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Risk Factors Associated with the Incidence and Progression of Mitral Annulus Calcification: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Background—Significant cardiovascular morbidity has been associated with mitral annulus calcification (MAC), but limited data exist regarding its progression. The purpose of this study was to examine the natural history of and risk factors for MAC progression.

Methods—The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of participants aged 45–84 years without clinical cardiovascular disease who underwent serial cardiac computed tomography studies with quantification of MAC. Regression models were used to identify risk factors associated with MAC incidence and progression.

Results—Prevalent MAC was observed in 534 of 5,895 (9%) participants. Over a median 2.3 years, 280 (5%) developed incident MAC. After adjustment, age was the strongest predictor of incident MAC (adjusted OR, 2.25 per 10 yrs; 95% CI, 1.97 to 2.58; $P<0.0001$). Female gender, white ethnicity, body mass index, diabetes, hypertension, hyperlipidemia, serum cholesterol, smoking, and interleukin-6 were also significant predictors of incident MAC. In participants with

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prevalent MAC, the median rate of change was 10.1 [IQR, −6.7, 60.7] Agatston units (AU)/year. Baseline MAC severity was the predominant predictor of rate of MAC progression (β-coefficient per 10 AU, 0.88; 95% CI, 0.85 to 0.91; $P<0.0001$), although ethnicity and smoking status possessed modest influence.

Conclusions—Several cardiovascular risk factors predicted incident MAC, as did female gender. Severity of baseline MAC was the primary predictor of MAC progression, suggesting that, while atherosclerotic processes may initiate MAC, they are only modestly associated with its progression over these time frames.

Keywords

calcification; mitral valve; progression; risk factors; gender

INTRODUCTION

Mitral annulus calcification (MAC) is a progressive disease that involves fibrosis and calcification. MAC is a common finding, with prevalence as high as 35% in patients with coronary artery disease.(1) When severe, the presence of MAC can cause mitral valve stenosis or regurgitation and the associated heart failure symptoms. Even in the early stages of disease, the presence of MAC has been associated with increased risk of cardiovascular morbidity and mortality, including myocardial infarction, stroke, and vascular death.(2–6) It is thought that MAC is a marker and consequence of an advanced atherosclerotic process, which would explain the associated adverse cardiovascular outcomes. Associations of prevalent MAC with traditional cardiovascular risk factors and the degree of coronary artery disease also support this notion.(1,7–9)

Minimal data exist regarding the natural history and progression of MAC.(10) Characterization of MAC progression and identification of predisposing risk factors may help confirm assumptions that MAC is a surrogate for the atherosclerotic process or may implicate alternate mechanistic pathways. We sought to examine the natural history of MAC progression and the hypothesis that the progression of MAC is associated with traditional cardiovascular risk factors within the longitudinal Multi-Ethnic Study of Atherosclerosis (MESA).

METHODS

Study Population and Data Collection

The Multi-Ethnic Study of Atherosclerosis (MESA) is a longitudinal cohort study of 6,814 community-dwelling men and women aged 45–84 years without evidence of clinical cardiovascular disease at baseline. Participants were recruited from 6 U.S. communities (Forsyth County, NC; Northern Manhattan and the Bronx, NY; Baltimore County, MD; St. Paul, MN; Chicago, IL; and Los Angeles County, CA). A description of the design of MESA has been published previously.(11) Participants attended study visits that included physical examination, prescription medication review, and assessment of subclinical cardiovascular disease by trained study staff using a variety of non-invasive modalities according to standardized protocols. Baseline examinations occurred from July 2000 to August 2002.

Measurement of Mitral Annulus Calcification

Mitral annulus calcification was assessed by electron-beam CT at 3 centers and multi-detector row helical CT at 3 centers. Participants underwent two consecutive scans at the same visit and results were averaged to enhance the accuracy of calcium assessments. Mitral

annulus calcification was quantified by the Agatston scoring method and was differentiated from calcification in the circumflex artery.(12,13) All studies were interpreted at a central reading center (Harbour-UCLA Research and Education Institute, Los Angeles, CA). Any detectable calcium was defined as a score >0 Agatston units (AU). A minimum focus of calcification was based on at least 4 contiguous voxels, resulting in identification of calcium of 1.15 mm^3 with the multi-detector row helical CT scanners (0.68 × 0.68 × 2.50 mm) and 1.38 mm^3 with the electron-beam CT scanners (0.68 × 0.68 × 3.00 mm). Details of the image acquisition and interpretation protocols, quality control measures and interobserver reliability characteristics have been reported.(14,15) Participants underwent serial CT scan with MAC quantification on one-half of the cohort (randomly selected) at a second exam (September 2002 to January 2004) and on the other half of the cohort at a third exam (March 2004 to July 2005), an average of 1.6 and 3.2 years after the first scan, respectively.

