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Coronary Calcification, Coronary Disease Risk Factors, C-Reactive Protein, and Atherosclerotic Cardiovascular Disease Events

The St. Francis Heart Study

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OBJECTIVES The purpose of this study was to determine the prognostic accuracy of electron beam computed tomographic (CT) scanning of the coronary arteries and the relationship of coronary calcification to standard coronary disease risk factors and C-reactive protein (CRP) in the prediction of atherosclerotic cardiovascular disease (ASCVD) events in apparently healthy middle-age persons.

BACKGROUND As a screening test for coronary artery disease (CAD), electron beam CT scanning remains controversial.

METHODS In a prospective, population-based study, 4,903 asymptomatic persons age 50 to 70 years underwent electron beam CT scanning of the coronary arteries.

RESULTS At 4.3 years, follow-up was available in 4,613 participants (94%), and 119 had sustained at least one ASCVD event. Subjects with ASCVD events had higher baseline coronary calcium scores (median [interquartile range], Agatston method) than those without events: 384 (127, 800) versus 10 (0, 86) ($p < 0.0001$). For coronary calcium score threshold ≥100 versus <100, relative risk (95% confidence interval) was 9.6 (6.7 to 13.9) for all ASCVD events, 11.1 (7.3 to 16.7) for all CAD events, and 9.2 (4.9 to 17.3) for non-fatal myocardial infarction and death. The coronary calcium score predicted CAD events independently of standard risk factors and CRP ($p = 0.004$), was superior to the Framingham risk index in the prediction of events (area under the receiver-operating characteristic curve of 0.79 ± 0.03 vs. 0.69 ± 0.03, $p = 0.0006$), and enhanced stratification of those falling into the Framingham categories of low, intermediate, and high risk ($p < 0.0001$).

CONCLUSIONS The electron beam CT coronary calcium score predicts CAD events independent of standard risk factors, more accurately than standard risk factors and CRP, and refines Framingham risk stratification. (J Am Coll Cardiol 2005;46:158–65) © 2005 by the American College of Cardiology Foundation

Most coronary artery disease (CAD) events occur on a substrate of moderate to severe atherosclerosis (1–4). This fact, together with recognition of the limitations of conventional risk fa ctor assessment and improvements in technology, has generated increasing interest in noninvasive measures of atherosclerosis. These include carotid intima-media thickness (5), ankle-brachial index (6), and fast computed tomographic (CT) scanning of the coronary arteries.

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Coronary calcification occurs in rough proportion to the severity of underlying atherosclerosis (7,8) and can be measured with a high degree of accuracy and reproducibility with electron beam CT (9,10). However, the use of electron beam CT scanning as a screening test for CAD has been and remains controversial (11,12). The strongest supporting evidence has come from retrospective analyses of commercial scanning databases (13–16), which are subject to referral bias, and the only prospective study has yielded conflicting results (17–19). Therefore, we sought to determine the prognostic accuracy of electron beam CT scanning of the coronary arteries and the relationship of coronary calcification to standard CAD risk factors and C-reactive protein (CRP) in the prediction of atherosclerotic cardiovascular disease (ASCVD) events in apparently healthy adults.

METHODS

General study design has been described in detail elsewhere (20) and is diagrammed in Figure 1.

The primary purpose of the St. Francis Heart Study was to compare the prognostic accuracy of electron beam CT scanning of the coronary arteries with that of standard and putative CAD risk factors in a setting of primary prevention. Accordingly, men and women age 50 to 70 years were considered eligible provided they had no history, symptoms (Rose questionnaire [21]), or signs of ASCVD.

