Mitral and Aortic Annular Calcification Are Highly Associated With Systemic Calcified Atherosclerosis

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Background—Atherosclerosis has been implicated as a cause of valvular calcification. The aim of this study was to determine whether atherosclerotic calcification in multiple vascular areas is significantly associated with aortic or mitral annular calcification independent of traditional risk factors.

Methods and Results—A total of 1242 consecutive asymptomatic patients free of clinical coronary heart disease were studied by electron-beam computed tomography for the extent of calcium due to atherosclerosis in 5 distinct vascular beds and calcium in the aortic and mitral annuli. Nearly 24% had calcium in the aortic annulus, whereas 8% were found to have mitral annular calcification. Age and a history of hypertension were the only traditional cardiovascular risk factors that were independently associated with prevalent calcification in the aortic and mitral annuli. After adjustment for age, gender, and cardiovascular disease risk factors, subjects with calcium in the thoracic aorta had the highest odds for the presence of aortic annular calcium (OR=3.9, $P<0.01$), whereas those with calcium in the abdominal aorta had the highest odds for mitral annular calcification (OR=5.1, $P=0.01$). Standardized increases in calcium in the abdominal aorta (OR=2.0, $P<0.01$) and iliacs (OR=1.8, $P=0.01$) were significantly associated with calcium in the aortic annulus after adjustment for the extent of calcium in the other vascular beds, whereas the thoracic aorta was significantly associated (OR=1.4, $P=0.02$) with calcium in the mitral annulus.

Conclusions—This study supports the hypothesis that calcification of the mitral and aortic annuli is related to atherosclerosis in other vascular beds. (***Circulation*. 2006;113:861-866.**)

Key Words: atherosclerosis ■ calcium ■ mitral valve ■ aorta ■ valves

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Atherosclerosis is a systemic[1] inflammatory process[2,3] with a predilection for certain anatomic locations.[4] Calcium deposition typically occurs in areas of atherosclerotic lipid accumulation and is a highly organized and regulated process[5–7] that is very similar to cortical bone formation.[8,9] Previous histopathologic research has shown that the amount of calcium in the coronary arteries is highly correlated with the extent of atherosclerotic plaque burden and, to a lesser extent, the degree of stenosis in these vessels.[10]

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Arterial branch points and vascular areas with decreased shear stress[11] or increased turbulence of blood flow[12] are sites where there is a tendency for atherosclerosis to initiate. Examples of such include the bifurcation of the left main coronary artery[4] and the distal abdominal aorta.[13] Furthermore, the attachment points of the aortic and mitral valves to their respective annuli are also sites of turbulent blood flow. As such, these sites would theoretically be at increased risk of developing atherosclerosis. Indeed, recent studies have demonstrated a significant relationship between cardiovascular risk factors[14–16] and calcification in the mitral annulus along with the aortic valve proper. Valvular calcium is also associated with atherosclerotic calcification in the coronary arteries and aorta.[17,18]

The preponderance of studies of the aortic valve have utilized echocardiography and focused on the valve itself, rather than the annulus. However, imaging the valve proper entails potential limitations due to motion artifact. Therefore, the aim of the present study was to determine whether atherosclerotic calcification in multiple vascular areas is significantly associated with aortic (AAC) or mitral (MAC) annular calcification. Furthermore, this study tested the hypothesis that calcium in the vascular beds would be independently associated with AAC or MAC even after adjustment for traditional cardiovascular disease (CVD) risk factors.

Methods

Subjects

From February 1, 2001, to June 13, 2001, 1242 consecutive asymptomatic patients who were free of clinical coronary heart disease (CHD; either myocardial infarction or coronary revascularization) presented for preventive medicine services at a university-affiliated disease-prevention center in San Diego, Calif, and were evaluated for the extent of calcified atherosclerosis in 5 different vascular beds: the carotid,

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coronary, thoracic aorta, abdominal aorta, and iliac vessels. Most subjects were self-referred or referred on the advice of their primary care provider. Those with a history of aortic or mitral valve repair or replacement or of carotid artery surgery were excluded.

All patients completed a detailed health history questionnaire before undergoing the scanning procedure. Smoking status was defined as current, former, or never. Hypertension was defined as systolic or diastolic blood pressure >140 or >90 mm Hg, respectively, or current use of antihypertensive medication. Diabetes was defined by self-report and current use of antiglycemic medications. Individuals with a total cholesterol–to–HDL cholesterol ratio >5 or who reported using a medication for this condition were classified as dyslipidemic. The study protocol was approved by the Human Research Protection Program at the University of California at San Diego, which granted a waiver of informed consent.

