

Transcatheter Therapy of Mitral Regurgitation

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The mitral valve apparatus is a complex structure that incorporates the leaflets, chordae tendinae, papillary muscles, annulus, and left ventricle (LV) in its function. As a result, diseases that affect any of these structures can result in severe mitral regurgitation (MR), which in turn, is associated with reduced survival.¹⁻³ Classification of MR often differentiates between primary or degenerative cause attributable to diseases that affect the leaflets (eg, fibroelastic dysplasia, rheumatic disease, Barlow disease, endocarditis, prolapse) and secondary cause. In the latter category are diseases of the atrium or left ventricle, including ischemic dysfunction and functional disease (eg., dilated cardiomyopathy). Current guidelines recommend surgery in symptomatic patients with severe MR (recommendation class I), in asymptomatic patients with abnormal LV function (class I) as well as in asymptomatic patients with normal LV function when there is a high likelihood of successful repair (class IIa).^{4,5} Surgery may also be considered for secondary MR in symptomatic patients after optimal medical management (class IIb). It should be noted that the European and American College of Cardiology (ACC)/American Heart Association (AHA) guidelines differ slightly in the definitions of LV dysfunction and the level of evidence assigned to several of these recommendations.^{4,5}

Rationale for Transcatheter Therapy

Although there are no randomized trials of surgery versus medical therapy for severe, symptomatic MR, observational studies have demonstrated improved survival with surgery, particularly with repair of primary mitral regurgitation.^{5,6} Nonetheless, surgery is associated with mortality rates of 1% to 5% and morbidity rates of 10% to 20%, including stroke, reoperation, renal failure, and prolonged ventilation.⁷ This is particularly true in elderly patients and those with left ventricular dysfunction; mortality in octogenarians may be as high as 17% with morbidity occurring in more than a third of patients.⁸ Furthermore, surgery in elderly patients carries a high rate (>20%) of rehospitalization in the first 30 days in Medicare-age patients.⁹ A reduction in morbidity and rehospitalization is an important goal of current health care policy.

For patients with secondary MR attributable to LV dysfunction, survival with or without surgery is worse than in patients with a primary cause.² Unfortunately, most studies have not demonstrated improved survival with surgical annuloplasty with or without revascularization.^{10,11} In both ischemic and nonischemic functional MR, age and comorbidities are the

most important predictors of survival.¹² In these patients, surgery is indicated to provide symptomatic improvement. For this reason, it is essential to consider the efficacy of surgery in terms of MR reduction. In younger patients with primary MR, long-term freedom from repeat surgery is well documented.^{13,14} However, recurrent moderately-severe or severe MR may occur in up to 30% of patients, and it may occur earlier and more frequently in patients with ischemic MR.¹³⁻¹⁸

For these reasons, a less invasive, less morbid, less costly transcatheter approach to MR, particularly for the elderly, high-risk patient would be attractive.^{17,18} In this regard, the goals of transcatheter therapy should be measured not only in terms of MR reduction, but also in terms of symptomatic improvement, possibly including a reduction in resource utilization such as hospitalization for heart failure.

When considering the complexity of the mitral valve apparatus, it is useful to classify the transcatheter approaches according to the major structural abnormality that they address.¹⁹ Unlike the extensive toolbox available to the mitral surgeon, transcatheter approaches are still limited and often able to address only a single major element of the dysfunctional valve that contributes to the MR (Table). The remainder of this review will describe the approaches either currently approved or in clinical trial, with an emphasis on those that have progressed beyond first-in-human demonstration.

Leaflet and Chordal Repair

Mitraclip

MitraClip (Abbott Vascular, Abbott Park, IL) was the first approved and remains the most widely used transcatheter therapy for MR. The concept that underlies this device is derived from the Alfieri stitch operation, in which the middle scallops of the posterior and anterior mitral leaflets (P2 and A2, respectively) are sutured together to create a double-orifice mitral valve. This operation, usually performed with adjunctive ring annuloplasty, is effective and durable in a wide variety of pathologies, and may also be effective without annuloplasty in selected patients.^{20,21} The percutaneous analogue uses a clip placed from the ventricular side of the leaflets via a transseptal approach with standard catheterization techniques.^{22,23} Feasibility of Mitraclip was first demonstrated in the Endovascular Valve Edge-to-Edge Repair Study (EVEREST) I trial and subsequently compared with surgery in the randomized EVEREST II trial.^{24,25}

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Table. Transcatheter Therapies for Mitral Regurgitation

