JACC: CARDIOVASCULAR IMAGING
VOL. 14, NO. 4, 2021
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AMERICAN COLLEGE OF CARDIOLOGY FOUNDATION

FOCUS ISSUE ON SECONDARY (FUNCTIONAL) MITRAL REGURGITATION

ORIGINAL RESEARCH

Impact of Right Ventricular Dysfunction on Outcomes After Transcatheter Edge-to-Edge Repair for Secondary Mitral Regurgitation

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ABSTRACT

OBJECTIVES This study sought to assess the impact of right ventricular dysfunction (RVD) as defined by impaired right ventricular-to-pulmonary artery (RV-PA) coupling, on survival after edge-to-edge transcatheter mitral valve repair (TMVR) for severe secondary mitral regurgitation (SMR).

BACKGROUND Conflicting data exist regarding the benefit of TMVR in severe SMR. A possible explanation could be differences in RVD.

METHODS Using data from the EuroSMR (European Registry on Outcomes in Secondary Mitral Regurgitation) registry, this study compared the characteristics and outcomes of SMR patients undergoing TMVR, according to their RV-PA coupling, assessed by tricuspid annular plane systolic excursion-to-systolic pulmonary artery pressure (TAPSE/sPAP) ratio.

RESULTS Overall, 817 patients with severe SMR and available RV-PA coupling assessment underwent TMVR in the participating centers. RVD was present in 211 patients (25.8% with a TAPSE/sPAP ratio $<$0.274 mm/mm Hg). Although all patients demonstrated significant improvement in their New York Heart Association (NYHA) functional class, there was a trend toward a lower rate of NYHA functional class I or II among patients with RVD (56.5% vs. 65.5%, respectively; $p = 0.086$) after TMVR. Survival rates at 1 and 2 years were lower among patients with RVD (70.2% vs. 84.0%, respectively; $p < 0.001$; and 53.4% vs. 73.1%, respectively; $p < 0.001$). On multivariate analysis, a reduced TAPSE/sPAP ratio was a strong predictor of mortality (odds ratio: 1.62; 95% confidence interval: 1.14 to 2.31; $p = 0.007$).

CONCLUSIONS RVD, as shown by impairment of RV-PA coupling, is a major predictor of adverse outcome in patients undergoing TMVR for severe SMR. The often neglected functional and anatomic RV parameters should be systematically assessed when planning TMVR procedures for patients with severe SMR. (J Am Coll Cardiol Img 2021;14:768–78)
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ISSN 1936-878X/$36.00
https://doi.org/10.1016/j.jcmg.2020.12.015

Chronic secondary mitral regurgitation (SMR) is frequently encountered in the setting of heart failure with reduced ejection fraction and is associated with adverse prognosis. Although the benefit of mitral valve surgery has not been demonstrated in this setting (1,2), transcatheter mitral valve repair (TMVR) was introduced as a treatment option in case of symptom persistence despite optimal medical therapy.

Initial TMVR experience provided promising results and suggested a potential mortality benefit (3–7). However, results of randomized trials assessing the benefit of edge-to-edge TMVR compared with those of optimal medical therapy were controversial, with the MITRA-FR (French Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial showing no benefit from TMVR (8) and the American COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial demonstrating significant reductions in mortality and hospitalizations for heart failure as well as improvements in quality of life (9,10). This highlights the need to optimize the selection of patients for TMVR in the setting of SMR.

Right ventricular dysfunction (RVD), severe tricuspid regurgitation, and pulmonary hypertension have been associated with adverse outcomes after TMVR (11–15). Right ventricular-to-pulmonary artery (RV-PA) coupling, which integrates the RV systolic performance at a given degree of afterload, may be a better functional prognostic parameter. The noninvasive tricuspid annular plane systolic excursion (TAPSE)-to-systolic pulmonary artery pressure (sPAP) ratio has been shown to accurately assess RV-PA coupling and has prognostic impact in various heart failure populations (16–18). This ratio has subsequently been used for predicting prognosis in patients undergoing transcatheter aortic valve implantation. Its roles as a descriptor of RVD and a predictor of prognosis in patients undergoing TMVR have not been investigated (19).

Accordingly, this study used the EuroSMR (European Registry on Outcomes in Secondary Mitral Regurgitation) registry to assess the characteristics and outcomes of patients with SMR undergoing edge-to-edge TMVR according to their RV-PA coupling.

METHODS

PATIENT COHORTS. The EuroSMR registry is a large, retrospective registry including patients undergoing TMVR for SMR using the MitraClip device (Abbott Structural Heart, Santa Clara, California) between November 2008 and January 2019 in 8 experienced European centers (Munich, Hamburg, Berlin-Bernau, Bern, Mainz, Cologne, Leipzig, and Paris-Pompidou). A heart team consensus was necessary before TMVR commenced to evaluate the best treatment option for individual patients, who were all symptomatic under medical treatment. The study was registered at Deutsches Register Klinischer Studien (DRKS00017428) and approved by local ethics committees in each of the participating centers.

TECHNICAL ASPECTS. The procedural steps of TMVR using the MitraClip have been previously described (20,21). Briefly, the procedure is performed with the patient under general anesthesia, with fluoroscopic and transesophageal echocardiographic guidance. The transcatheter edge-to-edge repair system is introduced through the femoral vein and advanced to the left atrium through a trans-septal puncture. The device is then aligned perpendicular to the mitral valve plane, with the MitraClip arms perpendicular to the line of coaptation. The mitral leaflets are grasped, and the device is closed, resulting in fixed approximation of the mitral leaflets. One or several clips may be needed to achieve optimal result.

DATA COLLECTION. Collected data included patient demographics (age and sex), medical history, and echocardiographic data. All echocardiograms were performed and analyzed by experienced operators at each site. All patients underwent transthoracic and transesophageal echocardiography before TMVR. Baseline MR severity was assessed using an

ABBREVIATIONS AND ACRONYMS

ERO = effective regurgitant orifice

FAC = fractional area change

NYHA = New York Heart Association

RV = right ventricle

RV-PA = right ventricle-to-pulmonary artery

SMR = secondary mitral regurgitation

sPAP = systolic pulmonary artery pressure

TAPSE = tricuspid annular plane systolic excursion

TMVR = transcatheter mitral valve repair

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

Manuscript received August 11, 2020; revised manuscript received November 24, 2020, accepted December 7, 2020.