Imaging

All patients underwent imaging with an Imatron C-150 scanner. Images for each vascular bed were obtained from a single scan with a 100-ms scan time and preceding caudally from the base of the skull to the symphysis pubis. Each bed was obtained by a distinct scan of the segment in question with the following slice thicknesses: 3 mm for the coronary bed; 6 mm through the neck, abdomen, and pelvis; and 5 mm for the thorax. Cardiac tomographic imaging was electrocardiographically triggered at 40% or 65% of the R-R interval, depending on the subject's heart rate. Imaging of the heart, thorax, and abdomen was conducted during separate breath holds at half-maximal inspiration.

Data from the left and right sides were combined to give the extent of calcium in the carotid and iliac beds. The coronary vascular bed was composed of the left main, left anterior descending, left circumflex, and right coronary arteries. The thoracic aorta was defined as the segment from the aortic root to the diaphragm, whereas the abdominal aorta was the segment from the diaphragm to the iliac bifurcation.

Atherosclerotic calcification was defined as a plaque of ≥ 1 mm^2 with a density of ≥ 130 Hounsfield units (HU). Quantitative calcium scores were determined according to the method described by Agatston et al.[19] In brief, the calcium score per lesion was calculated by multiplying the area of the contiguous pixels by the corresponding density number using the following scale for density: 1=130 to 199 HU, 2=200 to 299 HU, 3=300 to 399 HU, and 4=≥400 HU. The total coronary calcium score was then determined by summing all of the lesion scores from all of the slices. Agatston calcium scores for vascular beds other than the coronaries were adjusted for slice thickness with the following formula: adjusted score=original score×slice thickness/3.0. Volume averaging was avoided by scoring each homogeneous slice thickness segment separately.

Cardiac image files for all subjects were interrogated retrospectively for the presence and extent of calcium in the mitral and aorta annuli with the same software used in scoring the vascular beds. The former was defined as calcium detected just inferior to the origin of the coronary arteries and located at the point of attachment of the aortic valve, whereas mitral calcification was located at the junction between the left atria and left ventricle. Because of their proximity, care was taken to discriminate between the left circumflex coronary artery and the mitral annulus. The Agatston criteria were used to quantify AAC and MAC. Calcium scoring of the annuli was conducted blinded to the results for the vascular beds.

Laboratory

All subjects had blood pressure measured while in the seated position and after resting for 5 minutes. Random serum lipid and glucose measurements were obtained by finger stick with the Cholestec LDX system. Body mass index was calculated with the patient lightly clothed (without shoes). Body fat measurement was conducted with bioimpedance on the Omron HBF-300.

Statistical Analysis

A 2-tailed level of significance of 0.05 was used for all analyses. The analyses were conducted with SPSS version 12. Separate analyses were conducted for the mitral and aortic annuli. Tests for group differences for those with and without any annular calcium were conducted with ANOVA or the Kruskal-Wallis test (as appropriate) for continuous variables and the χ^2 test for categorical variables. Because it is well-known that coronary calcium distributions differ by age and gender, mean values by group were also adjusted for these factors with ANCOVA. Simple correlations were calculated with the Spearman rank correlation procedure.

The potential association between the traditional cardiovascular risk factors and the presence of annular calcification was explored by multivariable logistic regression.[20] The association between vascular bed calcification and annular calcium was tested separately for each vascular bed and annulus with multivariable logistic regression and adjustment for the cardiovascular risk factors. These analyses were conducted with (1) the presence or absence of calcium and (2) a 1-SD increase in the amount of calcium in each vascular bed.

Results

The characteristics of the study cohort stratified by the presence or absence of AAC and MAC are presented in Table 1. Overall, nearly 24% had calcium in the aortic annulus, whereas 8% were found to have MAC. Calcium in the aortic annulus was found in 176 men (25.8%) and 120 women (21.5%; $P=0.08$), whereas MAC was found in 60 men (8.8%) and 39 women (7.0%; $P=0.24$). Because of the high number of subjects with no AAC or MAC, the distributions of these variables were highly skewed. The median quantity of AAC and MAC was 0 for both, but the maximums were quite different: 2039 and 10 735, respectively.

