Novel transcatheter therapies for valvular heart disease have developed tremendously over the past decade. These innovative interventional methods are largely modeled from established surgical heart valve procedures, which have started to evolve to less-invasive approaches. Until a decade ago, interventional valve procedures included only balloon pulmonic, aortic, or mitral valvuloplasty, serving highly-selected patients. In 2000 and 2002, percutaneous valve therapy advanced greatly with the first catheter-based pulmonic and aortic valve replacement procedures (1,2). Since then, tens of thousands of high-risk patients have had percutaneous pulmonic and aortic valve replacement worldwide. Although a variety of mitral valve (MV) transcatheter therapies grew in parallel with aortic valve therapies, the MV therapies have had a slower development path. Challenges arising from the complex anatomy of the MV and mitral apparatus and the interplay of the MV with the left ventricle (LV) contribute to the greater difficulty in conceiving of and evaluating mitral devices.

Severe mitral regurgitation (MR) is an insidious disorder that develops gradually over many years and carries an annual mortality rate of at least 5% (3,4). Medical therapy relieves symptoms but does not reverse the underlying mitral pathology. Those with degenerative MR have excellent outcomes with repair surgery (5). The long-term benefits of surgical treatment of functional MR are harder to demonstrate and remain controversial (6–9).

A number of transcatheter MV therapies have been adapted from surgical techniques and are being applied in patients at high-risk for surgery as a result of coexisting comorbidities, among whom there is a large unmet clinical need (10). Catheter device approaches for leaflet repair, indirect and direct annuloplasty, chordal replacement, and LV remodeling for the treatment of MR are under development for these patients who otherwise do not have a good therapy option.

**Leaflet Repair**

In 1991, Alfieri et al. (11) described a simple surgical technique for suturing leaflets together to reduce MR in patients with degenerative MR. This repair technique, also known as the edge-to-edge leaflet repair, involves suturing the anterior and posterior mitral leaflet edges together near their midpoints, creating a double-orifice valve, and thereby reducing MR. Alfieri performed this surgical procedure in combination with mitral annuloplasty in most cases (12,13). In a select group of patients who underwent isolated surgical edge-to-edge repair without annuloplasty, longer-term outcomes up to 12 years were excellent (14). This concept is the basis of a catheter-based approach to mimic the edge-to-edge surgical repair.

**MitraClip.** The MitraClip (Abbott Laboratories, Abbott Park, Illinois) is a novel transvenous percutaneous device...
that creates an edge-to-edge repair for MR (15). The MitraClip remains investigational in the United States. It received CE mark approval in 2008. Catheter-based mitral repair with the MitraClip system was first performed in patients in 2003. To date, of the various transcatheter MV therapies, the largest clinical experience is with the MitraClip system, which has been implanted in over 10,000 patients worldwide.

The MitraClip is a mechanical clip that permanently opposes the middle of the anterior and posterior mitral leaflets (Fig. 1). A double-orifice is formed, and the subvalvular apparatus is spared. The procedure is performed in the cardiac catheterization laboratory in the beating heart, under general anesthesia, and with fluoroscopic and transesophageal echocardiographic guidance. The MitraClip system consists of the clip delivery system, to which the device is mounted at its distal end, and steerable guide catheter. The MitraClip comes in 1 size, made of cobalt-chromium metal alloy covered by polypropylene fabric. The clip delivery system and clip are passed through the steerable guide. The steerable catheter is 24-F at the skin and 22-F when it gains access to the left atrium, across the mitral ori-efet insertion is made to ensure stability of the device and leaflets, and then the clip is closed. The operator may release and re-adjust the position of the clip to optimize MR reduction. In approximately 40% of the cases a second clip might be required to achieve sufficient reduction in MR if the degree of MR reduction from the first device is insufficient. Three clips are used in approximately 1% of cases, and the use of as many as 4 clips has been described (16). The use of 2 clips is an integral part of the strategy of the procedure. The device manufacturer currently charges for the device on a per-procedure rather than a per-clip basis, so the expense of the procedure is not different when multiple clips are used.

The MitraClip device was used in carefully-selected patients in the initial trial experience. In addition to clinical selection criteria based verbatim on the valve guidelines (9), careful anatomic criteria were also required. These anatomic features were originally designed for degenerative MR. Subsequently, it has been recognized in real-world practice that patients with functional MR might be treated with less concern for the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) criteria. Specifically, a jet origin that extends beyond the central scallops of the line of coaptation, or is even pan-orificial, might respond to MitraClip therapy in patients with functional MR. The anatomic criteria are ideal in approximately 20% to 35% of patients with severe degenerative MR and acceptable in a larger proportion with functional MR.

