

Percutaneous Repair of Mitral Regurgitation

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ABSTRACT: Mitral regurgitation (MR) affects more than 2 million people in the United States annually and is the second leading cause of heart valve disease after aortic stenosis. Surgical intervention is the currently accepted treatment of choice in patients with either symptomatic degenerative MR or asymptomatic MR with pulmonary hypertension, atrial fibrillation, or left ventricular dysfunction. Based on robust evidence from clinical trials, the MitraClip Transcatheter Mitral Valve Repair system (Abbott Vascular) was approved in the United States for commercial use in 2013. To date, more than 4,000 patients have been treated with the MitraClip in the United States and more than 35,000 patients worldwide. The device is approved in the United States for symptomatic degenerative mitral regurgitation in patients who are at high risk for surgery, as registry data has shown the device to be safe and effective in high-risk patients. In fact, when evaluated in the real-world setting in the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry, the device appears to be more safe and effective than in the original clinical trials. This review summarizes the clinical trials and registry data, reviews ongoing trials evaluating the device's utility in expanding populations, and introduces novel mitral valve repair devices in various stages of development.

INTRODUCTION

Mitral regurgitation (MR) is the second leading cause of valvular heart disease in the United States after calcific aortic stenosis, affecting more than 2 million people annually.¹ Acute MR from a ruptured chordae or papillary muscle is a rare medical emergency that leads to refractory pulmonary edema and cardiogenic shock. A majority of patients have chronic MR, which progresses more insidiously as the heart compensates for increasing regurgitant volume with left-atrial enlargement. Progression of the disease leads to left-ventricular (LV) volume overload and dysfunction and ultimately decreased functional status, congestive heart failure, and death.

The etiology of MR is classified as primary regurgitation from intrinsic valvular disease or secondary regurgitation from LV dysfunction. Frequently, the pathology is mixed with both degenerative valve disease as well as disruption of the mitral valve apparatus from LV dysfunction. Regardless of the etiology, severe symptomatic regurgitation has a poor prognosis, with an annual mortality rate of 6% per year or up to 60% at 5 years when occurring in the setting of advanced heart failure.²

Medical therapy for MR is limited to symptom management with blood pressure control, afterload reduction, and diuresis. Further advanced heart failure interventions can improve functional MR as well, including revascularization, cardiac resynchronization, and maximal heart failure medication optimization. The timing of an intervention for MR depends on the severity of regurgitation, LV function, and symptoms.

Ultimately, surgical intervention is the currently accepted treatment of choice in patients with either symptomatic degenerative MR or asymptomatic MR with pulmonary hypertension, atrial fibrillation, or LV dysfunction.³ Generally, a valve repair improves outcome compared to valve replacement and reduces mortality of patients with degenerative MR by 70%.¹ The best short-term and long-term results are obtained in patients treated in advanced repair centers with low operative mortality (< 1%) and high successful repair rates (≥ 80-90%).

Percutaneous repair of the mitral valve using the MitraClip (Abbott Vascular) has been approved in the United States since 2013 as an alternative to mitral valve surgery. The indication is for symptomatic, degenerative MR in patients who have been determined by a heart team to be at prohibitive risk for mitral valve surgery. Currently, the device is not approved in the United States for functional MR and should only be used in this setting as part of a clinical trial. Many questions are unanswered about when and on whom this procedure should be performed. Interestingly, roughly 80% of the procedures done outside the United States are for functional MR, whereas in the United States, 85% of patients are treated for degenerative MR.⁴

PERCUTANEOUS REPAIR OF MITRAL REGURGITATION

Ottavio Alfieri developed a surgical technique in the 1990s whereby the free edge of the mitral leaflets is sutured at the site of regurgitation when the regurgitation originates from the middle scallops, creating a valve with two orifices. This

