The Use of Transcatheter Devices for Mitral Repair and Replacement

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ABSTRACT
Recent advances in device design have resulted in a wide variety of transcatheter treatment options for patients with symptomatic mitral valve disease. Surgery remains the gold standard for patients with symptomatic, primary mitral regurgitation, while transcatheter devices can be considered in higher-risk patients. For secondary mitral regurgitation, optimal medical therapy and cardiac resynchronization are recommended. Recent evidence suggests that transcatheter alternatives may be considered as well. This review will provide an overview of current transcatheter mitral repair and replacement technologies. These include those that mimic open surgical procedures such as edge-to-edge repair, choral replacement, direct annuloplasty, and valve replacement.
Valvular heart disease affects 2.5% of adults in the United States; among these individuals, mitral regurgitation (MR) is the most prevalent, with moderate to severe MR representing more than two thirds of cases.1 MR typically progresses insidiously and eventually leads to left ventricular (LV) dilation, dysfunction, and failure.2 MR represents a significant public health concern: it carries an annual mortality rate close to 5%, prevalence increases significantly with age, and the burden of disease is estimated to double by 2030, as the population simultaneously grows and ages.1 Surgery remains the gold standard for patients with symptomatic primary MR, while transcatheter alternatives can be considered in patients with high or prohibitive surgical risk.3,4 First-line treatments for secondary MR currently include optimal medical management and cardiac resynchronization therapy, while compelling evidence has recently emerged regarding the use of transcatheter technologies to treat secondary MR.3,4 This review will provide an overview of transcatheter mitral repair and replacement technologies for the management of mitral regurgitation.

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*Adapted from Tang et al.*39

**Transcatheter Mitral Repair**

Edge-to-edge

In 1991, Alfieri created the first mitral valve double orifice through a surgical approach. Initially, the procedure was designed to repair mitral valve prolapse through the attachment of the free edge of the prolapsed leaflet to the free edge of the opposing leaflet: the “edge-to-edge” technique. Creation of a double orifice lessens the degree of MR. Further studies demonstrated that this approach was not only viable in the case of prolapse, but also for the correction of MR due to lack of coaptation in the setting of rheumatic or ischemic disease.5

In patients for whom surgery is not an option, a percutaneous alternative has emerged: MitraClip™ (Abbott Structural Heart, Santa Clara, California). The Food and Drug Administration (FDA) first approved this device in October 2013 for use in the United States.
Figure 1. Transcatheter mitral repair technologies. a: MitraClip™; b: PASCAL™; c: HARPOON; d: NeoChord; e: ChordArt™; f: Cardioband™; and g: Millipede. All images reproduced from publicly available information. (1a from abbottvascular.com; 1b from edwards.com; 1c from tctmd.com; 1d from NeoChord.com; 1e from tctmd; 1f from edwards.com; 1g from millipedemedical.com.)

Figure 2. Transcatheter mitral replacement technologies. a: Intrepid™; b: Tendyne™; c: CardiAQ; d: Tiara; e: Caisson; f: Sapien M3; and g: Cephea. All images reproduced from publicly available information. (2a from medtronic.com; 2b-2g from tctmd.com.)
States in patients with primary MR that were deemed a prohibitive risk for surgery and, in March 2019, in patients with secondary MR deemed not a suitable candidate for surgery. MitraClip remains the sole FDA-approved option for transcatheter, edge-to-edge mitral valve repair. To date, >75,000 patients have been treated with the MitraClip™ device.

**Design and procedure details**

The MitraClip™ system (Fig. 1A) uses a tri-axial catheter with an implantable clip. A dial on the proximal end of the catheter allows the user to deflect its distal tip, which contains the MitraClip™. Further medial-lateral and anteroposterior movement is achieved through the use of two additional dials. The clip itself is a 4mm-wide cobalt/chromium implant with two polyester fabric-coated arms. The fabric component helps to facilitate tissue ingrowth.6

MitraClip™ relies on the same principles as AHFiee’s open-surgical approach (edge-to-edge repair) but is far less invasive; access to the left heart is achieved through a percutaneous femoral venous transseptal approach while the patient is under general anesthesia as the heart continues to beat. The procedure can be divided into five separate components: (I) baseline imaging, (II) transseptal puncture, (III) guiding and appropriately positioning the MitraClip™ device, (IV) leaflet grasping, positional assessment, and deployment, and (V) final assessment and device removal.

