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## ORIGINAL RESEARCH

# Changes in Right Ventricular-to-Pulmonary Artery Coupling After Transcatheter Edge-to-Edge Repair in Secondary Mitral Regurgitation

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## ABSTRACT

**BACKGROUND** Preprocedural right ventricular-to-pulmonary artery (RV-PA) coupling is a major predictor of outcome in patients with secondary mitral regurgitation (SMR) undergoing transcatheter edge-to-edge mitral valve repair (M-TEER). However, clinical significance of changes in RV-PA coupling after M-TEER is unknown.

**OBJECTIVES** The aim of this study was to evaluate changes in RV-PA coupling after M-TEER, their prognostic value, and predictors of improvement.

**METHODS** This was a retrospective observational study, including patients undergoing successful M-TEER (residual mitral regurgitation  $\leq 2+$  at discharge) for SMR at 13 European centers and with complete echocardiographic data at baseline and short-term follow-up (30-180 days). RV-PA coupling was assessed with the use of echocardiography as the ratio of tricuspid annular plane systolic excursion to pulmonary artery systolic pressure (TAPSE/PASP). All-cause death was assessed at the longest available follow-up starting from the time of the echocardiographic reassessment.

**RESULTS** Among 501 patients included, 331 (66%) improved their TAPSE/PASP after M-TEER (responders) at short-term follow-up (median: 89 days; IQR: 43-159 days), whereas 170 (34%) did not (nonresponders). Lack of previous cardiac surgery, low postprocedural mitral mean gradient, low baseline TAPSE, high baseline PASP, and baseline tricuspid regurgitation were independently associated with TAPSE/PASP improvement after M-TEER. Compared with nonresponders, responders had lower New York Heart Association functional class and less heart failure hospitalizations at short-term follow-up. Improvement in TAPSE/PASP was independently associated with reduced risk of mortality at long-term follow-up (584 days; IQR: 191-1,243 days) (HR: 0.65 [95% CI: 0.42-0.92];  $P = 0.017$ ).

**CONCLUSIONS** In patients with SMR, improvement in TAPSE/PASP after successful M-TEER is predicted by baseline clinical and echocardiographic variables and postprocedural mitral gradient, and is associated with a better outcome. (J Am Coll Cardiol Img 2022;■:■-■) © 2022 Published by Elsevier on behalf of the American College of Cardiology Foundation.

**ABBREVIATIONS  
AND ACRONYMS****HF** = heart failure**MR** = mitral regurgitation**M-TEER** = transcatheter edge-to-edge mitral valve repair**PA** = pulmonary artery**PASP** = pulmonary artery systolic pressure**RV** = right ventricle**SMR** = secondary mitral regurgitation**TAPSE** = tricuspid annular plane systolic excursion**TR** = tricuspid regurgitation

**T**ranscatheter edge-to-edge mitral valve repair (M-TEER) is classified in recent guidelines as a treatment that should be considered for outcome improvement in selected patients with secondary mitral regurgitation (SMR) and heart failure (HF).<sup>1,2</sup> This recommendation is based on the results of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial showing clear benefits of M-TEER on top of optimal medical therapy in SMR.<sup>3-5</sup>

Moderate to severe right ventricular (RV) dysfunction was one of the key exclusion criteria of the COAPT trial. In contrast, patients with RV dysfunction were not excluded from the MITRA-FR (French Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study, which showed similar outcomes in patients receiving M-TEER vs control subjects.<sup>6,7</sup> RV dysfunction is a well-known predictor of worse outcome in patients with SMR undergoing M-TEER,<sup>8-11</sup> and its lack among the exclusion criteria of MITRA-FR may explain part of the discrepant results between the 2 trials.

Right ventricle-to-pulmonary artery (RV-PA) coupling, noninvasively assessed by means of echocardiography as the ratio between tricuspid annular plane systolic excursion and pulmonary artery systolic pressure (TAPSE/PASP), can be considered as a surrogate for RV length-force relationship and was found to be of clinical and prognostic relevance in HF populations.<sup>12-16</sup> Moreover, TAPSE/PASP was recently shown to be a major predictor of adverse events in M-TEER recipients.<sup>17-19</sup> Nevertheless, those studies

assessed the TAPSE/PASP ratio only at baseline, before M-TEER.

Several small studies have shown that RV dysfunction may recover after M-TEER<sup>20-25</sup> and that this improvement seems associated with a better outcome.<sup>25</sup> However, no data are available regarding the evolution of RV-PA coupling after M-TEER, and predictors of recovery of RV function are unsettled.

Therefore, our aim was to evaluate changes in TAPSE/PASP after successful M-TEER and their impact on prognosis, as well as to identify predictors of RV-PA coupling improvement after SMR correction.

**METHODS**

**STUDY POPULATION.** This was a retrospective multicenter analysis including patients undergoing M-TEER with the MitraClip system (Abbott Vascular) from December 2009 to February 2021 at 13 European centers. For the purpose of this analysis, only patients with a complete echocardiographic evaluation at baseline and short-term follow-up (30 to 180 days) and undergoing a successful M-TEER procedure (defined as residual mitral regurgitation [MR]  $\leq 2+$  at discharge) were included.

All patients were evaluated before M-TEER by a local multidisciplinary team including cardiologists, cardiac surgeons, and anesthesiologists. All patients gave their consent after extensive explanation of the benefits and risks of the procedure. The present study was approved by the local ethical committee.

**DATA COLLECTION AND DEFINITIONS.** Demographic, clinical, echocardiographic, procedural data, and outcomes were assessed for quality and entered into a dedicated computerized database.

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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](#).

