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Coronary Artery Calcium and Incident Cerebrovascular Events in an Asymptomatic Cohort

The MESA Study

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ABSTRACT

OBJECTIVES This study assessed the predictive value of coronary artery calcium (CAC) score for cerebrovascular events (CVE) in an asymptomatic multiethnic cohort.

BACKGROUND The CAC score, a measure of atherosclerotic burden, has been shown to improve prediction of coronary heart disease events. However, the predictive value of CAC for CVE is unclear.

METHODS CAC was measured at baseline examination of participants (N = 6,779) of MESA (Multi-Ethnic Study of Atherosclerosis) and then followed for an average of 9.5 ± 2.4 years for the diagnosis of incident CVE, defined as all strokes or transient ischemic attacks.

RESULTS During the follow-up, 234 (3.5%) adjudicated CVE occurred. In Kaplan-Meier analysis, the presence of CAC was associated with a lower CVE event-free survival versus the absence of CAC (log-rank chi-square: 59.8, $p < 0.0001$). Log-transformed CAC was associated with increased risk for CVE after adjusting for age, sex, race/ethnicity, body mass index, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, cigarette smoking status, blood pressure medication use, statin use, and interim atrial fibrillation (hazard ratio [HR]: 1.13 [95% confidence interval (CI): 1.07 to 1.20], $p < 0.0001$). The American College of Cardiology/American Heart Association–recommended CAC cutoff was also an independent predictor of CVE and strokes (HR: 1.70 [95% CI: 1.24 to 2.35], $p = 0.001$, and HR: 1.59 [95% CI: 1.11 to 2.27], $p = 0.01$, respectively). CAC was an independent predictor of CVE when analysis was stratified by sex or race/ethnicity and improved discrimination for CVE when added to the full model (c-statistic: 0.744 vs. 0.755). CAC also improved the discriminative ability of the Framingham stroke risk score for CVE.

CONCLUSIONS CAC is an independent predictor of CVE and improves the discrimination afforded by current stroke risk factors or the Framingham stroke risk score for incident CVE in an initially asymptomatic multiethnic adult cohort. (J Am Coll Cardiol Img 2014;7:1108–15) © 2014 by the American College of Cardiology Foundation.

Coronary artery calcium (CAC) is an independent predictor of cardiovascular disease (CVD) events (1-3), a composite that often include strokes and has also been shown to improve discrimination for CVD events in the general population beyond current risk prediction tools such as the Framingham risk score and Reynolds score (4-6). However, in almost all of these studies (1-3), the association between CAC and stroke failed to achieve statistical significance due to relatively small sample sizes. Some authors have questioned the use of CAC to improve stroke risk

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prediction in the general population based on these data (7).

The recent American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for risk prediction adopted a new composite: atherosclerotic cardiovascular disease (ASCVD), which includes coronary death, nonfatal myocardial infarction, and fatal and nonfatal stroke (8). The new AHA/ACC ASCVD risk score does not consider current subclinical atherosclerosis measures. Given persuasive data on the improvement of discrimination for CVD by subclinical atherosclerotic measures (4,5) and the

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similarity of the constituents of the pooled ASCVD risk prediction tool with the Framingham risk score (8,9), there are ongoing efforts to improve the risk prediction afforded by the new pooled ASCVD risk tool with these subclinical atherosclerotic measures in the general population. However, adding subclinical atherosclerotic measures to the new pooled ASCVD risk tool would only make sense if these measures were associated with strokes. A recent publication from the HNR (Heinz Nixdorf Recall) study with a larger number of strokes than that of prior published data (1–3) showed an independent association between CAC and strokes in low- to intermediate-risk Caucasian subjects (10). However, the racial homogeneity of the HNR cohort limits its external validity. Thus, the association between CAC and strokes in the general population remains unclear.

In this report, we examined the relationship of CAC measured during the baseline examination to adjudicated cerebrovascular events (CVE) in participants of the MESA (Multi-Ethnic Study of Atherosclerosis) over a 10-year follow-up.

