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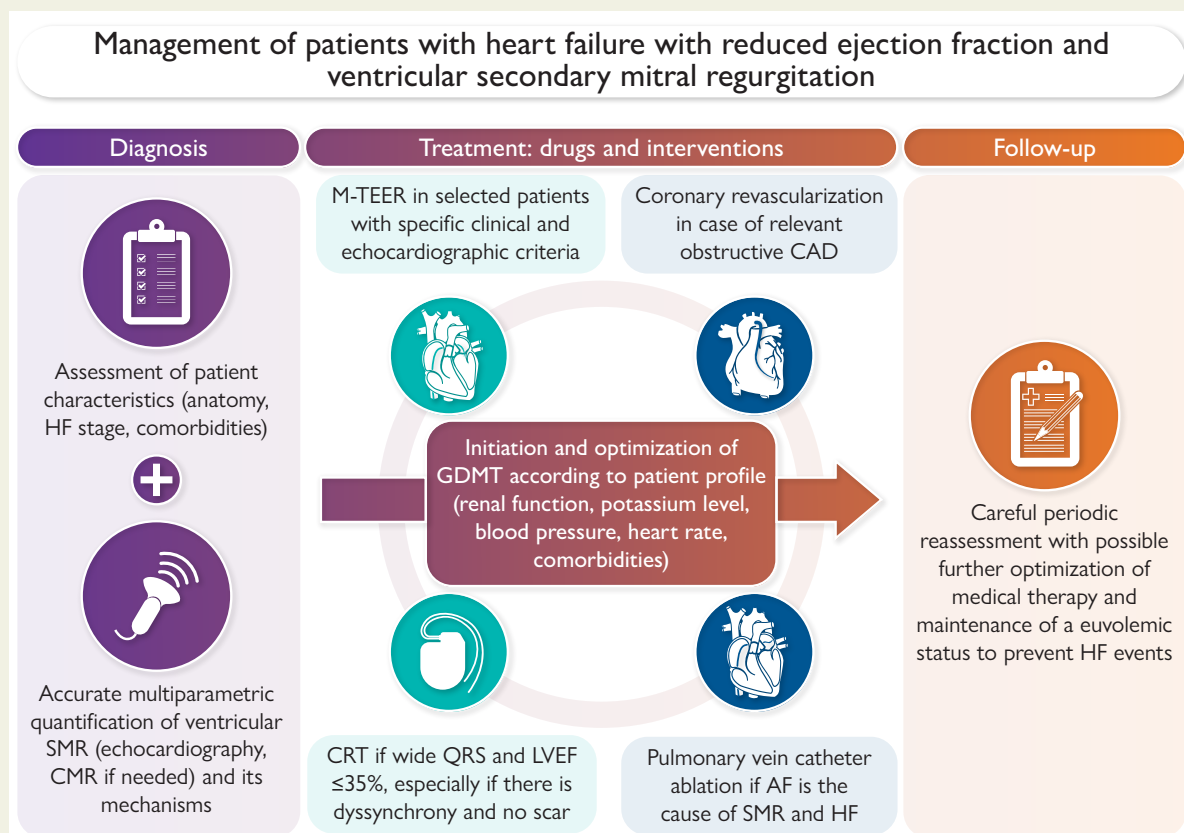
Heart failure with reduced ejection fraction and ventricular secondary mitral regurgitation: a holistic approach

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Graphical Abstract



AF, atrial fibrillation; CAD, coronary artery disease; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; GDMT, guideline-directed medical therapy; HF, heart failure; LVEF, left ventricular ejection fraction; M-TEER, mitral transcatheter edge-to-edge repair; SMR, secondary mitral regurgitation.

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Abstract

Optimal management of patients with heart failure with reduced ejection fraction (HFrEF) and secondary mitral regurgitation (SMR) requires the integration of multiple competencies with the interplay of guideline-directed medical therapy (GDMT) for HFrEF, devices, namely cardiac resynchronization therapy (CRT), when indicated, and mitral transcatheter edge-to-edge repair (M-TEER). Both GDMT and CRT can reduce SMR severity. However, GDMT may not be tolerated in patients with HFrEF who develop hypotension and worsening kidney function following uptitration. On the other hand, a successful M-TEER can increase forward stroke volume and blood pressure and improve kidney perfusion so that GDMT may be better tolerated after rather than before this procedure. Thus, similarly to CRT, M-TEER may serve as enabling therapy for GDMT. Notably, catheter ablation for atrial fibrillation and coronary revascularization may have a role in very selected patients. Furthermore, these patients with HFrEF and SMR remain at high risk of clinical events even after successful transcatheter treatments (i.e. M-TEER). Careful follow-up and continuous implementation of GDMT remain a major priority both before and after any intervention. The aim of this state-of-the-art review is to summarize current knowledge about management of HFrEF and ventricular SMR including the entire patient pathway (i.e. diagnosis, treatment and follow-up) with a focus on the effects of GDMT and CRT on SMR as well as on the effects of successful M-TEER on GDMT tolerability.

