

The EVEREST Percutaneous Mitral Leaflet Repair Trials

An overview of the safety and efficacy data of the MitraClip system for treating mitral regurgitation.

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Mitral regurgitation (MR) is the most common type of heart valve insufficiency affecting several million people in the United States. Available medical therapy for MR is suboptimal. Although medical therapy may relieve symptoms in some patients with functional MR, it has no effect on the natural history of the lesion. Surgical intervention is the therapy of choice for symptomatic patients with preserved left ventricular function, particularly if the etiology of MR is degenerative. The recommended guidelines for MR intervention are summarized in Table 1.^{1,2} Surgical candidates include symptomatic patients with moderate-to-severe or severe (3+ or 4+) MR, or asymptomatic patients with left ventricular dysfunction, new atrial fibrillation, or pulmonary hypertension. In this context, left ventricular dysfunction is defined as an ejection fraction < 60% because MR is associated with afterload reduction into the left atrium and may mask the deterioration of left ventricular performance.

A sizable proportion of patients with severe symptomatic MR are not referred for an operation due to elevated surgical risk. Patients with previous coronary artery bypass graft surgery, various comorbidities, and older age constitute the majority of this group. The morbidity and mortality of surgical approaches have led to the development of less invasive, percutaneous, catheter-based approaches to treating MR. Available percutaneous approaches include an implantable clip (MitraClip, Abbott Vascular, Santa Clara, CA), several annuloplasty

devices, and valve replacement. Currently, all such therapies are investigational in nature in the United States. The most studied and perhaps most promising of these therapies is the MitraClip, an implantable clip system based on the Alfieri method of edge-to-edge repair. This device mimics a surgical procedure in which the free edges of the mitral leaflets are sutured together to create a double orifice mitral opening.

The MitraClip system involves delivery of an implantable clip to the left atrium via a transseptal approach, which approximates the edges of the mitral leaflets.^{3,4} Extensive testing of the MitraClip device in animal models preceded human implantations by several years and proved that the sheath and delivery system are reliable and the clip is stable and durable after implantation.^{5,6} After the clip is placed, a fibrous tissue bridge develops. In addition to encapsulating the MitraClip device, the tissue bridge may also stabilize the septal-lateral annular dimension with resultant stabilization of annular dilatation.

The first MitraClip implantation in a human was performed in Caracas, Venezuela, in June 2003,⁷ and use of the device has continued internationally. Outcomes of therapy with the MitraClip device have been evaluated in the United States in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) registry, EVEREST Randomized, and EVEREST II High-Risk Registry trials. This article discusses these studies in detail and highlights lessons learned and future directions suggested by the EVEREST trial experience.

TABLE 1. INDICATIONS FOR MITRAL VALVE OPERATION: VALVE DISEASE GUIDELINES 2008**CLASS I**

1. Mitral valve surgery is recommended for the symptomatic patient with acute severe MR (level of evidence: B).
2. Mitral valve surgery is beneficial for patients with chronic severe MR and NYHA functional class II, III, or IV symptoms in the absence of severe LV dysfunction (severe LV dysfunction is defined as ejection fraction < 0.30) and/or end-systolic dimension > 55 mm (level of evidence: B).
3. Mitral valve surgery is beneficial for asymptomatic patients with chronic severe MR and mild-to-moderate LV dysfunction, ejection fraction 0.30 to 0.60, and/or end-systolic dimension $\geq$ 40 mm (level of evidence: B).
4. Mitral valve repair is recommended over mitral valve replacement in the majority of patients with severe chronic MR who require surgery, and patients should be referred to surgical centers experienced in mitral valve repair (level of evidence: C).

CLASS IIa

1. Mitral valve repair is reasonable in experienced surgical centers for asymptomatic patients with chronic severe MR with preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom the likelihood of successful repair without residual MR is > 90% (level of evidence: B).
2. Mitral valve surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and new onset of atrial fibrillation (level of evidence: C).
3. Mitral valve surgery is reasonable for asymptomatic patients with chronic severe MR, preserved LV function, and pulmonary hypertension (pulmonary artery systolic pressure > 50 mm Hg at rest or > 60 mm Hg with exercise) (level of evidence: C).
4. Mitral valve surgery is reasonable for patients with chronic severe MR due to a primary abnormality of the mitral apparatus and NYHA functional class III–IV symptoms and severe LV dysfunction (ejection fraction < 0.30 and/or end-systolic dimension > 55 mm) in whom mitral valve repair is highly likely (level of evidence: C).

