Transcatheter Mitral Valve Repair: For Whom Is It Still Better Than Replacement?

Current transcatheter options for mitral valve intervention.

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Mitral regurgitation (MR) is the most common valvular heart disease in the world. The natural history of MR in the modern era has been well documented and is not benign. In patients with primary MR, nearly 30% will develop atrial fibrillation, 50% will develop heart failure, and nearly 90% of patients on medical therapy will die or need surgery at the end of 8 years.[1] The prognosis of ischemic secondary MR is even more grave, with an estimated 5-year mortality of 60%.[2] Despite poor prognosis, it has been estimated that nearly 50% of patients with symptomatic severe MR are not referred for surgery because of older age and left ventricular (LV) dysfunction that results in high surgical risk.[3] Transcatheter intervention of the mitral valve (MV), either repair or replacement, offers a glimmer of hope to a large subset of patients who are either not treated or denied surgery due to high surgical risk. This article discusses the various mitral transcatheter repair options that are currently available and the decisions involved in choosing transcatheter repair over replacement.

REPAIR VERSUS REPLACEMENT

The long-term outcomes after surgical MV repair for degenerative MR (primary MR) compared with MV replacement has been well documented through multiple studies, all of which consistently show lower operative mortality, improved survival, better preservation of LV function, shorter postoperative hospital stays, lower total costs, and fewer valve-related complications, including thromboembolism, anticoagulation-related bleeding events, and late prosthetic dysfunction.[4] Hence, whenever anatomically feasible, MV repair is preferred over replacement because these advantages become even more apparent with longer-term follow-up.[5]

The preservation of the submitral apparatus leads to preservation of LV geometry and overall systolic performance, especially in functional MR.[6] Moreover, there are data showing a survival advantage of repair over replacement, even in those patients who undergo redo surgery for failed initial repair.[7] Despite the evidence for surgical correction for primary MR, nearly 50% of patients are not referred for surgery due to advanced age, poor LV function, and comorbidities contributing to high/prohibitive surgical risk. In older patients, surgical treatment of MR is associated with high perioperative mortality (7% for repair vs 13% for replacement) and poor long-term survival, with an uncertain benefit on quality of life.[8]

Surgical repair of functional MR (FMR) has less favorable outcomes, with increased perioperative mortality and MR recurrence rates as high as 60% at 2 years.[9] Preprocedure echocardiographic parameters that predict MV repair failure include a mitral annular diameter > 3.7 cm (sensitivity, 84%; specificity, 76%), a tenting area > 1.6 cm^2 (sensitivity, 80%; specificity, 54%), and a preoperative grade of MR > 3.5 (sensitivity, 42%; specificity, 81%).[10] Data from the Cardiothoracic Surgical Trials Network comparing MV repair and chord-sparing replacement in ischemic MR has shown similar 2-year mortality rates (19% vs 23%) and much higher recurrence rates of severe MR in the repair

group (58.8% vs 3.8%), resulting in more heart failure–related adverse events and cardiovascular admissions.[11]

Transcatheter therapy (either repair or replacement) offers a safe and effective treatment modality in high-risk patients with MR who are untreated or at high surgical risk, with uncertain clinical benefit with surgery.

Over the past decade, several transcatheter mitral valve (TMV) repair technologies have been adapted from different surgical techniques to target different components of the MV apparatus depending on the predominant pathology of MR. The armamentarium for transcatheter mitral repair is rapidly expanding, with up to five devices already approved for use in Europe: MitraClip (Abbott), Pascal (Edwards Lifesciences), the DS1000 device (NeoChord, Inc.), Carillon (Cardiac Dimensions, Inc.), and Cardioband (Edwards Lifesciences). In current clinical practice, transcatheter edge-to-edge therapy with MitraClip is the most commonly performed procedure, with up to 100,000 patients treated worldwide[12] with high success, good durable results in MR reduction, and excellent safety profile.[13]

TMV replacement offers theoretical advantages over MV repair. By replacing the entire valve itself, it offers a more predictable and complete resolution in MR severity, especially in anatomies unsuitable for repair. The development of transcatheter aortic valve implantation has been a revolution in the field of interventional cardiology and likewise, the development of a similar MV replacement device to treat all pathologies seems only logical. However, unlike the aortic valve, the MV anatomy is complex and heterogeneous, and the development of a TMV replacement device to target all anatomic variations and patient risk profiles is difficult and presents several challenges. To ensure a fully percutaneous approach, the development of a highly flexible transseptal delivery catheter is necessary to implant a relatively large device. LV outflow tract (LVOT) obstruction is the most dreaded complication of TMV replacement, occurring in up to 40% of valve-in–mitral annular calcification, 5% of valve-in-ring, and 2% of valve-in-valve cases,[14] and with 62% in-hospital mortality.[15] Other challenges include achieving adequate anchoring and sealing to prevent paravalvular leak/antegrade competitive flow, concerns with durability, valve thrombosis, and structural degeneration over time.

