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Transcatheter edge-to-edge repair for mitral regurgitation

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ABSTRACT

Mitral valve transcatheter edge-to-edge repair (M-TEER) has emerged as a transformative therapy for mitral regurgitation (MR), addressing the unmet needs of patients unsuitable for surgery. Landmark trials such as EVEREST II, COAPT, and MITRA-FR have established the safety and efficacy of M-TEER, in both patients with primary (PMR) and secondary MR (SMR). Recent trials, including RESHAPE-HF2 and MATTERHORN, have expanded our understanding and refueled discussions regarding patient selection and appropriate treatment indications in SMR. These trials have also contributed to the discussion regarding SMR phenotypes most appropriate for M-TEER. This review summarizes the evidence from pivotal trials, discusses patient selection, device advancements, potential future directions, and outlines ongoing trials that may shape future clinical practice.

Introduction

Mitral regurgitation (MR) is the most prevalent valvular heart disease, affecting approximately 2-3 % of the general population and nearly 10 % of individuals over 75 years old [1]. Despite the well-documented safety and efficacy of surgical mitral valve (MV) repair and the poor prognosis of untreated symptomatic MR, only a small subset of patients undergo surgery, largely due to concerns over high surgical risk [2,3]. This treatment gap has spurred the development of MV transcatheter edge-to-edge repair (M-TEER), now recognized as a safe and effective alternative for patients at high surgical risk (Fig. 1). M-TEER has been endorsed in American and European guidelines with a Class IIb recommendation for primary MR (PMR)—a disease of the MV apparatus—and a Class IIa recommendation for secondary MR (SMR), where structurally intact MV leaflets are affected by a disease of the left ventricle (LV) and/or left atrium (LA) [4,5].

Landmark trials like EVEREST II ("Endovascular Valve Edge-to-Edge Repair Study", [NCT00209274]), COAPT ("Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation", [NCT01626079]), and MITRA-FR ("Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation", [NCT01920698]), along with continued innovation of M-TEER devices, have facilitated its integration into clinical practice. To date, over 200,000 patients have been treated with this technique [6–9]. The recently published RESHAPE-HF2 ("A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation", [NCT02444338]) and MATTERHORN ("Transcatheter versus Surgical Mitral Valve Repair in Patients with Heart Failure and Secondary Mitral Regurgitation", [NCT02371512]) trials have reignited discussions about SMR patient selection and expanding M-TEER's treatment indications, making a review on M-TEER timely [10,11].

Evidence from landmark trials

Initial data and the EVEREST II trial

The safety, efficacy, and feasibility of M-TEER were first demonstrated in the United States Food and Drug Administration (FDA) Investigational Device Exemption-approved EVEREST I trial, initiated based on the observation that isolated surgical MV edge-to-edge repair can yield satisfactory outcomes in selected patients [12–14]. Building on these findings, the EVEREST II trial was designed as a 2:1 randomized non-inferiority trial to compare M-TEER with MV surgical repair or replacement, aiming to evaluate the safety and efficacy of M-TEER [15]. Anatomical exclusion criteria in EVEREST II included a MV orifice area (MVOA) <4.0 cm^2, flail gap ≥ 10 mm, flail width ≥ 15 mm, and leaflet tethering with a coaptation gap >11 mm [15].

Guided by these anatomical thresholds, the trial randomized 279 patients (73 % PMR, 27 % SMR) to M-TEER ($n = 184$) or MV surgery ($n = 95$) and concluded that M-TEER offered supe-

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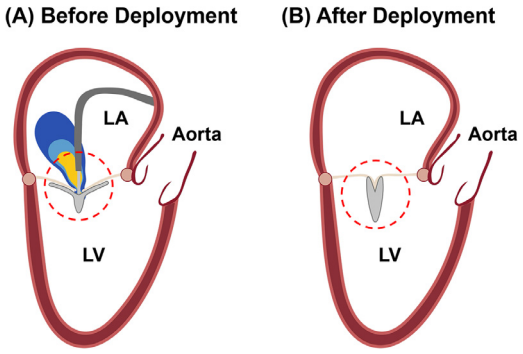