Anatomic Target	Device Name	Manufacturer	Development Status
Leaflet/Chordal	MitraClip	Abbott Vascular, Abbott Park, IL	CE Mark FDA approved
	NeoChord DS1000 System	Neochord Inc, Eden Prairie, MN	CE Mark
	Mitra-Spacer	Cardiosolutions Inc, West Bridgewater, MA	Phase 1 (OUS)
	MitraFlex	TransCardiac Therapeutics LLC, Atlanta, GA	Preclinical
	Middle Peak Medical	Middle Peak Medical Inc, Palo Alto, CA	Preclinical
	V-Chordal	Valtech Cardio Inc, Or Yehuda, Israel	Preclinical
Indirect annuloplasty	CARILLON XE2 Mitral Contour System	Cardiac Dimensions Inc, Kirkland, WI	CE Mark
	Kardium MR	Kardium Inc, Richmond, British Columbia, Canada	Preclinical
	Cerclage annuloplasty	National Heart, Lung, and Blood Institute, Bethesda, Maryland	Preclinical
Direct or LV annuloplasty	Percutaneous Annuloplasty System	Mitralign Inc, Tewksbury, MA	Phase 1 (OUS)
	GDS Accucinch System	Guided Delivery Systems, Santa Clara, CA	Phase 1 (OUS)
	Boa RF Catheter	QuantumCor, Inc., Laguna Niguel, California	Preclinical
	Cardioband	Valtech Cardio, Or Yehuda, Israel	Phase 1 (OUS)
	Millipede system	Millipede LLC, Ann Arbor, Michigan	Preclinical
Hybrid surgical	TASRA	MitraSpan Inc, Belmont, MA	Preclinical
	Adjustable Annuloplasty Ring	St. Jude Medical, St. Paul, MN	CE Mark
	enCor Dynaplasty ring	MiCardia Corporation, Irvine, California	CE Mark
	Cardinal Ring	Valtech Cardio Inc, Or Yehuda, Israel	CE Mark US IDE trial underway
LV remodeling	The Basal Annuloplasty of the Cardia Externally (BACE)	Mardil Medical, Minneapolis, MN	Phase 1
	Tendyne Repair	Tendyne Holdings Inc, Baltimore, MD	Preclinical
Replacement	CardiAQ	CardiAQ Valve Technologies Inc, Irvine, CA	Phase 1 (OUS)
	Tiara	Neovasc Inc, Richmond, British Columbia, Canada	Phase 1 (OUS)
	Fortis	Edwards Lifesciences Inc, Irvine, CA	Phase 1 (OUS)
	Lutter	Tendyne Holdings Inc, Roseville, MN	Preclinical with temporary human implants
	Medtronic Mitral Endovalve	Medtronic Inc, Minneapolis, MN Micro Interventional Devices Inc, Newtown, PA	Preclinical Preclinical

CE indicates Conformite Europeene; FDA, Food and Drug Administration; IDE, Investigational Device Exemption; LV, left ventricular; and OUS, Outside United States.

The clip is introduced through a 24F sheath from the right femoral vein into the left atrium via a transseptal puncture. It is then guided using a series of turning knobs and trans-esophageal echocardiographic imaging through the mitral valve into the left ventricle. A properly aligned and oriented clip can be placed on the P2 and A2 leaflet segments to create leaflet apposition before release. Repositioning before release is feasible and a second or more clips can be placed as needed for optimal MR reduction (Figure 1).²³

In the randomized EVEREST II trial, 184 patients were designated (2:1) to receive MitraClip therapy and

95 patients to undergo surgical repair or replacement.²⁶ Baseline characteristics of the study population revealed a mean age of 67 years, almost a decade older than usual surgical series of repair, as well as more comorbidities. Major adverse events at 30 days were significantly less frequent with MitraClip therapy (9.6% versus 57% with surgery, $P < 0.0001$), although much of this difference was attributable to the greater need for blood transfusion with surgery.²⁶ The primary end point of freedom from death, mitral valve surgery, and MR severity $>2+$ at 12 months in patients with initial clinical success was similar, but by intent to treat

analysis was lower with MitraClip (55%) as compared with surgery (73%, $P=0.0007$).

Subsequent analyses of this trial have demonstrated that in patients with acute MitraClip therapy success, the results are durable with persistent reductions in MR grade and a very low rate of later mitral valve surgery. At 4 years, overall mortality was similar in the 2 groups, mitral valve surgery was used more often after MitraClip (25% versus 5% after surgery), and moderate or severe MR was more common after transcatheter therapy. The primary combined end point of freedom from death, surgery, or 3+ or 4+ MR in the intention-to-treat population was lower (40%) with percutaneous repair and 53% with surgery ($P=0.070$). However, patients with a good result after MitraClip had sustained improvement for 4 years (Figure 2).²⁷ These patients have improvement in New York Heart Association class and a reduction in LV dimensions.^{26,27} Other studies have demonstrated a lack of mitral stenosis, no effect of initial rhythm on the results, and benefit in high-risk subjects.^{28–30}

High-risk patient subgroups have been a particular area of interest, given the failure to achieve efficacy that is equivalent

to surgery in low-risk patients with primary MR suitable for repair. In the EVEREST II High-Risk Study, 78 patients with an estimated surgical risk of 30-day mortality of 14% were treated with MitraClip with an actual mortality of 8%. These patients had a 1-year survival of 76%, significantly better than a concurrently screened comparison group treated medically.³⁰ Of note, these patients had improved MR grade (78% $\leq 2+$), reverse LV remodeling, improved functional class and quality of life, and a reduced need for hospitalization.³⁰ Similar benefit was demonstrated in a European series of extreme-risk patients.³¹ Recently, a group of European investigators demonstrated feasibility of MitraClip therapy in 51 severely symptomatic patients with secondary ischemic or functional MR who failed to respond to cardiac resynchronization therapy.³² Overall 30-day mortality was low at 4%, and $\approx 70\%$ of patients experienced improvement in functional class, LV ejection fraction, and a reduction in ventricular volumes at 1 year.³² In a recent European registry, investigators demonstrated that patients being treated commercially tended to be high-risk, elderly, and most (77%) had a functional cause.³³ Overall 30-day mortality was 3.4% with

