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Associations of Long-Term and Early Adult Atherosclerosis Risk Factors With Aortic and Mitral Valve Calcium

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Objectives To determine the association of long-term exposure to atherosclerosis risk factors with valvular calcification.

Background Traditional atherosclerosis risk factors have been associated with aortic and mitral valve calcium in cross-sectional studies, but long-term prospective data are lacking.

Methods This was a prospective, community-based cohort study with 27-year follow-up (median follow-up 26.9 years; range 23.1 to 29.6 years). Participants from the Framingham Offspring Study (n = 1,323, enrolled between 1971 and 1975, mean age at enrollment 34 ± 9 years; 52% women) underwent cardiac multidetector computed tomography assessment between 2002 and 2005. Associations between the long-term average of each cardiovascular risk factor and valve calcium were estimated using logistic regression.

Results Aortic valve calcium was present in 39% of participants and mitral valve calcium in 20%. In multivariable models, the odds ratio for aortic valve calcium associated with every SD increment in long-term mean total cholesterol was 1.74 ($p < 0.0001$); with every SD increment in high-density lipoprotein cholesterol, it was 0.77 ($p = 0.002$); and with every 9 cigarettes smoked per day, it was 1.23 ($p = 0.002$). Associations of similar magnitude were seen for mitral valve calcium. The mean of 3 serum C-reactive protein measurements was associated with mitral valve calcium (odds ratio: 1.29 per SD increment in C-reactive protein levels; $p = 0.002$). A higher Framingham risk score in early adulthood (40 years age or younger) was associated with increased prevalence and severity of aortic valve calcium measured 3 decades later.

Conclusions Exposure to multiple atherosclerotic risk factors starting in early to mid-adulthood is associated with aortic and mitral valve calcium. Studies evaluating early risk factor modification to reduce the burden of valve disease are warranted. (J Am Coll Cardiol 2010;55:2491–8) © 2010 by the American College of Cardiology Foundation

Aortic and mitral stenosis are among the most common forms of valvular heart disease affecting the elderly. Valve calcification precedes clinical stenosis and may represent an important intermediate phenotype for valve disease (1). Previously considered a degenerative consequence of aging, valve calcification and the resulting valvular stenosis are now recognized as "active" processes with marked histological similarities to atherosclerosis (2–7). However, the failure of lipid-lowering strategies to prevent or slow the progression of valvular disease has raised questions about the role of atherosclerosis risk factors in valvular stenosis (8–11). Improved understanding of the role of cardiovascular risk factors in valvular disease and the appropri-

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Abbreviations and Acronyms

BMI = body mass index
CRP = C-reactive protein
CT = computed tomography
HDL-C = high-density lipoprotein cholesterol
MDCT = multidetector computed tomography

ate timing for their control could provide insights into the prevention of valvular disease. Atherosclerosis risk factors such as lipoproteins, cigarette smoking, and metabolic syndrome have been associated with valvular calcium in several cross-sectional studies but in only few prospective studies. Prospective studies to date have been limited by short-term follow-up (2,12,13) and single assessments of risk factors (14), which may underestimate the long-term cumulative effects of cardiovascular risk factors on valve calcium. In addition, contemporary rates of treatment for cholesterol and other risk factors may attenuate the associations of valvular disease with risk factors.

Prospective, longitudinal studies with repeated measurements of risk factors could overcome these limitations. Accordingly, using >25 years of longitudinal data from the Framingham Offspring Study, we sought to evaluate the association of long-term exposure to atherosclerosis risk factors with the prevalence of aortic valve and mitral valve calcium in a community-based sample. We also sought to establish the association between an adverse risk factor profile in early to mid-adulthood and valvular calcification measured nearly 3 decades later.