Fig. 1. Mitral valve transcatheter edge-to-edge repair
Schematic representation of M-TEER in a long-axis view as seen in transesophageal echocardiography. (A) M-TEER device in the "grasping" position (red dashed circle), with mitral regurgitation depicted in blue and yellow. (B) M-TEER device in the closed position (red dashed circle), with mitral regurgitation no longer present. *Abbreviations: LA = left atrium, LV = left ventricle, M-TEER = mitral valve transcatheter edge-to-edge repair.*

rior safety and comparable symptomatic improvement, though it was less effective at reducing MR [6]. These results led to FDA approval of the MitraClip (Abbott Structural) in October 2013 for patients at prohibitive surgical risk with severe PMR, while Conformité Européenne (CE) mark approval was already granted in Europe in March 2008 for MR of any etiology. Notably, the abovementioned EVEREST II anatomical thresholds remain relevant today for M-TEER patient selection [16].

MITRA-FR and COAPT trials—defining SMR management

Prospective European registries and findings from the SMR subgroup of the EVEREST II trial suggested that M-TEER could alleviate symptoms and improve functional capacity and quality of life also in SMR patients. This formed the basis of the MITRA-FR and COAPT trials, initiated in December 2013 and 2012, respectively [7,8].

MITRA-FR trial

The French multicenter, randomized MITRA-FR trial compared M-TEER plus guideline-directed medical therapy (GDMT) to GDMT alone in patients with heart failure (HF) and severe SMR. Key inclusion criteria were regurgitant volume >30 mL/beat or effective regurgitant orifice area [EROA] >20 mm², LVEF of 15–40 %, and NYHA class ≥II despite optimized GDMT. Between December 2013 and March 2017, 307 patients (152 intervention, 155 control) were enrolled. The trial found no significant difference in the primary composite endpoint of all-cause mortality or unplanned HF hospitalization at 12 months (54.6 % vs. 51.3 %; $P = 0.53$), with similar all-cause mortality (24.3 % vs. 22.4 %) [8].

COAPT

Published a mere month after MITRA-FR, the COAPT trial famously provided contrasting findings [7]. In COAPT patients were randomized 1:1 to receive either M-TEER and GDMT (device group) or GDMT alone (control group). Key echocardiographic eligibility criteria included LVEF of 20–50 %, LVESD ≤70 mm, and echocardiographically estimated pulmonary artery systolic pressure (PASP) of <70 mmHg [7]. From December 2012 to June 2017, 614 patients were enrolled (302 in the device group, 312 in the control group). The primary effectiveness endpoint—hospitalization for HF within 24 months—significantly favored the device group, with a number needed to treat (NNT) of three. All-cause mortality at 24 months was also lower in the device group, with an NNT of six [7].

The differing outcomes prompted the FDA in 2019 to expand MitraClip approval for SMR, with eligibility criteria closely aligned to those established in the COAPT trial (LVEF 20–50 %, LVESD ≤70 mm). American and European Guidelines were also updated, granting M-TEER a Class IIa recommendation for this population [4,5].

Take-aways from MITRA-FR and COAPT: sweet spot for COAPT

Contradictory results reported in the MITRA-FR and COAPT trials have sparked a continuous debate over patient selection for M-TEER in SMR. Shortly after COAPT was published, patient selection was assumed to be of pivotal importance to explain the staggering difference between MITRA-FR and COAPT. Despite various proposed explanations for these discrepancies over the years, none have consistently delineated these outcome variations [17–21]. Retrospective analyses, however, support the idea that COAPT defined the "sweet spot" for M-TEER SMR patient selection [22–25]. In conclusion, it seems to be pivotal to select SMR patients within the boundaries of the COAPT trial to leverage the remarkably low NNT demonstrated in the trial.