CLASS IIb

1. Mitral valve repair may be considered for patients with chronic severe secondary MR due to severe LV dysfunction (ejection fraction < 0.30) who have persistent NYHA functional class III–IV symptoms despite optimal therapy for heart failure, including biventricular pacing (level of evidence: C).

CLASS III

1. Mitral valve surgery is not indicated for asymptomatic patients with MR and preserved LV function (ejection fraction > 0.60 and end-systolic dimension < 40 mm) in whom significant doubt about the feasibility of repair exists (level of evidence: C).
2. Isolated mitral valve surgery is not indicated for patients with mild or moderate MR (level of evidence: C).

EVEREST I REGISTRY

The first of the EVEREST trials was a prospective, multi-center, phase 1 trial designed to evaluate the safety and feasibility of the MitraClip procedure.⁴ The registry enrolled 107 patients meeting the American Heart Association/American College of Cardiology guideline recommendations for surgical mitral valve repair.⁸ All patients had moderate-to-severe (3+) or severe (4+) MR, as assessed by the American Society for Echocardiography quantitative scoring system. Pure functional MR was present in 21% of patients, with the remainder having degenerative or combined degenerative and functional MR. At baseline, mean MR grade was 3.3 ± 0.7 , representing a more severe grade of MR than reported in most surgical series. Successful clip placement occurred in 90% of

patients; two clips were required in 32%. All echocardiograms were evaluated by a core laboratory before patient enrollment. This was the first trial of an MR device therapy to utilize both an echo core lab and also prospective qualification of patients. The severity of MR before intervention has usually been site reported and unmonitored. For example, a trial utilizing surgical annuloplasty required at least 2+ MR for entry. After patients were operated, the qualifying echo examinations were sent for retrospective core lab review. Eighteen percent of patients had 0 or 1+ MR by core lab review.⁹

In the EVEREST I registry, MitraClip placement was associated with no procedural mortality. The major adverse event rate was 9%, with blood transfusions $\geq$ 2 units representing the majority of these events.

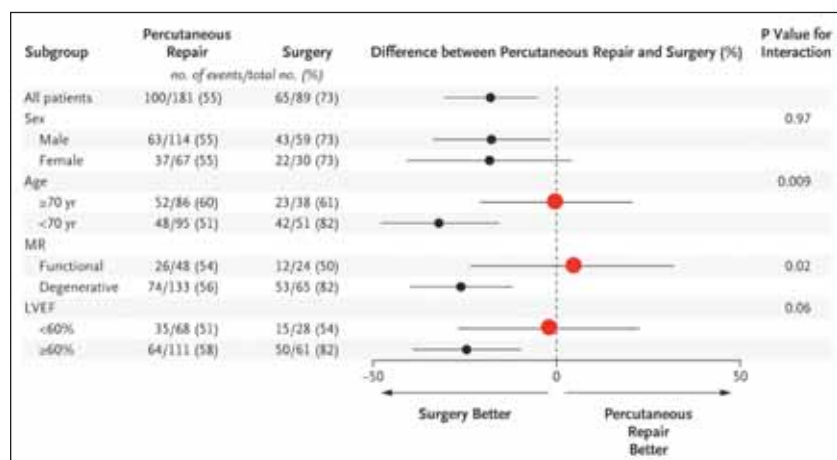


Figure 1. EVEREST II Randomized trial. Subgroup analyses for the primary endpoint at 12 months. Shown are the differences in rates of the primary efficacy endpoint (freedom from death, from mitral valve surgery, and from grade 3+ or 4+ mitral regurgitation) between patients in the percutaneous repair group and those in the surgery group for all randomized patients and those in four post hoc subgroups. The horizontal lines indicate 95% confidence intervals. Reproduced with permission from Feldman T et al. *N Engl J Med.* 2011;364:1395-1406. 10.1056/NEJMoa1009355.

Prolonged mechanical ventilation, postprocedure death, and periprocedural stroke represented less common adverse events, each affecting less than 1%. Partial clip detachment (detachment of a single leaflet from the clip) occurred in 9%, the majority of which were asymptomatic and detected on 30-day echocardiography. The majority of partial clip detachments were successfully treated with mitral valve surgery. No clip embolization occurred.

