

Mitral Valve Repair Using the MitraClip System

What the EVEREST trials have told us about this first-generation percutaneous option for treating heart valve disease.

BY D. SCOTT LIM, MD

Just as the previous decade has witnessed the maturity of percutaneous and surgical therapies for coronary artery disease, the next decade is likely to witness a tremendous change in our approach to therapy for heart valve disease. Already, we have seen a remarkable growth of percutaneously implanted heart valves in Europe and a number of novel devices being developed for repair or replacement of diseased heart valves from a transcatheter approach. This article will review the MitraClip device (Abbott Vascular, Santa Clara, CA), a novel percutaneous option for treating mitral valve disease.

PERSPECTIVE ON MITRAL REGURGITATION

Mitral regurgitation (MR) from a nonrheumatic etiology may be due to either degenerative valve disease, such as prolapse, chordal rupture, or myxomatous degeneration, or functional etiologies, such as ischemic cardiomyopathy and secondary MR. Significant MR (3 or 4+) occurs in 0.5% of the population,¹ with approximately 250,000 new cases annually in the United States. For patients with significant MR, medical therapy is ineffective in treating the underlying pathophysiology and is unable to retard disease progression. Surgical repair or replacement is the standard of care because it has been proven to be effective and low risk (1.4%–3.8% operative mortality rate).² However, it is estimated that only approximately 20% of patients with



(Courtesy of Abbott Vascular.)

Figure 1. A schematic view of the MitraClip device. The blue arms are mechanically hinged and allow the operator to change the angle between them. These arms are designed to be pulled from the ventricular side of the mitral leaflets to bring them together. The red, spiked, frictional elements may be lowered onto the atrial side of the leaflets, thereby sandwiching each leaflet between the blue arm and the red frictional element.

significant MR undergo surgery. Therefore, there is an unmet therapeutic need for patients with mitral valve disease and a significant opportunity for novel catheter-based therapies.



(Courtesy of Abbott Vascular)

Figure 2. The MitraClip in place on the mitral valve leaflets.

THE MITRACLIP SYSTEM

Since 2003, a novel percutaneous approach was developed to treat patients with nonrheumatic MR, which involves placing a metal clip (Figure 1) on the regurgitant portions of the mitral valve (Figure 2).^{3,4} This approach was derived from the known surgical approach of edge-to-edge leaflet repair as described by Alfieri.^{5,6} The MitraClip is introduced from a percutaneous, transvenous, transseptal approach to the mitral valve (Figure 3). The traditional imaging modality of fluoroscopy in the catheterization laboratory is of limited utility in this procedure because it cannot visualize the mitral leaflets. Therefore, the procedure is guided by simultaneous transesophageal imaging using both two- and three-dimensional echocardiography (Figures 4 and 5). The interventionist must be skilled in transesophageal imaging to complement the necessary catheter skills.

By placing the MitraClip on the central portions of the anterior and posterior leaflets, it acts to anchor prolapsing or flail segments, as well as coapting tethered leaflets, so that it reduces the time and force required to close the valve. By decreasing MR, the left ventricular volumes are in turn reduced, leading to beneficial left ventricular remodeling.⁷ Anatomically, the MitraClip creates a tissue bridge between the two leaflets, which limits dilation of the mitral annulus in the septal-lateral dimension, supporting the durability of this repair.⁴

EVEREST I & II TRIALS

This novel approach to percutaneous mitral valve repair was evaluated in the EVEREST trials. EVEREST I was a safety and feasibility registry in which 55 patients were enrolled for participation in the nonrandomized clinical trial.⁸ EVEREST II was the pivotal clinical trial in which 279 patients with 3 or 4+ MR were randomized to either MitraClip therapy or standard surgical therapy



Figure 3. Fluoroscopic image shows the transvenous/transseptal approach to introduce the MitraClip to the mitral valve.

