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Improving the CAC Score by Addition of Regional Measures of Calcium Distribution

Multi-Ethnic Study of Atherosclerosis

Michael J. Blaha, MD, MPH,[a] Matthew J. Budoff, MD,[b] Rajesh Tota-Maharaj, MD,[a,c] Zeina A. Dardari, MS,[a] Nathan D. Wong, PhD,[d] Richard A. Kronmal, PhD,[e] John Eng, MD,[f] Wendy S. Post, MD, MS,[a] Roger S. Blumenthal, MD,[a] Khurram Nasir, MD, MPH[a,g]

ABSTRACT

OBJECTIVES The aim of this study was to investigate whether inclusion of simple measures of calcified plaque distribution might improve the ability of the traditional Agatston coronary artery calcium (CAC) score to predict cardiovascular events.

BACKGROUND Agatston CAC scoring does not include information on the location and distributional pattern of detectable calcified plaque.

METHODS We studied 3,262 (50%) individuals with baseline CAC >0 from the Multi-Ethnic Study of Atherosclerosis. Multivessel CAC was defined by the number of coronary vessels with CAC (scored 1 to 4, including the left main). The "diffusivity index" was calculated as 1 - (CAC in most affected vessel/total CAC), and was used to group participants into concentrated and diffuse CAC patterns. Multivariable Cox proportional hazards regression, area under the curve, and net reclassification improvement analyses were performed for both coronary heart disease (CHD) and cardiovascular disease (CVD) events to assess whether measures of regional CAC distribution add to the traditional Agatston CAC score.

RESULTS Mean age of the population was 66 ± 10 years, with 42% women. Median follow-up was 10.0 (9.5 to 10.7) years and there were 368 CHD and 493 CVD events during follow-up. Considerable heterogeneity existed between CAC score group and number of vessels with CAC ($p < 0.01$). Addition of number of vessels with CAC significantly improved capacity to predict CHD and CVD events in survival analysis (hazard ratio: 1.9 to 3.5 for 4-vessel vs. 1-vessel CAC), area under the curve analysis (C-statistic improvement of 0.01 to 0.033), and net reclassification improvement analysis (category-less net reclassification improvement 0.10 to 0.45). Although a diffuse CAC pattern was associated with worse outcomes in participants with ≥2 vessels with CAC (hazard ratio: 1.33 to 1.41; $p < 0.05$), adding this variable to the Agatston CAC score and number of vessels with CAC did not further improve global risk prediction.

CONCLUSIONS The number of coronary arteries with calcified plaque, indicating increasingly "diffuse" multivessel subclinical atherosclerosis, adds significantly to the traditional Agatston CAC score for the prediction of CHD and CVD events. (J Am Coll Cardiol Img 2016;■:■-■) © 2016 by the American College of Cardiology Foundation.

From the [a]Johns Hopkins Ciccarone Center for the Prevention of Heart Disease, Baltimore, Maryland; [b]Division of Cardiology, Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, California; [c]Division of Cardiology, Danbury Hospital, Danbury, Connecticut; [d]Division of Cardiology, University of California-Irvine, Irvine, California; [e]Department of Biostatistics, University of Washington, Seattle, Washington; [f]Department of Radiology, Johns Hopkins, Baltimore, Maryland; and the [g]Center for Prevention and Wellness Research, Baptist Health Medical Group, Miami Beach, Florida. This research was supported by contracts N01-HC-95159, N01-HC-95160, N01-HC-95161, N01-HC-95162, N01-HC-95163, N01-HC-95164, N01-HC-95165, N01-HC-95166, N01-HC-95167, N01-HC-95168, and N01-HC-95169 from the National Heart, Lung, and Blood Institute and by grants UL1-TR-000040 and UL1-TR-001079 from NCRR. Dr. Budoff has received grant support from GE. Dr. Nasir is a consultant for Regeneron. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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ABBREVIATIONS AND ACRONYMS

AUC = area under the curve

CAC = coronary artery calcium

CHD = coronary heart disease

CT = computed tomography

CVD = cardiovascular disease

MESA = Multi-Ethnic Study of Atherosclerosis

NRI = net reclassification improvement

Coronary artery calcium (CAC) scores derived from noncontrast cardiac computed tomography (CT) are one of the strongest individual predictors of adverse cardiovascular events (1). The association of CAC with cardiovascular disease (CVD) is thought to be driven by the strong correlation between detectable subintimal coronary calcium and total coronary atherosclerosis burden (1). Indeed, several studies have suggested a direct relationship between the quantity of calcium and the total amount of coronary atherosclerotic plaque (2,3).

