Transcatheter Edge-to-Edge Repair in Proportionate Versus Disproportionate Functional Mitral Regurgitation

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Background: Functional mitral regurgitation (FMR) can be subclassified on the basis of its proportionality relative to left ventricular (LV) volume and function, indicating potential differences in underlying etiology. The aim of this study was to evaluate the association of FMR proportionality with FMR reduction, heart failure hospitalization and mortality after transcatheter edge-to-edge mitral valve repair (TEER).

Methods: This multicenter registry included 241 patients with symptomatic heart failure with reduced LV ejection fraction treated with TEER for moderate to severe or greater FMR. FMR proportionality was graded on preprocedural transthoracic echocardiography using the ratio of the effective regurgitant orifice area to LV end-diastolic volume. Baseline characteristics, follow-up transthoracic echocardiography, and 2-year clinical outcomes were compared between groups.

Results: Median LV ejection fraction, effective regurgitant orifice area and LV end-diastolic volume index were 30% (interquartile range [IQR], 25%–35%), 27 mm^2, and 107 mL/m^2 (IQR, 90–135 mL/m^2), respectively. Median effective regurgitant orifice area/LV end-diastolic volume ratio was 0.13 (IQR, 0.10–0.18). Proportionate FMR (pFMR) and disproportionate FMR (dFMR) was present in 123 and 118 patients, respectively. Compared with patients with pFMR, those with dFMR had higher baseline LV ejection fractions (median, 32% [IQR, 27%–39%] vs 26% [IQR, 22%–33%]; $P < .01$). Early FMR reduction with TEER was more pronounced in patients with dFMR (odds ratio, 0.45; 95% CI, 0.28–0.74; $P < .01$) than those with pFMR, but not at 12 months (odds ratio, 0.93; 95% CI, 0.53–1.63; $P = .80$). Overall, in 35% of patients with initial FMR reduction after TEER, FMR deteriorated again at 1-year follow-up. Rates of 2-year all-cause mortality and heart failure hospitalization were 30% ($n = 66$) and 37% ($n = 76$), with no differences between dFMR and pFMR.

Conclusions: TEER resulted in more pronounced early FMR reduction in patients with dFMR compared with those with pFMR. Yet after initial improvement, FMR deteriorated in a substantial number of patients, calling into question durable mitral regurgitation reductions with TEER in selected patients. The proportionality framework may not identify durable TEER responders. (J Am Soc Echocardiogr 2022;35:105-15.)

Keywords: Functional mitral regurgitation, Edge-to-edge mitral valve repair, Heart failure

Transcatheter edge-to-edge mitral valve repair (TEER) for functional mitral regurgitation (FMR) remains a subject of controversy.[1] In FMR, mitral valve incompetence is the result of structural and functional abnormalities of the left ventricle, and the mitral valve remains relatively intact. Currently, (medical) therapies for FMR are directed to reduce or reverse left ventricular (LV) remodeling.[2]

Two randomized controlled trials investigating percutaneous mitral valve repair with TEER for FMR in patients with heart failure (HF) and reduced ejection fraction produced conflicting results in terms of mortality and hospitalizations for HF.[3,4] FMR (dis)proportionality is a conceptual framework that may reconcile these data.[5] In disproportionate FMR (dFMR), the amount of mitral regurgitation (MR) as determined by quantitative echocardiographic parameters is larger than would be expected from the LV volumes and ejection fraction. The expected FMR is referred to as proportionate FMR (pFMR). dFMR was more frequent in Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation (COAPT) and pFMR in the Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation (MITRA-FR).[5] TEER improved clinical outcomes only in the COAPT trial, suggesting that TEER was particularly effective in the context of dFMR.[6]

Recently, we performed a small cohort study examining impact of FMR proportionality on TEER outcomes in patients with HF with reduced LV ejection fraction (LVEF) and demonstrated that more clips were required in patients with dFMR compared with those with pFMR.[7] However, the proportionality concept proved challenging, with large margins of error. The present multicenter study complements the previous small single-center cohort, with the aim of investigating the associations between FMR proportionality and FMR reduction, HF hospitalization, and mortality after TEER.

METHODS

In this retrospective, multicenter, observational cohort study, we evaluated FMR proportionality and clinical outcomes in consecutive symptomatic patients with HF and reduced LVEF who had moderate to severe or greater FMR and underwent TEER using the MitraClip device (Abbott Vascular, Santa Clara, CA).

