Percutaneous therapy for the treatment of mitral regurgitation has emerged rapidly over the past few years. Most of the percutaneous approaches are modifications of existing surgical approaches to mitral annuloplasty or leaflet repair. Catheter-based devices mimic these surgical approaches with less procedural morbidity and mortality as a consequence of their less invasive nature. Percutaneous annuloplasty can be achieved indirectly via the coronary sinus or directly from retrograde left ventricular access. Catheter-based leaflet repair is accomplished using an implantable clip to mimic the surgical edge-to-edge technique. Several of these percutaneous approaches have been successfully used in patients to demonstrate proof of concept, while others have already stopped further development. There is increasing experience in both trials and practice to begin to define the clinical utility of percutaneous leaflet repair, and annuloplasty approaches are undergoing significant development. (J Am Coll Cardiol 2011;57:529–37) © 2011 by the American College of Cardiology Foundation

Minimally invasive approaches have been developed in almost every field in surgery. Beating-heart surgery and port surgery are 2 approaches that have been used for many years for valvular heart disease, including the development of robotic operations to minimize invasiveness and diminish the recovery time and morbidity of traditional surgery. Over the last several years, the potential to treat patients with valvular disease using entirely catheter-based, percutaneous methods has undergone rapid development. The new concepts and improvements in technology responsible for this development are remarkable, and illustrate a substantial effort by cardiovascular surgeons working in concert with cardiologists, engineers, and clinicians (1,2).

Percutaneous therapies for mitral regurgitation (MR) parallel surgical approaches that have been in use for many years, and have been largely evolved from concepts developed by surgeons. The predominant form of surgical mitral repair is annuloplasty. The placement of a ring around the mitral annulus, fixed by sutures to diminish the mitral orifice, is the most frequently used surgical therapy. Annuloplasty brings the leaflet edges closer together by diminishing the circumference of the mitral orifice, and also decreases the distance between the septal and lateral dimensions of the mitral orifice. The unique geometry of the mitral valve (MV) and apparatus creates some challenges for annuloplasty, and has led to the development of a variety of asymmetric annuloplasty ring shapes to accommodate the saddle shape of the MV, and the displacement of the posterior leaflet in cases of ischemic MR. Annuloplasty is used as an adjunctive therapy in all forms of MR repair, including functional ischemic and functional heart failure-related MR, and in conjunction with leaflet resection for patients with degenerative MR from MV prolapse. The other form of repair that is commonly used in surgery is leaflet repair. This is applied to patients with mitral prolapse or fibroelastic deficiency.

Annuloplasty Approaches

Annuloplasty is the mainstay of surgery in patients with functional MR. Annular dilation due to dilation of the left ventricle and geometric distortion of the mitral apparatus is the mechanism of MR in this group of patients. Surgical annuloplasty has been the predominant approach for functional MR. Importantly, it has been difficult to demonstrate clinical benefit from surgical mitral repair in the heart failure population. Pivotal trials of percutaneous annuloplasty devices may thus make comparisons of device therapy with medical therapy for heart failure rather than being compared to surgical annuloplasty. The degree of efficacy necessary to effect clinical improvements from any form of annuloplasty in the heart failure population has not been clearly established from prior surgical experience, and the trial pathway for developing these devices will necessarily answer many of these long-standing questions (3,4).

Percutaneous annuloplasty approaches have been both direct and indirect. Indirect approaches use the coronary sinus as a route to deliver a device that partially encircles the
mitral annulus. The coronary sinus parallels the posterior mitral leaflet, and since there is a long history of implantation of devices in the coronary sinus, this appeared to be an attractive route. Access to the coronary sinus through jugular puncture is well developed and simple. The coronary sinus encircles about two-thirds of the mitral annulus, so a device can capture most of the annular circumference. Early animal work demonstrated that coronary sinus devices could reduce the annular circumference significantly both in the normal MV and in models of MR created using pacing-induced heart failure (5).