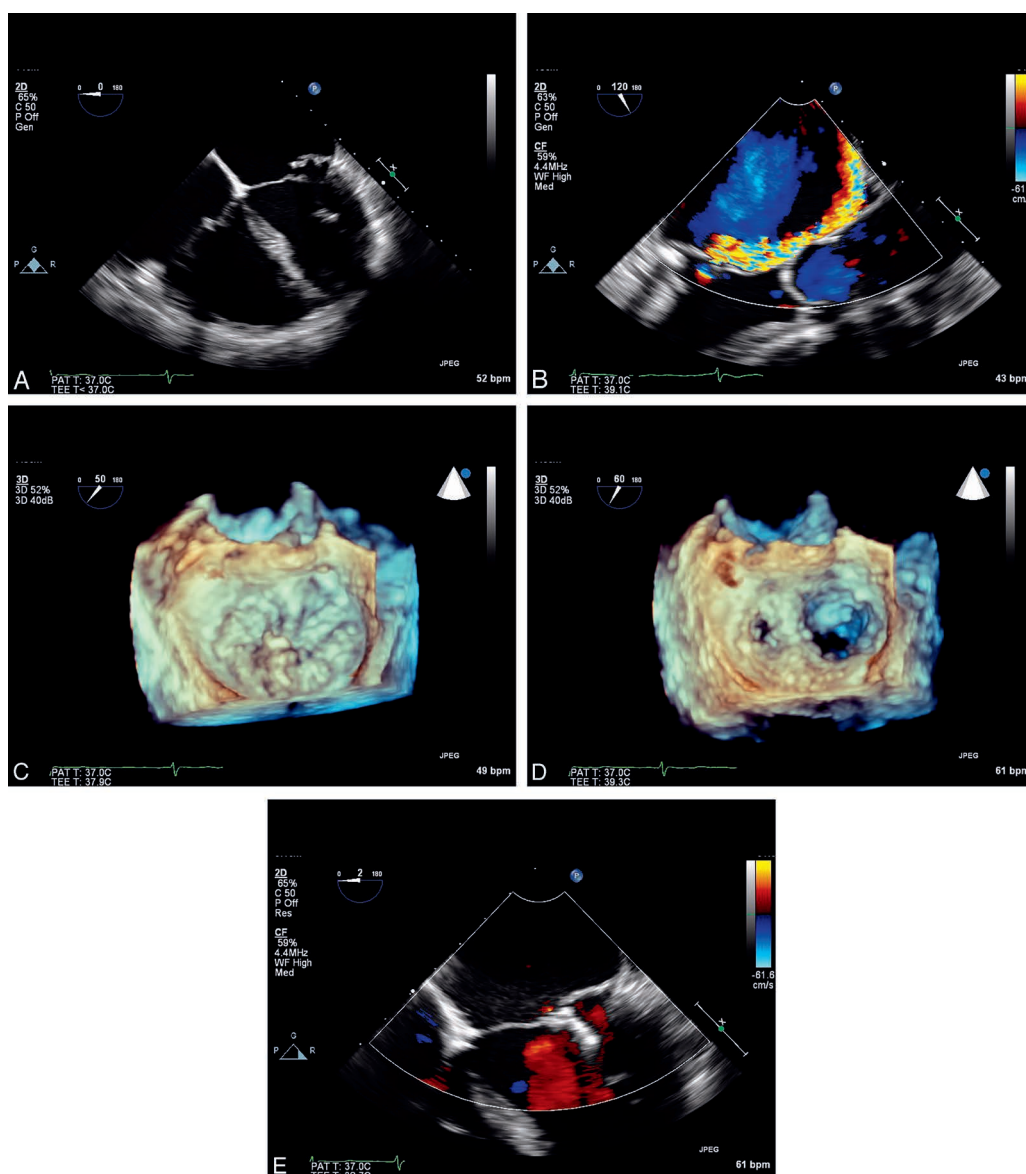


Figure 1.

