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Current Percutaneous Approaches to Treat Mitral Valve Regurgitation

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Abstract

Purpose of review In recent years, our understanding of mitral regurgitation and its management has evolved substantially. In particular, as percutaneous mitral valve interventions have proven safe and effective, it has become possible to offer expanded therapeutic options to patients who are deemed inoperable or at high surgical risk. This review provides an overview of currently available transcatheter mitral valve interventions and summarizes recently published findings that may allow for better risk stratification, patient selection, and procedural safety and efficacy.

Recent findings In the last 1–2 years, numerous studies have provided important insights that help to better characterize patients in clinical practice and to select them more optimally for specific interventional mitral valve procedures.

Summary The evolution of percutaneous MV therapy has been substantial and extremely beneficial for patient care. Nonetheless, this is an area underdevelopment and newer or enhanced devices are likely to emerge in the future.

Opinion statement

With the introduction of transcatheter procedures, the options for treating mitral regurgitation have expanded considerably, which is of particular benefit to patients who are not surgical candidates. Although both transcatheter mitral repair and transcatheter mitral valve replacement techniques have been shown to be safe and effective, it is crucial to characterize patient groups that either particularly benefit from therapy or, on the other hand, do not benefit as accurately as possible in order to select the best possible therapeutic procedure in each case. This underlines the importance of studies that help to optimize the selection process for mitral valve intervention. Therefore, in this review, we focus on recent studies describing the results with percutaneous mitral valve procedures.

Introduction

Mitral regurgitation (MR) is the most common cardiac valve disease, affecting more than 10% of individuals aged over 75 years [1, 2]. If left untreated, severe symptomatic MR leads to progressive left ventricular (LV) dilatation and dysfunction and, ultimately, congestive heart failure (HF), all of which are associated with excess morbidity and mortality [3, 4]. In recent years, the understanding of disease pathology and natural history has greatly improved, paralleling the evolution in imaging modalities. Concurrently, the management of significant MR has evolved dramatically, with developments in surgical approaches and the introduction of percutaneous mitral interventions. Percutaneous mitral therapies have been shown to be safe, feasible, and effective, extending our ability to treat patients with MR who were previously considered inoperable or at high surgical risk.

The purpose of this review is to provide an updated summary of currently available transcatheter interventions for MR, including transcatheter MV repair (TMVr) and replacement (TMVR). The findings presented in this review hold promise in enhancing risk stratification, patient selection, procedural safety, and efficacy in patients undergoing percutaneous mitral intervention.

Mitral transcatheter edge-to-edge-repair

With more than 150,000 cases performed worldwide, the mitral transcatheter edge-to-edge repair (M-TEER) is by far the most frequently utilized TMVr procedure and, accordingly, the data for this procedure is also the most well established.

Notwithstanding the high morbidity profile of patients referred to M-TEER, this procedure has been proven to be safe and effective [5•]. Consequently, it is recommended by current guidelines for the treatment of both primary (PMR) and secondary (SMR) MR [6••, 7••].

Devices for M-TEER

Currently, two M-TEER systems are commercially available, the MitraClip (Abbott Vascular, Santa Clara, California) and PASCAL (Edward Lifesciences, Irving, California).

The MitraClip system was the first M-TEER device to have a CE mark in 2008 and FDA approval for PMR in 2013. Approval was mainly based on the results of the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial which demonstrated superior safety and sustained clinical improvement with the MitraClip compared to surgical MV repair [8]. The MitraClip system later received FDA approval for SMR patients in 2019, based largely on the results of the clinical outcomes assessment of the MitraClip percutaneous therapy for the High Surgical Risk Patients (COAPT) study [9]. The inclusion criteria for this study (Fig. 1) were adopted by current practice guidelines as M-TEER indications [7••].

The PASCAL system, available since 2016, has technical differences from the MitraClip that relate to both steerability and grasping functions. The specific characteristics of the two devices are summarized in Table 1.

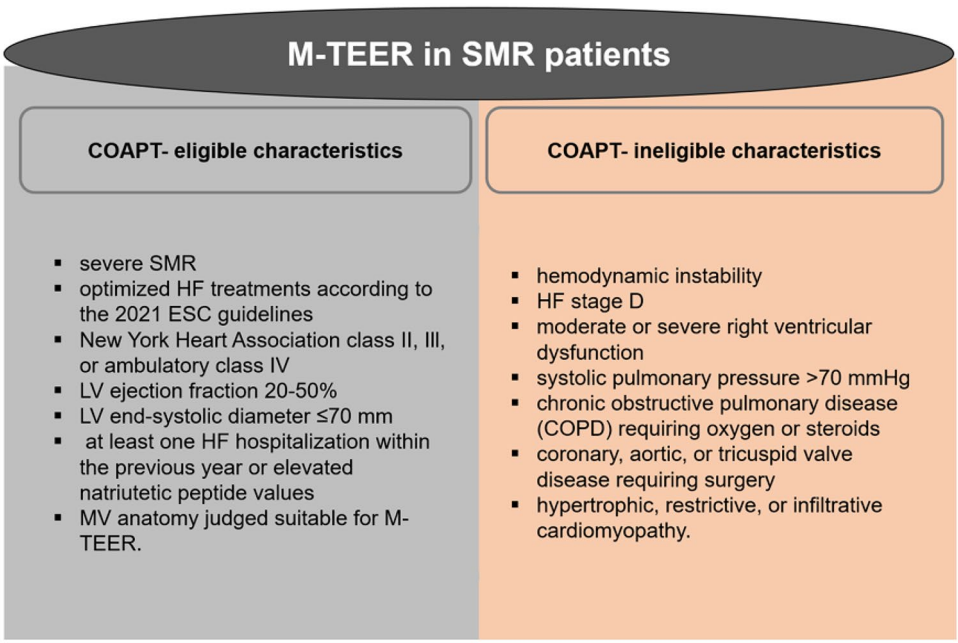
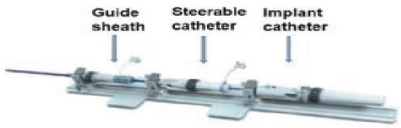


Fig. 1 Main characteristics of COAPT eligible and ineligible patients. SMR, secondary mitral regurgitation; HF, heart failure; LV, left ventricle; M-TEER, mitral transcatheter edge-to-edge repair; MV, mitral valve; ESC, European Society of Cardiology.

