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Resting heart rate and the incidence and progression of valvular calcium: The Multi-Ethnic Study of Atherosclerosis (MESA)

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Abstract

Background and aims—Left-sided valvular calcification is associated with cardiovascular disease (CVD) morbidity and mortality. Resting heart rate (RHR) may influence valvular calcium progression through shear stress. Whether RHR, an established CVD risk factor, is associated with valvular calcium progression is unknown. We assessed whether RHR predicts incidence and progression of mitral annular calcium (MAC) and aortic valve calcium (AVC) in a community-based cohort free of CVD at baseline.

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Conflicts of interest

Dr. Michos has received an honorarium from Siemens Healthcare Diagnostics (unrelated to this topic). Dr. Budoff has received research funds from GE Healthcare. No other authors declare a conflict of interest.

Author contributions

Drs. Amoakwa, Tibuakuu, and Michos designed the study. Dr. Fashanu performed the statistical analyses under the supervision of Dr. Zhao. Dr. Amoakwa wrote the initial draft of the manuscript. Dr. Budoff obtained the funding and performed the interpretation for the valvular calcium assessment from the cardiac CT scans, and provided critical revisions to the paper. Drs. Fashanu, Guallar, Zhao, Whelton, O'Neal, Post, Budoff, Tibuakuu and Michos provided critical revisions to the paper. Drs. Amoakwa, Fashanu, and Michos take fully responsibility for its content. All authors reviewed the final draft and approve of its submission.

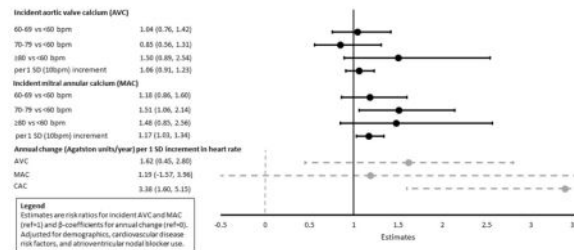
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Methods—RHR was obtained from baseline electrocardiograms of 5,498 MESA participants. MAC and AVC were quantified using Agatston scoring from cardiac computed tomography scans obtained at baseline and at a second examination during follow-up. We examined associations of RHR with incident MAC/AVC and annual change in MAC/AVC scores, after adjusting for demographics, CVD risk factors, physical activity, and atrioventricular nodal blocker use.

Results—At baseline, participants had mean age of 62 ± 10 years and mean RHR of 63 ± 10 bpm; 12.3% and 8.9% had prevalent AVC and MAC, respectively. Over median of 2.3 years, 4.1% and 4.5% developed incident AVC and MAC, respectively. Each 10 bpm higher RHR was significantly associated with incident MAC [Risk Ratio 1.17 (95% CI 1.03–1.34)], but not incident AVC. However, RHR was associated with AVC progression [$\beta = 1.62$ (0.45–2.80) Agatston units/year for every 10 bpm increment], but not MAC progression.

Conclusions—Higher RHR was associated with MAC incidence and AVC progression, independent of traditional CVD risk factors. Future studies are needed to determine whether modification of RHR through lifestyle or pharmacologic interventions can reduce valvular calcium incidence or progression.

Graphical Abstract



Keywords

resting heart rate; aortic valve calcium; mitral annular calcium; progression; cardiovascular; computed tomography

Introduction

Calcification of the left-sided heart valves, even when asymptomatic, has been independently associated with increased risk of cardiovascular (CVD) morbidity and mortality.^{1–3} Valvular calcification detected by computed tomography (CT) imaging also predicts valve dysfunction (i.e. stenosis).⁴ Valvular calcification is a form of subclinical CVD and identifies individuals who might benefit from more intensive risk factor modification.² However, only a few modifiable factors have been associated with progression of Mitral Annular Calcium (MAC) and Aortic Valve Calcium (AVC), and no treatment has demonstrated a slowing or reduction in valvular calcification.^{5, 6} Thus, more work is needed to identify other risk factors that may potentially be targets for treatment. An elevated Resting Heart Rate (RHR) is a potentially modifiable factor that can increase cardiac shear stress and mechanical strain, which in turn could potentially play a role in the pathogenesis and progression of valvular calcification. Prior work from the Multi-Ethnic

Study of Atherosclerosis (MESA) examined the associations of several CVD risk factors for AVC and MAC incidence and progression, but did not evaluate RHR in those studies.^{6, 7}

RHR already has been established as an independent risk factor for CVD in people with and without heart disease,^{8–11} with somewhat stronger associations for men compared to women.¹¹ An independent association between RHR and coronary artery calcium (CAC), a marker of subclinical atherosclerosis burden, has also been reported.¹² CAC and left-sided valvular calcification [MAC and AVC] are strongly associated¹³ and share similar CVD risk factors.^{6, 7, 14} In a small study of older adults (predominantly men) with aortic stenosis (n=405), a higher RHR was associated with faster progression of aortic stenosis, particularly in men and older patients.¹⁵ In MESA and in the Framingham Offspring Study, higher RHR was associated with prevalent AVC in both study populations;¹⁶ however, in the CHARGE consortium, a genetic risk score related to RHR was not associated with AVC.¹⁶ The association of RHR with prevalent MAC has not been previously examined. Furthermore, whether RHR is associated with the incidence or progression of valvular calcification over time is unknown.

