Keynote Lecture Series

Mitral annular calcification: implications on clinical outcomes and interventions

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Mitral annular calcification (MAC) is a chronic process that presents a complex clinical pathology. In the setting of a growing elderly population, the incidence of MAC has been increasing and it is often associated with other degenerative conditions most importantly atherosclerosis. While its clinical impact has previously been underappreciated, more recent evidence suggests that MAC has significant implications on cardiovascular and cerebrovascular morbidity as well as mortality. Commonly MAC is associated with mitral valve disease, which can require non-medical treatment in the form of conventional mitral valve surgery, transcatheter mitral valve replacement or a hybrid approach. The presence of MAC has important implications on both the interventional methods and subsequently on clinical outcomes. This review focuses on the diagnosis, clinical implications, and implications on mitral valve surgery and/or transcatheter interventions of MAC.

Keywords: Mitral annular calcification (MAC); mitral valve disease (MVD); clinical implications; interventional implications

Submitted Aug 21, 2025. Accepted for publication Nov 11, 2025. Published online Nov 29, 2025.
doi: 10.21037/acs-2025-mac-12
View this article at: https://dx.doi.org/10.21037/acs-2025-mac-12

Introduction

Mitral annular calcification (MAC) is a chronic and degenerative process involving progressive calcium accumulation around the fibrous mitral valve annulus (1). Often discovered incidentally on routine imaging, the prevalence of MAC ranges between 8–15%, with an increased frequency in the elderly population and females (2,3). It is crucial to properly diagnose MAC and classify its severity based on cardiac (4) and extra-cardiac (5) characteristics as it has ample implications on clinical outcomes and on available treatment options.

While MAC can directly impact the function of the mitral valve causing mitral valve disease (MVD), it has also been strongly associated with numerous cardiovascular risk factors as well as coronary artery disease (CAD), atrial fibrillation (AF), and heart failure (6-12). Moreover, patients presenting with MAC are at an increased risk for cardiovascular and cerebrovascular events (8,13). Subsequently, MAC has been associated with an increased rate of cardiovascular and all-cause mortality (2,13-17).

Based on the MAC severity and concomitant diseases, different therapeutic treatment options have developed (4,18). This includes conventional mitral valve surgery, transcatheter interventions, and a hybrid approach. MAC has important intraprocedural implications on both surgical and transcatheter interventions making them increasingly challenging and it also significantly impacts postprocedural outcomes and mortality (19). Thus, it is crucial to evaluate patients carefully so the ideal therapeutic treatment option can be chosen.

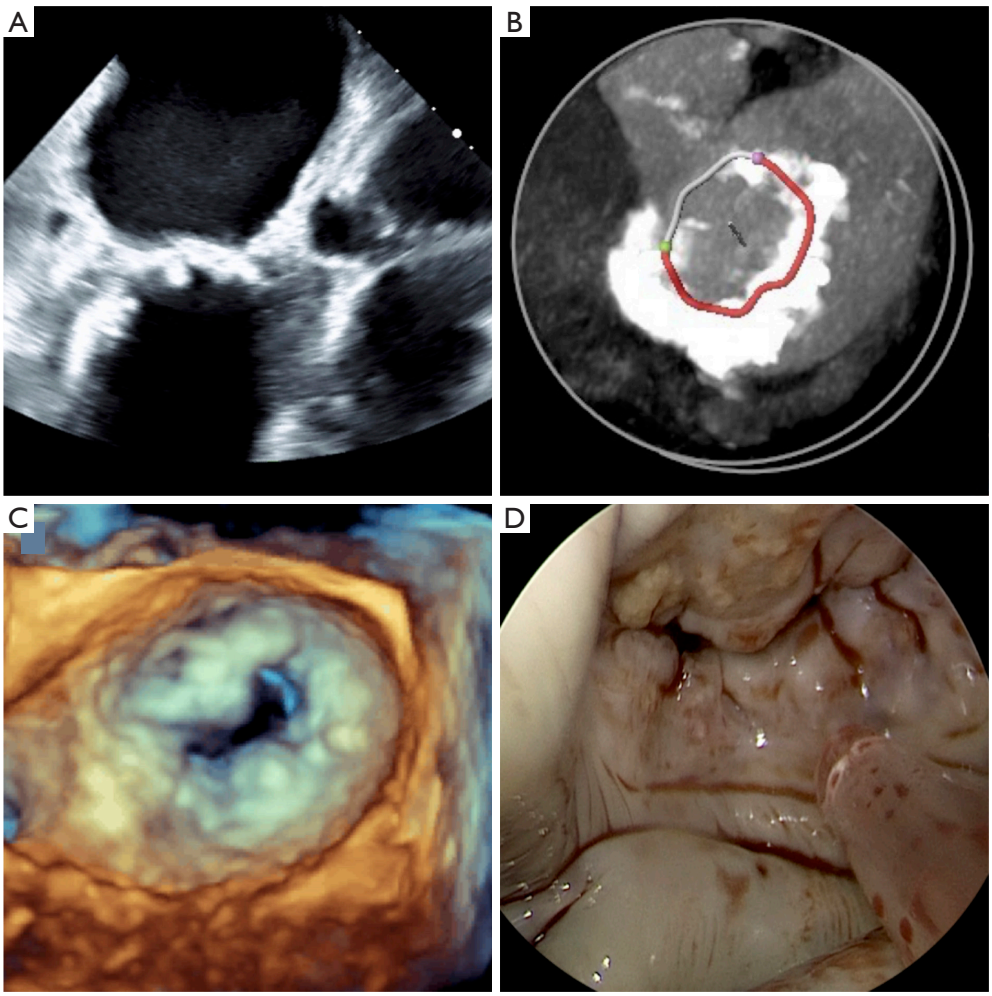

Figure 1 Extensive mitral annular calcifications as seen on: (A) 2D and (B) 3D transesophageal echocardiography; (C) multidetector computer tomography; and (D) surgical view. 2D, two-dimensional; 3D, three-dimensional.

