Probabilistic Model for Prediction of Angiographically Defined Obstructive Coronary Artery Disease Using Electron Beam Computed Tomography Calcium Score Strata

Lawrence F. Bielak, DDS, MPH; John A. Rumberger, PhD, MD; Patrick F. Sheedy II, MD; Robert S. Schwartz, MD; Patricia A. Peyser, PhD

Background—Electron beam CT (EBCT) is an accurate, noninvasive method to detect and quantify coronary artery calcification, a marker of coronary artery disease (CAD). This investigation examined the accuracy of EBCT to detect obstructive CAD (≥50% stenosis) and determined the optimal strata for quantity of coronary artery calcification to facilitate clinical decision-making.

Methods and Results—Clinical research patients (n=213) were examined with coronary angiography and EBCT (angiography group), and 765 research participants were examined with only EBCT (nonangiography group). Of the angiography group, 53% had obstructive CAD. After adjustment for verification bias, the estimated sensitivity and specificity for calcium score ≥1 were 97.0% and 72.4%, respectively. Likelihood ratios for strata of calcium score associated with obstructive CAD were calculated in each sex and 2 age groups. Among those ≥50 years old, the same 4 strata of EBCT calcium scores were identified in each sex; likelihood ratios ranged from 0.03 (calcium score 0) to 12.85 (calcium score ≥200). The same 3 strata of EBCT calcium scores were identified in each sex among those <50 years old; likelihood ratios ranged from 0.13 (calcium score 0) to 190 (calcium score ≥100).

Conclusions—A calcium score ≥200 among those ≥50 years old and calcium score ≥100 among those <50 years old provided strong evidence that patients of either sex had obstructive CAD. A calcium score of 0 provided strong evidence that patients <50 years old did not have obstructive CAD. (Circulation. 2000;102:380-385.)

Key Words: coronary disease ▪ calcium ▪ tomography

Coronary artery calcification (CAC) is an active part of the atherosclerotic process and predicts coronary artery disease (CAD) events in asymptomatic and symptomatic individuals.1–4 Electron beam CT (EBCT) is an accurate, noninvasive method to detect and quantify CAC.5 In symptomatic men and women, EBCT scanning for CAC adds to the power of conventional CAD risk factors to predict CAD at angiography.6,7

The usefulness of EBCT in diagnostic clinical decision-making has not been clearly established in a probabilistic model. Application of cardiac testing (eg, exercise-induced ST-segment response8) is predicated on first defining the probability of CAD on the basis of clinical information (pretest probability) and then revising the probability up or down based on test results (posttest probability).

Estimates of the sensitivity and specificity of CAC at EBCT to detect obstructive CAD, defined as ≥50% stenosis at angiography, are high, and the negative predictive value approaches 100% in most studies.9–14 The estimates of sensitivity and specificity are biased, however, because the information regarding the ability of EBCT to predict obstructive CAD comes to us through studies of symptomatic patients who had their CAD status verified with coronary angiography. Generally, as a result of this “verification” bias, sensitivity will be overestimated (because positive EBCT results will be overrepresented) and specificity will be underestimated (because negative EBCT results will be underrepresented) in those receiving angiography. Methods to adjust for its presence have been demonstrated for other noninvasive tests for CAD, such as exercise echocardiography15,16 and 201TI single photon emission CT17 but not for EBCT.

The clinical interpretation of quantity of CAC to estimate the probability of obstructive CAD remains ill-defined and has not been investigated via a traditional Bayesian approach to pretest and posttest probabilities of disease. The posttest probability of disease is derived from the pretest probability
and the likelihood ratio. A likelihood ratio is an expression of the odds that a given test result will occur in an individual with the disease as opposed to an individual without the disease. Likelihood ratios can be calculated simultaneously for different levels (strata) of quantitative test results; therefore, it is possible to separate a slightly positive test result from a markedly positive test result and to weigh the value of each accordingly.

The purpose of this investigation was to (1) estimate sex- and age-group--specific likelihood ratios for EBCT to predict obstructive CAD after adjustment for verification bias and (2) use these adjusted likelihood ratios to determine strata of probability of obstructive CAD within sex and age groups to facilitate probabilistic clinical decision-making.

Methods

Sample

Participants in this study consisted of 213 clinical research patients who were examined with EBCT of the heart and coronary angiography (angiography group) and 765 research participants who were examined with EBCT but not with coronary angiography (nonangiography group). All 978 individuals participated in research studies between January 1, 1989, and October 31, 1994, at the Mayo Clinic in Rochester, Minn. All were examined with the same EBCT scanning protocol, scoring system, and reporting method. The study protocols were approved by the Mayo Clinic Institutional Review Board, and patients gave informed consent before participating in the studies.

