JACC: CARDIOVASCULAR INTERVENTIONS VOL. 18, NO. 16, 2025

ORIGINAL RESEARCH

STRUCTURAL

Transcatheter Edge-to-Edge Repair for Atrial and Ventricular Secondary Mitral Regurgitation

Insights From the REPAIR Study

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ABSTRACT

BACKGROUND Secondary mitral regurgitation (SMR) has 2 phenotypes: atrial (aSMR) and ventricular (vSMR). The role of mitral valve transcatheter edge-to-edge repair (M-TEER) in aSMR remains less defined, with limited evidence on the PASCAL implant (Edwards Lifesciences).

OBJECTIVES The authors sought to evaluate and compare outcomes of SMR phenotypes undergoing M-TEER.

METHODS REPAIR (REgistry of PAscal for mItral Regurgitation) is an investigator-initiated, multicenter registry of patients undergoing M-TEER. aSMR was defined by left atrial dilation with preserved left ventricular size and ejection fraction. Outcomes included MR ≤1+ at discharge, technical success, NYHA functional class improvement, and 1-year survival.

RESULTS Among 915 patients (166 [18%] aSMR, 749 [82%] vSMR), the median follow-up was 491 days (Q1-Q3: 360-833 days). MR ≤1+ was achieved in 77.2% vs 71.4% ($P = 0.162$), with technical success in 97.0% vs 98.3% ($P = 0.446$). NYHA functional class improved in both phenotypes ($P < 0.001$), with 61.2% vs 61.3% in functional class ≤II at follow-up ($P > 0.999$). One-year survival was 88.4% (95% CI: 82.8%-94.4%) vs 86.0% (95% CI: 83.1%-89.0%; $P = 0.346$). In aSMR patients, 1-year survival was significantly lower in patients with baseline tricuspid regurgitation (TR) grade ≥moderate compared with those with <moderate TR (84.3% [95% CI: 77.0%-92.3%] vs 100.0% [95% CI: 100.0%-100.0%]; $P = 0.041$). In vSMR patients, survival was similar between ≥moderate and <moderate baseline TR (83.9% [95% CI: 79.8%-88.2%] vs 89.3% [95% CI: 85.0%-93.8%]; $P = 0.051$).

CONCLUSIONS M-TEER effectively reduces MR to ≤1+ and improves symptoms in both aSMR and vSMR. Particularly in aSMR, ≥moderate baseline TR is linked to worse outcomes, warranting consideration as an additional treatment target. (JACC Cardiovasc Interv. 2025;18:2020-2032) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2025.05.031

Secondary mitral regurgitation (SMR) is the most prevalent cause for moderate-to-severe or severe mitral regurgitation (MR), with 2 main phenotypes currently recognized: atrial secondary mitral regurgitation (aSMR) and ventricular secondary mitral regurgitation (vSMR).[1] While vSMR originates from left ventricular (LV) dysfunction, aSMR arises from left atrial (LA) and mitral annular remodeling in the context of preserved LV function and dimensions.[2] Notably, aSMR is anticipated to surpass vSMR in prevalence, driven by an aging population and the rising burden of atrial fibrillation and heart failure (HF) with preserved ejection fraction (HFpEF).[3] Although the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrated superiority of mitral valve transcatheter edge-to-edge repair (M-TEER) combined with guideline-directed medical therapy (GDMT) over GDMT alone for vSMR, the same has not yet been established for aSMR, because patients with preserved left ventricular ejection fraction (LVEF) (>50%), a hallmark of aSMR, were excluded from the trial.[4] Retrospective studies evaluating M-TEER for aSMR have demonstrated feasibility, with high technical success rates and improvements in quality of life.[5-11] However, these studies are limited by small patient numbers and their exclusive use of the MitraClip (Abbott Structural Heart). The PASCAL M-TEER system (Edwards Lifesciences) has emerged as a safe and effective M-TEER alternative.[12-14] Drawing on data from the REPAIR (REgistry of PAscal for mItral Regurgitation) study, the largest real-world PASCAL M-TEER registry, this study addresses this knowledge gap by comparing outcomes between aSMR and vSMR patients undergoing PASCAL M-TEER and identifying predictors of outcome.

METHODS

STUDY DESIGN AND PATIENT POPULATION.

The design and methodology of the REPAIR study have been detailed previously.[14] In brief, REPAIR is an ongoing, investigator-initiated, observational, multicenter registry enrolling MR patients treated with the PASCAL M-TEER system between 2019 and 2024 at 14 centers. All patients were evaluated by local interdisciplinary heart teams for M-TEER eligibility based on clinical characteristics, anatomical suitability, and optimization of maximum tolerated GDMT.

All M-TEER procedures were performed using the PASCAL system, of which the implantation procedure has been previously described.[15] In the absence of established consensus criteria, the choice between the PASCAL and MitraClip systems was left to the discretion of local physicians. Echocardiographic assessments were conducted by experienced clinicians at each center in accordance with established guidelines. MR severity was evaluated pre-intervention, at discharge, at 30 days, and during follow-up using a multiparametric approach, with severity classified as none/trace (0), mild (1+), mild-to-moderate (2+), moderate-to-severe (3+), and severe (4+).[16,17] Tricuspid regurgitation (TR) was also

ABBREVIATIONS AND ACRONYMS

aSMR = atrial secondary mitral regurgitation

GDMT = guideline-directed medical therapy

HF = heart failure

HFpEF = heart failure with preserved ejection fraction

LA = left atrial

LV = left ventricular

MPG = mean mitral valve pressure gradient

MR = mitral regurgitation

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

MVARC = Mitral Valve Academic Research Consortium

rMR = residual mitral regurgitation

SMR = secondary mitral regurgitation

TR = tricuspid regurgitation

vSMR = ventricular secondary mitral regurgitation

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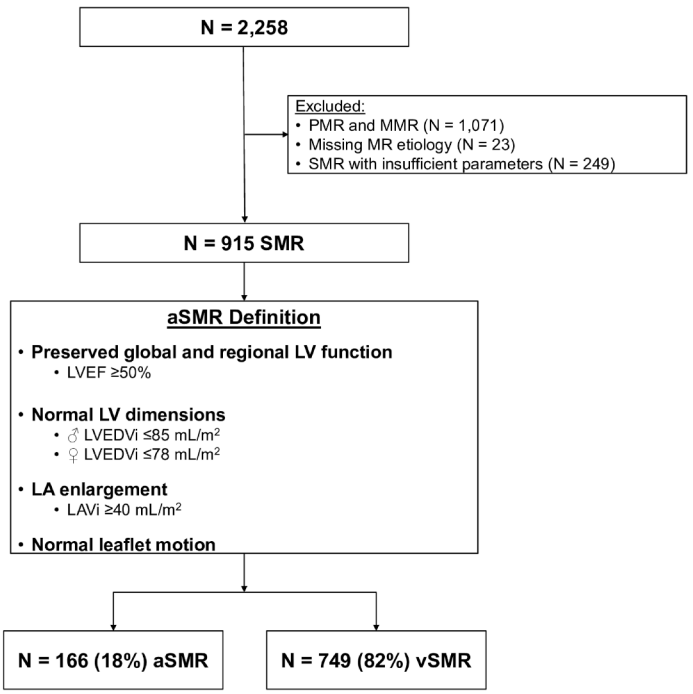
The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

Manuscript received March 22, 2025; revised manuscript received May 21, 2025, accepted May 27, 2025.

