Degenerative Mitral Stenosis: From Pathophysiology to Challenging Interventional Treatment

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Abstract: Mitral stenosis (MS) is characterized by obstruction of left ventricular inflow as a result of narrowing of the mitral valve orifice. Although its prevalence has declined over the last decade, especially in developed countries, it remains an important cause of morbidity and mortality. The most often cause of MS worldwide is still postrheumatic mitral valve disease. However, in developed countries, degenerative or calcific changes cause MS in a siginificant proportion of patients. Although the range of treatment for mitral valve disease has grown over the years in parallel with transcatheter therapies for aortic valve disease, these improvements in mitral valve disease therapy have experienced slower development. This is mainly due to the more complex anatomy of the mitral valve and entire mitral apparatus, and the interplay of the mitral valve with the left ventricle which hinders the development of effective implantable mitral valve devices. This is especially the case with degenerative MS where percutaneous or surgical comissurotomy is rarely employed due to the presence of extensive annular calcification and at the base of leaflets, without associated commissural fusion. However, the last few years have witnessed innovations in transcatheter interventional procedures for degenerative MS which consequently hinted that in the future, transcatheter mitral valve replacement could be the treatment of choice for these patients. (Curr Probl Cardiol 2019;44:10–35.)

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Introduction

Mitral stenosis (MS) is characterized by obstruction of left ventricular (LV) inflow as a result of constriction of the mitral valve orifice. Although its prevalence has declined in 21st century, especially in developed countries, it is still an important cause of morbidity and mortality.[1] It still accounts for approximately 10% of native valve diseases, frequently affecting young immigrants and the elderly.[1,2] MS most often occurs decades after the occurrence of rheumatic fever[2] with the main mechanism being postrheumatic commissural fusion. The prevalence of rheumatic heart disease remains constant in less developed countries, being estimated from 1 to 7 per 1000 children when employing clinical assessment only, but with a 10-fold increase in detection when using systematic echocardiographic screening.[3,4]

However, in developed countries, calcific changes of the mitral annulus cause degenerative MS (DMS) in a sizeable proportion of patients, especially in the elderly.[5] In most patients, calcification and degenerative changes seldom lead to significant valve stenosis as calcified nodules are most often located at the base of the leaflets and associated with valve leaflet thickening, but without causing significant restriction of leaflet movement and obstruction to flow.[6] Other causes of DMS are rare and may include systemic inflammatory disease (ie, systemic lupus erythematosus), infiltrative diseases, and drug-induced valve diseases.[5]

DMS As a Target of Clinical or Scientific Research

Although the range of treatments for mitral valve disease have grown over the years in parallel with transcatheter therapies for aortic valve disease, the improvements in mitral valve disease therapies have experienced slower development. This is mostly due to the more complex anatomy of the mitral valve and whole mitral apparatus, and the interplay of the mitral valve with the LV which interfers with the development of effective implantable mitral valve devices. This is especially the case with DMS where percutaneous or surgical comissurotomy have been rarely been employed due to the presence of extensive annular calcification and at the base of leaflets, without associated commissural fusion. However, the last few years have witnessed significant innovations in transcatheter interventional procedures for mitral valve disease which consequently hinted that in the future transcatheter mitral valve replacement (TMVRT) could be the choice for the treatment of these patients.

At present, treatment strategies, as well as risk stratification and investigation in asymptomatic or symptomatic patients with DMS, have still not been subject to thorough clinical and scientific investigation as is the case with patients with aortic stenosis (AS).[6-11] Despite the fact that the diagnosis of degenerative mitral valve disease and transcatheter management is evolving, this has been mostly related to mitral regurgitation (MR), and much less to DMS.[12] A case in point; a search result for the term "mitral regurgitation" on Pubmed revealed 30,145 publications, whereas the same search for the term "degenerative mitral stenosis" showed only 274 published papers. Likewise, search for the ongoing (recruiting or not yet recruiting) clinical trials showed that there are currently 308 trials evaluating patients with MR (primary and secondary) and only 33 are related to MS, of which only MITRAL (NCT02370511, transcatheter approach) and SITRAL trial (NCT02830204, surgical approach) are enrolling patients with DMS or significant mitral annulus calcification (MAC). With regard to multicenter Mitral Implantation of TRAnscatheter vaLves (MITRAL) trial, this is the only trial using transcatheter approach. The trial will evaluate the safety and feasibility of the Sapien XT or Sapien 3 (Edwards Lifesciences, Irvine, CA) transcatheter valves in the treatment of severe calcific mitral valve disease in patients who are not surgical candidates. It aims to enroll 90 patients with severe mitral valve disease due to either severe calcific mitral valve disease with severe MAC or due to failing surgical rings or bioprostheses. This is probably the first of many studies that will be seeking to demonstrate the feasibility and safety of transcatheter mitral valve implantation in patients with DMS.

