Update on Transcatheter Mitral Valve Repair

A look at the current and soon-to-come transcatheter mitral valve repair options.

BY DALE J. MURDOCH, MBBS; ROBERT H. BOONE, MD; ROBERT MOSS, MBBS; JOHN WEBB, MD; AND DAVID A. WOOD, MD

Mitral valve (MV) regurgitation is common; approximately 4 million people in the United States have severe mitral regurgitation (MR), and 250,000 new diagnoses of MR are made each year.[1,2] Once MR is severe and symptomatic, annual mortality is approximately 5%,[3] and medical therapy has not been shown to increase survival.[4] However, approximately 50% of patients with severe MR are not treated with open surgery due to advanced age, left ventricular dysfunction, comorbidities, or other contraindications.[5] This unmet clinical need has largely driven the development of safer, catheter-based treatments for MV disease.

Transcatheter therapies for repair of MR aim to balance increased safety with sufficient efficacy in reducing MR to improve clinical outcomes. The distinct advantages offered by transcatheter repair include improved procedural safety, preservation of physiological hemodynamics, and often avoidance of long-term anticoagulation.[6] These advantages are offset by numerous challenges related to the complexity of the MV apparatus, variability in MR location and etiology, and engineering and imaging constraints of current-generation technologies.

Transcatheter approaches borrow heavily from more than 50 years of research and development in cardiac surgery. Leaflet repair, annuloplasty, and chordal repair are all targets of intense research, and a combination of methods may provide optimal results for some patients (Table 1).

LEAFLET REPAIR

MitraClip

The MitraClip device (Abbott Vascular) is a percutaneous adaptation of the Alfieri stitch surgical technique. For the percutaneous approach, a clip (made of two polyester-covered arms that are roughly 8 mm long and 4 mm wide) is used instead of sutures. The clip is delivered by means of a 24-F steerable catheter and triaxial delivery system via a femoral venous and transseptal approach.

The first-in-human MitraClip implantation was performed in 2003.[7] Subsequently, the procedure and clinical outcomes have been studied extensively as part of the EVEREST studies and numerous registries.[8-10] More than 30,000 patients have now been treated worldwide.[11]

Primary (Degenerative) MR. Based on the outcomes of EVEREST, the US Food and Drug Administration (FDA) approved percutaneous MV repair with the MitraClip device for "symptomatic MR > 3+ due to primary abnormality of the mitral apparatus (degenerative MR) in patients who have been determined to be at prohibitive risk for MV surgery by a heart team."[12] Patients in the United States undergoing commercial MV repair with MitraClip are enrolled in the Society of Thoracic Surgeons (STS)/American College of Cardiology (ACC) Transcatheter Valve Therapy (TVT) Registry, and 30-day follow-up results have recently been published.[13] Between November 2013 and August 2014, 583 patients with predominantly degenerative MR (90.8%, isolated functional MR in just 9.2%) and at high risk for surgery (STS predicted risk of mortality scores for MV repair and replacement were 7.9% and 10%, respectively) were treated with MitraClip. Overall procedural success was high (90.6%) with one or more MitraClip device implanted in 94% and residual MR was grade ≤ 2 in 93%. Early safety was once again demonstrated with a 30-day mortality rate of 5.8%, a stroke rate of 1.8%, a bleeding risk of 1.8%, and a device-related complication rate of 1.4%.

These results further support the indication for percutaneous MV repair in patients with primary MR who are at high risk for surgery, accepting that patients treated commercially are different to those enrolled in EVEREST II—they are older, are more frail, and have higher surgical risk estimates. Although excellent clinical outcomes and improvement in mortality have been shown for open MV surgery for primary MR, further research is required to determine if the same is true for the patient population now treated with transcatheter MV repair in the United States.

