JACC: ADVANCES VOL. ■, NO. ■, 2026

ORIGINAL RESEARCH

Sex-Based Differences in Outcomes After Transcatheter Edge-to-Edge Repair for Severe Mitral Regurgitation

Reinhard J. Sauter, MD,[a,b] Tobias Schupp, MD,[a] Manuela Sauter, PhD,[a,b,c,d,e] Tina Sieburg, MD,[a] Simone Britsch, MD,[a] Serena Gregori, MD,[a] Nada Alnaggar, MD,[a] Johannes Patzelt, MD,[f] Michael Behnes, MD,[a] Yingying Zhang, MD,[f,g] Daniel Duerschmied, MD,[a,c,d,e] Christine S. Meyer-Zuern, MD,[h] Harry Magunia, MD,[i] Meinrad P. Gawaz, MD,[f] Tobias Geisler, MD,[f] Ibrahim Akin, MD,[a] Harald F. Langer, MD[a,b,c,d,e]

ABSTRACT

BACKGROUND Whether differences in outcomes exist between men and women after transcatheter edge-to-edge repair is currently unknown.

OBJECTIVES This study investigated sex-based differences in outcomes after mitral transcatheter edge-to-edge repair (M-TEER) for severe mitral regurgitation (MR).

METHODS Patients undergoing M-TEER were included from May 2014 to October 2025. The prognostic impact of sex was investigated with regard to the primary endpoint all-cause mortality at 6 months. The secondary endpoints comprised the reduction of MR, rehospitalization for heart failure (HF) and functional capacity as assessed by the 6-minute walk test.

RESULTS Of the 293 patients enrolled in the study, 119 (40.6%) were women. Compared with men, women had a similar severity of MR independent of its etiology. The prevalence of coronary artery disease (81% vs 65%; $P = 0.002$), and the proportion of functional MR (47% vs 37%) were higher in males. The risk of all-cause mortality at 6 months did not significantly differ in males and females (22% vs 17%; $P = 0.301$; adjusted OR = 0.929; 95% CI: 0.474-1.822; $P = 0.830$), paralleled by comparable rates of HF-related rehospitalization (10% vs 13%; $P = 0.576$; adjusted OR = 1.151; 95% CI: 0.520-2.548; $P = 0.729$). By contrast, women demonstrated a significantly lower functional capacity at baseline ($P = 0.001$). Interestingly, at 6 months mean improvement of functional capacity was similar between male and female patients ($P = 0.778$).

CONCLUSIONS Women undergoing M-TEER presented at a more advanced age and with higher symptom burden than men, potentially reflecting sex-specific clinical trajectories and differing MR etiologies. However, midterm outcomes, including all-cause mortality and HF rehospitalization, were comparable between sexes. (JACC Adv. 2026;■:103120)

From the [a]Cardiology, Haemostaseology and Medical Intensive Care, Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [b]Cardiovascular Systems Biology, Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [c]Helmholtz-Institute for Translational AngioCardioScience (HI-TAC), Mannheim, Germany; [d]European Center for AngioScience (ECAS), Medical Faculty Mannheim, Heidelberg University, Mannheim, Germany; [e]German Center for Cardiovascular Research (DZHK) Partner Site Heidelberg/Mannheim, Mannheim, Germany; [f]University Hospital, Department of Cardiology and Cardiovascular Medicine, Eberhard Karls University Tuebingen, Tuebingen, Germany; [g]University Hospital, Department of Cardiology, Qingdao University, Qingdao, China; [h]Division of Cardiology, Department of Medicine, Inselspital, Bern University Hospital, University of Bern, Bern, Switzerland; and the [i]University Hospital, Department of Anaesthesiology and Intensive Care Medicine, Eberhard Karls University Tuebingen, Tuebingen, Germany.

ISSN 2772-963X https://doi.org/10.1016/j.jacadv.2026.103120

ABBREVIATIONS AND ACRONYMS

6MWT = 6-minute walk test

BSA = body surface area

DMR = degenerative mitral regurgitation

FMR = functional mitral regurgitation

HF = heart failure

LVEDD = left ventricular end-diastolic diameter

MR = mitral regurgitation

M-TEER = mitral transcatheter edge-to-edge repair

PA = pulmonary artery

SpO_2 = oxygen saturation

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Mitral regurgitation (MR) affects >2 million patients in the United States and is associated with significant morbidity and mortality.[1] For primary MR, registry data suggest that women are less likely to undergo MV surgery[2] and will have worse long-term outcomes than men.[3,4] The underlying causes responsible for these differences are not entirely understood. However, to treat male and female patients for MR optimally, a detailed understanding of these causes is crucial.

Mitral transcatheter edge-to-edge repair (M-TEER) was developed to treat patients with MR not suitable for conventional surgery, described in the EVEREST I trial.[5] The clinical application of M-TEER was further established by the EVEREST II trial analyzing more patients and comparing the intervention with surgical valve repair in a randomized fashion, which suggested that percutaneous repair was associated with superior safety and similar improvements in clinical outcomes, with more favorable TEER outcomes for secondary vs primary MR.[6] Since then, the evidence base has significantly expanded with a stronger emphasis on secondary MR, most notably through the COAPT trial, which demonstrated substantial reductions in mortality and heart failure (HF) hospitalizations.[7,8] Five year-follow up, data of the COAPT trial confirmed that M-TEER is a beneficial therapy in these patients, and there was no difference in the prevalence of moderate-severe or severe MR or mortality compared to conventional surgery.[9] Furthermore, recent trials suggest that early treatment of MR offers clinical benefits regarding rehospitalization, mortality, and functional capacity, when patients are treated already at stage C (asymptomatic severe MR) of MR. For instance, early intervention before the onset of irreversible left ventricular remodeling has been shown to significantly improve long-term survival and quality of life compared to a “watchful waiting” strategy.[10-12]

Significant disparities are present between males and females regarding the prevalence, pathophysiological mechanisms, therapeutic responses, and prognostic outcomes across various cardiovascular disorders.[13,14] Despite this obvious central difference, women have been historically underrepresented in cardiovascular trials.[13,15] For MR, analysis of surgical treatment has demonstrated that women often present with more advanced disease stages and higher risk profiles, particularly in the context of ischemic MR, where the choice between repair and replacement remains a clinical challenge and is associated with significant rates of recurrent MR and adverse events.[14] Recent data on the conservative management of functional mitral regurgitation (FMR) suggest comparable survival rates between sexes, with prognosis being more closely tied to frailty than to sex-specific disparities.[16] For interventional therapy, however, only few data exist on whether female and male patients have similar outcomes in MR. The different clinical courses of MR between male and female patients, potential sex-specific anatomical or functional differences, and the role of concomitant comorbidities important for MR pathophysiology and outcomes prompted us to investigate differences between male and female patients regarding treatment, outcomes, and structural issues related to the procedure.

METHODS

STUDY POPULATION. We reviewed 293 data sets of consecutive patients with severe MR who underwent M-TEER using the MitraClip system[17] at the Department of Cardiology and Cardiovascular Medicine of the University Hospital of the University of Tübingen, Tübingen, Germany, from May 2014 until May 2018 and at the University Medical Centre Mannheim, Mannheim, Germany, from October 2024 until October 2025.

