Keynote Lecture Series

Transcatheter mitral valve options for severe mitral annular calcification

Takayuki Onishi[1], Ahmed El-Eshmawi[2], Stamatios Lerakis[1], Lucy M. Safi[1], Sahil Khera[1], Annapoorna S. Kini[1], David H. Adams[2], Gilbert H. L. Tang[1,2]

[1]Mount Sinai Fuster Heart Hospital, New York, NY, USA; [2]Department of Cardiovascular Surgery, Mount Sinai Health System, New York, NY, USA

Correspondence to: Gilbert H. L. Tang, MD, MSc, MBA. Mount Sinai Fuster Heart Hospital, New York, NY, USA; Department of Cardiovascular Surgery, Mount Sinai Health System, 1190 Fifth Avenue, Box 1028, New York, NY 10029, USA. Email: gilbert.tang@mountsinai.org.

Transcatheter mitral valve intervention (TMVI) has emerged as a potential alternative to surgery for patients with mitral annular calcification (MAC)-associated mitral valve disease, a population often deemed high-risk due to clinical and anatomic complexities. However, MAC also presents significant challenges to TMVI itself. In transcatheter edge-to-edge repair (TEER), procedural success may be limited by fibrotic and short leaflets, reduced mitral valve area, and subvalvular calcium protrusion. Transcatheter mitral valve replacement (TMVR) poses further anatomical hurdles, including a small, eccentric, or non-conforming annuli; insufficient MAC to ensure anchoring; narrow aortomitral angle; septal hypertrophy; elongated anterior mitral leaflet predisposing to left ventricular outflow tract (LVOT) obstruction; and heterogeneous MAC morphology leading to paravalvular leak or suboptimal fixation. Mechanical injury to adjacent structures such as the circumflex artery and atrioventricular groove is also a concern. Balloon-expandable valves, used off-label for TMVR, may be delivered via transapical, transfemoral, transseptal, or hybrid transatrial approaches. While early data show high mortality for valve-in-MAC (ViMAC) procedures, a shift toward transfemoral transseptal access has improved outcomes. The hybrid transatrial approach offers advantages including resection of the anterior leaflet, septal myectomy, and reinforcement of the valve skirt with Teflon felt. Among dedicated self-expanding TMVR systems, only Tendyne has both CE mark and US Food and Drug Administration (FDA) approval and is delivered transapically. New transfemoral transseptal systems—such as Intrepid, AltaValve, and Cephea—are under active investigation. Techniques like LAMPOON (Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN) and BATMAN (Balloon-Assisted Translocation of the Mitral Anterior Leaflet) have been developed to mitigate the risk of fatal LVOT obstruction. Despite progress, mid-term mortality after ViMAC TMVR remains high. Continued innovations in technique, device design, and patient selection are critical to establishing TMVI as a viable treatment for MAC-associated mitral valve disease.

Keywords: Mitral annular calcification (MAC); transcatheter edge-to-edge repair (TEER); transcatheter mitral valve replacement (TMVR); left ventricular outflow tract obstruction (LVOT obstruction)

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Introduction

Transcatheter mitral valve intervention (TMVI) has emerged as an alternative treatment for mitral annular calcification (MAC)-associated mitral valve (MV) disease, given that patients with MAC are often at high surgical risk (1-5) and because MAC presents significant technical challenges during mitral surgery (6-11). Transcatheter edge-to-edge repair (TEER) may be feasible in patients with moderate-to-severe or greater mitral regurgitation (MR) and in anatomies with sufficiently long leaflets and

large MV area to reduce the risk of mitral stenosis (MS). Transcatheter mitral valve replacement (TMVR) offers the potential to eliminate MR and/or MS but faces inherent challenges such as device under-expansion, migration, and paravalvular leak (PVL) due to insufficient radial anchoring force to the native anatomy. Additional risks include mechanical injury to the atrioventricular (AV) groove and left circumflex coronary artery (LCX), as well as left ventricular outflow tract (LVOT) obstruction caused by the device itself or displacement of the native anterior mitral leaflet by the stent frame. Although advances in technology and patient selection have improved outcomes of valve-in-MAC (ViMAC) TMVR, both short- and long-term results remain sobering (12). In this lecture, we review the current status of TMVI for MAC-associated MV disease, focusing on recent technological developments, clinical studies, outcomes, and future directions.

Reasons why anatomical MAC is challenging for TMVI

Heterogeneous etiology: TMVI

The size, location, and extent of MAC determine the phenotype of MAC-associated MV dysfunction, which can present as predominant MR, predominant MS, or mixed MS/MR (10,13,14). Consequently, the TMVI strategy must be individualized based on each patient's specific anatomy and pathology.

TEER

TEER may be a treatment option for MAC-related MR; however, several anatomic barriers limit its applicability. These include fibrotic and shortened leaflets, a small MV area, and sub-annular calcium protrusion.

The minimal leaflet length required for adequate grasping is 6 mm for MitraClip NT(W), 9 mm for MitraClip XT(W) (Abbott Structural Heart, USA), and 8 mm for PASCAL devices (Edwards Lifesciences LLC, USA). Therefore, detailed assessment of leaflet involvement by MAC—including leaflet length, mobility, and presence of calcium—using transesophageal echocardiography (TEE) is essential before the procedure. These factors influence the feasibility of device grasping. Additionally, a minimal MV area of 4.0 cm^2 by planimetry is required to avoid MS after TEER. Baseline transmitral gradient also needs to be considered to determine procedural expectations in terms of a tradeoff between MR reduction and the risk of causing MS. Sub-annular calcium protrusion can interfere with device deployment and manipulation, further complicating the procedure.

Given these anatomic challenges, realistic expectations for MR reduction should be established pre-procedure. It is important to recognize that TEER in MAC-associated MR carries a relatively high risk of single leaflet device attachment (SLDA) and post-procedural MS.

TMVR

TMVR is indicated for MAC-related MS, mixed MS/MR, and MR that is unsuitable for TEER. However, several challenging anatomic features complicate TMVR in MAC-associated MV disease.