Methods

Study sample. The Framingham Offspring Study was initiated in 1971 as described previously (15,16). As part of a substudy to measure subclinical cardiovascular disease, 1,422 Offspring Study participants underwent cardiac multidetector computed tomography (MDCT) between 2002 and 2005 (Fig. 1). The MDCT study was described previously (17). Of the 1,422 participants who underwent cardiac MDCT, we excluded 28 participants due to uninterpretable computed tomography (CT) images and/or previous valve surgery. Of the 1,394 participants with interpretable images, 20 participants were excluded for not attending examination 7, 38 participants were excluded for missing covariate data at examination 7, 9 participants who attended fewer than 4 of the 7 examinations were excluded, and 4 participants who attended at least 4 of the previous 7 examinations but had all risk factors measured at only 3 or fewer of the previous 7 examinations were excluded. After all exclusions, 1,323 participants remained eligible for the present investigation. Study protocols were approved by the Institutional Review Board of Boston University Medical Center and Massachusetts General Hospital. Written informed consent was obtained from all participants.

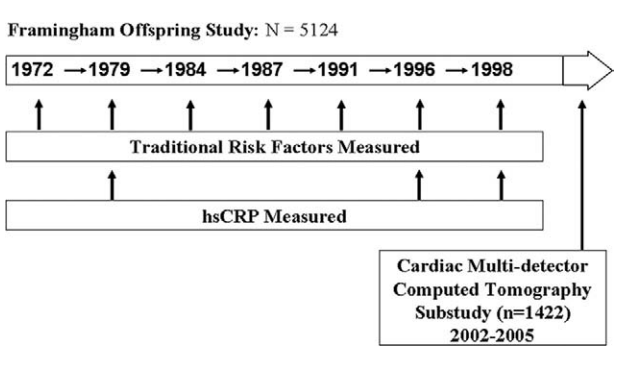

Figure 1 Description of the Framingham Offspring Study and Cardiac Multidetector Computed Tomography Substudy

hsCRP = high-sensitivity C-reactive protein.

Atherosclerosis risk factors. Risk factor information was collected from routine medical history, physical examination, and laboratory assessment. Total cholesterol and high-density lipoprotein cholesterol (HDL-C) were determined using fasting blood samples and conventional biochemical methods. C-reactive protein (CRP) level was measured for each participant with a Dade Behring BN100 nephelometer (Dade Behring, Deerfield, Illinois) on fasting morning serum samples. Body mass index (BMI) was calculated as the weight in kilograms divided by the square of the height in meters. A physician ascertained the number of cigarettes smoked daily and medication history during an interview. Blood pressure was determined in the left arm by a sphygmomanometer in subjects who had been seated for at least 5 min. Hypertension was defined as a systolic blood pressure ≥140 mm Hg, a diastolic blood pressure ≥90 mm Hg, or antihypertensive treatment.

Cardiac MDCT. Each participant underwent cardiac imaging using an 8-slice MDCT scanner (LightSpeed Ultra, GE Healthcare, Milwaukee, Wisconsin) as previously described (18). Two scans were performed for each participant using a sequential scan protocol with prospective gating of image acquisition. Calcium measurements were performed offline on an Aquarius workstation (TeraRecon, San Matteo, California).

Valve calcium measurement. Calcium was defined as an area of ≥3 connected pixels with an attenuation of ≥130 Hounsfield units. A modified Agatston scoring protocol was used to quantify the extent of calcium in the aortic and mitral valves. Aortic valve calcium was defined as calcium deposits of the aortic cusps or nodular deposits at the coaptation points of the aortic cusps. We excluded calcium deposits restricted to the aortic wall. Mitral valve calcium was defined as calcium deposits in the region of the annulus and/or the mitral valve leaflets.

Each set of 2 scans for each participant was initially read for the presence or absence of valve calcium by either of 2 observers (a cardiologist [S.K.] and a trained technician [E.M.]). If valve calcium was present on at least 1 of the 2 scans, the scan underwent an independent read, with the results of the first read blinded to a second observer (a

radiologist [R.C.]). Disagreement regarding the presence or absence of calcium was resolved by a consensus read involving the cardiologist and the radiologist. To determine a participant's valve calcium score, we first averaged the results from each of 2 scans read by the first observer and then averaged the results of the 2 observers. For scans requiring a consensus read to adjudicate valve calcium, we used the calcium score determined by consensus between the 2 observers. To determine interobserver variability, 2 observers independently read a random sample of 112 scans. Interobserver agreement for the presence or absence of aortic valve calcium and mitral valve calcium was kappa = 0.95 and kappa = 1.00, respectively. Intraclass correlation coefficients for aortic and mitral valve calcium scores were 0.98 and 0.99, respectively.

