

Mitral Valve Repair Using the MitraClip: From Concept to Reality

Early experience with the MitraClip device suggests that it may be a viable therapeutic option in selected patients with MR.

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Surgical repair of a diseased mitral valve has become the treatment of choice for significant mitral regurgitation (MR). A series of retrospective clinical studies that show that mitral valve repair, as compared to replacement, is associated with a good long-term outcome and lower mortality rate. One of the many surgical approaches for repair is called the *edge-to-edge repair*, whereby the leading edges of central scallops of the mitral leaflets are sutured together at the origin of MR, leading to stabilization of the flail/prolapsed segment and creation of a competent double-orifice mitral valve.^{1,2} Success of this surgical technique has inspired the development of a percutaneous edge-to-edge repair approach with the MitraClip system (Evalve, Inc., Menlo Park, CA). In selected patients, this innovative technique has the potential to treat MR as effectively as surgical repair while avoiding the mortality and morbidity associated with open heart surgery.

FUNCTIONAL ANATOMY OF THE MITRAL VALVE APPARATUS AND MECHANISM OF MR

The mitral valve is a complex structure with many integrated components (Figure 1A). The functional anatomy of the mitral valve includes the left ventricular myocardium, subvalvular apparatus (including papillary muscles and chordae tendineae), mitral annulus, mitral leaflets, and the left atrium. Abnormalities or malfunction of any of these components can result in MR. The mitral valve has two leaflets: the larger anterior leaflet and the smaller posterior leaflet. The posterior leaflet consists of three segments, or *scallops* (lateral, middle, and medial scallops), identified as *P1*, *P2*, and *P3*. The corresponding segments of the anterior leaflet are

referred to as the *A1*, *A2*, and *A3* segments (Figure 1B). Each leaflet is attached to the annulus and is connected to two papillary muscles by a web of strong chordae tendineae. The subvalvular apparatus withstands the left ventricular-to-left atrial systolic pressure gradient, prevents the leaflets from billowing into the left atrium, and helps to maintain ventricular shape and contractility. The experience of various approaches to mitral valve surgery has confirmed the importance of preserving the subvalvular apparatus due to its significant contribution to left ventricular contractility.^{3,4}

ETIOLOGY OF MR

Although mitral valve surgery can be performed for various types of mitral valve disease, mitral valve repair is most commonly used for degenerative mitral valve disease (myxomatous degeneration or fibroelastic deficiency) and less frequently for functional MR. Other less frequent causes, such as rheumatic mitral valve disease, infective endocarditis, or traumatic mitral valve disease, will not be discussed in this article.

DEGENERATIVE MITRAL VALVE DISEASE

Degenerative mitral valve disease can be due to either myxomatous degeneration or fibroelastic deficiency. Myxomatous degeneration, also known as *floppy mitral valve* or *Barlow's syndrome*, manifests as thickened and bulky leaflets and elongated and redundant chordae tendineae. As a result, usually several and sometimes all leaflet scallops prolapse into the left atrium, leading to ineffective coaptation and MR. On occasion, due to abnormal matrix structure, one or more chordae may rupture causing segmental leaflet flail and severe MR.

(Courtesy of Prof. Michael C. Fishbein.)

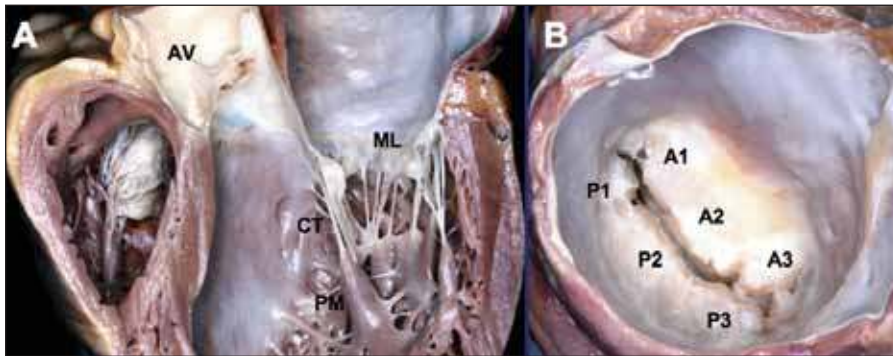


Figure 1. Normal mitral valve anatomy. The mitral valve apparatus consists of mitral leaflets (ML), chordae tendinae (CT), and papillary muscles (PM) (A). It also shows the relationship between the aortic valve (AV) and mitral leaflets (ML). This diagram shows the segments of anterior (A) and posterior (P) leaflets (B).

