Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 50, No. 10, 2007
ISSN 0735-1097/07/$32.00
doi:10.1016/j.jacc.2007.03.066

Ethnic Differences in the Prognostic Value of Coronary Artery Calcification for All-Cause Mortality

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Objectives The purpose of this study was to evaluate the prognostic value of coronary artery calcium (CAC), a known marker of subclinical atherosclerosis, in a large, ethnically diverse cohort of 14,812 patients for the prediction of all-cause mortality.

Background Disparities in case fatality rates for heart disease among ethnic groups are well known. In 2001, rates of death from heart disease were 30% higher among African Americans (AA) than non-Hispanic whites (NHW). Some of this variability may be due to differing pathophysiological mechanisms and effects of underlying atherosclerosis.

Methods Ten-year death rates from all causes (total deaths = 505) were compared using risk-adjusted Cox proportional hazards models in AA (n = 637), Hispanic (HS, n = 1,334), Asian (AS, n = 1,065), and NHW (n = 11,776) populations.

Results Ethnic minority patients were generally younger (0.3 to 4 years), more often persons with diabetes ($p < 0.0001$), hypertensive ($p < 0.0001$), and female ($p < 0.0001$). The prevalence of CAC scores ≥100 was highest in NHW (31%) and lowest for HS (18%) ($p < 0.0001$). Overall survival was 96%, 93%, and 92% for AS, NHW, and HS, respectively, as compared with 83% for AA ($p < 0.0001$). When comparing prognosis by CAC scores in ethnic minorities as compared with NHW, relative risk ratios were highest for AA with CAC scores ≥400 exceeding 16.1 ($p < 0.0001$). Hispanics with CAC scores ≥400 had relative risk ratios from 7.9 to 9.0, whereas AS with CAC scores ≥1,000 had relative risk ratios 6.6-fold higher than NHW ($p < 0.0001$).

Conclusions Consistent with population evidence, AA with increasing burden of subclinical coronary artery disease were the highest-risk ethnic minority population. These data support a growing body of evidence noting substantial differences in cardiovascular risk by ethnicity. (J Am Coll Cardiol 2007;50:953–60) © 2007 by the American College of Cardiology Foundation

Ethnic diversity in the U.S. is rapidly increasing, and information about differing cardiovascular disease (CVD) risk among different subgroups is sparse (1). Cardiovascular disease is still the leading cause of death in the U.S. (2).

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However, CVD-associated morbidity and mortality varies widely across different ethnic groups, and these differences are likely influenced by genetic and environmental factors as well as lifestyle (3). Moreover, the patterns of CVD may have evolved in these ethnic groups over time, complicating the simultaneous interpretation of current and earlier studies (4). The Cardiovascular Science and Health Care Disparities Minority Health Summit in 2003 encouraged additional research on ethnic disparities in CVD risk factors, outcomes, health care use, and effective risk factor modification as well as recommended increased minority participation in scientific studies (1).

Some of this ethnic variability may be due to differing pathophysiological mechanisms and effects of underlying atherosclerosis, which is the main cause of CVD mortality (5). A direct relationship has been established between coronary artery calcium (CAC) scores and atherosclerotic burden as well as future CVD events in asymptomatic individuals (6–11). Recent studies suggest that CAC differs among ethnic groups (12–16). Despite an ever-increasingly ethnically diverse U.S. population, our current understanding of the predictive accuracy of CAC in ethnic

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Manuscript received January 23, 2007; revised manuscript received March 8, 2007, accepted March 12, 2007.

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Abbreviations and Acronyms

AA = African American(s)
AS = Asian(s)
CAC = coronary artery calcium
CI = confidence interval
CVD = cardiovascular disease
EBT = electron beam tomography
HS = Hispanic(s)
NHW = non-Hispanic white(s)
RR = relative risk

minorities is lacking. The purpose of the current report was to evaluate the differential prognostic value of the extent and severity of CAC determined by electron beam tomography (EBT) in predicting all-cause mortality in an ethnically diverse asymptomatic population.

Methods

Study population. The study sample consisted of 14,812 asymptomatic subjects, including 637 African Americans (AA), 1,065 Asians (AS), 1,334 Hispanics (HS), and 11,776 non-Hispanic whites (NHW), referred by their primary care physicians between 1991 and 2004 for CAC screening with EBT. Among the Asians we excluded the 248 younger, Asian Indian patients where only 2 deaths were observed.

Individuals were referred for screening on the basis of the presence of established risk factors and, as such, were not an unselected cohort representative of the general population. Patients with a history of coronary disease (i.e., 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 EBT screening, and our study received the 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.

Risk factor data collection. Risk factor data were derived through patient interview, referring physician contact, and existing medical record data. Hypertension was defined as a documented history of high blood pressure or treatment with medication, diet, and/or exercise. A history of coronary disease in a first-degree relative was considered premature if reported in a male relative <55 years and in female relatives <65 years. A history of current smoking or cessation of smoking within 3 months before testing was defined as positive smoking status. A high cholesterol level was defined as reported hypercholesteromia and/or use of cholesterol-lowering medicine. 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.