Data Collection and Covariate Measurements

Data on age, sex, ethnicity, and medical history were collected from standardized questionnaires administered at the first study visit. Information regarding physical activity was collected using a combination of self–administered and interviewer–administered questionnaires. Smoking status was defined as current, former, or never with current smoking defined as having smoked a cigarette in the last 30 days. Blood pressure was measured 3 times in the seated position using a Dinamap model Pro 100 automated oscillometric sphygmomanometer (Critikon; General Electric, Madison, WI). The average of the second and third readings was recorded. Serum lipid levels were measured from blood samples obtained after a 12–hour fast.

Statistical Analysis

All participants with baseline and follow-up MAC measurements were included in this analysis. The presence of MAC was defined as an Agatston score >0 AU. Incident MAC was defined as detectable MAC at a follow-up examination in a participant free of MAC at baseline. Rate of change of prevalent MAC was defined as the difference in MAC Agatston scores divided by the between-scan time interval (years) in those participants with prevalent MAC on their baseline scan.

We used Student t-test for continuous variables and chi-square test for categorical variables. Variables that were highly skewed were logarithmically transformed in order to approximate a normal distribution. Multivariable regression models were used to identify risk factors associated with the progression of MAC. The incidence of MAC was <10% in our analysis, allowing for the use of logistic regression to model the probability of incident MAC. Due to the nature of the calcification process, we had a strong *a priori* expectation of extreme outliers in the MAC progression data. To minimize the impact of outliers, the rate of change of MAC in those participants with detectable MAC at baseline was modeled using robust linear regression analysis. Because a substantial proportion of participants with MAC at baseline demonstrated stabilization and regression of MAC at follow-up, we created a dichotomous variable such that those with a rate of change in MAC > 0 AU/yr were considered to have worsening MAC. In an exploratory analysis, this variable was modeled using multivariable logistic regression in order to identify predictors of worsening MAC. Multiplicative interaction terms were created to evaluate for effect modification by race/ethnicity, age, gender, and diabetes. These variables were selected *a priori* based on prior findings within MESA.(16–18)

Statistical analyses were performed using SAS (version 9.2, SAS institute, Inc., Cary, NC) and significance was accepted at $P<0.05$. Odds ratios (OR) are reported with 95% confidence intervals (CI).

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RESULTS

Baseline participant characteristics

Of the 6,814 participants within MESA, 5,895 underwent follow-up cardiac CT scans with assessment of MAC with a median between-scan interval of 2.3 [IQR 1.6, 3.1] years (Figure 1). The mean age was 62±10 years and 46% were male. The cohort was ethnically diverse with 26% reported as black, 22% Hispanic, and 13% Chinese (Table 1). Mitral annulus calcification was prevalent in 534 (9%) of participants at baseline, leaving 5,361 participants at risk for developing incident MAC.

Incident mitral annulus calcification

Of the 5,361 participants without prevalent MAC on baseline CT examination, 280 (5.2%) developed incident MAC with an annualized incidence rate of 2.2%/yr (Table 2). The rate of development of incident MAC was increased in women (2.5 %/yr) and in those with diabetes (3.8 %/yr), hypertension (2.9 %/yr), white ethnicity (2.5 %/yr), hyperlipidemia (2.8 %/yr), and prior smoking (2.4 %/yr). Stratification by age and ethnicity revealed a substantial impact of age on the incidence of MAC across all ethnic groups. Within the total cohort, those younger than 55 years had an annualized incidence rate of 0.4% compared to 4.7% in those 75 years or older ($P<0.0001$, Figure 2).

After adjusting for study site and follow-up period, increased age, white ethnicity, body mass index (BMI), and diabetes, reduced glomerular filtration rate (GFR), hypertension, hyperlipidemia, smoking status, statin use and serum levels of interleukin (IL)-6 and high-sensitivity C-reactive were each significantly associated with an increased risk of incident MAC (Table 3). In contrast to atherosclerotic disease, male gender appeared to be negatively associated with incident MAC (adjusted OR, 0.71; 95% CI, 0.55 to 0.91; $P=0.007$).

After full multivariable adjustment, age appeared to be the strongest predictor of (adjusted OR per 10 yrs, 2.27; 95% CI, 1.90 to 2.71; P<0.0001; Table 3) and male gender remained negatively associated (adjusted OR, 0.74; 95% CI 0.54 to 1.00; $P=0.05$) with incident MAC. Significant ethnic variability was noted with increased risk of incident MAC observed with white ethnicity. Baseline serum cholesterol levels, and not a history of hyperlipidemia or statin use, were significantly associated with the development of MAC (adjusted OR per 10 mg/dl increase, 1.07; 95% CI, 1.03 to 1.11; $P=0.0008$). In addition, IL-6 supplanted hs-CRP in predicting incident MAC.