Other exclusion criteria included indications for risk factor modification or conditions that might interfere with the conduct or conclusions of a natural history

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Abbreviations and Acronyms

ASCVD = atherosclerotic cardiovascular disease
CAD = coronary artery disease
CI = confidence interval
CRP = C-reactive protein
CT = computed tomography/tomographic
HDL = high-density lipoprotein
LDL = low-density lipoprotein
MI = myocardial infarction
ROC = receiver-operating characteristic

study. The former consisted of insulin-dependent diabetes, triglycerides >500 mg/dl, and in men, low-density lipoprotein (LDL) cholesterol >175 mg/dl (22). The upper limit for cholesterol in women, total cholesterol >300 mg/dl, was chosen in the absence of any proof (circa January 1996) of benefit of cholesterol-lowering therapy in a setting of primary prevention in women and to conform to local practice patterns.

Electron beam CT scanning was performed at the time of enrollment with an Imatron C-150 XP scanner (Imatron, South San Francisco, California) with a reconstruction field of view of 26 cm. Forty contiguous 3-mm slices were scanned during a single breath hold, beginning at the carina. Scan time was 100 ms/slice, synchronized to 80% of the RR interval. At least two adjacent pixels with an attenuation coefficient >130 Hounsfield units defined a calcified lesion, and coronary calcium scores were calculated using the method of Agatston et al. (23).

Subjects with coronary calcium scores above the 80th percentile for age and gender, as defined by an internal database comprising more than 5,000 asymptomatic persons, were invited to participate in a double-blind, placebo-controlled, randomized clinical trial of atorvastatin and antioxidant vitamins (Figure 1). In order to avoid the confounding effect of treatment, subjects assigned to the active treatment arm of the randomized clinical trial were excluded from this, the natural history component of the St. Francis Heart Study. In addition, at the insistence of the St. Francis Hospital Institutional Review Board, which approved this study, all subjects with calcium scores >80th percentile were given 81 mg of aspirin daily. Thus, the control arm of the randomized clinical trial represents the extension of the natural