Table 1. Characteristics of the MitraClip and PASCAL systems

	MitraClip (Abbott)				PASCAL Precision /Edwards-Lifesciences)	
Commercial introduction	**2008**				**2016**	
Delivery system	**2 working catheters** 				**3 working catheters** 	
Device generation	**4th**				**2nd**	
Number of available device sizes	**4**				**2**	
						
	NT	**NTW**	**XT**	**XTW**	**P 10**	**Ace**
Device width (mm)	**4**		**6**		**10**	**6**
Maximal tissue length than can be grasped(mm)	**9**(of which 6mm are captured by the active grippers)		**12** (of which 9mm are captured by the active grippers		**~9**(due to the larger central spacer, the maximum tissue length that can be grasped is minimally smaller than with the PASCAL Ace)	**~10**
Material characteristics	**Rigid arms of cobalt-chromium alloy**				**Flexible nitinol arms**	
Hook arrangements	**Longitudinally arranged small hooks**				**Horizontally arranged small hooks**	
Locking mechanism	**Active (locking element)**				**Passive (nitinol shape memory)**	
Independent grasping possible	**+**				**+**	
Continuous LA pressure measurement possible	**+**				**+**	
Central spacer to fill the coaptation gap	**-**				**+**	

The MitraClip device

With the introduction of the 4th generation of the MitraClip in 2020, the device portfolio now offers four distinct clip sizes, including NTW and XTW clips that feature wider clip designs with independent grasping capabilities (Table 1). The clips with the longer grasping arms (XTR/XTW) expand the scope of treatment to encompass a larger coaptation gap and address more complex anatomical presentations, extending beyond the initial EVEREST criteria [10].

In the prospective, multicenter, international, and single-arm EXPAND study that enrolled 1041 patients with PMR and SMR at 57 centers, it was demonstrated that treatment with the 3rd-generation MitraClip (XTR) in a contemporary real-world practice resulted in a substantially better and more durable MR reduction compared to prior studies with the MitraClip (EVEREST [8]/COAPT [9]), with 84.5% and 93.0% of subjects with PMR and SMR exhibiting a ≤ 1+ MR at 1 year, respectively. Similarly, the rate of all-cause mortality and re-hospitalization due to HF proved significantly lower among patients treated with the 3rd generation MitraClip compared to earlier iterations of the device (14.9% in PMR patients and 18.9% in SMR patients) [11].

Over the years, a few concerns have been raised regarding the potential for leaflet injury and single leaflet device attachment (SLDA), in view of a higher tension force brought about by the combination of the grasping of a larger amount of tissue, stiffness of the device, and active locking mechanism. However, a structured analysis of the EXPAND registry demonstrated comparable rates of adverse leaflet events following the use of either the longer-arm XTR or the NTR Clip [12].

The PASCAL device

The 2nd generation PASCAL Precision Platform was introduced in August 2022, bringing with it improvements in the stability and steerability of the catheter system. Three embedded catheters allow flexible maneuverability in the left atrium (LA). Two device sizes are currently available: PASCAL 10 and PASACL Ace (Table 1).

A recent meta-analysis encompassing 1028 patients with severe, symptomatic MR (84.0% in NYHA III–IV 84.0%, 99.7% with MR ≥ 3+) and high surgical risk (mean logistic EuroSCORE 16.4) from 12 retrospective and prospective observational studies and 1 randomized controlled trial supports the safety and efficacy of the PASACL system. Technical and procedural success rates were high (95.7% and 95.2%, respectively). MR grade ≤ 2+ was achieved in 94.7% of patients at discharge and in 94% at 30 days. The mean 30-day and 12-month mortality was 4.54% and12.2%, respectively [13].

In the CLASP IID study, a direct comparison of the two currently available M-TEER systems in high-risk patients with PMR showed the PASCAL device to be non-inferior to the MitraClip in terms of safety (major adverse event rate 3.4% vs 4.8%) and efficacy (MR ≤ 2+ 96.5% vs 96.8% [19].

M-TEER treatment of PMR

Severe, symptomatic untreated PMR has a poor prognosis [14]. According to current guidelines, surgical intervention is indicated in operable patients, with SMVr being preferable to MV replacement whenever possible, provided the MV morphology is favorable [7••, 15, 16].

This approach is supported by a recent study demonstrating the excellent results of SMVr in low surgical risk patients regardless of age (< 60 vs ≥ 60 years), sex, prior sternotomy, diabetes, atrial fibrillation, and type of leaflet repair [17].

In patients at high or prohibitive risk, M-TEER should be considered (IIb recommendation in the ESC guidelines [15] and IIa in the ACC/AHA guidelines for patients in NYHA stage III or IV [7••]).

A review of the data show that currently, almost 90% of high-risk patients with severe MR are referred for percutaneous intervention. Among these interventions, M-TEER predominates, accounting for 82% of all MV interventions. In about 10% of cases, medical therapy alone was attempted, primarily in situations marked by unfavorable anatomical features for M-TEER and TMVR. MV intervention was associated with both a lower risk of HF rehospitalization and improved functional status [18].

However, although some very complex anatomies such as failed surgical MV repair [20] or Barlow's disease [21] can be successfully treated in selected patients. There are conditions with definite contraindications for M-TEER such as severe calcification in the grasping zone, active endocarditis, and hemodynamically relevant MS persist. Considering the poor outcomes in very complex anatomies, other therapeutic options including new procedures of percutaneous valve replacement should be considered for these patients.

