# Preliminary Experience Using the Transcatheter Mitral Valve Leaflet Repair Procedure

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**ABSTRACT:** **Background:** Mitral regurgitation (MR) causes increased morbidity and mortality in heart failure patients and is often associated with augmented surgical risk.
**Objectives:** To assess the preliminary results of transcatheter mitral valve leaflet repair (TMLR) in a single academic center.
**Methods:** Data were collected prospectively in the cardiology department of Rabin Medical Center in 2012. Ten consecutive patients (age 69.3 ± 15.9 years, ejection fraction 36.5 ± 9.4) who were poor surgical candidates with severe functional MR underwent general anesthesia, followed by trans-septal puncture and a TMLR procedure using the MitraClip device.
**Results:** All 10 patients were considered to have severe functional MR prior to TMLR treatment and were all symptomatic; the mean New York Heart Association (NYHA) class was 3.4 ± 0.5. The MR severity was 4 ± 0. There were no immediate complications or failures of the procedure. One patient died on day 5 due to massive gastrointestinal bleeding. Immediately following TMLR all 10 patients showed a profound MR reduction to a mean severity grade of 1.6 ± 0.6. At one month after the procedure, NYHA had decreased to an average of 1.7 ± 1.0 and was at least grade 2 in all but one patient. After 6 months the MR remained ≤ 2 in six of eight patients, with a NYHA average of 1.4 ± 0.5.
**Conclusions:** The MitraClip procedure was shown to be relatively safe, providing significant clinical benefit to a relatively sick population with severe MR. It is therefore an important alternative to surgery in these high risk patients.

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**KEY WORDS:** mitral regurgitation (MR), MitraClip™, transcatheter mitral valve leaflet repair (TMLR), trans-septal puncture, heart failure

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Mitral regurgitation, detected clinically and/or by cardiac echo-Doppler, is a common disorder in the general population. In the Framingham Study, 1696 men and 1893 women underwent an echocardiography study as part of a routine examination. MR of at least mild severity was seen in 19.0% and 19.1% of the men and women respectively [1]. In heart failure patients, even in the absence of structural mitral valve disease, the condition is very common due to left ventricular dilatation, stretching of the mitral annulus, and regional wall motion abnormalities [2]. Robbins et al. [2] reported a 59% prevalence of at least moderate MR in patients with systolic failure. In another study, 50 patients referred for cardiac transplantation all had MR of at least moderate severity, regardless of etiology [3].

MR is caused by the lack of anterior and posterior leaflet coaptation, leading to a back flow of blood from the left ventricle into the left atrium in systole. Type IIIB MR, according to the functional classification named after the surgeon Alain Carpentier [4], is typically caused by ischemic or idiopathic (i.e., secondary) cardiomyopathy with impaired ventricular function and dilation but a "normal" morphology to the leaflets, chords and papillary muscles, commonly with restriction at the P3 segment [5].

In cases where MR is severe and the patient is symptomatic, the conventional treatment is surgical repair or replacement of the mitral valve. It is widely accepted that when feasible, valve repair is the optimal surgical treatment for patients with severe primary organic MR. However, in patients with secondary MR-type IIIB according to Carpentier's classification, the benefits of surgery alone are unclear, mostly because of severe comorbidities. In fact, most studies failed to demonstrate an improved long-term clinical outcome following surgical correction of secondary MR [6].

Surgical mitral valve edge-to-edge repair to create a double-orifice valve was first performed by Alfieri in the early 1990s [7]. It is important to note that this surgical technique offers better results when associated with ring annuloplasty, as later attested by Alfieri himself [8]. However, not all patients are suitable for such surgical procedures. The catheter-based mitral valve repair method, using a clip implant (manufactured by Abbott Vascular, Santa Clara, CA, USA) that simulates the Alfieri technique, approaching the mitral valve via a trans-atrial septal puncture, had been introduced as a potential

MR = mitral regurgitation

alternative for open heart surgery [9]. In this article we present our center's initial experience with a series of patients treated with the MitraClip device.

## PATIENTS AND METHODS

Our first 10 consecutive patients were selected according to several parameters: all had functional MR pathology, all had reduced LV function (LVEF < 40%) with significant symptoms, and all were deferred from surgery due to excessive procedural risk, i.e., both cardiac and non-cardiac comorbidites. Notably, in our experience so far, all the patients had functional MR as a result of ischemic cardiomyopathy.

