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The Evolving Role of Percutaneous Mitral Valve Repair

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Background: Mitral regurgitation (MR) is the second leading cause of valvular heart disease in the United States behind aortic stenosis. The percutaneous repair of the mitral valve (MitraClip, Abbott, Inc.) has been approved in the United States since 2013 as an alternative to traditional mitral valve surgery. However, many questions are left unanswered about when to perform this procedure and whom to perform it on.

Methods: We reviewed major published literature on the MitraClip from 2003-2016 to help guide clinical decision-making. A PubMed search was conducted using the phrase ''mitraclip'' or ''percutaneous mitral valve repair'' to identify relevant articles pertaining to the clip as well as surgical valve repair.

Results: The clinical trials EVEREST I and EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) demonstrated the safety and efficacy of the MitraClip but did not prove its superiority to surgical repair in the population studied. Numerous subsequent registries have suggested that the success of the MitraClip varies with the patient population studied. The currently enrolling Cardiovascular Outcomes for Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional MR (COAPT) trial hopes to answer some of these questions.

Conclusion: The MitraClip is a new and exciting technology for percutaneously treating disease processes traditionally managed with surgery. The future of the clip and its patient population is dependent on further studies.

Keywords: *Mitral valve, mitral valve annuloplasty, mitral valve insufficiency*

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INTRODUCTION

Mitral regurgitation (MR) is the second leading cause of valvular heart disease in the United States behind aortic stenosis.[1,2] Seen in up to 50% of patients after a myocardial infarction, MR is just as common in patients with left ventricular systolic dysfunction.[3,4] MR is classified as primary regurgitation from intrinsic valvular disease or secondary regurgitation resulting from left ventricular dysfunction. Severe symptomatic regurgitation of both types carries 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.[5-7] Surgical valve repair or replacement is the current recommended therapy for severe symptomatic primary MR and asymptomatic MR when associated with left ventricular dysfunction, atrial fibrillation, or pulmonary hypertension.[8] The role of mitral valve surgery in secondary MR is less clear; however, surgery has still proven beneficial in certain populations.[9,10] More than 40,000 mitral valve surgeries are performed every year in the United States, yet this number only accounts for 50% of the total population with an indication for surgery.[11] The patients who are denied surgery tend to be older (69 vs 63 years old), have a reduced ejection fraction (48% vs 56%), and have other comorbidities that increase their surgical risk.[2] In the absence of surgery, the only historic alternative has been medical therapy with blood pressure reduction and diuresis, but no medical therapy has been shown to improve survival.[12] Thus, there is a clear need for a less-invasive intervention in this high-risk population.

Percutaneous repair of the mitral valve with the MitraClip (Abbott, Inc.) has been an alternative to surgery since 2013, but questions about when this procedure should be performed and which patients are the best candidates have yet to be answered. To help guide clinical decision-making, we conducted a PubMed search of the published literature about the MitraClip from 2003-2016, using the search terms ''mitraclip'' and ''percutaneous mitral valve repair.''

THE DOUBLE-ORIFICE TECHNIQUE

Ottavio Alfieri developed a surgical technique in Milan in the 1990s in which he sewed a small section in the middle of the leading edge of the mitral leaflets together to create a double-orifice mitral valve.[13] The idea was born when Alfieri was operating on a patient with anterior leaflet prolapse one day after observing a patient with an asymptomatic fully functioning congenital double-orifice valve. Initial concerns about the development of mitral stenosis proved to be unfounded, and the procedure was shown to have normal hemodynamics.[14,15] The procedure was most effective when performed in conjunction with annuloplasty (repair

of the mitral valve annulus); however, two studies from 1998 and 2001 showed effectiveness when the procedure was done in isolation—85%-92% had a 6-year survival and 89%-95% were repeat operation free.[16,17] These studies were performed in a largely healthy population with isolated degenerative disease; nonetheless, the study results provided the clinical proof of concept for the development of a percutaneous leaflet procedure.[18]

PORCINE BEGINNINGS

In 2003, Evalve, Inc. developed a cardiovascular valve repair system that consisted of a steerable guide catheter with a distal tip that was placed in the left atrium via an atrium septal puncture. A V-shaped clip was introduced through the guide catheter into the left ventricle, and the open clip arms were oriented perpendicular to the leading edge of the leaflets using echocardiographic guidance. The arms were closed, and placement was verified by echocardiography. This technique was used successfully on 12 pigs in 2003 and replicated in another porcine study that showed durable results and clip integrity at 6 months.[19,20]

