

Cardiac Imaging

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Abbreviations:

A_z = area under the ROC curve
 ROC = receiver operating
 characteristic

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Prognostic Value of Cardiac Risk Factors and Coronary Artery Calcium Screening for All-Cause Mortality¹

PURPOSE: To develop risk-adjusted multivariable models that included risk factors and coronary calcium scores determined with electron-beam computed tomography (CT) in asymptomatic patients for the prediction of all-cause mortality.

MATERIALS AND METHODS: We followed up a cohort of 10,377 asymptomatic individuals undergoing cardiac risk factor evaluation and coronary calcium screening with electron-beam CT. Multivariable Cox proportional hazards models were developed to predict all-cause mortality. Risk-adjusted models incorporated traditional risk factors for coronary disease and coronary calcium scores.

RESULTS: Cardiac risk factors such as family history of coronary disease (69%), hypercholesterolemia (62%), hypertension (44%), smoking (40%), and diabetes (9%) were prevalent. The frequency of coronary calcium scores was 57%, 20%, 14%, 6%, and 3% for scores of 10 or less, 11–100, 101–400, 401–1,000, and greater than 1,000, respectively. During a mean follow-up of 5.0 years \pm 0.0086 (standard error of the mean), the death rate was 2.4%. In a risk-adjusted model (model $\chi^2 = 388.2$, $P < .001$), coronary calcium was an independent predictor of mortality ($P < .001$). Risk-adjusted relative risk values for coronary calcium were 1.64, 1.74, 2.54, and 4.03 for scores of 11–100, 101–400, 401–1,000, and greater than 1,000, respectively ($P < .001$ for all values), as compared with that for a score of 10 or less. Five-year risk-adjusted survival was 99.0% for a calcium score of 10 or less and 95.0% for a score of greater than 1,000 ($P < .001$). With a receiver operating characteristic curve, the concordance index increased from 0.72 for cardiac risk factors alone to 0.78 ($P < .001$) when the calcium score was added to a multivariable model for prediction of death.

CONCLUSION: This large observational data series shows that coronary calcium provides independent incremental information in addition to traditional risk factors in the prediction of all-cause mortality.

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The prognostic significance of coronary calcification discovered in asymptomatic individuals remains controversial (1). Though researchers in several publications demonstrate that the presence of coronary calcification helps to identify patients at high risk of events, they have been criticized for methodological weaknesses (2–10). The small size of the cohorts studied, the presence of a selection bias, the report of mixed outcomes (ie, revascularization, stroke, infarction, and death), and the use of nonstandard electron-beam computed tomography (CT) imaging techniques have all been cited as possible causes for the limited uniformity of the data published to date (1,7). The purpose of this study was to develop risk-adjusted multivariable models that included risk factors and coronary calcium scores determined with electron-beam CT to predict all-cause mortality in asymptomatic patients.

MATERIALS AND METHODS

Inclusion Criteria

We included a total of 10,377 asymptomatic individuals who were referred by their primary care physicians between 1996 and 2000 for coronary calcium screening with electron-beam CT. Individuals were referred for screening on the basis of the presence of established risk factors and, as such, are not an unselected cohort representative of the general population. All individuals were initially screened by their general internists and were considered to be at above-average risk for coronary disease because of the presence of cardiac risk factors, which included advanced age; a history of high blood pressure, hypercholesterolemia, diabetes mellitus, and current smoking; and a family history of premature coronary disease. Patients with a history of coronary disease (ie, a history that included admission to the hospital for chest pain, acute coronary syndrome, or myocardial infarction, as well as prior coronary angiography and revascularization) were excluded.

All screened individuals provided informed consent to undergo electron-beam CT screening, and our study received Human Investigations Committee approval. Furthermore, separate approval from the Human Investigations Committee was obtained, along with informed consent, for the patient interviews, collection of data and follow-up, and corroboration of the occurrence of death.

Data Collection

We (T.Q.C., P.R.) collected information in regard to the presence of categorical cardiac risk factors in every patient. Risk factor data were derived through patient interview, referring physician contact, and existing medical record data. Systemic arterial hypertension was defined as a documented history of high blood pressure or treatment with medication, diet, and/or exercise. A history of current smoking or cessation of smoking within 3 months before testing was defined as positive smoking status. Hypercholesterolemia was determined on the basis of the answers to the following questions: "Has your physician ever told you that you need medications for high cholesterol?" "Are you currently taking cholesterol medications?" Answers to these questions often identified patients who were currently receiving cholesterol-lowering medications. Individuals were classified as having diabetes mellitus if they

had received a previous diagnosis of diabetes mellitus that was determined with blood glucose levels or if they had received treatment with insulin or oral hypoglycemic agents.

Estimation of Framingham Risk

We calculated an expected 10-year risk of cardiac death or nonfatal myocardial infarction with range estimates published within the National Cholesterol Education Panel III risk calculator (11). A global risk score was devised for each patient on the basis of sex, age, and a history of hyperlipidemia, hypertension, and cigarette smoking. For each of the traditional risk factors for cardiovascular disease, individual points were summed for age and sex subsets of this cohort. Furthermore, the corresponding points for hyperlipidemia were based on a range of a total cholesterol level from 130 to 320 mg/dL (3.38–8.32 mmol/L) and on a range of a high-density lipoprotein cholesterol level from 25 to 55 mg/dL (0.65–1.43 mmol/L). Treated hypertension adds an average of 1%–2% risk for women and men, though the range was as high as 5%. Current history of cigarette smoking added a range in risk estimates from 4% to 12%. For the risk with diabetes mellitus, which is consistent with the coronary heart disease risk equivalent, a 20% risk of death or myocardial infarction was calculated. We then summed all point values for each of the previously mentioned risk factors to obtain a global risk score or the expected Framingham risk of death or myocardial infarction at 10 years. The median risk estimate was 15% (range, 1%–65%). Estimates were performed by one of us (L.J.S.).

