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ORIGINAL RESEARCH

Technical and Clinical Outcomes After Transcatheter Edge-to-Edge Repair of Mitral Regurgitation in Male and Female Patients: Is Equality Achieved?

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BACKGROUND: Currently, no clear impact of sex on short- and long-term survival following transcatheter edge-to-edge mitral valve repair (TEER) is evident, although no data are available on postprocedural life expectancy. Our aim was to assess sex-specific differences in outcomes of patients with mitral regurgitation (MR) treated by TEER.

METHODS AND RESULTS: Short-term and 5-year outcomes in men and women undergoing TEER between 2011 and 2018 who were included in the large, multicenter, real-world MitraSwiss registry were analyzed. Outcomes were compared stratified by sex and according to MR cause (primary versus secondary). The impact of TEER on postprocedural life expectancy was estimated by relative survival analysis. Among 1142 patients aged 60 to 89 years, 39.8% were women. They were older, with fewer cardiovascular risk factors and lower functional capacity compared with men. Thirty-day mortality was higher in men than in women (3.3% versus 1.1%; odds ratio, 3.16 [95% CI, 1.16–10.7]; *P*=0.020). Five-year survival was comparable in both sexes (adjusted hazard ratio for 5-year mortality in men, 1.14 [95% CI, 0.90–1.44], *P*=0.275). Both men and women with either primary or secondary MR showed similar clinical efficacy over time. TEER provided high relative survival estimates among all groups, and fully restored predicted life expectancy in women with primary MR (5-year relative survival estimate, 97.4% [95% CI, 85.5–107.0]).

CONCLUSIONS: TEER is not associated with increased short-term mortality in women, whereas 5-year outcomes are comparable between sexes. Moreover, TEER completely restored normal life expectancy in women with primary MR. A residual excess mortality persists in secondary MR, independently of sex.

Key Words: edge-to-edge mitral valve repair ■ mitral regurgitation ■ mortality ■ percutaneous mitral valve repair ■ sex

Mitral regurgitation (MR) is the most common valvular disease in Western countries and has a well-recognized prognostic impact.[1,2] Several sex-related disparities have been recognized in the incidence of MR, pathological findings, pathophysiological mechanisms, and the diagnostic accuracy of currently available imaging tools.[2]

In addition, the likelihood of access to treatments and outcomes for both surgical and interventional therapies appear to be dissimilar between sexes. Women

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CLINICAL PERSPECTIVE

What Is New?

- In women undergoing mitral transcatheter edge-to-edge mitral valve repair (TEER), despite an older age and a worse functional status at presentation, 30-day mortality was 3-fold lower than in men.
- Both men and women showed similar 5-year survival and major adverse clinical events rate (composite all-cause mortality, hospitalizations for heart failure, redo-TEER, or mitral valve surgery) confirmed even after stratification for mitral regurgitation cause.
- In elderly highly symptomatic women with primary mitral regurgitation, mitral TEER was able to fully restore postprocedural life expectancy.
- Despite residual excess mortality, patients with secondary mitral regurgitation treated by mitral TEER achieved high relative survival estimates at 5 years.

What Are the Clinical Implications?

- The risk for short-term mortality, consistently increased after surgery in women, might be effectively contained by a percutaneous approach.
- Although previous data hypothesized a reduced clinical efficacy over time in women, no outcome differences between sexes are evident at 5-year follow-up, even after stratification for mitral regurgitation cause.
- Once primary mitral regurgitation is treated by TEER, its prognostic impact is completely contained in women, because their life expectancy equals expected survival in age- and sex-matched subjects from the general population.

Nonstandard Abbreviations and Acronyms

MR	mitral regurgitation
PMR	primary mitral regurgitation
SMR	secondary mitral regurgitation
TEER	transcatheter edge-to-edge mitral valve repair

are significantly underreferred and show higher mortality after surgery, and a lower clinical efficacy following percutaneous treatments has been also suggested.[3–5]

Nonetheless, current European and American guidelines identify common diagnostic and therapeutic pathways for patients with MR that do not consider sex as a factor impacting on decision making.[6,7] At the same time, European guidelines acknowledge the presence of important gaps in evidence in sexual issues on pathophysiology, indications, and timing of treatment of valvular heart disease.[7]

Data from surgical series show that women are less likely to be referred to surgical correction of MR and are often scheduled at a later stage of the disease.[5] Presence of diffuse calcifications of the mitral apparatus and increased incidence of associated mitral stenosis impact on the choice between repair and replacement, with a lower likelihood of MV repair, whereas complexity of associated coronary artery disease leads to higher rates of incomplete revascularization, factors with clear prognostic impact.[8] Finally, life expectancy in women with primary MR is not as fully restored as in men, even after adequate surgical repair.[9]

Evidence derived from transcatheter edge-to-edge mitral valve repair (TEER) mirrors surgical experiences, showing that women are underrepresented in both trials and real-life registries, are often referred to TEER at an older age, and present with a worse functional capacity and with a higher perceived frailty that justifies a percutaneous approach.[4,10] Outcomes after TEER at short- and midterm follow-up seem to be comparable between sexes. Nonetheless, the reported persistence of limiting symptoms even after adequate management of MR in women represents an unmet need for treatment.[4]

The purpose of the present observational comparative study was to evaluate sex-specific differences in clinical and procedural characteristics, to report long-term outcomes, and to assess the impact on life expectancy in a large all-comer population of consecutive patients with MR treated by TEER enrolled in the multicenter MitraSwiss registry.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Study Overview, Registry Design, and Objectives

Since September 2011, all consecutive patients undergoing TEER using the MitraClip (Abbott, Chicago, IL) system in 10 Swiss centers were enrolled in the investigator-initiated, observational, prospective MitraSwiss registry. Details on registry design have been described previously.[11] Participating centers provide clinical, procedural, and follow-up data for each patient by a dedicated standardized online form. Data collection is centralized at the Division of Cardiology, Cardiocentro Ticino Institute (Lugano, Switzerland), where data are monitored and checked for consistency. Data acquisition was modified from 2019 onward, recording a reduced number of variables mainly for administrative reasons (details provided within Data S1).

Our primary objective was to assess in-hospital outcomes and 5-year survival of patients enrolled in the MitraSwiss registry, stratified according to sex and MR cause. As secondary objectives, we aimed to report observed survival while adjusting for expected mortality risks within the Swiss general population at 5 years as well as the clinical efficacy of TEER over time.