With this review we aimed to: (I) highlight the current state of diagnostics and contemporary imaging of MAC; (II) summarize its clinical implications; (III) discuss its impact on the various treatment options; and (IV) elucidate its implications on other cardiovascular disease (CAD) entities and corresponding interventions.

Diagnostics and imaging

The diagnostic workup of MAC relies on multi-modality imaging (*Figure 1*). The calcifications can be incidentally seen in standard chest X-ray or during fluoroscopy, visible as a C or O-shaped ring located at the left atrioventricular junction. However, the role of these methods is greatly limited to initial screening and prompting further diagnostics, as they do not allow for the assessment of the extent and severity of MAC (1).

Conventional transthoracic echocardiography (TTE) constitutes a first-in-line method to detect the presence of MAC given its accessibility and ability to assess the morphology and function of the valve apparatus. Systematic assessment includes evaluating the mitral valve annulus, leaflets, and sub-valvular apparatus for the presence, location, and extent of calcification and thickening (20). Moreover, it allows for the evaluation of heart chambers, ventricular function, left ventricular outflow tract (LVOT), pulmonary hypertension and potential pathologies of other valves. All this information in conjunction with MAC evaluation is crucial to delineate the significance of the pathology and impact the decision-making process.

The usual initial location of MAC is the posterior portion of the mitral annulus but with the progression of the disease, the calcium deposits can involve the whole mitral annulus and other parts of the valvular apparatus, being present on the leaflets, tendinous chords and even extending to LVOT and papillary muscles (21). The calcifications are visible as bright, reflective, echodense structures with distal acoustic shadowing. Fibrotic changes may sometimes mimic this picture, leading to the overestimation of MAC, given the echocardiography inability to discern both pathologies. Also, the TTE imaging may be impaired by the unfavorable anatomy and lack of optimal acoustic windows, making the accurate evaluation of MAC impossible. Moreover, the acoustic shadowing caused by extensive calcifications may hinder the assessment of underlying mitral regurgitation (MR)/stenosis (MS) (22).

Transesophageal echocardiography (TEE) offers a more direct visualization of the mitral annulus and is able to further characterize the extent of MAC and helps with differentiating other pathologies (such as tumors, thrombus, infection). Specifically, the 3D imaging is useful to reveal the annular calcium distribution providing a "surgeon's perspective" en face view and helps with guiding percutaneous interventions (23).

As of today, several echocardiographic classifications of MAC have been used but none is considered universal (6,14,24). Both the American and European guidelines underscore the role of echocardiography in initial screening and quantifying the degree of valvular pathology (stenosis/regurgitation), at the same time highlighting a definitive role of computed tomography (CT) imaging in MAC characterization and intervention planning (25,26).

Due to its high spatial resolution, the multidetector computed tomography (MDCT) is the method of choice in evaluating MAC patients. Not only does it allow for an accurate assessment of calcium distribution and structure, but also, with the use of contrast medium, enables an in-depth assessment of the surrounding structures (20,27). Moreover, CT helps differentiate MAC from other cardiac lesions, such as thrombus, vegetation/abscess, tumor and can distinguish the caseous MAC, which appears as a non-contrast enhancing hypoattenuating region surrounded by dense calcification (20,28).

MDCT imaging is essential for performing measurements, both annular and LVOT, as well as predicting neo-LVOT and skirt neo-LVOT—parameters that correlate with and help estimate the risk of LVOT obstruction and hemodynamic compromise post TMVR (29).

Similarly, to the echo imaging no universal CT classification of MAC exists as of today. Several solutions have been proposed utilizing both qualitative and quantitative approach by calculating the Agatston score (30-32). Also, a hybrid approach combining qualitative and quantitative measurements derived from echocardiography and cardiac CT was suggested (22). Notably, the Heart Valve Collaboratory proposed a comprehensive approach that integrates echocardiography, MDCT, as well as anatomical and clinical data (4). The classification relies on the previously described CT-based MAC score and includes other features such as extra-annular calcification (i.e., ventricular calcification), as well as echocardiographic and clinical features to stage MAC severity (33). Uniquely, based on these characteristics, the authors created categories that indicate the adequacy of the patient to undergo the selected intervention. The interventions included are standard MV replacement, surgical transatrial ViMAC replacement with a balloon-expandable aortic transcatheter heart valve (THV), transseptal ViMAC replacement using balloon-expandable aortic and dedicated mitral THVs, and self-expanding ViMAC using dedicated mitral THVs. Despite requiring further validation, this algorithm can be an indispensable adjunct tool in decision-making process.

The role of other modalities such as CMR and nuclear imaging in MAC diagnostics is limited. CMR fails with precise evaluation of calcifications as compared to MDCT (34). However, due to its ability to quantify the chamber size, function and flow, CMR can assist with defining the severity of MAC-related MR (35). The current role of nuclear imaging in MAC assessment is not well-defined. PET tomography can not only detect and evaluate the degree of calcification but also reveal the associated inflammation (36). Although further studies are warranted, it is speculated that reducing inflammation could potentially slow the calcification process, providing new therapeutic opportunities in the future, highlighting the role of nuclear imaging in MAC diagnostic workup.

Clinical implications

MVD

While a well-established definition of MAC-related mitral valve dysfunction is lacking, there are two proposed descriptions: (I) a pathological elevation [above 3–5 mmHg (37)] of the mean transmitral gradient (TMG) in the presence of MAC; (II) any MS and/or above moderate MR in the

presence of MAC (3). According to these definitions, the prevalence of MVD, including MR, MS, and mixed valve disease, due to MAC is estimated to be 8–16% compared to ~6% in patients without MAC (2,38,39). The underlying pathophysiology of how MAC can lead to these different MVD entities has been described as a multifactorial process (40).