Individuals with calcium in either the aortic or mitral annuli were significantly older and were more likely to have higher total body fat and a history of hypertension ($P<0.01$ for all). A history of smoking was significantly higher in those with any annular calcium. There was a significantly higher proportion of individuals with aortic (but not mitral) calcium in those with dyslipidemia. There were no significant differences between these groups with respect to body mass index. Interestingly, adjustment for age reversed the relationship between the calcification of the aortic annulus and total body fat (28.6% [those with AAC] versus 30.0% [no AAC], $P=0.01$), whereas these differences were of borderline significance for the mitral annulus (28.4% versus 29.8%, $P=0.10$).

Multivariable logistic regression revealed that increasing age and a history of hypertension were the only traditional cardiovascular risk factors that were independently associated with prevalent calcification in the aortic and mitral annuli (Table 2). Each 10-year increase in age was associated with a 4.0- and 3.7-fold increase in the likelihood for AAC and MAC, respectively, whereas the risk was 50% and 80% higher in those with hypertension. Subjects with hypercholesterolemia, who were current or former smokers, or who had a family history of CHD had a significantly higher risk for AAC but not MAC. Similarly, women had a 30% lower risk for AAC and MAC, respectively, but neither was statistically significant.

The Spearman rank correlation between calcification in the aortic and mitral annuli was moderate ($r=0.37$, $P<0.01$). In general, correlations between annular calcification and risk factors were larger for the aortic annulus than for the mitral annulus. Additionally, in both annuli, correlations were appreciably higher for calcium in any of the vascular beds than for the risk factors. The highest correlation was found between aortic annular calcium and atherosclerotic calcification in the thoracic aorta ($r=0.56$, $P<0.01$). Of note, all

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TABLE 1. Cohort Characteristics Stratified by the Presence of Aortic and Mitral Annular Calcium

	AAC			MAC		
Variable	Absent n=946 (76.2%)	Present n=296 (23.8%)	*P*	Absent n=1143 (92.0%)	Present n=99 (8.0%)	*P*
Age,* y	53.6 (9.9)	67.0 (9.0)	<0.01	55.6 (10.6)	70.5 (9.4)	<0.01
Female†	439 (46.4)	120 (40.5)	0.08	520 (45.5)	39 (39.4)	0.24
Body mass index,* kg/m^2	26.8 (4.6)	26.7 (4.5)	0.68	26.9 (4.6)	26.3 (4.1)	0.24
Total body fat,* %	29.1 (7.6)	31.3 (7.4)	<0.01	29.5 (7.6)	31.8 (7.5)	<0.01
Ever-smoker†	391 (41.3)	186 (62.8)	<0.01	518 (45.3)	59 (59.6)	<0.01
Diabetes mellitus†	27 (2.9)	15 (5.1)	0.07	37 (3.2)	5 (5.1)	0.34
Hypercholesterolemia†	254 (30.0)	100 (38.6)	<0.01	322 (31.7)	32 (35.6)	0.45
Hypertension†	202 (21.4)	119 (40.2)	<0.01	273 (23.9)	48 (48.5)	<0.01
Family history of premature CHD†	232 (24.5)	79 (26.7)	0.45	293 (25.6)	18 (18.2)	0.101
Carotid calcium score‡	0 (0–2035)	64 (0–2730)	<0.01	0 (0–2730)	157 (0–2365)	<0.01
Coronary calcium score‡	1 (0–3581)	164 (0–6056)	<0.01	3 (0–4124)	262 (0–6056)	<0.01
Thoracic aorta calcium score‡	0 (0–6241)	307 (0–12 676)	<0.01	0 (0–11 730)	575 (0–12 676)	<0.01
Abdominal aorta calcium score‡	0 (0–5131)	992 (0–11 111)	<0.01	9 (0–8777)	1663 (0–11 111)	<0.01
Iliac calcium score‡	0 (0–7698)	683 (0–16 446)	<0.01	18 (0–16 446)	1136 (0–13 875)	<0.01

Values are reported as *mean (SD), †count (%), or ‡median (minimum–maximum).

correlations with vascular bed calcification were of similar magnitude for a given annulus (aortic annulus 0.45 to 0.56, $P<0.01$ for all; mitral annulus 0.27 to 0.36, $P<0.01$ for all). Of the risk factors, only age and total body fat were significantly correlated with calcification in both annuli. Notably, the correlations between age and AAC ($r=0.51$) and MAC ($r=0.33$) were of similar magnitude to those between the annuli and calcium in the vascular beds.