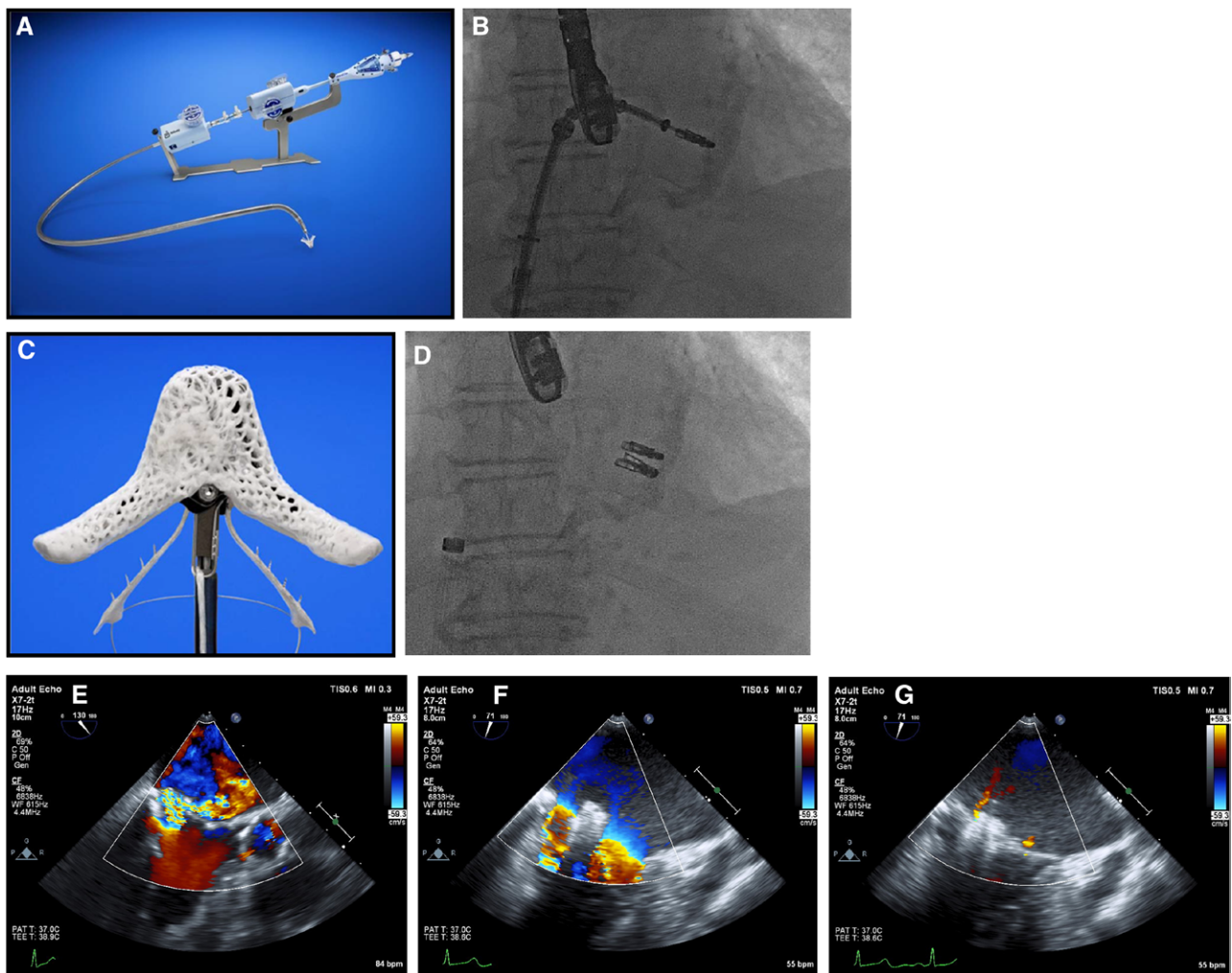


Figure 1. Top row shows the MitraClip clip delivery system (A) and its angiographic appearance during insertion of a clip (B). Second row shows a close up of a clip (C) and the angiogram in a patient after release of 2 clips (D). Bottom row shows transesophageal images from a patient with degenerative MR. From left to right: E shows systolic color flow of severe MR attributable to P2 prolapse before the procedure; F shows diastole after placement of 2 clips demonstrating the creation of a dual orifice with inflow medial and lateral to the clips; and G shows systolic color flow after clip placement with trace residual MR.

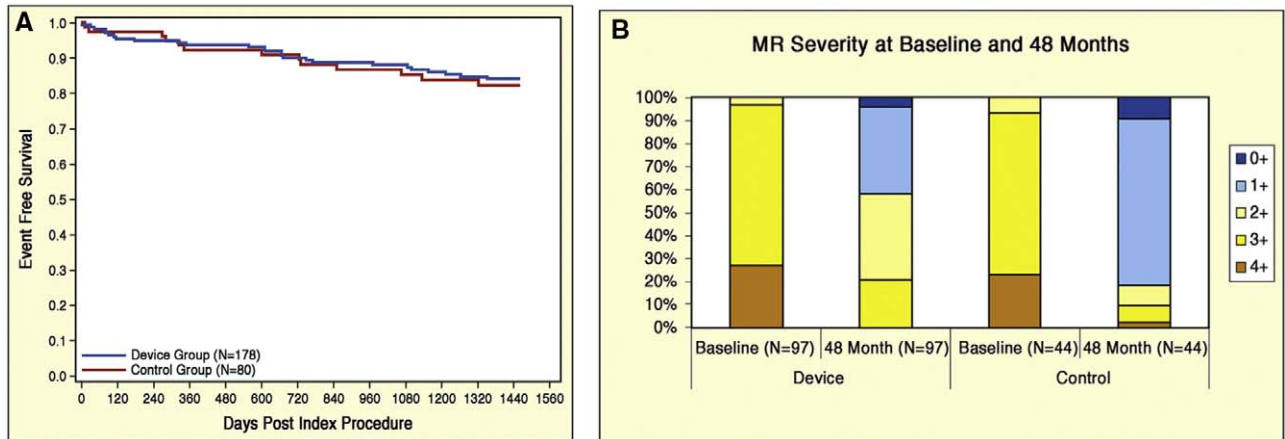


Figure 2. Event-free survival (A) and mitral regurgitation (MR) severity (B) are compared for MitraClip (device group) and surgery (control group) in the randomized, controlled Endovascular Valve Edge-to-Edge Repair Study (EVEREST) II trial with 4-year follow-up. Reproduced from Mauri et al²⁷ with permission of the publisher. Copyright ©2013, Elsevier.

