



Differential effects of transcatheter edge-to-edge repair on forward stroke volume in atrial and ventricular secondary mitral regurgitation

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Abstract

Introduction Transcatheter edge-to-edge mitral valve repair (M-TEER) is an established treatment for secondary mitral regurgitation (MR). Forward stroke volume (FSV), reflecting left ventricular forward flow, is a prognostic marker in heart failure and valvular disease. However, its clinical relevance in secondary MR has not been clearly defined.

Objective To assess the impact of M-TEER on FSV in atrial and ventricular secondary MR, identify predictors of FSV improvement, and evaluate its association with long-term outcomes.

Methods In this retrospective single-center study, 103 patients with moderate-to-severe or severe secondary MR (ventricular MR: $n=60$, atrial MR: $n=43$) underwent M-TEER. FSV was quantified using left ventricular outflow tract measurements before and 4 weeks post-procedure. Clinical outcomes were assessed over a 2-year follow-up period.

Results Procedural success (MR grade $\leq$ II) was high (ventricular MR: 95%, atrial MR: 100%). FSV remained unchanged in ventricular MR (49.4 ± 17.3 vs. 49.5 ± 16.5 ml, $p=0.960$) but increased significantly in atrial MR (60.5 ± 21.7 vs. 66.8 ± 19.6 ml, $p=0.037$). In multivariable analysis, atrial MR etiology (OR 5.12, $p=0.048$) and lower baseline FSV (OR 0.36 per 10 ml/m², $p=0.002$) independently predicted FSV improvement $> 10\%$. FSV responders and non-responders did not differ in functional status or residual MR grade. FSV improvement was not associated with reduced mortality or heart failure hospitalization.

Conclusion M-TEER enhances FSV in atrial but not ventricular secondary MR. Atrial MR etiology and low baseline FSV independently predict FSV improvement. Early FSV improvement does not translate into improved clinical outcomes, suggesting that FSV response reflects hemodynamic adaptation rather than serving as a prognostic marker.

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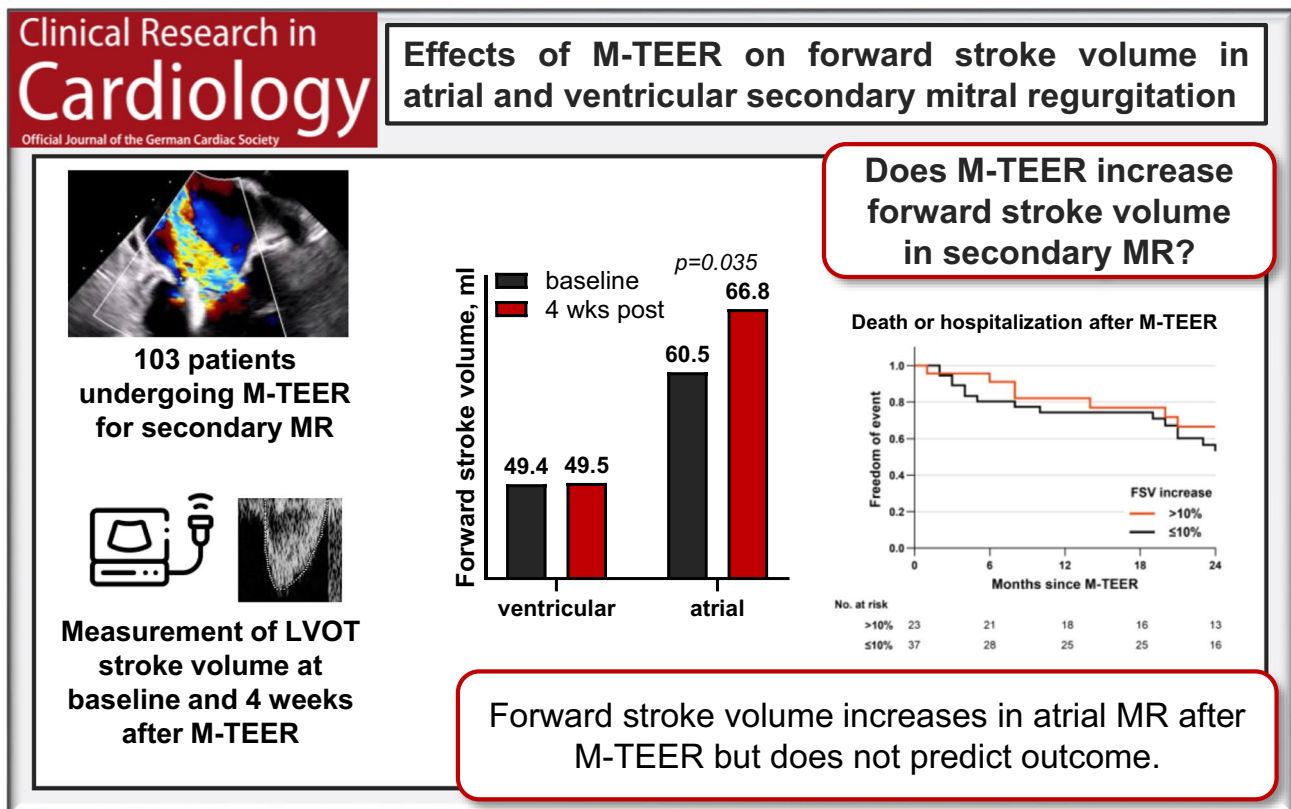
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Graphical Abstract



Keywords Atrial mitral regurgitation · Ventricular mitral regurgitation · Transcatheter edge-to-edge repair · Forward stroke volume · Echocardiography · Heart failure

Introduction

For patients with severe secondary ventricular mitral regurgitation (MR) at high surgical risk, transcatheter edge-to-edge mitral valve repair (M-TEER) is recommended by current guidelines [1, 2]. Yet, uncertainty remains regarding which patients benefit most, as COAPT and MITRA-FR reported conflicting results [3, 4]. More recently, the RESHAPE-HF2 trial demonstrated positive outcomes, further supporting the role of M-TEER [5]. The MATTERHORN trial showed that M-TEER is non-inferior to conventional mitral valve (MV) surgery in patients with severe secondary MR and heart failure (HF) [6]. Despite advances in patient selection, rates of HF hospitalization and all-cause mortality remain high [7, 8].

Left ventricular ejection fraction (LVEF) is commonly used for risk stratification in MR but often underestimates left ventricular (LV) dysfunction, as it is influenced by

regurgitant flow into the left atrium (LA) [9]. Forward stroke volume (FSV), representing forward flow through the LV outflow tract (LVOT), may serve as a more accurate marker [10]. Non-invasive FSV measurement correlates well with invasive thermodilution [11] and is recommended by guidelines [12]. In HF or severe aortic stenosis, FSV predicts survival and HF hospitalization [13, 14] with similar findings in primary MR [15]. Notably, a recently reported COAPT subgroup analysis demonstrated that patients with low baseline FSV derived the greatest absolute benefit from M-TEER, although FSV itself did not improve during follow-up [16].

Atrial MR has increasingly been recognized as a distinct phenotype. It occurs in patients with preserved LV function and results from LA enlargement, annular dilatation, and inadequate leaflet adaptation [17–20]. Evidence for M-TEER in atrial MR is limited, but recent studies suggest similar success and clinical benefit [17–20]. Current guidelines

recommend M-TEER in symptomatic patients with atrial MR [2].

