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Coronary Artery Calcium and Risk of Atrial Fibrillation (From the Multi-Ethnic Study of Atherosclerosis)

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Abstract

Calcified coronary arteries are associated with the development of cardiovascular disease and stroke. It is currently unknown whether coronary artery calcium (CAC) is associated with an increased risk of atrial fibrillation (AF). We addressed this question in 6,641 participants (mean age 62 ± 10; 53% women; 62% non-whites) from the Multi-Ethnic Study of Atherosclerosis (MESA) who were free of baseline clinical cardiovascular disease and AF. CAC measurements were assessed by cardiac computed tomography (CT) at study baseline. AF was ascertained by review of hospital discharge records and from Medicare claims data until December 31, 2010. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (95%CI) for the association between CAC and AF. During a median follow up of 8.5 years, 308 (4.6%) participants developed AF. In a model adjusted for socio-demographics, cardiovascular risk factors, and potential confounders, higher CAC scores were associated with an increased risk of

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AF (CAC=0: HR=1.0, referent; CAC=1–100: HR=1.4, 95%CI=1.01, 2.0; CAC=101–300: HR=1.6, 95%CI=1.1, 2.4; CAC>300: 2.1, 95%CI=1.4, 2.9). The addition of CAC to the Framingham Heart Study and the CHARGE AF risk scores yielded an integrated discrimination improvement (IDI) of 0.0033 (95%CI=0.0015, 0.0066) and 0.0028 (95%CI=0.0012, 0.0057) and with relative IDI of 0.10 (95%CI=0.061, 0.15) and 0.077 (95%CI=0.040, 0.11), respectively. In conclusion, CAC is independently associated with an increased risk of AF.

Keywords

coronary calcium; atrial fibrillation; epidemiology

INTRODUCTION

Coronary artery calcium (CAC) measured by cardiac computed tomography (CT) provides an estimate of total coronary plaque burden.[1] This technique largely has been studied to identify patients at-risk for obstructive coronary artery disease and has been shown to predict future coronary heart disease events.[2–6] The application of CAC to predict conditions that are not limited to the coronary arteries has recently been explored. In a large population-based cohort study, CAC independently predicted stroke events.[7] Additionally, highly calcified coronary arteries are associated with larger pulmonary veins and left atria, suggesting an association between CAC and atrial fibrillation (AF).[8] However, no studies have examined this potential association. The purpose of this study was to examine the association of CAC with incident AF using data from the Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Details of MESA have been reported previously.[9] Briefly, between July 2000 and September 2002, a total of 6,814 persons were recruited at 6 field centers (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles, California; New York, New York; and St. Paul, Minnesota). Participants were required to be between 45 and 84 years of age and to have no clinical cardiovascular disease. All participants provided informed consent and the study protocol was approved by the Institutional Review Boards at each participating institution. Our analysis examined the relationship between baseline CAC measurements and incident AF. Participants were excluded if they did not undergo baseline measurement of CAC, a baseline diagnosis of AF was present, baseline characteristics were missing, or follow-up data regarding AF follow-up were missing.

Participant characteristics were collected during the initial MESA visit. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized as < $20,000, $20,000–$49,999, and ≥ $50,000, and education was categorized as "high school or less," "some college," and "college or more." Smoking was defined as current or ever smoker. Blood samples were obtained after a 12-hour fast and measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, plasma glucose, and high sensitivity C-reactive protein (hs-CRP) were used. Diabetes was defined as fasting glucose values ≥126 mg/dL or a history of diabetes medication use. Blood pressure was measured for each

participant after 5 minutes in the seated position and systolic measurements were recorded 3 separate times and the mean of the last two values was used. Aspirin, statin, antihypertensive, and lipid-lowering medication use were self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude AV_L plus S wave amplitude $V_3 \geq 2800$ mm males and ≥ 2000 mm females) using baseline electrocardiogram data.[10] In a subgroup of MESA participants who had cardiac magnetic resonance imaging (MRI) data (N=4,896), left ventricular end-diastolic mass and left ventricular ejection fraction were recorded. Myocardial horizontal and vertical tagging were performed on three left ventricular short-axis slices (base, mid, and apex) by nonselective radiofrequency pulses separated by a spatial modulation of magnetization-encoding gradients. Imaging and analytical methods for this technique have been previously described.[11]