This study examined the association between RHR with incidence and progression of MAC and AVC in a large multi-ethnic community-based cohort free of clinical CVD at baseline. We hypothesized that higher RHR would be independently associated with increased incidence and progression of MAC and AVC, and that this association would be stronger in men and older adults.

Material and methods

Participants

MESA is a prospective cohort study designed to investigate subclinical CVD in people without clinical CVD or atrial fibrillation at baseline. 6,814 asymptomatic men and women, aged 45–84 years, representing 4 race/ethnicities were enrolled from 6 U.S. communities (Baltimore, Maryland; Chicago, Illinois; Forsyth County, North Carolina; Los Angeles county, California; Northern Manhattan, New York; and St. Paul, Minnesota) between the years of 2000–2002. A full description of the MESA study design has been published.¹⁷

We used data from the baseline examination (2000–2002), the time of the baseline cardiac CT, and from examinations 2 (2002–2004) and 3 (2004–2005), the times of the follow-up CTs. Participants were excluded if they had missing baseline RHR (n=48), atrial fibrillation or atrial flutter (n=1 incidentally found; MESA otherwise excluded individuals with atrial fibrillation at baseline), missing baseline AVC/MAC assessment (n=2), no follow-up CT (n=930), or missing covariates (n=335). A total of 5,498 participants are included in this analysis (Fig. 1).

MESA was approved by the Institutional Review Boards at all participating centers, and all participants provided written informed consent at each MESA examination.

Covariates

RHR was obtained from 12-lead electrocardiography performed at rest at the baseline examination. Other covariates were obtained from standardized questionnaires and physical examination at the baseline visit by trained staff.¹⁷ Medication use, including the use of antihypertensive medications, lipid lowering medications, and atrioventricular (AV)-nodal blocking medications (i.e. beta-blockers, verapamil, and diltiazem), were assessed by a medication inventory approach. Plasma glucose and cholesterol levels were measured from blood samples drawn after a 12-hour fast. Inflammatory markers including high-sensitivity C-reactive protein (hsCRP), interleukin-6 (IL-6) and fibrinogen were measured from stored serum samples.¹⁸ The Typical Week Physical Activity survey was used to assess physical activity¹⁹ and total MET-minutes/week of moderate and vigorous physical activity was calculated. Diabetes was defined as a fasting blood glucose level ≥ 126 mg/dl, self-reported diabetes or taking medication for lowering blood glucose. Estimated glomerular filtration rate (eGFR) was calculated with the Chronic Kidney Disease Epidemiology equation.²⁰

Valvular calcification

All participants underwent cardiac CT scanning at the baseline examination. Participants underwent a follow-up CT at either examination 2 or examination 3 based on random assignment. While some participants underwent additional CT scans at subsequent MESA examinations (Exams 4 and/or 5) for CAC assessment,¹² these latter scans have not yet been measured for valvular calcification and are not available for this analysis.

Three sites used electron-beam tomography and three sites used multi-detector CT. All cardiac CT scans were read in a central location (Harbor-UCLA Research and Education Institute, Los Angeles, California) by experienced readers. The scanning method, image reconstruction, and reading protocols have been previously reported for the MESA study.^{21, 22} Inter-scanner reproducibility was excellent (kappa statistic of 0.94–0.96 for the Agatston score between duplicate scans performed on the same patient using same scanner), and equivalence across scanner types has also been established.^{21, 22} Additionally, inter-reader variability between 2 CT analysts for the same cardiac scan images was also very good.²² In sum, this prior quality control work from MESA concluded there was sufficient reproducibility for MAC/AVC measurement to allow for serial investigations over time.^{21, 22}

AVC and MAC were quantified from the cardiac CTs using the Agatston scoring method.²³ Prevalent AVC or MAC was defined by an Agatston score >0 at the baseline examination. Incident AVC or MAC was defined as an AVC or MAC >0 at the follow-up CT scan for participants who had no AVC or MAC at baseline. Progression of AVC or MAC was defined as annual change in AVC and MAC Agatston scores from baseline, calculated for all participants.

Statistical analysis

RHR was examined both as a continuous variable [per 1 standard deviation (SD) increment] and as a categorical variable split at clinical cut points <60 , 60–69, 70–79, and ≥ 80 beats per minute (bpm). Baseline characteristics were reported stratified by categories of RHR. Means (SD) were used to present approximately normally distributed continuous variables while

medians (interquartile range) were used for skewed continuous variables. Categorical variables were presented as counts with percentages.

