

European Journal of Heart Failure expert consensus statement on transcatheter treatment of mitral regurgitation in heart failure

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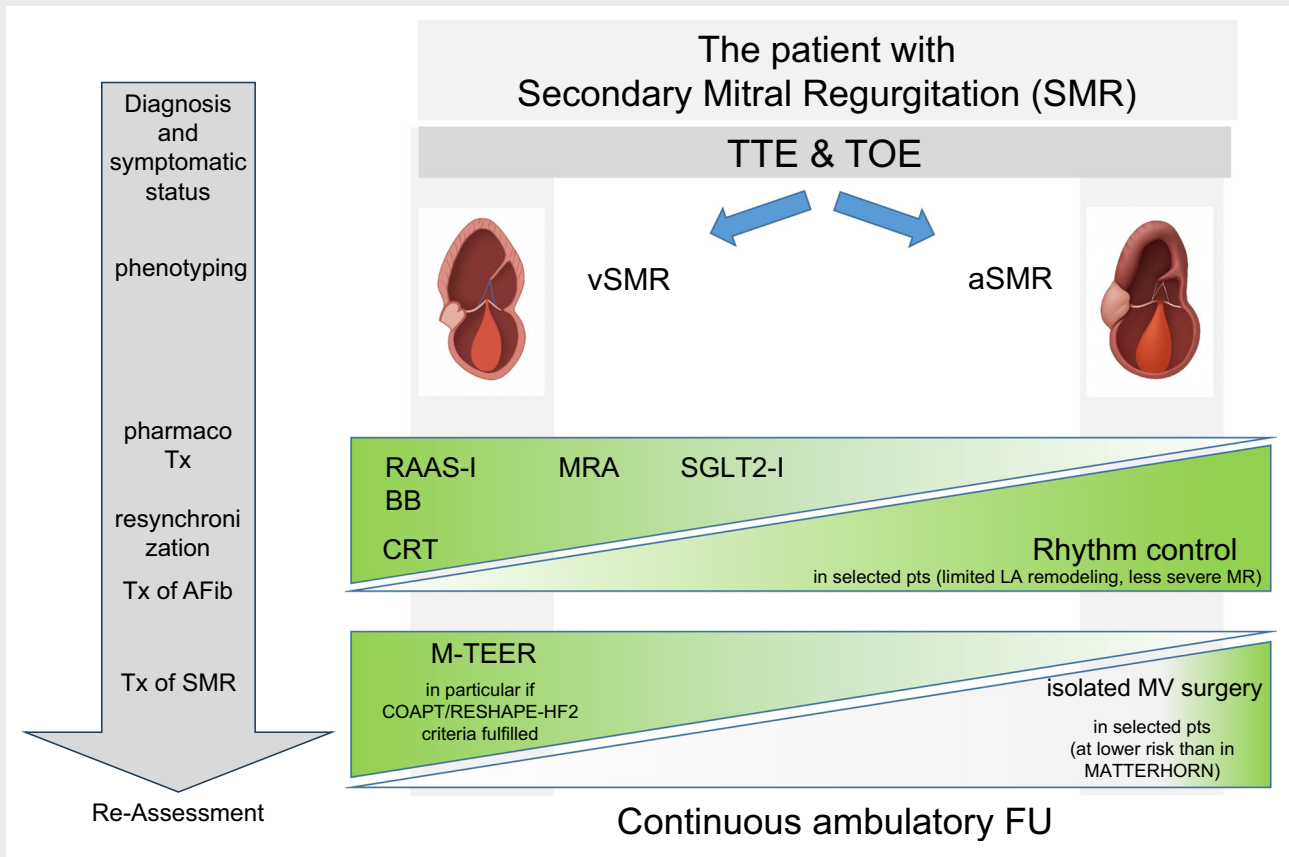
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Secondary mitral regurgitation (SMR) is highly prevalent in patients with heart failure (HF), associated with poor prognosis, and its treatment is typically preceded by implementing pharmacotherapy for HF as well as cardiac resynchronization therapy. Given the increase in experience and important technological iterations, transcatheter mitral valve repair has witnessed increasing safety and efficacy. Recently, two randomized controlled trials extended the level of evidence for this intervention in patients with SMR: RESHAPE-HF2 randomized patients with less severe SMR to either medical therapy alone versus adjunct transcatheter repair, whereas the MATTERHORN trial compared surgical therapy with transcatheter mitral valve repair in patients with SMR and increased risk for surgery. These two trials have a potential impact on the indications of transcatheter repair. Here we discuss updated indications for transcatheter mitral valve therapy across the different subtypes of SMR, revisit the current body of evidence for transcatheter mitral valve repair and classify this technique into the current treatment hierarchy of SMR in patients with HF.

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Graphical Abstract



The patient with SMR: From diagnostic assessment to treatment.

Keywords

Consensus statement • Heart failure • Mitral valve • Secondary mitral regurgitation • Transcatheter edge-to-edge repair

Introduction

Secondary mitral regurgitation (SMR) is highly prevalent in patients with heart failure (HF) and associated with poor prognosis. While the final common pathway is dysfunction of the mitral valve, the aetiology of SMR is heterogeneous, and can include any or a combination of left ventricular (LV) remodelling and/or isolated annular dilatation, driven by either atrial fibrillation (AF), atrial myopathy and/or LV diastolic dysfunction.

The algorithms for therapy follow the current guidelines of treatment of HF with guideline-directed medical therapy (GDMT) being the principal pillar. However, in addition to GDMT, mitral valve transcatheter edge-to-edge repair (M-TEER), and to a lesser extent surgical repair or replacement, have gained importance due to accumulating evidence of symptomatic improvement, reduced HF hospitalization (HFH) and, in some cases, also death.

Based on the outcomes of two large randomized trials (COAPT and RESHAPE-HF2), the new 2025 European Guidelines have updated their recommendations for intervention in SMR. In light of current data evaluating transcatheter therapy in combination with GDMT and in comparison with mitral valve surgery, this expert consensus revisits the current recommendations for treatment in patients with HF and SMR.