The EVEREST I clinical trial established safety of the device and feasibility of the procedure (17). In the phase II EVEREST trial, 279 patients selected by the guideline criteria for mitral operation were randomized in a 2:1 ratio to undergo percutaneous repair with MitraClip (n = 184) or conventional MV repair or replacement surgery (n = 95) (Table 1) (18). Most patients (73%) had degenerative MV as the etiology of MR. In the intention-to-treat analysis, the rates of death (6%) were similar for MitraClip and surgery at 1 year. The frequency of 2+ MR was significantly higher after MitraClip, but the proportion of patients with grade 3+ or 4+ MR was not significantly different between the 2 groups at 2 years of follow-up (20% percutaneous group vs. 22% surgical group). The rate of surgery for MV dysfunction was 20% for percutaneous group as compared with 2.2% in the surgical group. The combined primary efficacy endpoint of freedom from death, from surgery for MV dysfunction, and from grade 3+ or 4+ MR was 55% in the percutaneous-repair group and 73% in the surgery group (p = 0.007). This difference was driven largely by the high rate of surgery after the initial intervention in the MitraClip group. The EVEREST II trial showed superior safety in the percutaneous-repair group as compared with the surgery group in an intention-to-treat analysis (19). This was driven primarily by a higher rate of bleeding requiring transfusion in the surgery group. Importantly, the safety of the procedure even in high-risk patients has been a large part of the acceptance of the therapy in commercial use around the world. Device embolization was not observed, and mitral stenosis was not reported. Having a MitraClip in place did not take away the option for surgical MV reconstruction (20).

A number of studies have established favorable changes in LV dimensions, loading conditions, and MR severity after MitraClip implantation (21–24). Baseline versus 24-h echocardiographic measurements demonstrated significant reductions in MR grade (mean 3.3 to 1.6), regurgitant fraction (mean 46% to 28%) and volume (mean 51 to 27 ml), and LV end-systolic and -diastolic dimensions and volume (25). Other signs of significant reversal in LV remodeling include decrease in LV mass and LV wall stress (26). Left atrial volume reduction was associated with reduction in vena contracta area >50% (27). A novel mechanism for how the MitraClip might alter LV remodeling has been proposed (28). Tissue growth into the clip forms a bridge between the anterior and posterior mitral leaflets. The anatomic formation of this bridge might interact with adjacent myocardial tissue to enhance the
fibromuscular continuity that generates enough force to counteract or constrain the distending wall stress with retardation of adverse remodeling. Histopathological studies have found progressive “healing” over the course of several months, with eventual formation of mature collagen-rich matrix and complete fibrous encapsulation on the outer surface of the device that helps to maintain device integrity and stability (29). Despite this healing process, conventional surgical MV reconstruction can usually be done in patients who received MitraClip as late as 5 years after the implantation. Most of these cases have successful surgical repair (30). Due to the fibrous tissue bridge, it is important to perform careful dissection of and have a basic understanding of the mechanism to unlock the device such that the MitraClip can be explanted safely during surgery to preserve the mitral leaflets (31,32). Although occasionally MV replacement is required after MitraClip implantation due to MV injury or difficulty in removing the clip, presence of the MitraClip itself was not a major predictor of valve replacement, rather replacement was strongly associated with anterior or bi-leaflet MV pathology—also predictors for valve replacement during surgical repair (32).

**Figure 1** MitraClip System

(A) The partially open MitraClip (Abbott Laboratories, Abbott Park, Illinois) device is shown without its fabric covering. A fine wire runs through the barbed “grippers,” which is used to raise the grippers. (B) The device in closed configuration. (C) The MitraClip is attached to the clip delivery system, which protrudes from the steerable guide catheter. (D) Control knobs allow deflection of the guide and clip delivery system to steer the system through the left atrium and position the MitraClip above the mitral orifice.

