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Sex-Based Differences in Outcomes With Percutaneous Transcatheter Repair of Mitral Regurgitation With the MitraClip System: Transcatheter Valve Therapy Registry From 2011 to 2017

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Circulation: Cardiovascular Interventions

ORIGINAL ARTICLE

Sex-Based Differences in Outcomes With Percutaneous Transcatheter Repair of Mitral Regurgitation With the MitraClip System: Transcatheter Valve Therapy Registry From 2011 to 2017

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BACKGROUND: Women have a higher rate of adverse events after mitral valve surgery. We sought to evaluate whether outcomes after transcatheter edge-to-edge repair intervention by sex have similar trends to mitral valve surgery.

METHODS: The primary outcome was 1-year major adverse events defined as a composite of all-cause mortality, stroke, and any bleeding in the overall study cohort. Patients who underwent transcatheter edge-to-edge repair for mitral regurgitation with the MitraClip system in the Society of Thoracic Surgery/American College of Cardiology Transcatheter Valve Therapy registry were evaluated. Linked administrative claims from the Centers for Medicare and Medicaid Services were used to evaluate 1-year clinical outcomes. Associations between sex and outcomes were evaluated using a multivariable logistic regression model for in-hospital outcomes and Cox model for 1-year outcomes.

RESULTS: From November 2013 to March 2017, 5295 patients, 47.6% (n=2523) of whom were female, underwent transcatheter edge-to-edge repair. Females were less likely to have >1 clip implanted ($P<0.001$) and had a lower adjusted odds ratio of device success (adjusted odds ratio, 0.78 [95% CI, 0.67–0.90]), driven by lower odds of residual mitral gradient <5 mm Hg (adjusted odds ratio, 0.54 [CI, 0.46–0.63]) when compared with males. At 1-year follow-up, the primary outcome did not differ by sex. Female sex was associated with lower adjusted 1-year risk of all-cause mortality (adjusted hazard ratio, 0.80 [CI, 0.68–0.94]), but the adjusted 1-year risk of stroke and any bleeding did not differ by sex.

CONCLUSIONS: No difference in composite outcome of all-cause mortality, stroke, and any bleeding was observed between females and males. Adjusted 1-year all-cause mortality was lower in females compared with males.

Key Words: follow-up studies ■ mitral valve ■ mortality ■ sex ■ transcatheter mitral valve repair

See Editorial by Anwaruddin and Asgar

Mitral regurgitation (MR) is the most common valvular heart disease and characterized by a poor prognosis.[1] In 2013, percutaneous transcatheter mitral valve repair (transcatheter edge-to-edge repair [TEER]) using the MitraClip system (Abbott Vascular, Menlo Park, CA) was approved as commercial therapy

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WHAT IS KNOWN

- Sex differences exist in mitral valve anatomy, diagnosis, and treatment.

WHAT THE STUDY ADDS

- Although females are less likely to have >1 clip implanted due to higher residual gradients across the mitral valve, degree of postimplant mitral regurgitation does not differ when compared with males undergoing transcatheter mitral valve repair.
- Although females experience a lower adjusted odds of device success and more procedure-related complications, they have a lower adjusted 1-year mortality rate when compared with males undergoing transcatheter mitral valve repair.

Nonstandard Abbreviations and Acronyms

MR	mitral regurgitation
STS	Society of Thoracic Surgery
TEER	transcatheter mitral valve repair
TVT	Transcatheter Valve Therapy

for patients with severe symptomatic, primary MR and used in an investigational context for functional MR.[2,3] Although the prevalence of MR is noted to be similar in males and females in population studies, observational studies demonstrate sex-specific differences in mitral valve morphology/regurgitation mechanisms, and a greater proportion of patients undergoing surgical mitral valve repair are male versus female.[1,4] Female sex is also independently associated with lower long-term survival following mitral valve surgery.[5,6]

While small European registries have demonstrated safety and efficacy of TEER in both sexes,[7,8] data from larger US-based cohorts are lacking. This study aims to examine sex-based differences in patients undergoing TEER with the MitraClip system using the Society of Thoracic Surgery (STS)/American College of Cardiology Transcatheter Valve Therapy (TVT) registry.

METHODS

STS/American College of Cardiology TVT Registry and Study Cohort

The authors declare that all supporting data are available within the article.

The STS/American College of Cardiology TVT Registry was established in 2011 and is periodically audited and includes comprehensive baseline information, as well as 30-day and 1-year follow-up data. The registry data are linked with Medicare administrative claims for detection of events requiring hospitalization. This methodology of data acquisition, event ascertainment, and analysis in the STS/American College of Cardiology TVT Registry has been previously published in detail.[9]

All patients who underwent commercial therapy with the MitraClip system since the initial US Food and Drug Administration approval on October 24, 2013, and who were enrolled in the TVT registry through March 2017 were included in the present investigation. Patients who underwent implantation as part of a research study or received concomitant transcatheter aortic valve replacement were excluded. The clinical records of the TVT registry were linked to Medicare administrative claims data using direct patient identifiers. The Duke Clinical Research Institute serves as the data analysis center and has institutional review board approval to analyze the aggregate deidentified data for research purposes. The present investigation has been granted a waiver of the requirement to obtain informed consent. Data from TVT registry were used to determine procedural and in-hospital outcomes. For clinical events after hospital discharge (ie, 30-day and 1-year outcomes), data from the Centers for Medicare and Medicaid administrative claims were used.

