

Prediction of Coronary Events With Electron Beam Computed Tomography

Yadon Arad, MD, FACC,* Louise A. Spadaro, MD, FACC,* Ken Goodman, MD,† David Newstein, MS,*
Alan D. Guerci, MD, FACC*

Roslyn, New York

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.
CONCLUSIONS	In asymptomatic adults, EBCT of the coronary arteries predicts coronary death and nonfatal MI and the need for revascularization procedures. (J Am Coll Cardiol 2000;36:1253-60) © 2000 by the American College of Cardiology

Coronary atherosclerosis is the leading cause of death in industrialized Western nations, and in up to 50% of its victims, the first manifestation of coronary artery disease is sudden death or acute myocardial infarction (MI) (1-6). Thus, the early diagnosis of coronary disease remains a desirable goal. Unfortunately, conventional risk factor assessment is neither highly sensitive nor highly specific (7,8), and stress testing, even in high risk subgroups, has sensitivities and positive predictive values so low (9,10) that its use as a screening test has been questioned (11).

See page 1261

In 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 (12-16), 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

From the Departments of *Preventive Cardiology and †Radiology, St. Francis Hospital, Roslyn, New York. This study was supported by a grant from the St. Francis Hospital Foundation.

Manuscript received October 22, 1999; revised manuscript received March 7, 2000, accepted May 31, 2000.

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 end points. 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 $\geq 5\%$ 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 80% 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 (\pm 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 1. Descriptors of Test Performance for Electron Beam Computed Tomography for All Coronary Events at Various Calcium Score Thresholds

	Score*	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	OR (95% CI)
All subjects	≥80	0.85	0.75	0.10	0.99	0.75	16.1 (6.7-38.9)
	≥160	0.77	0.83	0.13	0.99	0.82	15.8 (7.4-33.9)
	≥600	0.44	0.95	0.22	0.98	0.93	13.8 (7.0-27.4)
Men	≥80	0.88	0.72	0.12	0.99	0.72	19.0 (6.6-54.6)
	≥160	0.79	0.81	0.15	0.99	0.81	16.3 (7.0-38.2)
	≥600	0.47	0.94	0.25	0.98	0.92	13.7 (6.6-28.6)
Women	≥80	0.60	0.82	0.05	0.99	0.81	6.7 (1.09-40.8)
	≥160	0.60	0.87	0.07	0.99	0.86	9.9 (1.6-61.0)
	≥600	0.20	0.97	0.08	0.99	0.95	7.2 (0.7-69.7)

*Coronary artery calcium threshold.
 CI = confidence interval; NPV = negative predictive value; OR = odds ratio; PPV = positive predictive value.

standard coronary risk factors were 42% for hypercholesterolemia, 10% for current smoking, 25% for hypertension, 5% for diabetes and 44% for family history of premature coronary disease. Of the five standard coronary disease risk factors—hypercholesterolemia, hypertension, smoking, diabetes and family history—7% of subjects had no risk factors, 23% had one risk factor, 36% had two risk factors, 26% had three risk factors, 6% had four risk factors and 1% had five risk factors.

Follow-up was obtained from 1,172 (99.6%) of 1,177 eligible subjects. Mean follow-up was 43 months (range 38 to 47). During the follow-up period, 39 subjects (3.33%) had coronary events: three deaths, 15 nonfatal MIs, 11 coronary artery bypass procedures and 10 coronary angioplasties.

For the entire study group, scores ranged from 0 to 8,155, and the 25th, 50th and 75th percentile scores were 0, 4 and 97, respectively. There were two events in the first quartile, one in the second quartile, four in the third quartile and 32 in the fourth quartile. Among subjects without events, the mean (±SD) value and 25th, 50th and 75th percentiles of the distribution of the coronary calcium score were 135 ± 432 and 0, 3 and 82, respectively, as compared with 764 ± 935 and 164, 511 and 972, respectively, for individuals with events (p < 0.0001). The mean calcium score was 844 ± 729 for subjects who sustained a MI or died, as compared

with 695 ± 1,094 for subjects who underwent revascularization without an antecedent MI (p = 0.7).