Epidemiology

MAC is a chronic, degenerative process affecting the fibrous support at the base of the mitral valve. It is most commonly asymptomatic and an incidental finding. MAC tends to be more common with aging, although other underlying processes, such as atherosclerosis, altered mineral metabolism (principally calcium-phosphorus homeostasis), or increased mechanical stress also promote development of MAC.[13] According to existing data, the prevalence of MAC is from 8%-15%, and increases with age and in patients with multiple cardiovascular risk factors or chronic kidney disease.[14-16] However, MAC is probably underdiagnosed and underrecognised due to the mainly asymptomatic status of MAC patients, which precludes true evaluation of its prevalence in the broader population.

Essentially, the underlying pathologic lesion of DMS is MAC.[13] Throughout the years many studies have explored the prevalence of

DMS, but the findings have been disparate. In studies conducted in the 1980s, it was estimated that ≈ 6% to 8% of patients with severe MAC will develop with MS.[17] The Euro Heart Survey reported that degenerative causes of MS account for 12.5% of cases from 336 patients with MS as diagnosed by echocardiographic screening, and the majority of these patients (≈74%) presented with severe and symptomatic disease.[1] The more recent study revealed that among patients noted to have mitral valve calcification on multidetector computed tomography, echocardiographic assessment was concordant in 26% of cases.[18] The study by Ukita et al[19] further showed that prevalence of DMS significantly increases in nonoctogenarians, is more often in females and is often associated with degenerative AS. This has been further validated in USA CDC National Health Report which demonstrated that DMS has become more prevalent over the last decade in general due to the increase in the life expectancy.[20] Thus, as the population ages, it is expected that the prevalence of DMS will also increase in years to come.

Pathophysiology

As discussed earlier, the underlying pathologic lesion of DMS is MAC.[13] The mitral annulus is a fibrofatty membrane that separates the left atrium and LV. The mitral annulus may be subjectively divided into anterior and posterior segments correlating with the attachments of the anterior and posterior mitral leaflets. The anterior segment of the annulus is in continuity with the fibrous skeleton of the heart and is confined by the left and right fibrous trigones and the aorto-mitral curtain (a fibrous sheet extending from the anterior mitral annulus superiorly to meet the aortic valve annulus at the level of the left and noncoronary cusps).[21] The posterior annulus encompasses the remainder of the annular perimeter and is composed of a discontinuous rim of fibrous tissue, here and there interrupted by fat.[21] MAC, as a precursor to DMS, more commonly affects the posterior rather than the anterior part of the annulus.[13] The *antero-posterior* diameter ≤35 mm (performed with echocardiography at end-systole in 3 chamber view) or an annular diameter to mid-diastolic anterior mitral valve leaflet length ratio of 1:3 is considered the upper limit of normal mitral annulus.[22] Functionally, the mitral annulus plays an important role in left atrial and LV function. The motion of the annulus itself is passive and determined by the contraction and relaxation of surrounding atrial and ventricular musculature. The overall circumference of the annulus may decrease by as much as 20% during systole.[23] Reduction in annular size begins with atrial contraction and peaks in mid-systole.

Yet, this passive motion of the mitral annulus is consequential as it prevents leaflet drilling during leaflet coaptation and unload mitral valve closing forces, thus reducing the leaflet closure stress as the LV systolic pressure rises.[24] The plausible mechanisms by which MAC contributes to DMS include reduced normal annular dilatation during diastole and impaired anterior mitral leaflet mobility such that the leaflet's hinge becomes displaced toward its free margin.[25-27] The importance of the mitral annulus is also evident from the effect of its damage on a number of disorders including functional or ischemic MR, mitral valve prolapse, atrial fibrillation, and annular submitral aneurysm.[24]

Elevated LV pressure (as is the case in significant AS or systemic hypertension) increases mitral annular tension and, if persistent, consequently leads to annular micro cracks and trauma. These sites of annular damage are believed to undergo typical degenerative dystrophic calcification, leading to MAC.[6,24] Consistent with the hypothesis that MAC and atherosclerosis in general share a similar pathophysiological process and have affined risk factors,[28-30] multiple studies have demonstrated a distinct association between the degree of MAC and the existence of aortic atheroma, increased carotid intima-media thickness, and peripheral arterial atherosclerotic disease.[31-33]

The association between MAC or DMS and degenerative AS, as shown in Figure 1, is common and demonstrated in number of previous studies, which is important as degenerative AS is the most frequent valve disease requiring some kind of intervention in developed countries.[34-37] In addition, severe MAC is increasingly encountered in patients undergoing mitral and aortic valve interventions, pointing to the importance of understanding the association between these 2 diseases. In both DMS and AS, plasma concentrations of natriuretic peptides are greater with increasing

