Percutaneous Mitral Valve Repair in the Initial EVEREST Cohort: Evidence of Reverse Left Ventricular Remodeling

Foster et al: Percutaneous Mitral Repair Reverses Remodeling for the EVEREST Investigators

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Abstract

Background—Percutaneous repair of MR permits examination of the effect of MR reduction without surgery and cardiopulmonary bypass on left ventricular (LV) dimensions and function. The goal of this analysis was to determine the extent of reverse remodeling at 12 months following successful percutaneous reduction of mitral regurgitation (MR) with the MitraClip device.

Methods and Results—Of 64 patients with 3 and 4+ MR who achieved acute procedural success after treatment with the MitraClip device, 49 patients had moderate or less MR at 12 month follow-up. Their baseline and 12 month echocardiograms were compared between the group with and without LV dysfunction. In patients with persistent MR reduction and pre-existing LV dysfunction, there was a reduction in LV wall stress, reduced LV end-diastolic volume (LVEDV), LV end-systolic volume (LVESV) and increase in LV ejection fraction (LVEF) in contrast to those with normal baseline LV function, who showed reduction in LVEDV, LV wall stress, no change in LVESV and a fall in LVEF.

Conclusions—Patients with pre-existing LV dysfunction demonstrate reverse remodeling and improved LVEF after percutaneous mitral valve repair.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifiers: NCT00209339, NCT00209274.

Key Words: mitral regurgitation; percutaneous mitral valve repair; echocardiography, reverse left ventricular remodeling, left ventricular dysfunction
Abbreviations List:

APS=acute procedural success
ASE=American Society of Echocardiography
CDS=clip delivery system
EDD=end diastolic dimension
EVEREST=endovascular valve edge-to-edge repair studies
FSV=forward stroke volume
LV=left ventricular
LVEDV=left ventricular end diastolic volume
LVESV=left ventricular end systolic volume
LVEF=left ventricular ejection fraction
LVIDd=left ventricular internal dimension at end-diastole
MR=mitral regurgitation
NYHA=New York Heart Association
PWT=peak wall stress
PWTd=posterior wall thickness in diastole
RCT=randomized clinical trial
RF=regurgitant fraction
RV=regurgitant volume
SAP=systolic arterial pressure
Left ventricular (LV) remodeling associated with mitral valve regurgitation (MR) is adaptive in that forward stroke volume is preserved, but may eventually become maladaptive, leading to irreversible LV dysfunction and adverse late outcomes even after correction of MR. Several studies have raised the specter of a “point of no return”, prompting the recommendation for intervention in asymptomatic patients with hemodynamically significant MR when the LV ejection fraction (LVEF) falls below 60% or the LV end-systolic dimension exceeds 40 mm.¹ A concern that surgery itself may contribute to post-operative LV dysfunction has led to modifications of surgical technique, with a strong preference for mitral valve repair over replacement.

Percutaneous repair of MR with the MitraClip system (Abbott Vascular, Menlo Park) offers a potential therapy for patients with 3-4+ MR. Safety and effectiveness outcomes in these patients have been previously reported from the EVEREST Clinical Trial (Endovascular Valve Edge-to-Edge REpair STudies) including a single-arm feasibility study², a randomized controlled trial comparing the treatment with mitral valve surgery³, and in a high surgical risk single-arm study.⁴ Percutaneous reduction of MR with the MitraClip procedure provides a unique opportunity to examine the extent of reverse LV remodeling in the absence of surgical intervention.

We hypothesized that sustained MR reduction would be associated with significant reversal in LV remodeling and sought to investigate the impact of pre-existing LV dysfunction on the extent of reverse remodeling. The primary aim of this analysis was to determine the extent of reverse remodeling at 12 months following successful percutaneous reduction of MR (Acute Procedural Success, APS) with the MitraClip device. We compared changes in indices of LV remodeling at
baseline, and 12, months in APS patients with and without sustained 12 month MR reduction. In addition we compared the extent of remodeling associated with sustained MR reduction in APS patients with and without baseline LV dysfunction. The patients in the EVEREST I safety and feasibility study and those in the roll-in phase of the EVEREST II Randomized Pivotal Trial form the basis of the current study. Patients in these studies were followed with echocardiography at pre-specified time points, and all of the echo studies were evaluated in a core laboratory as previously described\textsuperscript{5}.

**Methods**

**Study Design:** The study includes 55 patients from EVEREST I, a prospective multi-center, single-arm feasibility study and 52 patients from the roll-in phase of the EVEREST II Randomized Controlled Trial (RCT), representing the pre-randomization start-up experience. Each site performed up to 3 MitraClip procedures in the roll-in phase of the EVEREST II RCT. Thirty-one sites enrolled the 107 patients that comprise the study cohort. The EVEREST Clinical study was approved by the Food and Drug Administration, Health Canada, the participating local Institutional Review Boards/Independent Ethics Committees, and all patients signed informed written consent. The trials are registered at [www.clinicaltrials.gov](http://www.clinicaltrials.gov) (numbers: NCT00209339, NCT00209274).