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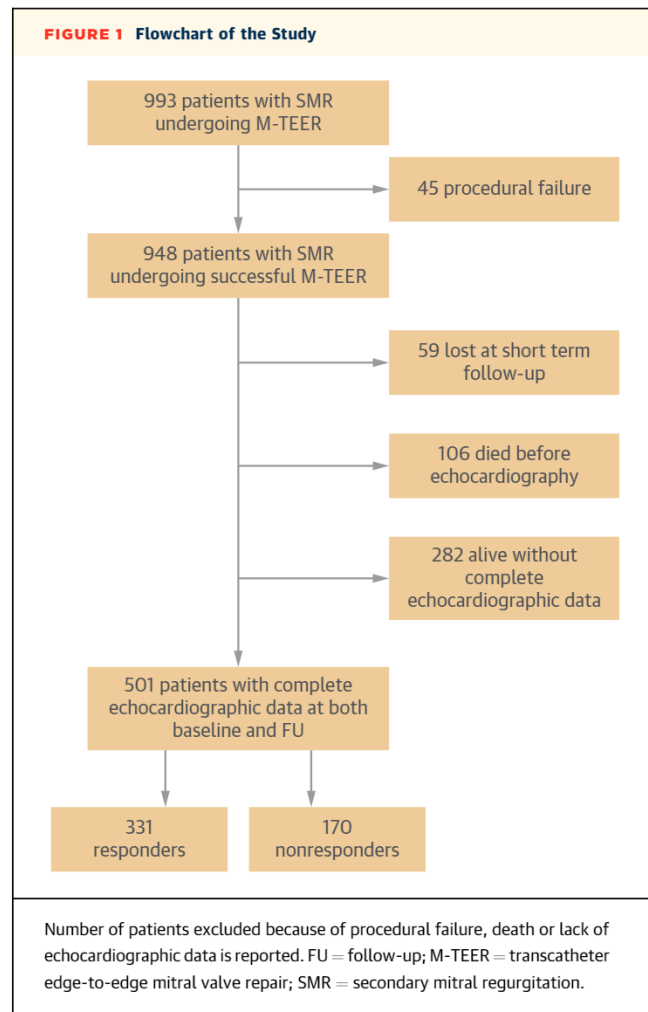
Echocardiographic parameters were measured at each center by expert operators at both baseline and short-term follow-up. TAPSE was measured using M-mode according to the American Society of Echocardiography recommendations.<sup>26</sup> PASP was obtained with the use of the following formula:  $4 \times (\text{peak TRV})^2 + \text{RAP}$ , where TRV is tricuspid regurgitation velocity and RAP is the estimated mean right atrial pressure. TRV was carefully assessed from multiple acoustic windows to accurately identify the velocity peak. RAP was estimated from the inferior vena cava diameter and collapsibility during inspiration. TAPSE/PASP ratio was then calculated.

Patients were stratified according to the changes in TAPSE/PASP between baseline and the echocardiographic reassessment in 2 groups: those with improved TAPSE/PASP, defined as responders, and those with unchanged or worsened TAPSE/PASP, defined as nonresponders.

Right ventricular dysfunction was defined by a TAPSE  $<15$  mm.<sup>8-10</sup> Short-term follow-up was defined as the time from M-TEER and echocardiographic reassessment. Echocardiographic reassessment was defined as a planned echocardiographic evaluation (not performed during HF hospitalization or unplanned visit). Long-term follow-up was defined as the time from the echocardiographic reassessment and the end of follow-up (last patient contact). New York Heart Association (NYHA) functional class and the rate of HF hospitalizations were assessed at short-term follow-up. All-cause mortality was evaluated at long-term follow-up.

**STATISTICAL ANALYSIS.** The normal distribution of continuous variables was explored with the use of Kolmogorov-Smirnov and Shapiro-Wilk tests. Continuous variables following a normal distribution are reported as mean  $\pm$  SD and were compared by means of Student's *t*-test, whereas those not following a normal distribution are presented as median (IQR) and compared by means of the Mann-Whitney *U*-test. Categorical variables are reported as n (%) and were compared by means of chi-square or Fisher's exact test, as appropriate.

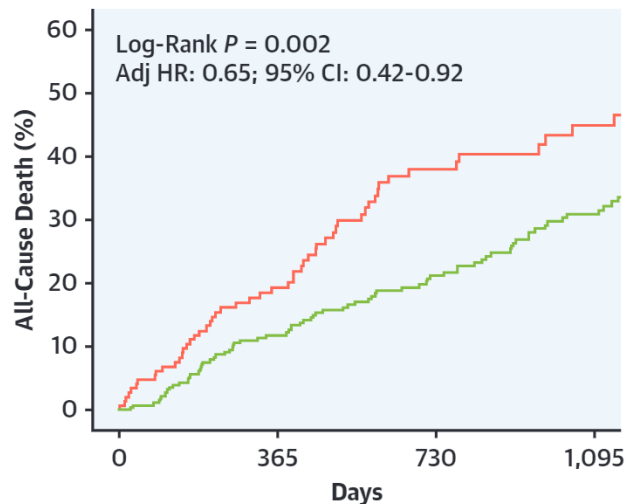
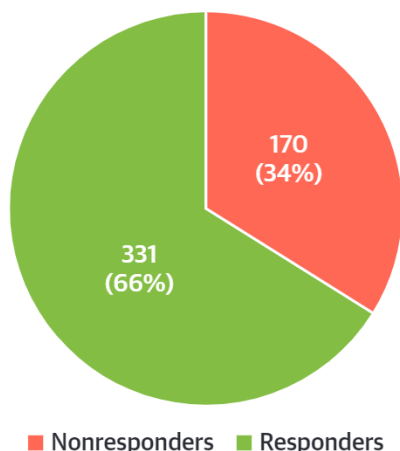
To exclude the regression to mean effect, we adjusted all changes in TAPSE, PASP, and their ratio for the baseline values by means of the analysis of covariance test.<sup>27</sup> The stratification into responders and nonresponders was done by using adjusted values of TAPSE/PASP changes. Correlation between TAPSE/PASP changes and baseline values was plotted with the use of scatter plots and tested by Pearson's test and linear regression analysis. Pearson's test was



also used to evaluate the correlation between TAPSE and PASP in different groups.

Interobserver and intraobserver variability regarding TAPSE, PASP and TAPSE/PASP measurements was verified in a sample size of 60 patients with the use of Pearson's statistics, intraclass correlation coefficient, and Bland-Altman method (bias and limits of agreement).

