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Impact of Mitral Annular Calcification on Cardiovascular Events in a Multiethnic Community

The Northern Manhattan Study

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OBJECTIVES We sought to determine the magnitude of the association between mitral annular calcification (MAC) and vascular events in a multiethnic cohort.

BACKGROUND Mitral annular calcification is common in the elderly and is associated with atherosclerotic risk factors. Its impact on the risk of cardiovascular events is controversial.

METHODS The study cohort consisted of 1,955 subjects, ages ≥40 years, and free of prior myocardial infarction (MI) and ischemic stroke (IS). Mitral annular calcification was assessed by transthoracic 2-dimensional echocardiography. The association between MAC and MI, IS, and vascular death (VD) was examined by Cox proportional hazard models with adjustment for established cardiovascular risk factors. The effect of MAC thickness was also analyzed.

RESULTS The mean age of the cohort was 68.0 ± 9.7 years and the majority of subjects were Hispanics (56.8%). A total of 519 subjects (26.6%) had MAC. Of 498 patients with MAC thickness measurements available, 253 (13.1%) had mild to moderate MAC (1 to 4 mm) and 245 (12.7%) severe MAC (>4 mm). During a mean follow-up of 7.4 ± 2.5 years, MI occurred in 100 (5.1%) subjects, IS in 104 (5.3%) subjects, and VD in 155 (8.0%) subjects. After adjustment for other cardiovascular risk factors, MAC was associated with an increased risk of MI (adjusted hazard ratio [HR]: 1.75; 95% confidence interval [CI]: 1.13 to 2.69, p = 0.011) and VD (adjusted HR: 1.53; 95% CI: 1.09 to 2.15, p = 0.015), but not IS (adjusted HR: 1.34; 95% CI: 0.87 to 2.05, p = 0.18). Further analysis revealed that the impact of MAC was related to its thickness, with MAC >4 mm being a strong and independent predictor of MI (adjusted HR: 1.89; 95% CI: 1.13 to 3.17, p = 0.008) and VD (adjusted HR: 1.81; 95% CI: 1.21 to 2.72, p = 0.002), and showing borderline association with IS (adjusted HR: 1.59; 95% CI: 0.95 to 2.67, p = 0.084).

CONCLUSIONS In this multiethnic cohort, MAC was a strong and independent predictor of cardiovascular events, especially MI and VD. The risk increase was directly related to MAC severity. (J Am Coll Cardiol Img 2008;1:617–23) © 2008 by the American College of Cardiology Foundation

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Mitral annular calcification (MAC) is a chronic process involving fibrosis and calcification of the mitral valve support ring. The prevalence of MAC has been reported to be as high as 15% in population-based studies (1) and up to 35% in patients with severe coronary artery disease (2). MAC has been associated with a high prevalence of risk factors for the development of atherosclerosis (3). Furthermore, association with clinical vascular events such as ischemic stroke (IS) has been reported in multiple community cohorts, although the incremental predictive value of MAC above other established risk markers has been questioned (4–6). The association of MAC with coronary heart disease has been less well demonstrated in the Framingham database (7), only modest association was observed with the combined outcome of myocardial infarction (MI), unstable angina, congestive heart failure, and nonhemorrhagic stroke.

We analyzed the relationship between MAC and the risk of MI, IS, and vascular death (VD) in the multiethnic population of the NOMAS (Northern Manhattan Study) study, adjusting for the effect of traditional cardiovascular risk factors.

ABBREVIATIONS AND ACRONYMS

IS = ischemic stroke

MAC = mitral annular calcification

MI = myocardial infarction

VD = vascular death

METHODS

Study design and subjects. Subjects were participants in NOMAS, a population-based prospective cohort study in northern Manhattan, New York. The methods of subject recruitment and enrollment into NOMAS have been described elsewhere (8,9). Briefly, random digit dialing was performed, and community participants were enrolled. The NOMAS entry criteria included: 1) age >39 years; 2) residence in northern Manhattan for at least 3 months; and 3) no prior diagnosis of stroke. Subjects with prior MI at enrollment were also excluded from this analysis. The study was approved by the Institutional Review Board at Columbia University Medical Center.

