Title

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Associations of Left Ventricular Hypertrophy with Prevalent and Incident Valve Calcification: The Multi-Ethnic Study of Atherosclerosis

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Abstract

Objectives—We aim to evaluate the relationship between percent of predicted left ventricular mass (%PredLVM) and valve calcification in the Multi-Ethnic Study of Atherosclerosis (MESA).

Background—Cardiac valve calcification has been associated with left ventricular hypertrophy (LVH), which portends cardiovascular events. However, this relationship and its mediators are poorly understood.

Methods—MESA is a longitudinal cohort study of men and women aged 45-84 years without clinical cardiovascular disease in whom serial cardiac magnetic resonance and computed tomography imaging were performed. The relationships between baseline %PredLVM and the prevalence, severity, and incidence of aortic valve (AVC) and mitral annulus calcification (MAC) were determined by regression modeling.

Results—Prevalent AVC was observed in 630 and MAC in 442 of 5,042 subjects (median 55.9 and 71.1 Agatston units, respectively). After adjustment for age, gender, body mass index, ethnicity, socioeconomic status, physical activity, diabetes, cholesterol levels, blood pressure,

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smoking, kidney function, serum lipids, and antihypertensive and statin medications, %PredLVM was associated with prevalent AVC (OR=1.18 per SD increase in %PredLVM [95%CI 1.08 – 1.30]; *p*=0.0004) and MAC (OR=1.18 [95%CI 1.06 – 1.32]; *p*=0.002). Similarly, %PredLVM was associated with increased severity of prevalent AVC (risk difference = 0.26 [95%CI 0.15 – 0.38]; p<0.0001) and MAC (risk difference = 0.20 [95%CI 0.03 – 0.37]; *p*=0.02). During follow-up (mean 2.4±0.9 years), 153 subjects (4%) developed AVC and 198 (5%) MAC. %PredLVM was associated with incident AVC (OR=1.24 [95%CI 1.04 – 1.47]; *p*=0.02) and MAC (OR=1.18 [1.01-1.40]; *p*=0.04). Further adjustment for inflammatory markers and coronary artery calcification did not attenuate these associations. Specifically, concentric LVH most strongly predicted incident valve calcification.

Conclusions—Within the MESA cohort, LVH was associated with prevalence, severity, and incidence of valve calcification independent of hypertension and other identified confounders.

Keywords

aortic valve; calcification; left ventricular mass; mitral valve annulus

INTRODUCTION

Calcification of the aortic and mitral valves is a progressive disease similar to atherosclerosis(1-4) that is associated with adverse cardiovascular outcomes.(5-7) Even without hemodynamically significant valve obstruction, calcific aortic and mitral valve disease have been associated with dramatic increases in the risk of myocardial infarction, stroke, and cardiovascular and all-cause mortality.(5-7) Valve calcification may be a marker of atherosclerosis, but discordance between coronary disease and calcific valve disease suggests that alternative mechanisms such as inflammation, neurohormonal activation, endothelial dysfunction, or other genetic factors also may play a role.(1-4)

Aortic stenosis (AS) causes compensatory left ventricular hypertrophy (LVH); however, two small cross-sectional analyses suggest an association between aortic valve disease and LVH even in the absence of significant valve obstruction.(3,8) Although LVH in this setting may be a consequence of low levels of outflow obstruction, similar associations between LVH and prevalent mitral annulus calcification (MAC) suggest that alternate processes may lead to both valvular calcification and left ventricular remodeling.(9,10) The longitudinal Multi-Ethnic Study of Atherosclerosis (MESA) provides a unique opportunity to explore relationships between LVH and calcific valve disease.

METHODS

Study Population and Data Collection

MESA is a prospective cohort study of 6,814 men and women aged 45 to 84 years recruited from six U.S. communities designed to evaluate risk factors for cardiovascular disease. At initial enrollment, subjects had no clinical evidence of cardiovascular disease. Participants attended study visits every 18 to 24 months. A detailed description of the study design has been published.(11) This analysis was limited to the 5,042 subjects who underwent cardiac magnetic resonance imaging (MRI) and computed tomography (CT).

