Mitral annular calcification progression and the risk of atrial fibrillation: results from MESA

Wesley T. O'Neal[1]*, Jimmy T. Efird[2], Saman Nazarian[3], Alvaro Alonso[4], Erin D. Michos[5], Moses Szklo[6], Susan R. Heckbert[7], and Elsayed Z. Soliman[8,9]

[1]Department of Medicine, Division of Cardiology, Emory University of School of Medicine, 101 Woodruff Circle, Woodruff Memorial Building, Atlanta, GA 30322, USA;
[2]Department of Cardiovascular Sciences, East Carolina Heart Institute, Brody School of Medicine, East Carolina University, 115 Heart Drive, Greenville, NC 27834, USA;
[3]Department of Medicine, Division of Cardiology, University of Pennsylvania School of Medicine, 9 Founders Pavilion, 3400 Spruce Street, Philadelphia, PA 19104, USA;
[4]Department of Epidemiology, Rollins School of Public Health, Emory University, 1518 Clifton Road NE, Atlanta, GA 30322, USA; [5]Department of Medicine, Division of Cardiology, and The Ciccarone Center for the Prevention of Heart Disease, Johns Hopkins University School of Medicine, 600 N. Wolfe Street, Baltimore, MD 21287, USA;
[6]Department of Epidemiology, Bloomberg School of Public Health, John Hopkins University, 615 N. Wolfe Street, Baltimore, MD 21205, USA; [7]Cardiovascular Health Research Unit and Department of Epidemiology, University of Washington, 1730 Minor Ave, Seattle, WA 98101, USA; [8]Department of Internal Medicine, Section on Cardiology, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA; and [9]Epidemiological Cardiology Research Center (EPICARE), Department of Epidemiology and Prevention, Wake Forest School of Medicine, Medical Center Blvd, Winston-Salem, NC 27157, USA

Aims	To determine if progression of mitral annular calcium (MAC) detected by cardiac computed tomography (CT) predicts incident atrial fibrillation (AF).
Methods and results	This analysis included 5683 participants (mean age 64 ± 10 years; 52% women; 40% whites; 27% blacks; 21% Hispanics; 12% Chinese–Americans) from the Multi-Ethnic Study of Atherosclerosis. MAC was measured by cardiac CT at baseline and at a follow-up CT scan over a mean time of 2.4 ± 0.84 years. AF was ascertained by review of hospital discharge records and from Medicare claims data through 31 December 2012. Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between MAC progression and AF. Over a median follow-up of 8.6 years, a total of 533 (9.4%) incident AF cases were detected. In a model adjusted for age, sex, race/ethnicity, education, income, baseline MAC, systolic blood pressure, body mass index, diabetes, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, and aspirin, any MAC progression (>0/year) was associated with an increased risk for AF (HR = 1.50, 95% CI = 1.20–1.87). Multiplicative interactions were not significant between MAC progression and AF by age (<65 year vs. older), sex, or race/ethnicity (whites vs. non-whites).
Conclusion	Important prognostic information regarding AF risk is obtained with follow-up MAC measurement, as the risk for participants with any MAC progression was substantively greater than participants without progression. MAC progression may detect underlying left atrial abnormalities that predispose to AF.
Keywords	mitral calcium • atrial fibrillation • cardiac CT

Introduction

Mitral annular calcification (MAC) is a chronic degenerative process that commonly affects the base of the mitral valve. Risk factors for its development include advanced age and female sex.[1,2] The presence of MAC has been shown to predict future cardiovascular events.[3–7] Additionally, reports from the Multi-Ethnic Study of Atherosclerosis (MESA) and the Framingham Heart Study have shown that MAC independently predicts the development of atrial fibrillation (AF).[8,9]

However, it is yet to be established whether the risk of AF associated with MAC also depends on the rate at which it develops (e.g. progression). It is possible that MAC progression is a better tool to identify individuals who are high risk for AF development than MAC measurements from a single point in time. Therefore, we hypothesized that MAC progression is an independent predictor of AF, and the predictive ability associated with this phenomenon exceeds the simple presence of MAC. Accordingly, we explored this hypothesis in MESA.

