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SPECIAL ARTICLE
Heart Failure and Cardiomyopathies

The management of secondary mitral regurgitation in patients with heart failure: a joint position statement from the Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI) of the ESC

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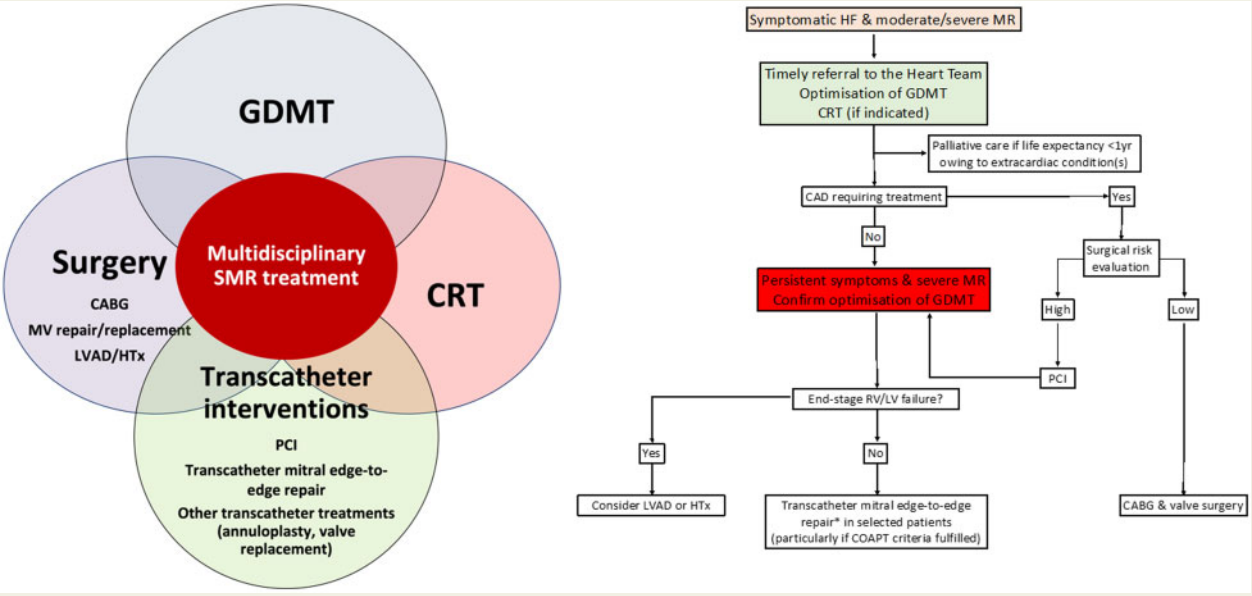
Secondary (or functional) mitral regurgitation (SMR) occurs frequently in chronic heart failure (HF) with reduced left ventricular (LV) ejection fraction, resulting from LV remodelling that prevents coaptation of the valve leaflets. Secondary mitral regurgitation contributes to progression of the symptoms and signs of HF and confers worse prognosis. The management of HF patients with SMR is complex and requires timely referral to a multidisciplinary Heart Team. Optimization of pharmacological and device therapy according to guideline recommendations is crucial. Further management requires careful clinical and imaging assessment, addressing the anatomical and functional features of the mitral valve and left ventricle, overall HF status, and relevant comorbidities. Evidence concerning surgical correction of SMR is sparse and it is doubtful whether this approach improves prognosis. Transcatheter repair has emerged as a promising alternative, but the conflicting results of current randomized trials require careful interpretation. This collaborative position statement, developed by four key associations of the European Society of Cardiology—the Heart Failure Association (HFA), European Association of Percutaneous Cardiovascular Interventions (EAPCI), European Association of Cardiovascular Imaging (EACVI), and European Heart Rhythm Association (EHRA)—presents an updated practical approach to the evaluation and management of patients with HF and SMR based upon a Heart Team approach.

Graphical Abstract



Keywords Heart failure • Secondary mitral regurgitation • Functional mitral regurgitation • Transcatheter mitral valve repair

Introduction and scope

Moderate or severe secondary (also known as functional) mitral regurgitation (SMR) accompanies heart failure (HF) in about one-third of patients[1] and contributes to clinical deterioration, progression of the syndrome, and adverse outcomes.[2–5] Secondary mitral regurgitation results from left ventricular (LV) remodelling as a consequence of ischaemic or non-ischaemic myocardial disease that leads to reduced coaptation of normal mitral valve leaflets via several mechanisms.[6] Since SMR is principally a disease of the left ventricle and not of the valve itself, current treatment strategies target the underlying LV disorder. However, SMR exaggerates LV remodelling by increasing volume load and mechanical correction has been proposed alongside guideline-directed medical therapy (GDMT) to improve symptoms and prognosis.

The interventional management of patients with HF and SMR is challenging. In contrast to primary (including degenerative) mitral regurgitation (MR), the outcomes of surgical mitral valve repair, either alone or combined with coronary artery bypass grafting (CABG), are of questionable benefit.[7–9] Transcatheter techniques for the correction of SMR have broadened the spectrum of patients who may benefit from mitral valve intervention, although current European Society of Cardiology (ESC) guidelines for the management of both HF and valvular heart disease (VHD) indicate the need for further clinical research in this area.[10,11] The recently published COAPT[12] and MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR)[13] randomized controlled trials have addressed this deficit but their conflicting results have generated considerable discussion and require careful interpretation.

This position statement, developed in collaboration by the ESC Heart Failure Association (HFA), European Association of Cardiovascular Imaging (EACVI), European Heart Rhythm Association (EHRA), and European Association of Percutaneous Cardiovascular Interventions (EAPCI), proposes an updated practical approach to the management of patients with HF and SMR based on a multidisciplinary Heart Team approach. We outline the current evidence (and its limitations), discuss open issues that need to be addressed by future research, and stress the importance of appropriate referral and selection of patients for transcatheter mitral valve intervention alongside guideline-recommended medical and device therapies.

Pathophysiology

The pathophysiology of SMR is complex (*Figure 1*), reflecting imbalance between valve closing and leaflet tethering forces, and the dynamic impact of factors affecting LV preload and afterload in patients with LV remodelling due to ischaemic or non-ischaemic myocardial disease.[6,15–18]

Progressive SMR is a marker of poor prognosis in patients with chronic HF[4,19] and the transition from LV disease 'marker' to HF 'contributor' is critical in determining the need for valve intervention. The concept of 'proportionate' and 'disproportionate' MR,[20] based upon a modelled relationship between LV end-diastolic volume and effective regurgitant orifice area (EROA), and its disruption in patients with ventricular dyssynchrony or papillary muscle dysfunction, has been proposed to guide the mode of treatment and predict the impact of transcatheter intervention. Although attractive from a pathophysiological point of view, this theoretical model overlooks the need to assess the severity of MR using an integrated multiparametric approach (and, in particular, fails to consider the frequently elliptical regurgitant orifice in SMR) and has not been validated to date.

