Identification of Patients at Increased Risk of First Unheralded Acute Myocardial Infarction by Electron-Beam Computed Tomography

Paolo Raggi, MD; Tracy Q. Callister, MD; Bruce Cooil, PhD; Zuo-Xiang He, MD; Nicholas J. Lippolis, MD; Donald J. Russo, MD; Alan Zelinger, MD; John J. Mahmarian, MD

Background—There is a clear relationship between absolute calcium scores (CS) and severity of coronary artery disease. However, hard coronary events have been shown to occur across all ranges of CS.

Methods and Results—We conducted 2 analyses: in group A, 172 patients underwent electron-beam CT (EBCT) imaging within 60 days of suffering an unheralded myocardial infarction. In group B, 632 patients screened by EBCT were followed up for a mean of 32±7 months for the development of acute myocardial infarction or cardiac death. The mean patient age and prevalence of coronary calcification were similar in the 2 groups (53±8 versus 52±9 years and 96% each). In group B, the annualized event rate was 0.11% for subjects with CS of 0, 2.1% for CS 1 to 99, 4.1% for CS 100 to 400, and 4.8% for CS >400, and only 7% of the patients had CS >400. However, mild, moderate, and extensive absolute CSs were distributed similarly between patients with events in both groups (34%, 35%, and 27%, respectively, in group A and 44%, 30%, and 22% in group B). In contrast, the majority of events in both groups occurred in patients with CS >75th percentile (70% in each group).

Conclusions—Coronary calcium is present in most patients who suffer acute coronary events. Although the event rate is greater for patients with high absolute CSs, few patients have this degree of calcification on a screening EBCT. Conversely, the majority of events occur in individuals with high CS percentiles. Hence, CS percentiles constitute a more effective screening method to stratify individuals at risk. (Circulation. 2000;101:850-855.)

Key Words: calcium ■ tomography ■ myocardial infarction ■ coronary disease
matched control subjects, for predicting hard cardiac events. We performed EBCT scanning in 2 distinct patient groups. (1) Group A consisted of 172 patients who had suffered an AMI as their first clinical manifestation of CAD and who underwent EBCT imaging shortly after their acute events. In this group, the imaging was conducted to estimate the extent of plaque burden that could have been identified had EBCT scanning been performed before the patients suffered an AMI. (2) A telephone survey for the occurrence of hard events was conducted in 632 patients who had originally been referred for a screening EBCT by their primary care physicians because of the presence of risk factors for CAD (group B). The average follow-up was 32±7 months. In both groups, absolute CSs and percentiles were calculated.

Methods

Patient Selection
One hundred seventy-two patients who had suffered an AMI with no previous clinical manifestation of CAD were enrolled in group A. The diagnosis of AMI was based on standard clinical and ECG criteria as well as a characteristic rise and fall in plasma creatine kinase MB fraction.

The number of patients in each group is in parentheses.

<table>
<thead>
<tr>
<th>Age, y</th>
<th>Men (5433)</th>
<th>25th percentile</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
<th>Women (4297)</th>
<th>25th percentile</th>
<th>50th percentile</th>
<th>75th percentile</th>
<th>90th percentile</th>
</tr>
</thead>
<tbody>
<tr>
<td>35–39</td>
<td>(479)</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>0</td>
<td>(288)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>40–44</td>
<td>(859)</td>
<td>0</td>
<td>3</td>
<td>11</td>
<td>21</td>
<td>(589)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>45–49</td>
<td>(1066)</td>
<td>0</td>
<td>16</td>
<td>44</td>
<td>64</td>
<td>(822)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>50–54</td>
<td>(1085)</td>
<td>3</td>
<td>41</td>
<td>101</td>
<td>176</td>
<td>(903)</td>
<td>10</td>
<td>0</td>
<td>0</td>
<td>4</td>
</tr>
<tr>
<td>55–59</td>
<td>(853)</td>
<td>14</td>
<td>118</td>
<td>187</td>
<td>320</td>
<td>(693)</td>
<td>33</td>
<td>87</td>
<td>0</td>
<td>24</td>
</tr>
<tr>
<td>60–64</td>
<td>(613)</td>
<td>28</td>
<td>151</td>
<td>434</td>
<td>502</td>
<td>(515)</td>
<td>87</td>
<td>123</td>
<td>87</td>
<td>0</td>
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<tr>
<td>65–70</td>
<td>(478)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(485)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The number of patients in each group is in parentheses.

was defined by current use of antihypertensive medications or known but untreated hypertension. Current smoking was necessary for the definition of positive smoking status. Hypercholesterolemia was defined as currently receiving cholesterol-lowering medications or the presence of known but untreated hypercholesterolemia. Patients currently receiving insulin or oral hypoglycemic agents were classified as diabetic. A family history of premature CAD was considered present if CAD had occurred in a first- or second-degree relative at <55 years of age.

