

ORIGINAL ARTICLE

Coronary Calcium as a Predictor of Coronary Events in Four Racial or Ethnic Groups

Robert Detrano, M.D., Ph.D., Alan D. Guerci, M.D., J. Jeffrey Carr, M.D., M.S.C.E., Diane E. Bild, M.D., M.P.H., Gregory Burke, M.D., Ph.D., Aaron R. Folsom, M.D., Kiang Liu, Ph.D., Steven Shea, M.D., Moyses Szklo, M.D., Dr.P.H., David A. Bluemke, M.D., Ph.D., Daniel H. O'Leary, M.D., Russell Tracy, Ph.D., Karol Watson, M.D., Ph.D., Nathan D. Wong, Ph.D., and Richard A. Kronmal, Ph.D.

ABSTRACT

BACKGROUND

In white populations, computed tomographic measurements of coronary-artery calcium predict coronary heart disease independently of traditional coronary risk factors. However, it is not known whether coronary-artery calcium predicts coronary heart disease in other racial or ethnic groups.

METHODS

We collected data on risk factors and performed scanning for coronary calcium in a population-based sample of 6722 men and women, of whom 38.6% were white, 27.6% were black, 21.9% were Hispanic, and 11.9% were Chinese. The study subjects had no clinical cardiovascular disease at entry and were followed for a median of 3.8 years.

RESULTS

There were 162 coronary events, of which 89 were major events (myocardial infarction or death from coronary heart disease). In comparison with participants with no coronary calcium, the adjusted risk of a coronary event was increased by a factor of 7.73 among participants with coronary calcium scores between 101 and 300 and by a factor of 9.67 among participants with scores above 300 ($P < 0.001$ for both comparisons). Among the four racial and ethnic groups, a doubling of the calcium score increased the risk of a major coronary event by 15 to 35% and the risk of any coronary event by 18 to 39%. The areas under the receiver-operating-characteristic curves for the prediction of both major coronary events and any coronary event were higher when the calcium score was added to the standard risk factors.

CONCLUSIONS

The coronary calcium score is a strong predictor of incident coronary heart disease and provides predictive information beyond that provided by standard risk factors in four major racial and ethnic groups in the United States. No major differences among racial and ethnic groups in the predictive value of calcium scores were detected.

From the University of California at Irvine, Irvine (R.D., N.D.W.); Saint Francis Hospital, Roslyn, NY (A.D.G.); Wake Forest Baptist Medical Center, Winston-Salem, NC (J.J.C., G.B.); the Division of Prevention and Population Sciences, National Heart, Lung, and Blood Institute, Bethesda, MD (D.E.B.); the University of Minnesota, Minneapolis (A.R.F.); Northwestern University, Chicago (K.L.); Columbia University, New York (S.S.); Johns Hopkins University, Baltimore (M.S., D.A.B.); Caritas Carney Hospital, Dorchester, MA (D.H.O.); the University of Vermont, Burlington (R.T.); the University of California at Los Angeles, Los Angeles (K.W.); and the University of Washington, Seattle (R.A.K.). Address reprint requests to Dr. Detrano at the Department of Radiological Sciences, University of California at Irvine, Medical Sciences Bldg., Irvine, CA 92697, or at robert@chinacal.org.

N Engl J Med 2008;358:1336-45.
Copyright © 2008 Massachusetts Medical Society.

THE FRAMINGHAM RISK SCORE USES STANDARD risk factors to estimate the risk of coronary events in persons without previous coronary heart disease.^{1,2} However, because this score predicts coronary events only moderately well, researchers have explored other methods to identify patients who would benefit most from intensive prevention efforts.³⁻⁷ Radiographically detectable coronary-artery calcium is a marker of subclinical coronary heart disease and predicts coronary events in white populations.⁸⁻¹⁸ As a result, there has been considerable interest in the potential use of measurements of coronary-artery calcium in models of risk prediction.

The potential role of this variable as a predictor of risk is complicated by evidence that there are substantial differences in the prevalence and extent of coronary calcification among various ethnic groups. Bild et al.¹⁹ reported that the prevalence of detectable coronary calcification was 22%, 15%, and 8% lower among blacks, Hispanics, and Chinese, respectively, than among whites. Other studies²⁰⁻²² have reported differences in coronary calcification between blacks and whites, although one study²³ found no difference. However, the relationship between the amount of coronary calcium and the incidence of coronary events in various ethnic groups has not been examined.

The Multi-Ethnic Study of Atherosclerosis (MESA)²⁴ investigates the prevalence, correlates, and progression of subclinical cardiovascular disease. The study cohort is a population-based sample from six urban communities, with oversampling of blacks, Chinese, and Hispanics. We used the data collected from the MESA cohort to study the relationship between coronary calcification and future coronary events in four major ethnic groups.