**Figure 2** Introducing the Clip

To introduce the clip, the clip delivery system is advanced through the guide into the left atrium (left). Under echocardiographic and fluoroscopic guidance, the clip is aligned perpendicular to the valve plane, with the clip arms perpendicular to the line of coaptation. It is then advanced into the left and then slowly retracted to grasp the leaflets (right). The clip is closed (right, inset), and if reduction of mitral regurgitation is satisfactory, it is released.
Historically, there has been concern for development of an acute low output state after open heart MV surgery among patients with poor LV function (33,34). A substudy of the EVEREST II trial examined acute hemodynamic effects and demonstrated that no patients developed an acute low output state immediately after MitraClip implantation (25). Favorable hemodynamic changes included improvement in forward stroke volume and cardiac index, lower LV end-diastolic pressure, reduction in systemic vascular resistance, and improvement in LV unloading conditions (35). Improvements in left-sided filling pressures and pulmonary arterial pressures have been demonstrated in those with elevated values at baseline (36).

Recently published 4-year EVEREST II follow-up showed stability of the earlier results of MitraClip (37). Freedom from death occurred in 83% of patients in the percutaneous group and 82% in the surgery group (p = 0.91). Rates of MR ≥3 to 4+ were not significantly different between the percutaneous repair group and the surgery group up to 4 years. Echocardiographic analysis demonstrated improved LV end-diastolic and -systolic volumes and dimensions, with significant improvements in clinical measures of functional status.

**High-risk subgroups.** Subgroup analysis of the randomized EVEREST II results suggested that patients with older age and functional rather than degenerative MR had outcomes most similar to conventional surgery. The EVEREST I and II trials included only surgical candidates, and it was recognized that many patients who were poor candidates for surgery were being excluded. This observation led to the EVEREST High Risk study in which patients with severe, predominantly functional MR who were high risk (estimated surgical mortality rate of ≥12%) for surgical repair or replacement were compared with a nonrandomized concurrent control group treated with standard medical therapy (38). At 1 year, there was a trend toward increased survival rate in the MitraClip group. Survival in clip-treated patients was 76% versus 55% in the control group. In addition, a 45% reduction in rate of repeat hospital stay was demonstrated. A prospective, multicenter registry involving high-risk surgical patients, the REALISM (Real World ExpAnded MuLticenter Study of the MitraClip System) registry, has found similar results (39).

Similar findings were demonstrated in the ACCESS-EU European registry for MitraClip, in which most patients treated were elderly, had multiple comorbidities, and were high-risk surgical candidates according to their European System for Cardiac Operative Risk Evaluation score (EuroSCORE) (39,40). One-year survival rate was 82%, and 70% were classified as New York Heart Association (NYHA) functional class I/II. Recently published findings from the German TRAMI (TRAnsCatheter Mitral valve Interventions) registry demonstrated similar results in which elderly patients (age >76 years) with LV dysfunction fared similarly to their younger counterparts (41).

A number of studies have shown feasibility and efficacy of the MitraClip device in patients who were deemed high risk for surgery or were inoperable (42–46). In a small, select group of 51 patients, acute outcomes of MitraClip therapy for MR were assessed (42). The average logistic EuroSCORE was 28%, and average Society of Thoracic Surgeons (STS) score was 15%. These patients were older (mean age 73 years) and had poorer LV function (mean LV ejection fraction 36%), functional MR (69%), complex valvar abnormalities, and pre-existing comorbidities. In fact, nearly 70% of these patients would have been excluded in the EVEREST trials. Most (94%) were discharged with MR grade ≤2+. All were hemodynamically stable throughout the procedure, and no major periprocedural complications were observed. Significant improvement in NYHA functional class was achieved in >90% who received the device.

The MitraClip device has been proven to have high procedural success clinical efficacy even in high-risk and critically ill patients (45). Short-term follow-up in a group with logistic EuroSCORE 41% and STS score 24% demonstrated a 92% successful MitraClip implantation rate, with reduction in MR and significant clinical improvement. Use in critically ill patients as a “bail-out” has been recently

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**Table 1  EVEREST II Randomized Trial**