Electron-Beam CT

Each patient signed an informed consent prior to undergoing screening. Electron-beam CT was performed with a scanner (C-100 or C-150; Imatron, South San Francisco, Calif), and images were obtained with 100-msec scanning time. The CT section thickness was 3 mm, and, in total, 40 sections were obtained starting at the level of the carina and proceeding to the level of the diaphragm. CT was electrocardiographically triggered at 60%–80% of the R-R interval. Coronary calcification was defined as a plaque of at least 3 consecutive pixels (area, 1.03 mm²) with attenuation of 130 HU or greater. Quantitative calcium scores were calculated according to the method described by Agatston et al (12). One of two experienced investigators (T.Q.C., P.R.) with 6 and 8

years of experience, respectively, reviewed all electron-beam CT scans in random order. Since calcium scoring was performed only once in each patient, intra- and inter-investigator score variability was not calculated.

Follow-up Procedures

Epidemiologic methods for follow-up included ascertainment of events by individuals who were blinded to historical and calcium score results (13–15). The occurrence of all-cause death was verified with the National Death Index (16). Individuals who underwent cardiovascular screening were followed up for a mean of 5 years \pm 0.0086 (standard error of the mean), with a range of 2–5 years, and we were able to perform follow-up in 100% of the patients.

Statistical Analysis

Statistical analysis was performed by two experienced statistical analysts (L.J.S., E.S.) who were blinded to patient identifiers. Categorical variables were compared with the χ^2 statistic. Comparisons of categorical variables with continuous measures were calculated with analysis-of-variance techniques. A general linear model was used to compare continuous measures of coronary calcium in subsets of the population according to age and sex groupings. A first-order test for interaction of coronary calcium according to sex was performed.

The primary end point for this analysis was all-cause mortality. For the outcome analysis, we used univariable and multivariable Cox proportional hazards models to estimate the time to all-cause death (13,15). For the univariable Cox proportional hazards regression models, we evaluated the statistical significance of cardiac risk factors and coronary calcium scores in separate models. Univariable models with a probability value of less than .20 were considered for the multivariable models. A final multivariable model was constructed that included variables with a *P* value of less than .10. Relative risk ratios and 95% CIs were calculated for the univariable and multivariable models. Stepwise Cox proportional hazards models were used to identify the strongest estimators of outcome by using a forward likelihood ratio method.

A concordance index, event classification ability, was determined for a model containing cardiac risk factors and then again with coronary calcium added to the Cox proportional hazards regression

TABLE 1
Clinical and Electron-Beam CT
Characteristics of the Study
Population

| Characteristic | Study Cohort (<i>n</i> = 10,377)* |
|------------------------------|---------------------------------------|
| Age (y)† | |
| 30–39 | 7.9 (820) |
| 40–49 | 30.0 (3,113) |
| 50–59 | 35.3 (3,663) |
| 60–69 | 19.2 (1,992) |
| 70–79 | 6.9 (716) |
| 80 or older | 0.7 (73) |
| Sex | |
| M | 59.6 (6,186) |
| F | 40.4 (4,191) |
| History of hyperlipidemia | |
| No | 38.5 (3,995) |
| Yes | 61.5 (6,382) |
| History of hypertension | |
| No | 56.4 (5,853) |
| Yes | 43.6 (4,524) |
| History of diabetes mellitus | |
| No | 91.3 (9,474) |
| Yes | 8.7 (903) |
| History of smoking | |
| No | 60.4 (6,268) |
| Yes | 39.6 (4,109) |
| Family history of CAD‡ | |
| No | 31.2 (3,238) |
| Yes | 68.7 (7,139) |
| Calcium score§ | |
| ≤10 | 57.3 (5,946) |
| 11–100 | 19.7 (2,044) |
| 101–400 | 13.8 (1,432) |
| 401–1,000 | 6.0 (623) |
| >1,000 | 3.2 (332) |

* Data are percentages. Data in parentheses are numbers of patients.

† Mean age was 53 ± 0.102 , and the range was 30–85 years.

‡ CAD = coronary artery disease.

§ Mean score was 133.1 ± 3.62 , and the score range was 0–4,380.

analysis. A split-sample test and validation set were used to verify the multivariable model results. Unadjusted and risk-adjusted (ie, controlling for cardiac risk factors) Cox proportional hazards survival curves were generated to compare coronary calcium scores of 10 or less, 11–100, 101–400, 401–1,000, and greater than 1,000.

In a final analysis, we evaluated the use of a predicted Framingham risk score in relation to the coronary calcium score. Initially, Cox proportional hazards models included the added value of coronary calcium scores above and beyond the estimated Framingham risk score. A receiver operating characteristic (ROC) curve (95% CI) was calculated and compared the ability to classify events on the basis of the Framingham risk score and a combination of the Framingham risk

TABLE 2
Coronary Calcium Scores according to Varying Age and Sex Subsets

| Age | Women (<i>n</i> = 4,191) | Men (<i>n</i> = 6,186) |
|-------------------------------------|------------------------------|----------------------------|
| Younger than 40 y (<i>n</i> = 820) | 7 ± 3.1 | 12 ± 3.3 |
| 40–49 y (<i>n</i> = 3,113) | 16 ± 3.1 | 56 ± 4.2 |
| 50–59 y (<i>n</i> = 3,663) | 51 ± 4.8 | 158 ± 7.9 |
| 60–69 y (<i>n</i> = 1,992) | 120 ± 9.8 | 352 ± 18.8 |
| 70–79 y (<i>n</i> = 716) | 267 ± 22.9 | 600 ± 42.1 |
| 80 y or older (<i>n</i> = 73) | 291 ± 90.6 | $1,070 \pm 181.6$ |

Note.—Values are the mean \pm standard error of the mean.

score and the coronary calcium score. Additionally, the predicted 5-year mortality from the multivariable model was compared for low, intermediate, and high Framingham risk groups according to their coronary calcium score.