Firstly, baseline imaging—via transesophageal echocardiography—is performed to determine the optimal location of transseptal puncture and to visualize the location of the regurgitant jet. Following transseptal puncture, the Clip Delivery System is introduced into the 24-French guide catheter, allowing the MitraClip™ to be advanced through the inferior vena cava and into the left atrium. A dial is then used to deflect the tip of the device downward toward the target pathology and through the mitral orifice. The device is then retracted inside the left ventricle until both valve leaflets are grasped by the clip’s two arms. The clip is then closed to restore/increase leaflet coaptation by tissue ingrowth.6

Clinical trials – EVEREST II

The phase II Endovascular Edge-to-Edge Repair Study (EVEREST II), is the only randomized-controlled trial that has been conducted to examine transcatheter edge-to-edge repair versus surgical intervention for patients with severe MR. In EVEREST II, 279 patients with moderately severe (3+) or severe (4+) MR were randomized in a 2-to-1 ratio to percutaneous repair with MitraClip™ (n=184) or to open surgical MV repair or replacement (n=95). The primary endpoint for efficacy was defined as a composite of: freedom from death, from 3+ or 4+ MR, and from mitral-repair surgery at 12 months. In the intention-to-treat analysis, the primary endpoint was achieved in 55% in the percutaneous group and 73% in the surgery group. The individual components of the composite primary endpoint were as follows: death, 6% in each group; freedom from mitral surgery, 20% versus 2%; and grade 3+ or 4+ MR, 21% versus 20%. The rate of major adverse events at 30 days was significantly different between the percutaneous group (15%) and the surgery group (48%). This was driven largely by the need for blood transfusion in the surgery group. At the 12-month follow-up, both groups showed significant improvement in left ventricular size, quality of life measures, and New York Heart Association functional class as compared to baseline.6 EVEREST II highlighted the safety of MitraClip™ and preliminarily identified two sub-populations who were more likely to have percutaneous outcomes similar to surgery: patients ≥ age 75 and those with functional, as opposed to degenerative, MR. Of note, EVEREST II excluded many higher-risk individuals and, thus, further studies were necessary to examine outcomes in these populations.

In the EVEREST II High Risk Study (HRS), 78 patients with symptomatic, significant (3+ or 4+) MR and prohibitive surgical risk were treated with MitraClip™. Twelve-month survival was 76% compared to controls treated with standard medical management (55%). Also at 12 months, left ventricular remodeling was observed as well as improved New York Heart Association Functional class, quality of life measures, and mental component scores.7

Clinical trials– COAPT and MITRA-FR

Based on subgroup analyses in the EVEREST II study, both the Cardiovascular Outcomes Assessment of the MitraClip™ Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and Percutaneous Repair with the MitraClip™ Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) studies were designed to investigate the use of MitraClip™ in patients with functional, rather than degenerative MR. In the United States and Canada, COAPT enrolled 614 patients with 3+ or 4+ functional MR that could not be successfully controlled despite optimal medical management and cardiac resynchronization therapy. Patients were assigned randomly in a 1-to-1 ratio to MitraClip™ plus medical therapy (n=302) or medical therapy alone (n=312). At 24 months, patients in the treatment arm had a lower rate of hospitalization for heart failure (35% vs. 68%) and death from any cause (29% vs. 46%) compared to the control arm.8 In France, MITRA-FR enrolled 302 patients with severe functional MR and assigned them in a 1-to-1 ratio to MitraClip™ plus optimal medical management (n=152) or medical management alone (n=155). At 12 months, there was no significant difference in mortality between the two groups (24% vs. 22%) or in the rate of unplanned hospitalization for heart failure (49% vs. 47%).9 These two trials paint vastly different pictures with regard to the efficacy of MitraClip™ for the treatment of severe functional MR.

Several possible explanations exist for the difference in outcomes between the COAPT and MITRA-FR trials. Firstly, COAPT utilized a run-in system of medical management prior to randomization. That is, an on-site team placed patients on the maximum-tolerated dose of standard therapy and subsequently excluded any patient from randomization whose symptoms were alleviated or whose MR was reduced. Thus, it is possible that COAPT captured patients who truly had MR that was refractory to medical therapy alone. Secondly, it is possible that differences in mitral valve and left ventricle characteristics contributed to the differ-
ence seen between these two trials. COAPT patients, at baseline, had worse regurgitation than Mitra-FR patients, as measured by the effective regurgitant orifice (ERO) area (41mm² vs. 31mm²). The only subgroup from COAPT that was not found to benefit from MitraClip™ was patients with a small amount of regurgitation (ERO <30mm²) and a very enlarged left ventricle (>96mL/mm²). Fifty-two percent of patients from Mitra-FR matched these baseline characteristics, compared to 14% of COAPT patients. This difference is a potential driver of the negative result of Mitra-FR because patients with a relatively small amount of MR from a very large LV are less likely to have a clinically significant benefit from correction. That is, MitraClip™ may not meaningfully benefit a patient with MR that is proportionate to the severity of LV dysfunction; however, patients with MR that is disproportionate relative to the severity of LV dysfunction, which COAPT enrolled more of, may benefit from MitraClip™.17,13 Finally, the two trials differ in their follow-up length: 24 months for COAPT and 12 months for Mitra-FR. Two-year data is not yet available for Mitra-FR, but it is possible that the Kaplan-Meier survival analyses would mirror one another more closely at this time point.10 Enrollment is ongoing for the RESHAPE-HF2 study, which may aim to resolve the issue of disparate findings between the COAPT and Mitra-FR studies.