1-year survival of 82%. At 12 months, 79% of patients had MR grade $\leq 2+$, 71% reported New York Heart Association class I or II symptoms, and there were significant improvements measured in 6-minute walk time (60 m) and Minnesota-living-with-heart-failure score (13.5 points).³³

Finally, Lim and colleagues reported on 127 prohibitive risk patients with degenerative MR and 1-year follow up.³⁴ These patients were elderly (mean age 82 years) and at high surgical risk (Society Thoracic Surgeons Predicted Risk of Mortality 13.2%). The 30-day mortality was less than predicted (6.3%) and 83% of surviving patients had MR $< 2+$ at 1 year, associated with a reduction in LV volumes and improved quality of life. There was a 73% reduction in hospitalization for heart failure in the year post MitraClip as compared with the year before implantation.³⁴

Although the EVEREST II trial failed to demonstrate efficacy equivalent to that of surgery for a diverse group of patients with varied (mostly low) risk and cause (mostly primary MR), the EVEREST High-Risk and Real World Expanded Multi-center Study of the MitraClip System [REALISM] registries, the European post Conformite Europeene [CE] Mark approval experience, and the prohibitive risk subset point to a more appropriate role for this technology in high-risk patients with

secondary (functional and ischemic) MR. Current European guidelines allow consideration of MitraClip for symptomatic patients with severe either primary or secondary MR despite optimal medical therapy who are judged by a heart team as inoperable or high risk for surgery with life expectancy greater than 1 year (recommendation class IIb, level of evidence C).⁴

In the United States, MitraClip received Food and Drug Administration approval in October 2013 for patients with primary (degenerative) MR who are deemed prohibitive risk for surgery by a multidisciplinary heart team. Recent ACC/AHA guidelines recommend (class IIb, level of evidence B) consideration of transcatheter repair for severely symptomatic patients with chronic severe primary MR, reasonable life expectancy, and prohibitive surgical risk attributable to severe comorbidities.⁵ A randomized trial (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk Patients [COAPT]) is underway to compare the device with medical therapy in patients with functional MR (clinicaltrials.gov NCT01626079). This study will examine the safety and effectiveness of MitraClip in high-surgical-risk patients with MR and heart failure with a primary effectiveness end point of superiority for recurrent heart failure hospitalizations at 1 year and a primary composite safety end point

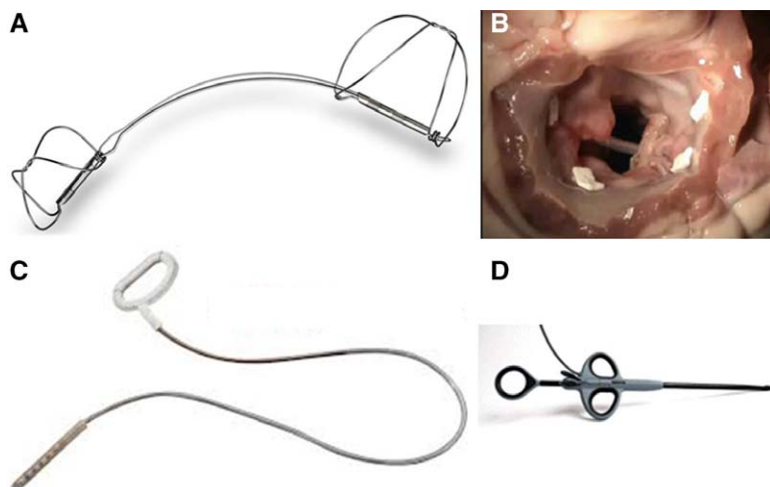


Figure 3. Several new technologies that have entered clinical investigation are illustrated. Clockwise from the top left: Carillon indirect annuloplasty (A), Mitralign direct annuloplasty in vitro result (B), enCor dynaplasty hybrid surgical ring (C), and Neochord transapical chordal device for leaflet repair (D).

of all-cause mortality, stroke, worsening renal function, or LV assist device/transplant at 1 year in about 430 patients. A similar trial in Europe, A Randomized Study of the MitraClip Device of Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation [RESHAPE-HF], is powered for a primary end point of all-cause mortality and recurrent heart failure hospitalizations with 800 patients (clinicaltrials.gov NCT01772108).

Other Leaflet and Chordal Repair Approaches

As shown in the Table, a number of other devices are in pre-clinical development or early phase 1 evaluation for transcatheter MR repair at the leaflet or chordal level. These include NeoChord, Mitra-Spacer, MitraSpan, MitraFlex, and V-Chordal (Figure 3). The NeoChord DS1000 system is a transapically inserted device that can capture a flail leaflet, pierce it with a semidull needle, attach a standard polytetrafluoroethylene artificial chord, and then anchor the chord to the apical entry site with a pledgeted suture without cardiopulmonary bypass.³⁵ Early experience with this device was obtained in 30 patients at 7 centers in the Transapical Artificial Chordae Tendinae (TACT) trial.³⁶ At 30 days, 17 patients (59%) achieved MR grade $\leq 2+$.³⁶ V-Chordal (ValtechCardio Inc, Or Yehuda, Israel) is being developed as a similar adjustable sutureless neochordal implant. This device, which is in preclinical evaluation, is implanted transseptally in the head of the papillary muscle. It has the potential advantages of avoiding the more invasive transapical approach as well as tension and wear on the implant due to apical tethering.