Cumulative incidence of all-cause death was assessed by means of the Kaplan-Meier method with a landmark analysis: survival assessed starting from the time of the echocardiographic reassessment. Differences between groups were calculated by means of the log-rank test. The proportionality assumptions were checked by visual estimation after plotting the log cumulative hazard vs (log) time at follow-up after the index procedure and by applying a test for non-proportional hazards with the use of Schoenfeld residuals, which failed to reject the null hypothesis that HR remains constant over time. A multivariable Cox

**CENTRAL ILLUSTRATION** Prevalence, Prognostic Impact, and Predictors of TAPSE/PASP Improvement After M-TEER

Number at risk

— Nonresponders	170	98	53	35
— Responders	331	224	161	105

#### Responders' Profile (TAPSE/PASP Improvement After M-TEER)

- Lack of prior cardiac surgery
- Low post-procedural mitral mean gradient
- Low TAPSE
- High PASP
- Significant TR
- High LVEF and high PASP in presence of RV dysfunction (TAPSE <15 mm)

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Responders (**green**) underwent improvement of their TAPSE/PASP ratio after M-TEER, whereas nonresponders (**red**) did not improve their TAPSE/PASP ratio after M-TEER. M-TEER = transcatheter edge-to-edge mitral valve repair; LVEF = left ventricular ejection fraction; PASP = pulmonary artery systolic pressure; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

regression analysis was performed to calculate the adjusted relative risk of all-cause death in responders vs nonresponders, which was expressed as HR and corresponding 95% CI. The continuous association between the incidence rates of all-cause death and TAPSE, PASP, and their ratio at baseline, follow-up, and their changes was assessed with the use of restricted cubic splines with 3 knots, resulting in the lowest model Akaike information criterion (3-6 knots were assessed).

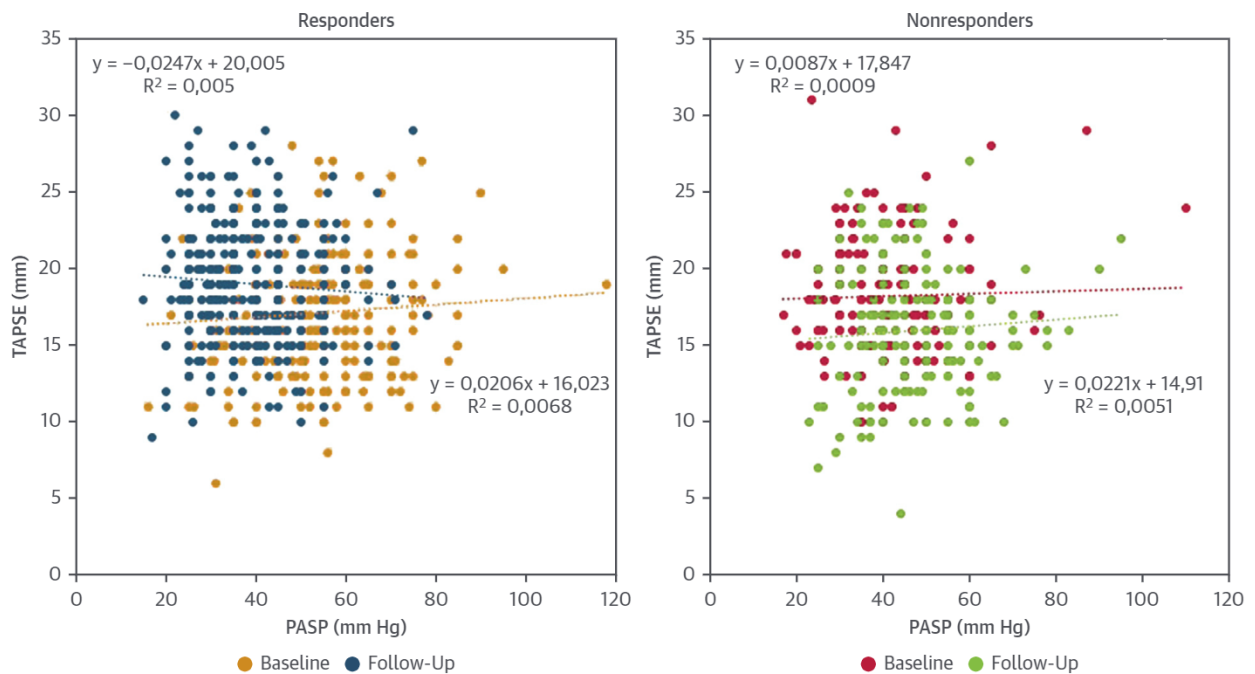
Baseline variables differently distributed at an alpha level of 0.10 were entered in a stepwise logistic regression model to calculate independent

predictors of TAPSE/PASP improvement. Each result was reported as OR and corresponding 95% CI. Multicollinearity was tested by variance inflation factor.

For all analyses, a 2-sided value of  $P < 0.05$  was considered to be significant. All statistical analyses were performed with the use of Stata version 14 (Statacorp).

## RESULTS

Among 993 patients with SMR screened for this study, 45 were excluded because of acute procedural failure

**FIGURE 2** Correlation Between TAPSE and PASP in Responders and Nonresponders

Scatter plots showing the relationship between TAPSE and PASP in responders (**left**) and nonresponders (**right**) at baseline and short-term follow-up. PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

(postprocedural MR >2+) and 447 because of a lack of echocardiographic data. In particular, 106 patients did not receive a short-term echocardiographic reassessment because they died within 180 days after the procedure, 59 were lost at follow-up before echocardiographic reassessment, and 282 did not have complete echocardiographic data including TAPSE and/or PASP values at baseline, short-term follow-up, or both (Figure 1).

Comparison between patients excluded and included in the study is presented in Supplemental Table 1. Patients screened and enrolled at each center are presented in Supplemental Table 2.