Approval and indications

Following the results of EVEREST II, MitraClip™ was approved for the treatment of primary MR in the United States. Per 2017 American Heart Association/American College of Cardiology guidelines, a patient is eligible for transcatheter edge-to-edge repair if they have symptoms (NYHA class III/IV) with chronic, severe primary MR (stage D) and are deemed a prohibitive risk for open surgery due to the presence of multiple co-morbidities, but have a reasonable life expectancy. In March 2019, on the basis of COAPT study results, MitraClip™’s FDA approval was broadened to include patients with secondary MR who are not surgical candidates. This represents a potentially significant paradigm shift in how patients with secondary MR are treated.

STS/ACC TVT registry

Analyses from the Society of Thoracic Surgeons (STS) and the American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) registry, a database of MitraClip™ procedures done commercially, have shown that the device is being used in predominantly elderly, high-risk patients with degenerative MR. Outcomes at the one-year mark indicate similar rates of technical success and MR reduction in this population as compared to prior study populations. However, at the one-year mark, there was a 49% cumulative risk of death or repeat hospitalization for heart failure in patients with residual 3+/4+ MR, compared to 24% in patients with 1+/2+ residual MR. Additionally, one-year mortality and rehospitalization rates were significantly lower in patients with degenerative (24.7% and 20.5%, respectively) versus functional MR (31.2% and 32.6%, respectively).14

MitraClip™ XTR and NTR

The third generation of MitraClip™ devices, the XTR and NTR, are currently in use and differ from the original device in terms of both clip and delivery system specifications. In the XTR system, the clip arms are 3mm longer than in previous generations and are able to extend outward further. Combined, these two factors allow the XTR to achieve a grasping width 5mm greater than its predecessor. In practice, the goal is to allow physicians to better customize their mitral valve repair based on the patient’s anatomy and pathology and optimize MR reduction while minimizing the risk of functional stenosis.15 The EXPAND post-market registry will evaluate the efficacy and safety of these next-generation devices for the treatment of MR. Preliminary 30-day follow-up analyses from the first 500 patients enrolled showed MR reduction to ≤2+ in 96% of patients. Thirty-day complication rates were as follows: 2.8% mortality, 0.4% stroke, and 1.4% need for surgery due to device-related complications.16

Edwards PASCAL™

In the EVEREST II trial, several anatomical exclusion criteria were applied. These included any leaflet abnormality that might preclude proper clip implantation, such as: evidence of calcification in the middle scallop of either the anterior or posterior leaflet (A2 or P2), presence of a significant A2 or P2 cleft, bileaflet flail, or severe bileaflet prolapse.17 As a result, the patients included in EVEREST II likely do not represent the range of anatomy seen in today’s clinical practice. The PASCAL™ transcatheter mitral valve repair system (Edwards Lifesciences Corp., Irvine, California) was designed with these limitations in mind. In comparison to MitraClip™, PASCAL™ (Fig. 1B) has gripper arms that can be independently controlled, a central spacer, and novel steering capabilities meant to facilitate positioning of the device within the left atrium. Specifically, each PASCAL™ arm is 10mm long, in comparison to MitraClip™, which has 9mm arms. The width of the two devices is also a substantial point of contrast; with the addition of a 10mm central spacer, PASCAL™ is almost twice as wide as MitraClip™. The spacer is a novel design feature and is meant to further reduce the degree of MR by filling the regurgitant orifice area. The additional width of the device is also thought to facilitate grasping deeper on the leaflet.19

