

# MitraClip® Implantation for High Risk Patients with Severe Mitral Regurgitation: The Sheba Experience

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**ABSTRACT:** **Background:** Percutaneous edge-to-edge mitral valve repair using the MitraClip® system has evolved as a new tool in the treatment of mitral regurgitation (MR).

**Objectives:** To present our initial experience with MitraClip implantation in 20 high risk patients at Sheba Medical Center.

**Methods:** Twenty high surgical risk patients with symptomatic significant MR underwent MitraClip implantation. Clinical and echocardiographic parameters were recorded at baseline and at follow-up.

**Results:** The patients' mean age was 76 years and 65% were male. Coronary artery disease was present in 85% and 45% had previous bypass surgery. Renal failure was present in 65%, atrial fibrillation in 60%, and 30% had an implantable cardioverter defibrillator/cardiac resynchronization therapy device. Mean left ventricular ejection fraction was 36%. Grade III-IV MR was present in all patients with the vast majority suffering from functional MR secondary to ventricular remodeling. New York Heart Association (NYHA) class was III-IV in 90%. Patients were followed for a mean of 231 days. Acute reduction of MR grade to  $\leq 2$  was accomplished in 19 of the 20 patients (95%) with a 30 day mortality of 5%. At follow-up MR was reduced to  $\leq 2$  in 64% of patients, and NYHA class improved in 70% of patients. An additional 2 patients (11%) died during follow-up.

**Conclusions:** MitraClip implantation is feasible and safe in high risk highly symptomatic patients with significant MR. Acute and mid-term results are comparable to similar high risk patient cohorts in the literature. Continued surveillance and longer follow-up are needed to elucidate which patients are most likely to benefit from the procedure.

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**KEY WORDS:** mitral regurgitation (MR), percutaneous edge-to-edge repair, MitraClip®, heart failure

**M**itral regurgitation is a common valvular disease with a huge impact on morbidity and mortality [1,2]. Current guidelines recommend surgical repair or replacement of the mitral valve in patients with severe MR and symptoms of

heart failure or left ventricular dysfunction [3,4]. However, despite improvements in surgical technique, perioperative morbidity and mortality continue to be a significant problem in high risk patients with advanced age, multiple comorbidities and advanced heart failure. Thus, a large proportion of MR patients eligible for surgery are deprived of this option [5]. A large proportion of patients with significant MR present with severe heart failure and LV dysfunction not amenable to surgical treatment.

In recent years a percutaneous technique based on the Alfieri edge-to-edge surgical method [6,7], involving approximation of the mitral leaflets using a suture, was developed [8]. The MitraClip® device (Abbot Vascular, Menlo Park, CA, USA) was compared with conventional surgical repair in a randomized controlled trial, the Endovascular Valve Edge-to-Edge Repair Study (EVEREST II) [9]. All patients included in this study were eligible for surgery and were predominantly patients with primary MR. Results of the EVEREST II trial demonstrated similar clinical benefit compared with surgery and lower peri-procedural complications rate. A number of reports have described experience with mitral clip implantation in patients with high surgical risk, predominantly patients with functional MR secondary to ventricular remodeling. These series have shown improved outcomes compared with expected life expectancy in similar patients [10-12].

Since 4 April 2011, 20 patients have undergone mitral clip implantation at the Sheba Medical Center, Tel Hashomer. We report our initial experience with the MitraClip device in symptomatic MR patients treated at our center.