The sample and study protocol of the angiography group have been described previously. Patients undergoing clinically indicated angiography for the diagnosis of obstructive CAD were invited to participate in the study and be examined with EBCT if they had not had previous angioplasty, bypass surgery, or heart transplantation. Seventy-five percent (n=160) underwent angiography for assessment of chest pain, 12% (n=25) had abnormal stress tests, 8% (n=17) had unexplained heart failure, and the remainder (5%, n=11) had a questionable history of prior infarction, pericarditis, or unexplained dyspnea.

Patients were not preselected for angiography on the basis of the results of their EBCT examinations, and most had EBCT after their angiography, usually on the following morning. These patients were selected for angiography on the basis of conventional clinical factors and at the request of their consulting cardiologist. Most were men (162 of 213, 76%) and were ≥50 years old (155 of 213, 73%). Because of the sex and age distribution and given that these patients were highly “likely” to have obstructive CAD, they would be expected to have a higher prevalence and quantity of CAC than individuals chosen from a random sample of the general population. Thus, verification bias would be present in this angiography group.

To adjust for this bias, data on sex, age, and calcium score from 765 research participants who were examined with EBCT but not with angiography during the same time period were incorporated into these analyses. Individuals in this nonangiography group were examined as part of a community-based study of the epidemiology of CAC as described in detail elsewhere. These participants were not physician- or self-referred. None had a history of previous angioplasty, bypass surgery, or other coronary surgery. Approximately half of the nonangiography group were men (375 of 765, 49%), and half were ≥50 years old (383 of 765, 50%).

Measures

All angiograms were visually assessed by 2 angiographers. In the case of disagreement in the interpretation of an angiogram, it was read by a third angiographer, and the interpretation was arbitrated. CAD was defined as obstructive CAD (≥50% stenosis in ≥1 major artery). Quantity of CAC was defined as the calcium score according to Agatston et al.

Statistical Analysis

The method of Begg and Greenes was used to estimate the adjusted sensitivity and specificity of EBCT for obstructive CAD in all patients undergoing EBCT. In the angiography group, logistic regression models were used to estimate the probability of having obstructive CAD. Variables included in the models were age, sex, and a calcium score within a given stratum as described below. By use of parameter estimates from these models, the predicted probability of obstructive CAD was calculated for each patient in the nonangiography group. These predicted probabilities were then summed separately for those with a calcium score within the given calcium score stratum and those with calcium scores outside the calcium score stratum for each sex and for 2 age groups (those ≥50 years old and those <50 years old). The adjusted sensitivities and specificities within specific sex and age groups were estimated by combining these sums for the nonangiography group with the observed numbers in the angiography group. This process was repeated for each calcium score stratum. The adjusted sensitivities and specificities were then used to calculate stratum-specific likelihood ratios (SSLRs) for EBCT.

The likelihood ratio of a positive test is defined as sensitivity/(1–specificity), and the likelihood ratio of a negative test is defined as (1–sensitivity)/specificity. Likelihood ratios are the odds that a given test result will occur in an individual with the disease as opposed to an individual without the disease. Likelihood ratios range from zero to infinity.

The method of Peirce and Cornell was used to determine SSLRs along with their 95% CIs for stratum of calcium score in detecting obstructive CAD. This method has been used to investigate the validity of prostate-specific antigen levels in detecting prostate cancer. A likelihood ratio equal to 1 indicates that the given stratum of calcium score is not able to discriminate between those with and those without the disease, and there should be no revision of the pretest probability based on the test result. The pretest probability would be revised upward if the SSLR were >1 or downward if the SSLR were <1. The magnitude of the SSLR defines the amount of the revision.

Initially, the following 7 strata of EBCT coronary calcium scores were evaluated: 0, 1 to 9, 10 to 49, 50 to 99, 100 to 199, 200 to 499, and ≥500. Two adjacent strata of calcium scores were combined into one if the 95% CI of one SSLR overlapped an adjacent SSLR. The process was repeated in each sex- and age-specific subgroup until there was a monotonic increase in the SSLRs and the 95% CI of one stratum did not overlap with the SSLRs of adjacent strata.

To compare the findings with those presented by others, we estimated the unadjusted sensitivity and specificity in the angiography group and the adjusted sensitivity and specificity in the entire study group for calcium score ≥1.

