Journal of the American Heart Association

ORIGINAL RESEARCH

Risk Factors and Outcomes With Progressive Mitral Annular Calcification

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BACKGROUND: Mitral annular calcification (MAC) is a chronic degenerative process that may progress. This study aimed to investigate associating factors and clinical implications of MAC progression.

METHODS AND RESULTS: Among 560 patients with MAC identified by transthoracic echocardiography between January 2012 and June 2016, 138 patients (mean±SD age 72.7±10.2 years, 73 women) with mild or moderate MAC who received follow-up examination within 18 to 36 months were retrospectively analyzed. Progressive MAC was defined as hemodynamic or structural profiles that had worsened by more than 1 grade. Hemodynamic features were assessed by the transmitral mean diastolic pressure gradient (MDPG), and structural features were assessed by the MAC angle in the parasternal short-axis view. The clinical outcome was defined as a composite of all-cause mortality, hospitalization for heart failure, and occurrence of ischemic stroke. Forty-three patients (31.2%) showed progressive MAC. Patients with progressive MAC had higher systolic blood pressure, pulse pressure, MAC angle, and MDPG than those with stable MAC. Patients with progressive MAC had smaller left ventricular (LV) end-systolic dimensions and higher LV ejection fractions compared with those with stable MAC. In multivariate analysis, pulse pressure, LV ejection fraction, MAC angle, and MDPG at baseline were significantly associated with MAC progression. During a median of 39.2 months' follow-up, patients with progressive MAC showed poorer clinical outcomes than those with stable MAC (log-rank P=0.015).

CONCLUSIONS: MAC progression is not rare and is associated with structural substrate and hemodynamic loads that result in mechanical stress. Patients with progressive MAC have poor outcomes.

Key Words: mitral annular calcification ■ outcome ■ progression ■ risk factor

Mitral annular calcification (MAC) is a chronic degenerative process in the fibrous base of the mitral valves.[1–3] The main contributing factors for the occurrence of MAC include age-related degeneration, elevated left ventricular (LV) afterloads, an atherosclerotic factor, and aberrant calcium-phosphate metabolism.[2,4,5] With the introduction of transcatheter intervention, MAC is now considered a disease entity, not just an incidental imaging finding.[1]

The severity and morphological and functional features of MAC vary.[6,7] The characteristics of MAC, along with its clinical risk factors, have been reported to be associated with morbidities and mortality.[6–9] In addition, a recent study demonstrated that patients who developed a significantly elevated mean diastolic pressure gradient (MDPG) with MAC had an increase in all-cause mortality.[10] However, most MAC studies have focused on the clinical significance of MAC evaluated at a single time point. Data on MAC progression is scant, although MAC pathophysiology can progress over time. Therefore, in the present study, we hypothesized that MAC progresses in at least some patients. Second, we hypothesized that there would be differences in clinical and echocardiographic features in

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This manuscript was sent to Amgad Mentias, MD, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.123.030620

For Sources of Funding and Disclosures, see page 10.

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CLINICAL PERSPECTIVE

What Is New?

- The progression of mitral annular calcification is not rare during a follow-up period.
- It is associated with higher left ventricular ejection fraction and wider pulse pressure, as well as structural and functional characteristics.
- Patients with progressive mitral annular calcification showed worse clinical outcomes compared with those with stable mitral annular calcification.

What Are the Clinical Implications?

- Patients with mitral annular calcification who have characteristics that can progress require closer clinical and imaging surveillance.

Nonstandard Abbreviations and Acronyms

MAC	mitral annular calcification
MDPG	mean diastolic pressure gradient
PP	pulse pressure

patients with progressive MAC compared with those without progression. Third, we hypothesized that patients with progressive MAC would have worse clinical outcomes than those who were stable.

METHODS

A total of 560 patients with MAC were retrospectively identified by transthoracic echocardiography at a single tertiary institution (Severance Cardiovascular Hospital, Seoul, Republic of Korea) from January 2010 to June 2016. Patients with MAC were identified by extracting patients whose mitral annulus calcification was described in the part describing mitral valve morphology in the echocardiography database and confirmed by reviewing the echocardiographic images. Patients with rheumatic mitral stenosis (MS), insufficient echocardiographic data for MAC assessment, or prior mitral intervention were excluded. We initially selected 212 patients who received follow-up echocardiography between 18 and 36 months after the first-indexed echocardiographic study. Cases without echocardiography or follow-up, patients with a pulse rate of 100 beats per minute or more, and subjects with severe grade MAC or MDPG >10 mm Hg at the time of the first examination were also excluded. Data from the remaining 138 patients were analyzed. The study was approved by the institutional review board of the Yonsei University Health System and complied with the Declaration of Helsinki. This was a registry-based retrospective study, and the data were analyzed anonymously; therefore, informed consent was not required from the study subjects. The data that support the findings of this study are available from the corresponding author upon reasonable request.