After adjustment for age, gender, percent body fat, dyslipidemia, hypertension, diabetes, and family history of CHD, the presence of atherosclerotic calcification in each vascular bed was significantly associated with calcium in the aortic annulus ($P<0.05$). For the mitral annulus, all beds were significant predictors except the coronary and iliac vascular beds (Figure 1). Subjects with calcium in the thoracic aorta had the highest odds for the presence of aortic annular calcium (OR=3.9, 95% CI=2.5 to 6.1), whereas those with calcium in the abdominal aorta had the highest likelihood for mitral annular calcification (OR=5.1, 95% CI=1.5 to 17.7). Interestingly, coronary calcium was a relatively weak predictor of calcium in either annulus, whereas calcium in the thoracic aorta was a strong and consistent predictor of annular calcium in either valve. Of the cardiovascular risk factors, only age was significantly and independently associated with calcium in either annulus for all models ($P<0.01$ for all).

The odds associated with a standardized increase (1 SD) in vascular bed calcium and the presence of AAC or MAC are presented in Figure 2. As with the analysis that used prevalent vascular bed calcium (above), all associations between 1-SD increases of calcium for each vascular bed and calcium in the aortic annulus were significant ($P<0.01$). Furthermore, only the iliac vascular bed was not significantly (OR=1.2, 95% CI=0.7 to 2.0) associated with mitral annular calcification when we used a standardized increase in calcium. Notably, the odds associated with a 1-SD increase in the total calcium score ("All" in Figure 2) were associated with the highest odds for calcium in the aortic annuli (OR=2.6, 95% CI=1.9 to 3.7).

To determine which vascular beds were significantly and independently associated with the presence of mitral or aortic annular calcium after adjustment for the other beds, we

TABLE 2. Multivariable Risk Factor Analysis for AAC and MAC

	AAC			MAC		
Variable	OR	95% CI	*P*	OR	95% CI	*P*
Age (10 y)	4.0	3.9–4.1	<0.01	3.7	3.6–3.9	<0.01
Gender (F vs M)	0.7	0.4–1.2	0.08	0.7	0.4–1.2	0.16
Body mass index (3 units)	1.0	0.9–1.1	0.55	0.9	0.9–1.3	0.35
Hypercholesterolemia (Y vs N)	1.5	1.3–1.7	0.04	1.3	0.8–2.3	0.30
Hypertension (Y vs N)	1.5	1.1–2.9	0.02	1.8	1.1–2.9	0.02
Diabetes (Y vs N)	1.5	0.6–5.0	0.35	1.7	0.6–5.0	0.34
Current smoker (Y vs N)	1.6	1.3–1.7	0.01	1.0	0.6–1.7	0.95
Former smoker (Y vs N)	2.1	1.3–3.4	0.02	1.2	0.5–3.1	0.67
Family history of CHD (Y vs N)	1.6	1.3–1.9	0.02	0.8	0.4–1.4	0.38

F indicates female; M, male; Y, yes; and N, no.

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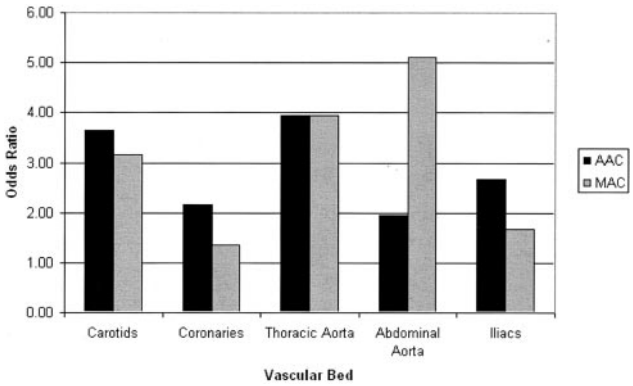

Figure 1. Odds of MAC or AAC by prevalence of calcium in each vascular bed. All models adjusted for age, gender, percent body fat, dyslipidemia, hypertension, diabetes, smoking and family history of CHD.

constructed multivariable logistic regression models. Notably, the extent of calcium in the abdominal aorta was highly correlated with that in the iliacs (r=0.82) with a significant tolerance (0.1) that indicated that parameter estimates for these 2 variables would cause inflated standard errors and potentially incorrect probability values if used in the same regression model. We therefore performed separate regressions that contained either the abdominal aorta or the iliacs along with carotids, coronaries, and thoracic aorta. Standardized increases in calcium in the abdominal aorta (OR=2.0, $P<0.01$) and iliacs (OR=1.8, $P<0.01$) were significantly associated with calcium in the aortic annulus after adjustment for age, gender, CVD risk factors, and the extent of calcium in the other vascular beds. For the mitral annulus, the thoracic aorta was significantly associated (OR=1.4 P=0.02), whereas the abdominal aorta was of borderline significance (OR=1.3, P=0.06).