TABLE 1. MITRAL VALVE REPAIR DEVICES AND INDICATIONS

Device	Indication	Design	Advantages	CE Mark	Number of Procedures Worldwide (approximate)
MitraClip and MitraClip NT (Abbott Vascular)	Primary MR (FDA approved) and secondary MR	Transvenous transeptal edge-to-edge repair clip	Ability to treat primary and secondary MR; broad clinical experience; improved clip and delivery system design (MitraClip NT)	2008	> 45,000
Pascal (Edwards Lifesciences)	Primary and secondary MR	Transvenous transeptal edge-to-edge repair paddles with central spacer	Broad grasping zone and spacer reduce multiple device implant; single leaflet grasping	Trial underway	20
NeoChord DS1000 (NeoChord, Inc.)	Primary MR (especially posterior leaflet prolapse)	Transapical artificial chordal repair (sutures at edge of leaflets)	Precise placement and tensioning of ePTFE artificial chords under physiological conditions using TEE guidance	2013	650
Harpoon TSD-5 (Harpoon Medical, Inc.)	Primary MR (especially posterior leaflet prolapse)	Transapical artificial chordal repair (sutures can insert anywhere in leaflet)	Precise placement and tensioning of ePTFE artificial chords under physiological conditions using TEE guidance; ability to place sutures anywhere in valve leaflet	Expected Q4 2017	50
V-Chordal off-pump transeptal (Edwards Lifesciences)	Primary MR	Transeptal adaptation of artificial chord off-pump tensioning system	Adaptation of surgical technique	No	Preclinical
Carillon (Cardiac Dimensions, Inc.)	Secondary MR	Transvenous preshaped nitinol device placed in coronary sinus	Multiple anchor sizes and lengths available (37 combinations); treatment effect and complications (circumflex artery compression) can be evaluated before device release	2011	700
Arto (MVRx, Inc.)	Secondary MR	Suture-based tether between interatrial septum and coronary sinus	Simplified annuloplasty with brief learning curve; adjustable device tension titrated to effect	No	45
Mitral Loop Cerclage (Tau-PNU Medical Co, Ltd.)	Secondary MR	Transvenous adjustable stainless steel loop delivered via coronary sinus	Annuloplasty delivered to circumference of mitral annulus; adjustable device tension titrated to effect	No	5
Mitralign (Mitralign, Inc.)	Secondary MR	Retrograde femoral arterial access and bident catheter-suture system direct annuloplasty	Customizable to patient anatomy with variable bident catheter size; asymmetrical or symmetrical annuloplasty can be performed (one or two pledget pairs)	2016	100
Cardioband (Edwards Lifesciences)	Secondary MR	Transvenous transeptal direct posterior leaflet annuloplasty	Surgical-like direct annuloplasty from atrial surface; homogeneous circumferential annular cinching	2015	200

Abbreviations: ePTFE, expanded polytetrafluoroethylene; FDA, US Food and Drug Administration; MR, mitral regurgitation; TEE, transesophageal echocardiography.

Secondary (Functional) MR. In patients with severe MR and heart failure, the etiology is much more commonly functional.[14] These patients are inherently at high risk due to left ventricular (LV) dysfunction and comorbidities, and guidelines recommend against isolated MV surgery in this setting due to limited evidence of improved outcomes and frequent recurrence of MR.[15] However, outcomes are poor with medical therapy alone, with mortality of up to 50% at 5 years and a rate of hospital readmission for heart failure at 90% in the same period.[14] Thus, percutaneous repair has been suggested as an alternative therapy in these patients and adopted with enthusiasm, particularly in Europe. Numerous large registries have been published, with the majority of patients treated for secondary MR.[16-19]

In the United States, use of the MitraClip system was continued after the EVEREST trials in a high-risk arm (EVEREST II HRR) and in the REALISM study of the MitraClip system.[20] Patients were high risk, either with an STS predicted risk of mortality > 12% or a prespecified risk factor, and most had functional MR (70%). Mortality was 4.8% at 30 days (less than predicted by the STS model for MV surgery), three of 351 subjects (0.9%) required MV surgery within 12 months of the procedure, and no cases of MitraClip embolization were reported, once again highlighting the safety of a percutaneous approach. Efficacy was acceptable, with an MR grade ≤ 2+ in 83.6% at 12 months and significant reduction in LV end-diastolic and end-systolic volumes. Functional class improved substantially, with 17.1% of patients in New York Heart Association (NYHA) class III or IV at 12 months, compared to 82.1% at baseline ($P < .0001$).[21]