Echocardiography

Standard 2-dimensional and Doppler echocardiography measurements were performed following the American Society of Echocardiography guidelines.[11] MAC was defined as a thick and echo-dense area in the mitral annulus, occasionally extending to the mitral valve leaflets, as described in previous studies.[9,12] Comprehensive echocardiography reviews were performed to define the functional and structural characteristics of MAC (thickness, location, extent, and functional MS). MAC was evaluated along the parasternal long-axis and short-axis and via apical 4-chamber, 3-chamber, and 2-chamber views to determine the most severely affected annulus. In the parasternal short-axis view at the level of the mitral annulus, the severity of MAC was qualitatively determined as mild (focal, limited increase in echodensity within 120° of the mitral annulus), moderate (marked echodensity within 120–180° of the mitral annulus), or severe (marked echodensity at >180° of the mitral annulus) (Figure 1A).[7] MAC thickness was measured from the leading anterior edge to the trailing posterior edge at its greatest width.[9] The estimation of the diastolic pressure gradient was derived from the transmitral velocity flow curve using continuous wave Doppler echocardiography. The severity of functional MS was graded as none (transmitral MDPG <3 mm Hg), mild (3 ≤MDPG <5 mm Hg), moderate (5≤MDPG<10 mm Hg), and severe (MDPG ≥10 mm Hg).[10] Significant functional MS was defined as a transmitral MDPG ≥5 mm Hg.[7,9] In patients with atrial fibrillation, the mean gradient was calculated as the average of 3 cycles with the least variation in R–R intervals as close as possible to the normal heart rate. The severities of mitral regurgitation and aortic stenosis were assessed in accordance with the current guidelines.[13] Significant valvular dysfunction was defined as moderate or severe grades of dysfunction.

Definition of MAC Progression

In this study, MAC progression was defined as either a structural progression or hemodynamic progression as compared with each patient's index and follow-up echocardiogram. Structural progression was defined as an increase in the MAC by 1 or more grades based on

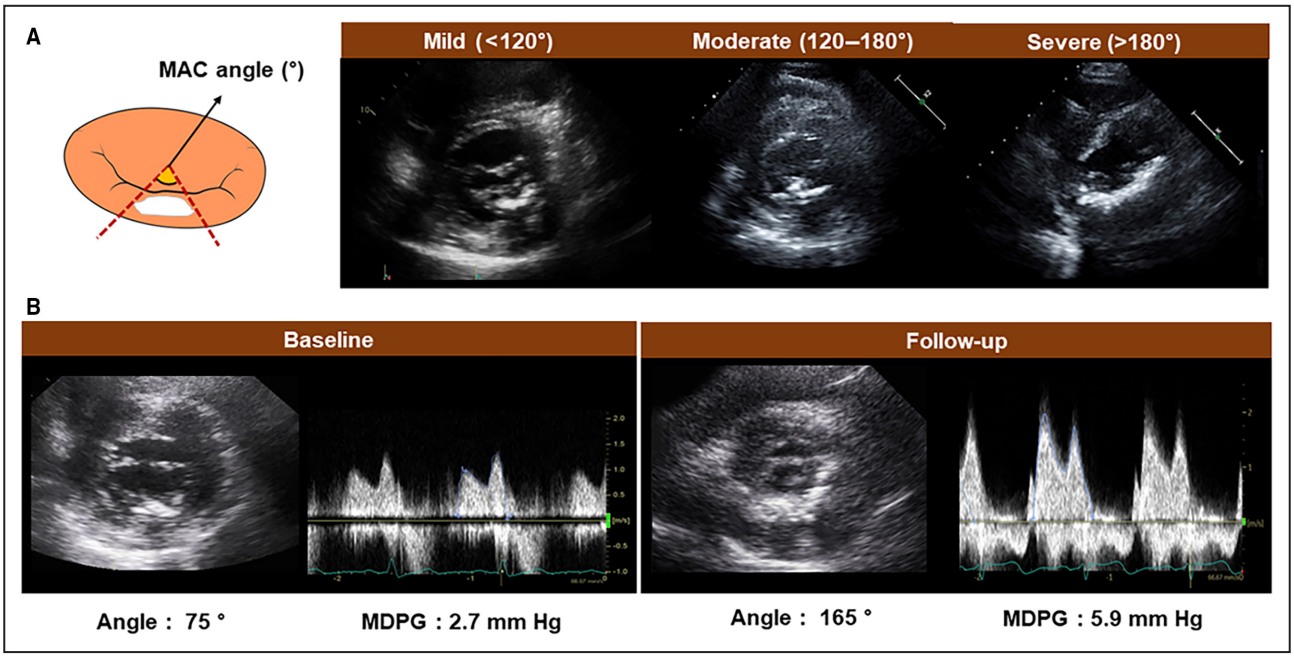

Figure 1. Representative cases of mild, moderate, and severe mitral annular calcification (A), and structural or hemodynamically progressive mitral annular calcification (B).
MAC indicates mitral annular calcification; and MDPG, mean diastolic pressure gradient.

the MAC angle measured in the parasternal short-axis view at the level of the mitral annulus. Hemodynamic progression was also defined as a case in which the hemodynamic grade divided by MDPG was increased by 1 level or more. A representative example of MAC progression is demonstrated in Figure 1B.

Clinical Data

Demographic, anthropometric, and laboratory data at the time of index echocardiography were collected from electronic medical records. Blood pressure measurements were performed automatically at the brachial artery of the nondominant arm in a relaxed seated position. Pulse pressure (PP) was defined as the difference between systolic and diastolic blood pressure. Coronary artery disease was defined as significant (>50%) coronary artery stenosis by angiography or computed tomography. Chronic kidney disease was defined as an estimated glomerular filtration rate of <60 mL/min per 1.73 m^2, and end-stage renal disease was a medical condition requiring a regular course of long-term dialysis due to renal dysfunction. Atrial fibrillation included both paroxysmal and persistent cases. Statin was prescribed between the index echocardiography and follow-up examination. Patients' clinical events were also reviewed from the electronic medical records. The clinical outcome was defined as a composite of all-cause mortality, hospitalization for heart failure, and occurrence of ischemic stroke from the date of follow-up echocardiogram.