Primary and Secondary Outcomes

The primary outcome was 1-year major adverse events defined as a composite of all-cause mortality, stroke, and any bleeding in the overall study cohort. These events were identified from the Centers for Medicare and Medicaid database. Stroke events reported in the TVT registry were defined per the Mitral Valve Academic Research Consortium[10] criteria and adjudicated by a board-certified cardiologist at the Duke Clinical Research Institute.

Secondary outcomes included individual components of the primary outcome at 1-year follow-up and the following in-hospital outcomes: all-cause mortality, stroke, major bleeding, major vascular complication, readmission for heart failure, adverse event related to device or delivery system, and device success. In accordance with the Mitral Valve Academic Research Consortium, standard definitions were used for the collection of data elements in the registry.[10]

Statistical Analyses

Groups were evaluated by sex. Categorical data are described as frequencies (percentages) and were compared using the Pearson χ^2 test. Continuous variables are presented as median (interquartile range) and were compared using the Wilcoxon rank-sum test.

Association between sex and in-hospital outcomes was examined using logistic regression and presented as estimated odds ratio and 95% CIs. The Generalized Estimating Equation method with exchangeable working correlation structure was used to account for within-hospital clustering, as patients at the same hospital are more likely to have similar responses relative to patients in other hospitals (ie, within-center correlation for response). The unadjusted cumulative incidence of outcomes from the index procedure date through 1 year were examined using the log-rank test and Kaplan-Meier methods for death and utilizing Gray method to account for mortality as a competing risk for nonfatal outcomes. Estimated hazard ratios for 1-year outcomes were generated by a Cox proportional hazard model, with robust variance estimation to account for within-center clustering.

All modeling assumptions were tested and transformations performed when needed.

The following variables were adjusted for in the regression models: age, race, ethnicity, body surface area, prior myocardial infarction, prior coronary revascularization, number of prior cardiac operations (2 versus 1 versus 0), diabetes, any atrial fibrillation or flutter, prior stroke or transient ischemic attack, prior peripheral arterial disease, carotid stenosis, dialysis, severe chronic lung disease, home oxygen, endocarditis, smoking status, New York Heart Association functional class IV, glomerular filtration rate, hemoglobin, left ventricular ejection fraction, left main stenosis >50%, hostile chest, porcelain aorta, aortic insufficiency (moderate/severe versus other), and procedural acuity (elective versus urgent versus shock or inotropes or assist device versus emergency or salvage or cardiac arrest). One-year models also included the following additional variables: hypertension, immunocompromised status, left ventricular systolic dimension, left ventricular diastolic dimension, triple vessel disease, prior mitral valve procedure, prior nonmitral valve procedure, mitral etiology (degenerative versus functional), mean mitral valve gradient, mitral leaflet calcification, mitral annular calcification, and years of performing procedure (site level). The majority of the variables in the registry were missing at a rate of <2%, with the exception of detailed echocardiographic data. For missing continuous measures, the missing measure was set to the median value for that measure. For missing categorical measures, the missing was set to No.

Significance was tested at a 2-sided α-level of 0.05. All statistical analyses were performed using SAS 9.4 (SAS Institute, Inc, Cary, NC). All analyses were performed at the Duke Clinical Research Institute.

RESULTS

Baseline Characteristics

During the study period from November 2013 to March 2017, a total of 5295 patients underwent TEER, including 2523 (47.6%) female and 2772 (52.4%) male patients. Female patients were older than male patients, less likely to be of White race, and had a lower body surface area. Female patients had lower prevalence of coronary artery disease, coronary revascularization with either percutaneous coronary intervention or coronary artery bypass graft surgery, cardiomyopathy, and prior cardiac surgery compared with male patients. Comorbidities, including diabetes, peripheral artery disease, end-stage renal disease on dialysis, and hostile chest, were also lower among females compared with males, while home oxygen use was higher in females than males. Prevalence of New York Heart Association III-IV was higher, and health status as assessed by the Kansas City Cardiomyopathy Questionnaire was poorer among females compared with males (Table 1).

On transthoracic echocardiogram, females had a higher left ventricular ejection fraction, smaller left ventricular dimensions, and smaller left atrial volume compared with males. Though no difference was observed in the degree of MR severity, females had a smaller effective regurgitant orifice area when compared with males. Females also had a smaller mitral valve area with more leaflet calcification, mitral annular calcification, and a higher baseline mitral valve gradient when compared with males. Overall, the median STS-Predicted Risk of Mortality for mitral valve repair was not different by sex (Table 1).

Procedural Characteristics and Complications

Both male and female patients predominantly underwent TEER for degenerative MR (Table 1). While functional MR only made up less than a fifth of the cohort, this etiology was less prevalent in females compared with males (Table 1). General anesthesia and femoral access were used in almost all the cases, and most procedures were undertaken electively (91%), though female patients had a higher prevalence of urgent/emergent procedures when compared with male patients (Table 2).

