Prediction of Coronary Events With Electron Beam Computed Tomography
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OBJECTIVES We sought to determine the prognostic accuracy of electron beam computed tomographic (EBCT) scanning of the coronary arteries at three to four years.

BACKGROUND Coronary artery calcium scores determined by EBCT correlate with the severity of coronary artery disease. However, previous reports of the prognostic accuracy of EBCT scanning for coronary events in asymptomatic individuals are conflicting.

METHODS Asymptomatic men and women undergoing coronary EBCT completed initial and follow-up evaluations, which included past medical history, the Rose angina questionnaire and interim cardiovascular events. Reported coronary events (death, nonfatal myocardial infarction [MI] and revascularization procedures) were confirmed without knowledge of the scan results.

RESULTS Information was obtained in 1,172 (99.6%) of 1,177 eligible subjects (baseline age 53 ± 11 years, 71% men). During an average follow-up of 3.6 years, 39 subjects sustained coronary events: three coronary deaths, 15 nonfatal MIs and 21 coronary artery revascularization procedures. The mean coronary artery calcium score was 764 ± 935 among subjects with events as compared with 135 ± 432 among those without events (p < 0.0001). For the prediction of all coronary events and of nonfatal MIs and deaths, the areas under the receiver-operator characteristics curve were 0.84 and 0.86, respectively, and a coronary calcium score ≥160 was associated with odds ratios of 15.8 and 22.2, respectively. The odds ratios for all events remained high (14.3 to 20.2) after adjustment for self-reported cardiovascular risk factors.

Recent years, an alternative approach to the early diagnosis of coronary disease, based on noninvasive quantification of atherosclerotic plaque with electron beam computed tomographic (EBCT) scanning of the coronary arteries, has been proposed. In that the severity and extent of coronary atherosclerosis are closely related to coronary events (1216), a noninvasive, anatomically based method of screening for coronary disease might offer substantial advantages over the current strategy, which is limited by unquantifiable and incompletely elucidated risk factors. Coronary calcium scores determined by EBCT correlate with angiographic (r = 0.85), intravascular ultrasound (r = 0.75 to 0.90) and autopsy (r = 0.93) measurements of coronary disease (17-19). However, because the calcified atherosclerotic plaque is not consistently associated with plaque rupture and coronary thrombosis (20,21), and because previous reports of the prognostic accuracy of coronary EBCT scanning in asymptomatic individuals have yielded conflicting results (22,23), this approach remains controversial.

The purpose of this study was to determine the accuracy of EBCT scanning of the coronary arteries for the prediction of coronary atherosclerotic events at three to four years in asymptomatic individuals.

METHODS Study protocol. All 1,238 subjects scanned between September 1, 1993, and March 11, 1994, were asked to complete initial and follow-up questionnaires (this study was approved by the Institutional Review Board of the St. Francis Hospital). After signing consent for periodic future follow-up, the subjects completed an initial questionnaires that included educational status, past medical history and the Rose angina questionnaire (24). After excluding subjects with previously documented coronary disease and those who were symptomatic at entry (central or left chest discomfort precipitated by physical exertion and relieved in > 10 min by...
Abbreviations and Acronyms

CI = confidence interval
EBCT = electron beam computed tomography
MI = myocardial infarction
OR = odds ratio
ROC = receiver-operator characteristics

rest or sublingual nitroglycerin, n = 56), and those who refused consent for follow-up (n = 5), 1,177 eligible subjects were questioned regarding interim cardiovascular events. Events were verified by review of medical records or, in the case of out-of-hospital death, by conversation with family members, by investigators (Y.A., A.D.G.) who had no knowledge of the coronary calcium scores.

The subjects were self-referred or referred by physicians in response to information in newspapers and direct mail by a commercial scanning venture.

Standard coronary disease risk factors (e.g., hypercholesterolemia, hypertension, diabetes, smoking, family history of premature coronary disease) were recorded by questionnaire, but were not measured directly. Patients were determined to have hypercholesterolemia if they were so informed by their physician, if they stated that their total cholesterol was >240 mg/dl or if they were treated with diet or cholesterol-lowering medications. Subjects were considered to have hypertension if they were diagnosed as such by their physicians and advised of dietary or medical treatment.