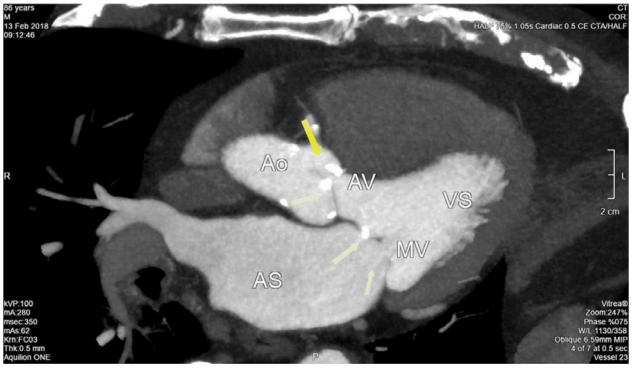

FIG 1. Pronounced calcification of mitral and aortic valve (courtesy of Dr Oliver Radmili).

severity of disease due to the pronounced atrial or ventricular remodeling and increased wall stress, which might help in risk stratification of these patients when asymptomatic.[38-40] Another similarity between severe AS and DMS is impaired coronary flow reserve (CFR), even in patients with normal epicardial coronary arteries.[41-43] Mahfouz et al[42] also demonstrated that CFR negatively correlates with LV ejection fraction in patients with MS, and that CFR value is directly proportional to mitral valve area (MVA). As observed in AS patients, the reduction in CFR could be the key factor responsible for myocardial ischemia[44] and together with structured changes in myocardium can be the cause of potentially fatal arrhythmias. However, the prognostic importance of CFR in patients with severe MS is yet to be demonstrated. MAC itself is marker of increased risk for cardiovascular death.[45] Moreover, Sheng et al have recently demonstrated that global cardiac calcification is associated and correlates with MS severity and coronary artery disease in patients with severe calcific AS. They have also showed that simple echocardiographic calcium scoring measurement shows ability to predict the presence of MS and at a same time may be used as part of a risk-stratification in patients with severe calcific AS.[46] Furthermore, the concomitant presence of even mild AS increases mortality in patients both with MAC or DMS.[47] Obviously, risk stratification in asymptomatic patients with severe MS is important; as once they become symptomatic their reported prognosis is variable, but generally poor.[48,49] Importantly and in addition, approximately half of the patients experience sudden and progressive symptom development and clinical deterioration.[5] Thus, a critical appraisal and identification of concrete markers or parameters that might help in risk stratification of asymptomatic DMS patients is necessary.

Assessment of DMS Severity

Echocardiography is the cornerstone in the evaluation of suspected or known MS and is used to confirm the diagnosis, evaluate the severity of the disease, and to plan a management strategy. Standard 2-dimensional (2D) transthoracic echocardiography (TTE) enable adequate analysis of mitral valve anatomy and morphology. TTE also allows visualization of MAC as an echodense structure with an irregular, lumpy appearance with associated acoustic shadowing. With respect to echocardiographic analysis of DMS, there is frequently extensive MAC and thickening that extends into the leaflet bases, but the body of the leaflets is generally thin (the width <5 mm) and mobile.[50] When TTE image quality is suboptimal, transesophageal echocardiography (TEE) may be helpful. Three-dimensional

echocardiography (3D) may be also helpful in evaluation of DMS severity, especially through accurate planimetric measurements of the MVA.[51] Furthermore, recently introduced real-time 3D TEE, if available, yields excellent images of mitral valve and might give additional information when needed.[52]

The most important parameter for assessing DMS severity is MVA. The normal MVA is approximately 4-6 cm^2. A 2D parasternal short-axis view enables direct planimetry, which is the reference measurement of MVA.[53] This is the only method that directly measures the valve area, and is importantly, independent of loading conditions and associated heart diseases.[5] The 2D image frame should be stopped and valve measured at the level of the leaflet tips. As emphasized in the text earlier, 3D echocardiography can facilitate positioning the measurement plan. All studies showed good correlation of 3D-guided 2D planimetry with 2D methods but some showed that MVA obtained by 3D approach is smaller, probably due to a better alignment with the narrowest portion of the valve.[54] However, both 3D, and especially 2D planimetry measurement can be difficult, sometimes even impossible, in the case of heavily calcified mitral valve, or in patients with poor acoustic windows. Beside planimetry, the parasternal short-axis view is helpful in differentiating between rheumatic MS and DMS, as in the latter the commissures are not fused. The pressure half-time method for measuring MVA is generally easier to perform and is widely used, but may be misleading in concomitant aortic regurgitation or decreased LV compliance.[53,54] The biggest discrepancies between planimetry method and pressure half-time method for measuring MVA are seen in elderly and in patients with atrial fibrillation.[55] The use of continuity equation is somewhat more difficult than previous methods due to the number of variables that need to be included and calculated, and is limited by concomitant aortic or pulmonary valve insufficiency.[22] The MVA can also be measured by dint of multislice computed tomography planimetry, with the results compatible to those obtained by cardiac catheterization (with Gorlin's formula) or 2D TTE planimetry.[56,57] In their analysis Oktay et al[57] pointed out that, bearing in mind the aforementioned limitations of echocardiography, multislice computed tomography can be especially of help when evaluating the patients for which there is intention for subsequent MV intervention.

