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Mitral annular calcification and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis

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Aims The associations of mitral annular calcification (MAC) with atrial fibrillation (AF) risk factors and related outcomes suggest a possible association between MAC and AF. The aim of this study was to examine the association between MAC and AF in a racially and ethnically diverse population.

Methods and results This analysis included 6641 participants (mean age 62 ± 10 years; 53% women; 27% Blacks; 22% Hispanics; 12% Chinese-Americans) from the Multi-Ethnic Study of Atherosclerosis (MESA) who were free of clinical cardiovascular disease and AF at baseline. The presence of MAC was defined by cardiac computed tomography (CT) as an Agatston score >0. Atrial fibrillation was ascertained by hospital discharge records and from Medicare claims data until 31 December 2010. Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (95% CIs) for the association between MAC and AF. At baseline, 619 (9.3%) participants had MAC. Over a median follow-up of 8.5 years, 308 (4.6%) participants developed AF. In a multivariable adjusted model, MAC was associated with an increased risk of AF (HR = 1.9, 95% CI = 1.5, 2.5). This association was consistent across subgroups of age, sex, race/ethnicity (Whites vs. non-Whites), hypertension, diabetes, and left atrial enlargement. The addition of MAC to the Framingham Heart Study and CHARGE AF risk scores for AF improved the C-statistics from 0.769 to 0.776 ($P = 0.038$) and 0.788 to 0.792 ($P = 0.089$), respectively.

Conclusion The presence of MAC was predictive of incident AF in MESA. Potentially, these findings suggest a usefulness of cardiac CT to identify individuals at risk for AF.

Keywords Mitral annulus calcification • Epidemiology • Atrial fibrillation

Introduction

Mitral annular calcification (MAC) is a chronic degenerative process that affects the base of the mitral valve. Several atrial fibrillation (AF) risk factors such as diabetes and hypertension have been associated with the presence of MAC.[1,2] Also, it has been shown that MAC is an independent predictor of future cardiovascular events.[3–6] This includes outcomes that have been linked to AF such as myocardial infarction and ischaemic stroke.[7,8] These findings suggest a potential association between MAC and AF.

In the Framingham Heart Study, MAC was associated with the development of AF.[9] However, this study consists of a predominantly White population and MAC was measured by echocardiography. Currently, it is unknown whether MAC, detected by a more precise imaging modality such as computed tomography (CT), is a risk factor for AF and whether such an association exists in a racially and ethnically diverse population.

The purpose of this study was to examine the association between MAC and incident AF in the Multi-Ethnic Study of Atherosclerosis (MESA). The diverse population of MESA allowed us to examine

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What's new?

- Currently, it is unknown if mitral annular calcium (MAC), detected by a more precise imaging modality such as cardiac computed tomography (CT), is a risk factor for atrial fibrillation (AF) and whether such an association exists in a racially and ethnically diverse population.
- Using data from the Multi-Ethnic Study of Atherosclerosis, we showed that MAC is associated with incident AF and this association does not differ by age, sex, race/ethnicity, hypertension, diabetes, or left atrial enlargement. Additionally, we showed that MAC improves discrimination of AF prediction beyond variables included in common risk scores for AF.
- These findings suggest a potential usefulness of cardiac CT to identify individuals at risk for developing AF.

whether differences between MAC and incident AF exist by race and/or ethnicity. Also, cardiac CT was used to measure MAC and the association between MAC and AF has not been examined using this technique.

Methods

Study population

Details of MESA have been described previously.[10] Briefly, between July 2000 and September 2002, 6814 participants were recruited at six field centres in the USA (Baltimore, ML; Chicago, IL; Forsyth County, NC; Los Angeles, CA; New York, NY; and St. Paul, MN). Requirement for study participation included age between 45 and 84 years and for participants not to have clinical cardiovascular disease at the time of study enrollment. For the purpose of this analysis, participants were excluded if they did not undergo baseline MAC measurement, baseline AF was present, or if baseline characteristics and/or follow-up data were missing.

Mitral annular calcification

Mitral annular calcification was assessed by cardiac CT at study enrollment using either cardiac-gated electron-beam CT or multi-detector CT systems depending on the study site.[11] All participants in MESA underwent two consecutive scans and the mean MAC value was recorded. The two scans were analysed separately for MAC by two independent analysts. Inter-observer and intra-observer agreement between different CT image analysts who measured MAC on the same cardiac CT image were excellent and have been previously reported.[11,12] The MAC score was computed using the phantom-adjusted Agatston method.[13] Mitral annular calcification was defined by the presence of calcium (Agatston score >0) on the mitral valve.