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<tr>
<th>Description</th>
<th>Primary Effectiveness Endpoint</th>
<th>Primary Safety Endpoint</th>
<th>Key Inclusion Criteria</th>
<th>Key Exclusion Criteria</th>
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<tr>
<td>Completed and reported prospective multicenter trial comparing MitraClip vs. control surgical repair or replacement 279 patients enrolled at 37 sites</td>
<td>Clinical success rate Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, and MR &gt;2+ at 12 months</td>
<td>Major adverse event rate at 30 days Superiority hypothesis</td>
<td>Candidate for MV surgery Moderate to severe (3+) or severe (4+) MR Symptomatic &gt;25% EF and LVESD &lt;55 mm Asymptomatic with 1 or more of the following: LVEF 25%–60% LVESD &gt;40 mm New-onset atrial fibrillation Pulmonary hypertension</td>
<td>AMI within 12 weeks Need for other cardiac surgery Renal insufficiency Creatinine &gt;2.5 mg/dl Endocarditis Rheumatic heart disease MV anatomical exclusions MV area &lt;4.0 cm² Leaflet tip width (&lt;15 mm) and gap (&gt;3.0 mm) Leaflet tethering/coaptation depth (&gt;11 mm) and length (&lt;2 mm)</td>
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AMI = acute myocardial infarction; EF = ejection fraction; EVEREST = Endovascular Valve Edge-to-Edge Repair Study; LV = left ventricle/ventricular; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MR = mitral regurgitation; MV = mitral valve.
described with rapid improvement in hemodynamic status, allowing de-escalation and discontinuation of inotropic therapy with eventual discharge to home (44). A unique case of MitraClip as a successful rescue therapy was described in a patient with acute MR due to ruptured papillary muscle after suffering an acute myocardial infarction (47). Similar therapeutic efficacy has been demonstrated in inoperable patients (46).

A recent meta-analysis of high-risk cohorts who underwent MitraClip implantation found safety and feasibility of the device in patients with primarily functional MR and STS scores ≥12% or equivalent logistic EuroSCORE (48). Acute procedural success demonstrated MR grade ≤2+ could be achieved between 73% and 100% of a high-risk subpopulation that was sustained through 12 months. Need for MV surgery ranged from 0% to 6%. Survival rate ranged from 75% to 90% at 1 year. At 12 months, clinical outcomes demonstrated approximately 75% of patients in NYHA functional class I/II had significant improvements in 6-min walk test and quality of life and parallel improvements in echocardiographic measures.

An additional subgroup that has benefited from MitraClip therapy includes nonresponders to cardiac resynchronization therapy (CRT) (49). CRT improves morbidity, mortality, and NYHA functional class and reduces MR in advanced heart failure patients by reducing LV dyssynchrony and thereby decreasing tethering forces of the mitral apparatus (50). However, patients with persistent severe MR despite CRT have increased rates of hospital stay and major arrhythmic events, lower ejection fraction, less reverse remodeling, and a higher incidence of mortality (51–53). In the European PERMIT-CARE (Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy) trial, patients with symptomatic persistent severe MR despite optimal pharmacologic therapy and a CRT device received MitraClip (50). These patients, with predominantly functional MR and dilated ischemic cardiomyopathy (average LV ejection fraction 27%), were considered ineligible for surgery. Those who underwent MitraClip repair demonstrated a trend in significant MR improvement and reverse LV remodeling. Additionally, 75% demonstrated improved NYHA functional class I/II at 1 year.

A number of European registries have reported therapeutic success with the MitraClip in commercial practice (39,41,49,54–57). Low rates of procedure-related mortality or major complications are highly consistent across these reports. There are significant reductions in MR grade and improvements in exercise capacity lasting beyond 1 year in most patients. Taken together, consistent safety and high procedural success rates, high clinical efficacy, and improved functional status and quality have been reported in patients who are considered high risk for mitral surgery or for whom there are no options. There remain questions with regard to the magnitude and duration of the efficacy or MR reduction, the durability of clinical improvements, and the optimal selection of patients.

Before the March 2013 Food and Drug Administration (FDA) panel review on MitraClip therapy, the FDA expressed several concerns on the basis of the available data at that time. Although EVEREST II and registry experiences are consistent with regard to the procedural safety and the clinical benefits of MitraClip therapy, particularly in higher-risk–for-surgery patients, there are no current randomized trial data in higher–risk patients. The FDA commented that the REALISM and High Risk Registries were continued access protocols not intended to be used as a pivotal dataset. Thus, “FDA believes the evidence necessary for determination of safety and effectiveness sufficient for approval of a first of a kind device should not be based on a retrospective evaluation of registry data.” The FDA panel considered the proposed indication for “MitraClip use in patients with significant symptomatic MR who have been determined by a cardiac surgeon to be too high–risk for open MV surgery and in whom existing co-morbidities would not preclude the expected benefit from correction of the MR.” Ultimately, the FDA panel review resulted in a vote of 8 to 0 in favor of a reasonable assurance of safety, 4 to 5 against reasonable assurance of effectiveness, and 5 to 3 that the benefits outweigh the risks. On October 24, 2013, the FDA approved MitraClip in a carefully-defined patient subgroup “for the percutaneous reduction of significant 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, which includes a cardiac surgeon experienced in MV surgery and a cardiologist experienced in MV disease and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation” (58). An important consideration after FDA approval is how the therapy will be disseminated. The international experience has shown that new sites can be initiated with a high level of procedure success, demonstrating that the overall group learning can be transmitted to new operators and teams. The procedure technical success rate has improved from ≤90% in the EVEREST trial experience to 95% to 100% in recent international reports (42,44).

