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RESEARCH ARTICLE

Transcatheter mitral valve replacement or repair for secondary mitral regurgitation: a propensity score-matched analysis

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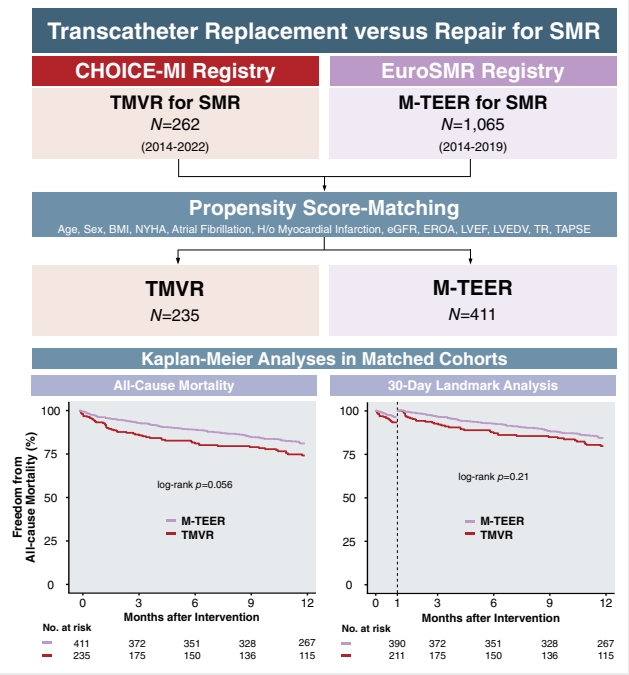
Aims This study aimed to compare outcomes after transcatheter mitral valve replacement (TMVR) and mitral valve transcatheter edge-to-edge repair (M-TEER) for the treatment of secondary mitral regurgitation (SMR).

Methods and results The CHOICE-MI registry included 262 patients with SMR treated with TMVR between 2014 and 2022. The EuroSMR registry included 1065 patients with SMR treated with M-TEER between 2014 and 2019. Propensity score (PS) matching was performed for 12 demographic, clinical and echocardiographic parameters. Echocardiographic, functional and clinical outcomes out to 1 year were compared in the matched cohorts. After PS matching, 235 TMVR patients (75.5 years [70.0, 80.0], 60.2% male, EuroSCORE II 6.3% [interquartile range 3.8, 12.4]) were compared to 411 M-TEER patients (76.7 years [70.1, 80.5], 59.0% male, EuroSCORE II 6.7% [3.9, 12.4]). All-cause mortality was 6.8% after TMVR and 3.8% after M-TEER at 30 days ($p = 0.11$), and 25.8% after TMVR and 18.9% after M-TEER at 1 year ($p = 0.056$). No differences in mortality after 1 year were found between both groups in a 30-day landmark analysis (TMVR: 20.4%, M-TEER: 15.8%, $p = 0.21$). Compared to M-TEER, TMVR resulted in more effective mitral regurgitation (MR) reduction (residual MR ≤1+ at discharge for TMVR vs. M-TEER: 95.8% vs. 68.8%, $p < 0.001$), and superior symptomatic improvement (New York Heart Association class ≤II at 1 year: 77.8% vs. 64.3%, $p = 0.015$).

Conclusion In this PS-matched comparison between TMVR and M-TEER in patients with severe SMR, TMVR was associated with superior reduction of MR and superior symptomatic improvement. While post-procedural mortality tended to be higher after TMVR, no significant differences in mortality were found beyond 30 days.

Graphical Abstract



Transcatheter replacement versus repair for secondary mitral regurgitation (SMR). BMI, body mass index; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; H/o, history of; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; M-TEER, mitral valve transcatheter edge-to-edge repair; NYHA, New York Heart Association; TMVR, transcatheter mitral valve replacement; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

Keywords Functional mitral regurgitation • Secondary mitral regurgitation • Transcatheter edge-to-edge repair • Transcatheter mitral valve replacement

Introduction

Secondary mitral regurgitation (SMR) affecting heart failure (HF) patients adversely impacts prognosis and disease progression, independent of HF severity.[1,2] Progressive SMR, found in one of five SMR patients, is particularly associated with poor outcomes.[3] Treatment of SMR is complex and requires guideline-directed medical therapy (GDMT).[4] Patients with persistent severe, symptomatic SMR despite GDMT should be referred to a multidisciplinary heart team for consideration of surgical or transcatheter intervention.[5] Current guidelines recommend concomitant mitral valve surgery if coronary artery bypass grafting (CABG) is indicated, whereas mitral valve transcatheter edge-to-edge repair (M-TEER) should be considered in symptomatic patients with suitable anatomy.[4–6] The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial demonstrated a significant benefit of M-TEER in addition to GDMT with regard to both all-cause mortality and HF hospitalization in a well-defined patient cohort.[7] However, a relevant proportion of SMR patients is neither amenable to open-heart surgery, due to advanced age or comorbidities, nor to M-TEER, mainly for anatomical reasons.[8] Transcatheter mitral valve replacement (TMVR), a novel technology to treat native mitral regurgitation (MR), is rapidly evolving and represents a complementary option for patients ineligible for surgery and M-TEER.[9] While various TMVR devices are still under early clinical investigation, data on patient selection, predictors of treatment success and clinical endpoints are incomprehensive.[10–13] Moreover, in the absence of randomized controlled trials, there is currently no data comparing outcomes of patients undergoing TMVR to established SMR therapies.

The CHoice of Optlmal transCatheter trEatment for Mitral Insufficiency Registry (CHOICE-MI) is an international multicentre study for patients undergoing TMVR screening and includes a large number of patients who underwent TMVR with different available devices.[14] The European Registry of transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR) is a large European registry including SMR patients treated with M-TEER.[15] With this study, we aimed to provide first comparative data on early clinical, echocardiographic and functional outcomes in propensity score (PS)-matched SMR patients undergoing TMVR or M-TEER using data from these two large, international multicentre registries.

Methods

Registry designs

The CHOICE-MI registry (ClinicalTrials.gov Identifier: NCT04688190) is a global, multicentre study investigating outcomes of MR patients screened for TMVR irrespective of MR aetiology. Patients from 31 centres undergoing TMVR evaluation from May 2014 until July 2022 were retrospectively enrolled. All patients were at high or prohibitive surgical risk and considered suboptimal candidates for M-TEER by local heart team consensus. Reasons for M-TEER ineligibility are summarized in online supplementary *Table S1*.

The EuroSMR registry (German Clinical Trials Register Identifier: DRKS00017428) is a retrospective, multicentre study including SMR patients undergoing M-TEER at 11 European academic centres between November 2008 and September 2019. All patients were deemed to be at high or prohibitive surgical risk.