In a study by Kato *et al.* (2) analyzing 24,414 patients using TTE, MAC was found in 5,502 patients (23%) and of that cohort 9.5% presented with MR compared to 6.1% of patients without MAC (P<0.001). Another echocardiographic study by Okura *et al.* (39) including 13,483 patients showed a 14% prevalence of MAC with the presence of significant MR in 11.9% in MAC compared to 5% in non-MAC patients (P<0.0001). The mechanisms of how MAC causes regurgitation depend on both its severity as well as its level of extension (40). Calcification of the leaflets as well as the chordae can cause restricted leaflet motion and incomplete coaptation. Subvalvular calcification, particularly underneath the posterior leaflet, can push the leaflets up resulting in a reduction of the coaptation surface. As this puts continued tension on the chordae, it can cause chordal elongation and even rupture (40). Lastly, annular calcium may impair the physiological dynamics of the annulus causing a loss of contraction, especially along the anteroposterior diameter, and a loss of the ability to fold during the early systole along the intercommissural diameter (41).

The prevalence of MS is much lower than MR in patients presenting with MAC. While Kato *et al.* (2) reported 6.6% of MAC versus 0.5% of non-MAC patients with MS (P<0.001), Okura *et al.* (39) only reported 2.2% of MAC versus 0.6% of non-MAC patients with significant MS (P<0.0001). The main mechanisms of MAC causing stenosis include annular as well as subvalvular calcium encroaching upon the mitral orifice area and the LVOT, respectively, thus leading to a diastolic transmitral flow obstruction (40). While calcification of the annulus distorts its dynamics leading to regurgitation, it does not make it smaller causing stenotic physiology (41). Extension of the calcification to the leaflets, especially the anterior leaflet, can lead to restricted leaflet mobility further increasing the mean TMG (40).

AF and conduction disturbances

The association of MAC with AF has been well established through both the Framingham Heart Study (9) and the more recent Multi-Ethnic Study of Atherosclerosis (MESA) (10) as well as a recent large-scale meta-analysis by Li *et al.* (11). In the Framingham Heart Study, a multivariable analysis including 1,126 patients adjusting for age, sex, systolic blood pressure (SBP), hypertension treatment, diabetes, baseline valvular disease, baseline myocardial infarction, and baseline heart failure demonstrated the independent association of MAC with an increased risk of AF [hazard ratio (HR): 1.6; 95% confidence interval (CI): 1.1–2.2]. Similarly, the MESA study showed a significant independent association of MAC with an increased risk of AF in a multivariable model including 6,641 patients adjusting for age, sex, race/ethnicity, income, education, smoking status, SBP, diabetes, bodymass index (BMI), total cholesterol, high-density lipoprotein (HDL)-cholesterol, antihypertensive and lipid-lowering medications, aspirin, high-sensitivity C-reactive protein (hs-CRP), left ventricular hypertrophy (LVH), and left atrial (LA) enlargement (HR: 1.9; 95% CI: 1.5–2.5). Moreover, a follow-up analysis of the MESA study with a median follow-up period of 8.5 years demonstrated an association of any MAC progression (>0/year) with an increased risk of AF (HR: 1.50; 95% CI: 1.20–1.87) (42). A pooled analysis by Li *et al.* (11) including 6,232 MAC and 15,199 non-MAC patients also showed an increased risk of developing incident AF in patients with compared to those without MAC [random effects odds ratio (OR): 2.34; 95% CI: 1.91–2.85; P=0.000]. The mechanism of how MAC causes AF is most likely multifactorial. However, LA enlargement has been suggested as the main driver of the increased risk of AF. This was further strengthened through the attenuation of the association between MAC and AF when additionally adjusting for the size of the LA in the Framingham Heart Study (HR: 1.4; 95% CI: 0.9–2.0) (9). Additionally, MAC is an independent predictor of AF recurrence after successful catheter ablation (43), which can most likely be explained through the presence of increased LA dimensions in patients with MAC. Of note, including LA enlargement in the multivariable model in the MESA study did not affect the association of MAC and the risk of AF. A possible explanation for the differing results that was suggested by the authors was the wide diversity of the study population compared to the predominantly white population in the Framingham Heart Study. Other potential pathophysiological mechanisms that have been suggested are interruptions of the interatrial and/or intraatrial conduction system through MAC leading to AF (44).

The presence of MAC has also been associated with various conduction disturbances, particularly

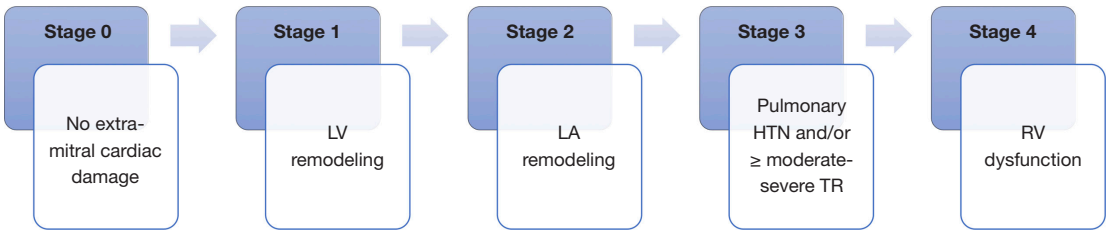

Figure 2 Classification system of cardiac damage beyond the mitral valve based on echocardiographic changes in MAC. Stage 0: MAC with MVD and no extramitral cardiac damage. Stage 1: MAC with MVD and LV remodeling (LV end-systolic indexed volume >31 mL/m^2 in male patients or >24 mL/m^2 in female patients, or LV end-diastolic indexed volume >74 mL/m^2 in male patients or >61 mL/m^2 in female patients). Stage 2: MAC with MVD and LA remodeling (left atrial volume index >34 mL/m^2, or an enlarged LA by visual estimate and/or the presence of atrial fibrillation). Stage 3: MAC with MVD and pulmonary HTN (RV) systolic pressure >50 mmHg) and/or ≥ moderate to severe TR. Stage 4: MAC with MVD and RV dysfunction (RV fractional area change <35%, RV free wall S' <9.5 cm/s, TAPSE <17 mm, or visual estimate of RV enlargement or RV systolic dysfunction (5). HTN, hypertension; LA, left atrial; LV, left ventricular; MAC, mitral annular calcification; MVD, mitral valve disease; RV, right ventricular; TR, tricuspid regurgitation.

