Review

Learning from Controversy and Revisiting the Randomized Trials of Secondary Mitral Regurgitation

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Abstract

Until recently, conventional mitral valve surgery has been the treatment of choice even in secondary mitral regurgitation. Recent evidence, however, advocates the use of transcatheter edge-to-edge mitral valve repair (TEER) of the mitral valve. This has been reflected by the change in guidelines of the American College of Cardiology/American Heart Association. We reviewed the literature to shed light on the risks and benefits of all interventions, surgical, transcatheter and guideline-directed medical therapy. Secondary mitral regurgitation occurs due to an imbalance between closing forces and tethering forces. Given the pathology extends beyond the valve alone, treatment should be directed at restoring the geometrical shape of the left ventricle alongside the valve. Myocardial revascularization plays a pivotal role in preventing recurrence. The role of papillary muscle approximation in addition to restrictive mitral annuloplasty should be considered in a select group of patients. We also reviewed the current literature on TEERs from the COAPT and Mitra-FR trials while highlighting the concept of proportionate/disproportionate MR which may help identify which patients benefit from mitral valve restoration. Treatment of this condition will require robust randomized trials alongside the use of state-of-the-art imaging technologies available with the full complement of the multidisciplinary team to ensure the best outcomes for each patient.

Keywords: secondary mitral regurgitation; mitral valve replacement; mitral valve repair; subannular repair; transcatheter edge to edge repair

1. Introduction

The evidence that has emerged in the latest international guidelines on the use of conventional mitral valve surgery and transcatheter edge-to-edge mitral valve repair (TEER) places a veil of uncertainty about the risk-benefit ratio of the recommendations for the treatment of secondary mitral regurgitation (SMR) [1,2]. The lack of high-level quality of evidence supported by multicenter randomized clinical trials may partly explain the conundrum indicating both the use of conventional mitral valve surgery and the TEER procedure [3–6].

However, the clinical evidence and the results emerging from randomized clinical trials or observational studies using the surgical approach or transcatheter procedures suggest food for thought and warrant a review of the literature [3–11] (Fig. 1, Ref. [11]).

Specifically, we revisited the mitral valve repair procedures, including valvular or subvalvular apparatus versus chordal-sparing mitral replacement, and the TEER approach. The TEER procedure has been extensively revisited due to concerns regarding its upcoming role as a pivotal part of the new platforms for the treatment of structural heart disease. We herein discuss the current evidence basis for the use of different treatment options for SMR and an evidence-based algorithm for the choice of more suitable mechanical intervention is proposed.

2. Pathophysiological Mechanisms of Secondary Mitral Regurgitation and Its Clinical Implications

In secondary mitral valve (MV) regurgitation, the geometric left ventricular (LV) shape is altered with distortion of the normal spatial relationships of the elements of the MV apparatus leading to incomplete mitral leaflet coaptation and SMR. This pathological SMR is characterized by the abnormal imbalance between tethering and closing forces. The tethering forces are depicted by annular dilatation, LV dilatation, papillary muscles displacement, increasing LV sphericity while closing forces are represented by the reduction of LV contractility, global LV dyssynchrony, papillary muscle dyssynchrony, and, altered mitral systolic annular contraction. For example, in patients who develop ischemic mitral regurgitation, the pathophysiological mechanism that supports it is a consequence of adverse left ventricular remodeling related to the myocardial injury. Patients experienced enlargement of the left ventricular chamber and mitral annulus, posterolateral and lateral migration of the papillary muscles, leaflet tethering,
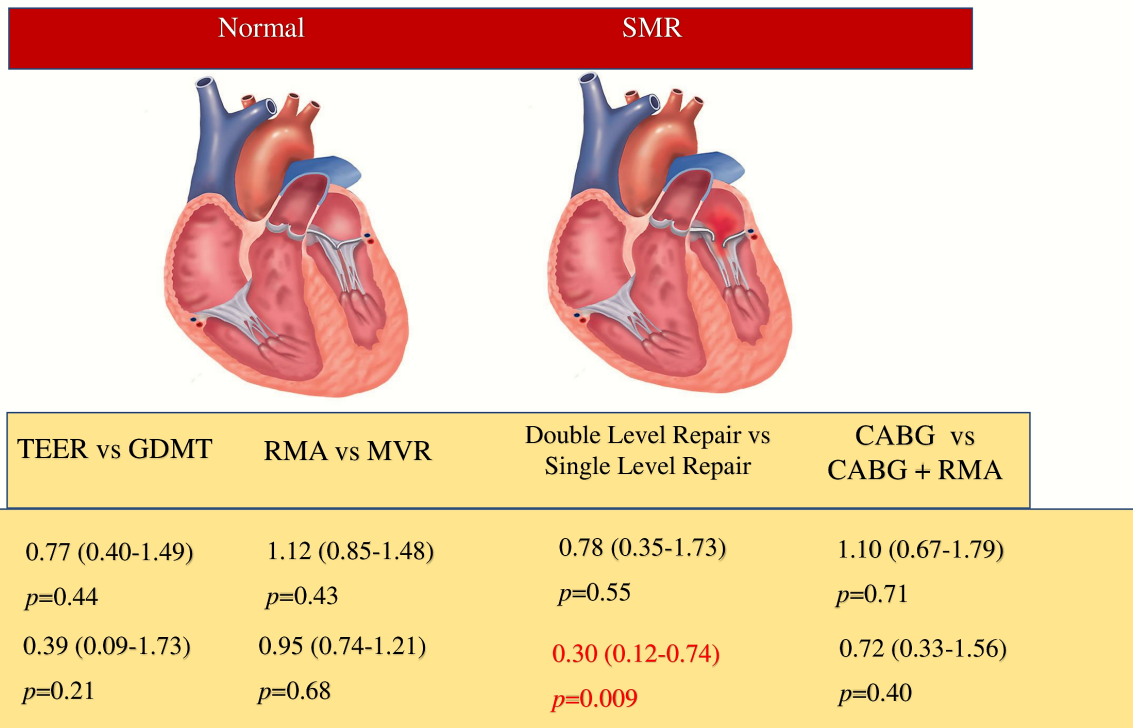
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	TEER vs GDMT	RMA vs MVR	Double Level Repair vs Single Level Repair	CABG vs CABG + RMA
Long-term mortality	0.77 (0.40-1.49) p=0.44	1.12 (0.85-1.48) p=0.43	0.78 (0.35-1.73) p=0.55	1.10 (0.67-1.79) p=0.71
Composite endpoint	0.39 (0.09-1.73) p=0.21	0.95 (0.74-1.21) p=0.68	0.30 (0.12-0.74) p=0.009	0.72 (0.33-1.56) p=0.40