Pathophysiology

Secondary mitral regurgitation is a complex disease, resulting from an imbalance between increased tethering forces (due to global and/or focal LV dilatation, papillary muscle displacement and/or dysfunction) and decreased closing forces (reduced LV contractility and/or synchronicity) in the presence of a structurally normal

mitral valve. Typically, SMR emerges as a chronic disease resulting from progressive remodelling of the left chambers. Acute mitral regurgitation (MR) results from instantaneous disintegration of different constituents of the mitral valve apparatus, which is not included in SMR. For example, ruptured papillary muscle secondary to myocardial infarction is classified as primary ischaemic MR. Carpentier's classification highlights two principal mechanisms of leaflet motion in SMR: type I, with normal leaflet motion due to annular dilatation from the adjacent chambers (left ventricle and/or left atrium); and type IIIb, characterized by restricted leaflet motion due to global or regional LV/left atrial (LA) remodelling. Rarely, such as in chronic ischaemic SMR, fibrosis and elongation of the papillary muscle yielding leaflet prolapse can provoke MR which resembles type II disease according to Carpentier's classification, despite the fact that the disease is originating in the ventricle.¹ Annular dilatation provokes tethering and reduced annular dynamics hamper adequate mitral valve closing, leading to SMR. Further, in more advanced stages of LV and/or (LA) dilatation, tethering becomes more pronounced in the subvalvular region.² Dilated cardiomyopathy causes leaflet tethering due to mainly symmetric enlargement of the left ventricle. In ischaemic cardiomyopathy, MR can be a result of either anterior myocardial infarction causing papillary displacement or apical tethering. Conversely, posterior wall infarction is associated with apical displacement of the posterior papillary muscle provoking asymmetric tethering with a larger posterior leaflet angle,^{3,4} causing insufficient closure of the mitral valve. Both are hallmarks of ventricular SMR (vSMR). In contrast, atrial SMR (aSMR) is the result of higher tethering forces due to LA dilatation and impaired annular dynamics resulting from increased LA pressure and atrial dysfunction as observed in HF with preserved ejection fraction (HFpEF) and/or AF.⁵ Atriogenic leaflet tethering is a complex pathoanatomic subtype of aSMR disease, which is based on marked LA dilatation posteriorly, and thus bending of the posterior leaflet over the LV crest, leading to reduced coaptation and typically eccentric MR.⁶ Importantly, this subgroup of aSMR is associated with worse procedural and clinical outcomes after M-TEER.⁷

Epidemiology and prognosis

The prevalence of moderate or severe MR is high in the community, affecting about 0.6% of all adults.⁸ Of these, 65% are diagnosed for SMR, being the most frequent MR aetiology.⁹ Within this patient population, SMR was characterized as vSMR driven in 58% and as aSMR in 42%. Patients with vSMR were slightly younger than patients with aSMR (73 ± 14 years vs. 80 ± 10 years). Female sex was predominant in aSMR (67%), whereas male sex was slightly more prevalent in vSMR (59%). Patients diagnosed for vSMR share similar characteristics as patients with HF with reduced ejection fraction (HFrEF) based on atherosclerotic disease; in contrast, patients with aSMR are typically diagnosed for HFpEF and/or AF. In patients hospitalized for acute HF, the prevalence of MR is reported to be between 24% and 53% in different registries and associated with worse outcomes.¹⁰

Overall, patients with SMR have dismal prognosis.⁹ Irrespective of the underlying myocardial disease, SMR has been shown to

impact on outcomes, independent of other variables, including those related with severity of HF, pulmonary hypertension, right ventricular dysfunction, tricuspid regurgitation and chronic obstructive pulmonary disease.^{9,11–15} Patients with SMR experience an excess risk of mortality during a follow-up time of 4.6 ± 3.1 years: patients with vSMR revealed the highest mortality, with a risk ratio of 3.45 (2.98–3.99) whereas patients with aSMR demonstrated a slightly better prognosis (risk ratio 1.88; 1.52–2.25). Further, the risk for progression of HF is considerable, reaching $83 \pm 3\%$ in vSMR and $59 \pm 4\%$ in aSMR over 5 years, respectively.⁹

Diagnosis of secondary mitral regurgitation

Clinical examination of SMR is often difficult, as it is the consequence of initial ventricular/annular disease, which are present long before SMR develops. Thus, symptom severity may not correlate with SMR severity. Further, as patients with chronic HF may present with acute deterioration and fluid overload, measures to optimize decongestion are mandated to avoid overestimation of SMR severity in the acute phase. Detailed assessment of SMR by imaging has the objective of defining the underlying aetiology (ventricular vs. atrial), the regurgitation grade, suitability for transcatheter intervention and concomitant insults of the ventricles and the pulmonary circulation. Transthoracic echocardiography (TTE) is the principal imaging technique to assess the majority of the above indicated pathoanatomic characteristics. Key differences have been highlighted in the section on pathophysiology above. Both types of SMR can display varying grades of mitral annulus calcification which may pose therapeutic challenges, particularly if the calcification extends to the mitral leaflets. The anatomic characteristics (extent of tethering, tenting angle, coaptation gap, leaflet length, jet eccentricity and localization, as well as the dilatation of the mitral valve annulus) are better appreciated using transoesophageal echocardiography (TOE), with three-dimensional data being a prerequisite for assessing the suitability of (transcatheter) repair regarding mitral valve orifice and calcifications in each scallop in detail. Moreover, three-dimensional TOE allows the display of multiplanar reconstructions of the mitral valve and the identification of the precise site of disease and origination of the jet.

Assessment of the MR grade using echocardiographic techniques requires a multiparametric approach evaluating qualitative, semi-quantitative and quantitative parameters (Table 1). When four or more of the qualitative and semi-quantitative parameters coincide, in the presence of LV dilatation and dysfunction and LA dilatation, MR can be graded as 'severe'. However, for complete assessment, current recommendations advocate for quantification of the effective regurgitant orifice area (EROA), the regurgitant volume and the regurgitant fraction. The EROA and the regurgitant volume are usually measured with the two-dimensional proximal isovelocity surface area (PISA). This method has several limitations that may lead to underestimation of MR severity. First, the PISA method assumes that the regurgitant orifice is circular which is not common in SMR. Usually, the anatomical regurgitant

Table 1 Qualitative, semi-quantitative, and quantitative parameters of severe secondary mitral regurgitation on transthoracic echocardiography

