Usefulness of Coronary Artery Calcium to Predict Heart Failure With Preserved Ejection Fraction in Men Versus Women (from the Multi-Ethnic Study of Atherosclerosis)

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We studied the association of coronary artery calcium (CAC) and risk of heart failure with preserved ejection fraction (HFpEF) among men and women in a multiethnic cohort. Coronary artery disease is a risk factor for development of HFpEF and assessment of subclinical atherosclerosis using CAC may allow for the early identification of patients at risk for HFpEF. We used data from the Multi-Ethnic Study of Atherosclerosis. CAC was measured at baseline in all participants. Incident HFpEF was defined as heart failure hospitalization with left ventricular ejection fraction ≥50%. Multivariable-adjusted Cox proportional hazards models were used to calculate HFpEF risk by CAC categories (0, 1 to 100, 101 to 300, and >300) and by CAC (continuous), stratified by gender and race/ethnicity. Of 6809 total participants, 127 incident HFpEF cases (1.8%) were ascertained. Mean age was 62 years (±10 years), and the participants were 53% female, 38% White, and 12% Black. In adjusted analysis, CAC >300 was associated with increased risk of HFpEF (hazard ratio [HR] 1.68, 95% confidence interval [95 CI] 1.00, 1.83); however, this was significant only in women (HR 2.82, 95% CI 1.32, 6.00 vs HR 0.91, 95% CI 0.46, 1.82 for men, interaction p = 0.03). Similarly, CAC modeled as a continuous variable was strongly predictive in women but not in men. In conclusion, measurement of CAC, a marker of coronary atherosclerosis, may stratify risk of HFpEF beyond traditional risk factors for women. Further investigation is needed to better understand potential gender differences in pathophysiology and presentation of HFpEF. © 2017 Elsevier Inc. All rights reserved. (Am J Cardiol 2017;120:1847–1853)

The prevalence and hospitalization rate for heart failure with preserved ejection fraction (HFpEF) is on the rise with population aging, such that HFpEF constitutes half of all heart failure (HF), with a female predominance.[1–3] Unlike proven therapies for patients with reduced ejection fraction (HFrEF), HFpEF treatment has been unsuccessful to date, partly due to a lack of understanding of its pathophysiology, but most likely due to heterogeneity of mechanisms of disease and patient population.[4] As such, considerable efforts are underway to clinically and pathophysiologically phenotype patients with the aim to target therapies to specific patient subgroups. Overt coronary artery disease (CAD) is associated with increased HFpEF risk, affecting up to 50% of HFpEF patients, and is associated with worse outcomes.[5–7] We investigated whether the presence of coronary artery calcium (CAC), an established marker of subclinical CAD, allows for identification of those at risk of incident HFpEF in the Multi-Ethnic Study of Atherosclerosis (MESA), and whether the potential association of CAC with HFpEF varies by gender.

Methods

MESA is a study of prevalence and characteristics of subclinical cardiovascular disease (CVD), and of determinants of progression from subclinical disease to clinically overt CVD. The MESA study design and objectives are described elsewhere.[8] Briefly, 6,814 asymptomatic men and women aged 45 to 84 years were recruited from six U.S. field centers from 2000 to 2002. Approximately 38% of the participants were White, 28% African-American, 22% Hispanic, and 12% Chinese-American. All participants were free of clinical CVD

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at enrollment. The protocols were approved by the institutional review boards of all collaborating institutions. All participants provided written informed consent.

At baseline, each participant was assessed for presence of CAC using noncontrast cardiac-gated computed tomography (CT) scan. CAC was measured either with an electron-beam CT scanner (Chicago, Los Angeles, New York), or a multidetector CT scanner (Baltimore, Forsyth County, St. Paul, Minnesota). Details of the MESA scanning protocol are reported elsewhere.[9] Participants were scanned twice, and the average Agatston score was calculated and used for all analyses.[10] All images were interpreted at the MESA CT reading center (Los Angeles Biomedical Research Institute, Torrance, California). The intraobserver and interobserver agreement were excellent (kappa statistics of 0.93 and 0.90 were found for intra- and interobserver variation, respectively). The effective radiation dose was approximately 1 mSv.[11]

Demographic data were collected using questionnaires. Systolic and diastolic blood pressures (SBP and DBP) were measured three times using an automated sphygmomanometer (Critikon, Tampa, Florida). The mean of the last two measurements was used. A central laboratory (University of Vermont, Burlington, Vermont) measured levels of total and high-density lipoprotein cholesterol (HDL-C) and plasma glucose in blood samples obtained after a 12-hour fast. Hypertension was defined as a blood pressure ≥140/90 mmHg or use of antihypertensive medications.[12] Physical activity was based on the amount of time and frequency of various activities during a typical week in the month before the baseline study visit. Minutes of activity were summed for each discrete activity type and multiplied by metabolic equivalent level. Education level was categorized as follows: <high school, completed high school but <bachelors, completed bachelors and higher. Estimated glomerular filtration rate (eGFR) was calculated using the CKD-EPI formula.[13]