Fig. 1. Secondary MR in Heart Failure: Success was defined as freedom from MACCEs (combined cardiac and cerebrovascular outcome red words). Data are presented as odds ratio (OR) with 95% confidence interval, with the corresponding overall p value. OR refer to the comparison between the first group and the second group in the treatment group. From Nappi F, *et al*. [11]. Abbreviations: CABG, coronary artery bypass grafting; GDMT, guide direct medical therapy; MVR, mitral valve replacement; OR, Odd ratio; RMA, restrictive mitral annuloplasty.

and reduced closing forces. These processes lead to malcoaptation of the valve leaflets and variable grades of MV regurgitation that can vary dynamically and is contingent on volume conditions, afterload, heart rhythm, and residual myocardial ischemia. Therefore, the pathogenesis of secondary mitral regurgitation is determined by the interactions between the mitral valve leaflets, mitral subvalvular apparatus, atrium, and left ventricle. This implies that the treatment of SMR diverges substantially from that of primary, degenerative mitral regurgitation [12–18].

Secondary mitral regurgitation sustained by a primarily ventricular pathology may be due to either ischemic or non-ischemic remodelling. There are some points of convergence concerning the underlying remodeling that link these two categories of patients in whom SMR with cardiomyopathy occurs. Concerns related to the increasing ventricular size with lateral or posterolateral displacement of the papillary muscles (PMs) affects both forms of SMR and leads to aberrant tethering forces on the leaflets [16].

The physiological functioning of the mitral valve (MV) prevents prolapse during systole by the action of the subvalvular apparatus which applies a vertical strain. Ventricular remodeling alters this dynamic. A second negative factor is represented by the ventricular and atrial increase in size leading to annular expansion and resulting in fur-

ther malcoaptation of the MV leaflets. A third intervening component in the pathophysiological mechanism of SMR is the reduced closing forces due to the decrease in systolic tension which amplifies the mechanism of mitral regurgitation. Furthermore, patients may experience left bundle branch block that progresses to heart failure with decreased left ventricular ejection fraction (LVEF), thereby worsening left ventricular remodeling through dyssynchrony. The latter leads to further impairment of the closure forces by altering the function of the dyssynchronous papillary muscles which supports the persistence of the SMR [17–20].

There are numerous determinants of mitral regurgitation (MR) within non-ischemic cardiomyopathy and these contribute to the onset of all the disorders previously described.

Bothe *et al*. [18] disclosed that although posterolateral displacement of posterior papillary muscle was a predominant pathomechanism leading to apical leaflet tethering during ischemic and non-ischemic SMR, the anterior papillary muscle was displaced laterally specifically in non-ischemic SMR. El Sabbagh *et al*. [19] found that the predominant mechanism supporting the secondary mitral regurgitation in patients with non-ischemic cardiomyopathy was the result of an increase in effective regurgitant orifice area (EROA) due to annular dilation and loss of annular contraction. Con-
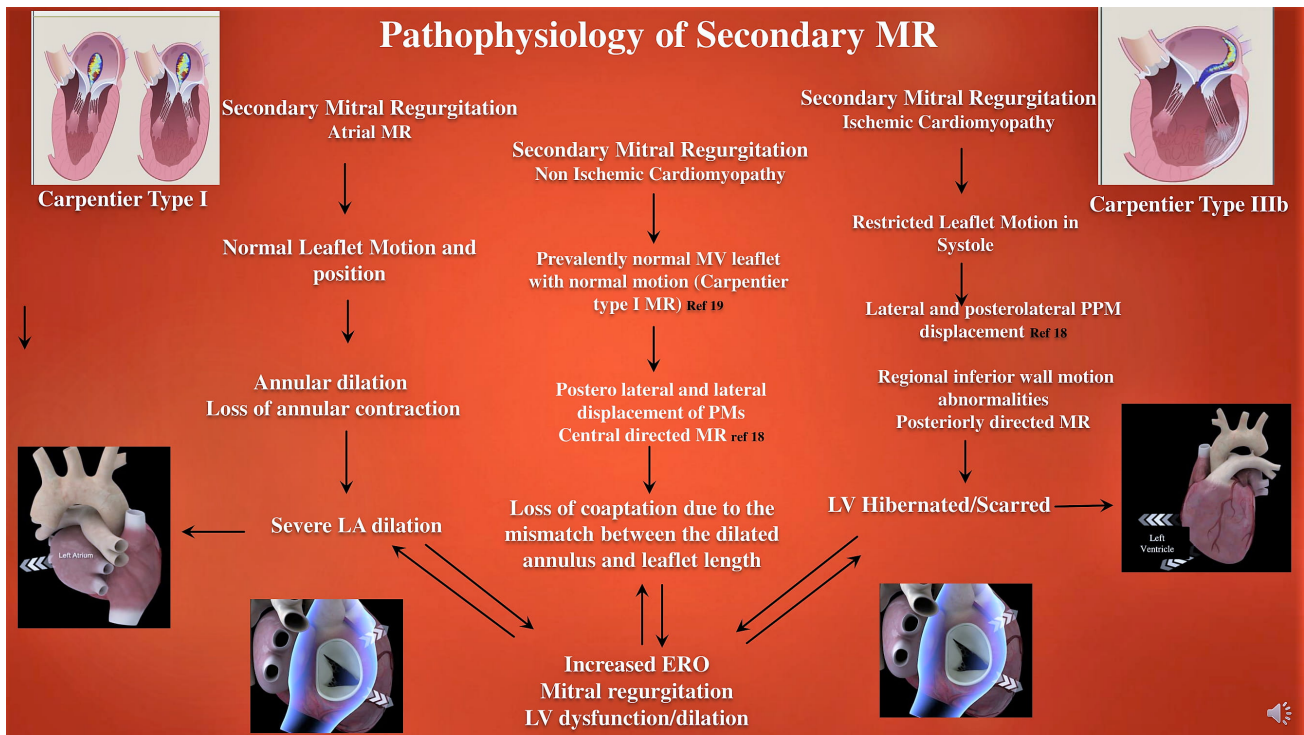
Fig. 2. Depicts the pathophysiology of SMR that differently to primary MR is not a disease of the MV. SMR is chacterized by a disease of the atrium or ventricle and as concern the ventricular disease SMR can be due to either nonischemic or ischemic remodeling. From Bothe *et al.*; El Sabbagh A *et al.*; O'Gara PT *et al.* [18–20]. Abbreviation: ERO, effective regurgitant orifice; LA, left atrium; LV, left ventricle; MR, mitral regurgitation; PPM, posterior papillary muscle; PMs, papillary muscles; SMR, Secondary Mitral regurgitation.