Statistical analyses. Spearman correlation coefficients were calculated for the relationship between aortic calcium and mitral valve calcium. We assessed agreement between aortic and mitral valve calcium scores by cross-classifying the aortic and mitral calcium scores into a 5×5 matrix (the first category consisted of scores of 0 and the other 4 categories consisted of scores within the first, second, third, and fourth quartiles of valve calcium scores for those with detectable calcium). A weighted kappa statistic was then calculated to summarize agreement between scores.

To examine the association of long-term average risk factors with valve calcium, we constructed multivariable logistic regression models using $p < 0.10$ as the significance criterion for covariates to be retained in the forward stepwise model selection process. The outcome variable was the presence or absence of valve calcium. Separate logistic regression models were fit with aortic valve calcium and mitral valve calcium as the outcome measures. In addition, we separately modeled blood pressure as a continuous variable (systolic and diastolic blood pressures separately) and as a dichotomous variable based on our definition of hypertension (i.e., blood pressure ≥140/90 mm Hg or antihypertensive treatment). Age (at examination 7) and sex were forced in as covariates in all models. The candidate predictor variables were total cholesterol, HDL-C, BMI, fasting glucose, CRP level, cigarettes smoked daily, lipid-lowering therapy, hypertension, and antihypertensive therapy. For continuous risk factors, we modeled the exposure to be the average of available values from the 7 examination cycle time points (3 examinations were available for CRP). For categorical variables (lipid-lowering therapy, hypertension), we modeled the exposure as the proportion of examinations (out of a maximum of 7) where hypertension or lipid-lowering therapy was present.

In a secondary analysis, to determine whether atherosclerosis risk factors present in early adulthood were related to valve calcium, we restricted the risk factor determinations to examination cycles 1, 2, and 3 and studied the association of risk factors measured at these early examinations with the presence of valve calcium. For these analyses, participants were required to have attended at least 2 of the 3 examinations. For continuous risk factors, we considered the average of available values, and for categorical risk factors, we modeled the proportion of examinations (out of a maximum of 3) where the risk factor was present.

Last, we evaluated the relationships between risk factors measured at the baseline examination (1971 to 1975) and valve calcium. Specifically, we estimated the prevalence and severity of aortic and mitral valve calcium across categories of Framingham coronary heart disease risk scores (19) based on baseline risk factors (i.e., examination cycle 1). Trend tests across cardiovascular risk categories were adjusted for age and sex. In a sensitivity analysis, we repeated this analysis in a sample restricted to participants 40 years of age or younger (871 participants). All analyses were conducted in SAS version 9.0 (SAS Institute, Cary, North Carolina). Odds ratios and 95% confidence intervals (CIs) are reported for a 1-SD change in the predictor variable. A 2-sided p value <0.05 was considered significant.

Results

Participant characteristics. Participant characteristics for the baseline examination (1971 to 1975) and for all 7 examinations (1971 to 2001) are shown in Table 1. The mean age of the participants at the baseline examination was 34 ± 9 years and 64 ± 9 years at the time of the CT scan. Median follow-up time from baseline examination was 26.8 years (range 23.1 to 29.6 years). On MDCT scans performed from 2002 to 2005, aortic valve calcium was detectable in 39% (95% CI: 37% to 42%) of participants and mitral valve calcium was detectable in 20% (95% CI: 18% to 23%) of participants. The correlation between aortic and mitral valve calcium was 0.45 ($p < 0.0001$). The agreement between aortic and mitral valve calcium scores was low (weighted kappa = 0.34).

Multivariable associations of long-term risk factors and aortic valve calcium. In multivariable models, older age at baseline and higher values of the long-term average of several risk factors (mean total cholesterol, BMI, and number of cigarettes smoked daily) were significantly associated with increased odds of aortic valve calcium, whereas female sex and higher values of the long-term average of HDL-C were associated with reduced odds of aortic valve calcium (Table 2). The average of CRP from 3 examinations (spanning ~22 years) was not associated with aortic valve calcium.