An interdisciplinary “heart team” comprising interventional cardiologists and cardiac surgeons determined the eligibility for M-TEER treatment predicated on either the EuroSCORE or the identification of particular surgical risk factors that are not encapsulated within the EuroSCORE methodology. The exclusion criteria for M-TEER were delineated as previously articulated.[18] Prior to the intervention, patients underwent transthoracic echocardiography (TTE), transesophageal echocardiography (TEE), and comprehensive clinical evaluation to accurately

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors’ institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received April 14, 2026; revised manuscript received July 7, 2026, accepted July 11, 2026.

delineate the severity of MR, the morphological characteristics of the mitral valve, and the NYHA functional classification. Patients with HF were mandated to be under optimal medical therapy in accordance with prevailing clinical guidelines for a minimum duration of 3 months prior to the initiation of M-TEER.

The study received endorsement from the Institutional Ethics Committees (260/2015R; 2022-818), and informed consent was duly obtained from all participants.

ECHOCARDIOGRAPHIC ASSESSMENT. TTE and TEE were performed in all patients within 30 days prior to the procedure. TEE was utilized for intraprocedural guidance. Additionally, TTE was performed in all patients prior to hospital discharge. MR severity at baseline and the etiology of the mechanism of regurgitation were determined according to the current EAE (European Association of Echocardiography) guidelines.[19] The technique described by Foster et al[20] was used to assess the severity of MR post-intervention. All echocardiographic sequences were meticulously documented. Echocardiographic examinations were initially evaluated by the performing investigator. Subsequently, all stored loops and images were re-evaluated by 2 additional independent examiners who were blinded to the initial clinical and echocardiographic findings. The average of these 3 independent measurements was computed and utilized as the final conclusive value for statistical analysis.

M-TEER PROCEDURE. The procedure was carried out either in general anesthesia or in deep sedation.[21] After sedation of the patient or induction of general anesthesia, the TEE probe was introduced into the esophagus and vascular access to the femoral vein was established.[22] The MitraClip device was advanced via the transseptal route across the mitral annulus into the left ventricle using fluoroscopic and transesophageal 2- and 3-dimensional echocardiographic guidance.[23] The device was retracted with the 2 arms of the clip extended to capture and subsequently closed, to coapt the mitral leaflets thereby emulating the surgical double-orifice technique introduced by Alfieri et al.[24] Leaflet insertion and the mean mitral pressure gradient were measured before the clip was released. After clip deployment, pulmonary capillary wedge and pulmonary artery (PA) pressure curves, blood samples and final TEE and TTE measurements were obtained a second time.[25]

HEMODYNAMIC MEASUREMENTS. Pressure transponders were calibrated to atmospheric pressure at right atrial height. Arterial blood pressure and arterial blood gas sampling were obtained via cannulation of the radial artery. A Swan-Ganz catheter (7.0-F) (Edwards Lifesciences) was introduced and pulmonary capillary wedge pressure and PA pressure curves before and after M-TEER deployment were obtained as well as PA blood samples. Wedge position was confirmed via fluoroscopy and pulmonary capillary blood sampling in comparison to arterial blood sampling. During M-TEER, we monitored changes in hemodynamics via the indirect Fick method.

ALL-CAUSE MORTALITY AND REHOSPITALIZATION FOR HF. All-cause mortality was defined as death from any cause; survival status was ascertained through electronic hospital records, municipal civil registries, or direct contact with the patients' primary care physicians or relatives. Rehospitalization for HF was defined as an unplanned hospital admission (duration ≥24 hours) necessitated by worsening symptoms of HF (eg, progressive dyspnea or peripheral edema) requiring the administration of intravenous diuretics or a significant intensification of HF therapy.

SIX-MINUTE WALK TEST. Functional capacity was evaluated using the 6-minute walk test (6MWT) at baseline and at the 6-month follow-up. The test was performed according to a standardized protocol on a flat, 30-m indoor corridor. Patients were instructed to walk as far as possible within 6 minutes, with the total distance recorded in meters. Predefined safety criteria for premature termination of the test included the onset of angina pectoris, severe dyspnea, dizziness, gait instability, or leg cramps/claudication. Furthermore, peripheral oxygen saturation (SpO_2) was monitored; a drop in SpO_2 <90% required a rest period with supplemental oxygen (2 L/min), after which the test was resumed. A definitive termination of the test was mandatory if SpO_2 fell below 85%.

STATISTICAL ANALYSIS. Statistical analyses were performed with SPSS, version 25 (IBM Deutschland GmbH). Categorical variables were presented as absolute numbers and percentages and were compared using the chi-square test or Fisher exact test, as appropriate. Continuous variables were expressed as mean ± SD or mean ± SEM, as specified in the respective figure legends.

Data distribution was assessed for normality using the Shapiro-Wilk test. For comparison of continuous variables between 2 independent groups (men vs women), the independent Student's *t*-test was used for normally distributed data, while the Mann-Whitney *U* test was applied for non-normally

TABLE 1 Baseline Clinical and Procedural Characteristics in Women and Men Undergoing M-TEER for Severe MR (N = 293)

	Women (n = 119)	Men (n = 174)	*P* Value
Age, y	78.6 ± 6.6	75.6 ± 9.3	0.003
Coronary heart disease	77 (65)	141 (81)	0.002
Atrial fibrillation	78 (66)	114 (66)	0.996
Hypertension	89 (75)	117 (67)	0.165
Active smoker	12 (10)	38 (22)	0.009
Hyperlipoproteinemia	48 (40)	75 (43)	0.637
Diabetes mellitus	33 (28)	53 (30)	0.614
Renal insufficiency[a]	54 (45)	99 (56)	0.053
Pulmonary hypertension[a]	73 (61)	118 (68)	0.234
EuroSCORE II	9.3 ± 0.9	11.1 ± 1.0	0.110
LVEDD	50 ± 9.5	56 ± 9.1	0.001
LVEDD/BSA, cm/m^2	29.6 ± 5.6	29.6 ± 5.8	0.829
Etiology of MR			
Functional	44 (37)	100 (57)	0.001
Degenerative	75 (63)	74 (43)	0.001
LVEF			
≤35%	37 (31)	107 (61)	0.001
36%-50%	32 (27)	47 (27)	
>50%	50 (42)	20 (11)	

Values are mean ± SD or n (%), unless otherwise indicated. [a]Definitions as used for EuroSCORE II.

BSA = body surface area; LV = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; MR = mitral regurgitation; M-TEER = mitral transcatheter edge-to-edge repair.

distributed data. To assess longitudinal changes within groups (baseline to 6-month follow-up), the paired Student's *t*-test or Wilcoxon signed rank test was performed. Comparisons across multiple groups or time points were conducted using ANOVA.

To identify the independent impact of sex on clinical outcomes, multivariable logistic regression analyses were performed with regard to the risk of all-cause mortality and HF-related rehospitalization at 6 months, and results were reported as OR with 95% CIs. Multivariable logistic regression analyses were adjusted for key baseline characteristics and comorbidities, including age, sex, chronic kidney disease, coronary artery disease, and MR etiology.

All P values are 2-tailed, and a value of $P \leq 0.05$ was considered statistically significant.

