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Predictive Value of Coronary Artery Calcium Score Categories for Coronary Events versus Strokes: Impact of Sex and Race:

The Multi-Ethnic Study of Atherosclerosis (MESA) and Dallas Heart Study (DHS)

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Abstract

Background—Coronary artery calcium (CAC) predicts atherosclerotic cardiovascular disease (ASCVD) events, inclusive of coronary heart disease (CHD) and stroke, and is a decision-making aid for primary prevention. The predictive value of CAC categories for CHD and stroke separately, and across sex and race groups of an asymptomatic population is unclear.

Methods—White, Black, and Hispanic participants of Multi-Ethnic Study of Atherosclerosis and Dallas Heart Study underwent CAC measurement at enrollment and were followed for incident ASCVD events. Ten-year CHD-to-stroke incidence ratios across CAC score categories 0, 1 to 99, and ≥100 were assessed. Associations of CAC with incident CHD and stroke events were evaluated using multivariable-adjusted Cox models and multiplicative interactions of CAC with sex/race were tested.

Results—Among 7,042 participants (mean age 57 years, 54% women, 36% Black, 23% Hispanic, 49% CAC=0, 19% CAC ≥100), 574 incident ASCVD events (333 CHD and 241 stroke) were observed over 12.3-year follow-up. 10-year CHD-to-stroke incidence ratio increased

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significantly across CAC categories in men, women, Whites, Blacks, and Hispanics (all p<0.001). High CAC burden (score ≥100) was independently associated with ASCVD and CHD risk in all groups, and with stroke risk in the overall cohort and Blacks. No sex- or race-based CAC interactions for ASCVD, CHD, and stroke events were observed. Adding CAC to a traditional risk factor model improved risk discrimination and reclassification for CHD, but not for stroke events.

Conclusions—In two population-based cohorts of asymptomatic individuals, 10-year CHD-to-stroke incidence ratio was higher with increasing CAC score categories across sex and race groups, and CAC was consistently a better predictor of CHD than stroke. High CAC burden comparably associated with ASCVD risk across sex and race groups.

Keywords

Calcium score; atherosclerotic cardiovascular disease; risk prediction; primary prevention

Journal Subject Terms:

Computerized Tomography (CT); Prognosis; Epidemiology

INTRODUCTION

The 2013 American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for cardiovascular risk assessment recommended using the pooled cohort equations (PCE) for estimating the 10-year risk of developing a first atherosclerotic cardiovascular disease (ASCVD) event, defined as coronary death, nonfatal myocardial infarction, or fatal/nonfatal stroke.(1) These guidelines changed the landscape of cardiovascular risk assessment by using racially diverse cohorts that allowed creation of separate risk estimation equations for Non-Hispanic White and Non-Hispanic Black men and women.(1) Furthermore, the cardiovascular end-point of interest was expanded beyond coronary heart disease (CHD) to include strokes in order to better identify modifiable ASCVD risk in women and in Blacks.(2) However, frequently there is uncertainty in clinical practice over the use of preventive therapies, even after utilizing the PCE, particularly for patients at borderline or intermediate risk.(2) In such a situation, testing for subclinical coronary atherosclerosis is thought to be reasonable.(3)

Coronary artery calcium (CAC) score, a marker of subclinical coronary atherosclerosis, reflects the cumulative exposure to cardiovascular risk factors over the lifetime and can inform shared decision-making regarding the use of preventive therapies.(4, 5) CAC burden independently predicts CHD events, improves CHD risk-discrimination, and correctly reclassifies individuals to appropriate risk categories.(6-9) However, fewer reports have examined the association of CAC with stroke,(10, 11) and the strength of this association is weaker than observed with CHD.(12) The collective evidence regarding the clinical utility of CAC is reflected in the 2018 AHA/ACC Multi-society Cholesterol management guidelines that recommend using CAC score categories 0, 1 to 99, and ≥100 if the decision about statin therapy is uncertain.(3)

The proportion of the two ASCVD subtypes, CHD and stroke, differs across sex and race/ethnic groups.(13) However, the relative predictive value of CAC categories for CHD vs. stroke has not been explored in detail across different demographic groups. Given the importance placed on stroke as an outcome along with the sex and racial variation in ASCVD risk, we sought to understand the performance of guideline-recommended CAC score thresholds to predict CHD and stroke risk in sex and race groups of an asymptomatic population. In this framework, two population-based, multi-ethnic American cohorts – the Multi-Ethnic Study of Atherosclerosis (MESA) and Dallas Heart Study (DHS) offer a unique opportunity to fill this knowledge gap.

METHODS

We performed individual-level data pooling of participants from MESA examination-1 and DHS phase-1 for the current analysis. The data that support the findings of this study are available from the corresponding author upon reasonable request. The MESA and DHS were selected because a pooled sample of these cohorts would be racially diverse and have a large number of participants with CAC scanning performed at enrollment. Additionally, these cohorts were recruited over similar time periods, and CHD and stroke events in both studies were adjudicated over long-term follow-up.

Study cohorts

The study designs for MESA and DHS have been previously published.(14, 15) Briefly, MESA is a population-based cohort study of White, Black, Hispanic, and Chinese individuals aged 45–84 years.(14) Examination-1 was performed between 2000 and 2002, and participants were recruited from six field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota).(14) The DHS is a probability-based, population cohort study of Dallas County (Texas) adults, with deliberate over-sampling of Blacks.(15) DHS phase-1 was conducted between 2000 and 2002 with participants aged 30–65 years completing a detailed in-home survey, laboratory testing, and multiple imaging studies.(15)

Both MESA and DHS were approved by Institutional Review Boards at each site and all participants provided written informed consent at enrollment. For the present analysis, we included White, Black, and Hispanic MESA (N=4838) and DHS (N=2971) participants who were free of prevalent clinical cardiovascular disease, had CAC score measured at time of study enrollment, and were followed for adjudicated ASCVD events. We excluded Chinese MESA participants in this analysis because DHS did not enroll Chinese participants. Cardiovascular risk factor measurement and CAC scanning procedures for both cohorts have been described previously and are discussed in detail in the Supplement.