Multivariable associations of long-term risk factors and mitral valve calcium. Similar risk factors were associated with mitral valve calcium including age and the long-term averages of total cholesterol, HDL-C, and number of cigarettes smoked daily (Table 2). In contrast to our findings with aortic valve calcium, long-term average CRP level was associated with increased odds of mitral valve calcium (odds ratio: 1.29 per SD increment of CRP level; 95% CI: 1.10 to 1.52; $p = 0.002$).

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Table 1 Participant Characteristics at Baseline Examination and Longitudinal Risk Factors According to the Presence or Absence of Aortic and Mitral Valve Calcium

Characteristic	Entire Sample (N = 1,323)	Aortic Valve Calcium		Mitral Valve Calcium	
		Absent (n = 804)	Present (Score >0) (n = 519)	Absent (n = 1,053)	Present (Score >0) (n = 270)
Baseline data (1971–1975)					
Age, yrs	34 ± 9	30 ± 8	39 ± 8	32 ± 9	41 ± 8
Female sex, %	52	59	42	52	52
Body mass index, kg/m^2	24.7 ± 4.1	23.9 ± 4.1	25.8 ± 3.9	24.4 ± 4.1	25.8 ± 3.7
Hypertension, %	14	10	20	12	21
Systolic blood pressure, mm Hg	119 ± 14	117 ± 14	122 ± 14	119 ± 14	122 ± 14
Diastolic blood pressure, mm Hg	78 ± 10	76 ± 10	80 ± 9	77 ± 10	80 ± 9
Total cholesterol, mg/dl	191 ± 35	180 ± 32	207 ± 34	187 ± 34	207 ± 35
High-density lipoprotein cholesterol, mg/dl	52 ± 16	53 ± 15	51 ± 16	52 ± 16	52 ± 16
Lipid-lowering therapy, %	0.3	0.3	0.4	0.1	1.1
Cigarette smoking, %	35	33	39	35	36
Cigarettes smoked daily	19 ± 12	18 ± 11	21 ± 12	19 ± 11	22 ± 13
Diabetes, %	0.3	0.1	0.6	0.0	1.5
Fasting glucose, mg/dl	100 ± 9	99 ± 8	101 ± 9	99 ± 8	101 ± 10
C-reactive protein, mg/dl	2.0 ± 4.2	1.9 ± 4.6	2.1 ± 3.5	1.9 ± 4.4	2.3 ± 3.3
Longitudinal data* (examinations 1 to 7)					
Body mass index, kg/m^2	26.6 ± 4.3	26.0 ± 4.4	27.5 ± 4.1	26.4 ± 4.4	27.5 ± 4.0
Hypertension, %	49	45	53	47	54
Systolic blood pressure, mm Hg	122 ± 12	120 ± 12	126 ± 12	121 ± 13	128 ± 12
Diastolic blood pressure, mm Hg	77 ± 7	76 ± 7	78 ± 7	76 ± 7	78 ± 7
Total cholesterol, mg/dl	200 ± 29	193 ± 27	211 ± 28	198 ± 28	211 ± 27
High-density lipoprotein cholesterol, mg/dl	51 ± 13	53 ± 13	48 ± 13	51 ± 13	49 ± 13
Lipid-lowering therapy, %	28	27	29	27	30
Cigarette smoking, %	50	48	52	50	50
Cigarettes smoked daily	10 ± 9	9 ± 9	11 ± 10	10 ± 9	11 ± 10
Diabetes, %	37	36	37	35	40
Fasting glucose, mg/dl	97 ± 14	95 ± 11	101 ± 16	96 ± 12	102 ± 18
C-reactive protein,† mg/dl	2.6 ± 2.9	2.4 ± 2.9	2.9 ± 2.9	2.4 ± 2.7	3.4 ± 3.5
Valve calcium score median (1st and 3rd quartiles)	—	0 (—)	46 (13, 140)	0 (—)	57 (15, 297)

Continuous variables presented as mean ± SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. *For longitudinal data, continuous variables are reported as mean ± SD of available values during follow-up (examinations 1 through 7), whereas categorical variables are reported as proportion of participants with presence of risk factor at any exam during follow-up (exams 1 through 7). †C-reactive protein values are the mean of measurement at a maximum of 3 time points (examinations 2, 6, and 7). †C-reactive protein values are the mean of measurement at a maximum of 3 time points (examinations 2, 6, and 7).