Patient Population

Symptomatic patients with moderate or severe MR in whom TEER was indicated and performed according to European guidelines at time of patient screening[12–14] were prospectively enrolled in the registry. Patients were referred for TEER after heart team assessment, considering surgical risk and anatomical suitability using the MitraClip system. Surgical risk was estimated by the logistic European System for Cardiac Operative Risk Evaluation I and later European System for Cardiac Operative Risk Evaluation II or the Society of Thoracic Surgeons Risk Model score. The presence of additional surgical risk factors (eg, frailty) was also considered.

For this analysis, all patients enrolled in the registry from September 2011 to December 31, 2018, aged between 60 and 89 years, were included. Survival analyses were performed including only patients with available follow-up data. Data on sex were available for all patients included in this analysis.

To avoid missing data resulting from modifications in data acquisition and extending patient follow-up, patients enrolled since 2019 were not included in the analysis.

All patients gave written informed consent for data collection. Our study conforms with principles of the Declaration of Helsinki, and the local ethics committees of each site approved registry protocol.

Echocardiography

Baseline transthoracic echocardiography and transesophageal echocardiography were performed according to a standardized protocol. Transthoracic echocardiography was performed at baseline and at all follow-up visits. MR severity was graded according to the American Society of Echocardiography recommendations.[15] Primary MR (PMR) was defined as MR associated with a structural abnormality of the mitral valve, whereas secondary MR (SMR) was defined as MR secondary to left ventricular dysfunction and/or atrial enlargement.

Increased pulmonary pressure was defined as a gradient between the right ventricle and atrium ≥30 mm Hg at echocardiography. Transesophageal echocardiography was performed at baseline and during the procedure to guide intervention and assess procedural success.

The MitraClip implantation technique has been described in previous reports.[16] Acute procedural success was defined as placement of 1 or more clips resulting in postprocedural MR severity of ≤2+.[16]

Follow-Up, Censoring, and End Points

Follow-up visits including clinical assessment and complete transthoracic echocardiography were scheduled at 1, 3, 6, and 12 months, and yearly thereafter, up to 5 years postprocedure.

Procedural details, acute procedural success, in-hospital adverse events, recurrent hospitalizations for heart failure (HF), and all-cause mortality data were extracted from the validated registry data. Vital status up to 5 years after TEER, with censoring at the end of follow-up on December 31, 2019, was ascertained. Survival time was defined as the time between procedure and death or censoring. According to the registry design, a set of prespecified clinical end points including all-cause mortality, hospitalizations for HF, redo-TEER, and mitral valve surgery due to TEER failure was defined. These were grouped into a major adverse clinical events (MACEs) combined end point. This, along with the evolution of New York Heart Association (NYHA) class and MR recurrence at follow-up, was used to assess clinical efficacy of TEER over time. Events were reviewed by a blinded clinical events adjudication committee, and disagreement was solved by consensus.

Statistical Analysis

Stata 17 (StataCorp, College Station, TX) was used for computation. Counts and percentages and median and 25th to 75th percentiles were used to describe categorical and continuous data, respectively. No imputation for missing data was performed.

Comparisons between sexes were performed using Mann-Whitney U and Fisher exact tests. Median follow-up was computed with the reverse Kaplan-Meier method. Cumulative and event-free survival was described with the Kaplan-Meier estimator. Comparisons were made with Cox regression models, and hazard ratios (HRs) and 95% CIs were computed.

Relative survival was computed and plotted according to the Ederer II method[17] up to 5 years after implant using the Swiss 2011 to 2019 mortality tables (open-access documents published by the Swiss Federal Bureau of Statistics).[18] Overall, survival was described with the life table method. Regression models (linear, logistic, or ordinal logistic depending on the variable) for repeated measures were used to assess changes over time. Robust standard errors were computed to account for intrapatient correlation of measures. Multivariable Cox regression analyses were performed to identify clinical correlates of all-cause mortality at

5 years. A confirmatory analysis was performed by weighing the role of sex for the inverse of the propensity score computed from a logistic model, where sex was the dependent variable, and age, renal impairment, anemia, functional class at admission, left ventricular ejection fraction (LVEF), MR cause, as well as center were the independent variables, all of them associated being known correlates of mortality. The balancing properties were satisfied and a common support was obtained. The Harrell C statistic was computed, and the calibration plot was plotted for model validation. The proportionality of hazards for the Cox models was satisfied. The log-rank test was also performed.

We followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines checklist for data reporting and the American Heart Association journal disparities guidelines reporting differences by race and/or ethnicity.[19]

RESULTS

Overall

Out of 1268 consecutive patients enrolled in the registry within the study period, a total of 1142 patients fulfilled study inclusion criteria. Figure S1 shows the patients' flow chart. The mean age was 78.5±6.4 years, and 454 (39.8%) were women. MR causes were balanced, with 581 patients (52.8%) having PMR and 519 (47.2%) having SMR. Surgical risk assessment qualified patients at intermediate to high risk, with a median European System for Cardiac Operative Risk Evaluation II of 4.1% and a Society of Thoracic Surgeons score of 3.7%. Table S1 reports additional details on patients' clinical characteristics.

Women were older (mean age 79.3±6.4 years versus 77.6±7.1 years, P<0.001), with a lower burden of associated cardiovascular risk factors and comorbidities than men. They also showed a lower functional capacity despite a higher mean LVEF and a higher Society of Thoracic Surgeons score.

Women received shorter procedures and a lower number of clips, whereas no differences on acute procedural success was noted between sexes (Table S2). Median transmitral gradient at procedure completion was higher in women (3 mm Hg [interquartile range [IQR], 2–4] versus 2 mm Hg [IQR, 2–3] in single-clip procedures and 3 mm Hg [IQR, 2–4.7] versus 2 mm Hg [IQR, 2–3] in double-clip procedures, both with P<0.001).

Thirty-day all-cause mortality was higher in men (1.1% versus 3.3%, unadjusted odds ratio [OR] for 30-day mortality for men 3.16 [95% CI, 1.16–10.7]; P=0.020).

Follow-up information was available in 1110 patients (97.2%). Median follow-up was 36.6 months (25th–75th percentile, 21.6–56.6), with a total time at risk of 34 410 person/months of follow-up. Over a 5-year period, 317 (28.5%) patients died, leading to a crude 5-year survival rate of 56.4% in men and 63.2% in women (P for the log-rank 0.024, unadjusted HR for 5-year mortality in men 1.30 [95% CI, 1.12–1.52]; P<0.001; Figure 1). Nonetheless, the association between men and 5-year mortality was not confirmed at multivariable Cox regression analysis (HR, 1.14 [95% CI, 0.90–1.44]; P=0.275; Table S3).