EVEREST I

Following the success of the porcine model, the cardiovascular valve repair system, or MitraClip, was first used in humans in 2005. Abbott, Inc. subsequently purchased Evalve, Inc. in 2009. The Endovascular Valve Edge-to-Edge Repair Study (EVEREST I) was designed to examine the feasibility, safety, and efficacy of the MitraClip.[21] The device was similar to the porcine model with 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.[19,22] The clip was advanced into the left ventricle, closed to 120 degrees, and retracted until both 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 of the clip. If clip placement was inadequate, the device could be opened and repositioned. Patients were treated with aspirin 325 mg daily for 6 months and clopidogrel 75 mg daily for 1 month after the procedure. The initial EVEREST I trial enrolled 55 patients, and the first 27 were evaluated at 6 months. The remainder were evaluated at 3 years in conjunction with 52 roll-in patients from the subsequent EVEREST II trial.[23] All patients met a Class I indication for mitral valve intervention as determined by 2006 American College of Cardiology/American Heart Association (ACC/AHA) guidelines.[24] Class I indications included patients with symptomatic moderate to severe MR or asymptomatic MR in the setting of reduced ejection fraction, left ventricular dilation, new-onset atrial fibrillation, or pulmonary hypertension. Several additional inclusion criteria were unique to the MitraClip such as the requirement for a central MR jet and a limited degree of degenerated leaflet.

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 2 transseptal complications requiring emergency surgery. No clip embolizations were reported, but detachment from one leaflet was seen in 9%. Overall, clips were implanted in 90% of patients with a 74% total acute procedural success rate; however, 25% eventually required mitral valve surgery for failed clip implantation or recurrent MR. Overall, 66% met the primary endpoint of freedom from surgery with $<2+$ MR or death at 3 years. The 55% of patients with New York Heart Association (NYHA) Class III/IV symptoms at baseline showed improvement in the secondary endpoint. Improvement to NYHA Class I/II classification was seen in 92% at 12 months. This symptomatic improvement persisted in the subset of patients with functional MR, with 80% having improved symptoms at 12 months. EVEREST I proved the safety of the clip and demonstrated evidence of symptom improvement but highlighted that further study was needed to demonstrate the degree of efficacy.

EVEREST II

After safety and feasibility were demonstrated in the EVEREST I trial, the EVEREST II trial aimed to demonstrate the efficacy of the MitraClip. From 2005-2008, 279 patients at 38 centers across the United States, including Ochsner Medical Center, were randomized 2:1 to MitraClip vs surgical replacement/repair for moderate to severe MR.[25] Inclusion criteria regarding the severity of regurgitation and the specifics of the MR jet were similar to those for EVEREST I. The composite endpoint was freedom from death, from surgery for mitral valve dysfunction, and from moderate to severe MR at 12 months. The endpoint was reached in 73% of the surgical group and 55% of the percutaneous group. The rate of death at 12 months was the same for both groups at 6%. However, a larger percentage of those in the percutaneous arm developed recurrent MR after the initial procedure, with 37 (20%) requiring follow-up mitral valve surgery compared with 2 (2%) in the surgical repair arm. After these follow-up surgeries, the incidence of moderate to severe MR at 12 months was similar in both groups at 38 (21%) and 18 (20%) for the percutaneous and surgical arms, respectively (Table 1).[26] These results proved durable at 4 years with the rate of moderate to severe MR in the percutaneous group unchanged at 21%.[26] Adverse events were largely the same for both groups with the only exception being a larger percentage of patients in the surgical arm requiring $\geq$2 units of blood (45% vs 13%). Two patients died within 30 days in each group, although the 2 deaths in the percutaneous cohort were patients who required subsequent mitral valve surgery for persistent MR.

The EVEREST II trial again demonstrated the safety of a percutaneous approach to mitral valve repair; however, traditional surgical repair/replacement was clearly more efficacious in this study population. An important point is that all patients enrolled in the trial were candidates for both valve surgery and percutaneous repair and were thus inherently low-risk patients. In contrast, among the US population, approximately half of patients with indications for mitral valve repair/replacement are not operative candidates secondary to comorbidities.[11] Operative mortality with mitral valve surgery increases with age, from 4% in patients $<$50 years old to 17% in patients $>$80 years old.[27] As a result, many subsequent studies have explored the

Table 1. EVEREST II Endpoints[26]

