Background—Neither clinical prediction models nor noninvasive imaging tests that detect coronary artery calcification identify all patients who experience acute coronary events. Variations in culprit plaque morphology may account for these inaccuracies.

Methods and Results—We compared the 10-year Framingham risk index, histologic coronary calcification, and culprit plaque morphology in 79 consecutive adults with sudden cardiac death. There was a modest relationship between the Framingham risk index and the extent of histologic coronary calcification ($r=0.35$, $P=0.002$). Agreement in risk classification between the histologic calcification score and the Framingham risk index occurred in 50 of 79 cases (63.3%, $P=0.039$). Either a focus of coronary artery calcification $\geq 40$ $\mu$mol/L (62% of cases) or a Framingham risk index score $\geq$ average risk for age (62% of cases) were present in 66 of 79 (83.5%) cases. Cases with plaque erosion ($n=22$) had significantly less coronary calcification ($P=0.003$) and lower Framingham risk index ($P=0.001$) scores than stable ($n=27$) or ruptured ($n=30$) plaques. Fourteen of 22 (63.6%) cases of plaque erosion were classified as low risk by both the Framingham risk index and the histologic calcification score.

Conclusions—The prediction of sudden cardiac death using the Framingham risk index and the measurement of coronary calcification are distinct methods of assessing risk for sudden cardiac death. Excessive reliance on either method alone will produce errors in risk classification, particularly for patients at risk of plaque erosion, but their combination may be complementary. (Circulation. 2000;101:1243-1248.)

Keywords: death, sudden • risk factors • atherosclerosis • prognosis • calcification

Sudden cardiac death accounts for half of an estimated 500,000 cardiac deaths per year.1 Recently, interest in the identification of patients at risk for cardiovascular events has increased. Available methods for this include simple, validated, clinical prediction algorithms, such as the Framingham risk index.2,3 Alternative methods for determining cardiovascular risk include anatomic assessments using expensive, noninvasive imaging modalities, such as electron beam computed tomography (CT), which can detect coronary calcification before clinical manifestations develop.4 The extent of coronary calcification is correlated with coronary plaque burden5,6 and the risk for future cardiovascular events.7-9 However, the comparative accuracy of coronary risk factors and the noninvasive detection of coronary calcification for the prediction of patients at risk for future cardiovascular events has been debated.10,11 Recently, Detrano and colleagues showed that the Framingham risk index and electron beam CT have similar accuracy for the prediction of developing manifest coronary heart disease.8 Both the Framingham risk index and the detection of coronary calcification also have significant limitations. Many acute coronary events are unexplained by conventional risk factors.12,13 Similarly, acute coronary events can occur in patients with little or no coronary calcification.8 We recently reported that the coronary plaque morphology in sudden cardiac death is variable.14 Most cases of sudden cardiac death are found to have stable plaques or plaque rupture with acute thrombosis, but an important minority of cases, possibly 25% or more, result from acute thrombosis due to plaque erosion.14,15 Thus, it is possible that the available methods for the prediction of coronary events differ in their accuracy on the basis of the underlying plaque morphology. To test this hypothesis, we evaluated the relationships between the Framingham risk index,
coronary calcification, and culprit plaque morphology in cases of sudden cardiac death.

Methods
We prospectively examined hearts of men and women with sudden, unexplained death who were consecutively referred to the Armed Forces Institute of Pathology through a cardiovascular pathology consultation service provided to the Office of the Chief Medical Examiner of the State of Maryland (Baltimore). Sudden cardiac death was defined as death occurring within 6 hours of the onset of symptoms (witnessed cardiac arrest) or within 24 hours of the time that the victim was last seen alive in a normal state of health. Coronary death was defined as natural death in which at least 1 major epicardial coronary artery had ≥75% cross-sectional luminal narrowing by an atherosclerotic plaque or acute thrombus. Noncardiac causes of death were ruled out by a complete forensic autopsy including postmortem toxicological testing. From 90 cases with sudden cardiac death from a coronary cause available for analysis (including adequate postmortem serum quality indicated by a serum albumin >2.5 g/dL), 79 had complete cardiovascular risk factor data available and are included in this analysis.