At 5-year follow-up, MACEs-free survival rate was numerically higher in women (50.5%) than in men (41.5%; unadjusted HR, 1.23 [95% CI, 1.00–1.52]; P=0.053), and no association was evident after multivariable Cox regression analysis (HR for men, 1.03 [95% CI, 0.80–1.31]; P=0.836; see Table S4). The risk of HF hospitalization at follow-up in the whole population was comparable between sexes (HR for men adjusted for MR cause, 1.28 [95% CI, 0.96–1.70;], P=0.092), whereas it was higher in patients with SMR (HR, 1.63 [95% CI, 1.16–2.27]; P=0.004; Figure S2). The risk of reintervention (redo-TEER or surgery) at follow-up was also comparable between sexes in the overall population (HR for men adjusted for MR cause, 1.59 [95% CI, 0.94–2.68]; P=0.080), whereas it was higher in PMR patients with PMR (HR for patients for PMR, 1.61 [95% CI, 1.03–2.50]; P=0.037; Figure S3).

The rate of recurrent moderate or severe mitral regurgitation over time did not differ between sexes (P=0.706) (Figure S4). Evolution of NYHA III/IV class was also comparable between sexes (P=0.260) (Figure S5).

Expected survival in an age- and calendar period-matched group was 84.7% in women, leading to a relative survival rate of 84.9% (95% CI, 75.8–92.9) and 72.4% in men, leading to a relative survival rate of 78.0% (95% CI, 70.2–85.3) without sex-related differences over time at Poisson regression analysis (P=0.137) (Figure 2).

Primary Mitral Regurgitation

Comparisons of baseline characteristics, echocardiographic findings, and surgical risk estimates in the subgroup of patients with PMR are shown in Table 1. A higher mean age at referral was evident in women with PMR. Despite a lower burden of associated comorbidities, a higher degree of functional impairment was evident in women at referral, with 74.5% presenting with NYHA III/IV and about 1 out of 3 patients with previous hospitalizations for HF.

No significant differences with respect to acute procedural success rates and procedural complications were evident between sexes in the setting of PMR (Table S5). Also, women received a lower number of clips and showed a higher median transmitral gradient at procedure completion (3 mm Hg [IQR, 2–4]

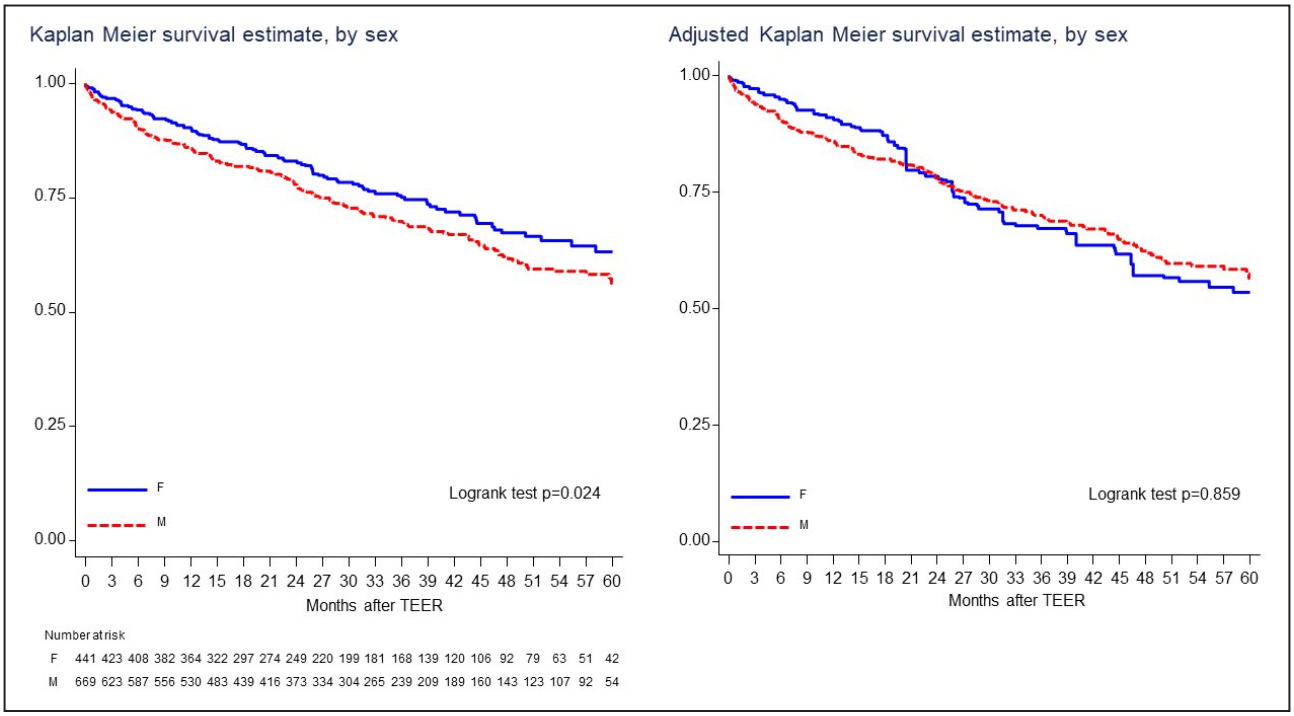

Figure 1. Unadjusted and adjusted Kaplan-Meier survival estimates of patients treated by TEER according to sex in the overall population.
F indicates female; M, male; and TEER, transcatheter edge-to-edge mitral repair.

versus 2 mm Hg [IQR, 2–3] in single-clip procedures and 3 mm Hg [IQR, 2–4] versus 2 mm Hg [IQR, 2–4] in double-clip procedures; *P*<0.001 and *P*=0.010, respectively). Notably, procedural complications and 30-day mortality rates were comparable between sexes (unadjusted OR for 30-day mortality in men, 3.20 [95% CI, 0.66–31.6]; *P*=0.193).

Over a 5-year period, 144 (24.7%) patients died, leading to a 5-year survival rate of 60.1% in men and 70.2% in women (*P* for the log-rank 0.034, HR for 5-year mortality in men, 1.45 [95% CI, 1.03–2.05]; *P*=0.035; Figure 3). Again, the association between men and all-cause 5-year mortality was not confirmed after multivariable Cox regression analysis (HR men, 1.04 [95% CI, 0.71–1.52]; *P*=0.829; Table S6).
Among patients with PMR, 5-year MACEs-free survival did not differ between sexes (58.3% in women versus 46.1% in men; unadjusted HR for men, 1.23 [95% CI, 0.83–1.82]; *P*=0.298). No differences on MR 3–4+ recurrence or evolution of NYHA class were evident between sexes over time (*P*=0.745 and 0.404, respectively; Figures S6 and S7). Expected 5-year survival in a matched group of subjects from the general Swiss population was 73.0% in women, leading to a relative survival rate of 97.4% (95% CI, 85.5–107.0), and 68.6% in men, leading to a relative survival rate of 86.8% (95% CI, 74.7–97.5), without differences between sexes at Poisson regression analysis (*P*=0.330) (Figure 4).