We investigated the early effect of M-TEER on FSV and examined whether FSV changes predict outcomes regarding all-cause mortality and HF hospitalization in patients with atrial or ventricular secondary MR.

Methods

Study population

This retrospective, single-center study included consecutive patients who underwent M-TEER at the University Heart Center Regensburg, Germany, between August 2017 and July 2024 (Fig. 1, Flowchart). Eligible patients were retrospectively identified from our institutional database. Inclusion criteria comprised the presence of symptomatic moderate-to-severe or severe secondary MR as defined by current recommendations [20], and treatment with M-TEER during the study period.

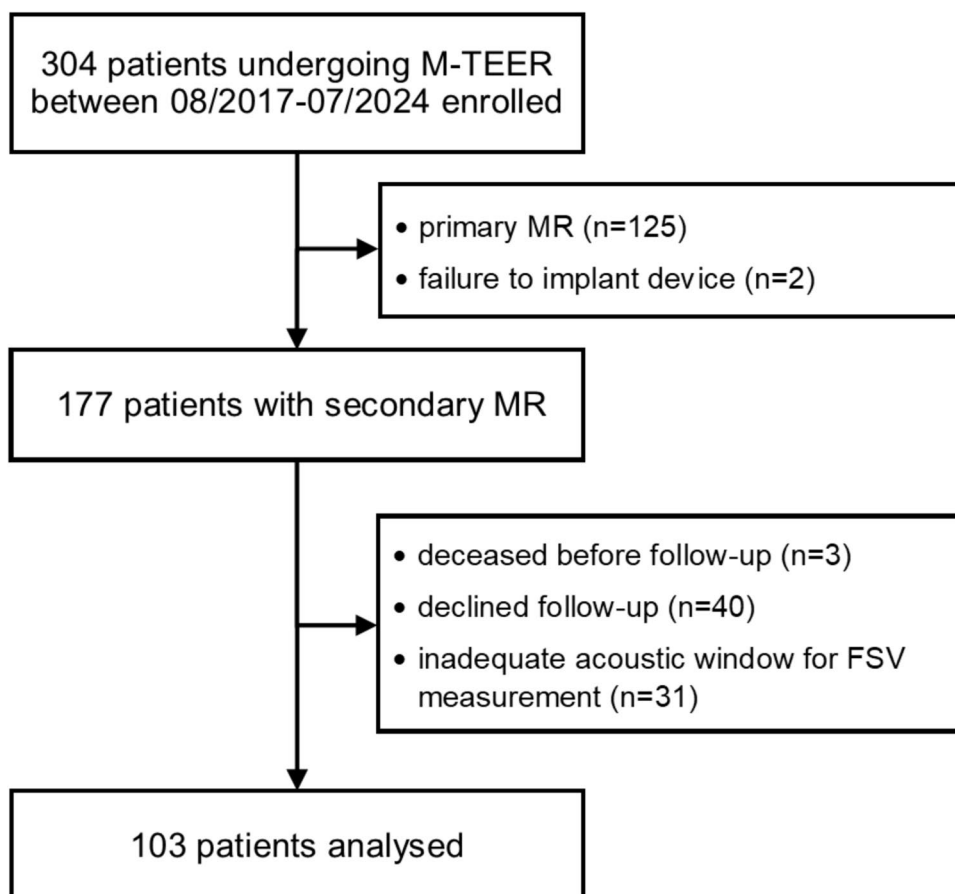
Secondary MR was categorized primarily according to LV function. Ventricular MR was defined as secondary

MR in patients with reduced LVEF ($<50\%$), whereas atrial MR was defined as secondary MR in patients with preserved LVEF ($\geq 50\%$) [21]. All procedures were performed under general anesthesia by experienced interventional cardiologists using fluoroscopic and three-dimensional transesophageal echocardiographic guidance. Depending on the anatomical characteristics and procedural strategy, either the MitraClip system (NT, NTW, XT, XTW; Abbott Vascular, Menlo Park, CA, USA) or the PASCAL system (PASCAL P10, PASCAL Ace; Edwards Lifesciences, Irvine, CA, USA) was employed, following established techniques [22, 23]. Patients were excluded in the event of unsuccessful device implantation, lack of follow-up data, or inadequate echocardiographic image quality precluding reliable FSV assessment. For all included patients, relevant clinical, procedural, and echocardiographic data were retrospectively retrieved from our database. The study was approved by the local ethics committee of the University of Regensburg. All patients had provided written informed consent.

Clinical assessment

The routine evaluation in our clinic includes a comprehensive clinical examination, a six-minute walk test, detailed

Fig. 1 Flowchart illustrating patient selection. A total of 304 patients undergoing transcatheter edge-to-edge repair (M-TEER) between August 2017 and July 2024 were screened. After exclusion of patients with primary mitral regurgitation (MR), unsuccessful device implantation, loss to follow-up, or inadequate acoustic quality for forward stroke volume (FSV) assessment, 103 patients with secondary MR were included in the final analysis



assessment of medical history, laboratory diagnostics, as well as the determination of the New York Heart Association (NYHA) functional class to evaluate the patient's functional capacity and symptomatology at baseline and 4 weeks after M-TEER procedure. To investigate clinical outcome, patients were followed up on the incidence of all-cause mortality or hospitalization for HF. Six-minute walk tests were performed according to previously described protocols [24].

Echocardiographic assessment

Echocardiographic assessment was performed at baseline and 4 weeks after M-TEER procedure. The assessment included the evaluation of left and right ventricular dimensions and function, the diastolic function, as well as the dimensions of the atria [25]. MR severity was assessed using an integrative, multiparametric approach in accordance with current ASE/EACVI guideline recommendations [26, 27]. MR grading incorporated qualitative and semiquantitative parameters, including color Doppler jet characteristics (jet direction, eccentricity, and spatial extent), vena contracta width, pulmonary venous flow patterns, and continuous-wave Doppler signal density and contour. PISA-derived parameters (e.g., EROA) were used only as supportive information when technically feasible and were not relied upon in isolation for MR grading, acknowledging their limitations in secondary MR with noncircular and dynamic regurgitant orifices.

After M-TEER, residual MR was graded using an integrative post-procedural assessment, emphasizing color Doppler evaluation of residual jet number, size, and eccentricity and distribution, vena contracta width where feasible, pulmonary venous flow pattern, flow convergence size (qualitatively), mitral inflow pattern and continuous-wave Doppler characteristics, in line with ASE recommendations for post M-TEER assessment, and recognizing the methodological limitations of quantitative PISA-based assessment in the multijet setting [28]. MR severity was categorized on a semiquantitative scale from 1 to 4 (1 = mild, 2 = moderate, 3 = moderate-to-severe, 4 = severe).