METHODS

STUDY PARTICIPANTS

Details of the design and organization of the MESA have been reported previously.¹⁹ Between July 2000 and September 2002, we selected 6814 persons to be members of the MESA cohort at six field centers (Baltimore; Chicago; Forsyth County, North Carolina; Los Angeles; New York; and St. Paul, Minnesota). The participants were required to be between 45 and 84 years of age and to have no clinical cardiovascular disease at the time of enrollment in the study. The participants were

recruited at each site from lists of residents, dwellings, and telephone-company customers. In the last few months of the recruitment period, participants were also recruited from lists of Medicare beneficiaries obtained from the Centers for Medicare and Medicaid Services and by referrals from other participants in order to ensure the enrollment of adequate numbers of elderly subjects and subjects from all four ethnic groups. Participants identified themselves as white, black, Hispanic, or Chinese at the time of enrollment. The study was approved by the institutional review boards of each site, and all participants gave written informed consent.

COMPUTED TOMOGRAPHIC SCANNING

Carr et al. have reported details of the methods used by the MESA for computed tomographic (CT) scanning and for interpretation of the scans.²⁵ Each of the six MESA centers assessed the amount of coronary calcium with the use of either an electron-beam CT scanner (at the Chicago, Los Angeles, and New York centers) or a multidetector CT system (at the Baltimore, Forsyth County, and St. Paul centers). Certified technologists placed radiographic phantoms containing identical and known concentrations of calcium beneath the thorax of each participant and then scanned the participant two times. A radiologist or cardiologist read all CT scans at a single center (the Los Angeles Biomedical Research Institute at Harbor–University of California Los Angeles Medical Center, Torrance) and used an interactive scoring system similar to that of Yaghoubi et al.²⁶ The reader–work station interface calibrated each tomographic image according to the estimated attenuation of the calcium phantom and then identified and quantified the coronary calcium in each image. The coronary calcium score (Agatston score)²⁷ was calculated for each scan, and the mean of the two scans was used in all analyses. Intraobserver and interobserver agreement was excellent (kappa statistics, 0.93 and 0.90, respectively). The participants were told either that they had no coronary calcification or that the amount was less than average, average, or greater than average and that they should discuss the results with their physicians.

RISK FACTORS

As part of the baseline examination, clinical teams at each of the six centers collected information on cardiovascular risk factors, including

family history of coronary heart disease, a history of smoking, level of low-density lipoprotein (LDL) cholesterol, level of high-density lipoprotein (HDL) cholesterol, hypertension, and diabetes. Using a Dinamap Pro 1000 automated oscillometric sphygmomanometer (Critikon), we measured resting blood pressure three times with the participant in the seated position. A central laboratory (University of Vermont, Burlington) measured levels of total and HDL cholesterol, triglycerides, plasma glucose, and high-sensitivity C-reactive protein in blood samples obtained after a 12-hour fast. Diabetes was defined as a fasting plasma glucose level greater than 140 mg per deciliter (7.8 mmol per liter) or a history of medical treatment for diabetes. The body-mass index was calculated as the weight in kilograms divided by the square of the height in meters. Family history of coronary heart disease was obtained by asking the participants whether any member of their immediate family (parents, siblings, and children) had had a fatal or nonfatal myocardial infarction, coronary angioplasty, or coronary-artery bypass surgery. The participants were classified as current cigarette smokers, former smokers, or persons who had never smoked.

FOLLOW-UP

We recorded new cardiovascular events for a median of 3.9 years (maximum, 5.3). At intervals of 9 to 12 months, an interviewer contacted each participant or a family member by telephone to inquire about interim hospital admissions, outpatient diagnoses of cardiovascular disease, and deaths. To verify self-reported diagnoses, we requested copies of medical records for participants who had been hospitalized or received an outpatient diagnosis of cardiovascular disease. We obtained records of 98% of reported cardiovascular events associated with hospitalization. For participants who had died of cardiovascular causes outside the hospital, we conducted interviews with the next of kin and requested copies of death certificates.

Trained personnel abstracted data from medical records that reported possible cardiovascular events. Two physicians who were members of the MESA mortality and morbidity review committee independently classified events and assigned incidence dates. If they disagreed, the full committee made the final classification. For the pur-

pose of this study, we classified myocardial infarction, death from coronary heart disease, definite angina followed by coronary revascularization, definite angina not followed by coronary revascularization, and probable angina followed by coronary revascularization as coronary heart disease events.

The diagnosis of myocardial infarction was based on a combination of symptoms, electrocardiographic findings, and levels of cardiac biomarkers. We used hospital records and family interviews to determine whether deaths were related to coronary heart disease. A death was considered related to coronary heart disease if it occurred within 28 days after a myocardial infarction, if the participant had had chest pain within the 72 hours before death, or if the participant had a history of coronary heart disease and there was no known nonatherosclerotic, noncardiac cause of death. The adjudicators graded angina as definite, probable, or absent on the basis of their clinical judgment. A classification of definite or probable angina required clear and definite documentation of symptoms distinct from the diagnosis of myocardial infarction. A classification of definite angina also required objective evidence of reversible myocardial ischemia or obstructive coronary artery disease. A more detailed description of the MESA follow-up methods is available at www.mesa-nhlbi.org.