Keywords Mitral regurgitation • Heart failure • Drugs • Interventions

Introduction

Treatment of patients with heart failure (HF) with reduced ejection fraction (HFrEF) and secondary ventricular mitral regurgitation (SMR) is complex. Secondary mitral regurgitation is a consequence of left ventricular (LV) remodelling and contributes to HF progression by worsening ventricle overload.¹ Guideline-directed medical therapy (GDMT) and devices [cardiac resynchronization therapy (CRT)] for HFrEF may reduce SMR severity through beneficial effects on LV remodelling.² Patients who continue to have significant SMR despite optimal HFrEF treatments may further benefit from SMR correction by a transcatheter approach [mitral transcatheter edge-to-edge repair (M-TEER)]. The improvement in haemodynamic conditions with increased forward stroke volume and blood pressure and possibly better kidney function after successful M-TEER may then increase tolerance to GDMT.³ Thus, HFrEF treatments (drugs and devices) may have a synergistic role (Figures 1 and 2).^{4,5} Furthermore, patients with HFrEF and significant SMR, even if effectively treated with medications and devices, remain at high risk of events so that a strict follow-up remains mandatory and implementation of GDMT maintained whenever possible (Graphical Abstract).^{6,7} The aim of this state-of-the-art review is to report current evidence on the treatment of patients with HFrEF and ventricular SMR, and to suggest a holistic management approach to these patients with the support of a multidisciplinary team. Management of atrial SMR will not be discussed here.

Epidemiology and natural history of secondary mitral regurgitation

Secondary mitral regurgitation is the most common valvular disease in patients with chronic HF, although its exact prevalence is difficult to estimate since available studies included heterogeneous populations in terms of HF stage, clinical setting or presentation, LV ejection fraction (LVEF), and type/aetiology of concomitant mitral regurgitation (MR).^{8–11} Prevalence of moderate–severe SMR ranged from 29% to 70% in available studies, and it is higher in HFrEF as compared with the other HF phenotypes based on LVEF.^{8–11} In the ESC Heart Failure Long-Term Registry, moderate–severe MR was observed in 35.6%, 28.4%, and 19.5% of patients with HFrEF, HF with mildly reduced ejection fraction (HFmrEF), and HF

with preserved ejection fraction (HFpEF), respectively.¹² In a recent large Austrian cohort study, severe MR was reported in 25%, 10.2%, and 4.5% of patients with HFrEF, HFmrEF, and HFpEF, respectively.⁹

Multiple studies have shown that significant SMR is an independent predictor of worse clinical outcomes in patients with chronic HF.^{9–11,13–15} There is a strong correlation between MR severity and outcomes.^{11,14,15} Patients with HFrEF and SMR are burdened by a particularly high risk of HF-related hospitalizations over time.⁹ In the control arm of the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial, cumulative 5-year rates of all-cause death or first HF hospitalization and of first HF hospitalization alone were 91.5% and 83.0%, respectively, in patients with moderate-to-severe or severe SMR and reduced LVEF on medical therapy.⁷

Management of patients with heart failure with reduced ejection fraction and secondary mitral regurgitation

Diagnosis

Echocardiography: when secondary mitral regurgitation should be considered significant

Transthoracic echocardiography (TTE) is the cornerstone imaging modality for the assessment of SMR and should integrate both 2D and 3D imaging, as well as Doppler techniques, to quantify SMR severity and define the exact underlying mechanisms.¹⁶ It should be performed in a eu-volemic state, but serial studies could be useful to detect changes related to haemodynamic conditions or initiation/uptitration of medical therapy. Transoesophageal echocardiography (TOE) may be required in cases of suboptimal TTE images or when a more detailed evaluation of the mitral apparatus is needed. Stress echocardiography is also valuable, as SMR severity often increases during exercise due to elevated afterload or worsening tethering forces, unmasking dynamic regurgitation not apparent at rest.

Assessment of SMR severity is currently recommended based on a multi-parametric echocardiographic approach.¹⁶ As first-line, qualitative