Measurement of Cardiovascular Calcification

Coronary artery, aortic valve and mitral annulus calcification were assessed by electron-beam CT at 3 centers and multi-detector row helical CT at 3 centers. All studies were interpreted centrally (Los Angeles Biomedical Research Institute at Harbor-UCLA, Torrance, CA). Calcification was quantified by Agatston scoring.(12) Prevalent

cardiovascular calcification was defined as a score >0 Agatston units (AU) Details of the image acquisition and interpretation protocols, quality control measures and inter-observer reliability characteristics have been reported previously.(13) Follow-up cardiac CT scans with assessment of AVC and MAC were performed 2 to 3 years after the initial scan.

Determination of Left Ventricular Mass

Magnetic resonance imaging was performed using 1.5-T magnets with 4-element phased-array surface coils, ECG gating, and blood pressure monitoring. LV mass was quantified as previously described.(14) Using an allometric approach, regression models for body size were derived from a sample of 1,746 MESA participants without obesity, hypertension, antihypertensive medication, diabetes, impaired fasting glucose or hypoglycemic medication and a multiplicative estimate derived from the regression of log(LV mass) on log(height), log(weight) and gender. LV mass was adjusted for body size by dividing LV mass by the predicted LV mass based on height, weight and gender as: $100^* \times \text{LV mass} / (a * \text{height}^{0.54} * \text{weight}^{0.61})$ where a = 6.82 for women and 8.25 for men with mass in grams, height in meters, weight in kilograms.(15) Similarly, LV end-diasolic volume was adjusted for body size and gender by dividing by the predicted LV volume as: 100* LV end-diasolic volume / $(b * \text{height}^{1.25} * \text{weight}^{0.43})$ where b = 10.0 for women and 10.5 for men. The resultant percent of predicted LV mass (%PredLVM) and percent of predicted LV end diastolic volume (%LVVol) were used for all analyses.

Covariates

Historical data were collected using a combination of self– and interviewer–administered questionnaires. Smoking status was defined as current, former, or never with current smoking defined as smoking a cigarette in the last 30 days. Diabetes was defined as a fasting glucose ≥126 mg/dL or hypoglycemic medication use. Hypertension was defined as systolic blood pressure ≥140 mmHg, diastolic blood pressure ≥90 mmHg, a reported history of hypertension, or antihypertensive therapy. Estimated glomerular filtration rate (eGFR) was calculated using the Modification of Diet in Renal Disease equation. Physical activity was assessed using the MESA Typical Week Physical Activity Survey and quantified for this analysis as minutes of vigorous activity per week multiplied by metabolic equivalent (MET) level.(16)

Statistical Analysis

Differences in patient characteristics across %PredLVM strata were evaluated using analysis of variance (ANOVA). Chi-square analyses were used for categorical variables. In order to approximate a normal distribution, calcium scores were log-transformed for use in analyses of severity. Logistic regression was used to derive odds ratios (OR) for the relationships between baseline %PredLVM and the prevalence and incidence of AVC and MAC. Linear regression models using log-transformed valve calcium scores were used to assess relationships between %PredLVM and severity of AVC and MAC in subjects with prevalent disease. Statistical analyses were performed using SAS (version 9.2, SAS Institute, Inc., Cary, NC), with significance accepted at $p<0.05$.

RESULTS

Subject Characteristics

A total of 5,042 subjects underwent both cardiac CT and MRI scans, with a mean age of 62±10 years; 46% were men (Table 1). The mean end-diastolic LV mass was 145±40 g. The mean %PredLVM, which adjusts for body size and gender, was 104±19%, indicating the LV mass of the population was 4% greater than the reference cohort of participants without

obesity, hypertension, antihypertensive medication, diabetes, impaired fasting glucose or hypoglycemic medication. Quartiles of %PredLVM were defined as: quartile 1: < 91.5%, quartile 2: 91.5 - 102.2%, quartile 3: 102.2 - 114.6%, quartile 4 ≥114.6% (Table 1). The proportion of subjects with diabetes mellitus, hypertension, and current smoking status increased by %PredLVM quartile. Significant ethnic variation in LV mass were observed with greater %PredLVM observed in Blacks and Hispanics (Table 1).