**CHANGES IN TAPSE/PASP.** Median time between baseline and short-term echocardiographic reassessment was 89 days (IQR: 43-159 days). TAPSE/PASP ratio improved in 331 of the 501 patients (66%: responders) whereas no change or worsening occurred in 170 patients (34%: nonresponders) (Central Illustration). There was no correlation between TAPSE and PASP at both baseline and at short-term follow-up, in responders and nonresponders (Figure 2). In responders, TAPSE/PASP improved from  $0.36 \pm 0.14$  mm/mm Hg at baseline to  $0.54 \pm 0.20$  mm/mm Hg at short-term follow-up, TAPSE increased

from  $17.1 \pm 3.6$  mm to  $19.1 \pm 3.9$  mm and PASP decreased from  $51.2 \pm 14.6$  mm Hg to  $38.4 \pm 11.1$  mm Hg (both  $P < 0.001$ ). On the other hand, in nonresponders, an overall worsening of TAPSE/PASP was observed, from  $0.49 \pm 0.19$  mm/mm Hg at baseline to  $0.36 \pm 0.13$  mm/mm Hg at short-term follow-up, with a decrease in TAPSE from  $18.2 \pm 3.8$  mm to  $16 \pm 4$  mm and an increase in PASP from  $41.1 \pm 13$  mm Hg to  $47.5 \pm 13$  mm Hg. Notably, among the 170 nonresponders, 94 (55%) had no RV dysfunction (TAPSE >15 mm) and 76 (45%) had a TAPSE/PASP >0.36 mm/mm Hg at short-term follow-up. Changes in TAPSE, PASP, and their ratio from baseline to short-term follow-up remained significant even after adjustment for baseline values in both responders and nonresponders (Supplemental Table 3). Correlation between changes in TAPSE/PASP and TAPSE/PASP at baseline is reported in Supplemental Figure 1. Interobserver and intraobserver variability for TAPSE, PASP, and TAPSE/PASP is presented in Supplemental Table 4.

**PREDICTORS OF TAPSE/PASP CHANGES.** Baseline demographic and clinical characteristics of the population stratified according to TAPSE/PASP changes (responders vs nonresponders) are presented in Table 1. Compared with nonresponders, responders

**TABLE 1** Baseline Demographic and Clinical Characteristics

	Responders (n = 331)	Nonresponders (n = 170)	P Value
Age, y	72.1 ± 10.1	73.2 ± 9.5	0.035
Male	246 (74)	106 (62)	0.007
Body mass index, kg/m <sup>2</sup>	26.7 ± 4.7	26.0 ± 4.4	0.127
EuroSCORE II, %	5.2 (2.7-9.8)	4.8 (2.7-11.5)	0.576
Hypertension	220 (66.5)	103 (60)	0.201
Diabetes	104 (31)	58 (34)	0.547
History of atrial fibrillation	159 (48)	94 (55)	0.132
Coronary artery disease	163 (61)	75 (61)	1.000
Peripheral artery disease	45 (14)	33 (19)	0.186
Chronic kidney disease	73 (59)	35 (66)	0.404
GFR, mL/min/1.73 m <sup>2</sup>	56.0 ± 24.6	55.2 ± 27.8	0.797
Chronic obstructive pulmonary disease	47 (14)	29 (17)	0.431
Previous cardiac surgery	112 (34)	75 (44)	0.025
Cardiac resynchronization therapy	119 (38)	63 (42)	0.418
Beta-blocker	283 (86)	148 (88)	0.585
ACEI/ARB/ARNI	191 (67)	86 (62)	0.278
Mineralocorticoid receptor antagonist	210 (63)	97 (57)	0.207
Furosemide daily dose, mg/d	75 (40-125)	80 (40-125)	0.188
NYHA functional class			0.783
II	44 (13)	19 (11)	
III	226 (68)	120 (71)	
IV	61 (18)	31 (18)	

Values are mean ± SD, n (%), or median (IQR).

ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; GFR = glomerular filtration rate; NYHA = New York Heart Association.

**TABLE 2** Baseline Echocardiographic Parameters

	Responders (n = 331)	Nonresponders (n = 170)	P Value
LVEF, %	32.9 ± 10.7	34.5 ± 11.6	0.173
LVEDD, mm	65.0 ± 10.1	62.5 ± 10.2	0.010
LVESD, mm	51.4 ± 12.6	49.9 ± 21.4	0.392
LVEDV, mL	200.2 ± 73.7	184.7 ± 73.5	0.040
LVESV, mL	134.6 ± 65.3	125.0 ± 63.2	0.147
LA volume, mL	122.4 ± 47.4	111.5 ± 44.0	0.030
MR degree			0.458
3+	55 (17)	33 (19)	
4+	276 (83)	137 (81)	
Tricuspid regurgitation degree			0.085
0/1+	72 (24)	45 (32)	
≥2+	232 (76)	98 (69)	
TAPSE, mm	17.1 ± 3.6	18.2 ± 3.8	0.001
TAPSE <15 mm	107 (32)	40 (24)	0.049
PASP, mm Hg	51.2 ± 14.6	41.1 ± 13.0	<0.001
TAPSE/PASP	0.363 ± 0.136	0.488 ± 0.192	<0.001
TAPSE/PASP <0.36 mm/mm Hg	136 (41)	122 (72)	<0.001

Values are mean ± SD or n (%).

LA = left atrium; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; TAPSE = tricuspid annular plane systolic excursion.

were younger, more likely to be male, and less likely to have a history of cardiac surgery. Regarding baseline echocardiographic data, responders had larger left ventricular and left atrial dimensions, higher PASP, and lower TAPSE and TAPSE/PASP compared with nonresponders (Table 2).

Procedural results were similar in responders and nonresponders, although responders showed a trend toward a higher rate of postprocedural MR 0/1+ vs MR 2+ and had a lower postprocedural transmitral mean gradient compared with nonresponders (Table 3). Lack of previous cardiac surgery, low baseline TAPSE, high baseline PASP, tricuspid regurgitation ≥2+ at baseline, and low postprocedural mitral mean gradient were independently associated with TAPSE/PASP improvement after M-TEER (Table 4, Central Illustration).

After excluding patients with previous cardiac surgery, baseline PASP, TAPSE, and degree of tricuspid regurgitation (TR) were the only independent predictors of TAPSE/PASP changes (Supplemental Table 5).

