MitraClip: Path to Approval and Future Directions

An overview of the key features, clinical use, and potential hurdles for this percutaneous mitral valve repair system.

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The path to approval for the MitraClip percutaneous mitral valve repair system (Abbott Vascular) began with the first-in-human device implantation in the United States in July 2003. This was the first time a percutaneous therapy of any kind had been successfully utilized for treating mitral regurgitation (MR). This first patient was treated as part of the EVEREST I feasibility study (Endovascular Valve Edge-to-Edge Repair Study), which demonstrated that the MitraClip procedure could be performed safely and with some degree of success.[1] The subsequent pivotal randomized trial, EVEREST II, compared the MitraClip with conventional repair or replacement surgery for MR. The broad conclusions of the EVEREST II randomized trial were that although the MitraClip device is not as effective as surgery at reducing MR, the clinical and quality-of-life outcomes are similar, and favorable left ventricular (LV) remodeling is produced similarly as it is with surgery.[2] As would be anticipated with a percutaneous therapy, safety was superior to surgery. Importantly, the majority of these patients had degenerative (DMR) rather than functional MR (FMR). A subgroup analysis of these good-surgical-candidate patients showed that the best results with the MitraClip device were achieved among patients with older age, poor LV function, and FMR rather than DMR.

It was recognized that patients who were at high risk for mitral surgery were being excluded from the EVEREST II randomized trial. As a response, a high-risk registry was developed to evaluate the potential use of the MitraClip as a therapy for patients with no other alternatives. Ultimately, more than 350 patients were enrolled in the high-risk registry.[3] In contrast to the randomized trial, the high-risk registry enrolled predominantly FMR rather than DMR patients. The broad findings in this experience were that the results for reduction in MR, favorable LV remodeling, and improved symptoms were similar to those seen in the EVEREST II randomized trial. The rate of rehospitalizations after MitraClip treatment was reduced by half compared to the year before treatment. Considering that the patient population for the registry was high risk for any form of therapy, the procedure could be performed with remarkable safety.

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It is well known that DMR has been successfully treated with surgery for many years. Still, many patients are older and have prohibitive risks for conventional surgery for DMR. A subgroup analysis of 127 patients with DMR in the high-risk registry showed excellent outcomes,[4] which ultimately led to FDA approval on October 24,

(Courtesy of Abbott Vascular.)

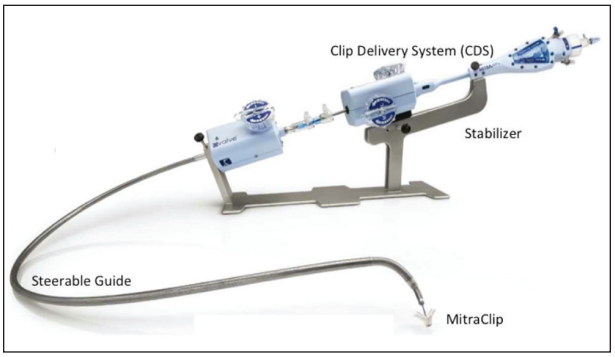
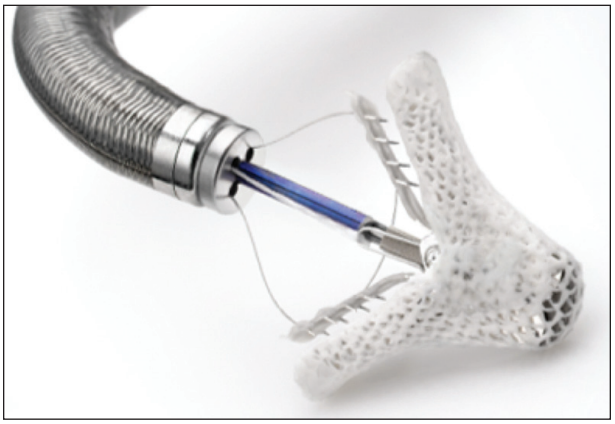


Figure 1. The MitraClip system is a triaxial catheter system. The guide catheter is 24 F proximally and tapers to 22 F. A steering knob on the proximal end of the guide catheter allows flexion and lateral movement of the distal tip. The clip delivery system, with a clip attached to its distal end, is passed through the guide catheter. This system is steerable using a two-knob coaxial system.



(Courtesy of Abbott Vascular.)

Figure 2. The clip is polyester covered with two arms that are opened and closed by control mechanisms on the clip delivery system. On the inner portion of the clip is a U-shaped, tined "gripper" that matches up to each arm and stabilizes the leaflets as they are grasped during clip closure.

2013, of the MitraClip for patients who have a prohibitive risk for surgery with a degenerative etiology of MR.