METHODS

STUDY POPULATION AND DATA COLLECTION. A detailed description of the study design for MESA has been published (11). In brief, MESA is a cohort study that began in July 2000 to investigate the prevalence, correlates, and progression of subclinical CVD. At baseline, the cohort included 6,814 women and men age 45 to 84 years recruited from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles County, California; northern Manhattan, New York; and St. Paul, Minnesota). MESA participants were 38% white, 28% black, 22% Hispanic, and 12% Chinese. Individuals with a history of physician-diagnosed myocardial infarction, angina, heart failure, stroke, or transient ischemic attack (TIA) or who had undergone an invasive procedure for CVD (coronary artery bypass graft, angioplasty, valve replacement, pacemaker placement, or other vascular surgeries) were excluded.

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcium
CVE = cerebrovascular events
TIA = transient ischemic attack

Demographics, medical history, and anthropometric and laboratory data for these analyses were obtained at the first MESA examination (July 2000 to August 2002). Current smoking was defined as having smoked a cigarette in the past 30 days. Diabetes mellitus was defined as fasting glucose ≥126 mg/100 dl or use of hypoglycemic medications. Use of antihypertensive and other medications was based on the review of prescribed medication containers. Resting blood pressure was measured 3 times in a seated position, and the average of the second and third readings was used. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, diastolic blood pressure ≥90 mm Hg, or use of medication prescribed for hypertension. Body mass index was calculated as weight (kg)/height^2 (m^2). Total and high-density lipoprotein cholesterol were measured from blood samples obtained after a 12-h fast. Low-density lipoprotein cholesterol was estimated by the Friedewald equation (12). The MESA study was approved by the institutional review boards of each study site, and written informed consent was obtained from all participants.

MEASUREMENT OF CAC SCORE. Details of the MESA computed tomography (CT) scanning and interpretation methods have been reported by Carr et al. (13). Scanning centers assessed CAC by noncontrast cardiac CT with either an electron-beam CT scanner (Chicago, Illinois; Los Angeles, California; and New York, New York field centers) or a multidetector CT system (Baltimore, Maryland; Forsyth County, North Carolina; and St. Paul, Minnesota field centers). Certified technologists scanned all participants twice over phantoms of known physical calcium concentration. A radiologist or cardiologist read all CT scans at a central reading center (Los Angeles Biomedical Research Institute at Harbor-University of California, Los Angeles, Torrance, California). We used the mean Agatston score for the 2 scans in all analyses (14). Intraobserver and interobserver agreements were excellent ($\kappa = 0.93$ and 0.90, respectively).

ASCERTAINMENT OF CVE. Strokes, TIAs, and other cardiovascular events were adjudicated by a MESA committee that included cardiologists, physician epidemiologists, and neurologists. A detailed description of the adjudication process has been published (11). For the purposes of this study, we defined CVE as fatal or nonfatal strokes due to hemorrhage or infarcts or TIA. TIAs and strokes

were also used individually as secondary outcomes for this analysis. Interim incident atrial fibrillation, which occurred during the follow-up period, was adjusted for in the full model as a time-varying covariate. Interim atrial fibrillation in MESA is a combination of adjudicated; International Classification of Diseases, Ninth Revision code; and self-reported cases.

STATISTICAL ANALYSIS. Demographic and other characteristics were compared according to cerebrovascular event. CAC was introduced into models as a binary variable (CAC present/absent), as a continuous variable (ln [CAC + 1]), or as 4 categories (CAC: 0, 0 to 100, >100 to 400, and >400 Agatston units). Kaplan-Meier and Cox proportional hazards analyses were used to evaluate the association between CAC and incident CVE. Among participants with more than 1 type of event adjudicated during the follow-up period, the first event was used in this analysis. Covariates entered in models were chosen on the basis of their association with incident CVE in the present analyses and in published data. The covariates include age, sex, race/ethnicity, body mass index, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, cigarette smoking status, blood pressure medication use, statin use, and interim atrial fibrillation that occurred during the follow-up period. The full multivariable model was then stratified by sex and race/ethnicity. The preceding analysis was repeated with all strokes and TIAs as the outcome.