In patients with RV dysfunction at baseline, high PASP and high left ventricular ejection fraction values were independently associated with an increased likelihood of TAPSE/PASP improvement after M-TEER (Supplemental Table 6, Central Illustration).

**SHORT- AND LONG-TERM OUTCOMES.** Median followup for clinical outcomes (from echocardiographic reassessment) was 584 days (IQR: 191-1243 days). Among the 501 patients included in the analysis, 171 died during clinical follow-up, 6 within 30 days after echocardiographic reassessment, 55 from 30 days to 1 year, and 113 after 1 year.

TAPSE/PASP ratio, whether assessed at baseline or at short-term follow-up, was significantly associated with long-term mortality (Supplemental Figure 2).

Cumulative incidence of all-cause mortality was lower in the responders vs nonresponders (31.5% vs 44.9%;  $P = 0.002$ ) (Figure 3, Central Illustration). On a continuous level, an increase in TAPSE/PASP was associated with a reduced mortality risk as well (HR: 0.34 per unit [95% CI: 0.18-0.65];  $P = 0.001$ ) (Figure 4).

The association with mortality was weaker for changes in TAPSE and PASP considered as separate variables compared with changes in TAPSE/PASP (Supplemental Figure 3). At multivariable analysis, changes in TAPSE/PASP (responders vs nonresponders) were significantly associated with mortality (HR: 0.65 [95% CI: 0.42-0.92],  $P = 0.017$ ), whereas changes in TAPSE or PASP alone did not (Supplemental Table 7).

## DISCUSSION

The main findings of the present study are the following: 1) two-thirds of patients with SMR undergoing successful M-TEER improved their RV-PA coupling; 2) patients with lower TAPSE, higher PASP, and TR  $\geq 2+$  at baseline were more likely to improve their TAPSE/PASP ratio after M-TEER; 3) previous cardiac surgery and high postprocedural mitral mean gradient after M-TEER were associated with a lower probability of improving TAPSE/PASP; and 4) improvement in TAPSE/PASP after M-TEER was associated with better outcomes.

Several parameters have been identified as predictors of clinical outcome in patients with SMR undergoing M-TEER and are currently used for patient selection before percutaneous SMR correction.<sup>28-32</sup> TAPSE/PASP is a noninvasive measurement of RV-PA coupling<sup>12</sup> and has been shown to have better prognostic value than each parameter alone in patients with HF.<sup>12-16</sup> Representing the RV systolic performance at a given degree of afterload, TAPSE/PASP can change after MR correction because of the decrease in pulmonary congestion and RV afterload.<sup>32</sup> Although TAPSE/PASP was shown as a powerful predictor of outcomes after M-TEER when assessed at baseline,<sup>17-19</sup> data regarding its changes after M-TEER are still lacking.

**CHANGES IN TAPSE/PASP.** To the best of our knowledge, this is the first study evaluating changes in TAPSE/PASP after M-TEER. Improvement in TAPSE/PASP was noted in 66% of SMR patients undergoing successful M-TEER. Interestingly, patients who improved their RV-PA coupling after MR correction (responders) experienced a decrease in PASP and an increase in TAPSE, probably due to the reduction in pulmonary congestion in the presence of RV contractile reserve. Conversely, in nonresponders, we observed an increase in PASP and a decrease in TAPSE, which may be, at least partially, explained by higher postprocedural mitral mean gradients and a trend toward lower rates of optimal procedural result after M-TEER. High transmitral gradient and residual MR could have contributed to the increase in PASP that probably led to a worsening in RV function.

Importantly, half of the nonresponders had no RV dysfunction or abnormal TAPSE/PASP at short-term follow-up. Thus, the lack of improvement in TAPSE/PASP after M-TEER did not have clinical impact in these patients as long as they maintained value within normal limits. The latter point may also explain the significant correlation between changes

**TABLE 3** Procedural and Short-Term Outcomes

	Responders (n = 331)	Nonresponders (n = 170)	P Value
<b>Procedure</b>			
Number of clips			0.499
1	143 (43)	73 (43)	
2	168 (51)	82 (48)	
>2	20 (6)	15 (9)	
<b>Discharge</b>			
MR degree			0.067
0/1+	134 (81)	64 (74)	
2+	63 (19)	45 (26)	
Transmitral mean gradient, mm Hg	3.5 $\pm$ 2	4.3 $\pm$ 3	0.034
<b>Short-term follow-up</b>			
Delta TAPSE, mm	1.8 $\pm$ 3.3	-2.2 $\pm$ 3.4	<0.001
Delta PASP, mm Hg	-12.8 $\pm$ 12.1	-6.5 $\pm$ 11.5	<0.001
Delta TAPSE/PASP, mm/mm Hg	0.18 $\pm$ 0.15	-0.13 $\pm$ 0.14	<0.001
NYHA functional class			<0.001
I	83 (25)	25 (15)	
II	203 (61)	98 (57)	
III	38 (12)	41 (24)	
IV	7 (2)	6 (4)	
HF hospitalization	20 (6)	21 (12)	0.024

Values are n (%) or mean  $\pm$  SD.

HF = heart failure; NYHA = New York Heart Association; other abbreviations as in Table 2.

in TAPSE/PASP and baseline TAPSE/PASP values in nonresponders, but not in responders.