versely, O' Gara noted restricted leaflet motion in systole [20], although the investigators in later publications argued that in non-ischemic cardiomyopathy the leaflets of the mitral valve have no anomalies and this movement was physiological. In particular, El Sabbagh *et al.* [19] suggested that this type of disorder may be classified as Carpentier type I mitral regurgitation in which the loss of coaptation was due to the mismatch between the dilated annulus and the leaflet length leading to MR [19]. Additionally, patients may develop severe left atrial enlargement which was often due to persistent atrial fibrillation which can be termed atrial functional MR [19]. O' Gara *et al.* [20] reported that the dilation of the mitral annulus caused by atrial fibrillation was protracted in time and by atrial remodeling, had a well-defined role in supporting the Carpentier type I form of secondary MR.

Another cause of functional atrial MR relies on the posterior enlargement of the left atrium which exerts traction on the posterior part of the mitral annulus where the posterior leaflet is inserted consequently causing MR [21] (Fig. 2, Ref. [18–20]).

In patients with ischemic MR, regional inferior wall motion abnormalities occur, leading to posterior asymmetric tethering and a posteriorly directed jet, related to mitral regurgitation. This type of SMR is classified as Carpentier type IIIb. The defining echocardiographic feature highlights the anterior leaflet override associated with is-

chemic MR. It should not be mistaken for prolapse because it does not pass through the annular plane [22]. It is important to note that the inferior wall motion disorder with ischemic MR may be coupled with the evidence of regional myocardial scar tissue and hibernation [23,24]. In some circumstances, ischemic MR with a central regurgitant jet can occur in patients with global wall motion abnormalities due to multivessel coronary disease. In these cases, an equivalent lateral displacement of both papillary muscles leads to the similar pathophysiological shape of nonischemic cardiomyopathy [25,26] (Fig. 2).

The presence of persistent ischemic MR portends an adverse prognosis. As demonstrated by the Survival and Ventricular Enlargement (SAVE) trial, the presence of even mild ischemic MR post-myocardial infarction significantly increases mortality at 3.5 years (29% versus 12%, $p < 0.001$) [27]. In the involutive phase, an impaired mitral valve, although supported by a pathological process that involves the left ventricle, will evolve to cardiomyopathy which then becomes the primary disease [28–32]. Severe ischemic MR has been associated with a range of survival between 40% [30] and $29 \pm 9\%$ [32] at 1-year and 5-year, respectively.

The clinical improvement of the patient with severe secondary mitral regurgitation is favored by any type of medical treatment that reduces the LV end-diastolic volume or causes reverse remodeling. The recommended ther-

apy of choice is that of acute decompensated heart failure with the use of angiotensin-converting enzyme (ACE) inhibitors/angiotensin receptor blockers (ARBs) or Entresto® (sacubitril (neprilysin inhibitor)/valsartan (ARB). Likewise, other medications such as beta-blockers and diuretic therapy including mineralocorticoid receptor antagonists (MRAs) like spironolactone, eplerenone, and canrenone have also been shown to significantly improve cardiac output. The benefit afforded by guideline-directed medical therapy (GDMT) is achieved in part through the reduction in secondary MR by means of reduction in EROA [33]. Secondary MR is primarily load-dependent. Therefore, this pathophysiological characteristic denotes the importance of re-evaluating MR in terms of preload and afterload, highlighting that both conditions have been optimized by the regulation of diuresis and vasodilation.

Although acute changes due to loading conditions represent the first line of GDMT, treatment of chronic left ventricular reverse remodeling (LVRR) responsible for heart failure with reduced EF, represents a delicate phase currently manageable through numerous medical therapies aimed at decreasing mortality. GDMT to improve LVRR includes diuretics, ACEi/ARBs, beta-blockers, aldosterone antagonists, combined with neprilysin inhibitors, and/or hydralazine/isosorbide dinitrate. The use of sodium-glucose co-transporter 2 inhibitors (SGLT-2i) and/or ivabradine, when indicated, represent another option of optimal therapeutic choice [2].

This therapeutic management can be associated with cardiac resynchronization and myocardial revascularization in patients with persistent/relapsing ischemia [34]. It is important to underline that the advantages of left ventricular reverse remodeling, achievable with optimal medical target treatment, therefore plays a significant role result on the severity of secondary MR.

3. Point and Counterpoint in Revisiting the Randomized Trials of Moderate to Severe Ischemic Mitral Regurgitation

In secondary mitral regurgitation classed as Carpentier type IIIb, the geometric malformation of the valve is due to the alteration of three measures; the interpapillary muscle distance (IPMD), the anteroposterior diameter of the annulus, and the area or volume of tenting. Patients who experienced the most extreme conditions of altered geometry had left ventricular end-diastolic diameter (LVEDD) $\geq$64 mm, left ventricular end-systolic diameter (LVESD) LVESD $\geq$55 mm, TH $\geq$12 mm, alfa-2 angle $\geq$45°, and IPMD >20 mm, whereby only the recovery of the three dimensions lead to a reduction of the mitral regurgitation [9,35,36]. In addition, the clinical benefit of associated mitral valve repair in patients with coronary artery disease suitable for CABG (coronary artery bypass grafting) is determined by reperfusion of these ischemic myocardial regions, optimizing left ventricular reverse remodeling over time [9,26,37]. Left ventricular reverse remodeling (LVRR) is the Achilles heel of mitral valve repair and it is improved by complete revascularization of the viable myocardium [8,9,23,24,26,37–39].