KEY FEATURES OF THE DEVICE

The MitraClip system uses a clip with a triaxial catheter system (Figure 1). The tip of the outer guide catheter is delivered to the left atrium via the right femoral vein using a standard transseptal approach over a guidewire and tapered dilator. The guide catheter is 24 F proximally and tapers to 22 F at the point where it crosses the atrial septum. A steering knob on the proximal end of the guide catheter allows flexion and lateral movement of the distal tip. A clip delivery system, with a clip attached to its distal end, is passed through the guide catheter. This system is steerable using a two-knob coaxial system that permits medial-lateral and anterior-posterior steering. The clip delivery system is advanced through the guide catheter into the left atrium, positioned using fluoroscopic and transesophageal guidance so that the clip is orthogonal to the three planes of the mitral valve and over the origin of the regurgitant jet. The clip is a polyester-covered metallic device with two arms that are opened and closed by control mechanisms on the clip delivery system (Figure 2). The two arms have a span of approximately 2 cm when opened in the grasping position. The width of the clip is 4 mm. On the inner portion of the clip is a U-shaped, tined "gripper" that matches up to each arm and helps to stabilize the leaflets from the atrial aspect as they are captured during closure of the clip arms. Leaflet tissue is secured between the closed arms and each side of the gripper, and the clip is then closed and locked to effect and maintain coaptation of the two leaflets percutaneously, creating a "double-orifice" configuration similar to that produced by the edge-to-edge surgical Alfieri repair technique.

PATIENT POPULATION

The data that supported the FDA approval included a subanalysis of high-risk patients with DMR. From the high-risk registry patients, a prohibitive-risk DMR cohort was identified by a multidisciplinary heart team that retrospectively evaluated high-risk DMR patients enrolled in the EVEREST II studies. This analysis included 127 prohibitive-risk DMR patients with 1-year follow-up (median, 1.47 years). Patients were elderly with a mean age of 82 years, severely symptomatic with 87% in NYHA class III/IV, and at prohibitive surgical risk with a mean STS score of 13.2% ± 7.3%. The MitraClip was successfully implanted in more than 95% of patients. The average hospital stay was 2.9 ± 3.1 days. Major adverse events at 30 days included death in 6.3%, myocardial infarction in 0.8%, and stroke in 2.4%. Through 1 year, there were 30 (23.6%) deaths, with no survival difference between patients discharged with MR ≤ 1+ or MR = 2+. A majority of surviving patients (82.9%) remained MR ≤ 2+ at 1 year, and 86.9% were in NYHA functional class I or II. LV diastolic volume decreased (125.1 ± 40.1 mL to 108.5 ± 37.9 mL; $P < .0001$). SF-36 quality-of-life scores improved, and hospitalizations for heart failure were decreased in patients whose MR was reduced. Thus, transcatheter mitral valve repair in prohibitive-surgical-risk patients is associated with safety and good clinical outcomes, including favorable ventricular remodeling, a decrease in rehospitalization, and functional improvements at 1 year.

ANATOMIC CONSIDERATIONS IN THE MITRACLIP IFU

For optimal results, the following anatomic patient characteristics should be considered. The safety and effectiveness of the MitraClip outside of these conditions has not been established. Use outside these conditions may interfere with placement of the MitraClip Device or mitral valve leaflet insertion.

- The primary regurgitant jet is noncommissural. If a secondary jet exists, it must be considered clinically insignificant
- Mitral valve area ≥ 4 cm^2
- Minimal calcification in the grasping area
- No leaflet cleft in the grasping area
- Flail width < 15 mm and flail gap < 10 mm

INSTITUTIONAL AND OPERATOR REQUIREMENTS FOR PERCUTANEOUS MITRAL REPAIR WITH THE MITRACLIP

- Interventional Program: 1,000 cath/400 PCI per year
- Interventionist: 50 structural procedures per year (including ASD/PFO and transseptal punctures)
- Surgical program: 25 total mitral valve procedures per year, of which at least 10 must be mitral valve repairs
- All cases must be submitted to a single national database
- Existing programs: 15 mitral (total experience)
- New programs: Because the indications are not defined, no volume criteria can be proposed yet; assuming approval would be for high-risk cohorts, a 10% to 15% mortality rate at 30 days, similar to registry or published results, is expected.

PATIENT SELECTION

The exact language in the instructions for use (IFU) is: "The MitraClip Delivery System is indicated for the percutaneous reduction of significant symptomatic MR (≥ 3+) due to primary abnormality of the mitral apparatus [degenerative MR] in patients who have been determined to be at prohibitive risk for mitral valve surgery by a heart team,[5] which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the MR."