FSV was determined using the LVOT method, with the LVOT diameter measured in the parasternal long-axis view during systole at baseline. For follow-up examinations, the baseline LVOT diameter was applied for FSV calculations to ensure methodological consistency and to minimize measurement variability, based on the assumption of an unchanged LVOT geometry over time. The cross-sectional area (CSA) was then calculated using the formula $CSA = \pi \times (LVOT\ Diameter/2)^2$. The LVOT velocity time integral (VTI) was obtained via pulsed-wave Doppler in the apical 5-chamber or 3-chamber view, and FSV was derived by multiplying the CSA by the VTI ($FSV = CSA \times VTI$) [29]. To obtain FSV index (FSVI), the

calculated FSV was indexed to the body surface area (BSA) using the formula $FSVI = FSV/BSA$ [15].

In patients with atrial fibrillation, FSV was determined using an index-beat approach. LVOT VTI was measured in a beat preceded by two cardiac cycles of similar RR duration, in order to reduce beat-to-beat variability related to irregular cycle length. This approach is supported by prior studies showing that index-beat analysis provides a reproducible and time-efficient assessment of echocardiographic parameters in atrial fibrillation [30, 31].

Statistical analysis

Continuous variables are reported as mean $\pm$ standard deviation when normally distributed, continuous variables with skewed distribution as median with interquartile range (first quartile-third quartile). Categorical variables are presented in numbers and percentages. Differences between groups were assessed using Student's *t*-test for continuous data, Mann–Whitney *U* test for ordinal data and Pearson's chi-squared test for nominal data. Differences in binary variables were analyzed applying Fisher's exact test. Differences in paired samples were tested using paired *t*-tests for normally distributed data, Wilcoxon signed-rank tests for skewed or ordinal data, and McNemar's test for dichotomous data. The incidence of clinical endpoints during follow-up was evaluated using time-to-event analysis with Kaplan–Meier curves. Kaplan–Meier estimates were utilized to account for varying follow-up durations among participants. Patients without events were censored at their last documented follow-up. The median follow-up period was determined through reverse Kaplan–Meier analysis. Differences in endpoint incidence between groups were assessed via log-rank tests. To identify independent predictors of improvement in FSV, a binary logistic regression analysis was conducted. The dependent variable was defined as improvement in $FSV > 10\%$ 1 month after M-TEER. Potential influencing factors were first examined through univariable analysis; variables with a *p*-value less than 0.10 were subsequently included in the multivariable model. Results are reported as odds ratios (OR) with 95% confidence intervals. Statistical significance was considered at a *p*-value less than 0.05. All statistical analyses were performed using SPSS Statistics 29 (IBM, Armonk, NY USA).

Results

Patient characteristics

A total of 103 patients, who underwent M-TEER for secondary MR, had complete echocardiographic and clinical

follow-up at 1 month and were included in the analysis (Fig. 1, Flowchart). Mean age was 74.9 ± 9.3 years and 40.8% were female. Sixty patients had ventricular MR, while 43 patients had atrial MR. Patients with ventricular MR were younger (73.0 ± 9.9 vs. 77.5 ± 7.7 years, $p = 0.015$) and more frequently male (68.3 vs. 46.5%, $p = 0.041$). Coronary artery disease, prior percutaneous coronary

intervention, myocardial infarction, implantable cardioverter-defibrillator, cardiac resynchronization therapy, dilative cardiomyopathy and HF medication were more common in ventricular MR (all $p < 0.01$, Table 1). NTproBNP levels were higher for ventricular MR compared to atrial MR (5875.7 [1710.0–6382.0] vs. 2990.6 [1064.0–3204.0] pg/ml, $p = 0.024$, respectively). Both groups exhibited a high

Table 1 Baseline patient characteristics

	All (<i>n</i> = 103)	Ventricular (<i>n</i> = 60)	Atrial (<i>n</i> = 43)	<i>p</i> -value
Age, years	74.9 ± 9.3	73.0 ± 9.9	77.5 ± 7.7	0.015
Female gender	42 (40.8)	19 (31.7)	23 (53.5)	0.041
BMI, kg/m ²	26.5 ± 5.0	26.7 ± 4.5	26.3 ± 5.6	0.642
Coronary artery disease	61 (59.2)	43 (71.7)	18 (41.9)	0.004
s/p PCI	51 (49.5)	37 (61.7)	14 (32.6)	0.005
s/p CABG	12 (11.7)	8 (13.3)	4 (9.3)	0.757
Dilative cardiomyopathy	20 (19.4)	20 (33.3)	0	< 0.001
Myocardial infarction	29 (28.2)	23 (38.3)	6 (14.0)	0.008
Atrial fibrillation	65 (63.1)	35 (58.3)	30 (69.8)	0.301
Arterial hypertension	66 (64.1)	36 (60.0)	30 (69.8)	0.405
Diabetes mellitus	30 (29.1)	21 (35.0)	9 (20.9)	0.131
COPD	13 (12.6)	11 (18.3)	2 (4.7)	0.068
Chronic kidney disease	81 (78.6)	48 (80.0)	33 (76.6)	0.808
Chronic hemodialysis	2 (1.9)	2 (3.3)	0	0.509
PAD	12 (11.7)	8 (13.3)	4 (9.3)	0.757
Cardiac resynchronization therapy	9 (8.7)	9 (15.0)	0	0.010
Pacemaker	25 (24.3)	16 (26.7)	9 (20.9)	0.642
ICD	18 (17.5)	17 (28.3)	1 (2.3)	< 0.001
EuroSCORE II, %	5.7 [3.5–9.4]	9.4 [4.3–9.9]	6.4 [2.9–7.6]	0.051
GFR, ml/min	47.9 ± 20.3	47.7 ± 23.1	48.2 ± 15.6	0.898
NTproBNP, pg/ml	2461.5 [1381.8–5028.3]	5875.7 [1710.0–6382.0]	2990.6 [1064.0–3204.0]	0.024
NYHA functional class				0.540
I	1 (1.0)	0	1 (2.3)	
II	20 (19.4)	11 (18.3)	9 (20.9)	
III	77 (74.8)	46 (76.7)	31 (72.1)	
IV	5 (4.9)	3 (5.0)	2 (4.7)	
Six-minute Walk distance, m	259.2 ± 111.4	249.4 ± 101.4	274.1 ± 125.3	0.332
Oral medication				
ASS	36 (35.0)	24 (40.0)	12 (27.9)	0.218
Oral anticoagulation	62 (60.2)	34 (56.7)	28 (65.1)	0.421
ACEI	49 (47.6)	23 (38.3)	26 (60.5)	0.030
ARB	12 (11.7)	6 (10.0)	6 (14.0)	0.550
ARNI	17 (16.5)	16 (26.3)	1 (2.3)	0.001
MRA	46 (44.7)	32 (53.3)	14 (32.6)	0.045
Betablocker	87 (84.5)	54 (90.0)	33 (76.7)	0.097

Variables are expressed as *n* (%), mean $\pm$ standard deviation, or median [interquartile range], as appropriate. Bold values indicate statistical significance ($p < 0.05$)

ACEI 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, GFR glomerular filtration rate, ICD implantable cardioverter-defibrillator, MRA mineralocorticoid receptor antagonist, NYHA New York Heart Association, PAD peripheral artery disease, PCI percutaneous coronary intervention

symptom burden (ventricular MR: NYHA III/IV: 81.7%, atrial MR: NYHA III/IV: 76.8%, Table 1).

