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THE PRESENT AND FUTURE

JACC STATE-OF-THE-ART REVIEW

Management of Patients With Severe Mitral Annular Calcification

JACC State-of-the-Art Review

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ABSTRACT

Mitral annular calcification (MAC) is a common and challenging pathologic condition, especially in the context of an aging society. Surgical mitral valve intervention in patients with MAC is difficult, with varying approaches to the calcified annular anatomy, and the advent of transcatheter valve interventions has provided additional treatment options. Advanced imaging provides the foundation for heart team discussions and management decisions concerning individual patients. This review focuses on the prognosis of, preoperative planning for, and management strategies for patients with MAC. (J Am Coll Cardiol 2022;80:722–738) © 2022 by the American College of Cardiology Foundation.

Mitral annular calcification (MAC) is a chronic disease process associated with atherosclerotic risk factors (age, female gender, diabetes, smoking, hypertension, ethnicity, obesity, interlukin-6, and renal failure) that occurs in 10% of those aged >60 years (33% of those aged >90 years) and results in deposition of calcium in and around the fibrous base of the mitral valve.[1]

Histopathological studies demonstrate that the cellular degradation products from apoptotic or necrotic interstitial cells accumulate as a result of mechanical stress, inflammation, and ischemia, providing a stimulus for calcification and lipid deposition.[2] The highest mechanical stresses on the mitral annulus are in the anteroposterior dimension, which may explain why the posterior annulus is most frequently involved.[3] Once MAC is established, the predominant factors that affect the rate of progression are calcium burden, ethnicity, smoking, and dialysis-dependent renal failure.[1]

The main pathophysiological consequences of MAC are mitral valve dysfunction (stenosis and/or regurgitation), atrial fibrillation (AF), stroke, infective endocarditis, and death. In the context of an aging population, clinicians are increasingly confronted by patients with mitral valve dysfunction and accompanying MAC who may benefit from surgical or transcatheter intervention. The aims of the current paper are to review the: 1) clinical features and prognosis of patients with MAC; 2) systems for the

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HIGHLIGHTS

- Disparate systems for grading severity and an array of technical approaches contribute to the variable outcomes of surgical mitral valve repair and replacement in patients with MAC.
- Transcatheter approaches are associated with high 30-day and 1-year mortality rates, the reasons for which are not clear.
- Preprocedural imaging can predict anatomical and clinical outcomes for patients with MAC and should be central to management decisions.

grading of its severity; and 3) factors governing clinical decision making and the outcomes of surgical and transcatheter interventions in this setting.

CLINICAL COURSE AND PROGNOSIS

VALVULAR HEART DISEASE. Clinicians need to distinguish between MAC as an incidental finding and MAC with accompanying mitral valve disease. Mitral valve dysfunction (stenosis or regurgitation) is the most common complication of MAC, although the classification of primary and secondary pathophysiological mechanisms is frequently difficult owing to interactions between annular and leaflet calcification. Moderate or severe mitral regurgitation (MR) may occur in up to 30% of patients with MAC, but mitral stenosis (MS) is much less frequent.[4] In 1 study of 24,380 echocardiograms, MAC was observed in 11.7% of patients with MR and 4.3% of those without (OR: 2.0; 95% CI: 1.6%-2.6%; $P < 0.0001$), indicating a clear association with MR.[5] Interestingly, tricuspid regurgitation may have an even stronger association with MAC (OR: 3.8; 95% CI: 2.9%-4.8%; $P < 0.0001$), likely related to pulmonary hypertension (secondary to mitral pathologic changes), tricuspid annular dilation secondary to AF, or local disruption of the tricuspid annulus at the base of the septal leaflet.[5] Among those undergoing surgery, the primary valve pathologic changes are equally distributed between MR, MS, and mixed mitral valve disease.[6] MR secondary to posterior leaflet restriction is most common, whereas MS usually involves the anterior leaflet (particularly A2).[7]

ATRIAL FIBRILLATION, STROKE, AND INFECTIVE ENDOCARDITIS. The Framingham study demonstrated a strong association between MAC and stroke mediated by an increased prevalence of AF (HR: 1.6; 95% CI: 1.1-2.2; $P < 0.001$)[8] resulting from left atrial enlargement secondary to valve or left ventricular (LV) dysfunction, extension of calcification into the atrial myocardium, or shared risk factors.[9] The relationship between MAC and stroke persists after adjustment for age, sex, blood pressure, diabetes, AF, smoking, and the presence of congestive cardiac failure, and it is proportionate to the depth of calcification (relative risk [RR]: 2.1; 95% CI: 1.2-3.6; $P = 0.006$; RR increased by 24%/mm [95% CI: 12%-37%; $P < 0.001$]).[8] MAC is also associated with increased frequency of IE.[10] *Staphylococcus aureus* is the predominant pathogen, and vegetations (attached preferentially to calcific deposits) are frequently thrombogenic.[11]

MORTALITY. Mortality is increased in patients with MAC. In the Framingham study, identification of MAC using M-mode echocardiography was associated with an increased risk of cardiovascular mortality (HR: 1.6; 95% CI: 1.1-2.3) and all-cause mortality (HR: 1.3; 95% CI: 1.0-1.6) after adjustment for other cardiovascular risk factors[12] that rose by approximately 10% for each 1-mm increase in depth of calcification. More recently, the incidental finding of MAC on chest computed tomography (CT) has been associated with a higher risk of cardiovascular events (heart failure, myocardial infarction, and stroke; adjusted HR: 1.6; 95% CI: 1.1-2.1)[13] that increases in proportion to the severity of calcification, most likely as a consequence of accelerated systemic atherogenesis.[14] Whether medical therapy or valve intervention reduce these risks remains unknown.

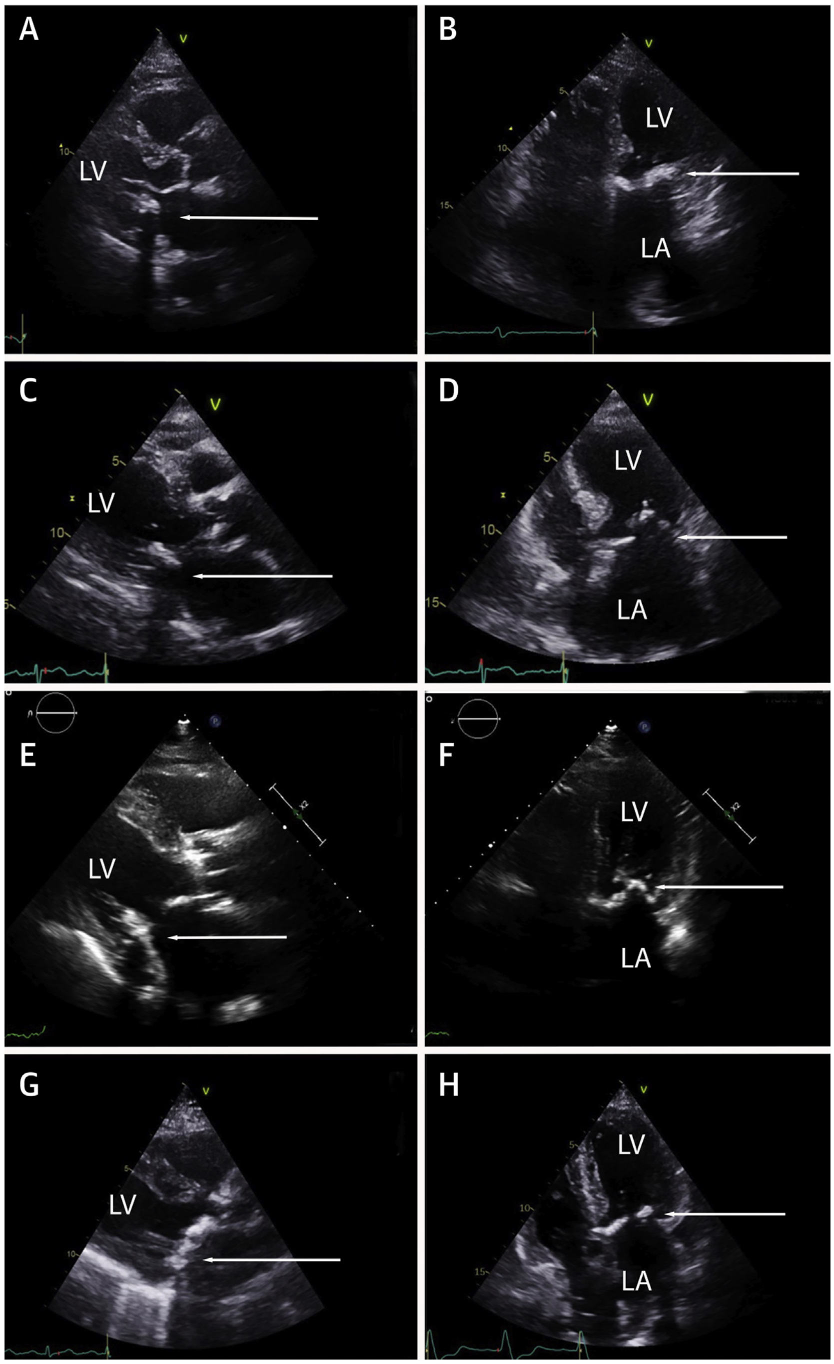
ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CT = computed tomography
LVOT = left ventricular outflow tract
MAC = mitral annular calcification
MDCT = multidetector computed tomographic imaging
MR = mitral regurgitation
MS = mitral stenosis
PTFE = polytetrafluoroethylene
PVL = paravalvular leak
THV = transcatheter heart valve
TMVR = transcatheter mitral valve replacement
ViMAC = transcatheter valve in mitral annular calcification