The coronary arteries were perfusion-fixed for 30 minutes with neutral buffered formalin at 100 mm Hg and then studied by serial sectioning at 3-mm intervals, with light decalcification performed on the basis of the presence of calcification assessed by postmortem radiography. Any 3-mm coronary arterial segment that showed cross-sectional narrowing ≥50% was submitted for histologic analysis (median value 3 sections per case), including hematoxylin and eosin and Movat pentachrome stains.

The culprit plaque was defined as the plaque with an acute thrombus, or, in the absence of an acute thrombus, the arterial segment with the greatest narrowing relative to the internal elastic lamina at the narrowest segment.17–19 Acute plaque rupture consisted of a ruptured fibrous cap with a luminal platelet-fibrin thrombus continuous with an underlying lipid-rich core. Plaque erosion was defined as an acute thrombus in direct contact with the intimal plaque without rupture of a lipid pool, as demonstrated by serial sections. Stable plaque was defined as cross-sectional luminal narrowing of ≥75% in the absence of a luminal thrombus. The location of the culprit plaque was the left anterior descending coronary artery in 50 cases (63.2%), the right coronary artery in 21 cases (26.6%), the left circumflex coronary artery in 7 cases (8.9%), and the left main coronary artery in 1 case (1.3%).

Histologic calcification was detected by the presence of calcified matrix with its tinctorial staining characteristic on hematoxylin- and eosin-stained sections. Coronary artery segments were digitized and areas of calcification were measured by computerized morphometry (IP Laboratory Spectrum 6.1, Vienna, Va). Coronary arterial sections with a ≥50% luminal narrowing were evaluated for the extent of calcification using a 5-point scale: grade 0, no calcification; grade 1, calcification <40 μm/L in diameter; grade 2, calcification ≥40 μm/L involving only 1 arterial quadrant; grade 3, calcification in 2 arterial quadrants; grade 4, calcification in 3 arterial quadrants; grade 5, calcification involving the entire arterial circumference. A total histologic calcification score for each case was determined using Pearson’s correlation coefficient. Continuous variables were compared among categories of culprit plaques using analysis of variance and unpaired t tests (2-tailed). Categorical variables were compared using a 2 by 2 contingency table, and the χ2 test. Agreement between categorical variables was assessed using the κ statistic. All data are expressed as mean±SD. For all statistical tests, a 2-tailed P<0.05 was considered significant.

Results
The mean age of the 79 subjects at the time of death was 49±11 years. There were 23 women and 56 men. The demographic variables and coronary risk factors of the 79 cases are shown in Table 1. The mean Framingham risk index was 12.2±9.9%. A total of 297 coronary segments with a luminal stenosis of ≥50% were examined from the 79 cases. The mean histologic calcification score was 3.9±4.1 (range 0 to 15). There was a significant relationship between the histologic calcification score and the area of radiographic calcification (r=0.69, P=0.01).

There was a modest, significant relationship between the histologic calcification score and Framingham risk index (r=0.35, P=0.002) (Figure 1). However, among categories of culprit plaque morphology, the histologic calcification score and the Framingham risk index differed significantly. Subjects with plaque erosion had significantly lower histologic calcium scores (1.9±3.0) compared with stable plaques.

### Table 1. Characteristics of the Study Cases

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Mean ± SD</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>79</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>49±11</td>
<td>33–82</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>228±74</td>
<td>109–380</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>43±20</td>
<td>13–96</td>
</tr>
<tr>
<td>Glycohemoglobin, %</td>
<td>7.5±2.6</td>
<td>5.3–17.2</td>
</tr>
<tr>
<td>Tobacco use, n (%)</td>
<td>51 (64.6)</td>
<td></td>
</tr>
<tr>
<td>10-year Framingham risk index, %</td>
<td>12.2±9.9</td>
<td>1–53</td>
</tr>
<tr>
<td>Pathology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Histologic calcification score</td>
<td>3.9±4.1</td>
<td>0–15</td>
</tr>
<tr>
<td>Culprit plaque morphology</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stable plaque, n (%)</td>
<td>27 (34.2)</td>
<td></td>
</tr>
<tr>
<td>Plaque erosion, n (%)</td>
<td>22 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Plaque rupture, n (%)</td>
<td>30 (40.0)</td>
<td></td>
</tr>
<tr>
<td>Healed myocardial infarction</td>
<td>22 (27.8)</td>
<td></td>
</tr>
<tr>
<td>Acute myocardial infarction</td>
<td>11 (13.9)</td>
<td></td>
</tr>
</tbody>
</table>
(4.5±4.6) and plaque ruptures (5.2±3.8) (Figure 2A, ANOVA P=0.003). Similar differences were observed for the calcification score of the culprit plaque alone, with plaque erosions containing significantly less calcium (0.7±0.9) than stable plaques (1.0±1.5) and plaque ruptures (1.7±1.2, ANOVA P=0.007). Likewise, the area of radiographic calcification in plaque erosions (0.27±0.26 cm² n=6) was less than the area of radiographic calcification in both stable plaques (0.74±0.95 cm² n=4) and plaque ruptures (0.68±0.36 cm² n=3), but the small number of cases with radiographs available for review limited the statistical power of this analysis (P=0.40).

