Mitral annular calcification (MAC) is a chronic degenerative process associated with advanced age and conditions predisposing to left ventricular hypertrophy. Assessment of mitral valve disease in patients with severe MAC can be a challenge. When severe MAC results in mitral stenosis or regurgitation, multimodality imaging with 2-dimensional, 3-dimensional, and Doppler echocardiography and cardiac computed tomography angiography can delineate the severity and pathoanatomic features to help guide therapeutic strategies. New approaches using computer-assisted simulation of transcatheter valves and novel percutaneous and surgical techniques are being used to devise effective alternative strategies to conventional mitral valve replacement in this high-risk group of patients.

(Mitral annular calcification (MAC) is a chronic degenerative process that, when severe, can result in mitral stenosis (MS) and/or mitral regurgitation (MR). The prevalence of significant MS due to severe MAC is increasing in the developed world due to the growing population of elderly patients and risk factors such as hypertensive and radiation heart disease. Treatment options for severe MAC are limited. With no specific medical therapy for MAC, treatment is symptomatic. Balloon valvuloplasty is not suitable for MS due to MAC and mitral valve surgery is associated with excessive morbidity and mortality in patients with extensive annular calcification. Additionally, the complex anatomy of the mitral apparatus and challenging left ventricular (LV) geometry in patients with severe MAC pose unique challenges to minimally invasive mitral valve implantation using transcatheter devices. Recent advances in multimodality cardiac imaging and novel percutaneous and surgical techniques are being investigated, offering hope for this challenging group of patients.

**PATHOPHYSIOLOGY OF MAC**

MAC is a result of slowly progressive calcification of the fibrous mitral annulus (Figure 1) (1). The estimated prevalence of MAC is 10%, with the posterior annulus being more commonly affected than the anterior annulus (1). MAC that results in an elevation in the mean transmural gradient is relatively rare, occurring in 0.2% of patients undergoing transoral echocardiography, with prevalence increasing to 2.5% in patients >90 years of age (2,3).

Risk factors for MAC include advanced age, female sex, chronic kidney disease, and conditions predisposing to LV hypertrophy including hypertension and aortic stenosis (4). Prior chest irradiation, most commonly as a treatment for Hodgkin’s lymphoma, is another cause of MAC, often in combination with...
aortic valve disease and restrictive cardiomyopathy. MAC appears to be a multifactorial condition resulting from a varying combination of abnormal calcium and phosphorus metabolism, increased mitral valve hemodynamic stress, and atherosclerotic processes. Although MAC is typically confined to the mitral annulus and the base of the leaflets, in some cases MS can occur when calcification extends further into the leaflets, particularly the anterior leaflet, resulting in restricted mobility. An important distinction compared to rheumatic MS is that in MS due to MAC, there is lack of mitral leaflet commissural fusion (Figure 2).

In isolated MAC, valve leaflet motion is preserved, and ventricular filling occurs unimpeded. However, over time calcific degeneration tends to further expand into the leaflets resulting in impaired mobility and geometric distortion. These anatomic changes typically lead to development of both MS and MR. Either lesion may be dominant in a given patient, but more commonly there is mixed disease. When MS or MR become severe, heart failure symptoms including dyspnea and exercise intolerance may ensue.

**ASSESSMENT OF MS IN SEVERE MAC**

Echocardiography is particularly well suited for anatomic and physiological assessment of valvular function, and is the cornerstone in assessment of calcific mitral valve disease. We recommend a systematic approach to diagnosis, which should include assessment of qualitative (visual appearance, calcification, thickening, leaflet mobility, adequacy of coaptation) and quantitative parameters (mitral valve area, gradients, indices of regurgitation severity). At the completion of the imaging study, internal consistency between visual cues, measured parameters, and clinical findings must be verified.

Visual inspection of the entire mitral apparatus should be systematic. We begin with assessment of extent of annular calcification (focal vs. circumferential), best achieved on short-axis views of the mitral valve (parasternal short-axis at the base on transthoracic echocardiography [TTE], or short-axis from the gastro-esophageal junction on transesophageal echocardiography [TEE]). If short-axis images are unavailable, inspection of the mitral annulus by rotating the imaging plane from the apical (TTE) or mid-esophageal (TEE) windows allows systematic evaluation of circumferential extent. Visual inspection of the mitral leaflets should describe presence and location of degenerative changes, their location according to the Carpentier nomenclature, and extent from base to coaptation line. While all information can be gathered by 2-dimensional (2D) imaging, the en face atrial and ventricular views of the mitral valve at 3-dimensional (3D) imaging provides the best information for topographical description of the mitral valve, and was a key development for the growing number of percutaneous interventions. Direct visualization of the extent and magnitude of MAC with 3D imaging is a useful adjunct to understand the severity of MS and for determination of therapeutic options.

Whenever MS is suspected on the 2D/3D images, careful quantitation of disease severity must be performed by measuring mitral valve gradient and mitral valve area. This information is critical for further clinical decisions in patient management.