At each of the six participating centers, a multidisciplinary heart team including imaging specialists, HF specialists, interventional cardiologists, cardiac surgeons, and geriatricians evaluated the clinical setting, comorbidities, frailty status, and echocardiograms to determine the indication for TEER by consensus. Patients with moderate to severe or greater FMR, as determined by multiparametric echocardiographic evaluation,[8] were considered eligible for TEER if HF symptoms persisted despite optimal HF therapy[2] and TEER was technically feasible. Procedures were performed according to device-specific instructions for use under general anesthesia and with transesophageal echocardiographic guidance. Written informed consent for TEER and subsequent data analysis for research purposes was provided by every patient.

All patients with HF with reduced ejection fraction and FMR aged ≥18 years who underwent TEER were retrospectively collected in a joint database. Exclusion criteria were previous mitral valve repair (either surgical or percutaneous), previous mitral valve replacement or heart transplantation, untreated clinically significant coronary artery disease requiring revascularization, LVEF > 55%,[9] the presence of other structural heart disease causing HF (i.e., hypertrophic cardiomyopathy, restrictive cardiomyopathy, and constrictive pericarditis), and uncontrolled arterial hypertension (systolic blood pressure at baseline > 180 mm Hg). Patient demographics, baseline comorbidities, echocardiographic parameters, and procedural data were collected. Clinical and echocardiographic follow-up was organized within the first months after discharge and at 1 year. Mortality up to 2 years was collected through clinical follow-up and contact with referring and general practitioners and complemented with a survival check in the municipal civil registry of the Netherlands. The study was conducted in accordance with the principles of the Declaration of Helsinki and did not fall under the scope of the Medical Research Involving Human Subjects Act as determined by the Erasmus University Medical Center institutional review board (EMC-2020-0678).

The primary end point was FMR reduction (by at least one grade) after TEER on the first available postprocedural transthoracic echocardiographic examination. Secondary end points were FMR on transthoracic echocardiography (TTE) at 12 months, 2-year all-cause mortality, and hospitalization for HF defined per Mitral Valve Academic Research Consortium criteria.[10] Technical success was also defined per Mitral Valve Academic Research Consortium criteria.

Echocardiographic Assessment

TTE was performed using commercially available equipment. Two-dimensional LVEF was assessed using guideline recommendations from the American Society of Echocardiography.[9] FMR was evaluated using a multiparametric integrative approach of both qualitative

HIGHLIGHTS

- Transcatheter treatment of FMR is a subject of debate.
- Proportionality of EROA to LV volumes could influence the outcome of TEER.
- Disproportionate mitral regurgitation showed greater reduction after TEER.
- A substantial part of initial FMR reduction deteriorated during follow-up.
- Clinical outcomes at 2 years did not differ between different proportionality groups.

and quantitative parameters and graded on a five-class grading scale (none, mild, moderate, moderate to severe, and severe). Main quantitative parameters were effective regurgitant orifice area (EROA; acquired using the proximal isovelocity surface area method) and regurgitant fraction (RF).[8,11] Regurgitant volume (RegVol) was derived from EROA and the mitral velocity-time integral. Reduction in FMR was evaluated by comparing baseline TTE, postprocedural TTE, and TTE at 12 months. The first available postprocedural transthoracic echocardiographic study was performed within 3 months after the index procedure. Patients who underwent redo TEER or surgical mitral valve repair during follow-up were scored as having severe MR at the time of the redo procedure. All echocardiographic parameters were site reported.

Assessment of FMR Proportionality

FMR severity was verified using the RF. Baseline $RF \geq 50\%$ was considered to indicate severe FMR, while $RF < 35\%$ was considered to indicate nonsevere FMR and was excluded from further analysis.[5,12] Subsequently, the ratio of EROA to LV end-diastolic volume (LVEDV) was calculated for each individual patient. After extended testing including different EROA/LVEDV ratios, the median EROA/LVEDV ratio provided an equal distribution and was selected to determine (dis)proportionality. An EROA/LVEDV ratio greater than or equal to the median value was considered disproportionate. Additionally, in a second analysis, the RegVol/LVEDV ratio was used to determine (dis)proportionality, with values greater than or equal to the median graded as dFMR.

