Coronary Calcium Does Not Accurately Predict Near-Term Future Coronary Events in High-Risk Adults

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Background—Prognostic risk models have had limited success in predicting coronary events in subjects with multiple risk factors. We and others have proposed an alternative approach using radiographically detectable coronary calcium. We evaluated and compared the predictive value of these 2 approaches for determining coronary event risk in asymptomatic adults with multiple coronary risk factors. In addition, we assessed the predictive value of a risk model that included calcium score and cardiac risk-factor data.

Methods and Results—We recruited 1196 asymptomatic high-coronary-risk subjects who then underwent risk-factor assessment and cardiac electron-beam CT (EBCT) scanning and were followed up for 41 months with a 99% success rate. We applied the Framingham model and our data-derived risk model to determine the 3-year likelihood of a coronary event. The mean age of our cohort was 66 years, and mean 3-year Framingham risk was 3.3 ± 3.6%. Sixty-eight percent (818 subjects) had detectable coronary calcium. There were 17 coronary deaths (1.4%) and 29 nonfatal infarctions (2.4%). The receiver operating characteristic (ROC) curve areas calculated from the Framingham model, our data-derived risk model, and the calcium score were 0.69 ± 0.05, 0.68 ± 0.05, and 0.64 ± 0.05, respectively (P = NS). When calcium score was included as a variable in the data-derived model, the ROC area did not change significantly (0.68 ± 0.05 to 0.71 ± 0.04; P = NS).

Conclusions—Neither risk-factor assessment nor EBCT calcium is an accurate event predictor in high-risk asymptomatic adults. EBCT calcium score does not add significant incremental information to risk factors, and its use in clinical screening is not justified at this time. (Circulation. 1999;99:2633-2638.)

Key Words: risk factors ■ calcium ■ coronary disease ■ tomography

Although coronary atherosclerosis is the leading cause of morbidity and mortality in persons with coronary risk factors,1 the majority of these individuals never develop coronary symptoms. Often, the first indication that coronary atherosclerosis is present is acute myocardial infarction or sudden death. Identification of those subjects with a high probability of suffering such a catastrophe is therefore of great interest, particularly because coronary disease is an increasingly treatable pathological entity.

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Asymptomatic persons with risk factors stand to benefit from aggressive risk-factor modification and/or further testing to reduce morbidity and mortality. Grover et al2 found that an algorithm derived from the Framingham Heart Study was an accurate predictor when applied to future events in the Lipid Research Clinic cohort.3

Recently, an alternative approach to risk stratification in this subset has been proposed4: noninvasive evaluation of coronary calcium by electron beam CT (EBCT). This approach is based on the close histopathological association of calcium with coronary atherosclerosis.4,5 Although coronary calcium assessment has been reported to be of moderate value in predicting coronary events,5 it is not known whether EBCT calcium scanning offers a significant advantage over either information obtained from risk factors or application of the Framingham algorithm.

The primary aim of this investigation was to prospectively compare calcium scanning with risk-factor assessment for predicting coronary heart disease events in asymptomatic high-risk subjects.

Methods

Recruitment of Subjects

The South Bay Heart Watch is a government-funded, prospective study designed to appraise the value of risk-factor assessments and coronary calcium or predicting coronary outcomes in asymptomatic...
Prognosis With CAC in Asymptomatic Adults

TABLE 1. Framingham Risk Model1,2, Data-Derived Risk Factor Model, and Data-Derived Model Including Calcium Score

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>Framingham*</th>
<th>P, Data-Derived,† CHD</th>
<th>P, Data-Derived,‡ CHD</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>CHD Death</td>
<td>MI</td>
<td>Death or MI</td>
</tr>
<tr>
<td>(\theta_0)</td>
<td>2.99</td>
<td>3.41</td>
<td>0.78§</td>
</tr>
<tr>
<td>(\theta_1)</td>
<td>-0.914</td>
<td>-0.858</td>
<td>0.00</td>
</tr>
<tr>
<td>Intercept</td>
<td>11.23</td>
<td>11.5</td>
<td>10.14 (0.0001)</td>
</tr>
<tr>
<td>Female=1</td>
<td>0.233</td>
<td>10.5</td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>-0.944</td>
<td>-0.797</td>
<td></td>
</tr>
<tr>
<td>(\log(\text{age})\times\text{female})</td>
<td>-5.42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\log(\text{age})^2\times\text{female})</td>
<td>0.710</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systolic BP</td>
<td>-0.588</td>
<td>-0.662</td>
<td></td>
</tr>
<tr>
<td>Mean BP</td>
<td>-0.137</td>
<td>-0.268</td>
<td>-0.02 (0.004)</td>
</tr>
<tr>
<td>Smoking=1</td>
<td>-0.345</td>
<td>-0.428</td>
<td></td>
</tr>
<tr>
<td>Total/HDL cholesterol</td>
<td>-0.047</td>
<td>-0.153</td>
<td>-0.17 (0.0002)</td>
</tr>
<tr>
<td>Diabetes=1</td>
<td>-0.223</td>
<td>-0.117</td>
<td>-0.77 (0.004)</td>
</tr>
<tr>
<td>Diabetes×female</td>
<td>-0.124</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH=1</td>
<td>-0.159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LVH×male</td>
<td>-0.159</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Log(Ca score + 1)</td>
<td></td>
<td></td>
<td>-0.14 (0.009)</td>
</tr>
</tbody>
</table>