Qualitative	<ul style="list-style-type: none"> • Large coaptation defect of the mitral leaflets • Severe tenting • Large regurgitant central jet occupying >50% of the left atrial area • Eccentric jet with Coanda effect (swirling along the atrial wall)
Semi-quantitative	<ul style="list-style-type: none"> • Large holosystolic convergence zone • Vena contracta width of the regurgitant jet of ≥ 7 mm (or ≥ 8 mm in the bicommissural view) • Pulmonary vein systolic flow reversal on pulsed-wave acquisitions • Velocity–time integral of the mitral valve relative to the that of the left ventricular outflow tract of >1.4
Quantitative	<ul style="list-style-type: none"> • E-wave dominant (1.2 m/s) • Effective regurgitant orifice area ≥ 0.4 cm² (or ≥ 0.3 cm² if elliptical orifice) • Regurgitant volume ≥ 60 ml (or ≥ 45 ml if low-flow) • Regurgitant fraction $\geq 50\%$

orifice is slit-like or oval. Colour Doppler three-dimensional echocardiography allows for multiplanar reconstructions of the regurgitant orifice and the planimetry of the anatomical regurgitant orifice area. This measurement has shown to provide a better estimation of the severity of MR than two-dimensional echocardiography, using as reference cardiac magnetic resonance. In addition, low-flow conditions in patients with SMR facilitate underestimation of the regurgitant volume and therefore, SMR should be assessed cautiously in particular during a state of low loading conditions. Moreover, assessment of regurgitant volume only considers the measurement of the convergence zone (PISA radius) in a single systolic frame despite its temporal changes, namely being maximal at the beginning and the end of the systole. The measurement of the regurgitant fraction may overcome this limitation in the absence of concomitant aortic regurgitation. The regurgitant fraction is calculated as the difference between the LV stroke volume and the forward stroke volume (measured at the LV outflow tract with pulsed-wave Doppler) relative to the LV stroke volume. The LV stroke volume can be measured as the difference between the end-diastolic and end-systolic volumes or based on pulsed-wave Doppler measurements of the mitral inflow, leading to discrepant results. Current guidelines consider MR severe when the EROA is ≥ 0.4 cm², the regurgitant volume is ≥ 60 ml, and the regurgitant fraction is $\geq 50\%$. In SMR specifically, considering the limitations of this quantification technique and the load dependency of SMR, EROA ≥ 0.3 cm² and/or a regurgitant volume ≥ 45 ml can define severe MR.¹ Additional techniques based on colour Doppler three-dimensional TOE have been developed to quantify the regurgitant volume along the systole similarly to cardiac magnetic resonance. Based on algorithms that track the

convergence zone of the regurgitant jet, the regurgitant volume is displayed as a function of time.¹⁶

When the symptoms of the patient do not match the severity of SMR on echocardiography at rest, exercise echocardiography can be useful and is recommended in unmasking severe SMR.¹⁷ The increase in EROA during peak exercise is associated with poor outcomes.¹⁸ Furthermore, when the echocardiographic assessment of SMR severity is inconclusive, cardiac magnetic resonance is the method of choice to quantify LV and LA volumes and regurgitant volume and fraction. There are several techniques to evaluate the regurgitant volume and fraction but the most frequently used are the standard method that calculates the stroke volume on cine images and the flow through the aorta with phase contrast images as well as four-dimensional flow that reconstructs the three-dimensional mitral regurgitant jet.¹⁹ Furthermore, cardiac magnetic resonance has the unique characteristic of providing the tissue characterization of the myocardium. In patients with SMR, the presence of myocardial scar and fibrosis has been associated with worse outcomes and less functional improvement after mitral valve intervention.^{20,21}

Treatment algorithm in patients with heart failure and secondary mitral regurgitation

A holistic therapeutic approach is required when dealing with patients with SMR and HF. In patients with HFrEF, optimization of medical treatment has to be achieved, or at least targeted, to the maximum tolerated individual patient's level. The goal is to reduce mortality and morbidity, but also to reduce the severity of SMR and thereby halt progression of ventricular disease. Indeed, among patients with SMR, all four mortality-modifying drug classes (angiotensin-converting enzyme inhibitors/angiotensin receptor blockers, and angiotensin receptor–neprilysin inhibitors; beta-blockers; mineralocorticoid receptor antagonists; and sodium–glucose co-transporter 2 inhibitors) have been shown to be associated with SMR reduction.^{22–29} In acute HF and MR, vasodilators are first line-therapy to reduce LV afterload in absence of hypotension, increasing forward stroke volume and reducing MR. Otherwise, inotropic (dobutamine) and inodilator drugs (milrinone) may be appropriate in patients with hypotension or hypoperfusion, whereas vasopressors may worsen MR and should be used at the lowest possible dose. Intravenous diuretics should be titrated until adequate decongestion is achieved.¹⁰

Cardiac resynchronization therapy (CRT) is endorsed as a class I recommendation for patients with LV ejection fraction (LVEF) $\leq 35\%$, a QRS duration ≥ 130 ms and left bundle branch block morphology who remain symptomatic despite optimal medical treatment both for symptomatic improvement and reduction in HFH and mortality. Interestingly, in CARE-HF those patients with moderate to severe MR, defined by a MR area ratio ≥ 0.218 , had a numerically larger reduction in the composite of death from any cause or an unplanned HFH for a major cardiovascular event with CRT, compared with those with less severe MR³⁰—further illustrating the prognostic relevance of SMR. MR reduction appears

Table 2 Criteria for mitral valve transcatheter edge-to-edge repair treatment success in secondary mitral regurgitation

M-TEER complexity	Non-complex	Complex	Very complex	Not feasible
M-TEER eligibility	Optimal	Suitable	Limited	Not recommended—consider replacement
Localization of pathology	A2-P2	Commissural (A1-P1 or A3-P3)	Over all mitral valve scallops	Over all mitral valve scallops
Mitral valve orifice area	>4 cm ²	3.5–4.0 cm ²	3.0–3.5 cm ²	<3.0 cm ²
PML length	>10 mm	7–10 mm	5–7 mm	<5 mm
Tenting height	<10 mm	>10 mm	>10 mm	>10 mm
Regurgitation jet extent	One isolated jet	Max 2 jets	Very wide/jet extent over all mitral valve scallops	Very wide/jet extent over all mitral valve scallops

M-TEER, mitral valve transcatheter edge-to-edge repair; PML, posterior mitral leaflet.

to be driven by instant effects of CRT on asynchrony, rather than by long-term LV reverse remodelling.³¹ Beneficial effects on MR reduction by CRT have been shown in several subsequent studies, further underlying the importance of CRT in this subpopulation.^{32,33} Of note, baseline moderate to severe SMR that remained unchanged at 6 months after CRT was independently associated with increased risk of mortality (hazard ratio [HR] 1.77; 95% confidence interval [CI] 1.41–2.22, $p < 0.001$).³⁴ Restoration of sinus rhythm, through pharmacological measures, cardioversion and ultimately catheter ablation has also been shown to reduce SMR, especially in patients with aSMR.^{35,36}