Due to the current lack of a "universal device" to treat all anatomies without all the inherent risks involved, a repair strategy is currently preferred in patients with suitable anatomy in light of its excellent safety profile. Moreover, the role of TMV replacement will need to be studied further because surgical MV repair has excellent results in patients with severe primary MR,[16] and it is unknown whether transcatheter replacement will result in any changes in outcome in patients with severe secondary MR.

TABLE 1. ANATOMIC FACTORS TO DETERMINE TRANSCATHETER REPAIR VERSUS REPLACEMENT

Consider Repair	Consider Replacement
A2-P2 defect	Severe calcification at the grasping zone
Mitral valve orifice area > 3.5 cm^2	Leaflet perforation
Mobile posterior leaflet length > 6 mm	Calcific mitral stenosis, MG > 5 mm Hg
Degenerative MR	Rheumatic valve disease
Poor LV function (EF < 35%)	Multiple MR jets
Contraindications to anticoagulation	Ischemic MR with severe leaflet tethering

Abbreviations: EF, ejection fraction; LV, left ventricular; MG, mean gradient; MR, mitral regurgitation.

Table 1 summarizes the anatomic characteristics that are taken into consideration to determine suitability of transcatheter repair versus replacement.

TRANSCATHETER REPAIR OPTIONS

The MV apparatus comprises the mitral annulus, leaflets, chordae tendinae, papillary muscles, subjacent LV myocardium, and posterior left atrial wall (Figure 1). Anatomic distortion of any of these components individually or in combination can cause the valve to malfunction and leak. Broadly speaking, MR is classified as "primary or degenerative" (related to anatomic abnormalities in valve leaflets and/or chordae tendinae) and "secondary or functional" (usually related to tethering of MV leaflets due to annular dilation and LV regional/global dysfunction). Multiple transcatheter devices have been developed to target or treat different components of the mitral apparatus or replace the valve.

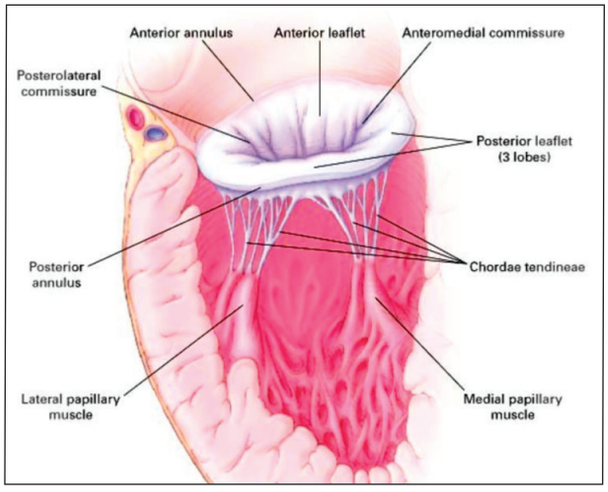


Figure 1. MV apparatus.

Transcatheter Edge-to-Edge Repair

Inspiration for transcatheter edge-to-edge repair was derived from the Alfieri surgical stitch, a procedure that was designed to reduce MR by placing a stitch joining the free edge of the anterior and posterior MV leaflets, thus resulting in a double orifice MV.[17] The MitraClip is currently the only percutaneous leaflet repair system with both FDA and CE Mark approval. The Pascal repair system recently received CE Mark approval, and a pivotal trial aimed at obtaining FDA approval is currently underway.