Before the FDA panel review, a pivotal randomized trial of MitraClip in a high-risk–for-surgery heart failure population was initiated. The COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High–Surgical–Risk Patients) trial is examining the safety and effectiveness of the MitraClip device in high-surgical-risk patients with MR and heart failure who are randomized to either percutaneous mitral repair or control group with standard medical therapy alone (Table 2). A similar trial in Europe, the RESHAPE–HF (A Randomized Study of the MitraClip Device of Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation), is taking place (Table 3). These randomized trials will add considerably to our understanding of the role of MitraClip therapy compared with medical therapy in a patient population that is too high risk to undergo MV surgery. These
**Table 2**

**COAPT High Risk Randomized Trial**

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<th>Description</th>
<th>Primary Effectiveness Endpoint</th>
<th>Primary Safety Endpoint</th>
<th>Key Inclusion Criteria</th>
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<tr>
<td>Prospective U.S. randomized multicenter comparison of MitraClip vs. medical therapy in extremely high-risk patients with HF</td>
<td>Superiority for recurrent HF hospital stays at 1 yr</td>
<td>Noninferiority hypothesis for composite of all-cause death, stroke, worsening kidney function, or LVAD or cardiac transplant at 1 yr</td>
<td>Functional MR $&gt;$3+ Ischemic or nonischemic cardiomyopathy Symptomatic NYHA functional class II, III, or ambulatory IV Local Site Heart Team concludes that comorbidities result in an extremely high operative risk of stroke or death $&gt;$1 HF hospital stay during prior yr and/or BNP $&gt;$400 pg/ml or NT-proBNP $&gt;$1,600 pg/ml in $&gt;$90 days treated per standards for CAD, LV dysfunction, MR, or HF including CRT, revascularization, OMT LVEF $&lt;$50% Primary MR jet originates from malcoaptation of A2-P2 scallops</td>
<td>Severe LV dysfunction is defined as LVEF $&lt;$70 mm or LVEF $&lt;$20% MV area $&lt;$4 cm$^2$ MI $&lt;$30 days Untreated clinically-significant CAD requiring revascularization CVA or TIA within 6 months or severe carotid stenosis Any percutaneous coronary, carotid, or endovascular intervention or carotid surgery within 30 days or any coronary or endovascular surgery within 6 months Untreated clinically-significant coronary artery disease requiring revascularization or tricuspid or aortic valve disease requiring surgery. CRT and/or ICD implant or revision within 90 days MVA by planimetry $&lt;$4.0 cm$^2$ Leaflet anatomy that might preclude MitraClip implantation, proper MitraClip positioning on the leaflets, or sufficient reduction in MR Severe right ventricular failure or severe tricuspid regurgitation</td>
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**CAD** — coronary artery disease; **COAPT** — Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for Extremely High Surgical Risk Patients; **CRT** — cardiac resynchronization therapy; **CVA** — cardiovascular accident; **HF** — heart failure; **ICD** — implantable cardioverter-defibrillator; **LVAD** — left ventricular assist device; **MI** — myocardial infarction; **MVA** — mitral valve area; **NT-proBNP** — N-terminal pro-B-type natriuretic peptide; **NYHA** — New York Heart Association; **OMT** — optimal medical therapy; **TIA** — transient ischemic attack; other abbreviations as in Table 1.