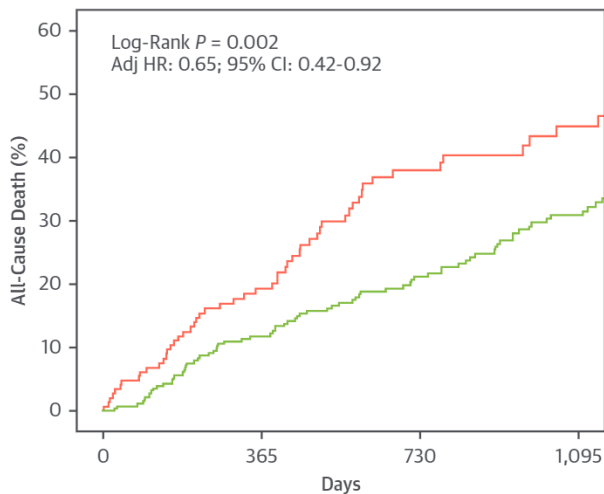
**VARIABLES ASSOCIATED WITH IMPROVEMENT IN TAPSE/PASP.** We found that TAPSE/PASP improvement was greater in patients with more impaired RV

**TABLE 4** Independent Predictors of TAPSE/PASP Improvement

	OR (95% CI)	P Value
<b>Demographics and clinical history</b>		
Age, y	0.99 (0.97-1.02)	0.494
Male	0.80 (0.46-1.39)	0.424
History of cardiac surgery	0.36 (0.21-0.60)	0.001
<b>Echocardiographic features</b>		
LA volume	1.00 (0.99-1.01)	0.199
LVEDD	1.00 (0.98-1.03)	0.962
Tricuspid regurgitation degree $\geq 2+$	1.80 (1.08-3.01)	0.024
Baseline PASP	1.06 (1.04-1.08)	<0.001
Baseline TAPSE	0.87 (0.81-0.93)	<0.001
<b>Procedural data</b>		
Postprocedural mitral regurgitation degree	1.15 (0.51-2.6)	0.742
Postprocedural mitral mean gradient	0.88 (0.78-0.99)	0.048

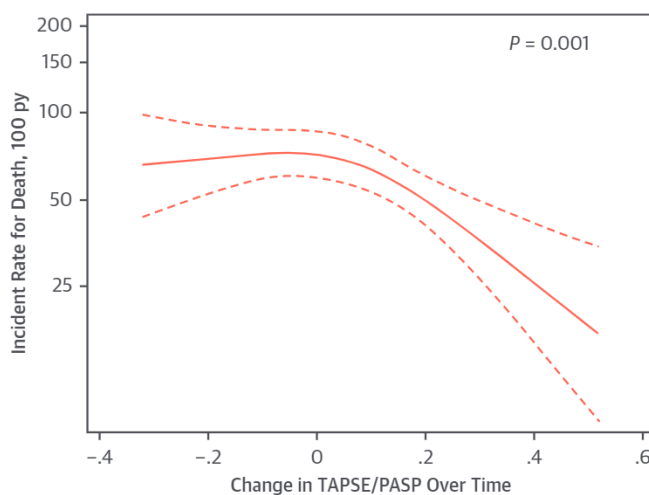
CI = confidence interval; LA = left atrium; LVEDD = left ventricle end diastolic diameter; OR = odds ratio; other abbreviations as in Table 2.



**FIGURE 3** Cumulative Incidence of All-Cause Mortality in Responders vs Nonresponders

Number at risk		0	365	730	1,095
— Nonresponders	170	98	53	35	
— Responders	331	224	161	105	

Kaplan-Meier estimates of all-cause death in responders (patients with improved TAPSE/PASP after M-TEER) vs nonresponders (patients with unchanged or worsened TAPSE/PASP after M-TEER). Abbreviations as in [Figures 1 and 2](#).

**FIGURE 4** Continuous Association Between Change in TAPSE/PASP and All-Cause Death

The **solid line** indicates the association between change in TAPSE/PASP and incident rate for all-cause death. The **dotted black lines** indicate the 95% CI. Abbreviations as in [Figure 2](#).

function and more severe pulmonary hypertension and TR degree at baseline.

This was already noted in a small single-center study investigating RV reverse remodeling after M-TEER by means of TAPSE and S'-wave at tissue Doppler imaging<sup>21</sup> and is probably consistent, as already mentioned above, with the presence of a RV contractile reserve in these patients.

Of note, a “regression to mean” effect was taken into consideration adjusting all changes for baseline values.

Interestingly, in patients with baseline RV dysfunction (TAPSE <15 mm) we found that high PASP and high left ventricular ejection fraction values were associated with a higher likelihood of TAPSE/PASP improvement after M-TEER. Our data show that RV-PA coupling may recover in patients with RV function reserve once RV afterload is reduced by effective M-TEER. Conversely, biventricular dysfunction in the absence of pulmonary hypertension represents an advanced clinical scenario where M-TEER may be futile. Notably, patients with low TAPSE and low PASP had a normal TAPSE/PASP ratio at baseline that did not change after M-TEER (nonresponders).

**VARIABLES ASSOCIATED WITH LACK OF IMPROVEMENT IN TAPSE/PASP.** We also observed that high transmitral gradients after M-TEER were associated with a lack of improvement in RV-PA coupling. This is consistent with previous results from smaller studies and may be explained by the persistence of high RV afterload hampering improvement in RV function.<sup>21,33-35</sup>

We also identified previous cardiac surgery as an independent predictor of lack of improvement in TAPSE/PASP after M-TEER. After pericardiectomy, echocardiographic longitudinal indexes of RV function were found to be significantly reduced.<sup>36</sup> Therefore, in these patients, an improvement in TAPSE is not expected after M-TEER, because the geometric and functional changes caused by previous pericardiectomy can be considered to be the main and irreversible cause of their baseline RV impairment. The lack of improvement in TAPSE may therefore explain the lack of improvement in TAPSE/PASP after M-TEER.

Of note, considering that TAPSE is possibly unreliable in this subgroup, we performed a sensitivity analysis excluding subjects undergoing previous cardiac surgery and found predictors of TAPSE/PASP improvement similar to those in the whole cohort.

**CHANGES IN TAPSE/PASP AND OUTCOME.** In our patients, improvement in TAPSE/PASP was associated with a concomitant lower rate of severe HF symptoms and hospitalizations at short-term follow-up and with a reduced risk of death at long-term follow-up. A greater improvement in NYHA functional class after M-TEER was also observed in patients who experienced a significant improvement in RV function, assessed as RV fractional area change (FAC)<sup>25</sup> or ejection fraction at 3-dimensional echocardiography,<sup>24</sup> compared with those who did not. In addition, a significant association between improvement in RV-FAC and clinical outcomes was recently reported. In particular, an increase in RV-FAC of  $\geq 5\%$  was associated with a 48% reduced risk of all-cause death or cardiac transplantation.<sup>25</sup> As reported in other settings,<sup>14,15</sup> also in our study, changes in TAPSE/PASP, but not changes in TAPSE and PASP considered alone, had an independent value in predicting clinical outcome. Indeed, TAPSE/PASP ratio can be considered as a comprehensive tool for assessing RV performance with a higher ability to detect RV dysfunction at a specific afterload.