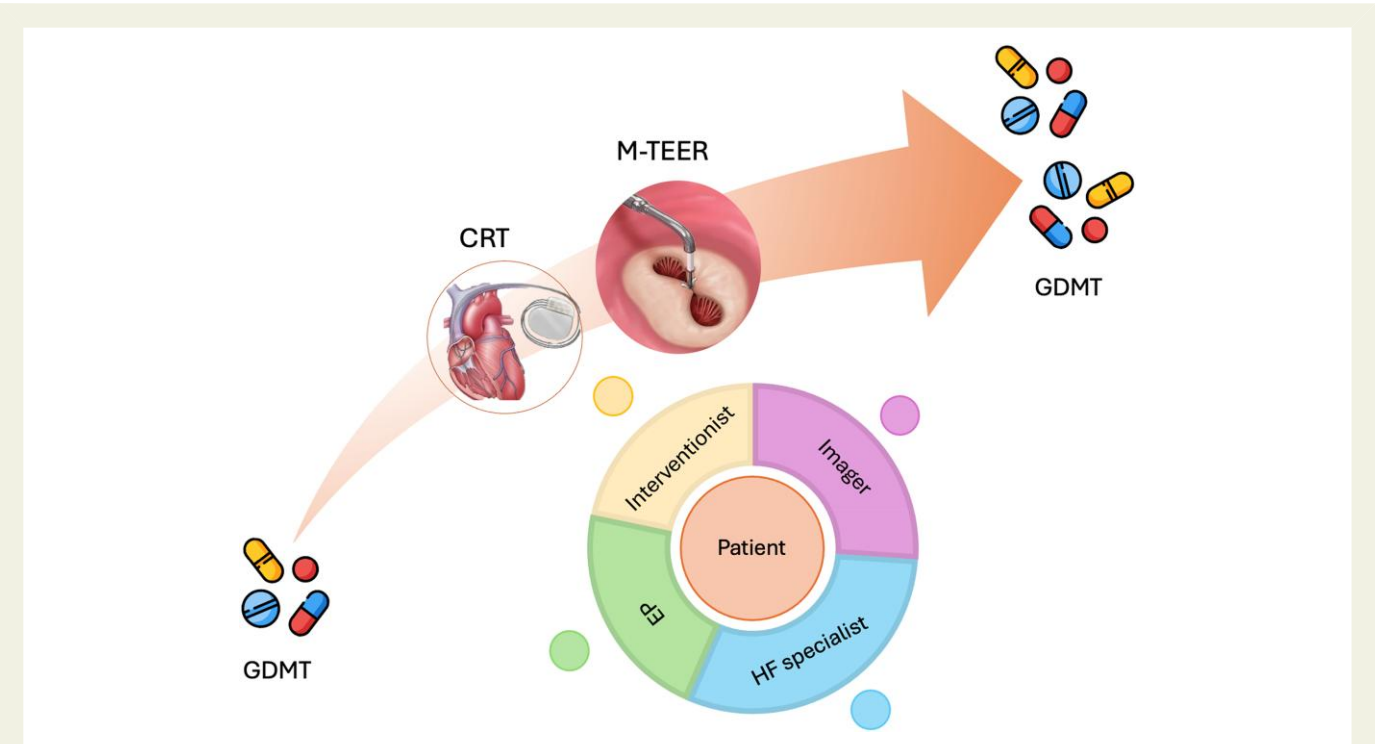


Figure 1 Multidisciplinary and multi-treatment approach to patients with heart failure with reduced ejection fraction and secondary mitral regurgitation. Guideline-directed medical therapy uptitration before and after device implementation. The entire patient pathway is managed by a multidisciplinary team. CRT, cardiac resynchronization therapy; EP, electrophysiologist; GDMT, guideline-directed medical therapy; HF, heart failure; M-TEER, mitral transcatheter edge-to-edge repair

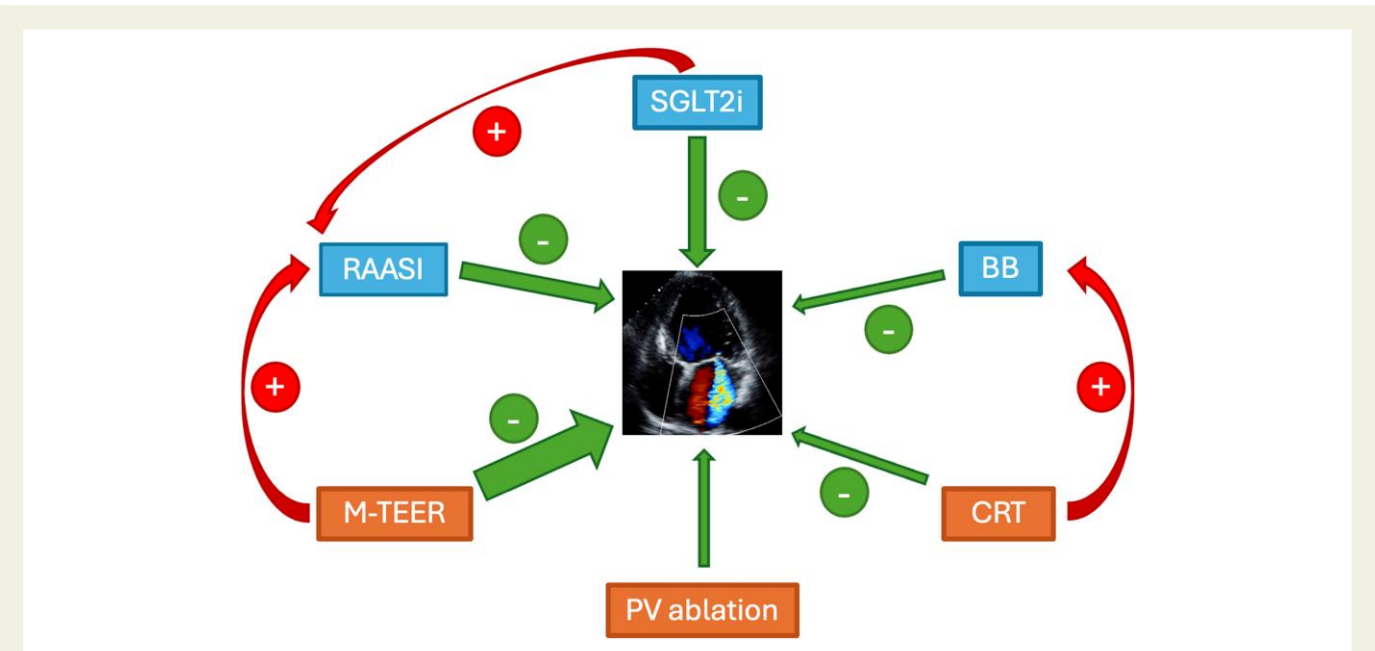


Figure 2 Synergistic therapies for secondary mitral regurgitation in patients with heart failure with reduced ejection fraction. Drugs and interventions may reduce SMR severity. The effect on SMR reduction can vary according to the treatment type (i.e. very high with M-TEER). Drugs as well as interventions may enable drug effects (i.e. SGLT2i may enable RAASI, CRT may enable betablocker, M-TEER may enable RAASI). BB, beta-blocker; CRT, cardiac resynchronization therapy; M-TEER, mitral transcatheter edge-to-edge repair; PV, pulmonary vein; RAASI, renin-angiotensin-aldosterone system inhibitors; SGLT2i, sodium-glucose cotransporter 2 inhibitor