For the present study, all patients undergoing TMVR for severe SMR from the CHOICE-MI registry and all patients undergoing M-TEER from the EuroSMR registry between 2014 and 2022 were included (*Figure 1*). The individual decision to perform TMVR or M-TEER was made by the local interdisciplinary heart team. Anonymized data were centrally collected for analysis. Both studies and all data collection were performed with the approval of the institutional review boards of the respective academic centres and the study was performed in accordance with the Declaration of Helsinki.

Transcatheter devices

Transcatheter mitral valve replacement was performed within clinical trials, as compassionate use or commercial implants. Ten dedicated mitral valve devices were implanted using either transapical (CardiAQ [Edwards Lifesciences LLC, Irvine, CA, USA], Fortis [Edwards Lifesciences LLC, Irvine, CA, USA], HighLife [HighLife SAS, Paris, France], Intrepid [Medtronic Inc., Redwood City, CA, USA], Tendyne [Abbott Structural Heart, Santa Clara, CA, USA], Tiara [Neovasc Inc., Richmond, Canada]) or transfemoral access (CardiAQ [Edwards Lifesciences LLC, Irvine, CA, USA], Cardiovalve [Cardiovalve Ltd., Or Yehuda, Israel], Cephea [Abbott Structural Heart, Santa Clara, CA, USA], Evoque [Edwards Lifesciences LLC, Irvine, CA, USA], HighLife [HighLife SAS, Paris, France], Sapien M3 [Edwards Lifesciences, Irvine, CA, USA]). Anatomical eligibility for TMVR was adjudicated by local heart teams and device manufacturers depending on local and/or clinical trial protocols.

Mitral valve transcatheter edge-to-edge repair was performed using the MitraClip device (Abbott Structural Heart, Santa Clara, CA, USA) via transfemoral access.

Echocardiographic analysis

Severity and aetiology of MR was assessed by each site using an integrative approach to grade MR severity based on an established five-grade system (none/trace, 1+, 2+, 3+, 4+). MR severity was assessed at baseline, discharge and 1 year after intervention. Standard echocardiographic assessment comprised effective regurgitant orifice area (EROA), left ventricular ejection fraction (LVEF), left ventricular end-diastolic and end-systolic diameters (LVEDD and LVESD), left ventricular end-diastolic and end-systolic volumes (LVEDV and LVESV), tricuspid annular plane systolic excursion (TAPSE), pulmonary artery systolic pressure (PASP), and tricuspid regurgitation (TR) severity. Right ventricular (RV)–pulmonary artery (PA) coupling was defined as the ratio of TAPSE per PASP (mm/mmHg). All echocardiograms were performed by experienced clinicians.

Study endpoints

The primary study endpoint was defined as all-cause mortality at 1 year after TMVR or M-TEER. Procedural mortality was defined as mortality occurring within 72 h after the index procedure. Incident HF hospitalization and the composite of all-cause mortality or HF hospitalization at 1 year were included as secondary clinical study endpoints. HF hospitalization was defined as new-onset or worsening signs and symptoms of HF requiring hospitalization. Echocardiographic outcome was assessed by transthoracic echocardiography at discharge

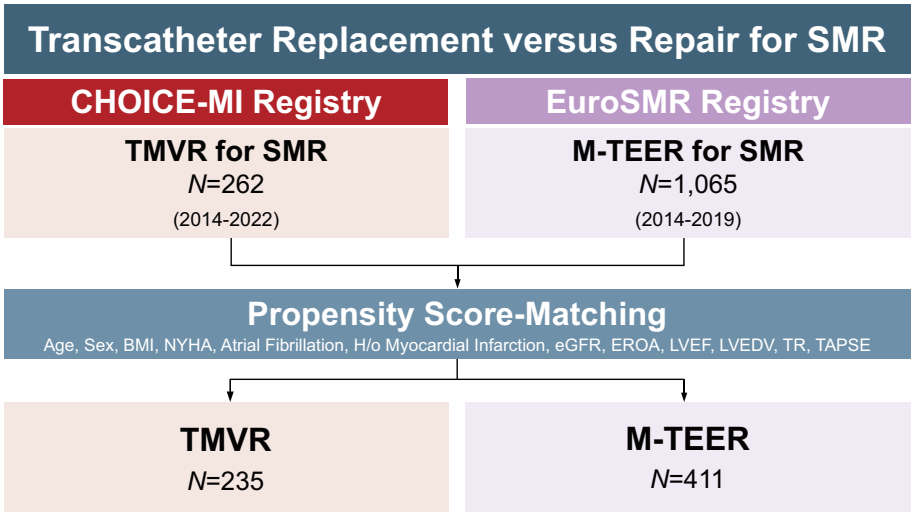


Figure 1 Study flow chart. The figure summarizes patient selection from two registries (CHOICE-MI and EuroSMR), parameters selected for propensity score calculation and matched patients undergoing transcatheter mitral valve replacement (TMVR) or mitral valve transcatheter edge-to-edge repair (M-TEER). BMI, body mass index; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; H/o, history of; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; NYHA, New York Heart Association; SMR, secondary mitral regurgitation; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

and at 1 year after intervention. Functional outcome was assessed according to New York Heart Association (NYHA) functional class at baseline and 1 year after intervention.

Statistical analysis

Continuous variables are shown as medians with interquartile range (IQR) and were compared using the Mann–Whitney U test. Binary variables are shown as counts (frequencies) and compared using the χ^2 test.

Missing data were handled by chained-equation multiple imputation (10 imputed data sets; R package mice). The amount of missing data is given in online supplementary *Table S2*. TMVR and M-TEER patients were matched using 1:2 nearest neighbour PS matching with Mahalanobis distance and caliper 0.2. PS calculation included age, sex, body mass index (BMI), NYHA functional class (III/IV), atrial fibrillation, history of myocardial infarction, estimated glomerular filtration rate (eGFR <30 ml/min/1.73 m^2), EROA, LVEF, LVEDV, TR severity ≥3+, and RV dysfunction (TAPSE <17 mm). PS matching was conducted in each imputed data set separately, so varying patients were matched per data set and all results are presented as approximated pooled results. Detailed ranges of group sizes for each category regarding MR severity and NYHA functional class are given in online supplementary *Table S3*. Alluvial plots were fitted for paired MR severity datasets at baseline, discharge and 1 year for TMVR and M-TEER.

