JACC: CARDIOVASCULAR IMAGING
VOL. 7, NO. 7, 2014

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC.
http://dx.doi.org/10.1016/j.jcmg.2014.04.004

Coronary Artery Calcification and Family History of Myocardial Infarction in the Dallas Heart Study

Andre R.M. Paixao, MD,* Jarett D. Berry, MD, MS,*† Ian J. Neeland, MD,* Colby R. Ayers, MS,† Anand Rohatgi, MD, MSCS,* James A. de Lemos, MD,* Amit Khera, MD, MSc*

ABSTRACT

OBJECTIVES This study aimed to investigate the independent and joint associations between family history of myocardial infarction (FH) and coronary artery calcification (CAC) with incident coronary heart disease (CHD).

BACKGROUND FH and CAC are associated with each other and with incident CHD. It is not known whether FH retains its predictive value after CAC results are accounted for.

METHODS Among 2,390 participants without cardiovascular disease enrolled in the Dallas Heart Study, we assessed FH (myocardial infarction in a first-degree relative) and prevalent CAC by electron-beam computed tomography. The primary outcome, a composite of CHD-related death, myocardial infarction, and percutaneous or surgical coronary revascularization, was assessed over a mean follow-up of 8.0 ± 1.2 years. The individual and joint associations with the CHD composite outcome were determined for FH and CAC.

RESULTS The mean age of the population was 44 ± 9 years; 32% had FH and 47% had a CAC score of 0. In multivariate models adjusted for traditional risk factors, FH was independently associated with CHD (adjusted hazard ratio: 2.6; 95% confidence interval: 1.6 to 4.2; $p < 0.001$). Further adjustment for prevalent CAC did not diminish this association (adjusted hazard ratio: 2.6; 95% confidence interval: 1.6 to 4.2; $p < 0.001$). FH and CAC were additive: CHD event rates in those with both FH and CAC were 8.8% vs. 3.3% in those with prevalent CAC alone ($p < 0.001$). CHD rates were 1.9% in those with FH alone compared with 0.4% in those with neither FH nor CAC ($p < 0.017$). Among subjects without CAC, FH characterized a group with a more unfavorable cardiometabolic profile.

CONCLUSIONS FH provided prognostic information that was independent of and additive to CAC. Among those with CAC, FH identified subjects at particularly high short-term risk, and, among those without it, selected a group with an adverse risk-factor profile. (J Am Coll Cardiol Img 2014;7:679–86) © 2014 by the American College of Cardiology Foundation.

Family history of myocardial infarction (FH) is consistently associated with coronary and cardiovascular events (1) and contributes modestly to short-term risk-prediction models (2,3). Although FH was not incorporated in the risk-prediction equations proposed by the most recent European and U.S. guidelines, both documents give FH a favorable recommendation as an additional cardiovascular risk marker (4,5). Coronary artery calcification (CAC), measured by computed tomography (CT), is thought to reflect the burden of coronary atherosclerosis and has emerged as 1 of the

From the *Division of Cardiology, University of Texas Southwestern Medical Center, Dallas, Texas; and the †Department of Clinical Sciences, University of Texas Southwestern Medical Center, Dallas, Texas. The Dallas Heart Study was funded by the Donald W. Reynolds Foundation and was partially supported by the National Center for Advancing Translational Sciences of the National Institutes of Health under award Number UL1TR001105. Dr. Berry has received honoraria for serving on the Speakers' Bureau of Merck & Co., Inc. Dr. Rohatgi has received honoraria for serving as an associate editor of a publication by the American College of Cardiology Foundation; and has received a research grant from Merck & Co., Inc. Dr. de Lemos has received honoraria grants from Abbott Diagnostics and Roche Diagnostics; has received honoraria from AstraZeneca Pharmaceuticals LP; and has received consulting fees from Abbott Diagnostics and Amgen Inc. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Manuscript received March 10, 2014; revised manuscript received April 10, 2014, accepted April 14, 2014.

ABBREVIATIONS AND ACRONYMS

CAC = coronary artery calcification

CHD = coronary heart disease

FH = family history of myocardial infarction

NRI = net reclassification improvement

TRF = traditional risk factor(s)

most powerful predictors of incident coronary heart disease (CHD) (6). Contrary to most other novel biomarkers, CAC significantly improves the *c* statistic and net reclassification when added to traditional risk factor (TRF) models (7).

