JACC: CARDIOVASCULAR IMAGING VOL. 17, NO. 6, 2024

STATE-OF-THE-ART REVIEW

The Evolving Concept of Secondary Mitral Regurgitation Phenotypes

Lessons From the M-TEER Trials

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ABSTRACT

Conflicting results from 2 randomized clinical trials of transcatheter mitral valve edge-to-edge repair in secondary mitral regurgitation (SMR) have led to the recognition that SMR is a heterogeneous disease entity presenting with different functional and morphological phenotypes. This review summarizes the current knowledge on SMR caused primarily by atrial secondary mitral regurgitation (aSMR) and ventricular SMR pathology. Although aSMR is generally characterized by severe left atrial enlargement in the setting of preserved left ventricular anatomy and function, different patterns of mitral annular distortion cause different phenotypes of aSMR. In ventricular SMR, the relation of SMR severity to left ventricular dilation as well as the degree of pulmonary hypertension and right ventricular dysfunction are important phenotypic characteristics, which are key for a better understanding of prognosis and treatment response. (J Am Coll Cardiol Img 2024;17:659-668) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

Secondary mitral regurgitation (SMR) is a major health and economic burden.[1,2] Two randomized clinical trials of transcatheter mitral valve edge-to-edge repair (M-TEER) in SMR yielded markedly different outcomes,[3,4] prompting the recognition that these trials enrolled different patient populations. Subsequently, we have learned that SMR needs to be understood as a broad spectrum of cardiac pathologies that results in systolic reflux of blood from the left ventricle (LV) into the left atrium (LA) with differing clinical consequences and responses to treatment.[5] In contrast to primary mitral regurgitation (MR), in which abnormalities of the valve leaflets or supporting chordae tendineae lead to inadequate systolic leaflet closure, SMR typically occurs in patients with a structurally normal valve.[6,7]

Currently, the published reports distinguish a predominantly ventricular origin of SMR (vSMR) from a primarily atrial cause (aSMR).[8-10] But even within these 2 entities there is significant heterogeneity and overlapping phenotypes may occur. Moreover, untreated SMR progresses over time and changes its structural and clinical picture due to development of secondary cardiac damage.[11,12] Understanding the etiology and natural disease course of SMR is crucial, as treatment should be targeted towards correcting the underlying pathology. Given these findings, the aim of this review was to summarize our current knowledge regarding different SMR phenotypes and their clinical implications, especially in the context of M-TEER (**Central Illustration**).

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received September 11, 2023; revised manuscript received January 17, 2024, accepted January 18, 2024.

ISSN 1936-878X https://doi.org/10.1016/j.jcmg.2024.01.012

JACC: CARDIOVASCULAR IMAGING, VOL. 17, NO. 6, 2024
JUNE 2024:659-668

ABBREVIATIONS AND ACRONYMS

aSMR = atrial secondary mitral regurgitation

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HFpEF = heart failure with preserved ejection fraction