In cross-sectional analyses, we used a Poisson regression model with robust variance estimation to estimate the adjusted prevalence ratios (PR) and 95% confidence intervals (95% CI) of having AVC or MAC >0 at baseline by RHR. We also used linear regression to examine the associations of RHR with baseline calcification extent [log-transformed (MAC or AVC+1)].

For longitudinal analyses, we used a modified Poisson regression model with robust variance estimation to estimate the adjusted relative risk (RR) and 95% CI of incident AVC and MAC for those with respective baseline scores of zero. We also used adjusted linear regression models to assess the association between baseline RHR and annual change in AVC and MAC scores.

Models were progressively adjusted as follows: Model 1 adjusted for participant demographics (age, sex, race/ ethnicity), field center, and CT scanner type. Model 2 further adjusted for education, body mass index, waist circumference, smoking status, and physical activity. Model 3 (our primary analytical model) additionally adjusted for CVD risk factors including systolic blood pressure, use of antihypertensive medication, total cholesterol, HDL-cholesterol, use of lipid-lowering medications, diabetes, eGFR, and AV-nodal blocking medication use. In a supplemental model, Model 4, we additionally adjusted for inflammatory biomarkers previously found to be associated with RHR (hsCRP, IL-6, and fibrinogen)¹⁸ which may potentially mediate associations between RHR and valvular calcification. In adjusted models, the variables of physical activity and inflammation were log-transformed due to their skewness.

We tested for linear trend across RHR categories by using an ordinal variable for each category and modeling this as a continuous variable. We evaluated for effect modification by age, sex, and race/ethnicity using our primary model (Model 3). We also performed the following sensitivity analyses: First, we repeated all analyses excluding participants on AV-nodal blocking medications. Second, although the association of RHR with CAC progression (through examination 4) has already been previously reported in MESA,¹² we also replicated our analyses using CAC (through examination 3) as a supplementary outcome to facilitate comparison with AVC and MAC progression for the same timeframe. Finally, for analyses of calcification progression (Agatston units/year), we additionally adjusted models for baseline Agatston score (log-transformed) as prior work in MESA has shown that the rate of valvular calcification progression was dependent on severity of baseline disease.⁶

All statistical analyses were performed using STATA 15 (StataCorp LP, College Station, TX) and significance was considered at p -value <0.05.

Results

Of the 5,498 participants included in this analysis, 52.4% were women. The racial/ethnic distribution was 39.7% white, 26.6% black, 12.2% Chinese-American, and 21.5% Hispanic.

The mean (SD) for age was 61.8 (10) years, and the mean (SD) for RHR was 63 (10) bpm, with a range of 36–130 bpm. Table 1 shows the baseline characteristics of the study population by RHR categories. Participants with higher RHR were more likely to be women, have lower physical activity levels, higher systolic blood pressures, lower HDL-cholesterol levels, were more likely diabetic, less likely to use AV-nodal blocking medications, and more likely to have higher levels of inflammatory markers.

Cross-sectional analysis

Prevalent valve calcification at baseline was found in 677 (12.3%) participants for AVC >0 and 492 (8.9%) for MAC >0 (Fig. 1). The association of RHR with prevalent AVC in MESA has been previously reported.¹⁶ We now additionally demonstrate that higher RHR (per 10 bpm increment) is independently associated with increased prevalence of MAC at baseline [PR 1.20 (95% CI 1.11, 1.31)], after adjusting for demographic and CVD risk factors in our primary model (Supplemental Table 1, Model 3). Participants with a RHR $\geq$ 80 bpm had a ~2-fold increased risk of prevalent MAC compared to those with RHR <60 bpm. These associations remained statistically significant after adjusting for potential mediating inflammatory markers (Model 4). Findings were consistent after excluding participants taking AV-nodal blocking medications (Supplemental Table 2). Higher RHR was also associated with greater MAC severity at the baseline exam but not AVC (Supplemental Table 3).

Longitudinal analysis

For participants who had no AVC or MAC at baseline, 4.1% developed incident AVC and 4.5% developed incident MAC during follow up over a median follow-up time of 2.3 years (Fig. 1). The mean (SD) annual change in Agatston units/year was 2.1 (40.4) for AVC and 8.5 (95.4) for MAC. In comparison, the mean annual change in CAC for the same timeframe was 23.2 (64.7) Agatston units/year.

MAC incidence/progression—A higher RHR was statistically significantly associated with incident MAC, with a RR of 1.17 (95% CI 1.03, 1.34) for every 10 bpm higher RHR, after adjusting for CVD risk factors (Table 2, Model 3). This association was similar, but no longer statistically significant, after adjusting for potentially mediating inflammatory markers [RR 1.14 (0.99, 1.30), Model 4]. After excluding those taking AV-nodal blocking medications at baseline, the association of RHR with incident MAC was not statistically significant (Supplemental Table 4).

In contrast to the association of RHR with CAC progression, there was no statistically significant association of RHR with MAC progression after adjustment for CVD risk factors [β = 1.19 (−1.57, 3.96) Agatston units/year] (Table 3, Model 3).