For the MitraClip, the evidence for safety is strong and consistent. Effectiveness is similar across trials, with approximately 80% of patients achieving ≤ 2+ MR at 12-month follow-up.[10] A propensity-matched comparison of EVEREST II HRR/REALISM patients and high-risk Duke Echocardiography Laboratory Database patients managed nonsurgically suggested a survival benefit with MitraClip therapy at 12 months (relative risk, 0.64; $P = .013$).[22] Similarly, a propensity-matched cohort of 120 patients with cardiomyopathy and functional MR showed improved rates of hospital readmission and overall survival when MitraClip therapy was compared to optimal medical therapy.[23]

Currently, a traffic light system is used by many institutions when interpreting echocardiographic suitability for MitraClip (Table 2). While this frequently corresponds with the EVEREST criteria, an experienced echocardiographer may identify features that make a patient well-suited or otherwise, in turn guiding the heart team discussion.

Obtaining excellent outcomes for MV repair with the MitraClip system requires mastery of complex catheterization and imaging skills along with a detailed understanding of cardiac anatomy, particularly the MV apparatus.[24]

MitraClip NT

MitraClip NT (Abbott Vascular) is an updated version of the original MitraClip system, which had not

TABLE 2. EVALUATION OF MITRAL REGURGITATION FOR TRANSCATHETER LEAFLET REPAIR

Traffic Light Color	Global Features	Primary MR	Functional MR	Comment
Red	Extreme anterolateral or posteromedial jet; leaflet cleft or perforation; calcification in the grasping zone; mitral valve area < 3.5 cm^2	Bileaflet flail valve	Rheumatic thickening or restriction	Unsuitable for MitraClip therapy; consider alternative therapy options
Amber	Anterolateral (A1/P1) or posteromedial (A3/P3) jet; mild calcification outside the grasping zone; mitral valve area 3.5 to 4 cm^2	Flail width > 15 mm; flail gap > 10 mm; prior annuloplasty/repair	Left ventricular ejection fraction < 25%; left ventricular end diastolic dimension ≤ 55 mm; coaptation depth > 11 mm	May be technically challenging for MitraClip therapy; Consider > one MitraClip; consider clinical history, indication, and alternative therapy options (most patients can be treated with MitraClip)
Green	A2/P2 regurgitant jet; no leaflet calcification; mitral valve area > 4 cm^2; mitral valve gradient < 4 mm Hg	Flail width < 15 mm; flail gap < 10 mm	Coaptation depth < 11 mm	Well suited for MitraClip therapy; consider clinical history and indication at heart team meeting

Abbreviation: MR, mitral regurgitation.

been substantially updated since its introduction more than 10 years ago. To improve steering and precision in the new system, the clip delivery system key material has been changed from stainless steel to nylon.[24] The steerable sleeve has also been improved, and there is a significantly improved response and reduced anterior movement with the M knob.

The gripper material has been changed from elgiloy to nitinol, allowing an increase in the gripper drop angle and therefore a more secure grasping arm angle, resulting in deeper leaflet insertion and more stable fixation of the edge-to-edge repair.

Pascal

The Pascal transcatheter mitral repair system (Edwards Lifesciences) is a percutaneous edge-to-edge repair device that uses a spacer in addition to the paddles and clasps that grasp the MV leaflets. The spacer and larger implant size are designed to occupy more of the regurgitant orifice and may reduce the number of multiple device implantations when compared to the MitraClip. Each clasp can be operated independently, allowing one leaflet to be grasped at a time. Successful procedures in humans have been presented, and a prospective multicenter study (CLASP) is underway.

CHORDAL REPAIR

Patients with predominant myxomatous degeneration and prolapsing or flail leaflets may benefit from repairing the chordae. Artificial chordae implantation has emerged as an attractive surgical technique and is often performed via a minimally invasive approach to reduce morbidity.[25,26] A natural extension, therefore, is to extend this strategy to a transcatheter system.