The anatomic criteria we used to select the patients for TMLR were based on specific anatomic features, estimated by both two- and three-dimensional trans-esophageal echocardiography. First, we confirmed the origin, direction and severity of the regurgitant jet. In the cases that were included, the origin of the MR jet was primarily from the central portion of the valve (A2 to P2). The resting mitral valve-effective orifice area was more than 4 $cm^2$ in the hope of minimizing the inevitable but small reduction in valve area at the transformation to a double orifice. In cases of ischemic functional MR, as in our series of patients thus far, where one or more leaflets may be tethered, a coaptation length of at least 2 mm is necessary [10-12]; all our patients conformed to these recommendations. Important exclusion criteria included rheumatic MR, apical tenting of > 10 mm, calcified leaflets, and significant mitral stenosis.

## RESULTS

Data were collected prospectively in the cardiology department of Rabin Medical Center in 2012. Mean patient age was 69.3 ± 15.9 years at the time of the procedure. All patients were considered to have severe MR (grade 4), and most were New York Heart Association class 4 at presentation. Ninety percent of the patients were considered to have coronary artery disease, and 40% had diabetes. Patient characteristics before the procedure are presented in Table 1.

The MitraClip™ system consists of two main parts: a MitraClip attached to the clip delivery system and a steerable guide catheter. The clip delivery system is advanced through the guide into the left atrium toward the mitral valve. The MitraClip is constructed from cobalt chromium and covered with polyester. It has two arms that are roughly 8 mm long and 4 mm wide. The arms are opened and closed by a control mechanism on the handle of the clip delivery system. On the inner aspect of the arms are two corresponding "grippers" that help secure the leaflets. Each leaflet is grasped between an arm and a gripper. The entire procedure is TEE guided, using real-time three-dimensional [Figure 1C] and X-plane technologies. These modalities enable a better understanding of both the position of the clip in its anatomic surroundings and in relation to the regurgitant jets. After verifying a profound reduction in MR severity, the clip can be locked in the final position and then deployed in this state.

In total, the length of the procedure was 123.50 ± 65.8 minutes on average (range 60–230 minutes), while the mean exposure time to fluoroscopy was 37.4 ± 12.7 minutes (range 18.5–59.7). The need for a second clip to further reduce the MR occurred in 6 of the 10 patients. One patient required three clips, as described below.

The results are shown in Table 2 and Figure 2. The mean MR grade after the TMLR was 1.6 ± 0.6. NYHA at 1 month and decreased to an average of 1.7 ± 1.0. Figure 1 shows echo-

**Table 1.** Patients' baseline characteristics

| | |
|---|---|
| Mean age (yr) | 69.3 ± 15.9 |
| Females | 1 (10%) |
| Hypertension | 7 (70%) |
| Diabetes mellitus | 4 (40%) |
| Coronary artery disease | 9 (90%) |
| Previous myocardial infarction | 5 (50%) |
| CABG surgery in the past | 6 (60%) |
| Heart failure | 9 (90%) |
| Past valvular surgery* | 1 (10%) |
| ICD/PM implant | 3 (30%) |
| Chronic renal failure | 5 (50%) |
| COPD | 3 (30%) |
| CVA | – |
| Atrial fibrillation | 5 (50%) |
| Mean MR severity | 4.0 |
| Mean NYHA class | 3.4 ± 0.5 |
| Mean LVEF | 36.5 ± 9.4% |
| Mean LVEDD | 61.5 ± 8.4 mm |
| Mean PAP | 56.8 ± 18.9 mmHg |
| Mean hospitalizations in previous 6 months** | 1.6 ± 0.8 |
| Mean STS score | 10.3 ± 5.8 |
| Mean EuroScore I | 28.5 ± 15.8 |

*One patient had undergone two aortic valve replacement surgeries in the past

**Admissions due to heart failure exacerbations in the previous 6 months prior to TMLR

CABG = coronary artery bypass surgery, ICD = implantable cardioverter defibrillator, PM = pacemaker, COPD = chronic obstructive pulmonary disease, CVA = cerebrovascular accident, LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, PAP = pulmonary artery pressure, STS = Society of Thoracic Surgeons Risk Score