Secondary Mitral Regurgitation

Women with SMR were older but with less comorbidities compared with men. No relevant differences in clinical presentation were evident, with similar rates of previous hospitalization for HF, NYHA III/IV, and surgical risk estimates (Table 2). Even among patients with SMR, women received a lower number of clips and showed a higher transmitral gradient at procedure completion (3 mm Hg [IQR, 2–4] versus 2 mm Hg [IQR, 2–3] in single-clip procedures and 3 mm Hg [IQR, 3–5] versus 3 mm Hg [IQR, 2–4] in double-clip procedures; *P*<0.001 and *P*=0.008, respectively). No differences in acute procedural success and procedural complication rates were evident between sexes (Table S7).

Thirty-day mortality rates did not differ between sexes (unadjusted OR for 30-day mortality in men, 2.63 [95% CI, 0.70–14.6]; *P*=0.190).

Over a 5-year period, 159 (31.3%) patients with SMR had died, leading to a 5-year survival rate of 53.0% in men and 59.3% in women (*P* for the log-rank 0.121; HR for 5-year mortality in men, 1.31 [95% CI, 0.96–1.78]; *P*=0.090) (Figure 3). Lack of association between sex and all-cause 5-year mortality was confirmed at multivariable Cox regression analysis (HR men, 1.25 [95% CI, 0.79–1.98]; *P*=0.342; Table S8). Five-year MACE rate did not differ between sexes (5-year MACE-free survival 40.4% in women and 36.3% in men; unadjusted HR for men; 1.20 [95% CI, 0.82–1.75]; *P*=0.337). No differences

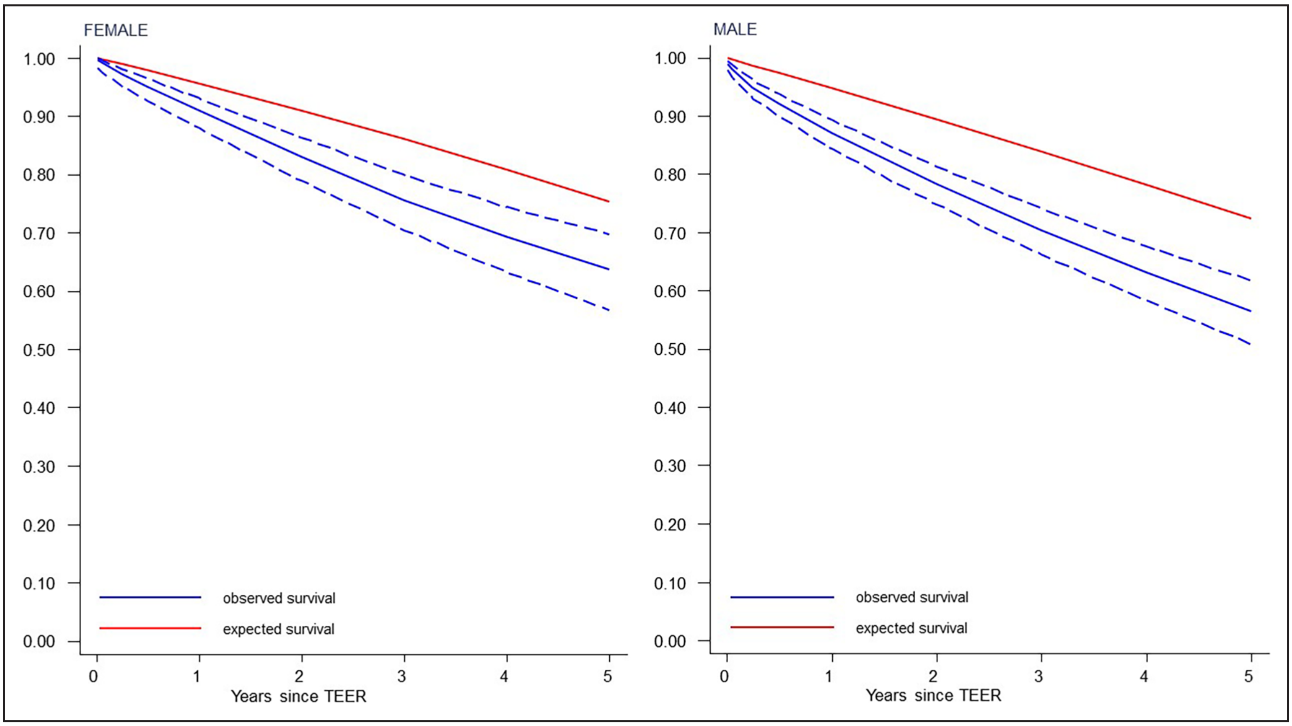

Figure 2. Observed and expected survival in study patients according to sex in the overall population.
Observed (blue solid line) with 95% CIs (blue dashed lines) and expected survival (red solid line). The displayed 95% CI allows assessment that the observed survival is inferior to the expected one, at the 5% level, given that the red line is above the upper confidence limit. TEER indicates transcatheter edge-to-edge mitral repair.

were evident between sexes on MR 3–4+ recurrence rate or evolution of NYHA class over time (*P*=0.792 and 0.178, respectively) (Figures S8 and S9).

The expected 5-year survival in a matched group of subjects derived from the general Swiss population was 79.0% in women, leading to a relative survival rate of 76.2% (95% CI, 61.5–88.6) and 76.9%, leading to a relative survival rate of 69.3% (95% CI, 58.8–78.9) in men, without differences over time between sexes at Poisson regression analysis (*P*=0.192) (Figure 4**)**.

A sensitivity analysis was performed by means of inverse probability weighting. This approach confirmed findings of the primary analysis (details provided in Data S1).

DISCUSSION

The present study reports a large analysis on sex-related long-term outcomes after TEER, the first to compare observed with expected survival stratified by sex in both primary and secondary MR.

Overall, women treated with TEER show a different clinical profile than their male counterparts. They present at an older age, more often with primary MR, with better LVEF, fewer comorbidities, but lower functional class. For the same severity of MR, women receive fewer clips and show higher postimplant mitral valve gradients, nonetheless with comparable procedural success rates. Clinically, these technical differences do not prevent them from enjoying a similar clinical benefit than men, irrespective of the cause of the MR. Late outcomes are dominated by comorbid conditions once MR is suppressed. Women do not show an increased risk of short-term mortality after TEER, which is common after surgery. Crude all-cause mortality estimates at 5 years were lower in women. Nonetheless, this difference was not ultimately associated with sex. Rates of rehospitalization for heart failure or reintervention were comparable between sexes at follow-up. As compared with the general population, residual excess mortality was evident after TEER, without sex-related differences.