**Patient Selection:** Patients were selected if they met Class I indications for mitral valve intervention from the 1998/2006 American College of Cardiology/American Heart Association Joint Task Force recommendations regarding therapy for valvular heart disease\textsuperscript{6,1}. Patients with moderate-to-severe (3+) or severe (4+) functional or degenerative MR with symptoms, or if
asymptomatic, with compromised LV function (ejection fraction 25 to 60\% or end-systolic
dimension $\geq$40 mm) were candidates for inclusion. Following the core laboratory analysis of
baseline MR, it was determined that 9 enrolled subjects had mild (n=2) or moderate MR (n=7).
Additionally, all patients were candidates for MV surgery, in the event surgery was required for complications.

**MitraClip System and Procedure:** The MitraClip system (Figure 1a) utilizes a tri-axial
catheter system with an implantable clip. The Guide Catheter is 24-French proximally, and 22-
French at the atrial septum, and is delivered with a tapered dilator. The Clip Delivery System
(CDS) has the MitraClip device attached to its distal end. The MitraClip device (Figure 1b) is a
4mm wide cobalt-chromium implant with two arms. Each leaflet is independently secured
between an arm and a gripper. The procedure has previously been described in detail\(^7\). The
procedure is performed under general anesthesia using fluoroscopy and transesophageal
echocardiographic guidance. The goal in the cardiac catheterization laboratory was to reduce
MR to mild-moderate (1+ or 2+) or less with optimal placement of one or two MitraClip devices.

**Echocardiography:** Transthoracic echocardiograms were performed using a pre-specified
protocol at baseline, pre-discharge, and at 1, 6, 12, 18, 24 months, and yearly up to five years.
All echocardiograms were reviewed by a core laboratory (UCSF, San Francisco CA). MR was
graded according to the criteria of the American Society of Echocardiography (ASE) guidelines
using quantitative (regurgitant volume, regurgitant fraction, regurgitant orifice area) and
qualitative criteria (color Doppler and pulmonary venous flow)\(^8\). To be included, moderate-to-
severe (3+) or severe (4+) MR using the integrative approach per the ASE guidelines was
required. Key anatomic inclusion criteria included a regurgitant jet origin associated with the A2-P2 segments of the mitral valve, and for patients with functional MR, a coaptation length of at least 2 mm, a coaptation depth of no more than 11 mm, and for patients with leaflet flail, a flail gap <10 mm, and a flail width <15 mm.9 LV volumes and ejection fraction were measured using the biplane method of disks. The sphericity index was computed as the ratio of the maximal LV minor to major dimension (end-diastole) from both the 4-chamber and 2-chamber views.10 LV mass was calculated using the Devereaux equation: 

\[
(0.8 \times \{1.04 \times [LVIDd + 2 \times PWTd]^3 - LVIDd^3]\}, \text{MD} + 0.6)
\]

where, LVIDd=LV internal dimension at end-diastole and PWTd = posterior wall thickness at end-diastole.11 Peak wall stress was calculated by the following equation: 

\[
0.86 \times (0.334 \times SAP \times EDD) / [\text{PWTd} \times (1 + (\text{PWTd} / \text{EDD}))] -2 \times 103 \text{ dynes/cm}^2,
\]

where, SAP=systolic arterial pressure, EDD=end diastolic dimension (LVIDd), and PWTd=posterior wall thickness in diastole. Measurement of 2 and 4 chamber sphericity indices, LV peak wall stress, and LV mass were only measured at baseline and 12 months for APS patients with echocardiographic follow-up at baseline and 12 months. Forward stroke volume (FSV) was calculated using LV outflow tract diameter and the velocity time integral.

**Patient Accountability:** 107 patients were enrolled in EVEREST I and the EVEREST II roll-in phase. 79 (74%) patients achieved acute procedural success (APS, defined as a reduction in MR grade to ≤2 at discharge). Within the APS group, there were 2 deaths (one death occurred following MV surgery), 3 withdrawals, 10 patients who underwent mitral valve surgery within 12 months, and one patient who did not have a 12 month echo, resulting in 64 patients with baseline and 12 month echocardiograms available for analysis (Figure 2). Patients who required surgery post MitraClip procedure, died, or withdrew were not included in these analyses.
**Patient Subgroup Analysis:** Reverse LV remodeling was assessed for all patients with successful MR reduction (APS) who had adequate echocardiograms for volumetric analysis (n=62). Comparisons were made between APS patients with sustained MR reduction (MR \( \leq 2 \)) at 12 months (Group 1) and APS patients with recurrent MR (MR \( > 2 \)) at 12 months (Group 2). Within Group 1, further analyses were performed comparing 12 month outcomes in patients with (Group 1a) and without (Group 1b) baseline LV dysfunction. For the purpose of this analysis, LV dysfunction was defined by the presence of either an LV end-systolic dimension greater than 40 mm or LV ejection fraction less than 60%.