Results

The prevalence of any measurable CAC was significantly higher among patients in the angiography group (81.2%) than the nonangiography group (40.8%) (P<0.001), as was the mean natural log–transformed calcium score (3.92 versus 1.52, respectively, P<0.0001). Table 1 shows the frequency distribution of patients in the angiography group with and without obstructive CAD and in the nonangiography group by calcium score stratum.

In the angiography group, half (112 of 213, 52.6%) of the patients had obstructive CAD, and calcium scores ranged from 0 to 4091.76. Only 1 patient with obstructive CAD (0.9%) had a calcium score of 0, but 39 patients without obstructive CAD (38.6%) had a calcium score of 0. Conversely, half (52 of 112, 46.4%) of the patients with obstruct-
tive CAD had calcium scores $\geq 500$, but few (3 of 101, 3.0%) patients without obstructive CAD had calcium scores $\geq 500$ (Table 1). In the nonangiography group, more than half had calcium scores of 0 (453 of 765, 59.2%), whereas few (33 of 765, 4.3%) had calcium scores $\geq 500$ (Table 1). Among patients $\geq 50$ years old, 116 men and 39 women were in the angiography group; 187 men and 196 women were in the nonangiography group. After adjustment for verification bias, there were 4 optimal strata of calcium score (Table 2). In both men and women, a calcium score equal to 0 had an SSLR close to 0. Calcium scores of $\geq 200$ had a high SSLR in both men [SSLR=12.85 (5.95, 27.76)] and women [SSLR=12.85 (5.46, 30.22)].

Among patients $<50$ years old, 46 men and 12 women were in the angiography group; 188 men and 194 women were in the nonangiography group. After adjustment for verification bias, there were 3 optimal strata of calcium score (Table 3). In men, a calcium score equal to 0 had an SSLR that was close to 0. Calcium scores $\geq 100$ had a very high SSLR in men [SSLR=54.44 (13.41, 220.98)] and women [SSLR=189.69 (15.6, 2306.13)].

In the angiography group, the unadjusted sensitivity and specificity for calcium score $\geq 1$ were 99.1% and 38.6%, respectively. After adjustment for verification bias, the estimated sensitivity and specificity for calcium score $\geq 1$ were 97.0% and 72.4%, respectively.

### Discussion

The results of the present study demonstrate 3 major points. First, after adjustment for verification bias, the estimated specificity of EBCT to detect obstructive CAD was markedly higher than the unadjusted specificity in the angiography group (72.4% versus 38.6%); however, there was little change in the estimated sensitivity (97.0% versus 99.1%). Other studies have also demonstrated this trend toward increasing specificity and decreasing sensitivity after adjustment for verification bias for other noninvasive tests for CAD.15–17 Second, use of different strata or levels of quantity of CAC were advantageous for detecting individuals with CAD. Third, the levels of quantity of CAC that were optimal for detecting CAD differed primarily by age but not sex within each age group.

### TABLE 1. Distribution of Patients by Study Group and CAC Score Stratum

<table>
<thead>
<tr>
<th>CAC Score Stratum</th>
<th>0</th>
<th>1–9</th>
<th>10–49</th>
<th>50–99</th>
<th>100–199</th>
<th>200–499</th>
<th>$&gt;500$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Angiography patients</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>With obstructive CAD</strong> (n=112)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>1</td>
<td>8</td>
<td>6</td>
<td>7</td>
<td>17</td>
<td>21</td>
<td>52</td>
</tr>
<tr>
<td>Percent</td>
<td>0.9</td>
<td>7.1</td>
<td>5.4</td>
<td>6.2</td>
<td>15.2</td>
<td>18.8</td>
<td>46.4</td>
</tr>
<tr>
<td><strong>With less than obstructive CAD</strong> (n=101)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>39</td>
<td>23</td>
<td>19</td>
<td>6</td>
<td>7</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>Percent</td>
<td>38.6</td>
<td>22.8</td>
<td>18.8</td>
<td>6.2</td>
<td>6.9</td>
<td>4.0</td>
<td>3.0</td>
</tr>
<tr>
<td><strong>Total</strong> (n=213)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>40</td>
<td>31</td>
<td>25</td>
<td>13</td>
<td>24</td>
<td>25</td>
<td>55</td>
</tr>
<tr>
<td>Percent</td>
<td>18.8</td>
<td>14.6</td>
<td>11.7</td>
<td>6.1</td>
<td>11.3</td>
<td>11.7</td>
<td>25.8</td>
</tr>
<tr>
<td><strong>Nonangiography patients</strong> (n=765)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No.</td>
<td>453</td>
<td>83</td>
<td>83</td>
<td>49</td>
<td>37</td>
<td>27</td>
<td>33</td>
</tr>
<tr>
<td>Percent</td>
<td>59.2</td>
<td>10.9</td>
<td>10.9</td>
<td>6.4</td>
<td>4.8</td>
<td>3.5</td>
<td>4.3</td>
</tr>
</tbody>
</table>