CLASSIFICATION AND GRADING OF SEVERITY

Usually, MAC is first detected using 2-dimensional echocardiography, which also enables assessment of mitral valve function (Figure 1). Electrocardiographic-gated multidetector computed tomographic imaging (MDCT) provides superior detail concerning the anatomical extent and severity of annular involvement, enables more reproducible quantification of the thickness and circumferential distribution, and is of particular value when intervention is contemplated (Figure 2). Agatston score, calcium volume, or mass can all be used to quantify the severity of MAC and enable the monitoring of temporal progression. Further prospective studies are required to validate the impact of MDCT on procedural outcomes and longer-term morbidity and mortality. Recognized

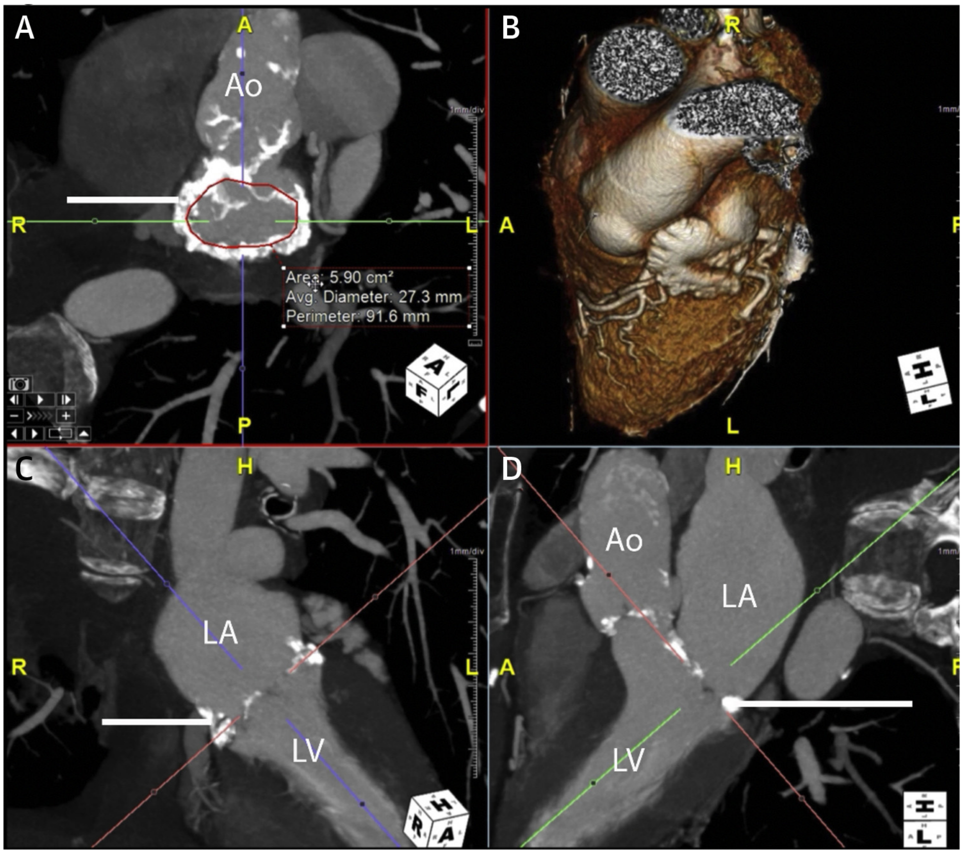
FIGURE 1 Transthoracic Echocardiogram Demonstrating MAC



Transthoracic echocardiography in a patient with severe mitral annular calcification **(white arrows)**. **(A, C, E, G)** Left column is the parasternal long axis view. **(B, D, F, H)** Right column is the apical 4-chamber view. LA = left atrium; LV = left ventricle; MAC = mitral annular calcification.

limitations include calcium blooming artefact and extension of calcification into adjacent cardiac structures (left ventricular outflow tract [LVOT], myocardium, and coronary arteries). The classification and grading of MAC severity is in itself a significant topic and is discussed here only superficially because it is beyond the scope of this review paper.

FIGURE 2 **Cardiac CT Multiplanar Reformatted Imaging**



Cardiac computed tomography multiplanar reformatted imaging is used to measure the projected mitral annular area and perimeter in patients being considered for transcatheter valve-in-MAC intervention **(A)**. **(B)** Three-dimensional volume rendered reconstruction of the heart. Crosshairs positioned in the 2-chamber **(C)** and 3-chamber **(D)** views identify the mitral annulus, and a wide maximal intensity projection (4-5 mm) is then used to assess MAC depth and guide device sizing. Ao = aorta; CT = computed tomography; other abbreviations as in Figure 1.

PROCEDURAL PLANNING

The 2 main strategies for dealing with mitral valve dysfunction accompanying MAC are surgical intervention and transcatheter intervention. Given the potential complexity of both approaches, all patients require comprehensive preprocedural imaging to facilitate heart team determination of the optimal treatment strategy.

VALVE SIZING. Intraoperative surgical valve sizing is undertaken using manufacturer-specific sizers to directly measure the internal dimensions of the mitral orifice after native valve resection. MDCT is the primary means for transcatheter heart valve (THV) sizing following earlier experience with echocardiographic or balloon-based techniques.[15,16] Our recommended approach is to localize the mitral valve annulus in the 2-chamber and 4-chamber views and to use a maximal intensity projection with 3- to 5-mm slice thickness to measure annular dimensions. A detailed report should include the distribution and eccentricity of calcification, and measurements of annular area, perimeter, intercommissural distance, and septal-lateral diameters. Using these parameters, an appropriate THV may be selected and positioned using dedicated mitral planning CT software to derive the anticipated neo-LVOT (see below). Uncertainties remain as to whether sizing is best performed along the inner boundary of the calcification or a few millimeters within, and these difficulties are compounded by the unpredictable behavior of the calcium once the annulus is circularized after THV deployment.