HFrEF = heart failure with reduced ejection fraction

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

M-TEER = mitral valve transcatheter edge-to-edge repair

PISA = proximal isovelocity surface area

RegVol = regurgitant volume

RVD = right ventricular dysfunction

SMR = secondary mitral regurgitation

vSMR = ventricular secondary mitral regurgitation

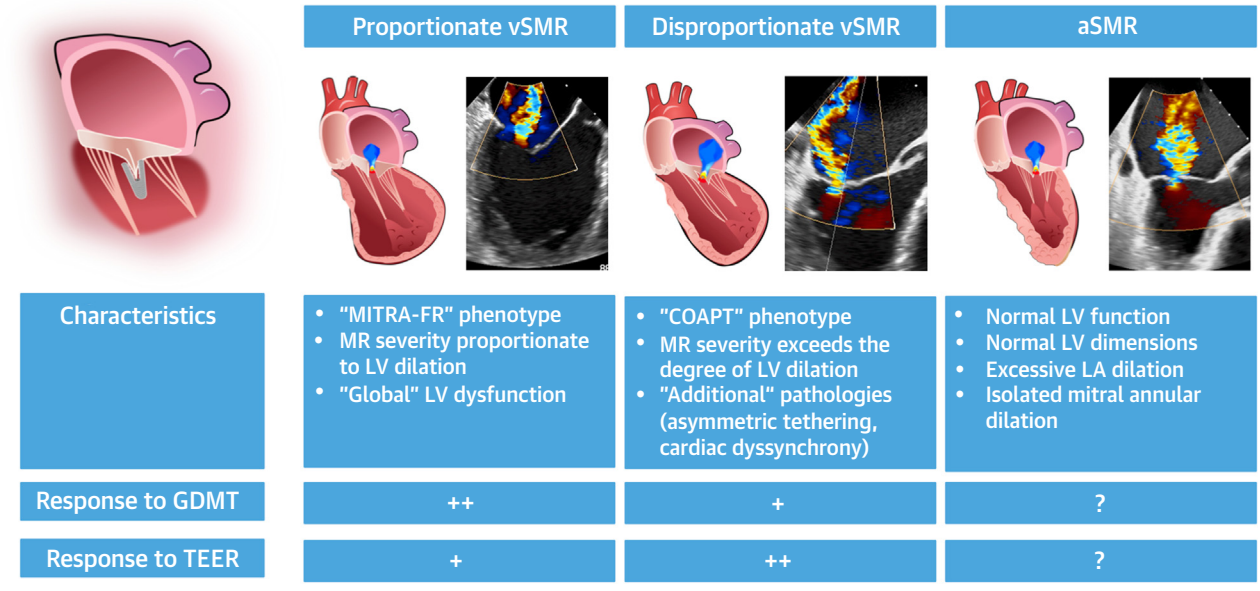
SMR: AN OVERVIEW

A wide variety of ventricular pathologies may lead to dilation, functional impairment, and geometric alteration of the LV in the setting of vSMR. Among the most common causes are ischemic cardiomyopathy, nonischemic dilated cardiomyopathy of various origins, aortic valve pathologies, hypertensive heart disease or hypertrophic cardiomyopathies, ventricular arrhythmias, and conduction disturbances.[7] vSMR is usually associated with heart failure with reduced ejection fraction (HFrEF), whereas aSMR expresses as heart failure with preserved ejection fraction (HFpEF) and/or atrial fibrillation (AF). Therefore, causal treatment of the underlying LV and/or LA pathology is paramount and includes guideline-directed medical therapy (GDMT) in all patients as well as coronary revascularization, ablation of atrial/ventricular arrhythmias, and cardiac resynchronization therapy in selected patients.[13,14] In the past few years, we have learned that not all patients respond to GDMT to the same degree, which is of crucial importance when selecting patients for surgical or transcatheter treatment of SMR.[13] One might suggest that patients whose LV does not respond to conservative treatment options (eg, no LV reverse remodeling, no decrease in regurgitant MR volume) could potentially profit the most from M-TEER or mitral valve (MV) surgery.

THE CONCEPT OF PROPORTIONATE AND DISPROPORTIONATE SMR. The concept of proportionate and disproportionate SMR was introduced to describe the relationship between MR severity (eg, effective regurgitant orifice area [EROA] or regurgitant volume [RegVol] to left ventricular end-diastolic volume [LVEDV]). SMR is referred to as *proportionate* if the degree of MR is secondary to severe LV enlargement (**Figure 1**, "Zone 4").[1] *Proportionate MR* is believed to be the consequence of global and homogeneous LV dysfunction and dilation with subsequent symmetric distortion of MV anatomy and predominantly symmetric MR jets that become more severe with increasing LV dilation. These individuals may be more likely to profit from uptitration of GDMT, which might lead to LV reverse remodeling and subsequent reduction of MR severity.[15,16] Patients with *disproportionate MR* (**Figure 1**, "Zone 3") often present with greater MR severity and less severe LV dilation (eg, due to prior myocardial infarction with subsequent asymmetric tethering[17] or cardiac dyssynchrony), which may be less likely to respond to GDMT,[15] because the LV has less potential for reverse remodeling. For example, Gaasch and Meyer[18] proposed the use of the RegVol/LVEDV ratio in 2018 before MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) were published. Using prior publications, they showed significantly larger ratios of MR RegVol to LVEDV in primary MR (mean: 0.29; range: 0.22-0.41) vs SMR (mean: 0.12; range: 0.08-0.18). In COAPT, the MR RegVol/LVEDV ratio (0.31) was virtually identical to prior studies of primary MR suggesting an SMR phenotype that resembles primary MR and thus may respond much better to M-TEER than to GDMT only.[18] Conversely, the MR RegVol/LVEDV ratio in MITRA-FR (0.18) is consistent with prior studies of SMR.[16] As depicted in **Figure 2**, most patients within the MITRA-FR study suffered from proportionate to hypoproportionate MR (LVEDV 252 mL, MR EROA 0.31 cm^2).[4] In contrast, patients from the COAPT trial presented with a magnitude of SMR that exceeded the degree of LV dilation (LVEDV 192 mL, MR EROA 0.41 cm^2).[3,19] The fact that the COAPT study reported very clear benefit of M-TEER on top of GDMT[3,20] supports the hypothesis that the trial likely selected patients with a suboptimal response to GDMT[3,13] in whom SMR was a primary driver of the pathology rather than a secondary phenomenon of severe LV dilation. However, limitations and pitfalls of quantitating LV volumes and MR severity make the application of the concept complicated on an individual patient basis.