CHD indicates coronary heart disease; MI, myocardial infarction; BP, blood pressure; and LVH, left ventricular hypertrophy.

*Probabilities of either CHD death or MI were summed.
†Negative coefficients imply increased risk; positive coefficients decreased risk.
‡This model included the calcium score as a variable.
§Each model contains a scale parameter. This is equal to \(\theta_0 + \theta_1 (B \times X)\) for the Framingham model and is equal to the constants shown for the other two models.
| Natural logarithm was used for this variable in this model. |

EBCT Scanning
We performed EBCT scans within 2±2 days after risk-factor evaluation, using an Imatron C-100 scanner. Exposure time was 100 ms per image slice, and total skin radiation was <600 mrad per scan. ECG triggering was used to acquire images at 80% of the RR interval. A standardized and reproducible thick-slice protocol using 6-mm image slices was used. In an initial preliminary report, we confirmed that this protocol has an accuracy for predicting events equivalent to that of more variable 3-mm protocols.

EBCT Analysis
A cardiologist experienced in coronary angiography and tomographic imaging assessed each scan. A region of interest 66 mm² was created that was precisely centered on each locus of calcification, defined as a volume of ≥8.16 mm³ with a CT number >130 Hounsfield units (HU) within the distribution of a coronary artery. The mean and peak CT number and the area of the subsets of pixels with a CT number >130 HU within these regions were calculated. The calcium score was calculated according to the method of Agatston et al.11

Risk Factors

Framingham Risk Model
Anderson et al.12 derived prognostically useful regression models from the Framingham data based on age, sex, and risk factors. The model we applied predicts the hard end points of acute myocardial infarction or coronary death12 and is summarized in Table 1.
Data-Derived Risk Model
To determine the data-derived risk-factor model, we fit an accelerated failure time (AFT) model to the time of coronary death or infarction with independent variables as listed in Table 2.12–14 An AFT model assumes that the effect of independent variables on an event-time distribution is multiplicative on the event time. The scale function is exp \(- (B \times X)\), where \(X\) is the vector of covariate values and \(B\) is the vector of parameters shown in Table 1. A positive value for a parameter implies that an increase in the value of its associated covariate will increase the time scale and thus lower the risk of an event; the opposite is true for a decrease in the covariate. Similarly, a negative value for a parameter implies that an increase in its associated covariate will increase the time scale and thus increase the risk.

Here, the baseline survival distribution was taken to be Weibull distribution, so as to closely approximate the derivation of the Framingham model. Although the Framingham model was based on a nonproportional hazards Weibull AFT,14 we chose to fit the simpler (constant-variance) model. Each model was fit by use of the 1196 time intervals until coronary death or infarction or until censoring occurred. Stepwise regression was used to choose variables for this model from the list of risk factors in Table 1 and their first-degree interactions. The criterion for entry into the model was a value of \(P<0.05\).

To appropriately determine the accuracy of a probability model in determining risk in a given population, the model should be derived and tested in separate samples. To accomplish this, we preserve maximum statistical power, we used a modified bootstrap approach,16 as follows. A recursive macro computer program deleted 1 observation, refit the accelerated failure time model to the remaining 1195 observations, and predicted the response value (probability of coronary death or infarction) for the deleted observation. This procedure was repeated for all 1196 observations. The resulting response values (risks) were used to determine sensitivities and false-positive rates for predicting myocardial infarction or coronary death.