The sensitivity, specificity, positive and negative predictive values, overall accuracy and ORs are listed in Table 1 for all events and in Table 2 for the composite end point of coronary death and nonfatal MI. In general, ORs were maximized at coronary calcium scores between 80 and 160 (16.1 for all events and 22.3 for nonfatal MI and coronary death), as were the sums of sensitivity and specificity (Fig. 1 and 2). Specificity and positive predictive value increased as a function of the coronary calcium score (p < 0.0001), whereas sensitivity decreased (p < 0.0001). The predictive value of the coronary calcium score was lower in women than in men, but the differences are not statistically significant.

The area under the ROC curve (±SE) was 0.84 ± 0.04 for all coronary events and 0.86 ± 0.07 for coronary death and nonfatal MI (p < 0.0001 for both).

On univariate analysis, age >55 years (p < 0.0001), self-reported elevated total cholesterol (p = 0.007), hypertension (p < 0.0001), smoking (p < 0.0001) and diabetes (p < 0.0001) were associated with a higher calcium score, whereas positive family history (p = 0.46) was not. Self-reported elevated total cholesterol (p = 0.007), hypertension (p = 0.014) and diabetes (p = 0.002) were also associated with the likelihood of future coronary events on univariate

Table 2. Descriptors of Test Performance for Electron Beam Computed Tomography for the Combined End Point of Myocardial Infarction and Death at Various Coronary Calcium Score Thresholds

	Score*	Sensitivity	Specificity	PPV	NPV	Overall Accuracy	OR (95% CI)
All subjects	≥80	0.89	0.74	0.05	0.99	0.74	22.3 (5.1-97.4)
	≥160	0.83	0.82	0.07	0.99	0.82	22.2 (6.4-77.4)
	≥600	0.55	0.94	0.13	0.98	0.94	20.3 (7.8-53.1)
Men	≥80	0.93	0.70	0.05	0.99	0.71	30.8 (4.0-236.9)
	≥160	0.86	0.80	0.07	0.99	0.80	23.3 (5.7-105.2)
	≥600	0.64	0.93	0.14	0.99	0.93	24.7 (8.0-76.3)
Women	≥80	0.75	0.82	0.05	0.99	0.82	13.4 (1.4-131.1)
	≥160	0.75	0.87	0.07	0.99	0.87	19.9 (2.0-195.5)
	≥600	0.25	0.97	0.08	0.99	0.96	9.6 (0.9-99.0)

*Coronary artery calcium threshold.
 Abbreviations as in Table 1.

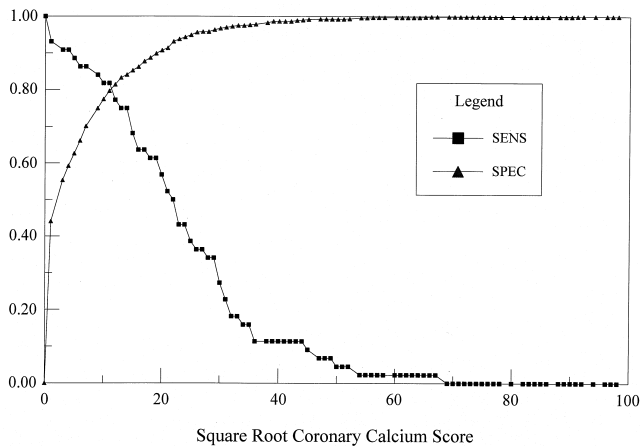


Figure 1. The relation between the square root of the coronary calcium score and the sensitivity (SENS, squares) and specificity (SPEC, triangles) for all events.

analysis, whereas age >55 years ($p = 0.057$), smoking ($p = 0.25$) and positive family history ($p = 0.44$) were not.