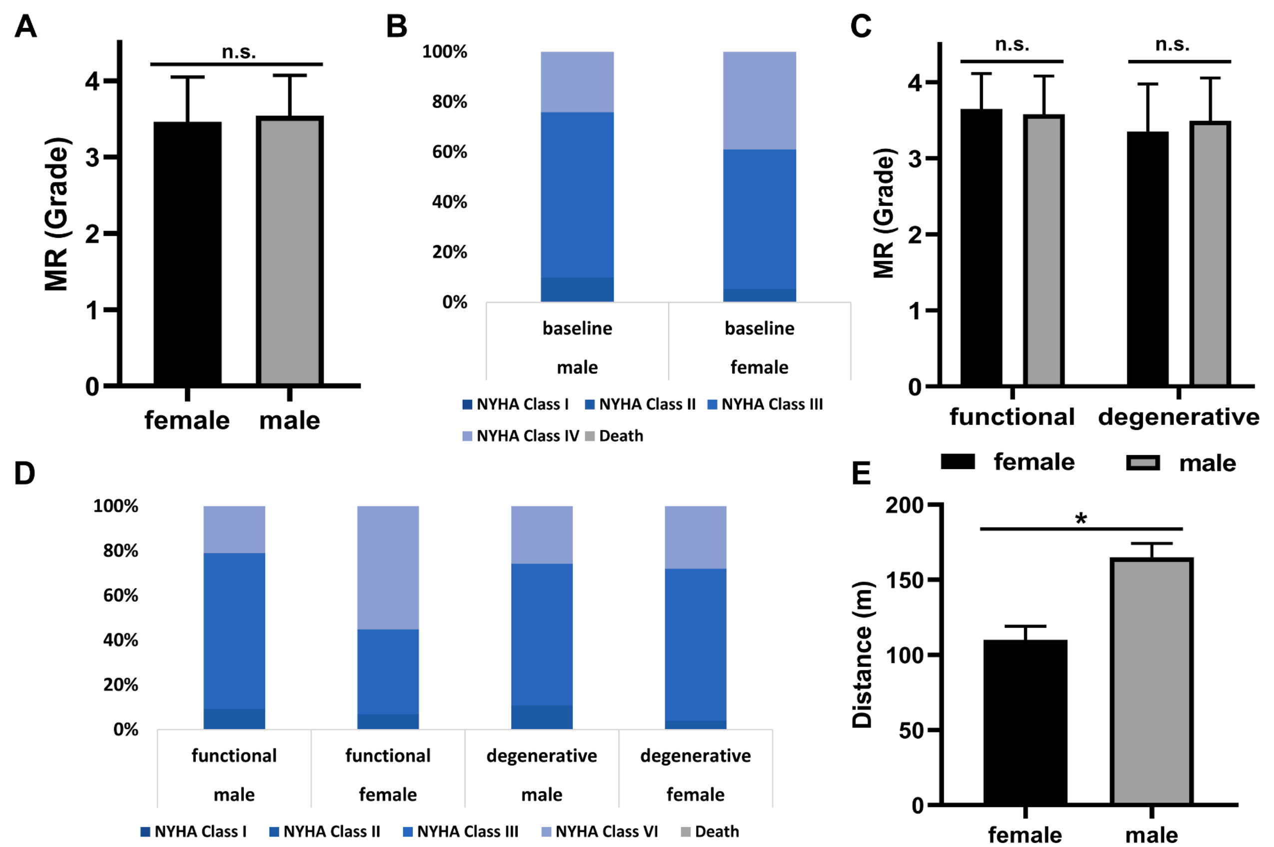
RESULTS

BASELINE CHARACTERISTICS AND FUNCTIONAL STATUS. A total of 293 patients (119 women, 174 men) undergoing M-TEER were included. Baseline clinical characteristics stratified by sex are summarized in Table 1. Women were significantly older than men (78.6 ± 6.6 vs 75.6 ± 9.3 years; $P = 0.003$) and presented with a distinct comorbidity profile, characterized by a lower prevalence of coronary heart disease (65% vs 81%; $P = 0.002$) and a significantly lower rate of active smoking at the time of intervention (10% vs 22%; $P = 0.009$). The etiology of MR differed significantly between groups (Table 1). While FMR was more common in men (57% vs 37%), women more frequently presented with degenerative mitral regurgitation (DMR) (63% vs 43%; $P = 0.001$). To account for differences in body habitus, left ventricular end-diastolic diameter (LVEDD) was indexed to body surface area (BSA) using the Mosteller formula.[26] Interestingly, the mean indexed LVEDD was identical between both groups, measuring 29.6 mm/m^2 in female patients and 29.6 mm/m^2 in male patients ($P > 0.05$), indicating a comparable relative degree of left ventricular dilation at the time of presentation (Table 1).

Despite these varying etiologies, baseline MR severity (Figures 1A and 1C) and symptomatic burden, as assessed by NYHA functional class (Figures 1B and 1D), were comparable between sexes (all $P > 0.05$). However, women demonstrated a significantly lower functional capacity at baseline, as evidenced by shorter distances covered in the 6MWT compared to their male counterparts (Figure 1E) (males $P < 0.001$).

PROCEDURAL OUTCOMES AND TECHNICAL SUCCESS. Technical success was achieved with high efficiency in both sexes. A reduction of MR severity to ≤2+ at discharge was achieved in the vast majority of patients, with only 7 women (6%) and 9 men (5%) not reaching this endpoint ($P = 0.348$). Following the procedure, no relevant mean mitral valve gradients were observed (3.4 mm Hg in women vs 2.8 mm Hg in men; $P > 0.05$), regardless of MR etiology (Supplemental Figure 1). Residual MR grades at discharge show no statistically significant difference between primary and secondary MR within either sex cohort (Supplemental Figure 2) ($P > 0.05$). Inhospital adverse events were infrequent and showed no significant sex-specific differences. Single-leaflet device attachment occurred in 3 patients in each group ($P = 0.690$). Similarly, rates of postprocedural pneumonia ($P = 0.461$), stroke ($P = 0.364$), and intrahospital mortality (8% vs 7%; $P = 0.661$) were comparable between women and men (Supplemental Table 1). Furthermore, there were no significant differences in fluoroscopy times (Supplemental Figure 3) ($P = 0.121$), though a trend toward shorter total procedure durations was noted in women ($P = 0.056$) (Supplemental Figure 4). Hemodynamic profiles, including cardiac index, remained similar between sexes at baseline ($P = 0.531$) and completion ($P = 0.284$) (Supplemental Figure 5).

FIGURE 1 Baseline Valvular Severity and Functional Capacity Stratified by Sex



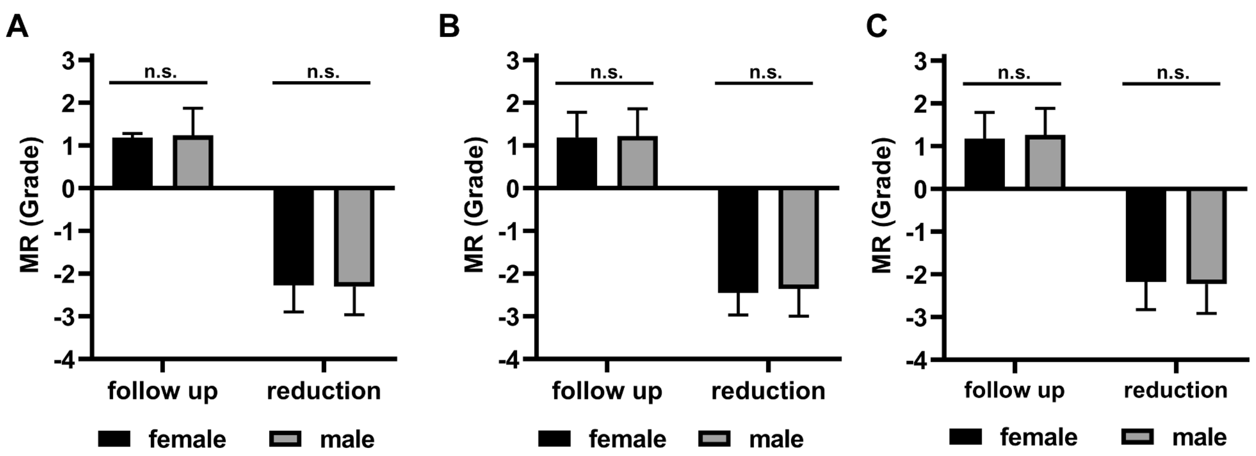
(A, C) Baseline MR grades were assessed via echocardiography and remained similar between men and women, independent of MR etiology (all $P > 0.05$). (B, D) Rates of NYHA functional classes are shown at baseline in women and men; symptomatic burden was comparable across all subgroups. (E) Conversely, functional capacity measured by 6MWT was significantly lower in women compared to men (*$P < 0.001$). These findings suggest that women present with more advanced functional impairment despite similar degrees of valvular severity. As a clinical frame of reference, normative 6MWT values for healthy individuals in this age group are approximately 450-550 m for men and 400-500 m for women, depending on age and height.[44] Data in A and C are mean ± SD; E represents mean ± SEM. 6MWT = 6-minute walk test; MR = mitral regurgitation.