Mitra-Spacer (Cardiosolutions Inc, West Bridgewater, MA) is a space-occupying occluder device that is anchored in the LV apex via either a transseptal or transapical insertion technique. The tethered balloon-like spacer floats in the mitral inflow pathway, providing a space occluder around which the mitral leaflets coalesce. First-in-human results in a small number of patients with various approaches and

lengths of implantation have been reported with a reduction of MR by 1 to 2 grades.³⁷ The Mitra-Flex device (Transcatheter Therapeutics) is also designed for transapical insertion with a thorascopy to implant artificial chords and remains in preclinical development. Finally, MitraAssist Medical Ltd. (Misgav, Israel) and Middle Peak Medical Inc (Palo Alto, CA) are developing prostheses that can be attached to the native leaflet to improve coaptation. The Middle Peak Medical device simulates the shape of the posterior leaflet at end-systole, when the valve is normally closed. It can be implanted either surgically or transcatheter, anchored to the posterior LV wall, and functions as a door stop for the normally moving anterior leaflet to improve coaptation.

Indirect Annuloplasty

Much early interest in the field of transcatheter mitral repair focused on the venous anatomy of the heart, because of its ease for access from the right internal jugular vein and the proximity of the great cardiac vein and distal coronary sinus to the posterior mitral annulus. The concept was thought to mimic surgical ring annuloplasty by placement of devices in the coronary sinus which would remodel the annulus and improve leaflet coaptation. Early attempts with the MONARC (Edwards Lifesciences Inc, Irvine, CA) and Viacor (Viacor Inc, Wilmington, MA) annuloplasty systems demonstrated feasibility, but highlighted some of the difficulties encountered with this approach. A modest reduction in MR severity was achieved in a subset of patients, but there was a high incidence of adverse cardiovascular events, including early and late myocardial infarction as well as coronary sinus rupture.^{38,39}

Although this class of devices has appeal because of its simplicity and ease of insertion, the MR reduction is likely to be limited as compared with surgery and applicable to only a subset of patients with secondary MR. The limited efficacy is likely related to the cranial location (up to 10

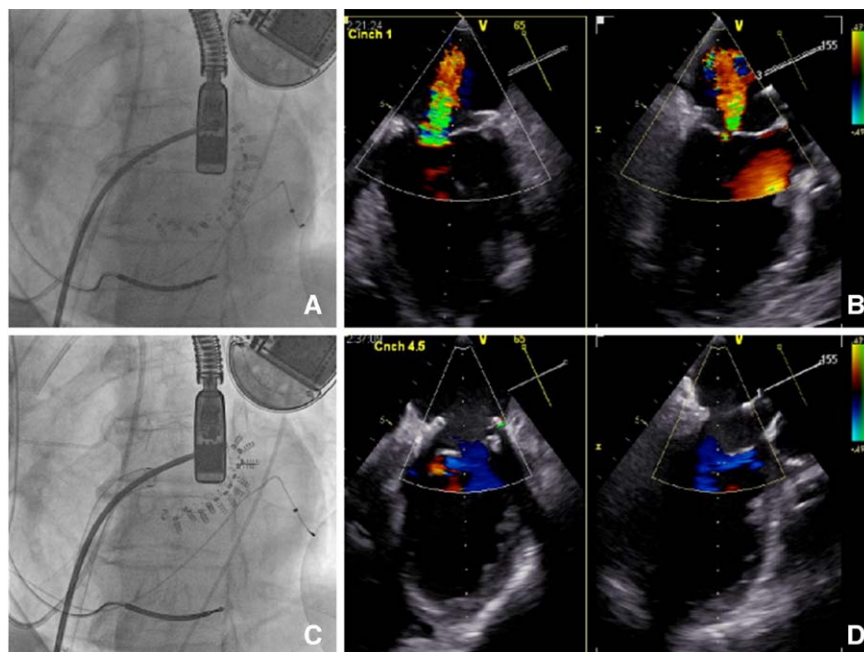


Figure 4. Angiographic image of Cardioband (A). B, Transesophageal image after Cardioband implantation but before cinching, demonstrating severe central mitral regurgitation (MR). After cinching of the device with 45% reduction of its length (C), only trace residual MR is present (D).

mm) of the coronary sinus relative to the actual mitral annulus, individual anatomic variability, and the limited benefit of partial annular remodeling.^{40,41} The risks of this approach include damage to the cardiac venous system and to the left circumflex or diagonal coronary arteries, which traverse between the coronary sinus and the mitral annulus in the majority of patients.⁴² Nonetheless, it is possible that some super-responders may be identifiable on the basis of careful preprocedure imaging and could gain benefit from this technique.