Per protocol, EVEREST I patients were withdrawn from the study if no MitraClip device was implanted or after mitral valve surgery was performed. In EVEREST II, patients were followed post-mitral valve surgery, however for this analysis, data post-mitral valve surgery is excluded.

**Statistical Analysis:** Continuous data are presented as mean ± standard deviation while categorical data is presented as n and percent. Baseline comparisons between groups were performed with t-tests for continuous data and Fisher’s exact test for dichotomous data. Within group comparisons (e.g., from baseline and 12 months) were performed using a paired t-test (all variables being continuous). Between-group comparisons on relative change from baseline were performed using an analysis of variance (ANOVA) (all variables being continuous). Bonferroni correction for multiple variables a p<0.0042 was considered statistically significant.
Results

Baseline Demographics and Echocardiographic Variables:

Group 1 vs Group 2: Sixty-four patients with acute procedural success (APS) were available for analysis at 12 months. 77% (49/64) of the APS patients had sustained MR reduction (MR ≤2) at 12 months (Group 1), and 23% (15/64) had recurrent MR (MR >2) at 12 months (Group 2). Baseline demographics and echocardiographic variables are presented in Table 1 for the overall patient group (n=107), and for patients in Groups 1 and 2. No significant baseline differences were noted between patients in Groups 1 and 2. For the overall cohort, mean age was 67 years, 38% were women, 70% had congestive heart failure, 19% prior cardiac surgery and 48% presented with New York Heart Association Class (NYHA) III or IV symptoms. Seventy-nine percent of patients (n=85) had degenerative mitral valve disease and 21% of patients (n=22) had functional MR. MR severity was moderate-severe (3+) in 54% and severe (4+) in 38%. LV measures were similar for the overall cohort and for Groups 1 and 2. At baseline, there was no difference in LVEDV (Group 1: 171±41 ml vs. Group 2: 168±35 ml, p=0.81), LVESV (Group 1: 70 ±29 ml vs. Group 2: 68±28 ml, p=0.77), ejection fraction (Group 1: 59.9±9.2 vs. Group 2: 60.2±8.8, p=0.92) and LV mass (Group 1: 180±57 g vs. Group 2: 205±40 g, p=0.14) and peak wall stress (Group 1: 216±56 dynes/cm² vs. Group 2: 191±36 dynes/cm², p=0.15) between those patients with sustained MR reduction (MR ≤2) at 12 months compared to those patients with recurrent MR (MR >2) at 12 months. Patients with sustained MR reduction at 12 months had a significantly smaller baseline sphericity index in the 2-chamber view than patients with recurrent MR at 12 months. There was no difference in the overall baseline MR grade (p=0.73), regurgitant volume (p=0.31) and regurgitant fraction (p=0.67) between the two groups.
Group 1a vs Group 1b: Of the 49 patients with sustained MR reduction (MR ≤ 2) at 12 months available for analysis, 41% (20/49) had existing baseline LV dysfunction (Group 1a) and 59% (29/49) did not have baseline LV dysfunction (Group 1b). Baseline demographics and echocardiographic variables for patients in Group 1a and Group 1b are presented in Table 1. Baseline demographics, co-morbidities, and MR grade were similar between the two groups. Significant differences in baseline echocardiographic variables were noted amongst the patients with and without baseline LV dysfunction. Those with pre-existing LV dysfunction were more likely to have functional MR (Group 1a: 40% FMR vs Group 1b: 10% FMR, p=0.033) and had lower ejection fractions (Group 1a: 51.8±8.1 % vs. Group 1b: 65.9±4.0 %, p<0.0001. All measures of LV remodeling were significantly greater including LVEDV (Group 1a: 196±36 ml vs. Group 1b: 152±35 ml, p=0.0001), LVESV (95±25 ml vs. 52±13 ml, p<0.0001) LV mass (209±55 g vs. 158 ±48 g, p=0.0021) and sphericity indices (2 chamber: 0.65±0.09 vs. 0.59±0.05, p=0.028, 4 chamber: 0.65±0.08 vs. 0.56±0.17, p=0.032) in patients with pre-existing LV dysfunction. Peak systolic wall stress, was however, no different at baseline.

12 Month MR Reduction and LV Remodeling:

Group 1 vs Group 2: In Group 1 there was significant improvement in overall MR grade at 12 months (51% mild and 49% moderate) (Figure 3a), regurgitant volume (Baseline: 45±18 ml vs 12 month: 21±10 ) and regurgitant fraction (Baseline: 42%±11 vs 12 month: 23%±10). In Group 2, 80% had moderate to severe MR compared to 53% at baseline and 20% had severe MR compared to 40% at baseline, suggesting modest improvement. However, there were no significant changes in regurgitant volume and regurgitant fraction. Group 1, exhibited significant reductions in diastolic and systolic LV dimensions and volumes (Figure 4), LV mass,
LV peak wall stress, and sphericity indices from baseline to 12 months whereas those in Group 2 demonstrated no significant changes except in sphericity in the 4-chamber view. Forward stroke volume increased in Group 1 although there was no observed change in LV ejection fraction. Group 2 did not demonstrate an improvement in FSV, or a change in EF (Table 2).