Continuous variables are presented as the mean and standard error of mean. The level of significance was chosen at a *P* value of less than .05.

RESULTS

Clinical Characteristics

The mean age of the subjects in the study cohort was 53 years \pm 0.102 (standard error of the mean), with a wide range in age of participants (ie, 30–85 years; Table 1). Individuals 40–59 years old were most frequently screened. Forty percent of the patients were women. Cardiac risk factors were prevalent. More than half of the individuals had hypercholesterolemia or had a family history of coronary artery disease, and approximately 40% had hypertension. Approximately 40% of the screened individuals were current smokers, and approximately 9% had diabetes mellitus. The mean number of cardiac risk factors was 2.2 ± 0.011 , and 74.2% (7,700 of 10,377) of individuals had two or more cardiac risk factors.

The mean coronary calcium score for the 10,377 asymptomatic individuals who were referred for screening was 133 ± 0.9 (score range, 0–4,380). Of the 10,377 individuals who underwent coronary calcium screening, 57% had a score of 10 or less. The prevalence of calcium scores of 11–100, 101–400, 401–1,000, and greater than 1,000 was 20%, 14%, 6%, and 3%, respectively. Table 2 presents the mean coronary calcium scores for varying age and sex subsets. Coronary calcium scores ranged, on average, from 12 to 1,070 for men younger than 40 years to 80 years or older ($F = 162$, $P < .001$). For women, mean coronary cal-

cium scores ranged from 7 to 291 for those younger than 40 years to 80 years or older. As calcium scores varied within age and sex subsets of this population, a test for interaction was significant ($F = 49$, $P < .001$).

Estimation of All-Cause Mortality

Mortality was significantly elevated in subjects older than 60 years compared with that in younger individuals ($P < .001$) and in subjects with established risk factors for atherosclerosis compared with that in those without risk factors. The *P* values were all less than .001 for the following risk factors: history of hypertension, diabetes mellitus, history of smoking, and a family history of premature coronary artery disease (Table 3). In this cohort of 10,377 asymptomatic individuals, diabetic patients had a mortality rate of 5.5% ($P < .001$ for comparison with nondiabetic individuals). The mortality rates for all patients were 1.0%, 2.6%, 3.8%, 6.3%, and 12.3% for calcium scores of 10 or less, 11–100, 101–400, 401–1,000, and greater than 1,000, respectively ($P < .001$).

Univariable Relative Risk Estimates of Mortality

Relative risk ratios increased from 1.31 for subjects 50–59 years of age to 13.50 for those 80 years or older ($P < .001$) (Table 4). Relative risk ratios were approximately twofold greater for hypertensive subjects and current smokers. For diabetic patients, the relative risk ratios were increased 2.69-fold (95% CI: 1.96, 3.67; $P < .001$). For calcium scores of 11–100, the relative risk of mortality was 2.47-fold greater (95% CI: 1.71, 3.58) than that for a score of 10 or less ($P < .001$). When the comparator of a calcium score of 10 or less was used, the relative risk ratio for mortality was 3.55 times greater (95% CI: 2.46, 5.13) for a score of 101–400, and it was 6.15 times greater

(95% CI: 4.11, 9.21) and 12.29 times greater (95% CI: 8.28, 18.23) for a calcium score of 401–1,000 and for a calcium score of greater than 1,000 ($P < .001$), respectively.

Multivariable Mortality Model

In a multivariable model, diabetes mellitus, hypertension, smoking, age, and coronary calcium were significant estimators of time to demise from all causes, with a P value less than .001 for all these factors (Table 5). In our series, hyperlipidemia was associated with a reduced risk of death ($P < .001$). Most of the patients with hyperlipidemia who were referred for electron-beam CT by their primary care physicians were already receiving a lipid-lowering drug, or their physicians prescribed such medication after the results of electron-beam CT became available. As shown in large primary prevention trials, the event rate in individuals with either elevated or average cholesterol levels who received lipid-lowering therapy was reduced by approximately 30% compared with the event rate in untreated subjects (17,18).

In the stepwise Cox proportional hazards regression analysis, coronary calcium (entered at step 1, $P < .001$) and age (entered at step 2, $P < .001$) were the strongest predictors of mortality.

Additionally, when compared with a model that was based on risk factors alone, the concordance index increased from 0.72 for cardiac risk factors to 0.78 when calcium was added to the multivariable model ($P < .001$). From this risk-adjusted model, the relative risk of mortality was 1.64, 1.74, 2.54, and 4.03 times greater for calcium scores of 11–100, 101–400, 401–1,000, and greater than 1,000, respectively, compared with the relative risk for a calcium score of 10 or less.

Split Sample: Test and Validation Sets

By using a split-sample approach, training and validation samples of the predictive accuracy of coronary calcium revealed similar results. The χ^2 test result for the training set was 18, and the χ^2 test for the validation set was 21 (Table 6). In both samples, the relative risk of death adjusted for all risk factors increased proportionally with the extent of coronary calcification.

Unadjusted and Risk-adjusted Survival Curves

Unadjusted survival according to coronary calcium scores is shown in Figure 1.