Echocardiographic methods and definition of MAC. Transthoracic echocardiograms were obtained in the 1,955 subjects between 1993 and 2001. Studies were performed and measurements taken according to the recommendations of the American Society of Echocardiography (10). Interpretation of echocardiographic studies was performed blinded to clinical and demographic characteristics. Interobserver reliability was periodically assessed by use of intraclass correlation coefficients for the variables measured, which ranged between 0.59 and 0.74. MAC was defined as an intense echocardiographic-producing structure with highly reflective characteristics that was located at the junction of the atrioventricular groove and the posterior or anterior mitral leaflet on the parasternal long-axis, apical 4- or 2-chamber, or parasternal short-axis view. The severity of MAC, expressed as maximal thickness in millimeters, was measured from the leading anterior to the trailing posterior edge at its greatest width. Calcification thickness >1 mm and <4 mm was considered mild to moderate, and >4 mm was considered severe.

Definition of covariates. Baseline evaluation was performed at enrollment as previously reported (8). Hypertensive status was defined as a systolic blood pressure recording ≥140 mm Hg or a diastolic blood pressure recording ≥90 mm Hg based on the mean of 2 measurements, a patient's self-reported history of hypertension, or antihypertensive treatment. Diabetes mellitus was defined by a patient's self-report, insulin use, oral hypoglycemic use, or a fasting glucose ≥126 mg/dl. Hypercholesterolemia was defined as total serum cholesterol >240 mg/dl, a patient's self-report, or the presence of lipid-lowering treatment. The presence of atrial fibrillation was based on a current or past electrocardiography. Body mass index was calculated as weight (kilograms) divided by height (meters) squared. Smoking was defined as current cigar or cigarette smoking. Alcohol consumption was defined as lifetime drinking of >1 drink per month.

Clinical end points. All subjects were followed at 6 months and then annually. In-person follow-up visits were conducted at the medical center and included interview, vital signs, and physical and neurological examinations. Over 80% of patients with MI or IS in northern Manhattan are hospitalized at Columbia University Medical Center. Subjects hospitalized at other local hospitals were identified through active hospital surveillance of admission and discharge in accordance with the International Classification of Diseases, 9th Revision codes, and through local physicians. All outcome events were reviewed by a specially trained research assistant and reported to a study physician for adjudication.

Myocardial infarction was defined by criteria adapted from the CAST (Cardiac Arrhythmia Suppression Trial) (11) and the LRC-CPPT (Lipid Research Clinics Coronary Primary Prevention Trial) (12), requiring at least 2 of the 3 following conditions: 1) cardiac pain determined to be typical angina; 2) cardiac enzyme abnormalities in creatine

phosphokinase myocardial band isoenzyme fraction or troponin I values; and/or 3) ischemic electrocardiography abnormalities.

Stroke was defined as the first symptomatic occurrence of any type of stroke, including intracerebral hemorrhage, subarachnoid hemorrhage, and cerebral infarction, based on the World Health Organization criteria (13). Only IS, defined by TOAST (Trial of ORG 10172 in Acute Stroke Treatment) trial criteria (14), was considered for this report. The vast majority (70%) of IS cases were hospitalized at Columbia University Medical Center, which allowed us access to information on clinical syndrome, blood test, and imaging studies. The presence of IS was determined by 2 neurologists independently, and the principal investigator of NOMAS (R.L.S.) adjudicated any disagreements.

For subjects who died, deaths were classified as vascular or nonvascular based on information obtained from the family, medical records, and death certificate. Causes of death were also validated by a study physician. Vascular causes of death included stroke, MI, heart failure, and cardiac arrhythmia (e.g., sudden or unwitnessed death).

Statistical methods. For principal analyses, MAC was both dichotomized (present/absent) and examined as a continuous variable. Mitral annular calcification was then categorized for further analysis into mild to moderate (1 to 4 mm) or severe (>4 mm), with 4 mm being the median value in subjects with MAC. We also performed an additional quantitative analysis with MAC categorized by the 75th percentile. The distribution of demographics and vascular risk factors was evaluated in the total cohort and in subjects with and without MAC. Comparisons were made using *t* tests for continuous variables and chi-square tests for categorical variables. Time to cardiovascular events was illustrated with Kaplan-Meier curves and log-rank test was used to compare different MAC subsets. Cox proportional hazard models were used to identify the risk factors of cardiovascular events, and hazard ratios (HRs) and 95% confidence intervals (CIs) of MAC were evaluated. Variables with association at the $p < 0.1$ level in univariable models were included in the multivariable models. An additional model was generated to adjust for additional variables such as higher education (higher than high school), work status (over 10 h/week), white blood cell count, and echocardiographically derived left ventricular mass index. We tested for interactions between MAC and significant covariates. Statistical analyses were conducted using SAS 9.1 software (SAS Institute, Cary, North Carolina).