The PASCAL™ device is currently CE-mark approved for use in Europe. PASCAL™ is not FDA approved in the United States; however, the device has been used in five countries (Germany, Switzerland, Canada, Greece, and the United States) as part of a prospective-, observational-, compassionate-use study. Twenty-three patients with severe functional and degenerative MR who were not candidates for intervention with MitraClip™ were enrolled in the trial and underwent transcatheter edge-to-edge repair with PASCAL™. Technical success was achieved in 96% of patients at the end of the procedure and device success—a composite that included successful implantation, absence of mortality, freedom from MR ≥2+, freedom from unplanned procedures, and lack of device-related complications—was 78% at 30 days.18 This study established the safety and feasibility of PASCAL™ for patients who were not eligible for the second-generation MitraClip™ for anatomical reasons. The study authors highlighted the technical advances of PASCAL™ and its ability to be used in patients with more varied anatomy—a population in which there is currently an unmet need for transcatheter repair options. Early results from the US feasibility trial—The Edwards PASCAL™ TrAnScatheter
Mitral Valve RePair System Study (CLASP)—show a favorable 30-day safety profile. Among 62 patients, the mortality rate was 1.6%, the rate of severe bleeding was 6.5%, and the re-intervention rate was 1.6%. At both 30 days and 6 months, MR was reduced to ≤2+ in 98% of patients. 19

The development of devices for transcatheter edge-to-edge repair of the mitral valve in patients with severe degenerative or functional mitral regurgitation represents a major step forward in treatment options for this complex, burdensome disease. However, edge-to-edge repair does not fully eliminate mitral regurgitation and is likely more palliative than curative. This reality has driven the design and development of devices for percutaneous and minimally invasive chordal replacement and annuloplasty as complementary adjuncts to edge-to-edge repair.

**CHORDAL REPLACEMENT**

In patients with degenerative MR caused by elongation or rupture of the chordae tendineae, minimally invasive and transcatheter options have emerged as an alternative to surgical repair. Traditionally, the surgical procedure involves repair of existing chordae and, starting in the early 1990s, creation of neochordae from expanded polytetrafluoroethylene (ePTFE) became an option. 20 These procedures require cardiopulmonary bypass, thoracotomy or sternotomy, cross clamping of the aorta, and cardiopelagic arrest. These invasive techniques are not without significant risk of morbidity and mortality. Additionally, in open surgery, residual MR is assessed intraoperatively through the use of saline injection in a flaccid heart, prior to reversal of cross clamp and cardiopulmonary bypass. Newer technologies, such as HARPOON (Edwards Lifesciences Corp., Irvine, California) and NeoChord DS1000 (NeoChord Inc., St. Louis Park, Minnesota) enable procedures to be performed on a beating heart and allow for real-time assessment via echocardiography.

**HARPOON**

The HARPOON device (Fig. 1C) is designed to anchor new ePTFE chords to the prolapsed mitral leaflet. Thus far, 65 patients have undergone the procedure worldwide. The 3mm device consists of a 21G needle apparatus that is coiled with 50 loops of ePTFE sutures in a preformed knot and is used in conjunction with a 14-French valved introducer. Transapical access to the anterior left ventricle is gained through a small left thoracotomy in the fourth or fifth intercostal space. An incision is made on the anterolateral surface of the left ventricle followed by the insertion of the 14-French sheath. The HARPOON device is then inserted through the introducer and, using transesophageal echocardiogram (TEE) guidance, its tip is used to stabilize the desired leaflet. The needle and its attached suture are then deployed to pierce the leaflet. As the needle is removed from the left ventricle, the sutures automatically form a knot on the atrial side of the valve. Additional chords can then be created in the same fashion. Finally, the free ends of suture from each new chord are attached to the epicardium via individual Teflon pledgets. TEE is then used to check for residual MR and chord length can be further adjusted to optimize the repair. 21

The Mitral TransApical NeoCordial Echo-Guided Repair (TRACER) study was used to evaluate the safety and performance of HARPOON in patients with severe MR. 22 The key inclusion criteria were: severe degenerative MR as the result of isolated posterior leaflet prolapse and anatomical suitability for the procedure. The latter was primarily determined by obtaining two measurements via TEE: 1) length of the posterior prolapsed segment and 2) distance between the free edge of the anterior leaflet and the base of the prolapsed posterior leaflet segment. If the ratio between these two measurements was ≥1.5, the patient was predicted to have a positive outcome and was included in the study. A variety of exclusion criteria were applied, including: anterior prolapse, bileaflet prolapse, severe leaflet calcification, moderate/severe aortic insufficiency or stenosis, functional MR, and tricuspid regurgitation. The primary endpoint of successful chord implantation and MR reduction from severe to mild or moderate at 30 days was achieved in 90% of patients. There were no deaths, or strokes, and no patient required implantation of a permanent pacemaker or a blood transfusion. Three patients required conversion to conventional mitral valve surgery. Also at 30 days, there was evidence of ventricular remodeling, as shown by reduced end diastolic dimension, end diastolic volume, and septal-lateral dimension. At six months, the results were reasonable—26/30 patients had mild or moderate MR. TRACER demonstrated the feasibility of HARPOON technology. It remains to be seen how the technology will perform in patients outside of isolated P2 prolapse, in more high-risk patients, and in comparison to other devices, such as MitraClip, in both high- and lower-risk patients.