When stratifying according to MR cause, both in PMR and SMR, TEER does not confer an increased risk for short-term mortality in women. Crude survival rates at 5 years after TEER is higher in women with PMR than in men, whereas no differences are evident between sexes in SMR. TEER approximated the expected survival trajectories in patients with PMR and completely restored normal life expectancy in women with PMR. A residual excess mortality persists in patients with SMR. Clinical efficacy over time does not differ between sexes, because no differences in evolution

Table 1. Clinical Baseline Characteristics of Patients With Primary Mitral Regurgitation

Characteristic	Overall n=581	Women n=246	Men n=335	*P* value
Age, y, mean±SD	80.3±6.1	81.3±5.5	79.5±6.3	0.008
BMI, kg/m², median (25th–75th)	24.6 (22.0–27.4)	23.8 (20.7–27.6)	24.9 (22.6–27.3)	0.012
BSA, m², median (25th–75th)	1.77 (1.61–1.92)	1.61 (1.51–1.75)	1.85 (1.76–1.98)	<0.001
Cardiovascular risk factors				
Hypertension, n (%)	414 (75.0)	170 (74.2)	244 (75.5)	0.765
Hyperlipidemia, n (%)	233 (42.3)	80 (34.9)	153 (47.5)	0.004
Diabetes, n (%)	80 (14.9)	26 (11.9)	54 (17.0)	0.110
Coronary artery disease, n (%)	230 (42.0)	67 (29.2)	163 (51.2)	<0.001
Comorbidities				
Previous myocardial infarction, n (%)	72 (13.1)	21 (9.0)	51 (16.0)	0.021
Previous PCI, n (%)	130 (23.8)	39 (17.1)	91 (28.6)	0.002
Previous CABG, n (%)	63 (11.5)	12 (5.3)	51 (15.9)	<0.001
Previous valve surgery, n (%)	60 (10.9)	21 (9.0)	39 (12.1)	0.271
Previous TAVI, n (%)	30 (5.4)	12 (5.2)	18 (5.6)	1.000
Previous hospitalization for heart failure, n (%)	150 (27.8)	75 (33.6)	75 (23.6)	0.011
Transplantation list, n (%)	0 (0.0)	0 (0.0)	0 (0.0)	
Atrial fibrillation, n (%)	310 (56.2)	127 (54.9)	183 (57.1)	0.664
Previous pacemaker/ICD, n (%)	78 (14.1)	34 (14.7)	44 (13.6)	0.804
Previous CRT, n (%)	25 (4.3)	8 (3.2)	17 (5.0)	0.309
COPD, n (%)	70 (12.7)	19 (8.2)	51 (15.9)	0.009
Previous major stroke, n (%)	14 (6.8)	5 (6.3)	9 (7.2)	1.000
Previous cancer, n (%)	79 (14.4)	25 (10.9)	54 (16.9)	0.050
End-stage renal disease, n (%)	7 (2.0)	2 (1.5)	5 (2.4)	0.708
Clinical presentation				
NYHA class III/IV, n (%)	379 (68.4)	173 (74.5)	206 (63.9)	0.009
Heart rate, bpm, median (25th–75th)	73 (64–82)	75 (66–85)	72 (62–81)	0.013
Hemoglobin, g/dL, median (25th–75th)	12.6 (11.3–13.7)	12.4 (11.4–13.4)	12.9 (11.2–14.0)	0.006
Creatinine, µmol/L, median (25th–75th)	102 (83–137)	92 (76–116)	109 (90–144)	<0.001
Creatinine >123 µmoL/L, n (%)	167 (30.7)	47 (20.6)	120 (38.1)	0.000
GFR, mL/min per 1.73 m², median (25th–75th)	46 (35–60)	45 (33–60)	46 (35–60)	0.390
NT-proBNP, pg/mL, median (25th–75th)	2129 (808–4017)	2279 (840–4564)	1971 (768–3826)	0.593
Echocardiography				
Moderate/severe MR, n (%)	568 (99.3)	241 (99.1)	327 (99.3)	1.000
LVEF, %, median (25th–75th)	60 (50–65)	60 (54–65)	58 (48–63)	<0.001
LVEDV, mL, median (25th–75th)	121 (92–155)	97 (78–125)	136 (108–175)	<0.001
Indexed LVEDV, mL/m², median (25th–75th)	67 (54–86)	60 (49–75)	72 (58–86)	<0.001
LVESV, mL, median (25th–75th)	47 (35–76)	38 (30–56)	56 (42–84)	<0.001
RV/RA gradient				
<30 mm Hg, n (%)	99 (22.6)	37 (19.0)	62 (25.5)	
30–50 mm Hg, n (%)	242 (55.3)	104 (53.6)	138 (56.7)	0.035
>50 mm Hg, n (%)	96 (21.9)	53 (27.3)	43 (17.7)	
LA area, cm², median (25th–75th)	30 (24–36)	29 (24–32)	32 (25–38)	0.003
Surgical risk assessment				
Logistic EuroSCORE I, %, median (25th–75th)	6.5 (4.2–13.0)	8.2 (5.0–14.3)	5.4 (3.4–10.8)	<0.001
EuroSCORE II, %, median (25th–75th)	3.4 (2.0–5.4)	3.9 (2.6–5.9)	2.9 (1.8–5.0)	<0.001
STS score, %, median (25th–75th)	3.6 (2.1–6.0)	4.1 (2.3–7.1)	3.2 (1.9–5.7)	0.001

Continuous data are provided as mean±SD or median (interquartile range). Categorical data are provided as count and percentage. End-stage renal disease is defined as patients with GFR <15 mL/min per 1.73 m². BMI indicates body mass index; BSA, body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV/RA, right ventricular to right atrial; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