COAPT vs MITRA-FR. Selection of such different patient populations in the 2 trials was in part due to diverging inclusion criteria. In line with European Guidelines, the MITRA-FR study considered an EROA of >0.2 cm^2 as severe MR, based on its association with an adverse prognosis. In contrast, COAPT used a multiparametric approach to define severe SMR as recommended in multiple guidelines.[3,4,21] In addition, the MITRA-FR study allowed inclusion of patients with lower left ventricular ejection fraction (LVEF) and significant LV dilation while not excluding severe right ventricular dysfunction (RVD).[4] Importantly, there have been many trials in cardiology that failed to show a response to treatment for parameters that were predictors of prognosis. Thus, although lower values for EROA are known to be associated with prognosis, that association does not necessarily imply causation nor response to

CENTRAL ILLUSTRATION **Secondary Mitral Regurgitation Phenotypes in the Context of Transcatheter Mitral Valve Edge-to-Edge Repair**



Stolz L, et al. J Am Coll Cardiol Img. 2024;17(6):659-668.

Secondary mitral regurgitation is a heterogeneous disease entity. aSMR is characterized by normal LV function and dimensions with excessive LA enlargement that leads to MR, which can present with a central or eccentric posterior directed jet. vSMR occurs in the setting of heart failure with reduced ejection fraction. Depending on the ratio of MR severity and LV dimensions, proportionate and disproportionate vSMR can be distinguished. aSMR = atrial secondary mitral regurgitation; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; GDMT = guideline-directed medical therapy; LA = left atrium; LV = left ventricle; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; MR = mitral regurgitation; SMR = secondary mitral regurgitation; TEER = transcatheter edge-to-edge repair; vSMR = ventricular secondary mitral regurgitation.

treatment. The hypothesis that combining EROA with LVEDV might identify patients who respond to GDMT is supported by a recent study, showing that SMR improved more after GDMT uptitration in patients with lower EROA/LVEDV ratio.[22]

Another important aspect of both randomized clinical trials—COAPT and MITRA-FR—is their generalizability to clinical practice in a real-world setting. As discussed previously, LV dimensions differed between both trials with significantly larger LV size in MITRA-FR, which indicates that many patients with advanced HFrEF might have been included. As depicted in **Figure 2**, it is important to realize that the 151 MITRA-FR patients treated by M-TEER do not resemble the patient population currently treated in "real-world" settings. The LV volumes of the 3 reported clinical registries (EuroSMR [European Registry of Transcatheter Repair for Secondary Mitral Regurgitation], EXPAND SMR [A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices], and COAPT PAS [COAPT Post-Approval Study]), which included >6,400 patients with SMR, were comparable to the COAPT trial, but considerably smaller than the MITRA-FR population.[23,24] Thus, the current application of M-TEER in clinical practice resembles patients enrolled in the COAPT trial.[25]

Proportionality and prognosis. First and foremost, the concept of SMR proportionality has been conceptualized to explain treatment response to M-TEER. Several retrospective analyses stratified data from registries or previously conducted trials by SMR proportionality and compared outcomes accordingly.

A European multicenter registry consisting of more than 1,000 patients with SMR identified patients with an LV-dominant pattern of SMR and thus proportionate to hypoproportionate MR (mean EROA/LVEDV ratio 0.0008 ± 0.0002 cm^2/mL) to be associated with higher 2-year mortality rates compared

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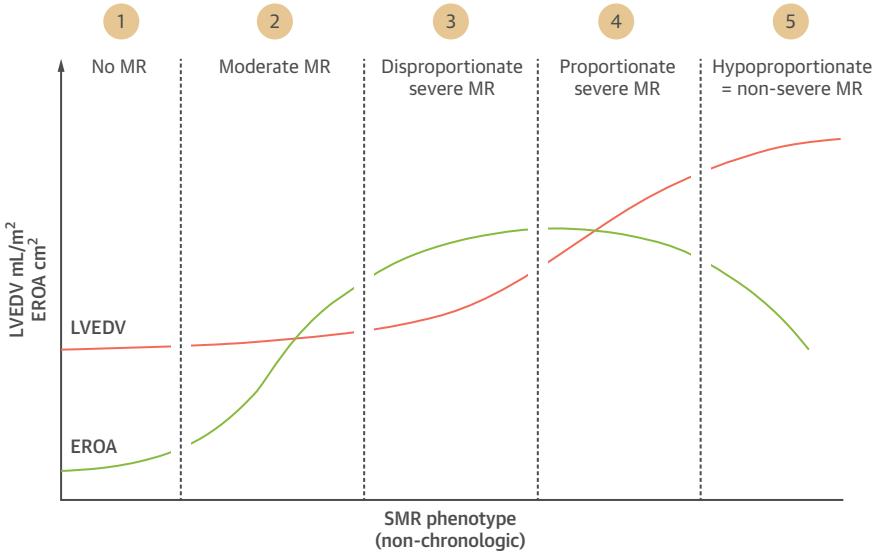
FIGURE 1 Relationship of MR Severity and LV Dilation