Female patients were less likely to have >1 clip implanted as compared with male patients, but their degree of postimplant MR did not differ by sex. Mean gradient across the mitral valve remained higher in females versus males. Although the incidence of any intra- or postprocedural adverse event did not differ by sex, female patients had a higher rate of conversion to open heart surgery, cardiac perforation, retroperitoneal bleeds, and blood transfusion when compared with male patients (Table 2).

In-Hospital Outcomes

Following TEER, the unadjusted in-hospital composite end point of all-cause mortality, stroke, and major bleeding was higher among females than males. This was driven by a higher rate of major bleeding among females than males. Although females had a lower rate of adverse events related to the device or delivery system when compared with males, they also had a lower rate of device success driven by a lower rate of achieving a mitral valve gradient <5 mm Hg post-implant, lower rate of freedom from unplanned cardiac surgery, and higher rate of readmission for heart failure (Table 3).

After adjustment for covariates, however, female sex did not emerge as an independent predictor of in-hospital adverse events, with the exception of lower procedural success (adjusted odds ratio, 0.78 [95% CI, 0.67–0.90]), again, driven by lower rate of achieving a mitral valve gradient <5 mm Hg post-implant (adjusted odds ratio, 0.54 [CI, 0.46–0.63]; Table 4).

One-Year Outcomes

At 1-year follow-up, the primary composite outcome of mortality, stroke, or any bleeding did not differ by sex. No difference was observed in the unadjusted cumulative incidence rate of mortality (23.2% [CI, 21.4%–25.0%] versus 23.6% [CI, 21.9%–25.3%]; P=0.45) or any bleeding (18.6% [CI, 17.0%–20.2%] versus 18.7% [CI, 17.2%–20.2%]; P=0.85). However, unadjusted

Table 1. Baseline Characteristics

	Overall (n=5295)	Male (n=2772)	Female (n=2523)	*P* value
Demographic variables				
Age, y	83 (77–87)	82 (76–86)	83 (77–87)	<0.001
Body surface area	1.8 (1.6–2.0)	1.9 (1.8–2.1)	1.6 (1.5–1.8)	<0.001
History and risk factors				
Cardiac history				
Coronary artery disease	2727 (51.5)	1726 (62.3)	1001 (39.7)	<0.001
Prior myocardial infarction	1357 (25.6)	860 (31.0)	497 (19.7)	<0.001
Prior percutaneous coronary intervention	1656 (31.3)	1040 (37.5)	616 (24.4)	<0.001
Prior coronary artery bypass surgery	1585 (29.9)	1159 (41.8)	426 (16.9)	<0.001
Cardiomyopathy	1920 (36.3)	1161 (41.9)	759 (30.1)	<0.001
Other risk factors and comorbidities				
Hypertension	4566 (86.2)	2378 (85.8)	2188 (86.7)	0.32
Diabetes	1334 (25.2)	756 (27.3)	578 (22.9)	<0.001
Atrial fibrillation/flutter	3434 (64.9)	1834 (66.2)	1600 (63.4)	0.04
Prior stroke/transient ischemic attack	882 (16.7)	468 (16.9)	414 (16.4)	0.64
Peripheral artery disease	988 (18.7)	585 (21.1)	403 (16.0)	<0.001
End-stage renal disease on dialysis	152 (2.9)	95 (3.4)	57 (2.3)	0.01
Preprocedure status				
New York Heart Association class				<0.001
I	93 (1.8)	50 (1.8)	43 (1.7)	
II	716 (13.5)	420 (15.2)	296 (11.7)	
III	3317 (62.6)	1719 (62.0)	1598 (63.3)	
IV	1128 (21.3)	563 (20.3)	565 (22.4)	
Heart failure within 2 wk	4397 (83.0)	2316 (83.5)	2081 (82.5)	0.30
STS-predicted risk of mortality for mitral valve repair, %	6.2 (4.1–9.5)	6.2 (4.0–9.4)	6.3 (4.1–9.5)	0.26
Echocardiographic variables				
Left ventricular ejection fraction, %	55 (41–60)	53 (38–60)	58 (47–63)	<0.001
Left ventricular ejection fraction categories				<0.001
<30%	498 (9.6)	333 (12.3)	165 (6.7)	
30%–45%	1140 (22.1)	704 (26.0)	436 (17.7)	
>45%	3532 (68.3)	1672 (61.7)	1860 (75.6)	
Degenerative MR	4633 (87.5)	2413 (87.0)	2220 (88.0)	0.30
Functional MR	930 (17.6)	524 (18.9)	406 (16.1)	0.007
Effective regurgitant orifice area, cm^2	0.4 (0.3–0.6)	0.4 (0.3–0.7)	0.4 (0.2–0.6)	<0.001
Mitral valve mean gradient, mm Hg	2 (2–4)	2 (2–3)	3 (2–4)	<0.001
Mitral valve area, cm^2	4.1 (3.0–5.1)	4.2 (3.0–5.5)	4.0 (3.0–4.9)	<0.001
Mitral leaflet calcification	1085 (20.5)	526 (19.0)	559 (22.2)	0.004
Mitral annular calcification	1989 (37.6)	969 (35.0)	1020 (40.4)	<0.001
Tricuspid regurgitation				<0.001
None	307 (5.8)	184 (6.7)	123 (4.9)	
Trace/trivial	511 (9.7)	286 (10.4)	225 (9.0)	
1+/mild	1716 (32.7)	980 (35.7)	736 (29.4)	
2+/moderate	1855 (35.3)	915 (33.3)	940 (37.5)	
3–4+/severe	865 (16.5)	381 (13.9)	484 (19.3)	