RISK OF THV EMBOLISM. The risk of valve embolism after transcatheter valve in MAC (ViMAC) implantation is higher than in mitral valve-in-valve or

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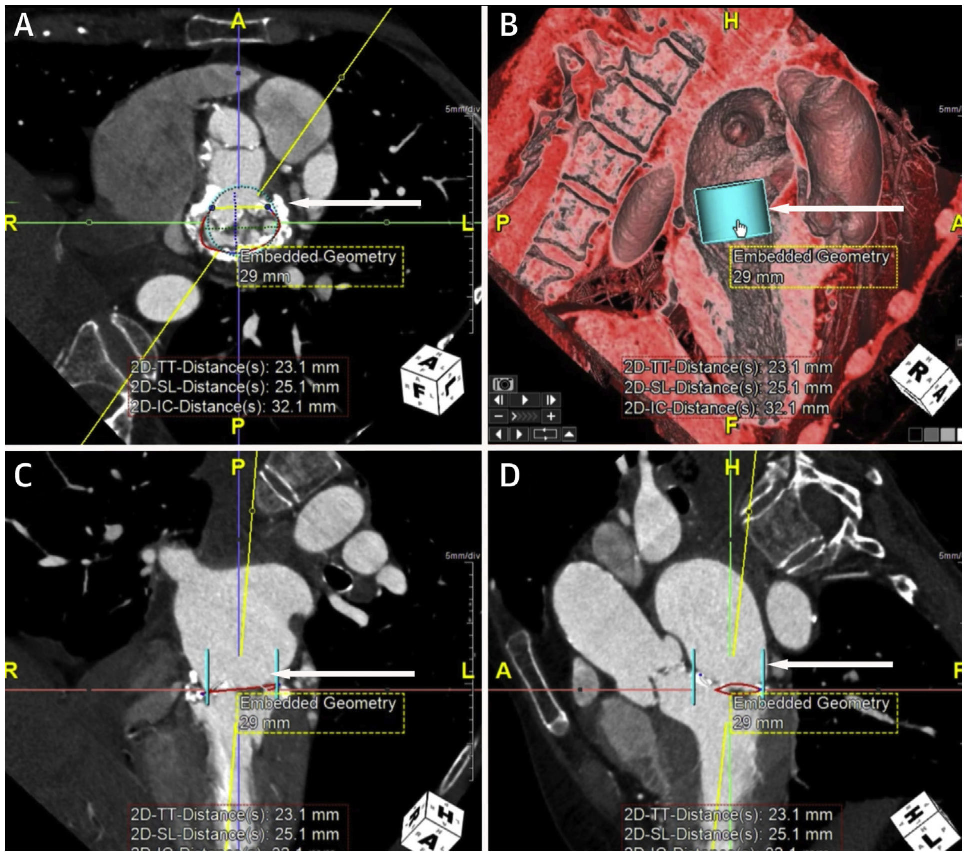
FIGURE 3 **Cardiac CT "Virtual" Valve Implantation**



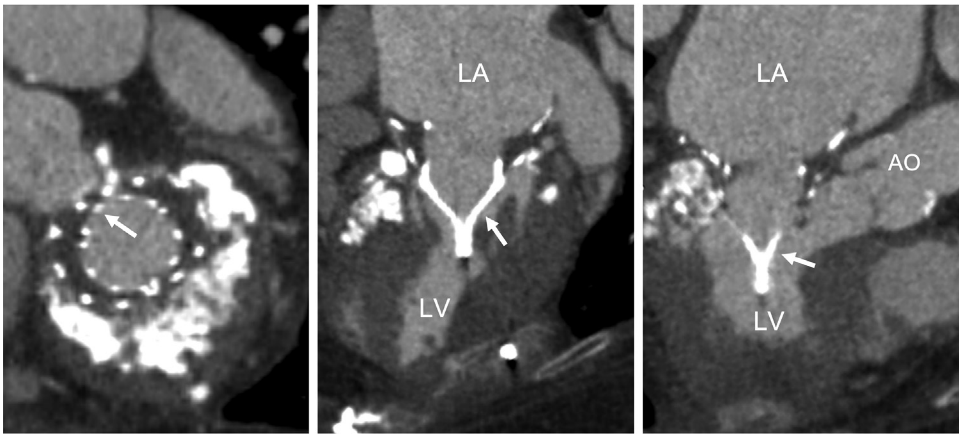
Cardiac CT dedicated mitral planning software packages allow "virtual" valve implantation and assessment of the optimal height to ensure sufficient device anchoring and neo-LVOT area (and thereby the lowest likelihood of device embolism and LVOT obstruction). **(A)** En-face view of the mitral valve annulus from which the annulus area, perimeter, trigone-to-trigone distance, septal-to-lateral and intercommissural distances are measured. **(B)** Modified volume rendered image of the left heart showing the intended transcatheter heart valve within the mitral valve annulus, which can be positioned at various heights. **(C)** Two-chamber view of the left ventricle and the position of the outer stent frame **(blue lines)** of the transcatheter heart valve. **(D)** Apical 3-chamber view. From this view, a center line extraction is performed from the aorta to the left ventricular apex. The neo-LVOT is the area between the lower margin of the stent between the lower margin of the stent frame and the interventricular septum. CT = computed tomography; LVOT = left ventricular outflow tract.

valve-in-ring procedures (6.9% vs 0.9% and 1.4%, respectively, in the TMVR Registry), reflecting difficulties related to valve sizing and insufficient or eccentrically calcified landing zones.[17-19] A more comprehensive and standardized approach to planning seems likely to reduce the risk of THV embolism by enabling more systematic evaluation.[20]

NEO-LVOT ASSESSMENT. The ventricular rim of THV devices displaces the anterior mitral valve leaflet toward the interventricular septum to create a new outflow tract (neo-LVOT), and LVOT obstruction contributes significantly to both 30-day and 1-year mortality. Factors contributing to neo-LVOT area include device protrusion and flaring, aortomitral angulation, and septal bulge.[21] Simulated implantation of the intended THV can now be undertaken using dedicated CT software packages to calculate the neo-LVOT area at various heights of deployment (Figure 3).[22] A neo-LVOT area <1.8 cm^2 predicts high rates of LVOT obstruction in preselected ViMAC patients.[23]

All preprocedural planning and neo-LVOT calculations are inherently dependent on deployment of the THV by the implanting interventionists at the site where measurements were made. This can be difficult to control, particularly when there are difficulties with device delivery or migration after deployment. Furthermore, preprocedural planning is unable to predict the radial or longitudinal displacement of MAC and its impact on the aortomitral angle,

FIGURE 4 **Post-TMVR Cardiac CT**



Postprocedural cardiac computed tomography of a Tendyne (Abbott Structural Heart) transcatheter mitral valve (**white arrow**) in situ after implantation in a patient with severe mitral annular calcification. (Adapted images provided by Dr. Alison Duncan, Royal Brompton and Harefield Hospitals.) TMVR = transcatheter mitral valve replacement; other abbreviations as in Figures 1 and 2.

neo-LVOT area, and risk of paravalvular regurgitation. An understanding of specific THV device designs and modes of deployment is essential to reduce complication rates. For instance, a cylindrical valve may result in greater reduction in neo-LVOT size than a D-shaped valve (Figure 4).