Atrial fibrillation

Follow-up phone calls to study participants every 9–12 months were used to identify hospitalizations and medical records, including discharge records. Additionally, for participants $\geq$65 years enrolled in fee-for-service Medicare, Medicare claims data were used to identify inpatient AF cases. Incident AF was defined by International Classification of Disease Ninth Revision codes 427.31 or 427.32.

Baseline characteristics

Participant characteristics collected during the initial MESA visit were used in this analysis. Age, sex, race/ethnicity, income, and education were self-reported. Annual income was categorized into three levels ($<$\$20 000, \$20 000–\$49 999, and $\geq$\$50 000). Similarly, education was categorized into 'high school or less,' 'some college,' and 'college or more.' Smoking was defined as ever (e.g. current or former) or never smoker. Blood samples were obtained after a 12 h fast and measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, plasma glucose, and high-sensitivity C-reactive protein (hs-CRP) were used in this analysis. Additionally, a subgroup of study participants' blood samples were analysed for levels of amino-terminal-pro-brain natriuretic peptide (NT-proBNP) and these values were used. Diabetes was defined as fasting glucose values $\geq$126 mg/dL or a history of diabetes medication use. After the participant rested for 5 min in a seated position, blood pressure was recorded three separate times and the mean of the last two values was used in this analysis. Hypertension was defined as a systolic/diastolic blood pressure values $\geq$140/90 mm Hg and/or a history of antihypertensive medication use. The use of aspirin, statins, and antihypertensive and lipid-lowering medications were self-reported. Body mass index was computed as the weight in kilograms divided by the square of the height in meters. Using baseline electrocardiogram data, left ventricular hypertrophy was defined by the Cornell criteria (R wave amplitude AV_L plus S wave amplitude V_3 $\geq$2800 mm for men and $\geq$2000 mm for women) and left atrial enlargement was defined by Novacode criteria (Novacode 7.1).[14,15] In a subgroup of MESA participants who had cardiac magnetic resonance imaging (MRI) data ($N = 4\,896$), left ventricular end-diastolic mass and left ventricular ejection fraction were recorded. Briefly, whole-body MRI scanners using electrocardiogram triggered segmented k-space fast gradient-echo pulse sequences during breath holds were used. Myocardial horizontal and vertical tagging were performed on three left ventricular short-axis slices (base, mid, and apex) by non-selective radio-frequency pulses separated by a spatial modulation of magnetization-encoding gradients. Imaging and analytical methods for this technique have been described.[16]

Statistical analysis

Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean $\pm$ standard deviation. Statistical significance for categorical variables was tested using the χ^2 method and the Wilcoxon rank-sum procedure for continuous variables. Follow-up time was defined as the time between the initial study visit until the diagnosis of AF or until death, loss to follow-up, or end of follow-up which was 31 December 2010. Kaplan–Meier estimates were used to compute cumulative incidence of AF by MAC and the difference in estimates was compared using the log-rank procedure.[17] Cox proportional-hazards regression was used to compute hazard ratios (HRs) and 95% confidence intervals (95% CI) for the association between MAC and AF. In all models, the association of MAC and AF was assessed by the presence of MAC (Agatston score >0) vs. no MAC (Agatston score $= 0$). Additionally, MAC scores were analysed as a continuous variable using the base-2 logarithm of the MAC score plus one ($\log_2[\text{MAC} + 1]$) to examine the risk of AF when the MAC score doubles. The addition of one allows for non-zero values to be included. We also constructed a restricted cubic spline model to examine the graphical dose–response relationship between MAC and the multivariable HR for AF and incorporated knots at the 5th, 50th, and 95th percentiles.[18] Multivariable models were constructed with incremental adjustments as follows: Model 1 adjusted for age, sex, race/ethnicity (Whites vs. non-Whites), income, and education; Model 2 adjusted for Model 1 covariates plus smoking status, systolic blood pressure, diabetes, body mass index, total cholesterol, HDL cholesterol, antihypertensive and lipid-lowering medication use, aspirin, hs-CRP, left ventricular hypertrophy, and left atrial enlargement. We tested for interactions between our main effect variable and

age (dichotomized at 65 years), sex, race/ethnicity (Whites vs. non-Whites), hypertension, diabetes, and left atrial enlargement.