M-TEER resulted in a similar reduction of MR severity in both groups (Figure 2A). This procedural efficacy remained consistent regardless of MR etiology; no sex-based disparities were found in residual MR grades or absolute MR reduction for either FMR (Figure 2B) or DMR (Figure 2C) (all $P > 0.05$).

CLINICAL OUTCOMES AND FUNCTIONAL RECOVERY AT 6 MONTHS. Clinical outcomes at the 6-month follow-up are detailed in Table 2. In the overall cohort, no significant differences were observed between women and men regarding all-cause mortality (17% vs 22%; $P = 0.301$) or rehospitalization for HF (13% vs 10%; $P = 0.576$). This equivalence in clinical endpoints was maintained across both FMR and DMR subgroups (Table 2). Even after multivariable adjustments, sex was not associated with the risk of all-cause mortality (OR = 0.929; 95% CI: 0.474-1.822; $P = 0.830$) and HF-related rehospitalization at 6 months (OR = 1.151; 95% CI: 0.520-2.548; $P = 0.729$) (Supplemental Table 2).

Consistent with the reduction in MR severity, both sexes showed significant and comparable improvements in NYHA functional class (Figures 3A and 3B). Regarding exercise tolerance, complete 6MWT data at both baseline and the 6-month follow-up were available for a subset of 150 patients (n = 87 men and n = 63 women); the remaining patients were excluded from this specific secondary analysis due to interim mortality, physical inability to perform the test or missing values. Within this analyzed

FIGURE 2 Procedural Efficacy and MR Reduction by Sex



(A to C) This figure evaluates the technical success of mitral transcatheter edge-to-edge repair by comparing residual MR and the magnitude of MR reduction between sexes. A displays the total cohort, while B and C specify functional and degenerative MR etiologies, respectively. No significant sex-specific differences were observed in residual MR grades at discharge or in the absolute MR reduction, regardless of the underlying MR entity (all $P > 0.05$). These findings indicate that M-TEER achieves comparable procedural outcomes for both men and women. Data are presented as mean ± SD. M-TEER = mitral transcatheter edge-to-edge repair; other abbreviation as in Figure 1.

subgroup, absolute 6MWT distances at the 6-month follow-up remained significantly shorter in women compared to men (Figure 3C) ($P = 0.02$).

Crucially, the mean improvement in walking distance (delta 6MWT) from baseline to 6 months was nearly identical between sexes (Figure 3D) ($P = 0.778$). This finding of equivalent functional gain was consistent across both functional and degenerative MR etiologies (Figures 3E and 3F), suggesting that the relative symptomatic benefit derived from M-TEER is independent of patient sex.

TABLE 2 Clinical Outcomes at 6 mo Between Women and Men Undergoing M-TEER for Severe MR (N = 293)

All Patients (N = 293)	Women (n = 119)	Men (n = 174)	OR (95% CI)	*P* Value
All-cause mortality	20 (17)	38 (22)	1.38 (0.76-2.52)	0.301
Rehospitalization for HF	15 (13)	18 (10)	0.80 (0.39-1.66)	0.576
Patients with functional MR (N = 144)	**Women (n = 44)**	**Men (n = 100)**	**OR (95% CI)**	***P* Value**
All-cause mortality	9 (20)	21 (21)	1.03 (0.43-2.48)	1.000
Rehospitalization for HF	3 (7)	14 (14)	2.23 (0.61-8.17)	0.272
Patients with degenerative MR (N = 149)	**Women (n = 75)**	**Men (n = 74)**	**OR (95% CI)**	***P* Value**
All-cause mortality	11 (15)	17 (23)	1.74 (0.75-4.01)	0.214
Rehospitalization for HF	12 (16)	4 (5)	0.30 (0.09-0.98)	0.061

Values are n (%), unless otherwise indicated. Univariable ORs and corresponding *P* values were estimated using Fisher exact test for all categorical endpoints.

HF = heart failure; other abbreviation as in Table 1.