MitraClip. The MitraClip is a cobalt chromium clip with two arms covered with polypropylene fabric. It works by grasping and approximating the edges of the anterior and posterior leaflet segments in patients with severe MR (Figure 2). The first iteration of the device was introduced in 2002, followed by a long latent period before the MitraClip NT was introduced in 2016. Subsequently, the MitraClip NTR and XTR systems were introduced in 2018 and included longer clip arms with the potential to treat wider flail gaps and more challenging anatomies. The latest iteration of the device is the MitraClip G4 system, which was released in the latter half of 2019. It offers multiple design advantages to treat wider and more challenging anatomies. The clip is offered in four sizes (NT, NTW, XT, and XTW). The NT clip has arms that measure 9 mm and an effective gripper length of 6 mm. The XT clip is longer, measuring 12 mm with an effective gripper length of 9 mm. The wide version of the clips (NTW/XTW), measures 6 mm in the center and is 50% wider than the 4-mm center of the normal clip. This has the potential advantage of grasping more leaflet tissue, which allows for a wider area of apposition between the anterior and posterior leaflets, allowing a more effective reduction in MR. This reduces the number of clips used and reduces the force applied per unit area, possibly reducing the risk of leaflet tear. However, there is a theoretical risk of inducing higher transmitral gradients with the wide version of the clip, which needs to be assessed in large-scale studies. The MitraClip G4 system permits controlled gripper actuation—the grippers can be dropped independently to capture the leaflets one at a time. This ability has the advantage of treating large coaptation gaps where simultaneous grasping of the leaflets is challenging or impossible. It also offers the option of optimizing leaflet insertion by raising one gripper and repositioning the clip to ensure maximum leaflet capture. In addition to a streamlined and faster system preparation (40% reduction), the steerable guide catheter has been redesigned to allow improved left atrial pressure monitoring during the procedure.

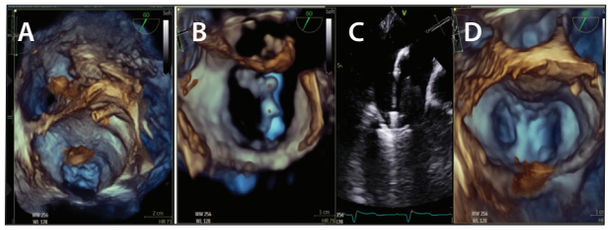


Figure 2. Transcatheter edge-to-edge repair of the MV. Steerable guide catheter in the left atrium (A), MitraClip (B), clip positioned at A2-P2 below the leaflets for grasp (C), grippers being dropped and leaflets grasped (D).

To facilitate safe positioning of the clip, preprocedural evaluation of certain anatomic criteria were recommended initially based on the EVEREST criteria.[18] The presence of a jet outside A2-P2, a large/wide jet, a commissural jet, a small valve, calcification at the landing zone, or the presence of a cleft are used to define complex cases as opposed to straightforward cases. Despite the initial stringent criteria, wider clinical experience and newer iterations of the device have allowed for successful treatment of complex anatomies with durable results.[19,20] The newer features of the MitraClip G4 system should allow for treatment of complex anatomies with potentially better results. Based on the leaflet length, MV area, jet width, and jet location (commissural or noncommissural), one can decide which of the four new clips to use (Table 2).

An initial postmarket analysis of 224 procedures across 24 sites in the United States and Canada with

TABLE 2. ANATOMIC CHARACTERISTICS THAT HELP DETERMINE CLIP CHOICE WITH THE MITRACLIP G4

Anatomic Characteristics		G4 NT	G4 NTW	G4 XT	G4 XTW
Length of mobile leaflet in grasping zone	< 9 mm	✓	✓		
	> 9 mm			✓	✓
Jet width	Wide jet		✓		✓
Commissural jet	–	✓			
Mitral valve area	Small valve < 3.5 cm^2	✓			
	Large valve > 3.5 cm^2		✓	✓	✓