TABLE 3
Overall Rates of All-Cause Mortality according to Clinical and Electron-Beam CT Characteristics of Study Population

| Characteristic | Study Population ($n = 10,377$) | | P Value |
|---------------------------------|-------------------------------------|----------------------------------|---------|
| | All-Cause Death ($n = 249$, 2.4%) | No Death ($n = 10,128$, 97.6%) | |
| Age | | | <.001 |
| 30–39 y ($n = 820$) | 1.3 (11) | 98.7 (809) | |
| 40–49 y ($n = 3,113$) | 0.7 (22) | 99.3 (3,091) | |
| 50–59 y ($n = 3,663$) | 1.7 (64) | 98.3 (3,599) | |
| 60–69 y ($n = 1,992$) | 4.1 (82) | 95.9 (1,910) | |
| 70–79 y ($n = 716$) | 8.4 (60) | 91.6 (656) | |
| 80 y or older ($n = 73$) | 14.5 (10) | 85.5 (63) | |
| Sex | | | .5 |
| M ($n = 6,186$) | 2.3 (144) | 97.7 (6,042) | |
| F ($n = 4,191$) | 2.5 (105) | 97.5 (4,086) | |
| History of hypercholesterolemia | | | .01 |
| No ($n = 3,995$) | 2.9 (115) | 97.1 (3,880) | |
| Yes ($n = 6,382$) | 2.1 (133) | 97.9 (6,249) | |
| History of hypertension | | | <.001 |
| No ($n = 5,853$) | 1.6 (93) | 98.4 (5,760) | |
| Yes ($n = 4,524$) | 3.4 (156) | 96.6 (4,368) | |
| History of diabetes mellitus | | | <.001 |
| No ($n = 9,474$) | 2.1 (50) | 97.9 (9,424) | |
| Yes ($n = 903$) | 5.5 (199) | 94.5 (704) | |
| History of smoking | | | <.001 |
| No ($n = 6,268$) | 1.6 (101) | 98.4 (6,167) | |
| Yes ($n = 4,109$) | 3.6 (148) | 96.4 (3,961) | |
| Family history of CAD* | | | <.001 |
| No ($n = 3,238$) | 3.0 (97) | 97.0 (3,141) | |
| Yes ($n = 7,139$) | 2.1 (151) | 97.9 (6,988) | |
| Calcium score | | | <.001 |
| ≤ 10 ($n = 5,946$) | 1.0 (62) | 99.0 (5,884) | |
| 11–100 ($n = 2,044$) | 2.6 (53) | 97.4 (1,991) | |
| 101–400 ($n = 1,432$) | 3.8 (54) | 96.2 (1,378) | |
| 401–1,000 ($n = 623$) | 6.3 (39) | 93.7 (584) | |
| $> 1,000$ ($n = 332$) | 12.3 (41) | 87.7 (293) | |

Note.—Data are percentages. Data in parentheses are numbers of patients.
* CAD = coronary artery disease.

TABLE 4
Univariable Cox Proportional Hazards Model for Estimation of All-Cause Mortality

| Characteristic | Relative Risk Ratio* | χ^2 Test | P Value |
|------------------------------------|----------------------|---------------|---------|
| Age | | 245.0 | <.001 |
| Younger than 40 y ($n = 820$) | ... [†] | | |
| 40–49 y ($n = 3,113$) | 0.53 (0.26, 1.11) | | |
| 50–59 y ($n = 3,663$) | 1.31 (0.69, 2.49) | | |
| 60–69 y ($n = 1,992$) | 3.21 (1.71, 6.00) | | |
| 70–79 y ($n = 716$) | 6.79 (3.56, 12.92) | | |
| 80 y or older ($n = 73$) | 13.50 (5.67, 31.45) | | |
| Female sex | 1.08 (0.84, 1.39) | 0.4 | .5 |
| Hypercholesterolemia | 0.71 (0.55, 0.91) | 7.0 | .008 |
| Hypertension | 2.18 (1.68, 2.82) | 37.0 | <.001 |
| Diabetes mellitus | 2.69 (1.96, 3.67) | 41.0 | <.001 |
| Smoking | 2.28 (1.77, 2.95) | 43.0 | <.001 |
| Family history of CAD [‡] | 0.71 (0.55, 0.92) | 7.0 | .009 |
| Calcium score | | 242.0 | <.001 |
| ≤ 10 ($n = 5,946$) | ... [†] | | |
| 11–100 ($n = 2,044$) | 2.47 (1.71, 3.58) | | |
| 101–400 ($n = 1,432$) | 3.55 (2.46, 5.13) | | |
| 401–1,000 ($n = 623$) | 6.15 (4.11, 9.21) | | |
| $> 1,000$ ($n = 332$) | 12.29 (8.28, 18.23) | | |

Note.—Study population is $n = 10,377$.
* Numbers in parentheses are the 95% CIs.
[†] Relative risk ratio comparator.
[‡] CAD = coronary artery disease.

TABLE 5
Multivariable Cox Proportional Hazards Model

| Model | Relative Risk* | χ^2 Test | P Value |
|---|-------------------|---------------|---------|
| Risk factor evaluation | | | |
| Age | 1.06 (1.04, 1.08) | 64 | <.001 |
| Female sex | 1.20 (0.91, 1.58) | 2 | .19 |
| History of diabetes mellitus | 1.62 (1.18, 2.24) | 9 | <.001 |
| Family history of coronary artery disease | 0.84 (0.65, 1.10) | 2 | .20 |
| History of hyperlipidemia | 0.64 (0.49, 0.82) | 12 | <.001 |
| History of hypertension | 1.59 (1.22, 2.08) | 12 | <.001 |
| History of smoking | 2.18 (1.68, 2.84) | 34 | <.001 |
| Coronary calcium score | | | |
| 11–100 | 1.64 (1.12, 2.41) | 6 | <.001 |
| 101–400 | 1.74 (1.16, 2.61) | 7 | <.001 |
| 401–1,000 | 2.54 (1.62, 3.99) | 16 | <.001 |
| >1,000 | 4.03 (2.52, 6.40) | 34 | <.001 |

Note.—The model χ^2 was 388.2 ($P < .001$).

* Numbers in parentheses are the 95% CIs.

