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Outcomes Stratified by Adapted Inclusion Criteria After Mitral Edge-to-Edge Repair

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ABSTRACT

BACKGROUND Although mitral valve transcatheter edge-to-edge repair (M-TEER) achieves symptomatic benefit for a broad spectrum of patients with relevant secondary mitral regurgitation, conflicting data exist on its prognostic impact.

OBJECTIVES Adapted enrollment criteria approaching those used in the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) trials were retrospectively applied to a European real-world registry to evaluate the influence of the respective criteria on outcomes.

METHODS A total of 1,022 patients included in the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry and treated with M-TEER (November 2008 to September 2019) were stratified into COAPT-eligible (n = 353 [34.5%]) and COAPT-ineligible (n = 669 [65.5%]) as well as MITRA-FR-eligible (n = 408 [48.3%]) and MITRA-FR-ineligible (n = 437 [51.7%]) groups.

RESULTS Although the stratification of patients according to adapted MITRA-FR criteria led to comparable outcomes regarding all-cause mortality ($P = 0.19$), the application of adapted COAPT enrollment criteria demonstrated lower mortality rates in COAPT-eligible compared with COAPT-ineligible patients ($P < 0.001$). Multivariable Cox regression analysis identified New York Heart Association functional class IV (hazard ratio [HR]: 2.29; 95% confidence interval [CI]: 1.53-3.42; $P < 0.001$), logarithmic N-terminal pro-brain natriuretic peptide (HR: 1.47; 95% CI: 1.24-1.75; $P < 0.001$), and right ventricular-to-pulmonary arterial coupling (HR: 0.10; 95% CI: 0.02-0.57; $P = 0.009$) as independent predictors of outcome. Yet improvement of functional outcome was demonstrated in a subset of patients irrespective of COAPT eligibility status.

CONCLUSIONS In this real-world cohort of patients with secondary mitral regurgitation undergoing M-TEER, the retrospective application of adapted COAPT enrollment criteria successfully identified a specific phenotype demonstrating lower mortality rates. On the contrary, stratification according to adapted MITRA-FR criteria resulted in comparable outcomes. (J Am Coll Cardiol 2021;78:2408–2421) © 2021 by the American College of Cardiology Foundation.

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Over the past decade, mitral valve transcatheter edge-to-edge repair (M-TEER) has been increasingly used to treat relevant primary and secondary mitral regurgitation (MR) in symptomatic patients with prohibitive surgical risk (1,2). Besides high procedural safety and success rates, quality-of-life improvement can be achieved in the vast majority of patients (3,4). Although the surgical approach remains the reference standard for primary MR, treatment of secondary MR (SMR) always involves guideline-directed medical therapy and requires a multidisciplinary approach. In terms of prognostic benefit, convincing surgical data are lacking, while controversial data exist for M-TEER (5-7). In 2018, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial demonstrated improved survival in patients with SMR treated using M-TEER on top of guideline-directed medical therapy in comparison with patients treated with guideline-directed medical therapy only. In light of the neutral results of the MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) trial, the applicability of the findings of the COAPT trial to a less selected population has been the subject of controversy (8), as well as the impact of differences in the trial protocols on the inconsistent results (9). Influenced by the divergent results of the COAPT and MITRA-FR trials, current American and European guidelines and a joint European position statement on SMR recommend the use of M-TEER, especially in patients meeting COAPT eligibility criteria (10-12). The aim of this retrospective study was to apply both adapted COAPT and MITRA-FR trial inclusion and exclusion criteria to patients treated with M-TEER for relevant SMR in a large, real-world, multicenter registry and investigate their influence on outcomes.

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METHODS

STUDY POPULATION AND ENDPOINT ANALYSIS. This retrospective analysis comprises anonymized patients with relevant SMR included in the EuroSMR (European Registry of Transcatheter Repair for Secondary Mitral Regurgitation) registry (German Clinical Trials Register; DRKS00017428) treated with M-TEER between November 2008 and September 2019 at 11 high-volume centers in France, Switzerland, Italy, Portugal, and Germany. All data collection and analysis were performed with the approval of the Institutional Review Board of the respective academic center. Patients received appropriate treatment with guideline-directed medical therapy and were determined to be not amenable to open heart surgery by an interdisciplinary heart team prior to M-TEER.

Follow-up was performed at the treating sites by clinical visits, phone calls, or hospital and civil record assessment, including mortality, transthoracic echocardiography, and the assessment of New York Heart Association (NYHA) functional class. In a subset of patients, 6-minute walk distance and quality of life by the Minnesota Living With Heart Failure Questionnaire (MLHFQ) were assessed. The primary study endpoint was defined as all-cause mortality (censored after 2-year follow-up).

PROCEDURAL TECHNIQUE AND ECHOCARDIOGRAPHIC ASSESSMENT. M-TEER was performed by MitraClip implantation (Abbott Medical) under general anesthesia using established protocols (13). All patients underwent echocardiography performed by experienced physicians at each site, including the assessment of left ventricular (LV) volumes (end-diastolic and end-systolic volumes), LV diameters (end-diastolic and end-systolic diameters), and function (LV ejection fraction by the Simpson biplane method). SMR severity was evaluated applying a multiparametric approach according to the European recommendations for native valve regurgitation, integrating vena contracta, effective regurgitant orifice area (EROA) derived using the proximal isovelocity surface area method, and regurgitant volumes (14). SMR severity was expressed using a 4-grade approach. Right ventricular (RV) function was assessed by tricuspid annular plane systolic excursion. Pulmonary artery systolic pressure was calculated from the tricuspid regurgitant jet velocity, adding the estimated right atrial pressure. RV-to-pulmonary arterial (PA) coupling was estimated using the ratio between tricuspid annular plane systolic

