Echocardiographic and Clinical Outcomes of MitraClip Therapy in Patients Not Amenable to Surgery

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Objectives
The aim of this study was to assess the outcomes of patients at prohibitive surgical risk undergoing MitraClip therapy (Abbott Vascular, Redwood City, California) for severe mitral regurgitation (MR).

Background
The safety of percutaneous mitral valve repair has been documented. However, midterm development of mitral valve function, ventricular remodeling, and clinical outcomes in patients not amenable to surgery are unknown.

Methods
A total of 104 consecutive patients (mean age 74 ± 9 years; 64 men; 49 and 54 with MR 3+ and 4+, respectively; 69 with functional MR; 59 and 45 in New York Heart Association classes III and IV, respectively) were followed for a median of 359 days.

Results
Device success was achieved in 96 patients (92%). In patients with successful index procedures, MR grade ≤2+ was present at follow-up in 82.5%, left ventricular end-diastolic and -systolic volumes were reduced, and forward stroke volumes were significantly increased. Improvements in New York Heart Association functional class were observed in 80% of patients, with 69% in class I or II; 75% improved in the 6-min walk test; and 74% reported improvements in quality of life. One-year estimates of mortality and rehospitalization were 22% and 31%, respectively. Forward stroke volume at discharge emerged as a predictor of event-free survival.

Conclusions
MitraClip therapy improves clinical and echocardiographic outcomes at 1 year in about three-quarters of critically ill, elderly patients with moderate to severe MR not amenable to surgery. (J Am Coll Cardiol 2011;58:2190–5) © 2011 by the American College of Cardiology Foundation

The MitraClip device (Abbott Vascular, Redwood City, California) is a novel percutaneous system to treat mitral regurgitation (MR). In the recent EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), MitraClip therapy was compared with mitral valve (MV) surgery for moderate to severe MR (1) and despite lower efficacy revealed similar improvements in clinical outcomes.

Whereas EVEREST II reported outcomes in selected patients amenable to surgery, in this study, we assessed the outcomes of patients not amenable for surgery undergoing MitraClip implantation.

Methods
Patients. Between September 2008 and March 2010, 104 consecutive patients with moderate to severe MR were determined to be at prohibitive surgical risk by joint evaluation of a panel of cardiovascular surgeons and cardiologists and thus underwent percutaneous mitral repair. All procedures were performed by 2 experienced operators (O.F., S.B.). Patient characteristics are given in Table 1. The patients’ clinical status was significantly different in several aspects from that of EVEREST II patients (Table 2). All patients included in the study provided written informed consent.
device success was pre-specified as a residual MR grade of $2^{+}$ or less after clip implantation. At 6 and 12 months, patients were subjected to a structured interview including the Minnesota Living With Heart Failure Questionnaire (MLHFQ), transthoracic echocardiography, a 6-min walk test, and assessment of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. If a return visit was hindered by comorbidities, re-evaluation was restricted to telephone follow-up.

**Echocardiography.** MR at baseline was graded according to American Society of Echocardiography guidelines (2). After the intervention, MR severity was assessed with the technique reported by Foster et al. (3). A description of echocardiographic methods is available in the Online Appendix. **Statistical analysis.** A summary of statistical methods is given in the Online Appendix.

**Results**

**Acute outcomes.** Initial device success was achieved in 96 patients (92%), with MR grade $2^{+}$ present in 60 patients and MR grade $1^{+}$ in 36. In the remaining 8 patients, clip implantation was not achieved (n = 3) or did not reduce MR to less than grade $3^{+}$ (n = 5). A single clip was implanted in 62 patients, 2 clips were implanted in 34, and $\geq 2$ clips were implanted in 5. The median length of hospital stay was 9 days (interquartile range: 7 to 14 days).

**Periprocedural complications.** Chordal rupture was encountered in 3 patients and clip detachment in 2 patients. Of the former patients, 2 underwent prompt surgical MV.
repair (Fig. 1), while minor residual MR was left untreated in the other patient. Clip detachments were remedied by placing another clip during the same procedure in 1 patient and on the next day in the other patient. One patient experienced intra-procedural ventricular tachycardia that was terminated by external defibrillation, and 1 patient developed transient third-degree atrioventricular conduction block that did not necessitate pacemaker implantation. This patient also required 2 U of blood transfusion, as did 8 other patients. Thus, overall, periprocedural complications were encountered in 14 patients (13.5%).

Clinical outcomes. Median follow-up duration was 359 days (interquartile range: 248 to 404 days).

PATIENTS WITH SUCCESSFUL INDEX PROCEDURES. Six of the 96 patients with successful index procedures underwent repeat clipping at a median of 140 days (interquartile range: 58 to 351 days), and 2 underwent MV surgery (1 repair, 1 replacement) at 47 and 58 days (Fig. 1). Surgical repair was also performed in 1 patient shortly after a failed attempt at repeat clipping.