STATISTICAL ANALYSIS

We used chi-square tests for discrete variables and one-way analysis-of-variance tests for continuous variables to test for differences in demographic and risk factors between ethnic groups and between participants with and without coronary events. To describe the frequency of coronary events according to time since the measurement of coronary calcium, we constructed Kaplan-Meier cumulative-event curves for major coronary events (myocardial infarction and death from coronary heart disease) and for any coronary event. The data were stratified according to coronary calcium score, with the use of the same cut-off points as those used by Greenland et al. (0, 1 to 100, 101 to 300, and >300).⁸

We used Cox proportional-hazards regression to estimate hazard ratios for major coronary events and for any coronary event according to the coronary calcium score. Tests for nonproportional-

tional hazards using Schoenfeld residuals resulted in nonsignificant findings in all analyses. The coronary calcium score was examined both as a stratified variable (with the same cutoff points as those used by Greenland et al.) and as a continuous variable. In the analysis treating coronary calcium score as a continuous variable, we used the base-2 logarithm of the sum of the coronary calcium score plus 1 ($\log_2[\text{CAC} + 1]$). The choice of base 2 for the logarithm allowed us to examine how a doubling of the calcium score affects the risk of events, since each unit difference in the log-transformed calcium score represents a doubling of the score. The addition of 1 to the calcium score before logarithmic transformation allowed us to include in the analysis those patients with a calcium score of zero.

After estimating the hazard ratios for coronary events for the entire study cohort, we performed additional regression analyses for each individual ethnic group, treating calcium score as a continuous variable. We computed receiver-operating-characteristic (ROC) curves and tested for equality of the areas under the curves for the individual ethnic groups.

All models were adjusted for age, sex, ethnic group, cigarette smoking, presence or absence of diabetes, total cholesterol level, HDL cholesterol level, systolic and diastolic blood pressure, and use or nonuse of lipid-lowering or antihypertensive medication. In addition, we allowed any of the following variables to enter the models if they were statistically significant at the $P < 0.05$ level: family history of coronary heart disease, C-reactive protein level, triglyceride level, creatinine level, body-mass index, waist circumference, and hip circumference. However, none of these variables met the criterion for statistical significance. We also carried out analyses that included terms for the interaction between ethnic group and calcium score, as well as any significant interactions ($P < 0.10$) between ethnic group and any of the risk factors. All analyses were performed with Stata software, version 9.2.

RESULTS

STUDY COHORT

Follow-up information was not available for 35 (0.5%) of the 6814 members of the MESA cohort, and 5 were discovered to have had a cardiovascu-

lar event before enrollment in the cohort. Measurements of one or more risk factors were missing for an additional 52 members (0.8%), none of whom had a coronary event after enrollment. The remaining 6722 participants are the subject of this report. Table 1 shows the baseline characteristics of the study cohort. As expected, the cardiovascular risk profile was less favorable in those in whom coronary heart disease subsequently developed than in those in whom it did not. The baseline characteristics of the study cohort varied significantly among the four ethnic groups, as shown in Table 2.

The prevalence of coronary calcification (coronary calcium score > 0) was 70.4% for white men, 52.0% for black men, 56.6% for Hispanic men, and 59.2% for Chinese men ($P < 0.001$). The corresponding figures for women were 44.7%, 37.0%, 34.8%, and 41.9%, respectively ($P < 0.001$). Details of the relationship between ethnic group and coronary calcification in the MESA have been published previously.²³

A total of 162 participants had coronary events. Eighty-nine had a major event (72 had a nonfatal myocardial infarction and 17 died of coronary heart disease), and 73 had angina (13 had definite angina not followed by revascularization, 56 had definite angina followed by revascularization, and 4 had probable angina followed by revascularization).

CORONARY CALCIUM AS A PREDICTOR OF CORONARY HEART DISEASE

Figure 1 shows the unadjusted Kaplan–Meier cumulative-event curves for major coronary events and for any coronary event according to coronary calcium score. The differences among these curves were statistically significant ($P < 0.001$).