signs, such as a large central jet and a holosystolic convergence zone, and semi-quantitative parameters should be used. Particularly, vena contracta width is considered one of the best measures, and a cut-off of 7 mm is proposed by both European and American guidelines to define severe SMR.^{17,18} However, considering the often elliptical shape of the regurgitant orifice in SMR, a cut-off value of 8 mm should be considered in biplane imaging or ideally use 3D vena contracta area to directly planimeter the regurgitant orifice area ($>0.4 \text{ cm}^2$). If vena contracta cannot be measured (e.g. in case of multiple jets) or shows intermediate values (3–6 mm), severe SMR needs confirmation by a quantitative method, including an effective regurgitant orifice area (EROA) $\geq 0.4 \text{ cm}^2$, a regurgitant volume (RVol) $\geq 60 \text{ mL}$ [both obtained by proximal isovelocity surface area (PISA) method], and a regurgitant fraction (RF) $\geq 50\%$. These cut-off values are in line with those used for primary MR, but if the impact of SMR on outcome is considered, lower cut-off values could be applied to define significant SMR, emphasizing the prognostic impact of SMR and possibly earlier identification of patients who may benefit from specific therapies.^{11,19,20} Current European guidelines therefore suggest considering a cut-off of 30 mm^2 for EROA and of 45 mL for RVol (i.e. consistent with moderate-to-severe SMR, but typically with RF of 50%), especially in case of elliptical regurgitant orifice and/or low-flow state.^{17,18}

However, even the application of these lower cut-offs may be problematic.²¹ Multi-modality imaging approach including integration of multiple echocardiographic parameters as well as an early use of TOE and cardiac magnetic resonance (CMR) should be considered in patients with clinically suspected significant SMR. This is of importance, because underestimation of SMR severity by TTE may result in significant under-treatment of HFrEF patients with clinically severe SMR.

Treatments

Medical therapy: advantages, limitations, and timing

Current guidelines recommend the optimization of medical therapy for HF in patients with SMR, before considering the potential candidacy to interventional treatments.^{18,22} Previous small studies have reported a reduction in SMR severity among patients with chronic HF receiving beta-blockers or renin-angiotensin-aldosterone system inhibitors (RAASi).^{23–26} In the Pharmacological Reduction of Functional, Ischemic Mitral Regurgitation (PRIME) trial, sacubitril/valsartan reduced SMR to a greater extent than valsartan in patients with chronic HFmrEF or HFrEF and concomitant significant SMR.²⁷ Similarly, the addition of ertugliflozin to GDMT for HF reduced SMR severity in the recent Ertugliflozin for Functional Mitral Regurgitation (EFFORT) trial.²⁸ Recent studies confirmed the efficacy of GDMT, above all when neurohormonal modulators [i.e. RAASi, beta-blockers, and mineralocorticoid receptor antagonists (MRAs)] are used together and showed that persistence of significant SMR after GDMT implementation has a strong prognostic impact.^{2,29}

However, in the real world, GDMT is initiated in only a fraction of patients with HFrEF and it is mostly underdosed, compared with the doses reached in randomized clinical trials (RCTs). Triple GDMT with RAASi, beta-blockers, and MRA was prescribed in 40% of patients undergoing M-TEER in the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) registry and was associated with higher survival after M-TEER.³⁰ The rate of triple GDMT prescription before M-TEER was even lower in a larger analysis from the US Transcatheter Valve Therapy Registry (19%) and with significant centre-level variability (0%–61%).³¹

Drug intolerance, caused by low blood pressure, kidney dysfunction, and hyperkalaemia, is a major cause of under-prescription, and these limitations may be larger in patients with HFrEF and concomitant SMR. In a

sub-analysis of the COAPT trial, where GDMT optimization was directed by HF specialists, most enrolled patients had medical intolerances prohibiting the prescription of one or more drug classes and the achievement of target doses.³² Causes of intolerances differed by GDMT class, with hypotension and kidney dysfunction being the most common for both RASi and MRA and hyperkalaemia also having an important role for MRA.³² Sodium-glucose cotransporter 2 inhibitors (SGLT2i) have been shown more recently to have beneficial effects on outcome of HF patients. They have beneficial effects also on cardiac function and SMR severity.^{28,33} As they lack of unfavourable short-term haemodynamic effects, their implementation seems easier in clinical practice and they should be administered before M-TEER in all patients with HF. Notably, SGLT2i should not be discontinued during hospitalization.