TABLE 1 Baseline Clinical Characteristics According to RV Coupling

	Overall Population (N = 817)	Impaired RV-PA Coupling (n = 211)	Normal RV-PA Coupling (n = 606)	p Value
Males	540 (66.3)	153 (72.5)	387 (64.1)	**0.026**
Age, yrs	73.8 ± 10.1	73.1 ± 9.9	74.0 ± 10.1	0.126
Diabetes	269 (33.0)	82 (38.9)	187 (30.9)	**0.034**
Arterial hypertension	566 (73.9)	150 (76.1)	416 (73.1)	0.404
Ischemic heart disease	356 (48.8)	106 (56.4)	250 (46.1)	**0.013**
Previous MI	198 (24.5)	61 (29.5)	137 (22.8)	0.050
Previous PCI	262 (44.1)	69 (46.9)	193 (43.2)	0.426
Previous CABG	124 (16.1)	39 (20.2)	85 (14.8)	0.075
Previous stroke	88 (10.8)	23 (10.9)	65 (10.7)	0.950
Pulmonary disease	132 (16.2)	30 (14.4)	102 (16.9)	0.392
Previous ICD	148 (25.6)	38 (25.3)	110 (25.8)	0.918
Previous CRT	170 (20.9)	45 (21.3)	125 (20.7)	0.854
Atrial fibrillation or flutter	520 (63.6)	151 (71.6)	369 (60.9)	**0.006**
EuroScore	19.9 ± 15.2	21.9 ± 16.9	19.4 ± 14.6	0.196
EuroScore II	8.4 ± 7.3	10.8 ± 9.9	7.6 ± 6.1	**<0.001**
NT-proBNP, pg/ml	3,540.0 (1,779.8-7,006.8)	4,540.0 (2,046.0-9,375.0)	3,330.5 (1,668.8-6,676.3)	**0.012**
eGFR, ml/min	49 ± 22	47 ± 22	49 ± 22	0.183
NYHA functional class				**0.039**
I	1 (0.1)	0 (0.0)	1 (0.2)	
II	111 (13.7)	23 (10.9)	88 (14.7)	
III	536 (66.1)	132 (62.6)	404 (67.3)	
IV	163 (20.1)	56 (26.5)	107 (17.8)	

Values are n (%), mean ± SD, or median (interquartile range [IQR]). The p values in **bold** indicate statistically significant difference. Parametric tests were used for continuous normal variables; non-parametric tests were used for continuous non-normal variables; and chi-squared tests were used for categorical variables.

CABG = coronary artery bypass grafting; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; ICD = implantable cardioverter-defibrillator; MI = myocardial infarction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RV = right ventricular; RV-PA = right ventricular-to-pulmonary artery.

integrative approach including quantitative (effective regurgitant orifice area [ERO] and regurgitant volume by the proximal isovelocity surface area method) and semiquantitative parameters (average of vena contracta width in long-axis and commissural views), as well as an assessment of the left ventricle using left ventricular ejection fraction and volumes (Simpson's biplane technique). MR was considered severe according to these combined criteria in all patients included in the registry. TAPSE was assessed through an apical 4-chamber view with an M-mode ultrasonography technique to measure the displacement of the tricuspid annular plane in the longitudinal direction toward the RV apex (2,22–25). sPAP was measured using transthoracic echocardiography by estimating the peak systolic tricuspid regurgitation (TR) gradient from the peak TR velocity, using the Bernoulli equation, and adding the estimated right atrial pressure (26). RV function and dimensions, tricuspid annular diameter, fractional area change (FAC), and grading of TR was performed using echocardiography by each participating site according to European guidelines for quantification of native valve regurgitation (27,28). RV-PA coupling was assessed using the TAPSE/sPAP ratio. In case of missing TAPSE values, these ratios were imputed from RV-FAC data.

Symptomatic status was assessed using the New York Heart Association (NYHA) functional class. Patients were followed routinely in their respective hospitals. Available follow-up data included survival status and NYHA functional class through outpatient visits or by telephone interviews with the patient or patient's relatives.

Data collection and follow-up examinations were performed according to protocols of the participating centers, in line with local ethical regulations, and adhered to international rules for scientific studies and Declaration of Helsinki principles. Patients needed to be of legal age and able to consent.

STATISTICAL ANALYSIS. Variables were described using median (interquartile range [IQR]) as well as mean ± SD for continuous measurements and counts (proportions) for categorical measurements. Normality of presented variables was assessed using the Shapiro test and graphical distribution. Comparisons between groups were performed using the

Pearson chi-squared test for categorical variables, Student's *t*-test or Mann-Whitney-Wilcoxon test for unpaired continuous variables, and Wilcoxon test for paired variables, as appropriate.

Receiver operator characteristic (ROC) analysis was performed in order to define the optimal cutoff for the TAPSE/sPAP ratio using the Youden index according to its discriminatory value for 2-year mortality. Patients' characteristics and outcomes were then described according to their baseline RV-PA coupling values (normal or low). NYHA functional classes were assessed and compared between the 2 RV-PA groups at baseline and last follow-up. The primary outcome was survival rate at 2 years. Mortality predictors were identified using a multivariate backward elimination Cox regression model that included all variables that were significant in univariate analysis. A sensitivity analysis was performed but excluded patients with TR >2. Cumulative survival rates at 2 years were analyzed using Kaplan-Meier models and compared using the log rank test.

The prognostic impact of TR and RV-PA coupling on 2-year survival prediction was compared to a base model that included relevant clinical and echocardiographic patient characteristics using 2 statistical methods: integrated discrimination improvement and continuous net reclassification improvement (29,30). All p values were calculated using 2-sided tests, and 0.05 was used to declare statistical significance. Statistical analyses were performed using SPSS version 25 software (IBM, Armonk, New York) and R version 1.2.5042 software (R Studio, Boston, Massachusetts).