In patients with persistent SMR and HF symptoms despite maximal tolerated GDMT including CRT if indicated, mitral valve repair, in particular M-TEER, should be considered the treatment of choice. However, also in the context of transcatheter therapy, careful risk stratification and appropriate patient selection is warranted, and several predictors indicating prognosis have been identified. Among those, pulmonary hypertension and right ventricular dysfunction should be systematically assessed, since they represent the most robust parameters to identify non-responders to M-TEER therapy.^{37–40} Conversely, the proportionality concept stratified SMR according to LV dimensions: disproportionate SMR, that is, severe SMR as assessed by EROA in relation to LV end-diastolic dimension, appears to represent a pathology, which identifies patients who reveal the most prognostic benefit. However, this concept remains controversial given that the benefit of M-TEER in the COAPT trial did not fully support this hypothesis in a post-hoc analysis.⁴¹ Recently, an artificial intelligence-derived risk score, the EuroSMR risk score, has been developed for the prediction of mortality and futility using clinical, echocardiographic, laboratory and data of pharmacological HF interventions.⁴² The most predictive parameters were N-terminal pro-B-type natriuretic peptide (NT-proBNP), haemoglobin, right atrial area, New York Heart Association (NYHA) class, systolic pulmonary artery pressure, and age. Developed specifically for the SMR population, the score was superior in predicting 1-year mortality after M-TEER when compared with EuroScore II, MitraScore, and the COAPT risk score.

Several studies, including randomized controlled trials and registries, revealed that patients treated with M-TEER are often

on suboptimal GDMT prior to the procedure, in large part due to hypotension. However, a significant fraction (38%) of patients experiences haemodynamic improvement after M-TEER, which subsequently allows for initiation of a new HF drug class and/or up-titration of at least one drug class, which translates into lower rates for mortality and HFH.⁴³ Accordingly, further optimization of GDMT should be targeted after M-TEER, which supports the potential catalytic role of M-TEER in optimizing medical treatment of HFREF. Improved haemodynamics after MR treatment seems not to be mediated by LV reverse remodelling, according to a post-hoc analysis of the COAPT trial, which contradicts findings from observational studies.⁴⁴

Current transcatheter devices for treatment of secondary mitral regurgitation

The development and clinical implementation of M-TEER, the transcatheter approach of approximation of anterior and posterior leaflet of the mitral valve using a clip-like system, has transformed the management of MR, and in particular SMR. M-TEER provides a minimally invasive therapeutic option for high-risk surgical candidates. The MitraClip (Abbott, Abbott Park, IL, USA) and PASCAL (Edwards Lifesciences, Irvine, CA, USA) are the two current commercially available M-TEER systems. After continuous iteration, both systems are now offered in multiple device sizes, in order to serve the wide range of anatomies.

The anatomic suitability criteria for procedural success for M-TEER include the achievement of favourable transeptal access to the left atrium, the absence of calcification in the treatment zone of the leaflets, adequate posterior mitral leaflet length (>10 mm), and the absence of perforations, significant clefts or a preexisting mitral stenosis (Table 2).⁴⁵ In fact, M-TEER treatment zone and the number of lesions to be treated are factors to be considered for the risk of mitral stenosis besides the mitral valve orifice area.⁴⁶ The aetiology of vSMR did not affect outcomes after M-TEER in the COAPT trial.⁴⁷ Given the risk of residual MR or MR recurrence following this type of mitral valve repair, we should consider

Table 3 Comparison of echocardiographic characteristics in mitral valve transcatheter edge-to-edge repair trials

	COAPT	MITRA-FR	RESHAPE-HF2	EXPANded (SMR cohort)		MiCLASP (SMR cohort)		MATTERHORN
				SMR 2+	SMR 3+	SMR 2+	SMR 3+	
LVEF (%)	31	33	32	40	39	44	39	43
LVEDV (ml)	192	252	205	164	174	156	196	165
EROA (cm ²)	0.41	0.31	0.23	0.20	0.30	0.22	0.36	0.22
PASP (mmHg)	44	54	41	46	49	40	46	39 + CVP

CVP, central venous pressure; EROA, effective regurgitant orifice area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PASP, pulmonary arterial systolic pressure; SMR, secondary mitral regurgitation.

important factors associated with higher residual or recurrent MR in patients screened for M-TEER. In vSMR specifically, LA volume has been identified as a risk factor for MR recurrence.⁴⁸ Further, a low leaflet-to-annulus index proved to be a significant predictor of higher residual MR after M-TEER.⁴⁹ In SMR, LA volume and a low leaflet-to-annulus index were similarly predictive of higher residual MR after M-TEER.⁵⁰

In contrast to M-TEER, transcatheter mitral valve replacement (TMVR) technologies for the treatment of SMR have emerged late. Until very recently, the only CE-marked bioprosthetic device, the Tendyne valve (Abbott Structural Heart, Santa Clara, CA, USA) was introduced into the market in 2020, requiring transapical minimal invasive surgical access and fixation of an apical tether. A second valve, the Sapien M3 (Edwards Lifesciences) has most lately received CE-mark, being the first approved transseptal device. Data from the ENCIRCLE trial (NCT04153292) are expected to be published soon. The paucity of TMVR devices is in part due to the complex anatomy of the mitral valve, requiring a valve that tethers inside the mitral valve annulus without obstructing the LV outflow tract. M-TEER is safe and efficacious, with 30-day mortality rates below 5%.^{51,52} In contrast, transapical TMVR has a 30-day mortality rate of up to 9%,⁵³ and therefore remains reserved for patients at increased risk for surgery and valvular anatomy not suitable for M-TEER.

Additional TMVR devices in current clinical trials include the Medtronic Intrepid valve, which has now achieved trial approval in the USA, Canada and EU, re-designed as a new 29F transseptal implant device that shows promising preliminary safety and efficacy data but is not yet subject of a randomized trial. Additional transseptal replacement devices include the CardioValve, and the AltaValve, the latter of which may overcome LV outflow tract obstruction, however, is dependent on atrial chamber fixation. Highlife may receive CE-mark in the near future and involves a combination of a mitral chordal and leaflet docking device and the implant of a transseptal conventional transcatheter aortic valve-like implant that seals within the docking implant. Most TMVR strategies still have high screen failure rates of 50%–80% due to size mismatch with annular diameters or the risk of LV outflow tract obstruction. Thus, in future, the benefits of TMVR, with the potential to achieve almost complete resolution of MR will have to be balanced against the exceptionally high safety profile of M-TEER, and randomized comparisons are needed to evaluate

the differences between both approaches with respect to quality of life, HFH and mortality.