TABLE 3. SUMMARY OF MITRA-FR AND COAPT TRIALS

	MITRA-FR[22,23]	COAPT[24-26]
Study design	Prospective, randomized	Prospective, randomized
Study groups	MitraClip (n = 152) vs medical therapy (n = 152)	MitraClip (n = 302) vs medical therapy (n = 312)
MR severity for inclusion	European guidelines: EROA > 20 mm^2 / RV > 30 mL	Multitiered approach[26]: Tier 1: EROA ≥ 30 mm^2 or PV flow reversal Tier 2: EROA 20-30 mm^2 + one of the following: RV ≥ 45 mL/beat, RF ≥ 40%, or VC width > 50 mm^2 Tier 3: EROA not measured or < 20 mm^2 with two of the following: RV ≥ 45 mL/beat, RF ≥ 40%, VC width > 50 mm^2, PISAr > 90 mm^2, large holosystolic jet around left atrium ≥ 6 cm, or peak E velocity ≥ 150 cm cm/s
Guideline-directed medical therapy	Variable as per real-world practice	Stable maximal tolerated doses adjudicated by central committee
Mean age	70 ± 10 years	72 ± 11 years
NYHA III or IV	67.1%	60.8%
Mean EROA	31 ± 10 mm^2	41 ± 15 mm^2
LVEF	33% ± 7%	31% ± 9%
LV end-diastolic volume index	135 ± 35 mL/m^2	101 ± 34 mL/m^2
Procedural success	96%	98%
Procedural complications	14.6%	8.5%
Postprocedural MR > +2 (immediately postprocedure and 1-year postprocedure)	9% and 17%	5% and 5%
1-year mortality	MitraClip: 24.2% Medical therapy: 22.4%	MitraClip: 19.1% Medical therapy: 23.2% *P* < .001
2- year mortality	MitraClip: 23.1% Medical therapy: 22.8%	MitraClip: 29.1% Medical therapy: 46.1% *P* < .001 (primary outcome)
1-year heart failure hospitalization	MitraClip: 48.7% Medical therapy:47.4%	MitraClip: 35.8% Medical therapy: 67.9% *P* < .001 (primary outcome)
2-year heart failure hospitalization	MitraClip: 55.9% Medical therapy: 62.3%	MitraClip: 35.8% Medical therapy: 67.9% *P* < .001
1-year mortality or heart failure hospitalization	MitraClip: 54.6% Medical therapy: 51.3% *P* = .53 (primary outcome)	MitraClip: 33.9% Medical therapy: 46.5% *P* < .001
2-year mortality or heart failure hospitalization	MitraClip: 63.8% Medical therapy: 65.4% HR: 1.01 (0.77-1.34)	MitraClip: 45.7% Medical therapy: 67.9% *P* < .001

Abbreviations: EROA, effective regurgitant orifice area; HR, hazard ratio; LV, left ventricular; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; MR, mitral regurgitation; PISAr, proximal isovelocity surface area radius; PV, pulmonary vein; RF, regurgitant fraction; RV, regurgitant volume; VC, vena contracta.

the new MitraClip G4 system has shown that the NTW was the most widely used clip in 47% of cases, followed by the XTW (25%), NT (23%), and XT(5%) systems.[21] Nearly half the cases were primary MR (49%), followed by FMR in 42% of cases. The perceived anatomic complexity for MitraClip according to physician perception was determined—nearly two-thirds of cases were believed to be of moderate anatomic difficulty, 20% were extremely difficult, and the remaining 13% were easy. Further large-scale studies are needed to determine clinical outcome and further refine clip selection according to anatomic characteristics.

The EVEREST II study was the first randomized trial to examine the MitraClip system in 279 patients with moderate-to-severe or severe MR, comparing percutaneous edge-to-edge therapy to conventional surgery in a 2:1 ratio; 74% of the patients had primary MR, whereas the remaining had secondary MR. The MitraClip arm demonstrated superior safety, with similar improvements in clinical outcomes. However, it was less effective at reducing MR compared with surgery at 1 year. The 5-year results found the composite endpoint (freedom from death, MV surgery, reintervention, and moderate-to-severe MR) in the treated population was 44.2% versus 64.3% in the percutaneous repair and surgical groups, respectively (P = .01), driven primarily by more MR (MR, 3+ or 4+; 12.3% vs 1.8%; P = .02) and more subsequent mitral surgery (27.9% vs 8.9%; P = .003) in the percutaneous arm. After percutaneous repair, 78% of surgeries occurred within the first 6 months; however, beyond 6 months, the rates of surgery and moderate-to-severe MR were comparable between groups, suggesting that if an excellent result is achieved with percutaneous therapy and sustained beyond 6 months, it is very likely to be durable and comparable to surgery.[13]

The MITRA-FR and COAPT trials both targeted patients with FMR using the same device but had diametrically opposite results, with MITRA-FR being neutral and COAPT being positive for the endpoints of heart failure hospitalization and mortality (Table 3).[22-26] The differences in outcomes have been explained by a number of factors. First, the definition of severe MR was different in the American and European guidelines (effective regurgitant orifice area [EROA] ≥ 40 mm^2 vs 20 mm^2, respectively), the indexed LV volumes were smaller in COAPT compared with MITRA-FR (101 ± 34 mL/m^2 vs 135 ± 35 mL/m^2), and the COAPT trial enforced a strict and aggressive medical therapy overseen by a central screening committee. Altogether, the patients in COAPT had worse MR with relatively more preserved and smaller left ventricles, representing a group of patients that benefit most from percutaneous edge-to-edge repair. To put it into perspective, these well-chosen, well-treated patients represent perhaps 5% of the heart failure population.