First, a small, eccentric, or non-conforming mitral annulus increases the risk of device under-expansion. Second, insufficient MAC severity may lead to device migration, particularly with balloon-expandable valves. A computed tomography (CT)-based MAC scoring system has been proposed to predict valve embolization and migration during TMVR (15) (*Figure 1*). This score incorporates average calcium thickness, the extent of annular circumference involved, calcification at one or both fibrous trigones, and calcification of one or both leaflets. Each component is assigned points according to severity, with a maximum total score of 10. A MAC score ≤6 independently predicts valve embolization or migration. Third, several anatomic factors predispose to LVOT obstruction, including a narrow aortomitral angle, prominent septal hypertrophy, a long native anterior mitral leaflet, and an eccentric mitral annulus (16,17). Smaller left ventricular end-diastolic dimension has also been implicated as a risk factor for LVOT obstruction (18). Devices that anchor more in the left ventricular cavity further increase this risk. Careful assessment is particularly warranted in female patients with small, hyperdynamic left ventricles. Fourth, heterogeneous MAC, especially calcified commissures, can result in inadequate sealing against the native annulus, particularly with balloon-expandable valves, leading to PVL as well as suboptimal fixation, and valve deformation. Finally, proximity of the LCX and AV groove may pose a risk of mechanical compromise if MAC is displaced toward the AV groove during valve deployment.

TEER in MAC

Optimal patient selection is key to the success of TEER in

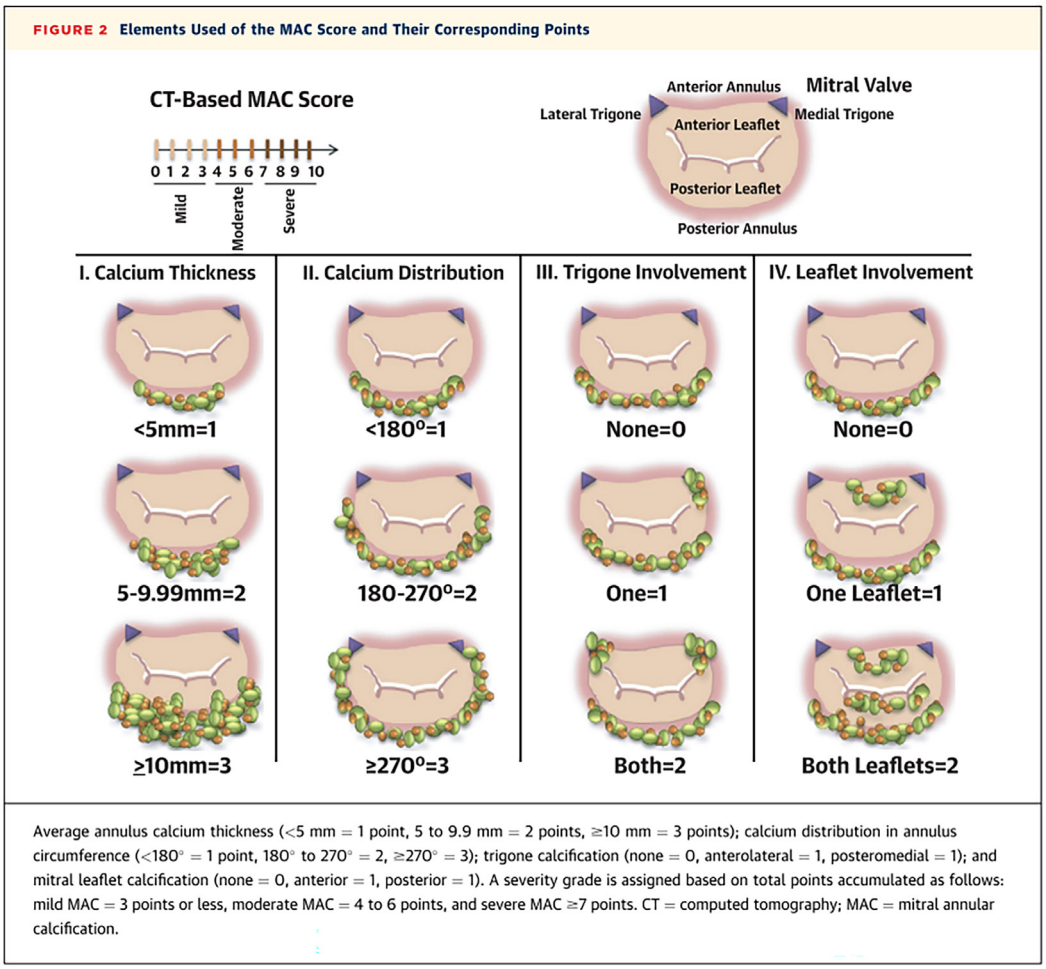

Figure 1 MAC score. A visual representation of the MAC scoring system. Reproduced with permission from Guerrero *et al.* © 2020 by the American College of Cardiology Foundation. This work is licensed under the CC BY-NC-ND 4.0 license (https://creativecommons.org/licenses/by-nc-nd/4.0/). CT, computed tomography; MAC, mitral annular calcification.

MAC-associated MR. The two critical factors to assess are the graspability of the mitral leaflets and the risk of post-TEER MS.

Graspability depends on leaflet length and mobility, as well as the presence and location of calcification. To avoid post-procedural MS, baseline MV area and transmitral gradients should be carefully evaluated pre-procedure.

In a single-center study of 260 patients undergoing mitral TEER, outcomes were compared between those with none or mild MAC (n=160) and those with moderate or severe MAC (n=100). Procedural success was comparable between the groups; however, the MAC cohort had three conversions to cardiac surgery and demonstrated higher rates of moderate to severe MR (22.1% *vs.* 7.5%) as well as higher mean transmitral gradients (5.3 *vs.* 4.0 mmHg) at 1 year (19).

In another single-center study of 280 patients undergoing mitral TEER, 31 patients with moderate or severe MAC demonstrated similar procedural success and rates of residual MR ≤2 at 1 year compared with 249 patients with no or mild MAC (86.7% *vs.* 93.2%). However, the moderate or severe MAC group experienced less symptomatic improvement and had lower cumulative 1-year survival (56.8% *vs.* 80.0%) (20).