ABBREVIATIONS AND ACRONYMS

CI = confidence interval

EROA = effective regurgitant orifice area

HR = hazard ratio

IQR = interquartile range

LV = left ventricular

MLHFQ = Minnesota Living With Heart Failure Questionnaire

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

MR = mitral regurgitation

NYHA = New York Heart Association

PA = pulmonary arterial

RV = right ventricular

SMR = secondary mitral regurgitation

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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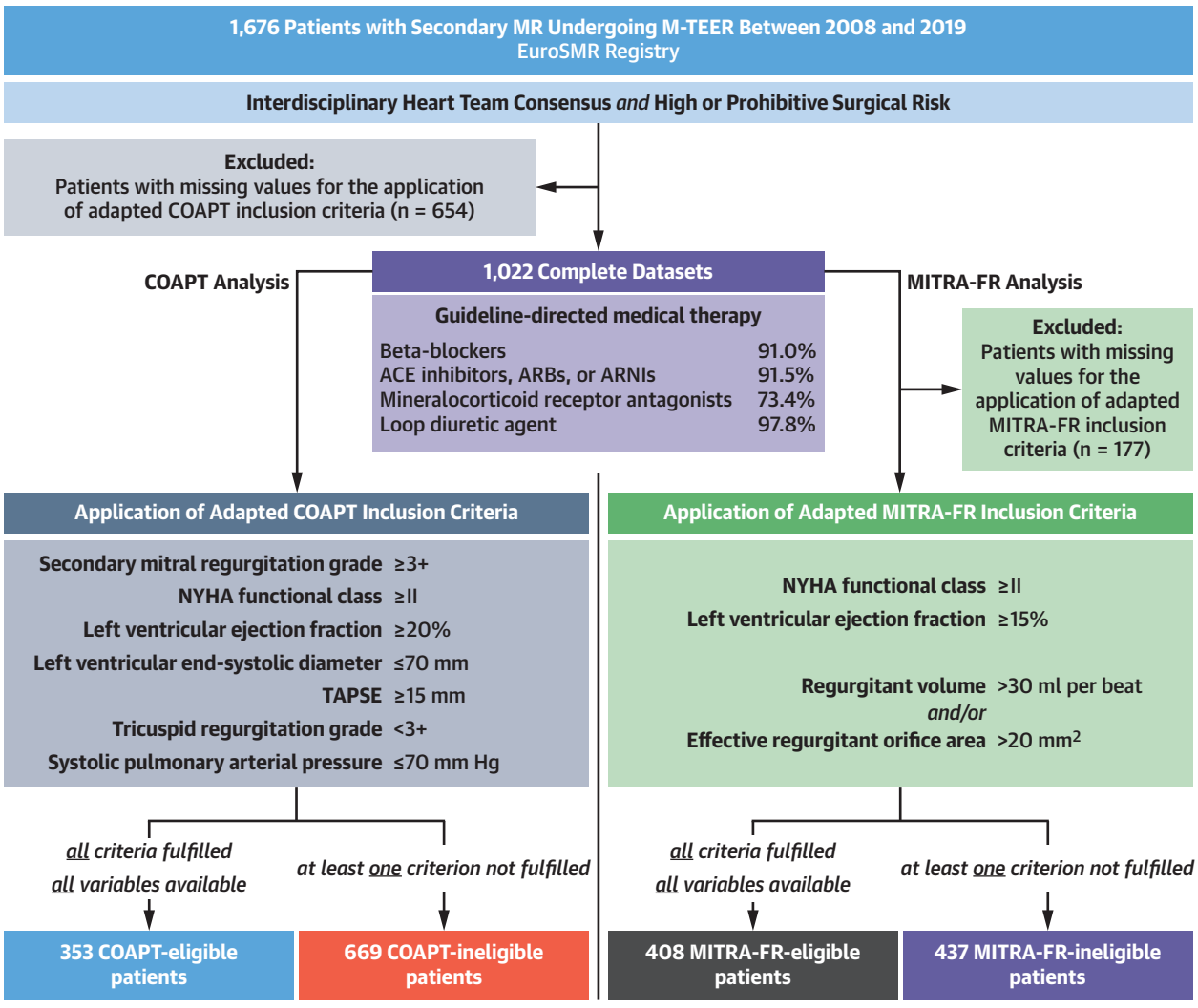
FIGURE 1 Study Flowchart



Adapted COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) and MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) inclusion criteria were applied to a real-world registry to evaluate the influence of the respective criteria on outcome. After exclusion, 1,022 patients with secondary mitral regurgitation (MR) and guideline-directed medical therapy treated with mitral valve transcatheter edge-to-edge repair (M-TEER) were examined in 2 independent analyses: COAPT analysis **(left)** and MITRA-FR analysis **(right)**. ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; EuroSMR = European Registry of Transcatheter Repair for Secondary Mitral Regurgitation; NYHA = New York Heart Association; TAPSE = tricuspid annular plane systolic excursion.

excursion and pulmonary artery systolic pressure as a noninvasive measure of RV-arterial coupling (15).

APPLICATION OF ADAPTED INCLUSION AND EXCLUSION CRITERIA. The application of adapted inclusion and exclusion criteria according to COAPT and MITRA-FR was performed in 2 independent analyses: 1) COAPT analysis; and 2) MITRA-FR analysis. To achieve a comparable cohort, especially with regard to the availability of RV parameters, patients with missing data for the application of adapted COAPT inclusion criteria were initially excluded from all further analyses.

The following parameters were used to identify patients as COAPT-eligible (16): SMR ≥3+, NYHA functional class ≥II, LV ejection fraction ≥20% and ≤50%, LV end-systolic diameter ≤70 mm, tricuspid regurgitation ≤2+, pulmonary artery systolic

pressure ≤ 70 mm Hg (echocardiographic assessment), and preserved RV function as assessed by tricuspid annular plane systolic excursion ≥15 mm (17). Only patients meeting all of the aforementioned criteria were classified as COAPT-eligible. Patients with missing variables were excluded. Conversely, COAPT-ineligible patients met at least 1 of the contrary criteria.

In contrast to the published inclusion criteria, no information on previous heart failure hospitalizations, the origin of the primary regurgitant jet, mitral valve orifice area, leaflet anatomy, creatine kinase-MB level, chronic obstructive lung disease requiring continuous home oxygen therapy, chronic outpatient oral steroid use, and modified Rankin scale score at baseline was available. Because of the availability of echocardiographic data, SMR ≥3+ was used for stratification instead of the previously published algorithm for MR quantification in the context of the COAPT trial (18). Supplemental Figure 1 depicts the classification of MR according to the published algorithm. In addition, the applied definition of RV dysfunction was not specified in COAPT. In accordance with a previously published analysis, tricuspid annular plane systolic excursion <15 mm was therefore used (17).

In a second independent analysis, the following adapted MITRA-FR inclusion criteria were applied: NYHA functional class ≥II, LV ejection fraction ≥15% and ≤40%, regurgitant volume >30 mL/beat, and/or EROA >20 mm^2. Only patients meeting all of the aforementioned criteria were classified as MITRA-FR-eligible. Patients with missing variables for the appropriate application of the MITRA-FR criteria were excluded. MITRA-FR-ineligible patients did fulfill at least 1 of the opposite criteria.

In contrast to the published inclusion criteria, no information on previous heart failure hospitalizations was available. Categorization of the predefined groups is depicted in **Figure 1**.

STATISTICAL ANALYSIS. Continuous variables are expressed as median (interquartile range [IQR]) and were compared using the Mann-Whitney *U* test. For selected continuous variables, the mean ± SD is given. Binary variables are shown as count (frequency) and were compared using the chi-square test.

Box plots for 6-minute walk distance and MLHFQ are expressed as the median (IQR) of all differences between time points. The whiskers mark the smallest and largest measurements. The Mann-Whitney *U* test was used to test for differences; in case of comparisons between time points, the paired Mann-Whitney *U* test was calculated, and missing values at any time point were excluded. To assess differences in outcomes, the predefined endpoint within 2 years of follow-up was analyzed. Median follow-up time was estimated by the reverse Kaplan-Meier estimator. Survival probabilities were evaluated using the Kaplan-Meier method. Groups were compared using the log-rank test. All survival analyses were conducted with the primary outcome censored at 2-year follow-up. A censoring curve is provided to describe the follow-up (Supplemental Figure 2). To examine predictors of all-cause mortality, univariable and multivariable Cox regression was calculated. Variables with *P* values <0.05 in univariable logistic regression for all-cause mortality were chosen for further multivariable analysis. COAPT-eligible patients were excluded for the multivariable analysis. *P* values <0.05 were considered to indicate statistical significance. *P* values and 95% confidence intervals (CIs) presented in this report were not adjusted for multiplicity, and therefore inferences drawn from these statistics may not be reproducible. All analyses were performed using R version 4.0.3 (R Foundation for Statistical Computing).