**NeoChord**

Similar to HARPOON, NeoChord uses a transapical approach to fix ePTFE sutures to the prolapsed leaflet and anchor them to the epicardium. Unique features of NeoChord (Fig. 1D) include a jaw-like mechanism used to grasp the prolapsed scallop and fiber-optic technology to confirm and optimize grasping of the appropriate location. Suture material does not come pre-knotted; instead, the device is used to form a hitch knot after piercing the leaflet. 23 As another point of contrast with HARPOON, because of the clamping jaw mechanism, NeoChord sutures are placed at a relatively uniform distance (3.5mm) inward from the free margin of the leaflet. HARPOON does not grasp the valve leaflet and, thus, can anchor a new chord from any location on the prolapsed segment.

The Transapical Artificial Chordae Tendinae (TACT) and Transapical Off-Pump Mitral Intervention with NeoChord Implantation (TOP-MINI) trials were designed to test the safety and efficacy of NeoChord in patients with posterior and/or anterior leaflet prolapse. TACT demonstrated that NeoChord was safe and feasible in a group of 30 patients with severe degenerative MR due to posterior leaflet prolapse. Acute procedural success, defined as implantation of at least one artificial chord and reduction of MR to ≤ 2+ was achieved in 87% of patients and technical success improved significantly with operator experience. 24 TOP-MINI expanded the inclusion criteria to include patients with anterior leaflet prolapse. Forty-nine patients with severe, degenerative MR were treated with NeoChord; 44 presented with posterior leaflet pathology, four with anterior leaflet prolapse,
and one with mixed disease. Acute procedural success, defined as successful implantation of three or more chords and reduction of MR to <2+, was achieved in 100% of patients. Freedom from reoperation at three months was 92%.25 Two-year follow up data is available for 64 patients from the TOP-MINI cohort. Patients were divided into four groups by lesion type: (A) P2 prolapse; (B) posterior prolapse with ≥1 scallop involved; (C) anterior leaflet prolapse; and (D) anterior and posterior prolapse, commissural disease, annular or leaflet calcification. At two years, 96% of patients with type-A disease were free of >moderate MR, mortality, stroke, and reintervention. This endpoint was met in 83%, 66%, and 57% of type B, C, and D patients, respectively.26 The NeoChord Independent International Registry (NIIR) followed 216 patients with severe MR due to flail/prolapse of one or both leaflets. Procedural success was achieved in 97% of patients and analysis of one-year follow-up data showed 98% survival. Of note, the composite endpoint (freedom from mortality, stroke, reintervention, severe MR, and rehospitalization) was met in 84% of the overall population, but it differed significantly between groups. The endpoint was met in 94%, 83%, and 64% of type A, B, and C patients, respectively.27

At present, there is little consensus regarding the ideal candidate for NeoChord. Although TOP-MINI demonstrated better outcomes in patients with lesions confined to a single scallop of the posterior leaflet, this study lacked a control arm and sample size was limited. Currently, the ReChord randomized-controlled trial aims to compare implantation of artificial chordae tendineae with NeoChord versus conventional surgical repair in patients with isolated A2 or P2 prolapse/flail. The device is currently CE-mark approved and over 1200 patients have undergone the procedure worldwide.

**DIRECT ANNULOPLASTY**

In patients with chronic MR, enlargement of the left atrium and left ventricle commonly cause enlargement of the mitral annulus. Beginning in the 1950s, mitral valve annuloplasty was proposed as a mechanism to correct this dilatation.29 Carpentier was the first to surgically implant a prosthetic ring directly into the mitral annulus; its shape was chosen in order to restore proper systolic annulus dimensions.30,31 Annuloplasty has since evolved to become a cornerstone of the surgical mitral valve repair armamentarium. Several percutaneous direct annuloplasty devices—Cardioband™ (Edwards Lifesciences Corp., Irvine, California) and Millipede (Boston Scientific, Marlborough, Massachusetts)—have recently emerged and have the potential to significantly impact the way MR is approached and treated.