EBT. Electron beam tomography was performed with either a C-100 or C-150 scanner (Imatron, South San Francisco, California), and images were obtained with 100-ms scanning time. The computed tomography 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. Computed tomography was electrocardiographically triggered at 60% to 80% of the R-R interval. Coronary artery calcium was defined as a plaque of at least 3 contiguous pixels (area = 1.03 mm^2) with attenuation of 130 HU or greater. Quantitative CAC scores were calculated according to the method described by Agatston et al. (17).

Follow-up data collection. Epidemiologic methods for follow-up included ascertainment of events by individuals blinded to historical and CAC results. The occurrence of all-cause death was verified with the National Death Index. Individuals who underwent cardiovascular screening were followed up for a mean of 6.8 ± 0.02 years (standard error of the mean), with a range of 0.7 to 14.5 years.

Statistical methods. Death from all causes was the primary end point for this registry. For comparisons between ethnic groups, categorical risk factors and CAC score subsets were compared using chi-square statistic. A logistic regression model was used to compare the likelihood of CAC across ethnic subsets. Time to death from all causes was estimated using a Cox proportional hazards model. For the Cox model, univariable and multivariable models were developed and included an evaluation of traditional cardiac risk factors and CAC score measurements in all ethnic groups. Specifically, risk-adjusted or multivariable prognostic models were employed to assess the independent prognostic value of CAC in ethnic groups while controlling for other cardiac risk factors including age, hypertension, hyperlipidemia, diabetes, and a family history of premature coronary artery disease. From the Cox models, relative risk (RR) ratios and 95% confidence intervals (CIs) were calculated. Relative risk ratios (95% CI) for calcium subsets of 11 to 100, 101 to 400, 401 to 99, and ≥1,000, respectively, were calculated for all ethnic subgroups.

Because the primary aim of the study was to assess whether the association of increasing levels of CAC differed across ethnic groups, a first-order test for interaction of ethnicity by CAC score was also entered into a Cox regression model. Furthermore, a stratified Cox survival analysis plotted survival by CAC subsets from 0 to 10, 11 to 100, 101 to 400, 401 to 999, and ≥1,000, respectively, for all ethnic groups. Survival rates were rounded to the nearest tenth of a percent.

We previously reported methods for the estimation of patient life expectancy based upon observed age at the time of testing (18,19). Based upon observed age at EBT imaging, expected life expectancy was assigned based upon national normative statistics for age and gender subsets from the Centers for Disease Control. A patient's life expectancy was assigned as their time to death from nonsurvivors. Normative life expectancy estimates were further revised based upon a multivariable model including age, CAC scores, and other cardiac risk factors resulting in a calculated predicted survival function. From this model, a total life

Table 1 Prevalence of Cardiac Risk Factors in 14,812 Asymptomatic Individuals Undergoing CAC Screening

	Non-Hispanic White (n = 11,776)	African American (n = 637)	Hispanic (n = 1,334)	Asian (n = 1,065)	p Value
Age (yrs)	57 ± 11	57 ± 11	53 ± 11	55 ± 12	<0.0001
Family history of premature CAD (%)	60	47	48	49	<0.0001
Smoking (%)	9	14	11	8	0.002
Diabetes mellitus (%)	6	18	17	12	<0.0001
Hypertension (%)	28	49	36	38	<0.0001
Female gender (%)	44	57	52	52	<0.0001
Hyperlipidemia (%)	47	44	43	45	0.105
Number of risk factors					<0.0001
0	19	20	21	23	
1–2	70	58	63	64	
≥3	11	22	16	13	

CAC = coronary artery calcium; CAD = coronary artery disease.

expectancy estimate was derived as a product of predicted survival function by the normative life expectancy estimate. All life expectancy estimates were stratified by ethnicity, age, and CAC score subsets of ≥100, ≥400, and ≥1,000, respectively. Life expectancy estimates for these latter subsets were compared using nonparametric statistics including 4 independent samples using the Kruskal-Wallis statistic.

Results

Cardiac risk factor and CAC prevalence rates. Coronary heart disease risk factor data across the ethnic groups are shown in Table 1. African American subjects had a significantly higher prevalence of diabetes mellitus ($p = 0.01$) and more frequent history of hypertension ($p = 0.03$) compared with NHW. However, NHW subjects were significantly older ($p = 0.0001$) with a greater prevalence of family history of coronary heart disease as compared with AA subjects ($p = 0.01$). In general, AA and HS had a greater frequency for clustering 3 or more traditional cardiac risk factors ($p < 0.0001$).

The mean (standard deviation) score range and median (interquartile range) CAC score for the 14,812 asymptomatic individuals who were referred for screening was 146.2 ± 463 (standard error of the mean) (score range 0 to 9,377) and 3 (0 to 78), respectively. Of the 14,812 individuals, 57% had a score of 10 or less. The prevalence of CAC scores of 11 to 100, 101 to 400, 401 to 999, and ≥1,000 was 20%, 14%, 6%, and 3%, respectively. Figure 1 demonstrates the prevalence of CAC categories across the ethnic groups. The prevalence of any CAC is 66%, 58%, 55%, and 55% for NHW, AA, HS, and AS, respectively ($p < 0.0001$). As compared with NHW, all ethnic groups had lower odds of having any as well as increasing burden of CAC ($p < 0.0001$).