* Corresponding author. Tel: 404-727-4724; Fax: 404-712-8335. E-mail: wesley.oneal@emory.edu

Methods

Study population

MESA is a prospective study with aims to determine characteristics related to the progression of subclinical to clinical cardiovascular disease, and details have been previously reported.[10] Briefly, between July 2000 and September 2002, a total of 6814 persons were recruited at 6 field centres (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.

This study was a retrospective analysis of prospectively collected data to examine the relationship between MAC progression and AF development. For the purpose of this analysis, we included participants with MAC measurements at baseline (2000–02) and follow-up (either Exam 2: 2002–04 or Exam 3: 2004–05). Participants were excluded if clinically recognized AF was present before the follow-up MAC measurement, or if they were missing baseline characteristics or follow-up data.

Mitral annular calcium

Mitral annular calcium (MAC) was assessed by cardiac computed tomography (CT) 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 CT scans. The two scans were independently analysed by two analysts and MAC was defined by the presence of calcium (Agatston score > 0) on the mitral valve. The MAC score was computed using the phantom-adjusted Agatston method,[12] and the mean MAC value was recorded. Inter-observer (κ-statistic, 0.90) and intra-observer (κ-statistic, 0.93) agreement between different CT image analysts who measured MAC on the same cardiac CT image was excellent.[11,13] Phantom-adjusted Agatston scores for baseline and follow-up measurements were used to compute the change in MAC per year. Participants who had >0 units of change/year were compared with those who had no change or reductions (≤0 units/year) in MAC values between CT scans.[14]

Participant characteristics

Participant characteristics were collected during the second MAC measurement (either Exam 2: 2002–04 or Exam 3: 2004–05). 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 the current use of cigarettes. Blood samples were obtained after a 12-h fast and measurements of total cholesterol, high-density lipoprotein cholesterol, and plasma glucose were used. Diabetes was defined as fasting glucose values ≥126 mg/dL or diabetes medication use. Blood pressure was measured for each participant after 5 min in the seated position. Systolic measurements were recorded three separate times and the mean of the last two values was used. Aspirin, antihypertensive, and lipid-lowering medication use were ascertained by self-report or pill bottle review. Body mass index was computed as the weight in kilograms divided by the square of the height in metres.

Atrial fibrillation

Follow-up phone calls to study participants every 9–12 months were used to identify hospitalizations. 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 and outpatient settings. Incident AF was defined by International Classification of Disease Ninth Revision codes 427.31 or 427.32.

Statistical analysis

Baseline characteristics were compared by those with and without MAC progression. Categorical variables were reported as frequency and percentage while continuous variables were recorded as mean ± standard deviation (SD). Statistical significance for categorical variables was tested using the chi-square method and for continuous variables using the Student's *t*-test. Follow-up time was defined as the time between the second CT scan until a diagnosis of AF, death, loss to follow-up, or end of follow-up (31 December 2012). Cox regression was used to compute hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between MAC progression and AF. Kaplan–Meier estimates were used to compute cumulative incidence of AF by MAC progression and the differences in estimates were compared using the log-rank procedure.[15] Multivariable models were constructed with incremental adjustment as follows: Model 1 adjusted for age, sex, race/ethnicity, education, income, and baseline MAC; Model 2 adjusted for Model 1 covariates with the addition of systolic blood pressure, body mass index, diabetes, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, and aspirin. The proportional hazards assumption was not violated in our analysis. Additionally, we tested for multiplicative interactions using the likelihood ratio method by age (dichotomized at 65 years), sex, and race/ethnicity (white vs. non-white). We also examined if the association between MAC progression and AF was dependent on baseline values by limiting the analysis to participants with baseline MAC (*n* = 495). To demonstrate that the association between MAC progression and AF possibly is stronger than MAC measured at one time period, we compared the magnitude of the association for MAC progression in persons who had baseline MAC (*n* = 495) and those who did not have baseline MAC (*n* = 5188) per 1-SD increase in MAC progression. Statistical significance for all comparisons and tests for interaction was defined as *P* < 0.05. SAS version 9.4 (Cary, NC) was used for all analyses.