Baseline echocardiographic characteristics

Moderate-to-severe (grade III) or severe (grade IV) MR was present in all patients. Compared with patients with ventricular MR, those with atrial MR showed a trend toward less severe MR, with grade III MR being more common in atrial MR (32.6% vs. 18.3%, respectively) and grade IV MR less frequent (67.4% vs. 81.7%, respectively, $p=0.098$). Patients with ventricular MR showed significantly reduced LVEF (32.8 ± 10.9 vs. $56.7 \pm 4.5\%$, $p < 0.001$), FSV (49.4 ± 17.3 vs. 60.5 ± 21.7 ml, $p=0.005$), and cardiac output (3.4 ± 1.2 vs. 4.1 ± 1.4 l/min, $p=0.016$), reflecting underlying ventricular dysfunction. Additionally, larger LV dimensions could be documented (Supplement Table 1).

Procedural data

A single device was implanted in 63.1% of patients, while 35.0% received two devices. The MitraClip was used in 78.6% of cases, whereas the remaining 21.4% were treated with the PASCAL device (Supplement Table 2), with no significant differences observed between ventricular and atrial MR. Complication rates were low, including one single-leaflet detachment, three major bleedings, and one cardiogenic shock (Supplement Table 3).

Echocardiographic and functional follow-up

In patients with ventricular and atrial MR, MR severity was significantly reduced at follow-up (Table 2). In ventricular MR, LVEF (32.8 ± 10.9 vs. $34.8 \pm 10.9\%$, $p=0.006$) and right ventricular function (TAPSE and TAPSE/PASP) improved, while LA volume index, pulmonary artery pressure (PASP), and tricuspid regurgitation (TR) grade significantly decreased (Table 2). However, FSV did not improve from baseline to 1-month follow-up (49.4 ± 17.3 vs. 49.5 ± 16.5 ml, $p=0.960$). Functional outcomes improved, including NYHA class and six-minute walk distance (Table 2).

In atrial MR, LVEF (56.7 ± 4.5 vs. $56.0 \pm 5.3\%$, $p=0.464$) and TAPSE remained unchanged, while LA volume index, PASP, and TR grade significantly decreased. FSV increased significantly (60.5 ± 21.7 vs. 66.8 ± 19.6 ml, $p=0.037$). This was accompanied by a numerically higher cardiac output (4.1 ± 1.4 vs. 4.5 ± 1.4 l/min, $p=0.082$), although statistical significance was not reached, possibly reflecting the limited sample size. Heart rate remained unchanged between baseline and follow-up. Additionally, functional improvement in NYHA class was observed (Table 2).

Functional and clinical outcomes according to FSV improvement

Patients were stratified according to the presence of FSV improvement of $\leq 10\%$ ($n=51$) or $> 10\%$ ($n=52$) 1 month after M-TEER (Table 3). Clinical status was comparable between groups. NT-proBNP levels, NYHA functional class distribution, and six-minute walk distance did not differ between patients with and without relevant FSV improvement. Similarly, echocardiographic assessment demonstrated effective MR reduction in both groups without differences in residual MR grade. Patients with an FSV improvement $> 10\%$ exhibited higher LVEF compared with those with $\leq 10\%$ improvement ($47.3 \pm 14.4\%$ vs. $39.9 \pm 12.3\%$, $p=0.006$). FSV was substantially higher in the $> 10\%$ improvement group, accompanied by a higher cardiac output (FSVI 33.6 ± 10.8 vs. 26.7 ± 8.3 ml/m², $p < 0.001$; cardiac output 4.3 ± 1.5 vs. 3.4 ± 1.1 l/min, $p=0.001$). In contrast, LV dimensions, LA volume index, right ventricular function, and TR severity did not differ between groups (Table 3).

Clinical outcomes after M-TEER were evaluated by monitoring patients for the occurrence of a composite endpoint comprising hospitalization due to HF or all-cause mortality. The median follow-up duration was 24 months (interquartile range, 12–24 months). During this period, 31 patients (30.1%) reached the combined endpoint of all-cause mortality or hospitalization for HF. In both patients with atrial or ventricular MR, an improvement in FSV exceeding 10% following M-TEER was not associated with a reduction in the incidence of the composite endpoint (Fig. 2). Furthermore, rates of all-cause mortality and HF hospitalization as individual endpoints did not differ between groups (Supplementary Fig. 1). Details on temporal distribution of clinical events across subgroups are provided in Supplementary Table 4.

Baseline predictors of FSV improvement after M-TEER

Baseline predictors of an FSV improvement $> 10\%$ after M-TEER were assessed using logistic regression analysis (Table 4). In univariable analysis, atrial MR, severe TR, higher LVEF, absence of coronary artery disease, absence of diabetes mellitus, and lower baseline FSV were associated with a higher likelihood of relevant FSV improvement.

In multivariable analysis, atrial MR remained independently associated with FSV improvement $> 10\%$, conferring a more than fivefold increase in odds compared with ventricular MR (OR 5.12 [1.04–25.90], $p=0.048$). In addition, a lower baseline FSV independently predicted significant FSV improvement (OR 0.36 [0.19–0.69] per 10 ml/m², $p=0.002$). Other variables, including age, sex, LVEF, coronary artery disease, diabetes mellitus, severe TR, MR grade,

Table 2 Functional and echocardiographic characteristics before and 1 month after M-TEER

	Ventricular MR (<i>n</i> =60)			Atrial MR (<i>n</i> =43)		
	Preprocedural	Follow-up	<i>P</i>	Preprocedural	Follow-up	<i>P</i>
NTproBNP, pg/ml	5875.7 [1710.0–6382.0]	5185.1 [1812.25–6175.75]	0.273	2990.6 [1064.0–3204.0]	3079.1 [1200.0–3750.0]	0.850
Six-minute walk distance, m	250.1 ± 102.3	285.1 ± 112.6	0.006	274.1 ± 125.3	296.3 ± 114.5	0.147
NYHA functional class			< 0.001			< 0.001
I	0	11 (18.3)		1 (2.3)	10 (23.3)	
II	11 (18.3)	41 (68.3)		9 (20.9)	22 (51.2)	
III	46 (76.7)	8 (13.3)		31 (72.1)	11 (25.6)	
IV	3 (5.0)	0		2 (4.7)	0	
Echocardiography						
MR grade			< 0.001			< 0.001
I	0	39 (65.0)		0	30 (69.8)	
II	0	18 (30.0)		0	13 (30.2)	
III	11 (18.3)	2 (3.3)		14 (32.6)	0	
IV	49 (81.7)	1 (1.7)		29 (67.4)	0	
LV ejection fraction, %	32.8 ± 10.9	34.8 ± 10.9	0.006	56.7 ± 4.5	56.0 ± 5.3	0.464
LV end diastolic diameter, mm	63.3 ± 8.4	62.8 ± 8.4	0.331	51.1 ± 7.7	50.1 ± 7.0	0.249
LV end systolic diameter, mm	54.7 ± 10.3	54.6 ± 9.6	0.886	37.5 ± 6.5	36.7 ± 6.6	0.419
LV mass index, g/m ²	147.4 ± 35.8	150.5 ± 37.5	0.409	129.7 ± 31.8	128.1 ± 27.8	0.702
LA volume index, ml/m ²	80.8 ± 32.8	68.9 ± 25.0	< 0.001	79.2 ± 33.4	66.6 ± 23.0	0.002
E/e'	15.8 ± 5.6	22.4 ± 7.6	< 0.001	12.9 ± 5.7	20.3 ± 7.3	< 0.001
RV basal diameter, mm	38.7 ± 6.7	37.9 ± 6.6	0.388	40.0 ± 7.6	38.2 ± 7.1	0.041
Right atrial area, cm ²	27.8 ± 9.9	25.1 ± 9.3	< 0.001	28.4 ± 10.0	26.8 ± 9.2	0.042
TAPSE, mm	17.1 ± 4.0	18.9 ± 3.7	0.001	18.2 ± 4.0	18.5 ± 3.8	0.484
PASP, mmHg	48.2 ± 14.6	43.4 ± 13.6	0.017	51.5 ± 16.2	44.4 ± 13.5	0.003
TAPSE/PASP, mm/mmHg	0.47 ± 0.19	0.58 ± 0.23	0.001	0.46 ± 0.19	0.55 ± 0.23	0.004
VCI, mm	2.59 ± 3.46	2.01 ± 1.62	0.261	2.01 ± 0.59	1.73 ± 0.52	0.006
Forward stroke volume, ml	49.4 ± 17.3	49.5 ± 16.5	0.960	60.5 ± 21.7	66.8 ± 19.6	0.037
Forward stroke volume index, ml/m ²	25.8 ± 8.2	25.9 ± 8.3	0.898	32.8 ± 11.1	36.2 ± 9.7	0.035
Heart rate,/min	71.2 ± 12.2	70.4 ± 14.0	0.614	68.9 ± 16.2	68.2 ± 13.4	0.782
Cardiac output, l/min	3.4 ± 1.2	3.4 ± 1.2	0.872	4.1 ± 1.4	4.5 ± 1.4	0.082
TR grade			0.003			0.025
Mild	20 (34.5)	30 (50.0)		10 (24.4)	18 (41.9)	
Moderate	17 (29.3)	18 (30.0)		13 (31.7)	11 (25.6)	
Severe	21 (36.2)	12 (20.0)		18 (43.9)	14 (32.6)	