Several sensitivity analyses were performed. In participants with available MRI data ($N = 4\,896$), we further adjusted for left ventricular end-diastolic mass and left ventricular ejection fraction, separately. Similarly, we further adjusted for NT-proBNP (ln[NT-proBNP]) among participants who had baseline measurements ($N = 5\,490$).[19] Additionally, due to a potential relationship between MAC and coronary artery calcium (CAC), we further adjusted for this variable ($\log_2[CAC + 1]$) among participants with CAC data ($N = 6\,614$).[20]

We assessed the ability of MAC to predict AF by computing the C-statistic using covariates from the Framingham Heart Study (age, sex, body mass index, systolic blood pressure, antihypertensive medication use, PR interval, clinically significant cardiac murmur, and heart failure) and the Cohorts for Heart and Aging Research in Genomic Epidemiology (CHARGE) AF (age, race, height, weight, systolic blood pressure, diastolic blood pressure, current smoking, antihypertensive medication use, diabetes, history of myocardial infarction, and history of heart failure, PR interval, and electrocardiogram-derived left ventricular hypertrophy) consortium risk models for AF.[21,22] The Multi-Ethnic Study of Atherosclerosis participants had no evidence of clinical cardiovascular disease at baseline and these covariates were coded as not being present. The added predictive ability of MAC was evaluated by the difference in C-statistics of the models before and after inclusion of MAC in the predictive models. We additionally investigated the integrated discrimination improvement (IDI) and relative IDI.[23] Integrated discrimination improvement quantifies the increase in the difference between the mean predicted risks for participants who do and do not develop AF after adding MAC to the model. Additionally, net reclassification improvement (NRI) which quantifies any desirable change in predicted risk was computed for the following risk categories: <2.5, 2.5–5%, >5%.[24]

The proportional-hazards assumption was not violated in our analysis. Statistical significance was defined as $P < 0.05$. SAS Version 9.3 was used for all analyses.

Results

Of the 6814 participants from the original MESA cohort, 58 participants had a diagnosis of AF before study enrollment. The majority of these cases were detected by Medicare linkage and only one case was present in the baseline electrocardiogram. Of those that remained, 6 participants with missing follow-up data, and 109 participants with either missing baseline characteristics or missing medication data also were excluded. A total of 6641 study participants (mean age 62 ± 10 years; 53% women; 38% Whites; 27% Blacks; 22% Hispanics; 12% Chinese-Americans) had available MAC measurements and were included in the final analysis.

A total of 619 (9.3%) study participants had baseline MAC. Baseline characteristics for study participants are shown in *Table 1*. Participants with MAC were more likely to be older, female, and to have lower levels of education and income compared with participants without MAC. A higher percentage of White participants (12%) were observed to have MAC compared with other races (7.4% Blacks; 10% Hispanics; 5.8% Chinese-Americans) ($P < 0.0001$). Participants with MAC had higher values for body mass index, hs-CRP, and systolic blood pressure, and also were more likely to be diabetic and to have left ventricular hypertrophy and left atrial enlargement. Additionally, these participants were more likely to use aspirin, statins, and antihypertensive and lipid-lowering medications.

Table 1 Baseline characteristics of study participants stratified by MAC ($N = 6641$)