The paired Mann–Whitney U test was used to test for differences between time points regarding MR severity or NYHA functional class. Survival probabilities of patients undergoing TMVR or M-TEER were estimated using the Kaplan–Meier method. Groups were compared using the log-rank test. A sensitivity analysis excluding TMVR devices with less than four implants was performed. Short-term and 1-year clinical and echocardiographic outcomes were also compared between TMVR and M-TEER for different periods (2014–2022). The median follow-up time was estimated by the reverse Kaplan–Meier estimator. A conditional Cox regression model was used to estimate hazard ratios (HR) and corresponding 95% confidence intervals (CI) for pre-specified subgroups. Spline curves were provided for the impact of LVEF and EROA on 1-year mortality in exemplary datasets for both groups.

Follow-up of outcomes was censored at 2 years. A p-value of <0.05 was considered statistically significant. All analyses were performed with R statistical software version 4.0.3 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Study population

A total of 1327 patients with SMR, 262 undergoing TMVR (CHOICE-MI registry) and 1065 undergoing M-TEER (EuroSMR registry) between 2014 and 2022, met the inclusion criteria and were assigned to PS matching. After PS calculation, 235 TMVR patients were matched to 411 M-TEER patients. After PS matching for age, sex, BMI, NYHA functional class, atrial fibrillation, history of myocardial infarction, eGFR, EROA, LVEF, LVEDV, TR severity, and RV dysfunction, baseline characteristics were overall equally distributed. Standardized differences before and after PS matching for parameters included for PS calculation are given in online supplementary *Table S4* and are illustrated in a balance plot in online supplementary *Figure S1*. There were no differences between groups with regard to age ([all following: TMVR vs. M-TEER] 75.5 years [IQR 70.0, 80.0] vs. 76.7 years [IQR 70.1, 80.5]; $p = 0.48$), male sex (60.2% [$n = 142$] vs. 59.0% [$n = 243$]; $p = 0.77$), EuroSCORE II (6.3% [IQR 3.8, 12.4] vs. 6.7% [IQR 3.9, 12.4]; $p = 0.69$), and LVEF (39.3% [IQR 32.3, 47.7] vs. 39.4% [IQR 32.0, 49.4]; $p = 0.98$) (*Table 1*). Severity of MR according

Table 1 Baseline characteristics in unmatched and matched cohorts

Variable	Unmatched cohorts				Matched cohorts			
	All (n = 1327)	TMVR (n = 262)	M-TEER (n = 1065)	p-value	All (n = 646)	TMVR (n = 235)	M-TEER (n = 411)	p-value
Age (years)	76.0 (69.0, 80.0)	76.0 (70.0, 80.0)	76.0 (69.0, 80.0)	0.63	76.0 (70.1, 80.2)	75.5 (70.0, 80.0)	76.7 (70.1, 80.5)	0.48
Male sex, n (%)	848 (63.9)	160 (61.1)	688 (64.6)	0.32	384 (59.5)	142 (60.2)	243 (59.0)	0.77
BMI (kg/m^2)	25.7 (23.1, 28.8)	25.69 (22.5, 28.8)	25.7 (23.2, 28.8)	0.56	25.8 (23.0, 28.6)	25.7 (22.6, 28.8)	25.7 (23.3, 28.6)	0.73
Risk stratification								
EuroSCORE II (%)	6.5 (3.9, 12.2)	6.3 (3.9, 12.4)	6.6 (3.9, 11.9)	0.76	6.5 (3.9, 12.4)	6.3 (3.8, 12.4)	6.7 (3.9, 12.4)	0.69
Cardiovascular risk factors, n (%)								
Hypertension	889 (73.5)	189 (72.4)	700 (73.8)	0.70	449 (74.6)	167 (71.5)	281 (76.5)	0.23
Diabetes	385 (30.7)	76 (29.0)	309 (31.2)	0.55	179 (28.8)	69 (29.3)	110 (28.6)	0.7
Cardiac disease, n (%)								
Atrial fibrillation	835 (62.9)	162 (61.8)	673 (63.2)	0.77	406 (62.9)	142 (60.7)	264 (64.2)	0.48
Prior myocardial infarction	396 (29.9)	117 (44.7)	279 (26.2)	<0.001	250 (38.7)	96 (40.9)	154 (37.4)	0.48
Prior CABG	272 (20.5)	86 (32.8)	186 (17.5)	<0.001	157 (24.3)	74 (31.4)	83 (20.2)	0.007
Prior PCI	445 (43.1)	117 (44.7)	328 (42.5)	0.60	251 (46.0)	104 (44.2)	147 (47.4)	0.60
Comorbidities, n (%)								
COPD	207 (15.6)	45 (17.2)	162 (15.2)	0.48	102 (15.9)	39 (16.5)	64 (15.5)	0.96
Prior stroke	135 (10.2)	32 (12.2)	103 (9.7)	0.27	64 (10.0)	27 (11.6)	37 (9.1)	0.46
eGFR <30 ml/min/1.73 m^2	259 (19.5)	46 (17.4)	214 (20.1)	0.38	104 (16.1)	42 (17.8)	62 (15.2)	0.52
Heart failure medication, n (%)								
Beta-blocker	1047 (93.5)	202 (89.4)	845 (94.5)	0.0082	506 (91.9)	181 (89.1)	325 (93.5)	0.15
ACE-I/ARB/ARNI	948 (76.0)	183 (80.6)	765 (75.0)	0.088	457 (76.2)	162 (79.5)	295 (74.5)	0.23
MRA	603 (71.5)	110 (53.7)	493 (77.2)	<0.001	272 (64.0)	97 (53.3)	175 (72.1)	<0.001
Echocardiographic parameters								
MR severity ≥3+, n (%)	1274 (96.0)	260 (99.2)	1014 (95.2)	0.0050	632 (97.8)	233 (99.2)	399 (97.1)	0.26
LVEF (%)	35.0 (27.0, 44.2)	40.0 (33.0, 48.0)	34.0 (25.7, 42.9)	<0.001	39.3 (32.0, 48.5)	39.3 (32.3, 47.7)	39.4 (32.0, 49.4)	0.98
LVEF <30%, n (%)	398 (30.0)	28 (10.8)	370 (34.8)	<0.001	103 (15.9)	28 (11.8)	75 (18.3)	0.055
LVEDD (mm)	60.0 (51.0, 67.0)	60.0 (54.4, 65.0)	60.0 (50.0, 68.0)	0.77	59.0 (50.9, 65.3)	59.9 (54.0, 64.8)	58.4 (47.3, 65.8)	0.064
LVESD (mm)	48.0 (39.0, 56.0)	46.0 (40.0, 53.2)	48.0 (37.2, 56.0)	0.32	46.3 (37.3, 54.2)	46.2 (40.0, 53.9)	46.3 (34.6, 54.5)	0.25
LVEDV (ml)	165.8 (121.3, 216.7)	166.2 (125.9, 207.4)	165.3 (119.3, 219.0)	0.63	156.9 (114.5, 205.2)	164.1 (125.2, 205.4)	153.0 (110.8, 205.6)	0.22
LVESV (ml)	106.0 (70.0, 150.0)	100.0 (67.8, 130.0)	108.5 (70.2, 156.0)	0.029	93.2 (61.8, 132.5)	99.6 (67.3, 131.1)	91.1 (56.8, 134.6)	0.22
EROA (mm^2)	0.29 (0.20, 0.40)	0.38 (0.26, 0.47)	0.26 (0.20, 0.37)	<0.001	0.32 (0.22, 0.44)	0.36 (0.26, 0.44)	0.30 (0.21, 0.42)	0.025
PASP (mmHg)	46.1 (37.7, 57.0)	47.0 (38.0, 59.2)	46.0 (37.3, 56.9)	0.33	46.3 (37.7, 57.6)	47.0 (38.1, 58.7)	46.0 (37.4, 57.1)	0.62
TAPSE (mm)	17.0 (14.0, 20.0)	16.3 (13.0, 20.0)	17.0 (14.0, 20.0)	0.20	16.6 (13.6, 20.0)	16.6 (13.1, 20.0)	16.7 (13.9, 19.8)	0.68
RV-PA coupling (mm/mmHg)	0.36 (0.27, 0.48)	0.35 (0.25, 0.45)	0.36 (0.28, 0.48)	0.14	0.35 (0.27, 0.47)	0.35 (0.26, 0.46)	0.35 (0.27, 0.48)	0.61
TR (≥ moderate)	695 (52.4)	124 (47.3)	571 (53.6)	0.079	317 (49.1)	111 (47.3)	206 (50.2)	0.56