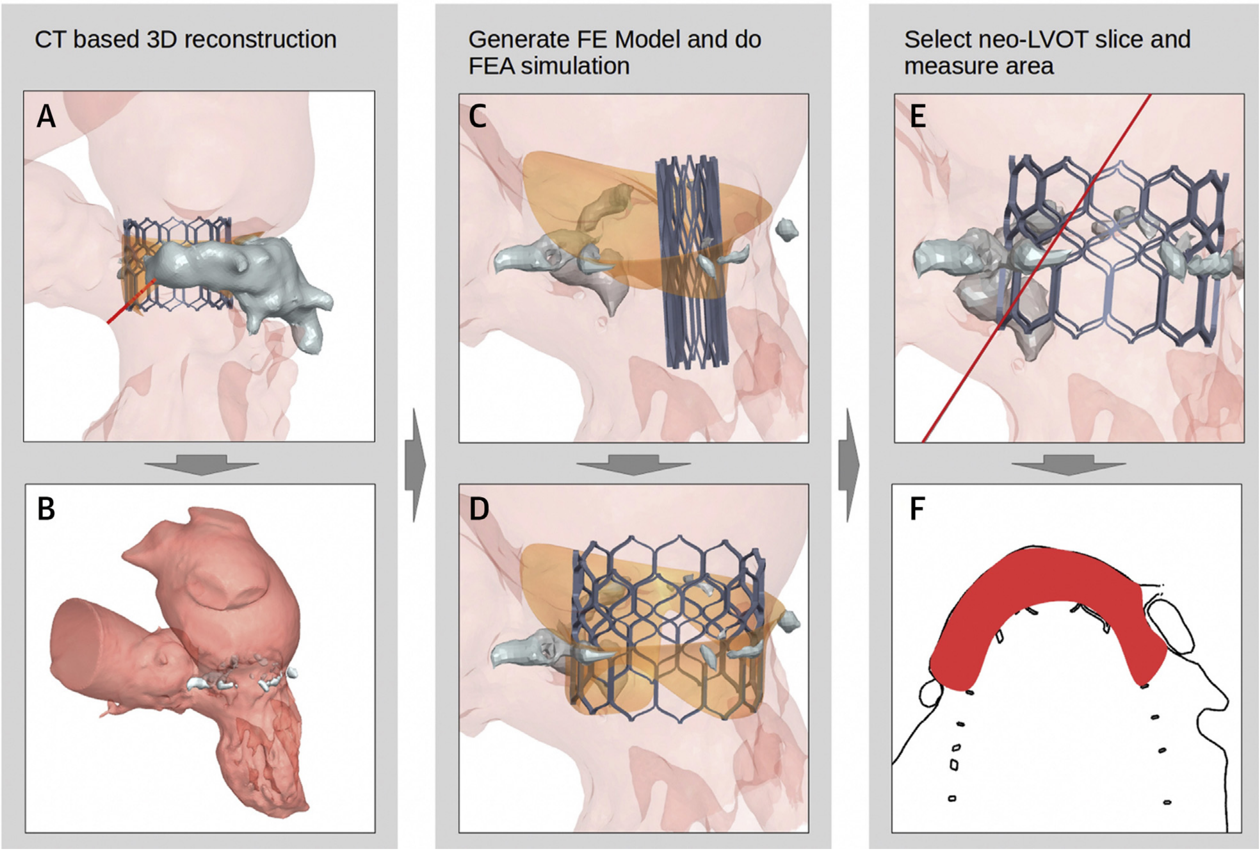
The application of bioengineering approaches to complex structural interventions potentially offers more reliable preprocedural planning.[24] Tissue properties of the mitral annulus and leaflets, left ventricle, and chordae tendinae can be incorporated using finite element modeling to enable better prediction of annular behavior after THV deployment (Figure 5). Simulated implantations allow calculation of the neo-LVOT area using varying sizes of the intended THV at differing left atrium/left ventricle height ratios. Early pilot data suggest that this technique reliably predicts calcium deformation and the neo-LVOT area.[24] Furthermore, the recent addition of computational fluid dynamics may permit measurement of mean and peak LVOT pressure gradients after THV deployment, potentially overcoming reliance on the neo-LVOT area as a surrogate for physiological flow obstruction.

SURGICAL INTERVENTION

The technical challenges posed by mitral valve dysfunction in the presence of MAC have long been recognized by surgeons and cardiologists. Generally, mild MAC localized to the posterior annulus and affecting less than one-third of the annular circumference does not affect surgical valve replacement or repair using conventional techniques. By contrast, the surgical management of moderate/severe MAC has required a range of innovative approaches, including extensive en bloc resection with annular reconstruction ("resect"),[25,26] more targeted conservative decalcification,[27] or no annular debridement ("respect").[28]

Coupled with these increased technical challenges, patients with significant MAC in the context of MS or MR tend to be older with multiple comorbidities and therefore at higher surgical risk.[29-31] Whereas surgery remains the gold standard treatment for severe mitral valve dysfunction accompanying MAC, the short-term and long-term surgical outcomes have historically been inferior compared with those in patients without significant MAC. Depending on the proposed procedure, surgery may result in unintended injury to the left circumflex coronary artery, rupture of the atrioventricular groove, conduction disturbances, paravalvular regurgitation, and patient-prosthesis mismatch.[32-35] Operative mortality rates including retrospective data from small or single-center studies range from 6% to 14%.[6,25,26,36,37] Low institutional volume (<50 cases/year) has also been shown to be independently associated with increased operative mortality.[35] Importantly, the lack of universally adopted precise definitions for grading MAC severity or the selected surgical approach limits the veracity of comparisons between studies.

FIGURE 5 Cardiac CT Finite Element Simulation



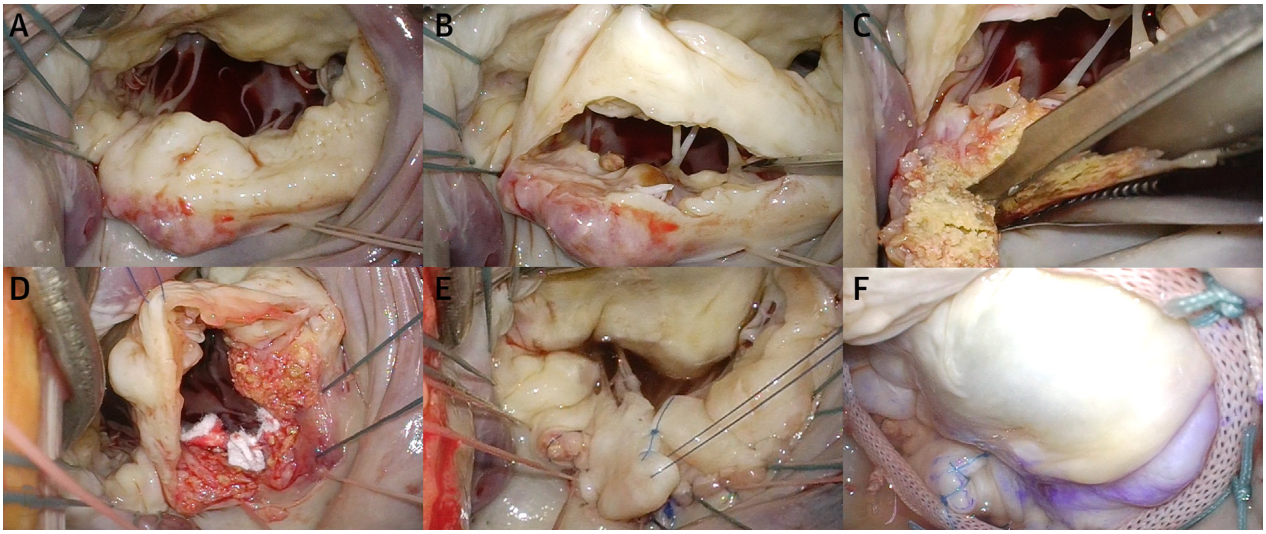
Finite element simulation (FEops HEARTguide, Ghent, Belgium) using computed segmentation of the imaging dataset allows simulated THV positioning at varying deployment heights between the left atrium and left ventricle **(A, B)**. It can help in the prediction of how the native anatomy will deform and displace after THV implantation **(C, D)** and indicates neo-LVOT area and sites of potential PVL at various deployment heights. **(E) Red line** indicates the narrowest point of the simulated neo-LVOT. **(F)** Neo-LVOT in cross-section and the **red area** is the measurement of the neo-LVOT area. FE = finite element; PVL = paravalvular leak; other abbreviations as in Figures 2 and 3.