(either mitral valve repair or replacement). This trial involved low- and moderate-risk patients, in comparison to the EVEREST High-Risk registry, which enrolled 79 nonoperative candidates for MitraClip therapy.

In the early nonrandomized experience with the MitraClip, procedural success (reduction of mitral regurgitation to 2+ or less) was achieved in 74% of patients, and 66% were free from death, mitral valve surgery, or MR > 2+ at 12 months.⁸ These outcomes were similar for patients with either a degenerative (79%) or functional (21%) etiology of MR. This represents the initial experience with this novel technology, which has a steep learning curve.

“... there is a significant unmet therapeutic need for patients with mitral valve disease and a significant opportunity for novel catheter-based therapies.”

The randomized EVEREST II trial included low- and moderate-risk patients with either 3 or 4+ MR who were candidates for mitral valve surgery. Patients were symptomatic with a left ventricular ejection fraction > 25% and left ventricular end-systolic dimension of < 55 mm or asymptomatic with ventricular dysfunction (defined as a left ventricular ejection fraction of 25% to 60% or left ventricular end-systolic dimension > 40 mm) or pulmonary hypertension. Patients were excluded if they had the need for other cardiac surgery, recent acute myocardial infarction (within 12 weeks), severe renal insufficiency (creatinine > 2.5 mg/dL), endocarditis, or a rheumatic etiology of valvular dys-

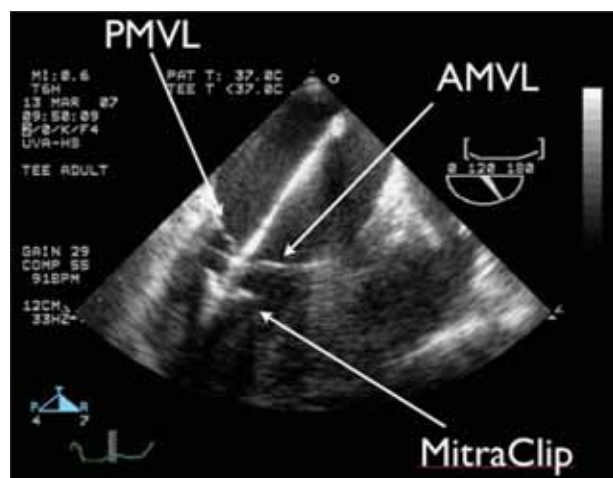


Figure 4. Two-dimensional transesophageal echocardiographic image of the MitraClip and its orientation to the anterior (AMVL) and posterior mitral valve leaflets (PMVL) is shown. This three-chamber view of the mitral valve is used to orient the MitraClip in an anterior-posterior direction on the valve.

function. Additionally, patients were excluded for certain anatomical issues of the mitral valve: stenosis with a mitral valve area $< 4 \text{ cm}^2$, a severely broad flail width ($> 15 \text{ mm}$) and flail gap ($> 10 \text{ mm}$), or deficient coaptation length ($< 2 \text{ mm}$).

Compared with patients from either the Society of Thoracic Surgeons database⁹ or patients undergoing first-time elective mitral valve surgery,¹⁰ those enrolling in the EVEREST II trial were significantly older and had more comorbidities. This is likely due to the fact that there is a preference to reserve the initial experience with novel percutaneous therapies for patients who are not ideal surgical candidates. This randomized trial was designed to have a primary safety endpoint powered for a superiority hypothesis for major adverse events at 30 days. The primary effectiveness endpoint was powered for a noninferiority hypothesis for the 12-month composite of freedom from death, mitral valve surgery or reoperation, or MR $> 2+$. Additional endpoints included MR severity, left ventricular function, New York Heart Association functional class, and quality-of-life indices.