Subjects with plaque erosions also had significantly lower cardiovascular risk (mean Framingham risk index 7.4±5.4) compared with those with stable plaques and plaque ruptures (Figure 2B, ANOVA P=0.001). The Framingham risk index in subjects with plaque rupture (17.3±10.4) was also significantly greater than stable plaques (10.5±9.9, P=0.014). These relationships were similar when examined separately for men and women.

A single focus of microscopic calcification was present in 81% of cases, and 62% had at least 1 focus of coronary calcification with an area ≥40 μm. A Framingham risk index at or above the predicted average risk for age² was present in 62% of cases. Coronary calcification ≥40 μm was present in 57% of cases with a below-average Framingham risk index score such that, overall, 66 of 79 cases (83.5%) had either characteristic (Figure 3).

There was significant disagreement between the histologic calcification score and the Framingham risk index for the classification of coronary heart disease risk in this sample of sudden death cases (Table 2) (P=0.021). Agreement was present in 50 of 79 (63.3%) cases (κ=0.25, P=0.024). Thirty of the 79 cases (38.0%) had both coronary calcification scores below the age-group median values and a Framingham risk index score <10%. Almost half (n=14) of these cases had plaque erosion. The remaining cases with discordance between the calcification score and the Framingham risk index were nearly equally divided between the categories of low calcification score/high Framingham risk index (n=15) and vice versa (n=14). When the calcification score and Framingham risk index were evaluated in subgroups of culprit plaque morphology, cases with plaque erosion were most commonly characterized by both a low calcification score and low Framingham risk index (κ=0.025, P=0.90).

**Discussion**

This study presents a comparison of the Framingham risk index and histologic coronary calcification in a group of
middle-aged patients with sudden cardiac death. Both the Framingham risk index and coronary calcification have been demonstrated to predict future cardiovascular events, but our results demonstrate significant discordance between these measures. When concordant, these predictive tools frequently underestimated risk, most commonly when atherosclerotic plaque erosion was responsible for sudden cardiac death.

The large degree of illness burden due to cardiovascular disease has created considerable interest in developing risk prediction models to identify patients at high risk. The success of prediction tools is crucial to appropriately utilize treatments for the primary prevention of cardiovascular disease. The Framingham risk index is a validated clinical prediction tool that incorporates measurable and treatable coronary risk factors. These features have established the Framingham risk index as the standard against which emerging technologies are measured. Our study found the highest Framingham risk index in cases of sudden cardiac death due to plaque rupture, consistent with past data on the influence of hypercholesterolemia and smoking on this coronary event.

Unfortunately, simple clinical prediction tools have limited accuracy with up to 25% of cardiovascular events remaining unexplained by traditional risk factors. This prognostic gap may be due to more recently recognized coronary risk factors, such as hemostatic factors (eg, fibrinogen), homocysteine, and possibly others (eg, infectious agents). Recent attention has also focused on biomarkers, such as coronary calcification, as a determinate of cardiovascular risk. There are several potential limitations to the anatomic approach to determining prognosis. Coronary calcification estimates only 20% of the total plaque burden because most atherosclerotic lesions are not calcified. As a likely consequence, acute coronary events can occur in both young and old patients with little or no coronary calcification. Thus, there is considerable controversy about the incremental value of expensive anatomic screening tests, such as electron beam CT, over simple clinical prediction algorithms. Preliminary data suggests that electron beam CT has limited specificity but may be superior for the angiographic diagnosis of coronary artery disease in symptomatic patients (not the target population of the Framingham risk index). However, the detection of coronary calcification may have no overall additive value for the determination of cardiovascular prognosis in asymptomatic patients.

