Usefulness of Age (≥85 Years) and Residual Mitral Regurgitation (>1+/4+) for the Prediction of Adverse Outcomes in Patients Receiving the MitraClip

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The goal of this study was to determine the predictors of adverse clinical outcomes in patients treated with the MitraClip for significant mitral regurgitation (MR) with a focus on acute changes in hemodynamics and cardiac function. This retrospective study included 63 patients (mean age 82 ± 8 years, 48% male) with moderate to severe or severe MR. Cardiac catheterization was performed before and immediately after MitraClip repair. Volumetric and functional changes were assessed in both ventricles. A major adverse cardiac event was defined as a composite of cardiac death and readmission for heart failure. Patients were followed up on average for 380 days. MR was improved in 92% of patients after MitraClip therapy from an average grade of 4+ to <2+ ($p < 0.001$). The pulmonary capillary wedge pressure decreased from 22 ± 7 mm Hg to 19 ± 6 mm Hg ($p < 0.001$), and the cardiac stroke volume increased by 28% from 102 ± 53 ml to 131 ± 54 ml ($p < 0.001$). The left ventricular end-diastolic volume was significantly reduced 24 hours after MitraClip therapy compared to that at baseline ($p = 0.001$). In the multivariate Cox proportion hazard regression model, an age ≥85 years ($p < 0.001$) and residual MR >1+ ($p < 0.048$) were predictors of an adverse prognosis at follow-up. In conclusion, a reduced left ventricular end-diastolic volume and improved hemodynamics occurred early after MitraClip therapy. An advanced age (≥85 years) and residual MR >1+ were associated with an increased risk of mortality and heart failure. **(Am J Cardiol 2019;124:1449−1453)**

MitraClip (Abbott Vascular, Abbott Park, Illinois) is a device used for transcatheter mitral valve repair for symptomatic and high-risk patients with significant mitral regurgitation (MR).[1] By 2018, more than 60,000 patients had been treated in over 50 countries worldwide.[2] Reduction in left ventricular (LV) volumes and improvement in clinical outcomes have been observed in clinical studies following surgical and percutaneous mitral valve repair.[3] However, some patients who have undergone mitral valve therapy still experience irreversible LV systolic dysfunction and a poor prognosis, especially those with longstanding volume overload due to severe MR.[4] Hence, screening appropriate patients who may respond to mitral valve therapy is essential.[5−7] In the present study, we evaluated the pre- and postprocedural MR grades, hemodynamic parameters, and LV geometric responses to MitraClip therapy and sought to identify factors that might be associated with the 1-year risk of adverse outcomes.

Methods

The study was performed with a retrospective approach. Between 2006 and 2017, 77 consecutive patients with an MR grade of 3+ or greater who received MitraClip therapy (Abbott Vascular, Abbott Park, Illinois) were enrolled at the Heart Center at St. Francis Hospital. All patients were at high or prohibitive surgical risk, which is defined by the Society of Thoracic Surgeons as a mortality risk ≥8%, frailty and other circumstances.[6,8] Each case was evaluated by a multidisciplinary team consisting of interventional cardiologists, echocardiologists, cardiac anesthetists, and cardiac surgeons. Patient information, including demographics, comorbidities, and the New York Heart Association (NYHA) functional class, were recorded in the institutional information system. Fourteen patients were excluded due to poor echocardiographic image quality ($n = 11$) and loss of follow-up ($n = 3$). The Institutional Review Board approved all procedures of the study, and each patient provided written informed consent before the intervention.

All patients underwent a baseline and postprocedural echocardiography using the Philips iE33 (Philips Medical System, Andover, Massachusetts) ultrasound system. Two-dimensional grayscale images were acquired 24 to 48 hours before and 24 hours after the MitraClip procedure. Digital images were prospectively stored for offline analysis using the TomTec workstation (TomTec Imaging Systems, Unterschleissheim, Germany). Echocardiographic measurements, including the left atrial volume, LV end-diastolic volume (LVEDV), and LV end-systolic volume (LVESV),

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were performed according to American Society of Echocardiography guidelines.[9] The LV ejection fraction (LVEF) was estimated using the biplane Simpson's method. The endocardial boundary delineation and measurement were performed by operators who were blinded to the patients' clinical information.