All patients gave informed consent to participate in the study, and the internal review boards of our institutions approved the research protocol.

Imaging Protocol

All patients underwent EBCT imaging with an Imatron C-100 or C-150 scanner, those in group A within 6 weeks of AMI. Images were obtained with 100-ms scan time and 3-mm single-slice thickness, with a total of 40 slices starting at the level of the carina and proceeding to the level of the diaphragm. Tomographic imaging was electrocardiographically triggered to 80% of the R-R interval. Coronary calcification was defined as a plaque of ≥4 consecutive pixels (area=1.37 mm²) with a density of ≥130 HU. Quantitative CSs were calculated according to the method described by Agatston et al.23 All EBCT scans were reviewed in random order by 3 separate investigators, and because calcium scoring was performed only once on each patient, interinvestigator score variability was not calculated.

Statistical Analysis

Four absolute CS categories were considered: zero, mild score (CS=1 to 99), moderate score (CS=100 to 400), and severe score (>400). CSs were also expressed as age- and sex-adjusted CS percentiles derived from a group of 9728 subjects who underwent EBCT imaging at 1 center (EBT Research Foundation, Nashville, Tenn; Table 1). These patients had a distribution of risk factors for CAD similar to those of the patients in the study groups: systemic hypertension, 47%; diabetes mellitus, 11%; smoking, 43%; hypercholesterolemia, 56%; and family history of CAD, 69% (see Table 2 for comparison).

For patients in the prospective cohort, the absolute event rates, risk ratios, and relative risk of events were calculated in each CS and risk factor quartile. The quartiles of CS percentile were created by subdividing the population into 4 numerically equal groups. The event rate was derived by assigning to each numerically balanced quartile group the observed number of events in each quartile. Risk factor quartile groups were created by including the following risk factors: men >45 years old, women >55 years old, current smoking, systemic hypertension, diabetes mellitus, hypercholesterolemia, and family history of premature CAD.
ANOVA and 2-sample t tests were used to compare the means of continuous variables. χ² analysis and the 2-sample test on proportions were used to compare categorical variables. All cited probability values are 2-tailed, and a value of P<0.05 was considered statistically significant. All data are expressed as mean±SD.

Results

Post-AMI Cohort

The clinical characteristics of group A patients are shown in Table 2. The overall mean CS was 367±535, and this was similar in the 126 men (389±559) and 46 women (307±534). The median CS for the entire group was 160. EBCT imaging showed CAC in 165 patients (96%). Four women and 3 men did not have CAC, and although their mean age was lower than that of patients with CAC, this difference did not reach statistical significance (47±8 versus 53±8; P=0.058). Of note, all patients without CAC at the time of AMI were smokers.

The individual CSs were mild (1 to 99) in 34%, moderate (100 to 400) in 35%, and severe (>{400} in 27% of the subjects (Table 3; P=NS for all comparisons by χ² analysis).

Table 3 shows the distribution of CS percentiles found in study patients in relation to the age- and sex-adjusted values presented in Table 1. The majority of group A patients (87%) had a CS >50th percentile for age and sex, 70% showed a CS >75th percentile, and 42% showed a CS >90th percentile. All comparisons of observed and expected prevalence of CSs were highly statistically significant (87% versus 50%, 70% versus 25%, and 42% versus 10%; P<0.001).

Prospective Cohort

The clinical characteristics of group B patients are shown in Table 2. In this cohort, 50% of patients were men, and 54% had CAC on the screening EBCT. The mean CS for the entire cohort was 101±254; median, 3.1. During 32±7 months, 27 patients (4%) had either a fatal cardiac event (n=8) or nonfatal AMI (n=19). Of these 27 patients, 26 (96%) had CAC on the initial EBCT, and their mean and median CSs were statistically greater than in the 605 individuals without events (303±441 versus 92±240, P<0.001, and 141 versus 2.4, P<0.001, respectively).

