Coronary Artery Calcium Progression and Atrial Fibrillation
The Multi-Ethnic Study of Atherosclerosis

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Background—Coronary artery calcium (CAC) measured at a single time point has been associated with an increased risk for atrial fibrillation (AF). It is unknown whether CAC progression over time carries a similar risk.

Methods and Results—This analysis included 5612 participants (mean age: 62±10; 52% women; 39% whites; 27% blacks; 20% Hispanics; 12% Chinese Americans) from the Multi-Ethnic Study of Atherosclerosis. Phantom-adjusted Agatston scores for baseline and follow-up measurements were used to compute change in CAC per year (≤0, 1–100, 101–300, and >300 U/year). AF was ascertained by review of hospital discharge records and from Medicare claims data through December 31, 2010. Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between CAC progression and AF. Over a median follow-up of 5.6 years (25th, 75th percentiles=5.1, 6.8), a total of 203 (3.6%) incident AF cases were detected. Any CAC progression (>0/year) was associated with an increased risk for AF (HR=1.55, 95% CI=1.10, 2.19), and the risk increased with higher levels of CAC progression (≤0/year: HR=1.0 [reference]; 1–100/year: HR=1.47, 95% CI=1.03, 2.09; 101–300/year: HR=1.92, 95%CI=1.15, 3.20; >300/year: HR=3.23, 95%CI=1.48, 7.05). An interaction was observed by age with the association of CAC progression with AF being stronger for younger (<61 years: HR=3.53, 95% CI=1.29, 9.69) compared with older (≥61 years: HR=1.42, 95% CI=0.99, 2.04) participants (P interaction=0.037).

Conclusions—CAC progression during an average of 5 to 6 years of follow-up is associated with an increased risk for AF.

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Key Words: atherosclerosis ■ atrial fibrillation ■ coronary calcium ■ coronary vessels ■ epidemiology

Atrial fibrillation (AF) is the most common arrhythmia encountered in clinical practice, affecting nearly 3 million Americans.1 AF represents a substantial burden to the healthcare system with incremental costs projected between $6 billion for AF-related care and $26 billion for AF-related care plus other cardiovascular and noncardiovascular care.2 Additionally, the prevalence of AF is projected to double by 2050, and this largely is explained by the expected growth in individuals over 65 years of age.4 Because of the rather large burden that will be placed on the healthcare system to treat AF and finance the care provided, an understanding of risk factors is of paramount importance for the development of targeted preventive interventions.

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Recently, we have shown that coronary artery calcium (CAC) is associated with an increased risk of AF, and the associated risk was found to be stronger for younger compared with older participants.4 These findings suggest that the presence of subclinical atherosclerosis is highly predictive of AF development and implicate vascular age as an important marker of AF risk. It is unclear, however, if the rate of CAC progression over time also will be predictive of AF. Such a finding would suggest that the risk of AF not only depends on the presence of CAC but also on the rate at which the coronary arteries age. Therefore, the purpose of this study was to examine the association of CAC progression with AF in the Multi-Ethnic Study of Atherosclerosis (MESA).

Methods

Study Population
Details of MESA have been reported previously.3 Briefly, between July 2000 and September 2002, a total of 6814 persons were recruited at 6 field centers (Baltimore, MD; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). Participants were required to be between 45 and 84 years of age and to have no...
clinical cardiovascular disease at baseline. All participants provided informed consent, and the study protocol was approved by the Institutional Review Boards at each participating institution.

For the purpose of this analysis, we included participants with CAC measurements at baseline (2000–2002) and follow-up (Examination 2: 2002–2004; Examination 3: 2004–2005). Participants were excluded if clinically recognized AF was present before the follow-up CAC measurement or if they were missing CAC measurements, baseline characteristics, or follow-up data.

Baseline Characteristics

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 or ≥$20,000, and education was categorized as high school or less or some college or more. Smoking was defined as ever (eg, current or former) versus never smoker. Blood samples were obtained after a 12-hour fast, and measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used. Diabetes mellitus was defined as a fasting glucose value ≥126 mg/dL or a history of diabetes mellitus medication use. Blood pressure was measured for each participant after 5 minutes in the seated position. Systolic measurements were recorded 3 separate times, and the mean of the last 2 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 A >V1 plus S wave amplitude V3 ≥28 mm males and ≥22 mm females) using baseline ECG data.