Table 3 shows the risk of major events and of any event associated with higher calcium score after adjustment for standard risk factors. The hazard ratio increases with an increase in stratum of calcium score. The largest increase in hazard ratio occurs for calcium scores greater than 100. The risk of both major coronary events and any event was increased by a factor of at least seven among participants with scores over 100 as compared with those without any coronary calcium. Table 3 also shows the increase in the risk of a major coronary event and of any coronary event associated with a doubling of

Table 1. Baseline Demographic Characteristics and Risk Factors According to Whether the Participant Had a Subsequent Coronary Event.*

| Variable | All Participants (N = 6722) | No Coronary Event (N = 6560) | Coronary Event (N = 162) | P Value |
|--|--------------------------------|------------------------------------|--------------------------------|---------|
| Age (yr) | 62.2±10.2 | 62.0±10.2 | 67.6±9.2 | <0.001 |
| Male sex (%) | 47.2 | 46.6 | 70.4 | <0.001 |
| Racial or ethnic group (%)† | | | | 0.26 |
| White | 38.6 | 38.5 | 45.7 | |
| Black | 27.6 | 27.7 | 23.5 | |
| Hispanic | 21.9 | 21.9 | 22.2 | |
| Chinese | 11.9 | 12.0 | 8.6 | |
| Systolic blood pressure (mm Hg) | 126.6±21.5 | 126.4±21.4 | 135.1±22.8 | <0.001 |
| Plasma cholesterol (mg/dl)‡ | | | | |
| Total | 194.2±35.7 | 194.0±35.5 | 199.6±42.8 | 0.05 |
| HDL | 51.0±14.8 | 51.1±14.8 | 47.3±15.4 | 0.001 |
| Use of lipid-lowering medication (%) | 16.3 | 16.0 | 28.4 | <0.001 |
| Current or former smoker (%) | 49.7 | 49.4 | 64.2 | <0.001 |
| Diabetes (%) | 11.7 | 11.4 | 24.1 | <0.001 |
| Hypertension (%) | 44.9 | 44.3 | 66.7 | <0.001 |
| Family history of coronary heart disease (%) | 42.7 | 42.4 | 56.4 | 0.001 |
| Serum C-reactive protein (mg/dl) | 3.76±5.84 | 3.76±5.84 | 3.67±4.68 | 0.81 |
| Serum triglycerides (mg/dl)§ | 131.7±89.0 | 131.3±89.1 | 148.8±80.5 | 0.007 |
| Serum creatinine (mg/dl)¶ | 0.96±0.28 | 0.95±0.29 | 1.05±0.37 | <0.001 |
| Body-mass index | 28.3±5.5 | 28.3±5.5 | 28.1±4.8 | 0.57 |
| Waist circumference (cm) | 98.1±14.4 | 98.1±14.4 | 100.4±12.5 | 0.02 |
| Hip circumference (cm) | 105.6±11.4 | 105.6±11.5 | 105.0±10.3 | 0.50 |

* Plus-minus values are means ±SD. Percentages may not total 100 because of rounding. HDL denotes high-density lipoprotein.

† Racial or ethnic group was self-assessed.

‡ To convert values for total and HDL cholesterol to millimoles per liter, multiply by 0.02586.

§ To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

¶ To convert values for creatinine to micromoles per liter, multiply by 88.4.

|| The body-mass index is the weight in kilograms divided by the square of the height in meters.

the coronary calcium score (a 1-unit increase in $\log_2[\text{CAC} + 1]$). After adjustment for standard risk factors, a doubling of the calcium score resulted in a 20% increase in the risk of a major event and a 26% increase in the risk of any event.

PREDICTING CORONARY HEART DISEASE IN INDIVIDUAL ETHNIC GROUPS

Table 4 shows the risk of coronary heart disease associated with increasing calcium score in each of the four ethnic groups, adjusted for standard risk factors and interactions. For each ethnic group, the risk associated with a doubling of the

calcium score increased by 15 to 35% for a major event and by 18 to 39% for any event. All adjusted hazard ratios are significant ($P < 0.02$), except for the hazard ratio for major coronary events among Chinese participants, who had only six such events. There was no interaction between ethnic group and the risk associated with increasing calcium score.

Table 5 shows the areas under the ROC curves for the prediction of major coronary events and of any coronary event according to ethnic group, calculated on the basis of the standard risk factors alone and on the basis of the standard risk

Table 2. Baseline Demographic Characteristics and Risk Factors According to Racial or Ethnic Group.*