Mitral valve gradients are estimated from the continuous wave (CW) Doppler spectrum obtained from apical (TTE) or mid-esophageal (TEE) windows. We recommend that color Doppler imaging is first performed to assess which imaging view allows for the best alignment of the CW Doppler line of interrogation with the direction of mitral inflow. The mean gradient is derived by integrating the CW velocity spectral envelope, and closely correlates with the gradient directly measured at catheterization. The mitral gradient cannot be used in isolation for quantitating MS severity because it is highly dependent on factors other than stenotic area, most notably on heart rate, cardiac output, and associated MR.

Mitral valve area by continuity equation is the recommended method in the case of calcific MS, but its value is limited in the presence of concomitant aortic and mitral valve regurgitation. Direct planimetry may be challenging in calcific degeneration of the valve; 3D technology seems to improve accuracy and reproducibility of planimetric measurements. Whenever TTE evaluation is inconclusive, we recommend additional TEE imaging; 3D-TEE planimetry of valve area is feasible in the majority of patients (Figure 3). Pressure half-time is influenced by numerous factors beyond MS severity (left atrial and ventricular compliance, delayed ventricular relaxation, concomitant aortic regurgitation), and has limited utility in estimating mitral valve area in elderly patients with calcific MS. The inflow proximal isovelocity surface area (PISA) method can also be used for estimating mitral valve area, but is highly dependent on operator experience, image quality, and correct measurement of the PISA radius and angle of leaflet correction. For patients with symptoms that are disproportionate to the resting mitral valve gradient and/or valve area, an exercise or
pharmacologic stress hemodynamic echocardiographic study examining the changes in mean gradient, valve area, and right ventricular systolic pressure with stress can help establish severity of MS.

In cases where the severity of MS is uncertain, a carefully performed invasive hemodynamic assessment with cardiac catheterization can be useful to clarify the severity of MS. Direct measurement of simultaneous left atrial and LV pressure is necessary for accurate assessment of the mean transmitral gradient and also provides valuable insight into the compliance properties of the left atrium and the LV diastolic function. Concomitant measurement of cardiac output with simultaneous right heart catheterization will allow for measurement of the mitral valve area using the Gorlin formula. Hemodynamics and loading conditions can be manipulated to assess valve function under conditions of higher heart rates and volume conditions.

ASSESSMENT OF MR IN SEVERE MAC

Beyond qualitative assessment of mitral valve apparatus (described in the preceding text), assessment of MR relies on color Doppler imaging and quantitative measurements of regurgitation severity. TTE evaluation of presence and extent of MR in calcific degenerative mitral disease is frequently hampered by the acoustic shadowing of the left atrium. The absence of color Doppler signal in the left atrium does not rule out MR. We recommend a “blind” CW sweep of the left atrium (which sometimes detects the signature MR spectrum), or imaging of the left atrial dome above the MAC (for instance in parasternal short-axis at aortic valve level) may also show presence of regurgitation, and is often an underutilized view.

TEE is excellent for detection and quantitation of MR, as the probe is located just behind the left atrium, with unimpeded views. 3D color Doppler is particularly useful in clarifying number and location of regurgitant jets, critical for planning percutaneous interventions. We find particularly useful the 3D en face view of the mitral valve from the ventricular side; this view allows reliable identification of jet(s) origin, as well as detection of functional and nonfunctional cleft-like indentations in the mitral leaflets (13).

We prefer the PISA method for quantitation of MR severity. The method is robust (14), allows estimation of anatomic disease severity (effective regurgitant orifice) and hemodynamic burden (regurgitant volume), and, unlike the continuity method, is not influenced by concomitant presence of aortic regurgitation. PISA-derived indexes have validated clinical impact, and are incorporated in all guidelines for management of MR (15,16).

FIGURE 1 Mitral Annular Calcification

(A) Parasternal short-axis at the level of the mitral annulus shows severe mitral annular calcification (MAC) involving the posterior annulus (arrows). (B) Gated cardiac computed tomographic angiography with 3-dimensional (3D) reconstruction shows nearly circumferential severe MAC in the same patient.
When MR severity remains unclear or there is discordance between physical examination findings and echocardiography, cardiac catheterization with left ventriculography is a useful adjunct to either confirm or rule out significant MR (15,17).

**COMPUTED TOMOGRAPHIC IMAGING OF MAC**

Computed tomography (CT) is a versatile noninvasive imaging modality that provides complementary data to echocardiography in the evaluation of the mitral valve and MAC (18–20). Calcification is especially well seen on CT due to its high x-ray attenuation and because of the high spatial resolution of CT. CT has been shown to have a higher accuracy for the detection of cardiac calcifications than other imaging modalities (3,21). Mitral calcifications are often detected incidentally on CT scans of the chest or abdomen (19). Dedicated electrocardiogram (ECG)-gated cardiac CT scans can be performed to evaluate for the presence, location, and extent of mitral calcifications as well as to evaluate other cardiac and extracardiac structures.