In a recent paper, Grayburn et al proposed a new framework to define secondary MR as proportionate or disproportionate to the degree of LV dilatation. This paper elegantly demonstrates how EROA is related to end-diastolic volume (EDV) and LV ejection fraction (LVEF). Using this model, in patients with reduced LVEF (−30%) and LV dilation (LVEDV, 200-250 mL), an EROA of 20 mm^2 is common and reflects only a moderate degree of MR, rather than severe.[27]

In a subgroup post hoc analysis of the COAPT trial, the COAPT patients were divided into six subgroups based on the EROA (30, > 30-40, and > 40 mm^2) and LVEDV index (96 mL/m^2 or greater than the median of 96 mL/m^2). Disproportionate MR was identified if the EROA indexed to LVEDV was > 0.14. After 1 year of follow-up among the five subgroups of patients in COAPT with disproportionate MR, transcatheter MV repair was accompanied by a decrease in the risk of all-cause mortality and hospitalization for heart failure. In contrast, in the subgroup that had proportionate MR (EROA < 30 mm^2 and EROA/EDV < 0.14), the hazard ratio for the effect of transcatheter MV repair was close to 1; this result is similar to that seen in the MITRA-FR trial. Essentially, when the EROA indexed to LVEDV in a COAPT subgroup was similar to that seen in the MITRA-FR trial, the efficacy of MV repair in the COAPT subgroup was also similar to that seen in MITRA-FR (Figure 3).[28] This logical framework helps to refine patient selection for intervention but is

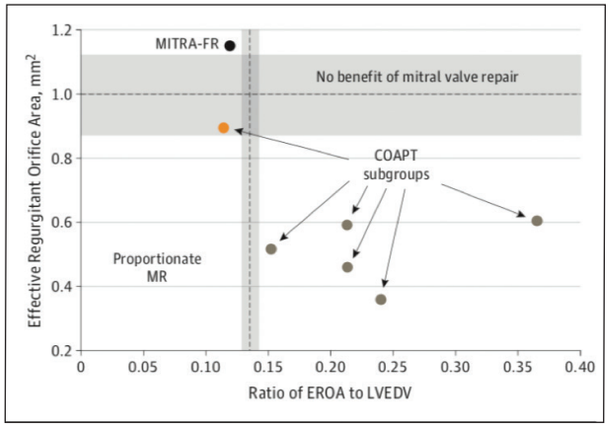


Figure 3. Ratio of EROA to LVEDV to the magnitude of the effect of transcatheter MV repair in the COAPT subgroups and the MITRA-FR trial. Reproduced with permission from Grayburn et al, JAMA Cardiol. doi:10.1001/jamacardio.2019.5971

hypothesis-generating and requires further validation in prospective large-scale studies.

COAPT and MITRA-FR are two important trials that looked at the role of MitraClip in FMR in two different populations. Taken together, the data help define a population subset that benefits from MitraClip as opposed to those that may not. Further ongoing trials Reshape-HF2 (NCT02444338) and MATTERHORN (NCT02371512) will potentially shed more light and further help refine patient selection for transcatheter edge-to-edge therapy for FMR in the future.