Follow-Up
One, 2, and 3 years after the EBCT examinations, we contacted participants by telephone. At that time, we assessed coronary heart disease using questions concerning intervening hospital admissions and review of medical records for these admissions. We considered a follow-up attempt successful when surviving subjects either returned to the clinic or completed a telephone interview and all relevant medical records were obtained. For deceased subjects, we defined successful follow-up as the procurement of relevant medical records, transcribed conversation with next of kin, death certificate, or autopsy report.

A committee of 3 board-certified cardiologists reviewed medical records and transcripts of conversations with next of kin, without knowledge of other data, and applied majority rule to determine the occurrence of myocardial infarction or coronary heart disease death.

Event Definitions
We defined myocardial infarction as the presence of 2 of the following 3 factors: (1) prolonged chest pain prompting hospital admission, (2) diagnostic evolutionary ECG changes, and (3) elevation of serum creatine kinase to twice the upper limits of normal or a positive serum creatine kinase MB fraction.

The research team confirmed all deaths with medical records or death certificates. The committee reviewing medical records considered coronary heart disease death to have occurred if the death (1) was proved to be due to coronary atherosclerosis by autopsy, (2) occurred within 1 hour after the onset of prolonged severe chest pain, or (3) occurred during hospital admission for acute myocardial infarction. Coronary heart disease was considered to be present if either myocardial infarction or coronary heart disease death had occurred.

Incremental Value of Calcium Score
To test the incremental effect of coronary calcium score on prognosis after risk factors had been considered, we repeated the derivation and testing of the AFT model described above, but with the calcium score as an additional variable. Once again, we applied the recursive bootstrap method to ensure independence between the training and testing sets.

Study Power
We prospectively determined that a study sample of 1200 subjects would be needed to detect ROC curve area differences of between 0.1 and 0.2. With this sample size, we calculated that the study would have a power of between 72% and 100% with an \(\alpha\) error of 0.05. Thus, this investigation had sufficient power to detect clinically important differences in discrimination if these existed.

Statistical Comparisons
We compared categorical data using \(\chi^2\) tests or \(t\) tests for trends, as appropriate. We constructed receiver operating characteristic (ROC) curves in the following manner. The probability values determined from the Framingham and data-derived models and the calcium scores were used as thresholds to categorize the results as either positive (higher than this threshold) or negative (no higher than this threshold). We thus determined true- and false-positive rates for each threshold and constructed ROC curves. We applied the method of Hanley and McNeil16 to calculate and compare areas under these curves. These areas represent the probability that the approach can discriminate between those who will suffer events from those who will not. An area of 1 represents perfect; an area of 0.5, random discrimination.

Results
Patient Characteristics
Of the 1461 subjects, 1196 (82%) were in the reconstituted study sample. The ethnic distribution of the study sample was similar to that of the population of the South Bay suburbs.17 The health and vital status of all but 1 of those who did not return for the EBCT scan were successfully determined in a manner identical to that described above. Of these 265 subjects, 67 had died, 78 had developed symptoms of coronary heart disease (either angina or acute myocardial infarction), and the remaining 119 had either moved from the Los Angeles area or for other reasons did not return for the EBCT study. The 119 surviving subjects who did not undergo scanning had a mean Framingham risk that was not signifi-

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Mean ± SD</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>66±8</td>
</tr>
<tr>
<td>Male sex, %</td>
<td>89</td>
</tr>
<tr>
<td>Total cholesterol, mg/dL</td>
<td>230±43</td>
</tr>
<tr>
<td>HDL cholesterol, mg/dL</td>
<td>45.3±15.6</td>
</tr>
<tr>
<td>Systolic blood pressure, mm Hg</td>
<td>142±20</td>
</tr>
<tr>
<td>Diastolic blood pressure, mm Hg</td>
<td>80±11</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>32</td>
</tr>
<tr>
<td>Smoking history, %</td>
<td>17</td>
</tr>
<tr>
<td>Family history, %</td>
<td>43</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>18</td>
</tr>
<tr>
<td>Framingham risk, %</td>
<td>3.3±3.6</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>31.0</td>
</tr>
</tbody>
</table>
TABLE 3. Calculated Risk From the Framingham Risk Equation, Data-Derived Risk, and Calcium Scores