CAC is usually scored by the method of Agatston et al. (4). The Agatston score is calculated as a summed product of the within-slice area of calcium multiplied by a weighting factor derived from the maximal CT attenuation of individual calcified lesions. Although elegant and simple, the Agatston score and other current CAC scoring algorithms (5–7) do not account for the distribution of CAC within the coronary tree. Therefore, 2 patients with the same CAC score may have significantly different patterns of CAC involvement (8). The implication of the heterogeneity in coronary atherosclerosis distribution within patients with similar CAC scores is not well known.

Given the large body of evidence supporting worse prognosis with diffuse coronary artery disease (9), we hypothesized that measures of diffuse CAC distribution might be associated with worse prognosis compared with identical CAC scores with a more concentrated pattern. To test this hypothesis, we sought to study the potential incremental prognostic value of adding simple measures of CAC distribution to the traditional Agatston score in a multiethnic population free of baseline CVD.

METHODS

STUDY DESIGN AND POPULATION. MESA (Multi-Ethnic Study of Atherosclerosis) is a multicenter population-based prospective cohort study aimed at describing the prevalence, progression, and clinical significance of subclinical atherosclerosis. In brief, MESA includes 6,814 men and women aged 45 to 84 years from different ethnic origins (white, black, Hispanic, and Chinese) with no known baseline clinical CVD at the time of enrollment. Full details of the MESA study design and methods have been previously published (10). The study protocol was approved by each institutional review board, and all participants provided written informed consent.

STUDY COVARIATES. As part of the baseline examination, staff members at each of the 6 centers collected information about cardiovascular risk factors, including medical history, smoking history, blood pressure measurement, anthropometric measurements, and laboratory data, as previously described (10). A central laboratory (University of Vermont, Burlington, Vermont) measured plasma glucose and high-sensitivity C-reactive protein, and levels of total and high-density lipoprotein cholesterol and triglycerides were measured after a 12-hour fast at the Collaborative Studies Clinical Laboratory at Fairview-University Medical Center (Minneapolis, Minnesota).

EVENT ASCERTAINMENT (FOLLOW-UP). Participants were followed for a median of 10.0 years (interquartile range: 9.5 to 10.7) for the first occurrence of a coronary heart disease (CHD) or CVD event. At intervals of 9 to 12 months, an interviewer contacted each participant or family member by telephone to inquire about interim revascularization, hospital admission, or death. To verify self-reported diagnoses, MESA obtained medical records for approximately 98% of hospital events and 95% of outpatient diagnoses. Two physicians from the MESA mortality and morbidity review committee independently classified events.

A CHD event was defined as myocardial infarction, death from CHD, resuscitated cardiac arrest definite angina, or revascularization if there was adjudicated preceding or concurrent angina. A CVD event was defined as a CHD event or stroke (not transient ischemic attack), cardiovascular death, or other atherosclerotic death. Full details of the MESA follow-up methods are available at the MESA website.

CT PROTOCOL. All MESA study participants underwent baseline measurement of CAC using noncontrast cardiac CT. Participants were scanned twice, and the score was reported as the average of the 2 scans. CAC scores were reported as the Agatston score, which is a single summary score reflecting the summed product of the within-slice calcified plaque area and a density weighting factor representing the peak CT attenuation within the individual calcified plaque (4). Regional distribution of CAC is not a factor in traditional Agatston CAC scoring. Subjects were told after the baseline visit (2000 to 2002) whether they had no, less than average, average, or greater than average CAC and were encouraged to discuss the results with their physicians.

DEFINITION OF CAC PARAMETERS. Vessel-specific CAC measurements were performed in 6,540 MESA participants (96%). A total of 3,262 (50%) individuals had baseline CAC >0 and form the population for this analysis.