In a multicenter registry study of 852 patients undergoing mitral TEER, 61 patients with moderate or severe MAC achieved similar procedural success and rates of MR grade ≤2 at 1 year compared with patients with none or mild MAC (90.6% *vs.* 79.5%). However, the MAC cohort exhibited a trend toward higher all-cause 1-year

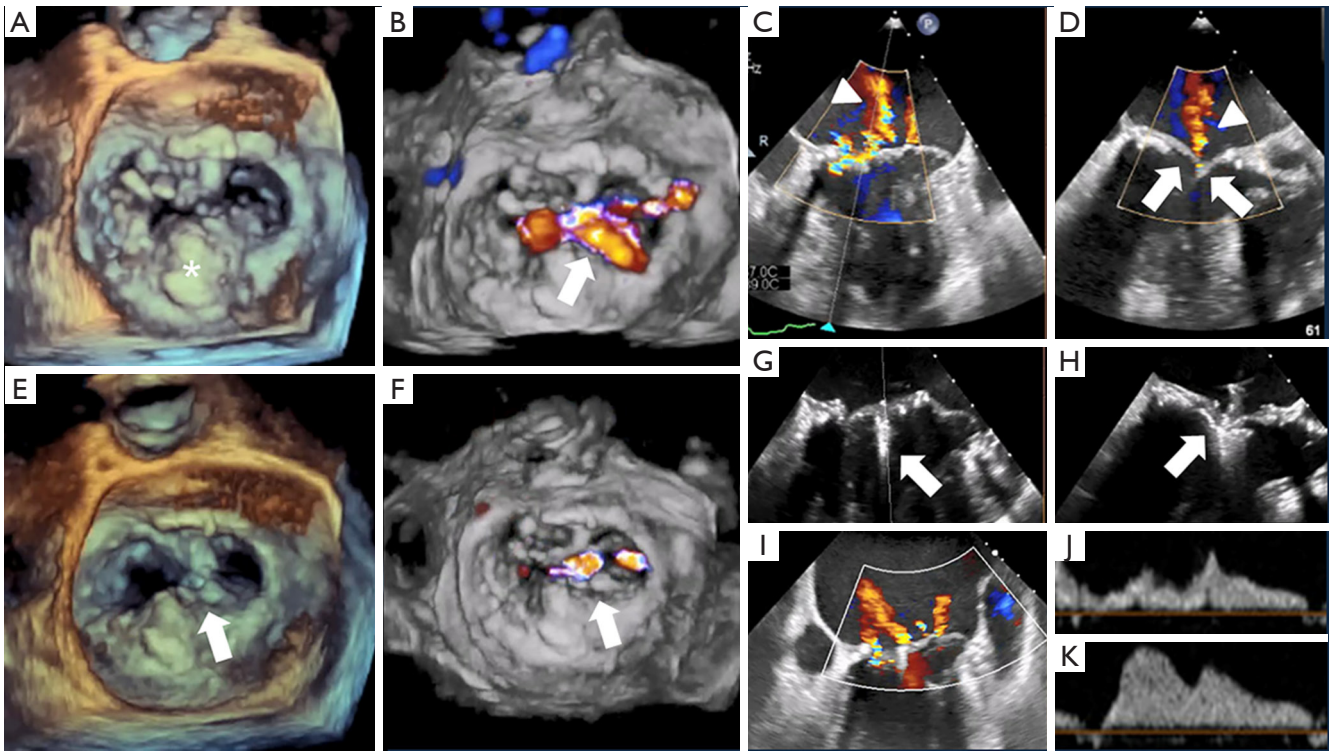

Figure 2 A case of TEER for MAC-associated MR. A 74-year-old female with a history of complex surgical MV repair for MAC, atrial fibrillation, severe COPD, and pacemaker implantation presented with NYHA class III heart failure symptoms. TEE revealed severe MR and MAC with a frozen P2 segment and a mean transmitral gradient of 2 mmHg. Left ventricular ejection fraction was preserved at 50%. The STS-PROM for MV repair was 4.26%, and the patient was deemed prohibitive risk for redo mitral surgery. TEE identified large MAC at central P2 (A, asterisk) and severe MR (B, white arrow; C,D, arrowheads) medial to the calcified segment. Bi-plane imaging at the MR site (C,D) revealed clippable leaflets without significant thickening or calcium, and with adequate length (D, white arrows). A MitraClip NT was successfully deployed at the central A2-P2 position (E,F,G,H, white arrows), resulting in reduction of MR from severe to minimal (F,I). Hemodynamics improved with a decrease in left atrial pressure (mean: from 28 to 15 mmHg; v-wave: from 35 to 22 mmHg), and pulmonary vein flow improved from systolic blunting (J) to normalized systolic dominance (K). COPD, chronic obstructive pulmonary disease; MAC, mitral annular calcification; MR, mitral regurgitation; MV, mitral valve; NYHA, New York Heart Association; STS-PROM, Society of Thoracic Surgeons predicted risk of operative mortality; TEE, transesophageal echocardiography; TEER, transcatheter edge-to-edge repair.

mortality (19.7% *vs.* 11.3%), while cardiovascular mortality was not significantly different between groups (15.3% *vs.* 9.2%) (21).

A meta-analysis incorporating five studies with a total of 2,533 patients demonstrated that those with moderate or severe MAC had comparable procedural success rates (87% *vs.* 94%), residual MR < moderate (80.4% *vs.* 87.7%), and New York Heart Association (NYHA) class III/IV symptoms (19.6% *vs.* 15.4%) at 1 year compared with patients with no or mild MAC. However, 1-year all-cause mortality was significantly higher in the MAC cohort (26% *vs.* 20%) (22).

Case example (*Figure 2*)

A 74-year-old woman with a history of complex MV repair for MAC, atrial fibrillation, severe chronic obstructive pulmonary disease, and prior pacemaker implantation presented with NYHA class III heart failure symptoms. TEE demonstrated severe MR and MAC involving a frozen P2 segment, with a mean transmitral gradient of 2 mmHg. Left ventricular ejection fraction was 50%, and the Society of Thoracic Surgeons predicted risk of operative mortality (STS-PROM) for MV repair was 4.26%. She was deemed to be at prohibitive risk for redo mitral surgery.

TEE revealed severe MAC at the central P2 segment (*Figure 2A*, asterisk) and severe MR primarily at the medial aspect of the P2 segment (*Figure 2B*, white arrow). Bi-plane imaging at the MR jet location (*Figure 2C,2D*) showed a clippable leaflet segment without significant thickening or calcification, and with sufficient length (*Figure 2D*, white arrows). Based on this evaluation, TEER using a MitraClip was planned.