CAC measurements were assessed by cardiac CT using either cardiac-gated electron-beam CT or multi-detector CT systems depending on the study site.[12] The CAC score was computed using the phantom-adjusted Agatston score for 2 consecutive scans for each participant and the mean value was used.[13] During the CT examinations, the 2 scans were independently analyzed for CAC by 2 analysts. Interobserver agreement between different CT image analysts who measured CAC on the same cardiac CT image was excellent (κ-statistic, 0.90). Similarly, intraobserver agreement was excellent when the same analyst measured CAC at separate time periods (κ-statistic, 0.93).

Follow-up phone calls to study participants every 9–12 months were used to identify AF events. Medical records, including discharge diagnoses, were obtained for each hospitalization. Additionally, for participants 65 years or older enrolled in fee-for-service Medicare, Medicare claims data were used to identify AF diagnoses in the inpatient setting. Incident AF was defined by International Classification of Disease Ninth Revision codes 427.31 or 427.32.

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean ± standard deviation. Statistical significance for categorical variables was tested using the chi-square method and the Wilcoxon rank-sum procedure for continuous variables. Kaplan-Meier estimates were used to compute cumulative incidence of AF by CAC score and the differences in incidence estimates were compared using the log-rank procedure.[14] Follow-up time was defined as the time between initial visit until the diagnosis of AF or until death, loss to follow-up, or end of follow-up (December 31, 2010). Cox proportional hazards regression was used to compute hazard ratios (HR) and 95% confidence intervals (95%CI) for the association between CAC scores and AF. CAC was examined using predefined categories (0, 1–100, 101–300, and >300).[6] Additionally, CAC scores were analyzed as a continuous variable using the base-2 logarithm of the CAC score plus 1 ($\log_2$[CAC + 1]) to examine the risk of AF when the CAC score doubles.[5] Multivariable models were constructed with incremental adjustments as follows: Model 1 adjusted for age, sex, race/ethnicity, income, and education; Model 2 adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, BMI, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medications, hs-CRP, and left

ventricular hypertrophy. The proportional hazards assumption was not violated in our analysis. We tested for interactions between our main effect variable and age, sex, and race/ethnicity. Additionally, we further adjusted for coronary heart disease events as a time-dependent variable to examine whether incident coronary heart disease events mediate the association between CAC and AF. In participants with cardiac MRI data, we further adjusted for left ventricular end-diastolic mass and left ventricular ejection fraction.

We assessed the ability of CAC to predict AF by computing the C-statistic using covariates from the Framingham Heart Study and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF consortium risk models for AF.[15,16] The added predictive ability of CAC was compared by the difference in C-statistics of the models before and after CAC inclusion. We also investigated the integrated discrimination improvement (IDI) and relative IDI. The integrated discrimination improvement (IDI) quantifies the increase in the difference between mean predicted risks for participants who do and do not develop AF after adding CAC to the model and this measure also was computed.[17,18] Additionally, net reclassification improvement (NRI) which quantifies any desirable change in predicted risk was computed for the following risk categories: <2.5%, 2.5% to 5%, >5%.[19] Statistical significance was defined as $p < 0.05$. SAS Version 9.3 (Cary, NC) was used for all analyses.

RESULTS

Of the 6,814 participants from the original MESA cohort, 58 participants had a diagnosis of AF before enrollment in MESA. These cases, detected by Centers for Medicare & Medicaid Services linkage, were excluded although they did not have AF in the baseline electrocardiogram. Of those that remained, 6 participants with missing follow-up data and 109 participants missing either baseline characteristics or medication data also were excluded. A total of 6,641 study participants (mean age 62 ± 10; 53% women; 38% whites; 27% blacks; 22% Hispanics; 12% Chinese-Americans) were included in the final analysis.