Secondary mitral regurgitation may also arise as a consequence of left atrial enlargement and mitral annular dilatation/flattening in patients with longstanding atrial fibrillation (AF), where left ventricular ejection fraction (LVEF) is often normal and LV dilatation less pronounced. So-called 'atrial'[21,22] MR may also contribute to SMR in patients with HF and AF. This pathophysiological distinction is important since treatment options differ.

Epidemiology and prognosis

Moderate or severe MR is present in about one-third of HF patients.[1] Early studies indicated that MR is an independent predictor of clinical HF and major cardiac events following acute myocardial infarction or in patients with LV dysfunction.[23,24] More contemporary data confirm that SMR is associated with adverse clinical outcomes, independent of clinical, haemodynamic, echocardiographic, and neurohormonal confounders. In a cohort of 576 HF patients with reduced LV ejection fraction (HFrEF) on optimal medical therapy, severe SMR was associated with mortality in intermediate-severity HF New York Heart Association (NYHA) class II/III, LVEF 30–40% and N-terminal pro brain natriuretic peptide (NT-proBNP) 871–2360 pg/mL], but not in those with more advanced disease.[4]

Clinical and imaging assessment

Initial evaluation of patients with HF and SMR should include:

- History and physical examination (to define functional, haemodynamic, and volume status, and HF severity).
- Electrocardiogram (to demonstrate baseline rhythm and QRS duration).
- Laboratory measurements (haemoglobin, renal function, and natriuretic peptides),
- Evaluation of LV function (including the presence of myocardial scar/viability),
- Invasive or non-invasive coronary angiography.

Imaging modalities

Transthoracic echocardiography facilitates integrated structural and functional assessment of the mitral valve, LV, and left atrium (together with associated valve disease, right ventricular function, and estimated pulmonary pressure) and is the key initial screening tool for standardized measurement of LV function and MR severity.[11,25]

Transoesophageal imaging provides more accurate anatomical evaluation, although the effects of sedation on blood pressure may alter LV loading conditions and result in underestimation of severity. Since SMR is a dynamic condition, stress echocardiography allows

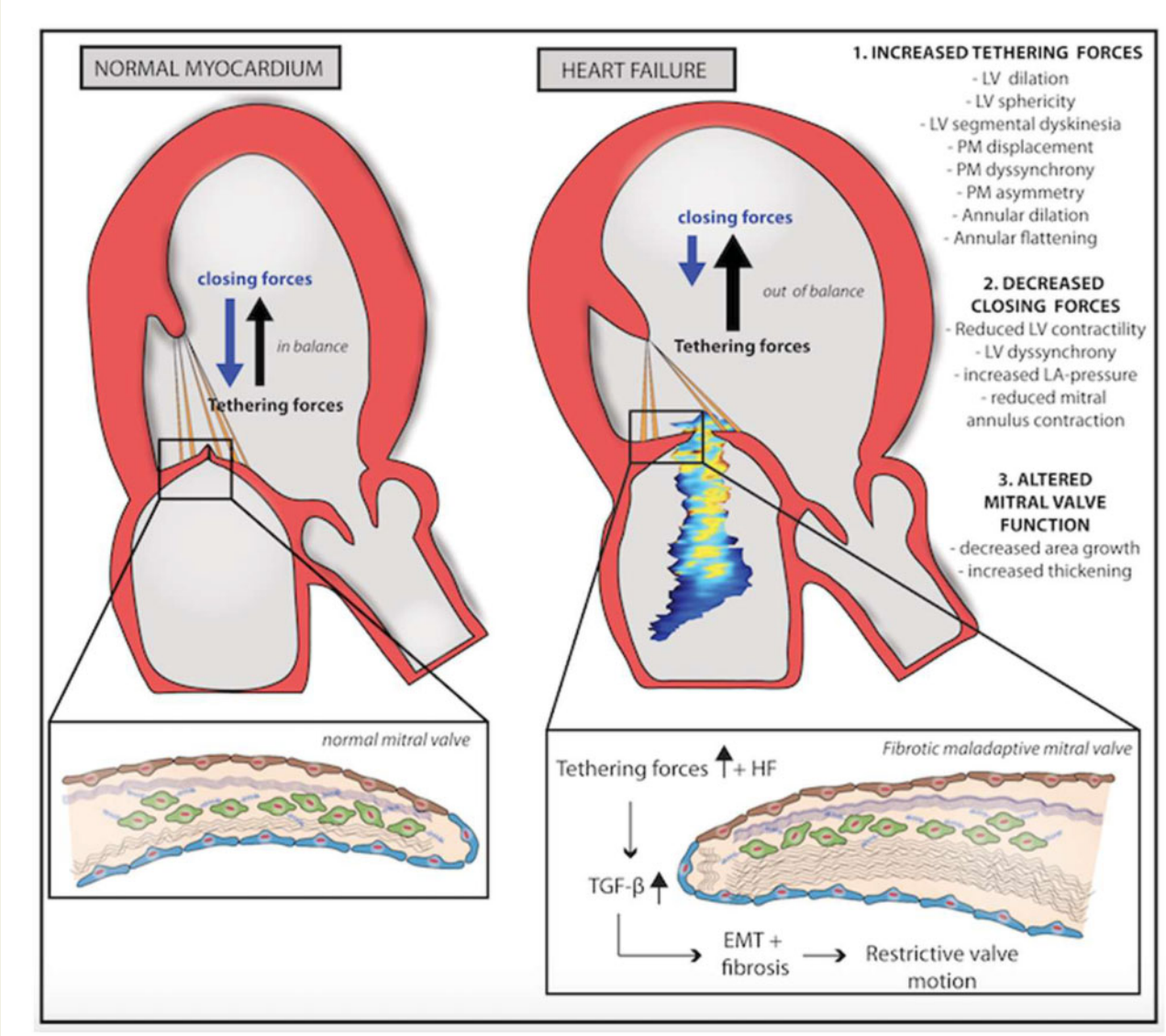


Figure 1 The pathophysiology of secondary mitral regurgitation (SMR). Primary disease of the left ventricular (LV) myocardium or damage secondary to ischaemic heart disease results in papillary muscle displacement, leaflet tethering, annular remodelling, and dilatation. Compensatory mechanisms of adaptive leaflet growth are typically insufficient (and frequently accompanied by maladaptive leaflet thickening and fibrosis),[14] resulting in failure of leaflet coaptation. Dynamic factors affecting LV preload (e.g. hydration status, medication) and afterload (e.g. blood pressure, exercise, medication) impact on the severity of resulting SMR. Progressive LV dilatation begets increasing SMR and the resulting increase in regurgitant fraction (with corresponding reduction in forward flow) impacts negatively on the Frank–Starling curve. Adapted with permission from Mullens and Martens.[15] EMT, epithelial-mesenchymal transition; HF, heart failure; LV, left ventricle; LA, left atrium; MR, mitral regurgitation; PM, papillary muscle; TGF-β, transforming growth factor beta.

assessment of its role during exercise (and possibly acute HF), as well as haemodynamic assessment of the interaction between MR severity and LV function,[26,27] but its precise role remains unclear. Multidetector computed tomography provides detailed anatomical information and is valuable in planning specific mitral interventions.[28,29] Cardiac magnetic resonance allows precise measurement of LV volume and ejection fraction, identification of fibrosis or scar, and accurate quantification of MR severity, though its availability and use in clinical practice are limited.[30]

Anatomical assessment

Determination of the precise mechanism of MR [using three-dimensional (3D) transthoracic and transoesophageal echocardiography if necessary] is essential to define the optimal treatment strategy. Although several aetiologies may coexist in an individual patient, the predominant mechanism should be identified to distinguish between those with primary MR and reduced LV function and those with true SMR.