Patients in zones (1) and (2) present with normal LV function and EROA values below guideline-recommended cutoffs for the definition of severe SMR. Although patients in zone (4) exhibit LV dilation proportional to increasing EROA, MR severity exceeds the degree of LV dilation in zone (3). In zone (5), LV dilation is the clinically predominating problem because SMR is less severe than expected by the degree of LV dilation. Of note, the figure does not represent a temporal development but phenotypes. EROA = effective regurgitant orifice area; LV = left ventricle; LVEDV = left ventricular end-diastolic volume; MR = mitral regurgitation; SMR = secondary mitral regurgitation.

with disproportionate SMR.[23] Of note, symptomatic outcomes were comparable across the spectrum of SMR proportionality.[23]

A smaller registry from the Netherlands included 241 patients who were divided into proportionate and disproportionate SMR. They observed SMR improvement of at least 2 grades to occur more frequently in patients with disproportionate SMR.[26] Of note, those differences were no longer observed at 1-year follow-up. Beyond that, the study reported no survival differences according to SMR proportionality.[26]

A subanalysis from the COAPT trial identified a proportionate "MITRA-FR like" subgroup with large LVEDV (236 mL) and low EROA (0.26 cm^2) that did not achieve improvement in terms of mortality or heart failure hospitalization at 24 months in patients receiving TEER compared with GDMT only.[27] Of note, patients with proportionate and disproportionate SMR achieved significant symptomatic and quality of life benefit.

Finally proving the prognostic importance of the proportionality concept in terms of treatment modalities used requires a dedicated randomized controlled study, which has not been done. Beyond that, as stated earlier, the proportionality concept is only a theoretical framework that is not easy to apply on an individual patient level because of the complexity of SMR quantification, which will be outlined in the next paragraph of this review.[19]

Complexity of SMR quantification and guideline differences. Even though current guidelines recommend a multiparametric approach toward SMR quantification, precise and reliable SMR grading, especially by transthoracic echocardiogram, is extremely challenging.[28] The most commonly used parameters (RegVol and EROA) are derived from the proximal isovelocity surface area (PISA) method, which is based on fundamental physics flow through a round orifice in a flat surface. The PISA method is subject to several important limitations and pitfalls in SMR and can either overestimate or underestimate the degree of MR. Because the PISA radius is measured in a single frame during systole, EROA may be overestimated in SMR by choosing the largest PISA zone that is of variable size during systole.[29] This can be improved using 3-dimensional PISA measurements averaged over each frame during systole.[30] However, this method is tedious and therefore rarely used in clinical practice. On the other hand, if the regurgitant orifice is markedly elliptical in shape, the PISA method may underestimate EROA and RegVol by measuring a smaller PISA radius. Of note, Doppler

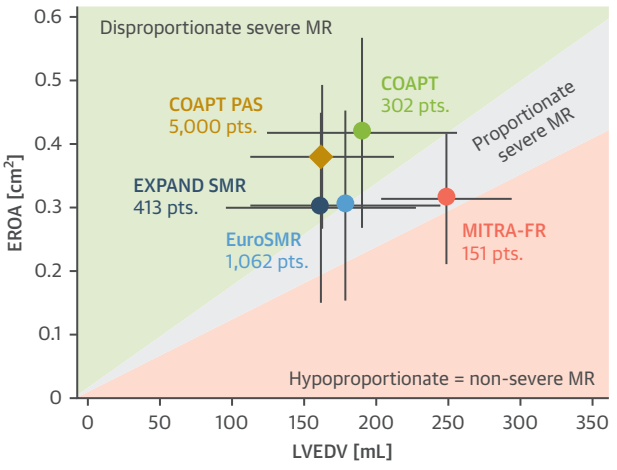
volumetric quantification is also considered difficult in the setting of SMR because of high variability. Uncertainties in the measurement of the PISA radius have a strong influence on the resulting error margin, because the radius is squared in the calculation of EROA and RegVol.[31] When having a look at a typical SMR patient with an LVEDV of 200 mL and an LVEF of 35%, the patient has a total stroke volume of 70 mL. According to American guidelines, in a multiparametric approach of MR quantification, a RegVol of 60 mL would be an indicator for the presence of severe SMR. This theoretically leads to a forward stroke volume of 10 mL, which equals a cardiac output of only 0.7 L/min, if a heart rate of 70 beats/min is considered.[32] This raises the question of whether in the setting of SMR with commonly reduced forward stroke volume a lower cutoff for the definition of severe SMR might be needed.