With respect to the timing of M-TEER after GDMT optimization in patients with HFrEF and SMR, the procedure should be performed once the benefits on cardiac function have reached their peak or are at least close to it. Evidence is, however, limited. Rapid GDMT uptitration has been found effective in patients recently hospitalized for acute HF.³⁴ Heart failure guidelines recommend rapid GDMT uptitration with achievement of the maximum tolerated dose within 6 weeks. Concomitant serial assessment of safety indicators, including blood pressure, heart rate, serum creatinine, potassium, and natriuretic peptides, is warranted.³⁵ Studies showing an improvement in SMR after medical therapies had an echocardiographic follow-up, which varied from 1 to 12 months.^{2,29} Studies showing LV reverse remodelling after HF treatment had an echocardiographic follow-up, which varied from 1 to 6 months.^{36,37} Therefore, it could be reasonable to reassess SMR and patient symptoms after 1–3 months after achievement of maximum tolerated dose of GDMT.

Cardiac resynchronization therapy: when, why, and how

Cardiac resynchronization therapy is an established treatment for patients with symptomatic HF despite GDMT, when they meet specific criteria reflecting LV dysfunction possibly related to electrical dyssynchrony, which is the specific target of this treatment. American and European guidelines therefore recommend CRT (Class I indication) for patients in New York Heart Association Class II–IV, reduced LVEF $\leq 35\%$, and a QRS duration $\geq 130 \text{ ms}$ with a left bundle branch block (LBBB) morphology. Lower class of recommendation (IIa and IIb) is given in case of QRS duration between 130 and 150 ms and non-LBBB morphology. Several clinical trials have demonstrated in these patients a significant reduction in HF symptoms and hospitalizations and in mortality.^{38–40} In a large percentage of patients undergoing CRT, reverse LV remodelling has been also demonstrated, with a reduction in LV size and an improvement in LVEF. Severity of SMR may also decrease in patients with significant SMR before CRT and this was associated with a clinical and prognostic benefit.^{41–43} The possible beneficial effect of CRT on SMR is attributed to several mechanisms. By restoring a synchronous contraction, CRT improves LV contractile efficiency, allowing more synchronous papillary muscle contraction and better mitral annular dynamics, leading to an immediate reduction of SMR. At mid- and long-term follow-up, when significant LV reverse remodelling occurs, the decrease in mitral leaflet tethering and in mitral annular dilatation results in better leaflet coaptation and in a further reduction of RVol. Echocardiography therefore plays a central role in assessing post-CRT changes in SMR severity, LV function, and remodelling.⁴⁴ However, the reported reduction in SMR severity after CRT is limited. van Bommel *et al.* reported an EROA reduction by only 16%

(from 0.51 ± 0.16 to 0.43 ± 0.18 cm²), Ypenburg *et al.* reported a SMR reduction in only 37% of patients while 63% presented with unchanged or increased SMR severity, and Michalski *et al.* reported no MR improvement in 38%, 1 grade improvement in 39% and ≥ 2 grade improvement in only 23% of patients.^{41–43} Thus, a considerable number of patients still remain with at least moderate SMR despite CRT implantation. Several factors might be responsible for this limited SMR improvement after CRT, including a suboptimal lead placement, severe impairment of LV function at baseline (e.g. because of an extensive myocardial scar), non-LBBB QRS morphology, and eventually a mixed aetiology of MR (with also an organic rather than functional component).^{38,44} It is unknown whether conduction system pacing, involving direct stimulation of the LBBB area, may have a role in reducing SMR. However, there is no evidence supporting this hypothesis. Advanced imaging modalities, such as echocardiography or CMR, can guide lead placement by identifying the latest activated areas (maximal delay) as target or avoid scar tissue that may impede proper pacing.^{45,46} In patients with SMR, successful CRT implementation therefore requires appropriate patient selection, precise lead placement, and ongoing multidisciplinary care to maximize therapeutic outcomes. Then, regardless of SMR, CRT may enable HF drug implementation by improving haemodynamic conditions and preventing bradycardia.⁴³

Studies showing an improvement in SMR after CRT had an echocardiographic follow-up, which varied from 3 to 12 months. Early improvement of SMR can be expected when dyssynchrony plays a major role in SMR aetiology.⁴³ Future trials are needed to evaluate the efficacy, the optimal timing and order of CRT placement, and M-TEER procedures to optimize outcomes of patients with SMR and HFrEF.

Transcatheter interventions

Nowadays, M-TEER can be considered the gold standard therapy for patients with HFrEF and significant SMR fulfilling specific clinical and echocardiographic criteria and after optimization of GDMT and CRT implantation, if indicated.²²