RESULTS

Of 1,955 subjects, 519 (26.6%) had MAC. The majority of the subjects were Hispanic (56.8%), followed by African American (22.7%) and white (20.5%). The cohort was predominantly elderly (mean age: 68.0 ± 9.7 years), female (61.4%), and hypertensive (67.3%). The average left ventricular mass in our cohort was 174.9 ± 57.4 g. Other baseline cohort characteristics are summarized in Table 1. Antiplatelet and anticoagulant agents were more frequently used in subjects with MAC compared with subjects without it (27.9% vs. 20.9%, $p = 0.001$, and 3.5% vs. 1.9%, $p = 0.06$, respectively). No difference in the use of cholesterol lowering agents was noted (11.8% vs. 12.7%, $p = 0.58$).

Subjects were followed for 7.4 ± 2.5 years. At follow-up, there were 100 MIs (50 [3.5%] vs. 50 [9.6%], no MAC vs. MAC, $p < 0.001$), 104 ISs (65 [4.5%] vs. 39 [7.8%], $p = 0.004$), and 155 VDs (81 [5.6%] vs. 74 [14.7%], $p < 0.001$). The incidence of MI, IS, and VD events was 13.8, 10.7, and 20.3/1,000 person-years, respectively, in subjects with MAC, and 4.7, 6.1, and 7.5/1,000 person-years, respectively, in subjects without MAC ($p < 0.001$ for MI, $p = 0.001$ for IS, $p < 0.001$ for VD). The event-free Kaplan-Meier curves for outcomes based on MAC presence and thickness are shown in Figures 1A to 1C.

Variables associated with each clinical outcome in univariable analysis are listed in Table 2. MAC, age, diabetes, and hypertension were associated with risk of all pre-defined clinical outcomes (MI, IS, and VD). After adjustment for other risk factors, MAC was associated with an increased risk of MI ($p = 0.011$) and VD ($p = 0.015$), but not IS ($p = 0.18$).

MAC was also associated with an increased risk of composite end point of death and MI (univariable HR: 2.28, 95% CI: 1.89 to 2.75, $p < 0.0001$; multivariable HR: 1.44, 95% CI: 1.18 to 1.77, $p = 0.0004$) as well as death and IS (univariable HR: 2.11, 95% CI: 1.75 to 2.54, $p < 0.0001$; multivariable HR: 1.38, 95% CI: 1.13 to 1.69, $p = 0.002$). The results were essentially unchanged when MAC was categorized by the 75th percentile ($n = 133$; HR: 1.55, 95% CI: 1.17 to 2.06, $p = 0.002$ for MI and death, and HR: 1.50, 95% CI: 1.13 to 2.00, $p = 0.005$ for IS and death). Further, when an even

Table 1. Baseline Characteristics of Participants With and Without MAC

	All Subjects N = 1,955	No MAC n = 1,436 (73.4%)	MAC n = 519 (26.6%)	p Value*
Age, yrs	68.0 ± 9.7	66.2 ± 9.1	72.9 ± 9.7	<0.001
Male gender, %	38.6	41.5	30.4	<0.001
Race-ethnicity, %				
African American	22.7	22.8	22.5	<0.001
Hispanic	56.8	60.0	48.2	
White	20.5	17.3	29.3	
Hypercholesterolemia, mg/dl				
Total cholesterol	204.2 ± 40.2	202.3 ± 39.2	209.3 ± 42.6	0.001
LDL	131.2 ± 35.8	129.9 ± 35.4	134.6 ± 36.6	0.012
HDL	46.6 ± 14.6	46.1 ± 14.4	47.8 ± 15.2	0.028
Hypertension, mm Hg (%)	67.3	65.0	73.4	0.001
SBP	143.9 ± 20.8	142.9 ± 20.1	146.7 ± 22.5	<0.001
DBP	83.4 ± 11.2	83.6 ± 11.0	82.8 ± 11.8	0.16
Diabetes, %	21.6	21.0	23.3	0.26
BMI, kg/m^2	27.7 ± 5.4	27.6 ± 5.3	27.9 ± 5.6	0.39
Smoking, %	53.2	53.1	53.3	0.95
Alcohol consumption, %	78.3	79.0	76.1	0.17
Atrial fibrillation, %	3.6	2.9	5.4	0.010
Left ventricular mass, g	174.9 ± 57.4	172.3 ± 56.2	182.1 ± 60.4	0.001