Results

A total of 5683 participants (mean age 64 ± 10 years; 52% women; 40% whites; 27% blacks; 21% Hispanics; 12% Chinese–Americans) were included in the final analysis. A total of 547 (9.6%) participants had MAC progression between CT scans and 5136 (90.4%) did not have MAC progression. Baseline characteristics for participants by MAC progression are shown in *Table 1*.

The mean time between CT scans for study participants was 2.4 ± 0.84 years. The mean change in MAC per year was 7.8 ± 95 units. Participants with baseline MAC (*n* = 495, 8.7%) were more likely to have MAC progression (*n* = 323, 65%) compared with participants without baseline MAC (*n* = 224, 4.3%) (*P* < 0.001).

Over a median follow-up of 8.6 years (25th, 75th percentile = 7.8, 9.6), a total of 533 (9.4%) incident AF cases were detected. A higher incidence (per 1000 person-years) of AF was observed in those with MAC (>0/year) progression (incidence rate = 28.9, 95% CI = 24.1–34.7) than those without MAC progression (incidence rate = 9.9, 95% CI = 8.9–10.8). The unadjusted cumulative incidence of AF among those with and without MAC progression is shown in *Figure 1* (log-rank *P* < 0.001).

When we adjusted for age, sex, race/ethnicity, education, income, and baseline MAC, any MAC progression (>0/year) was associated

Table 1 Participant characteristics from MESA visit 3 by MAC progression (N = 5683)

Characteristic	No MAC progression (n = 5136)	MAC progression (n = 547)	P-value[a]
Age, mean ± SD, years	63 ± 10	72 ± 8.1	<0.001
Male (%)	2481 (48)	225 (41)	0.0014
Race			
White (%)	1970 (38)	280 (51)	<0.001
Chinese–Americans (%)	625 (12)	41 (7.0)	
Black (%)	1434 (28)	107 (20)	
Hispanic (%)	1107 (22)	119 (22)	
Education, high school or less (%)	1741 (34)	216 (39)	0.0089
Income, <$20 000 (%)	1392 (27)	209 (38)	<0.001
Current smoker (%)	593 (12)	48 (9.0)	0.052
Diabetes (%)	754 (15)	119 (22)	<0.001
Body mass index, mean ± SD, kg/m^2	28 ± 5.5	29 ± 5.7	<0.001
Systolic blood pressure, mean ± SD, mmHg	123 ± 20	131 ± 23	<0.001
Total cholesterol, mean ± SD, mg/dL	191 ± 36	189 ± 35	0.34
HDL cholesterol, mean ± SD, mg/dL	52 ± 15	52 ± 15	0.58
Antihypertensive medications (%)	2063 (40)	312 (57)	<0.001
Aspirin (%)	1646 (32)	244 (45)	<0.001
Lipid-lowering therapies (%)	1164 (23)	171 (31)	<0.001