The IFU warns: "DO NOT use MitraClip outside of the labeled indication. Treatment of nonprohibitive-risk DMR patients should be conducted in accordance with standard hospital practices for surgical repair and replacement," and further notes that "the safety and effectiveness of the MitraClip device has not been established in patients with MR due to underlying ventricular pathology (FMR)." The approval specifies the anatomic requirements for treatment (see *Anatomic Considerations in the MitraClip IFU* sidebar).

IMPACT ON PRACTICE

The impact of the approval of the MitraClip on practice is demonstrated by the uptake of commercial use of the device internationally. Since the MitraClip received CE Mark approval in 2008, more than 14,000 cases have been performed at 355 sites in 30 countries. The majority of treated patients have FMR and are at high risk for conventional surgery. Technical success rates now approach 100%. A problem noted with the procedure in our early experience seen in almost 10% of cases was detachment of one leaflet from the clip, which has decreased to 1% as experience has grown. The safety of the procedure has been supported by low 30-day mortality despite the high-risk nature of the patients, and discharge to home rather than rehabilitation facilities in more than 85% of patients.[6]

Since the MitraClip's approval in October 2013, more than 250 patients have been treated at 40 sites in the United States. The population for which the device was approved represents high-risk patients for surgery with DMR, for whom results with the MitraClip have been clear in terms of improving symptoms and resulting in favorable LF chamber remodeling. These patients represent a population for whom historically there have been no other alternatives for therapy. These are generally elderly patients, often with fibroelastic deficiency as the etiology of their DMR. Interestingly, many of these patients have relatively preserved LV systolic function, in contrast to the severely depressed LF ejection fraction seen in the typical patient with ischemic cardiomyopathy and FMR. A January 20, 2014, *Wall Street Journal* article estimated that as many as 30,000 patients in the United States are currently eligible for the commercial indication for MitraClip therapy.[7]

REGULATION AND REIMBURSEMENT

Guidance for institutional and operator requirements are being developed by a multisociety working group similar in concept to the TAVR requirements[8] but specific to the MitraClip procedure (see *Institutional and Operator Requirements for Percutaneous Mitral Repair With the MitraClip* sidebar).[9] It is anticipated that requirements for other percutaneous mitral technologies, particularly transcatheter mitral valve replacement, will be technology- or approach-specific.

On August 4, 2014, the Centers for Medicare & Medicaid issued a fiscal year 2015 ruling on the inpatient prospective payment system. The Centers for Medicare & Medicaid approved a new technology add-on payment for MitraClip while maintaining MitraClip within its current diagnosis-related group classification. The device price for the hospital is $30,000. The hospital reimbursement has been based on percutaneous mitral valvuloplasty, usually less than $20,000.

UNRESOLVED CHALLENGES

Many challenges remain for this first-in-class percutaneous therapy for MR. The approval is for a narrow indication in a highly specific patient population with DMR. A greater number of patients have FMR rather than DMR. Although a large amount of registry data has been published on patients with FMR, showing excellent outcomes in terms of clinical response and favorable LF remodeling, it is yet to be demonstrated what the magnitude of this therapy benefit is compared to conventional medical therapy. To answer this question, two trials are ongoing. A randomized comparison of the MitraClip with medical therapy for heart failure, COAPT (Clinical Outcomes Assessment of the MitraClip Percutaneous Therapy for High Surgical Risk), has been initiated. The primary effectiveness endpoint is recurrent heart failure hospitalizations; the safety endpoint is the composite of death, stroke, worsening renal function, LVAD implantation, and heart transplantation at 12 months. The trial will enroll 430 patients at up to 75 sites in the United States. Enrollment criteria include significant FMR ≥ 3+ by core lab and LVEF < 50%. They must also have a heart failure hospitalization within the past year, or BNP > 300. The local heart team must agree that the patient would not be treated with surgery. A similar European trial, RESHAPE (Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation), is underway.

FUTURE DIRECTIONS

There are several other percutaneous mitral repair and replacement devices under development, including indirect and direct annuloplasty devices and percutaneous or transapical mitral replacement technologies.[10] Compared to more than 14,000 patients treated with the MitraClip, the next largest experience with patients is with the Carillon device (Cardiac Dimensions), a coronary sinus indirect annuloplasty device, with approximately 300 patients treated. For direct annuloplasy, Mitralign has enrolled 40 patients in a CE Mark approval trial studying the Mitralign system, and the Cardioband (Valtech) has been used in more than 25 cases. Catheter-based mitral replacement technology is in its infancy, with only a handful of implantations over the past 2 years. All of these devices will undergo significant future evaluation, and their time course for entry into United States practice will take several years. ■

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