Key anatomical features are as follows (*Figure 2*):

- *Mitral valve:* degree of leaflet tethering, tenting area, coaptation depth, jet location (central vs. commissural), presence or absence of leaflet calcification, angle between the posterior leaflet and annular plane, posterior leaflet length, and valve area (ideally >5 mm and ≥4 cm^2 for edge-to-edge repair, respectively).
- *Left ventricle:* end-diastolic and end-systolic diameters and volumes, LVEF, LV dyssynchrony, sphericity index (long/short LV axis), inter-papillary muscle distance, regional wall motion abnormalities.
- *Other structures:* left atrial volume, left atrial appendage (to exclude thrombus), right ventricular dimensions and function, concomitant tricuspid regurgitation, estimated pulmonary artery pressure.

Echocardiographic assessment of secondary mitral regurgitation severity

Severity of SMR should be assessed using an integrated multiparametric approach.[31,32] Two-dimensional transthoracic echocardiography has specific limitations in the setting of SMR and 3D imaging should be used whenever feasible. Importantly, SMR is a dynamic phenomenon and severity may vary significantly according to loading conditions[33]—assessment should be undertaken in stable clinical conditions (controlled blood pressure, optimal medical therapy), and interpreted cautiously in decompensated patients (fluid overload, inotropic support).

Definitions vary in Europe and the USA (*Table 1*)[11,34,35] and this discordance is of pivotal importance when considering the differing inclusion criteria of clinical trials. European guidelines define severe SMR as an EROA ≥20 mm^2 or regurgitant volume ≥30 mL, based upon adverse outcomes in observational studies using these specific thresholds.[23,26,36] However, quantitative assessment is highly operator-dependent with limited reproducibility, inaccurate in the presence of an elliptical regurgitant orifice (observed frequently in SMR) or multiple jets, and often overlooked in everyday clinical practice. To mitigate the risk of error, multiple parameters should be assessed [vena contracta, pulmonary vein systolic flow reversal, proximal isovelocity surface area (PISA) radius, and the subsequently derived EROA and regurgitant volume],[11,35] including 3D imaging (3D vena contracta area) if there is persisting diagnostic uncertainty.[37,38]

Management

The Heart Team

Heart failure is characterized by multiple cardiovascular and non-cardiovascular comorbidities and management of individual patients is frequently complex. Pharmacological, surgical, device, and transcatheter treatment options (and criteria for their optimal use) are constantly evolving.[39] Multidisciplinary management of HF is strongly recommended in the ESC guidelines (Class IC)[10,40] to achieve the best mode, sequence, and timing of treatment tailored to the needs of an individual patient. Although unsupported by a robust evidence base, the advantages of Heart Team management and decision-making have already been demonstrated in patients with complex coronary and VHD.[11,41] In the HF setting, the Heart Team should include an HF specialist, a cardiovascular imaging specialist, a cardiac electrophysiologist, an interventional cardiologist with expertise in transcatheter mitral valve intervention, and a cardiac surgeon with experience in mitral valve surgery. According to local institutional circumstances, this team should meet regularly, in particular to discuss patients with complex clinical and anatomical characteristics.

Pharmacological therapy

Optimization of GDMT is the first essential step in management of symptomatic moderate or severe SMR.[10] Neurohormonal inhibitors, including angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), beta-blockers, and mineralocorticoid receptor antagonists are mandatory in patients with HFrEF unless contraindicated or intolerable, and should be titrated to the guideline-directed dose (or maximum tolerated). These agents attenuate LV dysfunction and remodelling,[42,43] while some studies show that ACEi and beta-blockers may reduce SMR whilst improving LV geometry and function (although evidence remains inconclusive).[44,45]

Further pharmacological options in patients who remain symptomatic include ivabradine (if sinus rhythm is maintained with heart rate ≥70 b.p.m. despite beta-blockade, or if beta-blockers are not tolerated) and replacement of ACEI or ARB with sacubitril/valsartan.[10] In the PRIME study enrolling patients with HF and SMR, sacubitril/valsartan induced a significant reduction of EROA and regurgitant volume at 1 year follow-up on top of standard medical therapy (without inducing hypotension or other adverse events).[46] Diuretics, nitrates, and hydralazine also reduce LV preload and afterload and are associated with symptomatic improvement in patients with SMR.[18,47]

Oral anticoagulation is essential in patients with AF and SMR. Alternative therapeutic approaches focused on rhythm and rate control (including catheter ablation) may reduce the severity of 'atrial' MR[22,48] but are beyond the scope of this position statement.

Cardiac resynchronization therapy

Intraventricular dyssynchrony may itself precipitate SMR via various mechanisms.[49] Although no prospective randomized clinical trials have investigated cardiac resynchronization therapy (CRT) in the setting of severe MR, CRT improves global LV function, attenuates LV remodelling, and reduces papillary muscle dyssynchrony in patients with QRS prolongation, thereby reducing SMR by increasing mitral valve closing forces and reducing leaflet tethering both at rest and during exercise.

Large randomized trials have confirmed short- and long-term reduction of MR (assumed to be of secondary origin in the majority of patients) following CRT implantation[50] as a result of reverse remodelling,[51,52] although the magnitude of this reduction is modest (20–35% using different quantification methods). Short-term reduction in MR after CRT implantation predicts a favourable clinical response,[53] whereas persistent MR is associated with reduced survival.[54,55]

Coronary revascularization

Although the merits of surgical revascularization in HF have been well investigated,[56] there are only limited data demonstrating a lower incidence of cardiovascular adverse events compared with medical therapy in patients with SMR.[57–59] Following isolated CABG, MR improves in about 50% of patients.[60,61]

Data concerning the effects of percutaneous coronary intervention in SMR are limited. Reduction of MR was observed in about one-third of the patients in one small study and linked to better survival.[62]