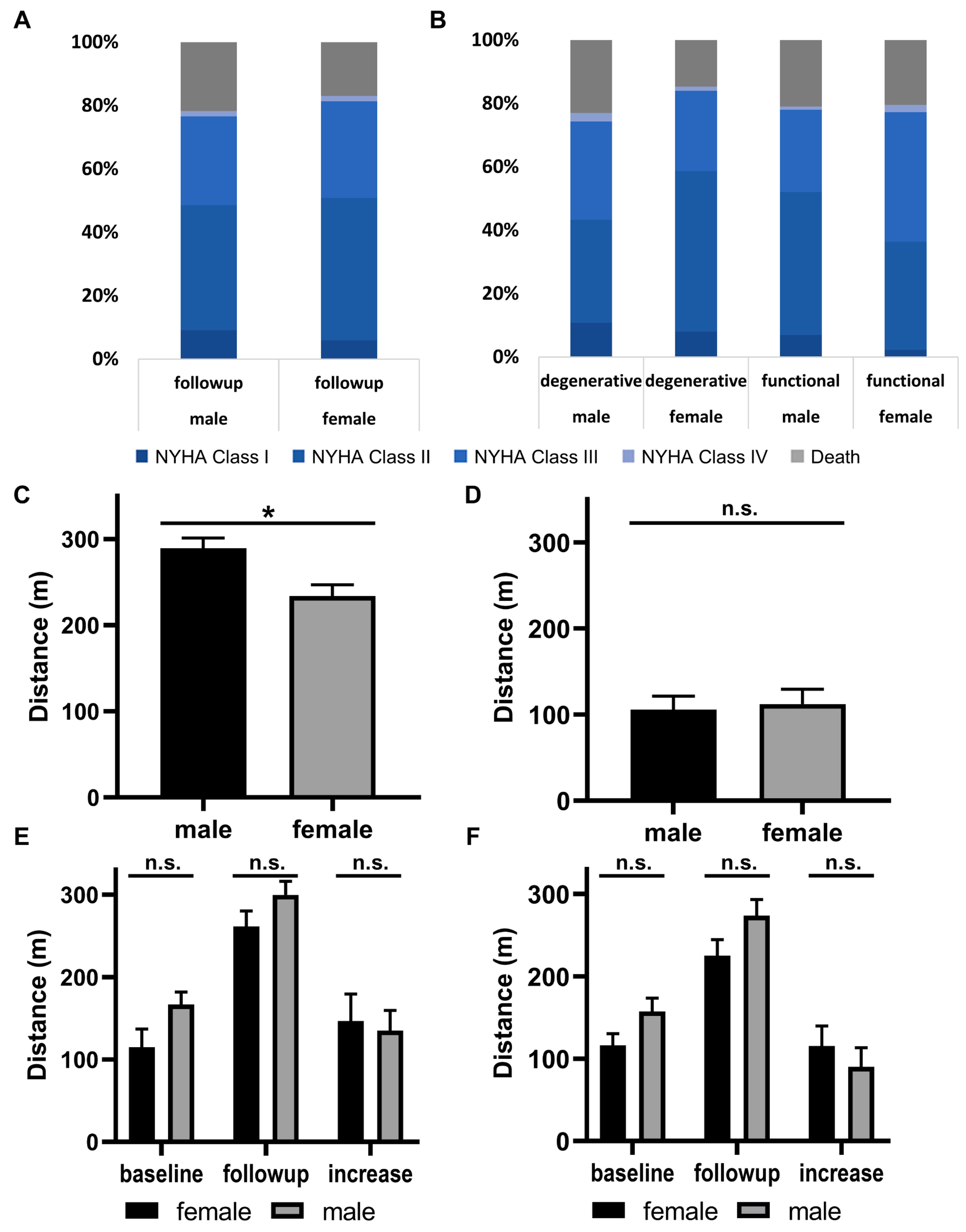
DISCUSSION

Interventional therapies are beneficial for patients beyond medical therapy but not eligible for surgery, and M-TEER is an established approach for secondary and primary MR.[8]

In this analysis, sex-based differences in baseline characteristics and outcomes were compared between men and women undergoing M-TEER for functional and degenerative MR. The major findings of the present study are: 1) male and female patients remained at similar improvement in functional capacity as assessed by the 6MWT 6 months after M-TEER. However, women had significantly lower functional capacity then men both at baseline and at follow-up; 2) alongside this observation, there was equal reduction in MR regardless of gender, an observation holding up for the etiology of MR; 3) at initial presentation, however, the prevalence of FMR was 20% lower in the female treatment group than in the male group; and 4) importantly, compared with men at first clinical presentation women were at average 3 years older that male patients.

SEX-BASED DIFFERENCES AT INITIAL CLINICAL PRESENTATION FOR M-TEER. Women feature an increased risk for thrombotic disease compared with

FIGURE 3 Midterm Clinical Outcomes and Functional Recovery Stratified by Sex



Continued on the next page

men, potentially related to increased platelet reactivity, higher levels of coagulation factors and sex-associated unique risk factors for cardiovascular disease.[27] Moreover, it is known that women with ischemic heart disease are less likely to undergo the necessary testing recommended according to current guidelines, pharmacological treatment or interventional therapy associated with less favorable clinical outcome, a phenomenon referred to as the "Yentl syndrome."[28] In our M-TEER cohort, we similarly observed that female patients presented with a reduced functional capacity and a 3-year difference in age, which night reflect a delayed clinical presentation after symptom onset. Interestingly, the grade of MR did not differ between sexes at the time of presentation. This observation suggests that a comparable absolute MR grade may impose a higher relative hemodynamic burden on women, likely due to their typically smaller ventricular dimensions and lower BSA. Consequently, the same degree of valvular incompetence may lead to more rapid symptomatic progression and a more advanced functional decline in female patients, contributing to their clinical presentation at a more compromised stage compared to men. On the other hand, there was a difference in the etiology of MR at presentation between female patients showing with 20% more degenerative MR and male patients presenting with 20% more FMR. This observation might at least partially be explained by the fact that female patients were older and exhibited a lower prevalence of coronary artery disease, which is a major driver of ischemic FMR in men, whereas degenerative etiology is more closely associated with advanced age.[29] Our observation is in line with published registry data for MR surgery suggesting that women with primary MR are referred to the clinic for treatment later than men, and among patients with primary severe MR, women have worse long-term outcomes than men.[30] Beyond potential referral bias, the advanced age of female patients at presentation likely reflects a combination of greater longevity—shifting disease manifestation to later in life—and distinct sex-specific natural histories of MR. Biologically, postmenopausal changes in sex hormones and smaller baseline cardiac geometry alter valvular mechanical stress and ventricular remodeling differently in primary and secondary MR. Although the exact time from initial diagnosis to intervention could not be retrospectively determined, these overlapping demographic and physiological factors suggest that women follow an inherently different clinical trajectory than men, rather than experiencing a simple delay in care.

The observed differences in clinical presentation must also be interpreted in light of the differing MR etiologies between sexes. In our cohort, men had a higher proportion of FMR, a condition often diagnosed and referred earlier as these patients are typically already established with a cardiologist for HF management. In contrast, the higher prevalence of degenerative MR among women may have contributed to their more advanced age and lower baseline functional status, as M-TEER in degenerative disease is primarily reserved for patients deemed high-risk for surgical repair. This etiological imbalance serves as a potential confounder, suggesting that the observed sex-specific disparities are a result of both biological differences and distinct clinical referral pathways for primary vs secondary MR.

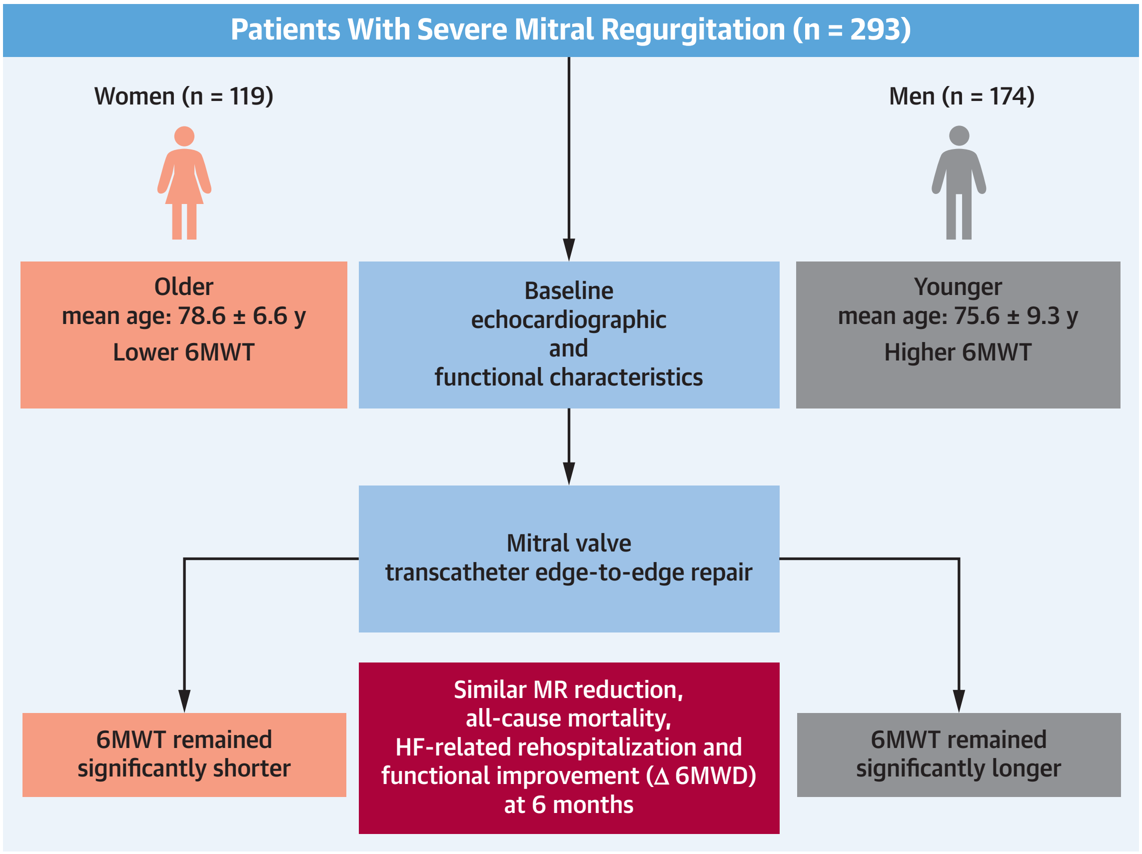
Although women in our cohort presented at a significantly more advanced age and with greater functional impairment, it is important to note that men exhibited a higher burden of specific comorbidities, such as coronary artery disease. This underlines that the "higher risk" profile of each sex is defined by different parameters—age and functional decline in women, vs atherosclerotic burden and FMR in men.