atrioventricular (AV) and bundle branch blocks (BBBs) (12,45,46), and an increased incidence of symptomatic bradyarrhythmias (47). A recent substudy of the population-based, multicenter Danish Cardiovascular Screening (DANCAVAS) trial including 14,771 patients showed significantly higher MAC scores in participants with pacemakers due to an AV conduction defect compared to participants without a pacemaker (OR: 1.11; 95% CI: 1.01–1.23) (48). Of note, this difference was not found when comparing patients with a pacemaker for other reasons to patients without a pacemaker. In an electrocardiographic analysis, a significant association of MAC with a prolonged QRS-interval (OR: 1.45; 95% CI: 1.04–2.04) but not a prolonged PQ-interval was demonstrated. This points to the hypothesis that MAC leads to AV conduction disturbances through calcium extension into the Bundle of His and its branches rather than the AV node. In addition to the direct extension of calcium, diffuse degenerative conduction disease has been associated with MAC as an increased prevalence of conduction disturbances has been described even in patients with MAC distant from the primary conduction system (44,49).

Heart failure

An increased incidence of heart failure (12,13) and heart failure rehospitalization (5,50) have been reported in patients presenting with MAC. The mechanisms for these associations are most likely multifactorial with a strong relationship of numerous cardiovascular risk factors with MAC as well as MAC leading to cardiac remodeling. Common cardiovascular risk factors in MAC patients include age, body mass index, diabetes, hypertension, hyperlipidemia, serum cholesterol, and smoking (46,51). Cardiac remodeling involving LVH, LA and left ventricular (LV) enlargement, and decreased LV compliance have been associated with MAC (5,46,50,52,53). A recent study by Al-Abcha *et al.* (5) demonstrated a new classification system of cardiac remodeling through the staging of extramitral cardiac damage in patients with MAC and concomitant MVD. The authors described 5 stages which all include MAC with MVD plus: Stage 0: no extramitral damage; Stage 1: LV remodeling; Stage 2: LA remodeling; Stage 3: pulmonary hypertension and/or tricuspid regurgitation; Stage 4: right ventricular dysfunction (*Figure 2*). At the 4-year follow-up, the incidence of heart failure rehospitalization in stages 2, 3, and 4 was significantly higher compared to stages 0–1 (P<0.001) and stages 3 and 4 were independently associated with heart failure hospitalization in a multivariable analysis (HR: 3.84; 95% CI: 1.37–10.77; P=0.010 and HR: 4.20; 95% CI: 1.52–11.59; P=0.006, respectively). In a study by Kato *et al.* (50) including 353 heart failure patients, 40 participants (11.3%) had MAC and the incidence of rehospitalization due to heart failure with preserved ejection fraction (HFpEF) was significantly higher in the MAC versus the non-MAC group (P<0.001), while the incidences of heart failure with mildly reduced and reduced ejection fraction (HFmrEF and HFrEF, respectively) were comparable between the two groups (P=0.101 and P=0.291, respectively). Moreover, MAC was independently associated with HFpEF rehospitalization in a multivariable model (HR: 3.379; 95% CI: 1.651–6.597;

P=0.001). In the echocardiographic analysis, MAC patients presented with a significantly increased E/e' (septum and lateral, P<0.05) and a significantly higher LV ejection fraction (LVEF) (52.4% *vs.* 40.2%, P=0.002) compared to participants without MAC suggesting a potential association of MAC with left ventricular diastolic dysfunction and thus HFpEF.

Cardiovascular and cerebrovascular disease

Both atherosclerosis and CAD have a strong association with MAC (6-8,54,55). This can be partially explained through the frequent coexistence of common cardiovascular risk factors and MAC (46,51). However, it has also been suggested that MAC and atherosclerosis are merely different forms of the same disease (56). In a histopathological study performed by Roberts (57), the examination of 300 patients with MAC revealed not only a strong association of MAC with CAD but also similar pathological features such as foam cells in the early stages of mitral annular calcium formation. Furthermore, it has been shown that MAC is an independent predictor of obstructive CAD (58) and is associated with an increased risk of incident CAD and myocardial infarction (MI) (13,14,24). In an angiographic study by Atar *et al.* (58), a significantly higher prevalence of obstructive CAD (88% *vs.* 68%; P=0.0004), left main CAD (14% *vs.* 4%; P=0.009), and triple vessel CAD (54% *vs.* 33%; P=0.002) in MAC versus non-MAC patients was reported. Correspondingly, MAC had a positive predictive value of 92% for finding obstructive CAD. In a subanalysis of the Framingham Heart Study, MAC was independently associated with an increased risk of incident CVD (HR: 1.5; 95% CI: 1.1–2.0) in an adjusted multivariable analysis (14). Kohsaka *et al.* (24) studied 1,955 patients, 519 (26.6%) of which had MAC, in the multiethnic Northern Manhattan Study and the presence of MAC was independently associated with an increased risk of MI (adjusted HR: 1.75; 95% CI: 1.13–2.69; P=0.011). Additional analyses demonstrated a strong correlation of this finding with MAC severity, with a mitral annular calcium thickness more than 4 mm being an independent predictor of MI (adjusted HR: 1.89; 95% CI: 1.13–3.17; P=0.008).