M-TEER treatment for SMR

SMR results from the geometric alteration/dysfunction of left-sided cardiac cavities and is associated with a very poor prognosis if left untreated [22]. While surgical studies have not demonstrated a survival benefit in patients with SMR, both GDMT and cardiac resynchronization therapy (CRT) have been associated with improved outcome.

The COAPT study, published in 2018, was the first randomized controlled trial (RCT) to demonstrate a survival benefit in patients treated with M-TEER in addition to GDMT [9] compared to patients treated with GDMT alone [9]. This study supported the use of M-TEER therapy for SMR. A recent study confirmed that a COAPT-like profile (Fig. 1) was an independent predictor of long-term outcome at 2 and 5 years (freedom from all-cause death and from a composite endpoint of cardiovascular death and HF hospitalization) [23, 24••].

Furthermore, in a recently published subanalysis of the COAPT study, both older (> 74 years) and younger (74 years) patients were shown to

benefit similarly from an M-TEER procedure in terms of the composite risk for death or HF hospitalization, improved survival, and quality of life. However, older patients did not have as large benefit in terms of HF hospitalization rate [25].

In a propensity score-matched analysis by Okuno et al. comparing M-TEER with SMVr, there was no difference in survival rates after 2 years, although MR reduction was greater and more persistent and left ventricular (LV) function improved in the surgically intervened group. A large meta-analysis published in 2022 directly comparing M-TEER and SMVr found advantages for the M-TEER cohort particularly with respect to in-hospital mortality despite a considerably higher age and comorbidity burden compared with surgically treated patients (3% (95% CI 0.02–0.03) vs 5% (95% CI 0.04–0.07)). In terms of 1-year mortality, functional status, and MR reduction, both cohorts were comparable [26].

In addition, it has been shown that M-TEER therapy in patients with SMR and moderate to severe or severe MR appears to be cost-effective [27].

M-TEER in COAPT-eligible patients

Current guideline recommendations are primarily based on the abovementioned COAPT study [9] and another RCT, the Mitra-FR study [28]. Both studies investigated the effect of M-TEER therapy using the MitraClip in addition to GDMT compared with GDMT therapy alone. This study confirmed the safety of the procedure, as well as a reduction in MR over a follow-up period of 2 to 5 years [24••, 29]. However, while the Mitra-FR study failed to show a beneficial prognostic effect of M-TEER in addition to optimal GDMT [29], the COAPT study at 2- [30] and 5-year [24••] follow-up documented significantly reduced annual HF hospitalization rates in patients treated with an M-TEER procedure (33.1% per year in the device group and 57.2% per year in the control group (hazard ratio, 0.53; 95% confidence interval [CI], 0.41 to 0.68)). In addition, all-cause mortality during the 5 years of follow-up was also significantly lower in the MitraClip device group (57.3% vs 67,2% in the control group; hazard ratio, 0.72; 95% CI, 0.58 to 0.89) [24••].

Several explanations for these contradictory results between the COAPT and MITRA-FR have been offered, among them differences in patient characteristics, medical treatment, severity of MR, procedural complication rates, and durability of the M-TEER result. Nonetheless, in 2021, both the European Guidelines for the Management of Valvular Heart Disease [6••] and the Guidelines for the Diagnosis and Treatment of Acute and Chronic Heart Failure [31] awarded a IIa recommendation for SMR patients who meet the COAPT criteria (Fig. 1).

M-TEER in COAPT-ineligible patients

With the aim of improving symptoms and quality of life (QoL), M-TEER can also be considered for patients who do not meet COAPT criteria (Fig. 1) according to current guidelines (IIb recommendation [6••]). This applies to patients with advanced HF and severely reduced LVEF and patients with a phenotype of atrial SMR (aSMR) and preserved LV function.

M-TEER in patients with severely impaired LV function

In a retrospective analysis of 96 patients with a median LV ejection fraction (LVEF) of 15%, an M-TEER procedure was performed urgently or in the setting of hemodynamic instability in 49% of cases with good technical (98%) and procedural success (≤ moderate MR was achieved in 94.7% and 90.7% of cases by 1 month and 1 year, respectively). A functional NYHA class ≤ II was maintained in 60.0% of patients, and 1-year survival and freedom from all-cause mortality or HF hospitalizations were 74.0% and 50.0%, respectively. Interestingly, mortality was not predicted by COAPT exclusion criteria [32].

Of 1022 patients included in the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry, 34.5% were retrospectively stratified as COAPT-eligible and 65.5% as COAPT-ineligible patients. Improvement in QoL and exercise capacity after M-TEER was achieved in both groups. Compared with stratification according to Mitra-FR criteria, COAPT-eligible patients had a lower rehospitalization and mortality rate. However, stratification according to Mitra-FR criteria did not predict outcomes [33].

Other multicenter studies also showed improvement in symptoms and QoL independent of parameters such as baseline right heart function [34], LVEF [35], pulmonary pressure [36], and LV reverse remodeling [37] after M-TEER In clinical situations, such as end-stage HF patients before LVAD implantation or HTx M-TEER may be considered a rescue or bridging strategy [38–41]. Overall, there is certainly a need to optimize preprocedural risk stratification in this very specific patient group.

M-TEER in patients with aSMR and preserved LV function

Atrial dilation/dysfunction without associated LV dilatation/dysfunction is often referred to as atrial SMR (aSMR). Compared with the more common phenotype of ventricular SMR (vSMR), aSMR is characterized by accentuated relative MV annulus dilation, mild, albeit perceptible, MV tenting, shorter leaflet length compared with MV annulus size, and normal papillary

muscle geometry, which may pose different challenges in M-TEER procedures [42]. In contrast, vSMR presents with apically and laterally displaced valve and akinetic posteromedial papillary muscles, resulting in pronounced leaflet tethering and leaflet elongation compared to controls, and generally only modest relative left atrial (LA) dilatation [3, 42].