Over a median follow-up of 8.5 years, 308 (4.6%) participants developed AF. Baseline characteristics for study participants stratified by AF are shown in Table 1. The incidence rate of AF increased with increasing CAC scores (Table 2). Unadjusted cumulative incidence curves for AF by CAC scores are shown in Figure 1 (log-rank $p<0.0001$). In an unadjusted Cox regression model, higher CAC scores were associated with an increased risk of AF (CAC=0: HR=1.0; CAC=1–100: HR=2.5, 95%CI=1.8, 3.4; CAC=101–300: HR=4.3, 95%CI=3.1, 6.1; CAC>300: HR=6.9, 95%CI=5.0, 9.4). Similarly, doubling of the CAC score was associated with a 23% increased risk of AF ($p<0.0001$). This pattern of increasing risk of AF associated with increasing CAC scores persisted after adjustment for socio-demographics, cardiovascular risk factors, and potential confounders (Table 2). These results were consistent in subgroup analyses by sex and race/ethnicity (Table 3). A significant interaction was observed for age, with the association being slightly stronger for participants less than 62 years (Table 3). The association between CAC and AF remained significant after further adjustment for coronary heart disease events as a time-dependent variable ($\log_2$[CAC + 1]; HR=1.1, 95%CI=1.05, 1.12), left ventricular end-diastolic mass

($\log_2$[CAC + 1]; HR=1.1, 95%CI=1.05, 1.14), and left ventricular ejection fraction ($\log_2$[CAC + 1]; HR=1.1, 95%CI=1.06, 1.15).

The addition of CAC to the Framingham Heart Study and CHARGE AF risk scores improved the C-statistic from 0.771 to 0.784 (p=0.0048) and 0.789 to 0.798 (p=0.0025), respectively. Also, the addition of CAC to the Framingham Heart Study and the CHARGE AF risk scores yielded an IDI of 0.0033 (95%CI=0.0015, 0.0066) and 0.0028 (95%CI=0.0012, 0.0057) and with relative IDI of 0.10 (95%CI=0.061, 0.15) and 0.077 (95%CI=0.040, 0.11), and a categorical NRI of 0.051 (95%CI=0.015, 0.089) and 0.039 (95%CI=0.0068, 0.075), respectively.

DISCUSSION

In this analysis from MESA, increasing CAC scores were independently associated with the development of AF. This association was consistent across subgroups stratified by sex and race/ethnicity. To our knowledge, this is the first study to show an association between CAC scores and incident AF.

The multi-ethnic population of MESA allowed us to examine if racial differences exist between the association of AF and CAC scores. The prevalence and severity of CAC has been shown to vary among the ethnic groups of MESA.[20] However, our results suggest that racial differences do not exist between CAC and AF.

An interaction by age was observed with a significantly stronger association in participants less than 62 years of age. The level of CAC varies with age and older persons have been shown to have increased CAC scores compared with younger persons.[21] However, young to early middle-aged persons with increased risk for coronary heart disease events also have increased levels of CAC.[22] Potentially, the stronger association of CAC with AF among younger study participants reflects a population subgroup with an increased predisposition for cardiovascular disease, including arrhythmias such as AF.

There are several explanations for the association between CAC and AF. Potentially, the association between CAC and AF is mediated by coronary heart disease events.[2–6,23,24] However, the association between CAC and AF remained significant after adjusting these events. Persons with increased levels of CAC have enlarged left atria and pulmonary veins and both structures are associated with AF.[8,25] Although unable to directly adjust for these structures, our results remained significant after adjusting for surrogate markers (electrocardiogram left ventricular hypertrophy and MRI left ventricular mass and function). Additionally, higher levels of inflammation are associated with the development of CAC and AF.[26,27] It is plausible that dysfunctional regulation of this biological process associated with CAC increases one's risk for AF. However, our results remained significant after adjustment for markers of inflammation (i.e. hs-CRP), suggesting that the relationship between CAC and AF unlikely is to be fully explained by inflammation. Nonetheless, the findings of this study suggest an association between CAC and AF and further studies are needed to determine the underlying pathophysiologic link between CAC and AF.

Our results show that CAC improves discrimination and reclassification of AF beyond variables included in the Framingham Heart Study and CHARGE AF risk scores for AF.[15,16] Cardiac CT is a relatively non-invasive technique that can easily detect the presence and severity of CAC.[1] Potentially, this imaging modality is able to improve the prediction of AF risk and identify persons who are high-risk for the development of AF. However, further research is needed to determine which populations will benefit from such screening as this was beyond the scope of the current study.