TABLE 6
Risk-adjusted Cox Proportional Hazards Model in Training and Validation Samples

| Coronary Calcium Score | χ^2 Test | P Value | Relative Risk Ratio | 95% CI for Relative Risk |
|------------------------|---------------|---------|---------------------|--------------------------|
| Training set | | | | |
| 0–10 | ... | ... | 1.00 | ... |
| 11–100 | 5 | .028 | 1.85 | 1.07, 3.20 |
| 101–400 | 9 | .003 | 2.31 | 1.32, 4.05 |
| 401–1,000 | 14 | <.001 | 3.24 | 1.74, 6.02 |
| >1,000 | 13 | <.001 | 3.75 | 1.85, 7.60 |
| Validation set | | | | |
| 0–10 | ... | ... | 1.00 | ... |
| 11–100 | 5 | .025 | 2.45 | 1.12, 5.36 |
| 101–400 | 8 | .006 | 2.38 | 1.28, 4.42 |
| 401–1,000 | 12 | .001 | 2.99 | 1.59, 5.65 |
| >1,000 | 21 | <.001 | 4.50 | 2.36, 8.60 |

Note.—With this model, age, sex, smoking status, family history of heart disease, history of diabetes, hypercholesterolemia, and hypertension were controlled. For the validation sample, the degrees of freedom for each multivariable model was 11.

Risk-adjusted survival estimates for coronary calcium scores generated from the multivariable model are plotted in Figure 2. Risk-adjusted survival was 98.8%, 98.1%, 98.0%, 96.8%, and 95.0% for calcium scores of 10 or less, 11–100, 101–400, 401–1,000, and greater than 1,000, respectively ($P < .001$).

Estimated Framingham Risk of 10-year Cardiac Death or Myocardial Infarction

By using an average expected risk of death or myocardial infarction at 10 years, the combined estimated Framingham risk score yielded a highly significant prediction of death (model $\chi^2 = 111$, $P < .001$). In a model that included both the estimated Framingham risk and coronary calcification, the calcium score was highly predictive of time to all-cause

mortality (model $\chi^2 = 238$, $P < .001$; coronary calcium score $\chi^2 = 69$, $P < .001$). An ROC curve analysis revealed that both the estimated Framingham risk (area under the ROC curve [A_z] = 0.67; 95% CI: 0.63, 0.71; $P < .001$) and coronary calcium scores ($A_z = 0.73$; 95% CI: 0.70, 0.76; $P < .001$) were significantly predictive of death. In this analysis, coronary calcium showed superior outcome classification ability when compared with the estimated Framingham risk (Fig 3; $A_z = 0.73$ vs 0.67, $P < .001$).

A multivariable model was used to derive the predicted 5-year mortality rates according to calcium scores in various Framingham risk subsets (Fig 4, $P < .001$). For low-risk patients, 5-year mortality rates ranged from 0.9% to 3.9% for coronary calcium scores of less than 10 to greater than 1,000 ($P < .001$). Similarly,

5-year mortality rates ranged from 1.1% to 9.0% for intermediate-risk ($P < .001$) and from 2.0% to 12.2% for high-risk ($P < .001$) Framingham risk subsets.

DISCUSSION

Background Information

Atherosclerosis, the leading cause of morbidity and mortality in Western countries, is a disease that infiltrates the arterial wall long before it causes obstruction of blood flow and symptoms (19,20). Recently, the screening of asymptomatic individuals to detect latent disease has become a topic of intense discussion. The rationale for investigating the presence of preclinical coronary atherosclerosis resides in the fact that more than half of all first coronary heart disease events are sudden cardiac deaths or acute myocardial infarctions in previously asymptomatic individuals (1). Thus, in prevention, the emphasis has recently been focused on the identification of high-risk individuals with the potential inclusion of screening for coronary calcification (1,21–24). Two critical questions that remain to be answered are to what degree coronary calcium screening can predict events in an asymptomatic population and whether coronary calcification adds to our ability to assess risk (1). To attempt to answer these questions, we evaluated a large population sample of asymptomatic subjects with risk factors for atherosclerosis who were referred by primary care physicians for electron-beam CT screening: The results show that coronary calcification adds prognostic information above and beyond knowledge of traditional risk factors. In fact, the ability to classify and predict an event improved (ie, the concordance index increased) once calcium scores were added to risk factors.

Calcification of the arterial wall is associated with the majority of atherosclerotic lesions, though only those in the more advanced stage of development may be visible at electron-beam CT screening (25). Electron-beam CT is widely used as a noninvasive tool to assess the presence and extent of coronary calcification, and more than 10 years of published evidence is available about its diagnostic and prognostic accuracy. In a recent expert consensus document prepared by the American College of Cardiology and the American Heart Association, key limitations to the existing body of evidence were discussed (1). Consistent with findings in prior publications

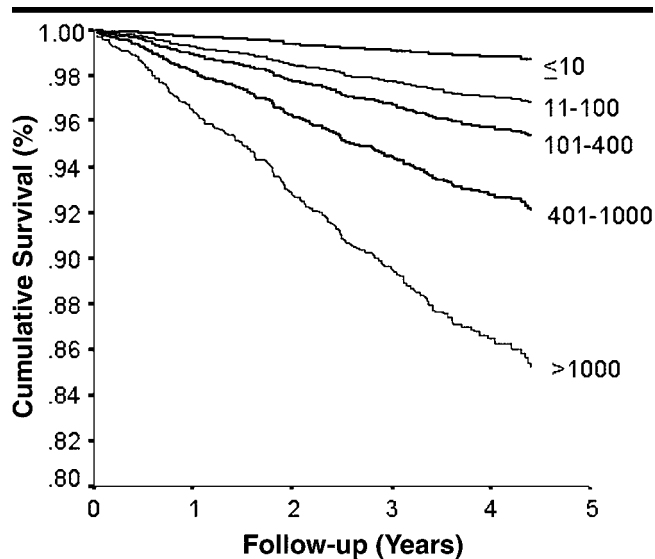


Figure 1. Graph shows unadjusted all-cause survival according to calcium score subsets. Survival rate is proportionally worse as the baseline calcium score increases.