**Indirect annuloplasty approaches.** Several approaches to the coronary sinus annuloplasty have been developed (Fig. 1). Fundamentally, all of them place a device that creates tension or a constricting force transmitted to the MV and the mitral annulus. The obvious appeal of the coronary sinus approach is simplicity and ease of use. The Cardiac Dimensions Carillon system (Cardiac Dimensions, Kirkland, Washington), the Edwards Monarc system (Edwards Lifesciences, Irvine, California), and the Viacor PTMA system (Viacor, Wilmington, Massachusetts) represent the coronary sinus devices that have some human implant experience.

The Cardiac Dimensions Carillon device (Fig. 1) is a simple nitinol wire that has been engineered into a form that includes distal and proximal anchors and a bridge element (6). After jugular puncture, a 9-F guide catheter is delivered into the distal coronary sinus. The distal anchor of the device is released, and using the guide catheter to pull from above and place tension on the coronary sinus, the mitral circumference is shortened; then, the proximal anchor is released. The first generation of the device was challenged by difficulty in anchoring. This problem was rapidly corrected with improvements in engineering, and some first-in-human experience has been successfully achieved. The major findings with this device include the ability to reduce MR by at least 1 grade in the majority of patients, with improvements in left ventricular (LV) volumes and dimensions. As a clinical measure, 6-min walk test results have been improved in this group as well, up to 6 months after treatment (7). Defining clinical success has been a challenge in the field of MR therapy. The subjectivity of New York Heart Association functional class is well appreciated. There has been no real study of the correlation between MR grade reduction and measures of functional improvement. While 6-min walk tests also have important limitations, this measure is at least quantitative, and is being

**Figure 1** Coronary Sinus Annuloplasty: The Cardiac Dimensions Carillon Device

The guide catheter is introduced through jugular venous access. The device is delivered in the distal coronary sinus, and then the guide catheter is pulled back to release the device in the coronary sinus ostium. The insets show the wireform, made of nitinol wire. Figure illustration by Craig Skaggs.
adopted with increasing frequency in trials evaluating percutaneous valve therapies.

The Edwards Monarc device is similarly implanted in the coronary sinus after cannulation with a guide catheter (8,9). The device is composed of proximal and distal self-expanding conventional nitinol stents connected by a bridge element. The distal anchor is delivered into the anterior interventricular vein, and the proximal anchor is placed near the coronary sinus ostium. Thus, this device captures a greater part of the circumference of the mitral annulus than does the Cardiac Dimensions device. The bridge is a spring that is held in its open position by the placement of absorbable suture material in the interstices of the spring. That holds the spring in an open position. The bioabsorbable material dissolves after 1 to 2 months, with slow and steady shortening of the device as the spring spaces approximate. The effect of the Cardiac Dimensions Carillon device can be assessed immediately at the time of implant, and even before complete release of the device. Thus, if the degree of reduction in MR is not sufficient, the device can be retrieved and the procedure abandoned. However, once the Edwards Monarc device is placed and released, there is no indication regarding the ultimate efficacy outcome until the spring has shortened several weeks later. Thus, there is no method to predict the outcome of MR reduction until after the implant has been completed and some time has passed. Early experience with the Edwards Monarc device has also demonstrated reductions in MR grade 1 or 2 grades in the majority of patients. Further study of the Monarc device has been stopped by the sponsor due to slow enrollment in the EVOLUTION II (Clinical Evaluation of the Edwards Lifesciences Percutaneous Mitral Annuloplasty System for the Treatment of Mitral Regurgitation) trial.

The Viacor PTMA device has a somewhat different mechanism (10–12). Subclavian puncture is used to deliver a trilumen plastic cannula into the coronary sinus. Stiff nitinol rods are passed through the lumens of the catheter to apply pressure to the central part of the posterior mitral leaflet and compress the septolateral dimension, rather than to encircle and constrict or cinch the mitral annulus. Rods of varying stiffness may be used. During the implant process, a sequence of rods may be placed through the lumens to determine the optimal amount of compression of the posterior annulus to result in a reduction in MR. Another attractive feature of this device is that the subclavian access may be re-accessed at a later date to remove rods if there is some problem with the device; or if efficacy for reduction of MR is diminished, stiffer rods may be used to replace those that were chosen during the initial implant process. The first several patients treated with this system have shown continued compression of the mitral orifice for as long as 1 year after initial implantation. The company has subsequently stopped further development of the device.