SEE PAGE 687

Patients with FH are often referred for CAC scanning and have an increased prevalence of CAC (8,9); yet, the significance of FH after CAC values are known is unclear. One possibility is that heritable factors reflected in FH will already be captured as coronary plaque and calcification by adulthood, such that FH provides no additional predictive information beyond CAC values. Alternatively, FH and CAC may be additive in predictive value, just as FH has been shown to be additive with other risk factors (8). Thus, in a large, population-based study, we sought to determine the independent and joint effects of FH and CAC on the risk for CHD events.

METHODS

STUDY SAMPLE. The DHS (Dallas Heart Study) is a multiethnic, probability-based, population cohort study in adults in Dallas County, Texas, with deliberate oversampling of African Americans. Detailed methods of DHS phase 1 (DHS-1) have been described previously (10). All subjects provided written informed consent, and the study protocol was approved by the institutional review board of the University of Texas Southwestern Medical Center. Briefly, between 2000 and 2002, 2,971 participants completed the 3 visits of DHS-1, including a detailed in-home survey, laboratory testing, and multiple imaging studies, as described subsequently. Of 2,971 patients, 228 did not have an interpretable CAC scan, 74 reported a history of cardiovascular disease, 88 had missing covariates, and 191 had incomplete follow-up for nonfatal endpoints (Online Fig. 1). The final study population comprised 2,390 participants free of cardiovascular disease and followed up for fatal and nonfatal CHD events.

DEFINITIONS. Race/ethnicity, history of cardiovascular disease, individual medication usage, family history, and smoking status were self-reported. Detailed definitions of the variables *hypertension, metabolic syndrome,* and *diabetes* in the DHS have been previously published (11). *FH* was defined as any first-degree relative with a history of myocardial infarction. *Family history of premature CHD* was defined as myocardial infarction occurring before the age of 50 years in a first-degree male relative or before the age of 55 years in a first-degree female relative, as predetermined in the original DHS questionnaire (8). Given the small number of subjects with premature FH, we used the more inclusive definition of any FH for the primary analyses. As part of our subgroup analysis, participants were stratified using prespecified age cutoffs of 45 years of age in men and 55 years in women (12). This definition was chosen on the basis of prior reports from the DHS, in which FH was a stronger predictor of CAC among younger participants (8).

MEASUREMENTS. Analytical methods for the biomarkers reported in this study have been previously described, including high-sensitivity C-reactive protein (13), highly sensitive troponin T (14), N-terminal pro-brain natriuretic peptide (15), and lipoprotein assessment (16). Glomerular filtration rate was calculated using the Modification of Diet in Renal Disease formula (17). Homeostasis model assessment of insulin resistance was calculated using the following formula (18):

$$\text{fasting insulin}\,(\mu\text{IU/ml}) \times \text{fasting glucose}\,(\text{mmol/l})/22.5$$

Electron-beam CT measurements of CAC were performed in duplicate, 1 to 2 min apart, on an Imatron 150 XP scanner (Imatron Inc., San Bruno, California). The 2 CAC scores were determined using the Agatston method and then averaged (19). Dual-energy x-ray absorptiometry (Delphi scanner, Hologic, and Discovery software version 12.2, Bedford, Massachusetts) was used to measure total body fat (20). Cardiac and aortic magnetic resonance imaging measurements were performed using a 1.5-T magnetic resonance imaging system (Intera, Philips Medical Systems, Best, the Netherlands). Left ventricular mass, aortic wall thickness, and aortic compliance were calculated according to previously published methods (14,21).

CLINICAL OUTCOMES. The primary outcome was a composite of CHD-related death, myocardial infarction, and/or coronary revascularization. All revascularization events (coronary artery bypass surgery and percutaneous revascularization) occurring within the first 3 months of CAC scanning were excluded from the analyses as they could have been driven by the CAC test result. Death events were ascertained through December 31, 2009, in all subjects in the DHS, using the National Death Index (14). Deaths were classified as secondary to CHD if they included International Statistical Classification of Diseases, 10th Revision codes I20 to I25. Subjects were contacted annually to participate in a detailed health survey regarding interval nonfatal cardiovascular events. In addition, subjects who provided