The effects of M-TEER in the subgroup of patients with aSMR are not yet sufficiently clear. However, results of the EXPAND study indicate that M-TEER in patients with aSMR leads to similar results as in patients with vSMR in terms of reduction of MR grade, improvement of QoL, and functional status. These findings suggest that M-TEER may provide clinical benefit in patients with atrial fibrillation and SMR in the setting of HF and preserved ejection fraction [43].

Another retrospective study verified a high technical success rate of M-TEER in 94.1% of cases and MR reduction ≤ 1+ in 79.1% of patients with aSMR. A large LA volume index and low leaflet-to-annulus index were associated with a lower probability of achieving an MR grade ≤ 1+ after M-TEER, so these parameters could be helpful in patient selection [44].

Also, the multicentric Mitra-Tune registry demonstrated a high technical success rate of an M-TEER in aSMR patients (97%), with all cause death occurring in 5% of patients at 30 days. An MR grade ≤ 2+ was achieved in 89% and NYHA stage I/II in 79% of cases. A residual MR grade > 2+ and an inter-commissural annular diameter ≥ 35 mm were independent predictors of all-cause death/HF hospitalization during the follow-up. The mean age of the patients was 81 years, underscoring that older patients with aSTR may also benefit from M-TEER [45].

Repeat M-TEER

In a real-world scenario by Sigiura et al., nearly 10% of patients are expected to have recurrence of severe MR 1 year after a first technical successful M-TEER procedure with the MitraClip. Flail leaflet and degree of post-procedural MR (MR grade 2+ vs ≤ 1+) were predictive of recurrence of severe MR in patients with PMR and LA volume and degree of residual post-procedural MR in patients with SMR [46]. Therapeutic options for recurrence of severe MR include surgery which has a relatively high mortality rate of 10% and a reduced rate of successful surgical repair (4.8% overall; 6.8% for PMR) [47] or alternatively a repeat M-TEER procedure.

Kaneko et al. reported on 11,396 patients who underwent M-TEER, of whom 4.8% required reintervention after a median time interval of 4.5 months. The overall 30-day mortality rate was high at 8.6%, as was the 30-day readmission rate (20.9%). A total of 53.7% of patients were treated with repeat M-TEER, and 46.3% underwent surgical intervention. Surgical patients tended to be younger and female but had a similar burden of comorbidities. Surgery was associated overall with a higher 30-day mortality than repeat M-TEER. The need for reintervention was an independent predictor of long-term mortality, underscoring the importance of ensuring procedural success in the index M-TEER procedure to prevent recurrent MR and reintervention [48].

In a retrospective single-center analysis of 52 patients, progression of the underlying mechanism of MR was the cause of recurrent MR. A repeat M-TEER procedure was technically successful in all cases, and most patients showed an improvement in MR and NYHA stage after 1 year. Just under 27% of patients died or were hospitalized for HF within the first year. These were higher-risk cases with predominantly SMR. They were mostly patients who underwent an urgent procedure and exhibited more severe HF indices before the intervention, as well as an attenuated 1-month clinical and echocardiographic response. Of note, tricuspid regurgitation > moderate was identified as the only baseline parameter that was predictive of a primary outcome [49].

Factors impacting outcome of M-TEER

Optimal outcome after M-TEER is currently defined by a residual MR ≤ 1+ [50–54] that is not accompanied by significant mitral stenosis (MS) (trans-mitral mean pressure gradient (TMPG) > 5 mmHg [55] and a MV area < 1.5cm^2). Risk predictors for increased post-procedural transvalvular MV gradients after M-TEER are calcification of the MV annulus or leaflets, baseline MVA < 4 cm^2 or TMPG ≥ 4 mmHg, and the presence of multiple MR jets [56, 57].

Real-world data regarding the prognostic value of TMPG is conflicting. According to a retrospective analysis, a cut-off of 1.94 cm^2 was already associated with a less pronounced decrease in pulmonary artery systolic pressure and a higher incidence of adverse events at 2 years [58]. In another study, a relative 100% increase in, rather than the absolute value of, the TMPG was associated with worse clinical and echocardiographic outcomes [51]. In a more recent study exploring PMR patients, an increase in TMPG quartile (1.9 ± 0.3 mmHg, 3.0 ± 0.1 mmHg, 4.0 ± 0.1 mmHg, and 6.0 ± 1.2 mmHg in Q1, Q2, Q3, and Q4, respectively) was not associated with adverse events [59]. These works suggest that, especially in complex M-TEER cases, the balance between the degree of MR reduction and the magnitude of MS augmentation is probably the most prognostically influential hemodynamic factor.

In addition to device-related factors and structural results, patient outcome after M-TEER is determined by anatomical and clinical factors, as well as the expertise of the treating center. Some recent aspects will be discussed in greater detail below.

Complexity of anatomy

Until recently, the most important factor to consider was the anatomy of the MV. Anatomic criteria for patient and device selection for both PMR and SMR were originally set by the EVEREST study and provide a high probability of achieving an optimal outcome [60]. Deviation from the EVEREST criteria, all implying increased anatomic complexity of the MV, have been associated with reduced likelihood of achieving an optimal result, which may subsequently affect outcome [61]. According to a study by Sorajja et al., if contemporary anatomic

criteria are used [50], 46% of patients can be assigned to an intermediate group, 36% to the suitable group, and 18% to a non-suitable category [62].

Additional anatomic predictors of procedural success include coaptation reserve (measured as the distance of continuous apposition of the A2 and P2 leaflet segments in 2-dimensional apical long-axis imaging at the site of the predominant MR jet) [63], asymmetric tethering degree [64], and leaflet-to-annulus angle which can be useful to identify patients who may require annuloplasty prior to M-TEER [65].