Continuous variables are presented as medians with interquartile percentiles, and categorical variables are expressed as frequencies (percentages). MR indicates mitral regurgitation; and STS, Society of Thoracic Surgery.

cumulative incidence rate of stroke was higher among females compared with males (3.0% [CI, 2.4%–3.8%] versus 2.1% [CI, 1.6%–2.7%]; *P*=0.008; Table 5).

After adjustment for demographics and comorbidities, the primary composite outcome of mortality, stroke, or any bleeding, as well as any bleeding alone, continued to

Table 2. Procedural Characteristics and Complications

	Overall (n=5295)	Male (n=2772)	Female (n=2523)	*P* value
Procedural variables				
Procedure status				0.01
Elective	4816 (91.0)	2547 (91.9)	2269 (89.9)	
Urgent	460 (8.7)	215 (7.8)	245 (9.7)	
Emergent	15 (0.3)	9 (0.3)	6 (0.2)	
Salvage	4 (0.1)	1 (0.0)	3 (0.1)	
No. of leaflet clips implanted				<0.001
0	153 (2.9)	70 (2.5)	83 (3.3)	
1	2864 (54.1)	1273 (45.9)	1591 (63.1)	
2+	2278 (43.0)	1429 (51.6)	849 (33.7)	
Procedure time, min; median (IQR)	118 (84–159)	124 (87–166)	112 (81–151)	<0.001
Postimplant echocardiogram				
MR				0.96
None	93 (1.8)	49 (1.8)	44 (1.7)	
Trace/trivial	777 (14.7)	406 (14.6)	371 (14.7)	
1+ (mild)	2664 (50.3)	1385 (50.0)	1279 (50.7)	
2+ (moderate)	1451 (27.4)	766 (27.6)	685 (27.2)	
3+ (moderate/severe)	148 (2.8)	78 (2.8)	70 (2.8)	
4+ (severe)	162 (3.1)	88 (3.2)	74 (2.9)	
Mitral valve mean gradient, mm Hg	3.0 (2.0–5.0)	3.0 (2.0–4.0)	4.0 (3.0–5.0)	<0.001
Intraprocedural adverse events/complications				
Occurrence of an intra- or postprocedure event	678 (12.8)	343 (12.4)	335 (13.3)	0.33
Cardiac				
Conversion to open heart surgery	26 (0.5)	7 (0.3)	19 (0.8)	0.009
Atrial fibrillation (new onset)	60 (1.1)	27 (1.0)	33 (1.3)	0.25
Cardiac arrest	59 (1.1)	26 (0.9)	33 (1.3)	0.20
Myocardial infarction	2 (0.0)	1 (0.0)	1 (0.0)	0.95
Perforation	42 (0.8)	10 (0.4)	32 (1.3)	<0.001
Valve				
Mitral leaflet injury (detected during surgery or echo)	18 (0.3)	11 (0.4)	7 (0.3)	0.46
Mitral subvalvular injury (during surgery or by echo)	6 (0.1)	5 (0.2)	1 (0.0)	0.22
Mitral valve reintervention	32 (0.6)	17 (0.6)	15 (0.6)	0.93
Renal				
New requirement for dialysis	34 (0.6)	16 (0.6)	18 (0.7)	0.54
Neuro				
In-hospital transient ischemic attack	5 (0.1)	4 (0.1)	1 (0.0)	0.22
In-hospital stroke*	31 (0.6)	15 (0.5)	16 (0.6)	0.66
Bleed/vascular				
In-hospital bleeding*				0.08
No major or life-threatening bleeding	5098 (96.3)	2681 (96.7)	2417 (95.8)	
Major bleeding event (but not life threatening)	132 (2.5)	60 (2.2)	72 (2.9)	
Life-threatening or disabling bleeding	65 (1.2)	31 (1.1)	34 (1.3)	
Bleeding at access site	47 (0.9)	25 (0.9)	22 (0.9)	0.91
Hematoma at access site	68 (1.3)	30 (1.1)	38 (1.5)	0.17
Retroperitoneal bleeding	22 (0.4)	3 (0.1)	19 (0.8)	<0.001
Blood transfusion	498 (9.4)	216 (7.8)	282 (11.2)	<0.001
Transseptal complication	23 (0.4)	10 (0.4)	13 (0.5)	0.39
Major vascular access complication	17 (0.3)	9 (0.3)	8 (0.3)	0.96
Minor vascular access	35 (0.7)	17 (0.6)	18 (0.7)	0.65

Continuous variables are presented as medians with interquartile percentiles, and categorical variables are expressed as frequencies (percentages). IQR indicates interquartile range; and MR, mitral regurgitation.