A MitraClip NT was successfully deployed at the medial aspect of the A2-P2 position (*Figure 2E,2F,2G,2H*, white arrows), reducing MR from severe to mild (*Figure 2F,2I*). Hemodynamically, left atrial pressure improved from a mean of 28 mmHg with v-waves of 35 mmHg to 15 and 22 mmHg, respectively. Pulmonary vein flow normalized, transitioning from a blunted systolic wave to a restored systolic dominance (*Figure 2J,2K*).

Potential complications of TEER in MAC include SLDA, MS, and suboptimal MR reduction. To optimize outcomes and reduce the risk of SLDA, meticulous steering and grasping techniques are essential. This includes slow device advancement, posterior guide torque during device closure to reduce system tension, and avoidance of excessive leaflet strain.

As demonstrated in this case and previous studies (19-21,23), carefully selected patients with MAC may be suitable candidates for TEER.

TMVR in MAC

Two main device types are used for TMVR: balloon-expandable valves and self-expanding valves.

Balloon-expandable valves

Transcatheter balloon-expandable aortic valves

Transcatheter balloon-expandable aortic valves [e.g., SAPIEN series (Edwards Lifesciences LLC, USA), MyVal (Merril, India)] are currently used off-label for TMVR. The first ViMAC procedure was performed using a classic SAPIEN valve via a transapical approach (24).

Because of the irregular and often calcified mitral annulus, oversizing is required to ensure valve anchoring. The MAC score is a helpful tool to assess the risk of valve migration or embolization (15) (*Figure 1*). This scoring system considers calcium thickness, annular circumference involved, and calcification of fibrous trigones and leaflets. However, due to the non-uniform morphology of MAC, incomplete sealing between the valve's outer skirt and the annulus is common, leading to PVL and suboptimal fixation. These challenges may necessitate adjunctive procedures, such as PVL closure or valve-in-valve implantation. A case example is shown in *Figure 3*.

The multicenter, prospective MITRAL Trial evaluated outcomes of balloon-expandable aortic transcatheter heart valves used for ViMAC procedures in 31 patients. Access included transatrial (48.4%), transseptal (48.4%), and transapical (3.2%) approaches. Technical success was achieved in 74.2%. LVOT obstruction with hemodynamic compromise occurred in 3 patients (9.7%), with no intraprocedural deaths or conversions to open surgery during the index procedures. At 30 days, all-cause mortality was 16.7% overall (transatrial 21.4%, transseptal 6.7%, and transapical 100%), and stroke occurred in 6.7% (transatrial 7.1%, transapical 100%). At 1 year, all-cause mortality increased to 34.5% (transatrial 38.5%, transseptal 26.7%, and transapical 100%), with stroke in 6.9%, MV reintervention in 13.8%, and heart failure hospitalization in 37.9%. At 5 years, all-cause mortality was 67.9% (28.6% cardiovascular), stroke occurred in 17.9%, MV reintervention in 17.8%, and heart failure rehospitalization in 42.9% (12). Despite these sobering statistics, patients who survived experienced sustained improvement in functional status and quality of life. Echocardiographic follow-up showed MR remained ≤ mild in 100% at 1 year and 96% at 5 years, with mean transmitral gradients of 7.3±2.7 mmHg at 1 year and 6.6±2.5 mmHg at 5 years. Notably, the ViMAC group had the lowest 5-year survival compared to valve-in-valve TMVR patients. Device innovation is needed to improve the outer skirt's conformability to irregular MAC anatomy, which could reduce PVL and improve outcomes.

The Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy (STS/ACC TVT) Registry reported on 3,597 high-risk patients treated with transcatheter balloon-expandable aortic valves for TMVR from 2014 to 2020. ViMAC comprised 10.3% of this cohort, while MViV and MViR accounted for 76.7% and 13%, respectively (25). The 30-day mortality for ViMAC was 20.3%, significantly higher than for MViR (9.4%) and MViV (4.7%). Moderate to severe post-procedural MR occurred in only 0.5% of all TMVR cases. One-year mortality, using inverse probability weighting, was 22.5% (95% confidence interval: 20.8–24.3). Importantly, a shift from transapical access (76% in 2014) to transfemoral/transseptal access (83% in 2020) was associated with reduced in-hospital and 30-day mortality, fewer blood transfusions,