*No MAC versus MAC.
BMI = body mass index; DBP = diastolic blood pressure; HDL = high-density lipoprotein; LDL = low-density lipoprotein; MAC = mitral annular calcification; SBP = systolic blood pressure.

more comprehensive set of confounding variables (e.g., education higher than high school, work status over 10 h/week, white blood cell counts, and echocardiographically derived left ventricular mass index) was added to the model, MAC was consistently associated with these end points (HR: 1.32, 95% CI: 1.06 to 1.65, p = 0.012 for MI and death; HR: 1.30, 95% CI: 1.05 to 1.61, p = 0.016 for IS and death; and HR: 1.48, 95% CI: 1.02 to 2.13, p = 0.024 for VD).

When MAC was categorized into mild to moderate (1 to 4 mm: n = 253; 13.1%) or severe MAC (>4 mm: n = 245; 12.7%), mild to moderate MAC was a significant predictor for MI and VD, but the association was no longer significant after adjusting for significant clinical variables (Table 3). Severe MAC, however, was a strong predictor of all pre-defined clinical outcomes (MI, IS, and VD), and its association with MI and VD remained significant after adjustment. The association of severe MAC with IS was of borderline significance (p = 0.08).

DISCUSSION

MAC was related to our pre-defined vascular clinical events including MI and VD in our multiethnic population-based cohort, but the association was not statistically significant for IS after adjustment for atherosclerotic risk factors. The impact of MAC was related to its thickness, with MAC >4 mm being a strong and independent predictor of MI and VD and borderline for IS. This dose-response relationship between MAC severity and outcome further strengthens the significance of the finding.

Several explanations may account for the predictive power of MAC for vascular clinical events. MAC has been associated with hypertension, left atrial enlargement, and atrial fibrillation (1–3). All of these do have predictive power for the specified outcomes. Thus, although there have been occasional reports of embolic calcification causing stroke (5), it is more likely that MAC represents a marker of risk rather than a causative factor. Mitral annular calcification could be an indicator of severity and duration of hypertension (similar to left atrial size) or hypercholesterolemia, or both.

Similarities exist between atherosclerosis in the vasculature and chronic degenerative changes in valvular structures although valve calcification is a more amorphous, disorganized process (15). Risk factors are common to both conditions. The attachment of the mitral valve to the annulus is a site of turbulence, and inflammation tends to initiate early

in the subclinical atherosclerotic phase in this area (3). The calcifying process of a valve is initially characterized by macrophage and T-cell infiltration in response to endothelial injury (16). The burden of atherosclerotic risk factors is likely reflected on the thickness of calcification, and MAC may be an accurate marker that reflects cumulative exposure to vascular metabolic and mechanical stresses.

MAC and risk of MI. Our study demonstrated a strong and independent association of MAC with MI. This is in partial agreement with a previously published study from the Framingham cohort (7). In that study, conducted in a predominantly white population, MAC was associated with the combined outcome of MI, unstable angina, congestive heart failure, and nonhemorrhagic stroke, but not with MI alone after adjustment for baseline covariates. This difference with our study might be explained in part by different participant characteristics, including the older age of our cohort and its triethnic race-ethnicity composition. Moreover, different echocardiographic methodologies used (M-mode evaluation of MAC in the Framingham cohort compared with 2-dimensional technique in the present study) may also contribute to these differences. The 2-dimensional evaluation provides better analysis of the spatial location and magnitude of MAC, and our definition of MAC (as any calcification >1 mm in multiplane 2-dimensional assessment), along with the older population, have lead to its higher prevalence (25%) compared with the Framingham cohort (15%) (1,7).

Further, our categorized multivariable analysis clearly revealed that it is the severity of MAC, rather than its presence, that drives the association with vascular events, but the available data are insufficient to suggest preventative strategies, such as the use of antiplatelet or anticoagulation therapy, in patients with MAC. As mentioned earlier, further investigation is needed to define whether the use of medical treatment to affect MAC might affect clinical outcome.