The improvement of discrimination for incident CVE afforded by the addition of CAC to our full model was evaluated using the receiver-operating curve analysis. The Framingham stroke risk score (FSRS) (15) was calculated for each MESA participant (using baseline data only) using the following variables: age, systolic blood pressure, diabetes mellitus, cigarette smoking, prior CVD, atrial fibrillation, left ventricular hypertrophy (ECG criteria), and blood pressure medications. No MESA participant had prior CVD or atrial fibrillation during the baseline examination. The improvement in discrimination afforded by the addition of CAC to the FSRS (and also using the constituents in the model) was also assessed using receiver-operating curve analysis. A 2-tailed value of $p < 0.05$ was considered significant. All statistical analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina).

TABLE 1 Demographic Characteristics of MESA Participants With and Without Cerebrovascular Events During the Follow-Up Period

	No Cerebrovascular Event (n = 6,545)	Cerebrovascular Event (n = 234)
Age, yrs	61.9 ± 10.2	67.9 ± 9.6
Male	3,089 (47.1)	111 (47.6)
Race/ethnicity		
Caucasian	2,526 (38.5)	93 (39.7)
Chinese	791 (12.0)	12 (5.2)
African American	1,823 (27.7)	69 (29.5)
Hispanic	1,435 (21.8)	60 (21.8)
Body mass index, kg/m^2	28.3 ± 5.5	28.7 ± 5.1
Cholesterol, mg/dl		
Total	194.1 ± 35.8	194.1 ± 33.8
LDL	117.2 ± 31.5	118.4 ± 30.4
HDL	51.1 ± 14.9	48.0 ± 12.5
Triglycerides	131.2 ± 89.1	140.8 ± 75.5
Cigarette smoking		
Never	3,302 (50.4)	114 (48.9)
Former	2,406 (36.7)	78 (33.5)
Current	846 (12.9)	41 (17.6)
Diabetes mellitus	804 (12.3)	52 (22.2)
Blood pressure, mm Hg		
Systolic	126.1 ± 21.2	140.0 ± 22.2
Diastolic	71.8 ± 10.2	74.9 ± 11.5
Antihypertensive use	2,144 (32.6)	121 (51.7)
Statin use	957 (14.8)	31 (13.3)
CAC score, Agatston units	80.8 (0.0–140.7)	289.8 (0.0–313.7)
Developed atrial fibrillation	368 (5.6)	40 (17.1)

Values are mean ± SD, n (%), or median (interquartile range). Mean follow-up was 9.5 ± 2.4 years.

CAC = coronary artery calcium score; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MESA = Multi-Ethnic Study of Atherosclerosis.

RESULTS

After a mean of 9.5 ± 2.4 years, 234 (3.5%) adjudicated CVE (180 strokes and 67 TIAs) were identified. Ischemic CVE (cerebral infarcts and TIAs) were observed in 206 (3.4%) participants, of whom 152 (2.2%) had cerebral infarcts. Participants who developed a cerebrovascular event were older, had a worse cardiovascular risk profile, and developed atrial fibrillation more often (17.1% vs. 5.6%) during the follow-up period than those who did not have a cerebrovascular event (Table 1). As shown in Table 2, similar proportions of the participants within each CAC category had hemorrhagic strokes during the follow-up period. However, an increased proportion of participants had cerebral infarcts, TIAs, and atrial fibrillation with higher CAC category.

CAC AND CEREBROVASCULAR EVENT PREDICTION. In Kaplan-Meier analyses, participants with CAC present during the baseline examination had a lower cerebrovascular event-free survival rate compared with participants with CAC absent at baseline (log-rank chi-square: 59.84, $p < 0.0001$) (Figure 1). When participants were divided into 4 groups according to baseline CAC (CAC: 0, 0 to 100, >100 to 400, and >400 Agatston units), a significant graded cerebrovascular event-free survival rate was observed

(log-rank chi-square for trend: 95.78, $p < 0.0001$) (Figure 2).