**Cardioband™**

Cardioband™ (Fig. 1F) is divided into two main components—the delivery system and the implantable device. The delivery system is used to position the device above the mitral annulus via a transseptal approach and has five degrees of movement to facilitate manipulation within the left atrium. After appropriate positioning of the device tip via 2D and 3D TEE, the first segment of polyester fabric band is attached to the posterior mitral annulus via a 6mm stainless steel anchor. The band, which is marked with radiopaque lines, is advanced forward an additional segment and another clip is placed. This segmental feature allows the implant to conform to an individual patient’s mitral annulus geometry.32 After the implant has been completely deployed, the size adjustment tool is introduced. A knob is turned and the length of the band can be adjusted to achieve optimal annular size and MR reduction. The first safety and feasibility study in Europe enrolled high-risk patients with symptomatic secondary MR, despite optimal medical therapy. The primary endpoints of the study included technical implantation success, technical adjustment success—defined as successful modification of Cardioband™ length—and reduction in both annular septolateral dimension and MR. At one-month follow up, both measures of technical success were achieved in 29/31 (94%) of patients, septolateral diameter was significantly reduced from an average of 37.8mm to 26.0mm, and MR was ≤2+ in 88% of patients.33 The device is currently CE-mark approved.

**Millipede IRIS**

Millipede IRIS (Fig. 1G) is the first transcatheter, transseptal annuloplasty system to include a complete semi-rigid ring. Other devices, such as Cardioband™, rely on a partial band that does not completely cover the perimeter of the annulus. Millipede is composed of laser-cut nickel-titanium alloy (nitinol); the base of the device contains eight evenly spaced, helical screws and the upper portion of the ring contains eight sliding collars, each of which can be individually advanced or retracted. During the TEE-guided procedure, the device is inserted into the femoral vein on a 24F deflectable catheter and advanced into the left atrium transeptally. Once in the left atrium, the device is positioned over the mitral annulus and the helical screws are individually fixed into the tissue.
Next, each individual segment of the collar apparatus on the upper portion of the band is adjusted to achieve optimal annular dimensions and MR reduction. Rodgers et al. report the use of Millipedes in seven patients with 3+ or 4+ secondary MR with annular dilation. The first four patients in the study underwent device implantation through a median sternotomy, while the percutaneous transeptal approach was used in the final three patients. There was no stroke, myocardial infarction, or device-related death. At 30 days, the average annular diameter was reduced from a baseline of 38.0 to 25.9 mm and MR was ≤1+. Reduction in LV volume and NYHA class improvement was also demonstrated. Currently, the device delivery catheter has an integrated intracardiac echocardiography (ICE) channel to better visualize the mitral annulus for accurate engagement of the Millipede anchors. Further study of the Millipede system is needed in larger cohorts and in comparison to surgical annuloplasty.

As with surgical annuloplasty, which is typically used in conjunction with other options for surgical repair, such as resection and chordal repair, it is unlikely that percutaneous annuloplasty technology will be used as a single therapy. Rather, it is likely to be combined and used in conjunction with existing percutaneous technologies, such as edge-to-edge repair and chordal replacement. Three recent cases demonstrate the feasibility of a combined approach—two patients underwent simultaneous implantation of Cardioband™ and MitraClip™, while one was treated with Cardioband™ and NeoChord. Limitations to this approach include the high cost and lack of data to drive appropriate patient selection. An interesting possibility is the use of Cardioband™ to reduce annular dimensions and improve coaptation distance, thus allowing patients previously considered anatomically ineligible for MitraClip™ to undergo the procedure.

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The first four patients in the study underwent device implantation through a median sternotomy, while the percutaneous transeptal approach was used in the final three patients. There was no stroke, myocardial infarction, or device-related death. At 30 days, the average annular diameter was reduced from a baseline of 38.0 to 25.9 mm and MR was ≤1+. Reduction in LV volume and NYHA class improvement was also demonstrated. Currently, the device delivery catheter has an integrated intracardiac echocardiography (ICE) channel to better visualize the mitral annulus for accurate engagement of the Millipede anchors. Further study of the Millipede system is needed in larger cohorts and in comparison to surgical annuloplasty.

As with surgical annuloplasty, which is typically used in conjunction with other options for surgical repair, such as resection and chordal repair, it is unlikely that percutaneous annuloplasty technology will be used as a single therapy. Rather, it is likely to be combined and used in conjunction with existing percutaneous technologies, such as edge-to-edge repair and chordal replacement. Three recent cases demonstrate the feasibility of a combined approach—two patients underwent simultaneous implantation of Cardioband™ and MitraClip™, while one was treated with Cardioband™ and NeoChord. Limitations to this approach include the high cost and lack of data to drive appropriate patient selection. An interesting possibility is the use of Cardioband™ to reduce annular dimensions and improve coaptation distance, thus allowing patients previously considered anatomically ineligible for MitraClip™ to undergo the procedure.