Determination of endpoints. The diagnosis of MI required two of the following three criteria: chest pain lasting at least 30 min, creatine phosphokinase elevation to more than twice the upper limit of normal with an MB fraction ≥596 or the development of new Q-waves ≥40 ms on the electrocardiogram.

Revascularization procedures (coronary artery bypass graft surgery or coronary angioplasty) without a preceding MI were counted as events only if they were performed because of the new onset of angina pectoris or shortness of breath, followed by a stress test, with objective evidence of myocardial ischemia or the new onset of unstable angina, leading directly to angiography. Coronary revascularization procedures were excluded (i.e., if the subject was considered not to have sustained an event) if the decision to perform stress testing or angiography in an otherwise asymptomatic individual was due solely to the results of EBCT (n = 5). This policy of exclusion of revascularization procedures in asymptomatic individuals was applied regardless of the results of stress testing or angiography.

Peripheral vascular procedures (one aortic aneurysm, one iliac-femoral bypass and two carotid endarterectomies), strokes (n = 2) and noncoronary deaths (n = 11) were not included in this analysis.

Electron beam computed tomography. Electron beam CT scanning was performed using an Imatron C-150XP scanner. Forty contiguous, 3-mm-thick slices were obtained during a single breath hold, beginning at the lower edge of the carina. The field of view was 35 cm, and the scan time was 100 ms per slice, with synchronized electrocardiographic triggering at 8096 of the RR interval. Coronary artery calcium scores were calculated according to the method of Agatston et al. (25). At least two adjacent pixels (i.e., area ≥0.93 mm2) with a density >130 Hounsfield units were required to define a lesion.

Analysis. The relations between coronary artery calcium scores and events, as well as between self-reported risk factors and events, were analyzed with contingency tables and the chi-square test. The relations between self-reported risk factors and calcium scores were analyzed by using the Wilcoxon rank-sum test. Only one event was counted for each patient in each analysis, in the following order of importance: a coronary death before a nonfatal MI before a revascularization procedure.

Receiver-operator characteristics (ROC) curves were generated to determine the predictive power of EBCT-derived coronary artery calcium scores for all events and for the combined end point of nonfatal MI and coronary death (26).

Multivariate logistic regression analyses were performed using models with the occurrence of any coronary event as the dependent variable. (Any event, rather than just coronary death and nonfatal MI, was chosen to maximize the number of events available for analysis.) Three hundred eighty six subjects were excluded from the multivariate analysis due to incomplete information, leaving 787 subjects for the multivariate analysis. Independent variables were selected for inclusion into the models from those variables (self-reported coronary artery disease risk factors and/or coronary calcium score) that were significantly correlated with outcome on univariate regression analyses. Variables were selected using a stepwise algorithm that started with the variable that yielded the lowest p value (if <0.05), followed progressively by the next lowest p value, while eliminating variables with p values >0.05 at each step until the final model was obtained. The analyses were performed using traditional risk factors (e.g., age, elevated total cholesterol, hypertension, diabetes mellitus, cigarette smoking and family history of premature coronary artery disease), with or without the coronary calcium score thresholds of 80, 160 and 600. Adjusted odds ratios (ORs) and confidence intervals (CIs) were calculated from the multivariate logistic regression variable estimates. The fit of the multiple logistic regression model was assessed using the Hosmer and Lemeshow goodness-of-fit test (27). The study was approved by the St. Francis Institutional Review Board.

RESULTS

At the time of EBCT scanning, the subjects mean (±SD) age was 53 ± 11 years (range 31 to 79), and the 25th, 50th and 75th percentiles were 46, 53 and 62, respectively. Seventy-one percent of the subjects were male and 95% were Caucasian. The prevalence figures for self-reported
Table 3. A multivariate analyses of the association of coronary artery calcium scores and self-reported traditional coronary risk factors, with ORs of 14.4, 19.7 and 20.2 for the calcium score after adjustments for self-reported coronary artery disease risk factors, with ORs of 14.4, 19.7 and 20.2 for the calcium score thresholds of 80, 160 and 600, respectively, indicating good fit of the models.