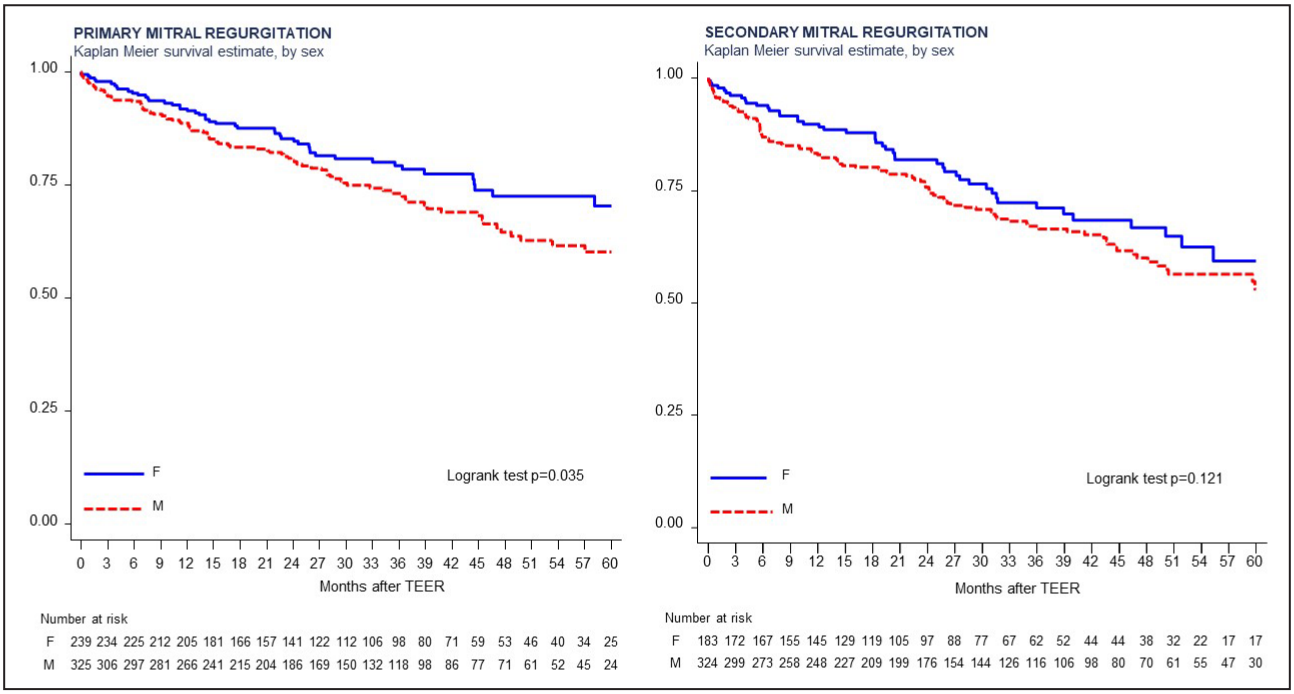

Figure 3. Crude Kaplan-Meier survival estimates of patients treated by TEER according to sex in primary and secondary mitral regurgitation.

Left, Primary mitral regurgitation. **Right**, Secondary mitral regurgitation. F indicates female; M, male; and TEER, transcatheter edge-to-edge mitral repair.

of NYHA class, recurrence of moderate–severe MR, or MACEs rate over time were evident between sexes, even after stratification according to MR cause.

Data derived from the present analysis support the adoption of TEER as a valid therapeutic option in elderly patients with MR, especially in women. To date, no sex-related differences in outcomes were evident when mitral TEER was compared with surgery in the EVEREST trial, which included patients with PMR and SMR, or when compared with medical management in SMR in both the COAPT and MITRA-FR trials.[16,20,21] The clinical profile of our population replicates data derived from surgical series and registries on TEER, indicating that women are referred for intervention at an older age and with a worse functional capacity as compared with men.[3]

From a technical perspective, despite comparable procedural success rates, women required fewer clip implants than men, and showed a higher median gradient at procedure completion, which is probably due to the smaller mitral annular dimensions in women.[22]

As evident from previous surgical series, women undergoing mitral valve surgery have a higher operative mortality and lower long-term survival than men.[9,23] These disparities, although still incompletely understood, might be partially explained by the presence of associated comorbidities and frailty.[9]

In our population, with a mean age of 79.3 years, women were independently associated with a 3-fold lower 30-day mortality than in men, confirmed after multiple correction for baseline differences. This was confirmed when stratifying according to primary or secondary causes, suggesting the risk for short-term mortality that consistently increased after surgery in women might be effectively contained by a percutaneous approach. Although the determinants of this finding are complex to analyze, because multiple factors might play a role, it is reasonable to hypothesize that a percutaneous procedure might mitigate the risk of early mortality in women, who are more frequently frail subjects with low body mass index and higher functional class at presentation, all factors associated with worse outcomes after surgery.

Disparities in outcomes at 5-year follow-up, although still favoring women with PMR in unadjusted analysis, are not ultimately associated with sex. While adjusting for baseline clinical differences by means of multivariable logistic regression analyses, the role of preoperative LVEF, functional class at presentation, anemia, and chronic kidney disease, all known correlates of mortality at follow-up in elderly patients with MR treated by TEER, overcome the impact of sex.[11]

Although our findings extend up to 5 years of previous evidence derived from registries confirming no sex-related differences in procedural and midterm outcomes after TEER,[10,22,24–27] we provide additional insights about sex-related differences and clinical outcomes according to MR cause.