MAC and risk of IS. In our study, MAC was marginally associated with IS risk, and only when MAC thickness was at least 4 mm. Multiple epidemiological studies have analyzed stroke risk in patients with MAC, but few adjusted for possible clinical confounders (17). The incremental predictive value of MAC over other established risk factors remains poorly defined. In the SPAF (Stroke Prevention in Atrial Fibrillation) study, MAC was no longer associated with stroke when patients with nonrheumatic atrial fibrillation were excluded from the

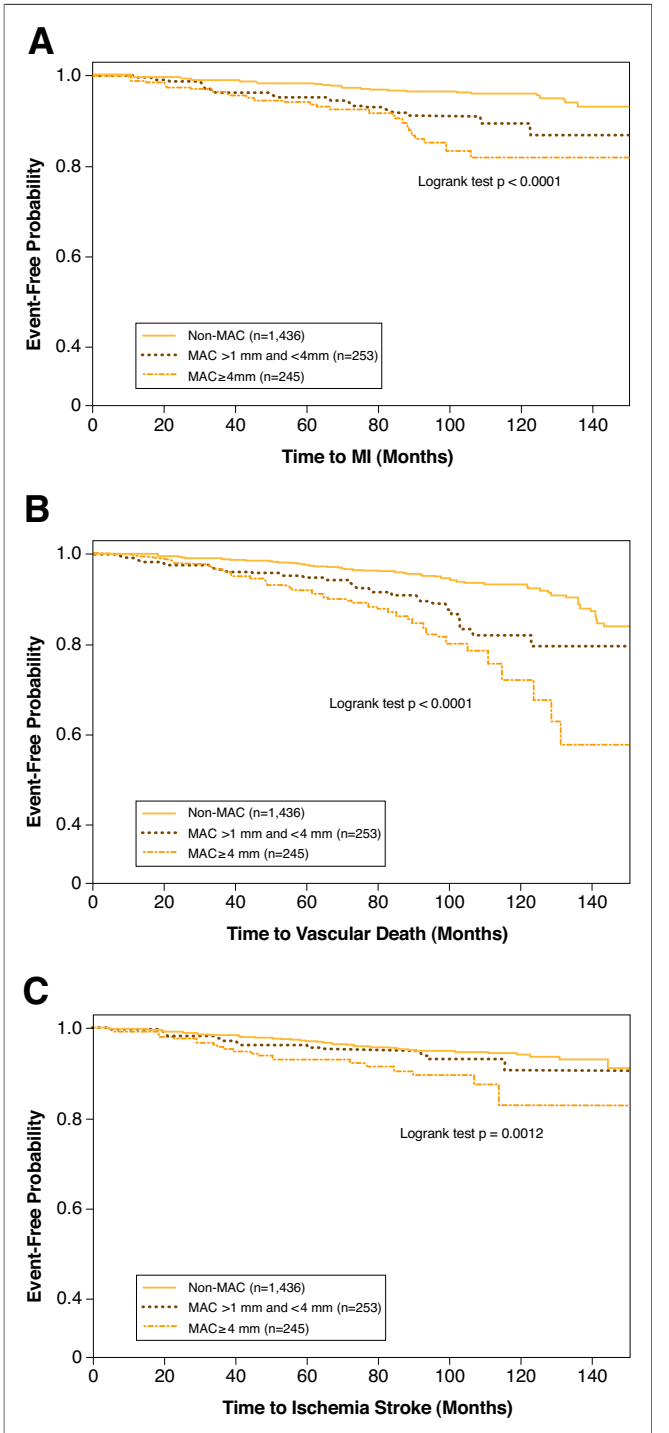

Figure 1. Event-Free Probability Curve for MI, VD, and IS

Event-free probability curve for myocardial infarction (MI) **(A)**, vascular death (VD) **(B)**, and ischemic stroke (IS) **(C)** based on presence of mitral annular calcification (MAC), which demonstrated a significant increase in each of these vascular outcomes related to its thickness. The incidence of MI, VD, and IS was 13.8, 20.3, and 10.7/1,000 person-years, respectively, in subjects with MAC, and 4.7, 7.5, and 6.1/1,000 person-years, respectively, in subjects without MAC.

