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4 **Impact of sex on outcomes after percutaneous repair of**
5 **functional mitral valve regurgitation**
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Abstract

Background

The role of percutaneous repair of functional mitral regurgitation (MR) is evolving. Left ventricle remodeling is known to be different between men and women; however, outcomes following percutaneous repair of functional MR have not considered the impact of sex.

Methods

Between 2012 and 2018, 175 patients underwent percutaneous repair of functional MR with the Mitra Clip NT/NTR (Abbott, Irvine CA) at our institution. Patients were assessed in a dedicated clinic with a follow-up that averaged 0.7 ± 1.2 years and extended to 5.7 years.

Results

Men had a larger body surface area than women ($p < 0.001$), whereas women were more likely than men to have diabetes preoperatively ($p = 0.02$). There were no deaths or instances of single leaflet detachment. Immediate post-procedure MR was $\leq 2+$ in 158 (90%) with a mean trans-mitral valve repair gradient of 3.4 ± 1.0 and 3.5 ± 2.1 mm Hg, respectively for women and men ($p = 0.8$). One- and 2-year freedom from MR $\geq 3+$ was $86.0 \pm 3.5\%$ and $77.6 \pm 5.1\%$, respectively. After adjusting for differences between male and female patients, women were more likely to have recurrent MR $\geq 3+$ (hazard ratio 4.7, 95% confidence interval 1.2-18.4, $p = 0.03$). Upon adjusted analysis, there was also no association between gender and survival ($p = 0.2$). One- and 2- year survival was $69.8 \pm 4.3\%$ and $54.3 \pm 5.5\%$, respectively.

Conclusion

Women are more likely to have recurrent severe MR after percutaneous repair of functional MR. The mechanism for this remains undetermined.

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Introduction

Functional mitral regurgitation (MR) is common and associated with adverse outcomes compared to individuals without MR [1-2]. Contemporary management primarily involves medical therapy and the treatment of coronary lesions in those patients with coronary disease [3]. As yet, no prospective data has demonstrated a survival benefit with surgical correction of functional MR. However, recent data suggests that percutaneous mitral repair may be associated with a survival benefit in selected patients [4-5].

Although the role of percutaneous repair of functional MR is evolving, early data suggests that patients with proportionate functional MR may benefit whereas those with disproportionate MR do not [6]. Overall, these landmark data have advanced the care of patients with heart failure. Ongoing refinement continues; however, few data are available advising on outcomes according to sex.

The data describing heart failure in men and women is complex. Contemporary data from the Framingham Heart Study suggests that women are more likely than men to develop heart failure symptoms at some point in their life [7]. Indeed, women are more likely to have heart failure with reduced ejection fraction than men, and women with ischemic cardiomyopathy have worse survival than men [8]. There also appears to be differing pharmacologic response to standard heart failure medications according to sex [9]. Women with heart failure who ultimately undergo cardiac surgery also have worse outcomes than men. We have previously shown that recurrent MR may be more likely and ventricle remodelling worse in women after repair of degenerative MR [10-11]. In a recent population study, women who underwent isolated mitral repair had worse survival than men [12].

In light of the above, assessing the role of female sex on outcomes after percutaneous repair may have clinical impact. We therefore performed a cohort study assessing outcomes following percutaneous repair of functional MR. This study is comprised of 175 consecutive patients who have been prospectively followed after percutaneous mitral repair with the MitraClip NT/NTR (Abbott, Irvine CA).

Methods

Patients and follow-up

Between 2012 and 2018, 175 patients underwent percutaneous repair of functional MR with the Mitra Clip NT/NTR (Abbott, Irvine CA) at our institution. Patients were assessed in a dedicated clinic with a follow-up that averaged 0.7 ± 1.2 years and extended to 5.7 years. Annular dilation without leaflet tethering was observed in 23 (13%) whereas the remainder of patients had leaflet tethering.

Procedure

Procedures were performed in a hybrid operating room after assessment by a Heart Team comprised of interventional cardiology, cardiac surgery, and cardiac anesthesia. Percutaneous mitral repair was performed through standard percutaneous femoral venous puncture, subsequent atrial balloon septostomy, and positioning of the 24Fr steerable guide in the left atrium. Overall, the median number of clips implanted was 2. Female patients received a mean of 1.5 ± 0.6 clips implanted whereas men had 1.8 ± 0.7 clips implanted ($p=0.01$). Fluoroscopic time averaged 31.6 ± 15.7 min and was not different between groups (33.2 ± 17.3 min in men versus 29.3 ± 12.8 min in women, $p=0.2$).