Coronary Artery Calcium

CAC was assessed by cardiac computed tomography (CT) using either cardiac-gated electron-beam CT or multi-detector CT systems, depending on the study site, and the average effective radiation dose per scan in millisieverts (mSv) ranged from 0.6 to 5.6 mSv.7 The CAC score was computed using the phantom-adjusted Agatston score for 2 consecutive scans for each participant, and the mean value was used.8 During the CT examinations, the 2 scans were independently analyzed by 2 analysts. Interobserver agreement between different 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). Phantom-adjusted Agatston scores for baseline and follow-up measurements were used to compute the change in CAC per year. For those with >100 U of change per year, intervals (eg, 1–100, 101–300, and >300 U/year) that have been described previously from MESA were used to compare with participants who had ≤100 U/year change (eg, no change or reduction in CAC score).9 Participants with any progression (>0/year change) also were compared with those without progression (≤0/year change).

Atrial Fibrillation

Follow-up phone calls to study participants every 9 to 12 months were used to identify AF events. Medical records, including discharge diagnoses, were obtained for each hospitalization. Additionally, for participants ≥65 years 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.

Statistical Analysis

Baseline characteristics were compared by the presence of baseline CAC. Categorical variables were reported as frequency and percentage, whereas continuous variables were recorded as mean±standard deviation. Statistical significance for categorical variables was tested using the χ2 method and for continuous variables using the student’s t test procedure. Kaplan–Meier estimates were used to compute cumulative incidence of AF by CAC progression, and the differences in estimates were compared using the log-rank procedure.10 Follow-up time was defined as the time between the follow-up CT scan until a diagnosis of AF, death, loss to follow-up, or end of follow-up (December 31, 2010). Cox regression was used to compute hazard ratios (HR) and 95% confidence intervals (CI) for the association between CAC progression and AF. Multivariable models were constructed with incremental adjustment as follows: Model 1 adjusted for age, sex, race/ethnicity, education, income, and baseline CAC; Model 2 adjusted for Model 1 covariates plus systolic blood pressure, body mass index, diabetes mellitus, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, aspirin, and left ventricular hypertrophy. The proportional hazards assumption was not violated in our analysis. Additionally, we tested for interactions by age (dichotomized at median age), sex, race/ethnicity (white versus nonwhite), and the presence of baseline CAC (CAC=0 versus CAC>0). We examined the graphical dose–response relationship between CAC progression and the multivariable HR for AF using a restricted cubic spline model with incorporated knots at the 5th, 50th, and 95th percentiles.11 Sensitivity analyses were conducted with adjustment for study visit 3 covariates, incident coronary heart disease, and incident heart failure. We also performed a secondary analysis to determine whether those with reductions in CAC score (<0/year) had a reduced risk of AF compared with those without change (0/year). Statistical significance was defined as P<0.05. SAS Version 9.4 (Cary, NC) was used for all analyses.

Results

A total of 5612 participants (mean age 62±10; 52% women; 39% whites; 27% blacks; 20% Hispanics; 12% Chinese-Americans) were included in the final analysis. At baseline, 2904 (52%) had no evidence of CAC and 2708 (48%) had CAC values >0. Participants with baseline CAC were more likely to be older, male, white, diabetic, and to report smoking, lower educational attainment, and lower income compared with participants without baseline CAC (Table 1). Participants with CAC also were more likely to have higher values for systolic blood pressure and lower values for high-density lipoprotein cholesterol than those without CAC. Antihypertensive medications, aspirin, and lipid-lowering therapies were reported more frequently among those with baseline CAC.

The mean time between CT scans for study participants was 2.4±0.84 years. The median change in CAC/year was 0.26 (25th, 75th percentiles=0, 16.9) units. Participants with baseline CAC were more likely to have CAC progression (n=2357, 87%; P<0.0001). The median CAC progression for those with baseline CAC was 18 (25th, 75th percentiles=4.4, 53) units per year, and for those without baseline CAC, it was 0 (25th, 75th percentiles=0, 0) units per year (P<0.0001).