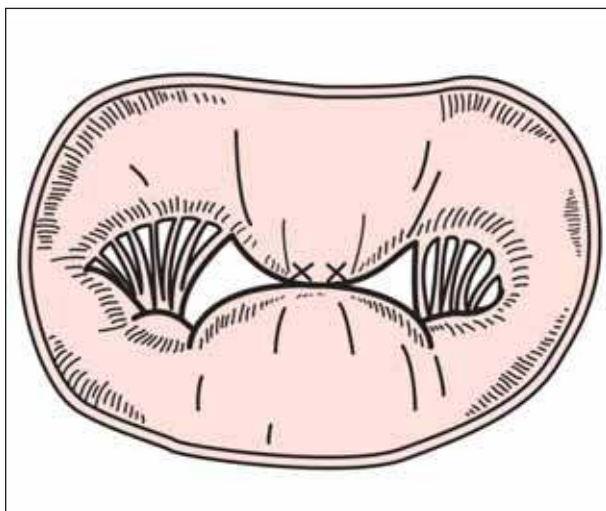


Figure 2. Alfieri edge-to-edge repair.

Fibroelastic deficiency can cause weakening of the leaflets and subvalvular apparatus, also leading to leaflet prolapse or ruptured chordae, usually limited to one scallop of the valve.

The exact pathophysiology and genetic basis of degenerative mitral valve disease are not well understood. However, there are some distinct differences between these two forms of degenerative mitral valve disease. Patients with myxomatous degeneration or Barlow's syndrome are usually younger and have redundant and thick leaflets, elongated chordae, and a high prevalence of multisegment prolapse. Patients with fibroelastic deficiency tend to be older, have normal thickness of leaflets, and have an isolated prolapsed or flail leaflet segment.

FUNCTIONAL MR

Functional MR is caused by geometric remodeling of the left ventricle without structural abnormalities of the

leaflets or chordae. This occurs in patients with idiopathic cardiomyopathy or postinfarction ventricular remodeling. MR occurs due to malcoaptation of the leaflets, which are tethered by displaced papillary muscles resulting from local or global dilation of the ventricle.

SURGICAL EDGE-TO-EDGE REPAIR

The edge-to-edge mitral valve repair technique was first described by the Italian sur-

geon Ottavio R. Alfieri, MD, and his colleagues. In 1991, while performing an open-heart surgical closure of an atrial septal defect in a 29-year-old woman, he noticed that the patient had a rare but well-described congenital abnormality (double-orifice mitral valve) and that this valve was functioning normally.⁵ Later that day, while performing a complex mitral valve repair in a patient with severe anterior leaflet prolapse, which did not restore competence with traditional techniques, Dr. Alfieri, based on what he had seen that morning, sutured the prolapsed segment of the anterior leaflet scallop to the middle scallop of the posterior leaflet. By stabilizing the prolapsed segment, he effectively reduced the MR and created a competent double-orifice mitral valve. This operation, often referred to as the *Alfieri edge-to-edge repair*, has been effectively used by Dr. Alfieri, his colleagues, and many other surgeons around the world in patients with MR of various pathologies (Figure 2).

The long-term results of this technique have been excellent. It has been successfully used for various causes of MR, including anterior prolapse, bileaflet prolapse, commissural malcoaptation, and functional MR. In one report, the long-term outcome of edge-to-edge repair in 133 patients with anterior prolapse was compared to 605 patients undergoing traditional posterior prolapse quadrangular resection. This study was conducted because traditional repair techniques are not as effective for anterior prolapse as compared to posterior prolapse. In that series, freedom from reoperation at 10 years was $9.6 \pm 2.3\%$ for the patients who underwent edge-to-edge repair for anterior prolapse, similar to those who had standard repair for posterior prolapse.⁶ Likewise, this technique has been successfully used in patients with bileaflet prolapse due to Barlow's disease.