Statistical analysis

Continuous data are described as a mean \pm standard deviation whereas count data are listed as a number and percentage. Female and male patients were compared in regards to a variety of covariates using either a Students t-test when the data were continuous and normally distributed or a chi-square test when applicable. Freedom from recurrent MR $\geq 3+$ was assessed via a

127 Kaplan-Meier method. Risk factors associated with recurrent MR and death were compared
128 separate Cox proportional hazards models. Procedural outcomes were qualified in accordance
129 with treatment guidelines from the Mitral Valve Academic Research Consortium [13].

Results

Demographics and Peri-procedural Outcomes

Women and men were of similar age in this cohort (Table 1) with an overall age of 73.3 ± 11.4 years. Not surprisingly, men were of larger body surface area than women ($p < 0.001$). Men were also more likely to be diabetics and had worse pre-procedure left ventricle ejection fraction than women (Table 1).

There were no deaths or single leaflet detachment. Immediate post-procedure MR was $\leq 2+$ in 158 (90%) with a mean trans-mitral valve repair gradient of 3.4 ± 1.0 and 3.5 ± 2.1 , respectively for women and men ($p = 0.8$). At the time of hospital discharge, 99 (57%) had MR $\leq 1+$. Twenty-eight women and 36 men had MR $\geq 2+$ at the time of discharge ($p = 0.4$). Discharge disposition included home in 152 (87%), peripheral hospital in 10 (9%), rehabilitation facility in 6 (3%), and a long-term care facility in 2 (1%).

Echocardiographic Outcomes

Of the 175 patients, 18 had persistent severe 3-4+ MR after implantation of whom 11 (10% were male and 7 (10%) were female ($p = 0.8$). Overall 25 patients had MR $\geq 3+$ at a mean of 325 days following percutaneous repair. One and 2-year freedom from MR $\geq 3+$ was $86.0 \pm 3.5\%$ and $77.6 \pm 5.1\%$. After adjusting for differences between male and female patients, women were more likely to have recurrent MR $\geq 3+$ (hazard ratio 4.7, 95% confidence interval 1.2-18.4, $p = 0.03$) (Table 2). At most recent follow-up, the mean LV ejection fraction was $34.3 \pm 13.5\%$ and similar between groups ($33.2 \pm 13.85\%$ in men and $36.0 \pm 13.6\%$ in women, $p = 0.3$).

Clinical Outcomes

157 Twelve patients died within 30 days of percutaneous mitral repair. Of these 12 patients, 2 had
158 residual severe MR immediate post procedure, both of whom were female. Upon adjusted
159 analysis, there was no association between gender and survival ($p=0.2$). One- and 2- year
160 survival was $69.8\pm4.3\%$ and $54.3\pm5.5\%$, respectively (Figure 1). At most recent follow-up, 133
161 (76%) of patients reported a New York Heart Association functional class ≤ 2 . Which was not
162 different between groups ($p=0.5$).

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Comment

In this study, we assessed the role of sex on outcomes following percutaneous repair of functional MR in a cohort of 175 patients. Early results were favorable with a 1-yr freedom from recurrent severe MR of 86%. Although there was no difference between men and women in terms of survival, recurrent MR $\geq 3+$ was more common in women even after adjusting for differences in patient groups.

Current evidence suggests a survival advantage for patients undergoing percutaneous repair of severe functional MR compared to patients treated with medical therapy alone [4]. In this study, the overall freedom from recurrent severe MR $\geq 3+$ was 86% at 1-year and 77% at 2-years, which compares favorably to studies evaluating MR after percutaneous repair [4,5]. Of note, men in this study were larger than women and had more clips placed at the time of procedure, which is congruent with observations from the German TRAMI (Transcatheter Mitral Valve Interventions) registry [14].

