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

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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

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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 participants, 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 55 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).

**METHODS.** 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):

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

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...
consent were tracked for hospital admissions using the Dallas Fort Worth Hospital Council Data Initiative database, which includes hospital admission data for 70 of 72 hospitals in the Dallas/Fort Worth metroplex. Greater than 90% of subjects from the initial imaging visit were followed up for nonfatal events with these data sources. Primary records were requested for all suspected cardiovascular events, and these events were each adjudicated separately by 2 cardiologists blinded to CAC assessment and all study variables.

**STATISTICAL ANALYSIS.** Baseline demographic and clinical variables were compared between participants with and without FH using the chi-square test for categorical variables and Wilcoxon rank sum test for continuous variables. Kaplan-Meier cumulative-events curves were constructed for CHD events and compared using log-rank statistics. Cox proportional hazard analysis was used to assess the association between FH and incident CHD in univariate and multivariate models adjusted for age, sex, systolic blood pressure, presence of diabetes, total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), smoking status, and use of antihypertensive drugs or statins. For the primary analysis, CAC was added to the multivariate models as a categorical variable (0 vs. >0). Sensitivity analyses were performed with CAC ≤10 versus >10, as a continuous variable (in [CAC + 1]), and as an ordinal variable (0, >0 to 10, >10 to 100, >100 to 400, and >400). The proportional hazards assumption was tested by Schoenfeld residuals. The interaction between FH and CAC was tested by adding a multiplicative variable to the fully-adjusted Cox model. Improvement in discrimination was assessed by comparing the c statistics in models with and without FH and CAC, using the Harrell c statistic, and significance was determined using bootstrapping. Category-free or continuous net reclassification improvement (NRI) was also calculated by bootstrapping (22). We divided our cohort into 4 mutually exclusive groups on the basis of the presence or absence of CAC and FH. Traditional and novel markers were compared among those 4 groups. Because, after stratification by CAC, participants with and without FH had significant age and sex differences, logistic and linear regression models adjusted for age and sex were used for this analysis. All statistical analyses were performed using the SAS software package version 9.2 (SAS Institute Inc., Cary, North Carolina).

**RESULTS**

The characteristics of the study population stratified by the presence or absence of FH are displayed in Table 1. The overall mean age was 44 ± 9 years, 56% of subjects were female, and 48% were African American. Most participants were classified as low risk (<6% 10-year risk) on the basis of the Framingham risk score (80%), and 47% had a CAC score of 0. FH at any age was reported by 32% of patients, and premature FH was reported by 10%. Participants with a positive FH tended to be older, were more often female, had higher prevalences of hypertension and diabetes, and had a more unfavorable lipid profile.
A total of 76 first CHD events occurred over a mean follow-up of 8 ± 1.2 years (CHD-related death: 17; nonfatal myocardial infarction: 38; percutaneous coronary revascularization: 16; and coronary bypass surgery: 5). Coronary event rates in those with both FH and CAC were 8.8% versus 3.3% in those with prevalent CAC alone (p < 0.001). Among those without CAC, CHD rates were 1.9% in those with FH compared with 0.4% in those without FH (p < 0.017) (Fig. 1). In univariate models, FH carried a hazard ratio (HR) of 3.3 (95% confidence interval [CI]: 2.1 to 5.2; p < 0.001) (Table 2). In multivariate models adjusted for TRF, FH remained significantly associated with CHD (HRadj: 2.6; 95% CI: 1.6 to 4.2; p < 0.001). Further adjustment for CAC did not diminish this association (HRadj: 2.6; 95% CI: 1.6 to 4.2; p < 0.001). Other independent predictors of CHD in the fully-adjusted model were age, male sex, diabetes, TC, smoking, use of antihypertensive drugs, and CAC. In stratified analyses, FH was independently associated with CHD events among those with CAC (HRadj: 2.5; 95% CI: 1.5 to 4.2). Among those without CAC, only 9 CHD events were observed, with a trend toward higher CHD event rates among those with FH (HRadj: 3.8; 95% CI: 0.9 to 16.3; p = 0.07 in the fully-adjusted model). No significant interaction between FH and CAC was detected (p = 0.394).

Replacing FH with premature FH yielded similar findings (HRadj: 2.9; 95% CI: 1.7 to 5.0; p < 0.001 in the fully-adjusted model). When CAC was modeled as a continuous, ordinal, or categorical variable using the cutoff of 10, results were also not significantly different, and the independent association between FH and CHD was maintained (Online Table 1).

The addition of FH to a model with TRF and CAC modestly improved the c statistic (from 0.86 to 0.87; p = 0.037) and resulted in significant correct reclassification (category-free NRI = 0.55; 95% CI: 0.27 to 0.83; p < 0.001). Discrimination measurements for premature FH were virtually the same as for any FH (c statistic: 0.87).