Statistical Analysis

Continuous data are presented as mean±SD, and categorical data are expressed as numbers and percentages for each group. Comparisons of baseline clinical and echocardiographic variables were analyzed using an unpaired, 2-samples *t* test for continuous variables and χ^2 test for categorical variables. The receiver operating characteristic curve and the area under the curve were analyzed to evaluate the discrimination performance of the optimal cut-off value. The optimal cut-off value can be determined by finding points that maximize the Youden index. We also constructed a restricted cubic spline model to examine the graphical relationship between each variable and the odds ratios for MAC progression. Knot locations are based on Harrell's recommended percentiles.[14] Kaplan–Meier survival analysis was performed to evaluate the association of MAC progression with clinical outcomes. Univariable and multivariable linear regression analyses were performed to assess the factors that were associated with MAC progression. Variables with *P* value <0.10 in the univariate analysis were included in the multivariate model. Among the variables showing multicollinearity, the most significant variable was selected from the univariate analysis. Factors associated with composite events were analyzed using multivariate Cox regression models. The variables selected for entry into multivariate analysis were those with *P* <0.1 in Cox univariate analysis. In model 1, the baseline MAC grade was included; and in model 2, MAC

progression was added. Intraobserver and interobserver agreement for MAC grade were also assessed by interclass correlation coefficient for absolute agreement. All tests were 2-sided, and statistical significance was defined as P <0.05. All statistical analyses were performed using R statistical software (version 4.0.0; R Foundation for Statistical Computing, Vienna, Austria) and SPSS 20.0 software.

RESULTS

Baseline Characteristics

The average age of the initial 560 patients was 74.7±10.5 years, and 316 (58.8%) were women. Among the remaining 138 patients, the mean age was 72.7±10.2 years, and 73 patients (52.9%) were women. Of the total 138 patients, 43 patients (31.2%) showed MAC progression and 95 patients (68.8%) did not. The baseline characteristics of the groups are shown in Table 1. The average age and sex proportion of the groups were comparable. There was no difference between the 2 groups in comorbidities including hypertension, diabetes, dyslipidemia, and coronary artery disease. In addition, there was no difference in risk factors that may be related to the occurrence of MAC, such as chronic kidney disease, hypertrophic cardiomyopathy, and significant aortic stenosis, between the groups. Although not statistically significant, end-stage renal disease tended to be more prevalent in the progressive MAC group. In terms of hemodynamic characteristics, patients with progressive MAC showed significantly higher systolic blood pressure (141.1±25.3 versus 130.0±20.7 mm Hg, P=0.007) and wider PP (67.1±21.3 versus 58.0±18.1 mm Hg, P=0.011) than those with stable MAC.

Table 1. Baseline Characteristics Stratified by the Progression of MAC

	Stable MAC (n=95)	Progressive MAC (n=43)	*P* value
Demographic characteristics			
Age, y	72.5±10.7	73.2±9.2	0.72
Sex, female, n (%)	48 (50.5)	25 (58.1)	0.52
Body mass index, kg/m^2	24.2±4.6	23.1±3.6	0.20
Comorbidities			
Hypertension, n (%)	81 (85.3)	36 (83.7)	0.99
Diabetes, n (%)	41 (43.2)	15 (34.9)	0.47
Dyslipidemia, n (%)	72 (75.8)	27 (62.8)	0.17
Smoking, n (%)	18 (18.9)	12 (27.9)	0.34
Coronary artery disease, n (%)	57 (60.0)	24 (55.8)	0.78
Chronic kidney disease, n (%)	24 (25.3)	16 (37.2)	0.22
ESRD, n (%)	11 (11.6)	11 (25.6)	0.067
Atrial fibrillation, n (%)	24 (25.3)	8 (18.6)	0.52
HCM, n (%)	4 (4.2)	3 (7.0)	0.79
Moderate or severe AS, n (%)	42 (44.2)	16 (37.2)	0.56
Moderate or severe AR, n (%)	11 (11.6)	0 (0.0)	
Hyperthyroidism, n (%)	1 (0.1)	0 (0.0)	
Hemodynamic characteristics			
Heart rate, bpm	68.3±11.1	71.8±12.6	0.10
Systolic BP, mm Hg	130.0±20.7	141.1±25.3	0.007
Diastolic BP, mm Hg	72.0±11.3	74.0±15.2	0.43
Pulse pressure, mm Hg	58.0±18.1	67.1±21.3	0.011
Laboratory findings and medications			
Hemoglobin, g/dL	12.5±2.1	11.5±2.2	0.016
Serum creatinine, mg/dL	1.5±2.0	2.4±2.9	0.10
Statin use, n (%)	81 (85.3)	33 (76.7)	0.33

AR indicates aortic regurgitation; AS, aortic stenosis; BP, blood pressure; bpm, beats per minute; ESRD, end-stage renal disease; HCM, hypertrophic cardiomyopathy; and MAC, mitral annular calcification.

Echocardiographic Characteristics

Table 2 shows baseline echocardiographic characteristics stratified by the progression of MAC. In the progressive MAC group, the MAC thickness was significantly higher (5.1±2.2 versus 4.2±2.0 mm, P=0.02), and the average angle of MAC was significantly wider

Table 2. Baseline Echocardiographic Characteristics Stratified by the Progression of MAC

	Stable MAC (n=95)	Progressive MAC (n=43)	*P* value
Structural MAC characteristics			
MAC location			0.37
Posterior only, n (%)	80 (84.2)	34 (79.1)	
Bilateral, n (%)	13 (13.7)	9 (20.9)	
Maximal thickness, mm	4.2±2.0	5.1±2.2	0.020
Angle of MAC, °	53.0±35.8	79.1±31.5	<0.001
Mild MAC, n (%)	92 (96.8)	42 (97.7)	0.79
Moderate MAC, n (%)	3 (3.2)	1 (2.3)	
Functional MAC characteristics			
MDPG, mm Hg	2.0±1.3	3.1±1.5	<0.001
MDPG >5 mm Hg, n (%)	7 (7.4)	6 (14.0)	0.36
Significant MR, n (%)	17 (17.9)	5 (11.6)	0.57
Chamber characteristics			
LVEDD, mm	50.3±7.1	48.3±6.3	0.12
LVESD, mm	34.4±8.5	30.6±6.0	0.003
RWT, mm	0.5±0.2	0.5±0.1	0.93
LV mass index, g/m^2	129.3±36.9	126.2±41.2	0.68
LV ejection fraction, %	61.6±13.6	68.8±9.8	0.001
LA volume index, mL/m^2	43.9±15.0	46.2±14.5	0.41
PASP, mm Hg	32.5±17.4	37.3±15.2	0.12