RESULTS

A total of 1,676 patients were included in the EuroSMR registry. After excluding patients with missing data regarding adapted COAPT inclusion criteria, 1,022 patients (median age 74 years [IQR: 68.0-79.7 years], 70.4% men, median European System for Cardiac Operative Risk Evaluation II score 7.0% [IQR: 4.1%-12.5%]) were included in the COAPT analysis. Among patients with the complete dataset, 353 (34.5%) met all adapted inclusion and none of the exclusion criteria applicable and were therefore classified as COAPT-eligible. In contrast, 669 patients (65.5%) were labeled as COAPT-ineligible.

The MITRA-FR analysis included all patients eligible for the COAPT analysis. After a further exclusion of 177 patients because of missing data for the application of adapted MITRA-FR criteria, 408 patients (48.3%) were categorized as MITRA-FR-eligible. Conversely, 437 patients (51.7%) were identified as MITRA-FR-ineligible (**Figure 1**). Clinical baseline characteristics according to COAPT and MITRA-FR status are given in **Table 1**. For comparison, Supplemental Tables 1 and 2 depict baseline and postprocedural parameters for patients initially excluded from any analysis. Supplemental Tables 3 and 4 present the respective parameters for patients excluded from the MITRA-FR analysis. Although limited by the absence of individual dosage

TABLE 1 Baseline Characteristics According to Adapted COAPT and MITRA-FR Status

	COAPT Analysis			MITRA-FR Analysis		
	COAPT-Eligible (n = 353)	COAPT-Ineligible (n = 669)	*P* Value	MITRA-FR-Eligible (n = 408)	MITRA-FR-Ineligible (n = 437)	*P* Value
Sociodemographic						
Age, y	75.4 (68.0-80.0)	74.0 (68.0-79.3)	0.24[a]	74.0 (67.0-79.0)	75.0 (68.0-80.0)	0.059[a]
Male	234 (66.5)	485 (72.5)	0.54	295 (72.3)	289 (66.3)	0.69
Body mass index, kg/m^2	25.6 (23.4-28.6)	25.6 (23.2-28.7)	0.92[a]	25.1 (22.9-28.0)	25.6 (23.3-28.4)	0.059[a]
EuroSCORE II	6.0 (3.8-11.1)	7.7 (4.4-13.6)	0.0016[a]	7.3 (4.3-13.1)	7.1 (4.0-12.4)	0.37[a]
Cardiovascular risk factors						
Hypertension	240 (72.7)	428 (70.6)	0.55	251 (67.3)	300 (77.7)	0.0017
Diabetes	106 (30.1)	228 (36.1)	0.66	124 (31.4)	147 (35.7)	0.22
Cardiac comorbidities						
Previous myocardial infarction	110 (31.5)	216 (32.5)	0.81	134 (33.3)	119 (27.4)	0.78
Previous PCI	113 (40.8)	219 (43.5)	0.51	142 (41.6)	139 (42.8)	0.83
Previous CABG	59 (17.4)	137 (21.6)	0.13	68 (17.5)	87 (21.4)	0.19
History of atrial fibrillation	181 (51.3)	427 (63.8)	<0.001	228 (55.9)	280 (64.1)	0.18
Noncardiac comorbidities						
COPD	59 (16.8)	101 (15.2)	0.62	58 (14.3)	72 (16.6)	0.39
Previous stroke	27 (7.7)	65 (9.7)	0.33	34 (8.4)	41 (9.4)	0.69
Laboratory results						
NT-proBNP, pg/mL	2,638.0 (1,209.7-6,613.7)	3,817.0 (1,631.5-8,422.5)	0.015[a]	3,500.0 (1,781.3-8,330.2)	3,125.5 (1,323.4-6,877.7)	0.17[a]
eGFR, mL/min	46.0 (32.8-61.9)	45.0 (31.0-59.9)	0.54[a]	44.9 (32.8-61.0)	46.0 (31.3-60.0)	0.92[a]
eGFR ≤60, mL/min/1.73 m^2	239 (72.0)	480 (75.2)	0.31	287 (74.0)	297 (72.4)	0.68
Clinical presentation						
MLHFQ score, %	37.0 (24.7-52.0)	36.0 (25.7-55.0)	0.73[a]	42.5 (31.0-57.0)	35.0 (25.0-54.0)	0.022[a]
6-min walking distance, m	247.0 (140.0-372.9)	224.0 (133.3-340.0)	0.20[a]	260.0 (150.0-360.0)	221.0 (133.2-330.0)	0.079[a]
NYHA functional class						
II	61 (17.3)	70 (10.5)	0.003	54 (13.2)	51 (11.7)	0.57
III	235 (66.6)	405 (60.9)	0.87	260 (63.7)	272 (62.4)	0.74
IV	57 (16.1)	188 (28.3)	<0.001	94 (23.0)	111 (25.5)	0.46
Device therapy						
Previous CRT	87 (24.8)	182 (28.1)	0.29	104 (26.1)	99 (23.3)	0.41
Previous ICD	47 (27.5)	123 (30.2)	0.58	72 (31.9)	71 (26.6)	0.24

Continued on the next page

information, a high proportion of all patients received applicable guideline-directed medical therapy (Table 1). In particular, no information on the use of sodium-glucose transporter protein 2 inhibitors was available.

In a further analysis, 153 patients (37.2%) were identified as MITRA-FR and COAPT-eligible (Figure 2). Detailed characteristics and outcomes according to only MITRA-FR-eligible and both MITRA-FR and COAPT-eligible are provided (Supplemental Tables 5 and 6, Supplemental Figure 3).

BASELINE CHARACTERISTICS. Despite a higher prevalence of atrial fibrillation in COAPT-ineligible patients, no significant differences were found between the 2 groups regarding baseline demographic factors and cardiovascular risk factors (Table 1).

The retrospective application of adapted COAPT criteria resulted in a higher proportion of NYHA functional class IV in the COAPT-ineligible group (28.3% vs 16.1%; $P < 0.001$) as well as higher levels of N-terminal pro-brain natriuretic peptide in the COAPT-ineligible group (3,817 pg/mL [IQR: 1,631-8,422 pg/mL] vs 2,638 pg/mL [IQR: 1,209-6,613 pg/mL]; $P = 0.015$). No significant differences were found for quality of life as assessed by MLHFQ or 6-minute walk distance.

In the MITRA-FR analysis, MITRA-FR-ineligible patients showed a significantly higher percentage of hypertension. In other respects, no significant differences were found regarding baseline demographic factors and cardiovascular risk factors.