Progression of prevalent mitral annulus calcification

Within the 534 participants with prevalent MAC at baseline CT examination, the median MAC score was 78 [IQR 23.4, 297.7] AU. Prevalent MAC changed at a median rate of 10.1 [IQR −6.7, 60.7] AU/yr, a median annual change of 15% (Figure 3). Progression of MAC was observed in 64% of participants with a median rate of change of 35.7 [IQR 12.1, 122.7] AU/yr. Mitral annulus calcification remained stable or regressed in 37% (n=196) of participants at a rate of −20.2 [IQR −75.5, −6.21] AU/yr. Stratification by ethnicity and quartile of baseline MAC revealed that the rate of change is greatly influenced by the baseline severity of MAC such that those with higher MAC scores have more rapid progression (Figure 4). The pattern is preserved across ethnic groups, although does not reach statistical significance in Chinese and Blacks ($P= 0.18$ and 0.62, respectively).

As opposed to incident MAC, few factors were associated with the rate of change of MAC. After adjustment for study site and between-scan time interval, only baseline MAC score (β-coefficient per 10 AU, 0.89; 95% CI, 0.86 to 0.92; $P<0.0001$) and current smoking (β-coefficient per 10 mmHg, 25.52; 95% CI, 10.07 to 40.34; $P=0.001$) were significantly associated with change in MAC (Table 4, Model 1). Hyperlipidemia, diabetes mellitus, and logarithmically transformed IL-6 demonstrated borderline associations with MAC progression that did not reach statistical significance. Serial multivariable regression models including study site, between-scan time interval, age, gender, ethnicity, BMI, history of diabetes, hypertension, or hyperlipidemia, smoking status, statin use, blood pressure, estimated glomerular filtration rate, and baseline serum levels of total cholesterol, hs-CRP, and IL-6, with and without baseline MAC score were compared. When excluding baseline MAC score, black (β-coefficient, −13.97; 95% CI, −26.36 to −1.59; $P=0.03$) and Hispanic ethnicity (β-coefficient, −15.24; 95% CI, −28.26 to −2.22; $P=0.02$) were associated with slowed MAC progression; whereas, diabetes (β-coefficient, 12.54; 95% CI, 1.53 to 23.54; $P=0.03$) and current smoking (β-coefficient, 31.78; 95% CI, 14.73 to 48.83; $P=0.0003$) were associated with accelerated MAC progression (Table 4, Model 2). The addition of baseline MAC score to the multivariable model (Model 3) demonstrated a significant relationship between baseline MAC and the progression of MAC (β-coefficient per 10 AU, 0.88; 95% CI, 0.85 to 0.91; $P<0.0001$). Again, Hispanic ethnicity (β-coefficient, −15.89; 95% CI, −28.11 to −3.68; $P=0.01$) and current smoking (β-coefficient, 27.29; 95% CI, 11.29 to 43.29; $P=0.0008$) were independently associated with rate of change of MAC (Table 4; Model 3).

We found that MAC was stable or regressed in 37% of participants (%-change ≤0; Figure 3). Consequently, we performed an exploratory analysis in an attempt to predict worsening of prevalent MAC. A fully adjusted model identified active smoking as a significant predictor (adjusted OR vs non-smoker, 2.43; 95% CI, 1.06 to 5.59; $P=0.04$) of worsening MAC.

DISCUSSION

Epidemiologic associations between prevalent MAC and cardiovascular risk factors support the hypothesis that MAC is a marker of atherosclerotic disease burden;(1,7–9) however, the impact of atherosclerotic risk factors on MAC progression has never been addressed. The present analysis utilized the diverse MESA cohort in order to characterize the progression of MAC, specifically the development of incident MAC and the rate change in prevalent MAC. Using quantitative serial CT measurement of MAC, we identified several risk factors for the development of incident MAC. These included several traditional cardiovascular risk factors including increased age, BMI, history of diabetes or hypertension, smoking status, and baseline serum cholesterol levels. As previously demonstrated with coronary artery calcification, white ethnicity was independently associated with increased risk of developing MAC.(17) We also found systemic inflammation, as measured by IL-6 and not hs-CRP, predicted incident MAC.