DISCUSSION

This study demonstrates the prediction of coronary heart disease events in asymptomatic individuals at three to four years with EBCT scanning of the coronary arteries. As in the case of a previous report of 1.6 years of follow-up in the same cohort, the ORs for the prediction of final and non-fatal MI, as well as all coronary events, are of the same order of magnitude higher than those typically associated with standard coronary artery disease risk factors. For example, in men, the OR for all events peaked at 19.0 (CI 6.6 to 54.6) in association with a calcium score of 80. In contrast, in a recent report from the Framingham study, the OR for any coronary event was 1.9 (CI 1.2 to 2.9) for elevated lipoprotein (a), 1.8 (CI 1.2 to 2.6) for hypercholesterolemia, 1.8 (CI 1.2 to 2.6) for high density lipoprotein cholesterol <35 mg/dl and 3.6 (CI 2.2 to 5.5) for cigarette smoking for 2,191 men followed for 15 years.

A limitation of the multivariate analysis is that 386 subjects were missing data or more data points, leaving only 787 subjects available for the multivariate analysis. We feel that this is not a major issue for the following reasons: a) we have no reason to suspect that the excluded subjects were demographically different from those that provided all data points; b) results of the univariate analyses for traditional risk factors and coronary calcification were similar for the subgroup and the complete population; c) the analyzed subgroup is of sufficient size to make fortuitous correlations unlikely.

Odds ratios for the prediction of all coronary events, based on the results of EBCT scanning, remained high even...
after adjustment for self-reported standard risk factors. This finding is consistent with two previous reports in which standard coronary disease risk factors were measured, demonstrating the independent association of the coronary calcium score with angiographically defined coronary atherosclerosis (29,30). This observation suggests that while traditional risk factors must be considered in the evaluation of the asymptomatic individual, coronary calcium scores must be used to modify loci assessment.

Other quantitative aspects of the study results deserve comment. Coronary calcium score thresholds of 80 and 160 predicted coronary death and nonfatal MI with sensitivity, specificity and overall accuracy of 70.82, and the area under the ROC curve was 0.86. These same coronary calcium score thresholds predicted all coronary events almost as accurately. The -incidence of nonfatal MI plus coronary death and the incidence of all coronary events increased as a function of the coronary calcium score (p < 0.0001) from 0.24% and 0.796%, respectively, among subjects with calcium scores <80 to 13% and 22%, respectively, among those with calcium scores >600.

Comparisons with other screening tests. To put these figures in perspective, screening stress tests predict nonfatal MI, coronary death and hospital admission for angina pectoris, with a sensitivity of 0.34, a positive predictive value of 0.05 and an OR of <4 at six to eight years (31). Exercise thallium scintigraphy was recently shown to predict coronary death and nonfatal MI, with a sensitivity of 0.55, a positive predictive value of 0.10 and an OR of 4.4 at six years in a high risk cohort (32). The ratio of total cholesterol to high density lipoprotein cholesterol and the current National Cholesterol Education Program guidelines are associated with areas under the ROC curve of 0.72 and 0.74, respectively, for the prediction of coronary death (8). Finally, event rates of 13% for coronary death and nonfatal MI and 22% for all events at 3.6 years in subjects with coronary calcium scores >600 are not only high, but they also fall into the range of event rates observed in recent studies of secondary prevention (33,34).

These results are consistent with the phenomenology of coronary calcification and the known limitations of conventional screening tests for coronary artery disease. The coronary calcium score is related ro the total volume of atherosclerotic plaque (e.g., lipid-rich plaque as well as fibrocalcific plaque) (r = 0.75 to 0.93) (18,19) and to angiographic estimates of the severity of coronary disease (r = 0.85) (17). In turn, in middle-aged and elderly persons, atherosclerosis is the substrate for the vast majority of coronary events, and the risk of coronary events is closely related to the severity and extent of underlying coronary atherosclerosis (12-16). In contrast, stress testing cannot reliably detect nonobstructive coronary disease (35,36), which accounts for up to 50% of MI s and sudden coronary deaths (37). Furthermore, coronary risk factors, which are incompletely elucidated and sometimes unquantifiable, cannot be equated with coronary disease.