Both noncontrast and contrast-enhanced CT scans can be used to assess mitral calcifications. Methods have been developed using noncontrast CT scans to quantify the amount of mitral annular calcification (18). Noncontrast examinations, however, are limited for evaluation of other cardiac structures. Intravenous contrast is needed to opacify the cardiac blood pool so the mitral valve leaflets and myocardium can be differentiated from blood in the cardiac chambers as these structures have similar imaging characteristics on noncontrast examinations (Figure 4).

For this reason, we perform a retrospectively ECG-gated CT with intravenous contrast for preprocedural planning of patients with MAC. ECG gating reduces motion artifact from cardiac motion and with retrospective gating, multiphasic images
can be generated, allowing motion of the mitral valve leaflets and annulus to be evaluated. Intravenous contrast is injected at a rate of 4 to 6 ml/s depending on patient size and the scan is timed to optimize opacification of the left atrium and ventricle using contrast bolus tracking in the ascending aorta. The scan range includes the entire heart and ascending aorta. To optimize image quality throughout the entire cardiac cycle, we do not use dose modulation. Although this increases radiation dose, patients with significant MAC are usually elderly and the improved image quality is believed to be necessary for procedure planning.

The CT is used to determine the precise location and extent of MAC. The circumferential arch of calcifications is best viewed using multiplanar reformatting to create a short-axis view of the mitral annulus. Also, CT can be used to determine whether there are mitral leaflet calcifications, subvalvular apparatus calcifications, or myocardial extension of calcification (Figure 4) (19,20). CT is especially useful for detecting caseous calcification of the mitral annulus, which can be mistaken for an intracardiac tumor, but rather is due to liquefaction of mitral annular calcification. On CT, caseous calcification generally appears as a uniform hyperdense mass.

**FIGURE 3** Mitral Valve Area in Severe Mitral Annular Calcification  

Determining correct mitral valve area in calcific mitral stenosis can be challenging. Whenever 3D echocardiographic images are of good quality we recommend direct planimetry. This can be performed directly on the scanner on carefully selected ventricular en face views of the mitral valve (A), or on multiplanar-reconstructed images of the mitral orifice (C to F); note that cross-section plane is carefully aligned to the leaflet tips in orthogonal views. Pressure half-time (B) usually overestimates valve area due to concomitant diastolic dysfunction that is typically present in this elderly group. MVA = mitral valve area; PHT = pressure half-time; other abbreviation as in Figure 1.
Noncontrast computed tomography (CT) (A) and CT angiogram (B) in a patient with caseous degeneration of mitral annular calcification. Note that contrast allows for visualization of adjacent myocardial structures and blood pool. Extra-annular calcification can involve the mitral valve leaflets (C, arrow), subvalvular apparatus, or the myocardium (D, arrow).

The presence of circumferential annular calcification can be confirmed with reformatted CT images. Abbreviation as in Figure 4.
along the mitral annulus surrounded by dense calcifications (22) (Figure 4). Although it is not routinely performed, mitral valve planimetry can be used to calculate a valve area, especially in patients with limited quality echocardiographic images (23,24).

In addition to evaluation of mitral calcifications, CT is used to evaluate other cardiac structures during the same examination. For patients in whom cardiac surgical procedures are planned, CT angiography is often used to evaluate for coronary artery disease, as CT angiography is a well-established technique for noninvasive evaluation of the coronary arteries (25).

Cardiac CT can also be used to evaluate the cardiac anatomy, cardiac chamber volumes, ejection fraction, and wall motion and can be used to evaluate for intracardiac thrombus (26). In patients with planned interventional procedures on the mitral valve, CT is used to evaluate the systemic arterial and venous anatomy. CT is limited in that it does not allow for the visualization or quantification of mitral regurgitation or transmitral gradients.

**CARDIAC MAGNETIC RESONANCE OF MAC**

Calcifications are difficult to reliably visualize and accurately quantify with conventional cardiac magnetic resonance (CMR) sequences (27). Because of this, we do not routinely use CMR to evaluate MAC or use CMR for procedure planning. As with CT scans, CMR results have been used to evaluate suspected cases of caseous calcification of the mitral annulus (22,27,28). CMR can be used to evaluate the severity of mitral valve stenosis and regurgitation in cases where echocardiography is nondiagnostic; however, this is not routinely performed in patients with MAC.

**MULTIMODALITY IMAGING TO DETERMINE OPTIMAL TREATMENT STRATEGY**

**CARDIAC CT FOR PROCEDURAL PLANNING.** Cardiac CT has taken on an essential role in planning of structural heart procedures, best demonstrated by its use in planning transcatheter aortic valve replacement. As novel procedures are being developed to treat mitral valve disease, including obstruction due to MAC, cardiac CT is becoming an integral tool in the planning these procedures.