Echocardiographic parameters are reported in Table 1. Despite the absence of MR severity grade 2+ because of the applied criteria in the COAPT analysis, no significant differences were noted at baseline for MR severity grade 3+ or grade 4+ or for EROA in both groups. Conversely, the application of adapted MITRA-FR exclusion criteria resulted in significant differences in the severity of MR between MITRA-FR-ineligible and MITRA-FR-eligible patients

TABLE 1 Continued

	COAPT Analysis			MITRA-FR Analysis		
	COAPT-Eligible (n = 353)	COAPT-Ineligible (n = 669)	*P* Value	MITRA-FR-Eligible (n = 408)	MITRA-FR-Ineligible (n = 437)	*P* Value
Medication						
Beta-blockers	277 (90.5)	497 (91.2)	0.84	311 (88.6)	309 (93.4)	0.43
ACE inhibitors, ARBs, or ARNIs	325 (92.1)	610 (91.2)	0.71	362 (88.7)	414 (94.7)	0.0022
MRAs	184 (70.5)	327 (75.2)	0.21	204 (69.2)	188 (74.6)	0.19
Loop diuretic agents	292 (97.7)	522 (97.9)	0.99	324 (98.5)	325 (97.9)	0.78
Echocardiographic parameters						
Severity of baseline mitral regurgitation						
Moderate to severe, grade 3+	168 (47.6)	301 (45.1)	0.16	174 (42.6)	245 (56.1)	<0.001
Severe, grade 4+	185 (52.4)	318 (47.6)	0.16	228 (55.9)	157 (35.9)	<0.001
Effective regurgitant orifice area, mm^2	31.6 ± 19.5	33.5 ± 28.9	0.89[a]	41.3 ± 31.8	24.1 ± 14.2	<0.001[a]
Regurgitant volume, mL/beat	41.9 ± 19.5	41.1 ± 23.1	0.19[a]	53.5 ± 19.2	31.8 ± 19.2	<0.001[a]
Left ventricular parameters						
Left ventricular end-systolic dimension, mm	63.0 (55.0-69.0)	63.0 (56.0-72.0)	0.063[a]	66.0 (58.0-73.0)	60.0 (51.0-67.0)	<0.001[a]
Left ventricular end-diastolic dimension, mm	51.0 (43.0-58.0)	53.0 (43.0-61.3)	0.015[a]	54.0 (46.0-61.0)	48.0 (39.0-56.0)	<0.001[a]
Left ventricular end-systolic volume, mL	120.0 (84.7-154.0)	133.0 (90.9-180.0)	<0.001[a]	138.0 (104.1-179.0)	108.0 (72.0-155.3)	<0.001[a]
Left ventricular end-diastolic volume, mL	186.0 (142.2-220.0)	186.5 (141.5-240.0)	0.16[a]	196.9 (157.6-247.3)	170.5 (125.0-217.6)	<0.001[a]
Left ventricular ejection fraction						
LVEF, %	34.0 (27.8-39.5)	30.0 (21.0-36.2)	<0.001[a]	30.0 (24.0-34.9)	35.5 (25.0-44.0)	<0.001[a]
LVEF ≥30%	241 (68.3)	334 (50.4)	<0.001[a]	216 (52.9)	279 (63.8)	0.0017
Severity of baseline tricuspid regurgitation						
None to moderate	353 (100)	420 (63.5)	<0.001	317 (78.5)	323 (74.4)	0.20
Severe	0 (0)	241 (36.5)	<0.001	87 (21.5)	111 (25.6)	0.20
Vena contracta biplane, mm	4.0 (3.0-5.3)	6.0 (4.0-8.0)	<0.001[a]	5.0 (3.5-7.0)	5.3 (4.0-7.5)	0.060[a]
Right ventricular parameters						
Pulmonary artery systolic pressure, mm Hg	45.0 (37.2-55.0)	49.1 (39.0-60.0)	<0.001[a]	48.0 (39.0-58.0)	48.0 (37.9-58.0)	0.49[a]
TAPSE, mm	18.0 (16.6-21.0)	14.0 (12.0-17.0)	<0.001[a]	16.0 (13.0-19.0)	16.0 (13.0-19.0)	0.84[a]
RV-PA coupling, mm/mm Hg	0.4 (0.3-0.5)	0.3 (0.2-0.4)	<0.001[a]	0.3 (0.3-0.4)	0.3 (0.3-0.5)	0.73[a]

Values are median (interquartile range), n (%), or mean ± SD. [a]The Wilcoxon rank test was used for skewed continuous variables.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CABG = coronary artery bypass graft; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter-defibrillator; LVEF = left ventricular ejection fraction; MITRA-FR = Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation; MLHFQ = Minnesota Living With Heart Failure Questionnaire; MRA = mineralocorticoid receptor antagonists; NT-proBNP = N-terminal pro-brain natriuretic peptide; NYHA = New York Heart Association; PA = pulmonary arterial; PCI = percutaneous coronary intervention; RV = right ventricular; TAPSE = tricuspid annular plane systolic excursion.

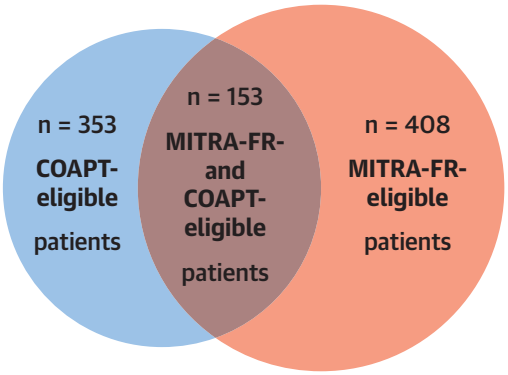
(EROA: 24.1 ± 14.2 mm^2 for MITRA-FR-ineligible patients vs 41.3 ± 31.8 mm^2 for MITRA-FR-eligible patients [$P < 0.001$]; regurgitant volume: 31.8 ± 19.2 mL/beat for MITRA-FR-ineligible patients vs 53.5 ± 19.2 mL/beat for MITRA-FR-eligible patients [$P < 0.001$]).

The median LV ejection fraction was 31% (IQR: 24%-38%), with significant differences between the groups (30% [IQR: 21%-36%] for COAPT-ineligible patients vs 34% [IQR: 28%-40%] for COAPT-eligible patients [$P < 0.001$]; 36% [IQR: 25%-44%] for MITRA-FR-ineligible patients vs 30% [IQR: 24%-35%] for MITRA-FR-eligible patients [$P < 0.001$]).

Regarding end-diastolic LV parameters, the COAPT analysis did not result in any significant differences between both groups. However, in the MITRA-FR analysis LV diameters and volumes differed significantly. MITRA-FR-eligible patients showed greater LV diameters and volumes (LV end-systolic volume: 171 mL [IQR: 125-218 mL] for MITRA-FR-ineligible patients vs 197 mL [IQR: 158-247 mL] for MITRA-FR-eligible patients; $P < 0.001$).

Although the application of adapted COAPT criteria caused significant differences regarding tricuspid regurgitation severity and RV function, the MITRA-FR analysis revealed no such differences. Considering the adapted COAPT criteria of tricuspid regurgitation ≤2+, pulmonary artery systolic pressure ≤70 mm Hg, and tricuspid annular plane systolic excursion ≥15 mm, COAPT-eligible patients consequently had smaller tricuspid regurgitation vena contracta (4.0 mm [IQR: 3.0-5.3 mm] for COAPT-eligible patients vs 6.0 mm [IQR: 4.0-8.0 mm] for COAPT-ineligible patients; $P < 0.001$), lower pulmonary artery systolic pressure (45.0 mm Hg [IQR: 37.2-55.0 mm Hg] for COAPT-eligible patients vs 49.1 mm Hg [IQR: 39.0-

FIGURE 2 Proportions of MITRA-FR-Eligible and COAPT-Eligible Patients



The Venn diagram depicts the proportions of COAPT-eligible patients (**blue circle**; n = 353) and MITRA-FR-eligible patients (**red circle**; n = 408) and the overlap of COAPT- and MITRA-FR-eligible patients (n = 153). Abbreviations as in Figure 1.