In (CAC + 1) was a predictor for CVE, strokes, and TIAs in both univariate and multivariable models across sex and race/ethnic strata, except Chinese (Table 3).

Table 4 shows univariate and multivariable hazard ratios for cerebrovascular event, strokes, and TIAs according to presence of CAC, stratified by sex and race/ethnicity. The hazard ratio for females and all race/ethnicities did not reach conventional statistical significance, although point estimates and directions were similar to those in Table 2.

Coronary heart disease (CHD) is a known predictor of CVEs; thus, as a sensitivity analysis, we excluded participants with incident CHD during the follow-up examination (n = 449). In (CAC + 1) was a predictor of CVE (n = 205 events) in univariate and full model (hazard ratio [HR]: 1.29 [95% confidence interval (CI): 1.22 to 1.36], $p < 0.0001$, and HR: 1.13 [95% CI: 1.06 to 1.20], $p < 0.001$, respectively), for all strokes (n = 153) (HR: 1.24 [95% CI: 1.16 to 1.31], $p < 0.001$, and HR: 1.10 [95% CI: 1.03 to 1.18], $p = 0.007$, respectively), and TIAs (n = 63) (HR: 1.26 [95% CI: 1.15 to 1.39], $p < 0.001$, and HR: 1.17 [95% CI: 1.05 to 1.31], $p = 0.006$, respectively) in this subcohort. CAC (present/absent) also showed similar associations with incident CVE, all strokes, and TIAs in this subcohort (data not shown). The new ACC/AHA recommended cutoff for improving risk assessment using CAC (≥300 Agatston units or ≥75 percentile for age, sex, and ethnicity) (8) was also an independent predictor of CVE and strokes in this cohort (for strokes HR: 3.02 [95% CI: 2.18 to 4.20], $p < 0.0001$, and HR: 1.59 [95% CI: 1.11 to 2.27], $p = 0.01$, respectively).

There was significant reduction in power when the analysis was stratified by CAC categories: 0, 0 to 100, >100 to 400, and >400 Agatston units. With CAC = 0 as the reference, the univariate and multivariable HRs in the Cox model were for CAC 0 to 100: 1.38 (95% CI: 1.08 to 1.78), $p = 0.01$, and 1.19 (95% CI: 0.92 to 1.55), $p = 0.18$; CAC >100 to 400: 2.27 (95% CI: 1.16 to 4.47), $p = 0.08$, and 2.26 (95% CI: 1.11 to 4.57), $p = 0.02$; and CAC >400: 1.56 (95% CI: 0.97 to 2.52), $p = 0.06$, and 1.38 (95% CI: 0.81 to 2.36), $p = 0.23$, respectively.

In age-stratified analysis (by median age of 62 years), CAC was a predictor of CVE and strokes in those greater than or equal to the median age in both the univariate and multivariable Cox model. For those below the median age (age <62 years), CAC was a predictor of CVE and strokes in only univariate Cox models but not in the multivariable Cox models (data not shown).

TABLE 2 Occurrence of Cerebrovascular Events, Hemorrhagic Strokes, Cerebral Infarcts, and TIAs

CAC Category (Agatston Units)	n	Cerebrovascular Events	Hemorrhagic Strokes	Cerebral Infarcts	TIAs
0	3,399	69 (2.0)	13 (0.4)	40 (1.2)	19 (0.6)
0–100	1,786	67 (3.8)	9 (0.5)	41 (2.3)	20 (1.1)
>100–400	923	52 (5.6)	4 (0.4)	36 (3.9)	15 (1.6)
>400	671	46 (6.9)	2 (0.3)	35 (5.2)	13 (1.9)
Total		234	28	152	67

Values are n (%). Events occurred within each CAC category after a mean of 9.5 ± 2.4 years of follow-up in the MESA cohort.