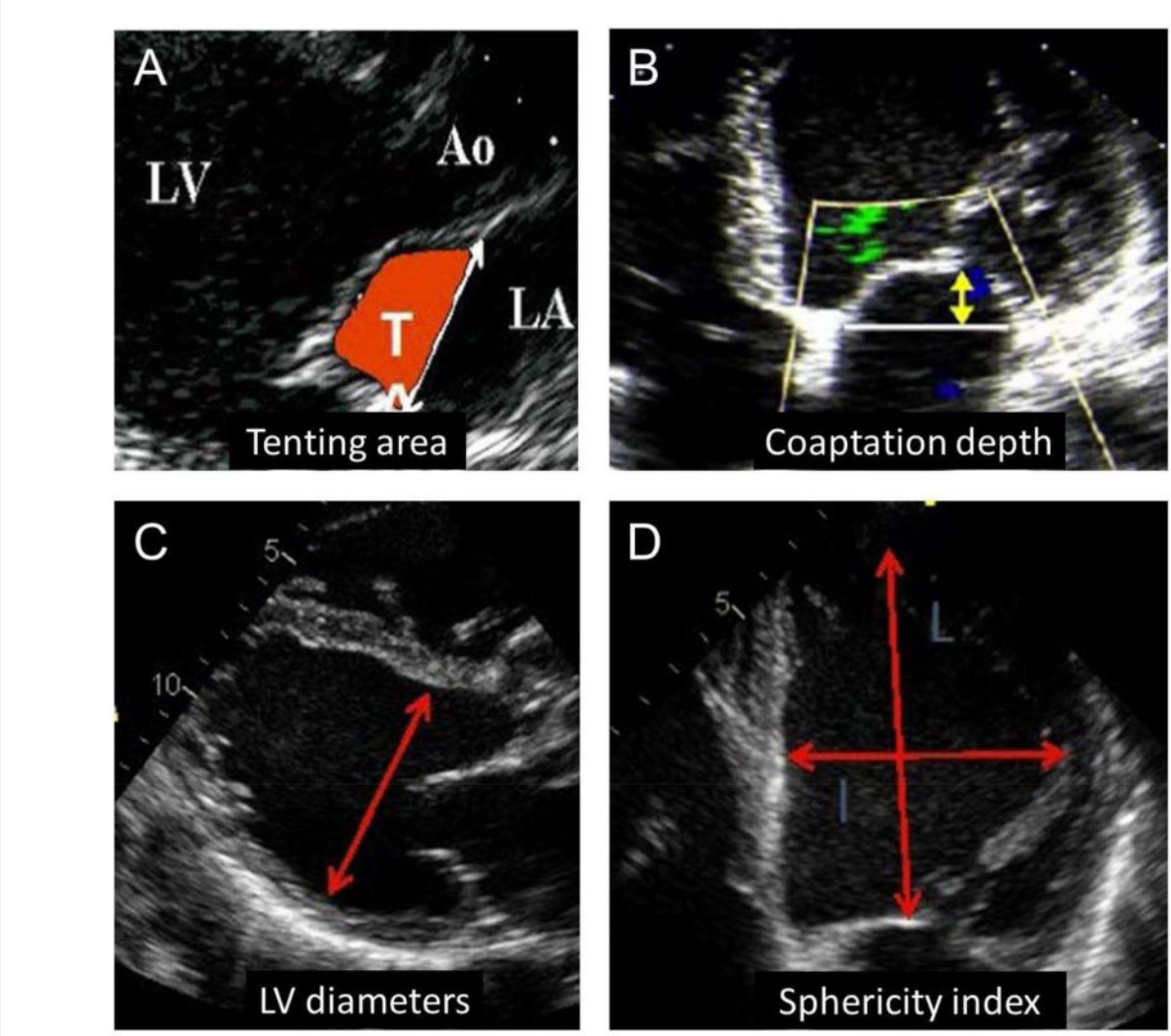


Figure 2 Key echocardiographic data in secondary mitral regurgitation concerning the mitral valve (*A, B*) and left ventricle (*C, D*). (*A*) The tenting area (highlighted in red) is bound by the anterior and posterior leaflets and the mitral annular plane (white arrow). (*B*) Coaptation depth represents the distance from the annular plane of the mitral valve to the leaflet coaptation point (yellow arrow). (*C*) The LV diameter (red arrow) must be measured in end-diastole and end-systole. (*D*) Sphericity index is the ratio between the measured end-diastolic volume (EDV) and a spherical volume based on the longitudinal dimension of the left ventricle. Ao, aorta; LA, left atrium; LV, left ventricle; T, tenting area.

The extent and distribution of myocardial perfusion defects appear to predict clinical response.[63]

Surgery

Current ESC/EACTS guidelines provide consensus recommendations for mitral valve surgery in patients with (i) severe SMR and LVEF >30% who are undergoing CABG (Class I Level C), (ii) symptomatic severe SMR and LVEF <30% with evidence of myocardial viability and revascularization options (Class IIa Level C), and (iii) symptomatic severe SMR and LVEF >30% but unsuitable for revascularization (Class IIb Level C).[11] However, it is important to emphasize that these recommendations were made before the availability of robust data supporting the potential benefits of transcatheter valve repair techniques.

The evidence supporting surgical intervention for SMR remains weak. Mitral annuloplasty, the most commonly used technique for surgical mitral valve repair, reduces MR, improves symptoms, and results in reverse LV remodelling in the short term.[64] It remains unclear whether these outcomes are durable or reduce mortality[7,8] although low rates of recurrent MR (28%) have been recently reported at 10-year follow-up in a single-centre study.[65] In a randomized controlled trial, additional surgical treatment of moderate SMR (EROA 0.2–0.39 cm^2) had no beneficial clinical effect in patients undergoing surgical revascularization at 2-year follow-up.[9] Besides repair, chordal sparing MV replacement presents a further surgical option. In a randomized study comparing mitral valve repair and chordal sparing mitral valve replacement in patients with severe SMR, there was no significant difference in 2-year mortality (19.0% vs. 23.2%; $P = 0.39$) or rates of LV reverse remodelling.[66] Although recurrent

Table 1 Summary of the European and US guideline definitions of severe SMR

	2017 ESC guidelines[11]		2017 ASE guidelines[35]	2020 AHA/ACC guidelines[34]
Semi-quantitative criteria				
Vena contracta (mm)	≥7 (>8 for biplane)		≥7	—
Pulmonary vein	Pulmonary vein systolic flow reversal		Pulmonary vein systolic flow reversal	—
Inflow	E-wave dominant ≥1.5 m/s		—	—
Other	TVI mitral/TVI aortic >1.4		Central large jet > 50% of LA area	—
Quantitative criteria	**Primary**	**Secondary**		
EROA (mm^2)	≥40	≥20	≥40 (or 30–39 with 3 other severity criteria or elliptical orifice)	≥40
PISA radius	—	—	≥1.0 cm at Nyquist 30–40 cm/s	—
Regurgitant volume (mL)	≥60	≥30	≥60	≥60
Regurgitant fraction (%)	—	—	≥50	≥50

ACC, American College of Cardiology; AHA, American Heart Association; ASE, American Society of Echocardiography; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; LA, left atrium; PISA, proximal isovelocity surface area; TVI, time velocity integrals.