AVC incidence/progression—The highest category of RHR ($\geq$ 80 bpm), compared to the lowest (<60 bpm) was associated with incident AVC after adjustment for demographic and lifestyle factors [RR 1.66 (1.01, 2.74)] (Table 2, Model 2). In contrast to the findings for incident MAC, RHR (per 10 bpm increment) was not significantly associated with incident

AVC after adjustment for CVD risk factors [RR 1.06 (0.91–1.23)] (Table 2, Model 3) and after exclusion of those taking AV-nodal blocking medications (Supplemental Table 4).

However, higher RHR was significantly associated with increased AVC progression. In multivariable analysis adjusted for traditional CVD risk factors, each 10 bpm higher RHR was significantly associated with an increase in AVC of 1.62 Agatston units/year (0.45, 2.80) (Table 3, Model 3). Participants with RHR ≥ 80 bpm had an average 8.32 (3.34, 13.29) Agatston units/year greater increase in AVC progression as compared with participants with RHR < 60 bpm. The association between RHR with AVC progression remained significant after further adjustment for potential inflammatory mediators (Model 4). Findings were similar after excluding those on AV-nodal blocking medications (Supplemental Table 5).

Since progression of calcification has been shown to be related to extent of baseline disease,⁶ we also repeated the analyses of valvular calcium progression (annual change) after further adjustment for baseline score (Supplemental Table 6). Results were similar to the primary analysis.

Finally, we examined the effects of RHR on valvular calcification progression by age, sex, and race/ethnicity. The association between RHR and annual change in AVC was modified by sex ($p=0.006$ for interaction) and age ($p=0.02$ for interaction), but not race/ethnicity ($p=0.43$ for interaction). In fully-adjusted models, higher RHR predicted AVC progression for men, but not for women, and predicted AVC progression for older adults [> 62 years (median age)] but not younger adults (Table 4). Subgroup analyses were consistent when repeated after excluding those taking AV-nodal blocking medications (Supplemental Table 7) and after adjustment for baseline Agatston score (Supplemental Table 8).

Discussion

In a large community-based cohort of individuals free of CVD at baseline, we found that higher RHR was associated with calcification of the left-sided heart valves, specifically with prevalent and incident MAC and with AVC progression, independent of traditional CVD risk factors. Thus, RHR, a vital sign measured at nearly all clinic encounters and self-monitored by many via fitness trackers and mobile devices, may provide prognostic information about valvular calcification risk.

Our findings are consistent with other large cardiovascular cohorts that have demonstrated an independent association between RHR and CVD events and mortality.^{8–11, 24} A recent meta-analysis of 45 prospective cohort studies found RHR was an independent predictor of coronary artery disease, stroke, sudden death and even non-CVD.²⁴ However previously the relation of RHR with incidence/progression for valvular calcification has not been studied.

MAC predicts CVD morbidity and mortality, independently of CVD risk factors.^{2, 3, 25} To our knowledge, our study is the first to report an independent association of RHR with prevalent and incident MAC. It is unclear why we found an elevated RHR was associated with the incidence of MAC (for those without MAC at baseline) but not with the progression of MAC. Elmariah et al also demonstrated from MESA that traditional CVD risk factors were associated more with the incidence rather than progression of MAC.⁶ It has been

postulated that different mechanisms may be involved in the initiation and progression of valvular calcium.^{6, 26} However it is important to note that the study by Elmariah, as well as ours, evaluated MAC progression over a relatively short median follow-up time of 2.3 years. A longer timeframe might be needed to evaluate for progression, although we did find an association of RHR with AVC and CAC progression over the same period.

Similar to MAC, the presence of AVC also independently predicts CVD events and CVD mortality.¹ Several known traditional risk factors for CVD are independently associated with incident AVC.⁷ However we did not find an independent association between RHR and incident AVC. Studies suggest that AVC may progress independent of known atherosclerotic disease risk factors and only baseline AVC has emerged as a consistent independent predictor of AVC progression.^{5, 7} Factors associated with shear stress, such as greater cardiac output, have been shown to correlate with more rapid progression of aortic stenosis.^{15, 27, 28} Subclinical AVC and clinical aortic valve stenosis are known to be associated with each other⁴ and share similar CVD risk factors.^{4, 29, 30} To our knowledge, our study is the first to look at the association between RHR and progression of subclinical AVC. Even after adjusting for baseline AVC we found RHR to be a strong independent predictor of AVC progression. This relationship appeared to be stronger in men (compared to women) and in older adults (compared to younger), although subgroup analysis should be considered exploratory given the multiple tests performed. However, similar to our findings, De Oliveira Moraes et al, who looked at the association between RHR and aortic valve stenosis progression, also found effect modification by sex and age.¹⁵ Other prior work has found RHR to be more strongly associated with mortality in men compared to women.¹¹