With the introduction of device iterations (such as independent grasping) or new device sizes, the clinical benefit associated with M-TEER is now more likely to be achieved despite adverse MV anatomy. The 3rd generation of the MitraClip was investigated in the EXPAND registry in high-risk patients with PMR or a mixed etiology. Of the 1041 patients included in the registry, 40.5% were treated with a 3rd generation device (NTR or XTR). With an all-cause mortality of 2.4%, a stroke rate of 1.2%, and 0% myocardial infarction, the 30-day event rate was remarkably low. MR reduction ≤ 1+ was achieved in 86.9% of cases and MR reduction to < 2+ in 97.3%, which is also remarkable because 29% of cases had complex anatomy with either severely degenerated leaflets, large flail gaps, or widths (62.6%), calcification in the grasping zone (35.7%), or extremely wide coadaptation gaps (29.6%). Even in the subgroup with complex anatomy, an MR grade ≤ 1+ was observed in 79.4% of patients at 30-day follow-up, and an MR grade ≤ 2+ was achieved in 96.9% of cases [11].

Also, among real-world patients with SMR, 93% sustained MR reduction ≤ 1+ following M-TEER with the 3rd generation MitraClip in the EXPAND study. These excellent results were associated with symptomatic improvement and low event rates. While MR reduction was comparable in NTR-only- and XTR-only-treated patients, fewer XTR Clips were required for achieving MR reduction [66].

Early results from patients treated with the latest-generation (G4) MitraClip indicate an even more effective reduction in MV annulus size compared with earlier generations of the MitraClip [67]. Recently published data from the Expand-G4 study with more than 1000 patients with PMR and SMR in a real-world scenario showed high implantation and procedural success rates (98.0% and 96.2%, respectively). On average, 1.4 ± 0.6 clips were implanted per procedure. MR was significantly reduced at 30 days compared to baseline, with MR ≤ 2 being achieved in 98% and MR ≤ 1 in 91% of patients; ($p < 0.0001$). Eighty-three percent of patients achieved a functional NYHA class of I or II, and an 18-point improvement was observed on KCCQ score. Composite rates of serious adverse events and all-cause mortality were low, at 2.7% and 1.3%, respectively, at 30 days [68•].

The CLASP IID registry within the Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical Trial (CLASP IID) also demonstrated the effectiveness of the PASCAL system in treating complex anatomy. Ninety-eight patients were included. 37.2% of patients had ≥ 2 independent significant jets, 15.0% had severe bileaflet /multi-scallop prolapse, 13.3% an effective regurgitant orifice area < 0.4 cm^2, and 10.6% a large flail gap and/or flail width. At 6 months, MR < 2+ was achieved in 92% of patients and MR ≤ 1+ in 56.1% ($p < 0.001$ vs baseline) [69].

The question of whether there are relevant differences in outcome in complex anatomies with respect to the two available M-TEER systems was addressed in a recently published retrospective meta-analysis including patients with severe SMR or PMR who underwent M-TEER with either the PASCAL device (785 patients) or the MitraClip (796 patients). No significant difference was found between the two device groups in terms of achieving residual MR < 1+. Remarkably, both devices also achieved similarly high technical success rates (96.9% and 96.7% for the PASCAL and MitraClip group, respectively), low 30-day all-cause mortality (risk ratio [RR] = 1.51, 95% CI 0.79–2.89), and an excellent NYHA improvement (RR = 0.98, 95% CI 0.84–1.15) [70].

Institutional expertise

The results of an M-TEER procedure are highly dependent on the experience of the performing interventionalist, so that the complexity of the selected cases should be adapted accordingly [5, 71].

This observation is supported by a recent analysis of a nationally representative database of 4922 M-TEER procedures from 250 institutions. Substantial inter-center variability in the number of annual procedures was found (median 25.0 [11.6–52.5] cases). A larger case volume was associated with a decreased risk of rehospitalization at 180 days. This association was accentuated in non-elective patients, emphasizing that patients in need of urgent MR treatment benefit from a highly experienced percutaneous MV operator team [72].

Clinical factors

Clinical factors to be considered include the severity of MR, the presence of HF signs and symptoms, the possibility of medical therapy optimization, the surgical risk, and the suitability for other advanced therapies (e.g., left ventricular assist device (LVAD), heart transplantation (HTx)) [73].

Prediction of MR severity following M-TEER

In SMR, the intraprocedural severity of MR may be underestimated by the altered loading conditions [74]. This explains why, although an MR grade ≤ 1 + is obtained intra-procedurally in the majority of cases, a higher grade of MR is detected at discharge. For this matter, intraprocedural dobutamine stress echocardiography (DSE) could be helpful in predicting the degree of residual MR [75]. According to one study, patients who developed an MR grade > moderate during the procedure under DSE also had an MR grade > moderate at discharge in 55% of cases, while none of the patients who did not show an increase in MR grade under DSE had an MR > moderate at discharge [75].

Risk stratification scores for patients undergoing M-TEER

Some scores have been developed to allow a better estimation of the outcome in patients after M-TEER.

The use of a multimodal MitraScore, which includes echocardiographic, angiographic, and LA hemodynamic parameters, has shown to be predictive of 1-year outcomes after M-TEER. Results of the MitraPro registry indicated a nearly linear relationship between intraprocedural MitraScore following M-TEER and mortality. The combined clinical end point of mortality and rehospitalization within the 1-year follow-up was also significantly lower in the MitraScore ≤ 3 group (31.5%) than in the MitraScore ≥ 4 group (40.8%). Subgroup analysis confirmed the predictive value of MitraScore in patients with PMR, SMR, or mixed MR etiology [76].

The CITE score was developed for patients with SMR and HF who do not meet COAPT criteria. It is a simple 7-item scoring tool (hemodynamic instability, LV impairment, NYHA class III/IV, peripheral artery disease, atrial fibrillation, brain natriuretic peptide, and hemoglobin) to predict death or HF hospitalization 2 years after M-TEER in patients ineligible for COAPT. The score is important as using it can help support clinical decision-making by identifying those patients who, although excluded from clinical trials, may still benefit from M-TEER [77].