MR was more frequent in the repair group (58.8% vs. 3.8%, $P < 0.001$) resulting in a higher rate of cardiovascular re-hospitalization (48.3 vs. 32.2 per 100 patient-years, $P = 0.01$), patients in the repair group without recurrent MR demonstrated significant reverse remodelling. In the absence of effective surgical approaches to the ventricular aspect of SMR, novel repair techniques that may reduce MR more effectively by combining subannular reconstruction (e.g. papillary muscle relocation) or leaflet augmentation with standard annuloplasty require further evaluation.[67]

Overall, however, isolated valve surgery is rarely performed for SMR in real-world clinical practice due to the high procedural risk and inconsistent evidence of clinical benefit.[68] Patients with advanced HF and severe SMR may be better served by cardiac transplantation or LV assist device implantation (either as destination therapy or a bridge to transplantation).

Transcatheter mitral valve repair

The 2017 ESC guidelines for the management of VHD provide a Class IIb Level C recommendation for the use of transcatheter edge-to-edge repair in patients with SMR and impaired LV function who remain symptomatic despite optimal medical therapy[11] but do not incorporate insights from recent randomized controlled trials investigating the role of transcatheter techniques in this patient group.

As a result of large-scale clinical experience (>100 000 patients) and high levels of patient safety, MitraClip has become the first-line interventional treatment option for SMR in Europe. Clinical improvement (change of NYHA class, increased 6-min walking distance and reverse LV remodelling)[69–72] and improved survival[73–75] have been reported after transcatheter mitral edge-to-edge repair in several observational studies. Predictors of poor outcome have also been identified: advanced HF (NYHA class IV), severe reduction in LVEF (<30%), very high EROA (>70 mm^2), extremely high NT-proBNP values (>10 000 pg/mL), significant right ventricular dysfunction (tricuspid annular plane systolic excursion <15 mm), severe pulmonary hypertension or tricuspid regurgitation, and the presence of major comorbidities (such as significant renal dysfunction).[71,72,76,77]

Two recent randomized controlled trials from France and the USA/Canada have evaluated the safety and efficacy of MitraClip implantation in patients with symptomatic HF and moderate-severe SMR despite medical therapy (*Table 2*).

In the French multicentre Percutaneous Repair with the MITRA-FR trial,[13] 304 patients with symptomatic HF (NYHA class II–IV), LVEF of 15–40% (but no limit of end-systolic dimension), a history of at least one HF hospitalization within 1 year and severe SMR (defined as EROA >20 mm^2 or regurgitant volume >30 mL) but unsuitable for surgery were randomized to undergo MitraClip implantation plus GDMT or GDMT alone. MitraClip implantation had no impact on the primary endpoint of all-cause mortality or HF hospitalization at 12 months compared with GDMT alone (HR 1.16, 95% CI 0.73–1.84) and no additional effect on functional status, 6-min walking distance, quality of life, or LV end-diastolic volumes (although incomplete assessment of these secondary outcome measures hampered meaningful statistical analysis). Recently reported extended observations showed no change in these findings at 24-month follow-up, with no impact of MitraClip implantation on all-cause mortality or HF hospitalization.[79]

In the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial,[12] 614 patients with symptomatic HF (NYHA class II, III, or ambulatory IV), LVEF 20–50%, LV end-systolic diameter ≤70 mm, at least one HF hospitalization within the previous year or increased natriuretic peptide levels, with moderate-to-severe or severe SMR (semi-quantitative grade 3+ or 4+ according to integrative assessment based on American Society of Echocardiography recommendations)[35,80] and in whom surgery was not considered the standard of care were randomized to undergo MitraClip implantation plus optimal GDMT or optimal GDMT alone. MitraClip implantation substantially reduced the primary endpoint (hospitalization for HF, 35.8% vs. 67.9% per patient-year: HR 0.53,

Table 2 Key differences between the COAPT and MITRA-FR trials (modified from Praz et al.[78])

	MITRA-FR	COAPT
Primary endpoint	All-cause death and hospitalization for HF at 12 months	All hospitalizations for HF within 24 months (including recurrent events)
Key exclusion criteria		
Heart failure severity	NYHA class < II	NYHA class < II ACC/AHA stage D HF
Left ventricular dimensions	No exclusion criteria	LVESD >70 mm
Coronary artery disease	CABG or PCI performed within 1 month	Untreated coronary artery disease requiring revascularization
Right ventricle	No exclusion criteria	Right-sided HF with moderate or severe right ventricular dysfunction Tricuspid valve disease requiring surgery
Pulmonary disease	No exclusion criteria	COPD with home oxygen therapy or chronic oral steroid use PAP >70 mmHg unresponsive to vasodilator therapy
Principal baseline characteristics		
Number of patients screened	450	1576
Number of patients enrolled (ITT)	304	614
Mean age (years)	70 ± 10	72 ± 12
Mean LVEF (%)	33 ± 7	31 ± 10
MR severity (EROA, cm^2)	0.31 ± 0.10	0.41 ± 0.15
<30 mm^2 (%)	52%	13%
30–40 mm^2 (%)	32%	46%
>40 mm^2	16%	41%
Mean indexed LVEDV, mL/m^2	135 ± 35	101 ± 34
Safety and efficacy endpoints in intervention arm		
Complications[a] (%)	14.6	8.5
No implant (%)	9	5
Implantation of multiple clips (%)	54	62
Post-procedural MR grade ≤2+ (%)	92	95
MR grade ≤2+ at 1 year (%)	83	95
Hospitalization for HF at 1 year (%)		
Edge-to-edge repair + GDMT	49	36
GDMT alone	47	68
Thirty-day mortality (%)		
Edge-to-edge repair + GDMT	3	2
GDMT alone	3	1
One-year mortality (%)		
Edge-to-edge repair + GDMT	24	19
GDMT alone	22	23
Two-year mortality (%)		
Edge-to-edge repair + GDMT	34	29
GDMT alone	35	46

BNP, brain natriuretic peptide; COPD, chronic obstructive pulmonary disease; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical treatment; HF, heart failure; ITT, intention to treat; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT-proBNP, N-terminal pro brain natriuretic peptide; PAP, pulmonary artery pressure.
[a]Device implant failure, transfusion, or vascular complication requiring surgery, ASD, cardiogenic shock, cardiac embolism/stroke, tamponade, and urgent cardiac surgery.