TABLE 2 Baseline Clinical Echocardiographic According to RV-PA Coupling

	Overall Population (N = 817)	Impaired RV-PA Coupling (n = 211)	Normal RV-PA Coupling (n = 606)	p Value
TAPSE/sPAP ratio	0.40 ± 0.21	0.22 ± 0.04	0.46 ± 0.20	
MR severity				**0.022**
2+	35 (4.3)	10 (4.7)	25 (4.1)	
3+	442 (54.1)	97 (46.0)	345 (56.9)	
4+	340 (41.6)	104 (49.3)	236 (38.9)	
MR vena contracta, mm	6.9 ± 1.9	7.1 ± 1.8	6.8 ± 1.9	**0.028**
MR EROA, cm^2	0.30 ± 0.15	0.31 ± 0.17	0.30 ± 0.15	0.712
EROA/LVEDV × 100, cm^2/ml	0.2 ± 0.1	0.2 ± 0.1	0.2 ± 0.1	0.207
MR volume, ml	42.9 ± 21.1	41.6 ± 22.6	43.3 ± 20.6	0.096
LVEF, %	35.0 ± 12.9	32.9 ± 11.9	35.8 ± 13.1	**0.013**
LVEDV, ml	180.1 ± 79.8	190.7 ± 87.6	176.2 ± 76.6	0.050
LVESV, ml	120.8 ± 69.4	131.4 ± 76.1	117.13 ± 66.57	**0.025**
LVSV, ml	59.8 ± 31.6	60.3 ± 31.2	59.6 ± 31.7	0.922
TR severity				**<0.001**
0+	13 (1.6)	0 (0.0)	13 (2.2)	
1+	329 (40.4)	56 (26.5)	273 (45.2)	
2+	331 (40.6)	98 (46.6)	233 (38.6)	
3+	142 (17.4)	57 (27.0)	85 (14.1)	
TR vena contracta, mm	5.5 ± 2.7	6.1 ± 2.7	5.3 ± 2.6	**<0.001**
RV-FAC	0.34 ± 0.11	0.30 ± 0.03	0.34 ± 0.03	**<0.001**
TAPSE, mm	17.1 ± 4.7	13.0 ± 3.5	18.5 ± 4.2	**<0.001**
RV-EDA, cm^2	23.1 ± 7.4	25.0 ± 7.0	22.5 ± 7.7	**<0.001**
RV-ESA, cm^2	16.3 ± 5.5	18.2 ± 5.3	15.7 ± 5.4	**<0.001**
Right atrial area, cm^2	25.0 ± 7.0	26.1 ± 6.2	24.1 ± 8.3	**<0.001**
TV annular diameter, mm	38.4 ± 8.0	39.4 ± 6.5	38.1 ± 7.1	**0.009**
RV mid-diameter, mm	35.6 ± 10.3	37.9 ± 9.3	34.7 ± 10.5	**<0.001**
IVC diameter, mm	21.8 ± 6.1	23.2 ± 4.6	21.0 ± 6.6	**<0.001**
sPAP, mm Hg	47.8 ± 14.4	60.5 ± 12.7	43.4 ± 12.1	**<0.001**

Values are mean ± SD or n (%). Values in **bold** indicate statistically significant difference.

EDA = end-diastolic area; EROA = effective regurgitant orifice area; ESA = end-systolic area; FAC = fractional area change; IVC = inferior vena cava; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left end-systolic volume; LVSV = left ventricular stroke volume; MR = mitral regurgitation; RV-PA = right ventricular-to-pulmonary artery; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; TV = tricuspid valve.

RESULTS

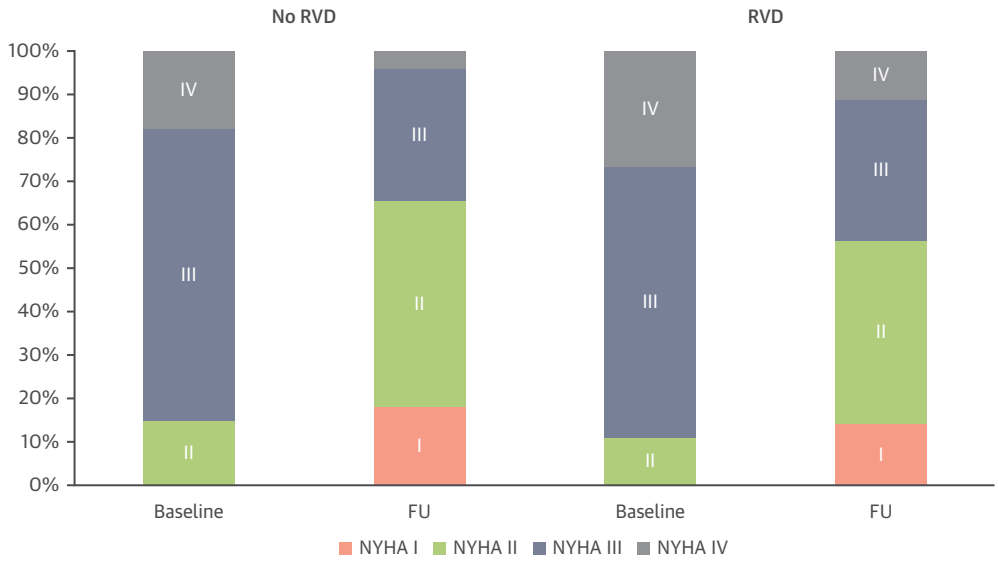
Between 2008 and 2019, 1,237 patients were included in the EuroSMR registry. In 39 patients (4.8%), RV function was determined by FAC, but no TAPSE data were reported. In those patients, TAPSE was approximated from the available FAC values by use of the linear regression equation (TAPSE = 12.18 + 14.98 • FAC). Patients with missing sPAP data (n = 190) and TAPSE and RV-FAC to approximate TAPSE (n = 100) or both (n = 165) were excluded from the analyses; therefore, 817 patients were included in the analyses.