Risk factors in early adulthood and valve calcium. As shown in Table 3, early risk factors obtained in the first 3 examinations (1971 to 1982) predicted the future presence of valve calcium in a manner largely similar to the long-term average across all 7 examinations. Exceptions included the presence of a relationship between early BMI and mitral valve calcium and the absence of a relationship between mitral valve calcium and either sex or HDL-C.

Table 2 Association of Long-Term Average of Individual Atherosclerosis Risk Factors (Examinations 1 Through 7) With the Presence of Aortic and Mitral Valve Calcium

	Aortic Valve Calcium			Mitral Valve Calcium		
	Adjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Age, per SD	3.25	2.76–3.82	<0.0001	3.11	2.58–3.75	<0.0001
Female (vs. male) sex	0.56	0.41–0.76	0.0003	—	—	—
Mean total cholesterol, per SD	1.74	1.50–2.01	<0.0001	1.26	1.08–1.48	0.004
Mean high-density lipoprotein cholesterol, per SD	0.77	0.66–0.91	0.002	0.85	0.71–1.02	0.07
Body mass index, per SD	1.21	1.05–1.40	0.008	—	—	—
Cigarettes smoked daily, per SD	1.23	1.08–1.41	0.002	1.18	1.02–1.36	0.03
Mean C-reactive protein, per SD	—	—	—	1.29	1.10–1.52	0.002

Stepwise logistic regression models were constructed with outcome variable of the presence of aortic valve calcium and the following candidate independent variables as long-term average (examinations 1 through 7): age, sex, total cholesterol, high-density lipoprotein cholesterol, hypertension, body mass index, number of cigarettes smoked per day, C-reactive protein, fasting glucose, and lipid-lowering therapy. Predictor variables with $p < 0.10$ are presented.

CI = confidence interval; OR = odds ratio.

Table 3 Association of Early Atherosclerosis Risk Factors (Examinations 1 Through 3) With the Presence of Aortic and Mitral Valve Calcium

	Aortic Valve Calcium			Mitral Valve Calcium		
	Adjusted OR	95% CI	p Value	Adjusted OR	95% CI	p Value
Age, per SD	2.81	2.39–3.31	<0.0001	2.89	2.39–3.50	<0.0001
Female sex	0.64	0.47–0.87	0.005	—	—	—
Mean total cholesterol, per SD	1.81	1.55–2.11	<0.0001	1.33	1.13–1.57	0.0005
Mean high-density lipoprotein cholesterol, per SD	0.84	0.72–0.99	0.03	—	—	—
Body mass index, per SD	1.15	0.99–1.33	0.06	1.26	1.08–1.47	0.003
Cigarettes smoked daily, per SD	1.22	1.06–1.39	0.005	1.21	1.05–1.39	0.009
C-reactive protein, per SD (from examination 2)	—	—	—	—	—	—

Stepwise logistic regression models were constructed with outcome variables of the presence of either aortic or mitral valve calcium and the following candidate predictor variables averaged over examinations 1 through 3: age, sex, total cholesterol, high-density lipoprotein cholesterol, body mass index, number of cigarettes smoked per day, fasting glucose, lipid-lowering therapy, and antihypertensive therapy. Predictor variables with $p < 0.10$ are presented.

Abbreviations as in Table 2.

Framingham coronary heart disease risk score and valve calcium. To evaluate the combined effect of multiple atherosclerotic risk factors in early adulthood on valvular calcification later in adulthood, we examined the prevalence of valve calcification across categories of coronary heart disease risk based on the Framingham risk score at the baseline examination (1971 to 1975). The prevalence of aortic valve calcium was 33.0%, 53.8%, and 61.1%, for low, intermediate, and high Framingham coronary heart disease risk score categories, respectively ($p < 0.0001$ for trend across risk categories) (Fig. 2). A similar relationship was also seen when we evaluated the severity of aortic valve calcium (determined by mean aortic valve calcium score) across increasing risk score categories ($p = 0.006$ for trend) (Fig. 3). We did not observe any significant trend for the presence or severity of mitral valve calcium across risk score categories.