Variables are expressed as *n* (%), mean ± standard deviation, or median [interquartile range], as appropriate. Bold values indicate statistical significance (*p* < 0.05)

EROA effective regurgitation orifice area, *LA* left atrial, *LV* left ventricular, *MR* mitral regurgitation, *NYHA* New York Heart Association, *PASP* pulmonary artery systolic pressure, *RV* right ventricular, *TAPSE* tricuspid annular plane systolic excursion, *TR* tricuspid regurgitation, *VCI* inferior vena cava

and atrial fibrillation, were not independently associated with FSV improvement in the adjusted model (see Table 4).

Discussion

Our study provides novel insights into the differential impact of M-TEER on FSV in secondary MR of atrial versus ventricular etiology. While patients with atrial MR

exhibited a significant increase in FSV, no overall improvement was observed in those with ventricular MR. Notably, lower baseline FSV emerged as a strong and independent predictor of relevant FSV improvement after M-TEER, suggesting that patients with more advanced hemodynamic compromise have the greatest capacity for hemodynamic recovery. However, FSV improvement did not translate into lower mortality or fewer HF-related hospitalizations in either group. FSV and its dynamic response

Table 3 Functional and echocardiographic results 1 month after M-TEER, stratified by FSV improvement

	FSV improvement		<i>p</i>
	≤ 10% (<i>n</i> = 51)	> 10% (<i>n</i> = 52)	
NTproBNP, pg/ml	2908 [1810–5470]	2491 [1632–4761]	0.827
NYHA functional class		0.994	
I	9 (17.6)	12 (23.1)	
II	34 (66.7)	29 (55.8)	
III	8 (15.7)	11 (21.2)	
IV	0	0	
Six-minute walk distance, m	283.6 ± 106.1	302.1 ± 116.8	0.414
Echocardiography			
MR grade			0.109
I	38 (74.5)	31 (59.6)	
II	12 (23.5)	19 (36.5)	
III	0	2 (3.8)	
IV	1 (2.0)	0	
MV pmean, mmHg	3.4 ± 1.5	3.5 ± 1.7	0.897
LV ejection fraction, %	39.9 ± 12.3	47.3 ± 14.4	0.006
LV end diastolic diameter, mm	58.4 ± 9.2	56.4 ± 10.8	0.325
LV end systolic diameter, mm	48.6 ± 10.2	44.5 ± 14.1	0.111
LA volume index, ml/m ²	62.8 ± 21.2	71.6 ± 26.1	0.063
RV basal diameter, mm	36.8 ± 5.4	39.3 ± 7.7	0.188
TAPSE, mm	18.3 ± 3.8	19.4 ± 3.7	0.134
PASP, mmHg	41.0 ± 12.6	45.8 ± 13.6	0.561
Forward stroke volume, ml	49.9 ± 16.2	63.4 ± 20.7	< 0.001
Forwards stroke volume index, ml/m ²	26.7 ± 8.3	33.6 ± 10.8	< 0.001
Heart rate, /min	69.9 ± 14.9	69.1 ± 12.7	0.766
Cardiac output, l/min	3.4 ± 1.1	4.3 ± 1.5	0.001
Tricuspid regurgitation grade			0.055
Mild	28 (54.9)	20 (38.5)	
Moderate	14 (27.5)	15 (28.8)	
Severe	9 (17.6)	17 (32.7)	

Variables are expressed as *n* (%), mean ± standard deviation, or median [interquartile range], as appropriate. Bold values indicate statistical significance (*p* < 0.05)

FSV forward stroke volume, LA left atrial, LV left ventricular, MR mitral regurgitation, MV mitral valve, NYHA New York Heart Association, PASP pulmonary artery systolic pressure, RV right ventricular, TAPSE tricuspid annular plane systolic excursion

may therefore serve as complementary echocardiographic markers for characterizing the hemodynamic response to M-TEER, while underscoring that atrial and ventricular MR represent two distinct pathophysiological phenotypes of secondary MR requiring individualized assessment.

Patient characteristics and procedural success

Significant baseline differences were observed between the two groups. Patients with ventricular MR had more severe LV dysfunction, lower FSV, and higher NTproBNP levels, whereas patients with atrial MR were older, predominantly female, and had preserved LV function. Consistent with

existing literature, these characteristics reflect the differing pathophysiological mechanisms underlying these MR subtypes [17, 19, 20]. Despite these differences, procedural success and safety were comparable for both groups and to current studies [32].