Baseline characteristics of the study population are presented in Table 1. Mean age of the patients was 73.8 ± 10.1 years, and 540 (66.3%) were men. Overall, 699 patients (86.2%) were in NYHA functional class I or IV at the time of the procedure. Medical history was relevant for atrial fibrillation in 520 patients (63.6%), a prior stroke in 88 patients (10.8%), and a chronic pulmonary disease in 132 patients (16.2%). Regarding surgical risk, mean EuroSCORE II was 8.4 ± 7.3%.

Baseline echocardiographic parameters are described in Table 2. Mean ERO was 0.30 ± 0.15 cm^2, with a mean vena contracta diameter of 6.9 ± 1.9 mm. Mean left ventricular ejection fraction was 35.0 ± 12.9% with a mean left ventricular (LV) end-diastolic volume of 180.1 ± 79.8 ml and an end-systolic volume of 118.2 ± 70.7 ml. TR grade ≥3+ was observed in 142 patients (17.4%). Regarding RV function, mean TAPSE and RV-FAC were 17.1 ± 4.7 mm and 0.3 ± 0.1%, respectively. Mean sPAP was 47.8 ± 14.4 mm Hg.

CHARACTERISTICS ACCORDING TO RV-PA COUPLING. The mean TAPSE/sPAP ratio was 0.40 ± 0.21 mm/mm Hg. ROC analysis revealed that a cutoff value of 0.274 mm/mm Hg of the TAPSE/sPAP ratio had the

FIGURE 1 NYHA Functional Class at Baseline and 1-Year Follow-Up According to Baseline RV-PA Coupling



Improvement in New York Heart Association (NYHA) functional class was observed in both groups. RV-PA = right ventricular-to-pulmonary artery.

best discriminatory value for 2-year survival. The TAPSE/sPAP ratio was therefore dichotomized accordingly. Using this cutoff, RVD, as expressed by impaired RV-PA coupling, was present in 211 patients (25.8%; TAPSE/sPAP ratio: ≤0.274 mm/mm Hg) and absent in 606 patients (74.2%).

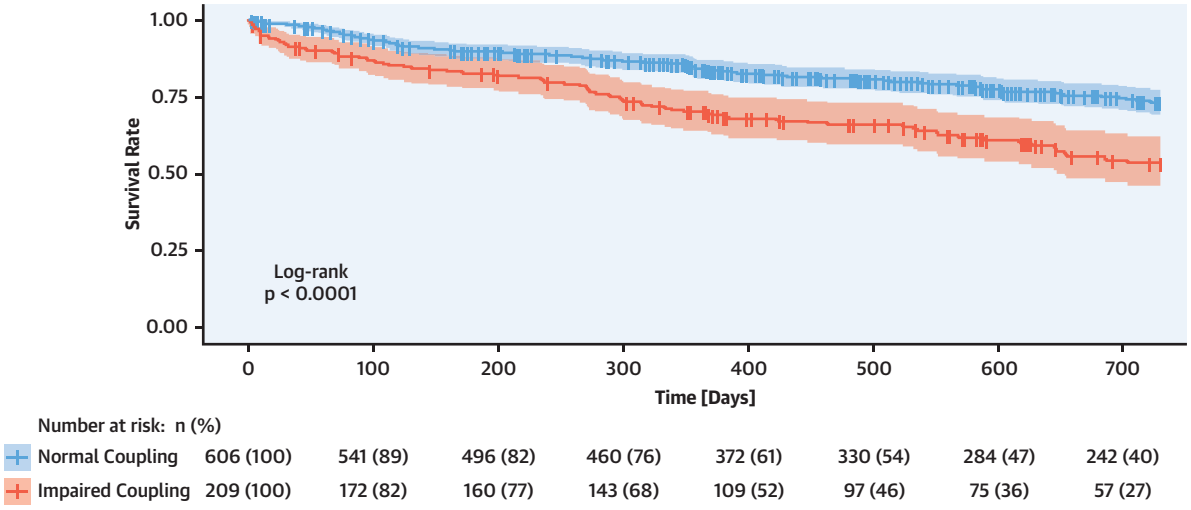
Baseline clinical characteristics of patients according to RV-PA coupling (with and without RVD) are presented in Table 1. Patients with RVD (impaired RV-PA coupling) were more frequently males (72.5 vs. 64.1% patients without RVD; p = 0.026) and more frequently presented with ischemic heart disease (56.4% vs. 46.1%, respectively; p = 0.013) and atrial fibrillation (71.6% vs. 60.9%, respectively; p = 0.006). Their median N-terminal pro-B-type natriuretic peptide concentrations were higher (7,537 vs. 6,473 pg/ml, respectively; p = 0.012).

Regarding baseline echocardiographic parameters, patients with impaired RV-PA coupling had a lower ejection fraction (32.9% vs. 35.8%, respectively; p = 0.013) and a higher LV end-diastolic volume (190.7 vs. 176.2 ml, respectively; p = 0.05). They more frequently presented with a TR grade ≥3+ (27.0% vs. 14.1%, respectively; p < 0.001), and their mean sPAP was higher (60.5 vs. 43.4 mm Hg, respectively; p < 0.001). Their RV volumes were larger (end-diastolic area: 25.0 vs. 22.5 cm^2, respectively; p < 0.001), and their mean fractional area change was lower (0.30% vs. 0.34%, respectively; p < 0.001) (Table 2).

OUTCOME ACCORDING TO RV-PA COUPLING. Post-procedural MR reduction of at least 1 grade was observed in 95.3% of patients (94.8% of patients with RVD vs. 95.5%, of patients without RVD; p = 0.659). Median MR reduction was 2.0 grades (range 1.0 to 3.0) in patients with RVD and 2.0 grades (range 2.0 to 3.0) in patients without RVD (p = 0.448). Residual MR grade was 1+ in 550 patients (67.5%) and ≤2+ in 758 patients (93%). There were no differences in residual MR grades according to RV-PA coupling (p = 0.537) (Supplemental Table 1).