TABLE 3. Distribution of Absolute CS Values and CS Percentiles

<table>
<thead>
<tr>
<th>Absolute CS</th>
<th>Group A (n=172)</th>
<th>Group B, Hard Event (n=27)</th>
<th>Group B, No Hard Event (n=605)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>7 (4)</td>
<td>1 (4)</td>
<td>291 (48)</td>
</tr>
<tr>
<td>1–99</td>
<td>58 (34)</td>
<td>12 (44)</td>
<td>207 (34)</td>
</tr>
<tr>
<td>100–400</td>
<td>60 (35)</td>
<td>8 (30)</td>
<td>66 (11)</td>
</tr>
<tr>
<td>&gt;400</td>
<td>47 (27)</td>
<td>6 (22)</td>
<td>41 (6)</td>
</tr>
<tr>
<td>CS percentiles</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50th percentile</td>
<td>150 (87)</td>
<td>23 (85)</td>
<td>258 (43)</td>
</tr>
<tr>
<td>&gt;75th percentile</td>
<td>121 (70)</td>
<td>19 (70)</td>
<td>162 (27)</td>
</tr>
<tr>
<td>&gt;90th percentile</td>
<td>72 (42)</td>
<td>11 (41)</td>
<td>82 (14)</td>
</tr>
</tbody>
</table>

Values are n (%).

Prevalence of mild, moderate, and severe CS and CS percentiles for the patients in group B are shown in Table 3. As in the retrospective analysis, >2/3 of the events occurred in patients with mild to moderate absolute CS values (74% in group B versus 69% in group A, P=NS), and >1/4 occurred in patients with severe CS (22% in group B versus 27% in group A; P=NS). These results are compatible with angiographic and pathological findings demonstrating that the majority of patients who suffer an AMI or sudden cardiac death have nonobstructive coronary artery lesions.24–26

The annualized event rate was 0.11% for the 292 subjects with a CS of 0, compared with 2.1% for those with a CS of 1 to 99, 4.1% for those with a CS of 100 to 400, and 4.8% for those with a CS >400. Although 22% of the events occurred in patients with a CS >400, only 7% of the entire cohort showed a CS in this range, and the majority of events occurred in patients with mild or moderate CSs. Hence, although a larger absolute CS identified a population at high risk of events, these values reflected only a small segment of the population at risk and would therefore not constitute an optimal screening method.

Conversely, as shown in the prospective group, the majority of patients who suffered an acute AMI in group B had a CS percentile value in the upper range of normal (85% >50th percentile, 70% >75th percentile, and 41% >90th percentile). Again, the comparisons of observed and expected prevalence of CS percentiles were all highly statistically significant (85% versus 50%, 70% versus 25%, and 41% versus 10%; P<0.001).

Limiting the analysis to patients who showed a CS >75th percentile demonstrated that a much greater proportion of events occurred in patients in this quartile group than in all other lower quartile groups considered together (19 events in 181 patients versus 8 events in 451 patients; P<0.001).

Risk Analysis of Prospective Patient Cohort

Table 4 shows a comparison of total number of events, annualized absolute event rates, and odds ratios for an event in the 27 prospective patients identified according to quartiles of CS percentiles and risk factors. The risk ratio for events in the highest risk factor quartile was 6.5-fold greater than in the
lowest quartile (13/2=6.5). In contrast, the risk ratio for patients in the highest CS quartile (ie, CS >75th percentile) was 19 times that of patients in the lowest quartile (19/1 = 19). Furthermore, the odds ratios for events in the upper 2 quartiles of CS percentiles were substantially greater than in the respective risk factor quartiles (6.2 and 21.5 versus 3.1 and 7.0, respectively), although there was some overlapping of the CIs. The annualized relative risk of events (Table 5) ranged from 0.09 to 1.05 (12-fold difference) between the lowest and the highest quartiles in patients identified according to risk factors and from 0.045 to 2.7 (59-fold difference) when the grouping was done according to CS quartiles. This analysis suggests that although traditional risk factors for CAD are very valuable predictors, percentiles of CS are a substantially better means of identifying patients at risk of hard coronary events.

### Discussion
Calcification of the coronary arteries, identified and measured on EBCT imaging, is highly prevalent in patients suffering an acute AMI and strongly predictive of hard events. This study demonstrates that CS percentiles, based on patient age and sex, are better predictors than absolute CS values and categorical risk factors for CAD. In this regard, Wilson et al\(^27\) recently showed that the presence of categorical risk factors for CAD is as predictive of cardiovascular events as the measurement of such continuous variables as systolic hypertension and LDL cholesterol levels. Therefore, the assumptions made in this study about the relative ability of risk factor categories to predict events in comparison to CS categories are pertinent.

As previously shown, CAC is present with a very high prevalence in patients who suffer a coronary event,\(^16,25,26,28,29\) indicating that this is a true marker of CAD. However, previous studies showed an apparent paradox: patients with high CSs were shown to be at high risk of hard events, but only a small portion of the population would show high CS, and events were evenly distributed across all ranges of absolute CS.\(^16,19\) Our study suggests that high CS percentiles are highly prevalent in patients suffering a hard event independent of the absolute CS and that these measurements may allow a better segregation of the portion of an asymptomatic population that may benefit from therapeutic interventions.