Long-term prognosis by ethnicity. In the 10-year follow-up, 505 all-cause deaths were observed. Overall survival was 96%, 93%, and 92% for AS, NHW, and HS as compared with 83% for AA, respectively ($p < 0.0001$) (Fig. 2). The unadjusted and risk-adjusted RRs for mortality across the ethnic groups are shown in Table 2. Multivariable analyses revealed that AA race was an independent predictor of death (RR 2.9; 95% CI 1.9 to 4.6). The results persisted with additional adjustment for CAC scores (RR 3.0; 95% CI 1.9 to 4.7). After adjusting for age, gender, hypertension, hyperlipidemia, diabetes, and a family history of premature coronary disease, HS and AS had a similar mortality risk as compared with NHW.

Survival by coronary calcium scores and ethnicity. The overall unadjusted survival for the study population were 99.5%, 96.7%, 92.8%, 85%, and 72% for CAC scores of 10 or less, 11 to 100, 101 to 400, 401 to 999, and ≥1,000, respectively ($p < 0.001$). The multivariable adjusted RR ratios for mortality with increasing CAC scores in all ethnic groups are shown in Table 3.

Risk-adjusted survival by ethnicity. Using risk-stratified Cox proportional hazard survival analyses (Fig. 3), survival for NHW ranged from 98% to 57% for CAC scores of 0 to

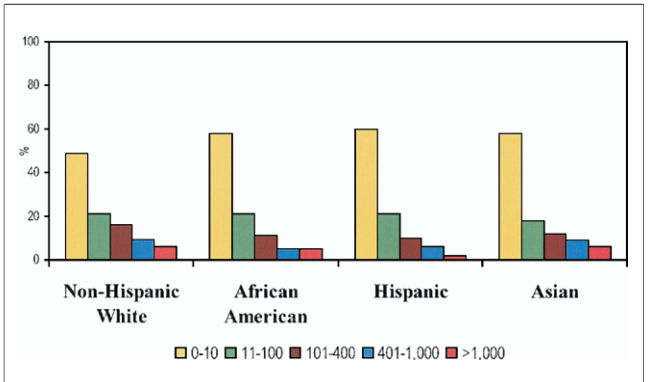

Figure 1 Observed Frequency of CAC Score Subsets by Ethnicity (n = 14,812)

Prevalence of any coronary artery calcium (CAC) is 66%, 58%, 55%, and 55% for non-Hispanic whites, African Americans, Hispanics, and Asians, respectively ($p < 0.0001$). As compared with non-Hispanic white, all ethnic groups had lower odds of having any as well as an increasing burden of CAC ($p < 0.0001$).

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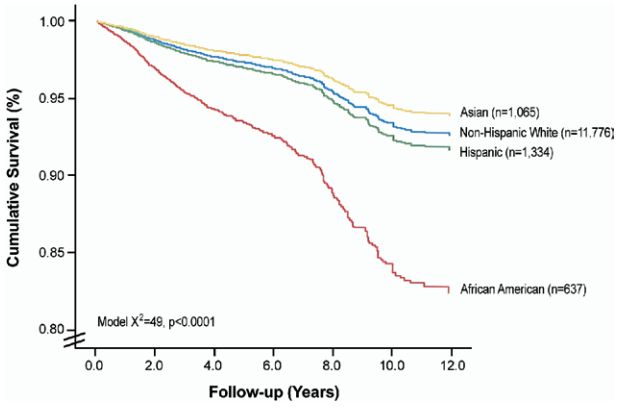

Figure 2 **Long-Term Survival in Ethnic Subsets (n = 14,812)**

Overall survival was 96%, 93%, and 92% for Asians, non-Hispanic whites, and Hispanics as compared with 83% for African Americans, respectively ($p < 0.0001$). Among all ethnic groups, the lowest survival was observed in African Americans (83%, $p < 0.0001$).

10 to ≥1,000. In comparison, survival ranged from 97% to 30% in AA, 99% to 60% in HS, and 100% to 80% in AS. Using a stratified Cox model, CAC remained predictive of death in a model controlling for age and risk factors in all ethnic subsets ($p < 0.0001$). For subset multivariable models, CAC was predictive of death for NHW ($p < 0.0001$), HS ($p < 0.0001$), AA ($p < 0.0001$), and for AS ($p = 0.002$), respectively. Furthermore, in a stepwise model, the CAC score was identified as the single greatest estimator of time to mortality for each ethnic subset.

A first-order interaction of CAC score with ethnicity was statistically significant in a model controlling for other cardiac risk factors indicating differential effect of CAC on mortality among the ethnic groups ($p < 0.0001$). When comparing the predictive value of CAC scores in ethnic minorities as compared with NHW, the RR ratio for CAC ≥1,000 is 9.0 for HS, 6.6 for AS, and 24 for AA (Fig. 4). Similarly, higher RR ratios were noted for HS and AA with CAC scores ≥400.