NeoChord

The NeoChord DS1000 system (NeoChord, Inc.) utilizes a transapical off-pump approach to implant and tension expanded polytetrafluoroethylene (ePTFE) neochordae under transesophageal echocardiographic (TEE) guidance. A leaflet verification display uses four fiber optic lights to confirm leaflet capture in the distal clamp of the device, and the suture is deployed in the free margin of the prolapsing leaflet. This is then secured at the apex and tensioned under TEE guidance, and one or more sutures are deployed in the prolapsing/flail segment to ensure adequate coaptation, reduction of MR, and stability.

Early feasibility was demonstrated in the TACT trial.[27] Thirty patients were treated at seven centers, with acute procedural success achieved in 26 patients (86.7%); neochordae were not placed for technical or patient-specific reasons in four patients. One patient died within 30 days, and four patients required early conversion to standard MV surgery. Seventeen patients (57%) achieved the primary outcome of ≤ 2+ MR at 30 days. Similar to open surgical isolated chordal repair, this procedure appears best suited to posterior leaflet prolapse/flail.

A single-center study of 49 patients treated with the NeoChord DS1000 system for degenerative MR (90% posterior leaflet) demonstrated excellent early clinical results.[28] Acute procedural success was achieved in all carefully selected patients, with three to six neochords used in each patient. MR was grade ≤ 2+ in 89.6%, and four patients (8.2%) required conventional MV surgery at 3 months. Patients with anterior or bileaflet disease were more prone to premature deterioration of the repair, likely related to higher neochordal tension.[29] Current limitations of this technique are intraprocedural blood loss and the potential need for blood transfusion.[28]

Harpoon

The first-in-human experience with the Harpoon TSD-5 (preformed ePTFE knot implantation device; Harpoon Medical, Inc.) has recently been reported.[30] The Harpoon device is similar to the NeoChord device: PTFE sutures are delivered via a transapical approach to perform chordal repair under TEE guidance. Key differences include a smaller diameter shaft (3 vs 8 mm), a hemostasis valve in the introducer to reduce bleeding, and the option to insert the PTFE suture anywhere on the mitral leaflet. However, it is not possible to remove a suture if it is improperly deployed in the leaflet.[31]

Eleven patients were included in the initial report, all with degenerative disease of the posterior leaflet.[30] All patients had acute procedural success using three to five pairs of artificial cords, and mild MR or less was achieved in all patients. At 30 days, no patients died, and there was no reoperation for MV disease. Initial results are promising, and a larger CE Mark trial enrolling 43 patients was recently completed.

V-Chordal

The V-chordal off-pump system (Edwards Lifesciences) allows precise tensioning of artificial cords off-pump, under echocardiographic guidance, after open surgical placement. A first-in-human study is complete, and adaptation for a transfemoral approach is currently in the preclinical stage.[32]

ANNULOPLASTY

Carillon

The Carillon mitral contour system (Cardiac Dimensions, Inc.) performs an indirect mitral annuloplasty by placing a nitinol device in the coronary sinus. Two self-expanding

anchors are attached to each end of a central curvilinear segment. By means of an internal jugular venous approach, the device is unsheathed under fluoroscopic and TEE guidance and the preshaped central segment (available in three lengths, 60, 70, and 80 mm) cinches the periannular tissue, particularly in the posterior segment. The device has CE Mark approval for use in functional MR, and approximately 700 implantations have been reported.[33]

Early and intermediate safety is excellent, with no device-related deaths reported in prospective multicenter trials, and very low rates of dissection or perforation of the coronary sinus.[33] Functional MR reduction can be evaluated in real-time, prior to final device deployment, and significant improvement seems to persist beyond 6 to 12 months.[34] Significant improvement in NYHA class and 6-minute walk distance has been reported at 30-day to 2-year follow-up, along with improvements in a host of echocardiographic markers of LV reverse remodelling.[34,35]

However, the circumflex coronary artery frequently lies between the mitral annulus and the coronary sinus, and compression by the Carillon device can occur, causing myocardial ischemia or infarction. This compression may occur in up to 42% of patients, but it can often be overcome through careful patient selection, monitoring coronary flow during implantation, changing device size, and even intracoronary stent implantation.[36] With experience, Carillon implantation without coronary compromise is possible in 85% to 90% of patients.[37]

A pivotal double-blind, randomized trial (REDUCE FMR) is currently underway and will guide future use of this device.