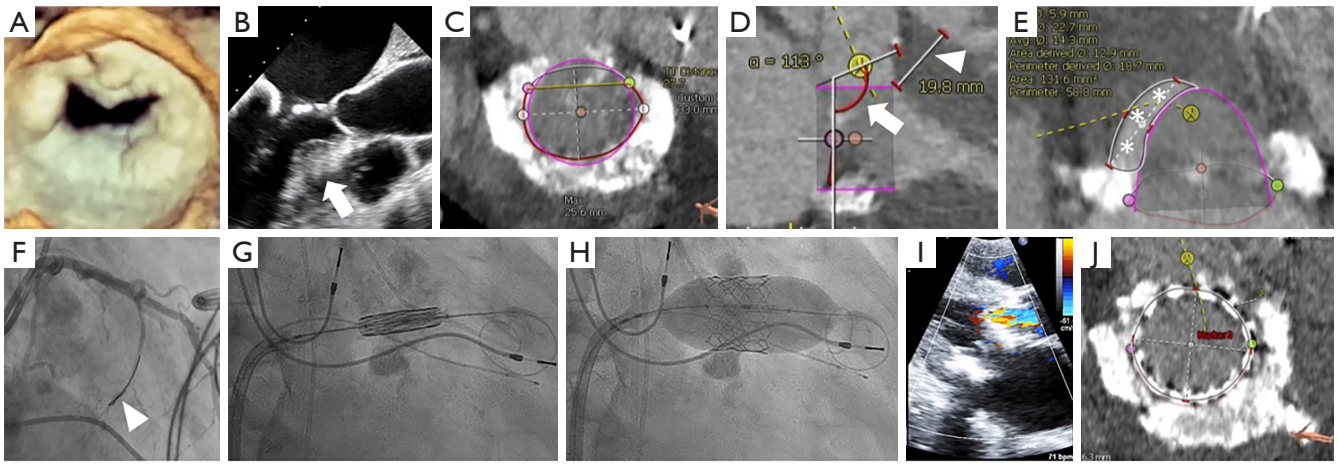

Figure 3 A case of transcatheter ViMAC using SAPIEN 3. An 85-year-old female with severe MS and moderate MR due to MAC. TEE (A) demonstrated a mean transmitral gradient of 13 mmHg and a thickened interventricular septum measuring 1.6 cm, with a bulge into the LVOT (B). CT showed a mitral annulus with maximal and minimal diameters of 33 and 25.6 mm, respectively, an area of 670 mm^2, and a perimeter of 94 mm (C). The aortomitral angle was 113° (D, white arrow), and the septal thickness was 19.8 mm (D, white arrowheads). The predicted neo-LVOT area was 131.6 mm^2 (E, asterisks). The MAC score was 9. ViMAC was considered feasible but associated with a high risk of LVOT obstruction. To mitigate this risk, a combined approach using alcohol septal ablation (F, white arrow) and transseptal ViMAC with a 29 mm SAPIEN 3 valve was performed (G,H). The patient's symptoms improved immediately following the procedure. At 30-day follow-up, TTE showed no MR, a mean transmitral gradient of 4 mmHg, and a peak LVOT gradient of 26 mmHg (I). CT confirmed a well-expanded SAPIEN 3 valve (J). CT, computed tomography; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; MR, mitral regurgitation; MS, mitral stenosis; TEE, transesophageal echocardiography; TTE, transthoracic echocardiography; ViMAC, valve-in-mitral annular calcification.

shorter hospital stays and improved 1-year survival. Given the TVT registry data are site reported, reporting bias may make the ViMAC outcomes more favorable than reality.

Transfemoral approach with SAPIEN M3 transcatheter heart valve

The SAPIEN M3 valve (Edwards Lifesciences LLC, USA) is a balloon-expandable transcatheter heart valve composed of three bovine pericardial leaflets mounted on a cobalt-chromium frame with a polyethylene terephthalate (PET) fabric inner skirt, and a full-frame outer skirt. The SAPIEN M3 dock encircles the native anterior and posterior mitral leaflets, applying inward force to the mitral apparatus that pulls the leaflets and chordae toward the dock center, thereby approximating the papillary muscles and creating a secure landing zone for valve implantation. The SAPIEN M3 valve is then positioned within the dock and deployed via balloon inflation under rapid pacing.

The ENCIRCLE trial (26), the first prospective, multicenter, single-arm, pivotal clinical trial evaluating outcomes of a percutaneous transseptal TMVR using the SAPIEN M3 system, was published recently. Among 1,171 patients screened for eligibility, 299 patients were treated. Seventy-three patients (24%) had MAC identified on echocardiography, all graded as mild to moderate on cardiac CT with a MAC score ≤4. Device implantation was completed in 287 patients (96%). No patients required a second valve or conversion to surgery, and there were no intraprocedural deaths. Two in-hospital deaths (0.7%) occurred post-procedure. The 1-year Kaplan-Meier estimates for all-cause mortality and heart failure rehospitalization were 13.9% and 16.7%, respectively. At 1 year, 88% of patients were NYHA class I or II. MR was none or trace in 79% and mild in 16%, with a mean transmitral gradient of 5.5 mmHg. Major adverse events through 1 year included disabling stroke in 3.9% and valve thrombosis in 7%. There were no cases of clinically significant TMVR-related LVOT obstruction, and the rate of MV reintervention was 6.4%.

Hybrid transatrial approach

The hybrid transatrial approach involves surgical exposure via

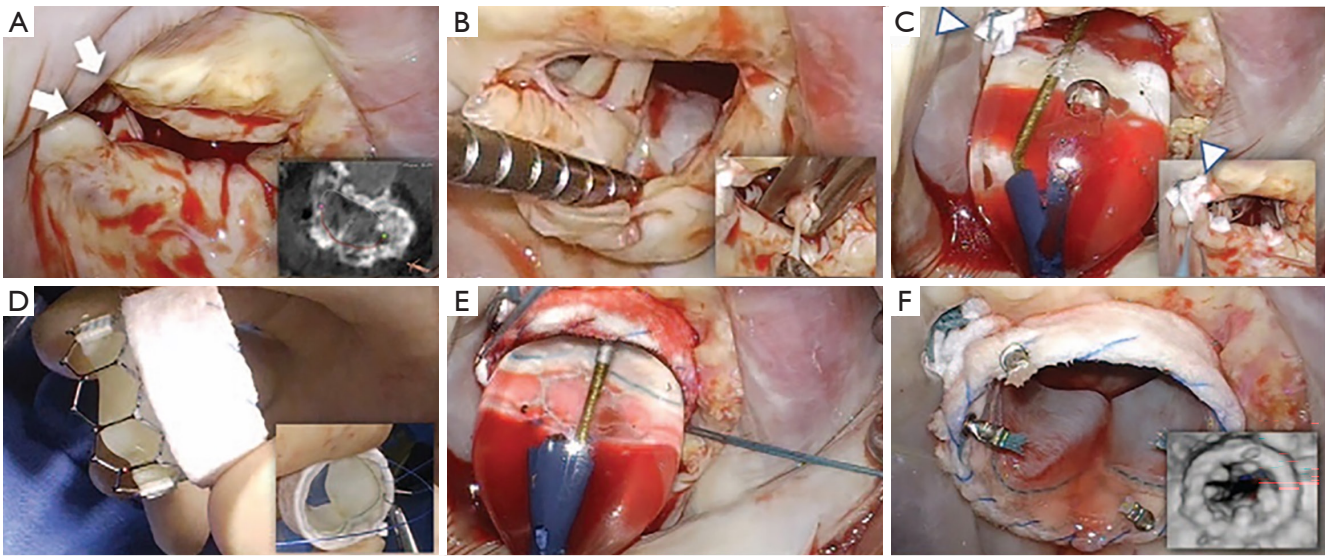

Figure 4 A case of hybrid transatrial TMVR. Hybrid TMVR in severe MAC. (A) Intraoperative surgeon's view of the calcified mitral valve—anterolateral commissure (white arrows) spared of severe MAC (PIP: computed tomography reconstruction of circumferential MAC); (B) partial resection of the anterior mitral leaflet from commissure to commissure with debulking of hypertrophic papillary muscle tips to increase intracavitary space (PIP); (C) plication of the anterolateral commissure (arrowheads) to circularize the orifice and initial prosthesis sizing following complete anterior leaflet flip (PIP); (D) a Teflon-felt cuff is fashioned and secured around the outer sealing skirt of the S3 prosthesis (see text for details); (E,F) the S3 is inflated under direct vision and secured *in situ* (PIP: 3D-Doppler reconstruction of the S3 in mid-systole showing no paravalvular leak). Reproduced with permission from El-Eshmawi *et al.* © 2020 Wolters Kluwer Health, Inc. MAC, mitral annular calcification; PIP, picture-in-picture; S3, SAPIEN 3; TMVR, transcatheter mitral valve replacement.