As with transcatheter aortic valve replacement planning, CT is an important tool both for assessment of surgical options and transcatheter device selection. Visual analysis of degree of MAC and measurements of the mitral annulus area can be performed with most standard CT post-processing software. Extension of MAC into extra-annular structures that would increase the risk of surgical debridement can be easily visualized by CT. The presence of circumferential annular calcification, needed for optimal device anchoring of balloon-expandable prostheses, can be confirmed with reformatted CT images (Figure 5). Methods for measuring the mitral annular area in patients with annular calcification have been reported; however, a consensus technique for making annular measurements has not been reached (29–31). More research is needed to determine the optimal technique for device sizing and for minimizing complications.

Three of the common conditions associated with MAC, advanced age, female sex, and LV hypertrophy, often lead to a management conundrum when devising percutaneous treatment strategies owing to a heightened risk of LVOT obstruction in the setting of small LV cavities with basal septal hypertrophy and more acute angulation between the aortic and mitral valve planes (Figure 6). Furthermore, transcatheter mitral valve implantations can result in elongation of the outflow tract by displacement of the anterior mitral valve leaflet (32), predisposing to LVOT obstruction. In the global transcatheter mitral valve replacement in native mitral valve disease with severe MAC registry, clinically significant LVOT
obstruction occurred in 6 of 64 (9.3%) patients undergoing balloon-expandable transcatheter mitral valve implantation (33). The angle between the aortic and mitral valves (termed “aortomitral angle”) may be predictive of LVOT obstruction (Figure 6). In addition to standard post-processing software, specialized software has been developed which can be used to place “virtual” prosthetic valves of various sizes in the mitral valve position. The virtual valve image is overlaid on the volumetric CT images showing relationship to the annular calcification and adjacent structures (Figure 7). Adequacy of valve fit, protrusion into the LVOT, and likelihood of LVOT obstruction can be assessed using these images (Figure 8). The measured LVOT area before and after mitral valve implantation is used to predict risk of obstruction using a formula proposed by Wang et al. (34) ([native LVOT area - neo LVOT area]/native LVOT area), although no specific cutpoint has been identified as of yet (Figure 9). These variables can then be calculated with different relative atrial and ventricular valve positions (e.g., 40% atrial 60% ventricular, 50% atrial 50% ventricular, etc.) to determine procedural options for an individual patient (34).

In addition to use in valve sizing and positioning, CT is useful for planning other aspects of the procedure. CT can also be used to predict optimal fluoroscopic angles for device placement. For transapical approaches, ideal rib space and LV access point for ideal catheter trajectory can be determined.
In patients where a transatrial approach is planned, extracardiac structures can be evaluated. CT can be used for evaluating the adequacy of the systemic arterial and venous system when needed depending on the planned approach.

**Echocardiography for Procedural Planning.** 2D and Doppler echocardiography is essential to characterize the LV geometry (LV dimensions and relative wall thickness), quantify the presence and severity of basal septal hypertrophy, LVOT width, the presence of outflow tract obstruction at baseline, systolic motion of the mitral apparatus, and the length of the anterior mitral valve leaflet. All of these variables are then integrated along with CT derived data to help predict the risk and anticipated risk of LVOT obstruction with either surgery or a transcatheter mitral valve implantation. In cases where severe basal septal hypertrophy is present and there is a high risk of LVOT obstruction with percutaneous mitral valve implantation, septal reduction therapy with either alcohol septal ablation or surgical myectomy with or without anterior mitral leaflet resection can expand the LVOT width to facilitate mitral valve replacement. For the transseptal approach, TEE assessment of the interatrial septum is important for planning of the most appropriate septal puncture location and for anticipated difficulty in crossing the septum.

**FIGURE 9** CT Measurement of Baseline and Projected Left Ventricular Outflow Tract Area

CT angiogram reformatted to show the LVOT without and with (“Neo-LVOT”) (arrows) a simulated 29-mm valve placed in the mitral position. The LVOT area without the valve is 335 mm² (top) and with the valve is 53 mm² (bottom). Predicted percentage of obstruction is 84%. Abbreviations as in Figures 4 and 8.
due to fibrosis, prior surgical repair, or lipomatous hypertrophy.

**3D PRINTING FOR PROCEDURAL SIMULATION.** 3D printing has emerged as a fabrication technique in many industries. Medical applications are also rapidly emerging, whether for fabrication of medical devices or modeling of anatomy. The heart is an extremely complex organ and it frequently is difficult to understand the precise 3D anatomy and spatial relationships using 2D imaging representations. Using specialized software, volumetric medical images (CT, CMR, 3D echocardiography), can be used to create 3D printed life-size physical models of anatomic structures. There are multiple different 3D printing technologies available that vary in material properties, geometries that can be printed, print speed, and print cost. These models are used to more intuitively visualize the extent of MAC, relationship of MAC and valve leaflets to adjacent structures such as the LVOT, and route of access to the mitral annulus. In certain cases, a physical 3D model can be printed using polymers that mimic tissue characteristics and which allow actual bench testing of valves into the printed models (Figure 10). This allows direct visual assessment of the LVOT and adequacy of fit. As of now, there are no controlled studies showing the usefulness of 3D printed models for improving procedure feasibility or success or improvements in patient outcomes.