LV = left ventricular
LVEF = left ventricular ejection fraction

TEE = trans-esophageal echocardiography
NYHA = New York Heart Association
TMLR = trans-catheter mitral valve leaflet repair

**Figure 1.** Trans-thoracic echocardiography before the procedure **[A]**, angiography during the procedure **[B]**, 4D TEE during the procedure **[C]** showing the MitraClip device (arrow), and trans-thoracic echocardiography 4 months after the procedure **[D]**

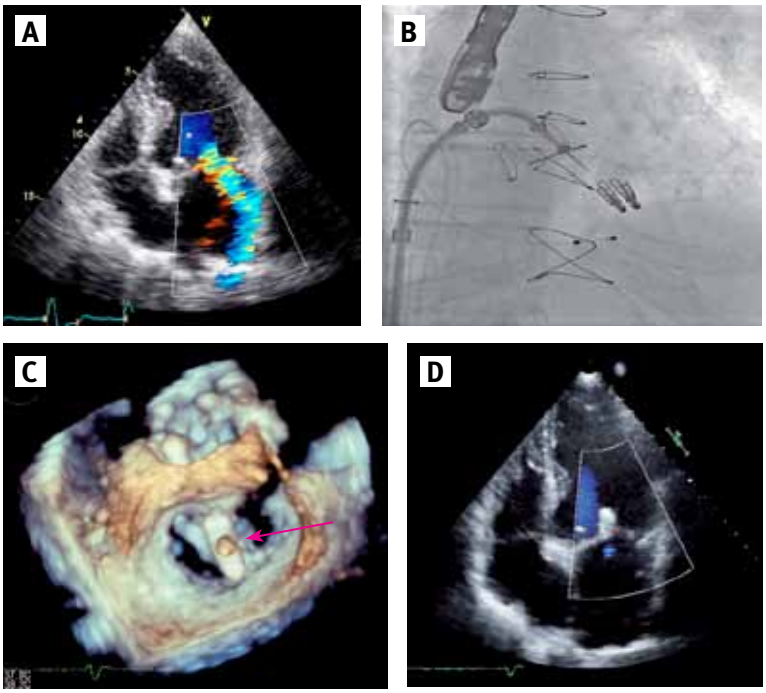
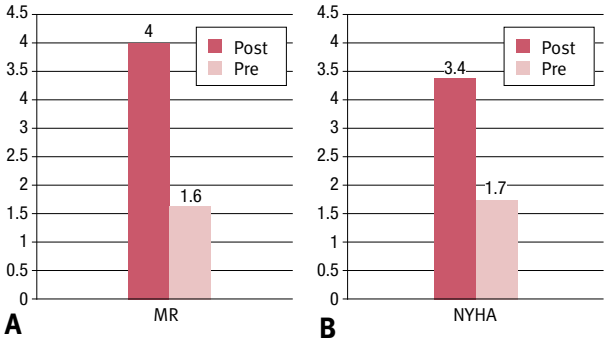



**Table 2.** Outcome

| | |
|---|---|
| Mean follow-up duration | 218.5 ± 124.6 days |
| Mean number of clips implanted | 1.7 ± 0.7 |
| Mean procedural length | 123.5 ± 65.8 min |
| Mean exposure time to fluoroscopy | 37.4 ± 12.7 min |
| Mean MR grade post-procedure | 1.5 ± 0.6 |
| LVEF-post | 36.9 ± 10.3% |
| LVEDD-post | 56.9 ± 4.6 mm |
| Pulmonary artery pressure-post | 43.0 ± 15.5 mmHg |
| Mean NYHA at 1 month | 1.7 ± 1.0 |
| Mean NYHA at 6 months | 1.6 ± 0.6 |
| Death | 1 (10%) |
| Acute myocardial infarction | – |
| Cardiovascular death | – |
| Urgent surgery | – |
| Renal failure | 1 (10%) |
| Stroke | – |
| Reoperation* | 1 (10%) |