Arto

The Arto system (MVRx, Inc.) system consists of a suture that tethers two anchors: one in the interatrial septum and another in the coronary sinus.[38] A connection is made using magnetic-tipped catheters, and tension is applied and adjusted to reduce the anteroposterior dimension of the native mitral annulus. This approach has been evaluated in the MAVERIC trial: a first-in-human study of 11 patients.[39] Mitral annular anteroposterior diameter decreased from 45 ± 3.3 mm to 38.7 ± 3 mm, with corresponding improvements in markers of MR and functional status. There were no periprocedural adverse events, and the procedural learning time appears to be brief.

Mitral Loop Cerclage Annuloplasty

The Mitral Loop Cerclage annuloplasty system (Tau-PNU Medical Co, Ltd.) consists of a stainless-steel cerclage tension element delivered using a multistep procedure to form a continuous loop from the coronary sinus to a basal septal perforator coronary vein and right ventricular outflow tract, with a bifid coronary sinus tricuspid bridge device (that straddles and protects the septal tricuspid leaflet and coronary conduction system) completing the loop. There is an arch-like coronary artery protection element to prevent compression of the circumflex artery, and the device can be tensioned in real-time under echocardiographic guidance to titrate the indirect annuloplasty. In a small feasibility study, the procedure was successful in four of five patients, with a reduction in MR and beneficial LV remodelling observed.[40]

Mitralign

The Mitralign transcatheter annuloplasty system (Mitralign, Inc.) is a retrograde direct annuloplasty system.[41] By means of a 14-F deflectable catheter placed in the left ventricle, a radiofrequency-assisted interventional wire crosses the posterior mitral annulus into the left atrium and allows fixation of a pledgeted suture. A bident system is then used to precisely place a second pledgeted suture, and the two sutures are cinched to complete the annuloplasty. If required, a second set of pledgets can be deployed.

Seventy-one high-risk patients with functional MR were included in the first-in-human trial reported by Nickenig et al.[42] Device success was achieved in 70.4%, and there was no intraprocedural death or conversion to MV surgery. Improvement in MR was modest, although patients treated with two pairs of pledgets may have more reduction in MR. Improvements in NYHA class and 6-minute walk distance were reported, but further follow-up in a larger cohort of patients is required to fully assess the procedure and outcomes.

Cardioband

Cardioband (Edwards Lifesciences) is a transcatheter mitral annuloplasty system that directly anchors to the mitral annulus from the left atrium, claiming "surgical-like" annuloplasty technique.[43,44] Via a transvenous, transeptal approach, a polyester fabric sleeve is delivered and fixed to the entire posterior mitral annulus using multiple stainless steel helical anchors. Tension is then applied to achieve homogeneous circumferential annular cinching.

A feasibility study included 31 patients with symptomatic moderate to severe functional MR and a left ventricular ejection fraction of 34 ± 11%. Six-month results were recently published.[11] Device success was achieved in all patients, and there was no periprocedural death or adverse events. Technical success was achieved in 29 of 31 patients, with the mean septolateral dimension reduced from 3.67 ± 0.47 cm before the procedure to 2.46 ± 0.37 mm

1 month after the procedure, with a sustained result at 6 months. Significant improvements were observed in MR grade, NYHA class, and 6-minute walk distance.

Feasibility and early safety have been demonstrated for the Cardioband system, with promising benefits with respect to reduction of MR and quality of life. Unfortunately, recurrence of MR after surgical annuloplasty repair is common, with 58.8% of patients experiencing recurrence of severe MR 2 years after repair for functional MR in the CTSNet trial.[45] Once again, more studies are required to evaluate the safety and efficacy of Cardioband.

FUTURE DIRECTIONS

The population of patients with significant MR is diverse, with a multitude of factors requiring consideration for any one patient. Most patients considered for transcatheter mitral repair are at high risk for open-heart surgery due to age and comorbidities, LV dysfunction, and a variety of other reasons.

Transcatheter MV repair currently offers improved early safety, often at the cost of reduced efficacy. For primary (degenerative) MR, this trade-off is acceptable in high-risk patients, and has led to FDA-approval of MitraClip and widespread use of the device. Improvements in the MitraClip NT system, along with improved TEE guidance and operator experience will increase the likelihood of an effective repair, improving patient outcomes. Availability of additional technologies, such as NeoChord and Harpoon, will provide additional less-invasive options for select patients with degenerative MR, particularly those with posterior leaflet prolapse.