A risk score derived from the COAPT trial recently showed poor performance in prognostic stratification of real-world patients in an external validation (the Italian Society of Interventional Cardiology (GIse) Registry of Transcatheter Treatment of Mitral Valve RegurgitaTiOn (GIOTTO) population was stratified according to COAPT score quartiles). However, after the application to patients with a COAPT-like profile, moderate discrimination and good calibration were observed [78].

The Mitral Regurgitation International Database (MIDA) score represents a mortality risk stratification tool that has been validated in a large-scale registry of patients with PMR [79]. In patients undergoing M-TEER, the predictive value of the MIDA score was recently confirmed in patients with PMR as well as in patients with SMR. It was predictive of worse event-free survival regarding a combined end point of mortality and HF hospitalization and was associated with postprocedural residual MR ≥ 2 and MR recurrence at 2-year follow-up [80].

Predictive value of a combination of echocardiographic and hemodynamic parameters

The combination of echocardiographic parameters (grade of residual MR) and hemodynamic parameters (LA pressure (LAP)) after M-TEER has a strong prognostic value for outcome after M-TEER. In a retrospective analysis, patients were divided into 3 groups according to the hemodynamic profile after M-TEER: group 1 had an optimal hemodynamic response with a residual MR ≤ 2 + and an LAP < 17 mmHg; group 2 showed intermediate hemodynamic response defined by either an MR grade > 2+ or an LAP > 17 mmHg; and group 3 had a poor hemodynamic response with an MR grade > 2+ and an LAP ≥ 17 mmHg. The rate of major adverse events at 1 year increased gradually from group 1 to group 3 and so did the rates of HF readmission (11.5%

vs 16.7% vs 23.7%; $p = 0.03$), MV surgery (3.1% vs 5.1% vs 10.5%; $p = 0.03$), mortality (12.8% vs 17.6% vs 28.9%; $p = 0.005$), and the composite outcome of HF and mortality (20.7% vs 28.7% vs 48%; $p < 0.001$). This highlights that invasive hemodynamic monitoring is additive to echo-Doppler in the evaluation of MR grade, with the advantage of potentially allowing for intraprocedural modifications [81].

Importance of optimal medical therapy in patients with SMR

In patients with SMR, guideline-directed medical therapy (GDMT) remains the fundamental therapeutic recommendation with the goal of favorably affecting cardiac function and remodeling [7, 15]. A recently published study supports the efficacy of medical therapy in patients with severe SMR and HF with reduced ejection fraction (HFrEF). In a retrospective analysis, 63 patients treated with GDMT alone were compared with 95 cases managed by TMVr in addition to GDMT. GDMT reduced the severity of SMR in 57% of patients. A final MR grade ≤ 2+ was associated with improved survival regardless of treatment strategy [82]. Another study showed that in patients with HFrEF and SMR, the use of 3 drugs in combination (beta-blockers, renin-angiotensin system inhibitors, and mineralocorticoid receptor antagonists) was associated with improved survival at 2-year follow-up after M-TEER compared with the use of only 2 drugs [83].

Another aspect of prognostic importance in relation to medical therapy relates to the possibility of up-titration of GDMT following M-TEER, which was possible in 38% of patients with SMR and HFrEF in the EuroSMR registry, and which was independently associated with lower mortality and HF rehospitalization rate. A greater reduction in MR was also predictive of the likelihood of GDMT up-titration [84].

Highly symptomatic patients

Advanced HF symptoms (NYHA class III and/or IV) were associated with poor outcomes in large observational studies [53, 85]. In the COAPT study, HF symptoms were associated with a 28% increase in mortality or HF hospitalization per NYHA class observed after 2 years [86].

A recently published sub-analysis of the EXPAND study showed even severely symptomatic patients may benefit from an M-TEER procedure. Of 1041 patients who received MitraClip therapy in the study, 118 were in stage NYHA IV. These patients had a significantly higher rate of baseline comorbidities and were more likely to have SMR compared with NYHA I/II/III patients. Procedural success rates were high in this patient population (92.4%) and significant improvement in MR grade to ≤ 1 + was achieved in 90.7% of subjects at 30 days and 92.9% at 1 year. QoL and long-term clinical outcome were also significantly improved [87].

Prognostic value of staging according to extramitral cardiac involvement

In a recent study by Stolz et al. a prognostic value was demonstrated by the extent of extra-mitral disease among patients with HFrEF and SMR. There was a gradual increase in 2-year mortality and decrease in symptomatic relief for higher HFrEF stages as well as more pronounced chamber dysfunction (going from left ventricular to left atrial to right ventricular to biventricular) [88].

Quality of life

QoL, which is typically measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ)-12) score, is of particular importance when ensuring optimized patient care and filtering out patients who are considered non-responders and thus have a higher risk of adverse outcome [89]. Natanzon et al. recently demonstrated that patients with a low KCCQ score had a higher prevalence of SMR, a higher Society of Thoracic Surgery (STS) score and, ultimately, a higher incidence of 1-year all-cause mortality or HF rehospitalization. The 30-day KCCQ was the strongest predictor of 1-year all-cause death or HF hospitalizations. QoL is thus an important prognostic factor after a TMVr procedure, helping to identify patients who are likely to experience an adverse outcome even after a successful TMVr [90].