RESHAPE-HF2 and MATTERHORN trials: sharpening SMR understanding

RESHAPE-HF2

The investigator-initiated, prospective, multicenter, and randomized RESHAPE-HF2 trial, the third trial comparing M-TEER plus GDMT (device group) to GDMT alone (control group) in patients with moderate to severe or severe SMR, enrolled symptomatic HF patients deemed ineligible for surgery [26]. The trial was supported by an unrestricted grant from Abbott Laboratories. Key inclusion criteria included an LVEF of 20–50 % (later revised to 15–45 %) and a prior HF hospitalization or an elevated plasma natriuretic peptide concentration within 90 days before enrollment. From March 2015 through October 2023 a total of 505 patients (250 in the device group, 255 in the control group) at 30 sites in 9 countries were enrolled. In the overall cohort, patients presented with a mean LVEF of 31±8 %, a mean LVEDV of 211±76 mL, a mean EROA of 25±8 mm^2, and a median regurgitant volume of 35.4 (28.9–43.9) mL/beat [10,27]. All three of the co-primary endpoints showed an improvement after M-TEER. The rate of first or recurrent HF hospitalization or cardiovascular mortality at 24 months was 37.0 events per 100 patient-years in the device group compared to 58.9 events per 100 patient-years in the control group (rate ratio 0.64, 95 %CI 0.48–0.85, $P = 0.002$). The rate of first or recurrent HF hospitalization at 24 months was 26.9 events per 100 patient-years versus 46.6 events per 100 patient-years (rate ratio 0.59, 95 %CI 0.42–0.82, $P = 0.002$). At 1 year, the mean increase in the Kansas City Cardiomyopathy Questionnaire–Overall Summary score was 21.6 ± 26.9 points in the device group versus 8.0 ± 24.5 points in the control group (mean difference, 10.9 points; 95 % CI, 6.8 to 15.0; $P < 0.001$). The rate of all-cause mortality during the complete follow-up was defined to be a secondary endpoint and showed no difference between the device group (17 events per 100 patient-years) and the control group (18.6 events per 100 patient-years), $P = 0.37$. The authors concluded that a broader application of M-TEER in addition to GDMT should be considered among patients with symptomatic HF and moderate to severe SMR, particularly in those with a history of a recent HF hospitalization [10].

MATTERHORN

Current European and American guidelines recommend either M-TEER or MV surgery in HF patients with severe SMR who remain symptomatic despite GDMT [4,5]. However, a direct comparison between these therapies in an SMR population was lacking. Therefore, the German, multicenter, non-inferiority MATTERHORN trial randomized symptomatic patients with SMR who received the maximum of tolerated GDMT to undergo either M-TEER

(intervention group) or MV surgery (surgery group) in a 1:1 fashion. The trial was funded by Abbott Vascular. Patient eligibility included those with clinically significant SMR (defined by meeting at least two of the following: EROA ≥20 mm^2, biplane vena contracta width >8 mm, regurgitant volume ≥30 mL, regurgitant fraction ≥50 %) or at least two hospitalizations for acute HF during the 12 months before enrollment. Further selection criteria included an LVEF ≥20 %, NYHA class ≥II despite GDMT, and eligibility for both M-TEER and MV surgery. From February 2015 through December 2022, a total of 210 patients from 16 German centers were randomized. Mean LVEF was 43.0 ± 11.7 %, mean LVEDV was 164.6 ± 57.3 mL, and median EROA was 22 (17–28) mm^2 [11]. MV repair was feasible in 72 % of patients in the surgery group. At 1 year, the primary efficacy endpoint (composite of mortality from any cause, HF hospitalization, MV reintervention, implantation of an LV assist device, or stroke within 1 year after the procedure) was met in 16.7 % of the intervention and 22.5 % of the surgery group at 1 year ($P < 0.001$ for non-inferiority). At 30 days, the primary safety endpoint (composite of all-cause mortality, myocardial infarction, major bleeding, stroke or transient ischemic attack, rehospitalization [from any or from cardiovascular causes], reintervention or nonelective cardiovascular surgery, renal failure [need for renal replacement therapy], deep wound infection, mechanical ventilation for >48 h, gastrointestinal complication requiring surgery, new-onset atrial fibrillation, septicemia, or endocarditis) occurred in 14.9 % in the intervention and in 54.8 % in the surgery group, with M-TEER again meeting non-inferiority ($P < 0.001$). Recurrence of MR grade ≥3+, a key secondary endpoint, was observed in 8.9 % in the intervention group compared to 1.5 % in the surgery group ($P = 0.02$ for non-inferiority).