There are plausible biological mechanisms of how a faster RHR could contribute to valvular calcification including increased sympathetic activity leading to higher blood pressure,³¹ vascular stiffness,³² endothelial dysfunction, and activation of an inflammatory milieu.¹⁸ Valvular calcification is thought to occur by an immune-inflammatory process similar to atherosclerosis.²⁶ Mechanical strain combined with transforming growth factor-B1 can both initiate and accelerate the aggregation of aortic valvular interstitial cells to form calcific nodules.³³

Despite biologic plausibility of mechanisms that could support a causal link between RHR and valve calcification, prior work has found that a genetic risk score associated with higher RHR was not associated with prevalent AVC.¹⁶ While this genetic study raises questions regarding causality, it is important to note that other non-genomic (environmental and lifestyle) factors influence RHR as well. For example, fitness is associated with improved autonomic function and a lower RHR.³⁴ Although we did not have a measure of fitness in our study, we adjusted for physical activity levels as a surrogate for fitness and associations remained statistically significant.

Our study has several strengths, which include a large sample size, multi-racial composition, and longitudinal evaluation. Our findings suggest a temporal association between RHR and valvular calcification, which reduces concerns for reverse causation. We were also able to adjust for multiple potential confounding and mediating factors, including physical activity and use of AV-nodal blocking medications. However, there may still be residual confounding

explaining our associations. Follow-up time was relatively short (median of 2.3 years) between scans. Also, participants in MESA did not have baseline or follow-up echocardiography to assess for valvular dysfunction (i.e. stenosis).

Conclusions

In summary, among an ethnically-diverse community cohort with no clinical CVD at baseline, we have demonstrated that higher RHR was statistically significantly associated with higher prevalence and incidence of MAC and faster progression of AVC independent of traditional CVD risk factors. The association between RHR and AVC progression appeared stronger for men and older adults, consistent with prior work. Our study results supports our hypothesis that higher RHR, possibly through increased mechanical strain, may enhance the initiation and progression of left-sided valvular calcification. However, further work is needed to determine whether associations seen are causal or due to another process. RHR is a vital sign that is underused for CVD risk assessment and can be readily measured at routine clinic visits. Whether modification of RHR through lifestyle or pharmacologic interventions can reduce valvular calcium progression warrants further study.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

MESA	Multi-Ethnic Study of Atherosclerosis
AVC	aortic valve calcium
MAC	mitral annular calcium
RHR	resting heart rate
CAC	coronary artery calcium
AV	atrio-ventricular
eGFR	estimated glomerular filtration rate

CRP C-reactive protein

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Highlights

- Mitral annular and aortic valve calcium are markers for cardiovascular disease (CVD)
- Resting heart rate (RHR) is a vital sign that is underused for CVD risk assessment
- We found RHR was associated with progression of left-sided valvular calcification
- This was independent of other CVD risk factors, and stronger for men & older adults
- Whether modification of RHR reduces valve calcium progression needs further study

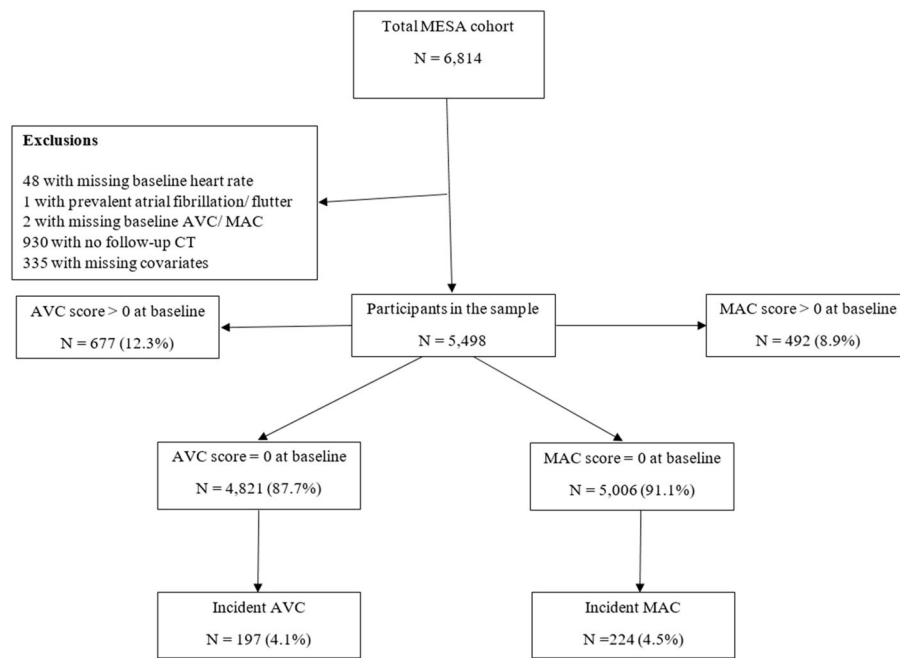


Figure 1.

A flow chart illustrating our exclusions, the prevalence of AVC and MAC at baseline, and the percentage of participants at risk who developed incident AVC/MAC on follow-up CT.