Predicted life expectancy by CAC scores in ethnic subsets. The predicted changes in life expectancy for ethnic subsets by CAC score are shown in Figure 5. In each case across ethnic subsets, younger patients with CAC scores ≥100 to ≥1,000 had a reduced life expectancy. For 40-year-old NHW, life expectancy declined 2.0 to 5.9 years for CAC scores ≥100 to ≥1,000. Declines in life expectancy were 2.3 to 0.9 years for 60- to 80-year-old NHW. The declines in life expectancy were higher for ethnic minority patients. That is, for 40-year-old subjects of diverse ethnicity, declines in life expectancy ranged from 8.3 to 15.0 years for AA, 6.3 to 15.0 years for HS, and 2.6 to 12.0 years for AS.

Discussion

During the past several decades, the U.S. population has become increasingly ethnically diverse (4). To achieve a meaningful impact from a preventive aspect on morbidity and mortality in the U.S., it is pragmatic to consider the demographic diversity within the U.S. (1). Recent data from American Heart Association 2005 statistical fact sheets indicate a significant disparity from CVD mortality in racial/ethnic groups (2).

The heterogeneity in CVD among ethnic subgroups may, in part, be explained by known issues such as risk-factor clustering (20), as well as underutilization of preventive therapies (21,22) and acculturation and diminished access to health care services (23,24). Some variability, however, may be due to differing mechanisms of plaque formation, pro-

Table 2 **Multivariable Model on the Impact of Ethnicity in Clinically Risk-Adjusted and Calcium-Adjusted Cox Proportional Hazards Models**

	Relative Risk	95% Confidence Intervals	Wald Chi-Square	p Value
Unadjusted model			49	<0.0001
Ethnicity			49	<0.0001
African American	2.54	1.92–3.36		<0.0001
Hispanic	1.13	0.85–1.52		0.40
Asian	0.82	0.55–1.21		0.31
Clinical risk adjustment*			367	<0.0001
Ethnicity			25	<0.0001
African American	2.93	1.86–4.62		<0.0001
Hispanic	1.67	1.02–2.73		0.04
Asian	0.88	0.50–1.56		0.66
Calcium risk adjustment†			577	<0.0001
Ethnicity			24	<0.0001
African American	2.97	1.87–4.72		<0.0001
Hispanic	1.58	0.92–2.71		0.096
Asian	0.85	0.47–1.54		0.60

For each of the models, the reference group is non-Hispanic whites. *Clinical risk adjustment includes adjustment for all of the cardiac risk factors reported in Table 1; †Calcium risk adjustment includes variables included in the clinical risk-adjusted model plus the coronary artery calcium score.

Table 3 Multivariable Model RRR for All-Cause Mortality by CAC Scores According to Ethnicity

CAC Score	Overall	Non-Hispanic White	African American	Hispanic	Asian
0–10	1 (reference)	1 (reference)	1 (reference)	1 (reference)	1 (reference)
11–100	4.9 (3.6–6.8)	3.8 (2.6–5.6)	4.1 (1.6–10.8) p = 0.004	4.2 (1.9–9.5) p = 0.001	9.3 (1.3–66.2) p = 0.026
100–400	10.5 (7.7–14.2)	6.9 (4.8–9.9)	12.3 (5.0–30.5)	3.7 (1.4–10.3) p = 0.011	13.1 (2.8–61.9) p = 0.001
401–1,000	22.0 (16.0–30.3)	10.8 (7.4–15.7)	25.6 (9.9–66.3)	19.1 (8.7–42.3)	17.6 (3.7–84.7)
>1,000	45.3 (33.4–61.6)	24.8 (17.3–35.4)	39.5 (16.1–97.4)	20.8 (7.5–57.7)	53.3 (11.3–251.2)

All comparisons are $p < 0.0001$ except where indicated.
CAC = coronary artery calcium; RRR = relative risk ratio.

gression, rupture, and thrombosis, which are known precursors of acute coronary syndromes and cardiac death (25). The possible ethnic/racial differences in rates of CVD can potentially be explored by identifying those with subclinical atherosclerosis and associated risk.

Coronary artery calcium is an established surrogate for the overall magnitude of coronary atherosclerotic plaque (26). Since more than one-half of all first coronary heart disease events are sudden cardiac deaths or acute myocardial infarctions in previously asymptomatic individuals, the emphasis has recently been focused on the identification of high-risk individuals with the potential inclusion of screening for CAC. It is now clearly established that increased CAC scores are consistent with increased cardiovascular risk. Shaw et al. (6) reported on all-cause mortality in a large cohort of 10,377 asymptomatic individuals followed for an