<table>
<thead>
<tr>
<th></th>
<th>Framingham Risk</th>
<th>Data-Derived Risk</th>
<th>Calcium Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean±SD</td>
<td>3.3±3.6</td>
<td>3.2±4.5</td>
<td>452±457</td>
</tr>
<tr>
<td>Median</td>
<td>2.56</td>
<td>2.00</td>
<td>44</td>
</tr>
<tr>
<td>Tertile 1</td>
<td>0.49–1.75</td>
<td>0.26–1.41</td>
<td>0.0–3.4</td>
</tr>
<tr>
<td>Tertile 2</td>
<td>1.75–3.60</td>
<td>1.41–2.79</td>
<td>3.4–151.0</td>
</tr>
<tr>
<td>Tertile 3</td>
<td>3.60–29.80</td>
<td>2.79–8.05</td>
<td>151.0–4576.0</td>
</tr>
</tbody>
</table>

Follow-Up

All but 2 of the 1196 subjects who underwent scanning were successfully followed up for 41±5 months. The mean age of the subjects at the time of scanning was 66±8 years; 89% were men. Table 2 shows the demographics and risk factors for these subjects. The enrollment strategy had aimed for a high-risk cohort; accordingly, the percentages of subjects with risk factors were high.

Coronary Events

Fifty coronary heart disease events occurred in 46 subjects (3.8%) during the 41±5-month period after scanning. These events included 17 coronary heart disease deaths and 33 acute myocardial infarctions (4 fatal). In addition, there were 46 deaths not attributable to coronary heart disease. Forty-two subjects underwent revascularization after their scans; all had complained of chest discomfort, prompting further evaluation. Eighteen of these revascularizations were performed in subjects who did not have coronary angiography. Eighteen of these revascularizations were performed in subjects who did not have coronary events (myocardial infarction or coronary death) either before or after revascularization. Thus, 64 subjects either suffered a serious coronary event or underwent revascularization.

Coronary Events and Risk Factors

The median 3-year Framingham risk of infarction or coronary death was 4.4%. The relative risk of a value higher than this for predicting these outcomes was 2.5 (P=0.003). The median data-derived risk was 2.7%. Subjects with data-derived risks >2.7% were 3.6 times as likely to suffer an event (P<0.001).

Coronary Events and EBCT Calcium Scores

Two-thirds of the subjects had detectable coronary calcium (score >0). The median coronary calcium score was 44. Subjects with a calcium score >44 were 2.3 times as likely to suffer infarction or coronary death than subjects with lower scores. Subjects were divided into equal tertiles based on risk or calcium scores. Table 3 shows the distributions of Framingham and data-derived risks and calcium scores in each tertile. Figures 1 and 2 show the distributions of coronary events and revascularizations by tertiles of Framingham risk and data-derived risk and calcium scores. The trends toward higher event incidence with increasing Framingham risk are significant for infarction (P<0.001), either coronary death or infarction (P<0.001), revascularizations (P=0.004), and any of these (P<0.001), and marginally significant for coronary death alone (P=0.04). These trends are significant for all types of events for the data-derived risks (P<0.001). Figures 1 and 2 show the distribution of events by tertiles of coronary calcium score. There was a significant trend toward greater frequency of infarctions (P=0.003), but not for coronary deaths (P=0.14). The composite end points of coronary death or infarction and coronary death, infarction, or revascularization were significantly increased in the higher tertiles of calcium score (P<0.01).

ROC Curve Analysis

Table 4 shows the ROC curve areas for predicting events (infarction or coronary death) calculated by risk-factor as-

![Figure 1](image1.png)  
**Figure 1.** Events (revascularization, myocardial infarction, coronary death; x axis) as a function of tertiles of calcium score, Framingham risk, data-derived risk, and data-derived risk with calcium score (z axis). Height of bars (y axis) represents 41-month incidence of events indicated under horizontal axis (x axis). Tertiles of calcium score (cylindrical bars), Framingham risk (conical bars), data-derived risk (rectangular bars), and data-derived risk with calcium (pyramidal bars) run from front to back (z axis). Only trends for coronary death (calcium score and Framingham risk) are not significant.

![Figure 2](image2.png)  
**Figure 2.** All events (infarction, coronary death, or revascularization) and hard events (infarction or coronary death) (x axis) as a function of tertiles of calcium score, Framingham risk, data-derived risk, and data-derived risk with calcium score (z axis). Height of bars (y axis) represents 41-month incidence of events indicated under horizontal (x axis). Tertiles of calcium score (cylindrical bars), Framingham risk (conical bars), data-derived risk (rectangular bars), and data-derived risk with calcium score (pyramidal bars) run from front to back (z axis).
The area under the curve for our data-derived model for predicting infarction or coronary heart disease death was not significantly higher than the areas under the other 2 curves (0.68 ± 0.05 for data-derived model; 0.69 ± 0.05 for Framingham; 0.64 ± 0.05 for calcium score; P = NS). The area under the curve representing the data-derived model including the calcium score was 0.71 ± 0.04. This ROC curve area also was not significantly higher than the areas under the other ROC curves. The similarity of the ROC curve areas for risk-factor assessment and calcium score indicates that both of these have equivalent discriminatory ability in predicting coronary death or infarction.