In the setting of primary MR, women display different anatomical characteristics, clinical risk profiles, and long-term outcomes.[15] Our study extends these previous observations from surgical collective to a M-TEER cohort with primary and secondary MR demonstrating a greater prevalence of some comorbidities such as coronary artery disease and active smoking, while others were not changed.

FIGURE 3 Continued

(A to F) Clinical trajectories and exercise tolerance were assessed at 6-month follow-up to evaluate the long-term impact of M-TEER. (A, B) Rates of death and NYHA functional classes were comparable between sexes across all MR etiologies. (C) Absolute 6MWT distance remained significantly lower in women ($P = 0.02$), but (D) the mean improvement in walking distance (delta) was similar between sexes ($P = 0.778$). (E, F) Stratification by functional and degenerative MR revealed no sex-specific differences in baseline, follow-up, or delta 6MWT distances. These findings suggest that while women maintain lower absolute functional levels, the relative symptomatic benefit from M-TEER is independent of sex. Data in C-F are mean ± SEM. Abbreviations as in Figures 1 and 2.

CENTRAL ILLUSTRATION Sex-Specific Outcomes of Patients Undergoing M-TEER



Sauter RJ, et al. JACC Adv. 2026;■(■):103120.

Among 293 patients (119 women) undergoing M-TEER for severe MR, women were older and had a lower functional capacity at baseline. At 6 months, clinical outcomes—all-cause mortality and HF rehospitalization—were comparable between sexes. Despite persistent absolute differences in 6MWT distances, both groups derived comparable relative functional improvement. These findings underscore M-TEER's efficacy in both sexes and suggest that earlier diagnosis and intervention in women may be necessary to maximize absolute functional recovery and close sex-based gaps in care. 6MWT = 6-minute walk test; HF = heart failure; MR = mitral regurgitation; M-TEER = mitral transcatheter edge-to-edge repair.

In general, and particularly for mitral valve diseases, women are underrepresented in clinical studies and randomized controlled trials investigating interventional treatment for MR are not available.[31-33] In our collective, only the rate of active smokers was significantly increased in male patients, the other comorbidities showed no sex-specific difference. In addition, we detected some echocardiographic differences between sexes. When evaluating echocardiographic parameters, women presented with a significantly lower absolute LVEDD, which initially reflects established sex-specific reference ranges.[34] However, when LVEDD was indexed to BSA, this difference completely disappeared, revealing an identical indexed LVEDD between sexes. Notably, this finding in our female cohort - despite their more advanced age—aligns with recent translational evidence describing sex-specific cardiac aging and remodeling trajectories.[35] Current evidence suggests that women with severe MR often exhibit smaller left ventricular cavities and lower absolute regurgitant volumes compared to men, which can lead to a significant underestimation of disease severity when using standard, nonindexed imaging thresholds. This sex-specific remodeling pattern—characterized by less pronounced ventricular dilatation in women—underscores the necessity of tailored diagnostic criteria to optimize the time of intervention.[36]

SEX-BASED DIFFERENCES IN OUTCOMES AFTER M-TEER. Our results are consistent with emerging evidence from large-scale registries and long-term cohorts. Although Biasco et al[37] confirmed comparable 5-year survival between sexes despite later referral for women, results from the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry show no sex-related differences in clinical outcomes up to 2 years of follow-up. However, the evidence is not entirely clear, because data from the COAPT trial show that the impact of M-TEER in reducing HF hospitalizations was less pronounced in women compared with men beyond the first year after treatment.[38] These findings are complemented by Hioki et al,[39] who demonstrated that women with FMR achieve favorable clinical outcomes, even though they are typically older and present with different risk profiles at the time of intervention.

Following adjustment for baseline confounders, we found that female sex was not significantly associated with a higher risk of mortality, a worse reduction in MR or an increased hospitalization for HF at 6 months after TEER. This observation seems to be in contradiction to previous results reported for patients undergoing surgery with worse outcomes in women with secondary ischemic MR.[1] This might be explained by the fact that the follow-up in this study was 2 years in comparison to the shorter observational period of our study. Another explanation could be that the increased age and differences in MR etiology outweigh potential sex-specific differences is MR outcome, which warrants further investigations. Alongside the increased percentage in FMR, female patients had a significantly lower absolute but an identical indexed LVEDD to the BSA at initial presentation mirroring an aggravated hemodynamic impairment by MR. It is known that changes in LVEDD over time are strongly associated with outcomes in patients with HF.[40]

CLINICAL IMPLICATIONS. The present study underscores the importance of timely interventional correction of MR in patients not eligible for surgical repair, regardless of sex (Central Illustration). While the COAPT trial established that M-TEER reduces mortality and HF-related rehospitalization in both men and women with secondary MR,[8] our findings extend this evidence by highlighting a critical functional aspect: despite presenting at a more advanced age and with significantly lower baseline functional capacity, women achieve a functional improvement (delta 6MWT) identical to that of men. These results demonstrate that female patients have the same symptomatic benefit from M-TEER once the intervention is performed. However, the persisting absolute functional gap at follow-up, which may be linked to the more advanced disease stage at presentation, warrants a plea for increased awareness and optimized screening for MR in women. Earlier identification and timely intervention may be essential to bridge this functional disparity and further enhance long-term recovery in female patients.

STUDY LIMITATIONS. One of the main limitations of this study is the rather small sample size, although our data represent a real-life all-comer collective. Given the scarce data on this most relevant topic and the complexity of the procedure, the patient number and retrospective study design appeared reasonable to generate hypotheses, which will have to be scrutinized in future trials. Another limitation lies in the rather long study period including patients from 2014 until 2025. During this time, not only did TEER devices and procedural techniques evolve, but the HF population itself also changed substantially, with increasingly older and more multimorbid patients following ongoing demographic changes. In parallel, significant advances in guideline-directed medical therapy—particularly the introduction and widespread adoption of sodium-glucose cotransporter 2 inhibitors—may have influenced clinical outcomes independently of the intervention.[41-43]

The long study period involves an inherent evolution in clinical practice, including the transition from predominantly primary to secondary MR indications, the inclusion of higher-risk cohorts (eg, cardiogenic shock), and advancements in device technology. These temporal shifts in patient selection and procedural techniques may have influenced clinical outcomes over time.

Additionally, a significant confounding factor is that women have a longer life expectancy, which may result in the development and clinical manifestation of mitral valve disease later in life. A major limitation of our study is the inability to retrospectively delineate the exact duration from the initial diagnosis of severe MR to the time of intervention. Consequently, we cannot definitively distinguish whether the more advanced age of women at presentation reflects a true delay in treatment or simply the natural demographic and biological trajectory of the disease in the female population.

