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4 **Impact of sex on outcomes after percutaneous repair of**
5 **functional mitral valve regurgitation**
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41

42 **Abstract**

43

44 **Background**

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

48

49 **Methods**

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

53

54 **Results**

55 Men had a larger body surface area than women ($p < 0.001$), whereas women were more likely
56 than men to have diabetes preoperatively ($p = 0.02$). There were no deaths or instances of single
57 leaflet detachment. Immediate post-procedure MR was $\leq 2+$ in 158 (90%) with a mean trans-
58 mitral valve repair gradient of 3.4 ± 1.0 and 3.5 ± 2.1 mm Hg, respectively for women and men
59 ($p = 0.8$). One- and 2-year freedom from MR $\geq 3+$ was $86.0 \pm 3.5\%$ and $77.6 \pm 5.1\%$, respectively.
60 After adjusting for differences between male and female patients, women were more likely to
61 have recurrent MR $\geq 3+$ (hazard ratio 4.7, 95% confidence interval 1.2-18.4, $p = 0.03$). Upon
62 adjusted analysis, there was also no association between gender and survival ($p = 0.2$). One- and
63 2- year survival was $69.8 \pm 4.3\%$ and $54.3 \pm 5.5\%$, respectively.

64

65 **Conclusion**

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

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70 **Introduction**

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

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

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

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

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99

100 **Methods**

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102 Patients and follow-up

103

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

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110 Procedure

111

112 Procedures were performed in a hybrid operating room after assessment by a Heart Team
113 comprised of interventional cardiology, cardiac surgery, and cardiac anesthesia. Percutaneous
114 mitral repair was performed through standard percutaneous femoral venous puncture, subsequent
115 atrial balloon septostomy, and positioning of the 24Fr steerable guide in the left atrium. Overall,
116 the median number of clips implanted was 2. Female patients received a mean of 1.5 ± 0.6 clips
117 implanted whereas men had 1.8 ± 0.7 clips implanted ($p=0.01$). Fluoroscopic time averaged
118 31.6 ± 15.7 min and was not different between groups (33.2 ± 17.3 min in men versus 29.3 ± 12.8
119 min in women, $p=0.2$).

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121 Statistical analysis

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123 Continuous data are described as a mean \pm standard deviation whereas count data are listed as a
124 number and percentage. Female and male patients were compared in regards to a variety of
125 covariates using either a Students t-test when the data were continuous and normally distributed
126 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].

130 **Results**

131

132 Demographics and Peri-procedural Outcomes

133

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

138 There were no deaths or single leaflet detachment. Immediate post-procedure MR was
139 $\leq 2+$ in 158 (90%) with a mean trans-mitral valve repair gradient of 3.4 ± 1.0 and 3.5 ± 2.1 ,
140 respectively for women and men ($p = 0.8$). At the time of hospital discharge, 99 (57%) had MR
141 $\leq 1+$. Twenty-eight women and 36 men had MR $\geq 2+$ at the time of discharge ($p = 0.4$). Discharge
142 disposition included home in 152 (87%), peripheral hospital in 10 (9%), rehabilitation facility in
143 6 (3%), and a long-term care facility in 2 (1%).

144

145 Echocardiographic Outcomes

146

147 Of the 175 patients, 18 had persistent severe 3-4+ MR after implantation of whom 11 (10% were
148 male and 7 (10%) were female ($p = 0.8$). Overall 25 patients had MR $\geq 3+$ at a mean of 325 days
149 following percutaneous repair. One and 2-year freedom from MR $\geq 3+$ was $86.0 \pm 3.5\%$ and
150 $77.6 \pm 5.1\%$. After adjusting for differences between male and female patients, women were more
151 likely to have recurrent MR $\geq 3+$ (hazard ratio 4.7, 95% confidence interval 1.2-18.4, $p = 0.03$)
152 (Table 2). At most recent follow-up, the mean LV ejection fraction was $34.3 \pm 13.5\%$ and similar
153 between groups ($33.2 \pm 13.85\%$ in men and $36.0 \pm 13.6\%$ in women, $p = 0.3$).

154

155 Clinical Outcomes

156

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 $69.8\pm 4.3\%$ and $54.3\pm 5.5\%$, 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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166 **Comment**
167

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

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

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

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

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

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

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

207

208 Limitations

209

210 There are a variety of limitations of this study. This study is a single center experience and is
211 comprised of non-randomized data. Although women were more likely than men to have
212 recurrent severe MR, the association is not conclusively causative and may be influenced by
213 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.

219

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>Demographic Features</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>Echocardiographic Features</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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