FIGURE 1 Study Flow Chart



Patients undergoing M-TEER were evaluated using a dedicated aSMR definition.[2]
aSMR = atrial secondary mitral regurgitation; LA = left atrium; LAVi = left atrial volume index; LV = left ventricle; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; MMR = mixed mitral regurgitation; PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation; vSMR = ventricular secondary mitral regurgitation.

graded using a multiparametric approach with severity classified as none/trace, mild, moderate, and severe.[16,17]

The study was conducted in accordance with the principles of the Declaration of Helsinki, received ethical approval from the appropriate institutional review boards, and was registered in the German Clinical Trials Register (DRKS00033959).

STUDY DEFINITIONS. For this analysis, only patients with SMR were included; those with primary MR or mixed MR etiology were excluded. aSMR was defined as LA enlargement (LA volume index ≥40 mL/m^2), preserved LV regional and global systolic function (LVEF ≥50%), normal LV size (LV end-diastolic volume index ≤78 mL/m^2 for females or ≤85 mL/m^2 for males), and normal mitral valve leaflet motion, in accordance with the dedicated aSMR definition proposed by Zoghbi et al.[2] SMR patients who did not meet all these criteria were considered as vSMR.

STUDY OUTCOMES AND SUBGROUP ANALYSES. The primary endpoint was MR reduction to residual mitral regurgitation (rMR) ≤1+ at discharge. Secondary endpoints included changes in NYHA functional class, 1-year survival, the composite rate of 1-year survival free from HF hospitalizations, and Mitral Valve Academic Research Consortium (MVARC)-defined technical success.[18] Subgroup analyses were performed based on combined stratification of rMR and mean mitral valve pressure gradient (MPG) at discharge, resulting in 4 groups: 1) MR ≤1+ and MPG <5 mm Hg; 2) MR ≤1+ and MPG ≥5 mm Hg; 3) MR ≥2+ and MPG <5 mm Hg; and 4) MR ≥2+ and MPG ≥5 mm Hg. Additionally, patients were stratified by TR grade at baseline (<moderate vs ≥moderate).

STATISTICAL ANALYSIS. Data were summarized as mean ± SD, median (Q1-Q3), or frequencies (n [%]). Between-group comparisons were performed using the chi-square test or Mann-Whitney *U* test, as appropriate. Paired analyses included the Wilcoxon signed rank test for continuous variables and McNemar's test for categorical variables. Survival was assessed using the Kaplan-Meier method and compared between groups with the log-rank test, considering time to first event. Time-to-event outcomes were further analyzed using Cox proportional hazards regression. The proportional hazards assumption was tested for all Cox models using Schoenfeld residuals, and no significant violations were observed. For the multivariable Cox regression model, variables with a univariable significance level of $P < 0.10$, as well as age, sex, and aSMR (vs vSMR) were included. Covariates with intercorrelation >0.7 were excluded. To address sparse events and separation issues, Firth's penalized likelihood approach was applied to obtain bias-reduced HR estimates. Binary logistic regression models were used to assess the association between baseline characteristics and the likelihood of achieving a ≥1 NYHA functional class improvement at 30 days. Multiplicative interaction terms were tested individually by including cross-product terms in the model. For all subgroup analyses, interaction with SMR phenotype (aSMR vs vSMR) was specifically assessed to evaluate potential effect modification. To assess potential learning curve effects in achieving residual MR ≤1+, logistic regression models stratified by SMR phenotype and adjusted for baseline MR severity were fitted using the logarithmized case number within each center as a surrogate for procedural experience. Two-sided *P* values <0.05 were considered statistically significant. All statistical analyses were conducted using R software version 4.4.0 (R Foundation for Statistical Computing).

RESULTS

BASELINE CHARACTERISTICS. Of the 2,258 patients who underwent M-TEER in the REPAIR study, 915 SMR patients were included in this analysis, with 166 (18.1%) classified as aSMR and 749 (81.9%) as vSMR (Figure 1). Median follow-up time was 491 days (Q1-Q3: 360 to 833 days).

Detailed demographic and clinical baseline characteristics are presented in Table 1. Compared with vSMR, those with aSMR were older (80 ± 7 years vs 74 ± 11 years; $P < 0.001$), more frequently female (61% vs 34%; $P < 0.001$) and had a lower European System for Cardiac Operative Risk Evaluation II score (4.0% [Q1-Q3: 2.7%-6.0%] vs 6.2% [Q1-Q3: 3.6%-10.6%]; $P < 0.001$). Atrial fibrillation was more frequent in aSMR (87.3% vs 63.8%; $P < 0.001$), as was arterial hypertension (91% vs 80%; $P = 0.002$). Symptomatically, aSMR patients were more often in NYHA functional class II (18.1% vs 11.8%) and less often in class IV (7.8% vs 16.6%; $P = 0.001$). N-terminal pro-B-type natriuretic peptide (NT-proBNP) was significantly lower in aSMR.

Baseline echocardiographic characteristics are summarized in Table 2. By definition, aSMR patients had higher LVEF, smaller LV dimensions, and larger LA volume indices. The degree of MR was similar between groups, though the effective regurgitant orifice area was smaller in aSMR patients (29 mm^2 [Q1-Q3: 21-39 mm^2] vs 32 mm^2 [Q1-Q3: 24-42 mm^2]; $P = 0.001$). Right ventricular function, assessed by tricuspid annular plane systolic excursion (TAPSE) and the TAPSE-to-pulmonary artery systolic pressure ratio, was better in aSMR patients, who also had a higher prevalence of ≥moderate TR (76.5% vs 58.3%), driven by severe TR (41.2% vs 25.3%).