Of the 107 registry patients, 96 (90%) achieved a reduction in MR from the clip or mitral valve surgery performed after a clip attempt. Acute procedural success occurred in 74% of patients and was defined as placement of one or more clips resulting in $\leq 2+$ MR. Approximately 75% of patients had improvement in clinical symptoms. In this early experience, all but 30% of patients remained free of surgical intervention at 3-year follow-up. Surgical procedures performed after clip placement had an 84% success rate.

The results of the initial EVEREST I registry demonstrated that percutaneous edge-to-edge repair clearly had a favorable safety profile and demonstrated feasibility. Early freedom from death, need for emergent or elective surgery, or recurrent MR could be achieved in a substantial proportion (66%) of patients. Clinical improvements were seen in the majority of patients, with New York Heart Association (NYHA) class III/IV symptoms decreasing from 55% at baseline to 8% at 12 months. The procedure also appeared to be extremely safe: there were no

intraprocedure and minimal periprocedural complications, and the rates of major and minor adverse events were low. The procedure was well tolerated, with hemodynamic stability maintained throughout the procedure. This latter finding is remarkable.

Manipulation of a device in the mitral orifice with a beating heart was almost uniformly tolerated, allowing the operator to concentrate on optimizing MR reduction rather than managing a hemodynamically unstable patient.

Extubation was possible within the first 24 hours in most patients.

In addition to preliminary safety and efficacy data, the initial EVEREST registry provided vital insights into patient selection and the technical nuances of the MitraClip device. It was clear from the EVEREST

registry experience that careful evaluation of mitral valve anatomy was critical for optimal patient selection. Examination of the mitral valve on short-axis color Doppler to ensure that the MR jet is within the central two-thirds of the line of coaptation was identified as a crucial step. In addition, EVEREST investigators appreciated during this initial experience that there was a significant learning curve associated with operation of the delivery system and implantation of the device. The majority of the cases included in the registry were the first three implantations performed at respective centers. Procedure times in the first third of the cohort were almost 1 hour longer than procedure times of the final third of the cohort, indicating that operators clearly became more proficient with the device on subsequent implantations. The success rate for clip implantation has increased from 90% in the early experience with the device to 98% in our recent registry experience.

EVEREST II RANDOMIZED TRIAL

EVEREST II was a multicenter, randomized, controlled trial designed to evaluate the safety and efficacy of percutaneous mitral repair versus conventional surgical repair or replacement for MR.^{9,10} Patients were included and excluded from the trial based on the same criteria as EVEREST I (ie, according to the Valve Guideline criteria for intervention for MR).¹ Patients were assigned to MitraClip repair versus conventional surgical repair or replacement in a 2:1 ratio. The primary efficacy endpoint

TABLE 2. EVEREST II PRIMARY ENDPOINT: FREEDOM FROM DEATH, SURGERY/REOPERATION FOR VALVE DYSFUNCTION OR 3+ OR 4+ MR (INTENTION-TO-TREAT ANALYSIS)

Components of Failure	Percutaneous		Surgery		P Value Percutaneous Versus Surgery at 2 Years
	1 year N = 181	2 years N = 172	1 year N = 89	2 years N = 83	
Death	6%	11%	6%	11%	> .999
MV surgery/ reoperation	20%	22%	2%	4%	< .001
3+ or 4+ MR	21%	20%	20%	22%	.84
Freedom from death, MV surgery or reoperation, or 3+ or 4+ MR	55%	52%	73%	66%	< .001

was defined as the composite of freedom from surgery for mitral valve dysfunction, 3 or 4+ MR, and death at 12 months. The primary safety endpoint was defined as a composite of death, myocardial infarction, reoperation for failed mitral valve surgery, nonelective cardiovascular surgery for adverse events, stroke, renal failure, deep wound infection, prolonged mechanical ventilation, gastrointestinal complication requiring surgery, septicemia, new onset permanent atrial fibrillation, and transfusion of 2 units or more of blood at 30 days.