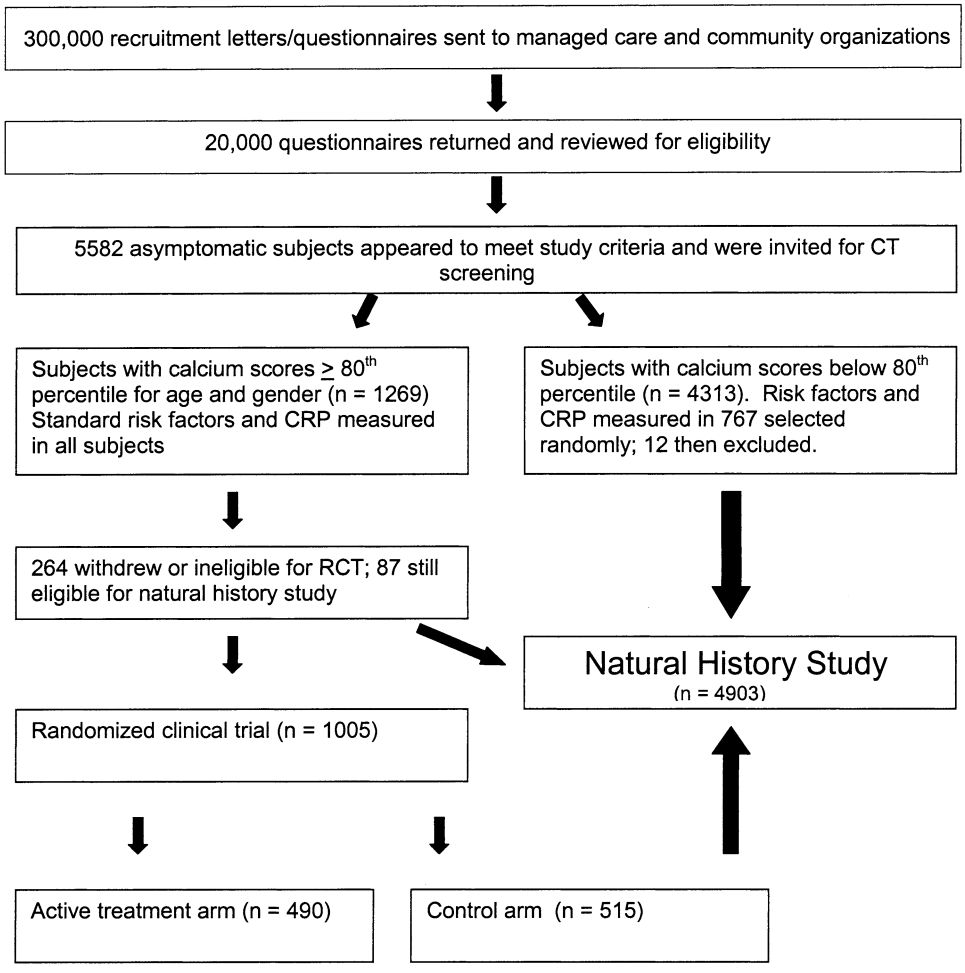

Figure 1. Flow diagram of the St. Francis Heart Study. Follow-up was available at 4.3 years on 4,613 of the 4,903 (94%) and 1,293 of the 1,357 (95%) eligible subjects in whom risk factors were measured. CRP = C-reactive protein; CT = computed tomographic; RCT = randomized clinical trial.

history study into the realm of high calcium scores but was perturbed by treatment with aspirin.

Whereas medical histories and the Rose questionnaire were obtained on all subjects, physical examinations, electrocardiograms, lipid levels, CRP, and other blood tests were obtained only on randomized clinical trial participants and, initially, one in five low-score subjects, later one in six low-score subjects, selected at random. C-reactive protein was measured by latex immunonephelometry on a BN Prospec analyzer (Dade Behring, Newark, Delaware [24]) using Dade Behring reagents by a technician blinded to all other patient information. All randomized clinical trial participants and the low-score subjects in whom risk factors were measured also underwent repeat electron beam CT scans at two and four years after enrollment.

This study was approved by the St. Francis Hospital Institutional Review Board. All participants gave informed consent.

The primary hypothesis tested by the natural history study was that the coronary calcium score would add incremental prognostic value to standard CAD risk factors. End points of interest, verified by an independent committee of current or former coronary care unit directors at academic medical centers, blinded to the coronary calcium score, included coronary death, nonfatal myocardial infarction (MI), surgical or percutaneous coronary revascularization procedures, non-hemorrhagic stroke, and peripheral vascular (i.e., arterial) surgery. In cases in which a study participant experienced more than one end point, only the first end point was counted.

Statistical analysis. Areas under receiver-operating characteristic (ROC) curves and their standard errors were calculated using the method of Hanley and McNeil (25). The statistical significance of differences in areas under ROC curves for the same patients, but for different tests (i.e., calcium score versus standard risk factors), were also calculated using the method of Hanley and McNeil (26), which adjusts for the correlation of the two areas due to the fact that the same patients are used for both ROC curves. The distributions of coronary calcium scores were highly skewed and were compared using Wilcoxon rank sum tests. Correlations of calcium scores with continuous variables were calculated using Spearman correlations. Associations of risk factors and dichotomized calcium scores with events were assessed in univariate analyses from the aforementioned descriptors of test performance as well as relative risks. Relative risks were calculated as the proportion of individuals experiencing an event in the exposed versus unexposed groups. The significance of relative risks were assessed by calculating their standard error using the first-order Taylor series approximation for the variance of the log-relative risk and determining if they were different from one. For assessing the significance of trends in proportions of individuals experiencing events over a variable with three ordinal categories, a Cochran-Mantel-Haenszel test for linear trend of proportions was used. Multiple logistic regression was used to determine if multiple risk factors with and without calcium score predicted events while simultaneously adjusting for all variables in the model (27–29). The statistical significance of risk factors and the calcium score was assessed by likelihood ratio tests, which enabled determination of incremental improvement in prediction of events after all other variables were considered. Multiple ordinary least-squares regression on log (calcium score +1) was used to assess the independent association of multiple risk factors with the coronary calcium score. Significant colinearity was ruled out by calculating variance inflation factors for each independent variable. Multiple logistic regression analyses were performed with and without CRP levels >10 mg/l. Unless otherwise noted, results of analyses including all CRP values are presented.