Right ventricular-pulmonary arterial coupling

As a surrogate for right ventricular-pulmonary arterial coupling, the ratio of tricuspid annular plane systolic excursion (TAPSE) to pulmonary artery systolic pressure (PASP) has been shown to be prognostically relevant in a variety of cardiac pathologies and interventions. In a retrospective single-center analysis that included 707 patients and encompassed 448 days, those with a baseline TAPSE/PASP ratio below the cohort's median of 0.37 mm/mmHg experienced higher prevalence of SMR and burden of comorbidities and worse clinical and echocardiographic indices of cardiac function. Post-procedure, they had a lower rate of technical success. In addition, a low TAPSE/PASP ratio independently predicted the composite of mortality or HF hospitalizations. Interestingly, the prognostic significance of the TAPSE/PASP ratio was confined to the patients with SMR [91]. Another study demonstrated that in SMR patients, improvement in TAPSE/PASP after successful M-TEER was predicted by baseline clinical and echocardiographic variables (lack of previous cardiac surgery, low baseline TAPSE, high baseline PASP, and baseline tricuspid regurgitation) and low postprocedural TMPG. Improvement in TAPSE/PASP was independently associated with reduced risk of mortality at long-term follow-up (584 days; IQR 191–1243 days) [92].

MV annuloplasty

Transcatheter annuloplasty may be useful in inoperable patients with SMR, or after M-TEER that resulted in a suboptimal outcome. Similar to surgical annuloplasty, percutaneous annuloplasty procedures aim to reduce the dimensions of the MV annulus, thereby restoring leaflet coaptation in patients who have intact leaflets and MR predominantly due to MV annulus dilation. In principle, this can be achieved by a direct annuloplasty using a device that is attached to the MV annulus or indirectly by accessing the coronary sinus (CS), which is located in the vicinity of the posterior MV annulus.

Direct mitral annuloplasty

Currently, 2 devices with a CE mark are available. With the Cardioband (Edwards Lifesciences, Irvine, CA, USA) implant, a significant MR reduction was achieved in the majority of patients in early studies, which was associated with a significant improvement in functional status and QoL [93, 94]. The randomized ACTIVE trial was designed to support these findings. The trial is ongoing; however, no recruitment is currently taking place.

The Mitralign (Mitralign Inc., Tewksbury, MA, USA) percutaneous annuloplasty system resulted in MR reduction and symptom improvement in only about 50% of patients within a 6-month follow-up period in a first-in-man study.

Indirect mitral annuloplasty

The coronary sinus (CS) is usually easily accessible by percutaneous methods, which makes this approach attractive. The largest clinical experience with the most robust long-term data is with the only CS device that also has a CE mark: the Carillon Mitral Contour System® (Cardiac Dimensions, Kirkland, WA). In the REDUCE-FMR study, 120 SMR patients with a mean LVEF of 34% were randomized in a 3:1 fashion (device to optimal GDMT ratio). In 14% of the patients, the device could not be implanted due to anatomical conditions (8 due to compression of the left circumflex coronary artery (LCx), 2 due to CS dissection, and 2 due to the distal anchor not allowing stable tension). After 12 months, a statistically significant reduction in regurgitant volume and LV end-diastolic and end-systolic volumes was observed, and clinical parameters such as NYHA class and 6-min walk test were significantly improved. Intraprocedural perforations, device fractures, or embolizations were not observed, but 3 patients in the device group suffered a myocardial infarction within 30 days after the index procedure due to LCx compression. According to a recent meta-analysis, which included the Carillon system as well as other non-CE marked CS devices, the main concern with a CS approach was LCx compression, which occurred in 10–15% of cases, whereas the risk of CS thrombosis or device migration (at least with the Carillon system) has been

low. To avoid LCx compression, a safety distance between the CS and LCx of > 8.6 mm measured on CT using 3D reconstruction proved useful [95].

Further real-world data are expected from the EMPOWER trial (The Carillon Mitral Contour System in Treating Heart Failure With at Least Mild Functional MR), which will enroll 400 patients [96].

Transcatheter mitral valve replacement (TMVR)

Due to the complexity and heterogeneity of MR mechanisms, it is difficult to adequately address all MV pathologies with current TMVr techniques. With the development of TMVR technologies, the range of options for treating MR is expanding.

Valve-in-valve, valve-in-ring, valve in mitral annular calcification

In the initial clinical experience, three main scenarios were considered: (1) a valve-in-valve (ViV) procedure for patients with a degenerated MV bioprosthesis; (2) a valve-in-ring (ViR) procedure for patients with an existing annuloplasty ring; and (3) a valve implantation into a native MV with severe mitral annulus calcification (ViMAC). Essentially, these procedures use valves designed for transcatheter aortic valve replacement (TAVR). There has been variable outcomes for these procedures and significantly increased morbidity in some cases. Thus, the VIVID registry reports significant mitral stenosis (TMPG > 5 mmHg) in approximately 60% of patients after ViV and ViR procedures and significant residual MR in 8.2% of the ViV and 12.0% of the ViR patients, each of which was associated with a need for repeat MV replacement. Patients after a ViR procedure had a significant mortality of almost 50% after 4 years [97]. In a registry-based prospective cohort study, a ViV procedure with a SAPIEN 3 valve (Edwards Lifesciences) showed more favorable outcomes with a high technical success rate of 96.8% and all-cause mortality of 5.4% at 30 days and 16.7% at 1 year. Transseptal access was associated with lower 1-year all-cause mortality than transapical access (15.8% vs 21.7%; $p = 0.03$) [98]. Two recently published studies demonstrated that ViV implantation in a degenerated bioprosthesis in mitral position was associated with lower early and 1-year mortality [99] and a lower complication rate compared with reoperation [100], excluding the occurrence of paravalvular leaks [99].

In the largest study with the longest follow-up to date, ViMAC procedures were associated with significantly higher all-cause mortality compared with ViR and ViV procedures at 30 days (34.5% vs 9.9% vs 6.2%; $p < 0.001$), and the 1-year mortality rate reached 62.8% for ViMAC procedures [101]. In the TMVR in MAC global registry, the 1-year all-cause mortality was slightly lower for ViMAC procedures, at 53.7%. Left ventricular outflow tract obstruction (LVOTO) with hemodynamic compromise occurred in 11.2% of cases in this study and was the most important and independent predictor of 30-day and 1-year mortality [102].