There are several limitations common to all of the coronary sinus devices. Long-standing prior experience with coronary sinus pacemaker lead implantation suggested that the integrity of the devices would not be a significant problem, but all 3 of these devices have experienced metal fatigue, with device fracture in several cases. Apparently, the mechanical stresses of the coronary sinus are greater than had been anticipated, and the complex geometric motion patterns of the coronary sinus create greater torsional forces on these devices than had been initially modeled using finite element analysis. Re-engineering of all 3 of these devices has led to better outcomes, with improvements in the frequency device fracture. Long-term study will be necessary to determine whether this remains a persistent late problem. Importantly, device fracture has not resulted in coronary sinus perforation or other important adverse events. Interestingly, device fracture in patients treated with the carillon device has not been associated with loss of efficacy in MR reduction.

A second important limitation common to this class of devices is the potential for compression of the circumflex coronary artery. The coronary sinus crosses over the circumflex coronary artery or 1 of its obtuse marginal branches in between two-thirds and three-quarters of patients (13–15). With the Cardiac Dimensions Carillon device, this compression can be appreciated at the time of implant. The position of the implant can be adjusted to diminish compression, or if needed, the device can be removed and the procedure abandoned. With the Edwards Monarc device, the potential for compression cannot be completely assessed until after shortening of the bridge element occurs several weeks later. Computed tomography scans to evaluate the relationship of the coronary sinus and the coronary arteries before device implantation are therefore particularly important with these devices. While the Viacor PTMA device does not encircle as much of the circumference of the mitral annulus, compression of the circumflex may still occur with this device as well (16). Thus, evaluation of the coronary circulation both before the procedure using computed tomography scanning and during the implant procedure using concurrent coronary arteriography is important as part of the implant procedure. In early human experience, this group of devices was successfully implanted in about two-thirds of patients. In the remaining one-third, the procedure was not successful because of either unfavorable coronary sinus geometry, difficult coronary sinus access by the guiding system, or coronary artery compression.

Despite the indirect nature of the coronary sinus approach and the challenges that have been encountered with these devices, the coronary sinus route remains highly attractive because of the simplicity of the approach. The potential for transvenous implantation makes the procedure accessible to a large population of patients and a wide range of physician operators.

**Direct annuloplasty approaches.** Direct implantation of a device into the mitral annulus would overcome some of the limitations of the indirect, coronary sinus approach (17). Direct annuloplasty might more closely mimic surgical annuloplasty ring implantation. Reaching the mitral anu-
Direct annuloplasty has the advantage of obviating coronary compression. A guide catheter must be passed retrograde transarterially across the aortic valve and maneuvered into a position within the left ventricle under the posterior mitral leaflet, adjacent to the mitral annulus. Two companies, Mitralign and Guided Delivery Systems, have utilized a direct access approach. Retrograde access to the left ventricle and posterior mitral annulus is shared by both of these devices, but each device is unique.

The Mitralign system (Mitralign, Tewksbury, Massachusetts) involves placement of the guide catheter under the middle scallop of the posterior mitral leaflet. Radiofrequency wires are used to penetrate the mitral annulus and gain access to the left atrial side of the annulus. Pledgets are passed over the wires and connected with a drawstring. Plication of the string results in drawing of the pledgets closer together. The current system employs 2 pairs of pledgets, and this results in shortening of the mitral circumference by 1 to 3 cm. The system has been employed in pre-clinical and first-in-human experiences. Clinical outcome data will require additional experience.

The second direct annuloplasty approach is the Guided Delivery Systems device (Guided Delivery Systems, Santa Clara, California) (Fig. 2). After access to the annulus, a series of as many as 12 nitinol anchors are placed in the mitral annulus. These are connected with a tether or cord that is tensioned to draw the anchors together. This device has been implanted surgically, and first-in-human experience has demonstrated the technical feasibility of percutaneous use.

Direct annuloplasty has the advantage of obviating coronary compression. Arterial access as the delivery route adds some complexity and morbidity to this procedure in comparison with a transvenous coronary sinus approach. The potential for greater efficacy in reduction of MR through the direct approach is highly attractive. The direct annuloplasty technologies are in early development, and more human experience is anticipated.