Mean mitral valve gradient assed by continuous wave Doppler echocardiography is not reliable for exact measurement of DMS severity due to its high dependence on the flow condition. It has been recently shown that mitral leaflet separation, measured by averaging the maximal leaflet tip distance in diastole with TEE 3D, might help in evaluation of MS

severity.[58] There was also significant positive correlation between maximal leaflet separation and 3DTEE planimetry measurement of mitral area. However, this method needs further validation, especially in patients with isolated severe DMS.

In summary, based on available data, 3D-guided 2D planimetry should be considered the "gold standard" in defining the MVA.[59] Nevertheless, the consistency of planimetry, pressure half-time, and mean gradient should always be checked, although limitations of each method should be kept in mind.[59] The severity of mitral valve stenosis can be further evaluated with Wilkins, Echo score "Revisited," or Cormier score, but these scores are more suitable for assessing rheumatic MS than DMS.[34,60,61]

Treatment Approach to DMS

The type of treatment, as well as its timing, should be decided on the basis of patient's characteristics, valve anatomy and local expertise. The basical therapy in patients with significant DMS is medical management with heart rate control and diuretic therapy.[34] However, medical therapy can only transiently improve symptoms in the short and medium term, but cannot cure the disease or improve prognosis. Thus, intervention should be performed in symptomatic patients. Majority of patients with favorable valve anatomy currently undergo percutaneous mitral commissurotomy (PMC), however, open commissurotomy may be the preferred operation by experienced surgeons when treating younger patients with concomitant mild to moderate MR.[34] As pointed in current ESC valvular guidelines, PMC may be even considered in symptomatic patients with a valve area >1.5 cm^2 if symptoms cannot be explained by another cause and if the valve anatomy is favorable.[34] In patients with unfavorable anatomy, decision making as to the type of intervention is still a matter of debate and must take into account multiple factors.[62-64] In patients with DMS who have heavily calcified valve, open surgery may be risky, especially in the elderly. As mentioned in the text earlier, in patients with DMS there is no commissural fusion and thus these patients are not amenable to PMC. This may be particularly important in elderly, high-risk patients who might be candidates for the transcatheter valve implantation, but so far this hypothesis is based on very preliminary experience and limited data.

The Transcatheter Treatment of DMS

Percutaneous catheter-based approaches to cardiac valve repair were initiated in the 1950s with the introduction of simple catheter devices for

treating pulmonary stenosis.[65] Treatment of stenotic lesions continued to develop and mature in the early 1980s with the advent of balloon valvuloplasty,[66] which has become the predominant therapy for rheumatic MS. Efforts to develop and refine percutaneous approaches to cardiac valve repair and replacement have thrived rapidly over the past few years, having exceeded even the most optimistic expectations. New innovations have been predominantly directed toward the 2 most frequent forms of valvular heart disease in the industrialized world; AS and MR, which account for more than 70% of the cases of acquired valve disease in the United States and Europe.[67] Approximately 350,000 transcatheter valve procedures have been performed worldwide to date. Transcatheter aortic valve implantation (TAVI), has been performed in about 300,000 patients around the world (and its use keeps growing 40% annually) (A Cribier, "A brief history of TAVI", EuroPCR 2017.[68-71] On the other hand, percutaneous Mitraclip implantation for MR has been performed in >50,000 procedures as of July 2017 (http://www.mitraclip.com/hcp). Evidently, there is a subtle but progressive paradigm shift in the treatment of valvular heart disease. However, at this point, the percutaneous transcatheter management of clinically significant DMS is still in its infancy.

That being said, surgical mitral valve replacement (SMVR) has been the method of choice for treating patients with symptomatic DMS, whereas transcatheter treatment of DMS has been, so far only used to treat patients on compassionate basis. Several dedicated mitral valve transcatheter valves are currently in their infancy or in development and are focused mainly on patients with severe MR.[71-73] Thus, the evolution of TMVRT in patients with DMS has lagged behind that of TAVI, primarily due to the increased complexity of the mitral valvular apparatus and veritable peril of postprocedural LV outflow tract obstruction. So far, it has been demonstrated that placing a bioprosthesis used in TAVI procedures in the mitral position is feasible for elderly people who are deemed inoperable or not suitable for open heart surgery.[74]