Echocardiographic images of posterior mitral valve prolapse treated with percutaneous mitral valve repair using a MitraClip. (A) 2-dimensional (2D) echocardiogram showing posterior leaflet flail. (B) 2D echocardiogram with color Doppler showing significant mitral regurgitation. (C) 3D echocardiogram showing location of posterior leaflet flail. (D) 3D echocardiogram after grasp with mitral clip illustrating resultant double orifice mitral valve. (E) 2D echocardiogram with color Doppler showing significant reduction of mitral regurgitation after treatment with MitraClip.

was subsequently combined with the use of an annuloplasty ring. The technical simplicity of this aptly named “double orifice” technique facilitated the development of a number of transcatheter technologies used in percutaneous mitral valve repair.⁵ In fact, the edge-to-edge technique was one of the major springboards transforming the standard surgical approach into a minimally invasive off-pump repair with a suture- or device-based (MitraClip) approach (Figures 1, 2).

After preclinical porcine data and the initial first-in-man treatment in 2005, clinical trials to test the safety and efficacy of the MitraClip device were initiated. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST I) was designed to examine the device’s feasibility, safety, and efficacy.⁶ The

original device had an open-arm clip span of 2 cm and a width of 4 mm. It was covered with a polyester fabric to successfully promote endothelialization and was introduced via an 8-mm sheath. There have been subsequent iterations, with the current being the MitraClip NT delivery system that improves precision and device success. The clip was positioned transeptally across the mitral valve and into the left ventricle, closed to 120 degrees, and retracted until the anterior and posterior leaflets had been captured. A gripper was lowered from the atrium to secure the leaflets to the clip while the MR was evaluated with echocardiography prior to final closure. If clip placement was inadequate, the device could be opened and repositioned. The initial EVEREST I trial enrolled 55 patients, with the first 27 evaluated at 6 months. The rest were evaluated at 3 years