Continuous variables are shown as medians (25th, 75th percentile) and were compared using the Mann–Whitney U test. Binary variables are shown as counts (frequencies) and compared using the χ^2 test.

ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BMI, body mass index; CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; LVESV, left-ventricular end-systolic volume; M-TEER, mitral valve transcatheter edge-to-edge repair; MR, mitral regurgitation; MRA, mineralocorticoid receptor antagonist; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TMVR, transcatheter mitral valve replacement; TR, tricuspid regurgitation.

Table 2 Study endpoints in the matched cohorts

Endpoints	TMVR (n = 235)	M-TEER (n = 411)	p-value
Procedural mortality, n (%)	4 (1.7)	2 (0.5)	0.30
All-cause mortality[a] (30 days) (%)	6.8	3.8	0.11
All-cause mortality[a] (1 year) (%)	25.8	18.9	0.056
HF hospitalization[a] (1 year) (%)	24.6	19.7	0.26
All-cause mortality or HF hospitalization[a] (1 year) (%)	39.2	34.9	0.27
MR ≥2+ (1 year), n (%)	4 (2.96)	67 (36.58)	<0.001
MR ≥3+ (1 year), n (%)	3 (2.58)	20 (10.73)	0.023
NYHA functional class I or II (1 year), n (%)	102 (77.78)	161 (64.31)	0.015

HF, heart failure; MR, mitral regurgitation; M-TEER, mitral valve transcatheter edge-to-edge repair; NYHA, New York Heart Association; TMVR, transcatheter mitral valve replacement.
[a]Kaplan–Meier estimates.

to EROA was higher in TMVR patients (0.36 cm^2 [IQR 0.26, 0.44] vs. 0.30 cm^2 [IQR 0.21, 0.42], p = 0.025). With the exception of mineralocorticoid receptor antagonists, used more frequently in M-TEER patients, no differences in the use of HF medication were noted. The rate of prior CABG was higher in the TMVR group (31.4% [n = 74] vs. 20.2% [n = 83], p = 0.007). Most patients in the TMVR cohort were treated with transapical TMVR devices (n = 220, 93.6%). A detailed list of implanted TMVR devices is given in online supplementary *Table S5*.

Outcome analyses

Primary and secondary study endpoints

In the PS-matched cohorts, a total of 221 deaths (34.2%) and 120 HF rehospitalizations (26.3%) occurred over a median follow-up of 2.1 years (95% CI 2.0–2.3; TMVR: 1.8 years [95% CI 1.4–2.3]; M-TEER: 2.2 years [95% CI 2.0–2.5]). All primary and secondary outcomes are given in *Table 2*.

Procedural mortality in the PS-matched cohorts occurred in four patients (1.7%) after TMVR and in two patients (0.5%) after M-TEER (p = 0.30). Kaplan–Meier estimated 30-day all-cause mortality in the matched cohorts was 6.8% after TMVR and 3.8% after M-TEER (p = 0.11). Kaplan–Meier analysis for the primary endpoint of all-cause mortality after 1 year is given in *Figure 2A*. The rate of all-cause mortality after 1 year was 25.8% in patients undergoing TMVR and 18.9% in patients receiving M-TEER (p = 0.056). In a 30-day landmark analysis, the rates of all-cause mortality after 1 year were 20.4% after TMVR and 15.8% after M-TEER (p = 0.21; *Figure 2B*). There were no differences between TMVR and M-TEER regarding the 1-year endpoints of HF hospitalization (TMVR: 24.6%, M-TEER: 19.7%; p = 0.26) and all-cause mortality or HF hospitalization (TMVR: 39.2%, M-TEER: 34.9%; p = 0.27; online supplementary *Figure S2*). A sensitivity analysis excluding TMVR devices with less than four implants showed similar results for the primary endpoint (online supplementary *Figure S3*). Outcomes according to different enrolment periods are presented in online supplementary *Table S6*. Kaplan–Meier analyses for all 2-year endpoints in the matched and unmatched cohorts are given in online supplementary *Figures S4* and *S5*.

The impact of M-TEER versus TMVR on the primary endpoint of all-cause mortality after 1 year in pre-specified subgroups is given in *Figure 3*. Formal testing for interaction was negative for all subgroups (p for interaction ≥0.05), however the data suggested a greater benefit after M-TEER compared to TMVR in patients aged 75 or older (HR 0.53 [95% CI 0.32–0.88], p = 0.016), female patients (HR 0.48 [95% CI 0.26–0.90], p = 0.024), patients with LVEF ≥30% (HR 0.60 [95% CI 0.38–0.96], p = 0.033), without RV dysfunction (TAPSE ≥17 mm: HR 0.42 [95% CI 0.20–0.86], p = 0.020; RV-PA coupling ratio ≥0.274 mm/mmHg: HR 0.53 [95% CI 0.31–0.92], p = 0.025), and without ≥ moderate TR (HR 0.56 [95% CI 0.31–0.99], p = 0.048). Spline curves for the impact of LVEF and EROA on 1-year mortality after TMVR and M-TEER are given for exemplary datasets in online supplementary *Figure S6*.