Discussion

In this cross-sectional study of 1242 asymptomatic men and women, atherosclerotic calcification in any of 5 distinct vascular beds was significantly associated with calcium in the aortic annulus even after adjustment for traditional CVD risk factors. The same was true for the mitral annulus except for the coronary and iliac vascular beds, which were not significantly associated. Furthermore, when we adjusted for risk factors and the extent of calcium in the other beds, the increases in calcium located in the abdominal aorta or iliac arteries were significant predictors of aortic annular calcium, whereas thoracic aortic calcium was significantly associated with calcium in the mitral annulus. Notably, age was the only CVD risk factor that remained significant in the multivariable models, which did not differ by gender.

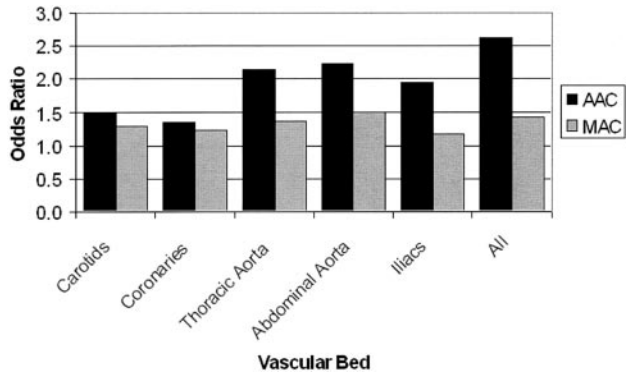

Figure 2. Odds for AAC or MAC by 1-SD increase in calcium in each vascular bed. All indicates carotids plus coronaries plus thoracic aorta plus abdominal aorta plus iliac arteries. All models adjusted for age, gender, percent body fat, dyslipidemia, hypertension, diabetes, smoking, and family history of CHD.

From population-based studies, the overall prevalence of AAC and MAC has been reported to be 28% and 13%, respectively.[14,21] The prevalence of the latter ranges from 4.6% to 15.8% in different genders and races,[22,23] up to 35% in symptomatic populations[24] and 36% in those with end-stage renal disease.[14] Notably, in the Framingham Heart Study, MAC was never found in those under the age of 40 years.[25]

Atherosclerosis of the large and medium-sized conduit vessels occurs via a relatively standard process that includes amorphous calcification of a lipid core, which progresses to endochondral bone formation similar to that found in skeletal bone.[8] Previous histopathologic research has demonstrated similarities between atherosclerosis in the vasculature and chronic degenerative changes in the aortic and mitral valves.[26,27] For example, the initiating event for valve disease is likely to be injury or dysfunction of the endothelium,[28] especially in areas of altered shear stress and blood rheology.[29] Furthermore, the calcified aortic valve lesion develops in the setting of inflammation[30] and displays hallmarks of atherosclerosis, including lipid accumulation,[31] matrix metalloproteinase activation,[32] and interaction with the renin-angiotensin system.[33] The aortic valve also contains cells similar to myofibroblasts that have been shown to differentiate into osteoblast-like cells that form calcific nodules in vitro.[34] These myofibroblasts are phenotypically analogous to vascular smooth muscle cells, which can also undergo differentiation into calcifying cells.[35]

Previous clinical studies have demonstrated significant associations between both CVD risk factors[17,36,37] and different measures of subclinical atherosclerosis[17,38,39] and valvular calcification, thereby providing additional evidence for the hypothesis that annular calcification is atherosclerotic in nature. Unfortunately, owing to their anatomic locations, similar research on the pathophysiology of calcification for the valvular annuli is not available. Nonetheless, the magnitude and consistency of significant associations found in the present study between annular calcification and calcium in different vascular beds provide further support for the hypothesis that calcification of the mitral and aortic annuli is due to atherosclerosis. Furthermore, because the associations between vascular and annular calcification are highly significant and independent of CVD risk factors, measurement of subclinical atherosclerosis may provide the opportunity for enhanced valvular disease prediction.