Furthermore, it should be noted that all patients underwent multidisciplinary Heart Team (consisting of a senior cardiologist, heart surgeon and anesthesiologist) evaluation. In cases of primary MR where surgery was initially considered, patients were frequently declined due to significant comorbidities or elevated surgical risk. Consequently, the elimination of healthier surgical candidates from this cohort likely introduced a selection bias, as M-TEER was reserved for those deemed unsuitable for conventional surgery.

When we analyzed the time of referral to the clinic for TEER, important variables were not assessed including left atrial end-systolic volume index, MR severity by effective regurgitant orifice area, remodeling parameters such as left ventricular end-diastolic volume and lab parameters such as N-terminal pro-B-type natriuretic peptide. These parameters will have to be further addressed in future studies. It should be noted that the 6MWT delta analysis at follow-up was available for 150 patients (n = 87 men, n = 63 women), with exclusions primarily due to mortality, physical inability to perform the test, or missing values. Patients without assessment of the 6MWT at 6 months were excluded for the evaluation of this secondary endpoint. Regarding follow-up, future studies will have to include later time points to assess mortality, rehospitalization for HF and other clinical parameters. Moreover, natriuretic peptides levels at baseline and at follow-up were not collected in this trial and should be included in future diagnostic approaches. In addition, frailty data were not available, which can influence 6MWT results. Last but not least, our data collection started, when the distinction between atrial and ventricular FMR was not clear, which is however important for example regarding effectiveness of comedication for HF.

CONCLUSIONS

In this study, M-TEER for primary and secondary MR demonstrated comparable midterm clinical outcomes, with no sex-based differences in mortality or HF-related rehospitalization. However, women presented at a significantly more advanced age and with lower absolute functional capacity. Notably, despite these baseline disparities, the relative symptomatic benefit and functional improvement (delta 6MWT) were identical between sexes and across MR etiologies. These findings underscore that M-TEER is highly effective in both sexes and suggest that optimized screening and intervention may be warranted to maximize their absolute functional recovery and close existing sex-based gaps in care.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by the Physician Scientist Program of the Helmholtz-Institute for Translational AngioCardioScience (HI-TAC) and the Carl Zeiss Foundation. This work was furthermore supported by the Else-Kröhner Fresenius Stiftung (Schlüsselprojekt, 2023_EKSE.46), the German Research Centre for Cardiovascular Research (partner site Mannheim/Heidelberg, FKZ81Z0700110), the BMWE (ZIM project, KK5118403BM4), and the SFB1366/2/project B08 (394046768) to Drs Langer and Duerschmied. Drs Langer and Sauter were reimbursed for M-TEER training courses by Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

ADDRESS FOR CORRESPONDENCE: Dr Harald F. Langer, Cardiology, Haemostaseology, and Medical Intensive Care, Medical Centre Mannheim, Medical Faculty Mannheim, Heidelberg University, Theodor-Kutzer-Ufer 1-3, Mannheim 68167, Germany. E-mail: harald.langer@umm.de. X handle: @CVSBMannheim.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: M-TEER provides comparable clinical outcomes in women and men regarding mortality and heart failure rehospitalization at 6 months. Although women currently seem to present at an older age with significantly lower baseline functional capacity (6MWT), they derive a similar relative functional benefit (delta 6MWT) compared to men. This confirms that M-TEER is highly effective regardless of sex.

TRANSLATIONAL OUTLOOK: Women presenting for M-TEER at present may exhibit more advanced functional impairment and distinct clinical trajectories compared to men. Thus, to optimize absolute functional recovery, increased clinical awareness and refined screening strategies for MR in women are warranted. Future research should focus on whether sex-specific thresholds for intervention—accounting for smaller cardiac dimensions and differing etiological profiles—can optimize the timing of treatment and further improve long-term outcomes in female patients.

REFERENCES

1. Giustino G, Overbey J, Taylor D, et al. Sex-based differences in outcomes after mitral valve surgery for severe ischemic mitral regurgitation. *JACC Heart Fail*. 2019;7:481–490. https://doi.org/10.1016/j.jchf.2019.03.001

2. Avierinos JF, Inamo J, Grigioni F, Gersh B, Shub C, Enriquez-Sarano M. Sex differences in morphology and outcomes of mitral valve prolapse. *Ann Intern Med*. 2008;149:787–795. https://doi.org/10.7326/0003-4819-149-11-200812020-00003

3. Mantovani F, Clavel MA, Michelena HI, Suri RM, Schaff HV, Enriquez-Sarano M. Comprehensive imaging in women with organic mitral regurgitation: implications for clinical outcome. *JACC Cardiovasc Imaging*. 2016;9:388–396. https://doi.org/10.1016/j.jcmg.2016.02.017

4. Grayburn PA. Sex differences in mitral regurgitation before and after mitral valve surgery. *JACC Cardiovasc Imaging*. 2016;9:397–399. https://doi.org/10.1016/j.jcmg.2016.02.013

5. Feldman T, Wasserman HS, Herrmann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST phase I clinical trial. *J Am Coll Cardiol*. 2005;46:2134–2140. https://doi.org/10.1016/j.jacc.2005.07.065

6. Feldman T, Foster E, Glower DD, et al. Percutaneous repair or surgery for mitral regurgitation. EVEREST II investigators. *N Engl J Med*. 2011;364:1395–1406. https://doi.org/10.1056/NEJMoa1009355

7. Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379:2297–2306. https://doi.org/10.1056/NEJMoa1805374

8. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379:2307–2318. https://doi.org/10.1056/NEJMoa1806640

9. Stone GW, Abraham WT, Lindenfeld J, et al. Five-year Follow-up after transcatheter repair of secondary mitral regurgitation. *N Engl J Med*. 2023;388:2037–2048. https://doi.org/10.1056/NEJMoa2300213

10. Anker SD, Friede T, von Bardeleben RS, et al. Transcatheter valve repair in heart failure with moderate to severe mitral regurgitation. *N Engl J Med*. 2024;391:1799–1809. https://doi.org/10.1056/NEJMoa2314328

11. Otto CM, Nishimura RA, Bonow RO, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: executive summary: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2021;77:450–500. https://doi.org/10.1016/j.jacc.2020.11.035

12. Asgar AW, Tang GHL, Rogers JH, et al. Evaluating mitral TEER in the management of moderate secondary mitral regurgitation among heart failure patients. *JACC Heart Fail*. 2025;13:213–225. https://doi.org/10.1016/j.jchf.2024.08.001

13. EUGenMed T, Group CCS, Regitz-Zagrosek V, et al. Gender in cardiovascular diseases: impact on clinical manifestations, management, and outcomes. *Eur Heart J*. 2015;37:24–34. https://doi.org/10.1093/eurheartj/ehv598

14. McNeely C, Vassileva C. Mitral valve surgery in women. *Circ Cardiovasc Qual Outcomes*. 2016;9:S94–S96. https://doi.org/10.1161/CIRCOUTCOMES.115.002603

15. Scott PE, Unger EF, Jenkins MR, et al. Participation of women in clinical trials supporting FDA approval of cardiovascular drugs. *J Am Coll Cardiol*. 2018;71:1960–1969. https://doi.org/10.1016/j.jacc.2018.02.070

16. Bruno RR, Uzel R, Spieker M, et al. The impact of gender and frailty on the outcome of older patients with functional mitral regurgitation. *ESC Heart Fail*. 2023;10:2948–2954. https://doi.org/10.1002/ehf2.14478