Current guideline recommendations and criteria for prognostic benefit

In the current HF and previous valvular heart disease guidelines, M-TEER received a class IIa level B recommendation for patients with significant secondary MR, which remained symptomatic despite optimized GDMT, and fulfilling the criteria that define a high probability of having a favourable response to the procedure (COAPT criteria).^{54–56} The current VHD guidelines raised the level of recommendation for M-TEER to class I. This is based not only on the long term outcome of patients in COAPT, but importantly on the results of the RESHAPE HF 2 trial.⁵⁷

RESHAPE-HF2 enrolled 505 patients with HFrEF and moderate-severe or severe SMR (EROA ≥ 0.2 mm²),⁵⁸ randomized 1:1 to receive optimized GDMT alone versus M-TEER in addition to GDMT. The trial included three prespecified primary endpoints: cardiovascular death or HFH, HFH (both assessed after 2 years), and quality of life measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ) at 1 year, respectively. At 2-year follow-up, there was a significant reduction in cardiovascular death or HFH (HR 0.64; 95% CI 0.48–0.85, $p=0.002$), HFH (HR 0.59; 95% CI 0.42–0.82, $p=0.002$). At 1-year follow-up, quality of life was improved with a KCCQ overall summary score mean difference of 10.9 points (95% CI 6.8–15.0, $p<0.001$). The reduction in HFH drove the primary endpoint, whereas all-cause mortality was numerically reduced but not statistically significant; this was potentially blunted by cross-over of 38 patients (15%) from the control arm in the first 2 years. In the study level meta-analysis published simultaneously with RESHAPE-HF2, which merges the primary results of RESHAPE-HF2, COAPT and MITRA-FR, a clear benefit of M-TEER in terms of 2-year HFH and a trend towards a mortality benefit of M-TEER was observed.^{59,60} RESHAPE-HF2, similarly to COAPT but conversely to MITRA-FR, excluded patients with severe right ventricular failure and severe tricuspid regurgitation, as well as haemodynamically unstable patients.⁶¹ Patients enrolled into the three trials were comparable for age and systolic LV function. However, patients included in RESHAPE-HF2 had a mean EROA of 0.23 cm² (only 14% of patients had an

EROA $>0.40\text{ cm}^2$, and 23% had an EROA $<0.20\text{ cm}^2$), whereas COAPT and MITRA-FR patients were indicative of a mean EROA of 0.40 and 0.31 cm^2 , respectively (Table 3). Furthermore, patients included in RESHAPE-HF2 compared with those included in the latter studies, revealed lower levels of NT-proBNP, higher glomerular filtration rates, and more frequently received optimized GDMT⁶²: in RESHAPE-HF2, 96% of patients received beta-blocker therapy (vs. 90% in COAPT and 90% in MITRA-FR), 82% were treated with mineralocorticoid receptor antagonists (vs. 50% in COAPT and 55% in MITRA-FR), 82% with renin-angiotensin system inhibitors (vs. 67% in COAPT and 84% in MITRA-FR).

The robust adherence to HF medication in the RESHAPE-HF2 population may further add to the blunted effect on mortality by M-TEER as compared with COAPT. By demonstrating the effectiveness of M-TEER even in patients with less severe MR, RESHAPE-HF2 may however indicate a state of disease in which M-TEER has also the potential to improve outcome at an earlier stage of disease, in particular in absence of severe right ventricular dysfunction and/or tricuspid regurgitation.^{37,63} At the same time, a prespecified analysis of RESHAPE-HF2^{58,64} revealed that study participants who required HFH in the year prior to randomization derived greater prognostic benefit from M-TEER than those without HFH prior to randomization (p for interaction = 0.03 for the composite of cardiovascular death and HFH at 2 years), illustrating the potential prognostic benefit of this therapy in those with subtle indices of disease progression.

Additional evidence for the benefit of M-TEER in patients with symptomatic but moderate SMR derives from sub-analyses of the MiCLASP and EXPANDED prospective studies: results from the MiCLASP study reported sustained MR reduction, as well as improved symptoms, functional status and hospitalization rates.⁶⁵ These results were echoed in the outcomes from the EXPANDED trial.⁶⁶ Importantly, both studies confirmed similar outcomes for mortality and HFH as well as patient-centred outcomes including NYHA class and KCCQ improvement after M-TEER in patients with 'moderate' or severe MR. It is important however to stress the limitations of assessing improvement in quality of life in unblinded observational studies. To reconcile the outcome of these trials, the 'disproportionate MR' theory has been revisited to place more emphasis on LV dilatation as a determinant of outcomes.⁶⁷ Considering the complex aetiology of SMR, it would seem more appropriate to contextualize SMR to the degree of LV dilatation, reflecting the stage of disease with more precision.

Highlighting the significance of the stages of cardiac failure on outcomes after M-TEER, results of a recent analysis from the EuroSMR registry demonstrated a prognostic impact on mortality and symptomatic improvement after M-TEER, based on the stages of cardiac failure, with the worst outcomes observed in patients with established LV and right ventricular failure.³⁹ Adding to this is the observation that pulmonary pressures in MITRA-FR were significantly higher than those measured in the COAPT, RESHAPE-HF2, EXPANDED, or MiCLASP cohorts (Table 3). This is in line with higher LV end-diastolic volumes in MITRA-FR, which may be a determinant for the lack of benefit for M-TEER in this trial.