Over a median follow-up of 5.6 years (25th, 75th percentiles=5.1, 6.8), a total of 203 (3.6%) incident AF cases were detected. A higher incidence (per 1000 person-years) of AF was observed in those with CAC (>0/year) progression (incidence rate=10.0, 95% CI=8.6, 11.7) than in those without CAC progression (incidence rate=3.0, 95% CI=2.2, 3.9). The unadjusted cumulative incidence of AF among those with and without CAC progression is shown in Figure 1 (log-rank P<0.0001). Additionally, the incidence rate of AF increased with higher levels of CAC progression (Table 2). The unadjusted cumulative incidence of AF by CAC progression level is shown in Figure 2 (log-rank P<0.0001).
When we adjusted for age, sex, race/ethnicity, education, income, and baseline CAC, any CAC progression (>0/year) was associated with an increased risk for AF, and the risk increased with higher levels of CAC progression (Table 2). Similar results were obtained with further adjustment in Model 2 (Table 2). When the analysis was stratified by sex, race/ethnicity, and the presence of baseline CAC, the association between CAC progression and AF remained similar (Table 3). However, a differential association was observed by age, with the association between CAC progression and AF being stronger for younger (<61 years) compared with older (≥61 years) participants (P interaction =0.037; Table 3).

We also observed a dose–response relationship between CAC progression and the risk of AF. Figure 3 shows the association of CAC progression with AF across change in CAC/year computed in Model 2.

Any CAC progression (>0/year) was associated with an increased risk for AF when we used time-updated baseline covariates from study visit 3 (HR=1.56, 95% CI=1.09, 2.23) and after adjusting for incident coronary heart disease events.
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Discussion

In this analysis from MESA, CAC progression was associated with an increased risk for AF. A dose–response relationship was observed, suggesting that the AF risk associated with CAC progression depends on the rate at which CAC develops. Additionally, an interaction was observed when the analysis was stratified by age, with the association being stronger in younger compared with older adults.

Recently, we have shown that single CAC measurements predict incident AF in MESA. It was clearly shown that the risk of AF is not different in those with reductions (<0/year) in CAC compared with those who had no change (0/year; HR=1.02, 95% CI=0.48, 2.17).

Additionally, our data provide evidence that CAC progression is an important risk factor for AF development in persons without CAC from a single measurement. These persons may be deemed low-risk by single CAC measurements and subsequently reclassified as a population more likely to develop AF if CAC progression occurs.

The association between CAC progression and AF was found to be stronger among participants <61 years compared with those who were ≥61 years of age. A similar difference in AF risk by age was detected in our previous work using single CAC measurements. Similarly, in the Coronary Artery Disease in Young Adults (CARDIA) study, the presence of CAC in young and middle-aged adults was associated with an increased risk for adverse cardiovascular outcomes, and this risk increased with higher levels of calcium burden.

These findings suggest that the presence of subclinical atherosclerosis is highly predictive of future coronary events and demonstrates that young individuals with high CAC burden have an increased predisposition for cardiovascular disease development (eg, vascular age hypothesis). Our data extend previous literature to show that young individuals with high CAC burden also have an increased risk for AF. Additionally, the current study suggests that the rate of CAC progression in young persons is important when assessing AF risk instead of

Table 2. Risk of Atrial Fibrillation With CAC Progression (n=5612)