*Defined per the Valve Academic Research Consortium 2 criteria.

Table 3. In-Hospital Outcomes

	Overall (n=5295)	Male (n=2772)	Female (n=2523)	*P* value
Composite outcome of in-hospital mortality, stroke, and major bleeding*	746 (14.1)	352 (12.7)	394 (15.6)	0.002
Mortality	114 (2.2)	59 (2.1)	55 (2.2)	0.90
Stroke	31 (0.6)	15 (0.5)	16 (0.6)	0.66
Major bleeding*	667 (12.6)	311 (11.2)	356 (14.1)	0.002
Major vascular complication	17 (0.3)	9 (0.3)	8 (0.3)	0.96
Readmission for heart failure	415 (7.8)	195 (7.0)	220 (8.7)	0.023
Adverse event related to device or deliver system	102 (1.9)	65 (2.3)	37 (1.5)	0.02
Device success	2679 (50.6)	1502 (54.2)	1177 (46.7)	<0.001
Postimplant MR ≤1+	3534 (66.7)	1840 (66.4)	1694 (67.1)	0.56
Mitral valve mean gradient <5 mm Hg	3871 (73.1)	2203 (79.5)	1668 (66.1)	<0.001
No in-hospital mortality	5181 (97.8)	2713 (97.9)	2468 (97.8)	0.90
No cardiac surgery	5269 (99.5)	2765 (99.7)	2504 (99.2)	0.009
Discharge location among discharged alive				<0.001
Home	4437 (85.6)	2403 (88.6)	2034 (82.4)	
Extended care	473 (9.1)	200 (7.4)	273 (11.1)	
Other acute care hospital	20 (0.4)	13 (0.5)	7 (0.3)	
Nursing home	197 (3.8)	76 (2.8)	121 (4.9)	
Hospice	23 (0.4)	8 (0.3)	15 (0.6)	
Other	31 (0.6)	13 (0.5)	18 (0.7)	
Length of stay, d	2.0 (1.0,4.0)	2.0 (1.0,4.0)	2.0 (1.0,5.0)	0.001
Discharge medications				
Aspirin alone	2152 (41.2)	1151 (42.1)	1001 (40.2)	0.18
Aspirin and P2Y12 inhibitor	1795 (34.3)	976 (35.6)	819 (32.9)	0.04
Anticoagulants	2691 (51.5)	1454 (53.1)	1237 (49.8)	0.02
ACE inhibitor/angiotensin receptor blockade	2143 (42.8)	1166 (44.4)	977 (40.9)	0.01
β-Blocker	3734 (71.9)	1944 (71.4)	1790 (72.4)	0.39
Aldosterone antagonists	566 (10.7)	311 (11.3)	255 (10.1)	0.19
Loop diuretics	3741 (70.9)	1932 (69.9)	1809 (72.0)	0.09
Thiazide diuretics	258 (4.9)	149 (5.4)	109 (4.3)	0.075

Continuous variables are presented as medians with interquartile percentiles, and categorical variables are expressed as frequencies (percentages). ACE indicates angiotensin-converting enzyme; and MR, mitral regurgitation.

*Defined per the Mitral Valve Academic Research Consortium criteria: major bleed is defined as a drop in the hemoglobin of ≥3.0 g/dL or requiring transfusion of ≥3 U of whole blood or packed red blood cells.

not differ by sex (Table 6). However, after adjustment for covariates of interest, female patients had a lower 1-year mortality when compared with male patients (adjusted hazard ratio, 0.80 [CI, 0.68–0.94]; *P*=0.008), and no difference was observed for 1-year stroke by sex (adjusted hazard ratio, 1.09 [CI, 0.66–1.82]; *P*=0.73; Table 6; Figure). The etiology of mitral valve disease (degenerative versus functional) did not modify the association between sex and the primary composite outcome (P_{int}=0.88).

DISCUSSION

This large observational analysis of sex-based differences in outcomes after TEER with the MitraClip system demonstrated several key findings. First, there is an even proportion of females to males who undergo TEER. Second, though adjusted device success rate was lower in females compared with males (driven by lower odds of achieving mean postimplant gradient <5 mm Hg across the mitral valve), there were no sex-based differences in the postimplant reduction of MR. Third, while unadjusted rate of stroke and readmission for heart failure were higher in females than males, there was no significant sex-based association observed after adjustment for covariates of interest. Finally, female patients have a lower adjusted 1-year mortality compared with male patients; however, there are no sex-based differences in the unadjusted 1-year composite outcome of all-cause mortality, stroke, and any bleeding.