Statistical Analysis

Continuous variables are presented as mean $\pm$ SD if normally distributed. Medians and interquartile ranges (IQRs) are provided for variables not normally distributed. Normality was tested using the Kolmogorov-Smirnov test. Differences in mean values of normally distributed continuous variables between independent groups were analyzed using unpaired t tests. For differences in pre- and postprocedural, normally distributed, continuous variables, paired t tests were used. Mann-Whitney U tests were used for variables that were not normally distributed. Nominal data are presented as numbers and percentages and were compared using either the Pearson χ^2 or Fisher exact test for unpaired data or the McNemar test for paired data.

FMR reduction was compared between patients with dFMR and those with pFMR (independent variable) using cumulative linked mixed models to account for the ordinal nature of the dependent variable. Difference in FMR grade (pre- vs postprocedural) was the

dependent variable, adjustment for year of procedure was performed, and random effects were used to take into account clustering per study site. A separate analysis was performed in subgroups according to LVEF. Associations between dFMR and pFMR and all-cause mortality and HF hospitalization within 2 years of the index procedure were evaluated using Cox proportional hazards models. Here, a grouped jackknife variance estimator was used to take into account clustering per study site. Models were adjusted for age, sex, ischemic cardiomyopathy, stroke or transient ischemic attack, and the presence of an implantable cardioverter-defibrillator.[2] Results are reported as hazard ratios with 95% CIs. Subgroup analysis was performed for categories of LVEF. Additionally, to account for semicompeting risks, a composite end point of mortality and HF hospitalization (nonterminal event) was tested using a win-loss approach calculating the unmatched win ratio.[13,14] Improvement in New York Heart Association functional class at 1 year in the surviving population was assessed using Pearson χ^2 analysis. Analyses of FMR grade difference and clinical outcomes were conducted for both EROA/LVEDV- and RegVol/LVEDV-determined (dis)proportionality. A two-sided P value of $<.05$ was considered to indicate statistical significance. Statistical analyses were performed using SPSS version 25.0 (IBM, Armonk, NY) and R (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

A total of 323 patients who underwent TEER between 2011 and 2019 at six centers in Belgium and the Netherlands were included in this registry. Incomplete echocardiographic studies at baseline precluded proportionality determination in 49 patients (15%; Supplemental Figure 1). On the basis of RF, another 33 patients had less than moderate to severe FMR and were also excluded from further analysis. The final cohort comprised a total of 241 patients with FMR. The median age was 72 years (IQR, 66–78 years), 70.5% were men, and 18.3% had received cardiac resynchronization therapy (Table 1). Ischemic cardiomyopathy was the underlying cause of HF in 68.5%. Median QRS duration in the overall cohort was 130 msec (IQR, 110–166 msec), and left bundle branch block (LBBB) at baseline was present in 115 patients (48.3%), of whom 29 had coexisting pacemakers and 38 had received cardiac resynchronization therapy. Renin-angiotensin system antagonists, β-blockers, angiotensin receptor–neprilysin inhibitors, mineralocorticoid-receptor antagonists, and diuretics were prescribed in 70.5%, 80.5%, 7.1%, 54.4%, and 90.9% of patients, respectively. The median EROA/LVEDV ratio was 0.13 (IQR, 0.10–0.18). dFMR and pFMR were found in 123 and 118 patients, respectively. Significant differences between dFMR and pFMR were observed for sex, stroke or transient ischemic attack, peripheral vascular disease, atrial fibrillation, and presence of an implantable cardioverter-defibrillator. Baseline QRS duration and LBBB did not differ between proportionality groups. Additionally, HF medication use at baseline was similar between the dFMR and pFMR cohorts.

Baseline echocardiographic parameters are displayed in Table 2. Overall median LVEF was 30% (IQR, 25%–35%), median LVEDV index was 107 mL/m^2 (IQR, 90–135 mL/m^2), median EROA was 27 mm^2 (IQR, 21–36 mm^2), and median mitral RegVol was 41 mL (IQR, 32–52 mL). Patients with dFMR had higher LVEFs, less dilated left ventricles, increased FMR severity, and increased RegVol at baseline compared with the pFMR group. No differences were found in