TABLE 1 Baseline Characteristics

	aSMR (n = 166)	vSMR (n = 749)	*P* Value
Age, y	81 (76-84)	77 (69-82)	**<0.001**
Body mass index, kg/m^2	25.4 (22.7-28.7)	25.3 (23.3-28.7)	0.839
Female	102/166 (61.4)	253/749 (33.8)	**<0.001**
NYHA functional class			**0.001**
I	2/166 (1.2)	1/748 (0.1)	
II	30/166 (18.1)	88/748 (11.8)	
III	121/166 (72.9)	527/748 (70.5)	
IV	13/166 (7.8)	132/748 (16.6)	
NT-proBNP, pg/mL, n = 697	1,904 (1,149-3,081)	4,268 (1,920-9,868)	**<0.001**
EuroSCORE II, %	4.0 (2.7-6.0)	6.2 (3.6-10.6)	**<0.001**
Comorbidities			
Arterial hypertension	151/166 (91.0)	600/746 (80.4)	**0.002**
Diabetes mellitus	28/166 (16.9)	227/749 (30.3)	**0.001**
Coronary artery disease	77/166 (46.4)	492/749 (65.7)	**<0.001**
Previous myocardial infarction	18/166 (10.8)	214/749 (28.6)	**<0.001**
Previous cardiac surgery	30/166 (18.1)	171/749 (22.8)	0.216
Previous stroke/TIA	25/155 (16.1)	89/692 (12.9)	0.343
CRT/ICD/PM	19/166 (11.4)	300/749 (40.0)	**<0.001**
Atrial fibrillation	145/166 (87.3)	478/749 (63.8)	**<0.001**
Chronic lung disease	50/166 (30.1)	200/749 (26.7)	0.425
Renal function			
eGFR, mL/min	47 (36-60)	47 (32-63)	0.752
eGFR <60 mL/min	123/166 (74.1)	527/746 (70.6)	0.427
On dialysis	2/161 (1.2)	20/719 (2.8)	0.394
Medication			
ACEi, ARB, or ARNI	97/149 (65.1)	542/695 (78.0)	**0.001**
ARNI	7/109 (6.4)	219/563 (38.9)	**<0.001**
Beta-blocker	125/149 (83.9)	602/695 (86.6)	0.457
MRA	46/149 (30.9)	395/695 (56.9)	**<0.001**
SGLT2 inhibitors	22/149 (14.9)	227/697 (32.6)	**<0.001**
Loop diuretic	135/149 (90.6)	607/695 (87.3)	0.331

Values are median (Q1-Q3) or n/N (%). **Bold** values indicate statistical significance.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor neprilysin inhibitor; aSMR = atrial secondary mitral regurgitation; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate (calculated using the Cockcroft-Gault equation); EuroSCORE II = European System for Cardiac Operative Risk Evaluation II; ICD = implantable cardioverter-defibrillator; MRA = mineralocorticoid receptor antagonist; NT-proBNP = N-terminal pro-B-type natriuretic peptide; PM = pacemaker; SGLT2 = sodium-glucose cotransporter-2; TIA = transient ischemic attack; vSMR = ventricular secondary mitral regurgitation.

PROCEDURAL OUTCOMES. Procedural outcomes are summarized in Table 3. MVARC technical success rates were similar between aSMR and vSMR patients (97.0% vs 98.3%; $P = 0.446$). No intraprocedural device detachment occurred in aSMR patients, whereas 2 vSMR patients (0.2%) had a partial detachment ($P = 0.965$). Procedure abortion was more frequent in aSMR (3.0% vs 0.8%; $P = 0.049$), primarily due to impending stenosis or insufficient MR reduction.

The median number of implanted devices was lower in aSMR patients (1 [1-1] devices vs 1 [1-2] devices; $P < 0.001$), with 1 device implanted in 77.1% of aSMR patients compared with 56.7% in vSMR patients. The PASCAL Ace was used in 41.6% of aSMR patients compared with 47.1% of vSMR patients, whereas the PASCAL P10 was implanted in 52.4% vs 49.4%, respectively. Both devices were used in 3.0% of aSMR patients and 2.7% of vSMR patients, with no significant difference in overall device selection between groups ($P = 0.081$).

ECHOCARDIOGRAPHIC OUTCOMES. Echocardiographic outcomes are displayed in Table 4. At discharge, MR reduction to ≤2+ was achieved in 98.7% of aSMR patients and 97.5% of vSMR patients ($P = 0.535$), with rMR ≤1+ in 77.2% and 71.4% ($P = 0.162$), respectively. A postprocedural MPG of >5 mm Hg was observed in 18.7% of aSMR patients and 13.8% of vSMR patients ($P = 0.163$).

Echocardiographic follow-up was available in 59.1% of patients at 30 days (531/899 patients; aSMR: 71.1% [118/166], vSMR: 56.3% [413/733]) and in 47.3%

TABLE 2 Baseline Echocardiographic Characteristics

	aSMR (n = 166)	vSMR (n = 749)	*P* Value
Left atrium			
LA volume index, mL/m^2	62 (50-81)	58 (45-75)	**0.006**
Left ventricle			
LVEF, %	58 (54-63)	33 (25-42)	**<0.001**
LVEDD, mm	50 (46-55)	62 (55-69)	**<0.001**
LVESD, mm	34 (30-40)	52 (44-60)	**<0.001**
LVEDV index, mL/m^2	49 (39-63)	90 (68-113)	**<0.001**
Female	46 (38-55)	79 (55-101)	**<0.001**
Male	57 (45-68)	94 (76-123)	**<0.001**
Mitral valve			
MPG, mm Hg	1.9 ± 1.0	1.9 ± 1.0	0.532
3D-MVOA, cm^2, n = 360	4.8 (4.2-6.1)	4.7 (4.1-5.8)	0.235
VC width, mm	7.5 (6.0-8.0)	7.5 (6.0-9.0)	0.115
EROA, mm^2, n = 736	29 (21-39)	32 (24-42)	**0.001**
Regurgitant volume, mL	43 (33-59)	46 (35-60)	0.368
MR severity			0.408
0+	0/166 (0.0)	0/748 (0.0)	
1+	0/166 (0.0)	0/748 (0.0)	
2+	0/166 (0.0)	8/748 (1.1)	
3+	109/166 (65.7)	484/748 (64.7)	
4+	57/166 (34.3)	256/748 (34.2)	
Right ventricle			
TR severity			**<0.001**
None/trace	2/153 (1.3)	18/684 (2.6)	
Mild	34/153 (22.2)	267/684 (39.0)	
Moderate	54/153 (35.3)	226/684 (33.0)	
Severe	63/153 (41.2)	173/684 (25.3)	
TAPSE, mm	18 (16-22)	17 (14-20)	**<0.001**
PASP, mm Hg	44 (35-54)	44 (35-55)	0.420
TAPSE/PASP, mm/mm Hg, n = 666	0.431 (0.350-0.558)	0.372 (0.286-0.500)	**<0.001**

Values are median (Q1-Q3), mean ± SD, or n/N (%). **Bold** values indicate statistical significance.

3D-MVOA = 3-dimensional mitral valve orifice area; EROA = effective regurgitant orifice area; LA = left atrium; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic diameter; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; MPG = mean mitral valve pressure gradient; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; VC = vena contracta; other abbreviations as in Table 1.

at 1 year (390/825 patients; aSMR: 53.3% [81/152], vSMR: 45.9% [309/673]). At 30 days, rMR ≤2+ was achieved in 96.6% of aSMR patients and 96.9% of vSMR patients ($P > 0.999$), with rMR ≤1+ in 73.7% and 69.1%, respectively ($P = 0.391$). A postprocedural MPG >5 mm Hg was more frequently observed in aSMR than vSMR (12.8% vs 5.9%; $P = 0.020$). At latest echocardiographic follow-up (median 435 days [Q1-Q3: 365-816 days]), rMR ≤2+ was observed in 96.4% of aSMR patients and 96.8% of vSMR patients ($P = 0.837$), with rMR ≤1+ achieved in 69.9% and 67.9%, respectively ($P > 0.999$). No significant difference was observed regarding MPG >5 mm Hg in aSMR compared with vSMR (Table 4). The paired MR development is presented in the Central Illustration.