The presence of MAC has also been associated with an increased risk of stroke ranging from 4.8% to 24.1% (8,13,59,60). A recent subanalysis of the MESA study demonstrated MAC as a predictor of stroke. In a multivariable analysis adjusting for age, sex, race/ethnicity, SBP, diabetes, smoking, fibrinogen, IL-6, hs-CRP, and coronary artery calcium score, MAC was independently associated with an increased risk for all strokes (HR: 1.68; 95% CI: 1.22–2.30; P=0.0013) (59). One of the major mechanisms that has been suggested for how MAC causes stroke, is its strong association with AF mediated through left atrial enlargement. Interestingly, Onuegbu *et al.* (59) reported that even after adding AF/flutter and LA size to the multivariable model, MAC remained an independent predictor of all strokes (HR: 1.93; 95% CI: 1.22–3.05; P<0.0051) and ischemic stroke (HR: 2.03; 95% CI: 1.24–3.31; P<0.0046). Other possible mechanisms include the embolization of caseous and necrotic debris (60) as well as the strong association of MAC with systemic atherosclerosis (7,8,54,55).

Mortality

MAC has been shown to be an independent predictor of both cardiovascular and all-cause mortality (2,13-17). The progression of MAC defined as the worsening of the hemodynamic profile, assessed by the mean TMG, or the structural profile, assessed by the MAC angle, by more than 1 grade, was independently associated with increased mortality compared to stable MAC in a study by Lee *et al.* (61) analyzing 560 patients over a median follow-up period of 39.2 months. When MVD is present concomitantly with MAC, the rate of mortality increases even further (2,17). Kato *et al.* (2) showed both the independent association of MAC with increased mortality (adjusted HR: 1.40; 95% CI: 1.31–1.49; P<0.001) as well as the even higher mortality with MVD and MAC (adjusted HR: 1.79; 95% CI: 1.58–2.01; P<0.001) in a large-scale multivariable model adjusting for age, diabetes, renal dysfunction, cancer, chest irradiation, EF below 50%, aortic stenosis (AS), tricuspid regurgitation, and pulmonary hypertension. In the recent study by Al-Abcha *et al.* (5) describing the staging of extramitral cardiac damage (see above) in patients with MAC-related mitral valve dysfunction, death occurred in 401 out of 953 patients (42.1%) with MAC and significant MVD at a median follow-up of 3.8 years. Mortality grew significantly with increasing stages of extramitral cardiac damage and stages 3 and 4 were independent predictors of mortality in a multivariable model.

Mitral valve interventions

The incidence of moderate/severe MAC is often associated

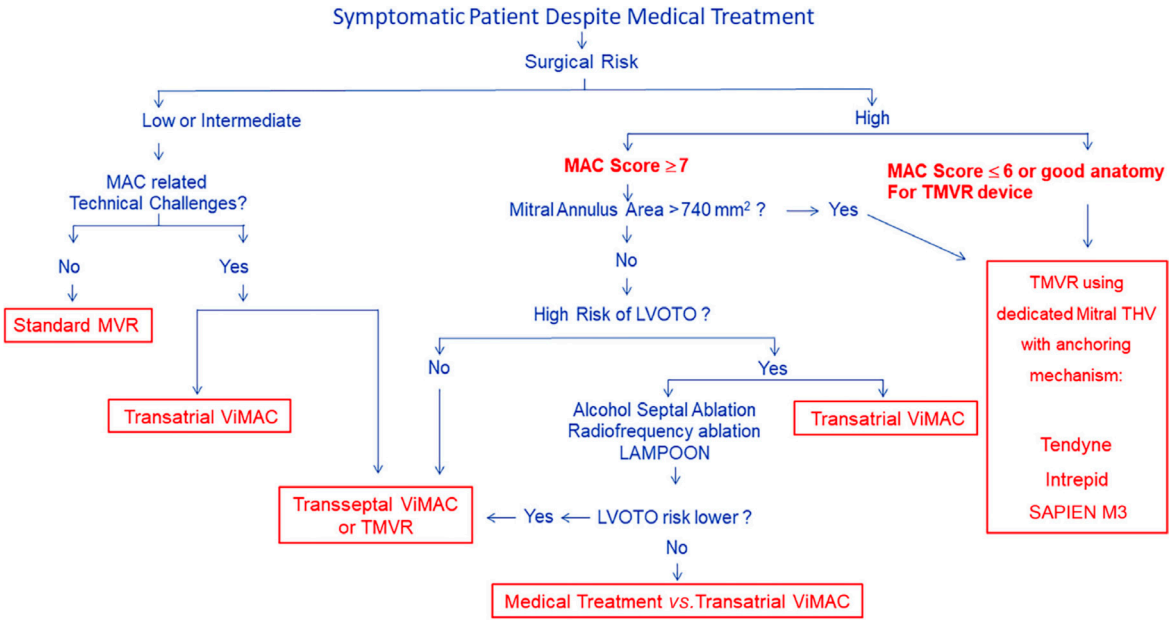

Figure 3 Proposed treatment algorithm for patients with MAC who remain symptomatic despite medical therapy. Reprinted with permission from Guerrero *et al.* (4). LVOTO, left ventricular outflow tract obstruction; MAC, mitral annular calcification; MVR, mitral valve replacement; THV, transcatheter heart valve; TMVR, transcatheter mitral valve replacement; ViMAC, valve-in-mitral annular calcification.