<table>
<thead>
<tr>
<th>Adjusted Absolute ∆CAC/y</th>
<th>Incidence Rate per 1000 Person-Years (95% CI)</th>
<th>Model 1* HR (95% CI)</th>
<th>P Value</th>
<th>Model 2† HR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤0</td>
<td>48/2789</td>
<td>3.0 (2.2, 3.9)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>1 to 100</td>
<td>109/2446</td>
<td>8.0 (6.7, 9.7)</td>
<td>1.52 (1.07, 2.17)</td>
<td>0.019</td>
<td>1.47 (1.03, 2.09)</td>
</tr>
<tr>
<td>101 to 300</td>
<td>33/315</td>
<td>20.3 (14.4, 28.6)</td>
<td>2.10 (1.27, 3.48)</td>
<td>0.0041</td>
<td>1.92 (1.15, 3.20)</td>
</tr>
<tr>
<td>&gt;300</td>
<td>13/62</td>
<td>45.8 (26.6, 78.8)</td>
<td>3.65 (1.66, 8.02)</td>
<td>0.0013</td>
<td>3.23 (1.48, 7.05)</td>
</tr>
<tr>
<td>No progression</td>
<td>48/2789</td>
<td>3.0 (2.2, 3.9)</td>
<td>1.0</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Any progression (&gt;0)</td>
<td>155/2823</td>
<td>10.0 (8.6, 11.7)</td>
<td>1.62 (1.15, 2.28)</td>
<td>0.0059</td>
<td>1.55 (1.10, 2.19)</td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CI, confidence interval; and HR, hazard ratio.

*Adjusted for age, sex, race/ethnicity, education, income, and baseline CAC.
†Adjusted for Model 1 covariates plus smoking, body mass index, diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, aspirin, and left ventricular hypertrophy.
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Table 3. Risk of Atrial Fibrillation With CAC Progression Stratified by Age, Sex, Race/Ethnicity, and Baseline CAC

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Events/No at Risk</th>
<th>Model 1† HR (95% CI)</th>
<th>P Value</th>
<th>Model 2‡ HR (95% CI)</th>
<th>P Value</th>
<th>Interaction P Value§</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;61</td>
<td>24/2665</td>
<td>4.45 (1.68, 11.75)</td>
<td>0.0026</td>
<td>3.53 (1.29, 9.69)</td>
<td>0.014</td>
<td>0.037</td>
</tr>
<tr>
<td>≥61</td>
<td>179/2947</td>
<td>1.48 (1.03, 2.11)</td>
<td>0.033</td>
<td>1.42 (0.99, 2.04)</td>
<td>0.055</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.31</td>
</tr>
<tr>
<td>Female</td>
<td>74/2946</td>
<td>1.93 (1.14, 3.29)</td>
<td>0.015</td>
<td>1.86 (1.09, 3.18)</td>
<td>0.024</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>129/2666</td>
<td>1.40 (0.90, 2.19)</td>
<td>0.14</td>
<td>1.34 (0.86, 2.10)</td>
<td>0.20</td>
<td></td>
</tr>
<tr>
<td>Race/ethnicity</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.53</td>
</tr>
<tr>
<td>White</td>
<td>114/2205</td>
<td>1.39 (0.87, 2.23)</td>
<td>0.17</td>
<td>1.44 (0.90, 2.30)</td>
<td>0.13</td>
<td></td>
</tr>
<tr>
<td>Non-White</td>
<td>89/3407</td>
<td>1.94 (1.17, 3.19)</td>
<td>0.0096</td>
<td>1.77 (1.07, 2.94)</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Baseline CAC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.24</td>
</tr>
<tr>
<td>CAC=0</td>
<td>50/2904</td>
<td>2.09 (1.16, 3.77)</td>
<td>0.015</td>
<td>2.10 (1.15, 3.84)</td>
<td>0.016</td>
<td></td>
</tr>
<tr>
<td>CAC&gt;0</td>
<td>153/2708</td>
<td>1.28 (0.76, 2.15)</td>
<td>0.35</td>
<td>1.32 (0.78, 2.22)</td>
<td>0.30</td>
<td></td>
</tr>
</tbody>
</table>

CAC indicates coronary artery calcium; CI, confidence interval; and HR, hazard ratio.
†HRs adjusted for age, sex, race/ethnicity, education, income, and baseline CAC.
‡Adjusted for Model 1 covariates plus smoking, body mass index, diabetes mellitus, systolic blood pressure, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, aspirin, and left ventricular hypertrophy.
§Interactions tested using Model 2.
||Dichotomized at the median age for study participants.

relying on single measurements of coronary calcium. Despite reports that have suggested the risk of radiation-induced cancer from whole body CT scanners is lower than the natural risk of cancer, future studies should assess the risk associated with repeated radiation exposure before serial measurements of CAC are recommended to identify persons who are at risk for AF development.