Unsupervised machine learning to identify SMR phenotypes. Recently, various study groups attempted to characterize and phenotype patients with SMR. Bartko et al[33] used principal component analysis including 32 morphological and functional parameters of LV, LA, and right ventricle (RV) to identify clusters among medically treated patients with SMR with HFrEF. Of note, their study included patients with none/mild to severe SMR (none/mild: 42.8%; moderate 34.2%; severe 23.0%).[33] The authors identified 4 different clusters of SMR patients. Clusters 1 and 2 were associated with favorable survival prognosis compared with clusters 3 and 4. Although clusters 1 and 2 were made up of patients with predominantly mild or moderate MR and relatively well-preserved LV and LA dimensions, the latter 2 clusters 3 and 4 showed a high prevalence of patients with severe MR (approximately 80%). Although EROA and RegVol were roughly comparable between clusters 3 and 4, patients in cluster 4 presented with significantly larger LVEDV (cluster 3: 188 mL; cluster 4: 315 mL).[33] Hence, cluster 3 resembles the phenotype treated in COAPT whereas those in cluster 4 resemble the phenotype treated in MITRA-FR. This assumption is supported by the fact that patients in cluster 3 presented with more dilated atria (indicating more severe and/or longer standing MR). Patients in cluster 3 presented with the worst survival prognosis in this medically treated cohort. They might have profited from further interventional treatment of MR and/or cardiac resynchronization therapy, as hypothesized for patients with *disproportionate MR*.[33,34]

A similar study by Trenkwalder et al[34] evaluated patients who underwent M-TEER using machine learning to develop phenotype clustering with both derivation and validation cohorts. This study included patients with both primary MR and SMR. Four clusters were identified, corresponding clinically to primary MR with and without pulmonary hypertension, vSMR, and aSMR. Both vSMR and aSMR had worse prognosis after M-TEER than either primary MR group. Further investigation using machine learning algorithms is under way to further understand SMR phenotypes as predictors of prognosis and response to therapy. Only randomized controlled data could either support or oppose the concept of disproportionate SMR as a predictor of response to treatment. A pooled analysis of MITRA-FR and COAPT would be of particular interest, as it could evaluate this hypothesis and apply the previously described machine learning/artificial intelligence applications to identify specific phenotypes that benefit from M-TEER.

Response of SMR to GDMT. As mentioned earlier, GDMT remains the cornerstone of SMR treatment.[22] Prior studies have shown that approximately 40% to 60% of patients with vSMR may have significant improvement in MR severity with appropriately titrated GDMT.[22,35,36] However, in severe SMR, low systolic blood pressure, abnormal renal function,

FIGURE 2 MR Proportionality in Different Trials and Registries



This figure depicts the mean proportionality of EROA and LVEDV among important SMR trials and registries. Although the COAPT study predominantly included patients with disproportionate and the MITRA-FR trial with proportionate to hypoproportionate SMR, real-world patients (EuroSMR, COAPT PAS, and EXPAND SMR) presented with predominantly disproportionate SMR. Circles represent mean ± SD, and diamonds represent median (IQR). COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation; COAPT PAS = COAPT Post-Approval Study; EuroSMR = European Registry of Transcatheter Repair for Secondary Mitral Regurgitation; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation; other abbreviations as in Figure 1.