17. Patzelt J, Zhang W, Sauter R, et al. Elevated mitral valve pressure gradient is predictive of long-term outcome after percutaneous edge-to-edge mitral valve repair in patients with degenerative mitral regurgitation (MR), but not in functional MR. *J Am Heart Assoc*. 2019;8:e011366. https://doi.org/10.1161/JAHA.118.011366

18. Patzelt J, Zhang Y, Seizer P, et al. Effects of mechanical ventilation on heart geometry and mitral valve leaflet coaptation during percutaneous edge-to-edge mitral valve repair. *JACC Cardiovasc Interv*. 2016;9:151–159. https://doi.org/10.1016/j.jcin.2015.09.038

19. Praz F, Borger MA, Lanz J, et al. 2025 ESC/EACTS guidelines for the management of valvular heart disease: developed by the task force for the management of valvular heart disease of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur Heart J*. 2025;46:4635–4736. https://doi.org/10.1093/eurheartj/ehaf194

20. Foster E, Wasserman HS, Gray W, et al. Quantitative assessment of severity of mitral regurgitation by serial echocardiography in a multicenter clinical trial of percutaneous mitral valve repair. *Am J Cardiol*. 2007;100:1577–1583. https://doi.org/10.1016/j.amjcard.2007.06.066

21. Patzelt J, Ulrich M, Magunia H, et al. Comparison of deep sedation with general anesthesia in patients undergoing percutaneous mitral valve repair. *J Am Heart Assoc*. 2017;6. https://doi.org/10.1161/JAHA.117.007485

22. Patzelt J, Seizer P, Zhang YY, et al. Percutaneous mitral valve edge-to-edge repair with simultaneous biatrial intracardiac echocardiography: first-in-human experience. *Circulation*. 2016;133:1517–1519. https://doi.org/10.1161/CIRCULATIONAHA.115.020923

23. Sauter R, Lin C, Magunia H, et al. Improved mid-term stability of MR reduction with an increased number of clips after percutaneous mitral valve repair in functional MR. *Int J Cardiol Heart Vasc*. 2023;45:101190. https://doi.org/10.1016/j.ijcha.2023.101190

24. Alfieri O, Maisano F, De Bonis M, et al. The double-orifice technique in mitral valve repair: a simple solution for complex problems. *J Thorac Cardiovasc Surg*. 2001;122:674–681. https://doi.org/10.1067/mtc.2001.117277

25. Sauter RJ, Patzelt J, Mezger M, et al. Conventional echocardiographic parameters or three-dimensional echocardiography to evaluate right ventricular function in percutaneous edge-to-edge mitral valve repair (PMVR). *Int J Cardiol Heart Vasc*. 2019;24:100413. https://doi.org/10.1016/j.ijcha.2019.100413

26. Mosteller RD. Simplified calculation of body-surface area. *N Engl J Med*. 1987;317:1098. https://doi.org/10.1056/NEJM198710223171717

27. Laborante R, Borovac JA, Galli M, et al. Gender-differences in antithrombotic therapy across the spectrum of ischemic heart disease: time to tackle the Yentl syndrome? *Front Cardiovasc Med*. 2022:9-2022. https://doi.org/10.3389/fcvm.2022.1009475

28. Healy B. The Yentl syndrome. *N Engl J Med*. 1991;325:274–276. https://doi.org/10.1056/NEJM199107253250408

29. Avierinos JF, Tribouilloy C, Grigioni F, et al. Impact of ageing on presentation and outcome of mitral regurgitation due to flail leaflet: a multicentre international study. *Eur Heart J*. 2013;34:2600–2609. https://doi.org/10.1093/eurheartj/eht250

30. McNeely C, Vassileva C. Mitral valve surgery in women: another target for eradicating sex inequality. *Circ Cardiovasc Qual Outcomes*. 2016;9:S94–S96. https://doi.org/10.1161/CIRCOUTCOMES.115.002603

31. Wu Y, Prasanna A, Miller HN, et al. Female recruitment into cardiovascular disease trials. *Am J Cardiol*. 2023;198:88–91. https://doi.org/10.1016/j.amjcard.2023.03.034

32. DesJardin JT, Chikwe J, Hahn RT, Hung JW, Delling FN. Sex differences and similarities in valvular heart disease. *Circ Res*. 2022;130:455–473. https://doi.org/10.1161/CIRCRESAHA.121.319914

33. Reddy KP, Faggioni M, Eberly LA, et al. Enrollment of older patients, women, and racial and ethnic minority individuals in valvular heart disease clinical trials: a systematic review. *JAMA Cardiol*. 2023;8:871–878. https://doi.org/10.1001/jamacardio.2023.2098

34. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. *Eur Heart J Cardiovasc Imaging*. 2015;16:233–270. https://doi.org/10.1093/ehjci/jev014

35. Haider A, Bengs S, Portmann A, et al. Sex-specific cardiac ageing and sympathetic compensation: a translational study. *Eur Heart J*. 2025. https://doi.org/10.1093/eurheartj/ehaf922

36. Springhetti P, Almeida AG, Muraru D, Clavel MA. The importance of sex differences in valvular heart disease from an imaging point of view. *Eur Heart J Cardiovasc Imaging*. 2026;27:85–103. https://doi.org/10.1093/ehjci/jeaf311

37. Biasco L, Tersalvi G, Klersy C, et al. Technical and clinical outcomes after transcatheter edge-to-edge repair of mitral regurgitation in male and female patients: is equality achieved? *J Am Heart Assoc*. 2024;13:e032706. https://doi.org/10.1161/JAHA.123.032706

38. Kosmidou I, Lindenfeld J, Abraham WT, et al. Sex-specific outcomes of transcatheter mitral-valve repair and medical therapy for mitral regurgitation in heart failure. *JACC Heart Fail*. 2021;9:674–683. https://doi.org/10.1016/j.jchf.2021.04.011

39. Hioki H, Watanabe Y, Kataoka A, et al. Impact of gender on mortality after transcatheter edge-to-edge repair for functional mitral regurgitation. *Am J Cardiol*. 2023;205:12–19. https://doi.org/10.1016/j.amjcard.2023.07.143

40. Konstam MA, Kramer DG, Patel AR, Maron MS, Udelson JE. Left ventricular remodeling in heart failure: current concepts in clinical significance and assessment. *JACC Cardiovasc Imaging*. 2011;4:98–108. https://doi.org/10.1016/j.jcmg.2010.10.008

41. Kubo S, Yamamoto M, Saji M, et al. Real-world outcomes of the initial clip selection for transcatheter edge-to-edge repair using the MitraClip G4 from the optimized catheter valvular intervention-mitral registry. *J Am Heart Assoc*. 2025;14:e041907. https://doi.org/10.1161/JAHA.125.041907

42. Thaw KM, Scalia W, Petersen R, et al. Comparison of outcomes of transcatheter edge-to-edge repair with early versus latest generation MitraClip for severe mitral regurgitation. *Heart Lung Circ*. 2025;34:1228–1234. https://doi.org/10.1016/j.hlc.2025.06.1033

43. Khan MS, Samman Tahhan A, Vaduganathan M, et al. Trends in prevalence of comorbidities in heart failure clinical trials. *Eur J Heart Fail*. 2020;22:1032–1042. https://doi.org/10.1002/ejhf.1818

44. Enright PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158:1384–1387. https://doi.org/10.1164/ajrccm.158.5.9710086

KEY WORDS echocardiography, gender, mitral regurgitation, mitral transcatheter edge-to-edge repair, sex

APPENDIX For supplemental tables and figures, please see the online version of this paper.