95% CI 0.40–0.70, $P < 0.001$; NNT 3.1, 95% CI 1.9–7.9) and every 1 of 10 pre-specified, statistically powered secondary endpoints [including 2-year all-cause mortality (29.1% vs. 46.1%: HR 0.62, 95% CI 0.46–0.82, $P < 0.001$; NNT 5.9, 95% CI 3.9–11.7), the composite of death and HF re-hospitalization (45.7% vs. 67.9%: HR 0.57, 95% CI 0.45–0.71, $P < 0.001$; NNT 4.5, 95% CI 3.3–7.2), symptomatic status (NYHA class I/II 72.2% vs. 49.6%; $P < 0.001$), change in quality of life (Kansas City Cardiomyopathy Questionnaire score +12.5 ± 1.8 vs. -3.6 ± 1.9 points; HR 16.1, 95% CI 11.0–21.2; $P < 0.001$), and 6-min walking distance (-2.2 ± 9.1 vs. -60.2 ± 9.0 m; HR: 57.9, 95% CI 32.7–

Table 3 Randomized trials of transcatheter mitral valve repair in patients with heart failure and secondary mitral regurgitation

Study acronym	HF status	LV status	SMR severity	*N*	Intervention	Primary endpoint	Hazard ratio
MITRA-FR[13]	II-IV and HF hospitalization within 12 months	LVEF 15–40%	EROA >20 mm^2 and/or Rvol >30 mL, unsuitable for mitral valve surgery	304	MitraClip vs. GDMT	Death HF hospitalization at 12 months	1.16 (0.73–1.84)
COAPT[12]	II-IV and HF hospitalization within 12 months or elevated NPs	LVEF 20–50% LVESD ≤70 mm	Grade 3+ or 4+ Surgery not an option	614	MitraClip vs. GDMT	Cumulative HF hospitalization at 24 months	0.53 (0.40–0.70)
RESHAPE-HF2 (Ongoing)	II-IV and HF hospitalization within 12 months or elevated NPs	LVEF 15–45% (NYHA III/IV) or LVEF 15–35% (NYHA II)	Moderate-severe or severe MR EROA ≥30 mm^2	650 (revised plan)	MitraClip vs. GDMT	Cardiovascular death and recurrent HF hospitalization during follow-up	—

EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HF, heart failure.; LV, left ventricular; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; NPs, natriuretic peptides; NYHA, New York Heart Association class; Rvol, regurgitant volume; SMR, secondary mitral regurgitation.

83.1, $P < 0.001$), and the need for LV assist device implantation or heart transplantation during the study period (4.4% vs. 9.5%: HR 0.37, 95% CI 0.17–0.81, $P = 0.01$)]. These benefits were even more pronounced at 3-year follow-up [composite endpoint of death and HF re-hospitalization 58.8% vs. 88.1%, HR 0.48 (95% CI 0.39–0.59), $P < 0.001$; NNT 3.4 (95% CI 2.7–4.6)].[81] Cost-effectiveness analysis at 2 years confirmed a higher cost of intervention overall ($73 416 vs. $38 345, $P < 0.001$; predominantly related to the price of the MitraClip device) despite the increased cost of follow-up in the GDMT group ($38 345 vs. $26 654; $P = 0.018$), and acceptable economic value based on current US thresholds (incremental cost-effectiveness ratio $40 361 per life-year gained, $55 600 per quality-adjusted life-year gained).[82]

Whilst these two trials appear superficially similar in design, a number of differences between them may partly explain their diverging results:

- *Patient selection:* In MITRA-FR, local investigators determined eligibility, while in COAPT, this was confirmed by a central eligibility committee.
- *Medical therapy:* In COAPT, a central eligibility committee directed up-titration of medical therapy to maximally tolerated doses prior to randomization. Patients were excluded from the trial if their symptoms subsided or MR decreased as a consequence. Subsequent modification of medical treatment was discouraged in both groups.

Conversely in MITRA-FR, up-titration of medical therapy before randomization was directed by the local Heart Team and constantly adapted to clinical circumstances after randomization in both groups, consistent with real-world practice.

Therefore, use of ACEi and ARB, and intensification of drug treatment (particularly beta-blockers) during follow-up was more frequent in the MitraClip group in COAPT, although the absolute impact of these differences on outcomes remains uncertain. The use of sacubitril/valsartan was low in both trials. Overall, these differences suggest that the COAPT trial enrolled more patients refractory to current evidence-based medical treatment than MITRA-FR.

- *Echocardiographic assessment:* Important differences in the severity of SMR, degree of LV dilatation, and accompanying parameters of right heart function are summarized in *Table 2*. Reflecting the echocardiographic trial inclusion criteria (*Figure 3*), patients in COAPT demonstrated greater severity of SMR based upon quantitative criteria (EROA 41 ± 15 mm^2 vs. 31 ± 10 mm^2) and less LV dilatation (mean indexed LV end-diastolic volume 101 ± 34 mL/m^2 vs. 135±35 mL/m^2) than those enrolled in MITRA-FR. Perhaps reflecting greater severity of MR in relation to LV dimensions, patients in COAPT were overall more likely to benefit from transcatheter edge-to-edge repair in terms of reduced mortality and need for HF hospitalization[20] (although improvements in quality of life appeared to be independent of these parameters).[83] Importantly, no single echocardiographic variable (whether prognostic or not) was able to predict the outcomes observed following MitraClip implantation in the COAPT trial.[80] In summary, echocardiographic assessment was undertaken using different parameters in the two studies—hence, only very limited conclusions can be drawn at this stage and composite assessment of both datasets by a single independent core laboratory may prove valuable.
- *Technical factors:* The results of MITRA-FR and COAPT indicate that transcatheter mitral edge-to-edge repair using the MitraClip

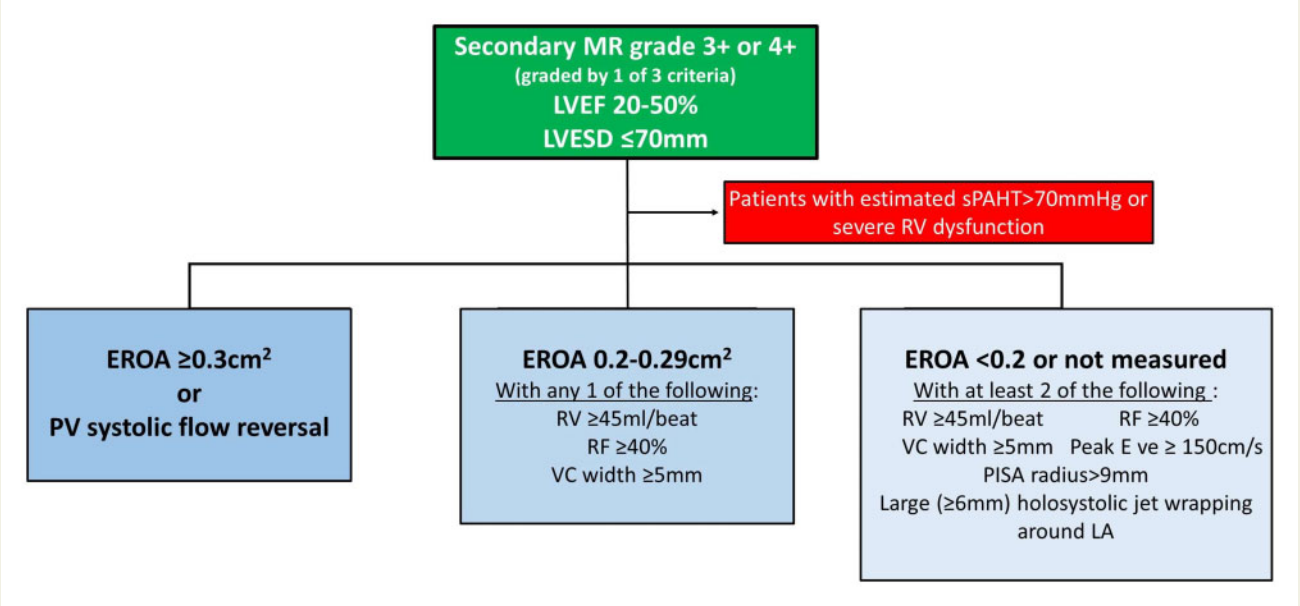


Figure 3 Echocardiographic inclusion criteria in the COAPT trial.[79] EROA, effective regurgitant orifice area; LA, left atrium; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; PISA, proximal isovelocity surface area; PV, pulmonary vein; RF, regurgitant fraction; RV, regurgitant volume; sPAHT, systolic pulmonary artery pressure; VC, vena contracta; ve, velocity.