Functional outcome

At baseline, there was no difference between the TMVR and M-TEERgroups regarding NYHA functional class (p = 0.17; *Figure 4*). Most patients in both groups were classified as NYHA functional class III or IV at baseline (TMVR: n = 196, 83.3%; M-TEER: n = 359, 87.4%; p = 0.22). At 1-year follow-up, significant functional improvement compared to baseline functional status was observed for both groups. The reported rate of patients at NYHA functional class ≤II at 1 year was significantly higher in the TMVR group (77.8%; 102 of 131 patients) compared to the M-TEER group (64.3%; 161 of 250 patients; p = 0.015). Group sizes and percentages are given as approximated values derived from 10 matched data sets.

Echocardiographic outcome

At baseline, MR severity was 3+ or 4+ in 99.2% (n = 233, TMVR) and 97.1% (n = 399, M-TEER; p = 0.26; *Figure 5*). According to echocardiography at discharge, residual MR ≤1+ was present in 95.8% (213 of 222 patients) of TMVR patients, compared to 68.8% (282 of 410 patients) of M-TEER patients (p < 0.001). At 1-year follow-up, the rates of residual MR ≤1+ were 94.5% (125 of 132 patients) after TMVR, compared to 50.1% (92 of 183 patients) after M-TEER (p < 0.001). Group sizes and percentages are given as approximated numbers derived from 10 matched data sets.

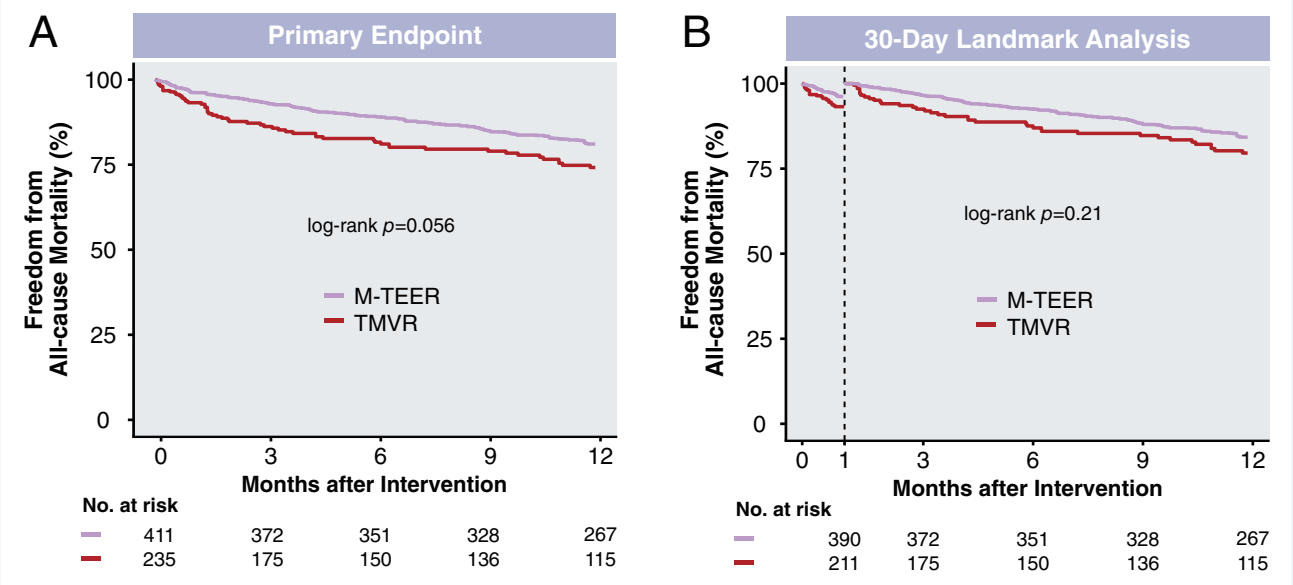


Figure 2 Primary endpoint outcomes. Kaplan–Meier analysis for freedom from the primary study endpoint of all-cause mortality after 1 year (*A*) and a Kaplan–Meier 30-day landmark analysis for freedom from all-cause mortality (*B*) are given for the propensity score-matched cohorts of transcatheter mitral valve replacement (TMVR) and mitral valve transcatheter edge-to-edge repair (M-TEER).

The evolution of MR severity for patients with paired data at baseline, discharge and 1 year (TMVR: $n = 125$; M-TEER: $n = 185$) is depicted in *Figure 6*. The rates of recurrent MR ≥2+ at 1 year among patients with successful reduction to MR ≤1+ at discharge were 2.5% (3 of 120 patients) in the TMVR group (*Figure 6A*) and 38.1% (53 of 139 patients) in the M-TEER group (*Figure 6B*). Among patients with residual MR ≥2+ at discharge, 20.0% (1 of 5 patients) in the TMVR group and 26.1% (12 of 46 patients) in the M-TEER group improved to MR ≤1+ at 1 year.

Discussion

This is the first and largest comparative analysis of SMR patients undergoing TMVR or M-TEER. This analysis is a PS-matched comparison of two real-world registries and does not bear comparison with a randomized controlled trial. However, our results allow for a differential, balanced and real-world comparison between both transcatheter therapies and provide important information on the potential role of TMVR as a complementary treatment alternative to M-TEER.

The main findings can be summarized as follows (*Graphical Abstract*): (i) although 30-day and 1-year mortality rates tended to be higher following TMVR, a 30-day landmark analysis demonstrated no differences regarding all-cause mortality beyond 30 days with an alignment of TMVR and M-TEER survival curves out to 1 year; (ii) especially in patients with less advanced left and right ventricular disease, M-TEER seemed to confer a lower risk of 1-year all-cause mortality compared to TMVR; (iii) following a more complete, predictable, and durable reduction of MR by TMVR, the symptomatic improvements after TMVR appeared to be superior compared to M-TEER; and (iv) TMVR as a novel transcatheter treatment represents a promising therapy for selected candidates suffering from SMR and complements established treatment options.