about other noninvasive tests for coronary artery disease, early evidence was based on small highly selected patient samples and, for purposes of prognosis, revascularization often was used as an end point. In this era of evidence-based medicine, ever-increasing rigor is being applied to the evaluation of new technologies, and current standards require the use of risk-adjusted analysis for the estimation of clinical outcomes. The present analysis provides supportive evidence that there is a linear relationship between the extent of coronary artery calcification and all-cause mortality. All-cause mortality is an appropriate end point to follow, since in the United States, when one accounts for both cardiac and systemic forms of the disease, nearly three-fourths of all deaths are related to atherosclerosis (26,27). Furthermore, this end point is not affected by the reporting and misclassification bias potentially introduced by a physician's filing of a death report (28). Finally, as noted according to Bayesian theory, the a priori limitation for low-risk populations imposed by the use of infrequent cardiac-specific end points may be overcome with the use of all-cause mortality as the primary outcome (7). Thus, our analysis that was conducted by using established epidemiologic methods in a sufficiently large population showed that the extent of coronary calcium is highly correlated with mortality risk.

Disruption of atherosclerotic plaques is the most frequent cause of acute thromboembolic events, and these events include

sudden death, acute coronary syndromes, and stroke (19). Further, calcification of the arterial wall often is found in ruptured plaques, as well as in plaques that show superficial erosion (29–31). It is not clear whether coronary calcium renders the individual plaque unstable, but as a marker and a measure of the atherosclerotic burden, it indicates an individual's predisposition to develop thromboembolic and ischemic events (32). Our prognostic models that were used to estimate all-cause mortality revealed that age and coronary calcium were the strongest risk markers in this 10,377-subject registry.

Risk Estimation

An evolution in thought has increasingly linked the intensity of therapeutic intervention to the estimation of risk (23,33). It is now recommended that a compilation of risk that is based on established cardiac risk factors be used to determine various outcome strata. This recommendation recently was implemented in the development of the National Cholesterol Education Program III guidelines in which the approach offered by the Framingham risk score to formulate a 10-year risk of cardiac death or myocardial infarction was embraced (34). In our article, many of the established risk factors were predictive of mortality, but when the coronary calcium score was added to the model, it was a highly significant predictor of outcome and added independently to the risk prediction ($P < .001$ for concordance index increase).

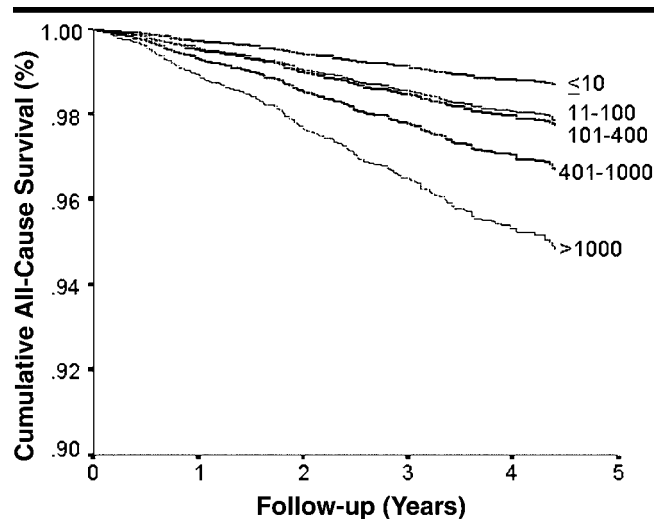


Figure 2. Graph shows risk-adjusted all-cause survival estimates according to calcium score subsets. Even after adjustment, survival rate is proportionally worse as the baseline calcium score increases.

Although many noninvasive markers have been evaluated for inclusion in the array of cardiac risk estimators, to date, the evidence for their utility has not been overwhelming. For any new marker or test to be judged as a valuable additional tool for the prediction of events, it should increase the precision of outcome estimation beyond information derived from integrated risk scores, such as the Framingham risk model (22). Nonetheless, current evidence also shows that established cardiac risk factors possess a limited ability in the estimation of risk. On average, only 50%–60% of the variability in outcome is explained by risk factors (22,33–35). Hence, there is a need to improve risk prediction. Markers of vascular wall abnormalities have been used in large epidemiologic studies, such as the Atherosclerotic Risk Factors in the Community study, to assess the future risk of major adverse cardiac events (36). In the Atherosclerotic Risk Factors in the Community study, the hazard ratio for events with an intima-media thickness of the carotid artery of 1 mm or thicker was increased 5.1-fold in women and 1.9-fold in men (36). It appears that coronary calcium may be an additional marker that provides unique information for risk assessment. A frequent criticism of the available literature about electron-beam CT is that findings therein have not firmly established that coronary calcification adds incremental value in addition to established cardiac risk factors (7). In an older population with high pre-test probability of disease, Detrano et al (37) reported that the concordance index,