In patients with severe secondary mitral regurgitation, the double-level repair is achieved using the combined annular and subannular mitral repair [9]. On the other hand, the use of the single-level repair (restrictive annuloplasty (RA)) allows closer approximation of the mitral leaflets. This procedure is effective at decreasing the anteroposterior diameter and the tenting area, leading to the recovery of the functional coaptation length [9,11–13]. Patients who received RA alone, however, have a constantly increased interpapillary muscle distance, which results in poor improvement despite favorable LVRR when the size of the left ventricular chamber is small. Without a more effective LVESD improvement, IPMD reduction is unlikely in the absence of PM approximation [9,36].

The benefit of RA with the improvement of mitral regurgitation are temporary and dependent on the LVEDD remaining less than 64 mm and LVESD less than 55 mm. Both the Papillary Muscle Approximation (PMA) randomized controlled trials (RCT) [9,26,35,36] (n = 33) and Cardiothoracic Surgical Trial Network (CTSN) [7] (n = 77) disclosed that patients with severe ischemic mitral regurgitation (IMR) who did not experience persistent or recurrent mitral regurgitation after restrictive annuloplasty, showed significantly reduced left ventricular sizes at 2-year follow up, compared to patients who experienced recurrent MR after single-level RA repair (PMA studies: LVEDD 52.2 ± 4.1 vs 60.4 ± 2.1; LVESD 44.2 ± 3.6 vs 50.8 ± 2.5 and CTSN: 43 ± 26 mL/m^2 vs 63 ± 27 mL/m^2) [7,18]. However, in patients with very dilated ventricles, undersizing the annulus may worsen ventricular function and has been criticized in a subanalysis of CTSN trial [40].

This specific condition is due to the abrupt decrease of the anteroposterior annular diameter in a severely enlarged left ventricle. Patients who do not experience a significant improvement of adverse LV remodeling (LVESD <50 mm) [9,36], reveal a discordance between the performance exerted by the annular restriction and the pulling forces applied in dilated left chamber [41].

Table 1 identifies the randomized clinical trials including patients with secondary mitral regurgitation undergoing standard surgical mitral valve operation or transcatheter edge to edge mitral valve repair (TEER). The new conceptual framework of proportionate/disproportionate condition that distinguishes between the heterogenous group of patients who have SMR due to LV disease includes patients either receiving standard surgical treatment or TEER. Patients may experience the estimated degree of MR which is expected or proportionate to the degree of LV dilatation, or they may experience the severity of MR which is unexpected or disproportionate to the degree of LV increased in size.

Table 1. Randomized Clinical Trial Reporting Proportionate/Disproportionate Secondary Mitral Regurgitation. Proportionate patients have the assessed grade of MR that is waited to the grade of LV dilatation. In disproportionate patients the severity of MR is unexpected or disproportionate to the degree of LV enlargement.

First Author or Study Acronym (Ref. *)	Type of Study	Number of Patients (N)	Treatment Option	Mean Follow-Up/Yrs	Criteria for SMR	Findings
Harmel 2019 [10]	Prospective	101	RMA (50)	1	Ischemic cardiomyopathy 100%	No differences in disproportionate vs proportionate patients for left ventricular remodelling outcome
			RMA plus PMR (51)		Average patients' value LVEDD >60 mm; LVEF <40%	MR >2+ at 1yr was more common among patients with RMA
					EROA >0.2 cm^2	Better survival in RMA plus PMR
Stone 2018 [5] COAPT	RCT	614	Mitra Clip (302) OMT (312)	2	Ischemic cardiomyopathy 62.5% Average patients' value LVEDV 192 mL LVEF 31 $\pm$ 9% (18% LVEF >40%) MR Grade 3/4 EROA mean value 0.41 cm^2; 14% EROA <0.3 cm^2; 41% $\geq$0.4 cm^2	Lover rate in unplanned hospitalization in disproportionate FMR. Slightly improvement of LVEDV/mL/min (from 194.4 $\pm$ 37.4 to 192.2 $\pm$ 76.5)
Obadia 2018 [3] MITRA Fr	RCT	306	Mitra Clip (152) OMT (154)	1	Ischemic cardiomyopathy 62.5% Average patients' value LVEDV 252 mL 33 $\pm$ 7% (all LVEF $\leq$40%) EROA mean value 0.31 cm^2 50% EROA <0.3 cm^2; 16% $\geq$0.4 cm^2	No difference in unplanned hospitalization rate between proportionate and disproportionate FMR. Slightly improvement of LVEDV/mL/min (from 136.2 $\pm$ 37.4 to 134.2 $\pm$ 37)
Nappi 2016 [9] PMA trial	RCT	96	RMA (48) RMA plus PMA (48)	5	Ischemic cardiomyopathy 100% Coronary artery disease with or without the need for coronary revascularization Average value LVEDD 62 mm LVEF 42% MR Grade 3/4 EROA >0.2 cm^2 or Regurgitant Volume >30 mL (ESC guidelines) EROA mean value 0.34 cm^2	Lover rate of unplanned hospitalization in PMA group. Better improvement of LVEDD in PMA (62.7 $\pm$ 3.4 to 56.5 $\pm$ 5.7) vs RMA (61.4 $\pm$ 3.7 to 60.6 $\pm$ 4.6). Reoperation in PMA with disproportionate FMR
Goldstein 2016 [7] CTS Net	RCT	250	MVR (125) RMA (126)	2	Ischemic cardiomyopathy 100% Average value LVESV 63.4 mL; LVEF 40% MR Grade 4 EROA $\geq$0.4 cm² with tethering Eligible for surgical repair and replacement of mitral valve Coronary artery disease with or without the need for coronary revascularization	RMA in disproportionate I-SMR with smaller left ventricle at 2-year follow up did not experience persistent or recurrent MR after surgery
Michler 2016 [24] CTS Net	RCT	351	CABG (151) CABG plus RMA (150)	2	Ischemic cardiomyopathy 100% Average value LVESV 57.2 mL; LVEF 45.8% MR Grade 3 EROA between 0.2 cm² to 0.3 cm² Coronary artery disease amenable to coronary artery bypass grafting and a clinical indication for revascularization	No significant difference between proportionate and disproportionate IMR. Better improvement of LVESV in CABG + RMA (59.6 $\pm$ 25.7 to 43.2 $\pm$ 20.6) compared to CABG alone