The results of the multivariate analyses, with or without the results of EBCT scanning, are listed in Table 3. When the calcium scores were excluded, only self-reported elevated total cholesterol, hypertension and diabetes were associated with events. When coronary calcium scores were included in the multivariate model, the association of age >55 years, self-reported elevated total cholesterol, hypertension and diabetes with events remained significant for all calcium score thresholds tested, whereas the association of family history and smoking with coronary events remained insignificant. Coronary calcium scores remained independently associated with outcome 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. The Hosmer and Lemeshow goodness-of-fit test of the multivariate models yielded p values of 0.89, 0.72 and 0.46 for the analyses incorporating

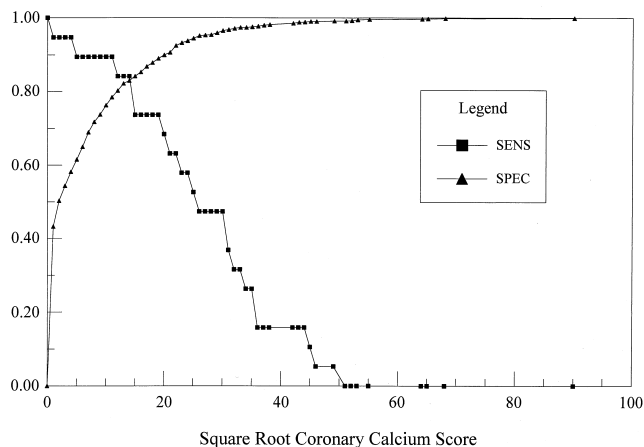


Figure 2. The relation between the square root of the coronary calcium score and the sensitivity (SENS, squares) and specificity (SPEC, triangles) for the combined end point of nonfatal MI and death.

Table 3. Multivariate Analyses of the Association of Coronary Artery Calcium Scores and Self-Reported Traditional Coronary Disease Risk Factors With All Events

	Variable	Odds Ratio (95% CI)
Independent of EBCT	Elevated cholesterol	3.9 (1.3-11.7)
	Hypertension	2.8 (1.2-6.5)
	Diabetes	5.4 (2.0-14.9)
With EBCT CACS ≥ 80	CACS >80	14.3 (4.9-42.3)
	Age >55 years	3.3 (1.3-8.4)
	Elevated cholesterol	4.0 (1.3-12.2)
	Hypertension	2.6 (1.1-6.1)
With EBCT CACS ≥ 160	Diabetes	4.8 (1.6-13.9)
	CACS >160	19.7 (6.9-56.4)
	Age >55 years	4.5 (1.6-12.2)
	Elevated cholesterol	3.7 (1.2-11.5)
With EBCT CACS ≥ 600	Hypertension	3.0 (1.2-7.4)
	Diabetes	5.8 (2.1-19.7)
	CACS >600	20.2 (7.3-55.8)
	Age >55 years	2.9 (1.1-7.9)
	Elevated cholesterol	3.5 (1.1-10.8)
	Hypertension	2.9 (1.2-7.3)
	Diabetes	4.4 (1.4-13.7)

Analyses were performed with and without the coronary artery calcium scores (CACS).

CI = confidence interval; EBCT = electron beam computed tomography.

coronary calcium scores 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 (22,28), the ORs for the prediction of fatal and nonfatal MI, as well as all coronary events, are an 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 ORs for any coronary event were 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 one or more data point, 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 or socially 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 such an 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 ≥ 0.82 , 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 0.7%, 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 to the total volume of atherosclerotic plaque (i.e., 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 MIs 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 across 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 disease events in such a highly 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 present study is the relatively large number of coronary deaths and nonfatal MIs in subjects with "low" calcium scores in the South Bay Heart Watch. This observation not only conflicts with the relations

Table 4. Clinical Characteristics of the Study Group

Risk Factors	St. Francis (n = 1,172)	South Bay Heart Watch (n = 326 of 5,023)	NHANES (n = 1,838 of 14,407)	ARIC (n = 15,800)
Age (yrs)	53	66	66	54
High cholesterol	42%	Mean LDL 144 mg/dl	37%	Mean LDL 136 mg/dl
Smoking (ever/current)	46/10%	2/17%	70/34%	55/27%
Hypertension	25%	50%	24%	33%
Diabetes	5.1%	21%	7.1%	12%
Family history	44%	44%	?	?
Male	71%	82%	100%	45%
Body mass index	Not done	32%	25%	28%

The prevalence of coronary risk factors in the present study is compared with that of the South Bay Heart Watch and two population-based studies.