HDL, high-density lipoprotein; MAC, mitral annular calcium; SD, standard deviation.
[a]Statistical significance for continuous data was tested using the Student's t-test and categorical data was tested using the chi-square test.
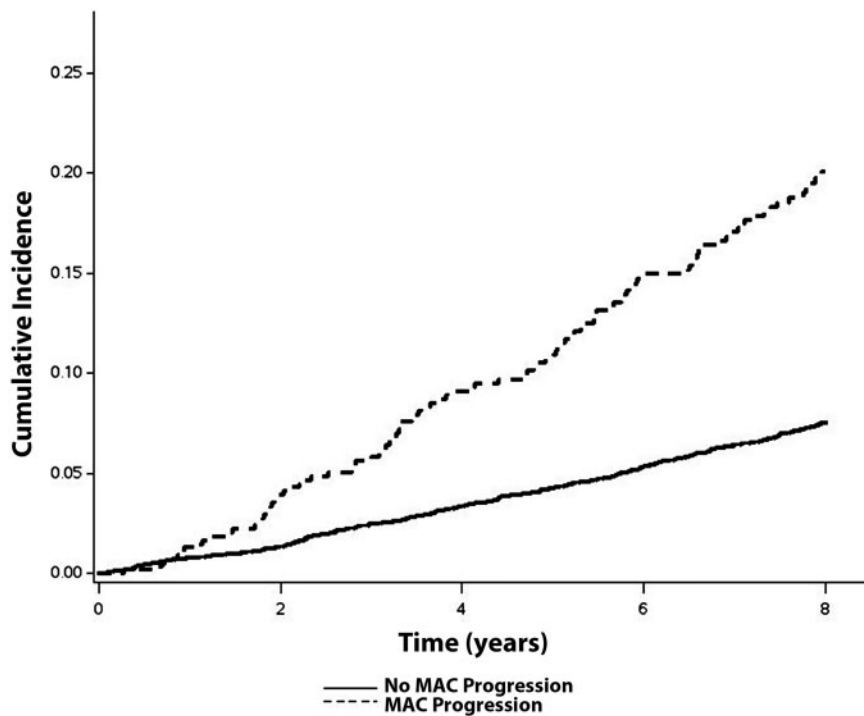
Figure 1 Unadjusted cumulative incidence of atrial fibrillation by MAC progression*. *Cumulative incidence curves are different (log-rank P < 0.001). MAC, mitral annular calcium.

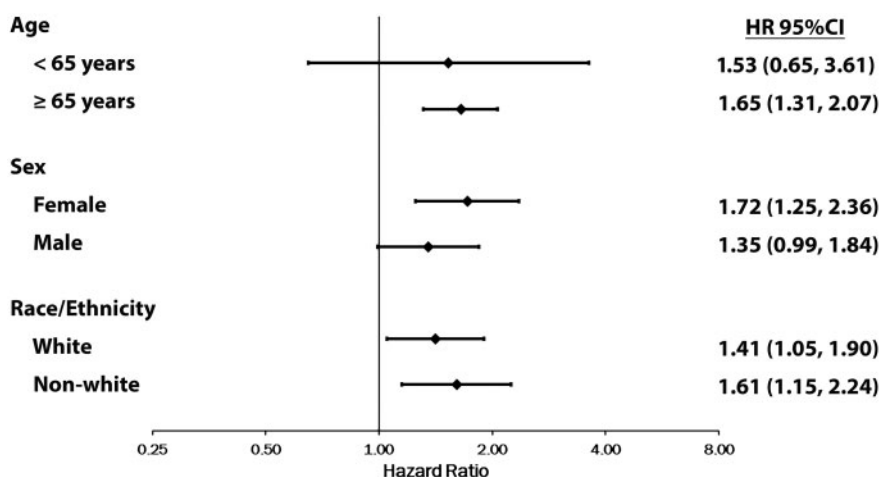**Table 2**   Risk of atrial fibrillation with MAC progression[a]

	Events/number at risk	Model 1[b] HR (95% CI)	P-value	Model 2[c] HR (95% CI)	P-value
MAC progression					
No	417/5136	Reference	—	Reference	—
Yes	116/547	1.54 (1.24–1.92)	<0.001	1.50 (1.20–1.87)	<0.001

CI, confidence interval; HR, hazard ratio; MAC, mitral annular calcium.

[a]HRs presented are for any progression (>0/year).