Contrary to the atherosclerosis paradigm,(19,20) we found that female gender is associated with an increased risk of developing incident of MAC. Previous studies have similarly found a predisposition for prevalent calcification within the mitral annulus in women;(1,9,21) however, this has not previously been documented with incident disease. Interestingly, the risk of incident coronary artery and aortic valve calcification within the MESA was lower in women than in men;(17,22) whereas, the prevalence of calcification in the descending thoracic aorta was greater in women.(23) These findings suggest a unique gender-related pathophysiologic process affecting the calcification at different anatomic sites. While identifying such a mechanism is beyond the scope of the current analysis, we suspect

calcium metabolism and the paradoxical relationship between bone and cardiovascular mineralization may have a role.(16,24,25) Mitral valve calcification may be more prone to this or other age-related pathophysiologic processes given its development later in life than coronary artery and aortic valve calcification.(16) The propensity of osteoporosis to affect women might thereby predispose them to calcification specifically within the mitral valve annulus. Other potential mechanisms for the increased risk of incident MAC in women include gender-based differences in hormone levels, calcium and vitamin D supplementation, changes in left-heart geometry, and mitral valve flow patterns and shear stress.

Factors associated with the development of incident MAC are different from those associated with the rate of change of prevalent MAC. We found that the predominant determinant of the rate of change in MAC appears to be the severity of baseline MAC such that those with more severe disease progress more rapidly. In addition, current smoking, and perhaps diabetes, portend an increased rate of MAC progression, while slower progression was noted in participants of black or Hispanic ethnicity. Smoking cessation would be expected to reduce the progression of MAC given the observed decrement in β-coefficients as one transitions from an active to a former smoker, but whether aggressive diabetes management modulates progression remains unclear.

The appropriateness of including baseline calcium scores in predicting disease progression has presented a challenging analytic problem. The severity of MAC at baseline may encompass the chronic effects of traditional risk factors on MAC, thereby obscuring their individual influence on MAC progression. In addition, those participants with more severe baseline MAC may have progressed rapidly prior to the “baseline” measurement, and we would expect the rapid rate of progression to persist. These concepts appear to play a role in coronary artery calcification progression.(17) Here, the addition of baseline MAC severity to regression models eliminated the chronic impact of black ethnicity and diabetes, both of which possessed borderline statistical significance. However, there was little change in the relationship between smoking status and MAC progression. Notably, both statistical approaches demonstrated that few clinically modifiable factors are associated with the rate MAC progression.

The discrepancy in risk factors associated with the incidence and progression of MAC suggests that different pathophysiology is responsible for each. Multiple cell culture and histopathologic studies have attributed valve calcification to valve myofibroblast activation and transdifferentiation into an osteoblast-like cell type.(25–27) This change in cell phenotype is triggered by an atherosclerosis-like process involving basement membrane disruption, lipid deposition, inflammatory cell infiltration, and cytokine release.(26) Once active, valve myofibroblasts themselves secrete a myriad of inflammatory cytokines that are instrumental in valve calcification.(28) Atherosclerosis, by activating valve myofibroblasts, thereby may trigger a self-perpetuating process of calcification that is less dependent on the initial cardiovascular risk factors than the mass of affected valve tissue. While this is speculative, the existing experimental data in combination with our group and others’ clinical findings suggests such a phenomenon is at play,(17,22,25–28) although other pathophysiologic processes may be involved as well.

We also found that approximately 40% of participants demonstrated stabilization or even regression of MAC on follow-up CT scans. This finding is similar to those in studies investigating the progression of coronary artery and aortic valve calcification using computed tomography scans.(17,22) Active smoking status was the only substantial predictor of worsening of MAC, although the dichotomization of the outcome into progression (yes/no) reduced our statistical power. It is possible that the observed regression

could be due to some degree of measurement error in the ascertainment of MAC; however, measurement of MAC within MESA has previously been shown to be highly reproducible with only 6% interscan variability.(13)

In addition to furthering our understanding of cardiovascular calcification, our findings hold significant clinical implications. Mitral annulus calcification is a commonly encountered entity that even when mild has been associated increased risk of myocardial infarction, stroke, and vascular death.(2–6) Our analysis identified relationships between cardiovascular risk factors and incident MAC, supporting the notion that MAC begins via an atherosclerotic process and emphasizing the importance of risk factor modification for the prevention of this morbid condition. When severe, MAC can encroach on the mitral valve, causing mitral valve stenosis and regurgitation. Extensive MAC also introduces formidable technical challenges for mitral valve surgery and places patients at increased risk of potentially fatal complications including intractable hemorrhage, atrioventricular disruption, and ventricular rupture.(29,30) Mitral annulus calcification has implications for aortic valve surgery as well; MAC increases the likelihood of cardiac conduction abnormalities after either surgical or transcatheter aortic valve replacement and denotes a risk of annular rupture during transcatheter aortic valve replacement.(31–33) Slowing MAC progression may mitigate these risks. However, we found that MAC progression is relatively independent of modifiable risk factors, further highlighting the importance of MAC primary prevention. The one apparent exception is smoking cessation, which is associated with attenuated MAC progression and also with MAC stabilization/regression.