ARIC = Atherosclerosis Risk In Communities study; LDL = low density lipoprotein; NHANES = National Health And Nutrition Examination Survey; ? = not reported.

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, 156 and 506, 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 to the 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 MI and coronary death in the lowest two terciles of the respective study groups was 2.01% at 2.8 years in the South Bay Heart Watch (42), as compared with 0.25% 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 MI and coronary death was 3.1% at 2.8 years for the entire study

group of the South Bay Heart Watch, as compared with 5.5% 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 with both 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

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 analysis.

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 usually contain many atherosclerotic 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.

Reprint requests and correspondence: Dr. Yadon Arad, Director of Preventive Cardiology, St. Francis Hospital, 100 Port Washington Boulevard, Roslyn, New York 11576. E-mail: yadon@earthlink.net.

REFERENCES

1. Froelicher VF, Thomas MM, Pillow C, Lancaster MC. Epidemiological study of asymptomatic men screened with exercise testing for latent coronary heart disease. *Am J Cardiol* 1974;34:770-9.
2. Aronow WS, Cassidy J. Five-year follow-up of double Master's test, maximal treadmill stress test, and resting and post exercise apex cardiogram in asymptomatic persons. *Circulation* 1975;52:616-23.
3. Bruce RA, DeRouen TA, Hossack KF. Value of maximal exercise test in risk assessment of primary coronary heart disease events in healthy men. *Am J Cardiol* 1980;46:371-8.
4. Giagnoni E, Secchi MB, Wu SC, et al. Prognostic value of exercise EKG testing in asymptomatic normotensive subjects. *N Engl J Med* 1983;309:1085-9.
5. McHenry PL, O'Donnell J, Morris SN, Jordan JJ. The abnormal exercise electrocardiogram in apparently healthy men: a predictor of angina pectoris as an initial coronary event during long-term follow-up. *Circulation* 1984;70:547-53.
6. Josephson RA, Shefrin E, Lakatta EG, Brant LJ, Fleg JL. Can serial exercise testing improve the prediction of coronary events in asymptomatic individuals? *Circulation* 1990;81:20-4.
7. Kinoshita B, Glick H, Garland G. Cholesterol and coronary heart disease: predicting risks by levels and ratios. *Ann Intern Med* 1994; 121:641-7.
8. Grover SA, Coupal L, Hu XP. Identifying adults at increased risk of coronary disease. How well do the current cholesterol guidelines work? *JAMA* 1995;274:801-6.
9. Gordon DJ, Ekelund LG, Karon JM, et al. Predictive value of the exercise test for mortality in North American men: the Lipid Research Clinics Mortality Follow-up Study. *Circulation* 1986;74:252-61.
10. Ekelund LG, Suchindran CM, McMahon RP, et al. Coronary heart disease morbidity and mortality in hypercholesterolemic men predicted from an exercise test: the Lipid Research Clinics Coronary Primary Prevention Trial. *J Am Coll Cardiol* 1989;14:556-63.
11. ACC/AHA Guidelines for Exercise Testing. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee on Exercise Testing). *J Am Coll Cardiol* 1997;30:290-3.
12. Gofman JW. The quantitative nature of the relationship of coronary artery atherosclerosis and coronary heart disease risk. *Cardiol Digest* 1969;4:28-38.