EDD indicates end diastolic dimension; ESD, end systolic dimension; LA, left atrium; LV, left ventricle; MAC, mitral annular calcification; MDPG, mean diastolic pressure gradient; MR, mitral regurgitation; PASP, pulmonary arterial systolic pressure; and RWT, relative wall thickness.

(79.1±31.5° versus 53.0±35.8°, *P*<0.001) on the index echocardiography. The progressive MAC group also had higher trans-mitral MDPG (3.1±1.5 versus 2.0±1.3 mm Hg, *P*<0.001) than the group with stable MAC. That is, patients with progressive MAC demonstrated more severe structural and hemodynamic features on index echocardiograms. In terms of chamber characteristics, patients with progressive MAC showed smaller LV end-systolic dimensions (30.6±6.0 versus 34.4±8.5 mm, *P*=0.003) and better LV ejection fractions (68.8±9.8% versus 61.6±13.6%, *P*=0.001) on index echocardiography than those with stable MAC.

Table 3 displays the echocardiographic characteristics of the 2 groups at follow-up. The mean periods between the 2 echocardiographic examinations were ≈25 months for both groups. There were 31 patients (22.5%) with structural progression, and hemodynamic progression was noted in 19 patients (13.8%). In patients with progressive MAC, the maximal thickness of MAC increased, and the proportion of moderate-to-severe MAC reached 74.4%. That is, the changes in MAC thickness and angle were larger in the progressive MAC group than in the stable MAC group; as a result, the increased rates of the MAC thickness and angle calculated annually were significantly larger. Concomitant with these MAC structural changes, significant elevation in MDPG occurred in some patients. In the follow-up echocardiography, the LV end-systolic dimension was smaller, and the LV ejection fraction was higher in patients with progressive MAC compared with those with stable MAC, similar to the index echocardiography results. In addition, a significant increase in left atrium volume index was found in patients with progressive MAC (50.7±18.0 versus 42.9±15.3, *P*=0.009), which did not vary between the 2 groups on index echocardiography.

Table 3. Follow-Up Echocardiographic Characteristics Stratified by the Progression of MAC

	Stable MAC (n=95)	Progressive MAC (n=43)	*P* value
Follow-up echo duration, mo	26.6±7.2	25.3±7.5	0.32
Structural MAC characteristics			
Structural progression, n (%)	0 (0.0)	31 (72.1)	
MAC location			0.17
Posterior only, n (%)	69 (72.6)	27 (62.8)	
Bilateral n (%)	23 (24.2)	16 (37.2)	
Maximal thickness, mm	5.0±2.4	7.3±2.6	<0.001
Change, mm	0.8±1.6	2.1±2.3	0.001
Progression rate, mm/y	0.3±0.8	1.0±1.1	<0.001
Angle of MAC, °	65.1±39.2	135.5±37.4	<0.001
Change, °	12.2±24.1	56.4±42.6	<0.001
Progression rate, °/y	5.9±11.6	27.8±20.7	<0.001
Mild MAC, n (%)	92 (96.8)	11 (25.6)	<0.001
Moderate MAC, n (%)	3 (3.2)	20 (46.5)	
Severe MAC, n (%)	0 (0.0)	12 (27.9)	
Functional MAC characteristics			
Hemodynamic progression, n (%)	0 (0.0)	19 (44.2)	
MDPG, mm Hg	2.0±1.2	3.7±2.1	<0.001
MDPG >5 mm Hg, n (%)	4 (4.2)	12 (27.9)	<0.001
Significant MR, n (%)	11 (11.7)	6 (13.9)	0.86
Chamber characteristics			
LVEDD, mm	48.5±6.1	46.5±7.2	0.081
LVESD, mm	32.5±6.9	29.6±6.3	0.019
RWT, mm	0.4±0.1	0.5±0.1	0.013
LV mass index, g/m^2	121.4±36.3	117.8±31.3	0.59
LV ejection fraction, %	62.3±12.7	66.6±13.0	0.073
LA volume index, mL/m^2	42.9±15.3	50.7±18.0	0.009
PASP, mm Hg	33.3±18.8	37.1±18.6	0.27

EDD indicates end diastolic dimension; ESD, end systolic dimension; LA, left atrium; LV, left ventricle; MAC, mitral annular calcification; MDPG, mean diastolic pressure gradient; MR, mitral regurgitation; PASP, pulmonary arterial systolic pressure; and RWT, relative wall thickness.

Interclass correlation coefficients of intra- and interobserver agreement of the extent of MAC established in 15 patients randomly selected from the study population were 0.959 (CI, 0.884–0.986, *P* <0.0001) and 0.948 (CI, 0.853–0.982, *P*<0.0001), respectively.