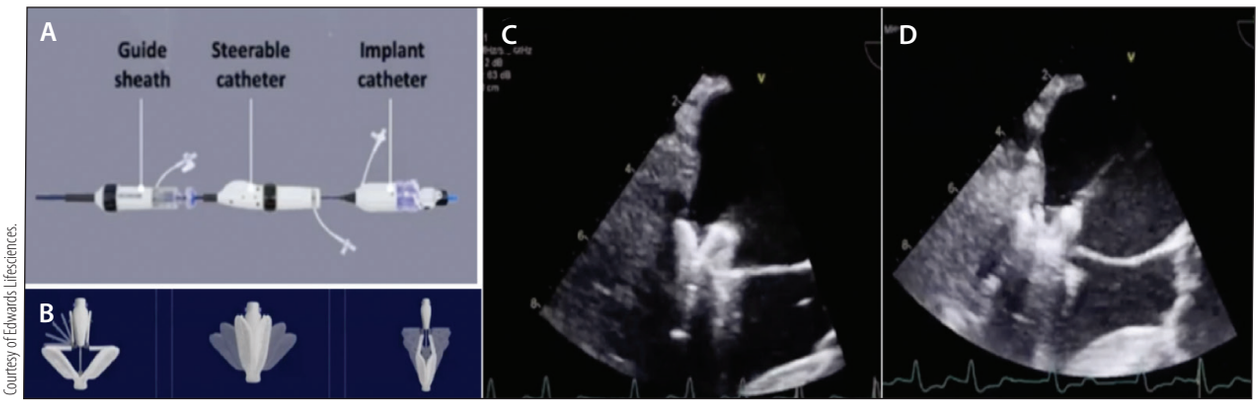
Pascal repair system. The Edwards Pascal transcatheter valve repair system also works on the principle of leaflet repair but has some additional design features. The Pascal implant has a 10-mm central spacer designed to reduce the tension on the leaflets and fill the regurgitant orifice area. The spring-loaded paddles and clasps, which can be operated either simultaneously or independently to facilitate leaflet capture in complex anatomies, are wide and allow distribution of load across the surface area of the inserted leaflets (Figure 4). The flexible delivery system allows navigation in three planes, and the Pascal device can be elongated, making it less prone to get stuck in the chords. A first-in-human feasibility experience of 23 compassionate-use cases has been described[29]; MR reduction to ≤ 2+ was achieved in 97% of the patients at discharge, without elevated gradients despite a larger device size.

The CLASP study was a multicenter, prospective trial of the Pascal system that recruited 62 patients with severe MR.[30] All clinical events were adjudicated by a central committee, and echocardiograms were assessed by a core lab. The mean age of patients was 76.5 years, with 52% in New York Heart Association (NYHA) functional class II; 56% of patients had FMR, 36% had degenerative/primary MR, and 8% had mixed MR etiology. Overall, 98% of patients achieved MR ≤ 2+, 86% had MR ≤ 1+, and 85% of the patients were NYHA class I/II at 6 months. The 1-year results of the CLASP trial were recently published by Webb et al.[31] At 1 year among the 109 patients treated (67% FMR, 33% degenerative/primary MR), Kaplan-Meier survival was 92% (89% FMR; 96% degenerative/primary MR) with 88% freedom from heart failure hospitalization (80% FMR; 100% degenerative/primary MR). MR was ≤ 1+ in 82% of patients (79% FMR; 86% degenerative/primary MR) and ≤ 2+ in 100% of patients, 88% were NYHA class I/II, and Kansas City Cardiomyopathy Questionnaire score improved 14 points (all $P < .001$).

Based on these promising results, the Pascal system gained CE Mark approval in early 2019. The pivotal CLASP IID/IIF randomized noninferiority trial is currently enrolling and will compare the efficacy and safety of Pascal versus MitraClip in patients with significant degenerative/primary MR or FMR.

Annuloplasty Devices

Annular dilatation is an important component driving FMR. Cardiac surgeons routinely use undersized rings during MV repair, which help reduce leaflet stress and stabilize the repair process. Drawing from this concept, various transcatheter devices have been developed to reduce annular dimensions. Though conceptually similar to surgery, it should be noted that the tissue forces that act to reduce annular dimensions and its implications are not well studied. In surgery, the surgeons bring the anatomy to the undersized ring, whereas percutaneous devices do the opposite, cinching the band together with the anatomy. Broadly speaking, percutaneous annular devices can be classified as direct or indirect

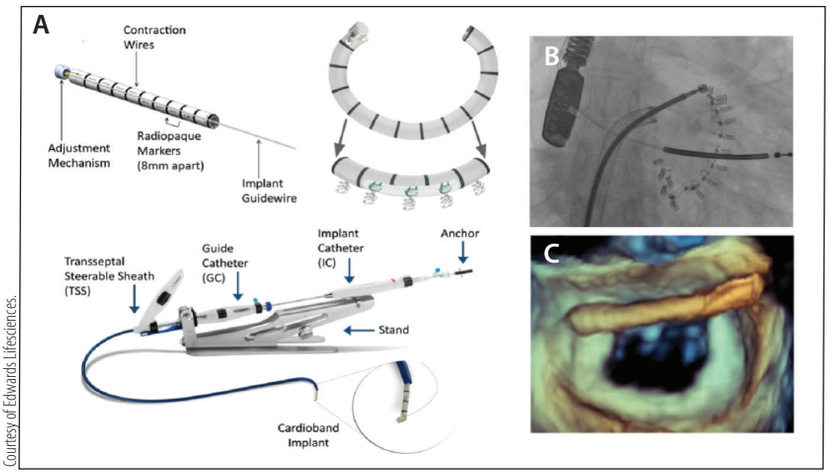


Courtesy of Edwards Lifesciences.