A subanalysis conducted on CTSN trial noted that the increased risk of persistent or recurrent MR was due to excessive annular restriction, with a strict relationship between LVESD and ring size equivalent to or higher than 2 [7,40]. The severe overcorrection with restrictive annuloplasty rings was coupled with an aggravation of the leaflet tethering between the papillary muscle and the edge of the leaflet. This overcorrection, associated with an undue lateral and posterior displacement of papillary muscles with respect to the mitral ring, leads to mitral regurgitation recurrence [42–44]. The CTSN investigators reported that in ninety-three percent of recipients a mitral valve ring measured 30 mm or less and the mean size of the valve annulus was 31.0 mm. Instead, the average size of the ring was 27.9 mm. These data are in discordance with the supplementary material from Goldstein *et al.* [7] where annuloplasty ring sizes typically used were 24 to 28 mm. The authors sized 2 ring sizes smaller than the measurement (on average, this will be 28 mm in males, and 26mm in females) which was the same procedure of measurement adopted during the restrictive mitral valve repair in PMA trials [7–9].

The ACC/AHA guidelines state that in patients classified as Stage D of cardiomyopathy, who experience concomitant coronary artery disease and chronic severe secondary IMR due to depressed left ventricular systolic dysfunction measured less than 50%, mitral valve surgery is recommended as a Class of Recommendation (COR) 2b/Level of Evidence (LOE) BR. These patients have severe symptoms, staged as NYHA class III or IV, which persist despite GDMT for heart failure, so cord-sparing mitral valve replacement may be reasonable to choose over the repair with reduced annuloplasty [1].

The use of double level repair confers a significantly lower risk of increased leaflet tethering due to anterior displacement of the posterior leaflet or apical tenting of the anterior leaflet because of the correction of interpapillary muscle diameter [9]. The clinical advantage associated with the use of double level repair, infarct plication, and leaflet or chordal cutting, aimed to reduce leaflet tethering, was more evident in patients with a lower LVEDD <60 mm, LVESD <50 mm, asymmetric tethering, and a well-circumscribed infarct of the inferior wall of the myocardium [9,26,45,46]. The use of papillary muscle approximation procedure did not achieve a significant effect modifier in 17% of patients with anterior myocardial infarctions and symmetrical patterns with predominantly severe apical tethering [26]. As the attrition rate of the double-level mitral valve repair increases with time for asymmetric tethering but not for the symmetric, it is not yet known if the clinical difference in outcomes between the groups at 5 years might increase with a longer follow-up period [9,26]. Undersizing annuloplasty was used in both symmetric and asymmetric tethering and sized 2 ring sizes smaller. It is indicated in subvalvular repair, by approximation of PMs, reduced the risk of augmented leaflet tethering [9] (Fig. 3).

26.2% of patients enrolled in the CTSN trial who underwent restrictive mitral annuloplasty did not receive concomitant revascularization (CABG). This finding may offer a biological mechanism to explain the observed advantage in clinical outcomes of patients who were managed with mitral valve surgery combined with a CABG operation [7]. It is important to note that in the randomized subannular repair trial all patients received complete myocardial revascularization [9]. Although the CABG operation was critical to ensure greater improvement of LVRR, criticisms related to the PMA approach were justified by the 23.8% of patients who had re-hospitalization for heart failure and 29 % of patients showing moderate to severe mitral regurgitation at 5 years follow-up (EROA 41.0 ± 5.3 vs 41.1 ± 1.1) [9,36].

The reasons for these adverse results can be relatively explained by the fact that the clinical benefit of PM approximation is related to multiple variables. As emerged in the PMA trial, surgery of PMs may be considered for patients with increased left ventricles sizes (cutoff of LVEDD 64 mm) [36], persistent dyskinesia, extensive areas of scar tissue formation, or basal aneurysm. However prospective trials on the use of double-level repair are currently scarce to prove significant improvements in postoperative tethering among patients with LV lateral wall dysfunction, predominant posterolateral displacement with apical tenting of both leaflets due to symmetric tethering, persistent LV dyskinesis, as well as severe alteration of LV sphericity [18].

Optimal myocardial revascularization cannot be considered the only determinant for achieving an improvement of left ventricular remodeling to obtain good long-term results.

An equipoise between optimal myocardial revascularization and improvement of reverse ventricular remodeling may be lacking in patients with severe and proportionate mitral regurgitation [2,9]. As reported in PMA trial, in recipients of double valve repair who had moderate to severe MR associated with markedly dilated left ventricles, the surgery may not directly improve the prognosis [9]. In fact 23.8% of these patients experienced ischemic cardiomyopathy which was the leading disease often independent to the degree of mitral regurgitation, revealing an echocardiographic pattern of adverse global and localized LVRR at the five-year follow-up (LVEDD 62.7 ± 3.4 vs LVEDD 63.5 ± 2.4. mean change from baseline -6.4 ± 0.49. EROA 41.0 ± 5.3 vs 41.1 ± 1.1) [9,26,36]. Despite an increase in further re-hospitalizations for heart failure in patients who received the double-level repair (PMA plus RMA), the rate of hospital readmission for heart failure was lower compared to those who had received RMA alone (23.8% vs 38%, $p = 0.136$) at 5th year follow-up after surgery [9,26,36].