Left Ventricular Mass and Prevalent Valve Calcium

At the baseline evaluation, cardiac CT identified AVC in 630 subjects (13%) and MAC in 442 (9%). Both AVC and MAC were observed in 183 (4%) subjects. Stratification by %PredLVM quartile demonstrated increasing prevalence of valve calcification with increasing %PredLVM, with AVC observed in 144 subjects (11%) in the lowest and 200 (15%) in the highest %PredLVM quartiles (p=0.0004; Figure 1A) and MAC observed in 97 subjects (8%) in the lowest %PredLVM quartile and 134 (11%) in the highest quartile (p=0.049; Figure 1A). This relationship was consistent across ethnic groups within MESA for both AVC and MAC (Figure 1B and C). After adjusting by multivariable analysis for age, gender, BMI, ethnicity, study site, socioeconomic status, physical activity, diabetes, history of hypercholesterolemia, hypertension, smoking, eGFR, total serum cholesterol and LDL-cholesterol levels, systolic and diastolic blood pressures, and use of antihypertensive agents and statins, %PredLVM was associated with prevalent AVC (OR=1.18 per SD increase in %PredLVM [95%CI 1.08 – 1.30]; p=0.0004) and MAC (OR=1.18 [95%CI 1.06 – 1.32]; p=0.002).

Left Ventricular Mass and the Severity of Valve Calcium

Among those subjects with valve calcium at baseline, the median AVC score was 55.9 (IQR 21.0, 149.1) AU and the MAC score was 71.1 (22.4, 290.2) AU. The severity of both AVC and MAC, defined as log (Agatston score), increased with increasing quartile of %PredLVM (AVC (mean (SD)): 3.7 (1.3), 4.0 (1.3), 4.1 (1.5), 4.3 (1.7), respectively; p=0.01; MAC: 4.3 (1.9), 4.2 (1.8), 4.5 (1.9), 4.8 (1.8), respectively; p=0.055). Multivariable regression analyses adjusting for the aforementioned variables demonstrated a robust relationship between %PredLVM and the severity of AVC (risk difference = 0.26 per SD increase in %PredLVM [95%CI 0.15 – 0.38]; p<0.0001) and MAC (risk difference = 0.20 [95%CI 0.03 – 0.37]; p=0.02).

Left Ventricular Mass and Incident Valve Calcium

Over a mean follow-up of 2.4±0.9 years, 153 (4%) of 3,902 subjects without AVC at baseline developed AVC, an annualized incidence rate of 1.6%. Of the 4,072 subjects without MAC at the first evaluation, 198 (5%) developed MAC during follow-up, an incidence rate of 2.0%/year. We found a relationship between incident AVC and baseline %PredLVM (incidence rate 1.2%/year in the lowest quartile and 1.9%/year in the highest quartile; p=0.05; Figure 2). Incident MAC was significantly greater among subjects in the highest %PredLVM quartile than in the lowest quartile (2.9 vs 1.9%/year; p=0.03).

Because of the racial variations in LV mass and valve calcification and the interaction of age with risk factors for valve calcification,(17-19) we tested for interactions between race and age with %PredLVM for incident valve calcification. Neither race nor age demonstrated significant interactions with %PredLVM for AVC (race: Chinese p=0.43, Black p=0.98, Hispanic p=0.20, each vs Caucasian ethnicity; age: p=0.63) or MAC (race: Chinese p=0.97, Black p=0.41, Hispanic p=0.98, each vs Caucasian ethnicity; age: p=0.20). After adjustment for age, gender, ethnicity, and study site, %PredLVM was significantly associated with incident AVC (OR=1.20 per SD increase in %PredLVM [95%CI 1.02 – 1.40]; p=0.03) and incident MAC (OR=1.16 [95%CI 1.00 – 1.35]; p=0.049). Sequential multivariable models

were constructed in an effort to identify mediators of this relationship (Table 2). Additional adjustments for cardiovascular risk factors including BMI, diabetes, hypercholesterolemia, hypertension, smoking, eGFR, cholesterol, blood pressure, antihypertensive or statin therapy, socioeconomic status, physical activity, inflammatory markers (serum IL-6, hs-CRP), and coronary artery calcification as a measure of subclinical atherosclerosis did not eliminate the association between %PredLVM and incident AVC (OR=1.23 per SD increase in %PredLVM [95%CI 1.03 – 1.46]; p=0.02) or incident MAC (OR=1.19 [95%CI 1.01 – 1.40]; p=0.04).