Figure 4. The delivery system of Pascal has a 22-F guide sheath and a steerable implant catheter that allows maneuvering in three independent planes (A). The device has two clasps and a central spacer (B). Demonstration of independent clasping of the anterior and posterior leaflets (C).

annuloplasty devices. Direct annuloplasty devices such as the Cardioband repair system and the Millipede Iris system (Boston Scientific Corporation) involve direct placement of anchors in the mitral annulus, with cinching to reduce annular dimensions. Indirect annuloplasty devices use the coronary sinus that runs behind the posterior mitral annulus to achieve annular reduction.

Cardioband repair system. The Cardioband transcatheter mitral repair system delivers direct anchors around the mitral annulus to connect the annuloplasty band, which is then contracted down sequentially in a stepwise manner, assessing reduction in MR in real time by echocardiography (Figure 5). The Cardioband repair system reduces the septolateral diameter and increases the coaptation zone between the anterior and posterior leaflets. The largest study of 60 patients with FMR treated with the Cardioband system was published in 2019. Early results raised concerns with the device design that had to be modified halfway through the study. Procedural success was achieved in 68% of cases according to Mitral Valve Academic Research Consortium criteria, and 60% of patients had ≤ 2+ MR at 1 year.[32] NYHA functional class and quality of life indices improved at 1 year compared to baseline in most patients. Further impetus to assess outcomes has been limited by the sometimes challenging procedural imaging and relatively modest results compared with other available therapies, resulting in the pivotal ACTIVE trial being placed on hold. Despite this, annuloplasty may still find a place in selected patients with "atriogenic" severe MR due to pure annular dilatation without leaflet tethering. Further studies are needed in this patient subgroup to assess outcomes and durability of repair.



Courtesy of Edwards Lifesciences.

Figure 5. Cardioband direct annuloplasty and delivery system (A). Fluoroscopic (B) and echocardiographic (C) appearance of Cardioband implantation.

Millipede Iris. The Millipede Iris annuloplasty ring is a semirigid, complete ring made of nitinol. Eight helical stainless-steel anchors are preattached to the base of the ring; the anchors can rotate independently and attach directly to the mitral annulus. If the operator is not satisfied with the initial placement, each anchor can be retracted/"unscrewed," then moved and redeployed. The initial clinical experience of seven patients with FMR and annular dilatation treated with the Millipede system was reported by Rogers et al.[33] The initial four patients had the ring implanted surgically, and the other three had the system delivered by the percutaneous transseptal approach. There was no procedural death or myocardial infarction. The mitral septal-lateral (SL) diameter was reduced from 38 ± 4.1 mm to 25.9 ± 4.9 mm at 30 days (31.8% SL reduction, n = 7). MR was reduced from baseline 3+ or 4+ to 0 or 1+ in all patients at 30 days. There were improvements in NYHA class, and there was a decrease in diastolic LV volumes from 182.4 ± 54.3 mL to 115.3 ± 98.8 mL at 30 days (36.8% reduction). Based on these initial positive findings, ongoing clinical trials (including an early feasibility trial) are underway to further evaluate the safety and efficacy of the Iris ring.

Carillon Mitral Contour System. The Carillon mitral contour system is an indirect annuloplasty device composed of two self-expanding nitinol anchors with a connecting curvilinear wire. It is positioned via the transjugular route with its distal anchor within the great cardiac vein and the proximal anchor at the coronary sinus ostium. As a nitinol-based device, it plicates the tissue next to the MV annulus, reducing mitral annular dilation and degree of MR by bringing the anterior and posterior leaflets closer. As with all annuloplasty devices, potential compression/kinking of the left circumflex artery is a potential complication. The device is recapturable, repositionable, and available in multiple sizes. Initial studies (AMADEUS and TITAN) with the earlier-generation device showed good improvement in MR reduction, quality of life, NYHA functional class, and evidence of reverse LV remodeling.[34,35] However, in 25% of cases in the TITAN trial, asymptomatic wire fracture was seen at the level of the proximal anchor where stresses were high.[35] This led to a newer device iteration to reduce strain at the proximal anchor, which was tested in a prospective, single-arm, multinational, safety study (TITAN II). TITAN II showed clinical