60.0 mm Hg] for COAPT-ineligible patients; $P < 0.001$) and higher tricuspid annular plane systolic excursion (18 mm [IQR: 16.6-21.0 mm] for COAPT-eligible patients vs 14 mm [IQR: 12-17 mm] for COAPT-ineligible patients; $P < 0.001$). Analyzing RV dysfunction defined by impaired RV-PA coupling (15), COAPT-ineligible patients showed a significant impairment of RV-PA coupling (0.3 mm/mm Hg [IQR: 0.2-0.4 mm/mm Hg] for COAPT-ineligible patients vs 0.4 mm/mm Hg [IQR: 0.3-0.5 mm/mm Hg] for COAPT-eligible patients; $P < 0.001$). In contrast, no significant differences regarding RV function and tricuspid regurgitation severity were found after applying the adapted MITRA-FR criteria.

COMPARABILITY WITH THE ORIGINAL TRIALS. Supplemental Table 7 shows clinical and echocardiographic parameters at baseline for COAPT-eligible and MITRA-FR-eligible patients compared with the respective "device group" of the original trials (5,16).

Patients included in the COAPT trial showed higher rates of previous myocardial infarction and previous strokes in comparison with patients classified as COAPT-eligible. Although LV and RV parameters were comparable, patients in the original trial had higher mean EROA values (0.41 ± 0.15 cm^2 vs 0.32 ± 0.20 cm^2 in COAPT-eligible patients).

In contrast, patients in the MITRA-FR trial showed higher median N-terminal pro-brain natriuretic peptide levels (3,407 pg/mL vs 2,484 pg/mL for MITRA-FR-eligible patients) and greater mean LV end-diastolic volumes (136.2 mL/m^2 vs 114.1 mL/m^2 for MITRA-FR-eligible patients), while MR severity, as assessed by EROA and regurgitant volume, was more severe in MITRA-FR-eligible patients (0.41 ± 0.32 cm^2 vs 0.31 ± 0.10 cm^2 in the "intervention group").

FOLLOW-UP, MORTALITY, AND COMBINED ENDPOINT RATES. The median follow-up time was 2.2 years (IQR: 2.09-2.44 years), with a maximum follow-up duration of 10.49 years. Outcome was censored at 2-year follow-up. Supplemental Figure 2 shows steady censoring across the whole follow-up period, with a greater amount at 1 year. Survival analyses were conducted, including the censored cases; thus sensitivity analysis (Supplemental Figure 4) showed that the assumption of independent censoring was likely to be met because of low variation of the logarithmic hazard ratio (HR) after gamma imputation. Procedural and overall outcomes are reported in **Table 2**. Overall, 359 patients (35.2%) died during the 2-year follow-up period, with 1-year and 2-year mortality rates of 21.8% and 34.1%, respectively. Kaplan-Meier curves for all-cause mortality within 2 years revealed significant differences between COAPT-eligible and COAPT-ineligible patients (log-rank $P < 0.001$), in contrast to MITRA-FR-eligible versus MITRA-FR-ineligible patients (log-rank $P = 0.19$) (**Central Illustration**).

Univariable Cox regression analysis for all-cause mortality indicated a significant association of COAPT-eligible status with improved survival (HR: 0.60; 95% CI: 0.45-0.81; $P < 0.001$). Multivariable Cox regression analysis identified NYHA functional class IV (HR: 2.29; 95% CI: 1.53-3.42; $P < 0.001$), logarithmic N-terminal pro-brain natriuretic peptide (HR: 1.47; 95% CI: 1.24-1.75; $P < 0.001$), and RV-PA coupling as independent predictors of outcome (HR: 0.10; 95% CI: 0.02-0.57; $P = 0.009$) (**Table 3**).

QUALITY OF LIFE AND FUNCTIONAL OUTCOMES. Irrespective of COAPT status, significant changes were found for 6-minute walk distance and MLHFQ score after M-TEER, with a significant increase in 6-minute walk distance after 6 weeks or latest follow-up for both subgroups (COAPT-eligible [n = 78]: median Δ +14 m [$P = 0.0047$]; COAPT-ineligible [n = 120]: median Δ +57 m [$P < 0.001$]) and a significant reduction for MLHFQ score (COAPT-eligible [n = 116]: median Δ −19.0 [$P < 0.001$]; COAPT-ineligible [n = 157]: median Δ −11.0 [$P < 0.001$]) (**Figure 3**). Changes in NYHA functional class are given in Supplemental Figure 5.

DISCUSSION

The aim of this study was to investigate the impact of the inclusion and exclusion criteria of the

TABLE 2 Overall Outcome and Postprocedural Parameters

	COAPT Analysis			MITRA-FR Analysis		
	COAPT-Eligible (n = 353)	COAPT-Ineligible (n = 669)	*P* Value	MITRA-FR-Eligible (n = 408)	MITRA-FR-Ineligible (n = 437)	*P* Value
Overall outcome						
All-cause death within 2 y	100 (25.2[a])	259 (38.2[a])	<0.001	155 (31.8[a])	154 (36.8[a])	0.19
Postprocedural outcome						
Severity of residual mitral regurgitation						
None to mild	236 (66.9)	441 (65.9)	0.82	257 (63.0)	305 (69.8)	0.043
Moderate	95 (26.9)	182 (27.2)	0.98	118 (28.9)	108 (24.7)	0.19
Moderate to severe	18 (5.1)	34 (5.1)	1.00	25 (6.1)	21 (4.8)	0.49
Severe	4 (1.1)	11 (1.6)	0.71	8 (2.0)	3 (0.7)	0.18
Latest follow-up (6 or 12 mo)						
Severity of mitral regurgitation						
None to mild	201 (56.9)	360 (53.8)	0.65	194 (47.5)	235 (53.7)	0.13
Moderate	57 (17.2)	70 (11.3)	0.70	69 (18.0)	36 (9.2)	<0.001
Moderate to severe	17 (5.1)	19 (3.1)	0.95	19 (4.9)	6 (1.5)	0.013
Severe	2 (0.6)	1 (0.2)	0.58	2 (0.5)	0 (0)	0.47
Clinical presentation						
MLHFQ score, %	21.0 (12.0-37.0)	25.0 (14.0-45.0)	0.070[b]	30.0 (16.2-41.8)	22.5 (11.0-37.1)	0.033[b]
6-min walking distance, m	293.5 (174.3-416.7)	285.0 (169.7-392.7)	0.63[b]	281.0 (167.4-420.0)	284.0 (170.8-389.7)	0.85[b]
NYHA functional class						
I	30 (16.7)	49 (14.1)	0.51	36 (18.0)	29 (12.4)	0.14
II	93 (51.7)	168 (48.3)	0.52	105 (52.5)	117 (50.2)	0.71
III	50 (27.8)	102 (29.3)	0.79	50 (25.0)	71 (30.5)	0.25
IV	7 (3.9)	29 (8.3)	0.82	9 (4.5)	16 (6.9)	0.40
Laboratory results						
NT-proBNP, pg/mL	1,917.0 (740.7-4,538.2)	2,228.5 (855.8-5,930.4)	0.35[b]	2,484.0 (1,084.4-9,209.2)	1,824.0 (819.1-4,918.7)	0.054[b]

Values are n (%) or median (interquartile range). [a]Cumulative event rates were calculated using Kaplan-Meier estimator. [b]The Wilcoxon rank test was used for skewed continuous variables.