**THERAPEUTIC OPTIONS FOR TREATMENT OF SEVERE MAC**

**STANDARD MITRAL VALVE REPLACEMENT.** Standard mitral valve replacement in the setting of severe MAC represents a real challenge to the surgeon. Proper debridement of the annulus with possible reconstruction is necessary to ensure a well-seated prosthesis with no periprosthetic regurgitation and serves
to minimize the risk of particulate embolization. The calcification process involves the posterior third of the mitral annulus in the majority of patients but it may involve the entire circumference of the annulus in approximately 1.5% of cases. On the vertical level, calcification is most commonly limited to the annulus; however, extension to the leaflet tissues, ventricular myocardium, and papillary muscle can occur in some cases (35). The Achilles heel of this operation is the risk of atroventricular groove disruption with subsequent increase in morbidity and mortality in addition to the time needed for the debridement and valve replacement (36).

There are several surgical techniques that have been described to overcome the challenges associated with the presence of severe MAC:

**STANDARD ANNUAL DEBRIDEMENT WITH RECONSTRUCTION.** This has been the standard technique in which the annulus is thoroughly debrided and all the calcium is removed (35). The calcium bar usually can be separated from the mitral annulus if the dissection is performed in the correct plane. When calcification extends to the underlying myocardium and/or includes one or both mitral leaflets as well as the subvalvular apparatus, the risk of debridement increases considerably. Because of these hazards, the decalcification process may not be suitable to apply for a large number of patients. After debridement and decalcification, the annulus must be reconstructed before placement of the prosthesis. This can be accomplished using either an autologous or a bovine pericardial patch. Local tissue reconstruction can be performed as well using the non-calcified anterior leaflet which can be transposed to the posterior annulus (Figure 11). Despite being the “gold standard” procedure for severe MAC, this technique requires prolonged cardiopulmonary bypass and aortic cross clamp times which further increases the morbidity of the procedure.

**ULTRASONIC PULVERIZATION.** Ultrasonic pulverization using the Cavitron Ultrasonic Surgical Aspirator device (Integra, Plainsboro, New Jersey) have been used in the presence of calcifications such as in cases of constrictive pericarditis (37) and debridement of calcific aortic valve leaflets. Some investigators have used this technique for debridement of MAC as well (38).

**DEEP PERIANNULAR SUTURE PLACEMENT.** Placing sutures deeply around the calcium bar is another potential option for prosthesis anchoring; however, this technique can result in injury of the circumflex coronary artery, which is close to the mitral valve annulus, especially in a left dominant coronary system (39). Furthermore, leaving the calcium bar untouched may increase the risk of periprosthetic regurgitation.

**INTRA-ATRIAL PROSTHESIS PLACEMENT.** Some authors suggest intra-atrial placement of the mitral prosthesis (40,41). In this technique a Dacron collar is added to enlarge the circumference of the prosthesis sewing ring and then the collar is sutured to the left atrial wall above the mitral annulus. This technique may be more appropriate for cases of severe mitral valve regurgitation due to the presence of a dilated annulus but is difficult to accomplish when the main pathology is severe mitral stenosis as a subvalvular...
level of obstruction will persist after placement of the prosthesis. This approach may also be associated with an increased risk of left atrial dissection and bleeding due to the presence of a left atrial segment below the prosthesis that will be under LV pressure.

**LEFT ATRIAL-TO-LEFT VENTRICULAR APICAL CONDUIT (MITRAL VALVE BYPASS).** The concept of mitral valve bypass using a valved conduit from the left atrium to the LV apex is not new and has been previously reported as a treatment for congenital mitral valve stenosis (42,43). For treatment of severe MS due to MAC, mitral valve bypass is an experimental therapy that avoids direct manipulation of the severely calcified mitral annulus. Importantly, this technique cannot be used as a stand-alone treatment for patients with significant MR due to MAC, as the bypass is only a treatment for MS.

The left atrial side of the conduit can be sewn either to the left atrial appendage or the left atriotomy incision site. Both bioprostheses and mechanical valves can be in the conduit depending on the patient age and related comorbidities (Figure 12). Our preference is to connect the inflow of the conduit to the left atrial appendage and place the valve as close to the LV apex as possible (44). This approach allows the conduit to take the shortest pathway, minimizing the high pressure zone between the LV apex and the

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**FIGURE 12 Left Atrial-to-Left Ventricular Valved Conduit Technique**

(Left) Artist illustration demonstrating left atrial-to-left ventricular valved conduit utilizing a mechanical prosthesis. Notice the direction and the location of the prosthesis in relation to the left ventricular apex. The inflow of the conduit is from the left atrial appendage. (Right) Post-operative CT scan with 3D reconstruction in the same patient showing the location and the direction of the conduit. This patient had previous coronary artery bypass surgery. Used with permission of Mayo Foundation for Medical Education and Research. All rights reserved. Abbreviations as in Figures 1 and 4.