Data on safety have been extensively reported in registries and RCTs.^{21,47–52} Efficacy in reducing SMR severity is higher with new-generation devices and at high volume centers.^{53–55} Outcome data were collected in three RCTs comparing M-TEER + GDMT vs GDMT alone in patients with SMR and LVEF $\leq 50\%$ (Table 1).^{48–50} The Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) was neutral. However, there was no eligibility committee to evaluate GDMT before intervention, and possible changes of GDMT during follow-up were not reported. In addition, patients with advanced HF, severe pulmonary hypertension, and right ventricular dysfunction could be included in this trial.⁴⁸ The COAPT trial showed, for the first time, a significant reduction in HF hospitalization (primary endpoint) as well as all-cause death in patients receiving M-TEER as compared with the control group. This trial has led to a specific indication, Class IIa level of evidence B, in current guidelines, for patients fulfilling inclusion criteria adopted in the study [LVEF 20%–50%, LV end-systolic diameter < 70 mm, and lack of advanced HF, haemodynamic instability, severe pulmonary hypertension, severe tricuspid regurgitation (TR), moderate or severe right ventricular function].⁴⁹ The Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation (RESHAPE-HF2) trial has been recently published. It met its three co-primary endpoints showing a significant reduction of HF hospitalization, HF hospitalization and cardiovascular death, and improvement in quality of life in patients treated with M-TEER as compared with those conservatively managed. Notably, 2-year mortality and all-

cause admissions did not differ between the two treatment arms.⁵⁰ RESHAPE-HF2 confirmed COAPT results in a lower-risk population (lower NT-proBNP levels, better renal function, better tolerance to GDMT, and less severe SMR by TTE), and this could explain the lack of mortality benefit. Importantly, both TTE and TOE studies were evaluated for eligibility determination,⁵⁰ which acknowledged the limitations of MR severity assessment by TTE and also explained the lower observed EROA values. Importantly, a pre-specified analysis of the RESHAPE-HF2 trial showed that HF hospitalizations in the year prior to randomization were associated with a greater prognostic benefit after M-TEER.⁵⁶ In the study-level meta-analysis summarizing the results of RESHAPE-HF2, COAPT, and MITRA-FR, a significant reduction of 2-year HF hospitalizations and a trend towards a reduction of all-cause death were observed with M-TEER + GDMT as compared with GDMT alone.³

The role of surgery

Patients with SMR and HFrEF are rarely surgical candidates since they have an intrinsic increased surgical risk, and especially in a modern era where a safer and similarly effective alternative is available. Notably, there are no RCTs demonstrating a possible benefit of mitral valve surgery vs conservative care in patients with isolated SMR and HFrEF. The Multicenter, Randomized, Controlled Study to Assess Mitral vAlve reconsTrucTion for advancEd Insufficiency of Functional or isChemic ORigin (MATTERHORN) trial showed that, in patients with SMR, M-TEER was non-inferior to mitral valve surgery with respect to a composite of death, rehospitalization for HF, stroke, reintervention, or implantation of a LV assist device at 1 year. In addition, as expected, M-TEER was safer than surgery.⁵⁷ Of note, many limitations of MATTERHORN have to be recognized including small sample size, lack of a conservative arm, use of combined surgery in the surgery arm (i.e. AF ablation), and use of a combined endpoint including surgery-related complications. In addition, longer follow-up data are needed to know whether efficacy results are maintained over time.

Finally, as mentioned above, surgery may maintain a role in low-risk patients with severe SMR and an obstructive CAD suitable for CABG.⁵⁸

Other treatments

Prevalence of atrial fibrillation (AF) in patients with ventricular SMR is $\sim 35\%$.⁵⁹ Current guidelines recommend AF catheter ablation to promote LV reverse remodelling in patients with HFrEF and high probability of tachycardia-induced cardiomyopathy.⁶⁰ The Catheter Ablation Versus Medical Rate Control in Atrial Fibrillation and Systolic Dysfunction-Magnetic Resonance Imaging (CAMERA-MRI) trial demonstrated a significant left atrial and ventricular reverse remodelling in patients with HFrEF undergoing AF catheter ablation vs rate control; however, no data on possible SMR reduction are reported in this randomized controlled trial (RCT).⁶¹ A few small retrospective registries suggest a possible role of AF catheter ablation in reducing SMR severity.^{62,63} However, in these patients with HFrEF, ventricular SMR, and AF, it is crucial to understand the contribute of AF to left chamber remodelling as well as the mechanism of SMR, specifically the atrial contribute to mitral annulus remodelling. In those patients with tachycardia-induced cardiomyopathy or in whom there is a mixed aetiology of SMR (both ventricular and atrial), catheter ablation may play a major role in the treatment of HFrEF and SMR.

Coronary artery disease (CAD) is common in patients with HFrEF.⁶⁴ It is known that percutaneous coronary intervention (PCI) may induce LV reverse remodelling and reduction of SMR after an acute myocardial infarction with reduced LVEF⁶⁵; however, the role of PCI in chronic

Table 1 Comparison between RESHAPE-HF2, COAPT, and MITRA-FR

	RESHAPE-HF2	COAPT	MITRA-FR
Inclusion criteria			
LVEF	20%–50%	20%–50%	15%–40%
LVEDD	Not required	<70 mm	Not required
EROA	>20 mm ²	>30 mm ²	>20 mm ²
Prior HFH	Yes (or high NPs)	Yes (or high NPs)	Yes (NPs not required)
Right HF, severe TR, severe PH	Excluded	Excluded	Not excluded
Baseline characteristics			
Sample size (n)	505	614	304
Male sex, % (n)	80 (406/505)	64 (393/612)	75 (227/304)
Age (years), mean	70	72	70
NYHA Class III–IV, % (n)	75 (380/504)	61 (373/612)	67 (204/304)
Prior HF hospitalization, % (n)	66 (333/505)	57 (351/612)	100 (304/304)
EROA (cm ²), mean	0.25	0.41	0.31
LVEF (%), mean	31	31	33
LVEDV (mL), mean	205	193	250
NT-proBNP (pg/mL)	4185 (mean) 2745 (median)	5558 (mean)	3400 (median)
eGFR (mL/min/1.73 m ²), mean	56	49	50
Medical therapy			
• Beta-blockers, % (n)	96	90	90
• MRA, % (n)	82	50	55
• RASI, % (n)	82	67	84
Two-year outcomes			
All-cause death, HR (95% CI)	0.73 (0.51–1.05)	0.62 (0.46–0.82)	1.02 (0.70–1.49)
HF hospitalization, HR (95% CI)	0.62 (0.46–0.83)	0.53 (0.40–0.70)	0.97 (0.72–1.30)