The edge-to-edge technique has been evaluated by the same group in the treatment of functional MR. Seventy-seven patients with functional MR due to idiopathic or ischemic cardiomyopathy were treated either with an



Figure 3. The MitraClip device.

undersized annuloplasty ring alone or an undersized ring and an edge-to-edge repair. The study showed that the addition of the edge-to-edge repair to an undersized annuloplasty ring significantly improved durability of repair without causing significant mitral stenosis.⁷ This study, although small, gives some insight into the mechanisms of benefit. The apposition of the leaflets leads to effective reduction of MR, and by anchoring the leaflets together through the chordae tendineae, it may exert a supporting, or reins, effect on the left ventricle, counteracting the progression of ventricular remodeling and recurrence of MR.

RESULTS OF CONVENTIONAL SURGICAL OPTIONS FOR MR

Surgery for MR, although effective and the current standard of care, does have significant morbidity and limited scientific documentation of durability of MR reduction. Traditional repair may include partial leaflet resection, placement of an annuloplasty ring, and chordal revision or replacement. Unfortunately, the evidence base for short- and

long-term outcomes using the various techniques is incomplete. Most surgical literature quotes up to 90% freedom from reoperation at long-term follow-up, although this tends to overestimate the success rates for several reasons. First, postoperative mortality is typically not included as the primary, and second, analysis has not been on an intent-to-treat basis. With regard to the latter, the 2007 Society of Thoracic Surgeons (STS) database, reports that as many as 50% of patients with isolated mitral valve disease had prosthetic valve replacement instead of repair, thus making it likely that the success rates for repair are grossly overestimated. It should also be noted that significant morbidity, in the range of 30%, is associated with mitral valve surgery. There is, therefore, a clinical need for a less invasive approach, as well as a better evidence base for safety and effectiveness.

DEVELOPMENT OF PERCUTANEOUS EDGE-TO-EDGE REPAIR USING THE MITRACLIP

Recognizing the successful results of surgical edge-to-edge repair, it was proposed that this surgical method could be adapted into a percutaneous approach.⁸ In 1999, inspired by seeing the technique used successfully in one of our own patients, we began work on developing a percutaneous method for edge-to-edge repair, which led to the founding of Evalve, Inc.

Initial attempts focused on reproducing the surgical paradigm of a suture-based approach. While performing preclinical testing in a porcine model, it was appreciated that for the suture system to work, the leaflets needed to be stabilized. The stabilization system eventually evolved in an iterative fashion into a permanent, deployable clip known as the *MitraClip device*. The clip was designed to be removable and repositionable without causing damage to the leaflets.

The delivery system was refined for percutaneous placement in an acute porcine model, and the chronic healing response of the clip on the leaflets was evaluated in a chronic porcine model.^{9,10} Chronic studies up to 1 year confirmed that the MitraClip became encapsulated by a



Figure 4. Three echo views used to guide transseptal puncture. (A) Bicaval view (inferior-superior orientation) showing tenting of the fossa (arrow) (A). Short axis at the base (anterior-posterior orientation) showing tenting of the fossa (arrow) (B). Four-chamber view showing tenting of the septum for estimation of distance between transseptal puncture and site of leaflet coaptation (C). LA, left atrium; RA, right atrium; LV, left ventricle; RV, right ventricle; AO, aorta.