*Obstructive CAD is defined as $\geq 50\%$ stenosis in $\geq 1$ major coronary artery.

### TABLE 2. Adjusted Likelihood Ratio Across Optimal Strata of CAC Score for Predicting Obstructive CAD* in All Participants $\geq 50$ Years Old

<table>
<thead>
<tr>
<th>CAC Score Stratum</th>
<th>0</th>
<th>1–49</th>
<th>50–199</th>
<th>$&gt;200$</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Men, n</strong></td>
<td>59</td>
<td>75</td>
<td>69</td>
<td>100</td>
</tr>
<tr>
<td>Adjusted likelihood ratio</td>
<td>0.03</td>
<td>0.36</td>
<td>1.95</td>
<td>12.85</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>0.01</td>
<td>0.24</td>
<td>1.23</td>
<td>5.95</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>0.09</td>
<td>0.56</td>
<td>3.10</td>
<td>27.76</td>
</tr>
<tr>
<td><strong>Women, n</strong></td>
<td>129</td>
<td>44</td>
<td>34</td>
<td>28</td>
</tr>
<tr>
<td>Adjusted likelihood ratio</td>
<td>0.07</td>
<td>1.25</td>
<td>4.17</td>
<td>12.85</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>0.02</td>
<td>0.71</td>
<td>2.29</td>
<td>5.46</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>0.19</td>
<td>2.21</td>
<td>7.60</td>
<td>30.22</td>
</tr>
</tbody>
</table>

*Obstructive CAD is defined as $\geq 50\%$ stenosis in $\geq 1$ major coronary artery.
TABLE 3. Adjusted Likelihood Ratio Across Optimal Strata of CAC Score for Predicting Obstructive CAD* in All Participants <50 Years Old

<table>
<thead>
<tr>
<th>CAC Score Stratum</th>
<th>0</th>
<th>1–99</th>
<th>&gt;100</th>
</tr>
</thead>
<tbody>
<tr>
<td>Men, n</td>
<td>129</td>
<td>87</td>
<td>18</td>
</tr>
<tr>
<td>Adjusted likelihood ratio</td>
<td>0.13</td>
<td>1.38</td>
<td>54.44</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>0.05</td>
<td>0.95</td>
<td>13.41</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>0.34</td>
<td>2.01</td>
<td>220.98</td>
</tr>
<tr>
<td>Women, n</td>
<td>176</td>
<td>28</td>
<td>2</td>
</tr>
<tr>
<td>Adjusted likelihood ratio</td>
<td>0.29</td>
<td>4.01</td>
<td>189.69</td>
</tr>
<tr>
<td>Lower 95% CI</td>
<td>0.10</td>
<td>1.86</td>
<td>15.60</td>
</tr>
<tr>
<td>Upper 95% CI</td>
<td>0.86</td>
<td>8.65</td>
<td>2306.13</td>
</tr>
</tbody>
</table>

*Obstructive CAD is defined as ≥50% stenosis in ≥1 major coronary artery.

The higher prevalence and quantity of CAC in the angiography group versus the nonangiography group indicate verification bias in the angiography group. Ideally, this bias would be avoided by randomly assigning patients having EBCT to CAD verification with angiography, without regard to clinical signs or symptoms. This is not possible because of the invasive nature of angiography. Using information from the nonangiography group, we adjusted for verification bias. The adjusted specificity of EBCT was substantially higher than the unadjusted estimate, whereas sensitivity was minimally lowered.