and echocardiographic benefits similar to those seen in TITAN, with a reduction in MR and mitral annular dimension and an improvement in NYHA functional class with improved safety.[36] The safety and efficacy of the device was then evaluated in a multicenter, randomized, sham-control trial (REDUCE FMR).[37] Patients with FMR and LVEF < 50% were randomized in a 3:1 fashion to device (n = 87) versus sham (n = 33) groups. In the treatment group, 73 of 87 (84%) patients had the device implanted. The primary endpoint was met, with a statistically significant reduction in MR volume in the treatment group compared with the control group (decrease of 7.1 mL/beat [95% CI, −11.7 to −2.5] vs an increase of 3.3 mL/beat [95% CI, −6 to 12.6], respectively; *P* = .049). Patients in the treatment group had a significant improvement in NYHA functional class at 12 months compared with their baseline measurements (*P* = .002), whereas patients allocated to the control group did not (*P* = .75). The pivotal CARILLON trial will further assess the impact of the device on clinical outcomes in patients with FMR.

CHORDAL REPLACEMENT DEVICES

Several transcatheter chordal replacement devices are being developed and studied, including the NeoChord DS1000 device, Harpoon MV repair system (Edwards Lifesciences), MitralStitch (Hangzhou Valgen Medtech Co., Ltd), ChordArt (Coremedic), V-Chordal adjustable artificial chordae system (Valtech), Pipeline (Gore & Associates), and CardioMech (CardioMech AS). All these devices deliver new artificial chordae to the MV for degenerative MR via a surgical approach. Currently, there are no transseptal/transfemoral devices available, although ChordArt is currently working on the development of a fully percutaneous transfemoral delivery system.

The NeoChord DS1000 device was the first transapical chordal implantation device available for clinical use in Europe. It is implanted transapically via left lateral thoracotomy under general anesthesia. CE Mark approval was gained in December 2012 after the results of the TACT trial.[38] It is currently under investigation in the United States, where it is the RECHORD investigational device exemption trial is ongoing and will compare surgical MV repair with NeoChord MV repair.

The Harpoon MV repair system is a sheeted 10-F device developed for transapical implantation of an expanded polytetrafluoroethylene chord that is fixed on the MV leaflet using a preformed double-helix coil knot. It received CE Mark in 2017 but is not yet commercially available. The prospective, nonrandomized, multicenter TRACER trial was conducted to test the safety and efficacy of the device. The trial included 30 patients from six different European centers with isolated P2 prolaspe and severe MR. Procedural success was achieved in 93% of cases, with two patients requiring conversion to open surgery. At 6-month follow-up, 76% of patients had mild or less MR, 7% moderate MR, and 7% severe MR; three (10%) patients underwent conventional reoperation for severe MR recurrence.[39]

COMBINED TRANSCATHETER MITRAL REPAIR

Surgical mitral repair typically combines annuloplasty with leaflet repair to achieve durable MR reduction. Similarly, transcatheter direct and indirect mitral annuloplasty has been combined with edge-to-edge repair or chordal implants in single-stage procedures for maximal MR reduction.[40,41] Although these early reports provide proof-of-concept, further studies are needed to determine the safety, efficacy, and cost-effectiveness of combination procedures.

SUMMARY

Transcatheter mitral leaflet repair is the most widely used percutaneous technique, with broad clinical experience and established safety and efficacy. Until the development of a TMV replacement device that is easy to deliver with negligible risk of LVOT obstruction and excellent safety profile to eliminate MR, in patients with suitable anatomy, repair strategies should be the first choice. Although there are currently no available trials comparing transcatheter repair versus replacement, data from the ongoing SUMMIT trial (MitraClip versus Tendyne MV replacement in patients with severe MR) will potentially shed more light on the efficacy and safety of one therapy over the other. The role of transcatheter annuloplasty and chordal implants continues to evolve and will likely become part of the mitral toolbox. Future pivotal studies comparing transcatheter repair versus replacement will further define their role in the management of patients with MR. ■

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