RESHAPE-HF2 and MATTERHORN: lessons learned and outlook

The recently published RESHAPE-HF2 trial, the third randomized controlled trial comparing M-TEER plus GDMT to GDMT alone in patients with moderate-to-severe or severe MR, was anticipated by some as the “tiebreaker” between the conflicting findings of MITRA-FR and COAPT. Involving a distinct patient population, RESHAPE-HF2 rekindled debates over optimal SMR patient selection and introduced new questions [27]. One major difference among MITRA-FR, COAPT, and RESHAPE-HF2, was the more comprehensive GDMT implementation achieved in RESHAPE-HF2 [27]. Specifically, mineralocorticoid receptor antagonists were administered in 82 % in RESHAPE-HF2 (compared to 55 % in MITRA-FR and 50 % in COAPT), while renin-angiotensin or neprilysin inhibitors were used in 82 % (vs. 67 % in COAPT) and beta-blockers in 96 % (vs. 90 % in COAPT and MITRA-FR). Notably, sodium-glucose cotransporter 2 inhibitors were introduced exclusively in RESHAPE-HF2, albeit in a small subset [7,8,27]. Differences in patient populations are further reflected in the 12-month all-cause mortality rates in the GDMT arms, with RESHAPE-HF2 reporting 14 % versus 23 % in both MITRA-FR and COAPT [7,8,10].

Arguably the most significant difference is that according to United States criteria RESHAPE-HF2 enrolled rather moderate than severe MR [4,10]. Mean EROA values illustrate this: 31 mm^2 in MITRA-FR, 40 mm^2 in COAPT, and 25 mm^2 in RESHAPE-HF2 [28]. Notably, RESHAPE-HF2 became the first trial to demonstrate a benefit of M-TEER within the lower European cut-off for severe SMR [10,27,28]. Of note, prior outcome studies have highlighted the poor prognosis associated with an EROA ≥20 mm^2 [4]. Beyond differences in MR severity, RESHAPE-HF2 patients also had a lower mean LVEDV than those in MITRA-FR (211 mL vs. 250 mL), suggesting that M-TEER's advantage might diminish in patients with markedly enlarged ventricles but still holds promise in those with less severe MR. In essence, RESHAPE-HF2 hints that early intervention—before extensive LV remodeling—may yield greater benefits, even under robust GDMT.

A study level meta-analysis, including MITRA-FR, COAPT, and RESHAPE-HF2, supports these observations, showing that M-TEER plus GDMT reduced unplanned HF hospitalizations within 24 months, reduced the composite of HF hospitalization or all-cause mortality within 24 months, and improved functional capacity at 12 months [29]. Yet, no significant differences were observed in cardiovascular or all-cause mortality. A more conservative random-effects sensitivity analysis showed similar point estimates but wider confidence intervals. Patient level meta-analysis and more adequately powered trials should give us further information and definitive answers on optimal treatment of the highly heterogenous SMR patient population [29–31].