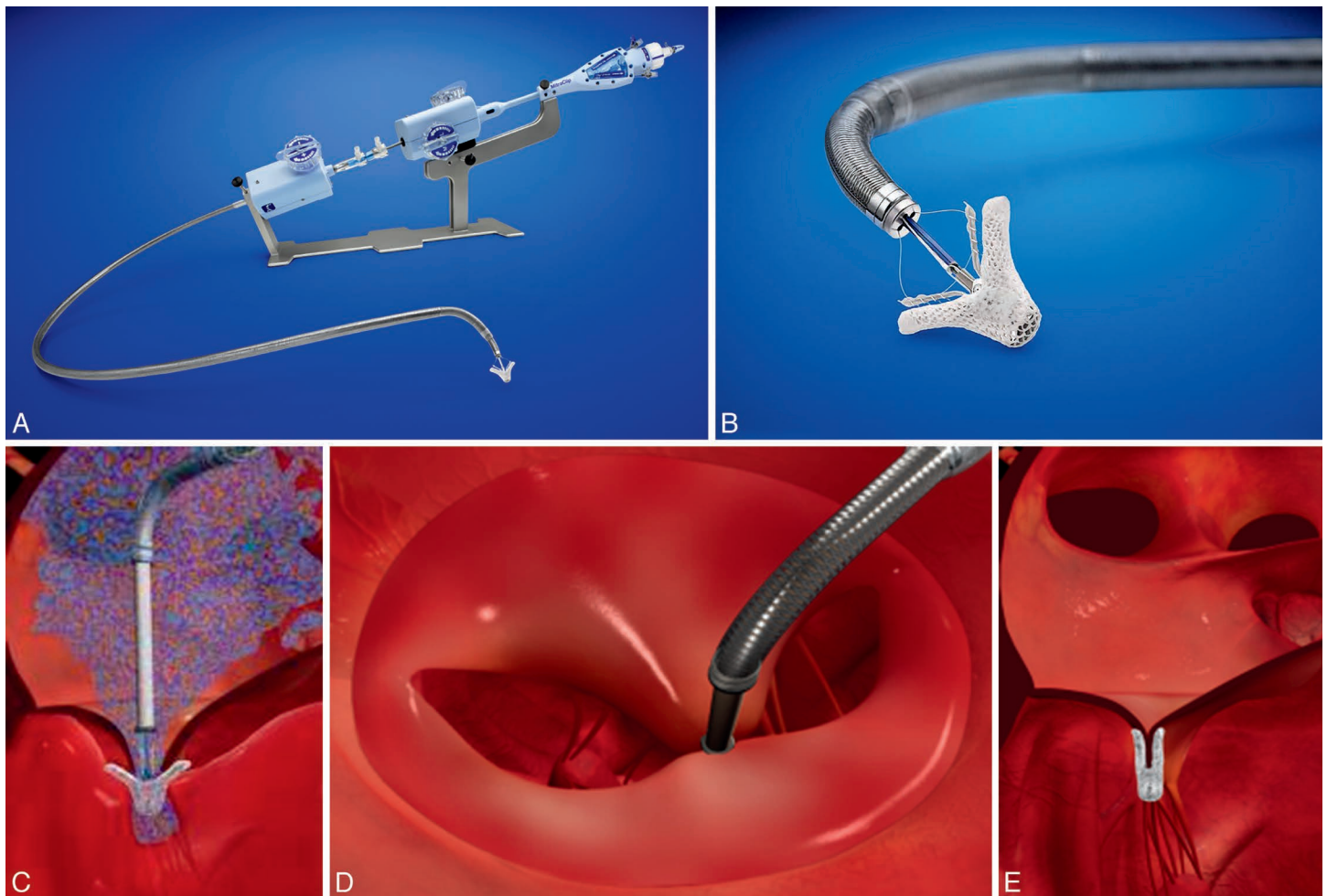


Figure 2.

Photographs and illustrations of the MitraClip System and procedure. (A) The MitraClip delivery system. (B) The MitraClip loaded on the delivery system open to 120 degrees with the grippers down. (C) Illustration of the MitraClip system engaging the mitral valve anterior and posterior leaflets at the site of the mitral regurgitation. (D) Illustration of the MitraClip grasping the mitral leaflets prior to being released. (E) Illustration of MitraClip after release.

in conjunction with 52 roll-in patients from the subsequent EVEREST II trial.⁷ EVEREST I had no exclusion criteria for the etiology of MR; 79% of patients had degenerative or primary MR, and 21% had functional or secondary MR. The 3-year analysis of 107 patients demonstrated a major adverse event rate of 9% at 30 days that consisted of bleeding, mechanical ventilation, one nonembolic cerebrovascular accident, one non-MitraClip-related death, and two transeptal complications requiring emergency surgery. No clip embolizations were reported, but detachment from one leaflet was seen in 9% of cases. Clips were implanted in 90% of patients with a 74% total acute procedural success rate. The primary end point of freedom from surgery with < 2+ MR or death at 3 years was met in 66% of patients. Improvement to NYHA Class I/II classification was seen in 92% at 12 months.

After safety and feasibility were demonstrated in the EVEREST I trial, the EVEREST II trial was designed to demonstrate the efficacy of the MitraClip. From 2005 to 2008, 279 patients with moderately severe or severe (grade 3+ or 4+) MR were randomized in a 2:1 ratio to undergo either percutaneous repair or conventional surgery for mitral valve repair or replacement. The primary composite end point for efficacy was freedom from death, surgery for mitral valve dysfunction, and grade 3+ or 4+ MR at 12 months. The primary safety end point was a composite of major adverse events within 30 days.⁸ At 12 months, the rates of the primary end point for efficacy were 55% in the percutaneous repair group and 73% in the surgery group ($P = .007$). The respective rates of the primary end point components in the percutaneous vs surgery groups were as follows: 6% vs 6% for death, 20% vs 2% for mitral

valve dysfunction surgery, and 21% vs 20% for grade 3+ or 4+ MR. Major adverse events occurred in 15% of patients in the percutaneous group and 48% of patients in the surgery group at 30 days ($P < .001$). At 12 months, both groups had improved LV size, New York Heart Association functional class, and quality-of-life measures compared with baseline. The investigators concluded that although percutaneous repair was less effective at reducing MR than conventional surgery, the procedure was associated with superior safety and similar improvements in clinical outcomes. At 4 years, the rate of the composite end point of freedom from death, surgery, or 3+ or 4+ MR in the intention-to-treat population was 39.8% vs 53.4% in the percutaneous vs surgical groups ($P = .070$). Rates of death were 17.4% vs 17.8% ($P = .914$), and 3+ or 4+ MR was present in 21.7% vs 24.7% ($P = .745$), respectively, at 4 years of follow-up. Surgery for mitral valve dysfunction, however, occurred in 20.4% vs 2.2% ($P < .001$) at 1 year and 24.8% vs 5.5% ($P < .001$) at 4 years.⁹ Nevertheless, the quality of the results in the surgical arm was criticized as not representative of that achieved in experienced centers.^{10,11} There were 80 repairs performed in 37 centers (2.2 repairs per center).