Atherosclerotic cardiovascular disease events

An ASCVD event was defined as coronary death, nonfatal myocardial infarction, or fatal/nonfatal stroke. In MESA, the primary means of identifying ASCVD events was participant self-report during telephone follow-up calls conducted at 9 to 12-month intervals.(16) A trained interviewer administered a standardized interview during the telephone call to

determine any new cardiovascular diagnoses, hospital admissions, and deaths. This information was supplemented by cardiovascular events identified by participant notification, during MESA clinic visits, investigations of other possible events, national death index search, and obituaries or public notices.(16) Medical records and death certificates were requested for all cases; and for participants who died of cardiovascular causes outside the hospital, interviewers contacted the next of kin and requested copies of death certificates. Trained personnel abstracted data from medical records with reports of cardiovascular events. Two blinded physician members of the MESA mortality and morbidity review committee independently classified all cardiovascular events and assigned incidence dates. In case of disagreement, the full mortality and morbidity review committee made the final decision.(16)

In DHS, multiple overlapping sources were utilized for identifying ASCVD events. The main source was the data coordinating center health survey, which is an annual formal survey administered by telephone to all participants to determine any new cardiovascular diagnoses, hospital admissions, and deaths.(9) This source was supplemented by the national death index and the Dallas Fort Worth (DFW) hospital council data initiative, which is a database comprising of 70 of 72 DFW area hospitals. The database consists of 100% of the discharge data from these institutions and is updated on a quarterly basis. The data retrieved from this database includes demographic data, hospitalization dates, discharge status (alive or deceased), primary and 10 secondary diagnoses by ICD-9 code, and in-hospital procedures. All potential cardiovascular events were reviewed by members of the clinical endpoints committee, which consists of DHS investigators. Each event was reviewed for adjudication by two blinded cardiologist reviewers. In the case of disagreement, a third review was required, and this review was considered final or could subsequently be referred to the entire clinical endpoints committee.(9) The detailed criteria for defining coronary death, nonfatal myocardial infarction, or fatal/nonfatal stroke events utilized during ASCVD event adjudication in MESA and DHS cohorts are provided in the Supplement.

Statistical analysis

Baseline characteristics of participants in the overall cohort, and among sex and race groups were described across three CAC score categories: 0, 1 to 99, and ≥100 Agatston Units (AU).(3) Categorical variables were presented as counts (proportions), continuous variables were presented as means (standard deviation) or medians [25^{th}-75^{th} percentile] depending on distribution. Categorical variables were compared using the Chi-square test and continuous variables were compared for a significant trend across CAC categories using the Kruskal Wallis test.

The unadjusted 10-year cumulative incidence of ASCVD and its sub-components, CHD and stroke events, were computed. Only the first ASCVD event for each participant was analyzed, and the 10-year CHD-to-stroke incidence ratio was additionally calculated. A similar analysis for participants stratified by CAC score categories was performed. The 10-year CHD-to-stroke incidence ratio was also compared across CAC score categories within the same sex and racial group participants. Furthermore, the CHD-to-stroke incidence ratio across CAC score categories and predicted 10-year ASCVD risk categories (<7.5%, 7.5–

20%, and ≥20%) in the overall cohort was also calculated. The risk prediction model used to estimate 10-year ASCVD risk is described later.

The independent associations of 'high' CAC burden (score ≥100 versus 0), 'moderate' CAC burden (score 1 to 99 versus 0), and CAC 'presence' (score >0 versus 0) with time-to-first cardiovascular event (ASCVD, CHD, or stroke) were assessed using Cox proportional hazards regression models. We stratified baseline hazards by study site, and participants from each site (6 in MESA and 1 in DHS) were given their own baseline hazard function in regression models. Cox models were adjusted for PCE risk factors (age, sex, race, diabetes, smoking, systolic blood pressure, antihypertensive use, total cholesterol, and HDL-C level), FHx, and statin use at baseline. This analysis was first performed in the overall cohort and the multiplicative interactions of CAC score with sex and race were tested. Cox models were further stratified into sex and race groups. Lastly, Cox models were stratified by cohort and were adjusted for educational attainment among MESA participants (education data not available in DHS).

We conducted two sensitivity analyses. First, the association of CAC with time-to-first ASCVD, CHD, or stroke event was determined using Fine and Gray competing risk regression models. Second, Cox regression analyses were performed in a subgroup of participants that met the 2018 Cholesterol Guideline criteria for CAC scanning. We sub-selected participants with predicted 10-year ASCVD risk between 7.5% and 20%, and no statin use at baseline for this analysis.

Finally, the impact of CAC on improving ASCVD, CHD, and stroke risk discrimination and reclassification in the overall cohort, sex and race groups was assessed by computing the change in model calibration (C)-statistic and the net reclassification index (NRI), respectively. A risk prediction model comprising of risk factors used during multivariable adjustment in Cox models was constructed, and change in C-statistic and NRI after CAC score categories were added to the model were studied. We used the 10-year predicted risk cut-off of 7.5% to create low- and high-risk categories for NRI analyses. Also, this risk prediction modeling approach was used for creating the three 10-year ASCVD risk categories (<7.5%, 7.5–20%, and ≥20%) used in the CHD-to-stroke incidence ratio analysis described previously. All statistical analyses were performed using SAS 9.4 (SAS Inc., Cary, North Carolina) and a two-sided p-value less than 0.05 was considered statistically significant.

RESULTS

Baseline characteristics

The study sample consisted of 7,042 participants (4,838 from MESA and 2,204 from DHS) and the mean age was 56.8 (12.7) years, 54.3% were women, 40.2% were White, 36.4% were Black, and 23.4% were Hispanic. No subclinical atherosclerosis was observed in 48.9% (N=3,443), while 31.7% (N=2,232) and 19.4% (N=1,367) had moderate (1 to 99 AU) and high (≥100 AU) CAC burden, respectively (Table 1). Traditional cardiovascular risk factor burden, apart from smoking history, increased across CAC categories and a high CAC burden was observed less frequently in DHS as compared with MESA participants (Table 1).