We subsequently evaluated parameters of LV geometry. After adjusting for age, gender, BMI, ethnicity, study site, socioeconomic status and physical activity, %PredLVM and the LV mass to volume ratio were associated with both incident AVC and MAC (Table 3). Concentric LVH, defined by LV mass to volume ratio, was the strongest predictor of incident valve calcification (AVC: OR=1.21 per SD increase [95%CI 1.03 – 1.43]; p=0.02; MAC: OR=1.27 [95%CI 1.09 – 1.47]; p=0.002]; whereas, there was no relationship between percent of predicted left ventricular volume and either AVC or MAC.

DISCUSSION

The association of increasing LV mass with the prevalence and severity of AVC are aligned with the paradigm that LVH develops in response to aortic valve disease. However, we also found associations between LV mass and the prevalence and severity of MAC, which does not increase LV afterload and has not been recognized as an independent cause of LVH. Furthermore, we demonstrate that increased LV mass, specifically concentric and not eccentric LVH, independently predicts the development of AVC and MAC over time. These observations suggest that concentric LVH may identify subjects at risk for valve calcification and possibly that common pathophysiological mechanisms may account for both the development of valvular calcification and LVH.

An obvious potential explanation for this association is hypertension, which has been consistently implicated as a factor in the development and progression of calcific valve disease (1,2,20) and is the most common cause of LVH in the general population.(21) Hypertension, broadly defined on the basis of patient reporting, increased systolic or diastolic blood pressure on the initial study visit, or the use of any antihypertensive therapy was prevalent among 2,281 subjects in the MESA cohort (45%). Multivariable analyses adjusting for hypertension suggest that the observed relationships between LVH and valve calcification are independent of this factor; however, residual confounding by hypertension cannot be excluded. More sensitive measures of hypertension, such as ambulatory blood pressure monitoring, would be necessary to more definitively exclude hypertension as a mediator of the observed relationships.

Inflammatory and neurohormonal mechanisms have also been implicated in the development of both cardiovascular calcification and LVH. Angiotensin II and several inflammatory cytokines are involved in both myocardial remodeling and valve calcification, and any or all of these could mediate the relationship between %PredLVM and incident valve calcification.(1,2,22-25) Exploring potential links, we adjusted for cardiovascular risk factors, the inflammatory markers hs-CRP and IL-6, and subclinical atherosclerosis by sequential multivariable analyses and found no attenuation of the association between LVH and valve calcification, suggesting that none of these factors entirely explains the relationship. However, we did not possess measures of other neurohormonal and inflammatory pathways. Alternatively, valve remodeling, inflammation, and calcification have been linked to changes in the hemodynamic environment. Conceivably, LVH-associated alterations in shear stress and cyclic pressures and stretch may induce or

propagate valve pathology.(26,27) Regardless of the etiology, our analyses suggest that concentric LVH identifies those subjects at risk for developing valve calcification.

Our study has several limitations. First is the limited power to fully evaluate factors that are associated with valve calcification and LVH given the relative good health of the MESA cohort, of which only 5% developed incident valve calcification. This restriction also hinders the ability to fully characterize the apparent non-linear relationship between %PredLVM and valve calcification. Second is the limited data on duration and severity of hypertension, which precludes a more robust adjustment for hypertension. Third is the relatively modest relationship between %PredLVM and incident valve calcification. Despite these limitations, the association between LVH, specifically concentric remodeling, and valve calcification has potentially important clinical implications and warrants further study.