The TVT registry study is the largest real-world database of MitraClip therapy reported to date and

Table 4. Association Between Female Sex and In-Hospital Outcomes

	Unadjusted				Adjusted			
		95% CI				95% CI		
Event	Odds ratio	Lower	Upper	*P* value	Odds ratio	Lower	Upper	*P* value
Composite outcome of in-hospital mortality, stroke, and major bleeding*	1.25	1.10	1.42	<0.001	1.00	0.82	1.21	0.99
Mortality	1.02	0.73	1.43	0.91	†	†	†	†
Stroke	1.17	0.64	2.14	0.61	†	†	†	†
Major bleeding*	1.28	1.11	1.46	<0.001	1.02	0.83	1.25	0.88
Major vascular complication	0.98	0.42	2.26	0.96	†	†	†	†
Readmission for heart failure	1.23	1.01	1.50	0.031	1.22	0.96	1.56	0.10
Adverse event related to device or deliver system	0.62	0.41	0.95	0.03	0.63	0.35	1.13	0.12
Device success	0.76	0.67	0.85	<0.001	0.78	0.67	0.90	<0.001
Postimplant MR ≤1+	1.05	0.94	1.17	0.39	1.08	0.94	1.24	0.28
Mitral valve mean gradient <5 mm Hg	0.51	0.45	0.59	<0.001	0.54	0.46	0.63	<0.001
No cardiac surgery	0.33	0.15	0.75	0.008	†	†	†	†

The multivariable logistic regression model adjusted for age, race, ethnicity, body surface area, prior myocardial infarction, prior coronary revascularization, number of prior cardiac operations (2 vs 1 vs 0), diabetes, any atrial fibrillation or flutter, prior stroke or transient ischemic attack, prior peripheral arterial disease, carotid stenosis, dialysis, severe chronic lung disease, home oxygen, endocarditis, smoking status, New York Heart Association functional class IV, GFR, hemoglobin, left ventricular ejection fraction, left main stenosis >50%, hostile chest, porcelain aorta, aortic insufficiency (moderate/severe vs other), and procedural acuity (elective vs urgent vs shock or inotropes or assist device vs emergency or salvage or cardiac arrest). The odds ratios and 95% CIs for odds ratio were presented for sex to examine the variation of the strength of its influence on outcomes. GFR indicates glomerular filtration rate; and MR, mitral regurgitation.

*Defined per the Mitral Valve Academic Research Consortium criteria: major bleed is defined as a drop in the hemoglobin of ≥3.0 g/dL or requiring transfusion of ≥3 U of whole blood or packed red blood cells.

†Too few events.

demonstrates no sex-based disparity in patients who are treated with TEER in the United States. Females have a better representation in the TVT database than pivotal randomized controlled trials (47% TVT registry versus 38% in the EVEREST II trial [Endovascular Valve Edge-to-Edge Repair Study]).[11] This underrepresentation of female in EVEREST II was also observed in 2 large European registries—37% in the European Sentinel Registry[12] and 36% in the ACCESS-Europe, a 2-phase observational study of the MitraClip system.[13] Female patients were likely underrepresented in randomized trials due to their older age and poorer baseline health status when compared with males.

Another interesting finding from this study is the lower device success rate in females as compared with males. This by definition was driven by higher postprocedure mitral gradients. Whether the higher residual gradients are due to baseline mitral valve anatomy or a similar degree of residual MR resulting in higher gradients across a smaller baseline mitral valve area remains unknown. In the current study, females had a higher rate of mitral stenosis at baseline with higher mean gradients and smaller valve areas likely due to lower body surface area and observed higher rates of mitral leaflet calcification and mitral annular calcification, when compared with males. These findings are similar to those reported in a large cohort of patients who underwent surgical mitral valve repair where females had a lower procedural success rate when compared with males that was thought to be due to the higher prevalence of increased leaflet calcification and mixed regurgitation/stenosis.[5] The current study only represents the early MitraClip systems. Appropriate selection of the different available newer generation MitraClip systems (NTR, XTr, and G4) may be important in patients with increased baseline gradient as XTr has a theoretical increase risk of higher residual mean gradient due to longer clip arms. However, the mean transvalvular gradient (3.5 mm Hg) of XTr in an early experience from a European multicenter observational study[14] was comparable with those reported in the initial experience with commercial TEER in the United States (4.0 mm Hg)[15] and the European Sentinel Registry (3.4 mm Hg).[12]

Although surgical cohorts have previously demonstrated poor clinical outcomes in females who undergo mitral valve surgery for the treatment of severe MR when compared with their male counterparts, data on sex-related outcomes following TEER are limited.[5,16] While few small series showed no difference in outcomes by sex after TEER,[7,8] our large cohort demonstrated a lower adjusted 1-year mortality in females compared with males. These data are consistent with one of the largest European cohorts of 592 patients, which demonstrated a higher long-term mortality in males versus females. The underlying mechanism of lower adjusted risk of 1-year mortality after TEER in females versus males, however, remains unclear. Females were more symptomatic than males with a higher prevalence of New York Heart Association class III-IV status and poorer baseline health status,