A total of 279 patients were enrolled and randomized 2:1 to MitraClip versus surgical repair or replacement. Seventy-three percent of patients in each treatment group had degenerative MR, and the remainder had functional MR. At 12-month follow-up, the device group achieved the primary efficacy endpoint (composite freedom from death, surgery for mitral valve dysfunction, or 3 or 4+ MR) in 55% compared to 73% in the surgical group ($P = .0007$) in an intention-to-treat analysis. The difference in the composite endpoint between the two therapies was driven by the increased rate of surgical referral after MitraClip therapy. During the first 12 months in the device group the need for subsequent surgery was 20%, compared to 2.2% for repeat mitral valve surgery in the surgical group. Thus, at 12 months, the need for any mitral valve surgery was avoided in 80% of the patients treated with the MitraClip. Importantly, the frequency of death and MR grade 3 to 4+ was not different in the device group versus the surgical group.

At 2-year follow-up, the primary efficacy endpoint was 52% in the percutaneous repair group versus 66% in the surgery group ($P = .04$), with surgery being superior for

better reduction in MR grade. The difference in composite endpoint was weighted by the increased need for surgery for valve dysfunction after the procedure in the percutaneous group (22% vs 4% in the surgical group). At 2-year follow-up, the number of patients receiving MitraClip therapy remaining free of surgical intervention remained close to 80% (Table 2).

Although surgical repair had an efficacy advantage over percutaneous repair in EVEREST II, it came at the price of safety. The major adverse event rates at 30 days were 48% in the surgical repair group versus 15% in the percutaneous repair group ($P = .001$) in an intent-to-treat analysis. Increased need for blood transfusions in the surgical group versus the percutaneous repair group (45% vs 13%; $P < .001$) drove the primary safety endpoint. The improved safety profile of the percutaneous approach was accompanied by sustained clinical improvements at 2 years.

EVEREST II was the first randomized trial to compare a catheter-based MR therapy with surgical intervention. Several important concepts were learned from this trial. First, although surgical repair was more effective at reducing MR at hospital discharge, at 12 and 24 months, the reduction in MR between the two therapies was similar. Second, the clinical improvements seen with percutaneous therapy were significant and sustained over 2 years. Although the reduction in MR severity and left ventricular end diastolic volume was significantly greater in the surgical group versus the percutaneous group, patients who underwent percutaneous repair had significantly reduced left ventricular end diastolic dimensions, improved NYHA grade, and improved quality of life compared to baseline.

There are several potential explanations for why MitraClip recipients derive significant clinical benefit despite modest reductions in MR compared to surgery. First, the effect of a double orifice on the echo assessment of MR grade must be considered. There is bench model evidence that the same volume of MR through a double orifice will appear to have a much greater MR area than the same volume through a single orifice, even when the area of the single and double orifice valves are equal.¹¹ Thus, the absolute degree of residual MR after MitraClip implantation may be overestimated. In addition, the absolute degree of MR reduction appears to be less important than reducing the regurgitation below a critical point where ventricular remodeling and symptom improvement may occur. The MitraClip appears to be effective in reducing MR below this threshold, accounting for the clinical improvements observed with MitraClip therapy.

Finally, the safety profile of the MitraClip device was clearly superior to that of surgical intervention, primarily based on the reduced need for blood transfusions in the percutaneous group. The importance of blood transfusions after surgery is a controversial topic, with many surgeons arguing that transfusion is a part of surgery and should not be considered an adverse event. This is analogous to the view in the interventional community that reintervention for restenosis after percutaneous coronary intervention should not be given the same weight as death, stroke, or myocardial infarction as an endpoint.

The surgical literature is clear regarding a mortality penalty associated with blood transfusions after open heart operations. Patients who receive transfusions after cardiac surgery have a clearly higher mortality rate beyond 5 years postoperatively compared with patients who do not receive transfusions.¹² The risks are correlated with the number of units of blood transfused, and persist after propensity adjustment with a relative risk > 1.7 .¹³⁻¹⁹ Although transfusion may not be proven to be causal in these studies, there is a clear strong association with mortality. As in percutaneous coronary interventions, transfusion is a marker for increased early and late postprocedure mortality.

In addition to safety and efficacy data, EVEREST II provided more insight into the patient populations that may benefit most from the MitraClip device. Subgroup analysis of EVEREST II showed the best outcomes in patients older than 75 years, with functional rather than degenerative MR, and with left ventricular ejection fraction $< 60\%$ (Figure 1). MitraClip therapy therefore may be most reasonable as a first option in select high-risk patients. These findings are consistent with the experience of European operators who have used the device with CE Mark

approval since 2008 and the results of the EVEREST II High-Risk Registry.