Table 1

Baseline characteristics of participants stratified by resting heart rate categories, the Multi-Ethnic Study of Atherosclerosis, 2000–2002 ^{a,b}

Characteristics	Resting heart rate (bpm)			p-for-trend
	< 60	60 – 69	70 – 79	≥ 80
N	2,083	2,154	953	308
Heart rate, bpm	54 (4)	64 (3)	73 (3)	85 (5)
Age, years	62.1 (10.2)	61.5 (10.1)	61.6 (10.3)	61.7 (9.8)
Women	940 (45.1%)	1,212 (56.3%)	546 (57.3%)	181 (58.8%)
Race/ethnicity				
White	835 (40.1%)	857 (39.8%)	372 (39.0%)	117 (38.0%)
Black	589 (28.3%)	528 (24.5%)	248 (26.0%)	98 (31.8%)
Hispanic	435 (20.9%)	466 (21.6%)	215 (22.6%)	65 (21.1%)
Chinese	224 (10.8%)	303 (14.1%)	118 (12.4%)	28 (9.1%)
Education				
Less than high school	322 (15.5%)	368 (17.1%)	171 (17.9%)	57 (18.5%)
High school or vocational school	837 (40.2%)	883 (41.0%)	393 (41.2%)	147 (47.7%)
College, graduate or professional school	924 (44.4%)	903 (41.9%)	389 (40.8%)	104 (33.8%)
BMI, kg/m ²	27.7 (5)	28.2 (5.5)	28.9 (5.6)	30.4 (6.4)
Waist circumference, cm	97 (14)	98 (14)	100 (15)	104 (16)
Smoking status				
Never	1,002 (48.1%)	1,107 (51.4%)	507 (53.2%)	172 (55.8%)
Former	831 (39.9%)	786 (36.5%)	320 (33.6%)	97 (31.5%)
Current	250 (12.0%)	261 (12.1%)	126 (13.2%)	39 (12.7%)
Physical activity, MET-minutes/week ^c	4,440 (2,273 – 8,280)	3,983 (2,025 – 7,410)	3,885 (1,845 – 7,080)	3,240 (1,478 – 6,105)
Systolic blood pressure, mmHg	125 (22)	126 (21)	127 (20)	130 (19)
eGFR, ml/min per 1.73 m ²	76.8 (15.5)	78.7 (15.7)	79.5 (16.7)	79.4 (18.3)
Total chol, mmol/L ^d	5.0 (0.8)	5.0 (0.9)	5.1 (0.9)	5.2 (1.2)
HDL-chol, mmol/L ^d	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)	1.3 (0.4)
Diabetes status	161 (7.7%)	231 (10.7%)	178 (18.9%)	89 (28.9%)

Characteristics	Resting heart rate (bpm)			<i>p</i> -for-trend
	< 60	60 – 69	70 – 79	
Medication use			≥ 80	-
Antihypertensive	768 (36.9%)	722 (33.5%)	359 (37.7%)	0.08
Lipid-lowering	332 (15.9%)	338 (15.7%)	171 (17.9%)	0.06
AV-nodal blocker	355 (17.0%)	236 (11.0%)	66 (6.9%)	<0.001
hsCRP, mg/L†	1.4 (0.7 – 3.3)	2.0 (0.9 – 4.2)	2.4 (1.0 – 5.0)	<0.001
IL-6, pg/mL†	1.1 (0.7 – 1.7)	1.2 (0.8 – 1.8)	1.3 (0.9 – 2.1)	<0.001
Fibrinogen, g/L†	3.3 (2.9 – 3.8)	3.4 (2.9 – 3.9)	3.5 (3.0 – 4.0)	<0.001
AVC Agastion score>0	244 (11.7%)	263 (12.2%)	126 (13.2%)	0.12
MAC Agastion score>0	147 (7.1%)	199 (9.2%)	100 (10.5%)	<0.001

^a AV = atrioventricular; AVC = aortic valve calcium; BMI = body mass index; bpm = beats per minute; chd = cholesterol; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; hsCRP = high-sensitivity C-reactive protein; IL-6 = interleukin-6; MAC = mitral annular calcium; MET = metabolic equivalent of task.

^b Data are presented as mean (standard deviation) for continuous variables and as count (percentages) for categorical variables, unless otherwise specified.

^c Data presented as median (interquartile interval).

^d To convert total cholesterol and HDL-C from mmol/L to mg/dL, multiply by 38.6. To convert fibrinogen from g/L to mg/dL multiply by 100.