The prevalence of antihypertensive medication use, FHx, and absent CAC was higher, while that of smoking and statin use was lower among women as compared with men (Online Table 1A). White participants were older, more frequently men, had higher CAC scores, higher prevalence of FHx, statin use, and lower prevalence of smoking and diabetes as compared with the other two race groups (Online Table 1B). Women and Black participants in the overall cohort were more frequently DHS participants.

Atherosclerotic cardiovascular disease incidence

Over a median follow-up of 12.3 [10.9–13.3] years, there were 574 adjudicated ASCVD events (130 in no CAC, 182 in moderate CAC, and 262 in high CAC category) in the study cohort. These comprised of 333 CHD (57 in no CAC [28 fatal], 97 in moderate CAC [46 fatal], and 179 in high CAC [100 fatal] category) and 241 stroke events (73 in no CAC [22 fatal], 85 in moderate CAC [34 fatal], and 83 in high CAC [40 fatal] category). The 10-year cumulative incidence of ASCVD, CHD, and stroke events along with CHD-to-stroke incidence ratio in the overall cohort, sex, and race groups is described in Figure 1 and Online Table 2. Overall, the 10-year CHD incidence was significantly higher than the stroke incidence, which was driven by a high CHD-to-stroke incidence ratio among men and White participants (Figure 1). Women on the other hand had a nominally higher incidence of stroke as compared with CHD and the ratio estimate was <1 (Figure 1).

Atherosclerotic cardiovascular disease incidence across CAC score categories

The 10-year cumulative incidence of ASCVD, CHD, and stroke events in the overall cohort, sex, and race groups across CAC score categories is described in Figure 2 and Online Table 2. The cumulative ASCVD incidence increased across CAC categories of none, moderate, and high, such that the estimates were <5%, 5–9%, and >13%, respectively, in all participant groups (Online Table 2). While the CHD and stroke incidence also increased across CAC score categories (Figure 2), there was a relatively greater increase in CHD incidence which is captured by the increasing CHD-to-stroke incidence ratio across CAC score categories (Figure 3) for the overall cohort as well as sex/race groups (p-trend for all groups <0.001). This observation remained consistent after the overall cohort was divided into predicted 10-year ASCVD risk groups (Online Table 3). Notably, in the moderate CAC burden category the ratio was significantly higher in men (1.73, 95% CI 1.19–2.48) as compared with women (0.55, 95% CI 0.31–0.84) (p<0.001). In the high CAC burden category, the CHD incidence was significantly higher than stroke in all groups except women where a nominal trend was observed (Figure 3).

Independent association of CAC with ASCVD events

Compared with no CAC, a high CAC burden was independently associated with a 2.3- to 3.4-fold increased risk of ASCVD, and a 3.3- to 5.6-fold increased risk of CHD events in the overall cohort and sex/race groups in Cox regression models (Figure 4). This relationship was similar in MESA and DHS separately (Online Table 4), and was only slightly attenuated after adjustment for educational attainment among MESA participants (Online Table 5). High CAC burden was independently associated with stroke risk in the overall cohort and Blacks, but this association was not statistically significant in rest of the demographic groups (Figure 4). Importantly, the strength of this association was consistently lower than what was

observed with CHD events in all groups (Figure 4). There was no high CAC-sex or -race interaction for ASCVD, CHD, or stroke events (all p-interaction>0.10).

Similar to high CAC burden, CAC presence was independently associated with ASCVD, CHD, and stroke risk in the overall cohort; and with ASCVD and CHD risk in all study groups when compared with no CAC (Table 2). A significant multiplicative interaction between CAC presence and sex for ASCVD and CHD risk was observed (p-interaction 0.048 and 0.043, respectively), such that the association of CAC presence with ASCVD and CHD risk was stronger among men as compared with women. There was no CAC presence-sex interaction for stroke events, and no CAC presence-race interaction for the three outcomes was observed.

Finally, compared with no CAC, moderate CAC burden was independently associated with ASCVD and CHD risk in the overall cohort, men, Whites, and Hispanics; while a nominal association was observed in women and Blacks (Table 2). Similar to CAC presence, there was a significant moderate CAC burden-sex interaction for CHD risk (p-interaction 0.022) and a nominal interaction for ASCVD risk (p=0.065), in that the association of moderate CAC burden with CHD and ASCVD was stronger among men than in women. Moderate CAC burden was independently associated with stroke in the overall cohort and a nominal association was observed in sex/race groups (Table 2). In this CAC category, there was no CAC-sex interaction for stroke and no race-based interactions were observed for the three outcomes.

During Fine and Gray competing risk regression analyses, the association of CAC presence, moderate burden, and high burden with cardiovascular events was qualitatively similar to Cox regression analyses as shown in Online Table 6. Among participants that met the 2018 cholesterol guideline criteria for CAC scanning (N=1,252), we observed that high CAC burden was independently associated with an increased risk of ASCVD events among all participant groups apart from Hispanics (Online Table 7). Additionally, the association of high CAC burden with CHD events was stronger than that for strokes.

Improvement in risk discrimination and reclassification with CAC

Addition of CAC score categories to a traditional risk factor model comprising of PCE risk factors, FHx, and statin use at baseline resulted in a significant improvement in ASCVD and CHD risk discrimination, but not stroke risk, as measured using the change in model c-statistic (Table 3). This observation was consistent across all study groups apart from CHD in Hispanics where a nominal improvement was seen likely due to small number of events. We also observed significant improvement in NRI for CHD events in the overall cohort, men, women, Whites, and Blacks (Online Tables 8A-F), but a similar improvement for stroke events was not observed in any study group.

DISCUSSION

We report three important findings in this study of the impact of sex and race on the predictive value of guideline recommended CAC score categories for CHD and stroke. First, CAC has a stronger association with CHD risk as compared with stroke risk. Second, the

guideline-recommended CAC score threshold of ≥100 AU is independently associated with a significant increase in ASCVD risk and its predictive value is comparable across sex and race groups. Third, the hazard associated with moderate CAC burden (CAC 1–99) for future ASCVD events appears to be higher among men as compared with women, primarily driven by lower CHD events among women.