Our results should be read in the context of certain limitations. Paroxysmal cases of AF possibly were missed due to the time-dependent nature of this condition. Incident AF cases were ascertained from hospitalization discharge records and inpatient Medicare claims using International Classification of Disease codes which possibly resulted in misclassification. However, these codes have adequate positive predictive value for the identification of AF events.[28] The ability of CAC to predict AF may vary by anatomic location and this was not examined. Additionally, cardiac CT is unable to distinguish medial and intimal calcification and results may vary by the location of calcium within the coronary artery.[29] We included several covariates in our multivariate models that likely are to influence the development of AF. However, we acknowledge that residual confounding remains a possibility.

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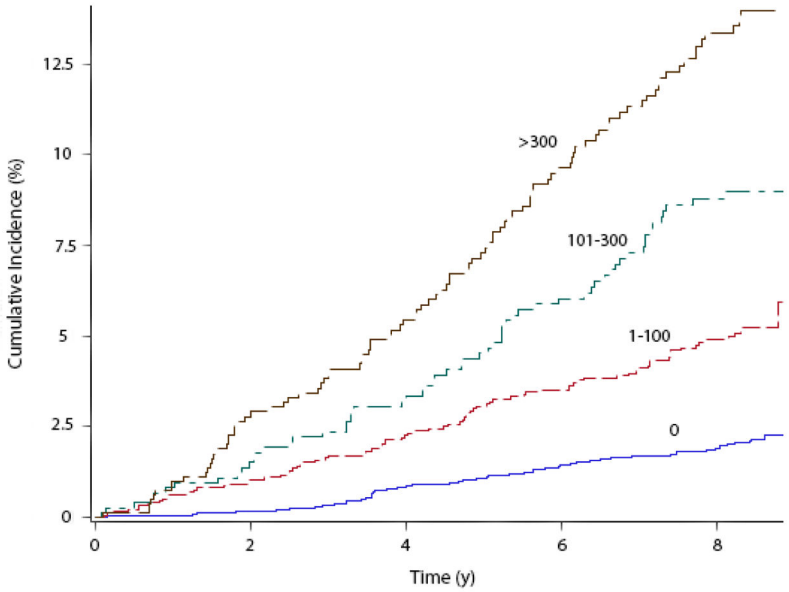

Figure 1. Unadjusted Cumulative Incidence of Atrial Fibrillation by Coronary Artery Calcium Score (N=6,641)*

*Cumulative incidence curves are different between all groups (log-rank p <0.0001).

y=years.

Table 1

Baseline Characteristics of Study Participants Stratified by Atrial Fibrillation (N=6,641)

Characteristic	AF (n=308)	No AF (n=6,333)	P-value*
Age, mean ± SD (years)	70 ± 8.0	62 ± 10	<0.0001
Male	189 (61%)	2,941 (46%)	<0.0001
White	168 (55%)	2,381 (38%)	
Black	66 (21%)	1,757 (28%)	
Chinese-American	21 (6.8%)	773 (12%)	
Hispanic	53 (17%)	1,422 (22%)	<0.0001
Education			
At least high school	118 (38%)	2,299 (36%)	
Some college	78 (25%)	1,814 (29%)	
College or more	112 (36%)	2,220 (35%)	0.45
Annual income			
<$20,000	99 (32%)	1,680 (27%)	
$20,000-$49,999	106 (34%)	2,219 (35%)	
≥$50,000	103 (33%)	2,434 (38%)	0.067
Body mass index, mean ± SD (kg/m^2)	29 ± 5.6	28 ± 5.5	0.19
Current or former smoker	180 (58%)	3,107 (49%)	0.0013
Diabetes	51 (17%)	878 (14%)	0.24
Systolic blood pressure, mean ± SD (mm Hg)	135 ± 22	126 ± 21	<0.0001
Total cholesterol, mean ± SD (mg/dL)	190 ± 36	194 ± 36	0.011
HDL-cholesterol, mean ± SD (mg/dL)	50 ± 15	51 ± 15	0.034
Antihypertensive medications	177 (57%)	2,262 (36%)	<0.0001
Statins	52 (17%)	924 (15%)	0.27
Aspirin	120 (39%)	1,452 (23%)	<0.0001
Lipid-lowering medications	56 (18%)	1,007 (16%)	0.29
hs-CRP, mean ± SD (mg/L)	3.9 ± 6.0	3.7 ± 5.9	0.31
Left ventricular hypertrophy	15 (4.9%)	241 (3.8%)	0.34
Coronary artery calcium score			
0	67 (22%)	3,283 (52%)	
<100	84 (27%)	1,660 (26%)	
100–300	60 (19%)	674 (11%)	
>300	97 (31%)	716 (11%)	<0.0001
Mean ± SD	444 ± 807	128 ± 377	<0.0001

* Statistical significance for continuous data was tested using Wilcoxon rank-sum procedure and categorical data was tested using the Chi-square test.