Right heart catheterization was performed before the intervention. Hemodynamic parameters, including the pulmonary capillary wedge pressure (PCWP), stroke volume (SV), cardiac output and cardiac index (CI), were obtained before and after the procedure using the thermodilution principle.[10–12] For MitraClip implantation, transseptal left heart catheterization and mitral valve edge-to-edge repair were performed under fluoroscopy and transesophageal echocardiography guidance.[3,13–15] Mitral regurgitation was graded using integrative criteria based on the American Society of Echocardiography guidelines.[16,17] The mean transmitral pressure gradient was measured by echocardiography before and after valvular repair during the procedure**.** A second or third clip was placed to achieve a residual MR grade of 2+ or lower if no evidence of mitral stenosis (mean transmitral pressure gradient >5 mm Hg) was detected.

Patients were followed up in the outpatient clinic by the physicians who performed the procedure. Postoperative follow-up information was obtained from the hospital medical records, including those for outpatient and emergency department visits. The primary end point was a composite of cardiac death and readmission for heart failure.

Continuous variables were tested for a normal distribution using the Kolmogorov-Smirnov test. Variables are expressed as the mean ± standard deviation. Continuous variables with a skewed distribution were assessed as dichotomous variables. Categorical variables are reported as frequencies and percentages. A paired Student's *t* Test (2-tailed) was used for comparison of continuous variables pre- and post-MitraClip procedure within groups. The Chi-square test or Fisher's exact test was used for comparisons between groups. Survival data were analyzed using Kaplan-Meier plots. Cox proportional hazards models were used to identify univariate and multivariate predictors of cardiac adverse events. Variables with $p < 0.10$ were tested with multivariate modeling. Hazards ratios (HRs) with 95% confidence intervals (CI) were calculated when appropriate. To exam the inter- and intraobserver variability, we used intraclass correlation coefficients (ICCs) to assess the reliability of the echocardiographic measurement. The ICC was considered poor if <0.4, acceptable if between 0.4 and 0.75, good if between 0.75 and 0.9, and excellent if >0.9. A $p < 0.05$ was considered statistically significant. Statistical analyses were performed using SPSS, version 19.0 (SPSS, Inc., Chicago, Illinois). GraphPad Prism software (San Diego, California) version 5.01 was used for drawing the figure.

Results

Sixty-three consecutive patients were included in this study. The demographics and clinical features are summarized in Table 1. The mean age was 82 years, and 48% of the patients were men. The baseline LVEF was 45% ± 12 %, and the majority of the patients had functional class NYHA III or IV (83%). One and 2 or more clips were implanted in 44% and 56% of the patients, respectively. Ninety-two percent of the patients achieved MR reduction to 2+ or less following MitraClip therapy. In them, 46 patients (73%) had a residual MR of 1+ or less (Table 1). The baseline PCWP was 22 ± 7 mm Hg, and the transmitral gradient was 2.2 ± 1.0 mm Hg (Table 2).