**Table 3**

**RESHAPE-HF Randomized Trial**

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<th>Key Inclusion Criteria</th>
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<td>Prospective, randomized, parallel-controlled, multicenter European clinical evaluation of the MitraClip device plus optimal standard-of-care therapy (Device group) compared with optimal standard-of-care therapy alone (Control group) Eligible subjects will be randomized in a 1:1 ratio to the device group or control group Approximately 800 subjects will be enrolled at up to 75 sites across Europe</td>
<td>Composite of all-cause mortality and recurrent HF hospital stays in the ITT randomized population Moderate-to-severe MR, NYHA functional class III–IV Minimum of 1 documented hospital stay for HF within 12 months or BNP $&gt;$350 pg/ml or NT-proBNP $&gt;$1,400 pg/ml LVEF $&lt;$15% and $&lt;$40% LVEDD $&gt;$55 mm</td>
<td>Degenerative MR Cardiovascular hospital stay within the last 2 weeks ACS, TIA, or CVA within 90 days Any percutaneous cardiovascular intervention, carotid surgery, cardiovascular surgery, or atrial fibrillation ablation within 90 days before randomization Implant of any rhythm management device (i.e., pacemaker, CRT or CRT-D, or ICD) within 90 days before randomization 6MWT distance $&gt;$450 m MVA by planimetry $&lt;$4.0 cm$^2$ Specific leaflet anatomy that might preclude MitraClip device implantation (evidence of calcification in the grasping area, presence of significant cleft in the grasping area, lack of both primary and secondary chordal support in the grasping area, prior mitral valve surgery, coaptation length $&lt;$2 mm, leaflet mobility length $&lt;$1 cm)</td>
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will be the first randomized clinical trials to compare nonsurgical standard-of-care medical treatment with an interventional therapy for MR. Notably, no such randomized comparison has been made for surgery compared with medical therapy for functional MR, despite ongoing controversy about the efficacy of surgery for functional MR. The COAPT and RESHAPE trials will not simply test the feasibility of percutaneous repair in patients who are too sick to undergo surgery, they also represent an important step in understanding whether MV repair offers an advantage at all in patients with failing ventricles.

**Annuloplasty**

Surgical plication of the mitral annulus with an undersized ring is the standard surgical treatment for functional MR (58,59). Annuloplasty reports describe restoration of MV competency, improved LV performance, decreased LV remodeling, and amelioration of symptoms in patients with functional MR (60–63). Despite the reduction of MR, a benefit of surgical annuloplasty on long-term mortality has not been demonstrated (8). Development of less invasive percutaneous devices has evolved over the years as an alternative to surgical annuloplasty, particularly in high-risk patients. Novel catheter-based devices have made use of the coronary sinus to achieve indirect annuloplasty, whereas other devices achieve more direct annuloplasty.

**Indirect annuloplasty.** Coronary sinus annuloplasty takes advantage of the proximity of the coronary sinus to the posterior and lateral mitral annulus (64–66). A device is placed in the coronary sinus to create tension that is transmitted to the annulus. Thus, the annular circumference is decreased, and mitral leaflet coaptation improves. The Carillon Mitral Contour System (Cardiac Dimension, Inc., Kirkland, Washington) is the only technology still using this approach. Indirect annuloplasty. Coronary sinus annuloplasty takes advantage of the proximity of the coronary sinus to the posterior and lateral mitral annulus (64–66). A device is placed in the coronary sinus to create tension that is transmitted to the annulus. Thus, the annular circumference is decreased, and mitral leaflet coaptation improves. The Carillon Mitral Contour System (Cardiac Dimension, Inc., Kirkland, Washington) is the only technology still using this approach.

It is implanted via the internal jugular vein with a 9-F delivery catheter (Fig. 3) (67). The nitinol device has a proximal and distal anchor connected by a ribbon (68). The distal anchor is released deep in the coronary sinus near the anterior commissure, whereas the proximal anchor resides near the coronary sinus ostium. To plicate tissue adjacent to the MV, direct tension is placed on the delivery system. Immediate assessment to determine its efficacy in reducing MR is possible, such that if the reduction of MR is insufficient, the device can be repositioned or removed.