With the exception of non-parametric analyses, and unless otherwise specified, observations in all analyses were weighted by the inverse probability of an individual being included in the sample. Thus, for example, in the calculation of baseline characteristics, subjects with scores above the 80th percentile for age and gender assigned to the control arm of the randomized clinical trial were counted twice relative to subjects with scores at or below the 80th percentile, since high-score subjects assigned to the active treatment arm were excluded from further analysis. All weights were then normalized so that the sum of the weights for the entire sample was equal to the original sample size. The descriptive statistics, measures of test performance, and p values presented should, therefore, be representative of an unweighted sample from a similar population.

RESULTS

Between July 1996 and March 1999, 5,582 apparently healthy men and women age 50 to 70 years underwent electron beam CT scanning of the coronary arteries. Of these, 28 subjects refused to stop taking cholesterol-lowering medicines or antioxidant vitamins and 161 were found to be ineligible (elevated cholesterol, ischemic changes on electrocardiogram, and so on). Of the remaining 5,393 subjects, 1,005 were invited to participate in the randomized clinical trial on the basis of a coronary calcium score above the 80th percentile for age and gender. Subjects assigned to active treatment (n = 490) were excluded, leaving 4,903 in the natural history component of the study. Follow-up was available at a mean of 4.3 years on 4,613 of the original 4,903 study participants (94%).

Baseline characteristics of the study population are listed in Table 1. Eighty-eight percent of study participants described themselves as Caucasian. Subjects lost to follow-up were younger (57 ± 7 years vs. 59 ± 6 years, p = 0.048) and had lower LDL cholesterol (129 ± 34 mg/dl vs. 144 ± 33 mg/dl, p = 0.03), but were otherwise similar to those for whom follow-up was available. After adjustment

Table 1. Baseline Characteristics of Study Population

Age (yrs)*	59 ± 6
Women (%)*	35
Total cholestrol (mg/dl)	224 ± 33
LDL cholestrol (mg/dl)	143 ± 33
HDL cholestrol (mg/dl)	52 ± 15
Triglycerides (mg/dl)	141 ± 104
Hypertension (%)	34
Diabetes (%)	6
Current smokers (%)	10
Family history of premature CAD (%)	21
Body mass index	28 ± 5
C-reactive protein (mg/l)	1.84 (0.89, 3.96)
Calcium score*	
All	10 (0, 105)
Men	30 (1, 174)
Women	0.5 (0, 20)

*n = 4,613. For all other variables, n = 1,293. Age, lipids, body mass index, and coronary calcium score are presented as mean ± SD. Because the distributions of C-reactive protein and calcium scores were skewed upward, results are presented as the median value (interquartile range). Approximately seven percent of C-reactive protein values exceeded 10 mg/l. To convert cholesterol levels from mg/dl to mmol/l, divide by 38.7. To convert triglycerides from mg/dl to mmol/l, divide by 88.6. Body mass index equals weight (kg) divided by height (m^2).

CAD = coronary artery disease; HDL = high-density lipoprotein; LDL = low-density lipoprotein.

for standard risk factors, calcium scores were similar among those with and without follow-up.

Atherosclerotic cardiovascular disease events occurred in 119 subjects (2.6%): nonfatal MI or coronary death in 40, coronary revascularization (bypass surgery or percutaneous angioplasty) in 59, non-hemorrhagic stroke in 7, and peripheral vascular surgery in 13. Of the 59 coronary revascularization procedures, 42% were performed in subjects hospitalized for unstable angina and 56% were performed after outpatient evaluation of recent onset chest pain. Time from baseline scan to coronary revascularization was >100 days in all of these cases, with a mean (± SD) of 2.1 ± 1.3 years. In just one case was a revascularization procedure performed on an asymptomatic subject.