TIA = transient ischemic attack; other abbreviations as in Table 1.

Figure 3 shows the effect of CAC predicting CVE across baseline Framingham stroke risk (stratified by the median: 5.7%) in this MESA cohort.

CAC AND CEREBROVASCULAR EVENT DISCRIMINATION. For CVE (n = 234), c-statistic for CAC (continuous) alone was 0.642, and it was 0.744 in the full multivariable model without CAC. The addition of CAC improved discrimination of our full multivariable model (Table 3) by 0.011 (c-statistic: 0.744 vs. 0.755).

The c-statistic for the FSRS was 0.664. The addition of CAC improved its discrimination, as reflected by a c-statistic of 0.706 ($p < 0.01$) (Figure 4). The

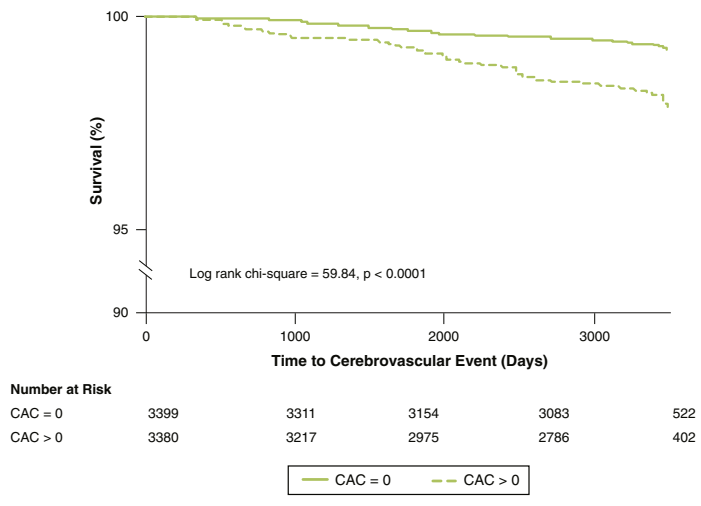

FIGURE 1 Incident CVE in Subjects With and Without CAC

Kaplan-Meier analysis showing the event-free survival of participants with and without coronary artery calcium (CAC) and incident cerebrovascular events (CVE) in the MESA (Multi-Ethnic Study of Atherosclerosis) cohort.

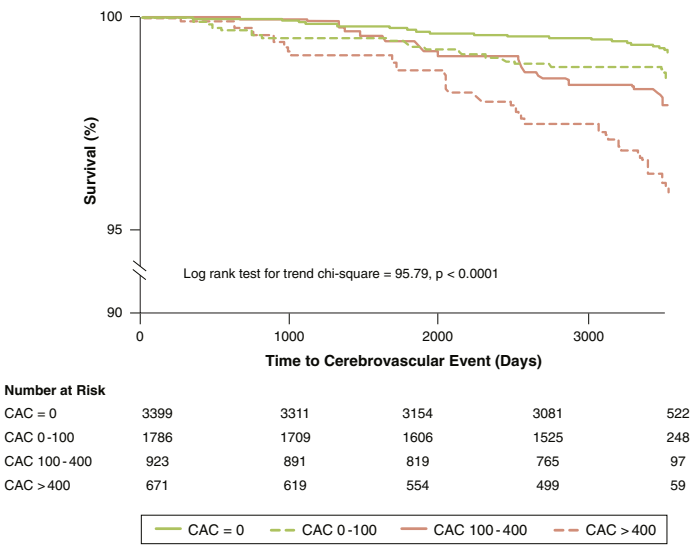

FIGURE 2 Incident CVE by CAC Categories

Kaplan-Meier analysis showing the CVE event-free survival of participants with 0, 0 to 100, >100 to 400, and >400 CAC (Agatston units) and incident CVE in the MESA cohort. Abbreviations as in Figure 1.

c-statistic when constituents of the FSRS (risk factors) were in the model was 0.721 and when CAC was added to the model was 0.735 (data not shown).