Whereas the stage and severity of LV failure are critical considerations in SMR cohorts, attention should also be given to the

criteria used to define severe SMR. In most real-world settings, including the RESHAPE-HF2, EXPANDED, and MiCLASP studies, SMR severity is assessed in the clinical context: patients were characterized with respect to clinical symptoms, a history of HF, laboratory values (e.g. NT-proBNP), followed by TTE and TOE and finally right heart catheterizations (e.g. v-wave of the pulmonary capillary wedge pressure). The core-lab readings of SMR severity in these studies were performed after study inclusion and based on the TTE studies. This is in contrast to trials like COAPT, in which core-lab based TTE assessment pre-selected patients prior to inclusion, resulting in a SMR subcohort of patients with higher EROA and regurgitant volume measurements. Quantification of EROA using the PISA method has well-recognized limitations. As a two-dimensional measurement, the PISA method fails to capture the true three-dimensional complexity and volume of SMR. This raises the important question of whether the 'moderate' MR reported in RESHAPE-HF2, EXPANDED, and MiCLASP was truly moderate, or in fact underestimated due to methodological limitations of EROA. To illustrate this, stroke volume estimates were extrapolated from EROA values in 'COAPT-like' patients (i.e. with LVEF 35%, LV end-diastolic volume 200 ml and heart rate 75 bpm), and shown to be unfeasible, suggesting that the current EROA and regurgitant volume thresholds for classifying severe SMR in HFrEF patients by TTE might need to be revisited.⁴⁵ Additionally, findings from over 1800 patients in the EuroSMR registry showed no correlation between EROA and mortality, challenging the utility of EROA as a prognostic metric in SMR.⁶⁸

Taken together, discrepancies among M-TEER HF trials may be attributed to differences in disease stage and HF severity. In addition, caution is warranted when interpreting these trial data based solely on classifications of 'moderate' MR, as current EROA thresholds may not accurately reflect true MR severity, particularly using only TTE. Therefore, when assessing the suitability for M-TEER, a more holistic approach is advisable and should replace the reliance on a single two-dimensional echocardiographic parameter: this should include clinical symptoms, LV size and function, markers of HF progression (such as LA function and pulmonary hypertension), and adherence to and tolerance of GDMT. Figure 1 summarizes a proposed management of HFrEF patients with moderate SMR.

Thus, RESHAPE-HF2 added important evidence for M-TEER in patients with HF and concomitant MR; however, rather than interpreting these results as evidence for a benefit of M-TEER in all patients with MR 2+, results should be contextualized to LV function, and interpreted with an understanding of the limitations of the EROA. Table 4 summarizes relevant limitations of SMR trials.

Mitral valve transcatheter edge-to-edge repair versus mitral valve surgery

The current European guidelines assign a class IIb level C recommendation to isolated mitral valve surgery and a class I level B recommendation to concomitant valve surgery in patients with SMR undergoing coronary artery bypass grafting or other

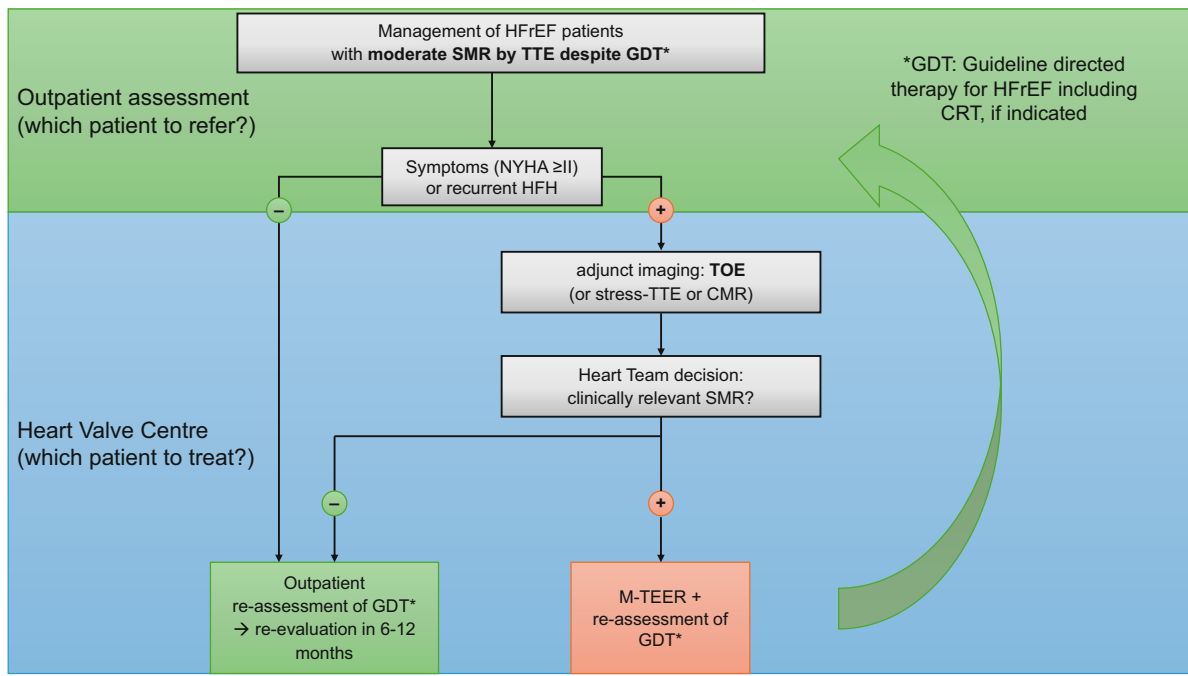


Figure 1 Proposed management of heart failure with reduced ejection fraction (HFrEF) patients with moderate secondary mitral regurgitation (SMR). CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; GDT, guideline-directed therapy; HFH, heart failure hospitalization; M-TEER, mitral valve transcatheter edge-to-edge repair; NYHA, New York Heart Association; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography.

Table 4 Limitations of secondary mitral regurgitation trials

- No RCT comparing M-TEER vs. OMT in aSMR
- No RCT comparing TMVR vs. OMT or vs. M-TEER
- EROA quantification as primary criterion for SMR severity is challenging
- No clear benefit of M-TEER in all patients with moderate SMR
- Patients with advanced HF or acute HF not included in trials
- Differences between SMR trials not explained through theoretical proportionality framework

EROA, effective regurgitant orifice area; HF, heart failure; M-TEER, mitral valve transcatheter edge-to-edge repair; OMT, optimal medical therapy; RCT, randomized controlled trial; SMR, secondary mitral regurgitation; TMVR, transcatheter mitral valve replacement.

cardiac surgery. At the same time, surgery for severe aSMR received a class IIa level B recommendation.⁵⁷