In summary, RESHAPE-HF2 reestablished what we had learned from MITRA-FR and COAPT; patient selection seems to be the key in improving outcomes in SMR patients and emphasized the role of GDMT in SMR. Interestingly, and in need of further and appropriately powered investigation, RESHAPE-HR2 ignited a discussion about the expansion of M-TEER indications to patients with moderate MR.

In contrast, the MATTERHORN trial addressed a different, though equally significant, question: how should symptomatic SMR patients eligible for both M-TEER and MV surgery be managed? MATTERHORN concluded that M-TEER was non-inferior to MV surgery in these patients. While this finding suggests that M-TEER may be an appropriate therapeutic option for SMR patients at low surgical risk, several caveats remain. As with MITRA-FR, COAPT, and RESHAPE-HF2, enrollment in MATTERHORN was slow (1.7 patients/center/year), indicating a highly selected SMR patient population. Moreover, MATTERHORN included patients with the lowest mean EROA (0.2 ± 0.1 cm^2), the highest mean LVEF (43±11.7 %), and the smallest LVEDV (164.6 ± 57.3 mL) among these trials. In fact, the investigators also identified an atrial SMR subpopulation, mirroring the results of the overall population [32]. Thus, MATTERHORN introduces yet another distinct SMR patient population, further raising the question regarding the expansion of treatment indications for SMR patients to moderate MR. However, concerns have been raised, among others, regarding the lack of a GDMT-only arm, and longer follow-up is needed to appreciate the full benefit of the trial.

Devices for mitral valve transcatheter edge-to-edge repair

The currently available 4th generation MitraClip, introduced in 2019, comes in four different device sizes to accommodate varying anatomical needs: NT (9 mm arm length, 4 mm arm width), NTW (9 mm arm length, 6 mm arm width), XT (12 mm arm length, 4 mm arm width), and XTW (12 mm arm length, 6 mm arm width). This iteration features independent leaflet grasping, enabling sequential treatment of MV pathologies. Its safety and efficacy across an expanding range of MV pathologies were confirmed in the EXPAND G4 study ("A Post-Market Study Assessment of the Safety and Performance of the MitraClip G4 System") [9,33].

The PASCAL transcatheter mitral valve repair system (Edwards Lifesciences) received CE mark approval in 2019, offering a second option for M-TEER. The PASCAL P10 device, constructed from nitinol, features a 5 mm central spacer, broad and contoured “paddles” (10 mm wide, 9 mm long), and a spring-loaded grasping mechanism (“clasps”) that allows for independent leaflet grasping. Notably, the device can also be elongated. In 2020, the smaller PASCAL Ace was introduced, featuring a 2 mm spacer and 6 mm wide and 10 mm long paddles. FDA approval for the PASCAL system for patients with severe PMR was granted in September 2022, based on the CLASP IID/IIF trial ("Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial: A Prospective, Multicenter, Randomized, Controlled Pivotal Trial to Evaluate the Safety and Effectiveness of Transcatheter Mitral Valve Repair With the Ed-

wards PASCAL Transcatheter Valve Repair System in Patients With Mitral Regurgitation," [NCT03706833]). Approval for SMR in the United States remains pending, contingent on the results of the ongoing CLASP IIF trial [34].

Given the lack of established consensus criteria, the choice between the MitraClip system and the PASCAL system are currently made at the physician's discretion based on their experience, device availability, and personal preference. Both devices achieved comparable effectiveness in the case of non-complex MV anatomy, demonstrated in the CLASP IID trial [35]. However, whether this holds true in cases of more complex MV anatomies is currently unclear and will be investigated in the LEAFLET I study ("Efficacy of MitraCLip Vs. PASCAL for the TrEAtment of MitraL REgurgiTation in an All-comer Population", [NCT06634121]).