CLINICAL OUTCOMES. Clinical outcomes at 30 days are summarized in Table 4. NYHA functional class follow-up was available in 58.4% of patients at 30 days (525/899 patients; aSMR: 74.7% [124/166], vSMR: 54.7% [401/733]) and in 53.6% at 1 year (442/825 patients; aSMR: 62.5% [95/152], vSMR: 51.6% [347/673]). NYHA functional class significantly improved from baseline to 30 days in both groups (both $P < 0.001$). An improvement of ≥1 NYHA functional class was observed in 54.8% of aSMR patients (68 of 124) and 63.4% of vSMR patients (256 of 404; $P = 0.093$), whereas improvement ≥2 functional classes occurred in 11.3% (14 of 124 patients) and 17.6% (71 of 404 patients), respectively ($P = 0.124$). NYHA functional class ≤II was achieved in 60.5% (75 of 124) of aSMR patients compared with 62.4% of vSMR patients (152 of 404; $P = 0.784$).

At latest NYHA follow-up (median 510 days [Q1-Q3: 370-941 days]), an improvement of ≥1 NYHA functional class was observed in 54.1% of aSMR patients (53 of 98) vs 61.6% of vSMR patients (221 of 359; $P = 0.201$), whereas improvement of ≥2 functional classes occurred in 12.2% (12 of 98 patients) and 13.1% (47 of 359 patients), respectively ($P > 0.999$). NYHA functional class ≤II was observed in 61.2% of aSMR patients (60 of 98) and 61.3% of vSMR patients (220 of 359) during follow-up ($P > 0.999$). Paired changes in NYHA functional class are depicted in the Central Illustration.

None of the examined variables, including SMR phenotype (aSMR vs vSMR; OR range: 1.31-2.15; all $P > 0.05$), MR ≤1+ at discharge (OR: 1.16 [95% CI: 0.48-2.77]; $P = 0.743$), MPG <5 mm Hg at discharge (OR: 1.70 [95% CI: 0.68-4.38]; $P = 0.260$), or <moderate TR (OR: 0.63 [95% CI: 0.26-1.54]; $P = 0.311$), were significantly associated with achieving a ≥1 NYHA functional class improvement at 30 days. No interaction terms were statistically significant (all $P_{\text{interaction}} > 0.05$).

One-year survival and survival free from HF hospitalization did not differ between patients with aSMR and vSMR (Figure 2). This finding was confirmed in multivariable Cox regression analysis (Table 5).

SUBGROUP ANALYSES. Subgroup analyses based on discharge rMR and MPG showed no significant differences in 1-year survival or survival free from HF hospitalization across the 4 defined groups in either aSMR or vSMR patients (Figure 3, Supplemental Figure 1). There was no significant interaction between subgroup and SMR phenotype

($P_{interaction} = 0.825$ for survival; $P_{interaction} = 0.640$ for survival free from HF hospitalization).

When stratified by discharge rMR (≤1+ vs ≥2+), both 1-year survival and survival free from HF hospitalization were similar between groups in both aSMR and vSMR patients (Supplemental Figures 2 and 3), with no significant interaction with SMR phenotype ($P_{interaction} = 0.491$ and $P_{interaction} = 0.850$, respectively).

Similarly, no significant differences were observed when stratifying by discharge MPG (<5 vs ≥5 mm Hg), and interaction terms were again nonsignificant ($P_{interaction} = 0.382$ for survival; $P_{interaction} = 0.902$ for survival free from HF hospitalization) (Supplemental Figures 4 and 5).

When stratified by baseline TR grade, both 1-year survival and survival free from HF hospitalization were significantly lower in aSMR patients with ≥moderate TR compared with those with <moderate TR ($P = 0.041$ and $P = 0.023$, respectively), whereas no statistically significant differences were observed in vSMR ($P = 0.051$ and $P = 0.096$, respectively) (**Figure 4**, Supplemental Figure 6). Interaction with SMR phenotype was not significant for either endpoint ($P_{interaction} = 0.996$ and 0.260, respectively).

LEARNING CURVE ANALYSES. Center experience, approximated by the logarithmized case number within each center and adjusted for baseline MR severity, was not significantly associated with achieving residual rMR ≤1+ at discharge in either SMR phenotype: aSMR (adjusted OR: 0.95; 95% CI: 0.83-1.07; $P = 0.399$) and vSMR (adjusted OR: 0.91; 95% CI: 0.79-1.06; $P = 0.229$).

TABLE 3 Procedural Outcomes

	aSMR (n = 166)	vSMR (n =749)	*P* Value
Technical success	161/166 (97.0)	736/749 (98.3)	0.446
Intraprocedural device detachment	0/150 (0.0)	3/701 (0.4)	0.965
Partial detachment	0/150 (0.0)	2/701 (0.3)	>0.999
SLDA	0/150 (0.0)	1/701 (0.1)	>0.999
Procedure aborted	5/166 (3.0)	6/749 (0.8)	**0.049**
Procedural death	0/166 (0.0)	0/749 (0.0)	
Conversion to open heart surgery	0/166 (0.0)	0/749 (0.0)	
Leaflet damage	0/165 (0.0)	1/749 (0.1)	>0.999
Devices implanted			**<0.001**
1	128/166 (77.1)	425/749 (56.7)	
2	31/166 (18.7)	296/749 (39.5)	
3	2/166 (1.2)	21/749 (2.8)	
4	0/166 (0.0)	1/749 (0.1)	
Number of devices implanted	1 (1-1)	1 (1-2)	**<0.001**
Independent grasping	64/122 (52.5)	207/395 (52.4)	>0.999
Postprocedural 3D-MVOA, cm^2, n = 247	2.4 (2.0-2.9)	2.3 (1.9-3.0)	0.525
Procedure duration, min	79 (58-109)	81 (63-107)	0.491

Values are n/N (%) or median (Q1-Q3). **Bold** values indicate statistical significance.
SLDA = single-leaflet device attachment; other abbreviations as in Tables 1 and 2.

DISCUSSION

To the best of our knowledge, this is the first analysis comparing aSMR and vSMR patients undergoing M-TEER with the PASCAL system. Among 915 SMR patients, approximately one-fifth with aSMR, the following principal findings were observed: First, M-TEER with the PASCAL system was associated with a high rate of achieving rMR ≤1+ and MVARC technical success in both aSMR and vSMR. Second, 1-year survival was similar in both aSMR and vSMR phenotypes. Third, ≥moderate TR was more prevalent in aSMR patients and significantly associated with worse 1-year survival, whereas a similar, but nonsignificant, trend was seen in vSMR; importantly, no significant interaction with SMR phenotype was detected. Fourth, both aSMR and vSMR patients experienced a significant and similar symptomatic improvement following M-TEER.