In a sensitivity analysis among participants 40 years of age or younger, we noted a similar graded increase in the prevalence and severity of aortic valve calcium across risk score categories (Fig. 4).

Discussion

Principal findings. In our study of >1,300 participants with >25 years of follow-up, we identified several traditional atherosclerosis risk factors that are associated with the presence of aortic and mitral valve calcium as detected by cardiac MDCT. Of the modifiable risk factors, we found that cigarette smoking and total cholesterol were strongly associated with valve calcium. We also noted important associations for HDL-C and BMI with valvular calcification. The observed associations were consistent whether we examined the risk factors averaged over the entire 27 years of observation or over the first 12 years of observation. Our study with >25 years of follow-up represents the longest community-based cohort to examine associations between atherosclerosis risk factors and valve calcium and provides new evidence that long-term exposure to an adverse risk

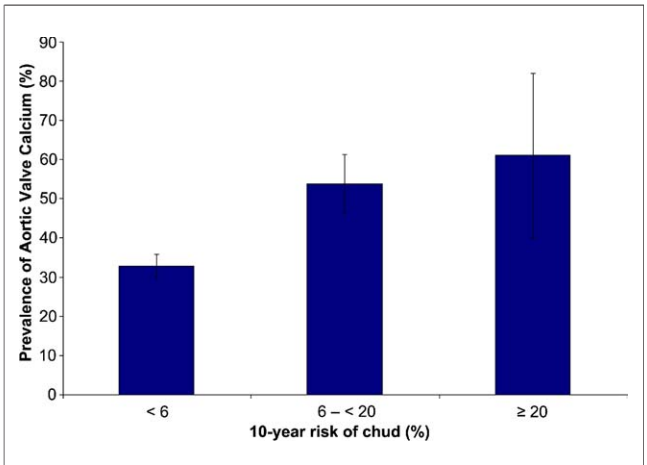

Figure 2 Prevalence of Aortic Valve Calcium Stratified by Framingham Risk Score Categories in Early Adulthood

Low, intermediate, and high cardiovascular risk corresponds to a <6%, 6% to <20%, and ≥20% 10-year risk of coronary heart disease (CHD), respectively. **Error bars** represent 95% confidence intervals.

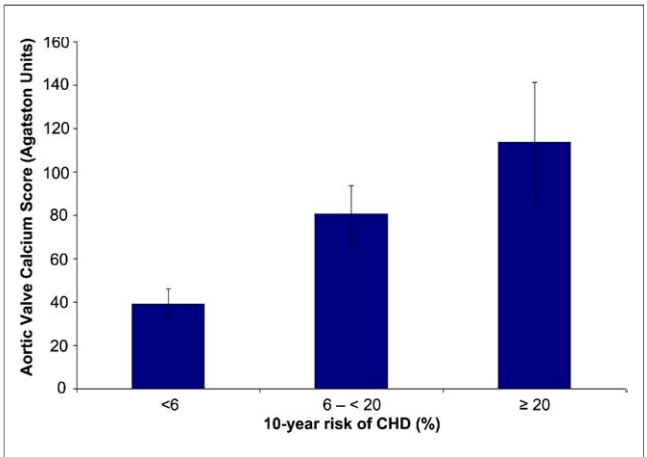

Figure 3 Mean Aortic Valve Calcium Score Stratified by Framingham Risk Score Categories in Early Adulthood

Low, intermediate, and high cardiovascular risk corresponds to a <6%, 6% to <20%, and ≥20% 10-year risk of coronary heart disease (CHD), respectively. **Error bars** represent SEs for calcium score.