Subjects with ASCVD events had higher baseline coronary calcium scores (median [interquartile range]) than those without events: 384 (127, 800) versus 10 (0, 86) ($p < 0.0001$).

Descriptors of test performance. For each of the three composite end points of interest (all ASCVD events, all CAD events, and the sum of nonfatal MI and coronary death), event rates increased as a function of the baseline calcium score ($p < 0.0001$). Relative risks were similar for different end points. For example, for the 15% of study participants with calcium scores of 100 to 399 compared with the 33% of subjects with scores of 0, relative risk (95% confidence interval [CI]) ranged only from 10.2 for all ASCVD events (95% CI 5.1 to 20.1) and all coronary events (95% CI 4.8 to 21.7) to 10.4 (95% CI 3.4 to 32.3) for death and nonfatal MI. Relative risks were also similar for weighted and unweighted analyses (Table 2). The sum of sensitivity and specificity reached a maximum of 1.51 to 1.55 at a calcium score threshold ≥100 (25% of the study population) for each of the three composite end points (Fig. 2).

Test performance was similar in the 1,357 subjects in whom risk factors were measured. For example, for subjects with calcium scores ≥100 versus subjects with calcium scores <100, relative risk was 13.0 (95% CI 5.7 to 29.6) for all ASCVD events, 14.5 (95% CI 5.8 to 36.0) for all CAD events, and 11.2 (95% CI 3.0 to 42.3) for nonfatal MI and coronary death, compared with relative risks of 9.6 (95% CI 6.7 to 13.9), 11.0 (95% CI 7.3 to 16.7), and 9.2 (95% CI 4.9 to 17.3), respectively, for all 4,613 participants.

Coronary calcium, coronary disease risk factors, and coronary disease events. In univariate correlation, most standard and conditional risk factors were associated with CRP and the coronary calcium score (Table 3). Exceptions were age and family history of premature coronary disease for CRP and LDL cholesterol for the calcium score. C-reactive protein and the coronary calcium score were weakly correlated ($r = 0.06$, $p = 0.01$).

In multivariate regression, the coronary calcium score was strongly predicted ($p < 0.0001$) by age, male gender, and family history of premature coronary disease. Associations with LDL cholesterol, current smoking, and hypertension became or remained significant ($0.01 > p > 0.001$), whereas associations with high-density lipoprotein (HDL) cholesterol ($p = 0.04$) and diabetes mellitus ($p = 0.06$) fell to borderline levels. After adjustment for standard risk factors, CRP levels no longer predicted the coronary calcium score ($p = 0.22$).

The calcium score predicted CAD events independently of standard risk factors (chi-square = 6.6, $p = 0.01$) and the combination of standard risk factors and CRP (chi-square = 6.6, $p = 0.01$) (Table 4). In contrast, after adjustment for standard risk factors alone or together with baseline calcium score, CRP did not predict CAD events ($p \geq 0.48$).

The calcium score predicted CAD events more accurately than the Framingham risk index (26); the area under the ROC curve was 0.79 ± 0.03 for the calcium score versus 0.68 ± 0.03 for the Framingham index ($p = 0.0006$). Consistent with this difference, the calcium score also enhanced risk stratification based on the Framingham index ($p < 0.0001$ for trend; Fig. 3).

Table 2. Coronary Calcium Score and All Coronary Disease Events*

Score	n (Weighted)	Event Rate (%)	Relative Risk (95% CI)
0	1,504	0.54	1.0
1–99	1,973	1.00	1.9 (0.8–4.2)
100–399	686	5.5	10.2 (4.8–21.6)
≥400	450	14.0	26.2 (12.6–53.7)

*Includes coronary death, nonfatal myocardial infarction, coronary bypass surgery, and percutaneous coronary angioplasty (n = 4,613). Relative risk is based on comparison to subjects with calcium scores of zero. Analysis of unweighted sample yielded similar results, with relative risks of 1.0, 1.9, 10.3, and 26.9, respectively, for the different strata of calcium scores.