Leaflet Repair

Surgical leaflet repair has mainly utilized annuloplasty in conjunction with the techniques of leaflet resection and sliding annuloplasty. Surgical leaflet approaches are used for MV prolapse to remove some of the redundant leaflet tissue, and help to restore leaflet coaptation. No percutaneous version of leaflet resection is currently available and has yet to be developed. A less commonly utilized surgical leaflet repair approach is the edge-to-edge, or double-orifice repair (18,19). The repair is accomplished by suturing the free edges of the mitral leaflets together to form a double orifice. This surgical procedure was pioneered by Alfieri et al. (18) in the early 1990s. In most cases, annuloplasty is performed in conjunction with leaflet surgical repair. Isolated use of the edge-to-edge repair has been controversial, because most surgical experience has utilized the combination of annuloplasty and the leaflet repair. Follow-up for as long as 12 years in a small group of patients who have undergone isolated surgical edge-to-edge repair without annuloplasty has demonstrated durable clinical outcome, and thus proof of principle, with this surgical technique (19). Additional study will be needed to show how well the principle translates into clinical outcome in various populations of patients.

Evalve MitraClip. A percutaneous approach has been developed that uses a clip to create the double-orifice repair (20,21). The MitraClip system uses a guide catheter, a clip delivery catheter, and an implantable clip (Fig. 3). The guide is placed using transseptal puncture. It is 24-F proximally and tapers to 22-F at the level of the atrial septum, and is delivered over a dilator. A knob on the end of the guide is used for deflection of the tip. The delivery catheter passes coaxially through the guide, and has the MitraClip attached to its distal end. This delivery system uses 2 knobs that control mediolateral and anteroposterior steering. The MitraClip device is a 4-mm-wide cobalt-chromium implant with 2 arms. The clip arms are opened
and closed by a knob on the delivery catheter handle. The clip has a locking mechanism to maintain closure. On the inner portion of the clip are small barbs or "grippers" to secure the leaflets when the clip arms are closed. The clip is covered with polyester fabric.

The procedure is performed with general anesthesia, using fluoroscopy and transesophageal echocardiography guidance (22). Most of the maneuvering of the system is done using echocardiography (Fig. 4). Transseptal access is used to place a guide catheter into the left atrium.
Through the guide catheter, the clip delivery system is maneuvered to center the clip over the mitral orifice. The clip is partially opened and passed across the leaflets, through the chordae tendineae, and into the left ventricle. The open clip is pulled back to grasp the mitral leaflets. When the leaflets have fallen into the clip arms, the grippers are lowered, and the clip is closed. A key step at that point is evaluation of the insertion of leaflet tissue into the clip. If the leaflets have been adequately grasped, a determination of the degree of reduction in MR can be made. If needed, a second clip can be placed. The clip may be opened and closed to grasp the mitral leaflets several times. If the leaflet insertion is not adequate, or if reduction of the MR is insufficient, the clip is opened, withdrawn into the left atrium, and repositioned before crossing the leaflets and attempting another grasp. If after several attempts it appears that the degree of MR cannot be effectively reduced, the clip can be completely removed. Thus, the ability to assess the results of the procedure in real time is an important asset of this therapy.

Patients have been referred for surgical mitral repair after unsuccessful clip procedures, both with and without a clip in place. Successful surgical repair has been accomplished in this setting (23). The appearance of the leaflets in the operating room after unsuccessful clip procedures without placement of a clip has demonstrated some reddening of the leaflets, but actual tissue damage or damage to the chordae has been rare. Successful surgical repair has also been accomplished after placement of a clip. In most of these instances, MR was either not adequately controlled or it recurred after placement of a clip. The clips can be removed and surgical repair can be accomplished in the majority of patients without needing valve replacement. Patients who have required valve replacement after failed clip therapy usually have predictors for replacement such as advanced age, annular calcification, or leaflet calcification. Thus, the potential for utilization of the clip without substantial penalties regarding future surgical repair is possible.