CAC score and ASCVD events

In the overall study population, the 10-year cumulative ASCVD incidence was 6.7%. After stratifying the cohort into guideline recommended CAC score categories, an overwhelming majority of ASCVD events occurred in the high CAC burden group. The observed 10-year ASCVD incidence increased from 2.7% to 7.0% to 16.5% across CAC score categories, supporting the 2018 Cholesterol Guideline's recommendation of considering CAC score thresholds of 0 AU, 1 to 99 AU, and ≥100 AU to guide statin use in primary prevention settings.(3)

CAC score for predicting Coronary risk versus Stroke risk

Several studies have assessed the predictive performance of CAC for CHD and strokes separately among asymptomatic individuals.(6-11) Our findings are consistent with prior work in terms of CAC score's strength of association with incident CHD and strokes, but we are the first to systematically study the differential impact of the guideline-recommended CAC score categories on CHD and stroke risk in a combined sample of two large, multi-ethnic, population-based cohorts. This is important in the context of current risk assessment and cholesterol management guidelines where the focus has shifted to ASCVD events.

There are several findings in our study highlighting the superior predictive ability of CAC for CHD as compared with strokes. The incidence of CHD events in the study cohort was 35% higher than strokes, and there was a significant increase in the CHD-to-stroke incidence ratio across CAC categories with a 106% relatively higher CHD incidence observed in the CAC ≥100 AU group. In multivariable adjusted analyses, the strength of the independent association of CAC presence, moderate or high CAC burden with CHD risk was higher than stroke risk. Furthermore, addition of CAC to a traditional risk factor model resulted in a significant improvement in risk discrimination and reclassification for CHD but not for stroke events.

However, despite the greater CHD predictive ability it is important to note that CAC presence and burden was an independent predictor of stroke risk in the overall cohort and high CAC burden independently predicted stroke risk in Blacks. The lack of a significant association in the remaining groups is possibly reflective of low statistical power in these subgroups.

Impact of sex and race on the predictive value of CAC

We explored the impact of sex and race on the predictive value of CAC because of variations in the relative contribution of CHD and stroke events to ASCVD incidence across sex and race/ethnicity.(13) Stroke incidence is known to be higher among women and Blacks. Given the relatively stronger association of CAC with CHD than stroke, it follows that the

predictive value of CAC for ASCVD risk would be higher in demographic groups where the relative contribution of CHD to ASCVD incidence is higher than stroke.

In the current analysis men had a similar mean age but a higher CAC score than in women, and White participants had a higher CAC score as compared with the other two race groups, similar to previous reports.(17) However, the unadjusted ASCVD incidence was higher among men and similar across race groups. The difference between men and women was primarily driven by a relatively higher CHD incidence in men such that the CHD-to-stroke incidence ratio estimate among men was 2.0 and among women was 0.8. Among race groups on the other hand, CHD incidence was significantly higher than stroke incidence among White participants with a nominal trend observed among Hispanics. The unadjusted CHD-to-stroke incidence ratio estimate was close to even (~1) for all five sex/race groups in the CAC zero category but changed differentially for men and women with increasing CAC score. While the ratio increased for both men and women, the ratio estimate among men was higher than women in the moderate and high CAC burden categories.

CAC presence and high burden were independently associated with ASCVD and CHD risk among both men and women in multivariable-adjusted Cox models. Moderate CAC burden had a significant association with ASCVD risk in men and a nominal association ($p=0.08$) was observed in women. Similarly, a significant sex-based interaction for CAC presence and moderate burden, but not high burden, for predicting ASCVD and CHD risk was observed. This is likely related to the relatively lower CHD incidence among women in the moderate CAC burden category.

Lastly, there were no interactions between CAC presence or burden and race for ASCVD, CHD, or stroke risk such that the predictive value of CAC score was similar for White, Black and Hispanic participants of the study cohort. These findings differ from a recent MESA study where CAC was analyzed as a continuous variable and no sex- or race-based interaction with CAC was observed for ASCVD events.(18) Indeed, we did not observe any significant interactions when we assessed continuous CAC scores in our combined cohort (data not shown). Nonetheless, our findings with CAC categories are perhaps more impactful as they align better with recommended use of CAC testing per recent guidelines. Furthermore, recent studies from the CAC consortium, wherein participants underwent *clinically indicated* CAC scanning, have shown that women as well as Blacks and Hispanics with elevated CAC have a higher risk of cardiovascular mortality as compared with men and Whites, respectively.(19, 20) Our findings among the moderate CAC group are different from the CAC consortium because of possible referral biases due to differences in the two study populations.

Study findings in context of current guidelines

Our findings are particularly relevant in light of the 2018 cholesterol guideline recommending consideration of CAC scanning as a decision-making aid when the decision about initiating statin therapy for primary ASCVD prevention is uncertain. Our findings support the paradigm that CAC=0 is associated with low ASCVD risk, while scores ≥100 AU are associated with a dramatically increased risk across sex and race groups.

Furthermore, we also found that CAC ≥100 AU is independently predictive of stroke risk among Blacks.

Strengths

This is the first study analyzing the impact of sex and race on the predictive value of guideline-recommended CAC score thresholds for CHD versus stroke events in middle-aged, asymptomatic American individuals. Our study cohort was large, multi-ethnic and participants had long-term follow-up for adjudicated ASCVD events.

Limitations

The results of our study should be interpreted in the context of its limitations. First, we report findings from observational, population-based cohorts of a pooled sample of adults aged 30 to 84 years (mean age 57 years) that were free of ASCVD at baseline; as such our results may not be generalizable to populations outside the United States and among patients undergoing clinically indicated CAC scanning. Second, we have not considered specific stroke types (ischemic, hemorrhagic, or embolic) and 'soft' ASCVD events like transient ischemic attacks and coronary revascularization via percutaneous intervention or coronary artery bypass grafting in our analysis. Third, MESA participants received information regarding their CAC score after scanning which could have altered participant health behavior and we have not accounted for incident use of cardioprotective medications like statins or more aggressive blood pressure management which might have biased our results to null.