Prior investigations of M-TEER in aSMR have focused exclusively on the MitraClip. By contrast, our analysis provides the first insight into outcomes following aSMR treatment with the PASCAL system. In our cohort, nearly all patients with either aSMR or vSMR achieved MR reduction to ≤2+, which is broadly in line with findings from MitraClip-treated patients in the EXPAND (A Contemporary, Prospective, Multi-Center Study Evaluating Real-World Experience of Performance and Safety for the Next Generation of MitraClip Devices) study (The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices).[5] However, in our population, rMR ≤1+ was somewhat less frequently achieved in both phenotypes, most likely reflecting the absence of predefined inclusion or exclusion criteria—an intrinsic difference from EXPAND, which enrolled patients according to regional instructions for use.[5] In accordance with this assumption, our results align more closely with the real-world EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry.[11] Another explanation for the discrepancy in achieving rMR ≤1+ might be that in EXPAND, 41.5% of aSMR and 48.8% of vSMR patients were subjected to M-TEER with baseline MR already at ≤2+.[5] When comparing EXPAND, EuroSMR, and

TABLE 4 Echocardiographic and Clinical Outcomes

	aSMR (n = 166)	vSMR (n = 749)	*P* Value
Echocardiographic outcomes			
At discharge			
rMR severity			0.435
0+	25/158 (15.8)	87/733 (11.9)	
1+	97/158 (61.4)	436/733 (59.5)	
2+	34/158 (21.5)	192/733 (26.2)	
3+	2/158 (1.3)	16/733 (2.2)	
4+	0/158 (0.0)	2/733 (0.3)	
rMR ≤2+	156/158 (98.7)	715/757 (97.5)	0.535
rMR ≤1+	122/158 (77.2)	523/733 (71.4)	0.162
MPG, mm Hg	3.57 ± 1.41	3.17 ± 1.46	**<0.001**
>5 mm Hg	28/150 (18.7)	96/695 (13.8)	0.163
Device detachment	0/123 (0.0)	0/604 (0.0)	
Partial detachment	0/123 (0.0)	0/604 (0.0)	
SLDA	0/123 (0.0)	0/604 (0.0)	
PASP, mm Hg	39 (30-48)	38 (30-46)	0.236
At 30 d			
rMR severity			0.762
0+	11/118 (9.3)	37/414 (8.9)	
1+	76/118 (64.4)	249/414 (60.1)	
2+	27/118 (22.9)	115/414 (27.8)	
3+	4/118 (3.4)	11/414 (2.7)	
4+	0/118 (0.0)	2/414 (0.5)	
rMR ≤2+	114/118 (96.6)	401/414 (96.9)	>0.999
rMR ≤1+	87/118 (73.7)	286/414 (69.1)	0.391
MPG, mm Hg	3.61 ± 1.52	3.17 ± 1.46	**<0.001**
>5 mm Hg	15/117 (12.8)	23/393 (5.9)	**0.020**
TAPSE, mm	18 (15-21)	18 (14-20)	0.672
PASP, mm Hg	40 (31-53)	40 (31-48)	0.184
At follow-up			
rMR severity			0.867
0+	8/83 (9.6)	24/315 (7.6)	
1+	50/83 (60.2)	190/315 (60.3)	
2+	22/83 (26.5)	91/315 (28.9)	
3+	3/83 (3.6)	8/315 (2.5)	
4+	0/83 (0.0)	2/315 (0.6)	
rMR ≤2+	80/83 (96.4)	305/315 (96.8)	>0.999
rMR ≤1+	58/83 (69.9)	214/315 (67.9)	0.837
MPG, mm Hg	3.55 ± 1.62	2.92 ± 1.68	**<0.001**
>5 mm Hg	8/83 (9.6)	23/315 (7.3)	0.634
TAPSE, mm	18 (16-20)	17 (14-20)	0.130
PASP, mm Hg	36 (26-45)	33 (15-44)	0.159
Clinical outcomes, NYHA functional class			
At 30 d			0.471
I	25/124 (20.2)	65/404 (16.1)	
II	50/124 (40.3)	187/404 (46.3)	
III	42/124 (33.9)	137/404 (33.9)	
IV	7/124 (5.7)	15/404 (3.7)	
At follow-up			0.227
I	15/98 (15.3)	44/359 (12.3)	
II	45/98 (45.9)	176/359 (49.0)	
III	37/98 (37.8)	120/359 (33.4)	
IV	1/98 (1.0)	19/359 (5.3)	

Values are n/total N (%), mean ± SD or median (Q1-Q3). **Bold** values indicate statistical significance.
rMR = residual mitral regurgitation; other abbreviations as in Tables 1 and 2.

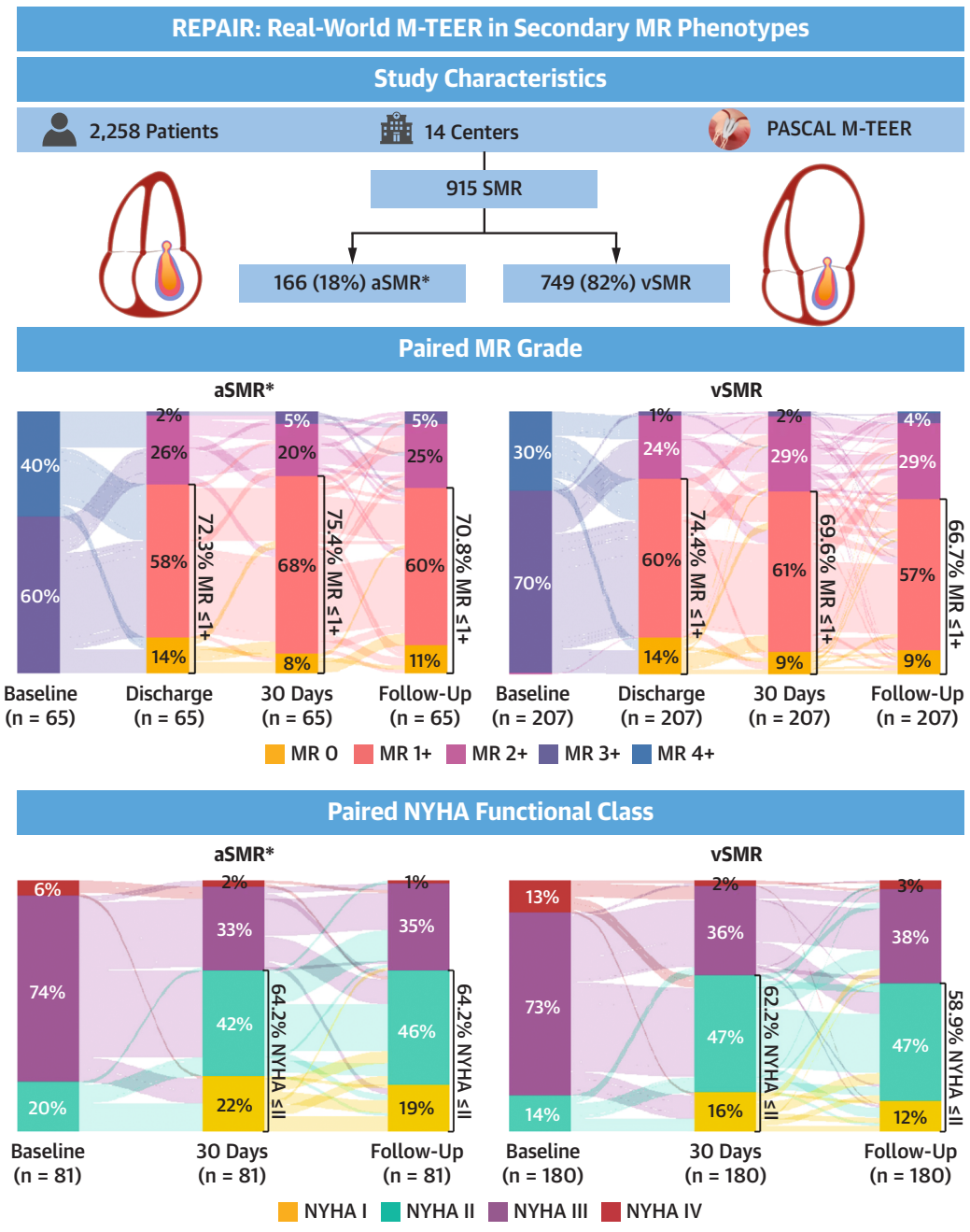
our present study, it is important to acknowledge that all 3 applied different definitions of aSMR, potentially resulting in distinct patient populations and limiting direct comparability.