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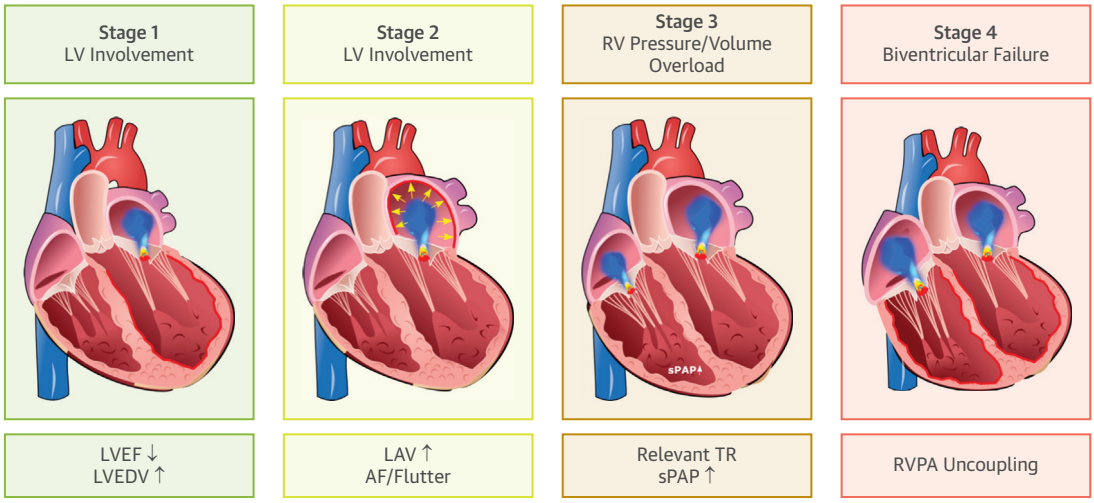
FIGURE 3 Heart Failure Stages in Patients With SMR Undergoing M-TEER



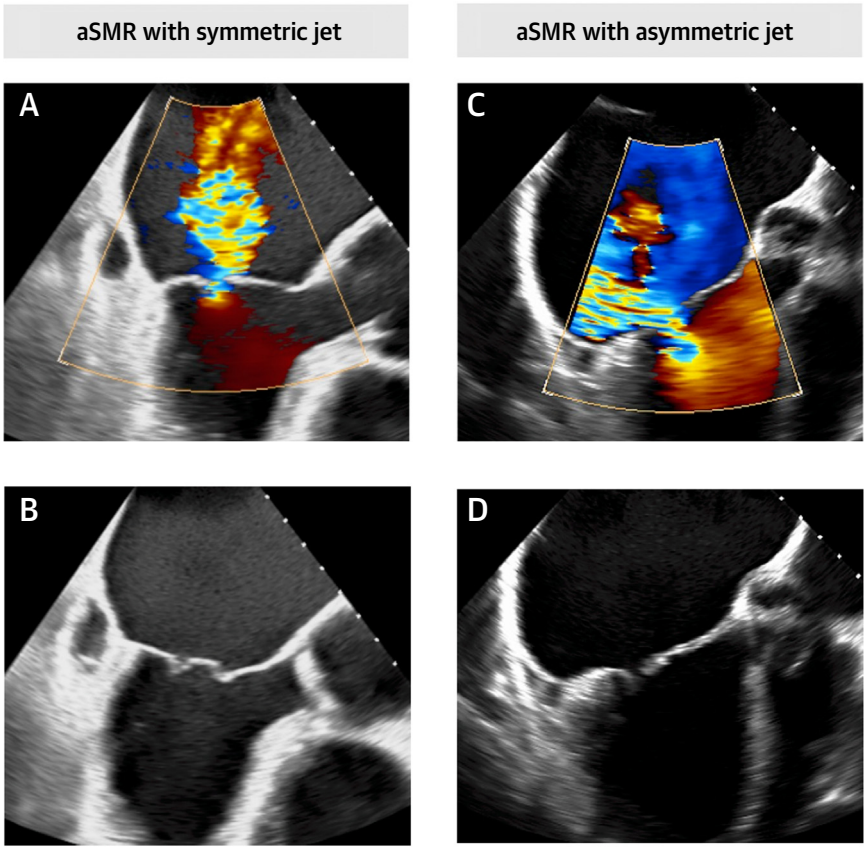
The figure represents heart failure stages according to extramitral cardiac involvement in patients with SMR. The staging concept might be applicable to patients with proportionate and disproportionate SMR. AF = atrial fibrillation; LAV = left atrial volume; LV = left ventricle; LVEF = left ventricle ejection fraction; M-TEER = transcatheter mitral valve edge-to-edge repair; RV = right ventricle; RVPA = right ventricular to pulmonary artery coupling; sPAP = systolic pulmonary artery pressure; TR = tricuspid regurgitation.

and/or electrolyte abnormalities might prevent GDMT uptitration to the recommended target doses. Of note, "optimal" GDMT uptitration before the procedure was judged by expert committees in both the MITRA-FR and COAPT trials. However, both trials were initiated before the demonstration of a survival benefit from sacubitril/valsartan and sodium glucose co-transporter 2 inhibitors (SGLT2is). Neither trial reported data on patients who were not randomized because SMR resolved with GDMT uptitration before enrollment. Recent data support the simultaneous initiation of the 4 classes of drugs shown to benefit patients with HFrEF, rather than the slow sequential uptitration used in COAPT or MITRA-FR.[37] This could potentially allow faster recognition of patients whose SMR is not responsive to GDMT and thus allow earlier treatment with M-TEER. Finally, it is important to recall that GDMT optimization is not only important before M-TEER[38] but also subsequently. Recently, a substudy from the EuroSMR registry demonstrated that M-TEER enabled GDMT uptitration during follow-up in 38% of patients, which was associated with a significantly improved survival prognosis.[16]