## PATIENTS AND METHODS

Patients were selected for the procedure if they were eligible for mitral valve intervention according to current guidelines [3,4], including at least moderate-to-severe MR with heart failure symptoms and suitable echocardiographic parameters for MitraClip implantation. All patients were evaluated by the 'heart team', which included an interventional cardiologist, a cardiac surgeon and a cardiologist specializing in echocardiography and valvular disease. Patients with an indication for mitral

\* The first two authors contributed equally to this study  
MR = mitral regurgitation

LV = left ventricular

valve surgery who were deemed to be too high risk for surgery, were inoperable and had a favorable anatomy suitable for clip implantation were referred for the procedure. Diagnostic workup included physical examination, functional capacity assessment according to the New York Heart Association class, electrocardiogram, blood tests, transthoracic and transesophageal echocardiography, and coronary angiography if indicated. MR was assessed according to current guidelines [13,14] and was classified as mild (1+), mild-to-moderate (2+), moderate-to-severe (3+), or severe (4+). Echocardiographic criteria for percutaneous mitral valve repair included:

- MR originating from the central two-thirds of the line of leaflet coaptation
- flail segment width of 15 mm or a flail gap of 10 mm
- mitral valve orifice area > 4 cm<sup>2</sup>
- coaptation length > 2 mm and coaptation depth < 11 mm
- mobile leaflet length > 1 cm
- absence of leaflet or excessive annular calcification.

#### MITRACLIP SYSTEM

The MitraClip system uses a clip with a tri-axial catheter system. The tip of the outer guide catheter is delivered to the left atrium using a standard trans-septal approach over a guidewire and tapered dilator. A steering knob on the proximal end of the guide catheter allows flexion and lateral movement of the distal tip. A steerable two-knob coaxial clip delivery system, with a clip attached to its distal end, is passed through the guide catheter. The clip delivery system is positioned 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 mechanical device with two arms at a span of approximately 2 cm when opened in the grasping position that are opened and closed by control mechanisms in the clip delivery system. The width of the clip is 4 mm. On the inner portion of the clip is a U-shaped “gripper” that 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.

#### PROCEDURE TECHNIQUE

The MitraClip procedure, which has been described previously [8], is performed under general anesthesia using fluoroscopy and TEE guidance. After trans-septal puncture using standard technique, heparin is administered to achieve an activated clotting time of 250–300 seconds. A guidewire is passed into the left atrium and positioned in the mid-left atrium. The clip delivery system is introduced into the guide catheter and advanced into the left atrial chamber. Using echocardiographic and fluoroscopic guidance, the clip is

moved in small iterations until it is centered over the mitral orifice. The arms of the clip are opened and oriented perpendicular to the long axis of the leaflet edges, and the clip is advanced into the left ventricle just below the mitral leaflet edges. The clip is closed at 120° and pulled back until the mitral leaflets are captured in the arms of the clip. The gripper is then lowered onto the atrial aspect of the leaflets. At this point, the degree of MR can be assessed using Doppler echocardiography. Next, the clip is closed incrementally under real-time echocardiography to assess the reduction of MR. If necessary, the clip can be opened, the mitral leaflets released, and the clip repositioned. In the event that the clip must be withdrawn back into the left atrium, the clip arms are everted so that they can be retracted through the mitral apparatus into the left atrium without entangling the chordae tendineae. Once adequate reduction of MR is achieved, the clip is released from the clip delivery system and the delivery system and guide catheter are withdrawn. Acute procedural success was defined as reduction of mitral regurgitation to a grade ≤ 2 as assessed by intra-procedural TEE, and additional clips were deployed to optimize the result if a suboptimal MR reduction was achieved with a single clip.

#### POST-PROCEDURE CARE AND FOLLOW-UP

Patients were followed for at least 24 hours post-clip implantation. Only one patient with severe heart failure was transferred to the intensive care unit post-procedure. All other patients were transferred to the cardiology department. Hospitalization duration was recorded, as were in-hospital course and complications.

On a follow-up visit at the cardiology clinic, patients were evaluated for functional class and echocardiographic features including MR severity, LV dimensions and function, and pulmonary pressure.

#### STATISTICAL ANALYSIS

Continuous variables are expressed as mean ± SD or median plus (interquartile) as appropriate. Categorical variables are presented as absolute numbers and percentages. Comparisons of continuous variables were performed by Wilcoxon's signed rank test for paired samples and the Mann-Whitney U test for unpaired samples; comparisons of categorical variables were performed by Fisher's exact test. A two-tailed *P* value ≤ 0.05 was regarded as statistically significant. All data were processed using the Statistical Package for Social Sciences, version 20 (SPSS, Chicago, IL, USA).