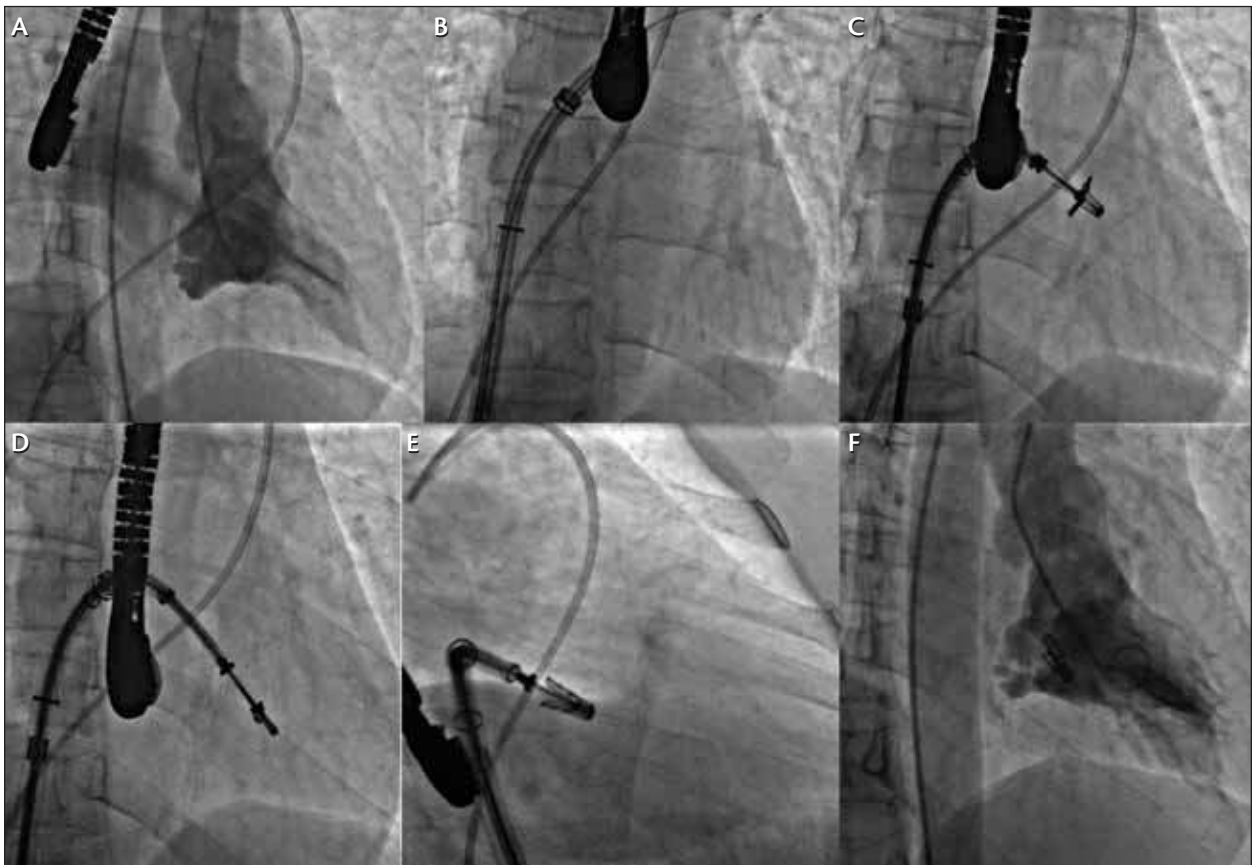


Figure 5. Fluoroscopic images of the steps of the procedure. Left ventriculogram showing severe MR (A). 22-F steerable guide catheter advanced into left atrium (B). The clip delivery system with the Mitraclip with open arms open advanced in the left atrium toward the mitral valve (C). The open MitraClip is advanced into the left ventricle (D). The MitraClip has been pulled to grasp leaflets (E). Left ventriculogram after clip placement showing trivial MR (F).

stable, fibrous tissue bridge. There was also no evidence of leaflet tissue necrosis.¹⁰ These findings were similar to a report of a human valve after surgical edge-to-edge repair, explanted 4 years later during a cardiac transplantation operation.¹¹ These acute and chronic animal studies led to approval for using this device in human clinical trials.

THE MITRACLIP PROCEDURE

The Evalve MitraClip system consists of three components: the MitraClip device, a Clip delivery system (CDS) used to position and deploy the clip, and a Steerable Guide Catheter through which the CDS is advanced into the left atrium toward the mitral valve.