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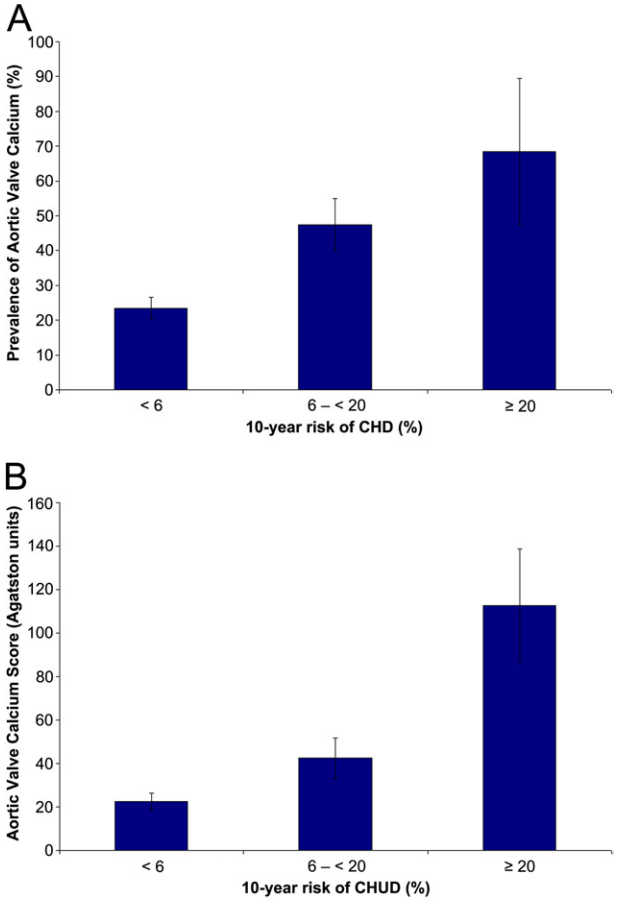

Figure 4 **Prevalence and Severity of Aortic Valve Calcification in Participants <40 Years of Age**

Prevalence of aortic valve calcium **(A)** and mean aortic valve calcium score **(B)** stratified by the Framingham risk score in early adulthood among participants 40 years of age or younger. Low, intermediate, and high cardiovascular risk corresponds to <6%, 6% to <20%, and ≥20% 10-year risk of coronary heart disease (CHD), respectively. **Error bars** represent 95% confidence intervals for prevalence and SEs for calcium score.

factor profile starting in early adulthood is associated with an increased prevalence of valvular calcification measured nearly 3 decades later.

In the context of the current literature. AORTIC VALVE CALCIUM. We found that 39% of participants had aortic valve calcium on CT. Our estimate of aortic valve calcium is higher than that of previous reports of aortic sclerosis by echocardiography, which have ranged from 26% to 29% (7,14) and aortic valve calcium by CT, which was reported to be 14% (20). This may be due to differences in baseline participant characteristics, a predominantly white sample, lower use of lipid-lowering therapies, differences in the imaging protocol, or differences in the CT reading methodology between our study and others.

Several previous studies reported associations with cholesterol and aortic valve disease (7,21–25). Our longitudinal data with serial serum cholesterol measurements over a 27-year period support the association between lipids and aortic valve calcium, demonstrating that for each 29-mg/dl increase in the long-term average of total cholesterol, there was a marked 74% increase in the odds of aortic valve calcium. Associations with valve calcium have also been reported for other cardiovascular risk factors including cigarette smoking (13,18,19,23,24), BMI (23,24), metabolic syndrome (12,17), and hypertension (7,18,19,22,23). Our results confirm that cigarette smoking is a potent risk factor for aortic valve calcification. In addition, we found a weak association between increased BMI and aortic valve calcium. Contrary to several previous reports (7,21,22,25,26), we did not find any association with hypertension or blood pressure; this may have been due to the younger age of our sample or other differences in baseline characteristics. In addition, despite histological evidence of inflammation in aortic calcification (27), we found no association with plasma CRP and aortic valve calcium, which is in agreement with a previous study evaluating CRP and the progression of aortic stenosis (28).

We are unaware of any previous studies that evaluated the presence of aortic valve calcification based on coronary heart disease risk factor profiles in early adulthood. However, our findings that an early adverse risk factor profile in the fourth decade of life is associated with increased prevalence of aortic valve disease later in life are supported by a recent study by Owens et al. (29), who reported that the association between low-density lipoprotein levels and prevalent valvular calcification was significant only among subjects younger than 65 years of age. These observations suggest that risk factors early in life, as opposed to later in life, may be more important for future valvular calcification. Whether risk factor modification at an earlier stage in life could arrest valvular damage and prevent valvular disease in old age requires further study.