CI, confidence interval; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; HF, heart failure; HFH, heart failure hospitalization; HR, hazard ratio; LVEF, left ventricular ejection fraction; LVEDV, left ventricular end-diastolic volume; LVEDD, left ventricular end-systolic diameter; MRA, mineralocorticoid receptor antagonist; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PH, pulmonary hypertension; RASI, renin–angiotensin system inhibitor; TR, tricuspid regurgitation.

HFrEF is less established. In the Study of Efficacy and Safety of Percutaneous Coronary Intervention to Improve Survival in Heart Failure (REVIVED-BCIS2) trial, enrolling patients with ischaemic HF with LVEF $\leq 35\%$ and multivessel CAD, changes in LVEF did not differ between the two arms of treatment (PCI + GDMT vs GDMT alone).⁶⁴ A small retrospective study suggests that PCI of the left main is associated with LV reverse remodelling in patients with HFrEF.⁶⁶ Notably, patients with CAD suitable for revascularization were excluded from RCTs evaluating M-TEER in HFrEF. The National Heart, Lung, and Blood Institute–sponsored Cardiothoracic Surgical Trials Network study, comparing coronary artery bypass grafting (CABG) alone vs CABG + mitral valve surgery in patients with CAD and moderate MR, showed a significant reduction of MR severity and lack of MR progression up to 2-year follow-up in patients receiving mitral valve surgery as compared with those who did not.⁶⁷ Based on this limited evidence, we can conclude that in patients with HFrEF and combined ventricular SMR and CAD, the first choice of treatment remains surgery, but PCI

can be considered in high-risk patients with proximal segment lesions. An extensive multidisciplinary discussion including HF specialists is mandatory to evaluate pros and cons of different approaches (conservative vs surgery vs percutaneous) as well as timing of intervention and ensure a tailored strategy according to specific patient characteristics (anatomy, comorbidities, and HF stage).

Follow-up

Procedural results

When a patient undergoes specific interventions targeting SMR, assessment of residual MR immediately after the procedure, at 30 days, and during longer follow-up is crucial to define procedural success and long-term prognosis and, accordingly, optimize further patient management.^{68,69} This assessment is typically performed with TTE and through serial studies. Currently, SMR reduction is considered optimal when post-procedure MR is reduced to at least mild, and acceptable when

reduced by at least 1 grade from baseline, and to no more than moderate. In case of mitral valve replacement, no greater than mild paravalvular MR (and without associated haemolysis) is accepted. Semi-quantitative and quantitative echocardiographic parameters are suggested, and specifically residual MR should have a vena contracta width < 3 mm, an EROA < 0.2 cm², and a RVOL < 30 mL. However, specifically in the setting of M-TEER, PISA-derived measures or volumetric assessments are not feasible as the TEER device typically creates multiple and eccentric jets with non-hemispheric proximal flow convergence, and these approaches have not been validated for double orifice geometry created after M-TEER. Vena contracta width, ideally with 3D echocardiography, should be therefore preferred, and optimal results are considered when the 3D vena contracta area is < 0.2 cm².⁷⁰

Assessment of the residual transvalvular gradient is another important evaluation to be performed by echocardiography, particularly after M-TEER, as the intervention should not result in obstructive gradients, which could compromise cardiac performance. Currently, a mitral valve area ≥ 1.5 cm² (ideally by using a 3D approach considering the double orifice) with a transmitral gradient < 5 mmHg is recommended post-procedure to avoid clinically significant mitral stenosis.^{69,70} However, in clinical practice, mean gradients up to 5 mmHg after M-TEER are considered as acceptable.²¹ This should be always evaluated intra-procedurally to eventually adjust number and position of TEER devices,^{71,72} but also during follow-up as flow conditions (pre- and afterload), heart rate and diastolic filling are altered during general anaesthesia and might change at follow-up. Notably, the prognostic role of high mean gradient in patients with SMR remains unclear.⁷³

Heart failure assessment

A careful follow-up by a dedicated HF team is of paramount importance after even after transcatheter or surgical interventions for SMR. Although the correction of SMR improves HF-related symptoms, quality of life, and clinical outcomes,^{3,49,50} the prognosis of these patients remains poor due to the severity of the impairment of myocardial function.^{6,7} A thorough monitoring of HF status to early treat congestion and prevent hospitalizations for worsening HF, further GDMT optimization after MR correction, and the identification of red flags for advanced HF are warranted.^{74–76}