The results of this study are similar to a large autopsy study (n = 1,288) that antedated EBCT scanning by more than 20 years and to a report from the EBCT Research Foundation in Nashville, Tennessee. In the first study, individuals dying of coronary artery disease had two to five times as much coronary calcium as age-matched subjects who died accidentally or of other natural causes (38). In the second study, the ORs for future events increased according to the deciles of coronary artery calcium scores from 4 to 30 as compared with a coronary artery calcium score of 0 (39), and the predictive value was independent of traditional risk factors. Conflicts with previous data. The results of this study and the Nashville study differ sharply from the results of the South Bay Heart Watch. The South Bay Heart Watch began as a study of the predictive accuracy of cardiac fluoroscopy in 1,461 asymptomatic, high risk adults, all of whom were at or above the 75th percentile for coronary risk by the Framingham criteria (40). These 1,461 subjects underwent fluoroscopy between 1990 and 1992; 1,289 surviving participants underwent EBCT scanning between 1992 and 1994. An early report of 2.7 years of follow-up in a subgroup of 326 study participants, which appears to have exerted considerable influence on the most recent American Heart Association statement on EBCT scanning (41), noted that the prediction of nonfatal MI and coronary death, based on the coronary calcium score, fell short of accepted levels of statistical significance (OR 3.1, p = 0.07) (23). More recently, with respect to the prediction of nonfatal MI and coronary death, the South Bay Heart Watch investigators reported an OR of 2.7 (CI 1.4 to 5.3, p = 0.007) in 1,196 subjects followed for 2.8 years (42), as well as an area under the ROC curve of 0.64 ± 0.05 at 3.4 years (p < 0.01) (43).

The lesser prognostic accuracy of the coronary calcium score in the South Bay Heart Watch is more likely due to a narrow range of observation than any inherent weakness in EBCT scanning as a screening test for coronary artery disease.

This may be appreciated by a simple thought experiment. Assume, as was the case among American men 20 years ago, that a total serum cholesterol level of 240 mg/dl marked the 75th percentile in the distribution of total cholesterol. Imagine trying to determine the relation between total serum cholesterol and atherosclerotic disease events in men by restricting a study to subjects with total serum cholesterol ≥240 mg/dl. One might find a statistically significant relation between cholesterol and disaccharide events in a population of men of selected group, but the relation would be weaker than the relation between cholesterol and events in a population that encompassed the entire range of cholesterol levels.

A second apparent difference between the South Bay Heart Watch and the prescript study is the relatively large number of coronary deaths and nonfatal MIs in subjects with low coronary calcium scores in the South Bay Heart Watch. This observation not only conflicts with the relations...
between coronary calcification, coronary atherosclerosis, and coronary events, but it is also a predictable consequence of patient selection.

Bayes' theorem states that the likelihood that a negative test result is a true negative is inversely proportional to the pretest probability of disease. Because the relation between coronary calcification and coronary atherosclerosis is imperfect, Bayes' theorem applies to EBCT scanning. Thus, with respect to the phenomenon of coronary calcification, a high risk population like that of the South Bay Heart Watch contains an unusually large number of false negative test results. Similar results have been obtained in a cohort of symptomatic patients undergoing coronary arteriography, in which obstructive coronary disease was present in the majority of patients with angina pectoris and four or five risk factors for coronary artery disease, regardless of the coronary calcium score (30).

Once these artifacts of patient selection are understood, it is actually easy to reconcile the results of the South Bay Heart Watch with those of the present study. Coronary calcium scores in the South Bay Heart Watch should be higher than those in the present study, and they are—the 25th, 50th, and 75th percentiles of the distribution of the coronary calcium scores in the South Bay Heart Watch population were 15, 15, and 30, respectively (23), as compared with 0, 4, and 97 for the present study (p < 0.0001). Event rates in the lowest two terciles of the South Bay Heart Watch, which correspond roughly to the 75th and 92nd percentiles of the general population (i.e., the lowest two terciles of the highest quartile), should be much higher than those in the present study, and they are—the incidence of nonfatal 1141 and coronary death in the lowest two terciles of the respective study groups was 2.0196 at 2.8 years in the South Bay Heart Watch (42), as compared with 0.2596 at 3.6 years in the present study (p = 0.001). Finally, the overall event rate in the South Bay Heart Watch study group should be similar to that in the highest 25% of the present study group (again because the South Bay Heart Watch included only persons above the 75th percentile of coronary risk), and it is—the incidence of nonfatal MT and coronary death was 3.196 at 2.8 years for the entire study group of the South Bay Heart Watch, as compared with 5.546 at 3.6 years for the highest 25% of the present study group.

