number of events was rather small, producing wide confidence intervals. An attempt at the influence of the results, EBCT was reported in the study by Arad et al. The participants in the Arad study constituted a group of intermediate-risk population, the participants in the study by Detrano study were, by definition, high risk. Indeed, Detrano et al. analyzed a relatively narrow range of observations (within the highest risk subgroup). This, but also the low event rate in the study by Arad et al. poses problems with regard to interpretation of the results.

An important question relates to the discrepancy between the studies. There were obvious differences in EBCT scanning protocol and image analysis. The sensitivity for detection of coronary calcium was decreased in the study by Detrano et al. Whereas the participants in the Arad study and Raggin studies constituted a low-to-intermediate-risk population, the participants in the study by Detrano study were, by definition, high risk. Indeed, Detrano et al. analyzed a relatively narrow range of observations (within the highest risk subgroup). This, but also the low event rate in the study by Arad et al. poses problems with regard to interpretation of the results.

To summarize these studies, there is data to suggest that coronary calcium provides very helpful prognostic information regarding subsequent acute coronary syndromes in subjects with no clinical CAD. The predictive power reported in 2 of the 3 studies was much better than traditional—albeit self-reported—risk factors. There is a serious question, however, as to the ability to extrapolate the results to other populations. Also, one study in high-risk subjects did not find an incremental value of EBCT compared with traditional risk assessment. Thus, further studies are warranted. This was also stated in the recent American College of Cardiology/American Heart Association expert consensus document on EBCT. An important focus of it was the ability of EBCT to diagnose CAD—that is, flow-limiting epicardial coronary stenoses. As discussed in the document and elsewhere, non–contrast-enhanced EBCT measures the extent of coronary atherosclerosis rather than the site-specific severity of stenoses. The trials discussed above clearly indicate that the potential of this method lies in risk prediction.

Summary and Outlook

Imaging of coronary calcium does not allow for reliable identification of unstable coronary plaques. Indeed, on the basis of the difficulties inherent in the histopathologic definitions, it is doubtful if any of the currently available noninvasive imaging techniques can prospectively identify vulnerable or complicated coronary plaques with some degree of accuracy.

Even in young age groups, subjects sustaining acute coronary syndromes have much more extensive and severe coronary atherosclerosis than age- and sex-matched controls. By virtue of the ability to determine overall plaque burden, direct visualization and quantification of coronary calcium appears to be very helpful for identification of subjects at increased risk. The available data suggest that even though we cannot at present define the unstable plaque, there is the potential to identify the “unstable patient.”

The only way to reach definitive conclusions at this point is to obtain more data from large prospective clinical trials that adhere to the principles of good clinical and epidemiologic practice. Such trials are now in the planning process or already underway. Two trials will examine the predictive value of EBCT-derived coronary calcium in the general population, one in the United States (Multi-Ethnic Study of Atherosclerosis [MESA]) and one in Germany (Heinz Nixdorf Recall Study). The latter study has begun recruitment of 4200 subjects who are being contacted through mandatory citizen registries. During an observation period of 5 years, there will be a direct comparison of the ability of EBCT and competing techniques, such as ultrasound measures of carotid intima-media thickness and the ankle-brachial index, to predict AMI and cardiac death. It is hoped that these studies will not only further elucidate the prognostic value of imaging coronary calcium but also will place this test in the public health and health-economic context.

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