CI = confidence interval.

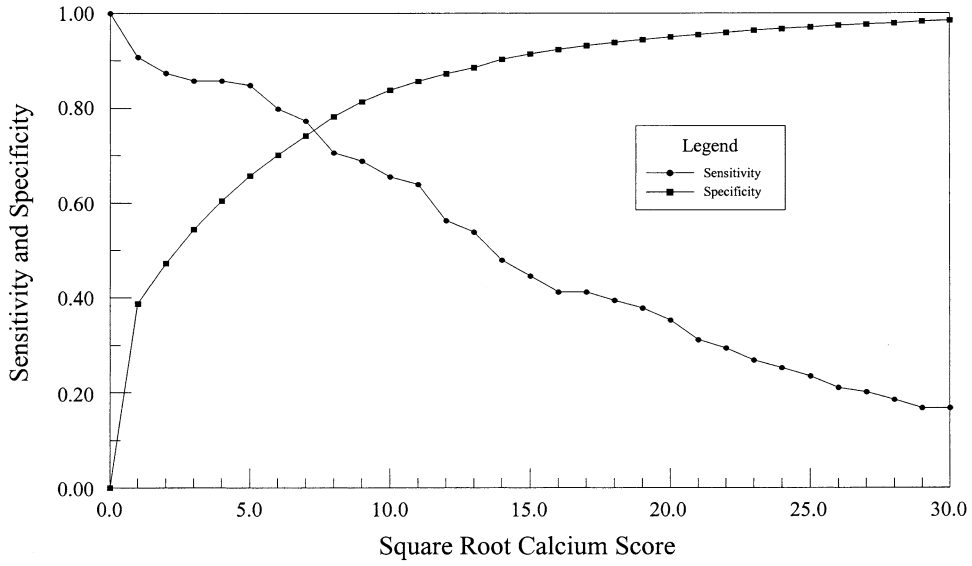

Figure 2. Sensitivity **(circles)** and specificity **(squares)** for the prediction of all coronary disease events as a function of the square root of the coronary calcium score (n = 4,613).

Change in calcium score and subsequent coronary disease events. Median (interquartile range) increased by 4 (0, 38) U from baseline to the year two scan in subjects who did not sustain a coronary event at any time during the study. In contrast, median (interquartile range) increased by 247 (40, 471) U between the baseline and two-year examinations in 49 subjects who first experienced a CAD event after the year two scan ($p < 0.0001$). (Subjects who experienced a CAD event in the first two years of the study were excluded from this analysis because most received one or more metallic stents, which cannot reliably be distinguished from coronary calcification.)

In univariate analysis, baseline age, male gender, current smoking, hypertension, diabetes, family history of premature coronary disease, HDL cholesterol, body mass index, and triglycerides, but not LDL cholesterol ($p = 0.08$) or current smoking ($p = 0.30$), were all correlated ($p < 0.01$) with change in calcium score. In multiple logistic regression, only age ($p = 0.03$), male gender ($p = 0.04$), LDL cholesterol ($p = 0.01$), HDL cholesterol ($p = 0.04$), and two-year change in calcium score ($p = 0.0001$) were significantly associated with subsequent CAD events. Two-year change in coronary calcium score was also highly correlated with baseline calcium score ($r = 0.92$).

Table 3. Univariate Correlations: Standard Risk Factors, C-Reactive Protein, and Coronary Calcium Score (n = 1,293)

	C-Reactive Protein		Calcium Score	
	r	p Value	r	p Value
Age	0.03	0.19	0.25	<0.0001
Gender (male)	0.07	0.003	0.33	<0.0001
LDL cholesterol	0.08	0.0006	0.03	0.15
HDL cholestrol	−0.21	<0.0001	−0.16	<0.0001
Hypertension	0.14	<0.0001	0.18	<0.0001
Diabetes mellitus	0.09	0.0003	0.10	<0.0001
Current smoking	0.08	0.001	0.05	0.03
Family history	0.01	0.67	0.09	<0.0001
Triglycerides	0.22	<0.0001	0.14	<0.001
Body mass index	0.44	<0.0001	0.16	<0.0001
Systolic blood pressure	0.18	<0.0001	0.21	<0.0001
Diastolic blood pressure	0.15	<0.0001	0.15	<0.0001
C-reactive protein	—	—	0.06	0.01
Calcium score	0.06	0.01	—	—

Abbreviations as in Table 1.