Structural deterioration of surgical bioprosthesis causing repeat intervention within the first 10 years of initial surgery is relatively common, with an incidence that increases with younger age, occurring in up to 35% of patients undergoing bioprosthetic mitral valve replacement.[75,76] Repeated mitral valve surgery is associated with significant morbidity and mortality, and therefore, a less-invasive approach is a desirable alternative in selected cases.[77] The feasibility of TMVRT has been already reported with balloon-expandable SAPIEN XT valve (Edwards Lifesciences, Irvine, CA) and Melody valve (Medtronic, MN) for valve-in-valve and valve-in-ring implantation in patients with dysfunctional mitral

bioprosthesis and annuloplasty rings.[78-81] The postprocedural results were very favorable with low postprocedural transvalvular gradient and perivalvular regurgitation. In addition, recently published single case hinted that TMVRT might be successful for valve-in-ring treatment of para-ring regurgitation.[82] Other transcatheter valves including the mechanically expanding Lotus (Boston Scientific, Marlborough, MA) and DirectFlow valves have also been used successfully for valve-in-valve, valve-in-ring treatment, and in patients with MAC. However, this experience is limited to few case reports at this time[83-85] and the Direct Flow valve is no longer available. The report from Cheung et al[79] described a series of 23 consecutive patients with failed mitral bioprostheses who were successfully treated with transcatheter valve replacement via a transapical approach using a 33 F Edwards SAPIEN type balloon expandable valve system. The device success rate was 100%, there was no intraprocedural or 30-day mortality and at a median follow-up of 753 days the survival rate was 90.4%. Descoutures et al[85] demonstrated favorable valve-in-ring outcomes using the Sapien XT valve, with a technical success rate of 89% using the transapical approach and 87% with the transseptal approach. The successful valve-in-ring implantation using transapical and antegrade approaches were also reported for Melody valve.[86,87] Very recently Elmously et al[88] demonstrated successful transapical mitral bioprosthetic valve-in-valve implantation in 19 high-risk patients with Edwards-SAPIEN valve. Clearly, most of the operators have used the Edwards SAPIEN XT aortic valve (Edwards Lifesciences, Irvine, CA) in the mitral position. As a result, in February 2014 Edwards received CE Mark approval and in 2017 Food and Drug Administration approval for transcatheter mitral valve-in-valve implantation for balloon-expandable SAPIEN valve, and with the vast majority of cases using a transapical approach.[77,89] An alternative may be the transvenous, transseptal approach, which involves obtaining femoral venous access followed by transseptal puncture in a posterior and superior location in the interatrial septum. The direct access and close proximity to the MV and possibility of achieving coaxial alignment to the mitral valve are advantages to the transapical route, whereas disadvantages of the transapical approach include prolonged recovery time, increased risk of pulmonary complications (especially in patients with existing lung disease), and higher bleeding incidence.[90] The majority of mitral valve-in-valve procedures in the largest so far published series were performed via the transapical approach in 67%, whereas 33% were performed using totally percutaneous transseptal access.[91] Interestingly, preliminary data from the Valve in Valve International Data Registry suggests that patients with transapical

approach are facing less improvement in LV ejection fraction compared to a transseptal approach following mitral valve-in-valve implantation.[92]

Experience with TMVRT in native DMS is limited. In 2014, Himbert et al[93] described a case series of 4 patients with isolated antegrade transvenous-transseptal TMVR with balloon-expandable SAPIEN XT valves in native valves with severe MAC. Lim et al[84] reported the first 2 cases of TMVRT with self-expanding and repositionable Lotus valves in patients with MAC. From the very beginning it was clear that TMVRT is not going to be an easy and straightforward procedure. This was demonstrated in 2 case-reports by Hulman et al,[94] which were complicated by periprocedural and postprocedural dislocation of balloon-expandable prosthetic valves which were successfully resolved. There is however, the largest registry of TMVRT for native DMS, which included 64 patients, published by Guerrero et al.[74] These cases were performed via a transapical (43.8%), transatrial (15.6%), or transfemoral or transseptal (40.6%) approach. The mean gradient decreased from 11 mm Hg to 4 mm Hg, successful valve implantation was achieved in 72% of patients and during 1 month follow-up all-cause mortality was 29.7%, pointing to the high risk of adverse events. However, the outcomes improved as the experience accumulated with more patients treated. A subsequent analysis of 104 patients from the MAC global registry evaluated outcomes relative to experience, dividing patients in tertiles in chronological order according to date of procedure. Most of the complications occurred in the first third of treated patients. Technical success in the first tertile was 62.5%, improved to 84.4% in the second third, and was 80% in the third tertile. Thirty-day mortality was 37.5% in the first tertile and lessened to 21.9% in the second tertile and to 15% in the last tertile.[95] Evidently, at this point, most TMVRT devices employ transapical delivery system, whose size ranges from 30-36-F, but as demonstrated, a transvenous-transseptal approach is also feasible. Recently, El Sabbagh et al[96] went a step further, demonstrating that 3-D computer prototyping for TMVRT in patients with severe MAC might be feasible and helpful for patients, simulating valve sizing, apposition, expansion, paravalvular leak (PVL), and LV outflow tract obstruction before the actual procedure. The registries and case reports, as well as ongoing studies investigating TMVRT in native DMS are shown in the Table.