CONCLUSIONS

In this large study of two contemporary, multi-ethnic, population-based cohorts we have shown that the predictive value of CAC categories for CHD is better than that for stroke. The CAC score threshold of ≥100 AU is highly predictive of ASCVD risk across demographic groups. CAC presence with a score <100 AU has a stronger association with ASCVD risk among men as compared with women, which is likely related to the relatively higher incidence of CHD events among men, for which CAC performs better. These nuances are important for guiding the patient-clinician shared decision-making process for deciding when to obtain a CAC scan and how to utilize CAC results to mitigate the risk of preventable CHD and stroke events.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS

ASCVD	Atherosclerotic Cardiovascular Disease
CAC	Coronary artery calcium
CI	Confidence Interval
DHS	Dallas Heart Study
EBCT	Electron Beam Computed Tomography
FHx	Family History of Myocardial Infarction
HR	Hazard Ratio
MDCT	Multi-Detector Computed Tomography
MESA	Multi-Ethnic Study of Atherosclerosis
NRI	net reclassification index
PCE	Pooled Cohort Equation
sHR	sub-distribution Hazard Ratio

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CLINICAL PERSPECTIVE

Coronary artery calcium (CAC) is a measure of subclinical coronary atherosclerosis and the 2018 American cholesterol management guidelines recommend that selective use of a CAC score can be helpful for guiding shared decision-making for primary atherosclerotic cardiovascular disease (ASCVD) prevention therapy. ASCVD is a composite of coronary and stroke events, and the incidence of ASCVD and its subtypes varies by sex and race. In this study, we have explored the predictive value of guideline-recommended CAC score categories (0, 1 to 99, and ≥100 Agatston Units) for incident ASCVD, CHD, and stroke events along with the impact of sex and race on this predictive value in a pooled sample of White, Black, and Hispanic participants from Multi-Ethnic Study of Atherosclerosis (MESA) and Dallas Heart Study (DHS). Across CAC categories, we observed an increase in 10-year cumulative ASCVD incidence and a greater increase in CHD incidence as compared with stroke, as captured by the CHD-to-stroke incidence ratio. Furthermore, high CAC burden (score ≥100) was independently associated ASCVD events and its subtypes, but the strength of this association was higher for CHD than for stroke. Lastly, CAC score categories resulted in significant improvement in CHD risk discrimination and reclassification, while such improvements were not seen for stroke risk. These observations were consistent across sex and race groups. Overall, our findings suggest that guideline-recommended CAC score categories are a better predictor of CHD than stroke risk and this predictive value is similar across sex and race groups.

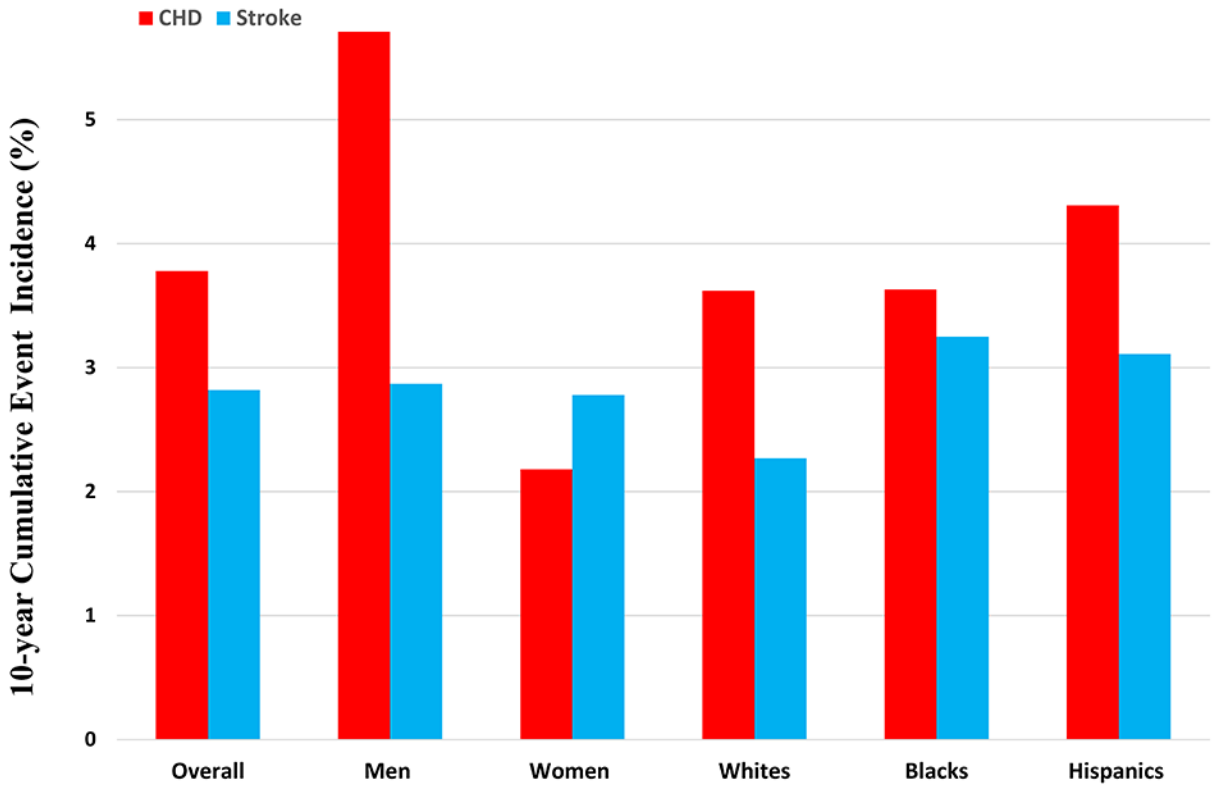

Figure 1. 10-year cumulative incidence of atherosclerotic cardiovascular disease, coronary heart disease, and stroke events

CHD-to-stroke incidence ratio (95% confidence interval) in the overall study cohort was 1.35 (1.15–1.57). This was primarily driven by men (ratio 2.01, 95% CI 1.63–2.49) and Whites (ratio 1.63, 95% CI 1.21–2.15). The ratios for Women, Blacks, and Hispanics were 0.79 (95% CI 0.59–1.01), 1.14 (95% CI 0.87–1.47), and 1.43 (95% CI 0.99–1.95), respectively.