EVEREST II HIGH-RISK REGISTRY

Patients enrolled in the EVEREST I phase 1 and EVEREST II randomized trials were considered acceptable candidates for mitral valve surgery. The aim of the EVEREST II High-Risk Registry (HRR) was to evaluate the MitraClip device in patients with elevated surgical risk due to previous cardiac surgery or multiple comorbidities. The HRR enrolled 78 patients with moderate-to-severe MR and an estimated surgical mortality risk of $\geq 12\%$ (measured with Society of Thoracic Surgery calculator or based on assessment by a surgeon). The prespecified mitral valve anatomic criteria were identical to those used in the randomized trial. Thirty-six patients who did not meet the anatomic screening criteria based on transthoracic or transesophageal echo assessment were used as a matched control group. All but 4% of the HRR received one or two MitraClips. Of the control group, 86% were managed medically, and 14% underwent mitral valve surgery.

Overall 30-day mortality in the HRR group and control groups were similar (7.7% and 8.3%, respectively) and significantly lower than the predicted surgical mortality of 16% ($P = .02$). At 1 year, survival was improved in the HRR group compared to the control group (76.4% vs 55.3%; $P = .047$). At 30 days, approximately 80% of patients had MR of 2+ or less, which was sustained to 1 year. In the HRR, significant improvements were seen in left ventricular dimensions, NYHA class, and quality-of-life scores at 30 days and 1 year. Annual hospitalizations for heart failure in the HRR were decreased as a result of MitraClip therapy by 45% from baseline. These beneficial effects were present in both the functional MR and degenerative MR groups.

Patients at high surgical risk have limited therapeutic options. The EVEREST II HRR supported the notion that high-risk patients, when appropriately selected, could benefit most from MitraClip therapy. The statistical outcomes from the HRR understate the clinical results. This patient group has never generally been treated with surgery in the past and represents a group with a dismal quality of life and a poor prognosis. With reduced MR, they often have dramatic quality-of-life improvements. The results of the HRR are largely consistent with the European experience for patient selection since commercialization of the device there in 2008, where a large proportion of patients undergoing the MitraClip procedure have functional MR, are at high risk for surgery, and have derived significant anatomical and functional benefits from this technology.²⁰

REALISM

The EVEREST II trial successfully completed patient enrollment in September 2008. In early 2009, continued access to the MitraClip technology for selected patients became available through the REALISM continued access registry. The REALISM study is a prospective, multicenter, continued access registry of the EVEREST II study. Patients with moderate-to-severe MR are currently being enrolled at 38 centers in the United States and assigned to one of two arms: high-risk arm and non-high-risk arm. Patients undergo 30-day, 6-month, and 12-month clinical follow-up. New information regarding quality of life and functional capacity after treatment with the MitraClip device is being collected as a part of this registry. Select preliminary results of REALISM were recently reported in abstract form at the 2011 SCAI Scientific Sessions, and data collection continues as a part of this continued access registry. To date, the registry has enrolled elderly patients with functional MR who tend to be high risk for mitral valve surgery. This pattern of patient selection is consistent with the subgroup analysis in EVEREST II (Figure 1) and also with the utilization of MitraClip in the European commercial use experience.

FUTURE DIRECTIONS

The EVEREST trials provided necessary phase 1 and phase 2 data regarding the safety and efficacy of the MitraClip system for the treatment of MR. It is important to note that these trials were designed to study this therapy in patients with degenerative MR, and those with functional MR represented a minority of the study populations. Conversely, three-quarters of the patient population currently being treated in Europe have functional MR. Franzen et al²¹ reported short-term durability and clinical outcomes in patients' functional MR who underwent MitraClip implantation, with a sustained reduction in MR severity in all patients and statistically significant improvements noted in 6-minute walking distance, left ventricular dimensions, and B-type natriuretic peptide levels. These findings suggest that the MitraClip therapy may be as effective in functional MR compared to degenerative MR.

As more patients are treated with the MitraClip device, patient populations who should be targeted for this therapy will become more apparent. Initial data indicate that patients at high risk for surgical intervention and those with functional MR with appropriate mitral valve anatomy may benefit most from MitraClip therapy. As additional endovascular mitral valve therapies with expanded indications undergo further development and testing, an even broader patient population will be treated nonoperatively for MR. ■

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