The pathophysiologic link between CAC burden and AF remains unclear. Shared risk factors between CAC development and AF possibly link both conditions (eg, high blood pressure, low high-density lipoprotein cholesterol, and obesity). However, the association between CAC progression and AF was not materially altered with adjustment for several of these factors. It has been suggested that persons with high levels of CAC also have enlarged left atria and pulmonary veins, structures associated with the arrhythmogenesis of AF. Potentially, persons who experience CAC progression are more likely to have enlargement of these structures, which provide the necessary substrate to maintain the arrhythmia. Therefore, the detection of CAC possibly identifies individuals who have the necessary abnormal electrophysiological connections that predispose to AF and also identifies those who will benefit from risk factor modification strategies (eg, lipid-lowering therapies) to reduce CAC burden and subsequent AF risk. Additionally, persons with CAC are more likely to develop coronary heart disease and heart failure, and these conditions are associated with an increased risk for AF development. Nonetheless, our findings were not substantively altered with adjustment for these potential mediators, suggesting that heart disease and heart failure do not completely explain our findings. In summary, the findings of this study suggest an association between CAC progression and AF, and further studies are needed to determine the underlying pathophysiologic link between these conditions.

Our results should be interpreted in the context of several limitations. CAC progression was based on 2 CT scans over an average interval of 2 years. The progression of CAC was presumed to be linear; however, it is possible that increases in CAC burden were not linear and the relationship between CAC progression and AF varies with different intervals. Additionally, we were unable to determine whether a baseline CAC value exists in which the AF risk is lowest and repeat CAC measurement is unnecessary. Paroxysmal and asymptomatic cases of AF possibly were missed. However, we do not know of any reason to suggest that the resulting bias, if any, would have been differential in nature, rather than merely reducing effect estimates toward the null (eg, diminishing power to detect a statistically significant result). Incident AF cases were ascertained from hospitalization discharge records and inpatient Medicare claims data using International Classification of Disease codes, which possibly resulted in misclassification. However, these codes have adequate positive predictive value for the identification of inpatient AF events, but miss AF cases managed entirely in the outpatient setting. Furthermore, we included several potential confounders in our multivariable models that likely influenced the development of AF, but we acknowledge that residual confounding remains a possibility similar to other epidemiological studies.

In this analysis from MESA, CAC progression was associated with an increased risk for AF development. Potentially, persons with low levels of CAC who subsequently have progression of CAC represent an at-risk population for AF. Additionally, we likely have identified a population with poor cardiovascular risk factor profiles who have the necessary substrate for AF to propagate. Therefore, targeted preventive programs that reduce the burden of subclinical atherosclerosis possibly will reduce the occurrence of AF.
Figure 3. Multivariable risk of atrial fibrillation by CAC progression. Each hazard ratio was computed using a restricted cubic spline model with the median change in CAC per year value of 0.26 as the reference and was adjusted for age, sex, race/ethnicity, education, income, baseline CAC, systolic blood pressure, body mass index, diabetes mellitus, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, aspirin, and left ventricular hypertrophy. Dotted lines represent the 95% confidence interval. CAC indicates coronary artery calcium.

References


**Clinical Perspective**

Atrial fibrillation is the most common arrhythmia encountered in clinical practice. Recently, increased levels of coronary artery calcium, a marker for subclinical atherosclerosis, obtained from single observations were shown to predict incident atrial fibrillation. It was unclear if the rate of coronary artery calcium progression also was predictive of atrial fibrillation. To address this question, we examined the association between coronary artery calcium progression and atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis. Coronary artery calcium progression was computed as the mean change per year in the phantom-adjusted Agatston score between 2 consecutive computed tomography scans. Incident cases of atrial fibrillation were identified by review of hospital discharge records and from Medicare claims data. In this prospective cohort study, coronary artery calcium progression was associated with an increased risk for atrial fibrillation, and a dose–response relationship was observed, suggesting that the atrial fibrillation risk depends on the rate at which coronary calcium develops. Potentially, we have identified a population with poor cardiovascular risk factor profiles who also have the necessary substrate for arrhythmia propagation. Our findings also suggest that targeted preventive programs that reduce the burden of subclinical atherosclerosis will reduce the occurrence of atrial fibrillation.
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