PATIENT SUITABILITY FOR SURGERY. The first step in the management of significant MAC-associated mitral valve dysfunction is a holistic and patient-centered assessment of surgical risk and suitability for intervention. As stated, patients with MAC tend to be older with multiple comorbidities, and they usually present with more advanced disease. More specifically, there are frequent additional factors that could complicate the outcome of any proposed surgical intervention, including a history of mediastinal radiation, chronic kidney, disease and frailty. Prior mediastinal radiation (especially mantle radiotherapy) has been linked to MAC (particularly affecting the anterior annulus and intervalvular fibrosa)[38,39] and is independently associated with increased risk of cardiovascular death after cardiac surgery.[40]

ANATOMICAL FEASIBILITY OF CONVENTIONAL SURGICAL VALVE TREATMENT. Detailed anatomical assessment of MAC distribution in both horizontal and vertical planes (including annular size and degree/distribution of calcium deposition: partial, horseshoe, circumferential) is a critical component of procedural planning. Involvement of the leaflets, extension into the left atrium or ventricle, and proximity to the left circumflex coronary artery are all important factors when considering treatment strategy.[41-43]

For example, patients with a Barlow deformity associated with a large annulus, myxomatous tissue, and severe MAC tend to have enough tissue above the calcium bar to permit valve repair or replacement. Those in whom the calcific shelf extends below the annular plane are good candidates for partial decalcification and conventional surgery (whereas

FIGURE 6 En Bloc Resection of Calcium and Surgical Mitral Valve Repair



Intraoperative images from surgeon's view looking through the left atrium. **(A)** Posterior mitral annular calcification encroaching on P2-P3 hinge point. **(B)** Posterior leaflet detachment and exposure of ventricular extension of calcium shelf. **(C)** Sharp dissection of the calcium shelf. **(D)** Placement of pledget-reinforced annuloplasty sutures. **(E)** Reattachment of posterior leaflet to annulus and cleft closure. **(F)** Completed mitral valve repair with placement of Physio Flex annuloplasty ring. (Figure courtesy of David H. Adams, MD, Icahn School of Medicine at Mount Sinai.)

transcatheter options are less suitable) because the leaflet hinge is often spared. Severe calcification extending beyond the anterior commissure and encroaching on the aortic mitral curtain may preclude conventional surgery without a "commando procedure" to replace the entire aortic mitral curtain.[41-43] Transcatheter strategies may be preferable in such patients if feasible, and they are discussed in greater detail below.

SURGICAL VALVE REPAIR. Mitral valve repair is consistently superior to replacement with respect to survival, postoperative left ventricular function, and complication rates (even in the context of MAC), although the frequency of conversion from repair to replacement is higher in MAC patients (8% vs 3%). MAC usually spares the commissures without distorting the leaflets, and resection or nonresection leaflet repair techniques can be used as part of a "resect" or "respect" approach.[41,42]

THE "RESECT" APPROACH. Beyond the traditional approach of complete annular decalcification using sharp dissection and removal of the calcium bar en bloc (with myocardial sparing), Carpentier et al[25] reported excellent mortality and durability at the 7-year follow-up visit using a sliding atrioventriculoplasty technique involving en bloc decalcification (Figure 8) followed by annular reconstruction with a dissected atrial flap and final valve repair (in-hospital mortality 2.9%, freedom from reoperation 87%, survival 93%, need for replacement 1.4%; n = 68). Similarly impressive 8-year outcomes were reported by David et al[26] using a pericardial patch technique involving trigone-to-trigone reconstruction of the posterior annulus after en bloc decalcification followed by valve repair or replacement (in-hospital mortality 9.3%, survival 65%, freedom from reoperation 89%, 42 replacements; n = 54). In a more contemporary series (2002-2015) of 55 patients treated by either of these techniques, there was only 1 death related to delayed circumflex artery compromise, and the durability of valve repair was comparable with that observed in patients without MAC.[44] However, these approaches are no longer frequently performed in high-volume centers, and contemporary practice favors more targeted MAC resection with debridement back to the annular plane while sparing the ventricle.[41]

THE "RESPECT" APPROACH. Respect strategies seek to work around the calcium to avoid the risk of atrioventricular groove disruption or circumflex artery injury. In the case of repair, sutures are placed below the calcium, either from the atrial or the ventricular side, and are often reinforced with felt or pericardium. In some situations, an oversized

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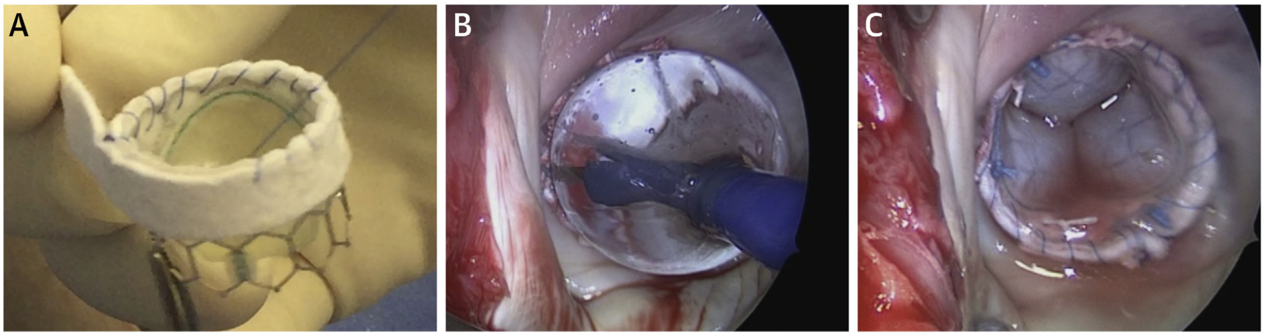
FIGURE 7 **Direct Transatrial Transcatheter Mitral Valve Replacement**



Intraoperative images of transatrial transcatheter mitral valve replacement. Initially, after exposing the mitral valve and resecting the anterior mitral valve leaflet, annular sutures are placed with caution, avoiding mitral annular calcification where possible. **(A)** Sapien 3 transcatheter aortic valve (Edwards Lifesciences, USA) valve is prepared before deployment by reinforcing the valve skirt with a polytetrafluoroethylene felt strip. **(B)** The valve is deployed with the skirt toward the delivery system handle. **(C)** Valve secured by tying down the annular sutures.

annuloplasty technique is used with the ring implanted behind the calcium bar. Partial annuloplasty bands can be implanted into noncalcified portions of the annulus when severe calcification extends above a commissure. These techniques are used alongside standard chordal and leaflet repair approaches where appropriate.[41]

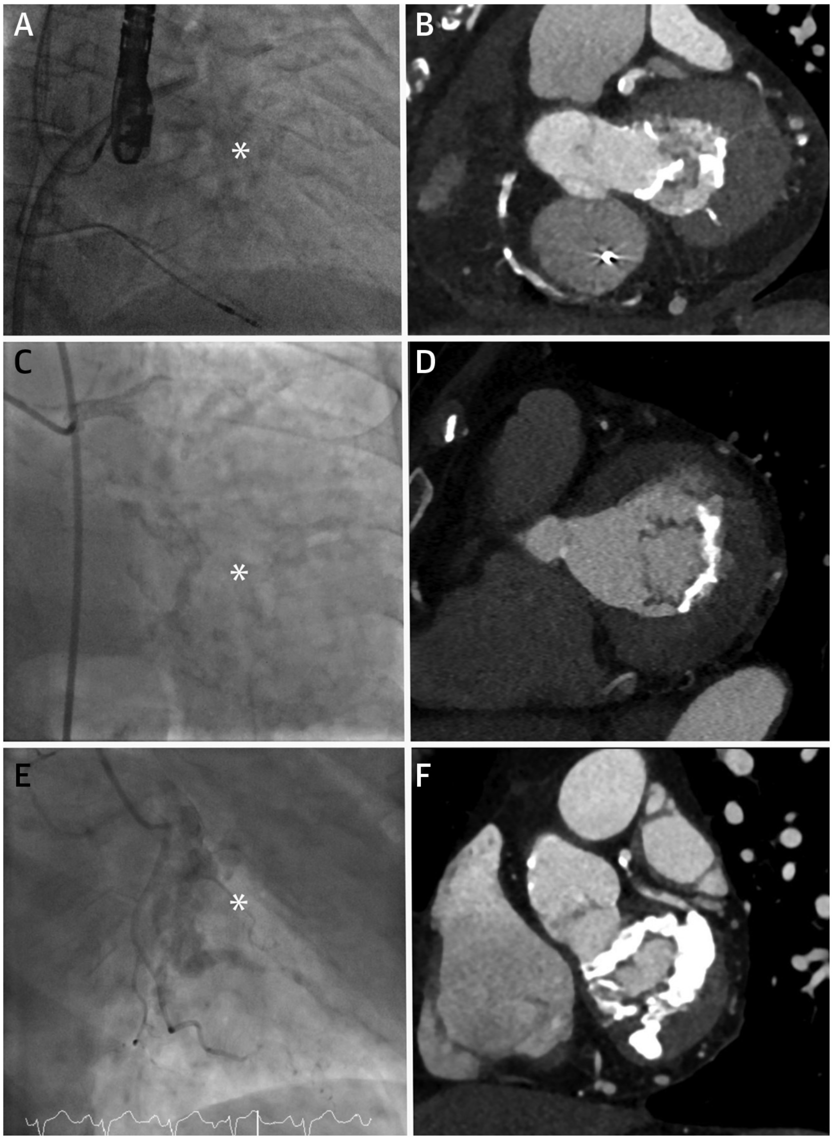
SURGICAL VALVE REPLACEMENT. Standard surgical valve replacement techniques can be used in patients with nonrepairable MAC. Preservation of the subvalvular apparatus is preferred to reduce the risk of midventricular tears.