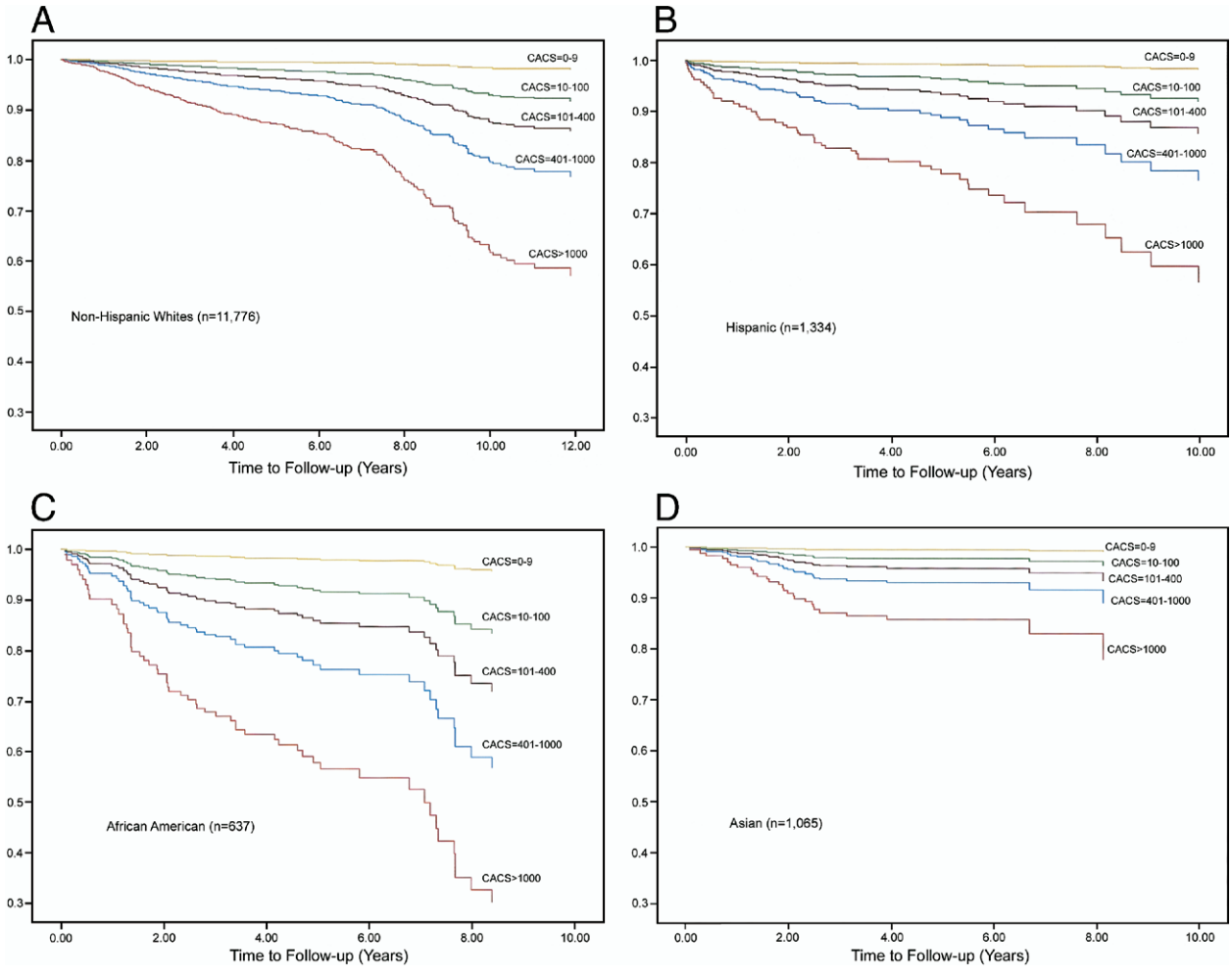

Figure 3 Cumulative Survival By CACS in Ethnic Subsets

(A to D) Using risk-stratified Cox proportional hazard survival analyses, the survival ranged from 98% to 57% in non-Hispanic whites, 97% to 30% in African Americans, 99% to 60% in Hispanics, and 100% to 80% in Asians for coronary artery calcium scores (CACS) of 0 to 10 to ≥1,000.

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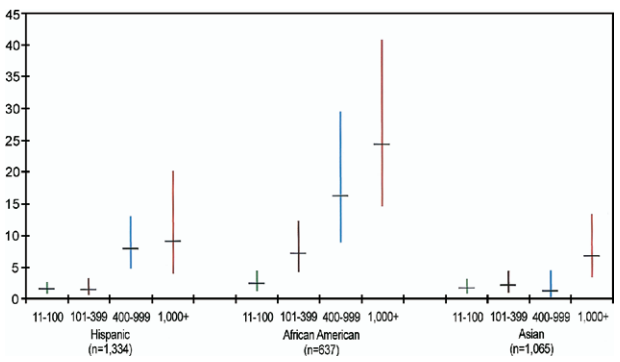

Figure 4 **RRRs (95% CIs) for CACS Subsets in HS, AA, and AS Patients as Compared With NHW**

The figure depicts the relative risk ratios (RRRs) of events for ethnic subsets with increasing coronary artery calcium scores (CACS) as compared with non-Hispanic whites (NHW). As compared with NHW, the relative risk ratio for CAC ≥1,000 is 9.0 for Hispanics (HS) (n = 1,334), 6.6 for Asians (AS) (n = 1,065), and 24 for African Americans (AA) (n = 637). CI = confidence interval.