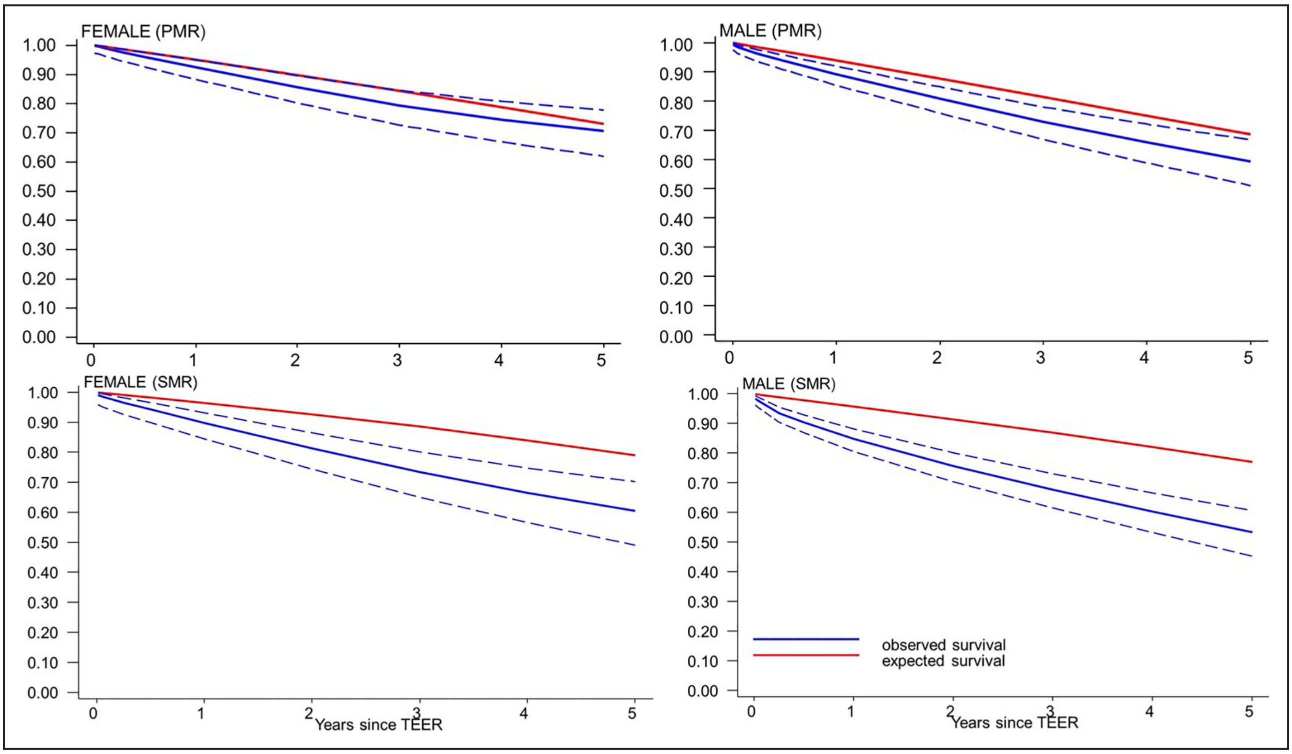

Figure 4. Observed and expected survival in study patients according to sex with primary and secondary mitral regurgitation. **Upper**, PMR. **Lower**, SMR. Observed (blue solid line) with 95% CIs (blue dashed lines) and expected survival (red solid line). The displayed 95% CI allows assessment that the observed survival is inferior to expected one, at the 5% level, given that the red line is above the upper confidence limit in all cases except for the upper left plot (female, PMR). PMR indicates primary mitral regurgitation; SMR, secondary mitral regurgitation; and TEER, transcatheter edge-to-edge mitral repair.

Women with PMR showed a higher crude survival rate at 5 years after TEER as compared with men. However, this difference was not ultimately dependent on sex, because no definitive confirmation was evident at multiple sensitivity analyses. Moreover, although surgical mitral valve repair was able to restore life expectancy in men with PMR and no or minimal symptoms,[28] women and the presence of NYHA class I triggers for surgery, such as HF symptoms or impaired LVEF, were associated with poor outcomes and excess mortality after surgery.[9,29] In our cohort, despite the presence of severe symptoms at presentation (74.5% of women with NYHA class III or IV), TEER was able to approximate expected to observed survival trajectories in men (5-year relative survival estimate, 86.8% [95% CI, 74.7–97.5]), whereas normal life expectancy was completely restored in women (5-year relative survival estimate, 97.4% [95% CI, 85.5–107.0]).

This finding is of clinical relevance and represents a peculiar effect of TEER. Data derived from surgery show, instead, that restoration of life expectancy after mitral valve repair is an expectation for patients with no or minimal symptoms, whereas those with lower functional status at presentation, such as in our cohort, pay a constant mortality price.[9,29] In addition, although mitral valve surgery showed similar postoperative survival rates[30] and reduced mortality in both sexes,[31] women do not seem to take full advantage of restoration of life expectancy.[9] Thus, this analysis confirms previous evidence from our group demonstrating restoration of life expectancy after TEER in elderly patients with PMR,[32] and supports considering the use of TEER in women, given the peculiar protective effect on TEER on short-term mortality and the ability to fully restore normal life expectancy up to 5 years, benefits that have not been observed after surgery.

In patients with SMR, 5-year survival after TEER was comparable between sexes. There was residual excess mortality in both sexes after relative survival analysis (5-year relative survival 76.2% [95% CI, 61.5–88.6] in women versus 69.3% [95% CI, 58.8–78.9] in men), due to the poor prognosis of HF that persists after treatment of MR. In SMR, indications for surgical interventions remains limited due to significant procedural risk, high rates of recurrent mitral regurgitation, and the absence of proven survival benefit conferred by surgery.[7,33] Hence, TEER might represent the only alternative for optimal medical treatment, particularly in the elderly population. Although the sustained clinical efficacy of TEER in selected patients with SMR was

Table 2. Clinical Baseline Characteristics of Study Patients With Secondary Mitral Regurgitation

Characteristic	Overall n=519	Women n=187	Men n=332	*P* value
Age, y, mean±SD	76.5±7.1	78.0±6.9	75.6±7.1	<0.001
BMI, kg/m^2, median (25th–75th)	25.4 (22.3–28.3)	24.7 (21.7–27.7)	25.6 (22.7–28.6)	<0.010
BSA, m^2, median (25th–75th)	1.82 (1.67–1.96)	1.64 (1.54–1.79)	1.89 (1.78–2.01)	<0.001
Cardiovascular risk factors				
Hypertension, n (%)	399 (79.0)	155 (86.6)	244 (74.8)	0.002
Hyperlipidemia, n (%)	284 (56.3)	92 (51.7)	192 (58.9)	0.133
Diabetes, n (%)	130 (26.7)	41 (23.5)	89 (28.5)	0.242
Coronary artery disease, n (%)	334 (66.6)	90 (50.5)	244 (75.5)	<0.001
Comorbidities				
Previous myocardial infarction, n (%)	212 (42.7)	45 (25.1)	167 (52.7)	<0.001
Previous PCI, n (%)	224 (44.9)	53 (29.6)	171 (53.4)	<0.001
Previous CABG, n (%)	138 (27.8)	23 (12.9)	115 (36.1)	<0.001
Previous valve surgery, n (%)	39 (7.7)	13 (7.2)	26 (8.0)	0.862
Previous TAVI, n (%)	20 (3.9)	5 (2.8)	15 (4.6)	0.353
Previous hospitalization for heart failure, n (%)	183 (37.1)	66 (38.1)	117 (36.5)	0.770
Transplantation list, n (%)	4 (0.86)	0 (0.0)	4 (1.3)	0.302
Atrial fibrillation, n (%)	299 (59.4)	104 (57.7)	195 (60.3)	0.571
Previous pacemaker/ICD, n (%)	161 (32.0)	38 (21.2)	123 (38.0)	<0.001
Previous CRT, n (%)	99 (19.1)	23 (12.3)	76 (22.9)	0.003
COPD, n (%)	73 (14.4)	24 (13.3)	49 (15.1)	0.692
Previous major stroke, n (%)	22 (12.7)	8 (14.3)	14 (11.9)	0.636
Previous cancer, n (%)	80 (16.0)	30 (16.9)	50 (15.4)	0.703
End-stage renal disease, n (%)	13 (3.5)	8 (5.9)	5 (2.0)	0.075
Clinical presentation				
NYHA class III/IV, n (%)	382 (75.3)	141 (77.0)	241 (74.4)	0.522
Heart rate, bpm, median (25th–75th)	72 (63–82)	73 (63–82)	71 (63–81)	0.269
Hemoglobin, g/dL, median (25th–75th)	12.5 (11.0–13.6)	11.9 (10.7–12.9)	12.8 (11.4–13.8)	<0.001
Creatinine, µmol/L, median (25th–75th)	121 (95–156)	109 (89–142)	128 (98–164)	<0.001
Creatinine >123 µmol/L, n (%)	230 (47.7)	64 (37.1)	166 (53.5)	0.001
GFR, mL/min per 1.73 m^2, median (25th–75th)	42.8 (31.0–55.1)	40.0 (29.0–51.7)	44.5 (32.0–59.9)	0.010
NT-proBNP pg/mL, median (25th–75th)	3822 (1283–8461)	3822 (1653–7821)	3848 (1283–8461)	0.907
Echocardiography				
Moderate/severe MR, n (%)	509 (98.4)	184 (98.9)	325 (98.1)	0.717
LVEF, %, median (25th–75th)	37 (29–51)	45 (34–58)	34 (26–45)	<0.001
LVEDV, mL, median (25th–75th)	163 (115–211)	108 (82–153)	189 (146–233)	<0.001
Indexed LVEDV, mL/m^2, median (25th-75th)	88 (65–117)	67 (47–91)	99 (75–123)	<0.001
LVESV, mL, median (25th-75th)	107 (66–153)	63 (37–101)	125 (97–167)	<0.001
RV/RA gradient				
<30 mmHg, n (%)	76 (19.6)	28 (19.7)	48 (19.5)	
30–50 mmHg, n (%)	223 (57.6)	84 (59.1)	139 (56.7)	0.867
>50 mmHg, n (%)	88 (22.7)	30 (21.1)	58 (23.7)	
LA area, cm^2, median (25th–75th)	30 (25–36)	26 (22–32)	32 (27–39)	<0.001
Surgical risk assessment				
Logistic EuroSCORE I, %, median (25th–75th)	8.98 (4.6–21.2)	9.99 (5.13–19.07)	8.50 (4.40–23.00)	0.861
EuroSCORE II, %, median (25th–75th)	5.25 (3.11–11.0)	4.81 (3.24–7.84)	5.54 (3.04–11.75)	0.231
STS score, %. median (25th–75th)	3.87 (2.05–8.48)	3.96 (2.25–8.6)	3.71 (1.92–8.47)	0.283