DISCUSSION

With nearly 20,000 person-years of observation, this study demonstrates that the electron beam CT scan-derived coronary calcium score predicts ASCVD events, CAD events, and the composite of coronary death and nonfatal MI independently of and more accurately than standard coronary risk factors. Although not sufficiently powerful to negate the prognostic value of standard risk factors, the calcium score enhanced risk stratification based on the Framingham index (30), identifying intermediate-risk subjects among those seemingly at low risk, low- and high-risk subjects among those apparently at intermediate risk, and intermediate-risk subjects among those classified as high risk. In contrast, after adjustment for standard risk factors and the baseline calcium score, CRP did not predict events.

For the entire study population, relative risk ranged from 9.2 to 11.1 for the composite end points of interest in subjects with calcium scores ≥100 (25% of the study population) compared to subjects with calcium scores <100 (the remaining 75% of the cohort). These relative risks are approximately five times higher than values typically reported for standard (5,31) and newer (32) coronary risk factors.

More likely than not, this study underestimated the true risk associated with a high coronary calcium score. Subjects

Table 4. Association of Standard Risk Factors, C-Reactive Protein, Calcium Score, and All Coronary Disease Events (n = 1,293)

	Without CRP		Without Calcium Score		With CRP and Calcium Score	
	Chi-Square	p Value	Chi-Square	p Value	Chi-Square	p Value
Age	4.1	0.04	5.4	0.02	4.1	0.04
Gender (male)	5.0	0.01	6.9	0.01	4.9	0.03
LDL cholesterol	5.6	0.02	6.5	0.01	6.4	0.01
HDL cholesterol	5.8	0.02	6.3	0.01	5.1	0.02
Hypertension	3.0	0.08	2.2	0.14	3.3	0.07
Diabetes mellitus	1.4	0.24	2.4	0.12	3.7	0.05
Current smoking	1.3	0.25	0.9	0.34	1.1	0.30
Family history	1.0	0.33	2.5	0.11	1.4	0.24
C-reactive protein	—	—	0.5	0.48	0.4	0.51
Calcium score	6.6	0.01	—	—	6.6	0.01
c-statistic	0.83		0.80		0.85	

Analyses including CRP are based on all values measured. Exclusion of subjects with CRP >10 mg/l reduced chi-square values to < 0.42. The c-statistic is analogous to the area under the receiver-operating characteristic curve (SAS PROC LOGISTIC [SAS v8.2: Association of predicted probabilities and observed responses]).

CRP = C-reactive protein; other abbreviations as in Table 1.

with high calcium scores were treated with aspirin, and only about 18% of subjects with low scores underwent physical examination, electrocardiography, or laboratory testing. Thus, the risk of ASCVD events was reduced by aspirin in subjects with high calcium scores (33,34), whereas the low score group undoubtedly contained subjects who should have been excluded from a study of primary prevention because of abnormalities on physical examination or electrocardiogram. A slightly higher relative risk in the subgroup in which risk factors were measured and a complete baseline examination was performed suggests that this was so. For budgetary and logistical reasons, these examinations were not performed on the majority of low-score subjects. This feature of study design also favored the null hypothesis.