Follow-up was obtained by telephone (n = 18) or clinical visit (n = 63) in 81 surviving patients. New York Heart Association (NYHA) functional class had improved in 65 patients (80%), with a total of 56 patients (69%) in NYHA functional class I or II at follow-up. The 6-min walk distance improved in 41 of 55 patients (75%), MLHFQ score improved in 35 of 47 patients (74%), and NT-proBNP decreased in 32 of 52 patients (62%). The overall changes in these variables from baseline to follow-up are shown in Figure 2. Baseline MR severity did not influence any outcome measure (Online Appendix). Of note, when counting patients who died (n = 15) as deteriorations, statistical significance was maintained for NYHA functional class, 6-min walk distance, and MLHFQ score, but not for NT-proBNP, in a sensitivity analysis using the sign test.

PATIENTS WITH FAILED INDEX PROCEDURES. Of 8 patients with failed index procedures, 1 patient underwent MV replacement on the same day and 1 patient had surgical MV repair after 2 days (Fig. 1). The latter patient underwent valve replacement 3 months later. Of 6 patients without immediate MV surgery, 1 patient underwent MV replacement at 49 days, and 2 patients had repeat MitraClip procedures. Both repeat interventions were failures (no clip in 1 patient, residual MR grade 3+ in the other), and 1 was followed by surgical valve repair 4 days later.

Echocardiographic follow-up. Compared with baseline, MR grade at follow-up was significantly improved; no change in left ventricular (LV) ejection fraction was observed, yet LV end-diastolic and end-systolic volumes decreased significantly. LV forward stroke volume increased significantly, whereas total stroke volume showed a significant reduction (Table 3). Major adverse events. Twenty-six patients (25%) died between 10 and 698 days after the intervention (median 162 days); there were 4 in-hospital deaths. Deaths were adjudicated as cardiac in 19 patients (18%).

Thirteen patients required reinterventions (13%). Repeat MitraClip procedures were performed in 8 patients and
failed in 2. MV surgery was performed in 7 patients (3 repairs, 5 replacements, 1 patient with both) (Fig. 1).

Twenty-eight patients (27%) were rehospitalized for cardiac decompensation. Independent predictors of cardiac rehospitalization were a baseline LV ejection fraction <45% (odds ratio: 3.90; p = 0.008) and a forward stroke volume at discharge <50 ml (odds ratio: 4.54; p = 0.007).

Overall, 57 patients (55%) experienced at least 1 major adverse event (i.e., cardiac rehospitalization, reintervention, or death). Kaplan–Meier estimates of freedom from death, cardiac rehospitalization, or reintervention are shown in Figure 3. Estimates of 1-year mortality and rehospitalization were 22% and 31%, respectively.

Baseline MR grade 4 and discharge forward stroke volume <50 ml independently predicted event-free survival on multivariate analysis (Table 4). For a comparison of patients with functional versus degenerative MR, see the Online Appendix.

<table>
<thead>
<tr>
<th>Variable</th>
<th>n</th>
<th>Baseline</th>
<th>Follow-Up</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>MR grade</td>
<td>63</td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>1+</td>
<td>0 (0%)</td>
<td>14 (22%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>1 (2%)</td>
<td>38 (60%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>3+</td>
<td>35 (56%)</td>
<td>10 (16%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4+</td>
<td>27 (43%)</td>
<td>1 (2%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Regurgitant jet/LA area ratio (%)</td>
<td>53</td>
<td>46 ± 12</td>
<td>21 ± 14</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-diastolic volume (ml)</td>
<td>63</td>
<td>221 (174–281)</td>
<td>183 (150–233)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV end-systolic volume (ml)</td>
<td>63</td>
<td>125 (87–193)</td>
<td>102 (73–166)</td>
<td>0.0002</td>
</tr>
<tr>
<td>LA volume (ml)</td>
<td>57</td>
<td>87 (59–113)</td>
<td>87 (61–119)</td>
<td>0.1130</td>
</tr>
<tr>
<td>Total stroke volume (ml)</td>
<td>63</td>
<td>90 (70–108)</td>
<td>69 (57–89)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>FSV (ml)</td>
<td>59</td>
<td>43 (31–53)</td>
<td>49 (42–59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant volume (ml)</td>
<td>59</td>
<td>45 (35–62)</td>
<td>19 (12–36)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Regurgitant fraction (%)</td>
<td>59</td>
<td>53 (42–60)</td>
<td>28 (17–37)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LV ejection fraction (%)</td>
<td>63</td>
<td>43 (31–52)</td>
<td>45 (30–53)</td>
<td>0.1577</td>
</tr>
<tr>
<td>LV end-diastolic diameter (mm)</td>
<td>59</td>
<td>65 ± 11</td>
<td>66 ± 11</td>
<td>0.7020</td>
</tr>
<tr>
<td>LV end-systolic diameter (mm)</td>
<td>59</td>
<td>54 ± 13</td>
<td>53 ± 14</td>
<td>0.6634</td>
</tr>
<tr>
<td>Mean transmitral gradient (mm Hg)</td>
<td>54</td>
<td>2.3 ± 2.0</td>
<td>3.7 ± 2.2</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Values are n (%), mean ± SD, or median (interquartile range).