Among participants with and without CAC, those with FH were older (mean age: 51 years vs. 46 years [p < 0.001] and 44 years vs. 40 years [p < 0.001], respectively), with a higher proportion of women (55% vs. 46% [p < 0.001] and 69% vs. 62% [p = 0.037], respectively). After adjustment for age and sex, among those with CAC, FH was associated only with hypertension and aortic wall thickness (Table 3). Among those without CAC, however, FH was associated with hypertension, diabetes, and metabolic syndrome, as well as higher triglycerides, total fat mass, and left ventricular mass (Table 3).

Among young participants, FH was associated with a higher fully-adjusted HR of CHD (5.1; 95% CI: 1.7 to 15.0) compared with that in older participants (HRadj: 2.0; 95% CI: 1.1 to 3.6; p = 0.007) (Fig. 2). Point estimates were numerically higher in participants with 0 or 1 versus 2 or more risk factors (HRadj: 3.2 [95% CI: 1.5 to 7.1] vs. 2.0 [95% CI: 1.1 to 3.7]), but the p value for interaction was not significant (0.07). The association between FH and CHD was significant in the subgroups with low (<6%) and intermediate (6% to 20%) Framingham risk scores (HRadj: 2.4 [95% CI: 1.0 to 5.7; p = 0.049] and 2.3 [95% CI: 1.2 to 4.6; p = 0.015], respectively, in the fully-adjusted model). In the small subgroup with high Framingham risk (>20%), only 11 events occurred, yet there was a trend toward higher CHD risk among those with FH (HRadj: 6.1; 95% CI: 0.9 to 37.4; p = 0.052 in the fully-adjusted

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**FIGURE 1** Cumulative Incidence of CHD Events

Patients are stratified by family history of myocardial infarction (FH) and presence (coronary artery calcification [CAC] score: >0) or absence (CAC score: 0) of coronary artery calcification. CHD = coronary heart disease.

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**TABLE 2** Hazard Ratios for Incident CHD on the Basis of Family History of MI

<table>
<thead>
<tr>
<th>Family History of MI</th>
<th>Premature Family History of MI</th>
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<tbody>
<tr>
<td><strong>HR (95% CI) p Value</strong></td>
<td><strong>HR (95% CI) p Value</strong></td>
</tr>
<tr>
<td>Model 1*</td>
<td>3.3 (2.1–5.2) &lt;0.001</td>
</tr>
<tr>
<td>Model 2†</td>
<td>2.6 (1.6–4.2) &lt;0.001</td>
</tr>
<tr>
<td>Model 3‡</td>
<td>2.6 (1.6–4.2) &lt;0.001</td>
</tr>
</tbody>
</table>

*Univariate analysis. †Adjusted for age, sex, systolic blood pressure, presence of diabetes, TC, HDL-C, smoking status, and antihypertensive drug and statin use. ‡Adjusted for age, sex, systolic blood pressure, presence of diabetes, TC, HDL-C, smoking status, antihypertensive drug and statin use, and CAC score.

**CHD** = coronary heart disease; **CI** = confidence interval; **HR** = hazard ratio; other abbreviations as in Table 1.
model). No interaction was noted between FH and Framingham risk score (p = 0.480).

**DISCUSSION**

In a large, population-based cohort, we evaluated the joint effects of FH and CAC on clinical CHD events and report several relevant findings. First, FH was independently associated with incident CHD, and this association was not attenuated after CAC was accounted for. Second, patients with both FH and CAC were at higher CHD risk than were those with each of these characteristics in isolation. Among those without CAC, although overall event rates were low, CHD risk was also higher in patients with FH. These findings have important implications for the interpretation of FH in the context of known CAC values and suggest that knowledge of FH provides additional relevant information.

Although FH has been shown to predict prevalent CAC as well as progression of CAC in multiple populations (8,23,24), few data are available integrating FH and CAC as predictors of future events. In an analysis of the Family Heart Study, Hopkins et al. (25) followed up a cohort for approximately 8 years and performed CAC scanning at the last examination. They then evaluated the cross-sectional association of CAC with prevalent CHD at the end of this interval. They reported that FH remained associated with CHD after adjusting for CAC. However, because participants with and without incident CHD were scanned at the last visit, it is possible that the clinical events themselves affected coronary calcification through subsequent revascularization or plaque rupture itself. Thus, to our knowledge, this is the first study to formally test the relationship between FH and CAC on clinical outcomes in a prospective, population-based cohort.