13. Proudfit WL, Bruschke AVG, Sones FM. Clinical course of patients with normal and moderately abnormal coronary arteriograms: 10-year follow-up of 521 patients. *Circulation* 1980;62:712-8.
14. Moise A, Lesperance J, Theroux P, Taeymans Y, Goulet C, Bourassa MG. Clinical and angiographic predictors of new total coronary occlusion in coronary artery disease: analysis of 313 nonoperated patients. *Am J Cardiol* 1984;54:1176-81.
15. Ellis S, Alderman E, Cain K, Fisher L, Sanders W, Bourassa M. Prediction of risk of anterior myocardial infarction by lesion severity and measurement method of stenoses in the left anterior descending coronary distribution: a CASS Registry study. *J Am Coll Cardiol* 1988;11:908-16.
16. Emond M, Mock MB, Davis KB, and Participants in the Coronary Artery Surgery Study (CASS). Long term survival of medically treated patients in the Coronary Artery Surgery Study (CASS) Registry. *Circulation* 1994;90:2645-57.
17. Guerci AD, Spadaro LA, Popma JJ, et al. Relation of coronary calcium score by electron beam computed tomography to arteriographic findings in asymptomatic and symptomatic adults. *Am J Cardiol* 1997;79: 128-33.
18. Chou TM, Redberg RF, Ko E, et al. Screening for coronary atherosclerosis by detection of calcium on electron beam computed tomography: correlation with intravascular ultrasound in asymptomatic patients with primary hyperlipidemia (abstr). *Circulation* 1996;94 Suppl I:I-360.
19. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron beam computed tomography and coronary atherosclerotic plaque area: a histopathologic correlative study. *Circulation* 1995;92:2157-62.
20. Tracy RE, Devaney K, Kissling G. Characteristics of the plaque under a coronary thrombus. *Virchows Arch* 1985;40:411-27.
21. Mintz G, Pichard A, Popma JJ, et al. Determinants and correlates of target lesion calcium in coronary artery disease: a clinical, angiographic, and intravascular ultrasound study. *J Am Coll Cardiol* 1997;29:268-74.
22. Arad Y, Spadaro LA, Goodman K, et al. Predictive value of electron beam computed tomography of the coronary arteries: 19-month follow-up of 1173 asymptomatic subjects. *Circulation* 1996;93: 1951-3.
23. Secci A, Wong N, Tang W, Wang S, Doherty T, Detrano R. Electron beam computed tomographic coronary calcium as a predictor of coronary events: comparison of two protocols. *Circulation* 1997;96: 1122-9.
24. Rose GA. The diagnosis of ischaemic heart pain and intermittent claudication in field surveys. *Bull World Health Organ* 1962;27: 654-8.
25. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;15:827-32.
26. Hanley JA, McNeil BJ. The meaning and use of the area under a receiver operating characteristic (ROC) curve. *Radiology* 1982;143: 29-36.
27. Hosmer DW, Lemeshow S. *Applied Logistic Regression*. New York: John Wiley & Sons, 1989.
28. Arad Y, Guerci AD. Letter to the editor. *Circulation* 1997;95:535-6.
29. Kennedy J, Shavelle R, Wang S, Budoff M, Detrano RC. Coronary calcium and standard risk factors in symptomatic patients referred for coronary angiography. *Am Heart J* 1998;135:696-702.
30. Guerci AD, Spadaro LA, Goodman KJ, et al. Comparison of electron beam CT scanning and conventional risk factor assessment for the prediction of angiographic coronary artery disease. *J Am Coll Cardiol* 1998;32:673-9.
31. Detrano R, Froelicher VF. Exercise testing: uses and limitations considering recent studies. *Prog Cardiovasc Dis* 1988;31:173-204.
32. Blumenthal RS, Becker DM, Moy TF, Coresh J, Wilder LB, Becker