Obviously, TMVRT in patients with DMS is at the very beginning of what is appearing to be a long road to success. More studies are needed to validate the outcomes of TMVRT in patients with DMS and to develop a better understanding of possible complications. From a more general perspective, positive results of TMVRT in high-risk patients with DMS

TABLE. Registries, case reports, and ongoing studies investigating TMVRT in patients with native MAC/DMS.

Study	No of patients	Valve type	Approach	Outcome
Hasan et al[97]	1	Edwards-SAPIEN valve	Transapical	Mean gradient from 14-7 mmHg, no complications
Himbert et al[93]	4	SAPIEN XT valves	Transvenous-transseptal	MG was 3-5 mm Hg NYHA functional class I/II at follow-up. One Patient had residual MR grade 2+
Lim et al[84]	2	Self-expandable Lotus valve	Transapical	The mean transvalvular gradients were 4 and 7 mm Hg, respectively, with no more than mild paravalvular regurgitation; no postprocedural complications
Ribeiro et al[98]	1	Sapien XT valve	Transapical	Mild paravalvular leak on follow-up
Mellert et al[83]	1	Direct Flow aortic valve	Transapical	Mild paravalvular leak, no residual stenosis
Guerrero et al[74]	64	Edwards-SAPIEN valve	Transapical (43.8%), transatrial (15.6%), transfemoral/ transseptal (40.6%)	Mean gradient decreased from 11 mmHg to 4 mmHg ± 2.2 mmHg, successful valve implantation was achieved in 72% of patients and during 1-mo follow-up all-cause mortality was 29.7%. Paravalvular regurgitation was mild or absent in all patients
Guerrero[95]	104	Edwards-SAPIEN valve	/	A subsequent analysis of 104 patients evaluated outcomes relative to experience, dividing patients in tertiles in chronological order according to date of procedure. Most of the complications occurred in the first third of the patients. Technical success in the first tertile was 62.5%, improved to 84.4% in the second third, and was 80% in the third tertile. Thirty-day mortality was 37.5% in the first tertile and decreased to 21.9% in the second tertile and to 15% in the last tertile.

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TABLE (*Continued*)

Study	No of patients	Valve type	Approach	Outcome
Sinning et al[99]	1	Edwards-SAPIEN XT	Transapical	After the procedure, the patient improved with a decrease in functional NYHA IV to class to grade II, with mean gradient 3 mmHg
MITRAL trial (NCT02370511)	90 (estimated)	Edwards SAPIEN XTTM and SAPIEN 3	/	Ongoing; The primary safety endpoint is technical success at exit from the cath laboratory and procedural success at 30 d. The primary effectiveness endpoint is individual patient success at 1 year

could have positive economic effect on the health care systems primarily due to the associated reductions in intensive care unit admissions and general hospital stay. In that context, very limited data show that TMVRT may be cost-effective relative to medical treatment in patients with DMS.[100] This potential cost-effectiveness could also serve as a boost for everyone involved in this field to improve technology and further investigate the use of TMVRT in high-risk patients with DMS, as there is obviously an unmet need in interventional treatment of these high-risk patients.

Surgical Management of DMS

Traditionally, SMVR with or without annular debridement of MAC, has been the method of choice for treating patients with symptomatic DMS. However, these patients are usually elderly with multiple comorbidities and thus carrying significant risk for surgery. Although there is some evidence to suggest that, even in elderly patients, SMVR before the occurrence of advanced symptoms may improve long term outcomes, there may be a delay in intervention until symptoms are severe and cannot be managed by medical therapy, but by then increasing the mortality and morbidity risk of surgery.[101]

Surgical correction in DMS can be broadly grouped into 2 approaches: SMVR with and SMVR without annular reconstruction.[102] The presence of annular calcium poses a significant challenge for surgeons attempting MVR in these high-risk patients. MAC with or without extension to the leaflets, annulus, or sub-annular extension into the ventricular myocardium gives rise to a variety of technical challenges in valve repair or replacement. In Figure 2 is shown pronounced MAC that involves posterior part