## RESULTS

#### SCREENING PROCEDURE

Seventy-eight patients were evaluated for percutaneous mitral valve repair. Of these, 20 underwent MitraClip implantation,

TEE = transesophageal echocardiography

and 58 were excluded because they had an unsuitable anatomy (n=18), refused the procedure (n=14), were referred for resynchronization therapy (n=2), were referred for mitral valve surgery (n=7), expired during the evaluation process (n=11), or had an estimated life expectancy of less than 12 months (6 patients).

**PATIENT CHARACTERISTICS**

Twenty patients (mean age 75.5 ± 10.5 years, 7 females) have undergone mitral valve repair with the MitraClip system at our center since April 2011. Baseline characteristics are shown in Table 1. The vast majority of patients had ischemic heart disease, almost half had undergone prior cardiac surgery, 60% had atrial fibrillation, and 30% had an implantable cardioverter defibrillator or cardiac resynchronization therapy device implanted. All patients had symptomatic grade III-IV MR, and 90% of patients had severe heart failure symptoms (NYHA class III-IV). Reduced LV ejection fraction (< 40%) was present in 68%. Only two patients had pure degenerative MR and the vast majority had functional MR or mixed etiology MR. Mean logistic EuroScore was calcu-

lated at 12% ± 9%. Both patients with degenerative MR were deemed very high operative risk due to advanced age and high frailty index.

**ACUTE PROCEDURAL OUTCOME AND SAFETY**

Implantation of a mitral clip was performed in 19 patients (95%). Inability to achieve a reduction in MR grade led to abortion of the procedure in one patient. Reduction of MR severity from grade 3-4 to ≤ 2 was achieved in 18 patients (94%) with MitraClip. Two clips were implanted in 11 patients (58%). No patients were implanted with more than two clips. Procedure median time was 90 minutes (interquartile range 66–130), with a significant difference between patients implanted with one (68 min, IQR 45–88) versus two clips (120 min, IQR 72–165) respectively (P = 0.02). Comparison between the first and second half of the cohort revealed a significant reduction in median device time (71 vs. 129 min, IQR 45–93 vs. 83–165, respectively, P = 0.02).

Patients were discharged at a mean of 2.8 ± 3.5 days post-implantation, 13 (65%) were discharged on the day after the procedure, but a number of patients had longer hospitalization periods. Notably, four patients were hospitalized for more than 5 days: two patients developed fever without an obvious source and were treated with antibiotics for 5 days; one patient had a large femoral artery pseudoaneurysm, probably resulting from inadvertent femoral artery puncture during venous cannulation, which underwent successful occlusion with thrombin injection; and another patient continued to suffer from intractable heart failure and thrombocytopenia and died following a massive stroke 2 weeks after clip implantation.

**FOLLOW-UP**

Of 19 patients with a successful procedure, 13 (68%) had a follow-up echocardiography exam performed at the end of a median 187 day follow-up (IQR 109–331). Compared with the baseline echocardiogram, a significant reduction in MR grade was observed on follow-up [Figure 1]. Nine patients (64%) had a reduction of MR grade to ≤ 2, while four patients had grade 3–4 MR. LVEF was reduced from 36 ± 16 at baseline to 34 ± 15 on follow-up (P = 0.01), as did other echocardiographic parameters: end-diastolic and end-systolic diameters and pulmonary pressure which were also slightly and non-significantly reduced [Table 2]. None of the patients suffered clip detachment or embolization.

Clinical follow-up after discharge (median 195 days, IQR 97–300) was available for 17 of 18 patients (94%) who underwent a successful procedure. Functional class was improved by at least one class in 12 patients (in 5 of whom it improved by ≥ 2 classes). No improvement in NYHA class was observed in five patients [Figure 2].