Outcomes and mitral regurgitation elimination

The outcomes of the first 100 patients treated with the transapical Tendyne TMVR system (Abbott Structural Heart, Santa Clara, CA, USA) included into the Global Feasibility Study demonstrated sustained MR elimination and improvements in quality of life out to 2-year follow-up in a cohort including mostly SMR patients.[16] The Kaplan–Meier estimate for all-cause mortality at 2 years was 41.6% in this study. Given a mortality rate of 46.1% in the control arm of the COAPT trial treated by GDMT only, this rate appears considerably high.[7] Notably, mortality and HF rehospitalization rates were highest within the first 3 months after implantation.[16] Our study confirms these findings with mortality rates of 25.8% and 39.4% at 1 and 2 years after TMVR, respectively. When compared to a PS-matched M-TEER group, higher event rates were observed within the first 30 days after TMVR followed by comparable mortality rates thereafter. A 30-day landmark analysis showing no mortality difference beyond 30 days confirmed that early post-procedural mortality currently represents the most important difference between TMVR and M-TEER. Although this finding appears to be attributable to the technique of TMVR itself, elevated mortality rates can somehow be expected in a high-risk cohort and seem acceptable in the context of learning curves with novel devices at early stages. However, for TMVR to become a truly competitive treatment alternative to M-TEER, the reduction of early mortality represents a key requirement.

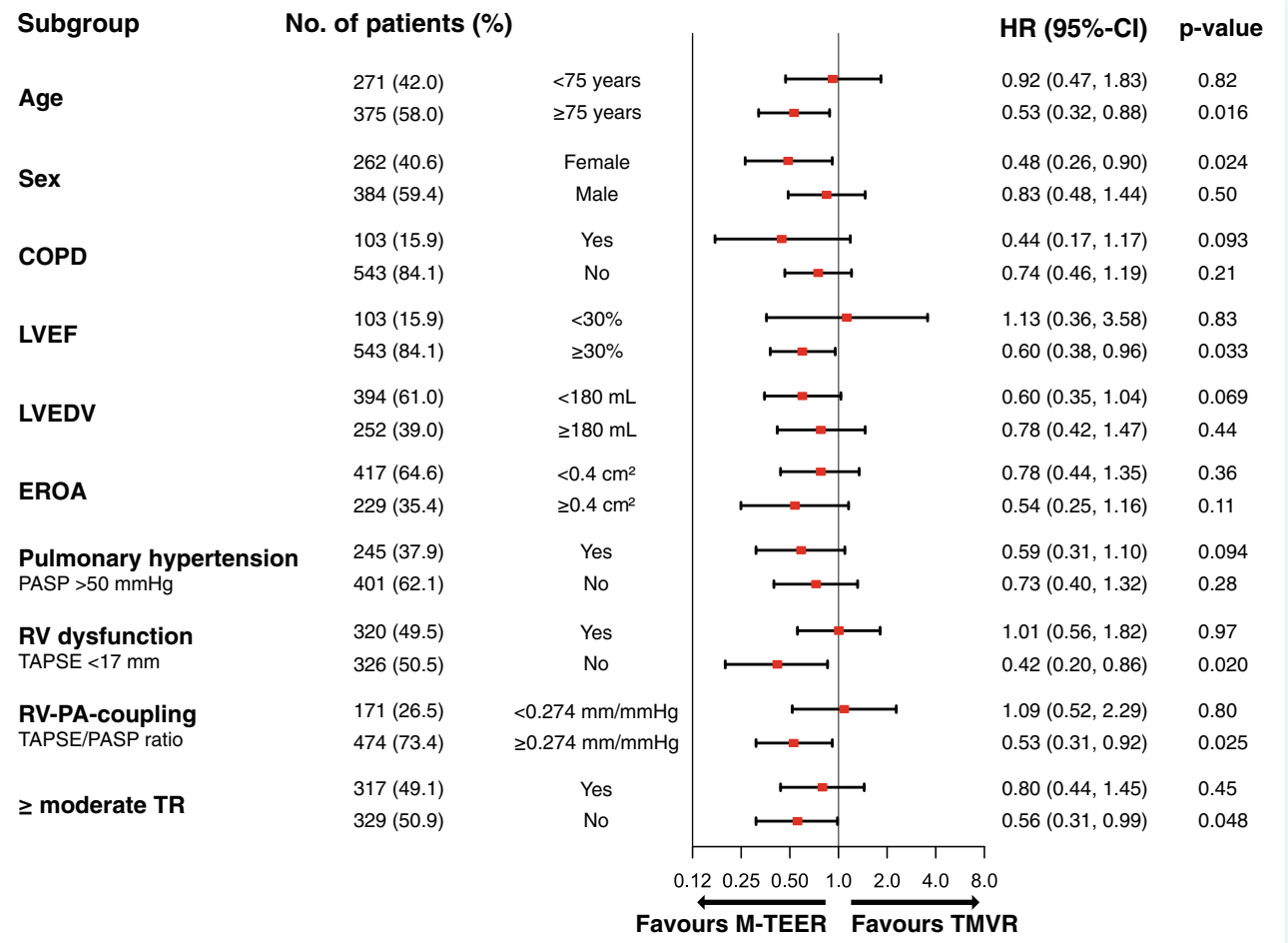


Figure 3 Subgroup analysis. Subgroup analysis for pre-specified subgroups is given for the primary endpoint of all-cause mortality after 1 year. Hazard ratios (HR) below 1.0 indicate lower risk after mitral valve transcatheter edge-to-edge repair (M-TEER), while HR exceeding 1.0 indicate lower risk after transcatheter mitral valve replacement (TMVR). Formal testing for interaction was negative for all subgroups (*p* for interaction ≥0.05). CI, confidence interval; COPD, chronic obstructive pulmonary disease; EROA, effective regurgitant orifice area; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; PA, pulmonary artery; PASP, pulmonary artery systolic pressure; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation.

In the context of SMR, higher grades of residual MR have been associated with inferior outcomes regarding mortality and rehospitalization after mitral valve surgery and M-TEER.[17,18] Our analysis demonstrates that complete MR elimination is achieved in most TMVR patients with very low rates of recurrent MR (2.5%) at follow-up. Following published data, this seems to be a clear advantage of TMVR over M-TEER, which might eventually translate into prognostic benefit. Yet, there appears to be a trade-off between the elimination of MR and the procedural impact of valve replacement. Moreover, while the rates of residual and recurrent MR ≥2+ in the M-TEER group were 31.2% and 38.1%, respectively, results with newer M-TEER generations have shown constant improvements with excellent MR reduction to ≤1+ in more than 90% of patients.[19] However, the possibility of recurrent MR after M-TEER remains an unsolved issue, which can currently only be addressed by TMVR or surgical valve replacement. The haemodynamic impact of complete MR elimination in patients with SMR is still uncertain and the question whether specific subgroups particularly qualify for MR elimination by TMVR (e.g. LV reverse remodeling) warrants further investigation. Superior symptomatic improvement with TMVR compared to M-TEER after 1 year found in our study might indicate a potential early benefit of MR elimination.