Finally, a sex-based difference in the improvement of adverse reverse left ventricular remodeling in patients who underwent combined surgery with the double-level repair was not clearly demonstrated [9]. Women with severe IMR experienced higher mortality compared to men after MV
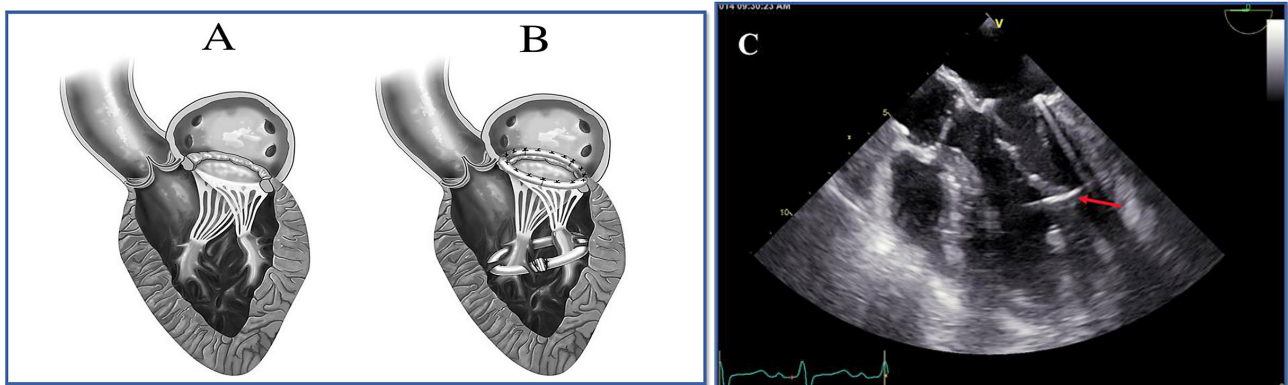
Fig. 3. Depicts the PMA procedure with the postoperative echocardiographic control. (A) Sagittal illustration of baseline with increased with interpapillary muscle distance. (B) Double level repair with restrictive mitral anuloplastie combined to papillary muscle approximation using a Expanded Politetrafluoroetilene graft. (C) 2D mid esophageal 4-chamber view status post double level repair. The papillary muscle graft is denoted by the red arrow.

surgery despite no significant differences in the degree of reverse LV remodeling in the sub-analysis of the CTSN RCT [47].

4. The Third "Wheel": Transcatheter Edge-To-Edge Repair

The transcatheter edge-to-edge repair with the MitraClip system is a percutaneous treatment option for secondary mitral regurgitation, and like the surgical interventions, targeting the mitral valve itself, which has debatable results. Secondary mitral regurgitation is a very heterogeneous disease with the demonstrated absence of a consistent correlation between the choice of mechanical intervention and clinical events [3,48,49].

Two recent RCTs, Multi-center Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR) [3] and Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) [5], have evaluated safety and efficacy of TEER for symptomatic patients with heart failure, reduced EF and severe SMR in addition to GDMT compared to GDMT alone.

The results of outcomes of trials were discordant and this has led to heated discussions and intense debates about the reasons for these differences.

In the COAPT trial and its ancillary report at 3-year [6], patients with TEER procedure showed a reduced risk of death from any cause, reduced risk of hospitalization for HF, and a significant reduction in MR and left ventricular volumes. The results of the MITRA-FR trials and its ancillary report at 2-years [4] were markedly discordant with no differences on the primary composite endpoint of all-cause mortality (ACM) or hospitalization for HF (HFH) and reduction of LV volumes.

Many factors have been postulated to partially explain the divergent outcomes: echocardiographic assessment of SMR severity, effect size and differences in trial design, optimal use of medical therapy, and patient selection.

A careful analysis of the patients enrolled in the 2 trials detected two important differences, patients enrolled in the MITRA-FR trial had a smaller mean EROA and a larger mean left ventricle end-diastolic volume index (LVEDVi). In the 307 patients enrolled, the mean (SD) EROA was 0.31 (10) cm^2, and the mean (SD) LVEDVi was 135 (37) mL/m^2. More than 50% of patients had an EROA <0.3 cm^2 and only 16% had an EROA $\geq$0.4 cm^2. Conversely, in patients from the COAPT trial, the mean (SD) EROA was 0.41 cm^2 [15] and the mean (SD) LVEDVi was 101 mL/m^2 [34]. Only 14% of patients had an EROA <0.3 cm^2 and 41% had an EROA $\geq$0.4 cm^2. It is interesting to note that in the COAPT patients the EROA was ~30% higher but their LV volumes were ~30% smaller than those enrolled in the MITRA-FR trial. Furthermore, in the COAPT trial, patients with an LV end-diastolic diameter (LVEDD) >70 mm were not eligible for randomization, while in MITRA-FR trial were not excluded and 70% of patients had LVEDD >65 mm [48,50,51].

Recently, a new conceptual framework has been established that attempts to reconcile the results of the MITRA-FR and COAPT trials [48,52]. By the introduction of the concept of disproportionate and proportionate SMR, the two RCTs now appear to have changed from divergent to complementary.