A prospective, single arm feasibility study, AMADEUS (CARILLON Mitral Annuloplasty Device European Union Study), was performed to examine the safety and efficacy of the Carillon device for treatment of functional MR (69). Patients who received the device demonstrated significant reduction in mitral annular diameter and MR by at least 1 grade and improvement in functional class and quality of life during the follow-up period through 24 months. A second-generation device was used in the TITAN (The Transcatheter Implantation of the Carillon Mitral Annuloplasty Device) trial, a prospective, nonrandomized study of patients with functional MR (70). Among the 53 patients enrolled, 36 patients underwent successful permanent device implantation. Patients who received the device had significant benefit in reductions in quantitative measures of functional MR, including regurgitant volume and effective regurgitant orifice area, and favorable changes in LV remodeling sustained at 12 months. Positive clinical outcomes were reflected in significant improvement in 6-min walk test, functional class, and quality of life sustained at 24 months. In 17 of the 53 patients, the device could not be permanently implanted, due to difficulty cannulating the coronary sinus, ineffective reduction in MR, or compression of a coronary artery. The Carillon device received CE mark approval in Europe in 2011.
Despite its ease of use and immediate reduction in MR, the Carillon device has several limitations. Some of the failures to deliver the device in the early experience are clearly related to the learning curve. Understanding the coronary sinus anatomy in its relation to the MV apparatus and coronary vessels is important to understanding the implications of percutaneous device annuloplasty. Noninvasive imaging has demonstrated that the separation between the coronary sinus and mitral apparatus increases significantly in dilated hearts compared with normal hearts, with the coronary sinus occasionally coursing along the left atrium, which might result in ineffective MR reduction (71). Between 16% and 80% of patients had a coronary vessel, particularly the left circumflex artery, that coursed inferiorly to the coronary sinus (i.e., coursing between the coronary sinus and mitral apparatus) (71–75). The implication of the close relationship between the coronary sinus and circumflex artery is that the directed forces of “cinching” the device has the potential to compress the circumflex artery or its major branches. This phenomenon was observed in both the AMADEUS and TITAN trials, in which 17% and 15% of the patients, respectively, did not receive a device due to impingement of the left circumflex coronary artery. With increasing experience, this limitation has interfered less and less with device placement (70).

Another concern is wire fracture. Several patients had fractures of the nitinol wire ribbon in both the AMADEUS and TITAN trials. Importantly, wire fractures were not associated with adverse clinical events. A third-generation of the device has not had wire fractures when tested in a model that reproduced the fractures seen in earlier versions.

Other earlier indirect percutaneous mitral annuloplasty devices have fallen by the wayside, but they add to our understanding of the complexity of the MV and apparatus and the long-term implications of a device implantation (75). The Monarc device (Edwards Lifesciences, Irvine, California) had been studied in a human trial with most patients showing reduction in MR by at least 1 grade, but further study was subsequently stopped due to slow enrollment (76). The Viacor PTMA system (Viacor, Wilmington, Massachusetts) has been taken off the market due to late, fatal coronary sinus laceration (77,78).
**Direct annuloplasty.** Although indirect annuloplasty exploits the coronary sinus for its ease of use, transvascular direct annuloplasty devices attempt to more closely reproduce surgical annuloplasty. Historically, surgical annular plication by suturing (without placement of an annular reduction ring) has demonstrated some efficacy in reducing MR (79). The Mitralign system (Mitralign, Inc., Tewksbury, Massachusetts) takes a retrograde transventricular approach to gain access to the mitral annulus on the basis of the concept of suture annuloplasty. With radiofrequency energy, guidewires penetrate the mitral annulus into the left atrium, whereby pairs of pledgets are implanted in the posterior mitral annulus near A1-P1 and A3-P3 target points (Fig. 4). The pledgets are cinched together by a suture to reduce the size of the mitral annulus and hence mitral orifice area. Early human experience is promising, and a CE approval study is underway (80). The Accucinch System (Guided Delivery Systems, Santa Clara, California) is another direct annuloplasty device that also uses the retrograde transventricular approach (Fig. 5). A series of anchors are implanted beneath the MV in the basilar LV. These anchors are connected by a nitinol wire in which tethering the cord cinches the basal LV and mitral annulus. The Accucinch System also causes remodeling of the basal portion of the LV and is unique in this respect.

Also under development is a percutaneously implanted annuloplasty ring that more closely resembles a surgical ring (Fig. 6). Whereas the Mitralign and Accucinch devices take a retrograde transventricular approach, the Valtech CardioBand system (Valtech Cardio, Or Yehuda, Israel) is delivered via transseptal atrial access. Thus, the ring is implanted in the atrial side of the mitral annulus. The screw anchors are deployed from the posteroomedial commissure to the anterolateral commissure in a counter-clockwise fashion, with the ring extruded from a delivery catheter in small segments. Annular circumference is reduced by controlling tension on the band, thereby reducing the degree of MR. Early animal studies demonstrated safety and feasibility in the device, and several patients have had successful percutaneous implants (81).