In conclusion, we found in the diverse MESA cohort that LVH is associated with the prevalence and severity of calcification of the aortic and mitral valves. Moreover, increased LV mass, specifically concentric LVH, at baseline was associated with the risk of incident AVC and MAC. These associations were independent of hypertension or other atherosclerotic risk factors, hs-CRP, IL-6, and subclinical atherosclerotic disease, suggesting that LVH may identify subjects at risk of developing valve calcification. Further study is needed to determine the pathophysiological links involved and to evaluate their reversibility and impact on patient outcomes.

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ABBREVIATIONS LIST

%PredLVM	percent of predicted left ventricular mass
%LVVol	percent of predicted left ventricular end diastolic volume
AU	Agatston units
AVC	aortic valve calcification
hs-CRP	high sensitivity C-reactive protein
IL	interleukin
LV	left ventricular
LVH	left ventricular hypertrophy
MAC	mitral annulus calcification
MESA	Multi-Ethnic Study of Atherosclerosis

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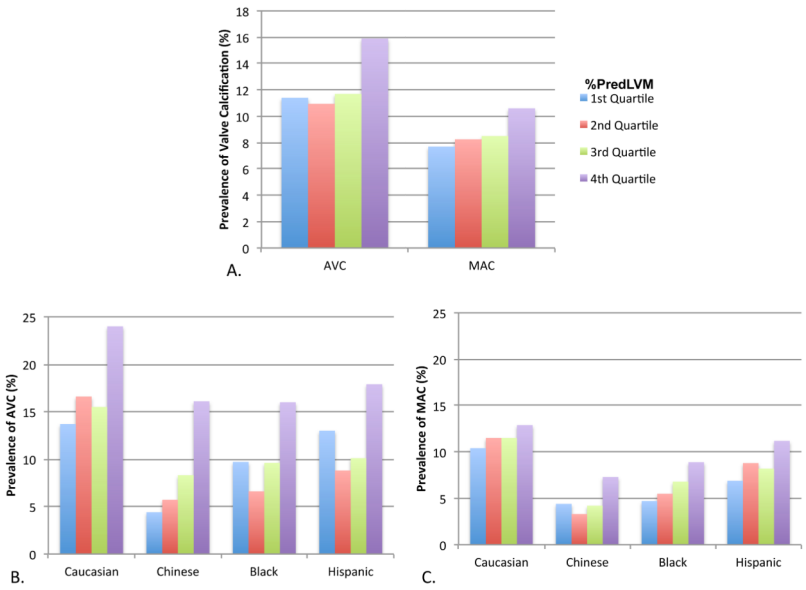

Figure 1. Relationship of LV mass to prevalent valve calcification

Unadjusted prevalence of aortic valve and mitral annulus calcification increases across quartiles of percent of predicted left ventricular mass. %PredLVM = percent of predicted left ventricular mass; LV = left ventricular.

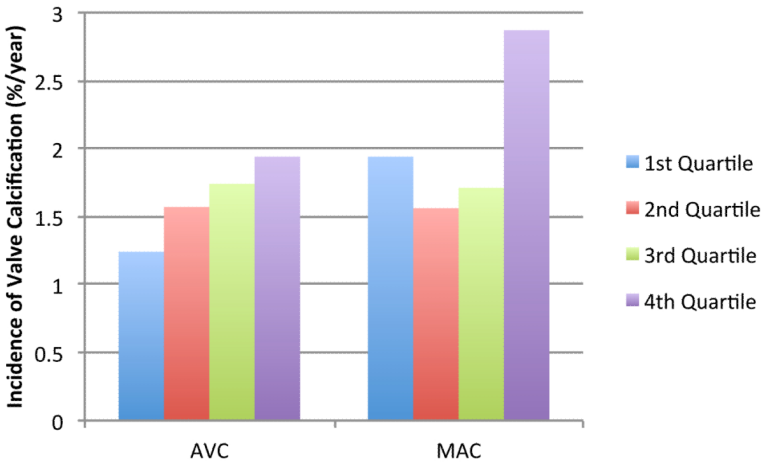

Figure 2. Relationship of LV mass to incident valve calcification

Unadjusted incidence of aortic valve and mitral annulus calcification stratified by quartile of percent of predicted left ventricular mass demonstrates that increased %PredLVM at baseline evaluation is associated with the development of incident valve calcification at both anatomic sites. %PredLVM = percent of predicted left ventricular mass; LV = left ventricular.