In contemporary literature on M-TEER for aSMR, aSMR has been reported in 8% to 28% of SMR patients, aligning well with the 18% observed in our cohort.[3,5,7,11] The wide range of reported rates likely reflects variability in the applied definitions of aSMR. Although aSMR is inherently characterized by LA and subsequent mitral annular dilatation, many existing definitions primarily focus on preserved LV function and dimensions, thereby effectively defining aSMR by exclusion, or, in some cases, incorporating clinical parameters into what is largely conceived as an echocardiographic definition. Given the anticipated—and, in 1 smaller analysis, already noted—rise of aSMR patients undergoing M-TEER, a unified definition of aSMR is needed to enhance comparability of outcomes and refine treatment strategies, especially in the context of more aSMR pathologies recognized.[3,19] In this regard, the echocardiographic framework proposed by Zoghbi et al[2] offers a comprehensive definition of aSMR, highlighting its key morphological hallmarks. However, like all other existing definitions, it has yet to undergo prospective validation. Ideally, such a definition should not only distinguish phenotypes but also enable risk stratification and predict clinical outcomes—criteria that, thus far, have not been met.

Given the older, predominantly female population, with high rates of atrial fibrillation and arterial hypertension, in combination with LA dilation, and preserved LVEF, it is conceivable that a substantial proportion of aSMR patients exhibit an HFpEF phenotype, or at least share overlapping characteristics, as previously demonstrated.[20] This might help explain the lack of prognostic separation, given the well-established observation that HFpEF carries a prognosis comparable to that of HF with reduced ejection fraction.[21] Supporting this notion, in our study, the aSMR phenotype was not independently associated with 1-year mortality in either univariable or multivariable analysis. Instead, NYHA functional class and the presence of baseline ≥moderate TR emerged as the strongest predictors of outcome.

This observation gains further relevance in light of the higher prevalence of ≥moderate TR among aSMR patients. In aSMR, TR may not represent a consequence secondary to MR—as is typically inferred in vSMR, where longstanding elevated pulmonary artery pressures lead to right ventricular dilation and secondary TR—but rather a parallel manifestation of a

CENTRAL ILLUSTRATION **Transcatheter Edge-to-Edge Repair in Atrial and Ventricular Secondary Mitral Regurgitation**

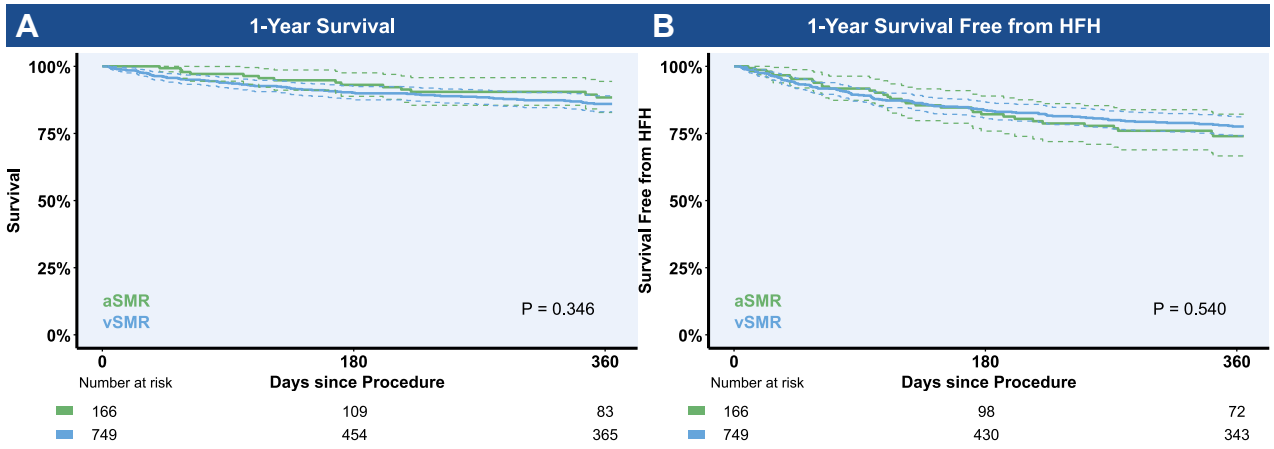


- M-TEER achieved MR reduction to ≤1+ in ≥70% and technical success in ≥97% in both aSMR and vSMR.
- 1-Year survival was similar between aSMR and vSMR.
- Baseline ≥ moderate TR was more common in aSMR and predicted 1-year outcomes in this phenotype.
- Both aSMR and vSMR patients showed significant symptomatic improvement after M-TEER.

von Stein P, et al. JACC Cardiovasc Interv. 2025;18(16):2020–2032.

Patients undergoing mitral valve transcatheter edge-to-edge repair (M-TEER) were stratified by secondary mitral regurgitation (SMR) phenotype,* and paired courses of mitral regurgitation (MR) and NYHA functional class are depicted. *Atrial secondary mitral regurgitation (aSMR) was defined as left atrial enlargement (left atrial volume index ≥40 mL/m^2), preserved left ventricular (LV) regional and global systolic function (LV ejection fraction ≥50%), normal LV size (LV end-diastolic volume index ≤78 mL/m^2 [♀], ≤85 mL^2 [♂]), and normal mitral valve leaflet motion. TR = tricuspid regurgitation; vSMR = ventricular secondary mitral regurgitation.