| Variable | White (N=2598) | Black (N=1852) | Hispanic (N=1474) | Chinese (N=798) | P Value† |
|--|-------------------|-------------------|----------------------|--------------------|----------|
| Age (yr) | 62.6±10.3 | 62.1±10.1 | 61.3±10.4 | 62.4±10.3 | 0.001 |
| Female sex (%) | 52.0 | 55.2 | 51.8 | 51.5 | 0.12 |
| Blood pressure (mm Hg) | | | | | |
| Systolic | 123.4±20.4 | 131.7±21.6 | 126.7±21.9 | 124.6±21.7 | <0.001 |
| Diastolic | 70.2±10.0 | 74.5±10.2 | 71.6±10.1 | 72.0±10.4 | <0.001 |
| Plasma cholesterol (mg/dl)‡ | | | | | |
| Total | 195.7±35.1 | 189.6±36.2 | 198.0±37.4 | 192.6±31.8 | <0.001 |
| HDL | 52.3±15.7 | 52.4±15.3 | 47.7±13.1 | 49.6±12.7 | <0.001 |
| Use of lipid-lowering medication (%) | 18.3 | 16.5 | 13.2 | 14.5 | <0.001 |
| Smoking status (%) | | | | | <0.001 |
| Current smoker | 11.5 | 18.0 | 13.5 | 5.6 | |
| Former smoker | 44.3 | 36.9 | 32.6 | 19.1 | |
| Never smoked | 44.2 | 45.1 | 53.9 | 75.3 | |
| Diabetes (%) | 5.5 | 16.7 | 16.8 | 11.2 | <0.001 |
| Hypertension (%) | 38.6 | 59.6 | 41.5 | 37.5 | <0.001 |
| Family history of coronary heart disease (%) | 51.5 | 42.1 | 40.4 | 19.9 | <0.001 |
| Serum C-reactive protein (mg/dl) | 3.41±5.10 | 4.78±7.04 | 4.15±5.59 | 1.85±4.81 | <0.001 |
| Serum triglycerides (mg/dl)§ | 132.9±90.1 | 104.9±69.1 | 157.3±101.3 | 142.7±85.0 | <0.001 |
| Serum creatinine (mg/dl)¶ | 0.95±0.20 | 1.02±0.34 | 0.91±0.36 | 0.90±0.22 | <0.001 |
| Body-mass index | 27.7±5.1 | 30.2±5.9 | 29.4±5.1 | 24.0±3.3 | <0.001 |
| Waist circumference (cm) | 97.9±14.4 | 101.2±14.7 | 100.6±13.0 | 87.1±9.9 | <0.001 |
| Hip circumference (cm) | 106.1±10.5 | 109.8±12.0 | 105.2±10.6 | 94.9±6.6 | <0.001 |

* The data differ slightly from those in previous publications from the MESA¹⁹ because of differences in the numbers of cases analyzed. Plus-minus values are means ±SD. Racial or ethnic group was self-assessed. HDL denotes high-density lipoprotein.

† P values for continuous variables were calculated by analysis of variance. P values for categorical variables were calculated by the chi-square test for equality of proportions in one-way tables.

‡ To convert values for total and HDL cholesterol to millimoles per liter, multiply by 0.02586.

§ To convert values for triglycerides to millimoles per liter, multiply by 0.01129.

¶ To convert values for creatinine to micromoles per liter, multiply by 88.4.

|| The body-mass index is the weight in kilograms divided by the square of the height in meters.

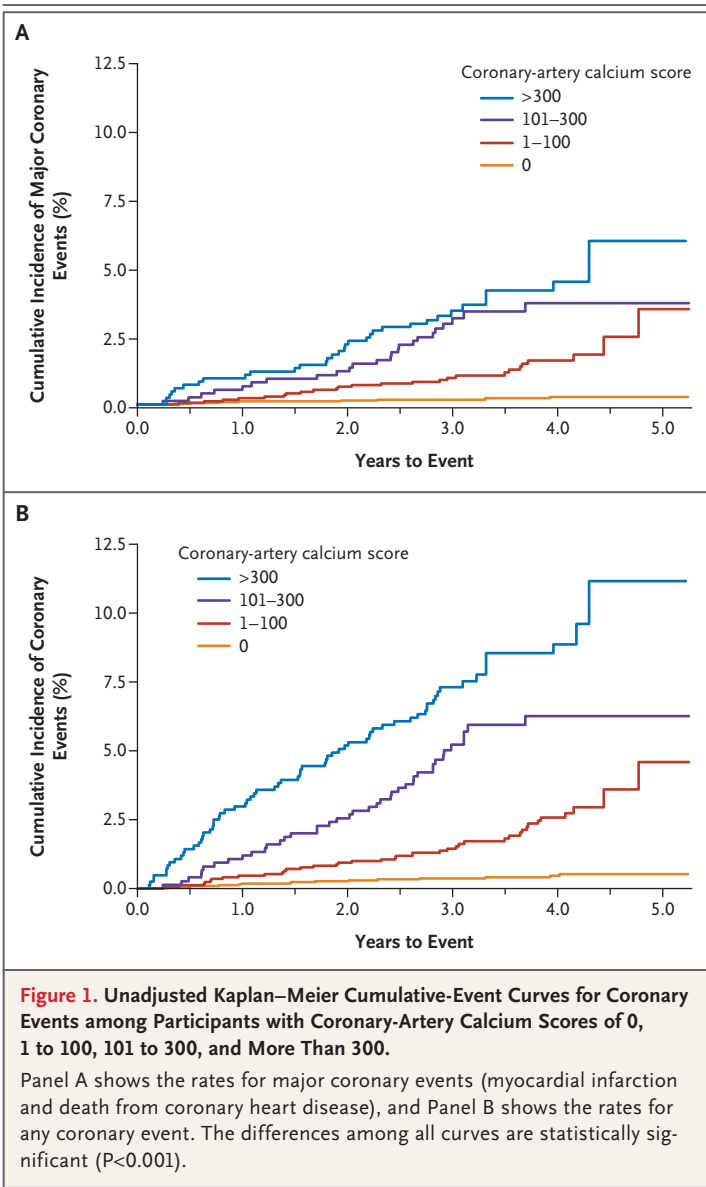
factors plus the coronary calcium score. The areas under the curve for the prediction of major events and those for the prediction of any event were greater when the calcium score was added to the standard risk factors. These increases were statistically significant for each ethnic group, except for the prediction of any event in Hispanics and of major events in Hispanics and whites.