Table 1
Baseline characteristics

Variable	Total (n = 63)
Age (years)	82 ± 8
Men	30 (48%)
Body surface area (m^2)	1.75 ± 0.25
New York Heart Association class II	11 (17%)
class III or IV	52 (83%)
Left ventricular ejection fraction (%)	45 ± 12
Left ventricular ejection fraction >50%	24 (38%)
STS PROM	12.4 ± 8.4%
Hypertension	53 (84%)
Diabetic mellitus	16 (25%)
Chronic obstructive pulmonary disease	8 (13%)
Prior myocardial infarction or intervention	38 (60%)
Cerebrovascular accident	17 (27%)
Prior cancer	22 (35%)
Atrial fibrillation	43 (68%)
Chronic renal insufficiency	14 (22%)
Mitral regurgitation etiology	
Degenerative	56 (89%)
Mixed*	7 (11%)
Degree of mitral regurgitation preprocedure	
3+	19 (30%)
4+	44 (70%)
Degree of mitral regurgitation postprocedure	
≤1+	46 (73%)
>1+ and ≤2+	12 (19%)
>2+	5 (8%)
Clips	
1 clip	28 (44%)
≥2 clips	35 (56%)

Values are presented as the mean ± SD or n (%). PROM = predicted risk of mortality; STS = Society of Thoracic Surgery.

* Mixed: functional and degenerative mitral regurgitation.

Hemodynamic improvement was achieved immediately after MitraClip deployment with a significant increase in the SV, cardiac output and CI and a decrease in the PCWP (Table 2). In the follow-up echo performed 24 hours after MitraClip implantation, the LVEDV and LVESV were significantly reduced, whereas the LVEF remained unchanged (Table 2).

During the mean follow-up of 380 days (range 178 to 1547 days), 17 cardiac deaths and 3 hospitalized heart failures occurred. The combined end point was met in 20 patients (32%). Univariate Cox regression analysis revealed that an age ≥85 years and a residual mitral regurgitation >1 + were associated with a higher incidence of adverse cardiac events. Multivariate Cox regression analysis showed that an age ≥85 years (HR 6.44, 95% CI 2.04 to 20.32, $p = 0.001$) and mitral regurgitation >1+ following the procedure (HR 4.56, 95% CI 1.48 to 14.10, $p = 0.008$) were independent factors for 1-year adverse cardiac events (Table 3). The Kaplan-Meier curves showed that elderly

Table 2
Cardiac remodeling and hemodynamic changes before and after MitraClip therapy

Variable	Pre-MitraClip	Post-MitraClip	p Value
Echocardiographic data			
Left ventricle end-diastolic volume (ml)	122 ± 42	109 ± 44	0.001
Left ventricle end-systolic volume (ml)	69 ± 35	63 ± 35	0.027
Left atrial end-diastolic volume (ml)	105 ± 57	98 ± 53	0.085
Left atrial end-systolic volume (ml)	149 ± 72	142 ± 62	0.223
Left ventricular ejection fraction (%)	45 ± 12	45 ± 12	0.669
Right ventricle fractional area change (%)	33 ± 12	37 ± 11	0.013
Mean transmitral pressure gradient (mmHg)	2.2 ± 1.0	4.1 ± 1.9	<0.001
Mitral regurgitation severity grade	3.8 ± 0.4	1.2 ± 0.7	<0.001
Hemodynamic data			
Pulmonary capillary wedge pressure (mmHg)	22 ± 7	19 ± 6	<0.001
Stroke volume (ml)	102 ± 53	131 ± 54	<0.001
Cardiac output (L/min)	6.9 ± 3.6	8.8 ± 3.0	<0.001
Cardiac index (L/min/m^2)	3.9 ± 1.9	5.0 ± 1.6	<0.001

Values are expressed as the mean ± SD.

Table 3
Univariate and multivariate predictors of the primary endpoint using COX proportional hazards models