Patients treated in the Evalve EVEREST (Endovascular Valve Edge-to-Edge Repair Study) have been selected using the American Heart Association/American College of Cardiology guideline recommendations for surgical MV repair. Patients with moderate to severe or severe MR (3 to 4+), judged by quantitative assessment of the degree of regurgitation using the American Society for Echocardiography quantitative scoring system have been included. All of the echocardiograms have been evaluated in a core laboratory. Use of the American Society for Echocardiography quantitative scoring system is important because, in usual practice, although noninvasive approaches have been widely accepted to assess severity of MR, there remain significant limitations. There is overlap in measurements for effective regurgitant orifice area, regurgitant volume, and regurgitant fraction between mild (1+) and severe (4+) angiographic MR. In practice, patients with qualitative “severe” MR by echocardiography are frequently found to have no or mild (1+) MR on angiography. In the EVEREST and EVEREST II trials, it was our experience that about one-quarter of patients referred with a clinical assessment of 3+ or 4+ MR had only ≤2+ MR in the core echocardiography laboratory. Patients were symptomatic, or if asymptomatic, had evidence of LV dysfunction for inclusion for treatment with the MitraClip. Importantly, patients with severely reduced LV dysfunction with LV ejection fraction of <25% were excluded.

On an intent-to-treat basis, 96 (90%) of the 107 EVEREST trial registry patients achieved a reduction in MR from either the clip or subsequent MV surgery after attempted clip. Of the patients with acute procedure success, 64% were discharged with mild MR (1+), and 13% had MR graded as mild to moderate (1 to 2+). Thus, 77% had ≤2+ MR. About 40% of patients were treated with 2 clips. The composite primary efficacy end point (freedom from MR >2+, cardiac surgery for valve dysfunction) and from death for the per-protocol population at 1 year was 66%, not including crossover to surgery. Three-year freedom from reoperation was just under 80%. Results have been similar in both degenerative and functional MR.

In-hospital and 30-day complications in the EVEREST trial registry included major adverse events in 9% of 107 patients. There was no procedural mortality. Bleeding requiring transfusion was the most common event, comprising almost one-half of the adverse events. There was 1 peri-procedural stroke and 1 post-procedure death. One patient underwent reoperation for failed surgical MV repair 19 days after valve repair after an unsuccessful MitraClip procedure, and 1 patient required ventilation for 20 days. No clip embolization has occurred at any time point. Partial clip detachment is the most important mechanical problem with the procedure. That occurred in 9% of the initial cohort, and was most often detected at the protocol-mandated 30-day echocardiography examination. These partial detachments were generally not associated with symptoms. Most were treated with mitral surgery, but more recently in the registry and in European experience, an additional clip has been placed. With better methods for assessment of leaflet insertion into the clip at the time of the procedure, the incidence of partial clip detachment has declined to <3%.

Careful evaluation of the echocardiographic morphology of the mitral leaflets is critical for good patient selection (Fig. 5). Patients with either degenerative or functional MR have been successfully treated. A coaptation length of at least 2 mm is needed. Thus, some tissue from both leaflets should be in contact, so there is some tissue to grasp with the clip. With a flail mitral leaflet, a flail gap ≤10 mm or a flail width on short-axis estimation <15 mm are also important anatomic features. The MR jet must arise from the central two-thirds of the line of coaptation as seen on short-axis color Doppler examination. It is common for most clinical transthoracic echocardiographic examinations to either omit or have very little short-axis color Doppler
interrogation of the MV. Adequate evaluation for this therapy requires careful scanning of the mitral funnel in the short-axis view to ensure that the jet origin is central, and ideally, relatively discrete. The baseline MV area should be >4 cm², because placement of the clip significantly diminishes the MV area, and this attention to baseline mitral area is necessary to avoid the creation of mitral stenosis. Clinically important mitral stenosis has not been created in our experience to date because of careful attention to the baseline MV area during the patient screening and selection process.

A randomized phase II clinical trial comparing the MitraClip with either surgical valve repair or replacement has been completed. In all, 279 patients have been randomized using a 2-to-1 scheme, and 12-month follow-up has been completed. The results of the trial were presented at the American College of Cardiology annual scientific sessions in 2010. Safety end points were reached in about 50% of surgery patients and 15% of MitraClip patients, showing superiority of safety for the percutaneous approach by intention to treat. A large component of the safety end point is blood transfusion, which is much more frequent with valve surgery than with the MitraClip procedure. Patients who receive transfusions after cardiac surgery have a higher mortality rate extending beyond 5 years post-operatively compared with that of patients who do not receive transfusions, demonstrating the importance of transfusion as a safety end point (24). The 1-year efficacy end point of the combined incidence of death, MV surgery, or reoperation for MV dysfunction was reached in about three-quarters of surgery patients and in two-thirds of MitraClip patients, meeting the noninferiority hypothesis for efficacy. A larger proportion of surgery patients had 0 to 1 MR. Reductions in LV volumes and dimensions were achieved in both groups after 1 year, as were improvements in New York Heart Association functional class.