Future directions, ongoing trials, and areas of uncertainty

Primary mitral regurgitation: PRIMARY, MITRA-HR, and repair MR trials

Real-world data from the STS/ACC TVT Registry ("Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapies Registry") demonstrate a substantial increase in procedural volume and success rates between 2014 and 2022, reflecting advancements in procedural techniques and device innovation [36]. Considering that the only randomized data comparing M-TEER with surgical MV repair originate from the now-dated EVEREST II trial—conducted with the 1st generation MitraClip in an era of less experienced operators and imaging techniques—there might be potential for more patients with PMR to be considered candidates for M-TEER.

As surgery remains the gold standard for patients with PMR, as evidenced by large databases showing an operative mortality rate of approximately 1 % for isolated surgical MR repair, the strategic PRIMARY ("Percutaneous or Surgical Repair In Mitral Prolapse And Regurgitation for ≥60 Year-olds (PRIMARY)", [NCT05051033]) trial began enrolling patients in February 2022 [37]. Supported by the National Heart, Lung, and Blood Institute and designed and conducted by the Cardiothoracic Surgical Trials Network, this prospective, international, multicenter, open-label, 1:1 randomized trial compares M-TEER with MV surgical repair in PMR. It is being carried out at 60 sites across the United States, Canada, Germany, and the United Kingdom, permitting the use of any legally marketed M-TEER device for PMR. Eligible patients are aged ≥60 years, present with moderate-to-severe or severe PMR and meet anatomical criteria for both M-TEER and surgical repair as determined by the local heart team. Importantly, patients across the entire surgical risk spectrum are included, as determined by the local heart team assessment. The primary endpoint is a composite of all-cause mortality, valve reintervention, hospitalizations and urgent visits for HF, or the onset of ≥3+ MR at three years post-randomization. The outcomes of the PRIMARY trial may substantially influence clinical guidelines and decision-making, potentially extending M-TEER indications to lower-risk PMR patients and making M-TEER a more widely accepted alternative to MV surgical repair.

The French and Monegasque MITRA-HR trial ("Multicentre Study of MITRACLIP® Transcatheter Mitral Valve Repair in Patients With Severe Primary Mitral Regurgitation Eligible for High-risk Surgery", [NCT03271762]) takes a slightly different approach. Funded by the French Ministry of Health (PHRC 2017) and Abbott Vascular, this prospective, multicenter, open-label, 1:1 randomized trial aims to establish non-inferiority for the clinical efficacy of the 3rd and 4th generation MitraClip devices compared to MV surgery in symptomatic patients with moderate-to-severe or severe PMR who are at high surgical risk. By focusing on this high-risk population, MITRA-HR targets those who stand to benefit most from less invasive therapy. Its primary endpoint, assessed at 12 months, is a composite of all-cause mortality, unplanned HF hospitalizations, and MV reintervention [38].

Similarly, the Abbott-funded REPAIR MR trial ("Percutaneous MitraClip Device or Surgical Mitral Valve REpair in PAtients with PrImaRy MItral Regurgitation Who Are Candidates for Surgery (REPAIR MR)", [NCT04198870]) is a prospective, 1:1 randomized, parallel-controlled, multicenter, non-inferiority trial. It aims to compare M-TEER with MV surgical repair over two-years in older or intermediate surgical risk patients with severe PMR. Both symptomatic and asymptomatic patients are considered, with eligibility guided by LVEF, PASP, LVESD, and a multiparametric surgical risk assessment. The local surgical team must deem MV repair feasible, and an independent committee must confirm that MR can be reduced to ≤1+ by both surgical repair and MitraClip with high certainty [39].

All these ongoing trials are expected to yield valuable insights over the next few years. They aim to clarify whether M-TEER can extend its benefits to a wider range of patients with PMR, including those at low, intermediate, and high surgical risk. The outcomes may influence clinical practice by potentially expanding the indications for M-TEER and providing evidence-based guidance for selecting the most appropriate intervention based on individual patient risk profiles.