Transcatheter mitral valve replacement candidacy

While M-TEER caseload has rapidly increased over the last decade, clinical use and adoption of TMVR has been much slower. Although TMVR cases with dedicated devices were not included, a recent analysis of the STS-ACC registry reports a 10-fold increase in transcatheter mitral valve procedures from 2014 to 2020 in the United States.[20] The main constraint regarding TMVR candidacy seems to be that it is more complex to find eligible patients, not only for anatomical and clinical limitations, but also due to limited

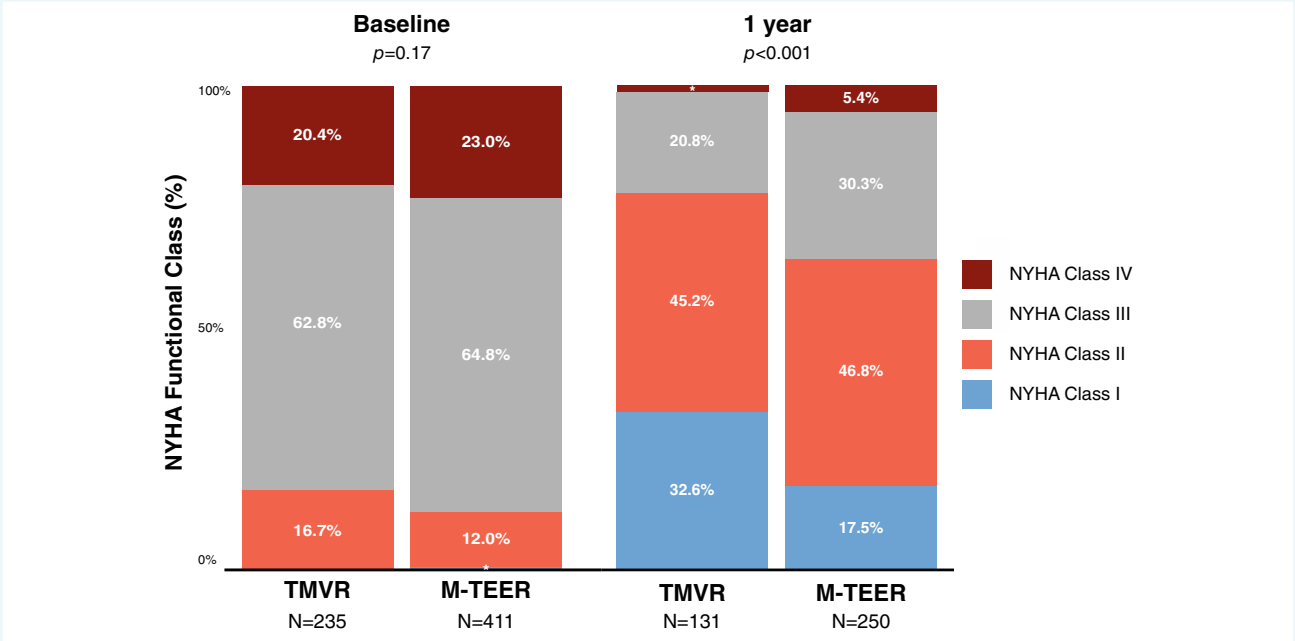


Figure 4 Functional outcome. Functional outcome according to New York Heart Association (NYHA) functional class is given for the propensity score-matched cohorts of transcatheter mitral valve replacement (TMVR) and mitral valve transcatheter edge-to-edge repair (M-TEER) at baseline and at 1-year follow-up. Asterisks (*) indicate percentages below 2.0%. The figure shows approximated values derived from 10 imputed and matched data sets. Detailed relative and absolute ranges are given in online supplementary *Table S3*.

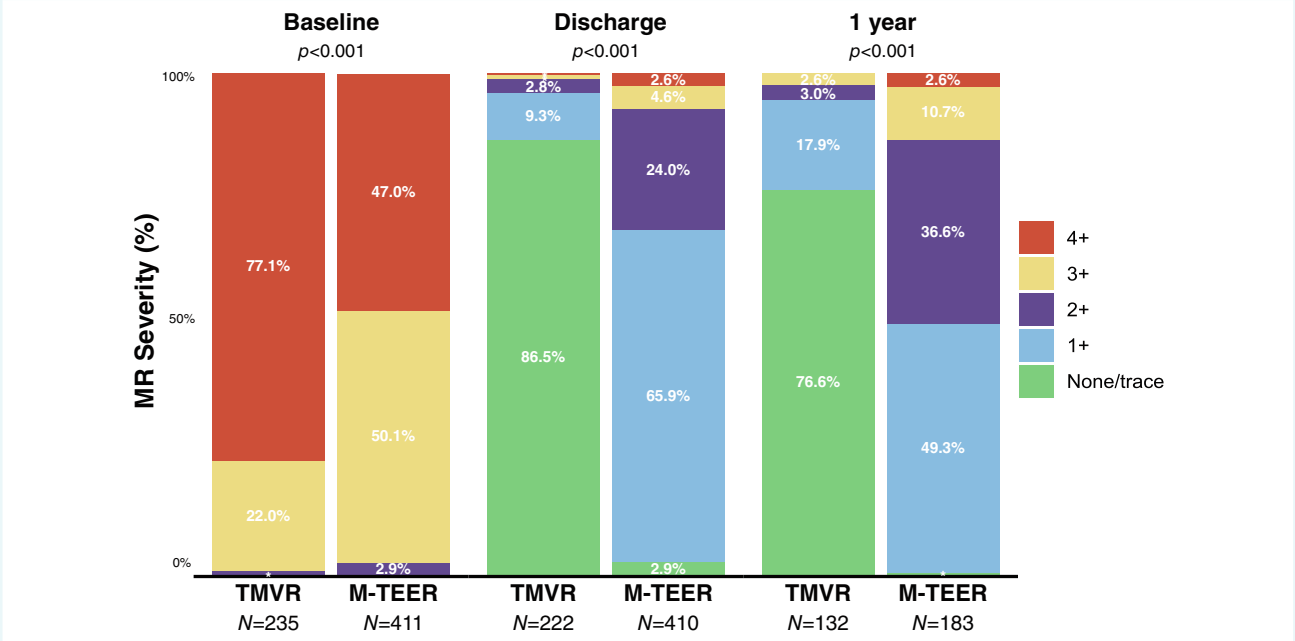


Figure 5 Echocardiographic outcome. Mitral regurgitation (MR) severity is shown for the propensity score-matched cohorts of transcatheter mitral valve replacement (TMVR) and mitral valve transcatheter edge-to-edge repair (M-TEER) at baseline, discharge and 1-year follow-up. Asterisks (*) indicate percentages below 2.0%. The figure shows approximated values derived from 10 imputed and matched data sets. Detailed relative and absolute ranges are given in online supplementary *Table S3*.