Factors Associated With Progression of MAC

Table 4 demonstrates the factors associated with MAC progression. In univariate Cox regression analysis, systolic blood pressure, PP, angle of MAC, MDPG, LV end-systolic dimension, and LV ejection fraction were significantly related to the progression of MAC. In the receiver operating characteristic curves, the PP and LV ejection fraction cut-off points for the prediction of MAC progression were 55.5 mm Hg and 68.5%, respectively (Figure 2A). In addition, the MAC angle and MDPG cut-off points for the prediction of MAC progression were 75° and 1.75 mm Hg, respectively (Figure 2B). Figure 2C shows the prevalence of MAC progression according to the 4 groups to which each PP and LV ejection fraction cut-off value was applied. The group with high PP and high LV ejection fraction exhibited considerably greater rates of total and structural MAC progression. Figure 3 displays the cubic spline curve for MAC progression according to PP, LV ejection fraction, angle of MAC, and MDPG. All 4 variables showed a positive linear relationship with MAC progression. Multivariate Cox regression analysis revealed that PP (hazard ratio, 1.02 [95% CI=1.00–1.04], *P*=0.047), angle of MAC (hazard ratio, 1.01 [95% CI, 1.00–1.03], *P*=0.013), MDPG (hazard ratio, 1.39 [95% CI, 1.05–1.86], *P*=0.023), and LV ejection fraction (hazard ratio, 1.05 [95% CI, 1.01–1.10], *P*=0.027) were significantly associated with MAC progression.

Table 4. Factors Associated With MAC Progression

	Univariate		Multivariate	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y	1.01 (0.97–1.04)	0.71		
Female sex	1.36 (0.66–2.84)	0.41		
Hypertension	0.89 (0.34–2.52)	0.82		
Diabetes	0.71 (0.33–1.48)	0.36		
Dyslipidemia	0.54 (0.25–1.18)	0.12		
Chronic kidney disease	1.75 (0.80–3.79)	0.15		
End-stage renal disease	2.62 (1.03–6.73)	0.04		
Atrial fibrillation	0.68 (0.26–1.61)	0.39		
Coronary artery disease	0.84 (0.41–1.76)	0.64		
Statin use	0.57 (0.23–1.44)	0.23		
Smoking	1.66 (0.70–3.82)	0.24		
HCM	1.70 (0.33–8.08)	0.50		
Significant AS	1.21 (0.54–2.66)	0.63		
Significant AR	0.26 (0.01–1.48)	0.21		
Prior AV replacement	0.80 (0.34–1.82)	0.61		
Systolic BP, mm Hg	1.02 (1.01–1.04)	0.010		
Pulse pressure, mm Hg	1.02 (1.01–1.04)	0.013	1.02 (1.00–1.04)	0.047
Angle of MAC, °	1.02 (1.01–1.03)	<0.001	1.01 (1.00–1.03)	0.013
MDPG, mm Hg	1.61 (1.26–2.12)	<0.001	1.39 (1.05–1.86)	0.023
LVEDD	0.95 (0.90–1.01)	0.12		
LVESD	0.92 (0.87–0.98)	0.012		
LV ejection fraction, %	1.06 (1.02–1.10)	0.004	1.05 (1.01–1.10)	0.027

AR indicates aortic regurgitation; AS, aortic stenosis; AV, aortic valve; BP, blood pressure; CMP, cardiomyopathy; EDD, end diastolic dimension; ESD, end systolic dimension; HCM, hypertrophic cardiomyopathy; LV, left ventricle; MAC, mitral annular calcification; MDPG, mean diastolic pressure gradient; and OR, odds ratio.

Clinical Outcomes in Patients With Progressive MAC

During a median 39.2 months follow-up (interquartile range, 12.1–57.0 months), 31 deaths, 23 hospital admissions for heart failure, and 7 ischemic strokes occurred. Patients who had progressive MAC demonstrated a poorer composite clinical outcome and all-cause death rate than patients with stable MAC (Figure 4A and 4B). There was no significant statistical difference between the 2 groups for heart failure hospitalization or stroke (Figure 4C and 4D). In Cox regression analysis, MAC progression was independently associated with composite clinical outcome (*P*=0.033) (Table 5) The main findings of this study were consistent even when analyzed after excluding 12 patients who had only hemodynamic progression without reaching the definition of structural progression of MAC (Figure S1).

DISCUSSION

The principal findings of the present study are that the progression of MAC was not rare during follow-up and that the progression of MAC was associated with wider PP, higher LV ejection fraction, baseline structural (angle of MAC) severity, and hemodynamic (MDPG) severity. These findings provide mechanistic insight into MAC progression and underscore the importance of structural substrate and hemodynamic loads resulting in mechanical stress. Finally, patients with progressive MAC showed worse clinical outcomes compared with those with stable MAC. We suggest that closer surveillance for MAC and its progression is especially necessary for patients with wider MAC angles and patients with wide PP and high LV ejection fraction.

The concept of MAC progression is generally accepted because MAC is a disease of degenerative nature. In fact, several studies have demonstrated the risk factors for MAC occurrence and their clinical significance regarding all-cause mortality and stroke,[4,5,7,9,15–21] Recently, Kato et al[22,23] also demonstrated that the prevalence of MAC was 23% in 24 414 patients. Patients with MAC had a higher risk of mortality, worse outcomes, and mitral valve dysfunction. However, in terms of MAC progression, there are only a few studies that have shown the risk factors and clinical outcomes,[4,24–26] and inconsistent results according to