Characteristic	MAC ($n = 619$)	No MAC ($n = 6022$)	*P*-value*
Age, mean (SD), years	72 (7.7)	61 (9.9)	<0.0001
Male sex (%)	248 (40)	2882 (48)	0.0002
Race/ethnicity			
White (%)	301 (49)	2248 (37)	
Black (%)	134 (22)	1689 (28)	
Chinese-American (%)	36 (5.8)	758 (13)	
Hispanic (%)	148 (24)	1327 (22)	<0.0001
Education			
High school or less (%)	285 (46)	2132 (35)	
Some college (%)	157 (25)	1735 (29)	
College or more (%)	177 (29)	2155 (36)	<0.0001
Annual income			
< $20 000 (%)	248 (40)	1531 (25)	
$20 000 to $49 999 (%)	216 (35)	2109 (35)	
≥$50 000 (%)	155 (25)	2382 (40)	<0.0001
Body mass index, mean (SD) kg/m^2	29 (5.7)	28 (5.5)	0.0010
Current or former smoker (%)	303 (49)	2984 (50)	0.78
Diabetes (%)	136 (22)	793 (13)	<0.0001
Hypertension (%)	423 (68)	2742 (46)	<0.0001
Systolic Blood Pressure, mean (SD), mm Hg	135 (23)	125 (21)	<0.0001
Total cholesterol, mean (SD), mg/dL	194 (38)	194 (35)	0.47
HDL cholesterol, mean (SD), mg/dL	52 (15)	51 (15)	0.082
Antihypertensive medications (%)	333 (54)	2106 (35)	<0.0001
Statins (%)	145 (23)	831 (14)	<0.0001
Aspirin (%)	204 (33)	1,368 (23)	<0.0001
Lipid-lowering medications (%)	159 (26)	904 (15)	<0.0001
hs-CRP, mean (SD), mg/L	3.9 (5.8)	3.8 (5.9)	0.017
ECG-left ventricular hypertrophy (%)	34 (5.5)	222 (3.7)	0.026
ECG-left atrial enlargement (%)	149 (24)	846 (14)	<0.0001

ECG, electrocardiogram; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; MAC, mitral annular calcium; SD, standard deviation.
*Statistical significance for continuous data was tested using the Wilcoxon rank-sum procedure and categorical data were tested using the χ^2 test.

Over a median follow-up of 8.5 years, 308 (4.6%) participants developed AF. The incidence rate of AF was almost four-fold greater in those with MAC than in those without MAC (incidence rates per 1000 person-years: MAC, 19.8 (95% CI = 16.0, 24.5); no MAC 4.8 (95% CI = 4.2, 5.5); $P < 0.0001$). Unadjusted cumulative incidence curves for AF by MAC are shown in *Figure 1* (log-rank $P < 0.0001$).

In a multivariable Cox regression analysis, the presence of MAC was associated with almost double the risk of AF (*Table 2*). These results were consistent across subgroups stratified by age, sex,

race/ethnicity (Whites vs. non-Whites), hypertension, diabetes, and left atrial enlargement (*Table 2*).

We observed a dose–response relationship between MAC and the risk of AF. When MAC was used in a restricted cubic spline model as a continuous variable ($\log_2$[MAC + 1]), doubling of the MAC score was associated with a 20% increase in the risk of AF in an unadjusted model (HR = 1.2, 95% CI = 1.18, 1.3) and a 10% increased risk when adjusted for covariates in Model 1 (HR = 1.1, 95% CI = 1.08, 1.2) and Model 2 (HR = 1.1, 95% CI = 1.08, 1.2). *Figure 2* shows the association of MAC with AF across MAC values.

The association between MAC and AF remained significant after further adjustment of Model 2 for left ventricular end-diastolic mass (HR = 2.2, 95% CI = 1.6, 3.1), left ventricular ejection fraction (HR = 2.4, 95% CI = 1.7, 3.3), NT-proBNP (HR = 1.6, 95% CI = 1.2, 2.1), and CAC (HR = 1.8, 95% CI = 1.3, 2.3), separately.

The addition of MAC to the Framingham Heart Study and CHARGE AF risk scores improved the C-statistics from 0.769 to 0.776 ($P = 0.038$) and 0.788 to 0.792 ($P = 0.089$), respectively. Also, the addition of MAC to the Framingham Heart Study and the CHARGE AF risk scores yielded an IDI of 0.0037 (95% CI = 0.0017, 0.073) and 0.0028 (95% CI = 0.0008, 0.0061) with relative IDI of 0.12 (95% CI = 0.055, 0.18) and 0.077 (95% CI = 0.023, 0.13), and categorical NRI of 0.050 (95% CI = 0.021, 0.093) and 0.039 (95% CI = 0.014, 0.078), respectively.

