Current Status of MitraClip

A review of the available data on the utility of this device for treating functional mitral regurgitation.

BY PETER S. FAIL, MD, FACC, FACP, FSCAI, AND VINOD NAIR, MD, FACC, FSCAI

It is difficult to pick up a cardiovascular journal or go to a meeting and not notice that the subspecialty of structural heart intervention has virtually exploded during the past decade. Transcatheter aortic valve replacement has lead the way with two valves currently approved in the United States,[1-4] several more in trials, and numerous others in various stages of development—all based on a similar premise of replacement. In the mitral valve space, there are various treatment strategies that target different parts of the mitral apparatus including the leaflets, annulus, commissures, chordae, papillary muscles, and left ventricle. This is largely attributed to the complex nature of the mitral valve apparatus.

Mitral regurgitation (MR) remains the most common structural heart valve disorder, with approximately 4 million estimated cases in the United States. Its prevalence increases with age, ranging from 0.7% (95% confidence interval, 0.5–1) in patients aged 18 to 44 years to 13.3% (95% confidence interval, 11.7–15) in patients aged 75 years and older ($P < .0001$).[5] Compared to surgery, medical therapy falls short in reducing all-cause and cardiovascular mortality, heart failure, and new-onset atrial fibrillation.[6] Despite the evidence, surgery is performed in only a significant minority of those patients (2%). Most are not offered the surgical option because of the risk (either real or perceived) associated with valve surgery.[7] The most recent American College of Cardiology/American Heart Association guidelines have reviewed the criteria for intervention, including symptomatic patients with moderate-to-severe MR and asymptomatic patients with left ventricular dysfunction, pulmonary hypertension, or atrial fibrillation.[8]

Current percutaneous technologies for mitral valve repair (PTMR) have been developed on the basis of some of the previously described surgical principles. These technologies have been grouped into those acting on the leaflets (as in the MitraClip [Abbott Vascular]), mitral annulus (direct annuloplasty or indirect annuloplasty via the coronary sinus), and chamber (left ventricle) remodeling.[9] Most of the technologies are somewhere between animal testing and phase I or feasibility trials with regard to development.

DATA REVIEW

The vast majority of patients who have been treated percutaneously for MR have undergone edge-to-edge repair using the MitraClip device. As of the end of 2014, MitraClip had been utilized in more than 19,000 patients worldwide (personal correspondence with Abbott Vascular, February 2015). The concept was derived from a recapitulation of the "Alferei Stitch."[10] In March of 2008, MitraClip received CE Mark approval as a less invasive alternative to conventional mitral valve surgery. The feasibility trial (EVEREST I) enrolled 107 patients who met the American College of Cardiology/American Heart Association criteria for mitral valve surgery.[11-13] Each patient enrolled in the study was prospectively evaluated by an echocardiography core lab to have moderate-to-severe (3+) or severe (4+) MR, as assessed by the American Society for Echocardiography quantitative scoring system, prior to the procedure. In EVEREST I, the mean MR grade was 3.3 ± 0.7; 90% of patients underwent successful device placement, and 32% required two MitraClips.[14]

EVEREST II was a trial based in the United States comparing MitraClip in a 2:1 randomization to surgical treatment of a relatively low-risk group of patients with moderate-to-severe (3+) or severe (4+) MR. The 1-year mortality was similar in both groups. The residual MR rate was better (lower overall grade) in the surgical group, whereas the safety profile was superior in the MitraClip cohort.[15] Interestingly, comparable results to surgery were seen in an older cohort and in those patients with functional MR. The EVEREST II high-surgical-risk arm (patients with a Society of Thoracic Surgeons score ≥ 12% or surgical coinvestigator-estimated mortality rate based on prespecified criteria) noted a significant improvement in left ventricular remodeling, along with improved clinical status, providing high-surgical-risk patients with MR a way to reduce hospitalizations for heart failure with a similar safety profile seen in the lower-risk cohort.[16]

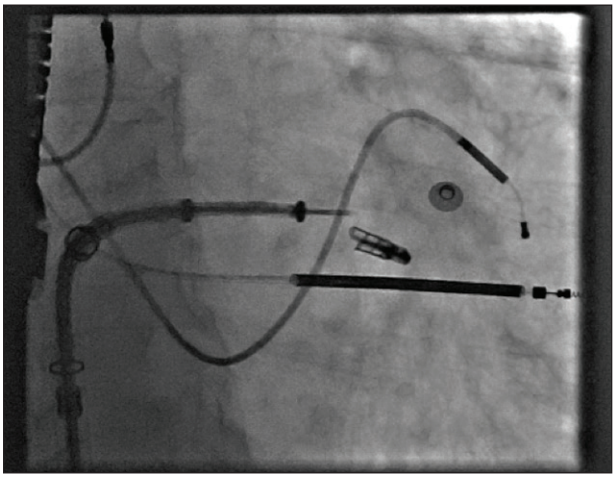

Figure 1. Successful implantation of a MitraClip device in a patient who was a CRT nonresponder.