**STUDY LIMITATIONS.** We acknowledge several limitations to this study. It is a retrospective observational single-arm study, so the reported associations need to be interpreted as hypothesis generating only. Although multivariable analyses were performed, many unknown biases may have affected our results. Moreover, there was not a core laboratory for the evaluation of echocardiographic images, which were locally analyzed by expert operators. A complete echocardiographic evaluation of RV function including peak systolic velocity (S-wave) of tricuspid annulus by pulsed-wave tissue Doppler imaging, RV longitudinal strain, FAC, and 3-dimensional ejection fraction was not available for the majority of patients. In addition, variables that may have affected TAPSE/PASP changes, such as changes in diuretic dose after M-TEER and presence/entity of iatrogenic atrial septal defect after trans-septal puncture, are lacking. Finally, a selection bias due to the exclusion of patients who died before the short-term echocardiographic reassessment or without complete echocardiographic data at both baseline and follow-up must be acknowledged. It must also be acknowledged that there was a high heterogeneity in the proportion of patients excluded among different centers.

## CONCLUSIONS

Two-thirds of patients with SMR undergoing successful M-TEER show an improvement in TAPSE/

PASP ratio, which is strongly and independently associated with mortality. Previous cardiac surgery, high postprocedural mitral mean gradient after M-TEER and biventricular dysfunction without pulmonary hypertension are negative predictors for RV reverse remodeling, whereas patients with low TAPSE, high PASP, and TR  $\geq 2+$  at baseline are more likely to improve their RV-PA coupling after M-TEER.

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Dr Adamo has received speaker fees from Abbott Vascular and Medtronic. Dr Estévez-Loureiro is a consultant for Abbott Vascular, Boston Scientific, and Edwards Lifesciences. Dr Pascual is a proctor for Abbott Vascular. Dr Jimenez-Quevedo has received speaker fees from Abbott Vascular. Dr Nombela-Franco is a proctor for Abbott and has received consulting fees for Abbott and Edwards Lifesciences. Dr Petronio is a consultant for Abbott Vascular, Boston Scientific, and Medtronic. Dr Bedogni is a consultant for Medtronic; and has received speaker fees from Abbott Vascular. Dr Sinagra has received personal fees Novartis, Bayer, AstraZeneca, Boston Scientific, Vifor Pharma, Menarini, and Akcea Therapeutics. Dr Metra has received consulting honoraria for participation in steering committees or advisory boards or for speeches from Abbott Vascular, Amgen, AstraZeneca, Bayer, Edwards, and Novartis. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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## PERSPECTIVES

### COMPETENCY IN PATIENT CARE AND PROCEDURAL

**SKILLS:** Most of the patients with SMR improve their RV-PA coupling after M-TEER. When RV impairment (low tricuspid annular plane systolic excursion and significant tricuspid regurgitation) is mainly due to RV afterload (high pulmonary artery systolic pressure), we can expect an improvement in the RV-PA coupling. On the other hand, lack of RV-PA recoupling can be predicted by conditions precluding increase in RV function (ie, previous cardiac surgery) or reduction in RV afterload (ie, high postprocedural mitral gradient) or associated with lack of contractile reserve and advanced heart failure (biventricular dysfunction without pulmonary hypertension).

**TRANSLATIONAL OUTLOOK:** Changes in RV-PA coupling after M-TEER might have a strong impact on clinical outcome and seem to be affected by several clinical and procedural variables. Further larger and randomized studies are needed to confirm our results and identify patients who may obtain RV reverse remodeling after SMR correction.