AF=atrial fibrillation; HDL=high-density lipoprotein; hs-CRP= high sensitivity C-reactive protein; SD=standard deviation.

Table 2

Risk of Atrial Fibrillation with Increasing Coronary Artery Calcium Score

CAC Score	Events/No. at risk	Incidence Rate per 1000 Person-Years (95%CI)	Model 1* HR (95%CI)	P-value	Model 2† HR (95%CI)	P-value
0	67/3,350	2.6 (2.0, 3.2)	1.0	-	1.0	-
1–100	84/1,744	6.4 (5.1, 7.9)	1.5 (1.04, 2.0)	0.027	1.4 (1.01, 2.0)	0.046
101–300	60/734	11 (8.5, 14)	1.8 (1.2, 2.6)	0.0017	1.6 (1.1, 2.4)	0.010
>300	97/813	17 (14, 21)	2.4 (1.7, 3.3)	<0.0001	2.1 (1.4, 2.9)	<0.0001
$Log_2(CAC + 1)$‡	308/6,641	6.1 (5.4, 6.8)	1.1 (1.07, 1.14)	<0.0001	1.1 (1.05, 1.13)	<0.0001

*Adjusted for age, sex, race/ethnicity, income, and education.

†Adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medications, hs-CRP, and left ventricular hypertrophy.

‡Denotes HR for AF with doubling of CAC score.

AF=atrial fibrillation; CAC=coronary artery calcium; CI=confidence interval; HDL=high-density lipoprotein; hs-CRP= high sensitivity C-reactive protein; HR=hazard ratio.

Table 3

Risk of Atrial Fibrillation with Increasing Coronary Artery Calcium Score Stratified by Age, Sex, and Race/Ethnicity*

Subgroup	Events/No. at risk	Unadjusted HR (95%CI)	P-value	Model 1† HR (95%CI)	P-value	Model 2‡ HR (95%CI)	P-value	Interaction P-value§
Age, years ‖								
<62	43/3,235	1.3 (1.2, 1.4)	<0.0001	1.3 (1.1, 1.4)	<0.0001	1.2 (1.1, 1.3)	0.0004	0.048
≥62	265/3,406	1.15 (1.1, 1.2)	<0.0001	1.1 (1.07, 1.15)	<0.0001	1.1 (1.06, 1.14)	<0.0001	
Sex								
Female	119/3,511	1.2 (1.19, 1.3)	<0.0001	1.1 (1.06, 1.2)	<0.0001	1.1 (1.05, 1.2)	0.0005	0.28
Male	189/3,130	1.2 (1.16, 1.3)	<0.0001	1.1 (1.05, 1.14)	0.0001	1.1 (1.03, 1.13)	0.0015	
Race/Ethnicity								
White	168/2,549	1.2 (1.15, 1.25)	<0.0001	1.1 (1.03, 1.13)	0.0026	1.1 (1.02, 1.12)	0.010	0.11
Non-White	140/4,092	1.3 (1.2, 1.31)	<0.0001	1.1 (1.08, 1.19)	<0.0001	1.1 (1.05, 1.17)	<0.0001	

*HRs presented are for the continuous variable, $\log_2(\text{CAC} + 1)$.

†Adjusted for age, sex, race/ethnicity, income, and education.

‡Adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL-cholesterol, aspirin, antihypertensive and lipid-lowering medications, hs-CRP, and left ventricular hypertrophy.

§Interactions tested using Model 2.

‖Dichotomized at the median age for study participants.

CAC=coronary artery calcium; CI=confidence interval; HDL=high-density lipoprotein; HR=hazard ratio; hs-CRP= high sensitivity C-reactive protein; y=years.