average of 5 ± 3.5 years. At the end of follow-up, a total of 249 deaths were recorded. The CAC score was an independent predictor of death ($p < 0.001$) with risk increasing proportionally to the baseline CAC scores. Greenland et al. (11) also demonstrated that high CAC scores can modify predicted risk obtained from the Framingham risk index alone, especially among patients in the intermediate risk category in whom clinical decision making is most uncertain. The results of the St. Francis Heart study, a prospective registry of 5,585 asymptomatic individuals, also demonstrated that higher CAC scores (>100) were associated with RRs of 12 to 32 for CVD events achieving secondary prevention equivalent event rates >2% per year (8). Similarly, Taylor et al. (9) showed CAC was associated with a nearly 12-fold increased risk for incident coronary heart disease controlling for the Framingham risk score in men age 40 to 50 years of age. In a recent study, Budoff et al. (10) followed 25,253 asymptomatic individuals for a mean of 7 years with nearly 21% followed for at least 10 years. Ten-year survival (after adjustment for risk factors, including age) was 99.4% for a CAC score of 0 and worsened to 87.8% for a score of >1,000 ($p < 0.0001$). The addition of CAC to traditional risk factors increased the C-index significantly (0.77 for age vs. 0.81 for the CAC score, $p < 0.0001$). However, the results from these studies are largely based on NHW, with data on ethnic minorities missing.

Recently published studies have indicated that there are ethnic differences in the prevalence and extent of CAC among asymptomatic individuals. In a large asymptomatic physician-referred cohort of over 16,000 men and women age 45 to 84 years, Budoff et al. (12) reported that NHW and HS men had a significantly higher prevalence of CAC when compared with AA and AS men, despite a lower prevalence of hypertension, diabetes, and smoking (12). These differences persisted after controlling for standard cardiac risk factors. The results of this study were similar to those reported in the MESA (Multi-Ethnic Study of Atherosclerosis) study (13). After multivariable adjustment, compared with whites, the odds ratios for having CAC were 0.78 (95% CI 0.74 to 0.82) in blacks, 0.85 (95% CI 0.79 to

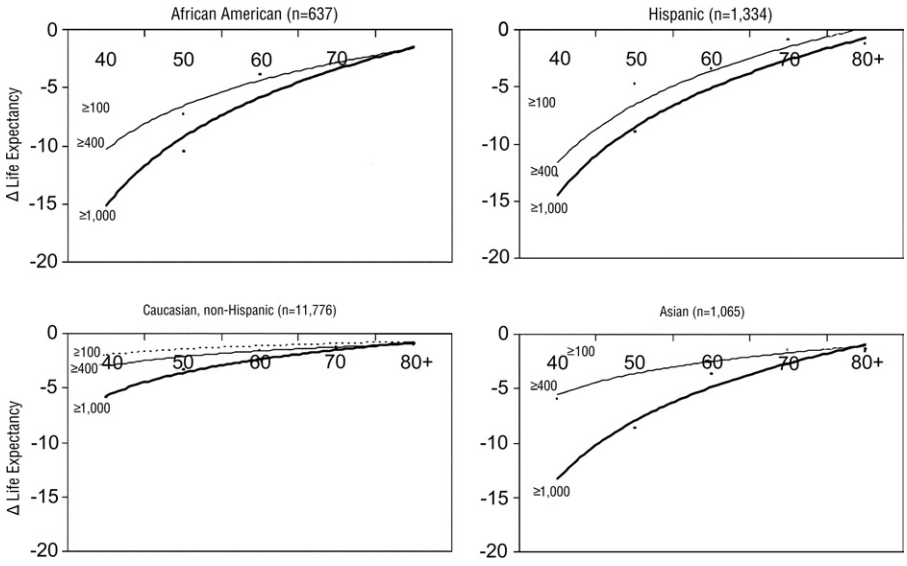

Figure 5 **Predicted Changes in Life Expectancy for Ethnic Subsets by CAC Scores ≥100, ≥400, and ≥1,000, Respectively**

The figure depicts the change in life expectancy for ethnic subsets of this registry for those with significant-to-extensive atherosclerosis including those with coronary artery calcium (CAC) scores ≥100, ≥400, and ≥1,000, respectively. The life expectancy (on the vertical axis) is plotted by age of individual (horizontal axis). The decline in life expectancy was highest among ethnic minorities with increasing levels of CAC burden.

0.91) in Hispanics, and 0.92 (95% CI 0.85 to 0.99) in Chinese enrollees in the MESA study ($p < 0.001$). Even after adjusting for risk factors, most studies have shown that the prevalence of CAC is lower in ethnic minorities (12,13).

Consistent with prior reports, we found that ethnic minorities largely had an increased clustering of risk factors and lower baseline CAC scores compared with NHW. However, our study is unique and adds to the literature by describing in detail for the first time the prognostic value of CAC in a large ethnically mixed cohort of asymptomatic individuals. In our study, increasing CAC burden was associated with a greater mortality in all ethnic/racial groups independent of baseline risk factors, gender, and age.