Fibrosis/scar. Besides looking at morphologic phenotypes of SMR from echocardiographic parameters, LV fibrosis/scar/infarction might also be important factors influencing the response to GDMT. Cardiac cine magnetic resonance imaging (MRI) offers high-quality measurement of cardiac chamber size and function, as well as myocardial abnormalities and scar burden.[39] Recently, a single-center study identified MRI-detected cardiac fibrosis as an important determinant of LV reverse remodeling.[40] The negative prognostic value of myocardial scar in the setting of heart failure patients with SMR has recently been demonstrated by Tayal et al.[41] Whether the degree of fibrosis predicts response to treatment requires further investigation.

The importance of RVD. RVD has emerged as an important outcome predictor in several cardiovascular disease entities,[42-45] including SMR. With a prevalence of 25% to 30%, RVD is a clinically relevant condition with distinctly increasing mortality rates.[43,45] Until today, it remains a subject of discussion whether RVD is a consequence of a long-standing MR with subsequent pulmonary venous hypertension or whether RVD is a part of the underlying cardiomyopathy at an earlier state of the disease, or whether it is associated with chronic pulmonary disease. It is possible that RV dysfunction could occur in some patients as a consequence of RV pacing or ventricular septal desynchrony. A retrospective analysis from the large EuroSMR registry clustered vSMR patients according to their extramitral cardiac involvement with the most progressive disease state being characterized by RVD.[12] Of note, patients with sole LV involvement (absence of AF/atrial dilation, pulmonary hypertension, and RVD) presented with

FIGURE 4 Phenotypes of aSMR



(A and B) Most commonly, aSMR occurs with a central jet in the middle of the valve due to malcoaptation of the leaflets. (C and D) In a smaller subgroup of patients, eccentric MR jets are located posterior due to "hamstringing of the posterior MV leaflet." aSMR = atrial secondary mitral regurgitation; MV = mitral valve; other abbreviation as in Figure 1.

comparable LV dimensions compared with patients in the most progressive disease state characterized by RVD (Figure 3). This raises the question about the relationship of MR proportionality and RVD. Although the EuroSMR registry reported a comparable EROA/LVEDV ratio in patients with and without RVD,[43] a subanalysis of the COAPT trial found RVD to be associated with lower EROA values against the background of comparable LV dimensions.[45] Unfortunately, data on RVD within the MITRA-FR trial are lacking. Understanding the relationship of RVD and SMR phenotypes is further complicated by the anatomic and functional complexity of the RV. To overcome the limitations of 2-dimensional imaging and approximation of RV function, cardiac magnetic resonance and 3-dimensional echocardiography are increasingly used.[46,47] Combining state-of-the art imaging with machine learning and/or artificial intelligence might be another important tool in understanding the complicated relationship of SMR and RVD.

Outcome prediction in SMR-TEER. The previously described heterogeneity of SMR-TEER patients makes reliable outcome prediction a challenging task. Even though there are several important singular outcome predictors (eg, RVD, GDMT, LVEF), comprehensive scores are needed to reflect the complexity of the disease and reliably predict procedural outcomes. Conventional risk scores in the field of SMR were subject to important limitations (derivation from surgical and/or mixed primary mitral regurgitation (PMR)/SMR cohorts, lack of proper validation).[48,49] Using an artificial intelligence–derived algorithm, the recently presented EuroSMR risk score was able to overcome those limitations, outperforming existing risk scores in terms of 1-year mortality prediction. It

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HIGHLIGHTS

- SMR is a heterogeneous disease entity presenting with different clinical phenotypes.
- Differentiation of SMR phenotypes (aSMR vs vSMR) and their subentities might facilitate our understanding of treatment response to medial and interventional SMR treatment.
- Further studies are needed to further improve our understanding of the disease and optimize treatment of SMR.

consists of 18 clinical, echocardiographic, laboratory, and medication parameters and thus provides a comprehensive picture of the individual risk for 1-year mortality and 1-year mortality free from NYHA functional class III or IV after SMR-TEER.[50]