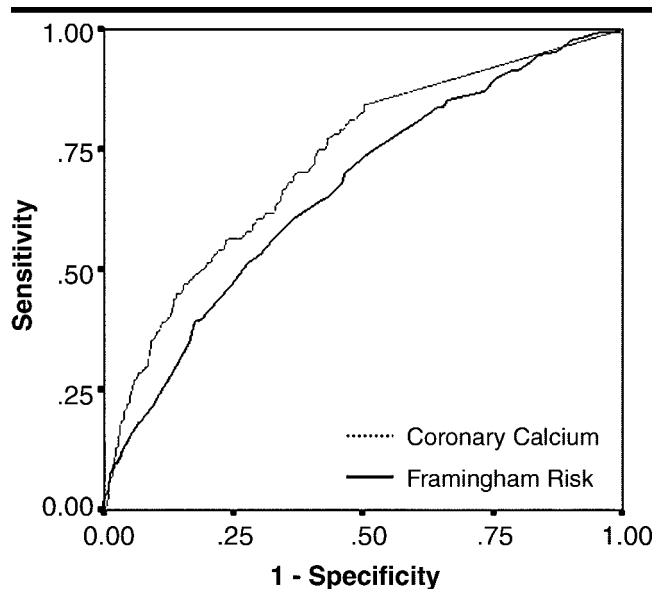


Figure 3. Graph shows ROC curves for comparison of estimated Framingham risk and coronary calcium scores for estimation of all-cause mortality. A_z for coronary calcium is larger than A_z for Framingham risk index ($P < .001$).

which reflects a measure of event classification, did not change when the calcium score was added to a model containing the Framingham risk index. Conversely, in an extended follow-up of their prior series, Arad et al (10) recently reported that moderate calcium scores (ie, ≥ 160) were associated with a relative risk of cardiac death or myocardial infarction that was 10-fold higher than that which was estimated with the Framingham risk index alone. Furthermore, Raggi et al (5) showed that coronary artery calcium provided incremental prognostic information to predict hard cardiac events in a cohort of 676 individuals who were followed up for approximately 3 years. Finally, in the current study, 21.5% of mortality information—or incremental value—was attributable to coronary calcium, and this finding indicates that calcification of the coronary arteries may provide additional documentation of risk independent of the presence of conventional cardiac risk factors.

Study Limitations

Although the current article includes a rigorous analysis of the prognostic value of coronary calcium, the majority of patients referred for electron-beam CT screening had cardiac risk factors and, as such, may not be representative of the general population. Furthermore, it is expected that the inclusion of measured risk factors, such as systolic blood pres-

sure, blood glucose level, and cholesterol values would provide a better estimation of risk than historical data alone. However, in many imaging laboratories, patients are referred on the basis of a brief history and measured values often are unavailable. Thus, we believe that our analysis is probably a close representation of the reality of daily laboratory practices. Furthermore, the use of categorical risk factors instead of continuous variables has been shown to constitute a valid approach to risk assessment (38). Hence, we believe that a risk assessment approach that is based on historical risk factors rather than on continuous variables does not significantly weaken the assumptions made in this study. Additionally, the National Death Index data do not include the cause of death and, as such, our models include mortality possibly unrelated to atherosclerotic disease. Furthermore, we do not have data on cardiac-specific procedures.

In conclusion, we collected mortality data in regard to 10,377 asymptomatic individuals with cardiac risk factors who were referred by their primary care physicians for coronary calcium screening with electron-beam CT. This large observational data series strongly indicates that coronary artery calcium is an independent estimator of all-cause mortality. Our results show that survival at 5 years worsens substantially as the screening calcium scores increase from levels of 10 or less to those of greater than 1,000.

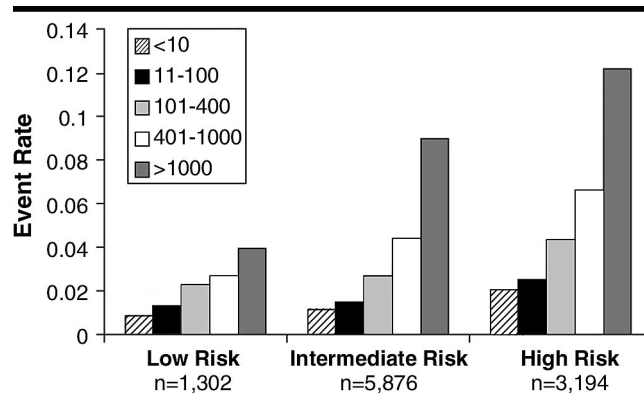


Figure 4. Graph shows risk stratification for each category of Framingham risk (from low to high) according to baseline calcium score. Event rate is predicted mortality at 5 years.

Therefore, it appears justified to use coronary calcium screening to identify intermediate-risk patients with traditional risk factors for whom aggressive risk-reducing strategies for the treatment of atherosclerotic disease should be indicated.

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References

- O'Rourke RA, Brundage BH, Froelicher VF, et al. American College of Cardiology/American Heart Association Expert Consensus document on electron-beam computed tomography for the diagnosis of coronary artery disease. *Circulation* 2000; 102:126–140.
- Detrano RC, Doherty TM, Davies MJ, Stary HC. Predicting coronary events with coronary calcium: pathophysiologic and clinical problems. *Curr Probl Cardiol* 2000; 25:374–402.
- O'Malley PG, Taylor AJ, Jackson JL, Doherty TM, Detrano RC. Prognostic value of coronary electron-beam computed tomography for coronary heart disease events in asymptomatic populations. *Am J Cardiol* 2000; 85:945–948.
- Raggi P. Prognostic implications of absolute and relative calcium scores. *Herz* 2001; 26:252–259.
- Raggi P, Cooil B, Callister TQ. Use of electron beam tomography data to develop models for the prediction of hard coronary events. *Am Heart J* 2001; 141:375–382.
- Raggi P, Callister TQ, Cooil B, et al. Identification of patients at increased risk of first unheralded acute myocardial infarction by electron beam computed tomography. *Circulation* 2000; 101:850–855.
- Shaw LJ, O'Rourke RA. The challenge of improving risk assessment in asymptomatic individuals: the additive prognostic value of electron beam tomography? *J Am Coll Cardiol* 2000; 36:1261–1264.
- Detrano R, Hsiai T, Wang S, et al. Prognostic value of coronary calcification and angiographic stenoses in patients under-

