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Original Research Article

Multisite extracoronary calcification indicates increased risk of coronary heart disease and all-cause mortality: The Multi-Ethnic Study of Atherosclerosis

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ARTICLE INFO

Article history:
Received 18 January 2015
Received in revised form
14 March 2015
Accepted 30 March 2015
Available online 7 April 2015

Keywords:
Extracoronary calcification
CHD events

ABSTRACT

Background: Cardiovascular calcification outside of the coronary tree, known as extracoronary calcification (ECC), is highly prevalent, often occurs concurrently in multiple sites, and yet its prognostic value is unclear.
Objective: To determine whether multisite ECC is associated with coronary heart disease (CHD) events, CHD mortality, and all-cause mortality.
Methods: We evaluated 5903 participants from the Multi-Ethnic Study of Atherosclerosis without diabetes who underwent CT imaging for calcification of the aortic valve, aortic root, mitral valve, and thoracic aorta. Participants were followed for 10.3 years. Multivariable adjusted hazard ratios estimated risk of outcomes for increasing numbers of ECC sites (0, 1, 2, 3, and 4), and receiver operator characteristic analysis assessed model discrimination.

Conflict of interest: Matthew J. Budoff is a consultant for General Electric, and Nathan Wong is a consultant for Reengineering Healthcare, Inc. The other authors declare no conflicts of interest.
Support: This work was supported by the National Heart, Lung, and Blood Institute at the National Institutes of Health grant R01 HL071739 and by contracts N01-HC-95159 through N01-HC-95169. The information contained herein was derived in part from data provided by the Bureau of Vital Statistics, New York City Department of Health and Mental Hygiene.
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http://dx.doi.org/10.1016/j.jcct.2015.03.012

Mortality
Risk prediction
Cardiovascular imaging

Results: Prevalence of any ECC was 45%; median age was 62 years. Compared with those without ECC, those with ECC in 4 sites had increased hazards of 4.5, 7.1 and 2.3 for CHD events, CHD mortality, and all-cause mortality, respectively, independent of traditional risk factors (TRF; all $P \leq .05$), and had ≥2-fold increased hazards for outcomes independent of coronary artery calcification (CAC). Each additional site of ECC was positively associated with each outcome in a graded fashion. When added to TRF, ECC significantly increased the area under the receiver operator characteristic curve for all outcomes and modestly increased the area under the curve for mortality beyond TRF + CAC (0.799 to 0.802; $P = .03$). *Conclusion:* Increasing multisite ECC has a graded association with higher CHD and mortality risk, contributing information beyond TRF. Multisite ECC incidentally identified on imaging can be used to improve individualized risk prediction.

1. Introduction

Despite vigorous prevention efforts, 2 times as many coronary heart disease (CHD) events occur as first-time, rather than recurrent, events,[1] highlighting the need for improved CHD risk assessment and earlier intervention. The existence of cardiovascular calcification has been identified for decades in various extracoronary sites, such as the aortic valve, mitral valve,[2] or aorta,[3] and is thought to be driven by a systemic calcific process.[4] However, extracoronary calcification (ECC) is rarely given consideration in clinical practice to inform individualized risk profiling. The preferential development of atherosclerosis in different cardiovascular locations among different patient populations invokes the possibility to improve subclinical CHD detection by measuring ECC.[5] Although studies have correlated individual sites of ECC with outcomes such as CHD events and mortality,[2,3,6] the significance of multisite ECC concurrently present in a given individual is not well characterized.

ECC has the advantage of being identifiable on the same CT scan as CAC, as well as on noncardiac CT scans and a wide variety of imaging modalities, including plain radiography, dual-energy X-ray absorptiometry, echocardiography, and ultrasonography.[2,6–8] Although calcification outside of the coronary tree (such as ECC) a priori is not expected to predict CHD events more effectively than coronary calcification, ECC represents readily available information—particularly when found incidentally—which can be used to inform clinical decision making beyond traditional risk scores. Determining the prognostic value of ECC may thus allow the use of ECC information from various sources, possibly even without additional cost or harm to the patient, to direct primary prevention and improve cardiovascular risk prediction. The aim of this study is to use a simple, clinically applicable assessment of ECC to evaluate the hypothesis that multisite ECC is associated with and incrementally improves risk prediction for CHD events, CHD mortality, and all-cause mortality.

2. Materials and methods

2.1. Study population

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal, population-based cohort study of 6814 people, free of clinical cardiovascular disease at baseline, aged 45 to 84 years from 6 US centers. Details of its design have been reported.[9] All participants gave informed consent, and the study protocol was approved by the institutional review board at each site in accordance with the Health Insurance Portability and Accountability Act. Approximately 53% of the cohort participants are female, and the ethnic distribution is 38% Caucasian, 12% Chinese, 28% African American, and 22% Hispanic. Participants were enrolled between August 2000 and July 2002, when a baseline examination was performed. For this study, to allow comparison with the Framingham risk score, we excluded all participants with diabetes, those missing ECC measurements and follow-up, for a total study population of 5903.

2.2. Data collection

Participants completed a self-administered questionnaire during the baseline examination, and clinical and laboratory data were obtained. Total and high-density lipoprotein cholesterol, as well as glucose levels were measured from blood samples after a 12-hour fast. Blood pressure was measured in a seated position 3 times with a Dinamap Pro-100 automated oscillometric sphygmomanometer (Critikon, Wipro GE Healthcare, Waukesha, WI); the average of the last 2 measurements was used in the analysis. Current smoking was defined as having smoked a cigarette in the last 30 days. Diabetes was defined as either a fasting glucose level ≥126 mg/dL or use of diabetes medication.

2.3. CT and ECC measures

After providing informed consent, all participants underwent 2 consecutive baseline noncontrast cardiac CT scans that were electrocardiographically gated to the R-R interval.[10] Three sites used the Imatron C-150XL CT scanner (GE Imatron, San Francisco, CA), and 3 sites used multidetector CT scanners (4 slices). The participant was supine for imaging, and a minimum of 35 contiguous images were obtained with a 2.5- or 3-mm slice thickness, starting above the left main coronary artery to the bottom of both ventricles. Each scan was obtained in a single breathhold. A section thickness of 3 mm, field of view of 35 cm, and a matrix of 512 × 512 were used to reconstruct raw image data. The nominal section thickness was 3.0 mm for electron-beam CT and 2.5 mm for 4-detector row CT. Spatial resolution can be described by the smallest volume element, or voxel, for