**Discussion**

The results of this investigation demonstrate that, in high-risk asymptomatic adults with risk factors, EBCT coronary calcium score is equivalent to risk-factor assessment in distinguishing individuals who will suffer coronary death or infarction from those who will not. Furthermore, coronary calcium assessment with EBCT added no prognostic information beyond that obtained by assessment of standard risk factors. Both approaches predicted death or infarction with only fair accuracy, as indicated by the magnitudes of the ROC curve areas.

Our subjects represented a subset of the spectrum of coronary risk in that they had relatively high coronary risk, and the distribution of risk factors was somewhat blunted at the lower end. Although a result of study design and power considerations, this somewhat select risk-factor distribution may not wield the same prognostic and discriminative power as in other cohorts with wider distributions of risk factors. For example, Grover et al applied the Framingham risk model in the Lipid Research Clinics subjects and found a better association between calculated and actual risk with an ROC curve area of 0.85, compared with 0.65 for our high-risk cohort. We attribute the relatively poorer performance of risk-factor assessment in our subjects to the uniformly high risk-factor levels seen in our subjects compared with that of the Lipid Research Clinics.

For example, our subjects were older than those in the Lipid Research Clinics trial (mean age, 66 compared with 47 years). Of pertinence, other studies have shown that hypercholesterolemia and low HDL cholesterol are only weak predictors of coronary mortality or infarction in older patients. Similarly, the relationship between hypertension and mortality has been found to be weaker in elderly subjects, and a history of diabetes was not significantly correlated with coronary disease in men or women >62 years old. It has been suggested that these findings may be attributed at least in part to the increased prevalence of chronic diseases and their correlated mortality, which are associated with aging. Thus, the effects of coronary risk factors on a chronic basis may in some cases result in mortality from diseases not directly related to coronary heart disease and preclude the occurrence of a cardiac end point.

Although it has been proposed that EBCT may be useful as a screening tool to prospectively identify high-risk subjects with preclinical atherosclerosis, studies conducted with asymptomatic patients are scarce and show conflicting results. A recent scientific advisory of the American Heart Association suggested that EBCT scanning should be applied clinically only to symptomatic subjects. The results of the present investigation support this advisory; the predictive value of coronary calcification, at least in high-risk subjects, is no better than that of evaluation of standard coronary risk factors—an approach that is simpler and cheaper and yields treatable entities.

**Limitations**

Our study cohort was predominantly male, and all subjects were ≥45 years old. Moreover, the distributions of risk factors in our subjects were, by design, limited because individuals with relatively low risk were excluded. Further prospective investigations addressing the prognostic significance of coronary calcium in women, as well as subjects of diverse ethnicity, age, and coronary risk, are clearly needed.
Coronary calcium may have a different significance in other populations, such as those with lower Framingham risk.

Subjects were advised as to their calcium scores and their risk factors. Although they were counseled to modify their risk factors accordingly, they were told that the calcium scores were research results of uncertain significance. Still, knowledge of risk factors and calcium scores might have caused behavioral changes and a bias of the results toward either of the approaches to screening.

The duration of follow-up (41 months) is the longest reported to date of any prospective investigation that used EBCT calcium scanning. Nevertheless, it is relatively short compared with other epidemiological studies. Further follow-up could demonstrate EBCT to be of value in selected asymptomatic subjects, and such follow-up is ongoing in our cohort.

Conclusions
The results of this investigation indicate that EBCT screening, although intuitively logical, is not more effective than the less expensive approach using risk-factor information in asymptomatic adults at high risk by conventional risk-factor analysis. Furthermore, the magnitude of the ROC curve areas reported here (≈0.65) indicates that neither EBCT nor risk-factor assessment discriminates, with high accuracy, those destined to suffer coronary death or infarction from those who will not. These results may not be valid for patients with chest pain syndromes for whom coronary calcium has been shown to have clinical validity.5

Acknowledgments
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References