Differential FSV response

M-TEER induces abrupt changes in LV loading. In both primary and secondary MR, total stroke volume (derived from LV end diastolic and LV end systolic volume) and LVEF decrease immediately after the procedure, while end systolic volume increases—reflecting the sudden reduction

Death or hospitalization for heart failure

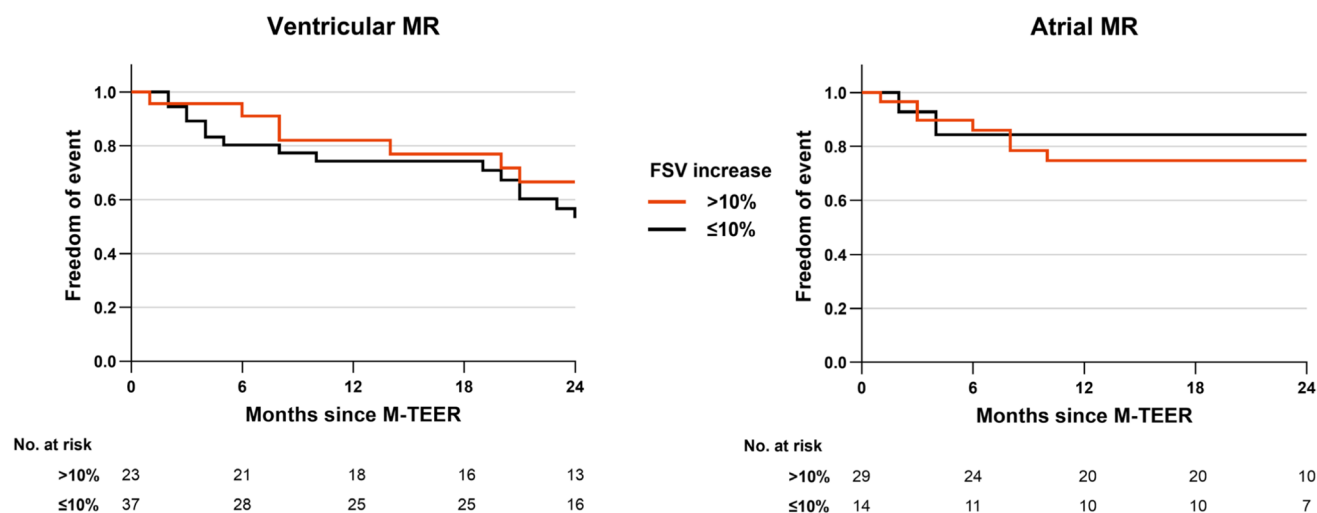


Fig. 2 Clinical outcomes after M-TEER stratified by forward stroke volume improvement in patients with atrial and ventricular secondary mitral regurgitation. Kaplan–Meier time-to-event analysis for the composite endpoint of all-cause mortality or hospitalization for heart failure in patients with ventricular (left) and atrial (right) secondary mitral regurgitation (MR) following transcatheter edge-to-edge repair

(M-TEER), stratified by forward stroke volume (FSV) improvement. Patients with an FSV improvement > 10% (red) were compared to those without FSV improvement (black). Patients were censored at the time of last available follow-up. No significant differences in event-free survival were observed between groups

Table 4 Baseline predictors of FSV improvement > 10% after M-TEER

	Univariable			Multivariable		
	OR	95% CI	<i>p</i>	OR	95% CI	<i>p</i>
Age (per year)	1.01	0.97–1.05	0.653			
Female gender (vs. male)	1.14	0.52–2.50	0.750			
Atrial MR (vs. ventricular)	3.33	1.46–7.59	0.004	5.12	1.04–25.90	0.048
MR grade IV (vs. III)	0.92	0.38–2.27	0.862			
Severe TR	2.92	1.27–6.72	0.012	2.31	0.89–6.01	0.086
LVEF (per 10%)	1.33	1.01–1.75	0.043	1.12	0.64–1.96	0.684
CAD	0.32	0.14–0.74	0.007	0.57	0.22–1.5	0.267
Diabetes mellitus	0.37	0.15–0.90	0.028	0.52	0.19–1.45	0.211
Atrial fibrillation	1.03	0.46–2.30	0.940			
Baseline FSVI (per 10 ml/m ²)	0.56	0.35–0.88	0.012	0.36	0.19–0.69	0.002

CAD coronary artery disease, FSVI forward stroke volume index, LVEF left ventricular ejection fraction, MR mitral regurgitation, TR tricuspid regurgitation. Bold values indicate statistical significance ($p < 0.05$)

of regurgitant flow into the low-pressure LA [33]. This decrease in total stroke volume and LVEF is mainly driven by decreased LV preload and increased LV afterload conditions after M-TEER, but not due to changes in LV contractility as demonstrated by Nagueh et al. with invasive measurements [34]. These findings are consistent with the landmark pressure–volume loop study by Gaemperli et al., who showed that M-TEER results in an acute increase in LV afterload (end-systolic wall stress) and a reduction in preload (end-diastolic wall stress), while LV contractility (end-systolic pressure–volume

relationship) remains unchanged [35]. Importantly, this reduction in LVEF should not be interpreted as deterioration of LV function but rather as a physiological adaptation to altered loading conditions. Despite the reduction in LVEF, forward cardiac output increases and pulmonary pressures decrease, indicating that the hemodynamic benefit of MR reduction outweighs the increase in afterload [36]. This concept has been further supported by Melisurgo et al., who demonstrated that afterload mismatch after MitraClip is a transient phenomenon without long-term prognostic implications [37].

Within the first 48 h after M-TEER, early hemodynamic improvements can be observed, initiating the process of subsequent ventricular remodeling. A study in patients with cardiogenic shock and severe MR, predominantly of secondary origin, demonstrated that M-TEER leads to an improvement in FSVI and cardiac index within this early period [38]. An improvement in LV global longitudinal strain precedes the increase in FSV in both atrial and ventricular MR [39]. Six months after M-TEER for secondary MR, some patients exhibited LV reverse remodeling, as reflected by an increase in FSV and cardiac index, while LVEF and LV strain remained unchanged [40].

In our study, FSV improvement > 10% after M-TEER was not associated with better functional status at follow-up, nor with improved clinical outcomes including all-cause mortality and HF hospitalization. This finding contrasts with the landmark study by Kubo et al., who showed that an FSV increase > 9% was associated with significantly lower 3-year all-cause mortality (17.6% vs. 42.3%, $p=0.002$), LV reverse remodeling, and improved functional status [41]. This discrepancy is most likely explained by fundamental differences in MR etiology between the study populations. The Kubo analysis was derived from the EVEREST II randomized trial and the REALISM continued access registry, which predominantly enrolled patients with primary (degenerative) MR and preserved LVEF. The EVEREST II trial explicitly excluded patients with $LVEF \leq 25\%$ and LV end-systolic diameter > 55 mm, thereby excluding patients with severely impaired ventricular function and advanced LV remodeling. Furthermore, atrial MR—characterized by preserved LV function, LA enlargement, and annular dilatation—was not recognized as a distinct phenotype at the time of these studies and was therefore not specifically addressed. In contrast, our cohort exclusively comprised patients with secondary MR, including both ventricular MR (with reduced LVEF and LV remodeling) and atrial MR (with preserved LVEF and LA-driven pathology). These entities represent fundamentally different pathophysiological substrates compared to primary MR, and therefore the findings of Kubo et al. cannot be directly extrapolated to our cohort.

The differential FSV response patterns observed in our study—with significant FSV improvement in atrial MR but not in ventricular MR—likely reflect these distinct pathophysiological mechanisms. In atrial MR, where MR originates primarily from atrial dilation and mitral annulus changes with preserved LV geometry [20], addressing the regurgitant lesion may more effectively enhance forward flow without the confounding influence of significant ventricular dysfunction [17, 18]. In contrast, ventricular MR is characterized by advanced LV remodeling and reduced contractility and the underlying LV dysfunction appears to impose limitations on the degree of hemodynamic improvement achievable after M-TEER [3, 4, 40, 42].