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Table 1

Baseline characteristics stratified by quartile of percent of predicted left ventricular mass.

		Total	Quartile 1 (< 91.5%)	Quartile 2 (91.5 - 102.2%)	Quartile 3 (102.2 - 114.6%)	Quartile 4 (>114.6%)	p-value
		(N=5042)	(N=1,260)	(N=1,261)	(N=1,261)	(N=1,260)	
Age, yrs		62 ± 10	62 ± 10	61 ± 10	61 ± 10	62 ± 10	<0.05
Male		2316 (46)	596 (47)	576 (46)	567 (45)	577 (46)	0.69
Race							<0.0001
	White	1952 (39)	575 (46)	505 (40)	478 (38)	394 (31)	
Black		1247 (25)	257 (20)	272 (22)	323 (26)	395 (31)	
	Hispanic	1135 (23)	247 (20)	274 (22)	267 (21)	347 (28)	
Chinese		708 (14)	181(14)	210 (17)	193 (15)	124 (10)	
BMI		28 ± 5	28 ± 5	28 ± 5	27 ± 5	28 ± 5	0.55
BSA, m^2		1.8 ± 0.2	1.9 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	1.8 ± 0.2	0.03
Serum cholesterol, mg/dl							
	Total Cholesterol	195 ± 36	198 ± 38	196 ± 35	194 ± 35	194 ± 37	<0.05
	LDL-cholesterol	117 ± 31	119 ± 33	117 ± 30	116 ± 31	116 ± 32	0.06
	HDL-cholesterol	52 ± 15	51 ± 16	51 ± 15	52 ± 15	52 ± 15	0.28
	Triglycerides	115 (81, 167)	121 (85, 171)	119 (84, 170)	113 (80, 159)	109 (76, 163)	<0.0001
Diabetes Mellitus		654 (13)	133 (11)	143 (11)	166 (13)	212 (17)	<0.0001
Hyperlipidemia		1859 (37)	463 (37)	497 (40)	437 (35)	462 (37)	0.11
Hypertension *		1468 (29)	263 (21)	303 (24)	391 (31)	511 (41)	<0.0001
eGFR, ml/min/1.73m^2		81 ± 17	80 ± 16	80 ± 16	82 ± 18	82 ± 19	0.0002
Smoking Status							
	Former	1790 (36)	476 (38)	452 (36)	462 (37)	400 (32)	<0.001
Current		627 (12)	110 (9)	131 (10)	142 (11)	244 (19)	<0.0001
Concurrent Medication							
	RAS inhibitor	593 (12)	108 (9)	123 (10)	144 (11)	218 (17)	<0.0001
	β-Blocker	463 (9)	92 (7)	90 (7)	126 (10)	155 (12)	<0.0001