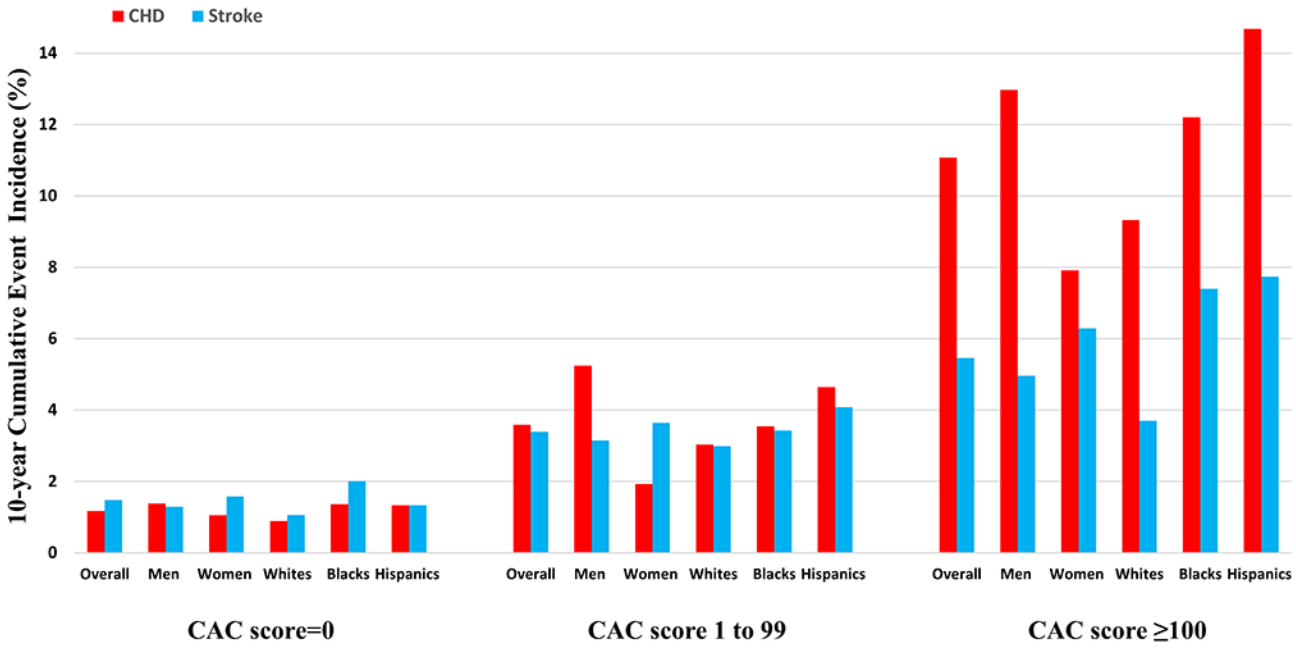

Figure 2. 10-year cumulative incidence of atherosclerotic cardiovascular disease, coronary heart disease, and stroke events across coronary artery calcium score categories

The 10-year cumulative incidence of ASCVD, CHD, and stroke events increased across CAC score categories in the overall cohort and all sex/race groups. The increase in CHD incidence across CAC categories was relatively higher compared with stroke incidence for all participant groups.