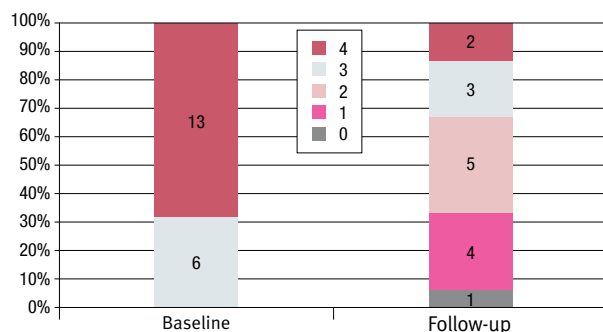
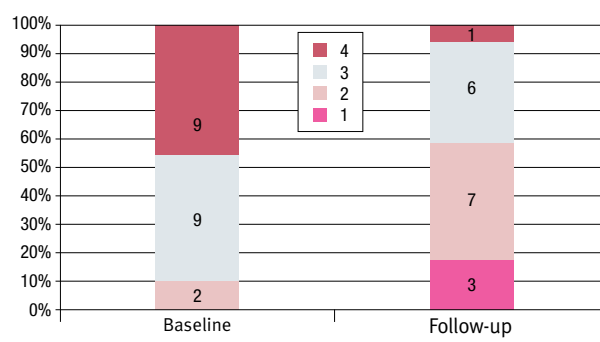
NYHA = New York Heart Association

**Table 1.** Baseline characteristics of mitral clip patients

Characteristic	n=20
Age (yr, mean ± SD)	75.5 ± 10.5
Female	7 (35%)
Diabetes mellitus	8 (40%)
Hypertension	17 (85%)
Chronic renal failure	13 (65%)
Ischemic heart disease	17 (85%)
Atrial fibrillation	12 (60%)
ICD/CRTD	6 (30%)
Prior cardiac surgery	9 (45%)
Chronic lung disease	4 (20%)
LVEF (mean ± SD)	36 ± 15
LVEF ≤ 40%	13 (68%)
Euroscore (mean ± SD)	12 ± 9
<b>MR etiology</b>	
Functional	14 (70%)
Degenerative	2 (10%)
Mixed	4 (20%)
<b>NYHA class</b>	
I	0
II	2 (10%)
III	9 (45%)
IV	9 (45%)
<b>MR grade</b>	
0	0
II	14 (74%)
IV	5 (26%)

ICD/CRTD = implantable cardioverter defibrillator/cardiac resynchronization therapy device

IQR = interquartile range  
LVEF = left ventricular ejection fraction

**Figure 1.** Comparison of baseline and follow-up MR grade ( $P = 0.005$ )**Figure 2.** Comparison of baseline and follow-up NYHA class ( $P = 0.002$ )**Table 2.** Comparison of baseline and follow-up echocardiographic parameters

	Baseline	Follow-Up	P value
LVEF (mm)	36 ( $\pm$ 16)	34 ( $\pm$ 15)	0.01
LVEDD (mm)	60 ( $\pm$ 9)	59 ( $\pm$ 9)	NS
LVESD (mm)	44 ( $\pm$ 11)	44 ( $\pm$ 10)	NS
PAP (mmHg)	62 ( $\pm$ 11)	60 ( $\pm$ 22)	NS

All values are presented as mean ( $\pm$  SD)

LVEF = left ventricular ejection fraction, LVEDD = left ventricular end-diastolic diameter, LVESD = left ventricular end-systolic diameter, PAP = pulmonary artery pressure

Among 18 patients with successful reduction of MR surviving to discharge, 2 patients died, one due to heart failure 7 months post-procedure and the other to non-cardiac causes 6 months post-procedure.

## DISCUSSION

The present study describes our initial experience using the MitraClip device in patients with a high risk profile, most of whom were considered inoperable. Acute reduction of MR grade was successful in 90% of patients; none had significant peri-procedural complications or need for prolonged hospital stay and most patients were discharged on the day following clip implantation. Mortality at 30 days was only 5% ( $n=1$ ) in this high risk group and was due to complications of his disease not directly attributable to clip implantation. On follow-up the majority of our cohort exhibited a sustained reduction in MR and a significant amelioration of heart failure symptoms, with a mortality rate of 11% after a median follow-up interval of more than 6 months.