Mean follow-up duration was 476 ± 251 days (median duration: 538 days [IQR: 287 to 730 days]). At last follow-up, improvement by at least 1 NYHA functional class was observed in 63.4% of patients. There was a trend toward a lower rate of NYHA functional class I or II among patients with RVD (56.5% vs. 65.5%, respectively; p = 0.086) (Figure 1). At 1 year, the mortality follow-up was completed for 87.2% of eligible patients (eligibility: 792 of 817 patients; in 25 patients, the time between intervention and database closure was <365 days). At the 2 year follow-up, the rate was 76.7% of eligible patients (criteria for eligibility was status alive at 1 year and time between intervention and database closure <730 days).

CENTRAL ILLUSTRATION **Kaplan-Meier Curve for Survival-Free According to RV-PA Coupling**



Karam, N. et al. J Am Coll Cardiol Img. 2021;14(4):768–78.

Survival rate at 2 years was lower among patients with impaired right ventricular-to pulmonary artery (RV-PA) coupling than those with normal RV-PA coupling.

Estimated all-cause mortality rates at 1 year and 2 years were 19.7% and 31.9%, respectively. Survival rates at 1 and 2 years were lower among patients with RVD (impaired RV-PA coupling; 70.2 vs. 84.0%, respectively; $p < 0.001$; and 53.4% vs. 73.1%, respectively; $p < 0.001$) (**Central Illustration**). Among patients with normal RV-PA coupling (Supplemental Table 2), there were no survival difference between patients with both normal RV function and sPAP and patients with concordantly reduced RV function and sPAP (Logrank $p = 0.583$).

There was a trend toward lower survival rates at 1 year among patients with a TR grade ≥3, even though survival at 2 years did not differ (74.8% vs. 81.5%, respectively; $p = 0.055$; and 64.0% vs. 68.8%, respectively; $p = 0.164$) (**Figure 2**).

PREDICTORS OF MORTALITY AND THEIR INCREMENTAL VALUE. Univariate analyses were performed to identify predictors for mortality (**Table 3**). On multivariate analysis factors associated with mortality after TMVR were a low TAPSE/sPAP ratio (HR: 1.62; 95% CI: 1.14 to 2.31; $p = 0.007$), a NYHA functional class of IV at baseline (HR: 2.21; 95% CI: 1.53 to 3.12; $p < 0.001$), and RV dilation (HR: 1.04; 95% CI: 1.01 to 1.07; $p = 0.005$ for RV end-systolic area) (**Table 3**). In order to rule out potential inaccuracies in sPAP estimation by echocardiography in patients with severe TR, a sensitivity analysis excluding patients with TR >2 was conducted. The analysis, performed on 673 patients, confirmed the adverse impact of a low TAPSE/sPAP ratio on outcome after TMVR.

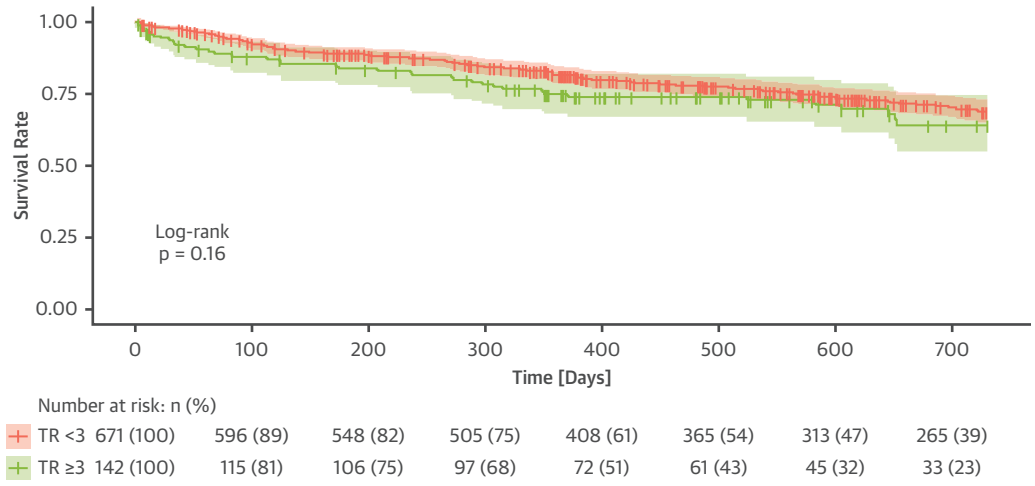
Although the addition of severe TR and sPAP to the base model did not provide an incremental value for mortality prediction, the addition of RV-PA coupling resulted in significant improvements in the integrated discrimination index and the continuous net reclassification index for mortality prediction beyond the incremental value of the addition of TAPSE alone (**Table 4**).

DISCUSSION

In the current analysis of the large multicentric EuroSMR registry, TMVR was associated with an improvement in NYHA functional class. However; patients with RVD determined by an impaired RV-PA coupling were less often in NYHA functional class I or II at last follow-up, and their survival rate was significantly lower. After adjustment for potential confounders, impaired RV-PA coupling was an independent and strong predictor of mortality after TMVR in patients with SMR.

The yield of TMVR in patients with severe symptomatic SMR is still unclear. Although several

FIGURE 2 Kaplan-Meier Curve for Survival According to Tricuspid Regurgitation Severity



Survival rate at 2 years was lower among patients with baseline tricuspid regurgitation (TR) grade ≥3+ than in patients with TR <3+.

preceding retrospective registries indicated a potential benefit from TMVR, 2 recent randomized trials (MITRA-FR and COAPT) provided conflicting results (8,9). Several differences were observed between the 2 studies and might account for the contradictory results, including differences in ERO, left ventricular diameters, heart failure medication, and MR proportionality. The role of RV dysfunction has not been investigated so far (19), even though differences in RV characteristics may exist between the 2 studies. Indeed, while physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe right ventricular dysfunction was an exclusion criteria in COAPT (21), such an exclusion criteria was not defined in MITRA-FR (31).