Abbreviations as in Table 1.

randomized controlled COAPT and MITRA-FR trials on outcomes among patients with relevant SMR undergoing M-TEER. Therefore, the respectively adapted inclusion and exclusion criteria of both trials were applied to a large European registry. The main findings are as follows: 1) in contrast to the inclusion and exclusion criteria used for the MITRA-FR trial, those used for the COAPT trial seem to adequately identify patients with superior survival after M-TEER; and 2) intraindividual significant symptomatic benefit was found in a subset of patients with available information regarding NYHA functional class, quality of life, and 6-minute walk distance, irrespective of COAPT eligibility status.

This is the largest study applying adapted COAPT and the first simultaneously applying MITRA-FR inclusion and exclusion criteria to a real-world M-TEER cohort. Regarding the COAPT analysis, in comparison with previously published analysis from a single-center retrospective study (Cologne, Germany) and a multicenter analysis (Italian/Portuguese), the lowest proportion of COAPT-eligible patients was found in our registry (n = 353 of 1,022 [34.5%] vs n = 62 of 122 [50.8%] in the Cologne study vs n = 197 of 304 [64.8%] in the Italian/Portuguese study) (17,19). All centers also participate in the EuroSMR registry, and at least a subset of previously analyzed patients were included in the present analysis. The discrepancy in the proportion of COAPT-eligible patients in all 3 cohorts is presumably attributable to the application of varying key inclusion and exclusion criteria of the COAPT trial, resulting in different approximations of the true percentage of patients eligible for the COAPT trial.

Despite a carefully executed translational application of the respective trial enrollment criteria on a real-world cohort of patients with SMR, noteworthy differences in baseline characteristics compared with the intervention arm of the original trials were present (Supplemental Table 7). It is essential to highlight that COAPT-eligible patients had smaller LV dimensions compared with patients in the original trial. MITRA-FR-eligible patients likewise had smaller LV end-diastolic volumes than patients in the original trial (114.1 ± 41.0 mL/m^2 among MITRA-FR-eligible patients vs 136.2 ± 37.4 mL/m^2 in the original trial).

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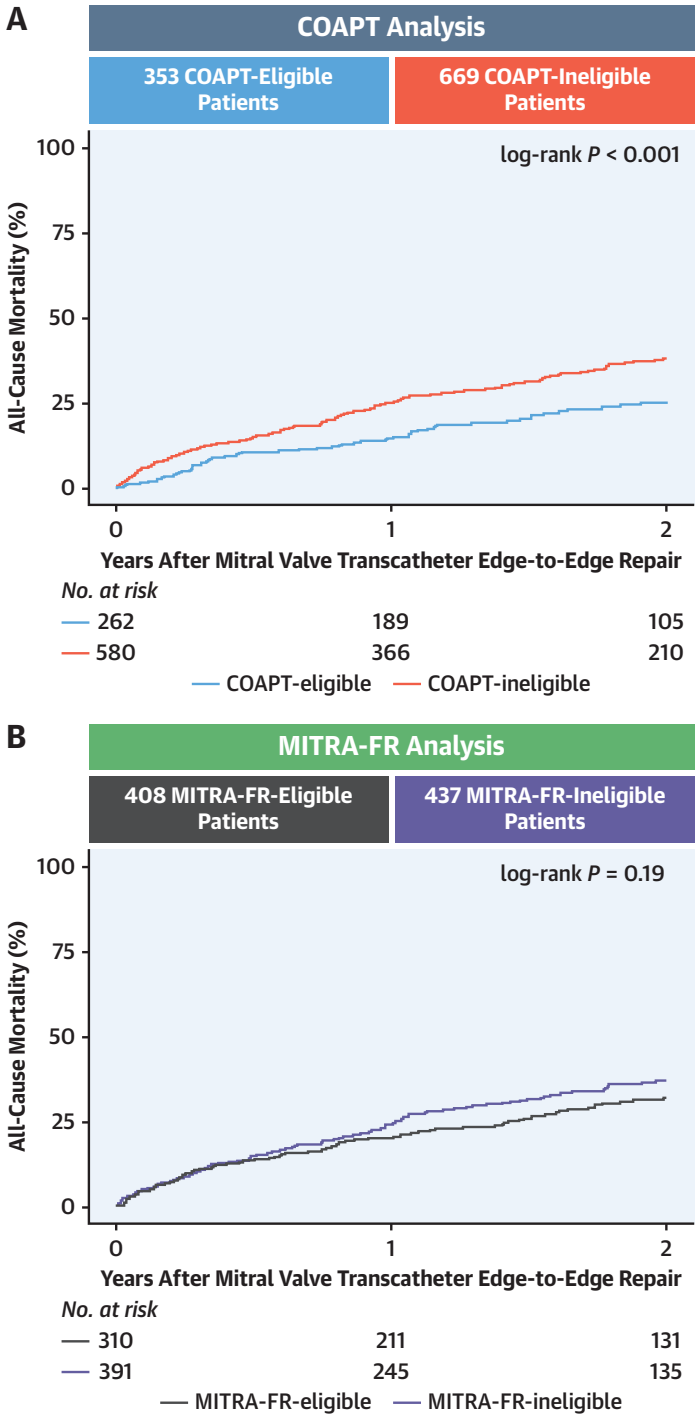
CENTRAL ILLUSTRATION **Outcomes Stratified by Adapted Inclusion Criteria**



Koell, B. et al. J Am Coll Cardiol. 2021;78(24):2408-2421.

Outcomes were examined in 2 independent analyses: COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) analysis **(left)** and MITRA-FR (Percutaneous Repair or Medical Treatment for Secondary Mitral Regurgitation) analysis **(right)**. Although the application of adapted COAPT criteria resulted in successful identification of patients with lower mortality rates (Kaplan-Meier analysis for all-cause mortality within 2 years; **A**), stratification according to adapted MITRA-FR criteria determined groups with comparable outcomes **(B)**.