However, the high mortality risk associated with CAC in AA seen in our study appears in conflict with a previous report (27). Doherty et al. (27) suggested that CAC may not be as significant a prognostic marker in AA as in NHW. In that study, CAC determined by fluoroscopy was present in 60% of white subjects but only 35% of AA subjects ($p = 0.0001$) (27). Nevertheless, after 70 months of follow-up, more AA than whites (24% vs. 15%; $p = 0.04$) suffered a CVD event. African Americans were more likely to suffer an event even after adjusting for age, CAC score, and other cardiac risk factors. As a result, the authors concluded: "Coronary calcium therefore does not carry the same pathobiological significance in blacks that it does in whites" (27). However, it must be kept in mind that Doherty et al. (27) did not report the relative prognosis with presence of CAC in AA as compared with NHW. Also, the small sample size of AA ($n = 93$) in the study by Doherty et al. (27) precluded any significant inference on ethnic differences in outcome. Additionally, CAC was not quantified, which might have provided improved risk stratification (27). By comparison, our study was sufficiently powered to detect differences between relatively large ethnic subsets from a well-controlled, prospective registry. Our results imply that, although AA have lower CAC scores, they display a sizeable increased mortality risk with more extensive CAC burden.

Thus, it is possible that our results may help explain the ethnic paradox of CAC and survival observed in earlier studies. To understand our hypothesis, it is necessary to consider the epidemiologic principle defining prevalence, which is the product of incidence and the duration of disease (28). As pointed out by Nieto and Blumenthal (28), the apparent paradox is analogous to an earlier survey showing that tuberculosis was less prevalent in American blacks than in whites (29). Indeed, subsequent studies demonstrated that tuberculosis incidence was much higher in blacks, and their case fatality rate was also higher. As a result, earlier baseline findings were found to be simply a product of the incidence-prevalence bias (29). Although we report that survival is shorter in ethnic minorities with elevated CAC scores, whether the incidence for CAC development is greater needs to be determined in future prospective studies.

Why do ethnic minority subsets, notably AA patients, with higher CAC scores have a greater mortality compared with NHW? Park et al. (30) have recently demonstrated that, in presence of higher CAC scores, higher levels of inflammation are associated with poor prognosis. In our study, we did not measure inflammatory markers, although a higher inflammatory burden in ethnic minorities, especially AA and HS, has been previously reported (31). Thus, it may be that a smaller amount of calcium in the setting of greater inflammation catapults CVD risk. Moreover, ethnic minorities had more risk factors, which are frequently associated with higher rates of inflammation. Also, substantially higher comorbidities, levels of risk factors, and lower access to health care treatment and preventive practices may contribute to shorter survival in the presence of advanced underlying subclinical atherosclerosis.

Study limitations. Although the current article includes a rigorous analysis of the prognostic value of CAC, the majority of patients referred for calcium scanning had cardiac risk factors and, as such, are not representative of the general population. Residual confounding due to deficient and/or incomplete adjustment, including lack of socioeconomic status information, are important limitations. Large prospective studies, such as the ongoing MESA study, may be better equipped to take into account the baseline socioeconomic status and health care access differences across ethnic groups and, as a result, provide clues to some of racial disparity in mortality (32). However, the current results are generalizable to large patient cohorts that undergo CAC imaging across the U.S. under the direction of a referring physician.

In our study, CVD risk factors were self-reported. Hoff et al. (33) noted good reliability of self-reported histories of CVD risk factors in referred individuals for EBT scanning. Because the CVD risk factors were self-reported, the potential "residual confounding" cannot be ruled out. However, in many imaging laboratories, patients are referred on the basis of a brief history with measured values frequently unavailable. The use of self-reported risk factors does represent standards for cardiac testing that are commonly applied in cardiovascular medicine. Thus, we believe that our analysis is a close representation of daily practice. The study populations were fairly homogeneous in the sense that they were highly motivated to assess their CVD risk and were able to afford the expense associated with the EBT scan. These findings raise the possibility that such physician-referred populations differ from the general population in their use of screening procedures and other preventive measures.

Our models do not include the cause of death and, as such, our models may be based on mortality unrelated to atherosclerotic disease. However, all-cause mortality is an appropriate end point to follow, since when one accounts for both cardiac and systemic forms of the disease, nearly three-fourths of all deaths have been related to atherosclerosis (5). Furthermore, this end point is unaffected by the

reporting and misclassification bias potentially introduced by a physician's filing of a death report (34).

Conclusions

There is currently a paucity of evidence as to the prognostic value of many commonly performed cardiac diagnostic tests in ethnic minority patients. Our results provide evidence that CAC screening provides prognostic information based upon the extent and severity of subclinical atherosclerosis among all ethnic subgroups. A greater intensity of treatment in the presence of CAC may reduce the excess morbidity and mortality for ethnic minority patients. Unfolding this evidence should aid in developing management strategies optimized for ethnically diverse patient populations. Finally, findings from our study provide support for the development of ethnic-specific guidelines and more aggressive population-specific screening and educational programs focused on ethnic minorities.