device is a safe procedure that effectively reduces SMR. However, procedural differences (particularly the more frequent use of multiple clips) may explain the better long-term reduction of SMR in COAPT with impact on overall clinical outcomes (notwithstanding the different systems for grading MR in the two trials). Arguably, these differences in technical outcomes are more relevant than differences in medical therapy and highlight the importance of achieving the best possible immediate result after MitraClip implantation.

The fact that differences in clinical characteristics, advanced echocardiographic findings and initial use of medical therapy are likely to have accounted for the diverging trial outcomes further emphasizes the critical importance of careful patient selection for transcatheter mitral valve intervention by a Heart Team (see Executive Summary section). The ongoing RESHAPE-HF2 trial will randomize 650 (according to the revised plan) patients with symptomatic HF (NYHA class II, III or ambulatory IV), LVEF 15–45%, a history of at least one HF hospitalization within the previous year or increased natriuretic peptide levels, and moderate-severe or severe SMR (EROA ≥30 mm^2) to MitraClip implantation plus GDMT or GDMT alone (*Table 3*). The primary endpoint is cardiovascular death or recurrent HF hospitalization and results are expected in 2022. Meanwhile, the MATTERHORN trial (ClinicalTrials.gov, NCT02371512) is comparing the merits of transcatheter edge-to-edge repair with surgery in patients at high-surgical risk with LVEF ≥20%. The results of these and future trials, combined with ongoing analyses of the MITRA-FR and COAPT databases to identify responders to edge-to-edge repair, are urgently needed to refine algorithms that ensure selection of the right patients by the right clinicians for transcatheter treatment of SMR with the right device at the right time (*Figure 4*).

Futility and end-of-life care

Expensive, high-risk and ultimately futile procedures should be avoided in patients who are expected to derive little symptomatic benefit or improvement in quality of life. Examples include those with very limited life expectancy (<1 year) due to extra-cardiac conditions, severe right ventricular impairment or pulmonary disease, impaired mobility as a result of neurological or musculoskeletal disease, or advanced dementia. Specialist palliative care should be available for these patients.

Open questions

The findings of the COAPT trial confirm the prognostic and symptomatic impact of SMR in HF patients. Although longer-term follow-up is essential, the diverging results of MITRA-FR and COAPT place even greater emphasis on the need for careful selection of patients for transcatheter repair techniques and identification of improved imaging parameters (including thresholds of MR severity) that will predict positive clinical outcomes. A greater relative degree of SMR in relation to LV dimensions may identify patients who are more likely to benefit from intervention and this concept warrants further investigation in future studies incorporating sophisticated imaging techniques (advanced echocardiography—including 3D imaging—and cardiac magnetic resonance).[20] Furthermore, better characterization and stratification of the SMR population may allow distinction between those patients who may obtain prognostic benefit and those who will derive symptom relief and reduced need for hospitalization alone. In practice, this may not be simple—no single echocardiographic variable predicted beneficial outcomes in the COAPT trial[80] and patient-level analysis of the MITRA-FR trial failed to identify any