Table 1 Baseline characteristics

	Total group (N = 241)	dFMR (n = 123)	pFMR (n = 118)	P
Age, y	72 (66–78)	73 (66–79)	72 (66–77)	.23
Gender, male	170 (70.5)	78 (63.4)	92 (78.0)	.01
Hypertension	132 (54.8)	67 (54.5)	65 (55.1)	.87
Diabetes mellitus	67 (27.8)	32 (26.0)	35 (29.7)	.53
Stroke/TIA	31 (12.9)	10 (8.1)	21 (17.8)	.03
Peripheral vascular disease	42 (17.4)	14 (11.4)	28 (23.7)	.01
COPD	40 (16.6)	21 (17.1)	19 (16.1)	.84
Previous myocardial infarction	144 (59.8)	67 (54.5)	77 (65.3)	.09
Ischemic cardiomyopathy	165 (68.5)	77 (62.6)	88 (74.6)	.06
Previous non–mitral valve surgery	13 (5.4)	9 (7.3)	4 (3.4)	.26
Previous TAVI	4 (1.7)	1 (0.8)	3 (2.5)	.36
Atrial fibrillation	131 (54.4)	75 (61.0)	56 (47.5)	.04
Cardiac resynchronization therapy	44 (18.3)	17 (13.8)	27 (22.9)	.07
Implantable cardioverter-defibrillator	103 (42.7)	42 (34.1)	61 (51.7)	.01
eGFR ≤ 35 mL/min	83 (34.4)	40 (32.5)	43 (36.4)	.58
Creatinine clearance, mL/min	44 ± 18	47 ± 19	42 ± 18	.08
NT-proBNP baseline, pmol/L	1,332 (400–4,447)	1,569 (489–3,812)	799 (298–4,645)	.34
NYHA functional class				.44
II	29 (12.0)	18 (14.6)	11 (9.3)	
III	151 (62.7)	74 (60.2)	77 (65.3)	
IV	61 (25.5)	31 (25.2)	30 (25.4)	
STS-PROM	2.7 (1.5–5.6)	2.4 (1.4–5.4)	3.4 (1.7–6.3)	.25
Conduction parameters				
QRS duration, msec	130 (110–166)	126 (106–164)	130 (111–170)	.12
LBBB*	115 (48.3)	54 (44.6)	61 (52.1)	.25
HF medications				
Renin-angiotensin system antagonist	170 (70.5)	83 (67.5)	78 (73.7)	.29
β-blocker	194 (80.5)	95 (77.2)	99 (83.9)	.19
Neprilysin inhibitor	17 (7.1)	7 (5.7)	10 (8.5)	.40
Mineralocorticoid receptor antagonist	131 (54.4)	67 (54.5)	64 (54.2)	.97
Any diuretic	219 (90.9)	111 (90.2)	108 (91.5)	.73

Data are expressed as median (IQR), number (percentage), or mean ± SD.

COPD, Chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *NT-proBNP*, N-terminal pro–brain natriuretic peptide; *NYHA*, New York Heart Association; *STS-PROM*, Society of Thoracic Surgeons Predicted Risk of Mortality; *TAVI*, transcatheter aortic valve replacement; *TIA*, transient ischemic attack.

*This includes patients with permanent LV pacing.

left atrial size. Moderate or greater tricuspid regurgitation was more prevalent in the dFMR group.

All patients received at least one MitraClip, and technical success was achieved in 96% of patients (*n* = 231). No significant differences between the dFMR and pFMR groups were observed for either number of clips or technical success. Conversion to surgery occurred in two patients with dFMR. Postprocedural transthoracic echocardiographic data are displayed in Table 3. The first available TTE after TEER was performed within 3 months of discharge in 99.6% of patients. Overall, FMR severity decreased by at least one grade in 91.2%, and postprocedural severe mitral stenosis (mean gradient > 10 mm Hg) occurred in 1.7% (*n* = 4). The dFMR cohort demonstrated a larger reduction in MR by first transthoracic echocardio-

graphic assessment after clipping (odds ratio [OR], 0.45; 95% CI, 0.28–0.74; *P* < .01; Figure 1). To clarify, the difference between pre- and postprocedural FMR grade was expressed as an ordinal variable. The OR of 0.45 denotes a greater FMR reduction in the dFMR group relative to the pFMR group, which was considered the reference. Analysis in subgroups of LVEF < 40% versus ≥40% showed similar effects. Twelve-month follow-up TTE was available in 167 of 199 alive patients (84%), and 1-year follow-up transthoracic echocardiographic findings are reported in Table 3. Changes in FMR severity in the dFMR and pFMR cohorts are displayed in Figure 2. Contrary to postprocedural TTE, there was no longer a significant difference in FMR reduction at 12 months (vs baseline) between proportionality groups (OR, 0.93; 95% CI, 0.53–1.63; *P* = .80).