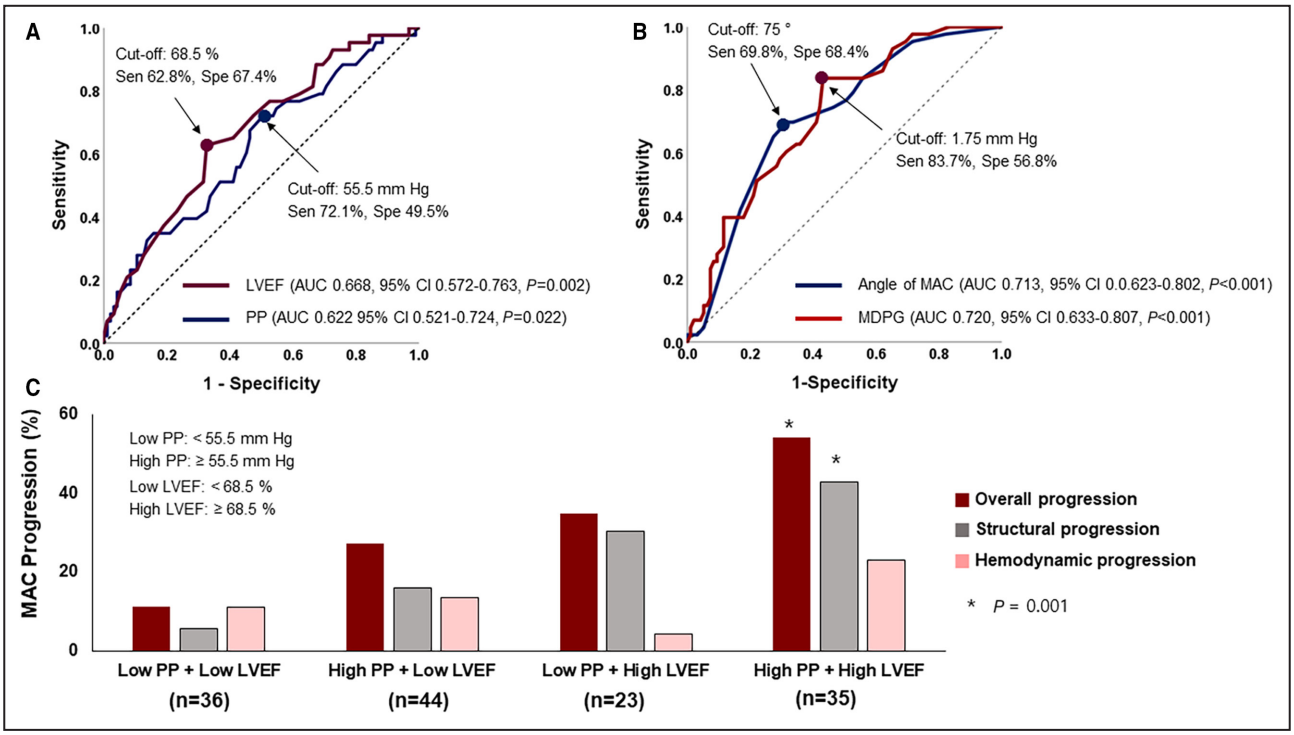

Figure 2. Receiver operating characteristic curves showing cut-off values to predict MAC progression.
A, Left ventricular ejection fraction and pulse pressure. **B**, Angle of MAC and mean diastolic pressure gradient. **C**, The prevalence of MAC progression in 4 groups according to the pulse pressure and left ventricular ejection fraction. AUC indicates area under the curve; LVEF, left ventricular ejection fraction; MAC, mitral annular calcification; MDPG, mean diastolic pressure gradient; and PP, pulse pressure.

the characteristics of the study participants or the definition of MAC progression.[4,24–26] Therefore, the clinical applications of these results are limited, although the results of each study can be understood conceptually. In the Multi-Ethnic Study of Atherosclerosis targeting the general population without cardiovascular disease, only 9% of participants were at risk for MAC progression.[4] Moreover, the median rate of change in MAC among those with MAC at baseline was 10 Agatston units/y, as assessed by computed tomography.[4] An analysis of the same population demonstrated an independent association between MAC progression and the occurrence of atrial fibrillation when MAC progressed to 10 Agatston units/y or more.[24] Although these population-based studies provided useful evidence for the concept of MAC progression, the severity of MAC observed in these studies was generally not clinically significant. More recently, single-center echocardiogram data from 11 605 patients with MAC over ≈4.2 years of follow-up have been reported.[25] In the study, the authors demonstrated that one third of the patients with mild or moderate MAC developed severe MAC.[25] Female sex was an important predictor of MAC progression and of the subsequent development of calcific mitral valve disease.[25] The present study has some similarities with that recently published study.[25] MAC grade was evaluated by echocardiographic methods; the average patient age was similar between the studies, ≈73 years old; and the male-to-female ratio was similar between the 2 studies.

The strength of the present study is its demonstration of several novel findings. First, in addition to structural progression, we analyzed hemodynamic progression based on MDPG elevation as a functional parameter that has recently been considered clinically important in patients with MAC.[10] Using clinically relevant and proven criteria from previous studies,[7,10] we defined MAC progression incorporating structural and hemodynamic changes. Since the structural grade of MAC might have a limit as a categorical grade assessed from the parasternal short-axis view on echocardiogram, complementary evaluation of MDPG for functional deterioration might be clinically important. In this study, hemodynamic progression occurred less often (13.8%) than structural progression, and hemodynamic progression presupposed some degree of structural progression.[26,27] Hemodynamic changes in all valvular diseases, in addition to structural alterations, are of clinical importance. The significant increase in left atrial volume index on follow-up echocardiography in the progressive MAC group was also a finding that supported the clinical significance of MAC progression