TABLE 2. Distribution of Cases With Different Culprit Plaque Morphology Grouped by the 10-Year Framingham Risk Index and the Histologic Calcification Score

<table>
<thead>
<tr>
<th>Framingham Risk Index</th>
<th>Stable Plaque n=27</th>
<th>Plaque Erosion n=22</th>
<th>Plaque Rupture n=30</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>≤10% &gt;10%</td>
<td>≤10% &gt;10%</td>
<td>≤10% &gt;10%</td>
</tr>
<tr>
<td>Histologic calcification score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>11 6</td>
<td>14 3</td>
<td>5 8</td>
</tr>
<tr>
<td>High</td>
<td>4 6</td>
<td>4 1</td>
<td>8 13</td>
</tr>
<tr>
<td>κ</td>
<td>0.24 (P=0.21)</td>
<td>0.025 (P=0.90)</td>
<td>0.16 (P=0.38)</td>
</tr>
</tbody>
</table>

Our data indicate that the correlation between coronary calcification and the Framingham risk index in patients with sudden cardiac death is modest. Furthermore, we found that the prognostic gap exists for both risk modeling and coronary calcification detection. The subjects in this sudden cardiac death study included 38% with a lower than average Framingham risk index score. Of these, 59% also had coronary calcification below the age-adjusted median value of the study group. However, most cases (83.5%) had either a high Framingham risk index score or at least a moderate (≥40 μmol/L in diameter) focus of coronary calcification. These data suggest a possible complementary role of both the Framingham risk index and coronary calcification for the prediction of cardiovascular risk in appropriately selected patients. Because the independent role of the noninvasive detection of coronary calcification for the assessment of cardiovascular prognosis has not yet been fully determined, any assessment of coronary calcification should include a comprehensive cardiovascular risk factor assessment.

Plaque erosion is a recently recognized cause of acute coronary arterial thrombosis. It represents a distinct pathological entity with morphological features and risk factor profiles that are distinct from stable and vulnerable plaques. This study supports the concept that plaque erosion is also a distinct clinical entity. The majority of sudden cardiac deaths due to plaque erosion occurred in subjects that had both a low predicted coronary risk and did not have extensive coronary calcification. Thus, the inability to accurately predict coronary events from plaque erosion provides an additional explanation beyond unmeasured or nontraditional coronary risk factors for the limited accuracy of currently available prediction tools. This limitation is particularly relevant because middle-aged patients are both an important target population for coronary risk screening and the ones with the greatest risk of plaque erosion. More data on the prevalence, clinical correlates, and noninvasive detection of plaque erosion in acute coronary syndromes, other than sudden cardiac death, are needed.

Limitations
This study is potentially limited by selection bias caused by autopsy sampling of fatal cases and may not be representative of patients with coronary thrombosis who survive. These data from relatively young patients with
sudden cardiac death cannot be generalized to older patients with coronary artery disease. This autopsy study necessarily focused on the “hard” event of coronary death, and the relationships that we have described between plaque morphology and risk prediction tools may not be the same for other cardiovascular events, such as the development of angina or the need for coronary revascularization. However, recent clinical data indicate similar predictive capability of the Framingham risk index and electron beam CT for all cardiovascular events. For determining high-risk calcification scores, we used the median calcium scores of this group of sudden cardiac death autopsies. It is possible that the concordance between coronary calcifications and the Framingham risk index would have been improved using population-based median scores as a cut off for high and low risk. However, such data are not available. Other recommendations suggest that using a coronary calcification score above the 75th percentile for age is an appropriate threshold for determining increased cardiovascular risk. Lastly, although the sensitivity of histology and clinically practical methods for the detection of coronary calcification differ, histology is required to distinguish plaque erosion from plaque rupture.

Conclusions
Coronary risk factors and coronary calcification are distinct determinants for the detection of patients at increased risk for sudden cardiac death. This study suggests that excessive reliance on any individual determinant will have limited predictive accuracy. Furthermore, an important minority of events, particularly those caused by plaque erosion, will remain poorly predicted. Alternative methods are needed that better predict sudden cardiac death secondary to plaque erosion.

Acknowledgment
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A Comparison of the Framingham Risk Index, Coronary Artery Calcification, and Culprit Plaque Morphology in Sudden Cardiac Death

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