For ischemic CVE (cerebral infarcts + TIAs, n = 206), the c-statistic values related to CAC alone, our full model (minus CAC), and the addition of CAC to the full model were 0.657, 0.751, and 0.763 ($p < 0.01$), respectively. For cerebral infarcts (non-TIA, nonhemorrhagic strokes) (n = 152 events), these values were 0.664, 0.767, and 0.777 ($p < 0.01$).

DISCUSSION

The goal of this study was to determine the predictive value of CAC for incident CVE and to assess the improvement in discrimination afforded by the addition of CAC to known risk factors for CVE in a multiethnic cohort. Our study, which is the largest and has the longest follow-up so far, shows that CAC is an independent predictor and improves the discrimination for CVE.

Compared with other subclinical and novel markers, CAC has been shown to be superior for predicting, in the general population, CHD and cardiovascular event composites, which include CVE (4,5,14,16). The predictive value of CAC with regard to CVE—which had been questionable before the present study—was clearly shown in our study.

Unlike the HNR study, we did not observe that CAC predicts stroke events in younger but not in older adults. Furthermore, our results strongly suggest that CAC improves the discrimination of incident CVE above and beyond that related to known risk factors and by a similar magnitude as the CHD risk prediction in the MESA cohort (6).

CAC is a measure of atherosclerosis burden in the coronary circulation (17). Atherosclerosis is a known systemic disease that is almost always present in other vascular beds once detected in the coronary bed (18,19). Thus, observation of atherosclerosis in the coronary bed suggests presence of atherosclerosis in the cerebral circulation and elsewhere. However, unlike CHD, the underlying pathophysiology, which is mainly atherosclerosis, cerebrovascular disease/events have a more heterogeneous pathophysiology (20), including hemorrhage, small-vessel lacunar

TABLE 3 Predictive Value of Coronary Artery Calcium Score [ln (CAC +1)] for Incident Cerebrovascular Events in the MESA Cohort

Outcome	Events, n	Univariate Model Hazard Ratio (95% CI)	p Value	Multivariable Model* Hazard Ratio (95% CI)	p Value
Cerebrovascular	234	1.28 (1.22-1.34)	<0.0001	1.13 (1.07-1.20)	<0.0001
All stroke	180	1.23 (1.17-1.31)	<0.0001	1.10 (1.03-1.18)	0.003
TIA	67	1.25 (1.14-1.37)	<0.0001	1.16 (1.04-1.31)	0.007
Sex stratified					
Male	111	1.26 (1.17-1.37)	<0.0001	1.15 (1.05-1.24)	0.001
Female	123	1.32 (1.23-1.42)	<0.0001	1.11 (1.03-1.21)	0.010
Race/ethnicity stratified					
Caucasian	93	1.32 (1.21-1.43)	<0.0001	1.14 (1.03-1.25)	0.008
Chinese	12	1.32 (1.04-1.67)	0.02	1.18 (0.89-1.56)	0.25
African American	69	1.24 (1.15-1.36)	<0.0001	1.14 (1.02-1.26)	0.016
Hispanic	60	1.33 (1.2-1.47)	<0.0001	1.14 (1.01-1.28)	0.036

Mean follow-up was 9.5 ± 2.4 years. *Multivariable model was adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, cigarette smoking status, blood pressure medication use, statin use, and interim atrial fibrillation that occurred during the follow-up period.

CI = confidence interval; other abbreviations as in Table 2.