## REFERENCES

- McDonagh TA, Metra M, Adamo M, et al. 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021;42(36):3599–3726.
- Vahanian A, Beyersdorf F, Praz F, et al. 2021 ESC/EACTS guidelines for the management of valvular heart disease. *Eur Heart J*. 2022;43(7):561–632.
- Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med*. 2018;379(24):2307–2318.
- Adamo M, Fiorelli F, Melica B, et al. COAPT-like profile predicts long-term outcomes in patients with secondary mitral regurgitation undergoing MitraClip implantation. *J Am Coll Cardiol Intv*. 2021;14(1):15–25.
- Koell B, Orban M, Weimann J, et al. Outcomes stratified by adapted inclusion criteria after mitral edge-to-edge repair. *J Am Coll Cardiol*. 2021;78(24):2408–2421.
- Obadia JF, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med*. 2018;379(24):2297–2306.
- Senni M, Adamo M, Metra M, et al. Treatment of functional mitral regurgitation in chronic heart failure: can we get a “proof of concept” from the MITRA-FR and COAPT trials? *Eur J Heart Fail*. 2019;21(7):852–861.
- Neuss M, Schau T, Schoepp M, et al. Patient selection criteria and midterm clinical outcome for MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure. *Eur J Heart Fail*. 2013;15(7):786–795.
- Kaneko H, Neuss M, Weissenborn J, et al. Prognostic significance of right ventricular dysfunction in patients with functional mitral regurgitation undergoing MitraClip. *Am J Cardiol*. 2016;118(11):1717–1722.
- Frea S, Crimi G, Gaemperli O, et al. Improving selection of MitraClip candidates in advanced chronic heart failure: look right to predict right. *J Card Fail*. 2019;25(4):312–313.
- Giannini C, Fiorelli F, Colombo A, et al. Right ventricular evaluation to improve survival outcome in patients with severe functional mitral regurgitation and advanced heart failure undergoing MitraClip therapy. *Int J Cardiol*. 2016;223:574–580.
- Guazzi M, Bandera F, Pelissero G, et al. Tricuspid annular plane systolic excursion and pulmonary arterial systolic pressure relationship in heart failure: an index of right ventricular contractile function and prognosis. *Am J Physiol Heart Circ Physiol*. 2013;305(9):H1373–H1381.
- Guazzi M, Naeije R, Arena R, et al. Echocardiography of right ventriculoarterial coupling combined with cardiopulmonary exercise testing to predict outcome in heart failure. *Chest*. 2015;148(1):226–234.
- Ghio S, Guazzi M, Scardovi AB, et al. Different correlates but similar prognostic implications for right ventricular dysfunction in heart failure patients with reduced or preserved ejection fraction. *Eur J Heart Fail*. 2017;19(7):873–879.
- Guazzi M, Dixon D, Labate V, et al. RV contractile function and its coupling to pulmonary circulation in heart failure with preserved ejection fraction: stratification of clinical phenotypes and outcomes. *J Am Coll Cardiol Img*. 2017;10(10 Pt B):1211–1221.
- Santas E, Palau P, Guazzi M, et al. Usefulness of right ventricular to pulmonary circulation coupling as an indicator of risk for recurrent admissions in heart failure with preserved ejection fraction. *Am J Cardiol*. 2019;124(4):567–572.
- Karam N, Stolz L, Orban M, et al. Impact of right ventricular dysfunction on outcomes after transcatheter edge-to-edge repair for secondary mitral regurgitation. *J Am Coll Cardiol Img*. 2021;14(4):768–778.
- Popolo Rubbio A, Testa L, Granata G, et al. Prognostic significance of right ventricle to pulmonary artery coupling in patients with mitral regurgitation treated with the MitraClip system. *Catheter Cardiovasc Interv*. 2022;99(4):1277–1286.
- Trejo-Velasco B, Estevez-Loureiro R, Carrasco-Chinchilla F, et al. Prognostic role of TAPSE to PASP ratio in patients undergoing MitraClip procedure. *J Clin Med*. 2021;10(5):1006.
- Giannini C, Petronio AS, de Carlo M, et al. Integrated reverse left and right ventricular remodeling after MitraClip implantation in functional mitral regurgitation: an echocardiographic study. *Eur Heart J Cardiovasc Imaging*. 2014;15(1):95–103.
- Godino C, Salerno A, Cera M, et al. Impact and evolution of right ventricular dysfunction after successful MitraClip implantation in patients with functional mitral regurgitation. *Int J Cardiol Heart Vasc*. 2016;11:90–98.
- Ledwoch J, Fellner C, Hoppmann P, et al. Impact of transcatheter mitral valve repair using MitraClip on right ventricular remodeling. *Int J Cardiovasc Imaging*. 2020;36(5):811–819.
- Vitarelli A, Mangieri E, Capotosto L, et al. Assessment of biventricular function by three-dimensional speckle-tracking echocardiography in secondary mitral regurgitation after repair with the MitraClip system. *J Am Soc Echocardiogr*. 2015;28(9):1070–1082.
- Sauter RJ, Patzelt J, Mezger M, et al. Conventional echocardiographic parameters or three-dimensional echocardiography to evaluate right ventricular function in percutaneous edge-to-edge mitral valve repair (PMVR). *Int J Cardiol Heart Vasc*. 2019;24:100413.
- Caiffa T, de Luca A, Biagini E, et al. Impact on clinical outcomes of right ventricular response to percutaneous correction of secondary mitral regurgitation. *Eur J Heart Fail*. 2021;23(10):1765–1774.
- Rudski LG, Lai WW, Afilalo J, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of the European Society of Cardiology, and the Canadian Society of Echocardiography. *J Am Soc Echocardiogr*. 2010;23:685–713.
- Barnett AG, van der Pols JC, Dobson AJ. Regression to the mean: what it is and how to deal with it. *Int J Epidemiol*. 2005;34(1):215–220.
- Bedogni F, Popolo Rubbio A, Grasso C, et al. Italian Society of Interventional Cardiology (GISE) Registry of Transcatheter Treatment of Mitral Valve Regurgitation (GIOTTO): impact of valve disease aetiology and residual mitral regurgitation after MitraClip implantation. *Eur J Heart Fail*. 2021;23(8):1364–1376.
- Adamo M, Grasso C, Capodanno D, et al. Five-year clinical outcomes after percutaneous edge-to-edge mitral valve repair: Insights from the multicenter GRASP-IT registry. *Am Heart J*. 2019;217:32–41.
- Adamo M, Cani DS, Gavazzoni M, et al. Impact of disproportionate secondary mitral regurgitation in patients undergoing edge-to-edge percutaneous mitral valve repair. *EuroIntervention*. 2020;16(5):413–420.
- Adamo M, Gavazzoni M, Castiello A, et al. Prognostic impact of heart failure history in patients with secondary mitral regurgitation treated by MitraClip. *Am J Cardiol*. 2020;135:120–127.
- Adamo M, Capodanno D, Cannata S, et al. Comparison of three contemporary surgical scores for predicting all-cause mortality of patients undergoing percutaneous mitral valve repair with the MitraClip system (from the multicenter GRASP-IT registry). *Am J Cardiol*. 2015;115(1):107–112.
- Italia L, Adamo M, Lupi L, et al. Percutaneous edge-to-edge mitral valve repair: beyond the left heart. *J Am Soc Echocardiogr*. 2021;34(10):1038–1045.
- van Riel AC, Boerlage-van Dijk K, de Bruin, Bon RH, et al. Percutaneous mitral valve repair preserves right ventricular function. *J Am Soc Echocardiogr*. 2014;27(10):1098–1106.
- Öztürk C, Friederich M, Werner N, et al. Single-center five-year outcomes after interventional edge-to-edge repair of the mitral valve. *Cardiol J*. 2021;28(2):215–222.
- Moya Mur JL, García Martín A, García Lledó A, et al. Geometrical and functional cardiac changes after cardiac surgery: a physiopathological explanation based on speckle tracking. *Int J Cardiovasc Imaging*. 2018;34(12):1905–1915.

**KEY WORDS** right ventricular to pulmonary artery coupling, secondary mitral regurgitation, transcatheter edge-to-edge mitral valve repair

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