Application of the method of Peirce and Cornell identified 4 strata of EBCT calcium scores in patients ≥50 years old and 3 strata of EBCT calcium scores in patients <50 years old for the determination of obstructive CAD. Although categorization of patients into 2 age groups (those ≥50 and those <50 years old) was useful for clinical purposes, it is important to note that age and calcium score are continuous variables. Future studies in a larger study group could investigate likelihood ratios in more age groups. Below are interpretations of the SSLRs, based on guidelines suggested by Jaeschke et al.29

In men and women ≥50 years old, a calcium score of 0 indicated a large downward revision of the probability of obstructive CAD. In men, scores between 1 and 49 provided small downward revisions in the pretest probability, whereas in women, there would be no revision in the pretest probability of obstructive CAD. For both sexes, scores between 50 and 199 provided a small upward revision in the pretest probability. Calcium scores of ≥200 provided strong evidence in both sexes of obstructive CAD, and the pretest probability should be revised upward. In the angiography group, 48% of the men and women ≥50 years old had calcium scores of ≥200; in the nonangiography group, 14% of the men and women ≥50 years old had calcium scores ≥200.

In men and women <50 years old, a calcium score of 0 indicated only a moderate downward revision in the probability of obstructive CAD. In men <50 years old, scores between 1 and 49 provided no revision in the pretest probability, whereas in women <50 years old, there would be a small upward revision in the pretest probability of obstructive CAD. Scores ≥100 provided very strong evidence in both sexes of obstructive CAD, and the pretest probability should be revised upward. In the angiography group, 14% of the men and women <50 years old had calcium scores ≥100; in the nonangiography group, 3% of the men and women <50 years old had calcium scores ≥100.

In previous studies, the negative predictive value of a calcium score of 0 for obstructive CAD approached 100%. In the present study, a calcium score of 0 provided very strong evidence that patients ≥50 years old did not have obstructive CAD, and the pretest probability would be revised downward. In patients <50 years old, however, a calcium score of 0 would provide for only a small downward revision in the pretest probability of CAD. This is consistent with the high prevalence of CAC and CAD found in individuals ≥50 years old and the low prevalence of CAC and CAD found in individuals <50 years old.20,21 Interestingly, among the 14 patients with obstructive CAD and positive calcium scores <50, 11 of 14 (78.6%) had CAC in the same artery as the obstructive lesion (data not shown).

Application

Graphs of the posttest probabilities illustrate the discriminating power of EBCT examinations for CAC for men and women ≥50 years old (Figures 1 and 2) and men and women <50 years old (Figures 3 and 4). These figures show the posttest probabilities of obstructive CAD as functions of the pretest probabilities and the SSLRs. The pretest probabilities range from 0% to 100%. For a specific pretest probability, the vertical distance between a point on the line indicating the posttest probability and the equity line indicates the size of the difference between the pretest and posttest probabilities as well as the direction of the revision.

For all strata of calcium score, differences between pretest and posttest probabilities were greatest for patients with an intermediate pretest probability. For pretest probabilities close to 0 or 1, the gain in information from the EBCT examination was relatively small. Thus, patients with a very
low or very high pretest likelihood of obstructive disease may not receive much benefit from testing with EBCT. This same trend has also been observed with other noninvasive tests for CAD, such as traditional stress testing.\(^{30}\)

The following examples illustrate how to interpret the figures. Consider a patient who, on the basis of clinical information, was judged to have a low to moderate pretest probability for having obstructive CAD. This could be a man, 60 years old, with nonanginal chest pain, described by Diamond and Forrester\(^ {31}\) to have a pretest probability of obstructive CAD of 0.28. For illustrative purposes, suppose that this patient had a calcium score of 250. The pretest probability for obstructive CAD of 0.28 would be noted on the x axis of Figure 1. Defining a vertical line to the uppermost curve indicating a calcium score \(\geq 200\) and then noting the corresponding coordinates on the y axis, the patient’s posttest probability of obstructive CAD has increased substantially, to \(\approx 0.85\). Thus, this patient is very likely to have obstructive CAD and may need to go on for further testing.

In the above example, if the same man had a score of 0 rather than a score of 250, the posttest probability of obstructive CAD would be revised to be very low (\(\approx 0.01\)). With a CAC score of 0, this patient and his clinician would most likely be reassured, and further testing could be directed toward investigation of noncardiac sources of chest pain.

Figure 2 for women \(\geq 50\), Figure 3 for men \(<50\), and Figure 4 for women \(<50\) years old may be used in the same way to evaluate pretest and posttest probabilities. If the tests are used in series (eg, Diamond and Forrester combined the results of fluoroscopy to detect CAC with stress testing in the diagnosis of obstructive CAD\(^ {31}\)), the uncertainty in the posttest probability from one test may be reduced by the use of another test. Thus, EBCT calcium scores can be used alone or combined with other tests to contribute to diagnostic clinical decision-making.

Acknowledgments

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References

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