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**TABLE 1 Proposed Mitral Annular Calcification Grading System**

<table>
<thead>
<tr>
<th>MAC Grade</th>
<th>Annular Calcification</th>
<th>Extra-Annular Calcification</th>
<th>Therapeutic Options</th>
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</table>
| Grade 1 (Mild) | Focal noncontiguous calcification limited to <180° total annular circumference | None | - Standard mitral valve replacement  
- Medical therapy alone |
| Grade 2 (Moderate) | Dense continuous calcification limited to <270° total annular circumference | Posterior and/or anterior leaflet calcification may be present | - Standard mitral valve replacement  
(if no anterior leaflet involvement)  
- Transcatheter mitral valve replacement with dedicated devices  
- LA-LV conduit (if < moderate MR)  
- Medical therapy alone |
| Grade 3 (Severe) | Dense continuous calcification extending past the commissures into anterior annulus or complete circumferential MAC (≥270° calcification arc) | Posterior and/or anterior leaflet calcification may be present. Papillary muscle or ventricular myocardial calcification may be present | - Transcatheter mitral valve replacement with balloon-expandable or dedicated devices  
- LA-LV conduit (if < moderate MR)  
- Medical therapy alone |

LA = left atrial; LV = left ventricular; MAC = mitral annular calcification; MR = mitral regurgitation.
FIGURE 13  MAC Grading

Short-axis parasternal transthoracic echocardiography images (left) and CT angiography images (right) in corresponding patients are shown.  
(Top) Grade 1 (mild) MAC is characterized by scattered noncontiguous calcification limited to <180° total annular circumference (arrows). 
(Middle) Grade 2 (moderate) MAC is composed of dense continuous calcification limited to <270° total annular circumference (arrows).  
(Bottom) Grade 3 (severe) MAC is defined as dense continuous calcification extending past the commissures into anterior annulus or complete circumferential MAC (≥270° calcification arc [arrows]). Abbreviations as in Figures 1 and 5.
prosthesis. In those patients where the left atrial appendage is too friable or has been ligated or removed in prior surgery, the inflow of the conduit can be from the left atriotomy incision site.

Using a valved conduit to bypass severe MAC is a new indication for the technique that has been performed in a small number of patients. As such, long-term outcomes are lacking; however, it seems to be a less morbid and safer technique than standard mitral valve replacement in this high-risk group of patients. Cardiopulmonary bypass and the aortic cross clamp times appear to be shorter with this technique compared to standard annular decalcification and mitral valve replacement. The risks of conduit-related complications such as thrombosis and kinking appear to be uncommon in the early experience but will need to be studied carefully.

TRANSCATHETER MITRAL VALVE IMPLANTATION

The concept of transcatheter mitral valve implantation for severe mitral valve disease due to MAC is an experimental emerging solution for a difficult problem. The initial experience with transcatheter balloon-expandable SAPIEN valve (first generation balloon expandable valve) (Edwards Lifesciences, Irvine, California) implantation for severe MAC has shown some promise in retrospective studies (45,46).

Among the 2 currently available transcatheter valves approved for clinical use in the United States, the first generation balloon expandable valve is the only device whose design also allows for implantation in the mitral position. In the largest multicenter experience of first generation balloon expandable valve implantation in 64 patients with severe MAC, technical success was achieved in 72% of cases, with a 30-day all-cause mortality rate of 29.7% (33). In this early experience including multiple access routes (transatrial 15.6%, transapical 43.8%, and transseptal in 40.6%) complications included the need for a second valve in 17.2% and LVOT obstruction in 9.3%, but no cases of significant paravalvular leak (33). The ongoing MITRAL (Mitral Implantation of Transcatheter Valves) trial will determine the feasibility and safety of this approach (47) and will also shed light on what criteria should be used to determine appropriate candidates for this technique. Up until now, CT-based evaluation has largely been empiric with application of some of the principles of patient selection from transcatheter aortic valve replacement, which has obvious limitations. On the basis of our experience and existing classifications of MAC, we propose a grading scheme based on pathoanatomic criteria relevant to guide therapeutic options with severe symptomatic MS and/or MR in the setting of MAC (Table 1, Figure 13).

DIRECT TRANSATRIAL IMPLANTATION. In the recent era of transcatheter interventions, surgical attempts have been made at direct transatrial implantation of transcatheter valves in a previously placed mitral ring or degenerated mitral bioprostheses (48). In the presence of severe MAC, this is still in the preliminary phase. Several limitations exist including the complex anatomy of the mitral
In this patient with circumferential MAC (A, side-by-side 3D en face views from left atrial and left ventricular side), a decision was made to implant a 26-mm SAPIEN XT (second generation balloon expandable valve) prosthesis via transseptal approach with the use of a transapical rail. Note the heavily calcified annulus on fluoroscopy (B), facilitating positioning of the valve. Post-deployment, the stent appears in stable position (C). Intraprocedure TEE reveals excellent opening of the bioprosthesis (D), with minor jets of peri-prosthetic regurgitation (E). TEE = transesophageal echocardiography; other abbreviation as in Figure 1.
valve and the risk of LVOT obstruction in the presence of an intact anterior mitral valve leaflet (49).