Table 5. Unadjusted Cumulative Incidence Rates of 1-Year Outcomes

		All (n=5295)			Male (n=2772)			Female (n=2523)			*P* value
		95% limit			95% limit			95% limit			Male vs female
Event		Rate	Lower	Upper	Rate	Lower	Upper	Rate	Lower	Upper	
Composite of mortality, stroke, and any bleeding	1 mo	12.3%	11.4%	13.2%	12.7%	11.5%	14.1%	11.9%	10.8%	13.2%	0.71
	3 mo	20.0%	18.9%	21.1%	20.7%	19.2%	22.3%	19.6%	18.2%	21.1%	
	6 mo	26.7%	25.5%	27.9%	27.6%	25.8%	29.4%	26.2%	24.6%	27.9%	
	9 mo	32.0%	30.7%	33.3%	32.4%	30.6%	34.3%	31.8%	30.1%	33.7%	
	12 mo	36.5%	35.1%	38.9%	36.5%	34.5%	38.5%	36.5%	34.6%	38.5%	
Mortality	1 mo	4.5%	4.0%	5.1%	4.2%	3.5%	5.0%	4.8%	4.0%	5.7%	0.45
	3 mo	9.9%	9.1%	10.7%	9.5%	8.4%	10.6%	10.3%	9.2%	11.5%	
	6 mo	15.0%	14.1%	16.0%	14.8%	13.5%	16.2%	15.2%	13.9%	16.7%	
	9 mo	19.6%	18.5%	20.8%	19.7%	18.2%	21.3%	19.6%	18.0%	21.2%	
	12 mo	23.4%	22.2%	24.6%	23.6%	21.9%	25.3%	23.2%	21.4%	25.0%	
Stroke	1 mo	1.0%	0.8%	1.3%	0.9%	0.6%	1.3%	1.1%	0.8%	1.6%	0.008
	3 mo	1.3%	1.0%	1.6%	1.1%	0.7%	1.5%	1.5%	1.1%	2.1%	
	6 mo	1.7%	1.4%	2.1%	1.5%	1.1%	2.0%	2.0%	1.5%	2.6%	
	9 mo	2.2%	1.9%	2.7%	1.9%	1.4%	2.4%	2.6%	2.1%	3.4%	
	12 mo	2.5%	2.1%	3.0%	2.1%	1.6%	2.7%	3.0%	2.4%	3.8%	
Any bleeding	1 mo	8.0%	7.3%	8.8%	8.0%	7.1%	9.1%	8.0%	7.0%	9.2%	0.85
	3 mo	11.8%	10.9%	12.7%	11.8%	10.7%	13.1%	11.7%	10.5%	13.0%	
	6 mo	14.7%	13.7%	15.7%	14.5%	13.2%	15.9%	14.8%	13.5%	16.3%	
	9 mo	16.5%	15.5%	17.5%	16.5%	15.1%	17.9%	16.5%	15.1%	18.0%	
	12 mo	18.6%	17.5%	19.7%	18.7%	17.2%	20.2%	18.6%	17.0%	20.2%	

more likely to undergo urgent/emergent procedure, and had a higher rate of clinically important periprocedural events such as conversion to open heart surgery, cardiac perforation, and retroperitoneal bleeds. Females also had a trend for higher rates of readmission for heart failure. This disparity in outcomes may partially reflect the findings that (1) the degree of residual MR post-TEER did not differ by sex, (2) complication rates were numerically low at <2% while the cumulative incidence unadjusted mortality rate at 1 year is numerically high at about 23%, and (3) the lower prevalence of important comorbidities (coronary artery disease, peripheral vascular disease, diabetes, reduced left ventricular ejection fraction, and renal dysfunction) in females compared with males. Furthermore, females in this cohort had more concomitant severe tricuspid valve disease and higher left ejection fraction, which may suggest an additional contribution of diastolic heart failure, rather than mitral valve disease alone, to these higher heart failure readmission rates observed in females versus males. However, this remains speculative, and further study is needed for both reproducibility of these findings and to better delineate the potential mechanisms of benefit of

Table 6. Association Between Female Sex and 1-Year Outcomes

	Unadjusted				Adjusted			
	Hazard ratio	95% CI		*P* value	Hazard ratio	95% CI		*P* value
Event		Lower	Upper			Lower	Upper	
Composite outcome of mortality, stroke, and any bleeding	1.07	0.96	1.18	0.22	1.04	0.91	1.18	0.62
Mortality	1.00	0.88	1.13	0.96	0.80	0.68	0.94	0.008
Stroke	1.44	0.99	2.08	0.05	1.09	0.66	1.82	0.73
Any bleeding	1.00	0.88	1.15	0.95	0.98	0.81	1.18	0.82

The multivariable model was adjusted for age, race, body surface area, prior myocardial infarction, prior revascularization, prior cardiac operations (2 vs 1 vs 0), hypertension, diabetes, any atrial fibrillation or flutter, prior stroke or transient ischemic attack, prior peripheral arterial disease, carotid stenosis, dialysis, severe chronic lung disease, home oxygen, immunocompromised status, endocarditis, current/recent smoker, New York Heart Association functional class IV, GFR, hemoglobin, left ventricular ejection fraction, left ventricular systolic internal dimension, left ventricular diastolic internal dimension, left main stenosis >50%, triple vessel disease, hostile chest, porcelain aorta, prior mitral valve procedure, prior nonmitral valve procedure, mitral etiology (degenerative vs functional), mean mitral valve gradient, mitral leaflet calcification, mitral annular calcification, aortic insufficiency (moderate/severe vs other), procedural acuity (elective vs urgent vs shock or inotropes or assist device vs emergency or salvage or cardiac arrest), and years performing procedure. GFR indicates glomerular filtration rate.