Carillon

One device (Carillon XE2, Cardiac Dimensions Inc), however, has had sufficient success to receive CE Mark in 2011 and is commercialized in Europe. This device has novel anchors placed permanently in the coronary sinus, which are then pulled toward each other with a cinching device to reduce the mitral annular circumference by traction. In the Amadeus feasibility study, the device was successfully implanted in 30 of 48 (62.5%) patients with modest improvement in quantitative measures of MR with a risk of coronary compromise (15%) and death in 1 patient.⁴³ A newer version of the device was evaluated in the Transcatheter Implantation of Carillon Mitral Annuloplasty Device (TITAN) trial.⁴¹ Among 53 enrolled subjects with secondary (64% ischemic) MR, the device was successfully implanted in 36 patients (68%). The average age of

patients was 62 years, mean LV ejection fraction was 29%, and 3 to 4+ MR was present in 80%. Quantitative measures of MR as well as measures of LV remodeling, functional status, and quality of life were all improved at 6 and 12 months, both compared with baseline and to the 17 patients who were enrolled in the trial and did not receive implants.⁴⁴

Cerclage

One novel indirect approach to reduce septal-lateral dimension that appears successful in preclinical testing is the Cerclage annuloplasty technique. This technique creates a more complete circumferential annuloplasty under fluoroscopic guidance by placing a suture from the coronary sinus through a basal septal perforator vein across a short segment of interventricular septum into the right ventricle and then returning across a tricuspid valve commissure into the right atrium, where it is snared and tensioned with the proximal end to create a closed purse-string.⁴⁵ The tension is applied under image guidance. Coronary compression is avoided using a bridge-like protection device. The technique has not yet been tested in patients.

Direct Annuloplasty, LV Remodeling, and Hybrid Techniques

Because of the limitations and failings of several of the indirect coronary sinus approaches to annular remodeling, other

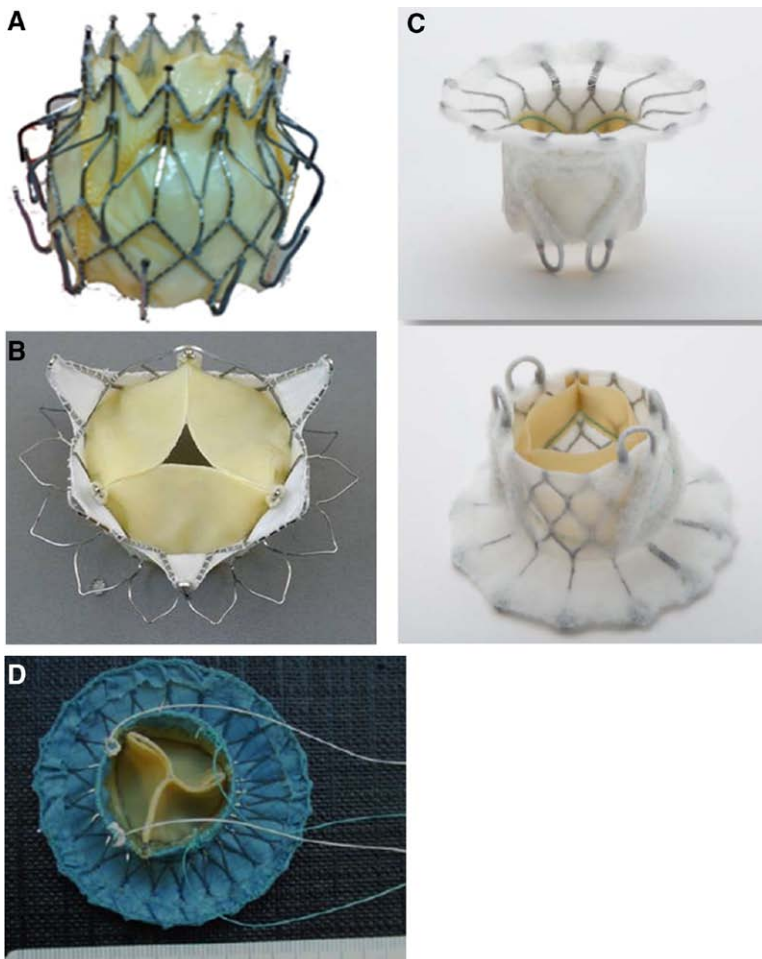


Figure 5. Transcatheter mitral valve replacement devices that are now in early clinical trials include CardiaQ (A), Tiara (B), Fortis (C), and Lutter/Tendyne (D) valves.

attempts have been made to more directly remodel the mitral annulus. These include some that work directly on the annulus and others that work on the left ventricle itself (Table), and are described below.

Cardioband

Cardioband (Valtech Medical Inc, Or Yehuda, Israel) is an adjustable, catheter-deliverable, sutureless device that is inserted transseptally. The insertion requires a steerable guide and device delivery system that is similar to the MitraClip system. The implant is a Dacron tube that is anchored to the annulus with multiple screw anchors from commissure to commissure (Figure 4). Once fully anchored, the implant is tensioned to create posterior annuloplasty with septal-lateral dimension reductions of $\approx 30\%$.⁴⁶ First-in-human was performed in 2013 in Milan, Italy and a European multi-center CE Mark trial with ≈ 25 treated patients to date is underway.