The strengths of the MESA include its large sample size, the inclusion of 4 racial/ethnic groups, its longitudinal evaluation of participants, and its use of cardiac CT with quantitative evaluation of valve and vascular calcification. However, several limitations of MESA and this analysis warrant acknowledgement. First, the MESA cohort is relatively healthy as participants with clinical cardiovascular disease were excluded. For this reason, we may not have had sufficient power to evaluate the relationship of some risk factors to MAC. For example, renal dysfunction (GFR <60 ml/min/1.73 m^2), which has previously been associated with prevalent MAC,(34) was present in less than 10% of our cohort. Technical factors associated with the measurement of MAC can result in considerable variability. This variability in turn limits the ability to detect modest associations with MAC progression. Despite these limitations, we were able to identify several risk factors for the progression of MAC, which in conjunction with prior clinical and experimental works furthers our understanding of valve calcification.

In conclusion, this is the first study to characterize MAC progression using quantitative CT measures and to identify predisposing risk factors. We found that several cardiovascular risk factors are associated with incident MAC. However, contrary to atherosclerosis, men are at lower risk of developing MAC than women. On the other hand, the rate of MAC progression is mostly dependent on the severity of MAC at baseline, although smoking status and ethnicity possessed more modest associations with MAC progression.

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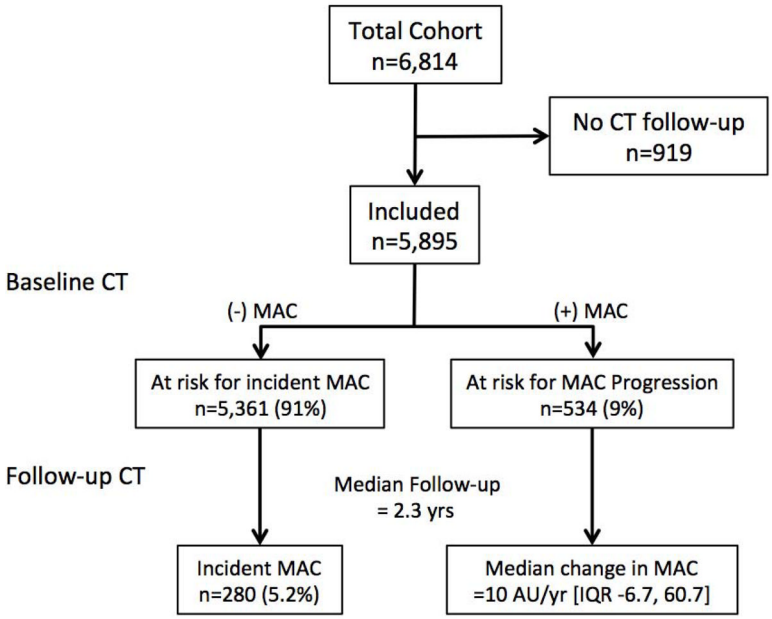

Figure 1.

MESA cohort categorized according to baseline and progression of mitral annulus calcification. A flow diagram illustrates the prevalence of MAC at baseline computer tomography (CT) scan, the percentage of participants without MAC at baseline who developed MAC on follow-up, and the median rate of change in MAC among those with MAC at baseline.

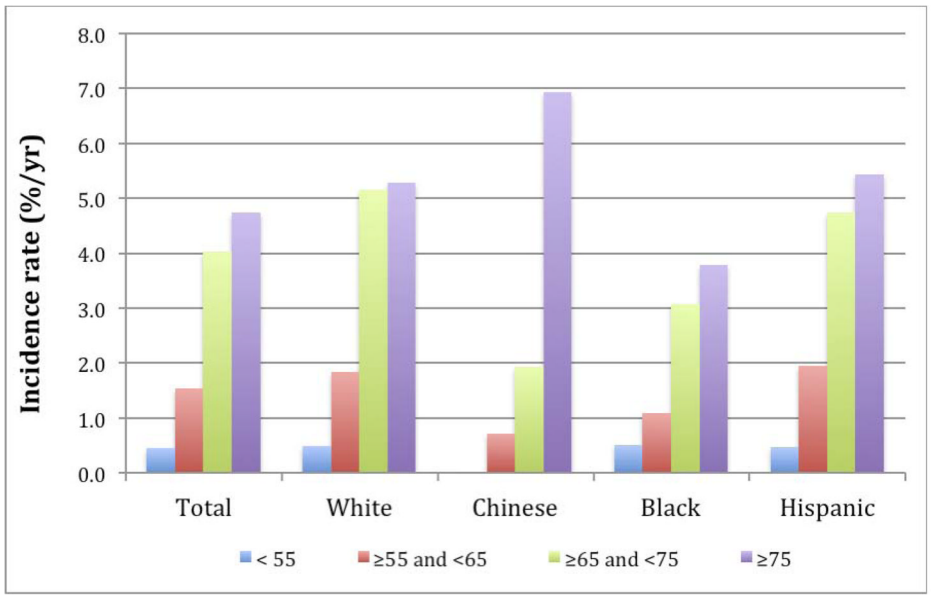

Figure 2.