		Total	Quartile 1 (< 91.5%)	Quartile 2 (91.5 - 102.2%)	Quartile 3 (102.2 - 114.6%)	Quartile 4 (>114.6%)	p-value
		(N=5042)	(N=1,260)	(N=1,261)	(N=1,261)	(N=1,260)	
	CCB	622 (12)	90 (7)	119 (9)	181 (14)	232 (18)	<0.0001
	Diuretic	683(14)	159 (13)	150 (12)	168 (13)	206 (16)	<0.01
	Vasodilator	226 (4)	42 (3)	47 (4)	59 (5)	78 (6)	<0.005
	Any Antihypertensive	1639 (33)	319 (25)	355 (28)	427 (34)	538 (43)	<0.0001
	Statin	748 (15)	187 (15)	200 (16)	178 (14)	183 (15)	0.65
	HRT	788 (16)	220 (38)	180 (30)	213 (35)	175 (27)	<0.0005
Blood Pressure, mmHg							
	Diastolic	72 ± 10	70 ± 10	70 ± 9	72 ± 10	75 ± 11	<0.0001
Systolic		125 ± 21	119 ± 19	122 ± 19	125 ± 20	134 ± 24	<0.0001
	Mean	93 ± 13	90 ± 12	91 ± 12	93 ± 13	99 ± 15	<0.0001
Heart Rate		63 ± 9	65 ± 9	63 ± 9	62 ± 9	61 ± 10	<0.0001
LV Measurements							
	LVeD mass, g	145 ± 40	117 ± 25	135 ± 27	150 ± 32	179 ± 42	<0.0001
	%PredLVM, %	104 ± 19	83 ± 8	97 ± 3	108 ± 4	129 ± 15	<0.0001
	LVeD Volume, ml	126 ± 31	113 ± 26	122 ± 27	128 ± 30	140 ± 36	<0.0001
	%LVVol, %	101 ± 19	90 ± 16	98 ± 15	103 ± 16	113 ± 22	<0.0001
	LV mass / volume ratio	1.17 ± 0.24	1.06 ± 0.21	1.12 ± 0.22	1.18 ± 0.22	1.30 ± 0.26	<0.0001
	LVEF, %	69 ± 7	70 ± 7	70 ± 7	69 ± 7	67 ± 9	<0.0001

%LVVol = percent of predicted left ventricular end diastolic volume; %PredLVM = percent of predicted left ventricular mass; BMI = body mass index; BSA = body surface area; CCB = calcium channel blocker; eGFR = estimated glomerular filtration rate; HDL = high-density lipoprotein; HRT = hormone replacement therapy; LDL = low-density lipoprotein; LV = left ventricular; LVeD = left ventricular end diastolic; LVEF = left ventricular ejection fraction; LVeS = left ventricular end systolic; RAS = renin-angiotenin system.

*Self reported history of hypertension.

Table 2

Association of increased left ventricular mass with incident valve calcification.

	Odds Ratio	95% Confidence Interval	p-value
Aortic Valve Calcification (N=4,412)			
Model 1 *	1.20	1.02 – 1.40	0.03
Model 2 †	1.24	1.04 – 1.47	0.02
Model 3 ‡	1.24	1.04 – 1.47	0.02
Model 4 §	1.23	1.03 – 1.46	0.02
Mitral Annulus Calcification (N=4,600)			
Model 1 *	1.16	1.00 – 1.35	0.049
Model 2 †	1.17	1.00 – 1.38	0.04
Model 3 ‡	1.18	1.01 – 1.39	0.04
Model 4 §	1.19	1.01 – 1.40	0.04

Odds ratios depicted are per SD increase in percent-predicted left ventricular mass.

*Adjusted for age, gender, ethnicity, and study site.

†Adjusted for Model 1 variables plus presence of BMI, diabetes, hypercholesterolemia, or hypertension, smoking status, eGFR, serum total and LDL-cholesterol levels, and systolic and diastolic blood pressures, and use of antihypertensive agents and statins.

‡Adjusted for Model 2 variables plus income level, health insurance status, and physical activity.

§Adjusted for Model 3 variables plus natural log-transformed (coronary artery calcification score + 1), interleukin-6, and C-reactive protein.

Table 3

Relationship of left ventricular parameters to incident valve calcification.

	Aortic Valve Calcification			Mitral Annulus Calcification		
	Odds Ratio	**95% Confidence Interval**	**p-value**	**Odds Ratio**	**95% Confidence Interval**	**p-value**
%PredLVM	1.21	1.04 - 1.42	0.02	1.18	1.02 - 1.37	0.03
%LVVol	1.00	0.84 – 1.18	0.95	0.89	0.75 - 1.04	0.14
LV Mass / Volume Ratio, g/ml	1.21	1.03 - 1.43	0.02	1.27	1.09 - 1.47	0.002

Odds ratios depicted are per 1 standard deviation increase.

%LVVol = percent of predicted left ventricular end diastolic volume; %PredLVM = percent of predicted left ventricular mass; LV = left ventricular Models adjust for age, gender, body mass index, ethnicity, and study site.