Mitralign

The Mitralign Percutaneous Annuloplasty System (Mitralign Inc, Tewksbury, MA) was originally based on the surgical technique of posterior suture plication of Paneth.⁴⁷ This procedure involves a retrograde approach to the annulus from the left ventricle with a guide catheter inserted across the aortic valve. Two pledgeted anchors are inserted with the aid of a radiofrequency wire puncture of the annulus and then pulled together to shorten or plicate the annulus and fixed with a stainless steel lock. Two sets of paired anchors are placed at both commissures. In a phase 1 report, septal-lateral dimension was reduced up to 8 mm, and a multicenter CE Mark trial in Germany, Poland, Brazil, and Colombia has completed enrollment.⁴⁸

Accucinch

The Accucinch device (Guided Delivery Systems Inc, Santa Clara, CA) also uses a LV catheter approach to place up to 15 anchors along the ventricular surface of the posterior mitral annulus and is undergoing safety and feasibility studies. A cable is run through the anchors, which can be tensioned to create posterior plication. In the original attempts, the anchors were placed in the annulus, but more recently they have been placed in the ventricular myocardium just below the valve plane (percutaneous ventriculoplasty) and the procedure is characterized as a form of ventricular remodeling. Since the first press release of a patient treated in 2009, no subsequent publications of clinical results have been made available.

Other

Several other devices in this category remain either preclinical or involve hybrid surgical placement. The BOA RF catheter (QuantumCor Inc, Bothell, WA) uses radiofrequency energy delivered via a transseptal catheter to heat shrink the collagen within the mitral annulus to mimic surgical ring annuloplasty. In animals, a 20% to 25% reduction in anterior-posterior dimension was achieved with 6-month durability. A first-in-human validation study during open heart surgery is planned. MitraSpan Inc is developing a transapical catheter-based approach to annuloplasty utilizing the placement of two sutures which span and cinch the mitral annulus

from the anterior trigones to the posterior annulus. An outside U.S. feasibility trial is planned.

Three devices that have entered clinical trial involve hybrid surgical and transcatheter therapy.^{49,50} The Adjustable Annuloplasty Ring (originally Mitral Solutions, recently acquired by St. Jude Medical Inc, St. Paul, MN), The Cardinal Ring (ValtechCardio Inc, Or Yehuda, Israel) and the enCor Dynaplasty ring (MiCardia Corp, Irvine, CA) are surgically implanted annuloplasty rings that can be adjusted after surgery off-pump under physiological conditions. Both the Adjustable Annuloplasty Ring and the Cardinal Ring allow circumferential reduction with a mechanical catheter attachment. The enCor device can be reshaped with radiofrequency energy supplied via removable leads passed externally from the left atrium through the incision for connection to an activation generator. All 3 devices have CE Mark and a U.S. IDE trial with the enCor ring is underway. A subcutaneous version that allows for late activation on an outpatient basis as well as transcatheter version are under development. The potential to improve surgical outcomes by allowing fine tuning of the ring size or shape under nonsurgical conditions or at a future time if further MR or ventricular enlargement occurs is intriguing, but requires clinical validation. A catheter-delivered ring is being developed both by MiCardia and Millipede Inc (Santa Rosa, CA).

Left Ventricular Remodeling Techniques

The rationale for therapies that affect the LV arises from an understanding of the pathophysiology of secondary ischemic and functional MR. Inferior and lateral myocardial infarction can lead to tethering or tenting of the posterior leaflet into the ventricle, allowing anterior leaflet override as the mechanism of MR.⁵¹ Failure of leaflet coaptation as a result of global LV enlargement causing annular distention is the major mechanism for MR in dilated cardiomyopathy.⁴⁵ Although ring annuloplasty can often ameliorate MR caused by LV distortion, recurrent MR resulting from progression of the underlying LV disease is common, providing further rationale for procedures that specifically address the underlying LV pathology.¹⁴⁻¹⁶

Proof of this concept was provided in the Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve (RESTOR-MV) trial utilizing the Coapsys system (Myocor Inc, Maple Grove, MN). This device used a transventricular subvalvular chord placed at the time of surgery to reshape and reduce LV end-diastolic dimension.⁵² Despite the benefit demonstrated in this trial, the company ceased operations. However, the Basal Annuloplasty of the Cardia Externally (BACE) device (Mardil Medical Inc, Plymouth, MN) has developed a surgically implanted external tension band that is placed around the heart at the time of surgical revascularization. In a preliminary report of 11 treated patients, MR grade was reduced acutely from grad 3.3 to 0.6.⁵³ Preclinical work with a transcatheter approach to approximate the papillary muscles is also in development (Tendyne Repair, Tendyne Holdings Inc, Baltimore, MD).

Transcatheter Valve Replacement

The rationale for transcatheter mitral valve replacement is derived from lessons learned from surgical valve replacement,

initial attempts with transcatheter repair described above, and the early feasibility demonstrations of transcatheter replacement in mitral prostheses using aortic transcatheter heart valves. Although surgical valve replacement is the most effective method to reliably reduce MR, the risks of surgery include significant morbidity and mortality related to the incision and the need for cardiopulmonary bypass.^{7-9,18} Surgical repair is associated with improved survival as compared with replacement, possibly related to better LV remodeling.⁶ However, this observational conclusion is confounded by differences in patient baseline conditions, comorbidities, and nonvalve-sparing surgical techniques. Other studies have suggested less difference between repair and replacement, particularly in higher risk patients.^{54,55} In addition, both surgical^{11,14,15} and transcatheter²⁴⁻²⁶ valve repairs are characterized by higher rates of MR recurrence than are seen after valve replacement. Recently, a randomized trial compared 251 patients with severe ischemic MR who underwent either surgical repair (mostly simple ring annuloplasty) or chordal-sparing replacement, most with coronary revascularization.¹⁶ At 12 months of follow-up, there was no difference in the primary end point of left ventricular end-systolic volume index and more frequent recurrent moderate or severe MR in the repair group (33%) as compared with replacement (2%).