Endpoint	Percutaneous Repair, n (%)	Surgery, n (%)
Freedom from death, surgery for mitral valve dysfunction, and grade 3+ or 4+ mitral regurgitation at 12 months	100 (55)	65 (73)
Surgery for mitral valve dysfunction	37 (20)	2 (2)
Death	11 (6)	5 (6)
Grade 3+ or 4+ mitral regurgitation at 12 months	38 (21)	18 (20)
30-day mortality	2 (1)	2 (2)
Mechanical ventilation >48 h	0 (0)	4 (4)
Transfusion of ≥2 units of blood	24 (13)	42 (45)

EVEREST, Endovascular Valve Edge-to-Edge Repair Study.

potential benefit of the MitraClip in high-risk populations who would not otherwise be surgical candidates and thus are relegated to medical therapy.[11,28,29]

HIGH RISK, HIGH REWARD

Whitlow et al first explored this high-risk population, examining 78 patients enrolled in the EVEREST II High Risk Registry (HRR), all of whom had a Society of Thoracic Surgeons (STS) expected procedural mortality rate ≥12% (14.9% ± 8.2%).[29] Seventy-five (96%) had a successful MitraClip implantation to treat severe symptomatic MR. At 1 year, 78% of the surviving patients had mild MR. Most notably, a significant symptomatic improvement was noted, with 89% having NYHA Class III/IV heart failure symptoms at baseline compared to 25% at 12 months. Hospitalizations also decreased, with 42% hospitalized in the year prior to the procedure and 12% hospitalized the year after. Mortality, however, was substantial in this high-risk population with 6 deaths (7.7%) at 30 days that were likely procedurally related and a 74% survival at 12 months. In an effort to understand the intrinsic mortality in this high-risk population, the study group was compared with 36 patients who were candidates for the procedure but either opted out or did not meet the strict anatomic criteria for the clip. This group had an 8% 30-day mortality and 55% survival at 12 months. Other studies have attempted to compare propensity-matched populations that have demonstrated comparable 30-day and 12-month mortality rates.[30]

The 78 patients in the initial EVEREST II HRR were rolled in with another 273 patients in the EVEREST REALISM (Real World Expanded Multicenter Study of the MitraClip System) registry, all of whom had an STS expected mortality with valvular surgery of ≥12%.[11,29] When these patients were considered together, the initial EVEREST II HRR results were validated. This combined cohort of 351 patients showed a similar 30-day mortality of 4.8% and a similar 12-month mortality of 22.8%. The reduction of MR was also similar, with 84% of patients having mild MR at 12 months (Figure 1). The percentage of patients with NYHA Class III/IV heart failure symptoms was reduced from 82% at baseline to 17% at 12 months (Figure 2).[11] This analysis did not include a comparison group.

Overall, the MitraClip appears to be effective at reducing symptoms, decreasing hospitalizations, and improving MR in high-risk patients who are not eligible for surgery. However, the MitraClip is associated with some procedure-related risk. Given the intrinsic high mortality of this population, long-term mortality benefits from the MitraClip remain uncertain. An additional concern is that while the EVEREST II HRR attempted to create a comparison group, both the EVEREST II HRR and EVEREST II REALISM studies were both registries. Problematic to all registries, including these, is the inherent potential for selection bias and other confounders that make the data difficult to generalize.

OFF TO THE REGISTRIES

Approved for commercial use in September 2008 in Europe and in October 2013 in the United States, the MitraClip has been used in more than 10,000 patients to reduce MR.[11] In addition to the registries mentioned above, several MitraClip registries during the past 7 years give us insight into its clinical outcomes and real-world use.

The ACCESS-EU (A Two-Phase Observational Study of the MitraClip System in Europe) registry enrolled 567 patients from April 2009 through April 2011 as phase 1 of a 2-phase study; the results of phase 1 were published in 2013.[31] Baseline preoperative mortality risk was determined by the European System for Cardiac Operative Risk Evaluation (EuroSCORE) instead of the STS score. The mean EuroSCORE was 23%, meaning these patients were high risk and more akin to the EVEREST II HRR than the patients originally studied in EVEREST II. The 30-day mortality was 3.4%, and the 12-month mortality was 18.2%. Seventy-nine percent of patients at 12 months had mild MR (Figure 1). Eighty-four percent had NYHA Class III/IV heart failure symptoms at baseline reduced to 29.6% at 12 months (Figure 2).[31] Other registries, such as the 628 patients from the Transcatheter Valve Treatment Sentinel Pilot Registry in Europe (TCVT-EU) from 2011-2012 or the 1,064 patients in the TRAMI (Transcatheter Mitral Valve Interventions) from 2010-2013 in Germany, are similar to EVEREST II HRR and ACCESS-EU. The patients, on average, tended to be high risk, with a similar short-term mortality at 2.9%-4.4% and a similar 1-year mortality at 15.3%-20.3%. The TCVT-EU and TRAMI registries also showed similar symptomatic success rates.[32,33]