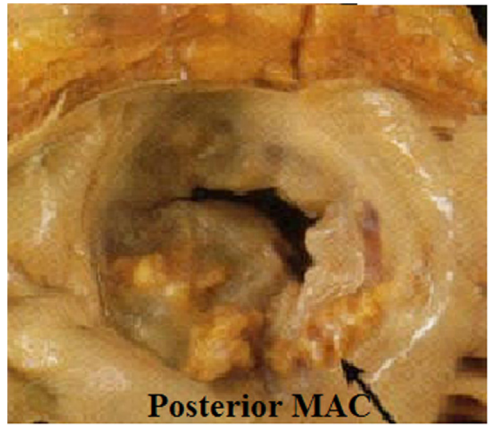

FIG 2. Pronounced MAC of posterior mitral annulus.

of mitral annulus. The calcium bar is described as being encapsulated in a fibrous sheath, distinct from the surrounding tissues except in the areas of infiltration into the myocardium. This suggests that the calcium bar can be excised en bloc, but in reality it is still a difficult and technically challenging procedure fraught with risk. As described earlier, MAC tends to exclusively involve the posterior leaflet, but in the minority of case may varyingly involve the anterior annulus as well. As the anteriorly annulus is much less pliable than the posterior annulus, the posterior annular calcium bar prevents reconstruction, reduction, and realignment of the mitral annulus. SMVR also depends on an intact fibrous mitral annulus to provide a secure anchor for the valve sutures, and this is absent in severe MAC. Furthermore, atrioventricular continuity is dependent on the integrity of the fibrous annulus. Thus debridement of the calcified tissue risks separation of the atrium and ventricle or damage the circumflex coronary artery.

Anatomically, the circumflex coronary artery is closely related to the posterior annulus. Passing sutures directly through the calcium bar to anchor the prosthesis is difficult, but is usually possible but risks calcium fragmentation, annular dehiscence, atrioventricular dissociation, or significant PVL (with an incidence of >10% in patients undergoing SMVR for MS[103]). Attempts to place deep sutures encircling the valve can avoid the need for debridement of the calcium bar, but this significantly risks circumflex artery injury. The choice of prosthesis is determined by patient choice in certain circumstances, age, concomitant need for anticoagulation and LV size.

Carpentier et al[104] has previously described the seminal technique of en bloc excision of the calcium bar in MAC. It is based on en bloc excision of the calcium bar instead of fragmentation, and reconstruction of the annulus with living tissue. Other forms of annular reconstruction have also been described in the intervening years. The reconstruction after en bloc excision of the calcium bar comprises closure of the 2 edges of the remnant fibrous sheath delineating the atrium and ventricle with a series of figure-of-8 mattress sutures. This technique achieves reduction in the size of the annulus, and also displaces the vessels and fat away from the reconstructed annulus. A further continuous suture is run along this reconstruction to reinforce the closure and prevent dissection of blood into the groove and risk atrioventricular dissociation.

If calcium extends into the ventricular myocardium, reconstruction requires coverage of exposed myocardium and a sliding atrium technique can be employed, which uses a flap of atrial edge to patch the defect.

If there is papillary muscle or chordal involvement, there have been various techniques described to preserve these structures if possible, or excision and replacement as part of the MVR.

Despite this, excision of MAC carries significant major risks. Spencer et al[105] reported 14 cases of LV rupture. In 4 patients, LV rupture was associated with posterior MAC, and 3 patients had undergone annular debridement. Although complete debridement is difficult, partial is often achieved, but there are hazards to this; the remaining calcium bar can fracture and embolise, or its motion can lead to lateral ventricular wall injury and rupture. Intractable hemorrhage from the ventricular wall is another complication that has been reported. MacVaugh et al[106] reported their experience of 5 cases among a total of 10 patients with posterior MAC in which SMVR was complicated with intraoperative hemorrhage from the LV.

In the past, various modifications of SMVR have been used to improve outcomes and to avoid potentially fatal complications. Said and Schaff[107] from the Mayo Clinic have recently used a previously described left atrial appendage to LV mitral valve bypass using a valved conduit in a 44-year old patient with end-stage renal failure, diabetes, and peripheral vascular disease, who presented with symptomatic, severe aortic and MS, and severe MAC. This completely avoids approaching the mitral valve and the attendant risks previously discussed. There are still risks of bleeding at the ventricular anastomosis especially in elderly patients with friable tissue. There are no large series looking at results with this technique.

A more novel surgical approach is being investigated in the SITRAL trial (NCT02830204). The purpose of this study is to establish the safety and feasibility of the Edwards SAPIEN 3 valve in subjects with MAC associated with MS or MR who are at high-risk for mitral valve surgery or deemed inoperable due to the extent of calcification (phase 1 and 2). It is a single group assignment, with 30 participants. The estimated completion date is the end of the 2018. Primary outcomes for the trial are procedural and technical success at 30 days, as well as device success at the time of deployment. Secondary outcomes being device success at 6 months and 1 year and subject success at 1 year.