cardiographic and angiographic samples taken before [Figure 1A], during [Figure 1B, 1C) and 4 months after [Figure 1D] the procedure. One patient died due to upper gastrointestinal bleeding during hospitalization. This patient was referred to our service following prolonged hospitalization in another hospital and was supported by mechanical respiratory ventilation due to intractable heart failure. He had severe stress ulcers and gastritis and was rushed to the operating room during the course of a massive gastrointestinal bleeding event; however, he did not recover from the hemorrhage and surgery and died 5 days after the procedure. Another patient required an additional TMLR procedure due to residual MR 5 months after a first single MitraClip implantation. During the second procedure a second and third clip were implanted, with an optimal final result: reduction of the MR to a severity grade of 1 per echocardiography. Clinically, the patient is now considered NYHA functional class 1.

**Figure 2. [A]** MR grades before and after the procedure. **[B]** NYHA class before and 6 months after the procedure




## DISCUSSION

In our experience, the technical aspects of the TMLR procedure seem to be manageable. With this treatment approach we were able to achieve a marked and durable reduction in MR for the first few months after TMLR. Unfortunately, we lost one patient due to massive gastrointestinal bleeding. These preliminary results encourage us to proceed with the TMLR program at our center.

The two major clinical trials involving the MitraClip device are the non-randomized study EVEREST I and the randomized controlled trial EVEREST II which demonstrated an acute MR reduction to grade 2 or lower at discharge in approximately 75% of patients [10-12]. In EVEREST (the Endovascular Valve Edge-to-Edge Repair Study) II, 279 patients with MR grade 2 or above were randomized 2:1 to the MitraClip procedure or to surgical repair/replacement. All patients were either symptomatic or had documented LV dysfunction. The trial was conducted at 37 centers in the United States and Canada and included patients with both functional (27%) and degenerative (73%) MR. Primary safety end-points at 30 days included death, major stroke, reoperation, urgent/emergent surgery, myocardial infarction, renal

failure, deep wound infection, gastrointestinal bleeding and more. Primary efficacy end-points were defined as survival and freedom from mitral valve surgery or reoperation for mitral valve dysfunction and lack of MR grade 2 or above at 12 months. For the primary efficacy end-point, rates were 55% in the percutaneous repair group and 73% in the surgery group ($P = 0.007$). The overall clinical success rate was numerically higher in the surgery group, 87.8% vs. 72.4%, but this difference, statistically, met the prespecified non-inferiority hypothesis of -31%. As for safety, events occurred less frequently in the MitraClip arm (15%) than in the surgical arm (48%, $P < 0.001$). Nonetheless, most adverse events in the surgical group were due to the need for peri-operative blood transfusion.

Seventy-eight patients who were considered high risk (> 12% surgical mortality rate) were compared with a group of 36 patients with similar degrees of mitral regurgitation, risks, and comorbidities who were screened for the study but were not enrolled for the procedure. The MitraClip patients appeared to have a better 1 year survival (76% vs. 55%, $P$ =0.047). In the treatment arm, after 12 months 78% of the surviving patients had an MR grade of 2 or less, NYHA functional class was 1 or 2 in 74% of patients, as compared to 89% class 3 or 4 at baseline, and the annual rate of hospitalization for congestive heart failure in patients with matched data decreased from 0.59 to 0.32 ($P = 0.034$). Finally, there were even signs of left reversed ventricular remodeling as end-diastolic and end-systolic volumes improved [12]. In a sub-analysis of patients with atrial fibrillation, comprising 27% of the total EVEREST II population, results were similar after the procedure, regardless of the type of rhythm [13].

In the prospective, observational, post-market study ACCESS-EUROPE, 567 patients were enrolled in 14 centers in Europe and were followed for 1 year. The mean age was 74 years; 85% were classified as NYHA class 3 or 4. Patients had significant comorbidities, such as coronary artery disease (in 63%) and renal disease (in 42%). The cause for MR was determined to be functional in 77% of the patients. After 1 year of follow-up, 82% of the patients were alive, 79% no longer had MR grade 2 or above, only 6% had to undergo mitral valve surgery, and 72% were considered NYHA class 1 or 2. There was also improvement in the 6 minute walking distance and in quality of life measurement, as assessed by the Minnesota Living with Heart Failure Questionnaire [14]. A recent trial dedicated to end-stage heart failure patients, all with LVEF < 25%, showed a 94% acute procedural success rate and an MR grade of 2 or below in 87% of the patients after 6 months. There were also significant reductions in LV dimensions and average β-natriuretic peptide levels [15].