THE "RESECT" APPROACH. The techniques of Carpentier et al[25] and David et al[25] just described provide a good surface area for valve replacement when successful and reduce the risk of paravalvular leak (PVL). Conversely, complete decalcification increases cardiopulmonary bypass time and the risks of bleeding, atrioventricular dehiscence, or circumflex artery injury (Figure 6).[27,28]

THE "RESPECT" APPROACH. Valve replacement can be performed using annular sutures around the calcium bar, through the leaflets, or a combination of these approaches. As mentioned above, contemporary surgical practice favors targeted decalcification or working around MAC where possible. The Mount Sinai group advocate a modified anterior leaflet flip technique wherein the anterior leaflet is detached from the annulus (while preserving the subvalvular apparatus) and flipped posteriorly to augment the suture line with the posterior leaflet above the calcium bar.[41] This approach reduces procedure time and the risk of serious complications, albeit with potentially higher rates of PVL and smaller valve implantation.[43] Nevertheless, data from several studies involving a conservative decalcification strategy and valve replacement demonstrate outcomes comparable with those in non-MAC patients.[27,28,45]

DIRECT TRANSATRIAL TRANSCATHETER MITRAL VALVE REPLACEMENT. Surgical ViMAC—insertion of a balloon-expandable THV via left atriotomy and deployment under direct vision—can avoid the need for annular decalcification in high-risk surgical patients.[46,47] Additional atrial sutures prevent migration, and supplementary pericardial/Teflon felt strips can be used to mitigate PVL, although improved outer skirt technology (as found on the Sapien 3 and Sapien Ultra THVs [Edwards Lifesciences]) may reduce the need for supplementary patches (Figure 7).[48] Use of a THV creates a larger effective orifice area compared with a surgical prosthesis. Resection of the anterior mitral valve leaflet can also be performed via a direct atrial approach, significantly reducing the risk of LVOT obstruction compared with transcatheter techniques. Small case series in high-risk patients demonstrate good echocardiographic and symptomatic improvement, but high in-patient and 30-day mortality (19% and 27%, respectively).[49] Although this approach is an appealing alternative in high-risk and comorbid patients, small retrospective studies show a longer-term mortality >30% at 1 year (Table 1).[50,51] The SITRAL (Surgical Implantation of TRAnscatheter vaLve in Native Mitral Annular Calcification; NCT02830204) study is underway and will

FIGURE 8 Examples of Mild and Circumferential MAC on Fluoroscopy and CT



(A) Mild MAC seen in the right anterior oblique caudal projection with **(B)** corresponding CT image. (**C)** Mild MAC seen in the posterior-anterior caudal projection with **(D)** corresponding CT image. **(E)** Severe MAC seen in the right anterior oblique projection with **(F)** corresponding CT image demonstrating extensive circumferential and ellipsoid calcification extending into basal segments of the LV. Abbreviations as in Figures 1 and 2.

provide comprehensive 30-day and 1-year outcomes for this cohort.

TRANSCATHETER INTERVENTION

The first transcatheter ViMAC procedures were performed in 2013 using a Sapien THV (Edwards Lifesciences) via a transapical approach,[15,16] and successful outcomes were subsequently replicated using the Lotus (Boston Scientific) and Inovare (Braile Biomedica) devices. Within 1 year, the first transvenous transeptal procedure was described,[52] and it has rapidly become the technique of choice, given the substantial advantages of avoiding transapical access. The outcomes of early transcatheter ViMAC procedures were highly variable, principally because of the hazards of valve embolism and LVOT obstruction, with significant mortality between 30 days and 1 year.

TABLE 1 Hybrid Surgical Approaches for MAC

Study	Time Period	Patients	Follow-Up	Technique	Complications	In-Hospital Mortality	Freedom From Late Reoperation	Long-Term Survival
El Sabbagh et al[46]	2014-2016	6 Mean age 81 y	30 d	Left atriotomy (n = 4), vertical transseptal (n = 2) deployment of balloon-expandable THV, postdilatation, anchoring sutures if needed	No LVOTO Mean MV gradient 5 mm Hg Valve migration (n = 1) Severe PVL (n = 4) Death (n = 3)	50% at 30 d	PVL closure in 1 patient	No long-term follow-up
Russell et al[47]	2017-2018	8 Mean age 75 y	30 d	Left atriotomy, PTFE felt strip anastomosed to atrial side of stent frame, AMVL excised, Sapien 3 THV deployed, secured with sutures	No >mild PVL No major complications	No operative, in-hospital, or 30-d mortality	PVL closure in 1 patient due to hemolysis	1 death at 7 mo
Praz et al[49]	2015-2017	26 Mean age 78 y	Mean 8 mo (n = 15)	Left atriotomy, AMVL resection, PMVL resection if restricted valve opening Occasional annular debridement to expand MVO Felt strip secured to base of THV stent frame Anchoring sutures after THV deployment 8% Sapien XT 92% Sapien 3	2 major bleeding requiring exploration, 1 stroke, 4 new RRT 2 PPM 1 LVOTO (MG ≥30 mm Hg)	19% (5 in-hospital deaths) 2 mesenteric ischemia, 1 respiratory failure, 2 multiorgan failure, 27% 30-d mortality (n = 7)	Postdilatation and PVL closure in 1 patient due to hemolysis	N = 15 2 deaths after 30 d of noncardiac causes
Guerrero et al[50] MITRAL Trial	2015-2017	15 Mean age 78 y	1 y	As described above 100% Sapien 3 13% after dilatation	1 LVOTO 2 ≥ 2+ residual MR 1 LV perforation 1 VSD (myectomy) 2 PPM 1 Stroke 4 new RRT	20% in-hospital and 30-d 1 LVOTO 1 VSD 1 sepsis	100%	38.5% 1-y mortality (n = 13) 2 CV 3 non-CV
Kaneko et al[61]	2018-2020	11 Mean age 74 y	30 d	Left atriotomy, AMVL ± PMVL resection ± SVA resection where necessary, THV (Sapien 3) cuff PTFE felt reinforcement, pledgeted annular sutures, minimal debridement, THV secured	1 Stroke 1 Reoperation (MVR due to LVOTO) 1 New RRT 2 PPM 2 LVOTO 0 ≥ 2+ residual MR	No in-hospital or 30-d mortality	N/A	N/A
Smith et al[51]	2015-2020	51 Mean age 74 y	1 y	Left atriotomy, AMVL ± PMVL resection, ventricular septal myectomy if high risk of LVOTO	2 Stroke (3.9%)	13.7% 30-d mortality	N/A	33.3% 1-y mortality

AMVL = anterior mitral valve leaflet; CC = cross-clamp; CHB = complete heart block; CV = cardiovascular; LVOTO = left ventricular outflow obstruction; MAC = mitral annular calcification; MG = mean gradient; MR = mitral regurgitation; MV = mitral valve; MVO = mitral valve orifice; N/A = not available; PMVL = posterior mitral valve leaflet; PPM = permanent pacemakers; PTFE = polytetrafluoroethylene; PVL = paravalvular leak; RRT = renal replacement therapy; SVA = subvalvular apparatus; THV = transcatheter heart valve; VSD = ventricular septal defect.

INTRAPROCEDURAL IMAGING. Accurate THV placement under imaging guidance is crucial to reduce the likelihood of embolism, LVOT obstruction, and PVL. Intraprocedural 3-dimensional transesophageal echocardiography is used to guide transseptal puncture, ensure satisfactory left ventricular wire and THV positioning, and evaluate valve function and hemodynamic status after deployment. Severe MAC is usually visible on standard fluoroscopy, which can provide supplementary information, particularly if the angle of deployment is known from preprocedural CT imaging.