Although current guidelines recommend mitral valve surgery for symptomatic patients with significant MR [3,4], in patients with high risk features such as severe LV dysfunction, prior surgery and multiple comorbidities, surgery entails a high rate of morbidity and mortality with a questionable benefit [15-19]. Our cohort had a very high risk profile: 50%

of our patients had severely reduced LV function, 45% had undergone prior cardiac surgery, and 70% had a glomerular filtration rate  $\leq 50$  ml/min. This was further accentuated by a high EuroScore [20] calculated at a mean of  $12 \pm 9\%$ .

The EVEREST II trial demonstrated the non-inferiority of percutaneous mitral valve repair compared with conventional surgery in terms of clinical improvement in patients with significant MR, along with superior safety outcomes [9]. However, this trial included younger patients with a mostly degenerative MR etiology who were good surgical candidates and is of little relevance to patients with significant comorbidities who are not eligible or are at high risk for mitral valve surgery, such as those included in our cohort. A growing number of reports have evaluated the results of percutaneous mitral valve repair in high risk populations. The EVEREST II High Risk Study [21] and data from European registries [11,22] included a higher risk population of older patients with lower functional capacity and a higher rate of reduced LV function together with mostly functional MR etiology.

Indeed, these studies [11,21,22] together with national registries from Italy [10] and Germany [12] reported a high success rate and low frequency of complications following percutaneous mitral valve repair in high risk patients. Acute MR reduction and 30 day mortality in our study was 90% and 5%, respectively, which is comparable to high risk series which showed acute MR reduction in 73–97% of patients and a mortality rate of 2.5–7.7% at 30 days [10-12,21-23]. The mid-term follow-up in our cohort, demonstrating MR reduction and NYHA class improvement in 64% and 70% of patients, respectively, resembles prior studies which reported sustained MR reduction in 64–87% of patients and amelioration of heart failure symptoms in 64–77% [11,12,21].

The 30 day and mid-term mortality rate was lower in the EVEREST II trial [9] compared with our study, which is consistent with the lower risk profile of patients in the EVEREST II trial. Mid-term mortality in our cohort was 11%, which compares well with the 15–25% rate reported by both the European studies [11,22] and the EVEREST II High Risk Registry [21].

A previous report in 75 consecutive patients undergoing MitraClip implantation at one center demonstrated a significant learning curve with a significant decrease in median clip time from 105 to 55 minutes. Accordingly, in our cohort, median clip time was reduced from 129 minutes with a mean of 1.67 clips per procedure in the first 10 procedures to 71 minutes in the second 10 procedures with a mean of 1.5 clips per procedure ( $P = 0.02$ ).

Follow-up echocardiography in the EVEREST II trial demonstrated remodeling of the left ventricle following percutaneous repair [9]. However, previous studies in patients with higher risk characteristics resembling our cohort reported mainly a reduction in LV volume, while systolic and diastolic LV diameters were reduced to a lesser extent. In the EVEREST II High Risk Study [21], and in European studies [11,22] which were conducted on a smaller number of patients, LV diameter reduction did not reach statistical significance. Similar to these high risk cohorts, in our study indices of LV remodeling were not significantly changed, probably reflecting small sample size and relatively short follow-up duration. Also, a large proportion of our patients had severe LV dysfunction, which may reduce the likelihood of the LV to undergo negative remodeling, as shown in previous studies of surgical therapy [16].

In conclusion, mitral valve repair using the MitraClip percutaneous technique is feasible and safe in high risk, mainly inoperable, highly symptomatic patients with significant MR. Acute and mid-term improvement in MR grade and functional class were observed in our cohort. These results are comparable to similar high risk patient cohorts in the literature. Continued surveillance and longer follow-up are needed to elucidate which patients are most likely to benefit from the procedure.

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