**Group 1a vs Group 1b:** At 12 months, there were similar reductions in MR by overall grade (Figure 3b), regurgitant volume and regurgitant fraction among those with (Group 1a) and without (Group 1b) baseline LV dysfunction. However, patients in Group 1a, (baseline LV dysfunction) exhibited significantly greater reductions in LVEDV (-41±30 ml, p<0.0001), LVESV (-24±17 ml, p<0.0001), LVEDD (-0.5±0.6 cm, p=0.0045) and LVESD (-0.5±0.5, p=0.0004) from baseline to 12 months whereas those in Group 1b exhibited a significant reduction in only LVEDV (-21±21 ml, p<0.0001) and LVEDD (-0.3±0.3 cm, p=0.0001) and LVEDD (-0.3±0.3 cm, p=0.0001) (Figure 5). Forward stroke volume (7.3±15.0, p=0.055) and LV ejection fraction increased (4.1±4.9, p=0.0019) in Group 1a; whereas in Group 1b, FSV increased (10.6±11.5, p=0.0002) and LVEF decreased (-4.9±6.3, p=0.0004). Significant decreases in LV mass, left peak wall stress, and sphericity indices were observed in Group 1a. In Group 1b, significant changes were observed in LV mass, left peak wall stress but not in sphericity indices (Table 3). Although the degree of MR reduction did not differ between Group 1a and Group 1b (change in RV and RF, p=NS), the extent of reduction in LVESV, LVIDs and improvement in ejection fraction was significantly greater in Group 1a.

The present analysis was also performed by removing two patients who were deemed to have baseline MR >2+ based on the sites’ assessment but who were later re-classified as having MR
We recently reported the acute hemodynamic effects of MR reduction with the MitraClip device associated with a reduction in LVEDV without a change in LVESV or sphericity. ejection fraction declined slightly but remained within normal limits. This finding was over a condition of isolated MR. In patients without LV dysfunction at baseline, the LV likely to have functional MR. Nevertheless, both groups of patients demonstrated a slight but end-systolic dimension >4.0 cm. The patients with pre-existing LV dysfunction were more likely to have functional MR. Nevertheless, both groups of patients demonstrated a slight but significant decline in peak wall stress, which is anticipated with the alleviation of the volume overload condition of isolated MR. In patients without LV dysfunction at baseline, the LV ejection fraction declined slightly but remained within normal limits. This finding was associated with a reduction in LVEDV without a change in LVESV or sphericity.

Discussion

In a careful analysis of 64 of 107 patients enrolled in EVEREST I Feasibility and Safety Trial and the roll-in phase of the EVEREST II Pivotal trial who had both acute procedural success following MitraClip therapy and echo analysis at 12 months, we demonstrate that reduction of MR is associated with sustained reverse remodeling of the left ventricle. These data are the first to demonstrate that mechanical correction of MR using a percutaneous approach is associated with improved LV function. In addition, we examined the association of pre-existing LV dysfunction with the extent of reverse remodeling and found that the reduction in LV end-systolic volume, improvement in LV ejection fraction and reduced sphericity were found only in those patients who had evidence of LV dysfunction at baseline as defined by LVEF <60% or LV end-systolic dimension >4.0 cm. The patients with pre-existing LV dysfunction were more likely to have functional MR. Nevertheless, both groups of patients demonstrated a slight but significant decline in peak wall stress, which is anticipated with the alleviation of the volume overload condition of isolated MR. In patients without LV dysfunction at baseline, the LV ejection fraction declined slightly but remained within normal limits. This finding was associated with a reduction in LVEDV without a change in LVESV or sphericity.
in the same cohort of patients described in this manuscript. Successful MitraClip treatment resulted in immediate increases in forward stroke volume and cardiac output with a decrease in systemic vascular resistance and in LV end-diastolic pressure.\textsuperscript{12} However, the pre-discharge echocardiogram performed 24 hours after the procedure showed a reduction in ejection fraction by approximately 4 percentage points. The observed reduction in ejection fraction was no longer present at 12 months although echocardiograms were not available in the entire cohort that was studied at 24 hours. Nevertheless, the current study demonstrates that the favorable changes in hemodynamics persisted in patients with sustained reduction in MR but not in those with recurrent MR. The current analysis also examines the differences in those with and without pre-existing LV dysfunction.