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Table 2. Predictors of MI, IS, and VD by Univariable Analysis

	MI			IS			VD		
	HR	95% CI	p Value	HR	95% CI	p Value	HR	95% CI	p Value
MAC									
For presence of any MAC	2.97	2.01–4.40	<0.001	1.78	1.20–2.66	0.004	2.77	2.03–3.79	<0.001
For each 1-mm increase in MAC	1.23	1.15–1.33	<0.001	1.14	1.05–1.24	0.001	1.24	1.17–1.32	<0.001
Age (per-yr increment)	1.09	1.07–1.11	<0.001	1.05	1.03–1.07	<0.001	1.10	1.08–1.12	<0.001
Male gender	1.42	0.96–2.10	0.082	1.58	1.07–2.32	0.020	1.02	0.74–1.41	0.90
Diabetes	1.88	1.24–2.86	0.003	2.12	1.42–3.16	0.000	1.54	1.09–2.18	0.014
Hypercholesterolemia	1.01	1.00–1.01	0.002	0.99	0.99–1.00	0.018	1.00	1.00–1.01	0.53
Hypertension	1.95	1.20–3.15	0.007	1.73	1.09–2.73	0.019	2.52	1.66–3.81	<0.001
Smoking	1.69	1.12–2.54	0.012	1.32	0.89–1.95	0.16	1.35	0.98–1.85	0.066
Atrial fibrillation	1.76	0.72–4.33	0.22	0.96	0.30–3.02	0.94	3.48	2.01–6.04	<0.001
LDL (per-U increment), mg/dl	1.01	1.00–1.01	0.001	0.99	0.99–1.00	0.018	1.00	0.99–1.01	0.62
HDL (per-U increment), mg/dl	0.98	0.97–1.00	0.017	0.99	0.98–1.01	0.18	1.00	0.98–1.01	0.36

IS = ischemic stroke; MI = myocardial infarction; VD = vascular death; other abbreviations as in Table 1.

Table 3. Association of MAC Thickness With Vascular End Points

	Any MAC (Any Thickness) n = 519 (26.7%)		Mild/Moderate MAC (Thickness <4 mm) n = 253 (13.1%)		Severe MAC (Thickness ≥4 mm) n = 245 (12.7%)	
	HR	95% CI	HR	95% CI	HR	95%CI
Univariable analysis						
MI	2.98	2.02–4.20	2.46	1.47–4.09	3.73	2.34–5.92
VD	2.71	1.98–3.72	2.18	1.44–3.29	3.55	2.44–5.16
IS	1.79	1.20–2.67	1.34	0.76–2.35	2.38	1.48–3.83
Multivariable analysis*						
MI	1.75	1.13–2.69	1.66	0.97–2.83	1.89	1.13–3.17
VD	1.53	1.09–2.15	1.35	0.87–2.09	1.81	1.21–2.72
IS	1.34	0.87–2.05	1.12	0.63–2.00	1.59	0.95–2.67

Reference group: No MAC. *Adjusted for age, gender, diabetes mellitus, hypertension, hypercholesterolemia, smoking history, and atrial fibrillation. Abbreviations as in Tables 1 and 2.

analysis (18). Mitral annular calcification was associated with a relative risk of stroke of 2.1 in the Framingham study after adjustment for clinical risk factors, and after exclusion of atrial fibrillation (4). However, by limiting outcomes to cerebral infarcts instead of including all incident strokes, the relative risk was reduced to a nonsignificant 1.78. Therefore, our results are consistent with previous reports, but underscore the importance the quantitative measurement of MAC, which may be a better risk indicator than the mere presence of MAC.

Study limitations. Renal failure, even in mild degree may be a significant confounding factor for the studied outcome variables. Our cohort did include 80 subjects with mild renal insufficiency (defined as serum creatinine above 1.5 mg/dl), but the exclusion of these subjects did not change the main results of our study (results not shown).

Lastly, novel inflammatory markers (e.g., C-reactive protein) were available only in a subset of our cohort, and could not be considered in the analysis. Further study is needed to examine the relationship between systemic biomarkers of inflammation, valvular or annular calcification, and vascular outcomes.

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Key Words: calcium ■ echocardiography ■ cardiovascular diseases ■ stroke ■ mortality.