We have adopted a different strategy in some patients, which is the hybrid approach with direct implantation of the first generation balloon expandable transcatheter valve in the native mitral position through either standard sternotomy or right mini-thoracotomy facilitated with the use of extracorporeal circulation to maintain hemodynamic stability (50). We have also performed this technique through an on-pump beating heart technique without the need for aortic cross clamp and cardioplegia.

Potential advantages for this hybrid strategy include: 1) using a combination of direct visualization and fluoroscopy can facilitate accurate placement of the prosthesis in a relatively short time; 2) open surgical approach allows resection of the anterior mitral leaflet to reduce the potential for LVOT obstruction; and 3) paravalvular leak can be detected at the time of implantation and attempts can be made to repair the site of the leak at the time of surgery or subsequently using percutaneous paravalvular leak closure techniques (51) (Figure 14).

The early experience with transatrial balloon-expandable valve implantation for severe MAC has been performed in few patients using both first generation balloon expandable valve and Melody (Medtronic, Minneapolis, Minnesota) valves (52) and it is expected that it will be only a matter of time before advances in technology address the limitations that have been previously discussed.

**PERCUTANEOUS TRANSSEPTAL DELIVERY.** Perhaps the most direct, but challenging, approach to transcatheter first generation balloon expandable valve implantation in the mitral position is the transseptal route. This approach has been increasingly used for treatment of bioprosthetic mitral valve dysfunction but also for patients with failed ring annuloplasties and severe MAC (46,53). Transseptal access has a number of important advantages such as avoiding thoracotomy or sternotomy, and using left atrial procedural techniques familiar to structural interventionalists. A slightly superior and slightly anterior transseptal puncture (relative to the long axis of the left ventricle) will allow placement of a wire guide that is directed posteroinferiorly, away from the LVOT. Following transseptal puncture, a steerable sheath can be placed in the left atrium. Through the steerable left atrial sheath, the LV cavity can be directly cannulated with a wire loaded into a 6-F or 7-F coronary guiding catheter. The initial wire can then be exteriorized via an LV apical puncture (Figure 15) (54). Following pre-dilation of the interatrial septum with a 10- to 14-mm balloon, the first generation balloon expandable valve delivery system is advanced through the femoral venous sheath into

![FIGURE 16 Septal Reduction Therapy Before Transcatheter Mitral Valve Replacement](https://example.com/figure16)

(Left) Cardiac CTA of a patient with severe MAC and severe basal septal hypertrophy (basal septal thickness 20 mm) who underwent alcohol septal ablation. (Right) Following ablation, the basal septum has thinned (arrows) with a corresponding increase in left ventricular outflow tract size. A simulated 29-mm SAPEIN 3 prosthesis is represented by a red rectangle. Abbreviations as in Figures 1 and 5.
the inferior vena cava, where the balloon and valve are articulated taking care the marker “E” is pointed downwards to allow the system to flex towards the left heart (46). The system is advanced into the left atrium as flexion is applied and subsequently into the left ventricle. If there is difficulty advancing across the septum, a second dilation can be performed from the contralateral femoral vein, but this is usually not necessary. Care must be taken to align the valve extremely carefully to the mitral annular plane. It is very helpful to have a fluoroscopic “marker” of calcification to target the distal and mid portions of the first generation balloon expandable valve, whether second or third generation. The valve is then deployed under rapid pacing in the usual fashion and the results carefully assessed with transesophageal echocardiography. Three things must be carefully evaluated: 1) LVOT obstruction due to anterior displacement of the anterior mitral leaflet, or excess protrusion of the first generation balloon expandable valve into the LVOT; 2) paravalvular leaks, which are commonplace since the annulus is not uniform; and 3) valve stability. A period of observation to ensure valve stability is important, as if the valve were to embolize into the left atrium, it is preferable to have it remain on the wire for stability rather than floating freely in the left atrium. Using these techniques the first generation balloon expandable valves can be delivered successfully in the vast majority of cases, and it is likely that this will become the preferred procedural technique for transcatheter mitral valve implantation in carefully selected patients.
**Transapical Delivery.** Transapical delivery of first generation balloon expandable valves for treatment of native aortic stenosis and for treatment of failed mitral bioprostheses (55) has led to widespread familiarity with the transapical approach for first generation balloon expandable valve delivery. Other valve systems have also been implanted successfully in the mitral position via transapical approach including the Lotus valve (Boston Scientific) in the setting of prior annuloplasty ring (56). The direct route from the LV apex to the mitral valve makes this approach appealing owing to less technical complexity compared to the transseptal or transatrial delivery options. Transapical delivery requires both surgical expertise for exposure of the LV apex and interventional cardiology expertise for creation of a wire rail with anchoring in a distal pulmonary vein. Pre-procedural cardiac computed tomography angiography (CTA) helps to identify any abnormalities of the LV apex such as myocardial fibrosis, overlying scar tissue, and the optimal rib space for approach. CTA delineates the coronary artery anatomy so that the major epicardial vessels can be avoided during apical access. The most coaxial access point to the mitral valve in patients with severe MR is typically located anterior and lateral to the true LV apex and can be predicted by cardiac CTA (57). Optimal location of ventricular puncture is further confirmed during intraprocedural TEE by digital indentation of the myocardium. A stiff J-tipped wire is advanced carefully across the mitral valve and positioned into a pulmonary vein which serves as a rail for valve delivery.