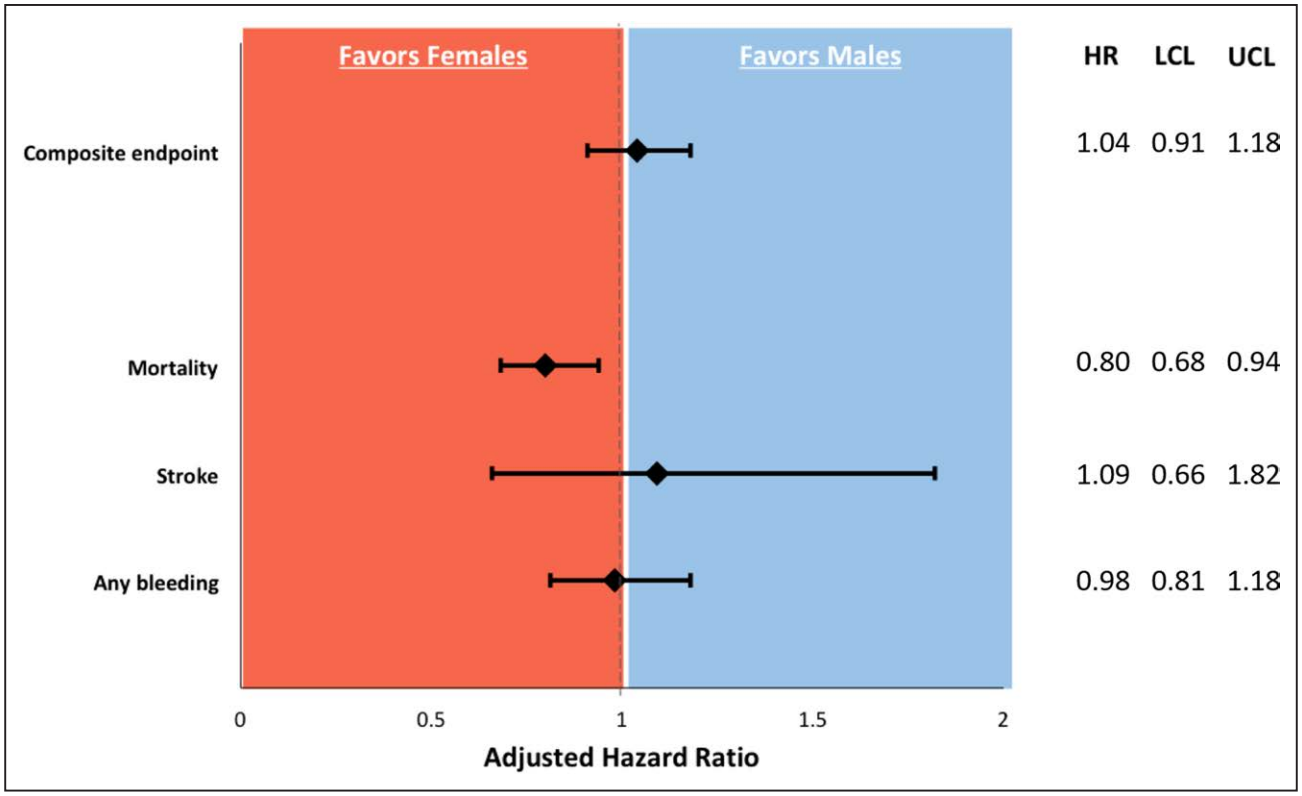

Figure. Forest plot comparing outcomes at 1 y between females and males, adjusted for demographics and comorbidities. HR indicates hazard ratio; LCL, lower confidence limit; and UCL, upper confidence limit.

TEER in females versus males. Furthermore, future investigations should incorporate sex-based differences into potential strategies to optimize procedure-related outcomes after TEER.

Limitations

There are several limitations of this study. First, this is an observational registry study and has the inherent limitations associated with retrospective analyses including residual measured and unmeasured confounding. Previous studies have reported the limitations of Centers for Medicare and Medicaid administrative claims data.[17] However, hospitals are required to participate in the currently utilized TVT registry for Centers for Medicare and Medicaid reimbursement, and the National Cardiovascular Data Registry system that includes the TVT registry has a long track record of data quality and management.[18] Second, the study presents data on only the early generation MitraClip devices (before availability of NTR, XRT, or the G4 system). Finally, the echocardiographic data were not reviewed by an independent core laboratory, and detailed data on mitral valve anatomy, such as mitral leaflet calcification, leaflet tethering, and mitral annular calcification, were missing in more than a third of the patients at baseline. Additionally, there are difficulties in reproducible quantification of MR grade after clip implantation due to the presence of a more complex regurgitant orifice. Nonetheless, this is the largest outcomes-based analysis of a real-world population evaluating sex-based differences in outcomes after TEER to date.

Conclusions

Female patients undergoing TEER with the MitraClip system for severe MR have a different risk profile compared with male patients. Although females had lower odds of procedural success (driven by lower odds of achieving mean mitral gradient <5 mm Hg post-implant) and higher rates of procedural complications, adjusted 1-year all-cause mortality was lower in females compared with males.

ARTICLE INFORMATION

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