From the primary safety endpoint, patients randomized to the MitraClip arm had a major adverse event rate of 9.6% at 30 days versus those in the surgical arm who had an event rate of 57% ($P_{\text{sup}} < .0001$) by a per-protocol statistical analysis. Further detailed analysis of the major adverse events, such as death, stroke, reoperation, or emergent surgery, showed no such events occurring in the MitraClip arm, but it did reveal these

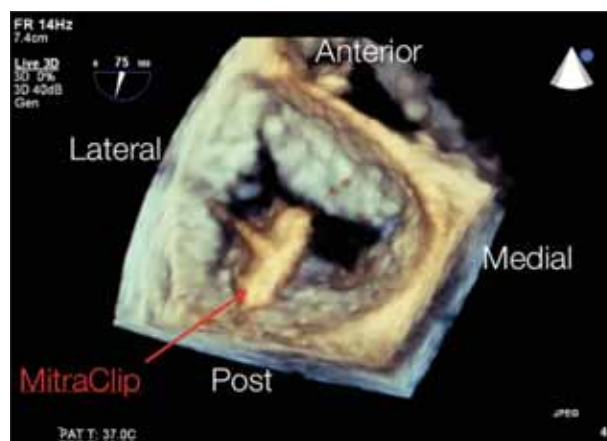


Figure 5. Three-dimensional transesophageal echocardiographic image of the MitraClip and its orientation to the mitral valve. The arms of the MitraClip are oriented perpendicular to the line of coaptation of the valve and over the point of pathology. To maintain operator orientation, the atrial septum is on the right side of the screen, with the aortic valve at approximately the 12-o'clock position.

events occurring in the surgical arm in 1.3% to 5.1% of patients. From the primary effectiveness endpoint, in terms of the clinical composite of freedom from death, mitral valve surgery/reoperation, or MR $> 2+$ at 12 months, the MitraClip arm had a success rate of 72.4% versus 87.8% with the surgical arm ($P_{\text{NI}} < .0012$). MR reduction to the endpoint and maintenance at 12 months of 2+ or less was achieved in 81.5% of the MitraClip patients versus 97% of the surgical patients, although this was achieved by mitral valve replacement in 12% of the surgical patients. Despite this difference in MR reduction as measured by echocardiography, there were similar reductions in left ventricular dimensions and volumes that were achieved at 12 months.

Additionally and paradoxically, despite the differences in apparent MR reduction, there was a greater percentage of patients from the MitraClip arm who were asymptomatic or minimally symptomatic at 12 months (97.6%) versus those in the surgical arm (87.9%). These apparent inconsistencies may be due to the difficulties in quantifying the degree of residual MR after the MitraClip has been placed in the center of the valve.

Quality-of-life indices, as measured by an SF-36 survey (a short-form, 36-question health survey to profile functional health and well-being), showed improved scores on both physical and mental evaluations in the MitraClip arm at 30 days versus impaired physical and indeterminate mental scores at 30 days in the surgical

“... collaboration among interventionists, echocardiologists, and cardiac surgeons is imperative for centers that wish to become involved in these exciting but early-stage technologies.”

arm. At 12 months, there were improvements in all study arms.

EVEREST HIGH-RISK REGISTRY

The EVEREST High-Risk registry was created as a separate registry for nonoperative patients with severe MR from either degenerative (prolapse or flail) or functional etiologies (MR secondary to ischemic or nonischemic cardiomyopathy). This registry rapidly enrolled 79 patients because it received significant support from surgical colleagues. The majority of patients in the EVEREST High-Risk registry had a functional etiology of their MR, which would be expected when finding more patients with ischemic etiologies in a higher-risk subgroup. Additionally, patients were older (average age, 76 y; 68% > 75 y) and more symptomatic (89% were New York Heart Association functional class III or IV) than the randomized EVEREST population.

Data were presented on the EVEREST High-Risk registry at the 2009 American College of Cardiology Scientific Sessions, which showed that although the predicted mortality rate for the group was 18.2% at 30 days, the actual mortality rate was 7.7%, with a 76% 1-year survival rate and 79% of the survivors in New York Heart Association symptom class I or II.¹¹ In a nonrandomized comparison to similar high-risk patients who were treated medically, there was a survival advantage at 1 year, with 76.4% of patients alive in the MitraClip group versus 54.7% in the medically treated group ($P = .037$). These data support the concept that novel percutaneous options are attractive, particularly for nonoperative patients.