**Dedicated Transcatheter Mitral Valve Devices**

To date, 5 different transcatheter mitral valve systems have been successfully implanted in humans with severe native mitral valve regurgitation, although no dedicated devices exist for treatment of MAC (CardiAQ valve system [Edwards Lifesciences], Tiara valve [Neovasc, Richmond, Canada], FORTIS valve [Edwards Lifesciences], Tendyne valve [Tendyne, Roseville, Minnesota] and Twelve valve [Twelve, Redwood City, California]) (58). Many other dedicated transcatheter mitral valve replacement devices are under development. Similar characteristics among these devices include trileaflet, bovine or porcine leaflets, nitinol self-expanding frames, fabric or pericardial sealing skirts, and transapical delivery (CardiAQ is also available for transseptal delivery). Additional valves in development include the Medtronic Mitral (Medtronic) and Highlife (Highlife, Paris, France) (59,60). The anchoring of these devices relies on unique fixation systems that do not rely on radial force that transcatheter aortic valve replacement devices use, and also are designed to minimize the risk of LV outflow tract obstruction. Although these valves were designed for treatment of severe mitral valve regurgitation, their design may permit them to have an important role in the treatment of severe MAC. Investigational studies of these devices currently exclude MAC; however, it is likely that some or all of these will be tested in the future as a treatment for MAC-associated mitral valve dysfunction. It is likely, however, that specifically designed devices will need to be developed for treatment of MAC. Special considerations include challenges in anchoring devices in MAC, difficulty in grasping leaflets and the inability to place screws into the annulus.

**Role of Septal Reduction Therapy**

Given the common coexistence of LV hypertrophy with severe MAC, consideration has recently been given to the use of septal reduction therapy to increase the size of the LVOT to minimize risk of LVOT obstruction following transcatheter mitral valve implantation. Especially in the setting of transseptal or transapical access where resection of the anterior leaflet is not currently an option, septal reduction therapy typically with alcohol septal ablation can be performed 4 to 6 weeks before mitral valve implantation to reduce basal septal hypertrophy (Figure 16). Using cardiac CT with simulation of valve deployment, patients anticipated to have a severe reduction in LVOT area after valve implantation or those with resting LVOT obstruction who also have significant basal septal hypertrophy may benefit from this approach to make them better candidates for transcatheter mitral valve implantation (Figure 16). Importantly, even patients without resting or provokable LVOT obstruction have the potential to benefit from septal reduction therapy if a transcatheter valve for severe MAC is planned, thus CT simulation techniques play an essential role in this group of patients.

**Conclusions**

Cardiac imaging approaches as well as percutaneous and surgical treatment options are rapidly evolving to improve care for the challenging group of patients with severe MAC resulting in MS or MR. Given the high morbidity and mortality associated with currently available treatment for severe MAC, there is a large need for ongoing research and technologies to better serve this patient population. A good understanding of the unique pathoanatomic features of MAC will be necessary for development of future transcatheter...
endavors targeted at this group. In summary: 1) severe MAC resulting in symptomatic mitral stenosis and/or regurgitation is associated with LV hypertrophy, advancing age, and history of mediastinal irradiation; 2) assessment of mitral valve disease severity in severe MAC can be challenging and often requires integration of multimodality imaging with trans-thoracic and transesophageal echocardiography and cardiac CT angiography; 3) surgical mitral valve replacement in the setting of severe MAC is associated with high operative morbidity and mortality; 4) novel therapeutic strategies for treatment of severe MAC are currently under development and are needed to improve care of this high risk group of patients; 5) major obstacles to transcatheter mitral valve implantation for treatment of severe MAC include prosthesis anchoring and stability, left ventricular outflow tract obstruction, and paravalvular leak (Central Illustration); and 6) dedicated transcatheter mitral valve replacement devices for treatment of severe MAC are needed.

REFERENCES


KEY WORDS: cardiac computed tomography angiography, echocardiography, mitral annular calcification, transcatheter mitral valve implantation