with elderly age and the presence of multiple comorbidities, implying a high periprocedural risk of cardiovascular and all-cause mortality (62,63). Coupled with this is the direct technical challenge of the intervention, both for surgical and transcatheter approaches, often requiring extensive debridement and reconstruction of atrioventricular groove or impairing proper stent expansion (64). Several different techniques have been utilized to treat MAC patients showing mixed results. Also, despite successful intervention, the mean left atrial pressure may remain elevated in the setting of poor left atrial and LV compliance, as is common in an elderly HFpEF population (65). Thus, the cohort of MAC patients who could potentially benefit from valvular intervention is limited and requires careful consideration employing a tailor-made, integrated approach, by the multidisciplinary heart valve team (26). Attempts have been made to establish an algorithm guiding MAC interventions. A Heart Valve Collaboratory Group created an integrated pathway incorporating CT MAC score, as well as echocardiographic and clinical features to stage MAC severity (4). This document serves as a clinical guide, with a specific focus on particular high-risk features including: obesity, re-operative status, severe diastolic dysfunction, severe RV dysfunction, severe lung disease, and severe renal disease. Pulmonary hypertension, even when severe, confers risk but has not been a significant contraindication unless the patient has concomitant severe lung disease, as pulmonary pressures generally improve considerably post-procedure. Based on this, they assigned suitability categories: green (adequate for proposed intervention, surgery or transcatheter), yellow (high risk for proposed intervention), and red (extremely high risk or not suitable for proposed intervention). The goal is to achieve the 30-day mortality of ≤10% in patients with acceptable anatomy. The interventions included were conventional cardiac surgery with standard MV replacement, surgical transatrial ViMAC replacement with a balloon-expandable aortic THV, transseptal ViMAC replacement using balloon-expandable aortic and dedicated mitral THVs, and self-expanding ViMAC using dedicated mitral THVs (*Figure 3*).

Surgery

Surgery remains the method of choice for most of the patients suffering from severe mitral valve dysfunction with coexisting MAC. Nevertheless, the reported retrospective results link MAC with significant periprocedural mortality, ranging from 6–14%, greatly surpassing the mortality

risk observed in the non-MAC cohort (21,66,67). The technical challenge associated with MAC impacts the increased incidence of complications such as unintended injury to the left circumflex coronary artery, rupture of the atrioventricular groove, conduction disturbances, paravalvular regurgitation, and patient-prosthesis mismatch (68,69). Interestingly, despite high periprocedural mortality, a single study reporting 5-year results of propensity-matched patients undergoing surgical intervention compared with those on conservative therapy showed lower mortality in the invasively treated cohort suggesting a benefit of MV intervention (49% *vs.* 68%; P=0.048) (70). Also, a study by Kato *et al.* compared the early intervention strategy (either surgical or transcatheter intervention) with optimal medical therapy and showed a survival benefit in people treated invasively up to 4 years of follow-up (80% *vs.* 72% at 1 year and 55% *vs.* 35% at 4-year, P<0.01) (71). Moreover, a clear link between the number of procedures performed annually and achieved results has been established with low volume centers (<50 cases per year) being reported with increased perioperative mortality (72).

The two main strategies of surgical intervention in MAC (including both repair and replacement interventions) are "resect" or "respect" suggesting a different handling of the present calcium (18,64). The first approach indicates the removal of a calcium bar by dissection followed by a repair or replacement procedure. Different extensions to this procedure have been proposed employing advanced reconstruction techniques. Carpentier *et al.* described a sliding atrioventriculoplasty technique involving an *en bloc* decalcification and annular reconstruction with a dissected atrial flap and final valve repair. The reported results of 68 patients showed low in-hospital mortality of 2.9% and excellent long-term outcomes with 7-year survival of 93% and freedom from reoperation in 87% of individuals (21). Another technique reported by David *et al.* incorporates the use of a pericardial patch and trigone-to-trigone reconstruction of the posterior annulus after an *en bloc* decalcification followed by valve repair or replacement. The reported results of 54 patients showed a relatively low in-hospital mortality (9.3%) with high survival (65%) and freedom from reoperation (89%) at 8 years (67). Similarly, in newer study that employed both techniques used in 55 patients only 1 death was directly related to the annular decalcification that caused the postoperative compression of the left circumflex coronary artery that resulted in fatal ventricular failure (73). Importantly, the durability of valve repair (freedom from recurrent MR) was comparable with that observed in patients without MAC (P=0.18) up to 8 years. Also, the recently published results of 2 single-center studies of totally endoscopic robotic mitral valve surgery showed low 30-day mortality (1.4% and 3.1%) and high 3-year survival—only reported for one study with two different groups based on the use of pericardial patch ventriculoplasty (97.4% in group without and 93.7% with patch) (64,74). Of note, direct comparison of the reported results between the studies is impossible due to the lack of universal MAC definition and different degree of calcium present. Despite the historically good results of aggressive full decalcification, the current practice favors more targeted MAC resection, limiting debridement to the annular plane, sparing the ventricle (75).

The "respect" strategy favors the preservation of MAC with working around the calcium bar to place the sutures. The potential downfalls of this approach are the increased risk of injury of the circumflex artery and disruption of the AVG. Additionally, tying the sutures around the calcium can cause fracture of the calcium bar resulting in embolism or drainage of a liquefied core. Also, leaving a high load of calcium often precludes implantation of a larger valve that can lead to patient-prosthesis mismatch. Ultrasonic aspiration with dedicated systems (Cavitron, Sonopet) offers a valuable tool to precisely aspirate or soften calcium only in areas where sutures will be placed (76,77). This can lead to an increase in technical success while decreasing the risk of AVG disruption, coronary injury, and stroke (76,77). Alternative approaches such as modified anterior leaflet flip technique have been proposed that decrease the risk of serious surgery-associated complications, but the potentially higher rates of PVL and smaller valves implanted remain (78).