Assessment of severity of SMR remains challenging because several factors are involved; the calculation of the EROA by echocardiography or its association with clinical outcomes requires caution [53]. Grayburn *et al.* [48] highlighted that for any given regurgitant fraction, the EROA is dependent on both the left ventricular end-diastolic volume (LVEDV) and the left ventricular ejection fraction (LVEF), hence, suggested that the EROA to LVEDV ratio identifies the degree of SMR as proportionate (when the degree of MR is expected or proportionate to the degree of LV dilata-
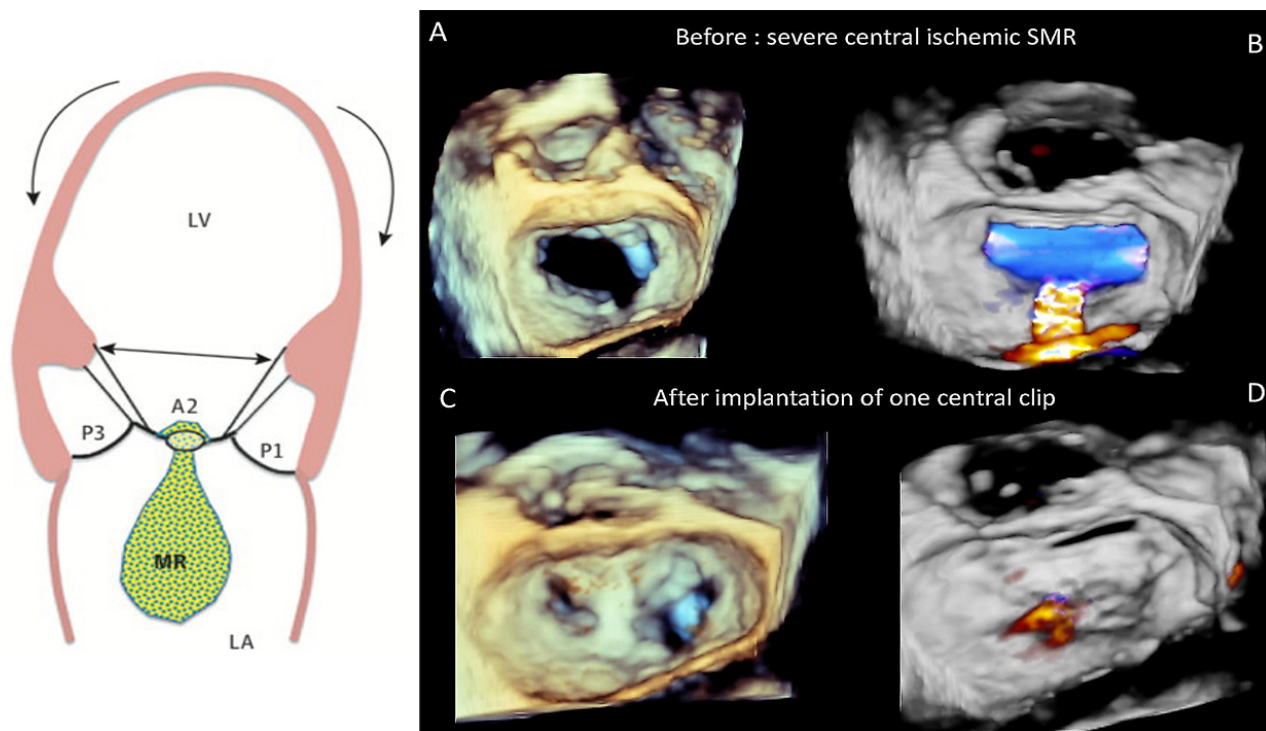
Fig. 4. Depicts a patient with proportionate SMR. Left: proportionate SMR sketch due to ischemic cardiomyopathy. Right: TEER procedure achieved in patient with SMR and proportionate framework. (A) three-dimensional (3D) transoesophageal echocardiography (TEE) and (B) 3D TEE color en-face view showing central SMR. (C) A 3D-TEE en face view after a successful procedure with implantation of 2 central MitraClip (Abbott Cardiovascular, Saint Paul, MN). (D) A 3D-TEE en face view shows persistent good results at 1 year with residual mild mitral regurgitation and a gradient at 4 mm Hg. Abbreviations: SMR, Secondary Mitral regurgitation; TEE, transthoracic echocardiography; TEER, Trancatheter Edge to Edge Repair.

tion and it is due to lateral but symmetrical displacement of papillary muscle) and disproportionate (when the severity of MR is unexpected or disproportionate to the degree of LV enlargement and it is due to unequal or uncoordinated activation of the papillary muscles) [52] (Fig. 4).

In patients with disproportionate MR, the mitral valve disease is the leading pathology, whereby effective and sustainable treatment toward restoration of normal papillary muscle synchrony or normal mitral valve function can directly improve the prognosis. In patients with proportionate MR, marked left ventricular dilatation and remodeling is the leading pathology and thus, the prognosis may not be linked to mitral valve treatment [52].

Based on this new conceptual framework, the analysis of the baseline characteristics of patients in the COAPT trial show that most of the patients enrolled had severe disproportionate MR and in contrast, those in the MITRA-FR trial had severe proportionate MR [48]. This can explain, at least in part, that the clinical benefit of adding edge-to-edge procedure in MITRA-Fr is minimal because the disease primarily affects the myocardium rather than the mitral valve with severe impairment of LV function. Grayburn *et al.* [52] in the COAPT cohorts showed that the EROA to LVEDVi ratio appeared to correlate with 12-month ACM or HFH, supporting the concept of proportionate/disproportionate SMR, with a cutoff ratio of 0.15 mm^2/mL to differentiate the two entities.

This new hypothesis is however questioned, Lindenfeld *et al.* [50], define 6 subgroups of the COAPT patients by EROA cutoffs and analysis show that TEER had no benefit on the composite rate of ACM or HFH at 24 months, using the new framework to explain results of MITRA-FR and COAPT trials. Other studies suggest that regurgitant volume-LVEDV association or regurgitant fraction and right ventricular dysfunction assessed by TAPSE (Tricuspid Annular Plane Systolic Excursion) may be considered more predictive of outcome than the EROA-LVEDV association and may help the selection of patients to TEER [54,55].