The importance and clinical relevance of the RV and its function have often been underestimated or even neglected. Assessing RVD is a difficult task, and several parameters have been used for this purpose, including TAPSE and FAC. A better approach would be to evaluate the RV to pulmonary artery (RV-PA) coupling, which integrates the RV systolic performance at a given degree of afterload. Until recently, this would require invasive evaluation of hemodynamics. However, validation of a noninvasive TAPSE/sPAP ratio has been shown to accurately provide similar results, which are prognostically significant in heart failure populations (16–18). Gorter at al. (32) demonstrated that the TAPSE/sPAP ratio, derived from right heart catheterization, is strongly correlated with the noninvasively determined TAPSE/sPAP ratio determined using continuous-wave Doppler echocardiography. The adverse prognosis prediction role of RVD, as assessed by the TAPSE/sPAP ratio, has been documented in heart failure with preserved ejection fraction, after transcatheter aortic valve implantation, as well as after transcatheter tricuspid valve repair (16,17,33). A similar role has not been documented after TMVR, even though both pulmonary hypertension and impairment of RV function have been shown to be associated with a poor prognosis among patients with severe MR undergoing TMVR (11–13).

The EuroSMR registry provides an excellent setting for identifying the optimal predictors of outcome after TMVR. In the 8 high-volume European heart valve centers, with long experience in the treatment of SMR by TMVR, a multidisciplinary heart team assessed each individual patient before the procedure to establish the severity of MR by using a multiparametric echocardiographic approach and the appropriateness of TMVR. In the current analysis, RVD, as determined by a low RV-PA ratio, is a strong independent predictor of outcome after TMVR, together with NYHA functional class IV and RV dilation. Accordingly, the nonexclusion of patients with right-sided heart failure and RV dilation in the MITRA-FR study, although they were excluded from the COAPT trial, may explain to some extent the differences in outcomes between the 2 studies. Systematic assessment of the RV and more particularly of

TABLE 3 Univariate and Multivariate Predictors of Survival Among Patients With Severe SMR Undergoing TMVR

	Univariate Analysis			Multivariate Analysis		
	HR	95% CI	p Value	HR	CI	p Value
Males	0.98	0.74–1.30	0.879			
Age, yrs	1.01	1.00–1.03	0.076			
Diabetes	**1.50**	**1.14–1.97**	**0.004**	1.23	0.86–1.74	0.260
Arterial hypertension	0.94	0.69–1.28	0.704			
Ischemic heart disease	0.92	0.69–1.24	0.592			
Previous MI	1.11	0.82–1.51	0.502			
Previous PCI	0.93	0.67–1.28	0.656			
Previous CABG	1.34	0.95–1.90	0.096			
Previous stroke	1.35	0.91–2.01	0.139			
Previous pulmonary disease	1.06	0.74–1.52	0.764			
Previous ICD	0.90	0.61–1.31	0.574			
Previous CRT	1.23	0.90–1.67	0.199			
Atrial fibrillation or flutter	0.97	0.74–1.28	0.844			
NT-proBNP, pg/ml	1.00	1.00–1.00	0.051			
eGFR, 10 ml/min	**0.87**	**0.81–0.93**	**0.000**	**0.85**	**0.78–0.92**	**<0.001**
NYHA functional class IV	**1.89**	**1.39–2.55**	**0.000**	**2.21**	**1.53–3.12**	**<0.001**
MR severity	-	-	-			
2+	Ref.	Ref.	Ref.			
3+	0.76	0.40–1.44	0.400			
4+	0.79	0.41–1.52	0.468			
MR vena contracta, mm	1.07	0.99–1.16	0.094			
MR EROA, cm^2	0.66	0.24–1.83	0.421			
MR volume, ml	1.00	0.99–1.00	0.207			
LVEF %	0.99	0.98–1.00	0.228			
LVEDV, ml	1.00	1.00–1.00	0.739			
LVESV, ml	1.00	1.00–1.00	0.496			
LVSV, ml	1.00	1.00–1.01	0.080			
ERO/LVEDV • 100, cm^2/ml	0.91	0.30–2.78	0.865			
TR Severity ≥ 3+	1.28	0.90–1.80	0.165			
TR vena contracta, mm	**1.09**	**1.03–1.15**	**0.002**	1.04	0.98–1.10	0.248
RV-EDA, cm^2	**1.02**	**1.00–1.04**	**0.013**	0.98	0.95–1.01	0.246
RV-ESA, cm^2	**1.05**	**1.02–1.07**	**0.000**	**1.04**	**1.01–1.07**	**0.005**
RAA, cm^2	**1.03**	**1.01–1.04**	**0.010**	1.00	0.98–1.03	0.774
TV annulus diameter, mm	**1.02**	**1.00–1.04**	**0.025**	0.99	0.96–1.02	0.488
IVC diameter, mm	1.01	0.98–1.04	0.585			
TAPSE/sPAP dichotomized	**2.02**	**1.53–2.66**	**0.000**	**1.62**	**1.14–2.31**	**0.007**

Values in **bold** indicate statistically significant difference.

CABG = coronary artery bypass grafting; CRT, cardiac resynchronization therapy; EDA = end-diastolic area; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; ESA = end-systolic area; FAC = fractional area change; ICD = implantable cardioverter-defibrillator; IVC = inferior vena cava; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left end-systolic volume; LVSV = left ventricular stroke volume; MI = myocardial infarction; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptiden-terminal pro brain natriuretic peptide; NYHA = New York Heart Association; PCI = percutaneous coronary intervention; RAA = right atrial area; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation; TV = tricuspid valve.