These observations underscore the importance of stratifying patients by MR etiology when evaluating hemodynamic outcomes and interpreting the prognostic significance of FSV response.

Impact of FSV response on LV function

At follow-up, patients with an FSV improvement > 10% exhibited higher LVEF and substantially higher FSV and cardiac output compared with those without relevant improvement, while clinical status, residual MR grade, LV dimensions, and right ventricular function did not differ between groups. Logistic regression identified two independent predictors of > 10% FSV improvement: atrial MR etiology (OR 5.12, $p=0.048$) and lower baseline FSVI (OR 0.36 per 10 ml/m², $p=0.002$). Variables such as age, sex, LVEF, coronary artery disease, diabetes, severe TR, MR grade, and atrial fibrillation showed no significant association.

These findings have important pathophysiological implications. The strong independent association between atrial MR and FSV improvement reflects the preserved LV geometry and contractility characteristic of this phenotype. In atrial MR, regurgitation originates primarily from LA dilation and mitral annular changes rather than ventricular dysfunction. Consequently, addressing the regurgitant lesion effectively enhances forward flow without the confounding influence of impaired LV contractility. The reduction in MR results in LV unloading, leading to a decrease in LV preload. Since LV function and dimensions are preserved in atrial MR, this unloading effect can enhance forward flow, as studies have shown that LV contractility remains stable [32, 43, 44].

The independent predictive value of low baseline FSV indicates that patients with more advanced hemodynamic compromise have greater capacity for improvement after successful MR reduction. This observation is strongly supported by the recent COAPT subgroup analysis by Gertz et al., who stratified patients by baseline FSV tertiles (low < 40 ml, intermediate 40–55 ml, high > 55 ml). Patients in the lowest FSV tertile experienced the greatest absolute benefit from M-TEER, with a significant reduction in the composite of death or HF hospitalization compared to medical therapy alone. Importantly, while FSV did not significantly improve after M-TEER across the overall cohort, patients with low baseline FSV demonstrated the largest relative gains in forward flow. The treatment effect of M-TEER was consistent across all FSV tertiles, but the absolute risk reduction was most pronounced in patients with the lowest baseline FSV, highlighting the prognostic relevance of baseline hemodynamic status for patient selection [16].

In contrast to our study, these hemodynamic improvements were accompanied by favorable clinical outcomes and

reverse remodeling, underscoring important differences in patient selection, baseline ventricular function, and follow-up duration.

Furthermore, Yedidya et al. showed that FSVI was the only echocardiographic parameter that consistently improved after M-TEER in patients with secondary MR, and that non-improvers demonstrated worsening of LVEF compared with improvers, in whom LVEF remained stable [45].

Notably, the absence of an independent association between baseline LVEF and FSV improvement underscores that LVEF alone may not adequately capture the hemodynamic substrate that determines response to M-TEER. FSV, as a direct measure of forward flow, appears to provide complementary information beyond traditional measures of LV systolic function.

Kamperidis et al. demonstrated that mitral valve repair for secondary MR in non-ischemic cardiomyopathy significantly improved FSVI (FSVI: from 20 ± 7 to 29 ± 8 ml/m², $p < 0.001$) and induced LV reverse remodeling, while LVEF remained unchanged [46]. This aligns with findings from a cardiac magnetic resonance study, where only one-third of patients with secondary MR demonstrated LV reverse remodeling after M-TEER after 6 months at mid-term follow-up [40].

Taken together, these results suggest that both—MR etiology and baseline hemodynamic status—should be considered when predicting the likelihood of hemodynamic improvement after M-TEER. Patients with atrial MR and those with low baseline FSV represent subgroups with the greatest potential for FSV response, which may have implications for patient selection and procedural counseling.

Impact of MR reduction on FSV response

In all patients, both with atrial and ventricular MR, a significant reduction in MR was achieved, aligning with current evidence [3, 4].

Importantly, while patients with ventricular MR did not demonstrate a significant increase in FSV at 1-month follow-up, FSV also did not decrease despite effective MR reduction. This finding is reassuring, as it suggests that M-TEER with maximal MR reduction does not compromise forward flow even in patients with reduced LVEF.

The current evidence clearly demonstrates that greater MR reduction is associated with improved outcomes. In the STS/ACC TVT Registry analysis by Makkar et al., MR success was associated with significantly lower 1-year mortality (14.0% vs. 26.7%; adjusted HR 0.49, 95% CI 0.42–0.56, $p < 0.001$) and HF readmission compared with unsuccessful procedures, with the lowest mortality observed in patients achieving mild or less residual MR [47]. Similarly, Ben-Shoshan et al. demonstrated that residual MR ≥ 2 + following M-TEER independently predicts device failure, HF

rehospitalization, and mortality [48]. Our observation that FSV remained stable supports the concept that concerns about excessive preload reduction should not deter clinicians from achieving optimal MR reduction.

The concept of afterload mismatch—where acute elimination of the low-resistance regurgitant pathway leads to increased LV afterload and potentially reduced forward output—has been described in patients with functional MR undergoing M-TEER.

Melisurgo et al. demonstrated that afterload mismatch occurs in approximately 26% of patients with functional MR and is more common in patients with larger LV dimensions and more severe RV dysfunction. Importantly, this phenomenon was shown to be transient and without long-term prognostic implications, as LVEF normalized before hospital discharge [37].

More recently, Angelini et al. specifically investigated afterload mismatch in patients with LVEF $\leq 35\%$ undergoing M-TEER and found that proportionate MR (where MR severity is proportional to LV dysfunction) was associated with a higher risk of afterload mismatch. While afterload mismatch was associated with higher in-hospital mortality, 2-year mortality rates were similar between groups, suggesting that this early hemodynamic phenomenon does not adversely affect long-term prognosis [49].

Our observation that FSV remained stable in patients with ventricular MR suggests that the feared hemodynamic deterioration due to afterload mismatch did not manifest at 1-month follow-up in our cohort, further supporting the safety of maximal MR reduction even in patients with advanced ventricular dysfunction.

It should be taken into account that our follow-up was performed after only 4 weeks following M-TEER, and therefore different hemodynamic changes may be observed compared to longer term follow-up.

Prior studies have characterized the acute hemodynamic shifts following MR correction. Historical surgical data indicate that MR reduction is associated with a decrease in LV end diastolic volume and an increase in LV end systolic volume, leading to an apparent drop in LVEF [50]. Similarly, an analysis of the EVEREST I and II trials by Siegel et al. confirmed that while M-TEER effectively reduces MR and improves cardiac output, it also lowers LV end diastolic volume and LVEF, highlighting the impact of acute hemodynamic shifts post-procedure [36]. A more recent study by Galli et al. further supports these findings, demonstrating a decline in global longitudinal strain in patients with primary MR after M-TEER, reinforcing the concept that abrupt preload reduction can transiently impair LV function parameters [51].

However, these changes in LVEF and strain parameters should not be interpreted as deterioration of intrinsic LV function, but rather as physiological adaptation to altered loading conditions, as LV contractility remains preserved.