Another important cohort of patients are those who are considered cardiac resynchronization therapy (CRT) nonresponders (Figure 1). Auricchio et al placed MitraClip devices in 51 symptomatic patients with functional MR who were considered CRT nonresponders. They concluded that MitraClip placement in CRT nonresponders who have functional MR was feasible, safe, and demonstrated improved functional class, increased left ventricular ejection fraction, and reduced ventricular volumes in a significant number of cases (70%).[17]

There are a few important points to keep in mind when reviewing the EVEREST II data. First, MitraClip implantation was performed by an interventionist with an average experience of three cases prior to randomization. Although it is difficult to calculate a learning curve for not only a new concept but also a new procedure, three previous implantations are clearly not adequate. For instance, if one looks at the procedural times as a surrogate for the complexity of the procedure, it might be 10 to 15 procedures before the structural team functions as a cohesive unit.

Franzen et al reported on their first 52 procedures, which reflected their learning curve. They found a trend toward shorter median device times in the second 26 procedures (66 minutes) as compared to the first 26 procedures (118 minutes). It should also be noted that multiple MitraClip devices were implanted in only 12% of patients in the first cohort, but in 50% of patients from the second cohort.[18] This probably reflects a better understanding of the procedure and how to achieve a better initial and long-term result. Similarly, Feldman et al noted similar results, with an overall procedural time reduction from 259 minutes in the first 30 cases to 165 minutes in the second 30 cases.[19]

As it has been stated previously, MitraClip recapitulates a specific surgical procedure that frequently includes the addition of an annular ring.[10] It is apparent that the addition of a ring improved the initial success of many of the patients in the original surgical report. The question that then must be asked is how does the lack of any annular manipulation or a secondary procedure (allowed in the surgical cohort), alter the device arm in the initial EVEREST II results? Another noteworthy observation is that the surgical arm in EVEREST II was permitted to perform the best surgical procedure that provided the patient the optimal reduction in MR and was compared to patients who underwent treatment with the MitraClip device alone. Can this really be considered an equivalent?

The last concern is accepting 2+ residual regurgitation as an acceptable endpoint for MitraClip patients, which is far greater then what would be considered a good mitral valve repair in surgery. Although 47% of MitraClip patients achieved < 2+ MR, there were still 33.6% with 2+ MR who were considered to have successful procedures. Could the implantation of a third or even a fourth MitraClip (EVEREST allowed a maximum of two MitraClips) in some of those patients result in a greater reduction in MR and therefore a better initial result compared to surgery (Figure 2)? In retrospect, the patients in EVEREST II who underwent a successful implantation of a MitraClip(s) clinically did as well as the surgical group. In the intention-to-treat analysis at 12 months, New York Heart Association functional class III or IV heart failure was present in 2% of patients in the percutaneous repair group and in 13% of those in the surgery group ($P = .002$).[15] Importantly, EVEREST investigators implanting the MitraClip attempted to achieve the best results possible in MR reduction. Despite the previously discussed criticisms, EVEREST II remains a landmark study in mitral valve intervention.

The REALISM study, a continued access registry of EVEREST, noted an increase in patient age of 74 ± 11 years (up from 67 ± 13 years). Functional MR was slightly more prevalent than seen in the EVEREST II trial (31% as opposed to 27%). Freedom from surgery improved to 90.1% (up from 80%). The 12-month survival rate, however, was slightly lower (91% as opposed to 93.7%) in the original EVEREST II cohort.[20] Some would argue that the investigators were taking on more difficult anatomy or complex patients, and as their familiarity with the procedure grew, their clinical experience improved (Figure 3).