Incidence of mitral annulus calcification stratified by age and race/ethnicity. Within the total cohort and each ethnic group, there is a robust relationship between incidence of MAC and increasing age such that older participants are at greater unadjusted risk of developing MAC. Incidence rate depicted as %/year.

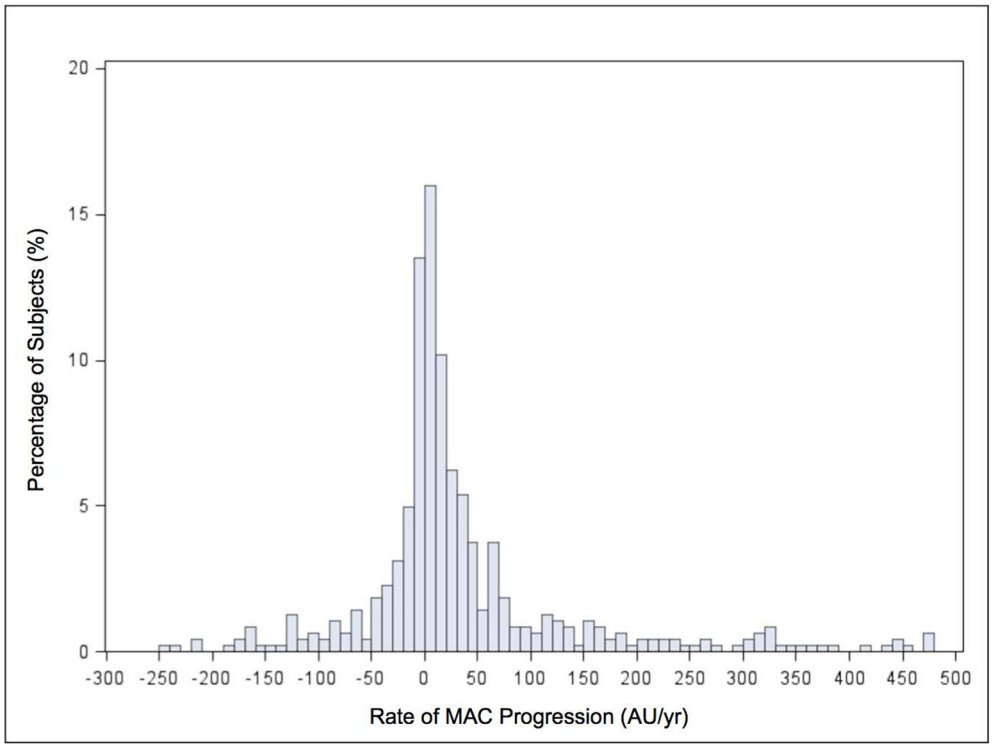

Figure 3.

Distribution of rate of change in mitral annulus calcification. Depicted is a histogram of the annual rate of change in MAC in those participants with detectable MAC on baseline computed tomography scan. The x-axis is truncated at −300 and 500 Agatston units/year (AU/yr). Fourteen participants had a rate of change <-300 AU/yr and 25 participants had a rate of progression >500 AU/yr. Regression of MAC (rate of change < 0 AU/yr) was observed in 37% of participants.

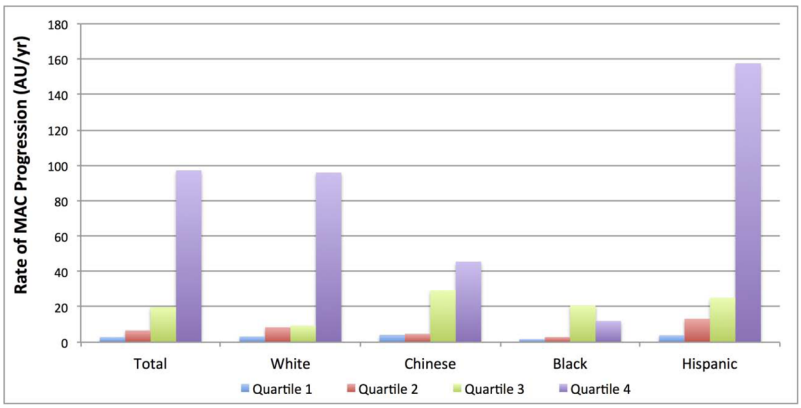

Figure 4.

Rate of change of mitral annulus calcification stratified by baseline severity of mitral annulus calcification and racial/ethnic group. Within the study cohort there is a robust relationship between severity of baseline MAC and the rate of change in MAC.

Table 1

Baseline participant characteristics stratified by progression of mitral annulus calcification.