The absence of significant attenuation of the association between FH and CHD after adding CAC to our models is intriguing and may indicate that FH reflects risk that is not proportional to the burden of coronary atherosclerosis as indirectly measured by calcium accumulation. FH may select heritable
Patients with FH have a significantly higher lifetime risk for CHD events and are often referred for CAC testing to better discern their individual risks (28). Our results suggest that FH and CAC may be additive in their information such that those with both characteristics are at particularly high short-term risk, with nearly double the risk of those with CAC alone. Interestingly, a recent study demonstrated that among patients with marked coronary calcification, FH may identify those who would most benefit from aggressive medical therapy (29). In a post-hoc analysis of the St. Francis Heart Study, in which patients with CAC above the 80th percentile were randomized to atorvastatin 20 mg or placebo, Mulders et al. (29) showed that the subgroup with FH benefitted from statin therapy (HR cardiovascular events: 0.55; 95% CI: 0.31 to 0.97; \( p = 0.04 \)), whereas there was no statistical reduction in patients without FH.

The trend toward higher adjusted CHD event rates associated with FH among patients without coronary calcification has potential clinical implications because these patients are thought to be at very low risk (6). Although the absolute short-term risk for CHD was still low in this young group, the presence of FH may signify the potential for future progression to a more aggressive phenotype and high lifetime risk for CHD (28). Indeed, participants with FH despite the absence of CAC had higher prevalences of hypertension, diabetes, and metabolic syndrome, as well as greater adiposity and left ventricular mass.

The improvement in risk classification evidenced by a modest change in \( c \) statistic and the significant category-free NRI support the clinical relevance of FH. This modest effect of FH on measurements of risk(6). Although, thought to be at particularly high risk and may require a lower short-term risk, with nearly double the risk of those with CAC alone.

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The improvement in risk classification evidenced by a modest change in \( c \) statistic and the significant category-free NRI support the clinical relevance of FH. This modest effect of FH on measurements of discrimination is consistent with data from prior studies (2). In a recent study by Yeboah et al. (3), participants in the intermediate-risk category were exclusively evaluated. Compared with other novel risk markers, CAC and FH were the strongest predictors of CHD, and the addition of FH to a model containing TRF resulted in a significant improvement in the \( c \) statistic (from 0.62 to 0.68; \( p = 0.001 \)) and a category-based NRI of 0.16. The large improvement in \( c \) statistic in this particular study was probably facilitated by the fairly low performance of the baseline model, unlike the high baseline \( c \) statistic for the TRF model (0.85) in our cohort.

The implications of our findings for the interpretation of CAC measurement in patients with FH are several-fold. The presence of FH is associated with a higher CHD risk, regardless of CAC results. In addition, patients who have both FH and CAC appear to be at particularly high risk and may require a lower
threshold for implementation of preventive therapies. Furthermore, the absence of CAC may not completely abrogate the increment in CHD risk in those with FH, and these patients may benefit from intensified life-style interventions as well as more vigilant surveillance for the development of risk factors. Finally, consistent with our prior report, FH may be particularly informative in younger patients (8).

STUDY LIMITATIONS. The relatively young age of our cohort (mean age at time of CAC scanning: 44 years) limits generalizability to older patients. It is known that CAC is more prevalent at older ages and may be more reflective of a longer exposure to FH. However, even in our subgroup analysis of older participants, adjusting for CAC did not significantly diminish the association between FH and CHD. We also had a limited number of clinical CHD events and thus limited power to detect potentially clinically meaningful differences in particularly informative subsets, such as patients without CAC and those in the high Framingham risk category. The DHS was designed as a population-based cohort with the goal of improving the mechanistic understanding and prevention of cardiovascular disease but not specifically to assess the association between FH, CAC, and CHD. Family history was therefore obtained through participant reporting, which is subject to misclassification and recall bias. This, however, is the norm in the field of cardiovascular epidemiology and consists of the same family history information available to practicing clinicians. Furthermore, reports from the Family Heart Study and the Newcastle Family History Study suggest that self-reported parental history has a sensitivity >80% and specificity approaching 90%, and that any misclassification of family history would bias associations toward the null (30–32). Therefore, we believe that our data represent a conservative estimate of the association between FH and CHD and its additive value to CAC. Finally, age definitions for FH and premature FH were determined by the original DHS questionnaire and differ from current guidelines (5). Prior studies, however, suggest that FH remains predictive of CHD across a wide range of parental ages (33).

CONCLUSIONS

FH was associated with incident CHD independent of baseline CAC, and its predictive value was not attenuated by CAC measurements. FH and CAC seem to be additive such that patients with both factors are at particularly high risk. In the subgroup of patients without significant coronary calcification, FH may still be informative by identifying patients at higher relative risk and selecting a group with a more unfavorable cardiometabolic profile. FH and CAC provide complementary information for CHD risk assessment.

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REFERENCES

**KEY WORDS** coronary artery calcification, family history of myocardial infarction, risk prediction

**APPENDIX** For a supplemental figure and table, please see the online version of this article.