ATRIAL SMR. Pathophysiology and definition of aSMR. With growing prevalence of HFpEF[51] and AF,[52] a new category of SMR referred to as atrial secondary mitral regurgitation (aSMR) has become recognized.[10] aSMR is generally characterized by preserved LV function and dimensions (in contrast to vSMR) and a structurally normal MV (in contrast to PMR).[53] The main mechanism of aSMR is enlargement of the LA, which leads to "isolated" MV annular dilation[10] and comes along with some typical anatomical features. Dilation of the MV annulus without distorting forces from the subvalvular apparatus leads to flattening of the valvular geometry.[54] In contrast to a nondiseased valve apparatus, MV leaflets usually lose their concavity toward the LV because of a lack of length reserve of the leaflets in the setting of aSMR.[53] Depending on the degree of atrial and hence MV annular dilation, 2 phenotypes of aSMR can be distinguished. Most commonly, aSMR occurs with a central jet in the middle of the valve due to malcoaptation of the leaflets[55] (**Figures 4A and 4B**). In a smaller subgroup of patients (20%-30%), eccentric MR jets are located posterior due to "hamstringing of the posterior MV leaflet" (**Figures 4C and 4D**).[9,55-57] Often, aSMR is accompanied by overriding of the anterior leaflet due to excessive annular dilation. The phenomenon is caused by excessive dilation of the LA especially in a posterior direction, which causes displacement of the posterior aspect of the MV annulus beyond the crest of the myocardial LV inlet.[56] This form of tethering is referred to as *atriogenic tethering* because the subvalvular apparatus and the LV remain completely intact.[58] Whether aSMR with asymmetric posterior jets is a consequence of progressing LA dilation or represents a distinct etiologic subentity of aSMR remains unclear.

Treatment and prognosis of aSMR. Current guidelines do not discriminate between aSMR and vSMR,[7] which might be problematic considering the distinctly different disease etiologies and outcomes. For patients with aSMR and AF, restoration of sinus rhythm can improve LA function and reduce MR severity.[10,59-61] In patients with HFpEF, SGLT2is have been proven to reduce the rates of heart failure hospitalizations or mortality.[62,63] So far, data regarding the impact of SGLT2is on aSMR severity are lacking. Even though the body of evidence is weak, single-center observational studies suggest good results after surgical MV annuloplasty in aSMR patients.[64,65] Because the prevalence of both AF and HFpEF are closely linked to increasing age, many patients are not good candidates for a surgical treatment approach. Retrospective data on M-TEER in patients with aSMR reported high rates of procedural success,[8,66] improvement in heart failure symptoms, and overall higher survival rates compared with vSMR but worse survival rates than patients with PMR.[8,55] Data on the performance of the transcatheter annuloplasty in the setting of aSMR are still lacking but highly anticipated.

CONCLUSIONS

Before the publication of the COAPT and MITRA-FR trials, there was little awareness about the heterogeneity of SMR. Within the past few years, our understanding of SMR has significantly improved and M-TEER for SMR became a guideline-recommended procedure.[7] The most important teaching points of this review can be summarized as follows:

1) SMR is a heterogeneous disease presenting with different clinical phenotypes.
2) Two predominant phenotypes with vSMR (ventricular dilation) and aSMR (atrial dilation) can be distinguished.
3) The concept of vSMR proportionality combines information on SMR severity and LV size and might influence the response to medical and/or interventional treatment.
4) Echocardiographic quantification of SMR is challenging because of methodological limitations.
5) RVD is a major outcome predictor even though its exact pathophysiologic role in the setting of SMR remains uncertain.
6) aSMR itself presents with different phenotypes depending on the exact mechanism of atrial and subsequent annular dilation.

7) Even though TEER treatment of aSMR was safe according to registry data, prospective randomized controlled data are lacking.

Despite the recent evolution in our understanding of SMR, many questions remain unsolved and require further investigation. aSMR is poorly understood and underrecognized by current guidelines because of a lack of high-quality evidence. A randomized comparison of transcatheter and surgical MR treatment has not been undertaken. This question is currently studied by the MATTERHORN trial (A Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or iscHemic ORigiN trial). Whether the concept of SMR proportionality can also be translated to surgical patients remains equally unsolved.

The field of interventional MV therapy is highly dynamic, and with unabated research efforts, some of these important open questions will likely be answered in the coming years.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Hausleiter has received research support and speaker honoraria from Edwards Lifesciences. Dr Sannino has received research support from Edwards, Neochord, and Cardiovalve Venus Medtech. Dr Stolz has received speaker honoraria from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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KEY WORDS atrial SMR, functional mitral regurgitation, phenotypes, proportionality, right ventricular dysfunction, secondary mitral regurgitation, ventricular SMR