- going coronary angiography. *J Am Coll Cardiol* 1996; 27:285–290.
9. 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; 93:1951–1953.
 10. Arad Y, Spadaro LA, Goodman K, Newstein D, Guerci AD. Prediction of coronary events with electron beam computed tomography. *J Am Coll Cardiol* 2000; 36:1253–1260.
 11. National Institutes of Health, National Heart, Lung, and Blood Institute. National Cholesterol Education Panel III. Available at: www.nhlbi.nih.gov/guidelines/cholesterol. Accessed June 30, 2002.
 12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990; 15:827–832.
 13. Marwick TH, Shaw LJ, Lauer MS, et al. The noninvasive prediction of cardiac mortality in men and women with known or suspected coronary artery disease. *Am J Med* 1999; 106:172–178.
 14. Shaw LJ, Hachamovitch R, Peterson ED, et al. Using an outcomes-based approach to identify candidates for risk stratification after exercise treadmill testing. *J Gen Intern Med* 1999; 14:1–9.
 15. Shaw LJ, Peterson ED, Kesler KL, et al. Use of a prognostic treadmill score in identifying diagnostic coronary disease subgroups and altering patient management. *Circulation* 1998; 98:1622–1630.
 16. Centers for Disease Control and Prevention. National Death Index. www.cdc.gov/nchs/rs&d/ndi/. Accessed January 20, 2001.
 17. Downs JR, Clearfield M, Weis S, et al. Primary prevention of acute coronary events with lovastatin in men and women with average cholesterol levels: results of AFCAPS/TexCAPS—Air Force/Texas Coronary Atherosclerosis Prevention Study. *JAMA* 1998; 279:1615–1622.
 18. West of Scotland Coronary Prevention Study: identification of high-risk groups and comparison with other cardiovascular intervention trials. *Lancet* 1996; 348:1339–1342.
 19. Fuster V, Badimon L, Badimon JJ, Chesebro JH. The pathogenesis of coronary artery disease and acute coronary syndromes. *N Engl J Med* 1992; 362:242–250.
 20. Fuster V. Mechanisms leading to myocardial infarction: insights from studies of vascular biology. *Circulation* 1994; 90:2126–2146.
 21. Califf RM, Armstrong PW, Carver JR, D'Agostino RB, Strauss WE. 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events—Task Force 5: stratification of patients into high, medium and low risk subgroups for purposes of risk factor management. *J Am Coll Cardiol* 1996; 27:1007–1019.
 22. Grundy SM, Pasternak R, Greenland P, Smith S Jr, Fuster V. Assessment of cardiovascular risk by use of multiple-risk-factor assessment equations. *Circulation* 1999; 34:1348–1359.
 23. Greenland P, Abrams J, Aurigemma GP, et al. Prevention Conference V: beyond secondary prevention—identifying the high-risk patient for primary prevention: noninvasive tests of atherosclerotic burden—Writing Group III. *Circulation* 2000; 101:E16–E22.
 24. Greenland P, Smith SC Jr, Grundy S. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation* 2001; 104:1863–1867.
 25. Becker CR, Knez A, Ohnesorge B, et al. Visualization and quantification of coronary calcifications with electron beam and spiral computed tomography. *Eur Radiol* 2000; 10:629–635.
 26. Thom TJ, Kannel WB, Silbershatz H, D'Agostino RB. Cardiovascular disease in the United States and prevention approaches. In: Fuster V, Alexander RW, O'Rourke RA, eds. *Hurst's the heart*. 10th ed. New York, NY: McGraw-Hill, 2001; 3–18.
 27. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary disease. *Lancet* 1999; 353:89–92.
 28. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? *J Am Coll Cardiol* 1999; 34:618–620.
 29. Farb A, Burke AP, Tang AL, et al. Coronary plaque erosion without rupture into a lipid core: a frequent cause of coronary thrombosis in sudden coronary death. *Circulation* 1996; 93:1354–1363.
 30. Burke AP, Taylor A, Farb A, Malcom GT, Virmani R. Coronary calcification: insights from sudden coronary death victims. *Z Kardiol* 2000; 89(suppl 2):49–53.
 31. Schmermund A, Schwartz RS, Adamzik M, et al. Coronary atherosclerosis in unheralded sudden coronary death under age 50: histo-pathologic comparison with 'healthy' subjects dying out of hospital. *Atherosclerosis* 2001; 155:499–508.
 32. Wahys R, Zellinger A, Raggi P. High calcium scores pose an extremely elevated risk for hard events. *J Am Coll Cardiol* 2002; 39:225–230.
 33. Furberg CD, Hennekens CH, Hulley SB, Manolio T, Psaty BM, Whelton PK. The 27th Bethesda Conference: matching the intensity of risk factor management with the hazard for coronary disease events—Task Force 2: clinical epidemiology—the conceptual basis for interpreting risk factors. *J Am Coll Cardiol* 1996; 25:976–978.
 34. Executive Summary of The Third Report of The National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, And Treatment of High Blood Cholesterol In Adults (Adult Treatment Panel III). *JAMA* 2001; 285:2486–2489.
 35. Kannel WB, Feinleib M. Natural history of angina pectoris in the Framingham study: prognosis and survival. *Am J Cardiol* 1972; 29:154–163.
 36. Chambless LE, Heiss G, Folsom AR, et al. Association of coronary heart disease incidence with carotid arterial wall thickness and major risk factors: the atherosclerosis risk in communities (ARIC) study, 1987–1993. *Am J Epidemiol* 1997; 146:483–494.
 37. Detrano RC, Wong ND, Doherty TM, et al. Coronary calcium does not accurately predict near-term future coronary events in high-risk adults. *Circulation* 1999; 99:2633–2638.
 38. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998; 97:1837–1847.