With regard to surgical techniques, the initially propagated restrictive annuloplasty failed to show superiority over valve replacement and resulted in MR recurrence rates of 33% and 59% after 1 and 2 years of follow-up, respectively.^{69,70} Nevertheless, post-hoc-analyses showed that patients with durable repair had a greater degree of reverse remodelling as compared with those having received mitral valve replacement.⁷⁰ Whereas a selection bias may contribute to this observation, more recent data on adjunctive

subvalvular surgical techniques lend support to further pursuing valvular repair in SMR. In particular, papillary repositioning and re-alignment in addition to annuloplasty potentially yields lower MR recurrence rates and more pronounced reverse LV remodelling as reported in a small single-centre randomized trial and in observational studies.^{71,72}

The current 2025 ESC guidelines however increased the level of recommendation for M-TEER over surgery for isolated SMR. This is in large part based on the results of the MATTERHORN trial. The multicentre MATTERHORN trial randomized patients with isolated SMR to M-TEER versus mitral valve surgery, with the choice between repair or replacement, as well as the addition of concomitant surgical procedures such as ablation at the discretion of the surgeon.⁷³ A total of 210 symptomatic HF patients were enrolled. Patients were on GDMT and at increased risk but suitable for surgery. The cohort differed substantially from other randomized M-TEER trials, with a mean LVEF as high as $43 \pm 12\%$ and annular dilatation rather than ventricular tethering as the predominant mechanism of SMR in approximately half of the patients. In the surgical group, valve repair was performed in 72% and replacement in 28%. The primary endpoint of death, HFH, MR recurrence, assist device implantation or stroke at 1 year occurred in 17% in the M-TEER group and 23% in the surgical group, demonstrating non-inferiority of M-TEER versus surgery ($p < 0.001$). Recurrence of MR grade $>2+$ at 1 year was 2% in the surgical group and 9% in the M-TEER group, which—despite the numerical difference—fulfilled prespecified criteria of non-inferiority. The

low MR recurrence rates in the surgical cohort may support the described recent advancements in MR repair techniques, however also reflect the high proportion of valve replacement in 28% of cases. The primary safety endpoint, a composite of major adverse events at 30 days, was reduced by an absolute difference of almost 40% in the M-TEER group (15% vs. 55%, $p < 0.001$), thus fulfilling the prespecified criterion of non-inferiority. This difference remained through 1 year, and after omitting bleeding and AF recurrence from the endpoint. A non-prespecified post-hoc analysis in patients with aSMR reproduced the overall results of MATTERHORN, supporting the new class IIb level B recommendation for M-TEER in patients with this pathology.⁷⁴ Clearly, longer-term data will be of importance, particularly for younger patients without overt surgical risk.

Taken together, critical re-appraisal of the role of surgery in SMR is warranted, in light of the paucity of evidence and the above-described trial results for M-TEER. This will extend to the evaluation of surgery in patients with additional valvular disease, in whom additional transcatheter valvular therapies can now be offered, or patients with concomitant coronary disease, in whom the effect of revascularization on LV remodelling still remains uncertain.

Open questions

Timing of mitral valve transcatheter edge-to-edge repair

There are many open questions about the correct sequence for implementing available medical and interventional treatment options. While GDMT is unquestionably the backbone of HF therapy, SMR patients with advanced HF are typically excluded or severely underrepresented in pharmacological trials for HF. Notably, dedicated trials in advanced HF, with presumably a high prevalence of SMR, provide equivocal results.⁷⁵ Importantly, less than 39% of patients in the COAPT trial were able to tolerate more than two GDMT substance classes, with the predominant reason for intolerance being hypotension.⁷⁶ Employing M-TEER in such patients improved GDMT tolerability and facilitated up-titration.⁴³ Enabling GDMT by M-TEER emerges as an intriguing concept, which should be evaluated further in future studies. Also, the event curves in COAPT early separated in favour of M-TEER, indicating that in patients adequately pre-treated and fulfilling the COAPT criteria, M-TEER should not be withheld unnecessarily.

Interaction with cardiac resynchronization therapy

Another open question relates to the timing of CRT in patients with SMR. Whereas CRT trials revealed some effect on MR grade, patients with truly severe SMR were underrepresented in CRT trials. Thus, while CRT is a valuable treatment option if otherwise indicated, its role in patients with severe SMR, who carry a high risk for acute or progressive HF, is less clear.⁷⁷ As mentioned above, sub-analyses of CARE-HF show a greater benefit

in patients with \geq moderate MR. Whether earlier introduction of CRT would be associated with improved clinical outcomes by facilitating up-titration of GDMT is currently under debate.⁷⁸

Interaction with interventions for atrial fibrillation

Catheter ablation of AF has recently been shown to confer a clinical benefit in patients with stable as well as advanced HF.^{79,80} In the context of MR, only observational data are available, and the majority of patients in these studies exhibit non-severe MR.⁸¹ Reductions in MR severity after AF treatment were modest.⁸² Whereas the existence of SMR is a predictor of AF recurrence after pulmonary vein isolation, the presence of AF does not blunt the beneficial treatment effects of M-TEER.⁸³ Whether the duration of AF or the extent of MR will ultimately help guide the sequence of the two interventions still remains to be determined. Data on the role of M-TEER in stabilizing sinus rhythm also need to be generated.

Mitral valve transcatheter edge-to-edge repair in acute heart failure

Acute HF complicated with MR is a challenging situation for patients and physicians and has many facets, encompassing acute HF with or without acute myocardial ischaemia. Data on M-TEER therapy in acute settings remain scarce compared with chronic MR. The most life-threatening condition resulting in severe acute MR is papillary muscle rupture after myocardial infarction, which requires immediate treatment. In patients with prohibitive surgical risk, M-TEER may be appropriate in expert centres, considering the very high risk for adverse events in severe comorbidity.¹⁰ Registry data show significantly worse outcomes in this subset of patients, compared with MR following LV failure in the chronic phase after myocardial infarction.⁸⁴ However, the optimal timing of intervention in the latter is unclear, and depends on the clinical course. Primary percutaneous coronary intervention and medical therapy potentially enables staged and not emergency M-TEER.¹⁰ In a recent meta-analysis, patients presenting with cardiogenic shock and MR without acute myocardial infarction had better 30-day but worse intermediate-term (mean 10.6 ± 6.4 months) outcomes despite similar acute device success as compared with patients with acute myocardial infarction.⁸⁵ These data support the tenet that patients with MR upon acute-on-chronic HF complicated by cardiogenic shock have worse prognosis—irrespective of and despite successful therapy of the valvular lesion.