Secondary mitral regurgitation: expanding indications and acknowledging SMR heterogeneity

The recent publication of the RESHAPE-HF2, the MATTERHORN, and the vortex around those two main publications have—once again—fueled discussion regarding patient selection in SMR. Particularly a patient level meta-analysis of the MITRA-FR, COAPT, and RESHAPE-HF2 trials is highly awaited. RESHAPE-HF2 and MATTERHORN further support the application of M-TEER for SMR, challenge traditional MR severity thresholds, and suggest (at least symptomatic) benefit even in moderate MR when combined with GDMT. These findings raise important questions about the potential need and benefit of an earlier intervention. However, further expansion of M-TEER indications for SMR patients requires dedicated and appropriately powered trials, applying lower thresholds for MR severity. In harmony with determining MR severity in SMR the growing understanding of SMR heterogeneity also requires further attention and investigation. SMR heterogeneity is currently classified into two predominant phenotypes: ventricular and atrial SMR, the latter representing an increasingly prevalent condition [40,41]. While randomized trials have predominantly focused on ventricular SMR, data on atrial SMR remain scarce, with no randomized trials conducted to date. Retrospective analyses, however, suggest high procedural success rates with M-TEER and significant improvements in HF symptoms [42]. Notably, atrial SMR itself encompasses at least two distinct phenotypes: isolated annular dilation and atriogenic hamstringing, with the latter associated with lower technical success rates [41]. Finally, recognizing that the current standard four-column GDMT approach was not yet (fully) available when the cited SMR studies began recruitment, this should also be investigated in future studies.

Further areas of uncertainty

A number of further unresolved questions remain, warranting attention. Among these, the role of M-TEER in acute MR represents a particularly intriguing area without randomized evidence, as these patients have been systematically excluded from previous M-TEER trials. A recently published meta-analysis suggested that M-TEER may provide favorable short-term outcomes even in hemodynamically unstable patients, highlighting its potential in

acute settings [43]. Furthermore, mixed MR remains a challenging population with poor outcomes and a lack of robust evidence to guide treatment. The long-term durability of the initial procedural success also remains a significant gap in the literature, with particularly limited data on outcomes many years (i.e., >5 years) post-intervention. However, long-term studies are essential to establish the durability of MV repair and further reinforce the efficacy of M-TEER across diverse patient populations. Currently, the longest available follow-up after M-TEER includes the 5-year outcomes from the EVEREST II and COAPT trials, along with a 5-year analysis from a large European SMR registry [44–46]. Moreover, the complex interplay of atrial fibrillation and atrial SMR has not yet been elucidated sufficiently. Whether rhythm control or M-TEER should be the first intervention is a matter of ongoing debate, with a pilot randomized study being underway (Treatment of Functional Mitral Regurgitation in Patients With Atrial Fibrillation (CAMERA-Pilot), [NCT05846412]). Finally, the optimal degree of MR reduction continues to be debated; while some evidence exists, no definitive answers have yet emerged. These uncertainties emphasize the need for further research to refine patient selection, procedural strategies, and long-term management in this evolving field.

Conclusions

M-TEER has transformed the treatment landscape for MR, providing a less invasive alternative to surgery for high-risk patients. Evidence from pivotal trials such as COAPT, RESHAPE-HF2, and MATTERHORN supports its safety and efficacy in carefully selected cases of SMR, while ongoing trials like the PRIMARY, MITRA-HR, and REPAIR MR trials will help clarify its broader applicability in PMR. With further advancements in technology, M-TEER holds promise for bridging the treatment gap in MR, enhancing quality of life and outcomes for patients in this challenging and evolving demographic. However, an array of uncertainties persists, underscoring the need for continued investigation and dialogue to fully leverage the potential of M-TEER.

Declaration of competing interest

Christos Iliadis has received travel support and consultant honoraria from Abbott and Edwards Lifesciences.

CRediT authorship contribution statement

Philipp von Stein: Writing – original draft, Conceptualization. **Christos Iliadis:** Writing – review & editing, Supervision, Project administration, Methodology, Conceptualization.

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