DISCUSSION

We examined the predictive value of measurements of coronary-artery calcium in a multiethnic

U.S. population. We found that a doubling of the calcium score increased the estimated probability of both major coronary events (myocardial infarction and death from coronary heart disease) and any coronary event by approximately 25% during a median follow-up period of 3.8 years. Moreover, the coronary calcium score contributed to the risk of both major events and any event in four major ethnic groups independently of other risk factors.

Other studies evaluating the prognostic accuracy of the measurement of coronary calcium by CT have shown that coronary calcification is



predictive of coronary events independently of standard risk factors or risk-factor scores.⁸⁻¹⁸ For example, a study by LaMonte et al. of nearly 11,000 adults from 22 to 96 years of age who underwent a screening medical examination reported hazard ratios for major coronary events of 8.7 among men and 6.3 among women with coronary calcium scores of 400 or more during a mean follow-up of 3.5 years.¹⁵ Among men and women 40 to 45 years of age in the Prospective

Army Coronary Calcium Project, the presence of coronary calcium was associated with an increase in the risk of coronary events by a factor of 12 during 3 years of follow-up.¹⁷ Finally, in the population-based Rotterdam Study of elderly asymptomatic subjects, during a mean follow-up of 3.3 years, the adjusted relative risks of coronary events associated with calcium scores of 101 to 400, 401 to 1000, and more than 1000 (as compared with scores of 0 to 100) were 3.1, 4.6, and 8.3, respectively.¹⁸ However, many previous studies included participants who were referred by themselves or their physicians or who were chosen because they were at high risk. In addition, previous analyses did not attempt to evaluate the effect of ethnic group on the predictive value of coronary calcification.

It has been reported previously that the prevalence and extent of coronary calcification differ substantially among ethnic groups.¹⁹⁻²² Our study suggests that these differences do not decrease the predictive value of this subclinical marker in American minority groups. Our results, in fact, suggest that the coronary calcium score is valuable for the prediction of future events even in ethnic groups in which coronary calcification is less prevalent.

Our study has several limitations. CT acquisition and reading methods differ among studies and clinical scanning centers. We calibrated images with the use of a calcium phantom to control for variability in some of the physical characteristics of the scanners.²⁸ We also chose a large field of view to include the phantom in all images, and we set the minimum lesion size used to define a calcified plaque conservatively large to reduce variability among scanners resulting from differences in the signal-to-noise ratio. These and other differences from the usual clinical scanning protocols are expected to have some effect on the absolute values of calcium measurements but will only minimally affect the ranking of participants' calcium scores. We suggest caution in using the absolute calcium-score numbers from our study in settings in which scanning and reading protocols differ greatly from those used in the MESA.

In our study, the participants and their physicians were informed of the coronary calcium

Table 3. Risk of Coronary Events Associated with Increasing Coronary-Artery Calcium Score after Adjustment for Standard Risk Factors.*

| Coronary-Artery Calcium Score | Major Coronary Event†‡ | | | Any Coronary Event | | |
|-------------------------------|------------------------|-----------------------|---------|--------------------|-----------------------|---------|
| | No./No. at Risk | Hazard Ratio (95% CI) | P Value | No./No. at Risk | Hazard Ratio (95% CI) | P Value |
| 0 | 8/3409 | 1.00 | | 15/3409 | 1.00 | |
| 1–100 | 25/1728 | 3.89 (1.72–8.79) | <0.001 | 39/1728 | 3.61 (1.96–6.65) | <0.001 |
| 101–300 | 24/752 | 7.08 (3.05–16.47) | <0.001 | 41/752 | 7.73 (4.13–14.47) | <0.001 |
| >300 | 32/833 | 6.84 (2.93–15.99) | <0.001 | 67/833 | 9.67 (5.20–17.98) | <0.001 |
| Log ₂ (CAC+1)‡ | | 1.20 (1.12–1.29) | <0.001 | | 1.26 (1.19–1.33) | <0.001 |

* CAC denotes coronary-artery calcium score, and CI confidence interval.

† Major coronary events were myocardial infarction and death from coronary heart disease.

‡ Each unit increase in log₂(CAC+1) represents a doubling of the coronary-artery calcium score.