TABLE 4 Predictive Value of Coronary Artery Calcium (Present vs. Absent) for Incident Cerebrovascular Events in the MESA Cohort

Outcome	Events, n	Univariate Model Hazard Ratio (95% CI)	p Value	Multivariable Model* Hazard Ratio (95% CI)	p Value
Cerebrovascular	234	2.88 (2.18–3.82)	<0.0001	1.13 (1.07–1.20)	<0.0001
Stroke	180	2.57 (1.86–3.55)	<0.0001	1.45 (1.01–2.07)	0.043
TIA	67	2.71 (1.59–4.61)	0.0002	1.81 (1.00–3.27)	0.049
Sex stratified					
Male	111	3.02 (1.88–4.81)	<0.0001	1.84 (1.11–3.05)	0.018
Female	123	2.95 (2.05–4.25)	<0.0001	1.33 (0.88–2.00)	0.174
Race/ethnicity stratified					
Caucasian	93	3.41 (2.08–5.60)	<0.0001	1.65 (0.95–2.89)	0.075
Chinese	12	2.74 (0.82–9.17)	0.10	1.57 (0.40–6.12)	0.513
African American	69	2.35 (1.45–3.83)	0.0005	1.53 (0.89–2.63)	0.123
Hispanic	60	3.71 (2.14–6.47)	<0.0001	1.79 (0.96–3.34)	0.061

Mean follow-up was 9.5 ± 2.4 years. *Multivariable model was adjusted for age, sex, race/ethnicity, body mass index, diabetes mellitus, systolic and diastolic blood pressure, total cholesterol, high-density lipoprotein, cigarette smoking status, blood pressure medication use, statin use, and interim atrial fibrillation that occurred during the follow-up period.

Abbreviations as in Table 2.

strokes, and ischemia. The heterogeneous pathophysiology of cerebrovascular disease/events makes predicting events using a single marker such as CAC in 1 of the pathophysiologic pathways unappealing. However, as evident from the present study and others, most cerebrovascular disease/events (approximately 85%, 152 of 180 strokes) are due to cerebral infarcts (21). With a few exceptions, such as cerebral infarcts from cardioembolic source, most of these cerebral infarcts may be due to in situ atherosclerosis, small-vessel disease including microatheroma, or embolism of plaques from extracranial vessels or the aorta; for all of these, CAC would be a good surrogate marker. Thus, despite the heterogeneous pathophysiology of cerebrovascular disease, CAC as a measure of atherosclerotic burden in the coronary bed can still be a good predictor and can be used to identify most subjects at risk for aggressive preventive therapy, such as statins.

Epidemiological and observational studies have shown a clear association between hypertension and incident CVE, suggesting that blood pressure control may be a good target for primary stroke prevention (22,23). Primary stroke prevention trials with upstream modification of blood pressure have shown a significant reduction in incident CVE (24–26). However, current data on the association between dyslipidemia and incident CVE are mixed (27–30). To date, no clinical trial data exist on the effects of lipid-lowering therapy on CVEs in asymptomatic individuals. However, a secondary analysis of primary prevention trials and long-term clinical trials, which evaluated CVE as a secondary outcome in patients with established coronary heart disease, showed a reduction in CVEs with statin therapy (31–35). Thus, CAC, a noninvasive test, can identify individuals for statin therapy with asymptomatic CHD but at high risk for CVE. Clinical trials primarily evaluating the effect of statins on CVEs in individuals without clinical cardiovascular disease but positive CAC are needed.

Although our study shows an improvement in discrimination by CAC over current risk factors, we caution the incorporation of CAC into primary