[b]Adjusted for age, sex, race/ethnicity, education, income, and baseline MAC.

[c]Adjusted for Model 1 covariates plus systolic blood pressure, body mass index, diabetes, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, and aspirin.

Figure 2 Risk of atrial fibrillation with MAC progression by age, sex, and race*. *HRs presented are for any progression (>0/year). Estimates adjusted for age, sex, race/ethnicity, education, income, baseline MAC, systolic blood pressure, body mass index, diabetes, smoking, total cholesterol, high-density lipoprotein cholesterol, antihypertensive medications, lipid-lowering therapies, and aspirin. Estimates were not different by age (P-interaction = 0.81), sex (P-interaction = 0.41), or race/ethnicity (P-interaction = 0.77). CI, confidence interval; HR, hazard ratio; MAC, mitral annular calcium.

with an increased risk for AF (*Table 2*). Similar results were obtained with further adjustment in Model 2 (*Table 2*). There was no evidence of multiplicative or additive interactions by age, sex, or race/ethnicity (*Figure 2*).

After excluding participants who did not have baseline MAC, a trend was observed for the association between MAC progression and AF (HR = 1.49, 95% CI = 0.94–2.16; P = 0.092). When we examined the risk of AF associated with MAC progression per 1-SD increase among participants with baseline MAC, a trend for significance was observed for increases in MAC progression (HR = 1.13, 95% CI = 0.99–1.27; P = 0.055). In contrast, MAC progression was not associated with AF risk among participants without baseline MAC (per 1-SD increase in MAC: HR = 0.99, 95% CI = 0.92–1.06; P = 0.76).

Discussion

In this analysis from MESA, we have demonstrated that the accumulation of higher levels of MAC over time is associated with an increased risk for AF development. Compared with participants who had no MAC progression, a 50% increase in AF risk was observed for those who had any progression, and this risk did not depend on the baseline level of MAC. Overall, our data suggest that important prognostic information regarding AF risk is obtained with follow-up MAC measurements.

Several reports have examined the predictive ability of MAC measurements in the prediction of AF events. Data from the racially and ethnically diverse population of MESA using cardiac CT have demonstrated that baseline MAC predicts incident AF.[8] Similar results were reported from

the Framingham Heart Study in which MAC, detected by echocardiography, was associated with an increased AF risk.[9] The aforementioned studies examined the predictive ability of MAC from measurements at single time points, and although different modalities were used to measure MAC, both studies implicate MAC in the prediction of AF.

To our knowledge, our findings are the first to report that increases in MAC measurements over time are associated with an increased risk for AF. Our data also suggest that MAC progression plays an important role in the development of AF among persons who have detectable levels of MAC at a single point in time. This is supported by the fact that participants who had baseline MAC had a greater risk for AF development if MAC progression was observed. In contrast, participants with baseline MAC who did not have MAC progression had a lower risk of AF development. Although participants with baseline MAC were more likely to have MAC progression, these findings suggest that the risk of AF increases with further accumulation of MAC. Overall, the data presented in this report demonstrate that follow-up MAC measurements provide important prognostic information in the prediction of AF events, especially among persons who already have detectable MAC.

The pathophysiologic link between MAC and AF remains unclear. Several cardiovascular risk factors have been implicated in the development and progression of MAC (e.g. advanced age, hypertension, and diabetes).[1,2] Notably, many of these risk factors are well-known AF risk factors.[16,17] Although MAC progression was associated with AF independent of these shared risk factors, it is possible that the accumulation of MAC reflects an unfavourable cardiovascular profile in which AF is likely to develop. This is supported by data that have demonstrated an association between MAC and left atrial enlargement,[9,18] a well-known risk factor for AF propagation.[19] Therefore, the severity of MAC, and rate of progression, possibly represent a surrogate marker for left atrial abnormalities in which the occurrence of AF is likely.