Up until recently the treatment of MR has required surgery, with the exception of a small minority of patients with functional MR who respond to medical therapy or cardiac resynchronization therapy. Percutaneous treatment for MR is now under investigation and has for the first time opened the door to non-surgical treatment of MR through a mechanical correction. Over the course of the past 40 years, earlier intervention with improved criteria for patient selection as well as major advances in surgical treatment and myocardial preservation, have improved the outlook for patients with MR.\textsuperscript{13,14} However, up to 20\% of patients with degenerative MR still demonstrate an early post-operative decline in ejection fraction.\textsuperscript{15} A number of studies have demonstrated that there is an early decline in LV ejection fraction after surgery that is associated with a decrease in LV diastolic volume with no change in LV systolic volume. Some investigators have demonstrated a post-operative increase in LV wall stress due to elimination of LV ejection into the lower pressure left atrium, but others have shown that there
is no net increase in LV afterload. However, LV reverse remodeling is likely to be important prognostically.

Prospective studies examining the extent of reverse remodeling after surgical correction of MR are not available. In a study by Suri et al, the recovery of LV function was investigated in 1063 patients undergoing surgical correction of MR who had 2,488 echocardiograms available for analysis. After the initial decline in ejection fraction immediately post-operatively, there was a progressive increase in ejection fraction as the left-ventricular end-systolic volume declined to a greater extent than the end-diastolic volume. Predictors of late normalization of the ejection fraction were valve repair as compared to replacement, greater preoperative ejection fraction and smaller LV dimensions. Other studies have linked late mortality, late ventricular dysfunction and lack of reverse remodeling to the presence of pre-operative LV dysfunction. The degree of LV dysfunction among patients in our cohort was relatively mild compared to those in previous surgical studies. Nevertheless, in one study of 27 patients, those with preoperative LV dysfunction who underwent mitral valve repair, there was an initial decline in fractional shortening, which improved over the course of one year, such that it returned to normal levels but remained lower than those without preoperative LV dysfunction although the differences at one year did not remain statistically significant. In this small study, a preoperative LV end-systolic dimension >40 mm was the best predictor of early LV dysfunction. In our study of percutaneous mitral valve, the patients with pre-existing LV dysfunction as defined by an LVESD >40 mm or LVEF <60%, showed significant reverse remodeling and an improvement in ejection fraction. The recently published mitral surgery cohort of the ACORN trial demonstrated a progressive decline in LV volumes and improvement in LV ejection fraction.
over 5 years of follow-up. There was an approximately 40 ml decrease in LVEDV among the 91 patients who received mitral valve replacement or repair without cardiac restraint, despite recurrent MR in approximately 20%. There are significant differences between this study and the EVEREST cohort. The mean ejection fraction in the ACORN study was 24% compared to 52% in our patients with pre-existing LV dysfunction. Another difference is that we report only matched data whereas the ACORN study reported results in the entire cohort. Given the 30% mortality at 5 years, it is likely that there was a survivor bias in the data reported at years 3, 4 and 5 years, exaggerating the impact of MR reduction on LV volumes. Finally, core laboratory analysis of mitral regurgitation in the ACORN study showed 3+ or 4+ MR in only 59% of the enrolled patients compared to 87% of our cohort.

The most salient difference between our study of patients treated with a percutaneous device and previous reports following surgery is that our patients were not subjected to the potentially adverse effects of cardiopulmonary bypass, which causes ischemic injury and can lead to impaired systolic as well as diastolic function. Furthermore, the percutaneous procedure has minimal likelihood of disrupting the subvalvular apparatus. Potential explanations for the differences in reverse remodeling that we observed between the cohort with normal function and those with pre-existing dysfunction can be related to changes in wall stress and the greater hemodynamic impact of a similar degree of MR on a compromised ventricle. The results of this study suggest that patients with mild pre-existing LV dysfunction in the setting of both functional and degenerative MR demonstrated improved LV systolic function and significant reverse remodeling up to one year after percutaneous repair. By comparison to data from the surgical literature, it appears that this mechanism of reverse remodeling in subjects with baseline
left ventricular dysfunction may be unique to percutaneous treatment. The study is also unique as one of the first reports to include a multiple clinical centers with prospective data collection an echocardiographic core laboratory and the ASE measures of MR severity.

Limitations

The limitations of the current analysis are the relatively small size of the subgroups available for analysis. The patients included in this study did not have severe LV dilatation or severe reductions in LV ejection fraction. Therefore the findings of this study cannot be extrapolated to patients with severe dilated cardiomyopathy. The group of patients with pre-existing LV dysfunction included those with both functional and degenerative MR and specific conclusions cannot be drawn between these two subgroups. We did not have complete data available on changes in medication between the two time points. Finally we cannot exclude a floor effect in the group without pre-existing LV dysfunction (Group 1b) below which there can be no further reduction in LV volumes.