Another recent registry with notable findings is the GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) that compared 2 cohorts: patients who met strict EVEREST echocardiographic leaflet criteria and patients who did not. The GRASP registry demonstrated similar success, safety, and efficacy among the 2 cohorts.[34]

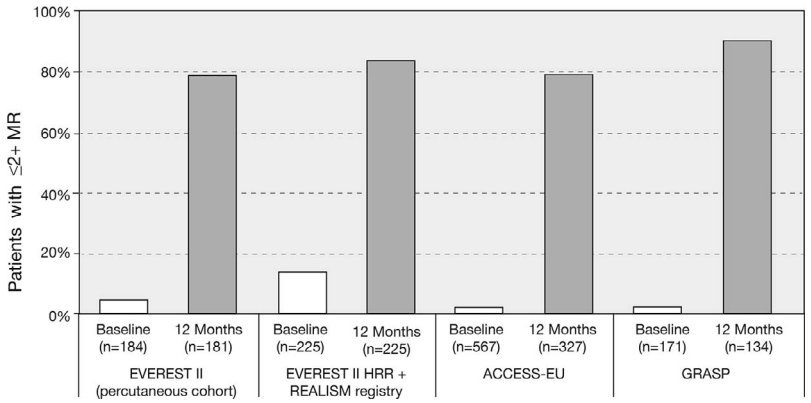

Figure 1. Percentage of patients with ≤2+ mitral regurgitation (MR) at baseline and 12 months after percutaneous MitraClip placement. The smaller cohorts represent the subset of patients from each registry who had MR qualified by imaging and were available for follow-up. Certain registries were able examine only those with follow-up and compare baseline MR; others measured baseline MR in all comers. ACCESS-EU, A Two-Phase Observational Study of the MitraClip System in Europe; GRASP, Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation; EVEREST II, Endovascular Valve Edge-to-Edge Repair Study II; HRR+REALISM, High Risk Registry/Real World Expanded Multicenter Study of the MitraClip System.[11,26,31,34]

The most recent registry release is the Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry (STS/ACC TVT). It is notable that this is the first commercial US registry with results released in March 2016. Five hundred sixty-four patients were enrolled from November 2013 through August 2014. Eighty-five percent of the patients had isolated degenerative/primary MR—a different patient population than the European registries because of the MitraClip US Food and Drug Administration (FDA)-approved indication for degenerative/primary MR. While the average STS score of the US registry was low (7.7%), the study authors did not feel it adequately reflected the true morbidity of the patient population. Currently, only 30-day results are available; the 12-month outcomes are pending. The 30-day mortality is similar to that of the European registries at 5.8%, and the incidence of mild MR at 30 days is 86%.[35]

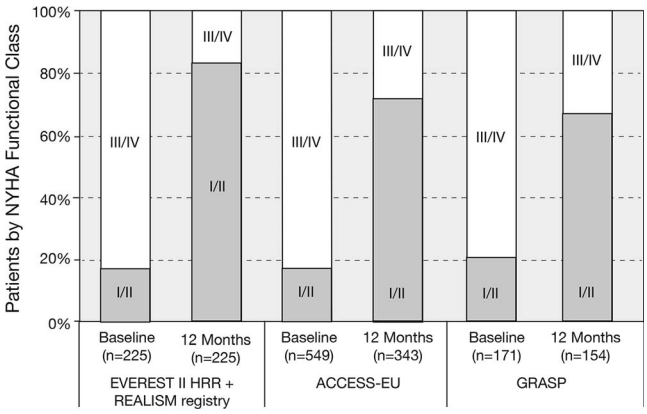

Figure 2. Percentage of patients with symptoms of heart failure (New York Heart Association [NYHA] functional class) at baseline and 12 months after percutaneous MitraClip placement. The smaller cohorts represent the subset of patients from each registry who had functional status measured on presentation and on follow-up. Certain registries were able to examine baseline symptoms of only those with follow-up; others measured baseline symptoms in all comers. ACCESS-EU, A Two-Phase Observational Study of the MitraClip System in Europe; GRASP, Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation; EVEREST II HRR+REALISM, Endovascular Valve Edge-to-Edge Repair Study II High Risk Registry/Real World Expanded Multicenter Study of the MitraClip System.[11,31,34]

Despite this plethora of data from the ACCESS-EU, GRASP, TRAMI, TCVT-EU, and STS/ACC TVT registries, we must still consider the fact that all of these studies are registries. As mentioned above, the potential for selection bias is apparent. Therefore, prospective, randomized data are needed about MitraClip outcomes in this high-risk population.