We describe here our preliminary experience using the TMLR technique in patients with severe functional MR who are at great surgical risk. Our results, while still preliminary and limited, are much in line with the results shown in the above-cited clinical trials.

The latest European Society of Cardiology Guidelines on valvular heart disease recommend consideration of the percutaneous mitral clip procedure in severe MR patients who are symptomatic "…despite optimal medical therapy, who fulfill the echo criteria of eligibility, are judged inoperable or at high surgical risk by a team of cardiologists and cardiac surgeons, and who have a life expectancy greater than 1 year" (recommendation class IIb, level of evidence C) [6]. It was previously proposed that patients with ischemic cardiomyopathy and functional MR fare better when the valvular disease is repaired rather than surgically replaced [16]. Taking into account the growing number of patients with ischemic cardiomyopathy and secondary MR, this population will likely expand. Future randomized controlled trials, particularly studies with long-term results, are necessary to assess the efficacy and safety of the TMLR in inoperable patients with functional MR.

Presently, the number of available percutaneous mitral valve repair techniques is very limited. However, following the success of TMLR, numerous new technologies of percutaneous mitral valve repair are now beginning to appear, including new end-to-end devices, as well as other innovative approaches to percutaneous repair (and perhaps replacement) of diseased mitral valves. Consequently, as recently occurred in the field of aortic valve disease, in the next few years we are likely to witness vast changes in our therapeutic algorithms for patients with mitral regurgitation.

## CONCLUSIONS

Our single-center experience with severe MR patients treated with the MitraClip procedure showed relatively good results, enabling significant clinical benefits for a very sick population. Our results concur with other trials assessing real-world experience, proving the TMLR to be an important alternative to surgery in these patients.

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**Capsule**

## Origin and function of myofibroblasts in kidney fibrosis

Myofibroblasts are associated with organ fibrosis, but their precise origin and functional role remain unknown. LeBleu and collaborators used multiple genetically engineered mice to track, fate map and ablate cells to determine the source and function of myofibroblasts in kidney fibrosis. Through this comprehensive analysis, they identified that the total pool of myofibroblasts is split, with 50% arising from local resident fibroblasts through proliferation. The non-proliferating myofibroblasts derive through differentiation from bone marrow (35%), the endothelial-to-mesenchymal transition program (10%) and the epithelial-to-mesenchymal transition program (5%). Specific deletion of *Tgfbr2* in α-smooth muscle actin (αSMA)+ cells revealed the importance of this pathway in the recruitment of myofibroblasts through differentiation. Using genetic mouse models and a fate-mapping strategy, the authors determined that vascular pericytes probably do not contribute to the emergence of myofibroblasts or fibrosis. These data suggest that targeting diverse pathways is required to substantially inhibit the composite accumulation of myofibroblasts in kidney fibrosis.

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**Capsule**

## The relationship of Asperger's syndrome to autism: a preliminary EEG coherence study

It has long been debated whether Asperger's Syndrome (ASP) should be considered part of the Autism Spectrum Disorders (ASD) or whether it constitutes a unique entity. Duffy et al. used EEG coherence, a measure of brain connectivity, to explore possible neurophysiological differences between ASP and ASD. Using prior EEG coherence-based DFA rules that successfully classified subjects as either controls or ASD, 96.2% of ASP subjects were classified as ASD. However, when ASP subjects were directly compared to ASD subjects using new DFA rules, 92.3% of ASP subjects were identified as separate from the ASD population. By contrast, five randomly selected subsamples of ASD subjects failed to reach significance when compared to the remaining ASD populations. When represented by the discriminant variable, both the ASD and ASD populations were normally distributed. Within a control-ASD dichotomy, an ASP population fell closer to ASD than controls. However, when compared directly with ASD, an ASP population was distinctly separate. The ASP population appears to constitute a neurophysiologically identifiable, normally distributed entity within the higher functioning tail of the ASD population distribution. These results must be replicated with a larger sample given their potentially immense clinical, emotional and financial implications for affected individuals, their families and their caregivers.

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