TABLE 3 Univariable and Multivariable Cox Regression Analysis of All-Cause Mortality in 2 Years for the COAPT-Analysis

		Univariable Cox Regression		Multivariable Cox Regression	
	n	HR (95% CI)	*P* Value	Multivariable HR (95% CI)	*P* Value
COAPT status					
COAPT-eligible	842	0.60 (0.45-0.81)	<0.001		
COAPT inclusion criteria					
TAPSE ≥15 mm	786	0.62 (0.48-0.81)	<0.001	0.95 (0.61-1.48)	0.82
Baseline TR ≤2+	834	0.81 (0.61-1.08)	0.16		
PASP ≤70 mm Hg	756	1.67 (0.88-3.14)	0.11		
LVEF 20%-50%	838	0.71 (0.51-0.98)	0.039	0.57 (0.34-0.98)	0.041
LVESD ≤70 mm	731	0.90 (0.56-1.44)	0.66		
Sociodemographic					
Age, y	841	1.02 (1.00-1.03)	0.018	1.01 (0.99-1.03)	0.26
Male	841	0.97 (0.74-1.27)	0.81		
Comorbidities					
eGFR ≤60 mL/min/1.73 m^2	791	1.63 (1.18-2.25)	0.003	1.27 (0.77-2.09)	0.36
History of atrial fibrillation	842	1.38 (1.05-1.81)	0.019	1.34 (0.87-2.06)	0.18
Clinical presentation					
NYHA functional class IV	838	1.85 (1.43-2.40)	<0.001	2.29 (1.53-3.42)	<0.001
Log NT-proBNP, pg/mL	488	1.44 (1.26-1.66)	<0.001	1.47 (1.24-1.75)	<0.001
Echocardiographic parameters					
RV-PA coupling, mm/mm Hg	708	0.21 (0.08-0.52)	<0.001	0.10 (0.02-0.57)	0.009
Effective regurgitant orifice area ≥40 mm^2	679	0.94 (0.68-1.31)	0.71		
LVEDVi, mL/m^2	795	1.00 (1.00-1.00)	0.63		
LVEF, %	838	0.99 (0.98-1.00)	0.13		

Variables with *P* values <0.05 in univariable logistic regression for all-cause mortality were chosen for further multivariable analysis. COAPT-eligible patients were excluded for the multivariable analysis.

CI = confidence interval; HR = hazard ratio; LVEDVi = left ventricular end-diastolic volume index; LVESD = left ventricular end-systolic diameter; MR = mitral regurgitation; PASP = pulmonary artery systolic pressure; TR = tricuspid regurgitation; other abbreviations as in Table 1.

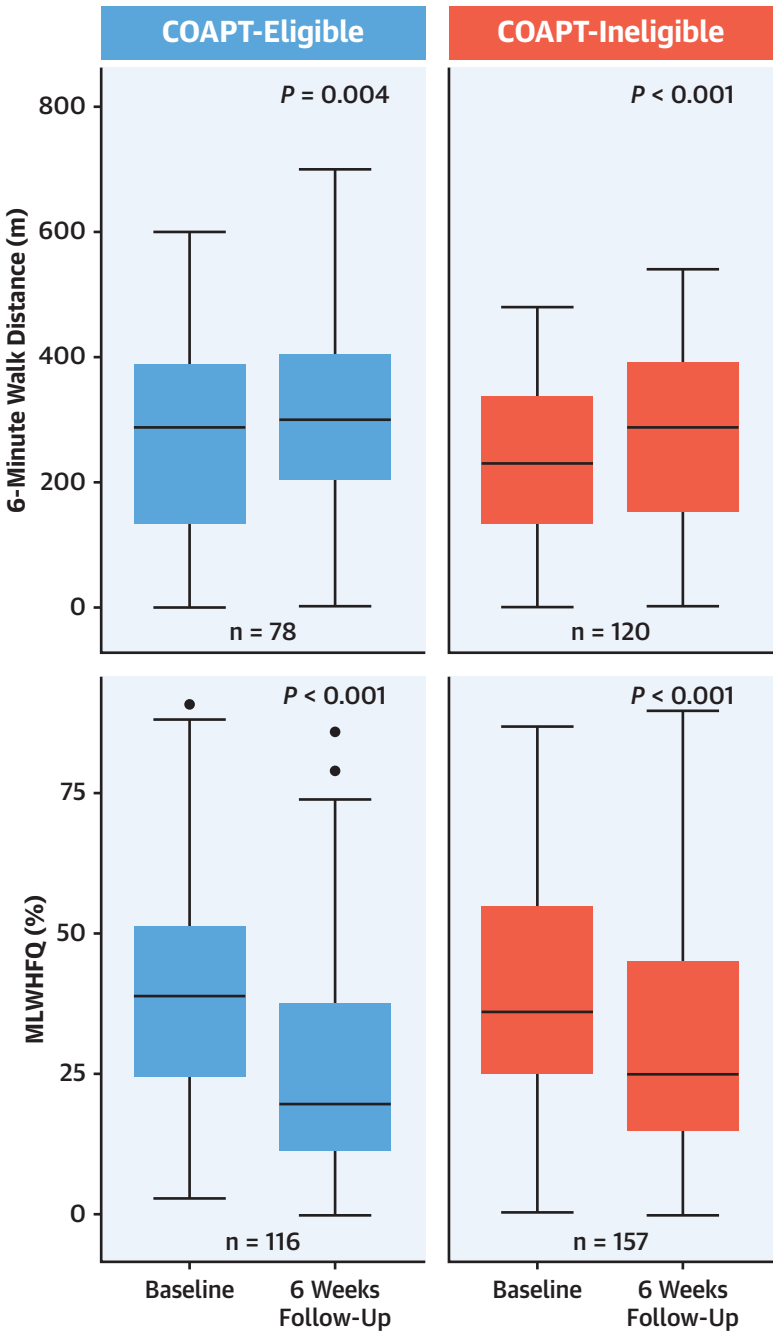
Even more crucially, the retrospective application of adapted enrollment criteria conversely resulted in diametrically opposing EROA values (median EROA 0.32 ± 0.20 cm^2 among COAPT-eligible patients vs 0.41 ± 0.15 cm^2 in the original COAPT trial; 0.41 ± 0.32 cm^2 among MITRA-FR-eligible patients vs 0.31 ± 0.10 cm^2 in the original MITRA-FR trial).

COAPT VERSUS MITRA-FR AND TRANSLATIONAL PERSPECTIVES TO THIS COHORT. The randomized controlled COAPT trial demonstrated superiority of M-TEER and guideline-directed medical therapy for relevant SMR compared with guideline-directed medical therapy alone (5), whereas the MITRA-FR trial failed to show significant benefits (6). Hence, it could conceivably be hypothesized that these differences may partly be explained by divergent inclusion and exclusion criteria used in both studies.

Both studies represent highly selected patient cohorts: during the 1,640 days of enrollment for the COAPT trial, merely 614 of 1,576 screened patients (38.9%) at 78 Canadian and U.S. centers were randomized (1.75 patients per center and year); in MITRA-FR, 304 of 452 screened patients (67.2%) were randomized during an enrollment period of 1,217 days at 37 sites in France (2.46 patients per center and year). There is ongoing discussion about the applicability of the divergent results of the MITRA-FR and COAPT trials with respect to advocating that patients undergo M-TEER for relevant SMR (20,21).