Given the number, size, and methodologic integrity of the studies that have established CRP as a risk factor for coronary disease (32), the failure of CRP to predict events independently of standard risk factors in the present study is most likely the result of sample size. Although the present findings do not invalidate CRP as a risk factor, they indicate that CRP, like standard risk factors, is not as powerful a predictor of events as the calcium score. The relative risk of CRP, highest tertile versus lowest tertile, is <2 (32), whereas the relative risk of a CAD event for the calcium score, highest tertile versus lowest tertile, in the present study was 13.9 (95% CI 7.1 to 27.3). Moreover, after adjustment for the calcium score, CRP failed to predict events ($p = 0.47$). In the only other published direct comparison of CRP and calcium score, after adjustment of each variable for the other, the association between the calcium score and events remained robust ($p \leq 0.004$), whereas the association between CRP and events fell to borderline levels ($0.02 \leq p \leq 0.09$; Park et al. [17]).

Less than 2% of age-eligible persons notified of this study eventually enrolled. This low level of participation raises questions about the generalizability of the study results. However, with the exception a low prevalence of current smoking and a high prevalence of family history of premature CAD disease, neither of which had independent prognostic significance, the prevalence of standard CAD risk factors is similar to that reported in recent, large, population-based studies (35–37). Although the area under the ROC curve for the Framingham risk index is at the low end of values reported from recent, large, population-based studies, the c-statistics reported in Table 4 are well within the range of previously reported values (38,39). Thus, it seems unlikely that the study results are inapplicable to asymptomatic, middle-age Caucasians. On the other hand,

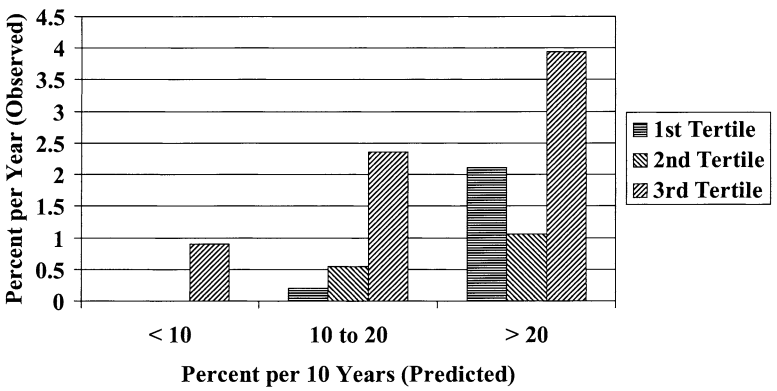

Figure 3. Coronary event rates as a function of calcium score within the Framingham risk groups (low: <10% per 10 years; intermediate: 10% to 20% per 10 years; and high: >20% per year). There were no coronary events in the first and second tertile of calcium scores in the Framingham low-risk group (n = 1,293).

the number of ASCVD events in non-white study participants is not yet sufficient to support conclusions. This point is important because African Americans appear to have less coronary calcium than whites (40,41), and data in Native Americans, whether English or Spanish speaking, or persons of East Asian ancestry, are scant.

All five previous longitudinal studies of electron beam CT scanning have established that the coronary calcium score predicts ASCVD events (13–18). However, due to methodologic limitations, these same studies have failed to end the debate over the incremental value of the coronary calcium score relative to standard risk factors (11,12). Specifically, because of concern about referral bias and/or inaccuracies in self-reported risk factors, the evidence presented in four positive, retrospective analyses of commercial databases has not been considered powerful enough to override the initially negative results from a prospective study of a highly selected population, even though the homogeneity of that population favored the null hypothesis (19).

The St. Francis Heart Study is unique in that it was both prospective and population based. To date, it is also the largest study of electron beam CT scanning for the early detection of CAD. In middle-aged Caucasians, the results of the St. Francis Heart Study speak for themselves: the electron beam CT-derived coronary calcium score predicted ASCVD events, including nonfatal MI and coronary death, independently of and more accurately than standard coronary risk factors. We eagerly await the results of the National Institutes of Health-sponsored Multiethnic Study of Atherosclerosis (MESA), which is sufficiently powered to address these issues in minorities.

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