Conclusions

The current study demonstrates significant reverse remodeling at 12 months following percutaneous correction of hemodynamically significant MR if there is sustained reduction in regurgitation. Significant improvements in LV volumes, shape and ejection fraction were most pronounced in those patients with echocardiographic evidence of mild pre-existing LV dysfunction. Long term follow-up of percutaneously-treated patients will determine whether the favorable impact of percutaneous treatment of mitral regurgitation on left ventricular remodeling
is sustained, and long term follow-up of the randomized cohort will elucidate whether this
benefit is unique to the percutaneous treatment.

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References


<table>
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<tr>
<th>Characteristics</th>
<th>All Subjects (N=107)</th>
<th>Group 1 Continued Success (N=49)</th>
<th>Group 2 Recurrent MR (N=15)</th>
<th>P-Value between Groups 1 and 2</th>
<th>Group 1a Continued Success + Pre-Existing LV dysfunction (N=20)</th>
<th>Group 1b Continued Success + No Pre-Existing LV dysfunction (N=29)</th>
<th>P-Value between Groups 1a and 1b</th>
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<tr>
<td>Demographics</td>
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<tr>
<td>Female gender (%)</td>
<td>38.3% (41/107)</td>
<td>36.7% (18/49)</td>
<td>46.7% (7/15)</td>
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<td>35.0% (7/20)</td>
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<td>Age (years)</td>
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<td>69.0±13.9 (49)</td>
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<td>Coronary Artery Disease (%)</td>
<td>31.9% (29/91)</td>
<td>40.2% (15/37)</td>
<td>35.3% (4/12)</td>
<td>&gt;0.999</td>
<td>31.3% (5/16)</td>
<td>29.6% (8/27)</td>
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<td>69.4% (34/49)</td>
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<td>85.0% (17/20)</td>
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<tr>
<td>Previous cardiac surgery (%)</td>
<td>18.7% (20/107)</td>
<td>20.4% (10/49)</td>
<td>20.0% (3/15)</td>
<td>&gt;0.999</td>
<td>25.0% (5/20)</td>
<td>17.2% (5/29)</td>
<td>0.72</td>
</tr>
<tr>
<td>NYHA Functional Class III or IV (%)</td>
<td>47.7% (51/107)</td>
<td>57.1% (28/49)</td>
<td>53.3% (8/15)</td>
<td>&gt;0.999</td>
<td>70.0% (14/20)</td>
<td>48.3% (14/29)</td>
<td>0.15</td>
</tr>
<tr>
<td>Mitral Regurgitation</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Functional MR (%)</td>
<td>20.6% (22/107)</td>
<td>22.4% (11/49)</td>
<td>20.0% (3/15)</td>
<td>&gt;0.999</td>
<td>40.0% (8/20)</td>
<td>10.3% (3/29)</td>
<td>0.033</td>
</tr>
<tr>
<td>Degenerative MR (%)</td>
<td>79.4% (85/107)</td>
<td>77.6% (38/49)</td>
<td>80.0% (12/15)</td>
<td>&gt;0.999</td>
<td>60.0% (12/20)</td>
<td>89.7% (26/29)</td>
<td>0.033</td>
</tr>
<tr>
<td>MR Grade (≥3) (%)</td>
<td>91.5% (97/106)</td>
<td>85.7% (42/49)</td>
<td>93.3% (14/15)</td>
<td>0.73</td>
<td>80.0% (16/20)</td>
<td>89.7% (26/29)</td>
<td>0.20</td>
</tr>
<tr>
<td>Echo Parameters</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RV (ml)</td>
<td>50.6±20.9 (99)</td>
<td>45.5±17.6 (45)</td>
<td>51.1±18.6 (14)</td>
<td>0.31</td>
<td>42.8±15.8 (19)</td>
<td>47.5±18.9 (26)</td>
<td>0.39</td>
</tr>
<tr>
<td>RF (%)</td>
<td>45.5±13.9 (99)</td>
<td>42.5±11.8 (45)</td>
<td>44.1±13.9 (14)</td>
<td>0.67</td>
<td>40.9±11.9 (19)</td>
<td>43.7±11.7 (26)</td>
<td>0.45</td>
</tr>
<tr>
<td>Characteristics</td>
<td>All Subjects (N=107)</td>
<td>Group 1 Continued Success (N=49)</td>
<td>Group 2 Recurrent MR (N=15)</td>
<td>P-Value between Groups 1 and 2</td>
<td>Group 1a Continued Success + Pre-Existing LV dysfunction (N=20)</td>
<td>Group 1b Continued Success + No Pre-Existing LV dysfunction (N=29)</td>
<td>P-Value between Groups 1a and 1b</td>
</tr>
<tr>
<td>--------------------------</td>
<td>----------------------</td>
<td>----------------------------------</td>
<td>-----------------------------</td>
<td>-------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>---------------------------------------------------------------</td>
<td>-------------------------------</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>171.4±37.5 (103)</td>
<td>170.7±41.1 (47)</td>
<td>167.9±34.5 (15)</td>
<td>0.81</td>
<td>195.5±36.2 (20)</td>
<td>152.2±34.7 (27)</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>69.6±24.8 (103)</td>
<td>70.0±28.5 (47)</td>
<td>67.6±27.6 (15)</td>
<td>0.77</td>
<td>94.5±25.3 (20)</td>
<td>51.8±12.8 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.6±0.6 (99)</td>
<td>5.5±0.7 (44)</td>
<td>5.7±0.5 (15)</td>
<td>0.27</td>
<td>5.8±0.7 (19)</td>
<td>5.2±0.5 (25)</td>
<td>0.0024</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>3.5±0.8 (102)</td>
<td>3.5±0.4 (45)</td>
<td>3.5±0.7 (15)</td>
<td>0.81</td>
<td>4.2±0.6 (20)</td>
<td>2.9±0.5 (25)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>60.1±8.2 (104)</td>
<td>59.4±9.2 (47)</td>
<td>60.2±8.8 (15)</td>
<td>0.92</td>
<td>51.8±8.1 (20)</td>
<td>65.9±4.0 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>56.8±13.8 (98)</td>
<td>59.0±14.7 (45)</td>
<td>58.4±12.0 (14)</td>
<td>0.89</td>
<td>60.6±16.4 (19)</td>
<td>57.9±13.5 (26)</td>
<td>0.55</td>
</tr>
<tr>
<td>Sphericity index (2C)</td>
<td>N/A</td>
<td>0.6±0.1 (44)</td>
<td>0.6±0.3 (12)</td>
<td>0.40</td>
<td>0.63±0.09 (20)</td>
<td>0.59±0.05 (24)</td>
<td>0.028</td>
</tr>
<tr>
<td>Sphericity index (4C)</td>
<td>N/A</td>
<td>0.53±0.14 (49)</td>
<td>0.62±0.18 (15)</td>
<td>0.69</td>
<td>0.65±0.08 (20)</td>
<td>0.56±0.17 (29)</td>
<td>0.032</td>
</tr>
<tr>
<td>LV Mass Indexed (Devereaux equation)</td>
<td>N/A</td>
<td>180.3±50.6 (44)</td>
<td>204.2±50.4 (14)</td>
<td>0.34</td>
<td>209.2±55.3 (19)</td>
<td>158.3±47.7 (25)</td>
<td>0.0021</td>
</tr>
<tr>
<td>LV peak wall stress (dynes/cm²)</td>
<td>N/A</td>
<td>216.0±55.7 (35)</td>
<td>191.2±36.3 (13)</td>
<td>0.15</td>
<td>229.0±69.7 (15)</td>
<td>205.0±41.4 (20)</td>
<td>0.21</td>
</tr>
</tbody>
</table>
Table 2. Change in Echocardiographic Variables From Baseline to 12 Months in Patients With MR $\leq$ 2+ at 12 Months Versus Patients With MR $>$ 2+ at 12 months