Alternate options for percutaneous mitral valve repair include annuloplasty approaches, which take advantage of the anatomic relationship between the coronary sinus and the mitral valve. Devices have been designed for insertion into the coronary sinus in attempts to create a mitral annuloplasty approach. However, most of these devices are still currently in the early stages of development.

COLLABORATIVE EFFORTS

Many of the steps to percutaneous mitral valve repair rely on skills and technology that are not always avail-

able to the cardiac interventionist alone. Therefore, collaboration among interventionists, echocardiologists, and cardiac surgeons is imperative for centers that wish to become involved in these exciting but early-stage technologies. It was no accident that the first United States trial of the transcatheter aortic valve was called PARTNER, as it emphasizes the very close working relationship that is required across disciplines.

CONCLUSION

Whereas the previous decade was noted for an explosion in the utility and maturity of transcatheter interventions for coronary artery disease, the next decade will bear a similar focus on transcatheter approaches to heart valve disease. The MitraClip system represents a first-generation step in this direction, and it is remarkable for its success as such. The pendulum of excitement for these novel technologies will likely swing a bit farther at first than where the real utility of these approaches lies, and careful patient selection will always be key. ■

D. Scott Lim, MD, is Associate Professor of Cardiology and Director of the Advanced Heart Valve Center at the University of Virginia in Charlottesville. He has disclosed that he holds no financial interest in any product or manufacturer mentioned herein. He has disclosed that he receives grant/research funding from Abbott Vascular. Dr. Lim may be reached at (434) 243-0884; sl9pc@virginia.edu.

1. Jones EC, Devereux RB, Roman MJ, et al. Prevalence and correlates of mitral regurgitation in a population-based sample (the Strong Heart Study). *Am J Cardiol*. 2001;87:298-304.
2. Gammie JS, Sheng S, Griffith BP, et al. Trends in mitral valve surgery in the United States: results from the Society of Thoracic Surgeons Adult Cardiac Surgery Database. *Ann Thorac Surg*. 2009;87:1431-1437; discussion 1437-1439.
3. Fann JJ, St Goar FG, Komtebedde J, et al. Beating heart catheter-based edge-to-edge mitral valve procedure in a porcine model: efficacy and healing response. *Circulation*. 2004;110:988-993.
4. St Goar FG, Fann JJ, Komtebedde J, et al. Endovascular edge-to-edge mitral valve repair: short-term results in a porcine model. *Circulation*. 2003;108:1990-1993.
5. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg*. 2001;122:674-681.
6. Maisano F, Torracca L, Oppizzi M, et al. The edge-to-edge technique: a simplified method to correct mitral insufficiency. *Eur J Cardiothorac Surg*. 1998;13:240-245; discussion 245-246.
7. Herrmann HC, Kar S, Siegel R, et al. Effect of percutaneous mitral repair with the MitraClip device on mitral valve area and gradient. *EuroIntervention*. 2009;4:437-442.
8. Feldman T, Kar S, Rinaldi M, et al. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge Repair Study) cohort. *J Am Coll Cardiol*. 2009;54:686-694.
9. STS National Database. Mitral valve repair and replacement patients. Incidence of complications summary. <http://209.220.160.181/STSWebRiskCalc261>. Accessed July 20, 2010.
10. Gammie JS, O'Brien SM, Griffith BP, et al. Influence of hospital procedural volume on care process and mortality for patients undergoing elective surgery for mitral regurgitation. *Circulation*. 2007;115:881-887.
11. Whitlow PL, Kar S, Pederson W, et al. MitraClip therapy in the EVEREST High-Risk registry: one-year results. *EuroIntervention*. 2008;4:437-442.