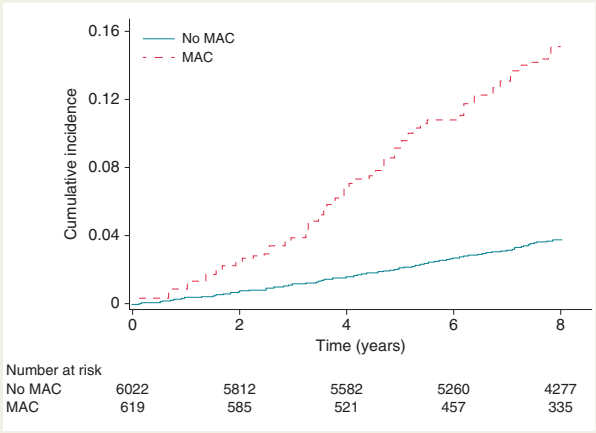

Figure 1 Unadjusted cumulative incidence of AF by MAC ($N = 6641$)*.
*Cumulative incidence curves are different (log-rank $P < 0.0001$).
AF, atrial fibrillation; MAC, mitral annular calcium.

Discussion

In this analysis from MESA, the presence of MAC was associated with an increased risk of incident AF. This association was consistent across subgroups stratified by age, sex, race/ethnicity, hypertension, diabetes, and left atrial enlargement. The risk of AF was shown to

Table 2 Risk of AF with MAC

	MAC events/no. at risk	No MAC events/no. at risk	Model 1[a] HR (95% CI)	*P*-value	Model 2[b] HR (95% CI)	*P*-value	Interaction *P*-value[c]
All participants	85/619	223/6022	2.0 (1.5, 2.6)	<0.0001	1.9 (1.5, 2.5)	<0.0001	–
Age, years							
<65	4/95	56/3683	2.5 (0.90, 6.9)	0.081	1.3 (0.44, 3.7)	0.66	0.88
≥65	81/524	167/2339	2.4 (1.8, 3.1)	<0.0001	2.3 (1.8, 3.0)	<0.0001	
Sex							
Female	39/371	80/3140	2.1 (1.4, 3.2)	0.0004	1.9 (1.3, 2.9)	0.0023	0.79
Male	46/248	143/2882	1.9 (1.4, 2.8)	0.0002	1.9 (1.3, 2.7)	0.0004	
Race							
White	50/301	118/2248	1.8 (1.3, 2.5)	0.0012	1.7 (1.2, 2.4)	0.0034	0.33
Non-White	35/318	105/3774	2.4 (1.6, 3.6)	<0.0001	2.2 (1.5, 3.4)	<0.0001	
Hypertension							
No	15/195	66/3259	1.4 (0.75, 2.5)	0.32	1.4 (0.74, 2.5)	0.32	0.76
Yes	70/424	157/2763	2.2 (1.6, 2.9)	<0.0001	2.1 (1.6, 2.8)	<0.0001	
Diabetes							
No	66/483	191/5229	1.8 (1.4, 2.5)	<0.0001	1.8 (1.3, 2.4)	0.0002	0.36
Yes	19/136	32/793	3.3 (1.8, 6.1)	0.0001	3.2 (1.7, 6.0)	0.0003	
Left atrial enlargement							
No	61/470	176/5176	1.9 (1.4, 2.6)	<0.0001	1.8 (1.3, 2.5)	0.0001	0.75
Yes	24/149	47/846	2.2 (1.3, 3.7)	0.0045	2.2 (1.3, 3.9)	0.0034	

AF, atrial fibrillation; CI, confidence interval; HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; HR, hazard ratio; MAC, mitral annular calcium.
[a]Adjusted for age, sex, race/ethnicity, income, and education.
[b]Adjusted for Model 1 plus smoking status, systolic blood pressure, diabetes, body-mass index, total cholesterol, HDL-cholesterol, antihypertensive and lipid-lowering medications, aspirin, hs-CRP, left ventricular hypertrophy, and left atrial enlargement.
[c]Interactions tested using Model 2.

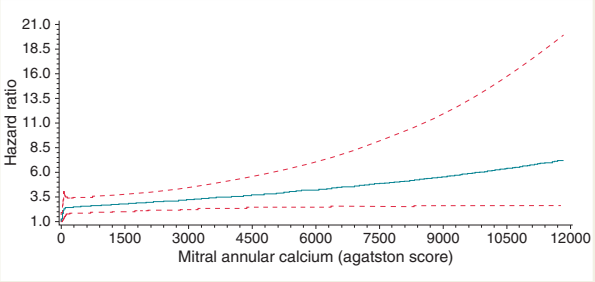

Figure 2 Multivariable-Adjusted Risk of AF by MAC*.
*Each HR was computed with the median MAC value of 0 as the reference and was adjusted for age, sex, and race/ethnicity. Dotted-lines represent the 95% confidence interval. AF, atrial fibrillation; MAC, mitral annular calcium; HR, hazard ratio.

increase with higher levels of MAC, suggesting that the level of MAC severity plays a role in the magnitude of AF risk. Additionally, MAC was found to improve reclassification beyond variables included in the Framingham Heart Study and CHARGE AF risk scores for AF prediction.