The device has received continuing education approval and is undergoing increasingly wide use in Europe. The experience in clinical practice has shown several trends. Current use in Europe includes a high proportion of patients at high risk for surgery. A majority of the patients in the EVEREST registry had degenerative MR, but about three-quarters of those being treated in European practice have functional MR. The learning curve for new clinical sites has benefitted from the aggregate experience with this novel procedure. New sites are having high implant success.

![Figure 5](image_url)

Figure 5: Echocardiographic Evaluation of Morphology of Mitral Leaflets Is Critical for Good Patient Selection

(Top) A coaptation length of at least 2 mm is needed. Thus, some tissue from both leaflets should be in contact, so there is some tissue to grasp with the clip.
(Bottom) With a flail mitral leaflet, a flail gap ≤10 mm and a flail width on short-axis estimation <15 mm are also important anatomic features. The mitral regurgitation jet must arise from the central two-thirds of the line of coaptation, as seen on short-axis color Doppler examination. Figure illustration by Craig Skaggs. Modified, with permission, from Feldman et al. (20).
rates and good clinical outcomes, with average procedure device times (guide catheter insertion to guide catheter removal) under 2 h, and for cases with 1 clip implanted, frequently under 1 h. This reflects continued improvements in procedure technique, and the ability to teach new operators proper patient selection, the technique, and the use of intraprocedure echocardiographic guidance.

Future Developments

The best methods for study of these new MV therapeutic approaches are difficult to establish. Percutaneous annuloplasty approaches have been directed primarily at functional MR. Surgical annuloplasty has been most commonly performed in conjunction with coronary bypass or other valve operations. Thus, isolated percutaneous annuloplasty is not easily compared with surgical annuloplasty. The EVEREST II trial was unique in being able to compare percutaneous leaflet therapy directly with surgery. Medical therapy is the other possible comparator, especially in high-risk surgery patients. Measurement of differences in outcome in comparisons of medical therapy with devices may be difficult if patients with $2 +$ MR are studied, whereas patients with 3 to $4 +$ functional MR are less common. In addition to assessing decreases in MR grade and LV dimensions, functional results such as 6-min walk tests, and quality of life measures such as the Short Form-36 and the Kansas City Cardiomyopathy questionnaires, are important to determine the utility of MR therapy devices.

Several novel concepts are in the earliest stages of development. Beating-heart transapical chordal replacement is 1 of these concepts. Another is catheter-based, percutaneous MV replacement. Percutaneous MV replacement is in pre-clinical evaluation. Challenges include the asymmetric shape of the mitral orifice, and finding an adequate anchoring mechanism for a percutaneous prosthesis. Radiofrequency energy has been used as an annuloplasty approach to shrink the mitral annulus (25).

A fundamental problem with annuloplasty for treatment of functional MR is that MV dysfunction is caused by LV geometric distortion and LV chamber dysfunction. While annuloplasty treats MR, it has no impact on the underlying LV dysfunction. A novel therapy that effected chamber remodeling has been developed and tested in a significant human experience (26–30). Unfortunately, lack of funding during the recent financial crisis led to the demise of this effort. The Coapsys system (Myocor, Maple Grove, Minnesota) used a tether placed through the LV cavity, either during beating-heart surgery or through transpericardial percutaneous access. The ventricle is compressed between 2 external pads placed on the epicardial surface of the anterior and posterior walls and connected by the transventricular tether. This device both remolds the LV chamber and compresses the mitral annular septolateral dimension. A randomized trial comparing Coapsys surgical therapy with mitral annuloplasty for ischemic MR without ventricular remodeling has been completed, and demonstrates both sustained reductions in MR and improved survival (31). It is hoped this technology will come back into development and further testing.

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