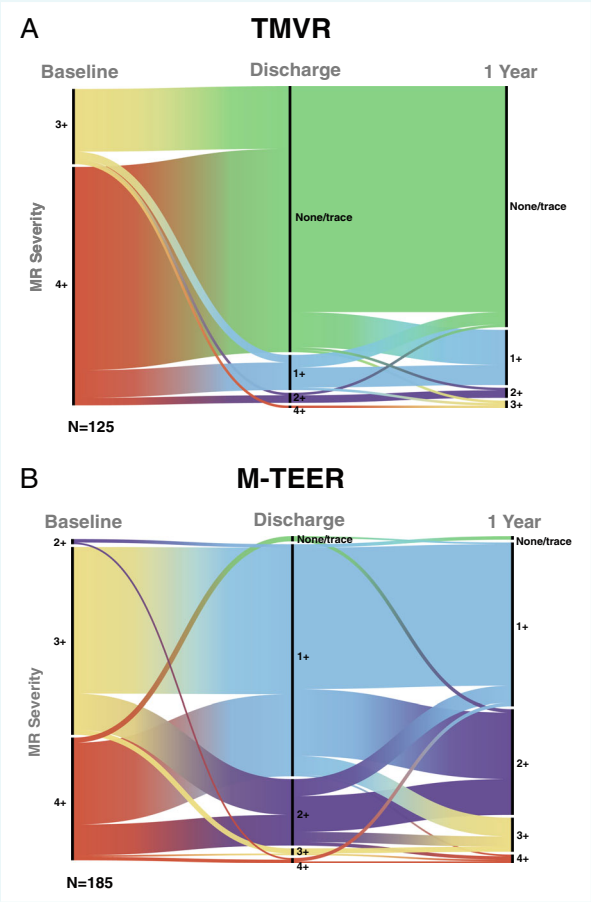


Figure 6 Evolution of mitral regurgitation (MR) after transcatheter replacement and repair. The evolution of MR severity after intervention (paired analysis) is given for the propensity score-matched cohorts of transcatheter mitral valve replacement (TMVR, $n = 139$) (*A*) and mitral valve transcatheter edge-to-edge repair (TEER, $n = 236$) (*B*).

availability (only one device with CE mark) and elevated costs of TMVR.[10] Consequently, screening failure rates of 60–70% have been reported.[11,12] With at least five different valve anchoring mechanisms in TMVR, it remains to be seen which approach will prevail combining safety and generalizability to different anatomic conditions and durable results.[16,21,22] Long-term data for TMVR are missing, especially regarding valve degeneration or thrombosis, which are important determinants of long-term clinical success and reintervention.[23] Neither therapeutic anticoagulation nor prosthetic valve degeneration represent concerns after M-TEER treatment. Overall, the simplicity, the broad availability, and the extraordinary safety profile of M-TEER are factors challenging TMVR development, especially in SMR patients.[9]

Access routes, learning curve effects and future developments

While M-TEER is exclusively conducted via the transfemoral/transseptal route, TMVR has historically been performed using transapical access. This is mainly owed to large-bore delivery sheaths of available TMVR devices and the direct trajectory to the mitral valve.[10] Accordingly, transapically delivered devices were used in 93.6% of TMVR patients in the analysis at hand. Transapical access has been shown to be associated with adverse procedural outcomes and increased mortality in patients undergoing transcatheter aortic valve replacement.[24] Therefore, analogous correlations can be assumed for transapical versus transfemoral access routes in TMVR.[21] In this context, the noted increase in 30-day mortality rates for patients undergoing TMVR compared to M-TEER in our study further strengthens the hypothesis that the choice of access route has a substantial impact on patient outcome. Especially in patients with SMR, transapical access may additionally burden failing ventricles. Hence, intentions exist to transfer TMVR to a predominance of transfemoral procedures.[25] The Intrepid TMVR system (Medtronic, Minneapolis, MN, USA), originally designed as a transapical device, is now available as transfemoral iteration. The 30-day outcomes after a pure endovascular TMVR approach in 15 patients demonstrated encouraging short-term results without strokes, reinterventions, or mortality.[22] Consequently, it seems probable that the less invasive nature of transfemoral systems may improve the 30-day outcomes achieved by the first-generation devices included in this analysis.

Since TMVR represents a more holistic therapeutic approach less dependent on leaflet length and geometry, it might become a complementary therapeutic approach for patients not eligible for M-TEER. In those eligible for M-TEER, the novel technique of TMVR will always have to face the comparison against M-TEER as the most established transcatheter treatment with prognostic impact and low procedural risk. The ongoing randomized controlled SUMMIT trial (NCT03433274) comparing TMVR to M-TEER for the treatment of patients with severe MR will provide important insights into this topic.

In our study, M-TEER conferred a greater impact on survival than TMVR, particularly in patients with less advanced left and right ventricular disease. Beneficial outcomes of M-TEER in these patient subsets is not surprising. Especially the absence of advanced RV dysfunction, defined by RV-PA uncoupling, has been described as an important predictor of survival in patients undergoing M-TEER for severe SMR.[26] However, randomized controlled trials will provide more reliable data on outcomes within different subgroups.

Study limitations

This analysis has multiple important limitations, and all conclusions should be considered as hypothesis-generating. First, comparative outcomes may be confounded despite extensive matching efforts, since most TMVR patients were considered not eligible for M-TEER, and had more severe MR according to EROA. However, ineligibility for M-TEER is somewhat relative and many patients initially considered suboptimal candidates undergo M-TEER after TMVR screening failure.[14,27] Second, patient allocation could have been biased by individual and local factors impacting decision-making. Third, core-lab adjudicated echocardiographic evaluation was not available. Fourth, increasing operator experience has been shown to yield higher rates of procedural success

with M-TEER.[28] Regarding this analysis, a high degree of individual operator experience can be assumed for all patients treated by M-TEER, while learning curve effects are inherent for the TMVR procedures included in this analysis. Finally, follow-up data for both cohorts are limited, therefore, not allowing for statements regarding long-term outcomes.

Conclusion

In a PS matching approach, this analysis compared outcomes of SMR patients undergoing TMVR to a real-world M-TEER cohort. While 30-day and 1-year mortality rates tended to be higher after TMVR, no significant mortality differences between TMVR and M-TEER were found in a landmark analysis beyond 30 days. Compared to M-TEER, TMVR resulted in a more complete and durable elimination of MR, as well as superior symptomatic improvement. Our results highlight the potential of TMVR as a therapeutic alternative for patients with SMR and support the need for randomized controlled trials. With increasing operator experience, device evolution and the transition to transfemoral devices, a larger patient population might become eligible and primarily considered for TMVR.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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