Table 4. Risk of Coronary Heart Disease Associated with Coronary-Artery Calcium Score in Four Racial or Ethnic Groups.*

| Racial or Ethnic Group | Major Coronary Event†‡ | | | Any Coronary Event | | |
|------------------------|------------------------|------------------------|---------|--------------------|------------------------|---------|
| | No. | Hazard Ratio (95% CI)‡ | P Value | No. | Hazard Ratio (95% CI)‡ | P Value |
| White | 41 | 1.17 (1.06–1.30) | <0.005 | 74 | 1.22 (1.13–1.32) | <0.001 |
| Chinese | 6 | 1.25 (0.95–1.63) | 0.11 | 14 | 1.36 (1.12–1.66) | <0.005 |
| Black | 18 | 1.35 (1.16–1.57) | <0.001 | 38 | 1.39 (1.25–1.56) | <0.001 |
| Hispanic | 24 | 1.15 (1.02–1.29) | <0.025 | 36 | 1.18 (1.07–1.30) | <0.001 |

* CAC denotes coronary-artery calcium score, and CI confidence interval.

† Major coronary events were myocardial infarction and death from coronary heart disease.

‡ Hazard ratios were calculated with the use of Cox regression for coronary heart disease (major event and any event) for baseline levels of log₂(CAC+1) after adjustment for risk factors and interactions between racial or ethnic group and coronary calcium score and between racial or ethnic group and diabetes (the only significant interaction). Hazard ratios are calculated on the basis of a doubling of CAC+1.

scores. This might have influenced our results in two ways. First, participants with high coronary calcium scores might have changed their behavior or received preventive treatment that would have lowered their risk of coronary events. This would have biased our results toward the null hypothesis for the relationship between coronary calcium and coronary disease. Second, knowledge of the calcium score might have influenced the diagnosis of angina, potentially biasing the results toward showing a stronger relationship between coronary calcium and coronary disease. However, the relationship between coronary calcium and major coronary events would not have been affected by this bias.

Although our findings suggest that coronary calcium predicts coronary heart disease in four ethnic groups, ethnic-specific calibration of calcium measures may be needed to adjust for baseline differences among the ethnic groups. Finally, our study was limited by the small number of clinical events. Further follow-up of the MESA cohort will allow refinement of our risk estimates.

In conclusion, we found that measurement of coronary-artery calcium in a multiethnic American cohort added incremental value to the prediction of coronary heart disease over that of the standard coronary risk factors in each of four ethnic groups.

Table 5. Use of Area under the Curve for Risk Factors Alone and for Risk Factors plus Coronary-Artery Calcium Score to Predict Major Coronary Events and Any Coronary Event, According to Racial or Ethnic Group.*

| Racial or Ethnic Group | Major Coronary Event† | | | Any Coronary Event | | |
|------------------------|----------------------------|---|---------|----------------------------|---|---------|
| | AUC for Risk Factors Alone | AUC for Risk Factors plus Coronary-Artery Calcium Score | P Value | AUC for Risk Factors Alone | AUC for Risk Factors plus Coronary-Artery Calcium Score | P Value |
| White | 0.76 | 0.79 | 0.10 | 0.75 | 0.79 | 0.02 |
| Chinese | 0.83 | 0.88 | 0.05 | 0.74 | 0.85 | <0.001 |
| Black | 0.79 | 0.87 | 0.04 | 0.81 | 0.87 | 0.005 |
| Hispanic | 0.84 | 0.86 | 0.11 | 0.80 | 0.84 | 0.10 |
| Total | 0.79 | 0.83 | 0.006 | 0.77 | 0.82 | <0.001 |

* Separate models are fitted for each racial or ethnic group. AUC denotes area under the receiver-operating-characteristic curve. P values are for the comparison between AUC without and AUC with the coronary-artery calcium score.

† Major coronary events were myocardial infarction and death from coronary heart disease.

Supported by grants (N01-HC-95159 to N01-HC-95166 and N01-HC-95169) from the National Heart, Lung, and Blood Institute.

Dr. Guerci reports receiving grant support from Pfizer. Dr. O'Leary reports receiving consulting fees from Schering, Sanofi Aventis, Eli Lilly, and Pfizer, receiving lecture fees from AstraZeneca, and owning stock in Medpace. Dr. Watson reports re-

ceiving consulting fees from Merck and lecture fees from Merck, Abbott, and Schering. No other potential conflict of interest relevant to this article was reported.

We thank the other investigators, the staff, and the participants in the MESA (www.mesa-nhlbi.org) for their valuable contributions.