sternotomy or thoracotomy with the use of cardiopulmonary bypass to allow direct implantation of a transcatheter valve for MV replacement (27). This requires the patient to be a surgical candidate. A representative case is shown in *Figure 4*. Key advantages include the ability to perform concomitant cardiac procedures, such as coronary artery bypass grafting or tricuspid valve repair; resection of anterior mitral leaflet and/or septal myectomy to reduce the risk of LVOT obstruction; and reinforcement of the valve's outer skirt with a Teflon felt strip to enhance sealing, minimizing PVL, and prevent AV groove injury. Additional benefits include improved annular circularization through surgical plication of the commissures and suturing the valve inflow to the left atrial wall to prevent device migration or embolization.

Self-expanding valves

All self-expanding valves for TMVR are currently investigational, with the exception of Tendyne (Abbott Structural Heart, USA), which received CE mark approval in January 2020 and US Food and Drug Administration (FDA) approval in May 2025.

The Choice of Optimal Transcatheter Treatment for Mitral Insufficiency (CHOICE-MI) registry investigated patients with MR who were considered unsuitable for conventional therapies (surgery or TEER) and subsequently underwent screening for TMVR (28). Key findings were: TMVR was performed in 229 patients (30.7%) out of 746 screened, using 10 different investigational devices, with a screening failure rate of 69.3%; TMVR was performed via the transapical approach in 89.5% of cases and transseptal in 10.5%, achieving a technical success rate of 95.2%; procedural complications were low: mortality 1.8%, prosthesis malposition 3.7%, LVOT obstruction 3.2%, and device migration 2.3%; The 30-day all-cause and cardiovascular mortality were 9.9% and 8.7%, respectively; MR ≤1+ was achieved in 95.1% of patients at discharge and 95.2% at 1-year follow-up, with comparable outcomes observed in patients with moderate or severe MAC.

Transapical approach with Tendyne

Tendyne consists of an outer frame that conforms to the

Figure 5 Tendyne.

native mitral annulus and an inner frame housing a trileaflet porcine pericardial valve. It is deployed in an intra-annular position via a braided polyethylene tether attached to an epicardial pad, delivered through a 36F sheath via left lateral thoracotomy (*Figure 5*).

In an early study of the first 9 patients treated with Tendyne for MV disease due to severe MAC, there were no procedural deaths, with a technical success rate of 89%. One case of LVOT obstruction due to device malrotation was successfully managed with alcohol septal ablation (29). During a median follow-up of 12 months, there was one cardiac and one non-cardiac death, with no cases of prosthetic dysfunction. The mean transmitral gradient was 3.8±1.9 mmHg.

The TENDER registry (Tendyne European Experience) recently reported 1-year outcomes from 195 patients, including 20 with severe MAC (30). Technical success was achieved in 95% of cases. At 1 year, all-cause mortality and cardiovascular mortality were 28.6% and 16.9%, respectively, while MR was reduced to mild or less in 97.9% of patients. Among the 20 patients with severe MAC, the 30-day and 1-year all-cause mortality were 10.0% and 21.1%, respectively. Two patients required periprocedural device retrieval due to incomplete unfolding or migration.

The 3-year outcomes of the Tendyne Expanded Clinical Study were recently published (31). This study included 191 patients (mean age 74.1±8.0 years; 62.8% male; 70.2% in NYHA class III/IV; STS-PROM for surgical MVR: 7.7%±6.6%; secondary MR: 88.5%) who were enrolled between November 2014 and June 2020 across 39 global sites. Notably, patients with MAC were excluded. The procedural success rate was 96.9%, with no intraprocedural deaths and no conversions to open surgery. At 3-year follow-up, 70 patients had completed follow-up assessments. All-cause mortality was 51.3%, and cardiovascular mortality was 45.6%. Rates of heart failure hospitalization, disabling stroke, and major or greater bleeding were 35.1%, 4.7%, and 27.7%, respectively (fatal bleeding: 2.6%). MV reintervention occurred in 3.1%, PVL in 8.9%, endocarditis in 6.3%, and asymptomatic valve thrombus in 5.8%. Importantly, there was no structural valve deterioration, embolization, or device fracture. At 3 years, no MR was observed in 98.3% of patients with only one patient exhibiting mild MR. The mean transmitral gradient was 3.8±1.5 mmHg, and the LVOT gradient was 1.7±0.8 mmHg. NYHA class III/IV symptoms persisted in 19.4% of patients.

The SUMMIT trial (NCT03433274) is a prospective, controlled, multicenter clinical study evaluating the safety and effectiveness of Tendyne for symptomatic MR. It includes four cohorts: randomized, non-repairable MR, severe MAC, and severe MAC continued access protocol. The MAC cohort has been completed and submitted to the FDA, with regulatory approval granted in May 2025. Recently, the SUMMIT-MAC study was published, reporting outcomes in 103 patients with severe MAC and MR or MS who underwent TMVR with Tendyne. Technical success was achieved in 94.2% of cases. Thirty-day all-cause mortality was 6.8%, including two intraprocedural deaths (due to unrepaired apical bleeding), and five post-procedural deaths. At 1 year, all-cause mortality and heart failure hospitalization rates were 21% and 30.1%, respectively. Echocardiographic follow-up demonstrated none or trivial MR in 98.9% at 30 days and 91.4% at 1 year, and no MR grade ≥3+ at any time through 1 year. One patient required tether length adjustment via mini-thoracotomy for PVL on post-operative day 13; otherwise, the incidence of moderate (2+) PVL was 1.2% at 30 days and 2.9% at 1 year. The mean transmitral gradient at 1 year was 3.8±1.4 mmHg (32).

Transfemoral approach

Intrepid (Medtronic Inc., USA) was originally developed for transapical delivery but has since evolved to a 35F and now 29F transfemoral transseptal delivery system (*Figure 6*). The device comprises an outer fixation frame that engages the mitral annulus and leaflets, and an inner stent housing a trileaflet bovine pericardial valve. Early feasibility studies have demonstrated the safety and efficacy of transfemoral transseptal TMVR with Intrepid at 30 days (33) and 1 year (34).