Outcomes of SMVR (with different techniques) for DMS have been published in very small series ranging from 6-11 patients, and short follow-up periods only. The outcomes are not particularly encouraging, demonstrating how difficult the surgical management of this condition can be, and how difficult it is to get consistently good results. Cammack et al reported 6 patients who underwent surgical MVR with mechanical or porcine valve and partial or complete debridement of MAC with mitral reconstruction in

1 patient. Follow up was 12-29 months. 3 patients died; 2 in hospital from LV rupture and low cardiac output, and 1 a year later from sudden cardiac death.[108] Nataf et al reported 7 patients (out of 212 patients with MAC), who underwent SMVR with intra-atrial placement of the prosthesis. Out of the 21 patients with MAC, 5 died in the perioperative period, 5 underwent redo-operations, and 2 developed perivalvular leak at follow-up.[109] There are some proponents of the use of ultrasonic energy for debridement of MAC, arguing that it carries less complication than traditional surgical debridement techniques. Baumgartner et al reported the use of Cavitron ultrasonic aspirator for decalcification of MAC followed by MVR in 11 patients. Thirty-day follow up demonstrated no mortality and no PVL.[110] Iida et al had similar results with ultrasonic debridement, but in only 2 patients. Follow up at 24 and 46 months showed no complications or mortality.[111] Bito et al[112] and Kato et al[113] used the half and half technique of suturing the SMVR prosthesis partially intra-annular and partially supra-annular in the atrium, thus avoiding the area of severe MAC. Bito only reported this in 1 patient with no mortality or complications at 10 months. The latter study included 4 patients. One patient died at 1 month, and another patient had trivial paravalvular regurgitation at the 6-month follow-up. Another half and half technique of implantation was reported by Takahashi et al[114] in 2014, in 2 patients, which were followed to 10-13 months with no complications. Finally, Hussain et al[115] reported SMVR after partial debridement of annular calcium and the use of an annulus washer in 9 patients. Follow up was to 8 months, but actual survival was 50% at 5 years.

A proposed algorithm for the management of patients with MAC and severe MS (MVA $< 1.5\ cm^2$), would be to first determine if the patient is asymptomatic or symptomatic. If asymptomatic, thus cohort should be followed up regularly with serial clinical and echocardiographic assessment. If symptomatic, the mainstay of treatment is heart rate control and diuretic therapy. If this modality of treatment renders the patient asymptomatic, then the pathway is through regular clinical and echocardiographic assessment. If the patient remains symptomatic, then surgery should be considered based on the assessment of surgical risk. Those with low to moderate surgical risk should be offered SMVR. Besides physical and clinical assessment of surgical risk (mortality and morbidity), the feasibility of successful SMVR based predominantly on the severity of MAC should also be given serious consideration. This is also determined by the experience of the surgical team in dealing with high risk of debridement MAC and the possibility of annular reconstruction. Patients considered too high a risk for surgery should be given palliative care or if

suitable, assessed for alternative new therapies or enrollment in pre-existing clinical trials.

Conclusion

Many patients with severe DMS are currently left untreated because of the presence of multiple comorbidities that significantly increase the risk of mortality with SMVR. It is apparent from the preceding discussion that the surgical management of DMS is difficult with no clear guidelines. Published series are small, use several different techniques, which produce mixed results. A percutaneous approach somewhat similar to TAVI may provide an alternative treatment option for otherwise inoperable or high-risk cases. However, attempts to treat DMS with or without MAC with mainly balloon-expandable valves have been made, and technology is improving, making this modality of treatment a possible choice for this condition. Decision-making should be done by a multidisciplinary "Heart Team," which would pool expertise and consensus opinion as to the best recommendations for individual patients. In other words, a joint approach among interventional cardiologists, imaging experts, clinical cardiologists, and cardiac surgeons might help to advance the interventional treatment options for this underserved population.

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The prevalence of mitral stenosis has declined over the last decade, however, it is important cause of morbidity and mortality. Post rheumatic mitral valve disease is the most common cause of mitral stenosis worldwide, but in development countries degenerative/calcific changes in the mitral valve is a significant cause of mitral stenosis.

Several perspectives can be taken from this provocative manuscript.

First, the authors state that many patients with severe degenerative mitral stenosis are currently left untreated because of multiple comorbidities that significantly increase the risk of mortality with surgical replacement.

Second, there are no clear guidelines how to treat these patients. A percutaneous approach somewhat similar to transcatheter aortic valve implantation, may provide an alternative treatment option for high risk surgical patients.

Finally, the authors state the importance of a multi-disciplinary team, consisting of interventional cardiologists, imaging experts, clinical cardiologists and cardiac surgeons in making the right decision of the management of these patients.

I want to thank the authors for this excellent review on degenerative mitral valve disease and I hope the readers of the Journal will find a very interesting approach to the management of these challenging patients.