FIGURE 2 1-Year Survival and 1-Year Survival Free From HF Hospitalization in aSMR and vSMR



Kaplan-Meier curves illustrate 1-year survival (A) and survival free from heart failure (HF) hospitalization (B) by SMR etiology. One-year survival was 88.4% (95% CI: 82.8-94.4%) in aSMR patients and 86.0% (95% CI: 83.1-89.0%) in vSMR patients ($P = 0.346$). Survival free from HF hospitalization was 74.0% (95% CI: 66.6%-82.2%) in aSMR patients and 77.6% (95% CI: 74.1%-81.2%) in vSMR patients ($P = 0.540$). Abbreviations as in Figure 1.

broader biatrial pathology. This consideration is supported by the frequent coexistence of aSMR and atrial fibrillation, a condition affecting both atria and implicated in the pathogenesis of both aSMR and atrial secondary TR.[5,8,10,22] Building on the concept of differential secondary TR pathophysiology in aSMR and vSMR, we hypothesize that the response of TR to M-TEER may also differ between SMR phenotypes. In vSMR, effective MR reduction may lead to a reduction in pulmonary pressures and subsequent right ventricular reverse remodeling, facilitating partial TR regression, as previously demonstrated by Adamo et al.[23] By contrast, TR in aSMR may reflect a more fixed, atrial-driven pathology that is less amendable to improvement following M-TEER. This notion is again supported by findings from the study by Adamo et al,[23] where smaller LA size was associated with a higher likelihood of achieving TR ≤moderate after M-TEER. Although the interaction between SMR phenotype and TR severity was not statistically significant, our data cautiously support this hypothesis: ≥moderate TR at baseline was associated with worse survival and survival free from HF hospitalization in aSMR patients, whereas in vSMR patients, the association did not reach statistical significance. These findings, particularly the development of TR after M-TEER for aSMR patients, remain to be investigated in future studies. Nevertheless, our finding that ≥moderate TR is prognostically significant in aSMR patients underscores TR as a compelling additional therapeutic target in these patients.

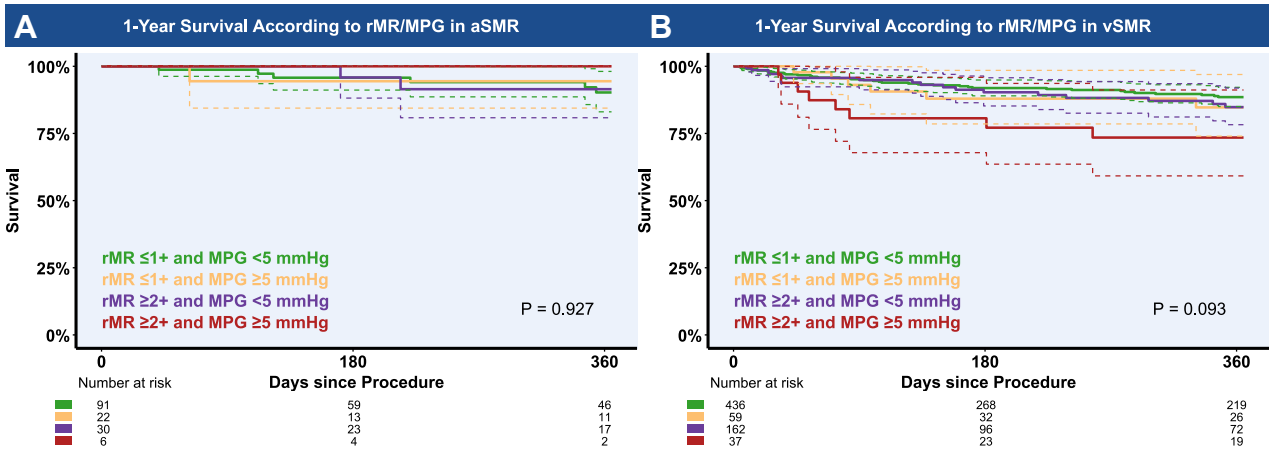
Importantly, aSMR patients derived a substantial symptomatic benefit from PASCAL M-TEER—analogous to the improvement seen in vSMR patients—such that two-thirds of aSMR patients remained in NYHA functional class II or better at

TABLE 5 Multivariable Cox Regression for 1-Year All-Cause Mortality

	Univariable			Multivariable		
	HR	95% CI	*P* Value	HR	95% CI	*P* Value
aSMR vs vSMR	1.31	0.74-2.32	0.348	1.05	0.57-1.92	0.868
NYHA, per functional class increase	2.26	1.60-3.20	**<0.001**	2.33	1.55-3.49	**<0.001**
History of cardiac surgery	1.76	1.19-2.61	**0.005**	1.28	0.78-2.10	0.323
TR ≥moderate	1.78	1.14-2.76	**0.011**	1.90	1.15-3.16	**0.013**
Coronary artery disease	1.51	1.02-2.24	**0.041**	1.45	0.87-2.42	0.154
eGFR <60 mL/min	1.48	0.95-2.31	**0.080**	1.23	0.71-2.14	0.459
Sex, female vs male	0.77	0.52-1.12	0.170	0.68	0.41-1.11	0.123
Chronic lung disease	1.28	0.87-1.88	0.216	–	–	–
Atrial fibrillation	1.24	0.81-1.89	0.320	–	–	–
History of stroke	1.20	0.72-2.02	0.484	–	–	–
Arterial hypertension	0.86	0.54-1.38	0.527	–	–	–
Diabetes	1.13	0.76-1.68	0.545	–	–	–
Age per y	1.00	0.99-1.02	0.747	1.003	0.98-1.03	0.811
History of myocardial infarction	1.02	0.66-1.59	0.924	–	–	–

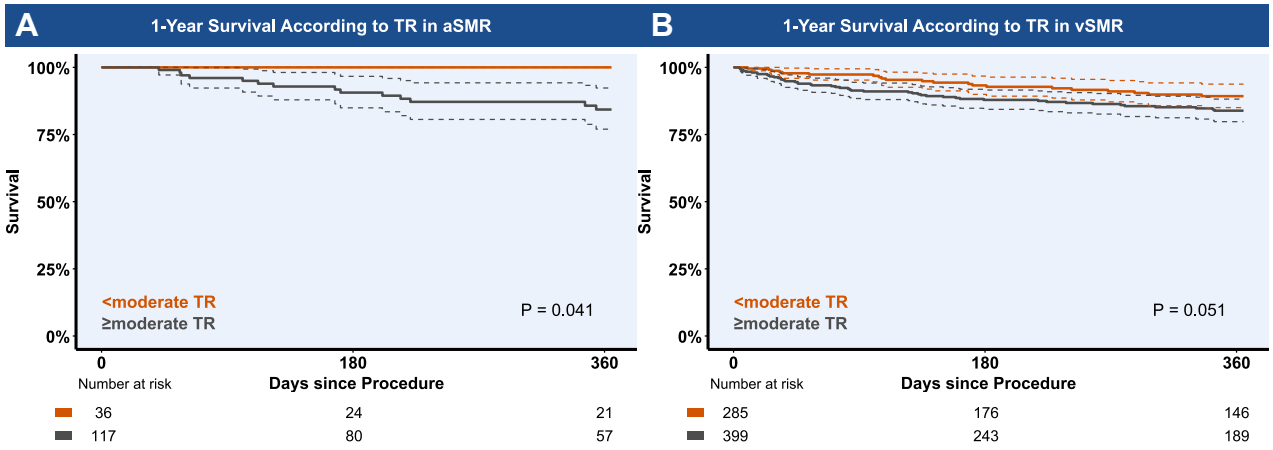
Bold values indicate statistical significance.
Abbreviations as in Tables 1 and 2.