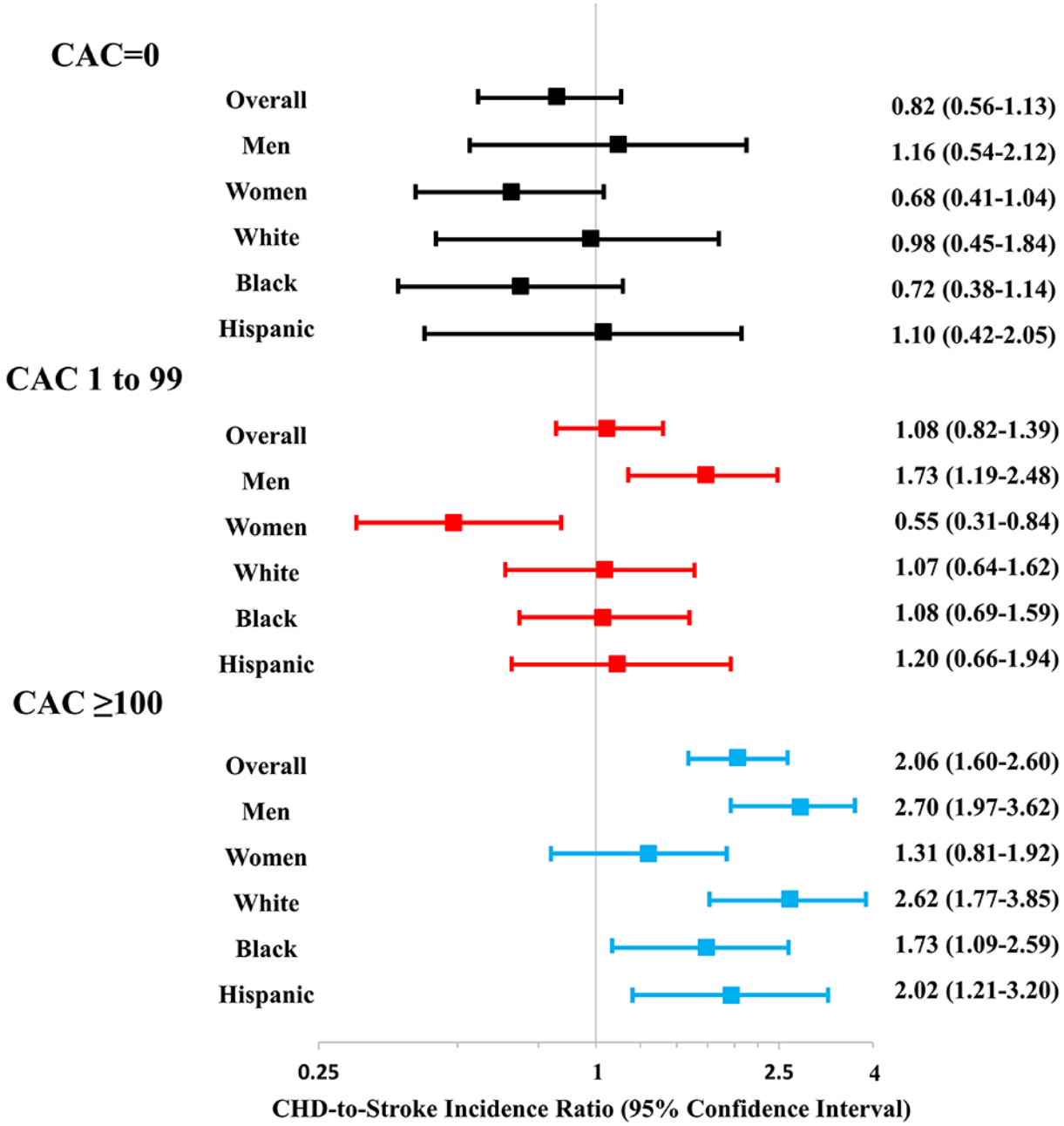

Figure 3. CHD-to-stroke cumulative incidence ratio across CAC score categories

The CHD-to-stroke cumulative incidence ratio increased across three CAC score categories for the overall cohort and the all sex/race groups (all p-trend <0.001)

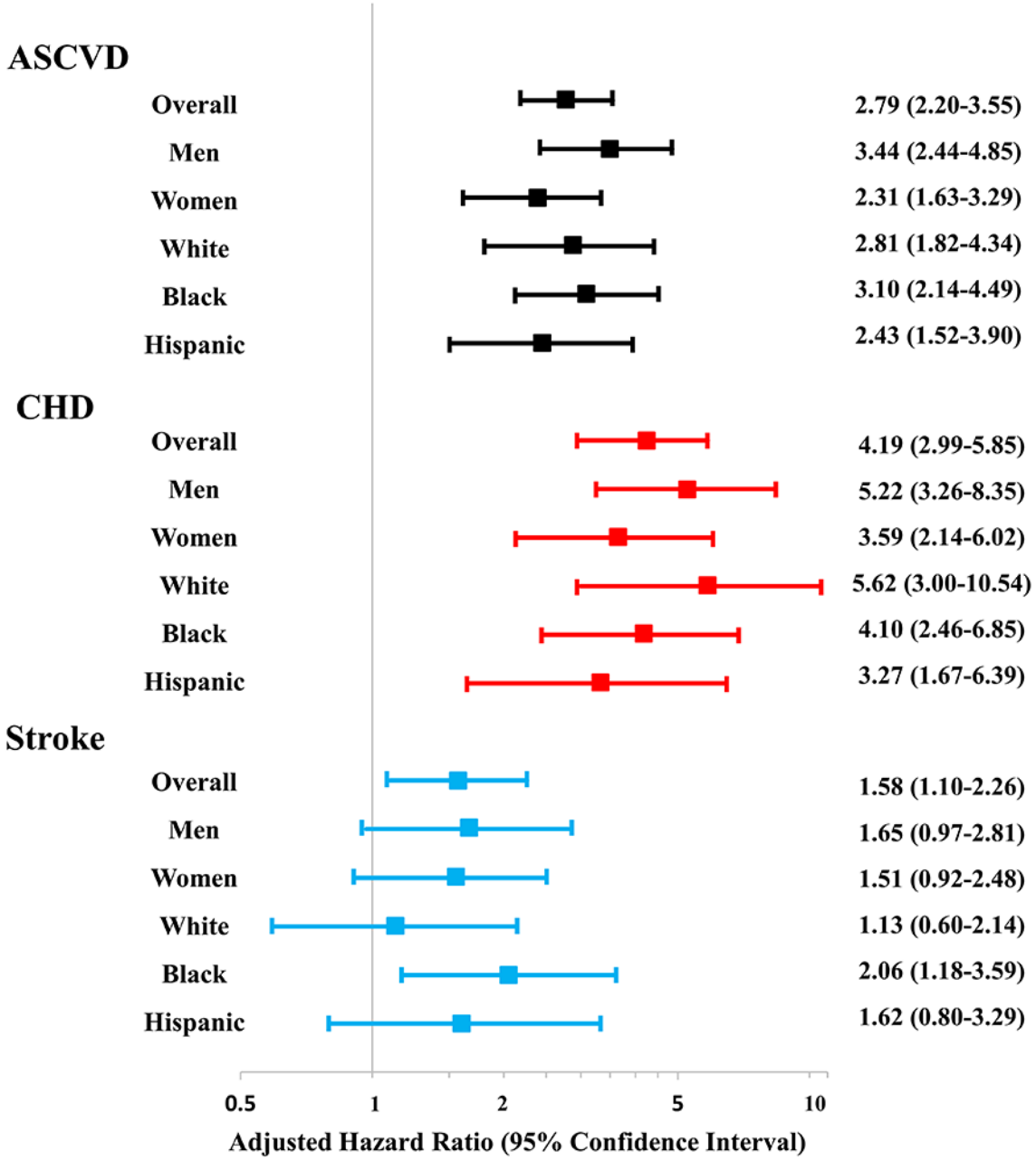

Figure 4. Association of high coronary artery calcium burden (score ≥100 AU) with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events

Results presented as adjusted hazard ratio (95% confidence interval) and referent group is participants with a zero CAC score. High CAC burden is independently associated with ASCVD, CHD, and stroke risk in the overall cohort; with ASCVD and CHD risk in all groups; and with stroke risk among Blacks. No significant sex- or race-based interactions for ASCVD, CHD, and stroke risk exist. Cox proportional hazards regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total

cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, and statin use.