The presence of annular calcification is important clinically. Individuals with MAC have been shown to have a higher prevalence and risk of severe coronary artery disease and of stroke and total cardiac death.[24,40] As may be expected, MAC has also been associated with an increased risk of incident atrial fibrillation (hazard ratio [HR] 1.6) on multivariable-adjusted analysis; however, this association

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was attenuated on further adjustment for left atrial size (HR 1.4).[21] Importantly, annular calcification has been associated with future CVD events. In the Framingham Heart Study, those who had echocardiographic evidence of MAC were at increased risk for stroke (relative risk 2.10), incident CVD (HR 1.5), CVD death (HR 1.6), and all-cause mortality (HR 1.3) over 16 years of follow-up.[22] In a study limited to blacks, the HR associated with prevalent MAC was 2.32 for incident CHD events (defined as fatal coronary event, hospitalized myocardial infarction, or cardiac procedure).[23]

The available literature on the clinical relevance of AAC is much less than for MAC. Jeon et al[41] found that hypertension was a significant risk factor for AAC, and individuals with calcification in multiple valve areas (including the AAC) had an increased risk for an abnormal myocardial perfusion scan with single photon emission computed tomography.

Patients often present with valvular disease as a primary symptom and may require complex surgical procedures to correct these anomalies. The data from the present study suggest that these calcific lesions are likely to be atherosclerotic in nature. As such, degenerative changes in the valves could potentially be prevented or attenuated by control of CVD risk factors. However, the suggested benefit of statin use in observational studies[42,43] was not confirmed in a recent randomized trial.[44] Further CVD risk factor modification research is warranted.

Study Limitations

The sample for this study may not be representative of the general population or populations from community-based samples. Because our definition of diabetes relies on self-report of medication use for this condition and not a fasting plasma glucose level, there is the potential for misclassification. Calcium detected by electron-beam computed tomography is primarily due to intimal changes associated with atherosclerosis; however, this technique does not distinguish between intimal calcification due to atherosclerosis and Mönckeberg's medial calcinosis. Because the latter occurs principally in those with diabetes[45] or chronic kidney disease[46] and is located in the lower extremities (below the knee), we believe the probability of misclassification is low. Additionally, although most existing data on atherosclerotic calcification are based on Agatston scoring, this method has several limitations. First, because this method relies on the maximum CT number, image noise may influence the calcium score. Second, the use of density numbers to categorize pixel intensity causes the calcium score to increase nonlinearly. Third, because the original Agatston scoring method used area-based calcium scores with contiguous, nonoverlapping 3-mm slices, the volumetric scores derived from the nonoverlapping 3-mm slices in the present study were adjusted to be equivalent to that for the original Agatston method. Finally, because the Agatston score may not represent the true volume of calcium in a lesion, the calcium score is not an exact physical measure.[47]

Conclusions

This study provides further support for the hypothesis that annular calcification is due to atherosclerosis and that the associations with traditional CHD risk factors are different. That is, smoking does not appear to be a risk factor for MAC, although it is significantly associated with AAC. These findings, coupled with previous reports of an association between MAC and future CVD events, support the hypothesis that identification of calcium in either annulus may a useful screening tool.

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Disclosures

None.

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CLINICAL PERSPECTIVE

Previous research studies have suggested that the origin of calcification of the mitral and aortic annuli is atherosclerosis. The findings of the present study provide further evidence that calcification of these annuli is likely to be due to this process. If this is true, early treatment of patients who have elevated cardiovascular risk factors may prevent the degenerative atherosclerotic changes of these valves. Conversely, if calcium in the annuli is detected, control of risk factor levels may retard the progression of the disease. Additionally, individuals with MAC have been shown to have a higher prevalence and risk of severe coronary artery disease, as well as stroke and total cardiac death. Similarly, those with AAC have an increased risk for an abnormal myocardial perfusion scan with single photon emission computed tomography. As may be expected, MAC has also been associated with an increased risk of incident atrial fibrillation on multivariable-adjusted analysis. Importantly, annular calcification has been associated with future CVD events. In the Framingham Heart Study, those who had echocardiographic evidence of MAC were at increased risk for stroke, incident CVD, CVD death, and all-cause mortality over 16 years of follow-up. Given the evidence for a link between atherosclerosis, future CVD events, and calcification of the valvular annuli, it would appear prudent to regard the latter as a focal manifestation of a systemic condition that warrants aggressive preventive therapies.

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