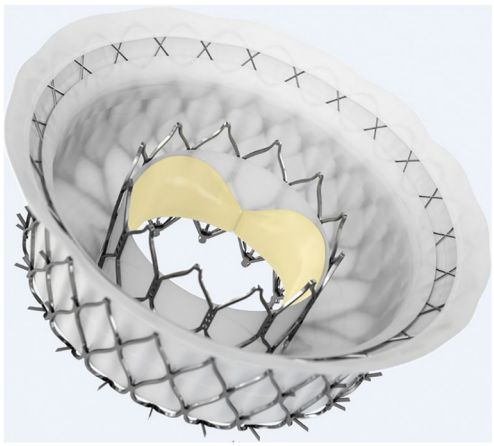

Figure 6 Interpid.

Figure 8 Cephea.

Figure 7 Alta.

The APOLLO trial (NCT03242642) is a global, prospective, non-randomized, interventional pre-market study evaluating TMVR using the Intrepid valve in patients with symptomatic moderate to severe or severe MR who are suboptimal candidates for TEER or surgery. The study includes two arms: the primary cohort and the MAC arm.

AltaValve (4C Medical Technologies, USA) features a self-expanding, spherical nitinol frame containing a supra-annular 27 mm trileaflet bovine pericardial valve (*Figure 7*). Its unique atrial-only anchoring mechanism, which deploys the large (50–95 mm) nitinol frame within the left atrium, aims to minimize risks of embolization, LVOT obstruction, and chordal interference. Initially introduced via a 34F transapical delivery system (35,36), it has since been adapted to a 29F transfemoral transseptal system. Because the AltaValve is not rigidly anchored to the native mitral annulus, it may offer particular advantages in patients with moderate or severe MAC. A recent study evaluated outcomes of TMVR with the AltaValve in six consecutive patients with severe MR and moderate or severe MAC (37). Of the six patients, five were treated as part of the AltaValve Early Feasibility Study, and one patient was treated under compassionate use considerations. Technical success was achieved in all patients. One patient died three days post-procedure due to complications related to the transapical access. Among the remaining five patients who were discharged, no deaths occurred through 3 months of follow-up. At 30 days, all patients were in NYHA class I/II. Echocardiographic assessment showed mild MR in one patient (20%), a mean transmitral gradient was 3.7± 1.4 mmHg, and the mean LVOT gradient was 1.9 mmHg. The ATLAS trial (A Transseptal Left Atrial System for Treatment of Mitral Regurgitation; NCT06465745) is a pivotal, prospective, single-arm, multicenter study evaluating the AltaValve device in patients with moderate to severe MAC (MAC cohort) as well as those without significant MAC (primary cohort). The trial is designed to support both CE mark certification and FDA approval.

Cephea (Abbott Structural Heart, USA) consists of an atrial disk, ventricular disk, and a central column housing a bovine pericardial trileaflet valve (*Figure 8*). The device anchors via axial compression across the mitral annulus, avoiding subvalvular structures. Its low frame height reduces the risk of LVOT obstruction. The valve is delivered via

transfemoral transseptal approach. A prior case report and case series have demonstrated favorable valve performance and procedural safety up to 6–7 months (38-40). The Cephea Early Feasibility Study (NCT05061004) is currently ongoing in the United States.

LVOT obstruction in TMVR

The risk of LVOT obstruction should be carefully evaluated preoperatively using cardiac CT and TEE. The neo-LVOT, formed between the basal interventricular septum and the anterior mitral leaflet displaced by the transcatheter valve, can be assessed using commercially available imaging software.

In a study of 194 patients undergoing TMVR with balloon-expandable valves (83.8%), Lotus (13.5%), and Direct Flow (2.7%), LVOT obstruction occurred in 13.4% overall, with higher incidence in ViMAC compared to MViR and MViV (54.1% *vs.* 8.0% *vs.* 1.9%, P<0.001). Patients who developed LVOT obstruction had significantly higher procedural mortality than those without (34.6% *vs.* 2.4%, P<0.001). A neo-LVOT area ≤1.7 cm^2 on CT predicted obstruction—defined as acute hemodynamic deterioration with a mean LVOT gradient ≥10 mmHg—with 96.2% sensitivity and 92.3% specificity (18). This value was obtained by planimetry at mid-to-late systole using cross-sectional CT images.

Another study evaluating multiphase CT analysis from the Intrepid Global Pilot Study identified several neo-LVOT thresholds predictive of obstruction at 30 days: 1.5 cm^2 at end-systole (40% cardiac phase) or multiphase averaging (10% to 40% in 10% increments); and 1.6 cm^2 at early systole (10% phase) (34). Neo-LVOT was measured at two key device locations: the widest point of the device, and the most ventricular portion. The smaller of the two values was used for each phase. For multiphase measurements, the minimum neo-LVOT area across all phases was averaged. Among 33 patients who were initially screen-failed on CT analysis, 18 (54.5%) would have met eligibility criteria if these thresholds had been applied. In the prospective cohort (6 patients approved using multiphase and 3 with early systolic criteria), none developed a peak LVOT gradient ≥30 mmHg at 30 days. These findings underscore that optimal neo-LVOT cutoff thresholds may vary by device type, and that the risk of LVOT obstruction differs across valve platforms.

In patients with an anticipated high risk of LVOT obstruction, prophylactic strategies should be considered. Alcohol septal ablation can be performed before TMVR, reducing septal bulging to enlarge the LVOT (41). For balloon-expandable valves, mitral leaflet laceration or modification techniques such as LAMPOON (Laceration of the Anterior Mitral leaflet to Prevent Outflow ObstructioN) (42,43), BATMAN (Balloon-Assisted Translocation of the Mitral Anterior Leaflet) (44-46), and CLEVE (Cleveland Valve Electrosurgery) (47,48) have been developed to prevent leaflet-mediated obstruction. Alternatively, surgical resection of the anterior mitral leaflet or septal myectomy can be performed during transatrial TMVR. In addition, transcatheter septal myotomy using the SESAME (Septal Scoring Along the Midline Endocardium) technique (49) has been proposed as a percutaneous option to relieve septal hypertrophy and expand the LVOT.