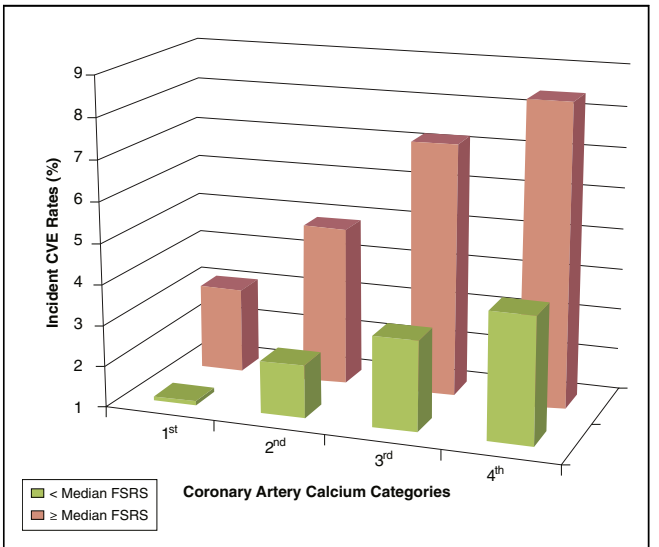

FIGURE 3 CAC Predicting CVE by Global Risk

Plot of incident CVE rates within CAC categories (CAC = 0 [1st], CAC = 0 to 100 [2nd], CAC = 101 to 400 [3rd], and CAC > 400 Agatston units) across the median Framingham stroke risk score (FSRS) in MESA participants after 9.5 years of follow-up. Abbreviations as in Figure 1.

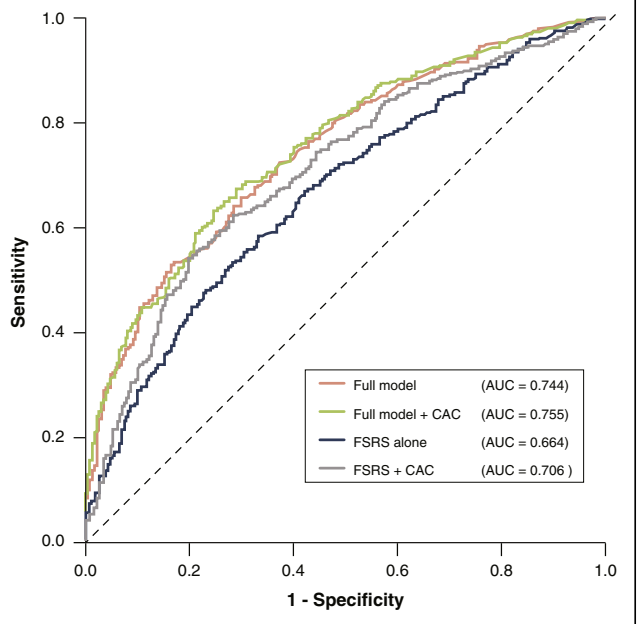

FIGURE 4 Predictive Accuracy of CAC, FSRS, and CAC + FSRS

Receiver-operating curves showing the discriminative ability of the full model, full model + CAC, the FSRS, and the FSRS + CAC for incident cerebrovascular events in the MESA cohort. AUC = area under the curve; other abbreviations as in Figures 1 and 3.

stroke prevention strategies until concerns about ionizing radiation exposure (~1 mSv) are weighed and this approach has been deemed cost-effective. Our results also need to be replicated in other cohorts.

STUDY LIMITATIONS. The strengths of our study include its large sample size, multiethnic cohort, relatively long follow-up, and the use of adjudicated CVE. The limitations include the relatively small number of CVE, which limited our ability to make definitive inferences in subgroups formed by sex and race/ethnicity. MESA is an observational study, and thus, residual confounding may have influenced our results. MESA does not include other ethnic groups, such as American Indians, or Asian groups other than Chinese. In addition, the proportion of each ethnic group in MESA does not accurately reflect that of the U.S. population. Although our primary outcome, CVE, and its constituents were adjudicated, atrial fibrillations that occurred during follow-up were a combination of adjudicated; International Classification of Diseases, Ninth Revision code-derived; and self-reports. The FSRS includes prior CVD and atrial fibrillation and was derived for stroke prediction in individuals with and without these comorbidities. MESA participants were free of CVD and atrial fibrillation at baseline but should not affect the discriminative ability of the FSRS in this cohort (asymptomatic multiethnic cohort). Last, because the present study involved individuals without clinical cardiovascular disease at baseline, our results may not be applicable to other populations.

CONCLUSIONS

CAC was found to be an independent predictor of CVE, strokes, and TIAs in a large multiethnic cohort. CAC also seems to have improved prediction over known risk factors for CVE, including atrial fibrillation and the FSRS.

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