- LC. Exercise thallium tomography predicts future clinically manifest coronary heart disease in a high risk asymptomatic population. *Circulation* 1996;93:915-23.
33. Scandinavian Simvastatin Survival Study Group. Randomized trial of cholesterol lowering in 4444 patients with coronary heart disease: the Scandinavian Simvastatin Survival Study (4S). *Lancet* 1994;344:1383-9.
34. Sacks FM, Pfeffer MA, Moye LA, et al. The effect of pravastatin on coronary events after myocardial infarction in patients with average cholesterol levels. *N Engl J Med* 1996;335:1001-9.
35. Kirkeeide RL, Gould KL, Parsel L. Assessment of coronary stenoses by myocardial perfusion imaging during pharmacologic coronary vasodilation. VII: Validation of coronary flow reserve as a single integrated functional measure of stenosis severity reflecting all its geometric dimensions. *J Am Coll Cardiol* 1986;7:103-13.
36. Arnesen M, Salustri A, Fioretti PM, et al. Quantitative angiographic measurements of isolated left anterior descending coronary artery stenosis correlation with exercise echocardiography and technetium-99m 2-methoxy isobutyl isonitrile single-photon emission computed tomography. *J Am Coll Cardiol* 1995;25:1486-91.
37. Fishbein MC, Siegel RJ. How big are coronary atherosclerotic plaques that rupture? *Circulation* 1996;94:2662-6.
38. Eggen DA, Strong JP, McGill HC. Coronary calcification: relationship to clinically significant coronary lesions and race, sex and topographic distribution. *Circulation* 1965;32:948-55.
39. Agatston AS, Janowitz WR, Kaplan GS, et al. Electron beam CT coronary calcium predicts future coronary events (abstr). *Circulation* 1996;94 Suppl I:I-360.
40. Detrano RC, Wong ND, Doherty TM, Shavelle R. Prognostic significance of coronary calcific deposits in asymptomatic high risk subjects. *Am J Med* 1997;102:344-9.
41. Wexler L, Brundage B, Crouse J, et al. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications. A statement for health professionals from the American Heart Association. *Circulation* 1996;94:1175-92.
42. Detrano RC, Wong N, Tang W, Doherty TM. Determining coronary event risk in asymptomatic high risk subjects: a risk factor versus an anatomic approach (abstr). *Circulation* 1997;96 Suppl I:I-404.
43. Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near term coronary events in high risk adults. *Circulation* 1999;99:2633-8.
44. Kajinami K, Seki H, Takekoshi N, Mabuchi H. Noninvasive prediction of coronary atherosclerosis by quantification of coronary artery calcification using electron beam computed tomography: comparison with electrocardiographic and thallium exercise stress test results. *J Am Coll Cardiol* 1995;26:1209-21.
45. Hsia J, Godinho C, Adams-Campbell L, Howard B, Wasserman AG. Coronary calcification in African-American and white women in the Women's Health Initiative Observational Study (abstr). *J Am Coll Cardiol* 1999;33 Suppl:415A.
46. Paganini-Hill A, Ross RK. Reliability of recall of drug usage and other health related information. *Am J Epidemiol* 1982;116:114-22.
47. Colditz GA, Martin P, Stampfer MJ, et al. Validation of questionnaire information on risk factors and disease outcomes in a prospective cohort study of women. *Am J Epidemiol* 1986;123:894-900.
48. Garg R, Madans JH, Kleinman JC. Regional variation in ischemic heart disease incidence. *J Clin Epidemiol* 1992;45:149-56.
49. Howard G, Manolio TA, Burke GL, Wolfson SK, O'Leary DH, the Atherosclerosis Risk in Communities (ARIC) and Cardiovascular Health Study (CHS) Investigators. Does the association of risk factors and atherosclerosis change with age? An analysis of the combined ARIC and CHS cohorts. *Stroke* 1997;28:1693-701.
50. Taylor AJ, Burke AP, O'Malley PG, Farb A, Virmani R. Insight into the "prognostic gap": the Framingham risk index, coronary calcification and culprit plaque morphology in sudden cardiac death (abstr). *Circulation* 1999;100 Suppl I:I-648.
51. Fuster V, Lewis A. Connor Memorial Lecture—mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994;90:2126-46 (Erratum: *Circulation* 1995;91:256).
52. Krangel AH, Reddy SG, Wittes JT, Roberts WC. Morphometric analysis of the composition of atherosclerotic plaques in the four major epicardial coronary arteries in acute myocardial infarction and sudden coronary death. *Circulation* 1989;80:1747-56.
53. Schmermund A, Baumgart D, Adamzik M, et al. Comparison of electron beam computed tomography and intracoronary ultrasound in detecting calcified and noncalcified plaques in patients with acute coronary syndromes and no or minimal to moderate angiographic coronary artery disease. *Am J Cardiol* 1998;81:141-6.