Leaflet modification strategies are limited with self-expanding TMVR, given the ventricular side is covered with a sealing skirt. Alcohol septal ablation or transcatheter septal myotomy would be necessary to improve the neo-LVOT clearance in these cases.

Future directions

The development of LVOT-friendly TMVR devices remains a critical need. Ideal future systems should provide secure annular anchoring with minimal ventricular protrusion, reducing the risk of LVOT obstruction. Lower-profile transfemoral transseptal delivery systems are essential to improve procedural safety and broaden patient eligibility. Additionally, more reliable and predictable leaflet modification techniques and dedicated low-profile devices should be developed to enhance procedural planning and outcomes. Given the high 5-year mortality associated with ViMAC TMVR with balloon-expandable valve (12), refined patient selection is paramount to avoid futile interventions and ensure clinical benefit.

Summary and conclusions

TMVI for MAC-associated MV disease has undergone significant evolution. However, to establish TMVR as a less invasive, reliable therapy for this high-risk population, continued research, technical refinement, and device innovation are imperative. Addressing the remaining challenges outlined in *Figure 9* will be key to advancing outcomes in this complex field.

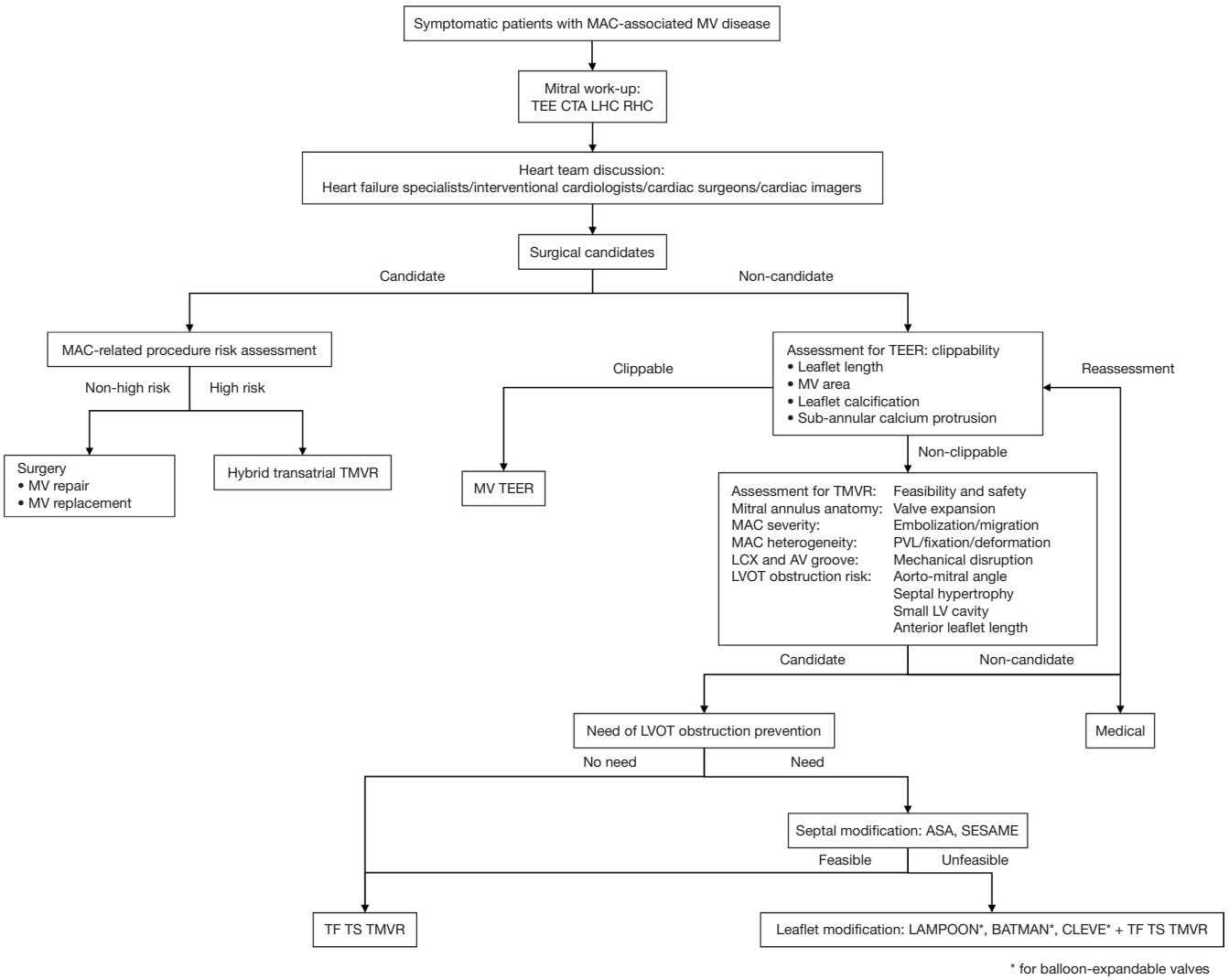

Figure 9 Decision making algorithm for MAC-associated MV disease. ASA, alcohol septal ablation; AV, atrioventricular; BATMAN, balloon-assisted translocation of the mitral anterior leaflet; CTA, computed tomography angiography; LAMPOOM, laceration of the anterior mitral leaflet to prevent outflow obstruction; LCX, left circumflex artery; LHC, left heart catheterization; LV, left ventricle; LVOT, left ventricular outflow tract; MAC, mitral annular calcification; MV, mitral valve; PVL, paravalvular leak; RHC, right heart catheterization; SESAME, septal scoring along the midline endocardium; TEE, transesophageal echocardiography; TEER, transcatheter edge-to-edge repair; TF, transfemoral; TMVR, transcatheter mitral valve replacement; TS, transseptal.

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Footnote

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publications committee member, RESTORE study steering committee member, APOLLO trial screening committee member and IMPACT MR steering committee member for Medtronic, has received speaker's honoraria and served as a physician proctor, consultant, advisory board member and TRILUMINATE trial anatomic eligibility and publications committee member for Abbott Structural Heart, has served as an advisory board member for Boston Scientific, a consultant and physician screening committee member for Shockwave Medical, a consultant for Philips and Edwards Lifesciences, Peija Medical and Shenqi Medical Technology, and has received speaker's honoraria from Siemens Healthineers. The other authors have no conflicts of interest to declare.

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