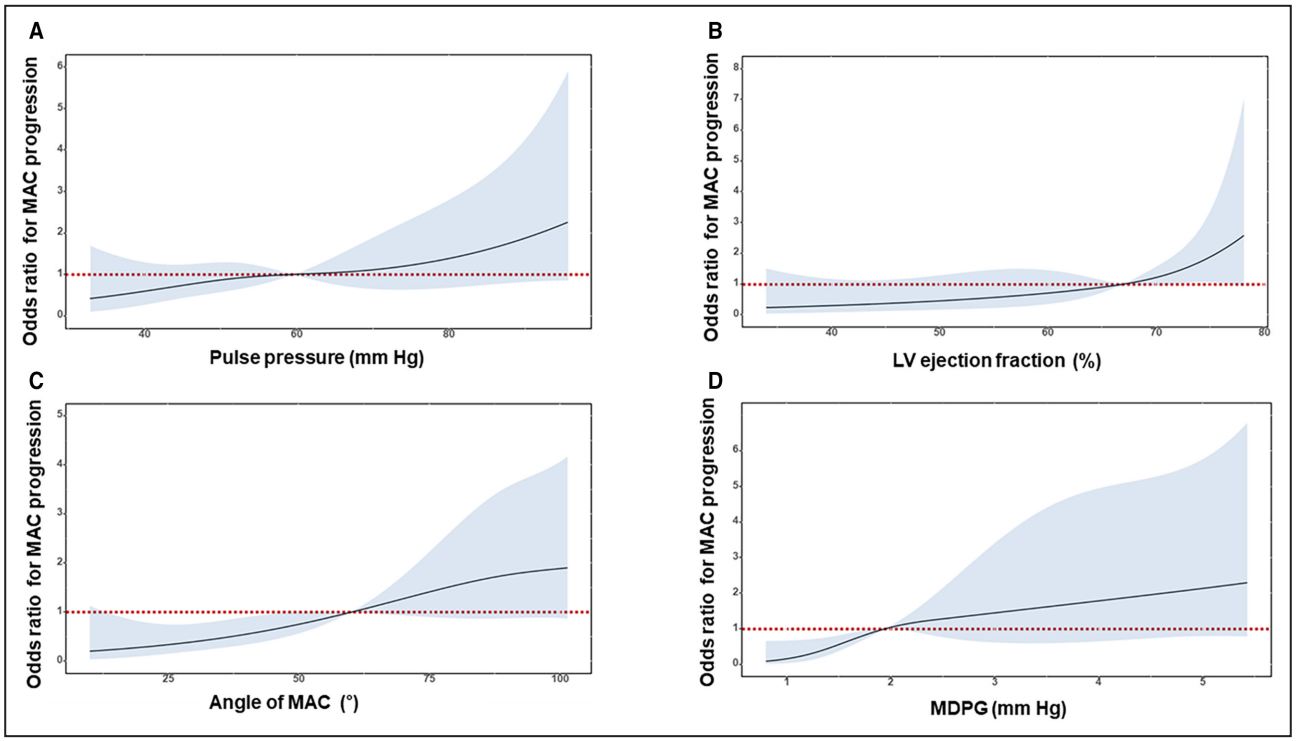

Figure 3. Restricted cubic spline curve to model showing relationship of (A) pulse pressure, (B) left ventricular ejection fraction, (C) angle of MAC, and (D) mean diastolic pressure gradient to MAC progression.
LV indicates left ventricular; MAC, mitral annular calcification; and MDPG, mean diastolic pressure gradient.

defined in this study. Second, in this study, hemodynamic factors such as PP widening and supernormal LV ejection fraction were found as independent factors related to MAC progression. PP is an index that reflects aortic stiffness and vascular aging and comorbidities.[28,29] Therefore, PP pressure widening induces a chronic and persistent increase in left ventricular afterload, a decrease in longitudinal myocardial function, and compensatory increase in radial or circumferential contraction.[7,30,31] Higher stress is related to endothelial injury resulting from mechanical stress, focal accumulation of oxidative stress, or a localized inflammatory process,[2,5] resulting in MAC progression during the follow-up period. Third, we reiterated the importance of baseline MAC structural and functional characteristics as substrates for further progression of the disease. In the receiver operating characteristic analysis, when the MAC angle was 75° or higher and the MDPG was 1.75 mm Hg or higher, the area under the curve values were 0.713 and 0.720, respectively. According to these cut-off values for MAC structure and function, closer imaging follow-up of MAC progression can be suggested for patients with MAC. Recently, aortic stenosis or prior aortic intervention was reported to be associated with the occurrence of significant degenerative MS,[31] and aortic regurgitation or hyperthyroidism also could theoretically be associated with abnormal cardiac status. However, these clinical factors did not demonstrate a significant difference between the 2 groups in this study.

In the present study, all-cause mortality in the progressive MAC group was significantly higher, creating a difference in the occurrence of the composite event between groups. We found that MAC is often accompanied by various comorbidities, and patients with progressive MAC are exposed to hemodynamic stress. The study subjects were relatively old and had various comorbidities, but MAC did not progress structurally or hemodynamically after ≈2 years in around two-thirds of the study population. Patients with progressive MAC had worse prognoses than those with stable MAC.

Study Limitations

Our study has several limitations. First, this study was conducted at a single tertiary center by comprehensively reviewing retrospective and prospective data; therefore, selection and referral bias were possible. As shown in Table S1, the characteristics of the entire MAC population and the study subjects were mostly similar, although there were differences in occurrence of hyperlipidemia, coronary artery disease, and previous stroke. Additionally, cardiovascular risk variables could be potential confounders of MAC progression as well as baseline MAC grades. Second, a lack of imaging