**Ventricular Remodeling**

The aforementioned catheter-based MR therapies indirectly produce favorable LV remodeling, but several novel systems aim to directly remodel the LV. The iCoapsys device (Myocor, Inc., Maple Grove, Minnesota) is a novel system that aims to reduce ventricular dilation by directly remodeling the LV while also compressing the mitral annular septal-lateral dimension. Through a pericardial subxiphoid approach, 2 epicardial pads connected by a flexible suture-like cord are placed on the LV surface, 1 anterior and 1 posterior. The cord is passed through the LV between the 2 papillary muscles, bisecting the ventricle. Shortening of the cord reduces LV size in an anteroposterior dimension with a corresponding decrease in the mitral annular size in the respective dimension. The Coapsys device not only decreases annular size but reshapes the distorted LV. The safety and feasibility of this device has been tested in RESTOR-MV (Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve), a randomized trial comparing the Coapsys device with surgical internal reduction annuloplasty. Patients who received the Coapsys device demonstrated significant sustained reductions in LV chamber dimensions and volume, reduced MR, and improved survival, compared with mitral annuloplasty (82–84). Shortly after this trial, the company (Myocor, Inc.) failed financially, and the device is no longer available; however, the approach merits mention, because of the positive RESTOR-MV trial results. The study is one of the only prospective, multicenter randomized trials to show a survival benefit in the arena of MV therapy.

Another ventricular remodeling device is the Mardil Medical BACE system (Basal Annuloplasty of the Cardia Externally, Mardil Medical, Inc., Plymouth, Minnesota),
which is a novel, minimally-invasive surgical technique that places a circular band with inflatable chambers around the base of the beating heart. When the chamber gently fills with saline, the annular and subannular structures are displaced and brought closer together, changing the shape and size of the distorted LV, diminishing posterior leaflet tethering, and reducing MR (85). Yet another novel beating heart surgical device implants artificial chordae tendineae anchored to the LV apex to restore MV competency (NeoChord, Inc., Eden Prairie, Minnesota). This procedure is performed through a transapical, off-pump, beating heart approach, whereby chordoplasty is effectively performed (86,87). It has been used successfully in several patients. The technology might be adaptable to a percutaneous system.

**Percutaneous MV Replacement**

The development of percutaneous MV replacement devices is in its early stages. The challenges for mitral replacement are more complex than for the aortic valve, and it is clear that the development and testing of these devices will take more time than with transcatheter aortic valve replacement. Replacement devices for direct left atrial, antegrade trans-septal, and apical delivery are being tested in bench and pre-clinical models. The number of patients treated with these devices remains small. Although the use of transcatheter aortic valve replacement valves for mitral replacement in patients with degenerated mitral bioprosthetic valves or prior annuloplasty shows feasibility and proof of concept, there remain many challenges in treating the diseased native MV. Device delivery and anchoring and the large size and eccentric geometry of the mitral orifice are the main complexities. Although the concept that a percutaneous replacement might make repair approaches obsolete is attractive, it is premature to make a conclusion.

**Conclusions**

Transcatheter-based techniques for the treatment of clinically-significant MR have evolved tremendously in the past decade. These novel devices are primarily based upon well-known surgical techniques that have subsequently progressed to less invasive approaches. It is important to emphasize that novel percutaneous techniques in the treatment of MR are not meant to replace surgical techniques in low-risk patients who are good candidates for surgery. Among all catheter-based mitral therapies, the leaflet repair MitraClip system to date has the largest clinical experience worldwide, with established and reproducible safety profile and effective reduction of MR with amelioration of symptoms and improved quality of life in high-risk surgical patients. A randomized study of MitraClip to standard medical therapy in high-risk patients with severe MR is underway. Indirect and direct annuloplasty approaches are promising, and further investigations are pending. Financing for these new device start-up companies remains challenging, and development of some has gone in stop and starts as a consequence. These studies will add to the armamentarium of catheter-based approaches for severe MR.

**REFERENCES**


Key Words: edge–to-edge leaflet repair • MitraClip • mitral regurgitation • percutaneous annuloplasty • percutaneous mitral valve repair • transcatheter mitral repair.