RV-PA coupling using a simple echocardiographic ratio and RV size may help to select the appropriate candidates for TMVR procedures among patients with severe SMR. The optimal cutoff value of the TAPSE/sPAP ratio for predicting outcome varies across studies and according to the underlying disease. While in patients with heart failure and preserved ejection fraction, Gorter et al. (32) identified a cut-off of 0.36 as the best discriminator for a diagnosis of post-capillary pulmonary hypertension and of mortality, cut-offs of 0.29 were identified as outcome predictors in TAVR and TTVR, which is close to the cutoff (0.274) identified in this study as an outcome predictor after TMVR (16,33). TR was not an independent predictor of prognosis in the present study. This result may seem surprising given that previous nonrandomized studies have shown TR to be an independent predictor of increased mortality (34,35). However, most previous studies included primary and secondary MR patients, and the impact of severe

TABLE 4 Mortality Prediction Models

Base Model (Sex, Age, eGFR, NYHA Functional Class IV, RV-ESA)	IDI (95% CI)	Continuous NRI (95% CI)
Base model + TR ≥3+	<0.01 (−0.001 to 0.010)	0.06 (−0.08 to 0.13)
p value, vs. base model	0.69	0.94
Base model + TAPSE	0.10 (0.000 to 0.03)	0.08 (−0.05 to 0.18)
p value, vs. base model	0.04	0.19
Base model + sPAP	0.003 (−0.001 to 0.017)	0.07 (−0.08 to 0.17)
p value, vs. base model	0.20	0.23
Base model + TAPSE/sPAP	0.02 (0.003 to 0.05)	0.17 (0.09 to 0.26)
p value vs. base model	<0.01	<0.01

eGFR = estimated glomerular filtration rate; LVEDV = left ventricular end-diastolic volume; MR-EROA = mitral regurgitation effective regurgitant orifice area; sPAP = systolic pulmonary artery pressure; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

TR on survival may be stronger in patients with primary MR and preserved LV function. In contrast, in patients with SMR, the probability for survival is more influenced by the underlying LV disease with its reduced LV function than by severe TR. Consistent with the present study findings, a recent echocardiographic substudy of COAPT also did not identify severe TR as independent predictor for mortality in TMVR-treated patients (36).

STUDY LIMITATIONS. This is an observational study without a control group, and there was no central adjudication of clinical status and echocardiographic parameters. However, 2 different observers remeasured TAPSE and sPAP in a subset of patients. Interclass correlation analysis showed excellent reliability for sPAP (interclass correlation coefficient >0.9) and good reliability for TAPSE and the TAPSE/sPAP ratio (interclass correlation coefficient >0.85). Additionally, all patients included were considered to be under optimal medical therapy, based on the local heart team's assessment; however, there was no clinical core laboratory to monitor this information, and the subsequent therapeutic adjustments were not documented. Finally, several patients were lost to follow-up, as is often the case in multicentric retrospective registries.

CONCLUSIONS

RVD, as shown by impairment of RV-PA coupling, is a strong and important predictor for increased mortality in patients with SMR undergoing TMVR. RV parameters, including RV dilation and RV-PA coupling, should therefore be systematically assessed when planning a TMVR procedure for severe SMR.

ACKNOWLEDGMENTS The authors acknowledge EuroSMR investigators in Munich: Mathias Orban, Daniel Braun, Michael Näbauer, Stephan Massberg, and Joerg Hausleiter, Medizinische Klinik und Poliklinik I. In Hamburg: Daniel Kalbacher, Edith Lubos, Dirk Westermann, Niklas Schofer, and Sebastian Ludwig in University Medical Centre Hamburg-Eppendorf. In Berlin, Christian Butter and Marvin Bannehr in Bernau. In Bern: Fabien Praz, Stephan Windecker, and Mohammad Kassar, Bern University. In Mainz: Aniela Petrescu and Stephan von Bardeleben, Mainz University Hospital. In Cologne: Roman Pfister, Christos Iliadis, and Stephan Baldus, Heart Center. In Leipzig: Philipp Lurz, Holger Thiele, Matthias Unterhuber Maximilian von Roeder, and Thilo Noack, Heart Center. In Paris: Nicole Karam, Tania Puscas, Alain Berrebi, Noemie Tence, Paul Achouh, and Christian Latremouille, European Hospital Georges Pompidou.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Dr. Karam is a consultant for Abbott Vascular. Dr. Orban has received speaker fees from Abbott Vascular. Dr. Windecker has received research and educational grants from Abbott, Amgen, Bristol Myers Squibb, Bayer, Boston Scientific, Biotronik, CSL, Medtronic, Edwards Lifesciences, Sinomed, and Polares. Dr. Pfister has received financial support for attending symposia by Abbot Vascular. Dr. von Bardeleben has received speaker fees from Abbott Vascular and Edwards Lifesciences. Dr. Hausleiter has received research support and speaker honoraria from Abbott Vascular and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: Conflicting data exist regarding the benefit of edge-to-edge TMVR in severe secondary mitral regurgitation. According to the present study, right ventricular dysfunction as defined by right ventricle-to-pulmonary artery coupling is a strong predictor of outcome and should be considered in the selection of appropriate candidates for TMVR.

TRANSLATIONAL OUTLOOK: Randomized studies are needed to confirm the yield of right ventricle to pulmonary artery coupling in selecting patients for TMVR procedures. More specifically, a randomized controlled trial is needed to compare optimal medical treatment to TMVR in patients with SMR and right ventricular dysfunction

REFERENCES

1. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739–91.

2. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Circulation 2017;135:e1159–95.

3. Puls M, Lubos E, Boekstegers P, et al. One-year outcomes and predictors of mortality after MitraClip therapy in contemporary clinical practice: results from the German transcatheter mitral valve interventions registry. Eur Heart J 2016;37:703–12.

4. Maisano F, Franzen O, Baldus S, et al. Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. J Am Coll Cardiol 2013;62:1052–61.

5. Swaans MJ, Bakker ALM, Alipour A, et al. Survival of transcatheter mitral valve repair compared with surgical and conservative treatment in high-surgical-risk patients. J Am Coll Cardiol Intv 2014;7:875–81.

6. Velazquez EJ, Samad Z, Al-Khalidi HR, et al. The MitraClip and survival in patients with mitral regurgitation at high risk for surgery: a propensity-matched comparison. Am Heart J 2015;170:1050–9.

7. Giannini C, Fiorelli F, De Carlo M, et al. Comparison of percutaneous mitral valve repair versus conservative treatment in severe functional mitral regurgitation. Am J Cardiol 2016;117:271–7.

8. Obadia J-F, Messika-Zeitoun D, Leurent G, et al. Percutaneous repair or medical treatment for secondary mitral regurgitation. N Engl J Med 2018;379:2297–306.