Table 2 Baseline echocardiographic parameters

	Total group (N = 241)	dFMR (n = 123)	pFMR (n = 118)	P
Systolic blood pressure	116 (101–128)	117 (102–130)	113 (100–126)	.42
LVEF, %	30 (25–35)	32 (27–39)	27 (22–33)	<.01
LVESV, mL	139 (110–190)	120 (82–150)	173 (136–224)	<.01
LVEDV, mL	209 (167–264)	176 (135–220)	243 (201–300)	<.01
LVEDV index, mL/m^2	107 (90–135)	97 (72–111)	124 (102–154)	<.01
LVEDD, mm	65 ± 10	61 ± 9	68 ± 10	<.01
LVESD, mm	54 (48–63)	52 (43–58)	58 (51–67)	<.01
LA dimension index, mm/m^2	27 ± 4	27 ± 4	27 ± 4	.40
MR grade				<.01
Moderate to severe	61 (25.3)	8 (6.5)	53 (44.9)	
Severe	180 (74.7)	115 (93.5)	65 (55.1)	
EROA, mm^2	27 (21–36)	34 (25–41)	23 (19–29)	<.01
MR VTI, cm	151 ± 33	147 ± 35	156 ± 31	.04
Mitral RegVol, mL	41 (32–52)	48 (35–57)	37 (28–44)	<.01
Aortic stenosis moderate or greater	4 (1.7)	2 (1.6)	2 (1.7)	.99
Aortic regurgitation moderate or greater	8 (3.3)	3 (2.4)	5 (4.2)	.72
TR moderate or greater	90 (37.3)	56 (45.5)	34 (28.8)	.01
Peak TR gradient, mm Hg*	37 (28–48)	37 (28–48)	36 (28–48)	.93
TAPSE, cm†	1.5 (1.3–1.9)	1.5 (1.2–1.8)	1.6 (1.2–2.0)	.16

Data are expressed as median (IQR), mean ± SD, or number (percentage).
LA, Left atrial; *LVEDD*, LV end-diastolic diameter; *LVESD*, LV end-systolic diameter; *LVESV*, LV end-systolic volume; *TR*, tricuspid regurgitation; *VTI*, velocity-time integral.
*Available in 115 of 123 patients with dFMR and 101 of 118 patients with pFMR.
†Available in 76 of 123 patients with dFMR and 72 of 118 patients with pFMR.

At 12 months, 27 of 167 patients (16.1%) did not show any FMR improvement. These nonresponders had lower rates of ischemic cardiomyopathy and less severe baseline FMR and more often LBBB (Supplemental Tables 1A–1C). Nonresponse rates were similar between proportionality groups (14 of 84 vs 13 of 83 in the dFMR and pFMR groups, respectively, *P* = .86). Of note, 70% of nonresponders at 12 months (19 of 27) had initial FMR improvement by first postprocedural TTE.

Overall, in 58 of 167 patients with 12 month TTE (35%), FMR had worsened in comparison with first TTE after TEER. This included nine patients who underwent redo mitral valve repair. Frequency of FMR deterioration did not differ between the dFMR and pFMR groups (31 of 84 vs 27 of 83, *P* = .55). In 93% of patients who deteriorated between postprocedural and 12 month TTE (54 of 58), initial FMR improvement was present at first postprocedural TTE. This corresponds to 35% (54 of 156; Supplemental Table 2) of patients experiencing decrements of FMR despite initial improvement (delayed deterioration) after TEER, with no difference between proportionality groups (29 of 84 vs 25 of 83, *P* = .54). Residual FMR at 12 months was moderate or less in 44% of these patients (24 of 54).