Hybrid

A surgical implantation of transcatheter ballon-expandable valve, so-called surgical ViMAC (transcatheter valve in mitral annular calcification) offers an alternative for patients not suitable for classical surgical intervention. ViMAC includes the insertion of a balloon-expandable THV via left atriotomy and its deployment under direct vision (79). The expansion of BE prosthesis allows for the avoidance of annular decalcification. The use of additional pledgeted atrial sutures anchors the valve and prevents migration. Usually, the prosthesis is reinforced with Teflon felt strips sewn to the base of THV frame to mitigate PVL. Alternatively, it can be sewn directly onto the mitral

annulus before implantation (80). Importantly, respective THV is characterized by a larger effective orifice area than its surgical counterpart, limiting the risk of PPM despite the high calcium burden. Also, the resection of the anterior mitral valve leaflet that can be performed surgically via a direct atrial approach and coupled with surgical myectomy significantly reduces the risk of LVOT obstruction (80). The study by Brener *et al.*, including the largest to date cohort of 126 patients showed a high technical success of this method (94.4% of cases) with a low incidence of above mild PVL (4.2%) and LVOT obstruction (6.3%) and acceptable valve hemodynamics (80). The reported in-hospital (11.1%) and 1-year mortality (35.4%) was high but was comparable with 1-year mortality reported in MITRAL trial (34.5% in overall ViMAC cohort, and 38.5% in the transatrial subgroup) (81). Interestingly, as mentioned by the authors, the frequency of observed adverse events (i.e., stroke, major bleeding, vascular injury) and valve replacement was low suggesting that mortality in this cohort may be driven by patients' underlying comorbidities as opposed to the procedure itself. The feasibility of this procedure and high technical success achieved was also shown in other small-series studies (82-85). However, the relative paucity of data warrants further studies, specifically ones concerning longer term follow-up and comparing the proposed intervention to optimal pharmacological treatment. A prospective study evaluating the results of surgical ViMAC (SITRAL study—Surgical Implantation of TRAnscatheter vaLve in Native Mitral Annular Calcification; NCT02830204) is underway.

Transcatheter

Transcatheter interventions offer an alternative for patients disqualified from any type of MAC surgery. This heterogenous group of interventions includes both transapical and transseptal approach, as well as the use of different platforms, such as off-label use of balloon-expandable TAVR systems (mainly Sapien valves) or implantation of dedicated mitral TMVR prostheses.

Comprehensive imaging and real-time guidance are essential to facilitate reliable valve implantation and to limit the risk of adverse events, especially the TMVR-induced LVOT obstruction. The TMVR-LVOTO is frequent (10.0–39.7% of cases) and serious complication that is independently associated with 30-day and 1-year mortality (86,87). Use of pre-procedural planning tools based on cardiac CT imaging allows for the simulation of virtual THV placement and estimation of neo-LVOT (29,88). Thus, the probability of TMVR-induced LVOTO can be stratified in advance and the high-risk features identified (end-systolic neo-LVOT area <170–200 mm^2, neo-LVOT area index <127 mm^2/m^2) allowing for the adequate implantation technique to be employed (89). Several pre-emptive strategies were reported to decrease the incidence of LVOTO, including alcohol septal ablation or radiofrequency septal ablation performed 3 to 4 weeks prior to intervention, surgical anterior leaflet resection during transatrial ViMAC, or percutaneous laceration of the anterior mitral leaflet during transseptal ViMAC (LAMPOON) (90-92). Similarly, the prosthesis embolization that was often reported (up to 6.9% of cases) in the initial trials with ViMAC has been nullified in newer prospective trials such as MITRAL due to thorough CT imaging evaluation and adequate valve oversizing (81,93). Overall, with the ViMAC patients being of prohibitive risk and the associated technical challenge, the reported 30-day mortality was high, reaching 21.8–34.5% (82,87). The recently published long-term results of prospective MITRAL trial showed an all-cause mortality of 67.9% in ViMAC patients at 5-year follow-up (94). Despite the relatively low long-term survival reported, to date there has not been a prospective randomized study comparing outcomes with MV intervention vs medical treatment alone. The MITRAL II pivotal study (NCT04408430) comparing patients treated with transseptal ViMAC to those managed conservatively is ongoing and may provide further valuable insights. Interestingly, hemolytic anemia, a specific complication of ViMAC procedures, was reported in 10% of patients at 30 days and in 17.2% at 1 year. The underlying mechanism of this phenomenon is not clearly understood, with high-flow hypothesis linked to the presence of PVL being the most likely cause. Hemolysis may resolve with supportive management while the stent frame endothelializes, but hemodynamic, renal, or hematological complications may necessitate repeated intervention with balloon overexpansion, implantation of a second THV or PVL closure device, or surgery (18).

Dedicated TMVR systems

Although infrequent, some of the dedicated TMVR platforms (i.e., Tendyne, Intrepid, Cephea, AltaValve) were seen to be used in MAC territory (4,18,95). Their unique design featuring larger skirt with lower radial force than TAVR platforms, as well as the ability to conform to the annulus and calcium debris (without displacing it) may