FSV = forward stroke volume; LA = left atrial; other abbreviations as in Table 1.
Discussion

Our study demonstrates that in patients with severe MR not amenable to surgery, MitraClip therapy leads to sustained reduction in MR severity and reverses ventricular remodeling. Significant clinical improvement was observed in three-quarters of patients followed.

Patient population. Compared with EVEREST II, the present study population differed considerably with respect to age, comorbidities, and the prevalence of functional MR. Moreover, 80% of our patients had valve morphologies that met EVEREST II exclusion criteria (1). Nevertheless, an overall procedural success rate of 92% was achieved in our study, demonstrating the general feasibility of the procedure in patients at prohibitive surgical risk. The higher procedural success rate compared with EVEREST II may be explained by 2 factors: 1) in the present study, 2 experienced operators performed all interventions; and 2) functional MR, which tends to be easier to intervene on, was more prevalent. The rate of periprocedural complications was low, with in-hospital mortality of 3.8%; expectedly, this is higher than the 1.1% mortality in the EVEREST II population but in the 2% to 10% range reported for MV surgery in high-risk patients (4,5). Importantly, the severity of comorbidities exceeded not only that commonly encountered in MV surgery studies but also that reported for patients denied MV surgery (6). Compared with EVEREST II, our patients exhibited higher NYHA functional classes, yet quantitative measures of MR severity tended to be lower, possibly because of the more advanced LV dysfunction in our patients. Thus, not only do patients with cardiomyopathy have a higher degree of functional impairment, but also the severity of mostly functional MR in these patients shows a high degree of variation, with a tendency toward underestimation in recompensated patients scheduled for intervention.

Clinical outcomes. Most of the patients followed exhibited significant improvements in clinical status. NYHA
functional class was reduced, with almost 70% of patients in class I or II. This effect was observed on top of optimal medical therapy and in highly symptomatic patients: as opposed to EVEREST II, with 49% of patients in NYHA functional class I or II, we included only patients in NYHA functional class III or IV. Also, MLHFQ score improved by almost 20 points, which is comparable with results reported for MV surgery (7). In accordance, 6-min walk distance increased in 75% of our patients, further underscoring the profound clinical benefit derived from this therapy in the majority of patients included.

Of the 13% of patients in whom reintervention was necessary, 6% could be retreated with the MitraClip, whereas 7% eventually required MV surgery. This incidence compares favorably with the 20% necessity for surgery in EVEREST II (1), implying that patients with prohibitive surgical risk do not exhibit higher reintervention rates.

**Echocardiography.** Echocardiographic baseline parameters in the present study underscore the population’s overall high morbidity. Yet, in concordance with EVEREST II (1), LV volumes were significantly reduced at follow-up.

**Major adverse events.** The 55% overall event rate was driven mainly by mortality and rehospitalization (25% and 27%, respectively). These data mirror the high morbidity of our cohort and are in accordance with data reported from the EVEREST II high-risk registry, which revealed a 1-year mortality of 24% after MitraClip implantation in patients with similar risk profiles, as opposed to 45% in patients on medical therapy only (8); these rates suggest that MitraClip implantation may indeed slow the progression of the disease. In the present study, a forward stroke volume at discharge of <50 ml emerged as the most powerful predictor for both rehospitalization and the composite endpoint of death, rehospitalization, and reintervention. This observation potentially indicates that LV contractile reserve (i.e., the ability of the left ventricle to procure sufficient contractility for enhancement of forward stroke volume) is of prognostic importance (9). Of note, MR etiology (i.e., functional vs. degenerative) had no influence on the patients’ clinical outcomes, implying that MitraClip therapy is equally effective for both conditions.

**Study limitations.** This study was relatively small in size, and a considerable number of patients were lost to follow-up. Those patients were on average older and more often in NYHA functional class IV at baseline. The lack of follow-up data in patients who died before assessment may have caused an optimistic selection bias. However, a sensitivity analysis revealed that only the decrease in NT-proBNP may be spurious.

**Conclusions**

This study extends the current body of evidence showing that MitraClip therapy is safe and efficacious in patients with significant MR deemed at prohibitive surgical risk; it resulted in significant clinical improvements at 1 year in about three-quarters of patients followed. The subgroup analyses of EVEREST II suggest that older age, functional MR, and reduced ejection fraction describe patients deriving particular benefit from this therapy (1). The present study, which largely included patients with these characteristics, reinforces this tenet and may point toward novel treatment options not only in patients considered at excessive surgical risk. Further research is needed to identify parameters that will more decisively discriminate between patients who will and those who will not derive benefit from the procedure in the long term.