The leaflets approximation with Mitraclip device G4, G4 NT and G4 NTW (Abbott Vascular, Santa Clara, CA, USA) is by far the most widespread percutaneous mitral valve repair strategy. Other percutaneous devices are being developed but their utility is still limited, like the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA, USA) that performs an indirect annuloplasty or the Cardioband Mitral System (Edwards Lifesciences, Irvine, CA, USA) that performs a direct annuloplasty. A direct competitor of Mitraclip device is the PASCAL device (Edwards Lifesciences, Irvine, CA, USA), which also allows leaflets approximation with edge-to-edge repair and with
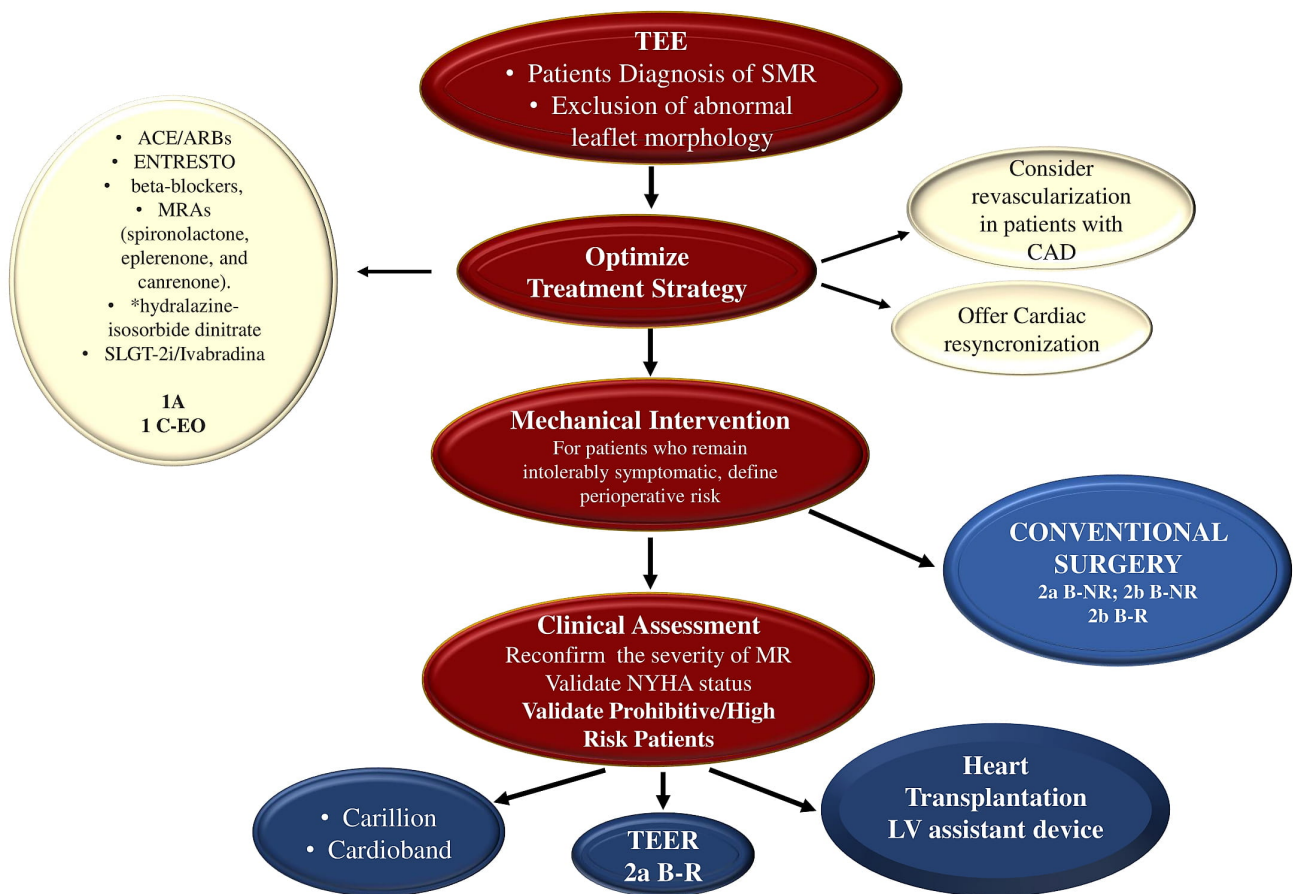
Fig. 5. Clinical Algorithm for the Management of Chronic MR Based on latest ACC/AHA guidelines. Decision Tree for Distinguishing Treatment Choice. Abbreviations: ACE, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; CAD, coronary artery disease; MRAs, mineralocorticoid receptor antagonists; LV, Left Ventricle; NYHA, New York Heart Association Class; TEE, transthoracic echocardiography; TEER, Trancatheter Edge to Edge Repair.

improved maneuverability, permitting independent leaflet capture, allowing theoretical high-quality leaflet grabbing. A recent article reports favorable outcomes at 2 years in functional and degenerative mitral regurgitation from the multicenter, prospective, single-arm CLASP study [56]. Although this study was not specific for SMR, the new device used alone or in combination with direct or indirect annuloplasty could provide encouraging results in the transcatheter mitral valve repair as well as the use of transcatheter mitral valve replacement devices for the treatment of SMR which could provide further insights into ventricular remodeling and the role of mitral regurgitation [57].

TEER should be considered in patients with severe MR that meet the COAPT trial criteria (LVEF between 20% and 50%, LVESD ≤70 mm, pulmonary artery systolic pressure ≤70 mmHg, and persistent symptoms) and receiving optimal medical therapy [1,2]. Nonetheless, a more rigorous selection of patients should be considered and the concept of proportionate/disproportionate MR can help identify patients who may benefit from mitral valve restoration [57–61].

Special considerations can be made for a particular form of SMR, the atrial functional MR. This entity should be differentiated from ventricular secondary MV because its pathophysiology is unique and therapeutic targets are different. Atrial fibrillation (AF) and/or heart failure with preserved ejection fraction (HFpEF) are responsible for isolated mitral annular dilation and inadequate leaflet adaptation, while the LV size and systolic function are typically normal. In this unique disease, restrictive mitral annuloplasty (which enhances leaflet coaptation by reducing annular dimensions) can be considered the interventional target. Therefore, direct or indirect transcatheter annuloplasty may have excellent results, as well as the transcatheter edge-to-edge devices in reduction of anterior-posterior MA diameter. The key to treatment of atrial functional MR may consist of early adapted strategies to prevent left atrial dilatation and restore sinus rhythm [62].

Given the multitude of choices available for the management of SMR, we have provided an algorithm to guide the optimal intervention based on the current guidelines by the ACC/AHA and ESC guidelines (Fig. 5).

5. Conclusions

Chronic SMR is a complex pathology associated with a poor prognosis where the pathophysiological mechanisms have probably not been fully elucidated. Interventional (surgical or percutaneous) management is controversial despite randomized trials. These must be backed by additional research that further clarifies the mechanisms underlying strong evidence correlating LVESVI with clinical outcomes, including the recurrence of mitral regurgitation, NYHA class, hospitalization, and survival in patients undergoing mechanical intervention. The concept of proportionate/disproportionate MR can help to identify which patients benefit from mitral valve restoration. The use of algorithms with up-to-date guidelines may help with ensuring the best management options are suited to individual patients.

Author contributions

AF, and FN designed the research study. AF, SSAS and FN performed the research. AF, SSAS and FN analyzed the data. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

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