	All (N=5,895)	At Risk of Incident MAC (N=5,361)		At Risk of MAC Progression (N=534)
		No Incident MAC (N=5,081)	Incident MAC (N=280)	
Age, mean (SD), yrs	62 (10)	61 (10)	68 (8)	71 (8)
Men, N (%)	2,705 (46)	2,387 (47)	109 (39)	209 (39)
Ethnicity, No. (%)				
White	2,339 (40)	1,926 (38)	138 (49)	275 (51)
Black	1,513 (26)	1,352 (27)	60 (21)	124 (23)
Hispanic	1,293 (22)	1,115 (22)	54 (19)	101 (19)
Chinese	750 (13)	688 (14)	28 (10)	34 (6)
Body Surface Area, mean (SD)	1.9 (0.2)	1.9 (0.2)	1.9 (0.2)	1.8 (0.2)
Body Mass Index, mean (SD)	28 (5)	28 (5)	29 (6)	29 (6)
Serum cholesterol, mean (SD), mg/dl				
Total Cholesterol	195 (35)	195 (35)	200 (33)	194 (37)
LDL-cholesterol	117 (32)	117 (31)	120 (29)	116 (32)
HDL-cholesterol	51 (15)	51 (15)	52 (15)	52 (15)
Triglycerides	115 [82, 166]	115 [81, 166]	123 [87, 183]	114 [83, 164]
Diabetes Mellitus, N (%)	789 (13)	620 (12)	57 (20)	112 (21)
Hyperlipidemia, N (%)	2,227 (38)	1,854 (37)	123 (44)	250 (47)
Hypertension, N (%)	1,936 (33)	2,227 (44)	181 (65)	332 (62)
Smoking Status, N (%)				
Former	2,155 (37)	1,826 (36)	121 (43)	208 (39)
Current	730 (12)	656 (13)	33 (12)	41 (8)
Concurrent Medication, N (%)				
RAS inhibitor	1,022 (17)	805 (16)	82 (29)	135 (25)
β-Blocker	540 (9)	427 (8)	37 (13)	76 (14)
Calcium Channel Blocker	726 (12)	573 (11)	52 (19)	101 (19)
Diuretic	823 (14)	651 (13)	61 (22)	111 (21)
Statin	905 (15)	716 (14)	61 (22)	128 (24)
Blood Pressure, mean (SD), mmHg				
Systolic	126 (21)	124 (20)	132 (21)	134 (23)
Diastolic	72 (10)	72 (10)	71 (10)	70 (10)
Mean	94 (13)	93 (13)	96 (13)	96 (14)
Estimated Glomerular Filtration Rate, mean (SD)	81 (17)	82 (17)	78 (18)	76 (19)
hs-CRP	1.8 [0.8, 4.1]	1.8 [0.8, 4.1]	2.4 [1.1, 4.6]	2.2 [0.9, 4.3]
IL-6	1.2 [0.8, 1.8]	1.1 [0.7, 1.8]	1.6 [1.0, 2.5]	1.5 [1.0, 2.2]

HDL, high-density lipoprotein; hs-CRP, high-sensitivity C-reactive protein; highIL, interleukin; LDL, low-density lipoprotein; MAC, mitral annulus calcification; RAS, renin-angiotensin system

Table 2

Cumulative and annualized incidence rate of mitral annulus calcification.

	At risk (n)	Incident AVC (n)	Cumulative Incidence (%)	Incidence Rate (%/yr)
Total	5,361	280	5.2	2.2
Women	2,865	171	6.0	2.5
Men	2,496	109	4.4	1.9
White	2,064	138	6.7	2.5
Black	1,412	60	4.2	1.9
Hispanic	1,169	54	4.6	2.1
Chinese	716	28	3.9	1.5
Diabetes mellitus	677	57	8.4	3.8
Hypertension	2,408	181	7.5	2.9
Hyperlipidemia	1,977	123	6.2	2.8
Smoker	689	33	4.8	2.2
Former smoker	1,947	121	6.2	2.4

Table 3

Unadjusted and multivariable risk estimates for factors associated with incident mitral annulus calcification.