9. Stone GW, Lindenfeld J, Abraham WT, et al. Transcatheter mitral-valve repair in patients with heart failure. N Engl J Med 2018;379:2307–18.

10. Arnold SV, Chinnakondepalli KM, Spertus JA, et al. Health status after transcatheter mitral-valve repair in heart failure and secondary mitral regurgitation: COAPT trial. J Am Coll Cardiol 2019;73:2123–32.

11. Matsumoto T, Nakamura M, Yeow W-L, et al. Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. Am J Cardiol 2014;114:1735–9.

12. Tigges E, Blankenberg S, von Bardeleben RS, et al. Implication of pulmonary hypertension in patients undergoing MitraClip therapy: results from the German transcatheter mitral valve interventions (TRAMI) registry. Eur J Heart Fail 2018;20:585–94.

13. 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;223:574–80.

14. Orban M, Braun D, Orban M, et al. Long-term outcome of patients with severe biventricular heart failure and severe mitral regurgitation after percutaneous edge-to-edge mitral valve repair. J Intervent Cardiol 2015;28:164–71.

15. Hahn RT, Asch F, Weissman NJ, et al. Impact of tricuspid regurgitation on clinical outcomes: the COAPT trial. J Am Coll Cardiol 2020;76:1305–14.

16. Sultan I, Cardounel A, Abdelkarim I, et al. Right ventricle to pulmonary artery coupling in patients undergoing transcatheter aortic valve implantation. Heart Br Card Soc 2019;105:117–21.

17. 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;10:1211–21.

18. Guazzi M, Villani S, Generati G, et al. Right ventricular contractile reserve and pulmonary circulation uncoupling during exercise challenge in heart failure: pathophysiology and clinical phenotypes. J Am Coll Cardiol HF 2016;4:625–35.

19. Mehmood M. Echocardiographic outcomes in the COAPT trial: asking the "right" question. J Am Coll Cardiol 2020;75:2095.

20. Wunderlich NC, Siegel RJ. Peri-interventional echo assessment for the MitraClip procedure. Eur Heart J Cardiovasc Imaging 2013;14:935–49.

21. Mack MJ, Abraham WT, Lindenfeld J, et al. Cardiovascular outcomes assessment of the MitraClip in patients with heart failure and secondary mitral regurgitation: design and rationale of the COAPT trial. Am Heart J 2018;205:1–11.

22. Galderisi M, Cosyns B, Edvardsen T, et al. Standardization of adult transthoracic echocardiography reporting in agreement with recent chamber quantification, diastolic function, and heart valve disease recommendations: an expert consensus document of the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2017;18:1301–10.

23. Kaul S, Tei C, Hopkins JM, Shah PM. Assessment of right ventricular function using two-dimensional echocardiography. Am Heart J 1984;107:526–31.

24. Aloia E, Cameli M, D'Ascenzi F, Sciaccaluga C, Mondillo S. TAPSE: an old but useful tool in different diseases. Int J Cardiol 2016;225:177–83.

25. Lang RM, Bierig M, Devereux RB, et al. Recommendations for chamber quantification: a report from the American Society of Echocardiography's Guidelines and Standards Committee and the Chamber Quantification Writing Group, developed in conjunction with the European Association of Echocardiography, a branch of the European Society of Cardiology. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2005;18:1440–63.

26. 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 Off Publ Am Soc Echocardiogr 2010;23:685–713, quiz 786–788.

27. Lancellotti P, Tribouilloy C, Hagendorff A, et al. Recommendations for the echocardiographic assessment of native valvular regurgitation: an executive summary from the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc. Imaging 2013;14:611–44.

28. Zoghbi WA, Adams D, Bonow RO, et al. Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American Society of Echocardiography Developed in Collaboration with the Society for Cardiovascular Magnetic Resonance. J Am Soc Echocardiogr Off Publ Am Soc Echocardiogr 2017;30:303–71.

29. Harrell FE, Lee KL, Mark DB. Multivariable prognostic models: issues in developing models, evaluating assumptions and adequacy, and measuring and reducing errors. Stat Med 1996;15:361–87.

30. Pencina MJ, D'Agostino RB, D'Agostino RB, Vasan RS. Evaluating the added predictive ability of a new marker: from area under the ROC curve to reclassification and beyond. Stat Med 2008;27:157–72; discussion 207–12.

31. Obadia J-F, Armoiry X, Iung B, et al. The MITRA-FR study: design and rationale of a randomised study of percutaneous mitral valve repair compared with optimal medical management alone for severe secondary mitral regurgitation. EuroIntervention 2015;10:1354–60.

32. Gorter TM, van Veldhuisen DJ, Voors AA, et al. Right ventricular-vascular coupling in heart failure with preserved ejection fraction and pre- vs. post-capillary pulmonary hypertension. Eur Heart J Cardiovasc Imaging 2018;19:425–32.

33. Lurz P, Orban M, Besler C, et al. Clinical characteristics, diagnosis, and risk stratification of pulmonary hypertension in severe tricuspid regurgitation and implications for transcatheter tricuspid valve repair. Eur Heart J 2020;41:2785–95.

34. Ohno Y, Attizzani GF, Capodanno D, et al. Association of tricuspid regurgitation with clinical and echocardiographic outcomes after percutaneous mitral valve repair with the MitraClip System: 30-day and 12-month follow-up from the GRASP registry. Eur Heart J Cardiovasc Imaging 2014;15:1246–55.

35. Kalbacher D, Schäfer U, V Bardeleben RS, et al. Long-term outcome, survival and

predictors of mortality after MitraClip therapy: results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry. Int J Cardiol 2019;277:35–41.

36. Asch FM, Grayburn PA, Siegel RJ, et al. Echocardiographic outcomes after transcatheter leaflet approximation in patients with secondary mitral regurgitation: the COAPT trial. J Am Coll Cardiol 2019;74:2969–79.

KEY WORDS edge-to-edge repair, outcome, right ventricular function, right ventricular-to-pulmonary artery coupling, secondary mitral regurgitation, tricuspid regurgitation

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