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Given the relatively high rate of residual MR following transcatheter edge-to-edge repair and recurrent MR after repair of functional regurgitation, transcatheter mitral valve replacement (TMVR) is perhaps a more definitive treatment. In terms of device design, the mitral valve poses a particular challenge because of its complex geometry and dynamic nature. Technologies currently in development have approached this issue from a variety of angles. Currently, proposed mechanisms include: 1) use of radial force (Intrepid™, Medtronic, Minneapolis, Minnesota); 2) anchoring of the device both proximally and distally (Tendyne™, Abbott Vascular, Abbott Park, Illinois); 3) grasping native leaflets (Tiara, Neovasc Inc., Richmond, Canada), 4) clamping of the mitral annulus (CardiaQ, Edwards Lifesciences, Corp., Irvine, California), and 5) creation of a docking system (Caisson, LivaNova, London, United Kingdom; Sapien M3; Edwards Lifesciences Corp., Irvine, California). Regardless of the particular device used, TMVR comes with a host of important considerations, including patient selection, anatomical screening—particularly for the risk of left ventricular outflow tract (LVOT) obstruction—and valve thrombosis.

Intrepid™
Intrepid™ (Fig. 2A) is a transapical, self-expanding, nitinol valve that relies on the creation of a cork-like seal to facilitate appropriate placement and anchoring within the mitral annulus. The device is composed of two concentric rings; the outer ring is directly involved in fixation, while the inner ring contains a tri-leaflet bovine valve. The outer ring is available in three different diameters (43, 46, and 53 mm), and a size is chosen after careful screening with cardiac computed tomography (CT). In order to minimize the risk of LVOT obstruction, the device profile is 17 to 18 mm. To study the safety and feasibility of transcatheter mitral valve replacement with Intrepid™, 50 consecutive patients with symptomatic, severe MR were enrolled in a recent study conducted by Bapat et al. Eighty-four percent of patients had secondary MR and 86% were NYHA Functional Class III or IV. Device implantation was successful in 96% of patients—30-day mortality was 14%. No strokes or repeat interventions occurred. At latest follow up (median 173 days), 78% of patients were NYHA Functional Class I or II and all patients had either mild or no residual MR. Currently, over 180 implants have been performed worldwide and a transcatheter system is under development with first in-human implant expected in late 2019.

Tendyne™
Tendyne™ (Fig. 2B), like Intrepid™, is a transapical, self-expanding, nitinol valve. It is composed of an inner band, which houses a trileaflet porcine pericardial valve and an outer band, which is coated in porcine pericardium and a polyethylene terephthalate cuff. The cuff material allows an appropriate seal to form between the implant and the mitral annulus. Additionally, the prosthesis is D-shaped in an effort to mimic native valve geometry. A unique feature of this device is its epicardial pad, which is secured to the apex and is connected to the prosthesis by a tether. Tether length is adjusted intraoperatively to ensure the device is optimally seated to the annulus. Of note, even if the device has been fully deployed, it can be repositioned or retrieved. The Global Feasibility Study enrolled 100 patients with symptomatic primary (n=11) or secondary (n=89) MR who were considered too high risk for surgery. Sixty-six patients were considered NYHA functional class III or IV. Device implantation was successful in 96% of patients. Stroke occurred in two patients and reintervention was necessary in one. At one-year follow up, mortality was 26% and 85% of surviving patients were NYHA class I or II. Thus far, over 220 implants have been performed worldwide and a hybrid transeptal/transapical system is currently under development.

CardiAQ/Evoque
CardiAQ (Fig. 2C) is a self-expanding, symmetrical, bioprosthetic valve on a nitinol frame. The inner frame features a trileaflet bovine pericardial valve, while the outer frame features two sets of anchors that help to fix the prosthesis in place. Unique features include inflow and outflow skirts—made of polyester fabric and designed to minimize any leakage around the device. Additionally, the valve can be delivered via the transapical or transeptal route. A limited number of patients have been treated thus far with CardiAQ. Analysis of 13 patients showed 92% procedure success; however, 30-day mortality was 53.8%. The transeptal CardiAQ—recently renamed Evoque—is currently undergoing an early feasibility study in the US in patients with symptomatic severe...
MR, with an expected primary completion date in late 2019.