The findings of this analysis have important clinical implications. MAC has been shown to predict incident stroke,[20] and it is possible that AF is an intermediate event. Additionally, patients with AF who have evidence of MAC have an increased risk of cardiovascular mortality.[3] Therefore, MAC not only predicts AF development but its presence confers an increased risk for adverse cardiovascular outcomes among those who already have the arrhythmia. Although the clinical utility of MAC measurements by cardiac CT to assess AF risk remains uncertain, the current study provides clinicians with important information, as they aim to implement strategies to prevent AF and to reduce the burden of adverse outcomes if AF is apparent. Furthermore, as the utilization of cardiac CT and other imaging modalities are incorporated into clinical practice,[21] the assessment of AF risk associated with MAC will be more widely available. Despite the potential clinical utility of MAC detection to identify persons in whom AF is likely to develop, further studies are needed before recommendations in clinical practice are made.

Our results should be interpreted in the context of certain limitations. The progression of MAC was presumed to be linear based on 2 CT scans over an average of 2 years. However it is possible that MAC progression was not linear and the relationship between MAC progression and AF varies with different intervals. Participants with complete MAC measurements were included in our analysis and possibly this resulted in selection bias. Incident AF cases were ascertained from hospitalization discharge records and 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.[22] Additionally, a trend was observed for the association between MAC progression and AF after excluding participants who did not have baseline MAC, as our analysis likely did not have the power to detect a statistically significant result. 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. For example, data on left atrial size were not collected and we were unable to incorporate this into our models.

In conclusion, the findings of this analysis suggest that MAC progression is an important marker of AF risk. MAC progression likely detects persons who have the necessary substrate for AF development. Further studies are needed to explore the utility of detecting MAC by cardiac CT, and its ability to reduce the occurrence of AF.

References

1. Kanjanauthai S, Nasir K, Katz R, Rivera JJ, Takasu J, Blumenthal RS et al. Relationships of mitral annular calcification to cardiovascular risk factors: the Multi-Ethnic Study of Atherosclerosis (MESA). *Atherosclerosis* 2010;**213**:558–62.
2. Elmariah S, Budoff MJ, Delaney JA, Hamirani Y, Eng J, Fuster V et al. Risk factors associated with the incidence and progression of mitral annulus calcification: the multi-ethnic study of atherosclerosis. *Am Heart J* 2013;**166**:904–12.
3. Potpara TS, Vasiljevic ZM, Vujisic-Tesic BD, Marinkovic JM, Polovina MM, Stepanovic JM et al. Mitral annular calcification predicts cardiovascular morbidity and mortality in middle-aged patients with atrial fibrillation: the Belgrade Atrial Fibrillation Study. *Chest* 2011;**140**:902–10.
4. Fox CS, Vasan RS, Parise H, Levy D, O'Donnell CJ, D'Agostino RB et al. Mitral annular calcification predicts cardiovascular morbidity and mortality: the Framingham Heart Study. *Circulation* 2003;**107**:1492–6.
5. Kohsaka S, Jin Z, Rundek T, Boden-Albala B, Homma S, Sacco RL et al. Impact of mitral annular calcification on cardiovascular events in a multiethnic community: the Northern Manhattan Study. *JACC Cardiovasc Imaging* 2008;**1**:617–23.
6. Fox E, Harkins D, Taylor H, McMullan M, Han H, Samdarshi T et al. Epidemiology of mitral annular calcification and its predictive value for coronary events in African Americans: the Jackson Cohort of the Atherosclerotic Risk in Communities Study. *Am Heart J* 2004;**148**:979–84.

7. Pradelli D, Faden G, Mureddu G, Rossi A, Cioffi G, Gaibazzi N et al. Impact of aortic or mitral valve sclerosis and calcification on cardiovascular events and mortality: A meta-analysis. *Int J Cardiol* 2013;**170**:e51–5.