Fusion imaging entails coregistration of 2 or more imaging modalities on a single screen to obtain complementary information. This approach has particular value during ViMAC procedures, enabling real-time access to the preprocedural planning MDCT dataset, superior anatomical detail, and identification of landmarks to ensure optimal THV deployment in the intended position, and reduced risk of complications (Figure 9).

CLINICAL OUTCOMES. Patients undergoing transcatheter ViMAC procedures are generally at high or prohibitive surgical risk, and substantial

TABLE 2 Outcomes of Transcatheter Valve-in-MAC Procedures in International Registries

	TMVR in MAC Global Registry (n = 116)[18]	STS/ACC TVT Registry (n = 100)[19]	TMVR Registry (n = 58)[17]	Tendyne (n = 20)[56]	MITRAL Trial (n = 16)[50]
First ViMAC enrollment	2012	2013	2015	2018	2015
Location	International	USA	International	USA and Europe	USA
Number of centers	51	49	40	Up to 10	13
Transseptal	40.5	43.0	53.4	Transapical	94.0 n = 1 transapical (transatrial n = 15 in Table 1)
Edwards Sapien	98.3	100.0	81.0	NA	100.0
30-d outcomes					
All-cause death	25.0	21.8	34.5	5.0	12.5
Cardiovascular death	13.0	12.0	N/A	0.0	12.5
Stroke	4.3	6.3	3.9	5.0	6.7
Valve embolism	4.3	1.6	6.9	N/A	N/A
MV re-intervention (including ASA)	7.7	6.3	13.8	10.0	12.5
LVOT obstruction	11.2[a]	10.0[b]	39.7[c]	0.0	12.5
Hemolytic anemia	3.4	N/A	N/A	5.0	20.0
MR grade >mild	15.5	5.7	13.2	0.0	6.7
1-y outcomes					
All-cause death	53.7	N/A	62.8	40.0	31.3
Cardiovascular death	23.5	N/A	N/A	20.0	18.7
Stroke	6.6	N/A	N/A	5.0	6.2

Values are % unless otherwise indicated. [a]No formal definition of LVOT obstruction. [b]Defined as hemodynamic compromise. [c]Defined as change in LVOT gradient ≥10 mm Hg. ASA = alcohol septal ablation; LVOT = left ventricular outflow tract; other abbreviations as in Table 1.

comorbidities (particularly lung disease) are more common than in those undergoing valve-in-valve or valve-in-ring procedures. Mitral stenosis or mixed mitral valve disease are the primary modes of valve dysfunction in this cohort, and the majority present in New York Heart Association functional class IV.[19] Complication rates are highly variable, reflecting operator experience and varying approaches to preprocedural planning between centers.

The TMVR in MAC Global Registry, Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry and TMVR Registry have collated data concerning the outcomes of transcatheter ViMAC procedures (Table 2). Transapical and transeptal access were used equally (both 40%), and remaining cases were undertaken via a direct atrial approach,[18] with relatively high rates of 30-day mortality (21.8%-34.5% independent of procedural approach),[18,19] device embolism (1.6%-6.9%), mitral valve surgery (6.3%-22.4%), and LVOT obstruction (10.0%-39.7%).[23] Beyond procedural mortality, analyses have also shown higher mortality rates between 30 days and 1 year, particularly in those with LVOT obstruction (85% mortality at 1 year).[18]

Hemolysis is a specific complication of transcatheter ViMAC procedures, with a prevalence of 3.8% at the 1-year follow-up visit in the TMVR in MAC Global Registry.[18] However, frequency may be underestimated in retrospective registries because of a lack of systematic screening, and rates are not reported by the STS/ACC TVT and TMVR Registries. The MITRAL (Mitral Implantation of TRAnscatheter vaLves; NCT02370511) trial is the first prospective study evaluating the safety and feasibility of ViMAC[50] and has actively screened for hemolysis, with rates of 10% and 17% at 30 days and 1 year, respectively.[53] The underlying mechanism is incompletely understood; high flow associated with PVL is likely to be the most important cause, although high-velocity passage of blood through the THV stent struts could also be a contributing factor. There are no clear predictors, although surgical series have demonstrated increased prevalence in patients with significant residual MR.[54] 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.

The total number of transcatheter ViMAC procedures performed worldwide remains small. Published international registries include many early cases and do not yet reflect improved outcomes associated with refined periprocedural imaging and improved implantation techniques. Recently presented 2-year outcomes from the MITRAL trial demonstrate improved results for ViMAC procedures compared

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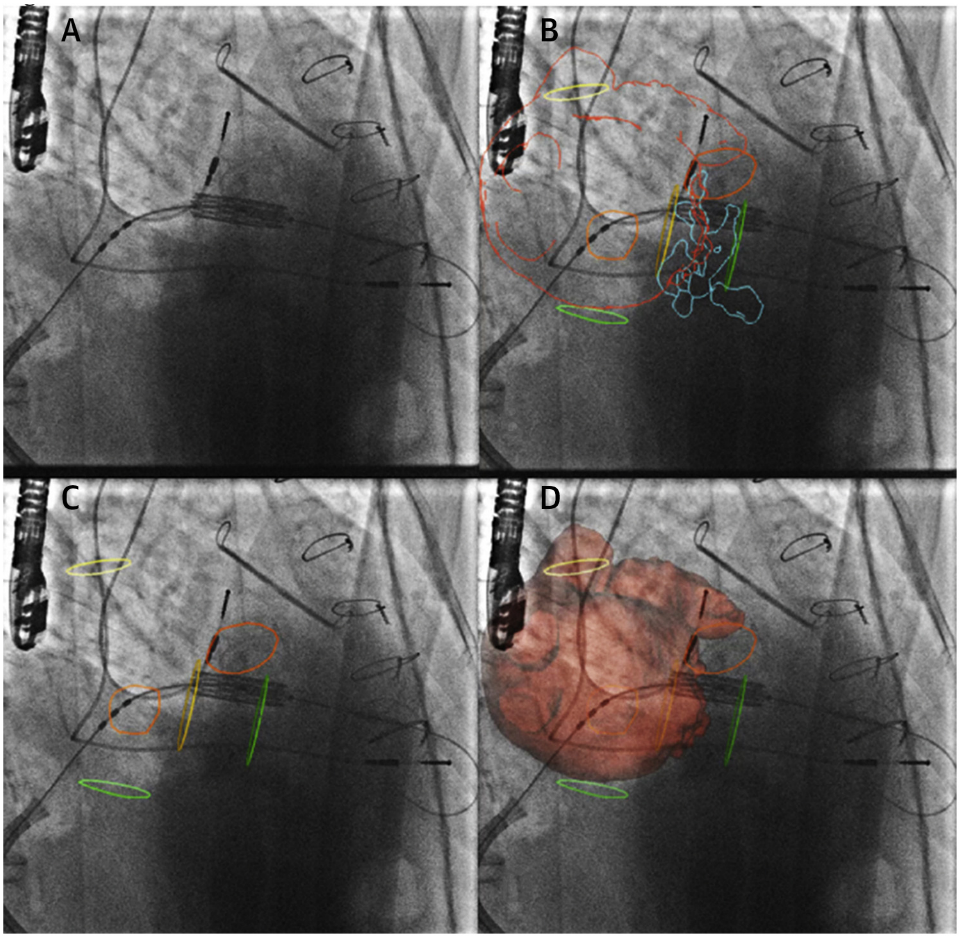
FIGURE 9 Periprocedural CT Fluorofusion