The Steerable Guide Catheter is 24 F proximally (22 F where it crosses the atrial septum) and is delivered with a dilator that has echocardiographically and fluoroscopically visible coils embedded in the tapered tip. A dial on the proximal end of the Guide Catheter allows controlled deflection of the distal tip. The CDS has the MitraClip device attached to its distal end. This system is steerable using two dials that

TABLE 1. CRITERIA FOR MODERATE-SEVERE OR SEVERE MR

MR severity of moderate-severe (3+) or severe (4+) grade as defined by a minimum of three of the following criteria, one of which must be quantitative (ie, 4, 5, or 6)

1. Color flow jet may be central and larger ($>6 \text{ cm}^2$ or $>30\%$ of the left atrial area as measured in all apical four chamber or a long-axis view) or smaller if eccentric, encircling the left atrium.
2. Pulmonary vein flow may show systolic blunting or systolic flow reversal.
3. Vena contracta width $>0.3 \text{ cm}$ measured in the parasternal long-axis view.
4. Regurgitation volume of $>45 \text{ mL/beat}$.
5. Regurgitation fraction $>40\%$.
6. Regurgitation orifice area $>0.3 \text{ cm}$.

Adapted from Silvestry F, et al. J Am Soc Echocardiog. 2007;20:1131-1140.



Figure 6. Short-axis transthoracic echo showing a double-orifice mitral valve with a clip at the center (arrow).

permit medial-lateral and anterior-posterior steering.

The MitraClip device (Figure 3) is a polyester fabric-covered, cobalt-chromium implant with two arms that are opened and closed by a control mechanism on the CDS handle. The width of the clip is approximately 4 mm. On the inner portion of the clip are two “grippers” that correspond to each arm to secure the leaflets from the atrial aspect as they are “captured” during closure of the arms. Each leaflet is independently secured between an arm and a gripper. The clip has a locking mechanism to maintain the desired degree of closure. The clip arms and grippers are covered with polyester fabric to promote tissue in growth.

PROCEDURAL TECHNIQUE

The procedure is performed in a catheterization laboratory using fluoroscopy and transesophageal, and on occasion, transthoracic, echocardiographic guidance. A transseptal puncture is performed using standard equipment. The site of puncture is important and approximately 3 to 4 cm above the plane of coaptation of the leaflets (Figure 4). After transseptal puncture and subsequent administration of intravenous heparin, a stiff .035-inch guidewire is passed into the left atrium, and the transseptal sheath is exchanged for the Steerable Guide Catheter and dilator. The CDS is introduced into the Guide Catheter, and the MitraClip device is advanced into the left atrium. Using echocardiographic and fluoroscopic guidance, the clip is positioned until it is axially aligned and centered over the

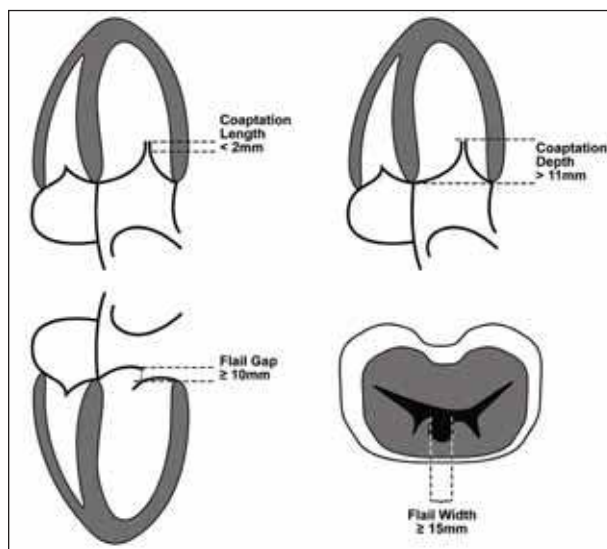


Figure 7. Key anatomical exclusion criteria.

origin of the regurgitant jet. The clip is opened, and the grippers are retracted. The arms are positioned so that they are perpendicular to the line of coaptation of the valve. The clip is advanced into the left ventricle (LV) just below the leaflets. The clip is then retracted to grasp the leaflets, the grippers are lowered, and the clip is partially closed to secure the leaflets. It usually takes more than one attempt to grasp the leaflets appropriately (Figures 5 and 6).