DEGENERATIVE VS FUNCTIONAL MITRAL REGURGITATION

In addition to the disparities in surgical risk between EVEREST II and the successive registries, the other fundamental difference is the etiology of MR in each of the studies. In the EVEREST II trial, only 75 patients (27%) had functional/secondary MR, while the majority (204 patients [73%]) had degenerative/primary MR.[25] In sharp contrast, the EVEREST II HRR/REALISM, GRASP, ACCESS-EU, TCVT-EU, and TRAMI registries were each comprised of at least 70% of patients with functional/secondary MR (Table 2).[11,29,31,33-35]

The mortality benefit of mitral surgery for degenerative MR has been demonstrated for appropriately selected patients, but a mortality benefit to surgical treatment of functional MR has not been shown.[7] Because a dysfunctional valve is the primary etiology behind the pathology of degenerative MR, the theory and practice are that correcting the valve reverses the pathological process. In contrast, secondary MR is a sequela of another pathology—most often dilated or ischemic cardiomyopathy. Repair of the valve and MR in this situation has been less straightforward because it does not reverse the underlying cause of the cardiomyopathy.

Table 2. Trial/Registry Composition by Functional vs Degenerative Etiology

Trial/Registry	Trial Size, n	Functional Mitral Regurgitation, %	Degenerative Mitral Regurgitation, %
EVEREST II[26]	279	27	73
EVEREST II HRR/REALISM[11]	351	70	30
ACCESS-EU[31]	567	77	23
GRASP[34]	171	76	24
TCVT-EU[32]	628	72	28
STS/ACC TVT[35]	564	14	86
TRAMI[33]	749	71	28

ACCESS-EU, A Two-Phase Observational Study of the MitraClip System in Europe; EVEREST II, Endovascular Valve Edge-to-Edge Repair Study II; GRASP, Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation; HRR/REALISM, High Risk Registry/Real World Expanded Multicenter Study of the MitraClip System; STS/ACC TVT, Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy Registry; TCVT-EU, Transcatheter Valve Treatment Sentinel Pilot Registry in Europe; TRAMI, Transcatheter Mitral Valve Interventions Registry.

Additionally, the greater comorbidities and greater surgical risk in the population with secondary MR increase the difficulty of demonstrating a surgical benefit.

Most major guidelines recommend against isolated mitral valve surgery in the setting of chronic severe secondary MR. Surgery is generally only recommended in this setting if aortic valve or coronary artery bypass graft (CABG) surgery is also being performed.[8] Mitral valve surgery for functional MR, when performed with CABG, has yielded mixed results, with some studies showing symptomatic and functional improvement and other studies remaining equivocal.[9,10,36] Nonetheless, as mentioned above, the registries have shown repeated significant symptomatic improvement in this population with functional MR, leading the way for further study and comparisons.

REGISTRY LEGACY

The registries have had several beneficial outcomes. They are largely comprised of a high-risk patient population with functional MR. These 2 factors are linked in that functional MR patients tend to have a reduced ejection fraction and numerous comorbidities that make them inherently high risk. With the lack of randomized trial data, the registries are a mechanism to study functional MR in a high-risk population that was not a part of the initial EVEREST II trial. Functional MR remains a more prevalent cause of MR in the United States than degenerative MR; thus, the registries have applicability to a broader potential indication than EVEREST II.[37] Nonetheless, we should still consider selection biases inherent to registries before drawing conclusions.

COAPT TRIAL

To clearly demonstrate the efficacy and safety of the MitraClip in this high-risk functional population, the Cardiovascular Outcomes for Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) trial was designed. It is a prospective, randomized, multicenter (including Ochsner Medical Center) 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 throughout the United States. Study participants are randomized 1:1 to device therapy (MitraClip) or to no device therapy, with all patients receiving maximal, guideline-directed medical therapy. The goal is to recruit 430 subjects, 215 in each cohort, with the primary efficacy endpoint being recurrent heart failure hospitalizations at 24 months and the primary safety endpoints including device embolization, mitral stenosis, left ventricular assist device, heart transplant, and any device complications requiring surgery. Many secondary endpoints 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 the use of the MitraClip in high-risk patients with functional MR.

CONCLUSION

The MitraClip is a new and exciting technology for percutaneously treating disease processes traditionally managed with thoracotomy, cardiopulmonary bypass, and surgery. However, many questions must still be answered about the most appropriate patient population to treat and when to treat them. With time and further research, these questions can be answered, and the future of the MitraClip will be determined.

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