INCREASING TREATMENT FOR FUNCTIONAL MR

In the EVEREST II trial, there was a minority of implantations in patients with functional MR (compared to degenerative MR), but was slightly higher than in REALISM. Reports from outside the United States reveal an increasing number of patients undergoing percutaneous mitral valve

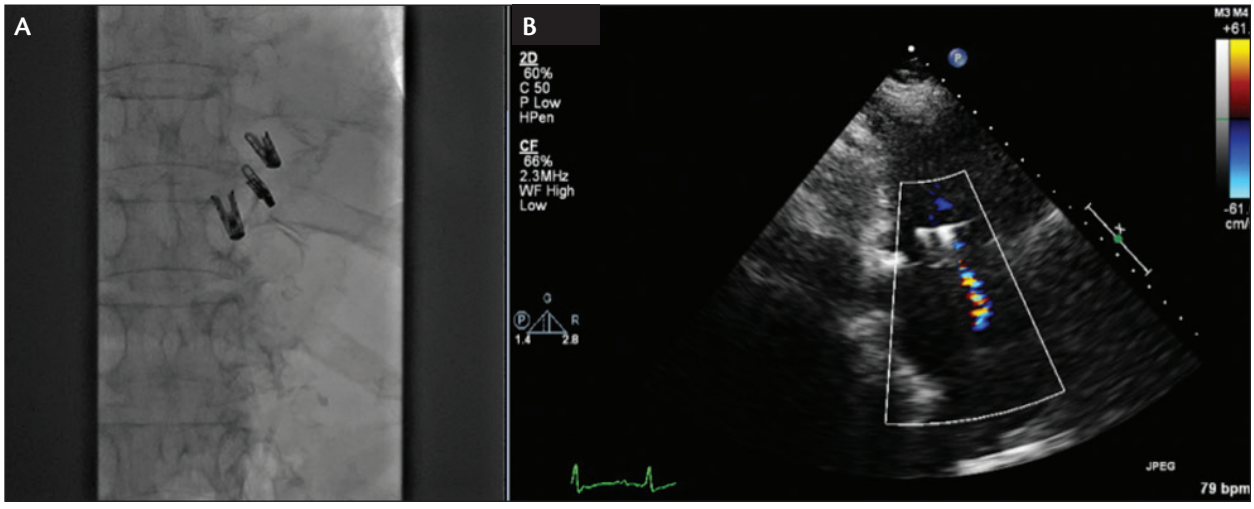

Figure 2. Panel A shows a patient with degenerative MR who required three MitraClips to achieve a successful repair. Panel B shows the echocardiographic results (trace MR).

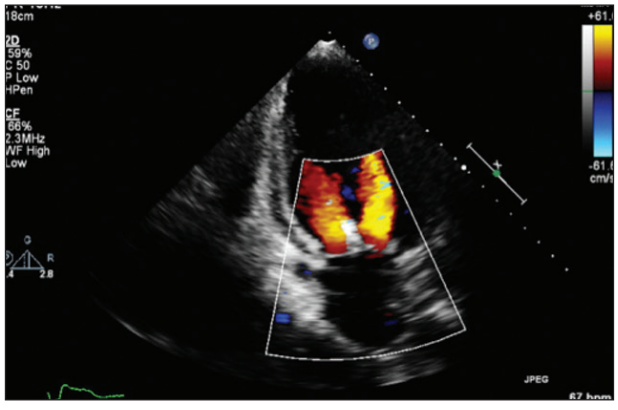

Figure 3. The pathognomonic echocardiographic results of a patient who has undergone MitraClip implantation, with the split jet entering the left ventricle during diastole.

repair who have functional MR.[21-23] Mitral valve surgery is the current treatment of choice for functional MR. Even with a recent report that in patients with moderate ischemic mitral regurgitation, the addition of mitral valve repair to coronary artery bypass grafting (CABG) did not result in a higher degree of left ventricular reverse remodeling and had an increased number of untoward events, there was however a reduced prevalence of moderate or severe mitral regurgitation.[24] Despite that, the authors concluded that the trial did not show a clinically meaningful advantage of adding mitral valve repair to CABG at 1 year.