Table 2

Relative risks (95% confidence intervals) of AVC and MAC by baseline heart rate, MESA, 2000 – 2005^a

Heart rate, bpm	< 60	60 – 69	70 – 79	≥ 80	p-for-trend	Per SD (10 bpm) increment in HR
Incident AVC, n	76	74	28	19	-	-
N	1,839	1,891	827	264	-	-
Model 1 ^b	1 (Reference)	1.07 (0.78 – 1.45)	0.92 (0.60 – 1.41)	1.84 (1.14 – 2.98)	0.19	1.11 (0.97 – 1.28)
Model 2 ^c	1 (Reference)	1.05 (0.77 – 1.43)	0.89 (0.58 – 1.37)	1.66 (1.01 – 2.74)	0.35	1.08 (0.94 – 1.25)
Model 3 ^d	1 (Reference)	1.04 (0.76 – 1.42)	0.85 (0.56 – 1.31)	1.50 (0.89 – 2.54)	0.55	1.06 (0.91 – 1.23)
Model 4 ^e	1 (Reference)	1.04 (0.76 – 1.42)	0.85 (0.55 – 1.31)	1.50 (0.89 – 2.53)	0.56	1.05 (0.90 – 1.22)
Incident MAC, n	72	84	51	17	-	-
N	1,936	1,955	853	262	-	-
Model 1 ^b	1 (Reference)	1.22 (0.90 – 1.66)	1.70 (1.20 – 2.41)	1.94 (1.16 – 3.25)	0.001	1.27 (1.11 – 1.44)
Model 2 ^c	1 (Reference)	1.18 (0.87 – 1.61)	1.57 (1.10 – 2.23)	1.71 (1.00 – 2.92)	0.006	1.22 (1.07 – 1.39)
Model 3 ^d	1 (Reference)	1.18 (0.86 – 1.60)	1.51 (1.06 – 2.14)	1.48 (0.85 – 2.56)	0.02	1.17 (1.03 – 1.34)
Model 4 ^e	1 (Reference)	1.17 (0.85 – 1.59)	1.42 (0.99 – 2.02)	1.38 (0.80 – 2.38)	0.06	1.140.99 – 1.30)

AVC = aortic valve calcium; bpm = beats per minute; HR = heart rate; MAC = mitral annular calcium; MESA = Multi-Ethnic Study of Atherosclerosis; SD = standard deviation

^bModel 1: adjusted for age, sex, race/ethnicity, study site, CT scanner type, and time between CT scans

^cModel 2: model 1 plus education, BMI, waist circumference, smoking status, and In physical activity

^dModel 3: model 2 plus systolic blood pressure, use of antihypertensive medication, total cholesterol, HDL-cholesterol, use of lipid-lowering medications, diabetes, eGFR, and atrioventricular-nodal blocker use

^eModel 4: model 3 plus In hsCRP, In IL-6, and In fibrinogen

Table 3Association of baseline heart rate with annual change in AVC, MAC, and CAC, MESA, 2000 – 2005^a

	Annual change (Agatston units/year) (95% confidence interval)		
Model 1^b	AVC	MAC	CAC
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	2.45 (0.01, 4.90)	0.95 (–4.79, 6.70)	2.62 (–1.14, 6.38)
70 – 79 bpm	1.63 (–1.48, 4.74)	8.82 (1.53, 16.12)	6.08 (1.31, 10.85)
≥ 80 bpm	7.80 (2.96, 12.65)	2.3 (–9.07, 13.67)	20.81 (13.37, 28.24)
Per 1 SD (10 bpm) increment in heart rate	1.46 (0.34, 2.59)	1.75 (–0.89, 4.38)	4.90 (3.18, 6.63)
Model 2^c			
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	2.37 (–0.08, 4.83)	0.68 (–5.07, 6.43)	2.13 (–1.63, 5.89)
70 – 79 bpm	1.53 (–1.60, 4.66)	8.23 (0.89, 15.57)	5.24 (0.44, 10.04)
≥ 80 bpm	7.55 (2.66, 12.45)	1.63 (–9.84, 13.11)	19.23 (11.73, 26.73)
Per 1 SD (10 bpm) increment in heart rate	1.40 (0.26, 2.54)	1.46 (–1.21, 4.14)	4.45 (2.70, 6.20)
Model 3^d			
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	2.59 (0.12, 5.06)	0.66 (–5.13, 6.45)	1.99 (–1.74, 5.71)
70 – 79 bpm	1.98 (–1.20, 5.17)	7.82 (0.36, 15.29)	3.27 (–1.53, 8.08)
≥ 80 bpm	8.32 (3.34, 13.29)	0.44 (–11.21, 12.1)	13.99 (6.49, 21.49)
Per 1 SD (10 bpm) increment in heart rate	1.62 (0.45, 2.80)	1.19 (–1.57, 3.96)	3.38 (1.60, 5.15)
Model 4^e			
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	2.61 (0.13, 5.09)	1.21 (–4.6, 7.02)	1.92 (–1.81, 5.66)
70 – 79 bpm	1.77 (–1.43, 4.98)	8.31 (0.81, 15.82)	2.76 (–2.07, 7.59)
≥ 80 bpm	8.09 (3.10, 13.08)	1.06 (–10.62, 12.74)	13.43 (5.92, 20.95)
Per 1 SD (10 bpm) increment in heart rate	1.53 (0.34, 2.71)	1.36 (–1.43, 4.14)	3.16 (1.37, 4.95)