**Applicability to screening for coronary artery disease.**

The critical question surrounding this study has to do with the generalizability of its results. The study group was overwhelmingly white and mostly male; many patients were self-referred; and risk factors were determined on the basis of a history rather than direct measurement. In each case, the error introduced by the sampling method and the method of ascertainment of risk factors is probably small. Coronary calcification is related to the severity of coronary atherosclerosis in blacks and Asians as well as in whites (38,44,45). The problem with self-referral is more complex, but it seems unlikely that subjects misrepresented themselves, as there was no penalty associated with reporting angina pectoris. With respect to the self-reporting of risk factors, previous studies indicate that self-reported coronary risk factors may be accurate in >90% of cases (46,47). There is no reason to think that this highly educated, affluent population was grossly ignorant of its coronary risk status, and the association of the coronary calcium score with standard coronary disease risk factors is similar to that found in studies in which the risk factors were measured (29,30). The reported risk factor profile of this group is also similar to that of the National Health and Nutrition Examination Survey (NHANES) and the Atherosclerosis Risk in Communities (ARIC) studies (Table 4) (48,49). Moreover, three of the four measurable standard risk factors (i.e., elevated total cholesterol, hypertension, and diabetes) correlated both with the coronary calcium score and coronary events, whereas the two history-dependent risk factors—family history and cigarette smoking—did not. In this regard, it should be noted that errors in the self-reporting of coronary risk factors would be expected to introduce bias toward the null hypothesis.

We certainly do not intend to imply that known coronary artery disease risk factors should be ignored. Our current data demonstrate that the presence of conventional risk factors, such as hypercholesterolemia, are correlated with the risk of subsequent cardiovascular events. As we have

**Table 4. Clinical Characteristics of the Study Group**

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>St. Francis (n = 1,171)</th>
<th>South Bay Heart Watch (n = 326 of 5,023)</th>
<th>NHANES (n = 1,838 of 14,407)</th>
<th>ARIC (n = 15,500)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>53</td>
<td>66</td>
<td>66</td>
<td>54</td>
</tr>
<tr>
<td>Smoking (ever/current)</td>
<td>42%</td>
<td>Man LDL 1-14 mg/dl</td>
<td>3796</td>
<td>Man LDL 136 mg/dl</td>
</tr>
<tr>
<td>Hypertension Diabetes</td>
<td>46/10%</td>
<td>7/17%</td>
<td>70/34%</td>
<td>55/27%</td>
</tr>
<tr>
<td>Family history/Diabetes</td>
<td>26%</td>
<td>59%</td>
<td>24%</td>
<td>33%</td>
</tr>
<tr>
<td>Body mass index</td>
<td>5.1%</td>
<td>21%</td>
<td>7.1%</td>
<td>12%</td>
</tr>
<tr>
<td>Not don'</td>
<td>71%</td>
<td>82%</td>
<td>100%</td>
<td>4596</td>
</tr>
</tbody>
</table>

*Mc prevalence of coronary risk factors in the present study is compared with that of the South Bay Heart Watch and nut polulation-baud studies.

ARIC = Atherosclerosis Risk in Communities study; LDL = low density lipoprotein; NHANES = National Health and Nutrition Examination Survey; MT = myocardial infarction.
demonstrated in an angiographic study (30), known risk factors are clearly associated with the likelihood of any coronary artery disease and obstructive coronary artery disease, independent of calcium scores. Similarly, in a pathologic study, Taylor et al. (50) showed that the Framingham score and coronary calcification are distinct and complementary for the prediction of sudden cardiac death. The coronary calcium score should be incorporated into the evaluation of coronary disease risk obtained from traditional risk factor analyses.

The relevance of plaque calcification to plaque rupture is controversial. Increasing evidence implicates rupture of lipid-rich atheromatous plaque in the pathogenesis of unstable angina, acute MI and sudden coronary death, but at least 40% of these lesions are not calcified (20,21). At the same time, the coronary arteries of patients with unstable coronary syndromes are often contain nontatherosclerotic lesions (51-53), and the histologic appearance of these lesions is typically mixed (20,52). Although the calcified plaque is not necessarily the lesion of interest, this study indicates that calcified plaque is a marker for the presence of the lesion of interest. Electron beam CT scanning of the coronary arteries cannot detect the lesion at risk, but it can identify the person at risk, and it may do so independently of standard coronary disease risk factors.

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