Leaflet insertion into the clip and MR reduction are carefully assessed using real-time echocardiography. If necessary, the leaflets can be released, and the clip can be repositioned. In the event the clip must be withdrawn back into the left atrium, the clip arms may be inverted in the ventricle providing a smooth profile for retraction, avoiding entanglement with chordae tendineae and catching on the leaflets. After adequate reduction of MR has been achieved and confirmed with appropriate hemodynamic challenge, the clip is deployed, and the CDS is withdrawn.

In cases in which there is significant residual MR, a second clip can be deployed adjacent to the first clip at the location of the residual MR. Repeat hemodynamic, angiographic, and echocardiographic assessments are performed after clip placement to verify the results, at which point the delivery system is removed. Groin hemostasis is achieved by manual compression after the activated clotting time has decreased appropriately. After repair, patients are treated with clopidogrel 75 mg daily for 30 days and with aspirin 325 mg daily for 6 months. Infective endocarditis prophylaxis is recommended.

The MitraClip procedure is best performed with a multi-specialty team of physicians and a well-trained catheterization laboratory support staff. Both the interventionist and the echocardiographer need to understand and communi-

cate information from essential transesophageal echocardiographic views.¹² The procedure is performed under general anesthesia, and a cardiac anesthesiologist plays a critical role. At various times during the procedure, the anesthesiologist may need to cease patient respiration to allow precise positioning of the clip. Manipulating the blood pressure, typically by increasing afterload, helps assess adequacy of the repair.

PATIENT SELECTION

Patients are screened for eligibility by transthoracic and transesophageal echocardiography. EVEREST study patients are required to meet basic criteria for intervention from the 1998/2006 American College of Cardiology/American Heart Association Joint Task Force recommendations regarding therapy for valvular heart disease.¹³ Patients with moderately (3+) or severe (4+) (Table 1) functional or degenerative MR who are symptomatic, or asymptomatic but with compromised LV function (LV ejection fraction <60% or LV end-systolic dimension >40 mm), are potential candidates. The origin of the MR jet should be at the A2-P2 scallops. The etiology of MR can be either functional or degenerative. Patients with MR due to rheumatic fever or endocarditis are excluded. An ejection fraction <25% and significant left ventricular dilatation (end systolic >55 mm) are other exclusion criteria. The mitral orifice needs to measure >4 cm². Other key anatomic inclusion criteria include: (1) for patients with functional MR, a coaptation length of at least 2 mm and a coaptation depth of <11 mm and (2) for patients with leaflet flail, a flail gap <10 mm and a flail width <15 mm (Figure 7).

HUMAN STUDIES USING THE MITRACLIP

The first human implant of a MitraClip was successfully performed on a 56-year-old woman in Caracas, Venezuela in June 2003, by a team lead by Dr. José Antonio Condado. Severe (4+) MR due to bileaflet prolapse was reduced to <2+ with concomitant clinical improvement. During a 2-year period, the LVEF improved (from 48% to 52%), and the enlarged left ventricle normalized in size (LV inner diameters reduced from 4.6 cm to 3.6 cm). Four years after the intervention, she remains asymptomatic and continues to have an MR grade <2+.¹⁴

After this first procedure, a phase 1 safety trial (EVEREST I) was initiated and successfully completed in the US. The 6-month results of the phase 1 data have been published.¹⁵ The primary endpoint of this study was acute safety at 30 days. There were no procedure-related complications; there were four 30-day major adverse events, including partial clip detachment in three patients, who subsequently underwent successful elective surgery, and one patient who had a post-procedure stroke that resolved at 1 month.

The presently enrolling pivotal multicenter EVEREST II

clinical trial is randomizing patients to MitraClip or surgical therapy in a 2:1 fashion. A high-risk registry arm for patients at significant risk for surgical morbidity and mortality (estimated STS score ≥ 12) has completed enrollment.

Preliminary data from nonrandomized patients enrolled in EVEREST I and in the roll-in phase of EVEREST II were presented recently.¹⁶ The patients had predominantly degenerative or combined degenerative and functional disease; the remainder had pure functional MR. Acute procedural success, defined as reduction of MR severity to <2+, was achieved in more than 75%. Less than 10% of patients had a major adverse event, including one death judged not to be device related. Few patients required surgery for complications related to transeptal puncture or the need for blood transfusions related to vascular access.