The process of coronary calcification is currently believed to be an active process similar in many aspects to true bone formation.\(^30–34\) Some investigators view this process as a repair mechanism to the damage caused by various noxious stimuli.\(^17\) A larger-than-expected amount of coronary calcium might indicate the presence of an aggressive damage of the arterial wall requiring either a faster or a more extensive repair. In this context, the amount of coronary calcium relative to the patient’s age and sex could be seen as an indicator of plaque activity rather than plaque quiescence.

Rosamond et al\(^1\) showed that in recent years, the incidence of AMI has continued to increase even though the mortality rate from AMI has declined. Hence, primary prevention of CAD must remain the focus of public health policies of industrialized nations. The Framingham equations\(^36,37\) provide a population-based method to assess the median risk of developing CAD but do not allow discernment of the individual’s risk. The National Cholesterol Education Program (NCEP)-II guidelines\(^38\) provide a very helpful aid for the prevention of CAD in people at risk, but published data suggest a maximum 3- to 5-fold increase in estimated risk between patients with the lowest and the highest risk profiles.\(^39–41\) Sophisticated computer simulations have been attempted to improve on the predictive ability of these models, but with poor applicability to the everyday clinical practice.\(^39\) Furthermore, according to the NCEP-II guidelines, 21.1 million Americans (≈17% of the adult population) need treatment for the presence of risk factors for CAD.\(^42\) However, even when more liberal treatment criteria are applied, as suggested in the recent Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS) trial,\(^1\) only 37% of the AMIs are prevented. Conversely, our EBCT analysis suggests that a larger number of hard events could be addressed by implementation of this screening strategy. If patients with CS >75th percentile were treated, ≈70% of the events could potentially be prevented, and if patients with CS >90th percentile were treated, ≈40% of the events could be prevented. Hence, EBCT screening for coronary calcification

![Table 4](attachment:image.png)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>CS%</th>
<th>Risk Factors</th>
<th>CS%</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>1 (0.2%)</td>
<td>2 (0.5%)</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2nd</td>
<td>1 (0.2%)</td>
<td>6 (1.4%)</td>
<td>1.0</td>
<td>0.1, 16.1</td>
</tr>
<tr>
<td>3rd</td>
<td>6 (1.4%)</td>
<td>6 (1.4%)</td>
<td>6.2</td>
<td>0.7, 52.1</td>
</tr>
<tr>
<td>4th</td>
<td>19 (4.5%)</td>
<td>13 (3.1%)</td>
<td>21.5</td>
<td>2.8, 162.4</td>
</tr>
</tbody>
</table>

CS% indicates calcium score percentile.

![Table 5](attachment:image.png)

<table>
<thead>
<tr>
<th>Quartile</th>
<th>CS Percentiles</th>
<th>Risk Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>0.045</td>
<td>0.09</td>
</tr>
<tr>
<td>4th</td>
<td>2.7</td>
<td>1.05</td>
</tr>
</tbody>
</table>
should improve the practicing physician’s ability to stratify individuals at high risk of events, to whom aggressive treatment of traditional risk factors for CAD can be more appropriately directed.

Of note, the data presented in this study confirm previous observations pertaining to the absence of CAC on EBCT imaging in a percentage of young smokers who suffer an acute coronary event. Similar findings have been reported in pathological studies conducted in young individuals who died of cardiac arrest or AMI. This indicates that prudence should be used in characterizing the absence of CAC or the presence of small amounts of CAC in young smokers as a nonthreatening marker for acute coronary events.

Study Limitations
Our postevent imaging analysis in group A was limited to nonfatal AMI cases. However, nonfatal AMI is the most prevalent clinical manifestation of coronary heart disease in men and the second most prevalent in women, and its incidence continues to rise in recent years. We can only conjecture that the amount of CAC found in patients who die of an acute coronary event is at least as extensive as, if not greater than, the amount found in patients who suffer a nonfatal event. Interestingly, in the prospective group, the patients who died had a larger amount of coronary calcification than those who suffered a nonfatal AMI (median CS, 391 versus 75, \( P<0.04 \)). Finally, the presence of risk factors for CAD was not directly assessed but rather inferred from current medical regimens or patient self-reporting.

Conclusions
The incidence of cardiovascular events is greatly increased in the presence of CAC. Although high CSs portend a high risk of events, only a relatively small portion of the AMIs occur in this fraction of the population, and the majority of events occur in patients with mild to moderate amounts of CAC. Conversely, high age- and sex-adjusted CS percentiles appear to be closely related to the occurrence of subsequent hard events, and we suggest that this measurement should be used in the assessment of the risk of a hard event in asymptomatic individuals undergoing EBCT screening.

Acknowledgment
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References


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