**Tiara**

Tiara (Fig. 2D) is a self-expanding, transapical, D-shaped, bioprosthetic valve on a nitinol frame. The inner band features a trileaflet valve made from bovine pericardium. The outer band features an atrial skirt, one anterior anchor, and one posterior anchor. The anchors are designed to dovetail with the existing valve leaflets, while the skirt interfaces with the atrial portion of the mitral annulus to facilitate proper seal formation. Combined, these features minimize paravalvular leakage and prevent device migration. To date, Tiara has been implanted in 70 patients, with a 93% technical success rate. Enrollment is currently ongoing for the Tiara-I Early Feasibility Study, with an expected primary completion date in early 2020.

**Caisson**

Caisson (Fig. 2E) is a self-expanding, transseptal, D-shaped, bioprosthetic valve on a nitinol frame. The trileaflet valve is made of porcine pericardium and is contained within the inner portion of the device. Caisson also features a docking component that attaches to the mitral annulus via a clamping mechanism. The inner portion with the valve nests inside the outer-docking mechanism. Of note, the device is fully recapturable and retrievable. The device is available in three sizes, increasing treatable population size. Out of 30 patients implanted thus far, analysis of a portion of the Percutaneous Mitral Valve Replacement Evaluation Utilizing IDE (PRELUDE) and INTERLUDE study data showed promising feasibility, with no acute LVOT obstruction. Seven patients required conversion to open surgery and mortality rate was 13% at 30 days. Significant functional improvement was also evident in a small cohort (n=17) at 30 days and was durable at one-year follow up (n=7). Data from the full PRELUDE study is pending. The ongoing INTERLUDE study aims to enroll 75 high-risk patients with 3+/4+ symptomatic MR and is expected to reach primary completion in mid-2020.

**Sapien M3**

Sapien M3 (Fig. 2F) is a self-expanding, transseptal, bioprosthetic valve. Notably, the system includes a novel nitinol dock, which is introduced transseptally and is guided to encircle the native leaflets; a polyethylene terephthalate (PET) skirt surrounds the dock and is designed to increase seal formation between the dock and native valve leaflets. Once the dock is anchored, the prosthetic valve itself is deployed within the docking system. As part of a compassionate use program in Canada, Sapien M3 was implanted in 10 patients with symptomatic, 4+ MR. Technical success was achieved in 90% of patients. At 30 days, the mortality rate was 0%, there were no complications, and MR was reduced to ≤1+ in 90% of patients. In the United States, the Sapien M3 Early Feasibility Study enrolled 15 high-risk patients with symptomatic, ≥3+ MR and LVEF ≥30%. The primary endpoint for technical success was achieved in 13 of the 15 patients. One patient who did not meet the endpoint required separate transseptal punctures for the docking system and valve; the other required percutaneous closure of paravalvular leak. No deaths were reported at 30 days, although there were three instances of rehospitalization for heart failure and one reported stroke. The secondary endpoint for reduction of MR to 0 or 1+ at 30 days was achieved in 93% of patients. The US pivotal trial for Sapien M3 is expected to be initiated in late 2019.

**Cephea**

Cephea (Abbott Structural Heart, Santa Clara, California; Fig. 2G) is a self-expanding, transseptal bioprosthetic device designed to be anchored subannularly. It features two frame components—an outer anchor and the inner leaflet bovine valve structure—that are decoupled from one another; this feature isolates leaflet function and helps to maintain circularity. Additionally, the external frame is highly conformable and can adapt to variable anatomy. The valve is low profile and, in animal models, causes minimal hemodynamic disruption. The first-in-human study is expected in the latter half of 2019.

**CONCLUSION**

Over the last decade, catheter-based therapies for the treatment of mitral regurgitation have progressed significantly. These technologies evolved from well-known surgical techniques and, importantly, they are not designed to replace surgery in lower-risk patients who are good candidates for an open procedure. Rather, they are a novel addition to current mitral regurgitation therapies and show promise in the treatment of high-risk patients with primary or secondary MR. To date, the most utilized therapy is the transcatheter edge-to-edge repair using MitraClip™ and, as a result, it has been FDA approved for use in both primary and secondary MR. Chordal replacement via HARPOON and NeoChord shows promising early results as does direct annuloplasty via Cardioband™ and Millipede. Given residual MR following percutaneous repair, transcatheter mitral valve replacement may be a more viable long-term solution. Pipeline TMVR technologies show promising early results, but more study is necessary.

**AUTHORS’ DISCLOSURES**

Dr. Tang is a consultant for Abbott Structural Heart, W. L. Gore & Associates, Inc., and NeoChord, Inc. All other authors have no conflicts of interest to disclose.

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