Despite evidence that percutaneous repair and surgical repair had similar meaningful clinical end points, the MitraClip continues to be scrutinized for the persistence of residual MR and need for reoperation or reintervention.¹² These criticisms can be countered with the following observations. In spite of persistent MR, those treated with percutaneous repair report feeling better, with similar improvements in NYHA functional class and quality of life measures compared to surgery. In addition, patients treated with the MitraClip show improvement in hemodynamics and LV size. The intervention bias is always an imbalanced limitation when comparing less-invasive with more-invasive therapies.¹³ Patients with persistent MR despite previous percutaneous MitraClip repair are appealing and low risk to refer for a surgical mitral valve repair or replacement, providing that only one or two clips have been applied.¹⁴ Thus, these patients are frequently referred for surgery after a MitraClip despite feeling well. On the contrary, we frequently follow patients with significant MR and prior mitral valve surgery for as long as possible and, in fact, commonly never refer for redo surgery or an attempt at percutaneous repair. Our bias is that it is low risk and easy to refer for surgery in the setting of persistent MR despite prior percutaneous repair, regardless of symptoms. On the other hand, those who have had a prior mitral valve surgery are high risk for a second intervention and are treated more conservatively. Consequently, the most powerful component of the primary composite end point for efficacy is inherently biased. Currently, there are no meaningful criteria to refer for a reintervention beyond refractory and convincing symptoms. Persistent MR without symptoms after MitraClip is not an indication for another procedure. Furthermore, the most

recent heart valve guidelines from the American College of Cardiology (ACC)/American Heart Association do not address post mitral repair interventions (surgical or percutaneous).¹⁵ Finally, the most recent data from the Society of Thoracic Surgeons (STS)/ACC Transcatheter Valve Therapy (TVT) Registry reported an in-hospital and 30 day reintervention rate of 0.7% and 0.9%, respectively.¹⁶ This is much lower than the 20% rate reported in EVEREST II.

The TVT Registry captures all procedures with FDA-approved transcatheter valve devices performed in the United States. This is a self-reporting, mandated condition of reimbursement by the Centers for Medicaid & Medicare Services.¹⁶ The most recent data reported from this registry regarding the MitraClip include the following highlights: 2,556 MitraClip procedures were reported in 2015, median age was 81 years, and 54.5% of patients were male. The STS Predicted Risk of Mortality (PROM) score for mitral valve repair was 6.1% from 2014 to 2015. In-hospital deaths occurred in an average of 2.3% of patients overall, with a slight reduction from 2.9% in 2014 to 2.1% in 2015 ($P = \text{nonsignificant [NS]}$). Thirty-day mortality occurred in 5% of patients overall, with a 4.7% rate in 2015 ($P = \text{NS}$). In-hospital stroke was present in 0.5% of patients overall and decreased to 0.3% in 2015 ($P < .05$). The 30-day stroke rate was 0.7% overall, decreasing to 0.6% in 2015 ($P = \text{NS}$). Overall morbidity was low, with new atrial fibrillation in 1.1% and acute renal injury requiring dialysis in 0.7%. The major vascular access site complication rate was 0.2% overall and remained consistent. Thirty-day readmission due to heart failure occurred in 2.4% of patients overall and was consistent over time. Mitral regurgitation at discharge or 30 days was less than or equal to moderate regurgitation (grade ≤ 2) in 85.2% of patients in 2014 and 86.6% in 2015. A mitral valve gradient of < 5 mm Hg occurred in 73.8% of patients overall with no significant difference over time.