To reconcile the divergent findings, the concept of disproportionate MR was introduced by Grayburn et al (22), distinguishing between proportionate and disproportionate MR on the basis of whether MR is greater than expected by end-diastolic volumes. In addition, no convincing explanation was found after regurgitant volume-based patient stratification in an analysis comparing the mean echocardiographic results in both the MITRA-FR and COAPT trials, questioning the concept of EROA/LV end-diastolic volume-based proportionality (23). A subsequent analysis of this particular concept in the EuroSMR registry could not confirm the EROA/LV end-diastolic volume ratio as a predictor of patient outcomes (24). In line with this, a subanalysis of the MITRA-FR trial

FIGURE 3 Functional Outcome According to COAPT Status



Clinical presentation at baseline and follow-up according to COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) status and determined by 6-minute walk distance (COAPT-eligible, n = 78; COAPT-ineligible, n = 120) and Minnesota Living With Heart Failure Questionnaire (MLWHFQ) (n = 116 and n = 157, respectively).

was not able to identify a subset of patients with superior outcomes after M-TEER, irrespective of echocardiographic MR or LV parameters or the combination thereof (25).

In the context of a retrospective analysis and in the absence of a control cohort, it seems crucial for all analyses and subsequent interpretations that our data cannot prove an overall survival benefit of M-TEER.

Accordingly, the survival benefit of COAPT-eligible compared with COAPT-ineligible patients is not to be equated with the results of the original COAPT trial. In contrast to those used in MITRA-FR, the application of adapted COAPT criteria in this cohort allowed simple and reliable prognostic stratification and, therefore, is in line with the current recommendations of the joint position European statement (12).

Comparing the respective inclusion and exclusion criteria used in both trials, noteworthy differences are present. Apart from LV ejection fraction and NYHA functional class, MITRA-FR criteria focused on the severity of MR by using EROA and regurgitant volume cutoffs for inclusion. In contrast, the COAPT criteria took RV dysfunction, pulmonary artery systolic pressure, and tricuspid regurgitation severity into account. Apart from NYHA functional class IV and logarithmic N-terminal pro-brain natriuretic peptide, our multivariable Cox regression analysis emphasizes the prognostic importance of RV function and the absence of pulmonary hypertension by identifying RV-PA coupling as an independent predictor of outcome. In a direct comparison, the COAPT trial considered even physical evidence of right-sided congestive heart failure with echocardiographic evidence of moderate or severe RV dysfunction as an exclusion criterion. In MITRA-FR, no RV functional parameter was regarded for trial enrollment, and only pulmonary artery systolic pressure and tricuspid regurgitation grade were collected within the course of the study. It is warranted that RV function and associated parameters might deserve more attention in future M-TEER outcome studies.

Long-standing relevant SMR drives adverse remodeling and is associated with an increase in left atrial size, a decrease in RV function, and the development of tricuspid regurgitation (26). By applying adapted COAPT criteria, a subset of patients with smaller LV diameters, preserved RV function, and absence of relevant tricuspid regurgitation were successfully identified. Subsequently, these COAPT-eligible patients are characterized by lower values of N-terminal pro-brain natriuretic peptide and superior NYHA functional class (27). Whether adapted COAPT criteria identify a subset of patients in an earlier stage of MR or a specific phenotype remains uncertain. Taking the natural history of SMR with its potential risk for subsequent RV dysfunction into account, the question of the optimal timing for M-TEER prevails.

SYMPTOMATIC BENEFITS. As demonstrated before, M-TEER holds the potential to significantly improve functional status as assessed by 6-minute walk distance (28,29) and symptom burden as assessed by NYHA functional class (2), even in critically ill, decompensated patients (30). Considering the safety profile of M-TEER, our data are in line with a recent European position paper on SMR emphasizing that this therapeutic approach should not be offered solely on the basis of COAPT eligibility criteria, but heart team adjudication may also focus on symptomatic relief in selected patients (12). Previously published registry data indicate that symptomatic benefit can be expected in a large proportion of patients undergoing M-TEER (2,31). For the subset of patients with the respective data on functional status, this analysis demonstrated symptomatic alleviation, irrespective of COAPT eligibility status. Therefore, it seems justified not to withhold M-TEER in symptomatic candidates identified as suitable and appropriate for interventional treatment by heart team consensus.

STUDY LIMITATIONS. By applying adapted inclusion and exclusion criteria to a retrospective real-life cohort, important inherent limitations must be taken into account, and findings should be interpreted with caution and can only be hypothesis generating. Of the criteria published in the COAPT trial, sufficient data in the registry are available only for a limited number of items. It seems to be particularly worth emphasizing that a control group for COAPT-ineligible patients is lacking, and their potential prognostic benefit after M-TEER cannot be judged on the basis of the available data. In addition, corrected N-terminal pro-brain natriuretic peptide was not used to stratify patients in the present analysis, as it was a combined criterion in the original COAPT trial: rehospitalization for heart failure within the previous 12 months and/or corrected N-terminal pro-brain natriuretic peptide ≥1,500 pg/mL. Furthermore, the comparability with the original trials may be biased, as COAPT included only patients in whom medical therapy had already failed, as adjudicated by an eligibility committee. In our analysis, no information about the duration of guideline-directed medical therapy or the daily dose was available. As this patient population has not been examined in randomized controlled trials, further data are warranted. Diametrical EROA and LV diameters of the COAPT and MITRA-FR analysis compared with the respective original trials may restrict comparability. However, neither EROA nor LV diameters were identified as independent predictors of outcomes in the performed Cox regression analysis. Data on functional outcome (ie, 6-minute walk distance and MLHFQ score) were available in only a modest proportion of patients. Therefore all results on functional outcome must be interpreted with caution.

CONCLUSIONS

In contrast to those used in MITRA-FR, adapted COAPT enrollment criteria appear to adequately identify a specific phenotype of patients with SMR with lower mortality rates following M-TEER. The retrospective application of adapted COAPT enrollment criteria in this real-world cohort enabled adequate prognostic stratification and, thus, conceivably contributes to future patient selection for M-TEER.

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Dr Orban has received speaker honoraria from Abbott Medical. Dr Kalbacher has received speaker honoraria from Abbott Medical and Edwards Lifesciences; has received travel expenses from Abbott Medical and Edwards Lifesciences; and has received proctor fees from Edwards Lifesciences. Dr Hausleiter has received speaker honoraria from Abbott Medical. Dr Pfister has received speaker honoraria and travel expenses from Abbott Medical. Dr Baldus has received speaker honoraria from Abbott Medical and Edwards Lifesciences; and has received research grants from Abbott Medical. Dr Lubos has received speaker honoraria, travel expenses, and research grants from Abbott Medical. Dr Lurz has received speaker honoraria from Abbott Medical; and has received consultant fees from Abbott Medical and Edwards Lifesciences. Dr Karam has received consultant fees from Abbott Medical. Dr Iliadis has received consultant fees from Abbott Medical and Edwards Lifesciences; and has received travel expenses from Abbott Medical. Dr Petrescu has received consultant fees and research grants from Abbott Medical. Dr Metra has received consultant fees from Abbott Medical; and has received speaker honoraria from Edwards Lifesciences. Dr Windecker has received research grants from Abbott Medical and Edwards Lifesciences. Dr Ludwig has received travel expenses from 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: The criteria for inclusion of participants in the COAPT and MITRA-FR trials differed, which may explain the disparate outcomes of these studies. The available data support the use of M-TEER in a substantial proportion of patients with symptomatic SMR.

TRANSLATIONAL OUTLOOK: The association of indexes of RV function with clinical outcomes warrants further study in patients undergoing catheter-based interventions for MR.

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KEY WORDS edge-to-edge repair, secondary mitral regurgitation, transcatheter mitral valve repair

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