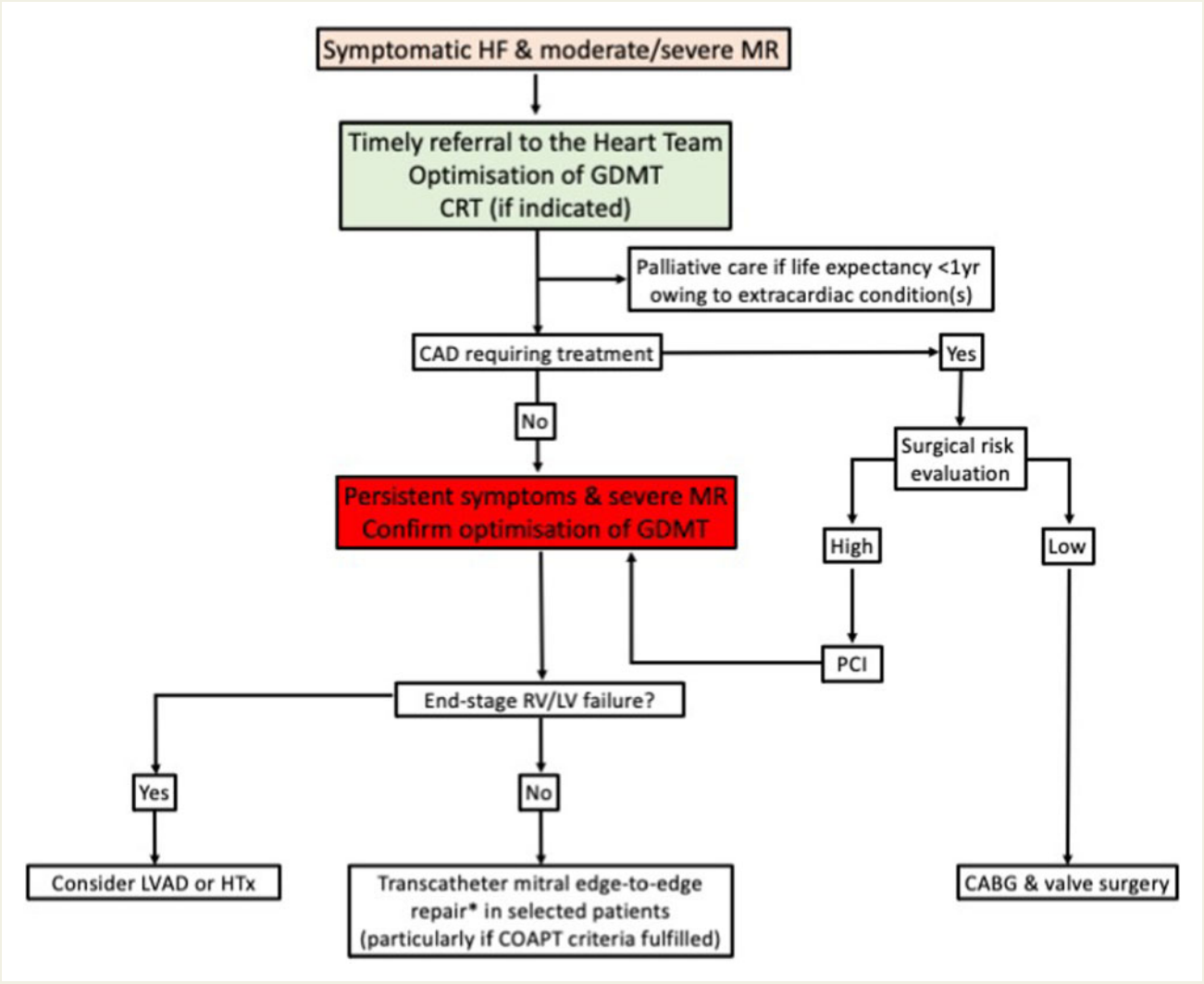


Figure 4 A practical algorithm for the management of secondary mitral regurgitation. Heart Team: HF specialist, cardiovascular imaging specialist, interventional cardiologist with expertise in transcatheter mitral valve repair, cardiac electrophysiologist, and cardiac surgeon with experience in mitral valve surgery. CABG, coronary artery bypass grafting; CAD, coronary artery disease; CRT, cardiac resynchronization therapy (with or without defibrillator); GDMT, guideline-directed medical therapy; HF, heart failure; HTx, heart transplantation; LV, left ventricular; LVAD, left ventricular assist device; MR, mitral regurgitation; PCI, percutaneous coronary intervention; RV, right ventricular; yr, year. *Current studies have established the safety and effectiveness of the MitraClip for this purpose—ongoing studies will determine whether other edge-to-edge mitral repair devices are as safe and effective.

combination of echocardiographic parameters associated with clinical benefit following intervention (including those with disproportionate MR).[84] Sub-studies from the COAPT trial showed that symptomatic and prognostic improvements were observed irrespective of NYHA class, exercise capacity, and the presence of CRT at baseline.[85–87]

Transcatheter mitral valve repair for SMR is a rapidly evolving field. Beyond the MitraClip device, other percutaneous techniques are now approved for commercial use in Europe: indirect annuloplasty using the Carillon Mitral Contour System (Cardiac Dimensions, Kirkland, WA, USA),[88] direct annuloplasty using the Cardioband Mitral System (Edwards Lifesciences, Irvine, CA, USA),[89] and edge-to-edge repair using the PASCAL Mitral Valve Repair System (Edwards Lifesciences, Irvine, CA, USA).[90,91] The Carillon system has been recently investigated in a randomized sham-controlled study (REDUCE-FMR) enrolling 120 patients receiving GDMT.[88] At 12 months, indirect annuloplasty using this system was associated with a significant 22% fall in MR regurgitant volume (the primary endpoint) accompanied by significant reduction in LV volumes and improvement in paired 6-min walking distance and NYHA functional class. However, the trial was not powered for clinical endpoints and between-group differences (including the incidence of mortality or HF re-hospitalization) did not differ significantly.

Since the safety and utility of MitraClip have now been proven in selected patients, the potential for intervention earlier in the natural history of the disease to prevent irreversible LV remodelling and systolic impairment will need to be rigorously evaluated in future studies. Further research is also needed for specific populations

Executive summary

The Management of Secondary Mitral Regurgitation in Heart Failure

- Secondary mitral regurgitation (SMR) is a common consequence of left ventricular remodelling and associated with adverse prognosis.
- Severity of SMR should be assessed by experienced echocardiographers using an integrated multi-parametric approach.
- Patients with symptomatic heart failure (HF) and moderate or severe SMR should be referred in a timely manner to a multidisciplinary Heart Team, including:
  - Heart failure specialist
  - Cardiovascular imaging specialist
  - Interventional cardiologist with expertise in transcatheter mitral valve repair
  - Cardiac electrophysiologist
  - Cardiac surgeon with experience in mitral valve surgery
- The Heart Team should first evaluate and optimize guideline-directed medical therapy (GDMT) and then consider the respective roles of device therapy (including cardiac resynchronization therapy, CRT), transcatheter mitral intervention and surgery (mitral repair, ventricular assist systems or transplantation), and their order of implementation.
- Decisions concerning treatments for mitral regurgitation, other than pharmacological therapy or circulatory support, should ideally be made in stable patients without fluid overload or the need for inotropic support.
- Surgical treatment of severe SMR should be considered in operable patients with coronary artery disease requiring surgical revascularization.
- Transcatheter edge-to-edge repair* is an evidence-based treatment option in patients with severe SMR who remain symptomatic despite GDMT (including CRT when indicated) and who have been carefully selected by a multidisciplinary Heart Team.
- Circulatory support devices and cardiac transplantation should be considered as an alternative in patients with advanced left and/or right ventricular failure.
- Interventions for mitral regurgitation should be avoided in patients with life expectancy <1 year due to conditions unrelated to the mitral regurgitation.

*Current studies have established the safety and effectiveness of the MitraClip for this purpose—ongoing studies will determine whether other edge-to-edge mitral repair devices are as safe and effective.

overlooked in recent studies, including those with advanced HF (excluded from COAPT) or marked LV dilation and severe SMR (EROA ≥30 mm^2, under-represented in MITRA-FR). Integrative approaches combining the benefits of pharmacological, electrophysiological, and transcatheter valve interventions and their relative priority in individual patients will ultimately determine the optimal management of SMR in HF.

Finally, and perhaps most importantly, timely assessment and management of SMR remain suboptimal.[89] Robust diagnostic criteria, earlier referral for specialist assessment and stricter evidence-based selection criteria will increase the net benefit of transcatheter valve and other advanced interventions.[92–95] These priorities need to be addressed urgently alongside improved education and training of the wider cardiovascular community—only then will outcomes for the high-risk group of patients with SMR and HF improve significantly.

Conclusions

SMR affects a large proportion of patients with HF and is independently associated with adverse prognosis. Timely diagnosis is therefore essential and requires high-quality imaging delivered by trained imaging specialists to appropriately define the severity and mechanism(s) of MR, and predict the potential response to treatment. Management is complex and these patients should be referred for timely Heart Team assessment and management. Medical therapy should be optimized and adjusted meticulously over long-term follow-up in all patients with SMR and HF, supplemented by CRT according to guideline recommendations. The COAPT trial provides robust evidence supporting the use of transcatheter mitral edge-to-edge repair using the MitraClip device in patients who remain symptomatic despite these measures and match the trial inclusion criteria. Given that these findings were not duplicated in the MITRA-FR trial, however, further data will be needed to refine optimal patient selection criteria. Heart Teams may also consider the use of transcatheter mitral edge-to-edge repair for symptomatic improvement in patients who do not match these criteria if alternative treatments (including LV assist device therapy or heart transplantation) are inappropriate or unavailable. Whilst international guidelines should be updated to reflect the findings of the recent randomized trials, further high-quality studies are required to refine selection criteria, explore indications beyond the current evidence base, and investigate the role of other transcatheter treatment options (annuloplasty, combined repair techniques, valve replacement).

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