positively impact the procedural outcomes and LVOT hemodynamics. The initial reports of both Tendyne compassionate use and Tendyne MAC feasibility study (NCT03539458) including 20 patients in total, showed promising results with 100% procedural success, no intraprocedural mortality and one death occurring at 30 days (96,97). Moreover, a TENDER European registry including 20 patients with severe MAC, reported an all-cause mortality at 30-day and 1-year of 10.0% and 21.1% respectively (98). Importantly, as mentioned by the authors, the periprocedural and 1-year outcomes regarding disabling stroke, valve migration, MV reintervention or surgery, and paravalvular leak (PVL) more than mild did not differ from patients without severe MAC. Most recently, the results of the SUMMIT-MAC study (NCT03433274) were released, which represents the first prospective clinical trial assessing the use of the Tendyne system in patients with significant MVD due to severe MAC and at prohibitive risk for surgery (99). A total of 103 patients were included, nearly all patients presenting with MR, and technical success was achieved in 94.2% with a 6.8% 30-day mortality rate. The primary endpoint of the study was freedom from all-cause mortality and heart failure hospitalization at 12-month and this was met in 60.4% of patients. More studies are underway including the Intrepid Apollo study, now including MAC patients in both their US (NCT03242642) and European (NCT05496998) arm, the Abbott Cephea Mitral Valve Disease Registry (NCT07069673), and the AltaValve Pivotal Trial (NCT06465745). The following TMVR devices have clinical experience in specific MAC registries or in small case series with clinical success: however, all of these devices remain in clinical trials and will require further clinical study before commercial approval. However, the upcoming results should shed more light on the use of dedicated TMVR systems in severe MAC population and help with establishing a treatment algorithm on the use of transcatheter systems in MAC.

Other implications of MAC

AS and transcatheter aortic valve replacement (TAVR)

With the frequent coexistence of MAC and AS, recent studies have aimed to better understand the possible implications of MAC for patients undergoing TAVR (53,56). The prevalence of MAC in TAVR patients ranges from 33.3% to 57.8% (100-103). Severe circumferential MAC has been associated with moderate PVLs, right BBB, and low cardiac output whereas subannular MAC at the anterolateral trigonum has been shown to be a risk factor for LVOT obstruction with balloon-expandable THVs (102). Also, a linear increase of the mean TMG post TAVR has been associated with increasing MAC severity (103). Therefore, it is recommended to use oversized self-expanding THVs to prevent significant PVL and any form of BBB. Severe MAC has also been associated with an increased risk of mortality following TAVR (100,102). In a study by Abramowitz *et al.* (100) including 761 patients, severe MAC was an independent predictor of both cardiovascular mortality (HR: 2.35; 95% CI: 1.19–4.66; P=0.01) and all-cause mortality (HR: 1.95; 95% CI: 1.24–3.07; P=0.004) following TAVR in a multivariable analysis. Moreover, severe MAC revealed to be an independent predictor of new permanent pacemaker implantation (OR: 2.83; 95% CI: 1.08–7.47; P=0.03) after TAVR. With these implication of MAC for patients undergoing TAVR, MAC should be considered when assessing risk stratification in the preprocedural evaluation prior to TAVR.

Hypertrophic (obstructive) cardiomyopathy (H(O)CM) and septal myectomy

The presence of MAC has been strongly associated with HCM, with a prevalence ranging from 10.8% to 46% (104-107), increasing significantly in the obstructive compared to the nonobstructive type (106). Recent studies have shown potential implications of MAC for patients with HCM, particularly those undergoing septal myectomy (104,106,107). An association of MAC with increased LVOT gradients as well as LVOT obstruction (LVOTO) has been demonstrated (105,107). A potential mechanism leading to LVOTO may be the increased risk of systolic anterior motion (SAM) of the mitral valve in patients with MAC (104-106). The prevalence of SAM in patients with MAC concomitant to HCM ranges from 84.2% to 87.5% (105,107), and is thought to be related to a combination of factors including the anterior displacement of the mitral valve towards the septum due to calcium accumulation and other risk factors for SAM found frequently in MAC patients particularly a long anterior mitral leaflet (108). MAC has also been associated with worse outcomes following septal myectomy in patients with HCOM (104,106,107). Wu *et al.* (107) performed a study with 1,035 HOCM patients undergoing myectomy and of that cohort 112 participants (10.8%) presented with MAC. All-cause mortality (3.57%

vs. 1.08%; P=0.031), major adverse cardiovascular and cerebrovascular events (MACCE) (23.32% *vs.* 13.65%; P=0.014), recurrent more than moderated MR (8.04% *vs.* 2.49%; P=0.001) and New York Heart Association class III-IV (11.61% *vs.* 5.53%; P=0.012) were more frequent in MAC versus non-MAC patients following myectomy. Moreover, MAC was an independent predictor of recurrent more than moderate MR postoperatively (HR: 2.47; 95% CI: 1.08–5.67; P=0.0329) and moderate to severe MAC was an independent predictor of long-term MACCE (HR: 2.03; 95% CI: 1.09–3.75; P=0.0244). Therefore, it is important to consider MAC in the preoperative evaluation and risk stratification in HOCM patients planned to undergo septal myectomy.

Conclusions

MAC constitutes a chronic process that is not bound to the mitral valve only but interferes with the whole heart function and physiology. The magnitude of this phenomenon is being increasingly recognized with links between MAC and other heart pathologies i.e., HFpEF, CAD, stroke and arrhythmias being established. Moreover, the presence of severe calcifications implies a significant technical challenge to the potential mitral valve intervention greatly impacting the periprocedural and long-term prognosis. New techniques and technologies aided with comprehensive scores and algorithms were proposed to limit the inherent risk and deliver a tailored therapy. However, more studies are needed to properly describe and understand their role and impact made. As of now, the timely diagnosis based on multi-modality imaging paired with a holistic approach to MAC as a dispersed rather than focal phenomenon is essential to detect, evaluate and limit the extent of damage caused.

Acknowledgments

None.

Footnote

Funding: None.

Conflicts of Interest: The authors have no conflicts of interest to declare.

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Cite this article as: Reisinger M, Kachel M, Kanade R, Roland J, Aly M, Gosden J, Wang C, Kurlansky P, Brener M, George I. Mitral annular calcification: implications on clinical outcomes and interventions. Ann Cardiothorac Surg 2025;14(6):423-437. doi: 10.21037/acs-2025-mac-12