	Unadjusted Model		Fully Adjusted Model	
	OR (95% CI)	***P***	**OR (95% CI)**	***P***
Age (per 10 yrs)	2.25 (1.97–2.58)	<0.0001	2.27 (1.90–2.71)	<0.0001
Male gender	0.71 (0.55–0.91)	0.007	0.74 (0.54–1.00)	0.05
Ethnicity				
White	referent (1.00)		referent (1.00)	
Chinese	0.45 (0.28–0.72)	0.0008	0.55 (0.33–0.92)	0.02
Black	0.59 (0.43–0.82)	0.002	0.43 (0.30–0.63)	<0.0001
Hispanic	0.70 (0.48 0 1.03)	0.07	0.57 (0.37–0.87)	0.009
Body Mass Index (per 5 kg/m^2)	1.17 (1.05–1.30)	0.005	1.17 (1.02–1.35)	0.02
Diabetes Mellitus	1.83 (1.34–2.49)	<0.0001	1.56 (1.11–2.21)	0.01
Hyperlipidemia	1.15 (1.01–1.32)	0.04		
Smoking Status				
Never	referent (1.00)		referent (1.00)	
Former	1.37 (1.06–1.78)	0.02	1.21 (0.91–1.61)	0.2
Current	1.07 (0.72–1.61)	0.72	1.54 (1.00–2.39)	0.052
Anti-hypertensive agent use	1.75 (1.36–2.24)	<0.0001		
Statin use	1.71 (1.27–2.31)	0.0004		
Systolic BP (per 10 mmHg)	1.17 (1.11–1.23)	<0.0001		
Diastolic BP (per 10 mmHg)	0.91 (0.81–1.03)	0.14		
eGFR (per 10 mL/min/1.73m^2)	0.87 (0.81–0.94)	0.0004		
Total cholesterol (per 10 mg/dl)	1.05 (1.01–1.08)	0.008	1.07 (1.03–1.11)	0.0008
Log (hs-CRP; per 1 SD change)	1.28 (1.13–1.44)	<0.0001		
Log (IL-6; per 1 SD change)	1.58 (1.40–1.79)	<0.0001	1.38 (1.17–1.62)	<0.0001

BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MAC, mitral annulus calcification; OR, odds ratio; SD, standard deviation

Both models include adjustment for study site and between-scan time interval. Fully adjusted model includes all listed variables in the model simultaneously.

Table 4

Median regression models for rate of change of mitral annulus calcification.

Annual Change in MAC						
	Model 1		**Model 2**		**Model 3**	
	Difference in mean progression (95% CI)	***P***	**Difference in mean progression (95% CI)**	***P***	**Difference in mean progression (95% CI)**	***P***
Baseline MAC score (per 10 AU)	0.89 (0.86–0.92)	<0.0001	EXCLUDED		0.88 (0.85–0.91)	<0.0001
Age (per 10 yrs)	3.08 (−1.69–7.85)	0.21				
Male gender	2.60 (−5.25–10.44)	0.52				
Ethnicity						
White	referent (0.00)		referent (0.00)		referent (0.00)	
Chinese	−0.86 (−17.03–18.76)	0.92	−0.31 (−19.86–19.24)	0.98	−6.35 (−24.68–11.98)	0.5
Black	−6.73 (−17.57–4.11)	0.22	−13.97 (−26.36–−1.59)	0.03	−8.71 (−20.35–2.93)	0.14
Hispanic	−8.64 (−20.45–3.17)	0.15	−15.24 (−28.26–−2.22)	0.02	−15.89 (−28.11–−3.68)	0.01
Body Mass Index (per 5 kg/m^2)	0.93 (−2.39–4.25)	0.58				
Diabetes Mellitus	8.53 (−1.05–18.12)	0.08	12.54 (1.53–23.54)	0.03		
Hyperlipidemia	−5.16 (−10.53–0.22)	0.06				
Smoking Status						
Never	referent (0.00)		referent (0.00)		referent (0.00)	
Former	7.24 (−1.15–15.62)	0.09	7.94 (−1.35–17.22)	0.09	4.83 (−3.88–13.54)	0.28
Current	25.21 (10.07–40.34)	0.001	31.78(14.73–48.83)	0.0003	27.29 (11.29–43.29)	0.0008
Anti-hypertensive agent use	1.86 (−5.77–9.49)	0.63				
Statin use	4.44 (−4.77–13.66)	0.34				
Systolic BP (per 10 mmHg)	0.76 (−0.96–2.48)	0.39				
Diastolic BP (per 10 mmHg)	1.31 (−2.71–5.33)	0.52				
eGFR (per 10 mL/min/1.73m^2)	0.19 (−1.91–2.28)	0.86				
Total cholesterol (per 10 mg/dl)	−0.70 (−1.78–0.39)	0.21				
Log (hs-CRP; per 1 SD change)	1.63 (−1.85–5.12)	0.36				
Log (IL-6; per 1 SD change)	5.61 (−0.75–11.99)	0.08				

AU, Agatston units, BP, blood pressure; CI, confidence interval; eGFR, estimated glomerular filtration rate; hs-CRP, high-sensitivity C-reactive protein; IL, interleukin; MAC, mitral annulus calcification; OR, odds ratio; SD, standard deviation

Model 1 includes adjustment for study site, between-scan time interval, and each listed variable individually. Model 2 includes adjustment for study site and between-scan time interval and all listed variables simultaneously, excluding baseline MAC score. Model 3 includes adjustment for all variables in Model 2 plus baseline MAC score.