Partial clip detachment, defined as detachment of a single leaflet from the clip, occurred in <10% of patients, almost all within 30 days. Detachments were not associated with clinical events and did not require urgent intervention. The overall in-hospital mortality rate was <1%, and 30-day major adverse events including partial clip detachment without embolization were all managed with successful elective surgery. Length of hospital stay averaged <2 days.

For patients with suboptimal results or in whom a clip could not be deployed, mitral repair using standard surgical techniques was performed as late as 18 months after the percutaneous intervention.¹⁷ The percutaneous repair did not appear to have an impact on the ability of surgeons to operate on the valve subsequently, a potentially important consideration for the eventual acceptance of this procedure.

Durability data for this procedure, admittedly midterm, now include, among patients discharged with a successful result, a Kaplan-Meier 2-year freedom from death, mitral valve surgery, or recurrent MR >2+ rate of almost 80%. Although these initial data are compelling, the strategy for application and indications for this procedure in the real world remain to be determined. The degree to which this therapy is clinically successful will require both an initial and a sustained MR reduction and, depending on the patient population, will need to be comparable to surgical benchmarks. New insights will be available after the completion of the randomized arm of the EVEREST II clinical trial. This will be the first prospective study comparing two different strategies for MR patients. It is also the first time that an independent core lab assessment of MR and LV function will be performed on a group of patients undergoing surgical versus percutaneous valve therapy.

EVEREST I and the ongoing EVEREST II randomized trial include patients with both degenerative and func-

tional MR who are candidates for mitral repair surgery, representing a broad patient population. At one end of the spectrum are younger healthier patients in whom the longer-term results of mitral repair surgery have been best characterized. At the other end of the spectrum are elderly patients who are at higher risk for surgery, often in their eighth decade or with significant comorbidities.

It is remarkable that EVEREST II is the first prospective randomized study comparing two different interventions for treating patients with MR. It will therefore begin to address a very large void in the literature. The study also incorporates clinical trials methodology previously lacking in this literature and is thus the first to use independent core lab assessment of MR and LV function in evaluating patients undergoing surgery versus percutaneous valve therapy.

Although untreated functional MR has been associated with decreased survival, no clear long-term survival benefit has been demonstrated in patients with severely compromised LV function undergoing surgery for functional MR.¹⁸ Although ring annuloplasty alone in functional MR patients results in good freedom from reoperation, early reoccurrence of moderate-to-severe MR may be frequent. McGee et al reported a 28% MR (>2+) reoccurrence rate as early as 6 months.¹⁹ The initial experience using the MitraClip in patients with pure functional MR is still relatively small; however, 23 patients had similar 12-month durability compared to the overall EVEREST I population.²⁰ These encouraging results are similar to the findings of Dr. Alfieri's group, which showed that the addition of the surgical edge-to-edge repair to undersized ring annuloplasty improved the durability of the repair.⁷

These preliminary results pose an interesting question. How does the edge-to-edge repair prevent recurrence of both degenerative and functional MR? There are three proposed concepts. First, this technique mechanically re-establishes effective coaptation of the leaflet scallops. Second, the development of a clip-induced tissue bridge between the anterior and posterior leaflet scallops may help stabilize the annulus and limit septolateral annular dilatation.^{6,7} Third, a continuity between annulus, leaflets, chordae, and papillary muscles may prevent ventricular dilatation.⁷ The long-term results will help determine whether these postulated mechanisms are responsible for the success of this procedure.

CONCLUSION

Percutaneous mitral repair using the MitraClip system is based on an existing surgical technique, and initial results have been encouraging in selected patients with significant MR. This first-in-class system is the only percutaneous device that appears to be beneficial for both functional and degenerative MR. Midterm durability results are also encouraging, with preservation of surgical

options. This device will hopefully be useful for both older, sicker, higher-surgical-risk patients, as well as younger patients who prefer a less-invasive alternative. ■

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