A high risk of HF-related hospitalizations during long-term follow-up after M-TEER has been reported in both RCTs and observational studies.^{6,7} Serial outpatient assessment of congestion status is therefore important to mitigate the risk of worsening HF events.⁷⁴ An integrative assessment combining patient's reported symptoms and quality of life, clinical signs of congestion, ultrasound imaging, and laboratory exams (including natriuretic peptides) should be performed during regular follow-up visits after interventions (i.e. M-TEER).⁷⁷ Continuous invasive haemodynamic monitoring or remote telemedical HF management may also be considered.⁷⁸

Irrespective of pre-procedural medical therapy optimization, further GDMT uptitration should be attempted after correction of SMR. Tolerability to GDMT may be improved after successful M-TEER due to several mechanisms, including increased forward stroke volume with consequently increased blood pressure levels and improved renal function.⁷⁹ Recent observational studies have shown that GDMT uptitration occurred in ~35%–40% of patients after M-TEER for SMR and was independently associated with better long-term outcomes, whereas GDMT downtitration was associated with worse prognosis.^{4,80} Notably, the likelihood of GDMT uptitration after M-TEER was higher among patients with a greater decrease in SMR (i.e. at least 3+).⁴

Gaps in evidence

Moderate MR may have a negative contribution to HF progression.⁹ The RESHAPE-HF2 trial showed a possible beneficial effect of M-TEER also in patients with less severe or moderate MR.⁵⁰ M-TEER with new-generation devices seems to be safe and effective in patients with moderate MR.⁸¹ However, the proportion of patients with moderate or less severe MR in these studies was limited. Thus, further studies are needed to expand the M-TEER indication to these patients.

Patients with advanced HF were not included in COAPT and RESHAPE-HF2.^{49,50} There are no specific RCTs on M-TEER focusing on these patients that need to be evaluated for LV assist device implantation or heart transplantation. Observational studies showed a prognostic role of severe MR also in patients with advanced HF¹³ and a possible beneficial effect on mortality of a successful vs non-successful M-TEER.⁸² Moreover, improvement in symptoms, quality of life, and functional status have been observed after M-TEER that may be considered as a bridge to advanced HF therapies.^{4,83} However, further studies are definitely needed to better understand whether SMR correction may have a role even in this setting.

Patients with SMR often present also with at least moderate TR and their long-term outcome is impaired.¹² Registry data indicate that TR may improve after successful M-TEER.⁸⁴ While COAPT and RESHAPE-HF2 excluded patients with severe SMR and severe TR, early experience indicates that concomitant (or staged) transcatheter treatment of both valvular diseases might result in improved outcomes.⁸⁵ However, specific RCTs are needed to demonstrate a possible benefit of M-TEER in patients with severe TR.

In recent years, advances have been made in the management of chronic HFrEF patients including among others: remote telemedical HF monitoring, use of implantable pressure sensors for HF monitoring, and intra-atrial shunt device placement.⁸⁶ The application of such technologies in HFrEF patients with severe SMR on top of M-TEER procedures needs to be further evaluated to improve patient outcomes.

Finally, patients with acute SMR (i.e. post-acute myocardial infarction) are excluded from RCTs. Limited evidence reported promising results. Specifically, M-TEER seems to play a major role in these high-risk patients.^{87,88} However, further studies are needed to confirm these findings and consequently expand M-TEER indication.

Conclusions

Patients with HFrEF and SMR have a poor prognosis and need to be carefully managed by using a multidisciplinary approach during all the patient pathway and offering all the possible treatment options where indicated ([Graphical Abstract](#)). Medical therapy, CRT, and M-TEER should be considered as complementary, since devices may enable drug initiation or uptitration. Treatment of AF and CAD can be considered in selected patients.

Supplementary data

Supplementary data are not available at [European Heart Journal online](#).

Declarations

Disclosure of Interest

M.A. received speaker honoraria from Abbott Vascular and Edwards Lifesciences; M.P. received personal fees from Abbott Vascular,

AstraZeneca, Boehringer Ingelheim, Novartis, Roche Diagnostics, and Vifor Pharma; N.A. reports speaker fees from GE Healthcare, Philips Ultrasound, and Abbott Vascular and research grants from Edwards Lifesciences, Alnylam, Pfizer, Pie Medical, and Astra Zeneca; J.H. reports research grant support and speaker honoraria from Edwards Lifesciences; J.B. received honoraria for lectures/consulting from Novartis, Abbott, Bayer, Pfizer, Boehringer Ingelheim, AstraZeneca, Cardior, CVRx, BMS, Amgen, Edwards, Roche, and Zoll, not related to this article and research support for the department from Zoll, CVRx, Abiomed, Norgine, and Roche, not related to this article; S.Z. received research grant support, served on advisory boards for or speaker engagements with Abbott, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, CSL Vifor, Cytokinetics, Edwards, Eli Lilly, GSK, Medtronic, Merck, Novo Nordisk, and Pfizer, and served on a clinical trial committee for studies sponsored by AstraZeneca, Boehringer Ingelheim, Cytokinetics, Merck, Novo Nordisk, Pfizer, and Salubris Bio; and M.M. received consulting honoraria from Bayer, AstraZeneca, Boehringer Ingelheim, Novartis, and Roche.

Data Availability

No data were generated or analysed for this manuscript.

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