	Univariate analysis HR (95% CI)	p Value	Multivariate model HR (95% CI)	p Value
Age ≥85 years	5.66 (2.03-15.76)	0.001	6.44 (2.04-20.32)	0.001
Left ventricle end-diastolic volume reduction	2.32 (0.84-6.41)	0.106		
Left ventricle end-systolic volume reduction	2.51 (0.88-7.11)	0.084		
Left atrial end-diastolic volume reduction	1.21 (0.49-2.98)	0.679		
Left atrial end-systolic volume reduction	1.21 (0.50-2.93)	0.672		
Baseline left ventricular ejection fraction ≥50%	0.44 (0.18-1.06)	0.066		
NYHA ≥III	0.93 (0.27-3.25)	0.913		
Right ventricle fractional area change increase	0.67 (0.27-1.67)	0.390		
Post mitral regurgitation >1+	3.27 (1.32-7.98)	0.009	4.56 (1.48-14.10)	0.008
Mean transmitral pressure gradient increase	0.50 (0.18-1.39)	0.184		
Pulmonary capillary wedge pressure decrease	1.08 (0.44-2.68)	0.861		
Stroke volume increase	0.53 (0.20-1.45)	0.220		

HR = Hazard ratio; the hazard ratio is given with its 95% confidence interval (CI).

patients with a residual MR >1+ following MitraClip had a significantly higher incidence of adverse outcomes. A significantly lower event rate was observed in patients with an age <85 years and a residual MR ≤1+. The highest cumulative adverse outcome rate was observed in those with an age ≥85 years and MR >1+ (p <0.001, Figure 1).

Interobserver variability in the ventricular volume and function analyses was tested for 10 randomly selected patients by 2 independent observers. Interobserver variability was excellent for the LVEDV and LVESV with an ICC of 0.92, and good for the LVEF, with an ICC of 0.87. The ICC of intraobserver variability was 0.91 for the LVEDV and LVESV and 0.93 for the LVEF.

Discussion

The present study investigated clinical variables before and after MitraClip therapy and their associations with clinical outcomes in patients with severe MR. We found that mitral regurgitation reduction was achieved in the majority of the patients and was associated with immediate improvement in the SV, CI, and PCWP. In addition, the LVEDV and LVESV were reduced after MitraClip repair without a change in the LVEF. Lastly, an age ≥85 years and residual mitral regurgitation >1+ were independent predictors of 1-year adverse clinical outcomes.

The endovascular valve edge-to-edge repair study (EVEREST II) was the first randomized clinical trial to evaluate the benefits and risks of MitraClip therapy compared with those of open mitral valve surgery.[14] The EVEREST II demonstrated similar survival and symptomatic improvement but a higher rate of recurrent MR than surgery. The corresponding 5-year follow-up study identified an older age, diabetes, functional MR, chronic obstructive pulmonary disease (COPD) and peripheral artery disease as independent predictors of 5-year mortality in this population.[14,18] With the rapidly increasing application of MitraClip and technological development, the patient population has largely expanded from surgical candidates to prohibitive surgical risk patients,[8,19–22], and from individuals with primary MR to those with functional MR.[23,24] Currently, elderly patients with symptomatic, severe MR and multiple co-morbidities are eligible candidates for MitraClip implantation.[25,26] The mean age of 82 years in our study is 13 years older than that in the EVEREST II trial[14] and 3 years older than that in the EVEREST II high-risk study.[3] Consistent with the EVEREST study,[16] our study found an immediate and significant improvement in the SV