Table 1

Baseline characteristics of study participants stratified by coronary artery calcium score category

Participant Characteristics	CAC score zero (n=3,443)	CAC score 1 to 99 (n=2,232)	CAC score ≥100 (n=1,367)	p-value
Age (years)	53.1 (11.5)	56.2 (12.7)	66.9 (6.7)	<0.001
Women	2204 (64.0)	1110 (49.7)	512 (37.5)	<0.001
Blacks	1284 (37.3)	906 (40.6)	376 (27.5)	<0.001
Hispanics	898 (26.1)	491 (22.0)	259 (18.9)	<0.001
Smoking	619 (18.0)	420 (18.8)	230 (16.8)	0.319
Diabetes	248 (7.2)	289 (12.9)	229 (16.8)	<0.001
Systolic blood pressure (mm Hg)	122.4 (18.9)	129.1 (18.8)	133.7 (21.8)	<0.001
Diastolic blood pressure (mm Hg)	72.8 (10.1)	75.7 (10.4)	73.9 (10.7)	<0.001
Antihypertensive use	861 (25.0)	753 (33.7)	682 (49.9)	<0.001
Total cholesterol (mg/dL)	189.0 (36.2)	191.0 (37.6)	194.0 (37.6)	0.002
High density lipoprotein-cholesterol (mg/dL)	52.5 (15.1)	49.2 (13.8)	49.8 (15.1)	<0.001
Low density lipoprotein-cholesterol (mg/dL)	113.0 (32.9)	116.1 (33.4)	118.0 (33.6)	<0.001
Family history of myocardial infarction	1392 (40.4)	1024 (45.9)	817 (59.8)	<0.001
Statin use	277 (8.1)	307 (13.8)	296 (21.7)	<0.001
CAC score (Agatston units)	0.0 [0.0–0.0]	10.5 [2.3–36.5]	329.5 [179.1–682.7]	<0.001
Dallas Heart Study cohort	1039 (30.2)	988 (44.3)	177 (12.9)	<0.001
ASCVD event	130 (3.8)	182 (8.2)	262 (19.2)	<0.001
CHD event	57 (1.7)	97 (4.4)	179 (13.1)	<0.001
Stroke event	73 (2.1)	85 (3.8)	83 (6.1)	<0.001

Values shown are mean (standard deviation) or median [25^{th}-75^{th} percentile] and number (proportion) depending on variable type. Abbreviations – CAC = coronary artery calcium, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease.

Table 2

Association of coronary artery calcium score with incident atherosclerotic cardiovascular disease, coronary heart disease, and stroke events

		ASCVD events		CHD events		Stroke events	
	Group	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**	**HR (95%CI)**	**p-value**
CAC score >0	**Overall**	2.06 (1.67–2.55)	**<0.001**	2.74 (2.02–3.72)	**<0.001**	1.48 (1.09–2.01)	**0.012**
	Men	2.59 (1.89–3.56) *	**<0.001**	3.66 (2.35–5.69) †	**<0.001**	1.51 (0.95–2.42)	0.084
	Women	1.68 (1.25–2.27) *	**<0.001**	1.99 (1.26–3.12) †	**0.003**	1.47 (0.98–2.20)	0.061
	Whites	2.28 (1.53–3.39)	**<0.001**	3.55 (1.98–6.37)	**<0.001**	1.38 (0.79–2.42)	0.259
	Blacks	1.84 (1.33–2.55)	**<0.001**	2.32 (1.47–3.68)	**<0.001**	1.39 (0.87–2.21)	0.171
	Hispanics	2.11 (1.40–3.19)	**<0.001**	2.56 (1.39–4.69)	**0.002**	1.69 (0.95–3.03)	0.076
CAC score 1 to 99	**Overall**	1.64 (1.30–2.08)	**<0.001**	1.92 (1.37–2.70)	**<0.001**	1.42 (1.02–1.98)	**0.039**
	Men	2.05 (1.45–2.89) ‡	**<0.001**	2.69 (1.97–4.32) §	**<0.001**	1.42 (0.85–2.37)	0.183
	Women	1.35 (0.96–1.90) ‡	0.080	1.24 (0.72–2.12) §	0.436	1.44 (0.93–2.24)	0.100
	Whites	1.90 (1.23–2.93)	**0.004**	2.30 (1.20–2.12)	**0.012**	1.62 (0.89–2.93)	0.112
	Blacks	1.30 (0.90–1.87)	0.161	1.54 (0.92–2.58)	0.101	1.09 (0.64–1.84)	0.753
	Hispanics	1.92 (1.23–3.01)	**0.004**	2.14 (1.11–4.13)	**0.023**	1.74 (0.93–3.24)	0.084

Referent group is participants with a zero CAC score. Cox proportional hazards regression models adjusted for age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, and statin use. Abbreviations: HR = hazard ratio, CI = confidence interval, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease. Bold values indicate statistically significant association (two-sided p-value <0.05).

* p-interaction=0.048

† p-interaction=0.043

‡ p-interaction=0.065

§ p-interaction=0.022

Table 3

Change in risk discrimination capability (C-statistic) of a traditional risk factor model* for predicting incident cardiovascular events after addition of coronary artery calcium score categories

	ASCVD events		CHD events		Stroke events	
Group	**Baseline**	**Change (95%CI)**	**Baseline**	**Change (95%CI)**	**Baseline**	**Change (95%CI)**
Overall	0.749	**0.021 (0.011,0.031)**	0.754	**0.035 (0.020,0.051)**	0.737	0.003 (−0.004,0.012)
Men	0.730	**0.026 (0.010,0.043)**	0.717	**0.047 (0.023,0.071)**	0.735	-0.002 (−0.015,0.011)
Women	0.757	**0.015 (0.003,0.026)**	0.749	**0.032 (0.007,0.057)**	0.761	0.003 (−0.006,0.012)
Whites	0.757	**0.015 (0.001,0.028)**	0.754	**0.037 (0.013,0.062)**	0.754	0.002 (−0.009,0.014)
Blacks	0.734	**0.031 (0.012,0.051)**	0.740	**0.040 (0.013,0.068)**	0.716	0.017 (−0.007,0.040)
Hispanics	0.776	**0.017 (0.002,0.033)**	0.790	0.022 (−0.002,0.046)	0.775	0.003 (−0.009,0.015)

*Traditional risk factor model contains age, sex, race, smoking, diabetes, systolic blood pressure, antihypertensive use, total cholesterol, high density lipoprotein-cholesterol level, family history of myocardial infarction, and statin use. Abbreviations: CI = confidence interval, ASCVD = atherosclerotic cardiovascular disease, CHD = coronary heart disease. Bold values indicate statistically significant association (two-sided p-value <0.05).