Transcatheter MV implantation (TMVI)

In high-risk patients who do not have suitable MV morphology for a TMVr approach and whose native mitral annulus does not have MAC, only valve designs specifically designed for MV implantation can be considered. The attractive features of transcatheter MV implantation (TMVI) are the relative simplicity of the procedure and a low risk of residual MR. Since TMVI has been mostly studied in patients with SMR, these patients seem to be the primary target group. However, this form of therapy also has some significant limitations:

1. Left ventricular outflow tract obstruction (LVOTO)
   LVOTO occurs when the prosthetic valve pushes the anterior mitral leaflet against the septum, which occurs in up to 40% of ViMAC cases [101] and is associated with high 1-year mortality [103]. LVOTO is defined according to MVARC (Mitral Valve Academic Research Consortium) by an increase in the peak gradient in LVOT measured by echocardiography of > 10 mmHg compared with baseline.
   Predictors of LVOTO include device-related factors such as the profile of the prosthesis and the anchoring mechanism; patient-related factors like multiple anatomic parameters, with particular importance given to neo-LVOT, which is evaluated pre-procedurally using computed tomography analysis; and procedure-related factors such as implantation depth. A deep implantation influences the neo-LVOT, a too high (atrial) implantation may increase the risk of thrombosis. LVOTO may be avoided by alcohol septal ablation, radiofrequency septal ablation, or anterior leaflet electrosurgical laceration [104, 105].
2. Access for device delivery
   Based on the experience with TAVR prostheses, a transseptal approach is in principle less complication-prone than a transapical approach. In ViV and ViR procedures, it was recently shown that a transseptal approach was associated with lower early mortality and lower 1-year mortality. Furthermore, the in-hospital stay after a transseptal access was shorter and there was a trend toward lower complication rates compared to an apical approach [106]
   Due to the size of the prostheses for TMVI, the current delivery system profiles are also large to accommodate the valves. To be more suitable for transfemoral/transseptal access, the delivery systems should be smaller and more flexible and the prostheses should be adapted accordingly for the TMVI.
3. Anatomy and anchoring
   Due to the much more complex anatomy of the MV apparatus compared to the aortic valve, secure sealing and anchoring within the dynamic, saddle-shaped MV annulus, which is usually not calcified, represent also an important concern in the context of TMVI. Fixation of an implanted prosthesis purely by radial force does not guarantee a secure hold and also increases the risk of compression and damage to surrounding structures such as the LVOT, the atrioventricular node, the LCx, and the CS as well as the aortic root. Different anchoring techniques have been developed in order to minimize the risk of device embolization, paravalvular leakage, and damage of surround-

ing structures. In ViR procedures, the stiffness and configuration of the previously implanted ring plays a crucial role in the anchorage of a prosthesis. In this scenario, complete, radiopaque semi-rigid rings are the most suitable.

4. Durability and thrombogenicity
   There are currently no long-term data on the durability of a transcatheter MV. According to the experience with biological surgical valves, deterioration of the implants can be expected after 5 years. After 10 years, 10–30% of the valves are affected by structural valve deterioration [107]. Contributing to thrombogenicity and valve deterioration are especially valve-associated factors, such as the device profile and the device shape, as well as the material properties of the leaflets and the stent frames. Based on experience with surgical bioprostheses, drug therapy with at least one antiplatelet/anticoagulant seems warranted, but standardized recommendations are lacking for TMVI.
5. Changing dynamics of the flow patterns.
   The current devices for TMVI have a 3-leaflet valve morphology, which may affect LV flow patterns and thus may have consequences for LV performance. Also, the dynamic flow patterns of the LA may potentially be altered, which may negatively impact the LV filling phase and, in the case of a highly implanted transcatheter valve, may lead to blood stagnation and consecutive thrombus formation.
   Currently, the only valve with CE marking is the Tendyne valve (Abbott). In the global feasibility study with 100 included patients (mostly patients with SMR), a high implantation success rate of 97% was observed, the 1-year motility was 26% and a total of 9 adverse events were reported (3 hemolysis and 6 thromboses) [108]. Clinical improvement and a sustained good echocardiographic result were observed in both short- and long-term follow-up. The Tendyne valve has also been successfully used in patients with MAC, providing a new option for this difficult-to-treat patient group [109].

Summary and future outlook

In this paper, we have provided an updated overview on percutaneous interventions for MR. This is an exciting and rapidly evolving field. Remarkable inroads have been made since the first MitraClip implantation in 2003. The evolution of percutaneous MV therapy has been noteworthy and extremely beneficial for patient care. Still, there remain uncertainties and potential for device improvements. The question of whether moderate-risk patients who are primarily operable may also benefit from an M-TEER will be addressed in the REPAIR MR study [110]. New MV repair devices have very good success rates and results, but device improvements are still required. Percutaneous MV replacement methodologies are in a rapid phase of trial and development. This may offer patients with MR in need of therapy more diversified treatment options better adapted to specific morphologies and clinical characteristics.

Author Contribution

All authors have contributed significantly to this manuscript. NCW, RJS and AS took part in the conception, design, and the writing of the paper. All authors revised the manuscript critically for important intellectual content.

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Compliance with Ethical Standards

Conflict of Interest
Nina C. Wunderlich reports honoraria for lectures and proctoring from Abbott Vascular, Edwards Lifesciences, GE, Philips, Siemens Healthcare, and Boston Scientific. Martin J. Swaans reports payment or honoraria for proctor/lecturer from Abbott Vascular, Boston Scientific, Edwards Lifesciences, Cardiac Dimensions, GE Healthcare, Philips Healthcare, and Bioventrix Inc. Alon Shechter declares that he has no conflict of interest. Ralf Lehmann declares that he has no conflict of interest. Robert J. Siegel declares that he has no conflict of interest.

Human and Animal Rights and Informed Consent
This article does not contain any studies with human or animal subjects performed by any of the authors.

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Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

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