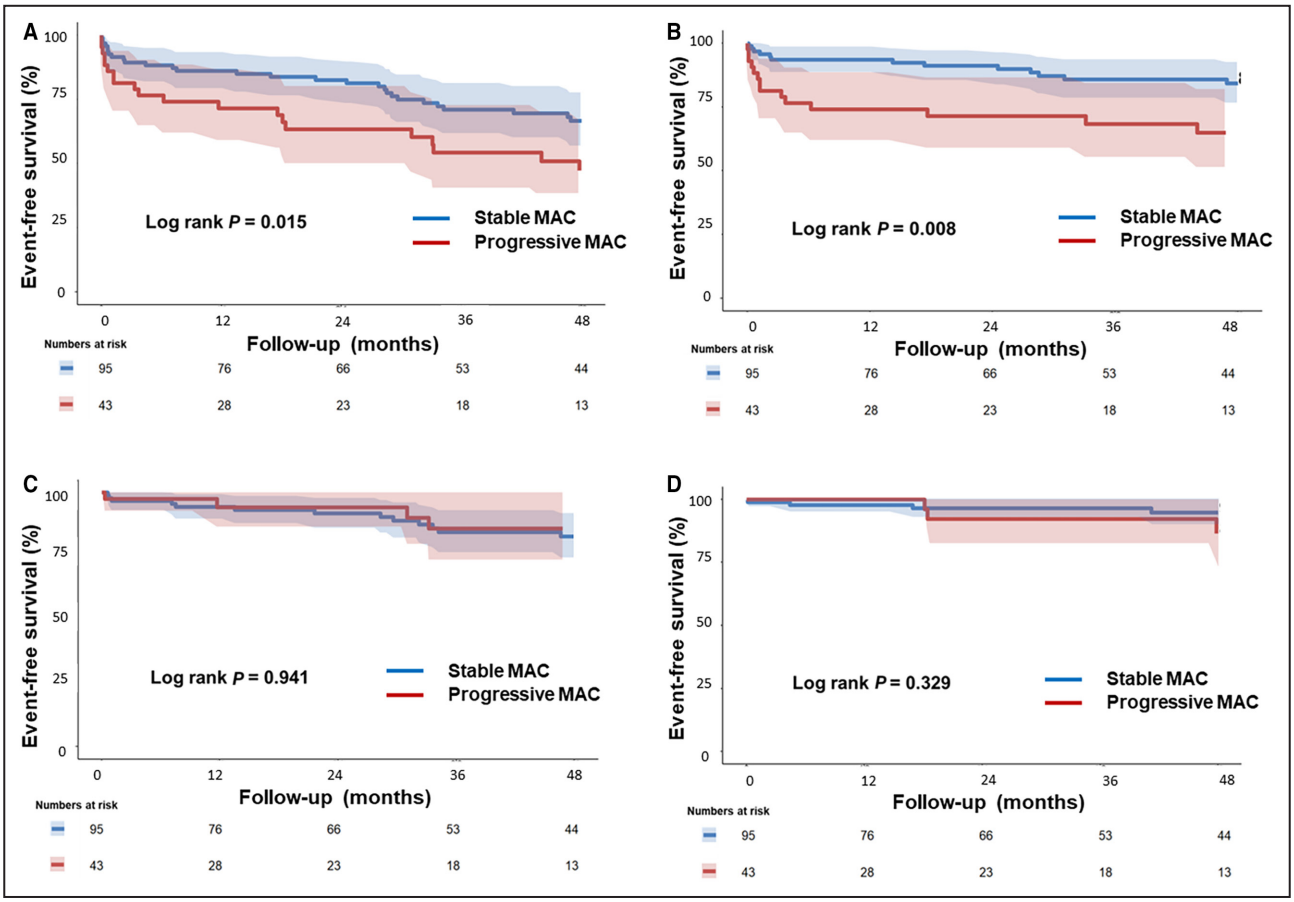

Figure 4. Kaplan–Meier survival curves showing poorer outcomes in patients with progressive MAC compared with those with stable MAC.
A, Composite events. **B**, All-cause death. **C**, Heart failure hospitalization. **D**, Ischemic stroke. MAC indicates mitral annular calcification.

modalities to assess MAC other than echocardiography may have limited the assessment of MAC severity. For example, computed tomography would be an objective imaging modality for assessing the extent of MAC.[32,33] Although an echocardiographic examination alone has limitations in evaluating MAC severity, this method is useful for routine follow-up imaging and can provide valuable hemodynamic data. Third, since the study subjects are all Asian, generalizability to other races is limited. However, because MAC is a degenerative disease that is increasing in the aging society, we believe that the Asian study population did not particularly change the results of this study. Moreover, additional meaning can be given to the fact that MAC progression was proven to have clinical significance in the Asian population. Fourth, 42% of studied patients had significant aortic stenosis. This requires further study in other populations. In addition, the potential link of end-stage renal disease to the MAC progression also needs further research in other populations, including a larger sample size of patients with end-stage renal disease.

Table 5. Factors Associated With Composite Clinical Outcomes

	Model 1		Model 2	
	OR (95% CI)	*P* value	OR (95% CI)	*P* value
Age, y	1.04 (1.00–1.07)	0.031	1.03 (1.00–1.07)	0.043
CKD or ESRD	2.05 (1.15–3.66)	0.016	1.88 (1.05–3.36)	0.035
Atrial fibrillation	1.67 (0.95–2.95)	0.077	1.76 (1.00–3.12)	0.052
Baseline MAC grade	3.21 (0.96–10.73)	0.059	3.26 (0.98–10.91)	0.055
MAC progression			1.81 (1.05–3.12)	0.033

CKD indicates chronic kidney disease; ESRD, end-stage renal disease; MAC, mitral annular calcification; and OR, odds ratio.

CONCLUSIONS

MAC progression is not a rare event during follow-up. Structural progression is more common than hemodynamic progression. MAC progression is associated with baseline MAC severity and hemodynamic loads resulting in mechanical stress. Patients with progressive MAC have poor clinical outcomes.

ARTICLE INFORMATION

Received April 16, 2023; accepted August 11, 2023.

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Sources of Funding

This research was supported by a grant from the Korean Society of Echocardiography and a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health and Welfare, Republic of Korea (grant number HI22C0154).

Disclosures

None.

Supplemental Material

Table S1
Figure S1

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