FIGURE 3 1-Year Survival According to rMR and MPG in aSMR and vSMR



Kaplan-Meier curves illustrate 1-year survival stratified by residual mitral regurgitation (rMR) and mitral valve pressure gradient (MPG) in aSMR (A) and vSMR (B) patients. In aSMR patients, survival was 90.3% (95% CI: 83.0%-98.1%) for rMR ≤1+ and MPG <5 mm Hg, 94.4% (95% CI: 84.4%-100.0%) for rMR ≤1+ and MPG ≥5 mm Hg, 91.5% (95% CI: 80.8%-100.0%) for rMR ≥2+ and MPG <5 mm Hg, and 100.0% (95% CI: 100.0%-100.0%) for rMR ≥2+ and MPG ≥5 mm Hg ($P = 0.927$). No pairwise comparisons were statistically significant (all $P_{Bonferroni} > 0.999$). In vSMR, survival was 88.5% (95% CI: 85.0%-92.2%) for rMR ≤1+ and MPG <5 mm Hg, 84.7% (95% CI: 74.0%-96.9%) for rMR ≤1+ and MPG ≥5 mm Hg, 84.8% (95% CI: 78.3%-91.9%) for rMR ≥2+ and MPG <5 mm Hg, and 73.5% (95% CI: 59.2-91.25) for rMR ≥2+ and MPG ≥5 mm Hg ($P = 0.093$). Bonferroni-adjusted pairwise comparisons were not significant (all $P_{Bonferroni} > 0.05$). Abbreviations as in Figure 1.

FIGURE 4 1-Year Survival According to TR in aSMR and vSMR



Kaplan-Meier curves illustrate 1-year survival stratified by tricuspid regurgitation (TR) grade (<moderate vs ≥moderate) in aSMR patients (A) and vSMR patients (B). In aSMR, 1-year survival was 100.0% (95% CI: 100.0%-100.0%) with <moderate TR and 84.3% (95% CI: 77.0%-92.3%) with ≥moderate TR ($P = 0.041$). In vSMR, survival was 89.3% (95% CI: 85.0%-93.8%) with <moderate TR and 83.9% (95% CI: 79.8%-88.2%) with ≥moderate TR ($P = 0.051$). M-TEER = mitral valve transcatheter edge-to-edge repair; other abbreviations as in Figures 1 and 3.

latest follow-up. Future randomized controlled trials are warranted to clarify whether M-TEER offers both symptomatic and prognostic advantages in aSMR, as proven for vSMR.[4]

STUDY STRENGTHS AND LIMITATIONS. This analysis represents the largest cohort of patients undergoing PASCAL M-TEER to date, encompassing multiple centers, and covering the entire period since the system's introduction. The investigator-driven, real-world nature of the study—conducted without predefined inclusion or exclusion criteria and independent of industry funding—further enhances its relevance and objectivity. Moreover, incorporating key aspects of a dedicated aSMR definition represents a significant methodological advantage.[2] Despite these strengths, several limitations must be considered. As a retrospective observational study, clinical data were obtained from local sites without independent adjudication, and echocardiographic assessments were performed by individual centers without review by an independent core laboratory. Although both iterations of the PASCAL implant (PASCAL P10 and Ace) are available today, the high proportion of PASCAL P10 use in this analysis does not reflect current clinical practice, where the PASCAL Ace is predominantly used.[14] Additionally, follow-up was limited by large referral areas, leading many patients to receive subsequent care from community cardiologists; this creates potential selection bias, capturing data primarily from either notably improved or significantly deteriorating cases. In addition, the study was conducted exclusively in Germany, which may constrain the generalizability of these findings to regions with less M-TEER experience. Finally, although the overall SMR cohort was sizable, analyses and subgroup analyses—particularly within the aSMR population—were constrained by smaller sample sizes, thereby warranting confirmation in larger, dedicated studies on aSMR.

CONCLUSIONS

M-TEER with the PASCAL system in aSMR patients is associated with high rates of achieving residual MR ≤1+ and technical success. At least moderate TR holds prognostic significance in aSMR and therefore might be regarded as an additional potential therapeutic target. Following M-TEER, both aSMR und vSMR patients derive significant and similar symptomatic improvement.

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FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr Gerçek has received a research grant from the Ruhr-University Bochum as Advanced Clinician Scientist; and served as a consultant for Edwards Lifesciences. Dr Baldus and Dr Mauri were supported by the Deutsche Forschungsgemeinschaft, Bonn, Germany (397484323). Dr Stolz has received speaker honoraria from Edwards Lifesciences. Dr Mahabadi has received honoraria, lecture fees, and/or grant support from Amgen, Daiichi-Sankyo, Edwards Lifesciences, Novartis, Sanofi, all unrelated to this work; and is cofounder of Mycor GmbH, a company focusing on AI-based ECG algorithms. Dr von Stein has received speaker honoraria from Edwards Lifesciences. Dr Lurz has received institutional fees and research grants from Abbott Cardiovascular, Edwards Lifesciences, and Medtronic. Dr Horn has received an unrestricted research grant from Edwards Lifesciences; and has received speaking honoraria from Abbott Cardiovascular. Dr Rassaf has received honoraria, lecture fees, and grant support from Edwards Lifesciences, AstraZeneca, Bayer, Novartis, Berlin Chemie, Daiichi-Sankyo, Boehringer Ingelheim, Novo Nordisk, Cardiac Dimensions, and Pfizer, all unrelated to this work; and is cofounder of Bimyo GmbH, a company that develops cardioprotective peptides, cofounder of Mycor GmbH, a company focusing on AI-based EKG-algorithms, and cofounder of Yes2NO, developing nitric oxide-based treatments. Dr Schindhelm has received speaker honoraria and travel expenses from Edwards Lifesciences, MedMile, and Björn Steiger Stiftung. Dr Möllmann has received speaker honoraria from Abbott Cardiovascular and Edwards Lifesciences. Dr Baldus has received honorarium for consultation by Edwards Lifesciences. Dr Rudolph has received research grants and honoraria for consultation from Edwards Lifesciences. Dr Hausleiter has received speaker honoraria from and serves as a consultant for Edwards Lifesciences. Dr Pfister has received an honorarium for consultation by Edwards Lifesciences. Dr Mauri has received speaker honoraria and travel compensation by Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? The PASCAL mitral valve transcatheter edge-to-edge repair system has emerged as a treatment option for mitral regurgitation and atrial secondary mitral regurgitation has come into view as an increasingly recognized secondary mitral regurgitation etiology.

WHAT IS NEW? Mitral valve transcatheter edge-to-edge repair with the PASCAL system is associated with both a high technical success rate and a high rate of achieving residual mitral regurgitation ≤1+ in both atrial and ventricular secondary mitral regurgitation. Clinical outcomes including symptomatic improvement are similar in patients with atrial and ventricular secondary mitral regurgitation undergoing mitral valve transcatheter edge-to-edge repair.

WHAT IS NEXT? A randomized controlled trial comparing mitral valve transcatheter edge-to-edge repair in addition to guideline-directed medical therapy vs medical therapy alone in patients with atrial secondary mitral regurgitation is warranted.

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KEY WORDS mitral regurgitation, mitral valve transcatheter edge-to-edge repair, M-TEER, PASCAL, real-world, REPAIR

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