Braun et al noted that patients undergoing restrictive mitral annuloplasty plus CABG whose left ventricular end-diastolic diameter was > 65 mm compared to < 65 mm had a higher 30-day mortality rate (17.7% vs 4.25%) and a higher all-cause mortality rate (50% vs 15.3%) at 4.3-year follow-up. These findings were associated with a higher readmission rate for heart failure (21.7% vs 8.7%).[25]

Despite a significant number of reports from Europe[22,26,27] on the success of the MitraClip in treating functional MR, the United States patients undergoing MitraClip implantation are required to have degenerative MR. They must be considered at prohibitive surgical risk as judged by a heart team that includes a cardiac surgeon experienced in mitral valve surgery and an interventional cardiologist experienced in mitral valve disease treatment. The patient should meet at least one of the following criteria: (1) 30-day Society of Thoracic Surgeons predicted operative mortality risk score of 8% for patients deemed likely to undergo mitral valve replacement, or 6% if repair is more likely; (2) a porcelain aorta or extensively calcified ascending aorta, hostile chest, severe liver disease with a Model for End-Stage Liver Disease score > 12; or (3) severe pulmonary hypertension that is more than two-thirds systemic. Other risk factors include severe frailty as assessed by the operating surgeons, right ventricular dysfunction with severe tricuspid regurgitation, severe dementia, AIDS, high aspiration risk, malignancy, or an increased risk of injury to the internal mammary artery.[28]

WHERE WE STAND TODAY

Two significant challenges remain for this predicate device for PTMR. First, as previously stated, the indication for PTMR is only for a very select group of patients who have degenerative MR and are believed to be too high risk for surgical repair or replacement. Functional MR patients remain a challenge, given the large number of patients who have this class of disease and the less-than-stellar surgical options that are currently available.

For now, we must wait for the COAPT and RESHAPE-HF studies results (see the following section).

The second challenge is that reimbursement remains a formidable issue for the MitraClip device. The Centers for Medicare & Medicaid did approve a technology add-on payment for fiscal year 2015, but maintained the current diagnosis-related group. This results in a $30,000 device that is only reimbursed for around $20,000 or less (for percutaneous mitral valvuloplasty), depending on the area of the country, forcing many programs to either not pursue PTMR, discontinue treating MR patients with MitraClip, or suffer a financial loss.

NEW DATA ON THE HORIZON

COAPT Trial

The COAPT trial (NCT identifier 01626079) was initiated in June 2012 to confirm the safety and effectiveness of MitraClip in heart failure patients with functional MR deemed to be at high surgical risk. Endpoints include a 1-year composite of single-leaflet device attachment, device embolization, endocarditis requiring surgery, echocardiography core laboratory–confirmed mitral stenosis requiring surgery, left ventricular assist device implantation, heart transplantation, and any device-related complications requiring nonelective cardiovascular surgery, or hospital readmission for heart failure. Secondary endpoints include a composite of all-cause death, stroke, myocardial infarction, or nonelective cardiovascular surgery for device-related complications; all-cause mortality; mitral regurgitation severity; or change in distance walked on a 6-minute walk test. As of December 22, 2014, the total enrollment is 159 randomized of an expected 420 (+42 roll-ins); there are 71 of 83 activated sites, with a projected date of completion in quarter one or two of 2017 (personal correspondence with Abbott Vascular, February 2015).

RESHAPE-HF

RESHAPE-HF (NCT identifier 17772108) was a European study sponsored by Abbott Vascular that looked at the safety and efficacy of MitraClip in patients with heart failure and severe cardiomyopathy. It has now been converted from a company-sponsored study to an investigator-sponsored study under RESHAPE-HF 2. It has not yet started enrolling patients, and the projected completion date will be determined after the first patient is enrolled. The plan is to include 40 centers. Until the results of both of these studies are reported, we will be limited to treating a very select subset of patients in the United States.

CONCLUSION

MitraClip remains the first of many devices yet to come for treating MR percutaneously. It is not without its issues (ie, the previously mentioned narrow treatment population and reimbursement), but we believe it will continue to lead the way in this arena for many years. For those who have been fortunate to witness patients improving following PTMR, it is nothing short of incredible. We anxiously await the results of the ongoing functional MR studies, with hopes that they will lead to an expanded indication. ■

Peter S. Fail, MD, FACC, FACP, FSCAI, is with the Cardiovascular Institute of the South in Houma, Louisiana. He has stated that he has no financial interests related to this article. Dr. Fail may be reached at peter.fail@cardio.com.

Vinod Nair, MD, FACC, FSCAI, is with the Cardiovascular Institute of the South in Houma, Louisiana. He has stated that he has no financial interests related to this article. Dr. Nair may be reached at vinor.nair@cardio.com.

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