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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.

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

ABBREVIATIONS AND ACRONYMS

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

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