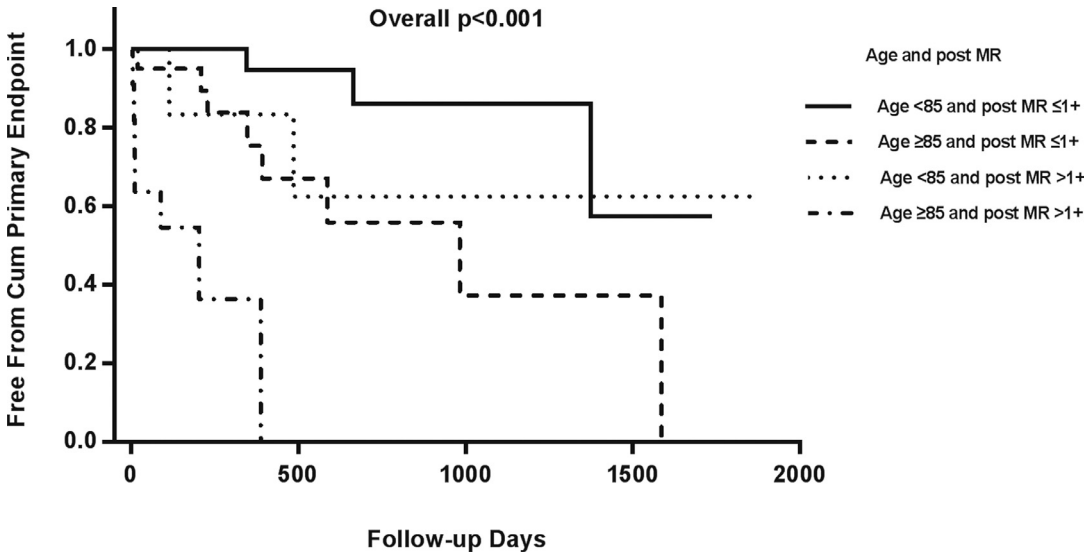

Figure 1. The graph shows the freedom of the primary end point according to age and the different extents of MR after the procedure. A significantly lower event rate was observed in patients with an age <85 years and a residual MR ≤1+. The highest cumulative adverse outcome was observed in patients with an age ≥85 years and an MR >1+.

and CI. MitraClip treatment, which reduces the low-impedance mitral regurgitant flow into the left atrium, leads to an increase in forward flow and thus a higher CI and concomitant decrease in systemic vascular resistance.[10,12] Considering that 83% of our patients had advanced congestive heart failure symptoms (NYHA functional class III to IV), the immediate improvement in hemodynamic parameters, such as the SV and CI, was particularly important. This outcome was more favorable than that reported for surgical mitral valve repair and replacement in a similar patient population.[27]

Although the vast majority of the patients in our study achieved a significant MR reduction, a residual MR greater than 1+ was still associated with unfavorable clinical outcomes. In general, an MR reduction to 2+ or less during the procedure is defined as acute procedural success and has been widely used as an echocardiographic predictor of a satisfactory procedure.[6] However, recent investigations have suggested that acute procedure success may need to be personalized.[28] For instance, Kaneko et al found that a residual MR of 2+ was associated with a poorer prognosis in patients with renal and LV dysfunction.[25,28] In the MitraSwiss registry, Sürder demonstrated that patients with a residual MR of 1+ or less had a better prognosis than those with grade 2+ or more, which was confirmed by Neuss et al.[6,29] These authors suggested that an echocardiographic MR grade of 1+ or less might be the optimal goal of MitraClip therapy. Nonetheless, our findings are consistent with their conclusion which suggests that pursuing a residual MR of 1+ or less as a therapeutic target in the elderly population may be important.

We recognize the study limitations. First, this study is a retrospective, observational study reflecting the experience of a single center with a small patient cohort. Compared to those in the literature, the patients in the present study are older and have a higher rate of co-morbidities. Nonetheless, our study has provided a unique opportunity to examine the outcomes of MitraClip in patients with an advanced age. Additionally, these observations are valuable for clinical care, because these patients are commonly underrepresented in clinical trials despite their high prevalence of disease. A large clinical trial is warranted to further investigate the clinical predictors of procedural success in elderly patients. Second, sedation is commonly used during the procedure. Inevitably, there is a hemodynamic impact that we are unable to exclude. Third, we had to exclude a number of cases with an inadequate echocardiographic image quality. As a result, we may have introduced selection bias. Finally, due to the retrospective study design, biochemical data sets were not complete for some patients and were not included in the study for prognostic analysis.

In conclusion, favorable cardiac remodeling and hemodynamic changes were observed immediately following MitraClip in the present study. An advanced age (≥85 years) and residual MR >1+ were associated with an increased risk of cardiac death and heart failure.

Disclosures

The authors have no conflicts of interest to disclose.

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