REFERENCES

- Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. *Circulation* 1998;97:1837-47.
- D'Agostino RB Sr, Grundy S, Sullivan LM, Wilson P. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. *JAMA* 2001;286:180-7.
- Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72. [Erratum, *JAMA* 2003;290:197.]
- Expert Panel on Detection Evaluation, and Treatment of High Blood Cholesterol in Adults. 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;285:2486-97.
- Smith SC Jr, Greenland P, Grundy SM. AHA conference proceedings — Prevention Conference V: beyond secondary prevention: identifying the high-risk patient for primary prevention: executive summary. *Circulation* 2000;101:111-6.
- Diverse Populations Collaborative Group. Prediction of mortality from coronary heart disease among diverse populations: is there a common predictive function? *Heart* 2002;88:222-8.
- Greenland P, Smith SC Jr, Grundy SM. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation* 2001;104:1863-7.
- Greenland P, LaBree L, Azen SP, Doherty TM, Detrano RC. Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 2004;291:210-5. [Erratum, *JAMA* 2004;291:563.]
- Arad Y, Goodman K, Roth M, Newstein D, Guerci AD. Coronary calcification, coronary disease risk factors, C-reactive protein, and atherosclerotic cardiovascular disease events: the St. Francis Heart Study. *J Am Coll Cardiol* 2005;46:158-65.
- 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;85:945-8.
- Raggi P, Callister TQ, Shaw LJ. Progression of coronary artery calcium and risk of first myocardial infarction in patients receiving cholesterol-lowering therapy. *Arterioscler Thromb Vasc Biol* 2004;24:1272-7.
- Kondos GT, Hoff JA, Sevrukov A, et al. Electron-beam tomography coronary artery calcium and cardiac events: a 37-month follow-up of 5635 initially asymptomatic low- to intermediate-risk adults. *Circulation* 2003;107:2571-6.
- Raggi P, Coolil B, Callister TQ. Use of electron beam tomography data to develop models for prediction of hard coronary events. *Am Heart J* 2001;141:375-82.
- Wong ND, Hsu JC, Detrano RC, Diamond G, Eisenberg H, Gardin JM. Coronary artery calcium evaluation by electron beam computed tomography and its relation to new cardiovascular events. *Am J Cardiol* 2000;86:495-8.
- LaMonte MJ, FitzGerald SJ, Church TS, et al. Coronary artery calcium score and coronary heart disease events in a large cohort of asymptomatic men and women. *Am J Epidemiol* 2005;162:421-9.
- Shaw LJ, Raggi P, Schisterman E, Berman DS, Callister TQ. Prognostic value of cardiac risk factors and coronary artery calcium screening for all-cause mortality. *Radiology* 2005;228:826-33.
- Taylor AJ, Bindeman J, Feuerstein I, Cao F, Brazaitis M, O'Malley PG. Coronary calcium independently predicts incident premature coronary heart disease

- over measured cardiovascular risk factors: mean three-year outcomes in the Prospective Army Coronary Calcium (PACC) project. *J Am Coll Cardiol* 2005;46:807-14.
18. Vliegenthart R, Oudkerk M, Hofman A, et al. Coronary calcification improves cardiovascular risk prediction in the elderly. *Circulation* 2005;112:572-7.
19. Bild DE, Detrano R, Peterson D, et al. Ethnic differences in coronary calcification: the Multi-Ethnic Study of Atherosclerosis (MESA). *Circulation* 2005;111:1313-20.
20. Tang W, Detrano RC, Brezden OS, et al. Racial differences in coronary calcium prevalence among high-risk adults. *Am J Cardiol* 1995;75:1088-91.
21. Newman AB, Naydeck BL, Whittle J, Sutton-Tyrrell K, Edmundowicz D, Kuller LH. Racial differences in coronary artery calcification in older adults. *Arterioscler Thromb Vasc Biol* 2002;22:424-30.
22. Lee TC, O'Malley PG, Feuerstein I, Taylor AJ. The prevalence and severity of coronary artery calcification on coronary artery computed tomography in black and white subjects. *J Am Coll Cardiol* 2003;41:39-44.
23. Jain T, Peshock R, McGuire DK, et al. African Americans and Caucasians have a similar prevalence of coronary calcium in the Dallas Heart Study. *J Am Coll Cardiol* 2004;44:1011-7.
24. Bild DE, Bluemke DA, Burke GL, et al. Multi-Ethnic Study of Atherosclerosis: objectives and design. *Am J Epidemiol* 2002;156:871-81.
25. Carr JJ, Nelson JC, Wong ND, et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology* 2005;234:35-43.
26. Yaghoubi S, Tang W, Wang S, et al. Offline assessment of atherosclerotic coronary calcium from electron beam tomograms. *Am J Card Imaging* 1995;9:231-6.
27. 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;15:827-32.
28. Nelson JC, Kronmal RA, Carr JJ, et al. Measuring coronary calcium on CT images adjusted for attenuation differences. *Radiology* 2005;235:403-14.

Copyright © 2008 Massachusetts Medical Society.

JOURNAL EDITORIAL FELLOW

The *Journal's* editorial office invites applications for a one-year research fellowship beginning in July 2009 from individuals at any stage of training. The editorial fellow will work on *Journal* projects and will participate in the day-to-day editorial activities of the *Journal* but is expected in addition to have his or her own independent projects. Please send curriculum vitae and research interests to the Editor-in-Chief, 10 Shattuck St., Boston, MA 02115 (fax, 617-739-9864), by September 30, 2008.