Heterogeneity of secondary mitral regurgitation populations

As discussed above, randomized controlled trials investigating the role of M-TEER in SMR used divergent measures for the definition of relevant MR and included patients with substantial differences in LV volumes.^{47,58–59} This raises the question of whether there is an upper LV volume at which M-TEER may be too late. To that end, a framework relating the clinical benefit of M-TEER to the degree

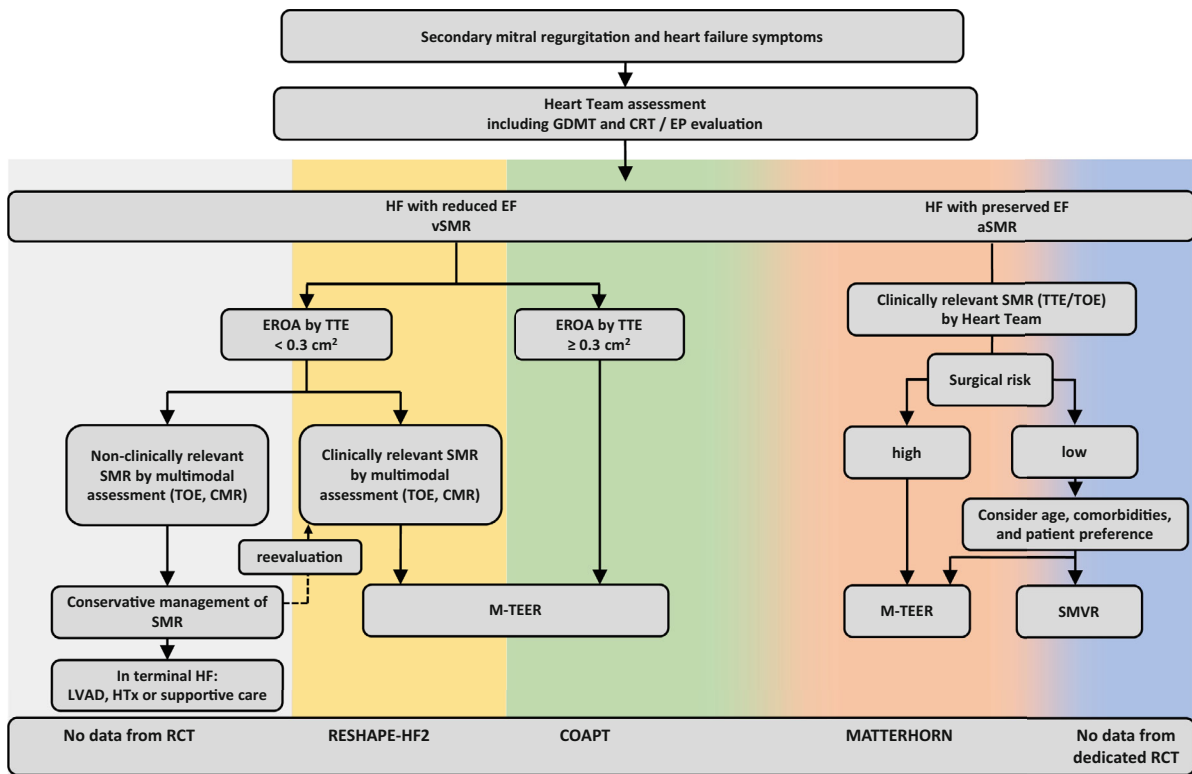


Figure 2 Proposed care pathway for patients with heart failure (HF) and secondary mitral regurgitation (SMR). aSMR, atrial secondary mitral regurgitation; CMR, cardiac magnetic resonance; CRT, cardiac resynchronization therapy; EF, ejection fraction; EP, electrophysiology; EROA, effective regurgitant orifice area; GDMT, guideline-directed medical therapy; HTx, heart transplantation; LVAD, left ventricular assist device; M-TEER, mitral valve transcatheter edge-to-edge repair; RCT, randomized controlled trial; SMVR, surgical mitral valve replacement; TOE, transoesophageal echocardiography; TTE, transthoracic echocardiography; vSMR, ventricular secondary mitral regurgitation.

of LV dilatation has recently been proposed, but requires further systematic investigation.⁶⁷

Despite the significant effects of M-TEER on mortality and HFH, the 5-year follow-up of the patients enrolled in COAPT showed a poor outcome with a 33% annualized rate of HFH, a 57% all-cause mortality through 5 years, and a death or HFH rate of 74%.⁸⁶ Thus, patients with severe SMR and HFrEF remain at high risk, and implementation of monitoring strategies and evidence-based treatment remains of paramount importance and includes shared decision-making along the patient's journey, when opting for mechanical circulatory support or transplantation or palliative care, respectively.

Conclusions

Secondary mitral regurgitation is highly prevalent in the community and is associated with reduced quality of life and substantial risk of recurrent HFH and mortality. M-TEER is effective in reducing symptoms and may improve outcomes in a larger subset of patients with symptomatic HFrEF than previously assumed. This includes patients with less severe MR and those at high risk for mitral valve surgery. Careful evaluation of MR pathology and LV size and

function, implementation of optimal GDMT and CRT as well as exclusion of those with prognosis-limiting comorbidities remain central prerequisites to define those who will benefit from this therapy. *Figure 2* summarizes evidence from randomized controlled studies for a proposed care pathway for patients with HF and SMR.

In aggregate, current data support earlier intervention in selected patients, and a reappraisal of the level of recommendation for this therapy in guidelines for treatment of HF in patients with SMR is warranted.

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MR-proANP (DE 102007010834 & DE 102007022367), but he does not benefit personally from the related issued patents. V.R. received research grant from Abbott Vascular, Boston Scientific, CoraMaze, Edwards Lifesciences, RealView. Advisory board Abbott Vascular, CoraMaze, Edwards Lifesciences, RealView (fees to institution); Speaker's honoraria Astra Zeneca, Boehringer Ingelheim, Bristol Myers Squibb, Edwards Lifesciences, Siemens Healthineers (fees to institution). N.K. is a consultant for Abbott and Medtronic. J. Hausleiter: speaker honoraria from and consultant to Edwards Lifesciences and TriCares. S.B. received research funds from Abbott and lecture fees from Abbott and Edwards. M.B. is supported by the Deutsche Forschungsgemeinschaft (German Research Foundation; TTR 219, project number 322900939) and reports personal fees from Abbott, Amgen, Astra Zeneca, Bayer, Boehringer Ingelheim, Cytokinetics, Edwards, Medtronic, Novartis, Servier and Vifor. Lifesciences.

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