^a AVC = aortic valve calcium; bpm = beats per minute; MAC = mitral annular calcium; MESA = Multi-Ethnic Study of Atherosclerosis; SD = standard deviation

^b Model 1: adjusted for age, sex, race/ethnicity, study site, and CT scanner type

^c Model 2: model 1 plus education, BMI, waist circumference, smoking status, and ln physical activity

^d Model 3: model 2 plus systolic blood pressure, use of antihypertensive medication, total cholesterol, HDL-cholesterol, use of lipid-lowering medications, diabetes, eGFR, and atrioventricular-nodal blocker use

^e Model 4: model 3 plus ln hsCRP, ln IL-6, and ln fibrinogen

Table 4

Association of baseline heart rate with annual change in AVC stratified by median age, and sex, MESA, 2000 – 2005^a

	Annual change in AVC (Agatston units/year) (95% confidence interval)			
Model 1^b	≤ 62 years	> 62 years	Women	Men
N, %	2,861	2,637	2,879	2,619
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	0.49 (–0.25, 1.23)	4.61 (–0.41, 9.62)	0.90 (–1.17, 2.98)	3.87 (–0.68, 8.43)
70 – 79 bpm	0.71 (–0.23, 1.65)	2.64 (–3.74, 9.01)	–0.79 (–3.35, 1.78)	4.30 (–1.66, 10.27)
≥ 80 bpm	1.45 (0.02, 2.88)	15.17 (4.98, 25.37)	0.43 (–3.44, 4.31)	17.28 (7.62, 26.95)
Per 1 SD (10 bpm) increment in heart rate	0.29 (–0.05, 0.63)	2.74 (0.45, 5.03)	–0.12 (–1.08, 0.84)	3.06 (1.01, 5.12)
Model 2^c				
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	0.49 (–0.25, 1.23)	4.54 (–0.49, 9.57)	0.89 (–1.19, 2.97)	3.44 (–1.15, 8.02)
70 – 79 bpm	0.69 (–0.25, 1.64)	2.41 (–4.05, 8.86)	–0.77 (–3.35, 1.82)	3.77 (–2.27, 9.82)
≥ 80 bpm	1.46 (0.01, 2.91)	15.04 (4.76, 25.32)	0.45 (–3.48, 4.38)	16.59 (6.83, 26.34)
Per 1 SD (10 bpm) increment in heart rate	0.28 (–0.07, 0.63)	2.66 (0.33, 4.99)	–0.11 (–1.09, 0.87)	2.8 (0.70, 4.91)
Model 3^d				
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	0.44 (–0.31, 1.19)	4.81 (–0.25, 9.88)	0.77 (–1.32, 2.86)	4.27 (–0.35, 8.90)
70 – 79 bpm	0.55 (–0.41, 1.51)	3.00 (–3.57, 9.57)	–0.87 (–3.49, 1.75)	5.18 (–0.98, 11.35)
≥ 80 bpm	1.15 (–0.35, 2.64)	15.92 (5.52, 26.31)	0.52 (–3.47, 4.52)	18.80 (8.86, 28.73)
Per 1 SD (10 bpm) increment in heart rate	0.19 (–0.17, 0.55)	2.94 (0.55, 5.34)	–0.18 (–1.19, 0.84)	3.49 (1.31, 5.67)
Model 4^e				
< 60 bpm	0 (Reference)	0 (Reference)	0 (Reference)	0 (Reference)
60 – 69 bpm	0.44 (–0.31, 1.19)	5.10 (0.01, 10.19)	0.76 (–1.34, 2.85)	4.30 (–0.35, 8.95)
70 – 79 bpm	0.58 (–0.39, 1.55)	2.68 (–3.92, 9.29)	–1.11 (–3.74, 1.52)	5.11 (–1.11, 11.32)
≥ 80 bpm	1.15 (–0.35, 2.65)	15.41 (5.00, 25.83)	0.45 (–3.54, 4.44)	18.60 (8.58, 28.62)
Per 1 SD (10 bpm) increment in heart rate	0.20 (–0.16, 0.57)	2.75 (0.33, 5.17)	–0.27 (–1.28, 0.75)	3.40 (1.19, 5.61)

^aAVC = aortic valve calcium; bpm = beats per minute; MESA = Multi-Ethnic Study of Atherosclerosis; SD = standard deviation

^bModel 1: adjusted for age (in sex subgroup analysis), sex (in age subgroup analysis), race/ethnicity, study site, and CT scanner type

^cModel 2: model 1 plus education, BMI, waist circumference, smoking status, and ln physical activity

^dModel 3: model 2 plus systolic blood pressure, use of antihypertensive medication, total cholesterol, HDL-cholesterol, use of lipid-lowering medications, diabetes, eGFR, and atrioventricular (AV)-nodal blocker use

^eModel 4: model 3 plus ln hsCRP, ln IL-6, and ln fibrinogen