The influence of sex on outcomes following percutaneous repair have been evaluated by several large registries [14-17]. Overall, men and women have similar survival in the intermediate term following percutaneous repair [15-17]. However, these studies have included patients with primary mitral regurgitation therefore the results of patients with functional MR remains unclear. Published data also suggests that left ventricle remodelling is different between men and women with systolic or diastolic dysfunction, which is particularly relevant in patients with functional MR [7-9].

One other observation from this study was that the post procedure MR grade appeared stable after the intervention. Although 10% of patients had persistent severe MR post procedure, overall freedom from severe MR was 86% at 1-year. And this did not appreciably change at 2-

years thereby suggesting percutaneous repair of functional MR is stable over the intermediate term. Although not only addressing functional MR, 5-year data from the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study) study also alludes to stability of Mitra clip therapy over time [18].

The survival of patients in this study also compares favorably to studies evaluating survival amongst patients with functional MR [4,5,19]. Indeed, 1-year survival in high-risk patients as part of the EVEREST II Investigational Device Exemption program was 74%, which compares to 70% in this cohort [18]. Importantly, the survival of 54% 2-years post procedure underscores the poor long-term survival of patients with severe functional MR.

The reason why women were more likely to have recurrent severe MR after percutaneous mitral repair remains incompletely understood. In this study, men and women were of similar NYHA functional class; however, they had a proportionately larger LV size even when considering differences between patient groups in regards to their body surface area or LV ejection fraction. This underscores the observation that women are more likely to have LV enlargement before a corresponding decrease in LV function [7-8]. As such, the influence on functional MR and its subsequent repair may be worse in women. These data highlights the importance of assessing LV size in women with symptomatic heart failure and MR.

Limitations

There are a variety of limitations of this study. This study is a single center experience and is comprised of non-randomized data. Although women were more likely than men to have recurrent severe MR, the association is not conclusively causative and may be influenced by unknown confounders. Furthermore, patients in this study received the Mitra clip NT/NTR

214 device. Although the XTR is often used for the treatment of functional MR since its release due
215 to its longer grasping arms, the resurgence of the NT, as well as its wide version, in the 4th
216 generation release of the Mitra clip may suggests that these data may be relevant in guiding the
217 treatment of patients with functional MR [20]. Data from the pre-market study remains yet to be
218 published.

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220 Nevertheless, this study comprises a large cohort of consecutive patients who have undergone
221 percutaneous repair of functional MR. These data provide insight not only on the intermediate
222 outcome of patients with functional MR, but also addresses the role of sex on outcomes.

223 **Table 1. Patient demographics**

	Female (N=70)	Male (N=105)	p-value
<i><u>Demographic Features</u></i>			
Age (years)	74.0±11.6	72.9±11.3	0.5
Body surface area (m ²)	1.73±0.22	1.93±0.23	<0.001
Diabetes Mellitus	13 (19%)	37 (35%)	0.02
Hypertension	45 (64%)	74 (70%)	0.4
NYHA			0.2
II	17 (24%)	14 (13%)	
III	42 (60%)	69 (66%)	
IV	11 (16%)	22 (21%)	
Preoperative atrial fibrillation	41 (59%)	64 (61%)	0.8
Society of Thoracic Surgeons			
Risk of mortality	5.8 (3.0-17.0)	6.9 (3.0-14.6)	0.5
<i><u>Echocardiographic Features</u></i>			
LV end-diastolic dimension (mm)	53.5±16.5	60.0±15.8	0.03
LV end-systolic dimension (mm)	43.9±16.3	51.4±15.9	0.01
LV ejection fraction	35.8±12.6	30.3±13.6	0.05
Mitral annular calcification	15 (21%)	15 (14%)	0.2
Pulmonary artery pressure (mm Hg)	49.4±15.9	52.0±15.6	0.5

224 Left ventricle, LV; Society of Thoracic Surgeons, STS

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227 **Table 2. Risk factors associated with recurrent MR $\geq 3+$**
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Variable	Hazard ratio (95% Confidence Interval)	p-value
Body mass index (kg/m ²)	0.9 (0.8-1.1)	0.4
Diabetes Mellitus	4.5 (1.2-17.3)	0.03
Female	4.6 (1.1-18.4)	0.03
Preoperative LV ejection fraction (%)	1.0 (1.0-1.1)	0.9

229 Left ventricle, LV
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