Although chronic secondary MR clearly reduces quality of life and survival, there are only sparse data to support correction, with poor repair success rates and overall survival at just 2 years.[15,45] Updated AHA/ACC guidelines suggest surgical replacement over repair if surgery is performed for severely symptomatic patients, highlighting the different disease processes between primary and secondary MR.

The COAPT trial is a prospective, randomized, multicenter trial evaluating patients with symptomatic functional MR in the setting of cardiomyopathy. All patients are treated with maximal guideline-directed medical therapy and randomized 1:1 to MitraClip or no device therapy, with aims to enroll more than 400 subjects, with 2-year follow-up. This trial will provide high-quality evidence regarding the use of MitraClip in patients with functional MR, which is already the predominant use of the device outside of the United States. Similarly, the MITRA-FR study is a French multicenter, randomized trial currently enrolling patients randomized to optimal medical therapy with or without MitraClip intervention.

For the Carillon device, the REDUCE FMR international, randomized trial will evaluate the safety and efficacy of indirect annuloplasty compared to guideline-directed medical therapy. If benefit is shown, this will pave the way for larger trials and evaluation of other transcatheter annuloplasty devices.

Contemporary surgical MV repair frequently combines multiple techniques, such as annuloplasty and chordal reconstruction, to improve the quality and durability of the repair. The surgical edge-to-edge repair technique has improved outcomes when performed in conjunction with an annuloplasty.[46,47] Although edge-to-edge repair provides some degree of annuloplasty via reduction of the anteroposterior diameter or the mitral annulus, many believe that additional benefit may be derived by adding percutaneous annuloplasty.[46]

Indirect annuloplasty with the Carillon mitral contour system has been reported in a high-risk patient with recurrent MR 14 months after MitraClip placement.[48] Similarly, Latib et al recently described Cardioband implantation after previous percutaneous MV repair with two MitraClips for functional MR.[49]

SUMMARY

Numerous transcatheter MV repair options are now either in routine clinical use or multicenter clinical trials. Severe symptomatic MR portends impaired survival and quality of life; however, many patients are not well suited to surgical MV repair or replacement.

Recent postapproval studies of MitraClip for primary MR demonstrate very good safety and efficacy in a high-risk population, and refinements of edge-to-edge repair technology and techniques will promote success. Patients with isolated posterior leaflet prolapse may be well suited to transapical chordal repair, and increased experience with the NeoChord and Harpoon technologies may expand durable results to a wider range of patients with degenerative MR.

Limited data show improved outcomes in patients with cardiomyopathy and functional MR. MitraClip repair is often utilized given an excellent safety profile despite the absence of randomized data. Ongoing randomized trials, such as COAPT, will guide future use of MitraClip in functional MR, and likely the utility of other transcatheter MV repair devices. Various percutaneous annuloplasty approaches have reported successful first-in-human trials and remain the subject of intense research. ■

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Dale J. Murdoch, MBBS
Centre for Heart Valve Innovation
University of British Cardiology
Vancouver, British Columbia, Canada
Disclosures: None.

Robert H. Boone, MD
Centre for Heart Valve Innovation
University of British Cardiology
Vancouver, British Columbia, Canada
Disclosures: Receives speaking honoraria from Abbott Vascular.

Robert Moss, MBBS
Centre for Heart Valve Innovation
University of British Cardiology
Vancouver, British Columbia, Canada
Disclosures: Consultant to Edwards Lifesciences.

John Webb, MD
Centre for Heart Valve Innovation
University of British Cardiology
Vancouver, British Columbia, Canada
Disclosures: Receives grant support from Edwards Lifesciences; consultant to Edwards Lifesciences and Abbott Vascular.

David A. Wood, MD
Centre for Heart Valve Innovation
University of British Cardiology
Vancouver, British Columbia, Canada
(604) 875-5601; david.wood@vch.ca
Disclosures: Receives grant support from Edwards Lifesciences.