HF events were adjudicated by a committee that included a cardiologist, cardiovascular physician-epidemiologist, and a neurologist. The definition of incident HF required HF symptoms, such as shortness of breath or edema, in addition to one or more objective criteria, such as pulmonary edema/congestion by chest x-ray, dilated ventricle or poor left ventricular (LV) function by echocardiography or ventriculography, or evidence of LV diastolic dysfunction. HFpEF was defined as a new HF event with a concomitant echocardiogram documenting a left ventricular ejection fraction (EF) ≥50%, or "normal" EF.

Baseline characteristics of participants who had a HFpEF hospitalization versus those who did not were summarized using means (standard deviation) for continuous and percentages for categorical variables. Differences between the two groups were tested using *t* tests and chi-square testing. We calculated absolute incident HFpEF rates (per 1,000 person-years) and plotted event-free survival using Kaplan-Meier curves for the overall study population and separately for each gender, race/ethnicity, and CAC category (0, 1 to 100, 101 to 300, and >300). Multivariable-adjusted Cox proportional hazards regression models were used to calculate risk of HFpEF for each CAC category relative to the CAC = 0 group. In addition, after graphically confirming linearity of effect, we also calculated HFpEF risk for each 1-unit increase in continuous CAC defined as ln (CAC + 1). The

proportional hazard assumption was confirmed using graphical methods (log-log plots). Hazards ratios (HRs) and 95% confidence intervals (CIs) were reported. The following hierarchal models were used: Model 1 was adjusted for demographic characteristics (age, gender, race/ethnicity, and education). Model 2 was further adjusted for traditional cardiovascular risk factors, including body mass index (BMI), SBP and DBP, hypertension, diabetes mellitus, total cholesterol, HDL-C, cigarette smoking status, and estimated glomerular filtration rate. Model 3 was additionally adjusted for baseline use of medications (antihypertensives and statins). Test for trend was performed by treating categorical CAC as an ordinal variable.

Multiplicative interaction terms between CAC (continuous and categorical) and each of gender, race/ethnicity, and age (≥60 years vs <60) were tested and, if significant, results were stratified by these variables. As an exploratory analysis, we evaluated the associations between CVD risk factors and HFpEF among participants with baseline CAC = 0 (i.e., no detectable calcified coronary atherosclerosis, n = 3,415). In this limited analysis with few HFpEF events, only variables that were significantly different between the two groups were included in Cox demographics-adjusted proportional models to prevent model overfitting.

In separate sensitivity analyses we excluded participants who had an interim coronary heart disease (CHD) event during follow-up before development of HFpEF (n = 31) during MESA follow-up, as well as those with any history of HFrEF. Although a CHD event may mediate the association of CAC with HFpEF, this analysis sought to explore whether subclinical disease (measured by CAC) in the absence of clinical events was associated with HFpEF. Statistical significance was defined by two-sided p <0.05.

Results

Over a median follow-up time of 11.2 years, there were 127 incident HFpEF hospitalizations. The baseline characteristics of the overall study population stratified by incident HFpEF are summarized in Table 1. The mean (SD) age overall was 62 (10) years, 53% were female, 38% were White, 28% were Black, 12% were Chinese-American, and 22% were Hispanic. The prevalence of cardiovascular risk factors was 45% for hypertension, 13% for diabetes, 43% for family history of CHD, and 13% for current cigarette smoking. Those who were hospitalized for HFpEF were older, with higher BMI and higher SBP, and more likely to be diabetic compared with those who were not hospitalized for HFpEF.

The overall incidence rate of HFpEF was 1.82 per 1,000 person-years. Incidence rates were slightly higher for men compared with women (2.00 vs 1.66 events per 1,000 person-years, respectively, p = 0.29). There was a graded increase in HFpEF incidence rates across the CAC categories. The absolute incidence rate for the CAC = 0 group was the lowest at 0.99 events per 1,000 person-years and it increased to 1.48, 2.95, and 5.39 events per 1,000 person-years for CAC 1 to 100, 101 to 300, and >300, respectively. A Kaplan-Meier plot of time to survival free of HFpEF stratified by gender and CAC groups is shown in Figure 1.

Hazard ratios (HRs) for the association between CAC and incident HFpEF for the overall study population and stratified