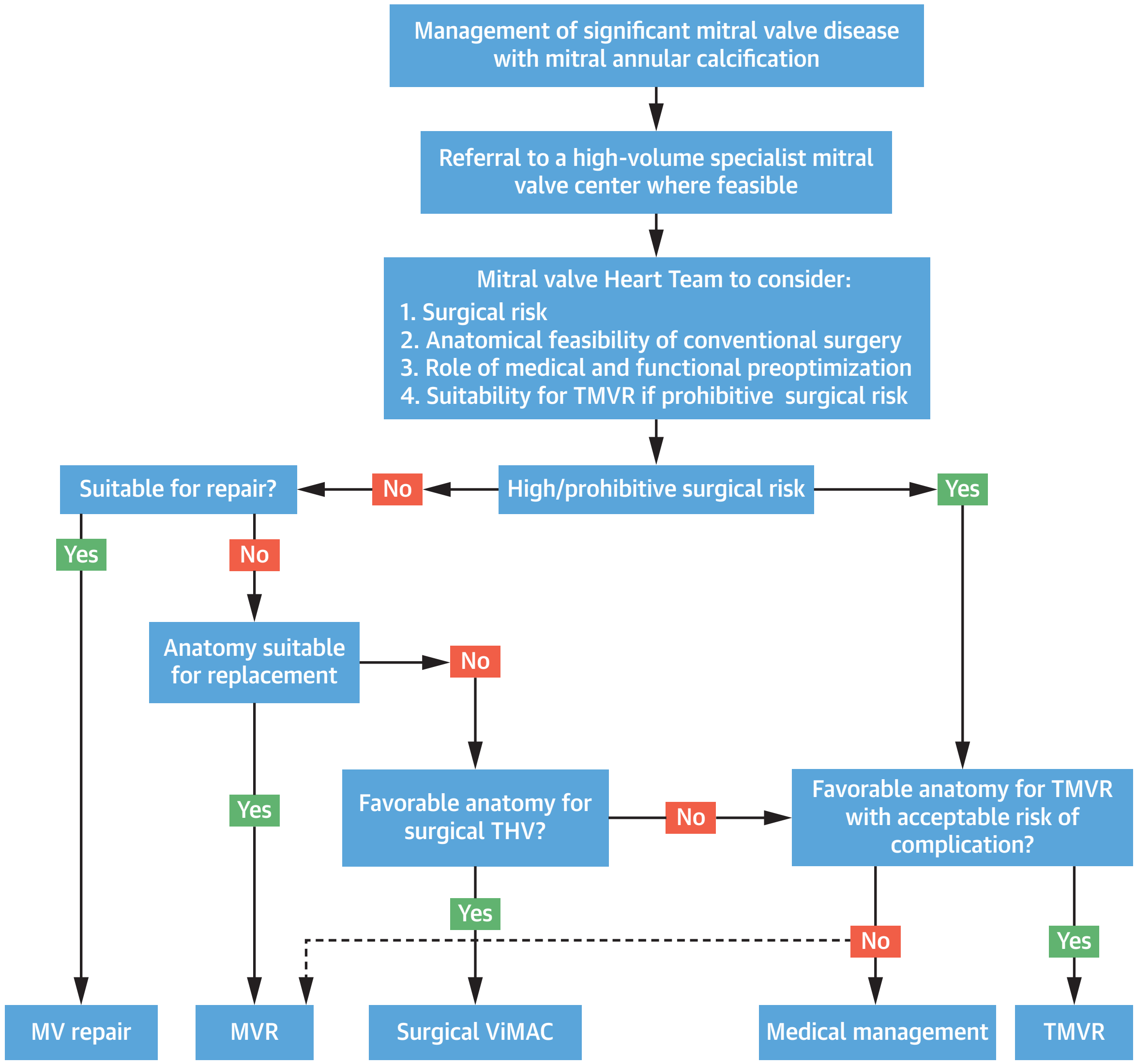


To ensure procedural outcomes are concordant with preprocedural planning, it is important that the THV is implanted at the optimal predicted height. **(A)** standard fluoroscopic appearances available during THV deployment. **(B)** CT finite element analysis-fluorofusion with anatomical landmarks coregistered against fluoroscopic images (**orange outline**: left atrial wall; **orange circle**: fossa ovalis; **yellow horizontal ellipse**: superior vena cava boundary; **green ellipse**: inferior vena cava boundary; **blue tracing**: MAC; **yellow and green lines**: atrial and ventricular margins for optimal THV deployment. **(C)** Simplified simulation-fluoroscopic fusion. **(D)** Full CT simulation and boundary fluoroscopic fusion. THV = transcatheter heart valve; other abbreviations as in Figures 1 and 2.

with registry data.[53] All-cause mortality at 2 years was 39.3%, comparing favorably with the 2-year mortality observed in patients treated with TAVI in the PARTNER I trial (43.3%).[55]

DEDICATED TMVR DEVICES. Dedicated transcatheter mitral valve replacement (TMVR) devices usually have a larger skirt with lower radial force than TAVI devices, enabling more predictable deployment and reduced annular deformation. Although severe MAC is often an exclusion criterion in studies using these devices, early results in a total of 36 patients with severe MAC treated using the CE-marked Tendyne valve (Abbott Structural Heart) in 3 multicenter registries have demonstrated good outcomes with relatively low mortality.[56-58] Whereas the D-shaped annulus of the Tendyne THV potentially mitigates the risk of LVOT obstruction and PVL, the case selection criteria are strict, and approximately two-thirds of patients were excluded from this study. Valves that conform to the calcium (rather than displace it) may also have more predictable post-procedural valve and LVOT hemodynamics. Dedicated substudies using both the Tendyne and Intrepid (Medtronic) THVs are under way and will provide further insights into the role of TMVR devices in this complex cohort.

CENTRAL ILLUSTRATION Proposed Treatment Algorithm for Patients With Mitral Annular Calcification Requiring Valve Intervention



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An algorithm for patients with mitral annular calcification requiring valve intervention, putting multidisciplinary decision making at the core of clinical decision making. The algorithm outlines 4 key considerations. 1) Assessment of surgical risk. 2) The anatomical distribution of mitral annular calcification and influence on surgical feasibility and risk. 3) Role of medical, physical, and nutritional preoptimization. 4) In cases of prohibitive anatomical/surgical risk, surgical transcatheter valve in mitral annular calcification or transcatheter mitral valve implantation can be considered. Conventional surgery may be considered **(dashed arrow)** in high-risk and highly symptomatic patients unsuitable for transcatheter mitral valve implantation. Medical management is reserved for cases in which procedural risk is prohibitive and a patient is unlikely to derive benefit. MV = mitral valve; MVR = mitral valve replacement; THV = transcatheter heart valve; TMVR = transcatheter mitral valve replacement; ViMAC = transcatheter valve in mitral annular calcification.

MULTIDISCIPLINARY DECISION MAKING IN MAC

Patients with MAC are predominantly elderly with multiple comorbidities, and careful adjustment of guideline-directed medical therapy coupled with improved physical and nutritional status is fundamentally important before any intervention. As outlined in this review, the array of surgical and transcatheter treatment options is complex and is heavily reliant on advanced preprocedural imaging, local expertise, and the availability of specific devices. Patients being considered for such intervention should therefore be referred to high-volume specialist heart valve centers where relevant expertise and experience are available and where the best outcomes are obtained.[59,60] Close collaboration of the heart team between imaging and interventional cardiologists, heart failure specialists, cardiac surgeons, geriatricians, and other relevant disciplines where necessary is then essential to ensure appropriate decision making and a bespoke management plan for an individual patient.

There are 4 key questions that require sequential consideration when surgical or transcatheter intervention is considered in patients with significant MAC (**Central Illustration**).

1. Is intervention warranted for a given patient based on the balance of symptoms, quality of life impairment, comorbidities, and life expectancy?
2. Is there a role for prior optimization of medical therapy or functional status?
3. Is the valve anatomically suitable for conventional mitral valve surgery?
4. If not, is THV implantation anatomically feasible at acceptable procedural risk?

CONCLUSIONS

MAC is more frequently encountered in the aging population and provides a unique challenge for the heart team. This review provides a standardized approach to grading the severity of MAC and the evaluation of patients for surgical or transcatheter intervention. Advanced and comprehensive preprocedural imaging has quickly become the cornerstone of all heart team decisions regarding these patients. Despite a limited evidence base, surgical valve repair remains the gold standard of treatment, and there are no robust data regarding the outcomes of surgical valve replacement. Surgical and transcatheter ViMAC procedures are still associated with high 30-day mortality. Furthermore, high mortality at 1 year despite initial procedural success reflects the age and comorbidities of this high-risk cohort and emphasizes the critical importance of a holistic heart team-guided approach to patient selection and management.

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