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1 — Continued Success (N=49)</th>
<th>Group 2 — Recurrent MR (N=15)</th>
<th>p-value* Group 1-2 Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline</td>
<td>12 months</td>
<td>p-value*</td>
</tr>
<tr>
<td>RV (ml)</td>
<td>45.4±17.6 (35)</td>
<td>20.7±9.9 (35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RF (%)</td>
<td>42.1±11.2 (35)</td>
<td>23.3±10.4 (35)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>170.7±41.1 (47)</td>
<td>141.2±34.2 (47)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>70.0±28.5 (47)</td>
<td>59.6±21.8 (47)</td>
<td>0.0004</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.5±0.7 (44)</td>
<td>5.1±0.6 (44)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>3.5±0.8 (45)</td>
<td>3.3±0.7 (45)</td>
<td>0.0079</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>59.9±9.3 (46)</td>
<td>58.3±9.2 (46)</td>
<td>0.0132</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>59.7±14.6 (42)</td>
<td>68.9±15.9 (42)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Sphericity index (2C)</td>
<td>0.61±0.07 (44)</td>
<td>0.58±0.06 (44)</td>
<td>0.0132</td>
</tr>
<tr>
<td>Sphericity index (4C)</td>
<td>0.60±0.14 (49)</td>
<td>0.57±0.14 (49)</td>
<td>0.0087</td>
</tr>
<tr>
<td>LV Mass Indexed</td>
<td>180.3±56.6 (44)</td>
<td>157.2±38.0 (44)</td>
<td>0.0002</td>
</tr>
<tr>
<td>(Devereaux equation)</td>
<td>215.5±55.7 (35)</td>
<td>185.2±43.8 (35)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

* The columns of p-values are not corrected for multiple testing. To be statistically significant after correction for multiple testing due to the 12 outcomes in a column, a p-value needs to be less than 0.05/12=0.0042.
Table 3. Change in Echocardiographic Variables from Baseline to 12 Months in Patients with MR ≤ 2+ at 12 Months With and Without Pre-Existing LV Dysfunction