The first target populations for transcatheter mitral valve replacement are the elderly and other patients considered at high surgical risk for whom the benefits of repair are unproven and the risks of surgery are high. Balloon-expandable transcatheter aortic valves have been implanted in degenerating bioprostheses⁵⁶⁻⁶¹ and previous surgical annuloplasty rings.⁶²⁻⁶⁴ Most success has been achieved with a transapical approach, although transseptal^{57,63,64} and transatrial^{57,59} delivery have also been demonstrated. These early results have been generally favorable with excellent reduction in MR grade and low residual transmitral gradients, although complications, including valve embolization, bleeding, and death, have been reported.

Placement of transcatheter mitral prostheses in native valves has proven more challenging than either aortic implants or valve-in-valve mitral implants. Challenges include the need for a prosthesis that is larger than most aortic devices, fixation to a diseased mitral apparatus with greater valve complexity, the lack of calcium, the potential need for orientation, and the noncircular annular shape. Paravalvular leaks, already demonstrated to reduce survival after transcatheter aortic valve replacement, will likely be even less well tolerated in the mitral valve, patients with LV dysfunction, and with the higher driving pressures which may make hemolysis more common. Finally, the needs to preserve the subvalvular apparatus and to not impinge on the LV outflow tract pose additional challenges. Nonetheless, several companies have now either demonstrated first-in-human feasibility or are about to and are described below (Figure 5).

CardiaQ

The CardiaQ valve (CardiaQ Valve Technologies Inc, Winchester, MA) is a self-expanding stent-based bovine pericardial bioprosthesis using a foreshortening frame and anchor barbs for fixation. It sits in a supraannular position with a significant portion of the prosthesis in the left atrium.

Investigators reported on its initial use in 82 pigs with acute and subchronic MR, with delivery system failure in 36% and unsuccessful implant positions in 21% of the remaining completed procedures.⁶⁵ Subsequently, a first-in-human demonstration in 2012 was performed with a transseptal approach and cardiopulmonary bypass support.⁶⁶ The valve was successfully implanted, but the patient did not survive. A current redesign is underway to allow for transapical implantation and a successful implant was recently reported.

Tiara

The Tiara device (Neovasc Inc, Richmond, BC, Canada) is a D-shaped self-expanding bovine pericardial bioprosthesis with an atrial sealing skirt that is implanted via a transapical approach with a 32F delivery catheter. It is anchored to the native leaflets at 3 points. The unique D shape is a potential mechanism to avoid LV outflow tract obstruction.⁶⁷ First-in-human implants in 2 patients were recently performed.

Fortis

A recent presentation reported the first-in-human results with 4 implants of the Fortis device (Edwards Lifesciences Inc, Irvine, CA).⁶⁸ This device is also a self-expanding stent-based bovine pericardial design inserted transapically. All patients were considered extreme risk for surgery, and 3 of the 4 died within 3 months post procedure.⁶⁸

Tendyne

This device (Tendyne Medical Inc, Roseville, MN) is based on initial technology of Lozonschi et al.⁶⁹ This group published their initial experience with a transapical, off-pump, porcine self-expanding stent prosthesis in pigs. Seven of the 8 animals died as a result of paravalvular leaks, suboptimal positioning, or failure of fixation.⁶⁹ A subsequent bovine pericardial design with a unique ventricular tethering fixation system reduced embolization, and all animals with initially successful implants maintained normal hemodynamics and stability to 8 weeks.⁷⁰ Initial first-in-human temporary implants during surgical mitral valve replacement were performed in 2013.

Others

Medtronic Inc (Minneapolis, MN) is developing a self-expanding prosthesis for insertion via a transatrial approach. It is fixated to the native valve with support arms that capture the anterior and posterior leaflets. Chronic animal studies are ongoing. The Endo Valve prosthesis (Microinterventional Devices Inc, Newtown, PA) is a foldable, nonstent based, nitinol prosthesis with proprietary gripper technology that was initially developed for insertion via a minimally invasive right mini-thoracotomy. Novel features of this device included cabling to contract, reposition, and release the device as well as a fabric skirt to provide perivalvular sealing. Valtech Cardio Ltd (Or-Yehuda, Israel) is developing a mitral valve replacement system for transfemoral implantation. It requires a 2-step insertion of an initial sealing skirt followed by valve implantation. Other companies who reportedly are also developing transcatheter mitral valve implantation systems include ValveXchange (Greenwood Village, CO), Vanguard Heart, Twelve Inc, and Highlife SAS.

Conclusions

The complexity of the mitral valve apparatus and the myriad causes of MR have caused the field of transcatheter mitral valve repair and replacement to lag the success of transcatheter aortic valve replacement. The success of MitraClip in Europe and now in the United States as well as the success of aortic valve therapy has reenergized this field. However, the wide spectrum of anatomic and functional mechanisms for MR will require multiple technological solutions to improve outcomes and expand indications. Transcatheter annuloplasty approaches and valve replacement will complete the therapeutic portfolio. Nonetheless, each device and procedure will require careful prospective evaluation and the results cannot be a priori extrapolated from those of surgical repair and replacement.

In addition, as detailed in a recent clinical joint society clinical guideline,⁷¹ similar to the development of TAVR, critical components of successful programs for transcatheter treatment of MR will include a heart team approach (particularly highlighting the importance of imaging and heart failure specialists), the need for regional specialized heart valve referral centers of excellence, development of joint professional society operator and institutional competency standards, and participation in a national analysis and reporting registry.⁷¹ Fueled by the ever-growing prevalence of heart failure, which is often accompanied by significant MR, it is likely that physicians and engineers will eventually develop successful transcatheter mitral valve therapies for many patients.

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