MITRAL VALVE CALCIUM. Mitral calcification also shares many risk factors with atherosclerosis and aortic calcification. Our findings of relationships between mitral calcification with cigarette smoking and lipid levels are in agreement with those of previous studies evaluating mitral annular calcification by echocardiography (22,23,30–32). We also observed an important relationship between serum CRP and mitral valve calcification, independent of other risk factors, which represents, to our knowledge, a novel association not previously reported in the literature. In our analysis, it remains unclear why CRP was associated only with mitral valve calcium and not aortic valve calcium. Whether this observation represents differences in the pathogenesis of mitral and aortic calcification or is a fortuitous finding requires further study.

Potential mechanisms. Valvular sclerosis and calcification seem to have marked similarities with coronary atherosclerosis. Histologically, early valve lesions are characterized by a disruption of valvular endothelium at areas of mechanical stress (33,34), accumulation of oxidized lipids and foam cells, and a prominent inflammatory infiltrate (3–6,35).

Changes in the valvular microenvironment promote differentiation of valvular cells to adopt an osteoblast-like phenotype leading to calcification, which characterizes the pathological process (36,37). Numerous lines of experimental evidence have demonstrated the importance of plasma cholesterol in this process (2,3). Once low-density lipoprotein is oxidized due to cigarette smoking or other factors, it has been shown to be a major stimulus for the deposition of extracellular matrix required for calcium deposition (36,38).

Animal models of hyperlipidemia have also provided additional evidence of the integral role of lipids in valvular calcification (39–41). In a recent study using hyperlipidemic transgenic mice with a "genetic switch" that allowed reversal of the hyperlipidemic phenotype, Miller et al. (42) demonstrated reductions in oxidative stress, lipid deposition, and calcium deposition with arrest of further valvular sclerosis after hyperlipidemia was reversed. These results provide new evidence of the role of lipids in the initiation and early stages of valvular disease.

Clinical implications. Randomized, controlled trials of lipid-lowering therapy to reduce the development or progression of aortic valve disease have been generally disappointing (8–10). These trials were limited to elderly patients (mean age across trials was 67 years) with established moderate or severe aortic valve stenosis (mean valve area across these trials was 1.3 cm^2 with a peak transvalvular gradient of 40 mm Hg). Our findings of strong and consistent associations between valve calcium and cardiovascular risk factors determined decades earlier raises the hypothesis that aggressive risk factor modification at an earlier age, among predisposed individuals, may be required to reduce the incidence of future valvular disease (29,42). However, the ASTRONOMER (Aortic Stenosis Progression Observation: Measuring Effects of Rosuvastatin) trial (11), which randomized patients with less severe aortic valve disease, also failed to demonstrate the efficacy of statins in slowing aortic valve disease. Although participants in this trial were younger than in previous trials, their mean age was still 58 years; therefore, it remains possible that earlier lipid-lowering drug therapy and risk-factor modification using alternative strategies (e.g., exercise) (43) before the initiation of valvular remodeling may be necessary to reduce the progression to aortic stenosis.

Study limitations. First, we used valve calcification, a subclinical surrogate marker for aortic or mitral valve sclerosis, as our outcome. We therefore could not assess the impact on physiological correlates (i.e., valve gradients) or on "hard outcomes" such as critical valve stenosis or valve replacement. However, valvular calcification is known to be an important risk factor for the development of clinical valvular disease and represents the same pathophysiological process involved in clinical disease (1). Second, participants did not have a CT scan on enrollment, and therefore any baseline calcification could not be quantified. However, given the young age at enrollment, it is unlikely that participants had any calcification at this early age. Third, due to the observational nature of our study, reported associations with atherosclerosis risk factors cannot imply causal relationships. Last, our sample was derived from a predominantly white population of European descent, and, as such, our results may not apply to other races or ethnicities.

Conclusions

We found that long-term exposure to atherosclerosis risk factors, such as plasma lipids and cigarette smoking, starting in early to mid-adulthood are associated with both aortic and mitral valvular calcification. Further study is warranted to evaluate whether early modification of cardiovascular risk factors may also decrease the development of valvular disease in the elderly.

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