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Group 1a — Continued Success + pre-existing LV dysfunction (N=20)</th>
<th>Group 1b — Continued Success + no pre-existing LV dysfunction (N=29)</th>
<th>p-value* Group 1a - 1b Change</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Baseline 12 months p-value*</td>
<td>Baseline 12 months p-value*</td>
<td></td>
</tr>
<tr>
<td>RV (ml)</td>
<td>40.5±13.8 (17)</td>
<td>49.9±19.9 (18)</td>
<td>0.0001</td>
</tr>
<tr>
<td>RF (%)</td>
<td>38.9±10.4 (17)</td>
<td>45.1±11.4 (18)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDV (ml)</td>
<td>195.5±36.2 (20)</td>
<td>152.2±34.7 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVESV (ml)</td>
<td>94.5±25.3 (20)</td>
<td>51.8±12.8 (27)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LVEDD (cm)</td>
<td>5.8±0.7 (19)</td>
<td>5.4±0.7 (19)</td>
<td>0.0045</td>
</tr>
<tr>
<td>LVESD (cm)</td>
<td>4.2±0.6 (20)</td>
<td>3.6±0.6 (20)</td>
<td>0.0045</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>51.4±8.1 (19)</td>
<td>65.9±4.0 (27)</td>
<td>0.0004</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>61.8±16.0 (18)</td>
<td>58.2±13.7 (24)</td>
<td>0.0002</td>
</tr>
<tr>
<td>Sphericity index (2C)</td>
<td>0.63±0.09 (20)</td>
<td>0.57±0.06 (20)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sphericity index (4C)</td>
<td>0.65±0.08 (20)</td>
<td>0.59±0.05 (24)</td>
<td>0.003</td>
</tr>
<tr>
<td>LV Mass Indexed (Devereaux equation)</td>
<td>209.2±55.3 (19)</td>
<td>173.3±39.2 (19)</td>
<td>158.3±47.7 (25)</td>
</tr>
<tr>
<td>LV peak wall stress (dynes/cm²)</td>
<td>229.2±69.7 (15)</td>
<td>197.6±56.5 (15)</td>
<td>205.2±41.4 (20)</td>
</tr>
</tbody>
</table>

* The columns of p-values are not corrected for multiple testing. To be statistically significant after correction for multiple testing due to the 12 outcomes in a column, a p-value needs to be less than 0.05/12=0.0042.
Figure Legends

Figure 1. The MitraClip System. A. The MitraClip System is composed by a sophisticated tri-axial catheter system (steerable guide catheter and clip delivery system catheter) and an implantable clip. The guide catheter is 24 Fr at the level of the groin and 22 Fr at the atrial septum. The clip delivery system can be steered in 4 directions and has the MitraClip device attached to its distal end. B. The MitraClip implantable clip is a cobalt/chromium device. It includes 2 arms and 2 “grippers” adjacent to each arm to independently secure the leaflets following grasping. The clip arms and grippers are covered with polyester to enhance tissue healing.

Figure 2. Patient Accountability Through 12 Months. The number of patients available are shown for each of the analysis subgroups.

Figure 3. Mitral Regurgitation Severity at Baseline and 12 Months
The change in mitral regurgitation (MR) grade (0 to 4+) by analysis group is shown at baseline and at 12 months. A. Continued Success (Group 1) versus Recurrent MR (Group B). B. Continued Success with pre-existing left ventricular dysfunction (Group 1a) versus Continued Success with pre-existing left ventricular dysfunction (Group 1b).

Figure 4. Changes of Echocardiographic Parameters in Patients With Sustained (Group 1) and Recurrent (Group 2) MR Reduction at 12 Months
A. Changes in left ventricular ejection fraction, B. left ventricular end diastolic volume, and C. left ventricular end systolic volume between baseline and 12 months.
Figure 5. Changes of Echocardiographic Parameters in Patients With Sustained MR Reduction at 12 Months (Groups 1, 1a, and 1b)

A. Changes in left ventricular ejection fraction, B. left ventricular end diastolic volume, and C. left ventricular end systolic volume between baseline and 12 months.
Patients Treated
N=107

Acute Procedural Success (N=79)

Mitral Valve Surgery = 10
Death = 2*
Withdrawals = 3
1 Echo Not Done

12-Month Follow-up (N=64)

Group 1
Continued Success at 12 Months (N=49)

Group 2
Recurrent MR at 12 Months (N=15)

Group 1a
Pre-Existing LV Dysfunction (N=20)

Group 1b
No Pre-Existing LV Dysfunction (N=29)

* 1 patient died after MV surgery
Percutaneous Mitral Valve Repair in the Initial EVEREST Cohort: Evidence of Reverse Left Ventricular Remodeling

Elyse Foster, Damon Kwan, Ted Feldman, Neil Weissman, Paul Grayburn, Allan Schwartz, Jason Rogers, Saibal Kar, Michael Rinaldi, Peter Fail, James Hermiller, Patrick L. Whitlow, Howard C. Herrmann, Scott Lim and Donald Glower

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