ONGOING CLINICAL TRIALS AND FUTURE APPLICATIONS

The utility of the MitraClip for functional MR is not yet determined. Despite this, a majority of patients treated worldwide with the MitraClip have isolated functional MR (64% of $> 35,000$ patients treated, data from Abbott Vascular). The Cardiovascular Outcomes for Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial was designed to test the efficacy and safety of the MitraClip in this high-risk functional MR population.¹⁷ It is a prospective, randomized, multicenter trial that evaluates patients with symptomatic functional MR in the setting of cardiomyopathy who have been determined to be nonsurgical candidates. The COAPT trial is still actively enrolling patients throughout the United States. Study participants are randomized 1:1 to device therapy (MitraClip)

or no device therapy, with all patients receiving maximal, guideline-directed medical therapy. The goal is to recruit 610 subjects, 305 in each cohort, with the primary efficacy end point being recurrent heart failure hospitalizations at 24 months and the primary safety end points including device embolization, mitral stenosis, LV assist device, heart transplant, and any device complications requiring surgery. Many secondary end points are being studied, including short- and long-term mortality, severity of MR at 12 months, quality of life, functional status, and chamber enlargement. While the registries have been informative, the COAPT trial will hopefully provide clarity on use of the MitraClip in high-risk patients with functional MR. Additional studies (MITRA-FR, RESHAPE-HF-2, MATTERHORN, and EVOLVE-HF) in treating patients with functional MR are ongoing and will add to the body of evidence to help guide therapy in these challenging patients.

We have initiated and are leading a multicenter study evaluating reverse cardiac remodeling with MitraClip treatment. The Effect of MitraClip on Reverse Cardiac Remodeling Assessed by CMR and Echocardiography Study (MITRA-REVERSE) is a prospective, multicenter, longitudinal study that ultimately will help optimize selection of patients who will benefit the most as well as potentially guide intraprocedural optimization of MitraClip therapy.

BEYOND THE MITRACLIP

The developing technology for percutaneous mitral valve repair is presently not as active as it is for transcatheter mitral valve replacement (TMVR), but there are some devices in various stages of development, clinical trial, and approval. These include the PASCAL transcatheter mitral repair system (Edwards Lifesciences), Carillon Mitral Contour System (Cardiac Dimensions Pty. Ltd), NeoChord artificial

chordae delivery system (NeoChord Corporation), and Cardioband Transcatheter System (Edwards Lifesciences). Currently, none of these devices are approved in the United States for commercial use; however, several are preparing to initiate U.S.-based pivotal randomized trials.

CONCLUSION

Based on robust evidence from clinical trials, the MitraClip percutaneous mitral valve repair system was approved in the United States for commercial use in 2013. To date, more than 4,000 patients have been treated with the MitraClip in the United States and more than 35,000 patients worldwide. The device is approved for symptomatic degenerative mitral regurgitation in patients who are high risk for surgery. Registry data has shown the device to be safe and effective, even more so than reported in EVEREST II. Whether or not this therapy will help patients with functional MR remains to be determined and is the subject of several ongoing studies. Many novel devices are in early stages of development and the approval process, and it remains to be seen how effective they will be and what utility they may have in the future.

Conflict of Interest Disclosure:

The author has completed and submitted the *Methodist DeBakey Cardiovascular Journal* Conflict of Interest Statement and none were reported.

Keywords:

mitral regurgitation, MitraClip, percutaneous transcatheter mitral valve repair

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KEY POINTS

- Surgical intervention is the currently accepted treatment of choice in patients with either symptomatic degenerative MR or asymptomatic MR with pulmonary hypertension, atrial fibrillation, or left ventricular dysfunction.
- The FDA has approved the MitraClip Transcatheter Mitral Valve Repair system for repair of symptomatic degenerative MR in patients who are at high risk for surgery.
- In patients with degenerative MR, valve repair generally improves outcomes compared to valve replacement and reduces mortality by 70%.¹
- The best short- and long-term results are seen in patients treated at advanced repair centers with low operative mortality and high success rates.

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