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REFERENCES

1. Yancy CW, Benjamin EJ, Fabunmi RP, Bonow RO. Discovering the full spectrum of cardiovascular disease: Minority Health Summit 2003: executive summary. Circulation 2005;111:1339–49.
2. Thom T, Haase N, Rosamond W, et al. Heart disease and stroke statistics—2006 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. Circulation 2006;113:e85–151.
3. Kuller LH. Ethnic differences in atherosclerosis, cardiovascular disease and lipid metabolism. Curr Opin Lipidol 2004;15:109–13.
4. Palaniappan L, Wang Y, Fortmann SP. Coronary heart disease mortality for six ethnic groups in California, 1990–2000. Ann Epidemiol 2004;14:499–506.
5. Lloyd-Jones DM, Larson MG, Beiser A, Levy D. Lifetime risk of developing coronary heart disease. Lancet 1999;353:89–92.
6. 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 2003;228:826–33.
7. 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.
8. Arad Y, Goodman KJ, 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.
9. 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.
10. Budoff MJ, Shaw LJ, Liu ST, et al. Long term prognosis associated with coronary calcification: observation from a registry of 25,253 patients. J Am Coll Cardiol 2007;49:1860–70.
11. 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.
12. Budoff MJ, Nasir K, Mao S, et al. Ethnic differences of the presence and severity of coronary atherosclerosis. Atherosclerosis 2006;187:343–50.
13. 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.
14. Hatwalkar A, Agrawal N, Reiss DS, Budoff MJ. Comparison of prevalence and severity of coronary calcium determined by electron beam tomography among various ethnic groups. Am J Cardiol 2003;91:1225–7.
15. Budoff MJ, Yang TP, Shavelle RM, Lamont DH, Brundage BH. Ethnic differences in coronary atherosclerosis. J Am Coll Cardiol 2002;39:408–12.
16. 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.
17. 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.
18. Shaw LJ, Raggi P, Callister TQ, Berman DS. Prognostic value of coronary artery calcium screening in asymptomatic smokers and non-smokers. Eur Heart J 2006;27:968–75.
19. Shaw LJ, Raggi P, Berman DS, Callister TQ. Coronary artery calcium as a measure of biologic age. Atherosclerosis 2006;188:112–9.
20. Hutchinson RG, Watson RL, Davis CE, et al. Racial differences in risk factors for atherosclerosis. The ARIC study. Atherosclerosis Risk in Communities. Angiology 1997;48:279–90.
21. Goff DC Jr., Bertoni AG, Kramer H, et al. Dyslipidemia prevalence, treatment, and control in the Multi-Ethnic Study of Atherosclerosis (MESA): gender, ethnicity, and coronary artery calcium. Circulation 2006;113:647–56.
22. Nelson K, Norris K, Mangione CM. Disparities in the diagnosis and pharmacologic treatment of high serum cholesterol by race and ethnicity: data from the Third National Health and Nutrition Examination Survey. Arch Intern Med 2002;162:929–35.
23. LaVeist TA, Arthur M, Morgan A, et al. The cardiac access longitudinal study. A study of access to invasive cardiology among African American and white patients. J Am Coll Cardiol 2003;41:1159–66.
24. Ibrahim SA, Whittle J, Bean-Mayberry B, Kelley ME, Good C, Conigliaro J. Racial/ethnic variations in physician recommendations for cardiac revascularization. Am J Public Health 2003;93:1689–93.
25. Fuster V, Moreno PR, Fayad ZA, Corti R, Badimon JJ. Atherothrombosis and high-risk plaque: part I: evolving concepts. J Am Coll Cardiol 2005;46:937–54.
26. Rumberger JA, Simons DB, Fitzpatrick LA, Sheedy PF, Schwartz RS. Coronary artery calcium area by electron-beam computed tomography and coronary atherosclerotic plaque area. A histopathologic correlative study. Circulation 1995;92:2157–62.
27. Doherty TM, Tang W, Detrano RC. Racial differences in the significance of coronary calcium in asymptomatic black and white subjects with coronary risk factors. J Am Coll Cardiol 1999;34:787–94.
28. Nieto FJ, Blumenthal RS. Explaining the race paradox of coronary calcium prevalence and survival. J Am Coll Cardiol 2000;36:308–9.
29. Comstock G, Sartwell P. Tuberculosis studies in Muscogee County, Georgia: IV. Evaluation of a community-wide X-ray survey on the basis of six years of observations. Am J Hyg 1955;61:261–8.
30. Park R, Detrano R, Xiang M, et al. Combined use of computed tomography coronary calcium scores and C-reactive protein levels in predicting cardiovascular events in nondiabetic individuals. Circulation 2002;106:2073–7.
31. Lakoski SG, Cushman M, Criqui M, et al. Gender and C-reactive protein: data from the Multiethnic Study of Atherosclerosis (MESA) cohort. Am Heart J 2006;152:593–8.
32. Bild DE, Bluemke DA, Burke GL, et al. Multi-ethnic study of atherosclerosis: objectives and design. Am J Epidemiol 2002;156:871–81.
33. Hoff JA, Chomka EV, Krainik AJ, Daviglus M, Rich S, Kondos GT. Age and gender distributions of coronary artery calcium detected by electron beam tomography in 35,246 adults. Am J Cardiol 2001;87:1335–9.
34. Lauer MS, Blackstone EH, Young JB, Topol EJ. Cause of death in clinical research: time for a reassessment? J Am Coll Cardiol 1999;34:618–20.