Continuous data are provided as mean±SD or median (interquartile range). Categorical data are provided as count (percentage). End-stage renal disease is defined as patients with GFR <15 mL/min per 1.73 m^2. BMI indicates body mass index; BSA, body surface area; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; EuroSCORE, European System for Cardiac Operative Risk Evaluation; GFR, glomerular filtration rate; ICD, implantable cardioverter defibrillator; LA, left atrial; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral regurgitation; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; RV/RA, right ventricular to right atrial; STS, Society of Thoracic Surgeons; and TAVI, transcatheter aortic valve implantation.

demonstrated by the 5-year results of the COAPT trial reporting a 5-year survival rate of 46.7%,[34] evidence from real-world experience was lacking. Our data fill this gap by providing outcomes and relative survival estimates stratified by sex, showing that high 5-year survival rates can be achieved after treating SMR with TEER in a real-world cohort.

Another issue raised by previous reports is related to the sustained clinical efficacy of TEER in women, with signals pointing toward a blunted effect over time in this class of patients. Reports from registries showed that women treated with TEER more frequently remained symptomatic after treatment, resulting in a lower functional class at follow-up.[10,24] Moreover, data derived from the COAPT trial showed that in patients with SMR, despite comparable procedural success rates and survival benefits conferred by percutaneous treatment between both sexes, the effect of TEER in reducing HF hospitalizations was less pronounced in women beyond the first year after treatment.[35] We demonstrated that the combined end point of all-cause mortality, HF hospitalizations, redo-TEER, and mitral valve surgery due to TEER failure, together with NYHA class evolution and MR recurrence at follow up, do not differ between sexes in the overall population, nor after stratification for MR cause, confirming a stable clinical effect over time in both sexes.

The results of our analysis have clinical implications on the management of patients with severe MR considered for mitral TEER. According to the lack of short-term excess mortality, TEER should be encouraged in elderly women deemed not to be candidates for surgery, irrespective from MR cause, with suitable anatomical characteristics. Moreover, in the setting of PMR, TEER was able to completely restore postprocedural life expectancy in women, filling the gap left by surgery in this subgroup of patients. This represents an additional justification supporting the adoption of TEER in this population.

Finally, a comparable clinical efficacy between sexes was observed at follow-up, not confirming previous reports suggesting persistence of limiting symptoms even after adequate management of MR in women.

Limitations

Our findings must be interpreted in the context of the following limitations. Five-year follow-up was not available in all patients, limiting median follow-up at 36 months. Younger patients aged <60 years were not included because of potential inaccuracies in relative survival estimations due to the peculiar clinical characteristics of this small patient subgroup (ie, advanced HF, bridge to transplantation). Similarly, patients aged ≥90 years were excluded due to their small sample size, which could limit comparisons with a matched group along with the risk of survivor bias with inaccuracies in relative survival estimations. Even if no data have been acquired in the registry on patients' race and/or ethnicity, a large majority of subjects included in the registry are White patients. Thus, our results might not fully apply to patient cohorts in which other races and ethnicities are widely represented. Nonetheless, in light of the similarities of the clinical profile of our cohort with previously reported data, the external validity of our analysis should be preserved.

Our data set did not include quantitative data on preprocedural MR, thus not allowing a further stratification of SMR proportionate/disproportionate MR,[36] nor echocardiographic data describing the location or complexity of the prolapse, proportion of anterior mitral valve prolapse, and Barlow disease in patients with PMR. However, all subjects were evaluated by a local heart team and deemed to have suitable anatomy for TEER. Frailty scores were not included in the data set. Our population was treated with first- and third-generation MitraClip devices; thus, the effect of a newer version of the device remains to be established. Finally, no data on baseline medical therapy, its evolution over time, or core laboratory evaluation of echocardiographic parameters are available.

CONCLUSIONS

Following mitral TEER, women are associated with a lower short-term mortality, whereas no outcome differences were observed at 5-year follow-up. Despite clinical and procedural differences between sexes, equality was achieved with similar clinical efficacy over time and confirmed after stratification for MR cause. TEER was able to confer high relative survival estimates and to restore life expectancy in elderly, highly symptomatic women with PMR. These findings, peculiar achievements of a percutaneous approach to MR treatment, emphasize the need to consider a patient's sex when tailoring the management of patients with MR.

ARTICLE INFORMATION

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Supplemental Material

Data S1
Tables S1–S8
Figures S1–S8

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