Mitral annular calcification has been shown to predict incident AF in the Framingham Heart Study and results were similar to those presented in this report (HR = 1.6, 95% CI = 1.1, 2.2).[9] In contrast with our study in which MAC was detected by cardiac CT, MAC was measured by echocardiography in the Framingham Study. Mitral annular calcification measurements by echocardiography were not obtained in MESA and we were unable to directly compare the results from the Framingham Study with our results. However, it has been proposed that CT is a better method to detect valvular calcification compared with echocardiography.[2] Additionally, the Framingham Heart Study is limited regarding racial and ethnic diversity. To our knowledge, our study is the first to report the association of MAC with incident AF in a racially and ethnically diverse population by cardiac CT.

Several cardiovascular risk factors which also are risk factors for AF have been associated with the progression of MAC.[1,2,21,25] These include older age, White race, diabetes, and hypertension.[25,26] Therefore, it is plausible that the presence of MAC reflects the detection of patients who are more likely to develop AF as they share similar risk factors. However, MAC was a significant predictor of AF after adjustment for these potential confounders, suggesting that MAC is independently associated with an increased risk of AF.

Mitral annular calcification has been associated with enlarged left atria in the Strong Heart Study and the association of left atrial size with AF is well established.[27–30] Furthermore, in the Framingham Heart Study, the association between MAC and incident AF was attenuated after adjustment for left atrial size measured by echocardiography (HR = 1.4, 95% CI = 0.9, 2.0).[9] These findings suggest that the association between MAC and AF is mediated by left atrial enlargement. It also is plausible that the presence of MAC coincides with enlarged left atria and MAC identifies persons who are more likely to have enlargement of these structures. However, our results show that the association between MAC and AF does not differ by electrocardiogram-diagnosed left atrial enlargement and our results remained significant after adjusting for this variable. The differences between the current study and the results reported from Framingham possibly are explained by differences in population diversity and/or the detection method of MAC. For example, Whites have a higher prevalence of AF and larger left atrial dimensions than Blacks.[31] Potentially, adjustment for left atrial enlargement did not have the same impact in the racially and ethnically diverse population of MESA compared with the predominantly White population of the Framingham Study. Additionally, left atrial enlargement in our study was defined by electrocardiographic data. However, this method has been shown to be specific and highly predictive of left atrial enlargement when measurements were confirmed by echocardiography.[32]

The degenerative calcification of the mitral valve has been closely linked with systemic inflammation.[33] Additionally, persons with AF have been shown to have higher levels of inflammatory markers than persons without AF.[34] Potentially, the association of MAC with AF is mediated through inflammatory processes as evidenced by systemic biomarkers. However, our results remained significant after adjustment for markers of inflammation, suggesting that the relationship between MAC and AF unlikely is to be fully explained by inflammation.

Our results should be read in the context of certain limitations. 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, this method has been reported to have adequate positive predictive value for identifying AF events.[35,36] Paroxysmal AF cases potentially were missed due to the time-dependent nature of this condition. Routine monitoring for AF (e.g. Holter monitors) was not performed in MESA and therefore 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 (e.g. diminishing power to detect a statistically significant result). Several potential confounders were included in our multivariable models that likely influenced the development of AF but we acknowledge that residual confounding remains a possibility. For example, the duration and severity of these potential confounders were unable to be fully adjusted for in our models (e.g. duration of hypertension, glucose control in diabetics, and continued tobacco use). Computed tomography allows excellent visualization of the anatomical details of the mitral valve and reliably measures the amount of calcification on the mitral valve annulus.[37] However, the utility of this measurement regarding AF risk assessment remains uncertain and further research is needed to determine its clinical significance. Potentially, persons who undergo cardiac CT for evaluation of chest pain are able to simultaneously be screened for AF risk using MAC measurements.[38]

Conclusion

In conclusion, we have shown that MAC is independently associated with an increased risk of AF and improves AF risk prediction. These findings suggest a potential usefulness of cardiac CT to identify individuals at risk for developing AF.

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