8. O'Neal WT, Efird JT, Nazarian S, Alonso A, Heckbert SR, Soliman EZ. Mitral annular calcification and incident atrial fibrillation in the Multi-Ethnic Study of Atherosclerosis. *Europace* 2015;**17**:358–63.

9. Fox CS, Parise H, Vasan RS, Levy D, O'Donnell CJ, D'Agostino RB et al. Mitral annular calcification is a predictor for incident atrial fibrillation. *Atherosclerosis* 2004;**173**:291–4.

10. Bild DE, Bluemke DA, Burke GL, Detrano R, Diez Roux AV, Folsom AR et al. Multi-ethnic study of atherosclerosis: objectives and design. *Am J Epidemiol* 2002;**156**:871–81.

11. Carr JJ, Nelson JC, Wong ND, McNitt-Gray M, Arad Y, Jacobs DR Jr et al. Calcified coronary artery plaque measurement with cardiac CT in population-based studies: standardized protocol of Multi-Ethnic Study of Atherosclerosis (MESA) and Coronary Artery Risk Development in Young Adults (CARDIA) study. *Radiology* 2005;**234**:35–43.

12. Agatston AS, Janowitz WR, Hildner FJ, Zusmer NR, Viamonte M Jr, Detrano R. Quantification of coronary artery calcium using ultrafast computed tomography. *J Am Coll Cardiol* 1990;**15**:827–32.

13. Budoff MJ, Takasu J, Katz R, Mao S, Shavelle DM, O'Brien KD et al. Reproducibility of CT measurements of aortic valve calcification, mitral annulus calcification, and aortic wall calcification in the multi-ethnic study of atherosclerosis. *Acad Radiol* 2006;**13**:166–72.

14. O'Neal WT, Efird JT, Qureshi WT, Yeboah J, Alonso A, Heckbert SR et al. Coronary artery calcium progression and atrial fibrillation: the Multi-Ethnic Study of Atherosclerosis. *Circ Cardiovasc Imaging* 2015;**8**:e003786.

15. Gray RJ, Tsiatis AA. A linear rank test for use when the main interest is in differences in cure rates. *Biometrics* 1989;**45**:899–904.

16. Schnabel RB, Sullivan LM, Levy D, Pencina MJ, Massaro JM, D'Agostino RB Sr et al. Development of a risk score for atrial fibrillation (Framingham Heart Study): a community-based cohort study. *Lancet* 2009;**373**:739–45.

17. Kannel WB, Wolf PA, Benjamin EJ, Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. *Am J Cardiol* 1998;**82**:2N–9.

18. Kizer JR, Bella JN, Palmieri V, Liu JE, Best LG, Lee ET et al. Left atrial diameter as an independent predictor of first clinical cardiovascular events in middle-aged and elderly adults: the Strong Heart Study (SHS). *Am Heart J* 2006;**151**:412–8.

19. Parkash R, Green MS, Kerr CR, Connolly SJ, Klein GJ, Sheldon R et al. The association of left atrial size and occurrence of atrial fibrillation: a prospective cohort study from the Canadian Registry of Atrial Fibrillation. *Am Heart J* 2004;**148**:649–54.

20. Benjamin EJ, Plehn JF, D'Agostino RB, Belanger AJ, Comai K, Fuller DL et al. Mitral annular calcification and the risk of stroke in an elderly cohort. *N Engl J Med* 1992;**327**:374–9.

21. Ladapo JA, Jaffer FA, Hoffmann U, Thomson CC, Bamberg F, Dec W et al. Clinical outcomes and cost-effectiveness of coronary computed tomography angiography in the evaluation of patients with chest pain. *J Am Coll Cardiol* 2009;**54**:2409–22.

22. Alonso A, Agarwal SK, Soliman EZ, Ambrose M, Chamberlain AM, Prineas RJ et al. Incidence of atrial fibrillation in whites and African-Americans: the Atherosclerosis Risk in Communities (ARIC) study. *Am Heart J* 2009;**158**:111–7.