Clinical implications

FSV improvement was not associated with lower rates of HF hospitalization or all-cause mortality, indicating that FSV improvement alone may not be a sufficient surrogate for clinical outcome in this population. This apparent lack of prognostic impact, however, requires careful interpretation. Notably, patients with low-baseline FSV—a well-established marker of poor prognosis—demonstrated the greatest absolute FSV gains after M-TEER, whereas patients with higher baseline FSV showed little or no improvement. This differential response pattern suggests that FSV improvement in the low-baseline group may elevate their hemodynamic and prognostic status to a level comparable to that of patients with preserved baseline FSV. Consequently, when comparing responders versus non-responders, the prognostic benefit of FSV improvement may be obscured, as responders “catch up” to the level of non-responders who already had favorable baseline hemodynamics. This interpretation is consistent with the COAPT subgroup analysis by Gertz et al. [16] and the findings of Kubo et al. [41], who identified higher baseline FSV as an independent predictor of non-response. Thus, baseline FSV appears to identify patients with greater capacity for hemodynamic improvement, and FSV response after M-TEER may represent a mechanism by which high-risk patients achieve prognostic alignment with lower-risk patients, rather than a simple surrogate marker of outcome.

Despite the lack of prognostic impact, functional improvements were evident in both MR etiologies. In ventricular MR, a significant improvement in both NYHA functional class and 6-min walk distance was observed from baseline to follow-up. In atrial MR, NYHA functional class improved significantly, while the increase in 6-min walk distance did not reach statistical significance. Of note, FSV responders and non-responders did not differ in their functional status at 1 month after M-TEER, suggesting that FSV response alone does not fully capture the functional benefit of the procedure. These findings underscore that FSV response should not be used as an isolated marker of procedural success in ventricular MR. Instead, baseline hemodynamics and patient selection are likely more relevant when evaluating procedural success.

In contrast, patients with atrial MR exhibited a significant increase in FSV, likely reflecting their distinct pathophysiological profile characterized by preserved LV function. However, this hemodynamic improvement did not translate into improved hard clinical endpoints, as no reduction in adverse outcomes was observed. This dissociation emphasizes the need to stratify patients by MR etiology to better predict therapeutic response and tailor procedural strategies. The differential FSV response patterns between atrial and ventricular MR further support the concept that these represent two distinct pathophysiological phenotypes requiring individualized management approaches.

Finally, FSV improvement may still serve as a surrogate marker for favorable ventricular remodeling, even in the absence of a direct association with hard clinical endpoints. Our findings support the concept of a hemodynamic–structural interplay, whereby unloading MR-induced volume excess can trigger reverse remodeling and improve ventricular function. Importantly, patients with low baseline FSV—who carry the highest risk—demonstrated the greatest capacity for hemodynamic recovery after M-TEER. As outlined above, this FSV response may enable high-risk patients to achieve prognostic alignment with those who had preserved baseline hemodynamics, thereby attenuating the apparent prognostic impact of FSV improvement when comparing responders versus non-responders. This mechanistic link warrants further investigation in larger cohorts with longer follow-up, as it may have prognostic value and refine patient selection for M-TEER. Future studies should specifically evaluate whether baseline FSV can serve as a selection criterion to identify patients with the greatest potential for hemodynamic and clinical benefit from M-TEER.

Limitations

This study has several limitations. First, it was a retrospective, single-center analysis with a limited sample size, which may restrict generalizability. Larger multicenter studies are warranted to confirm these findings. Although echocardiographic measurements followed standardized protocols, FSV estimation using the LVOT method remains subject to potential measurement variability. In patients with atrial fibrillation, Doppler-derived LVOT VTI is inherently subject to beat-to-beat variability because ventricular filling and subsequent FSV depend on both the preceding and pre-preceding RR intervals [52]. Although an index-beat approach was used to improve reproducibility, some measurement variability cannot be fully excluded. Alternative strategies have been described, including averaging multiple consecutive beats or selecting a single long cycle. Averaging multiple beats is widely applied but remains time-consuming and may still be affected by substantial cycle-length heterogeneity. Likewise, single long-cycle approaches may be appropriate for selected Doppler applications, but they can systematically yield larger stroke volume values and may therefore not fully reflect average hemodynamics in atrial fibrillation. These methodological considerations should be taken into account when interpreting Doppler-derived FSV in this rhythm [53, 54]. Furthermore, invasive hemodynamic data, including invasively measured FSV, were not routinely available in this study population, precluding a direct comparison with echocardiographic FSV measurements.

Echocardiographic follow-up was performed 1 month after M-TEER, focusing on short-term hemodynamic changes; longer-term effects related to reverse remodeling require further investigation. MR severity was assessed using an integrative, multiparametric approach in accordance with

guideline recommendations. Fully quantitative assessment using continuity equation or volumetry was not performed. However, these methods frequently necessitate contrast or three-dimensional echocardiography or cardiac magnetic resonance imaging to provide sufficient accuracy, which fell outside the scope of this study. Blinding of echocardiographic assessment was not feasible because the implanted devices are visible in the LVOT view. Finally, while the study provides new insights into differential FSV responses in atrial and ventricular MR, the underlying mechanisms remain incompletely understood.

Conclusion

Our study underscores the distinct hemodynamic response patterns to M-TEER in atrial versus ventricular secondary MR. FSV increased significantly in atrial MR but remained unchanged in ventricular MR. Low FSV at baseline was an independent predictor of relevant FSV improvement, suggesting that patients with more advanced hemodynamic compromise have the greatest capacity for hemodynamic recovery after M-TEER. Importantly, FSV remained stable in ventricular MR despite effective MR reduction, indicating that maximal MR correction does not compromise forward flow even in patients with reduced LVEF. Although FSV improvement was not associated with reduced mortality or fewer HF hospitalizations, this may reflect prognostic alignment—whereby high-risk patients with low baseline FSV achieve hemodynamic status comparable to lower-risk patients through FSV improvement. FSV response may therefore serve as a complementary echocardiographic marker to characterize the hemodynamic adaptation to M-TEER and to differentiate these two phenotypes. These findings support the concept that atrial and ventricular MR represent distinct pathophysiological entities requiring individualized assessment when evaluating procedural outcomes.

Abbreviations BSA: Body surface area; CSA: Cross-sectional area; FSV: Forward stroke volume; FSVI: Forward stroke volume index; HF: Heart failure; LA: Left atrial; LV: Left ventricular; LVEF: Left ventricular ejection fraction; LVOT: Left ventricular outflow tract; MR: Mitral regurgitation; M-TEER: Mitral valve transcatheter edge-to-edge repair; MV: Mitral valve; NYHA: New York Heart Association; PASP: Pulmonary artery pressure; VTI: Velocity time integral

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Schach, Christine Meindl. Writing—originaldraft preparation: Franziska Grewe. Resources: Lars Maier, Kurt Debl, Bernhard Unsöld. Supervision: Lars Maier, Bernhard Unsöld, Christoph Birner, Andreas Luchner.

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Declarations

Ethical approval This study has been reviewed by the local ethics committee. All study-related procedures were performed in accordance with the Declaration of Helsinki.

Consent to participate All patients had provided written informed consent.

Consent for publication Patients signed informed consent regarding publishing their data.

ICMJE and CRediT author statement All named authors meet the International Committee of Medical Journal Editors (ICMJE) criteria for authorship for this article, take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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