Data on clinical outcomes at 2-year follow-up are shown in Table 4 and Supplemental Figure 2. A total of 33 patients (13.7%) were lost to follow-up. Overall, 2-year all-cause mortality was 30.4% (*n* = 66), while HF hospitalization within 2 years of the index procedure occurred in 37.3% (*n* = 76). No significant differences were found when comparing mortality, HF hospitalization, the composite of mortality and HF hospitalization, and the composite of mortality, LV assist device implantation, and heart transplantation between the dFMR

and pFMR groups at 2-year follow-up (Table 4, Supplemental Figure 2, Supplemental Table 3). Separate analysis with correction for LVEF showed similar findings (Supplemental Tables 4). To quantify any potential heterogeneity between sites, we performed sensitivity analyses including a frailty term (random effect) in the Cox model instead of the jackknife estimator. The results showed that there was no significant heterogeneity among the sites, although we must acknowledge the limited sample size from each individual site. New York Heart Association functional class at 1-year follow-up had improved by at least one class in 68 of 88 (77%) and 58 of 89 (65%) patients in the dFMR and pFMR groups, respectively (*P* = .08).

RegVol/LVEDV Ratio–Derived Proportionality

The median RegVol/LVEDV ratio was 0.20 (IQR, 0.14–0.27). RegVol/LVEDV ratio–derived dFMR (RVdFMR) and pFMR (RVpFMR) were found in 120 and 121 patients, respectively. The median baseline LVEF was 34% (IQR, 29%–40%) in patients with RVdFMR and 26% (IQR, 21%–32%) in those with RVpFMR (*P* < .001). The RVdFMR cohort demonstrated a larger reduction in MR by first transthoracic echocardiographic assessment after clipping (OR, 0.39; 95% CI, 0.23–0.64; *P* < .01; Supplemental Table 5). In a subgroup of patients with LVEFs < 40%, a similar effect was observed. At 12 months, no significant difference in FMR reduction (vs baseline) was observed between proportionality groups (OR, 0.78; 95% CI, 0.44–1.38; *P* = .40). Additionally, the frequency of delayed FMR deterioration did not differ between RVdFMR and RVpFMR (31 of 86 vs 23 of 81; *P* = .29). All-cause mortality at 2-year follow-up

Table 3 Procedural characteristics and echocardiographic follow-up

Procedural variables	Total group (N = 241)	dFMR (n = 123)	pFMR (n = 118)	P
Number of clips				.69
1	106 (44.0)	55 (44.7)	51 (43.2)	
2	121 (50.2)	59 (48.0)	62 (52.5)	
3	12 (5.0)	8 (6.5)	4 (3.4)	
4	2 (0.8)	1 (0.8)	1 (0.8)	
Technical success*	231 (95.9)	116 (94.3)	115 (97.5)	.22
Conversion to surgery	2 (0.8)	2 (1.6)	—	.50
Postprocedural TTE	(n = 238)	(n = 122)	(n = 116)	
MR				.93
None	2 (0.8)	1 (0.8)	1 (0.9)	
Mild	100 (42.0)	54 (44.3)	46 (39.7)	
Moderate	100 (42.0)	48 (39.3)	52 (44.8)	
Moderate to severe	20 (8.4)	11 (9.0)	9 (7.8)	
Severe	16 (6.7)	8 (6.6)	8 (6.9)	
MR improvement (at least one grade)	217 (91.2)	113 (92.6)	104 (89.7)	.42
MR improvement (at least two grades)	179 (75.2)	100 (82.0)	79 (68.1)	.01
Mitral mean gradient, mm Hg	3 (2–4)	4 (3–5)	3 (2–4)	.01
Severe mitral stenosis	4 (1.7)	2 (1.7)	2 (1.8)	.99
Change in TR peak gradient vs baseline	1.8 ± 14.5	0.8 ± 14.3	3.0 ± 14.8	.32
12-mo TTE	(n = 167)	(n = 84)	(n = 83)	
MR				.96
Mild	57 (34.1)	28 (33.3)	29 (34.9)	
Moderate	66 (39.5)	32 (38.1)	34 (41.0)	
Moderate to severe	25 (15.0)	13 (15.5)	12 (14.5)	
Severe	10 (6.0)	6 (7.1)	4 (4.8)	
Redo mitral valve repair	9 (5.4)	5 (6.0)	4 (4.8)	
MR improvement (at least one grade)	140 (83.8)	70 (83.3)	70 (84.3)	.86
MR improvement (at least two grades)	106 (63.5)	53 (63.1)	53 (63.9)	.92
Mitral mean gradient, mm Hg[†]	3 (2–5)	4 (3–5)	3 (2–4)	.01
Severe mitral stenosis[‡]	2 (1.5)	—	2 (2.8)	.50
Change in TR peak gradient vs baseline[§]	4.4 ± 12.8	3.6 ± 13.6	5.3 ± 11.8	.45

Data are expressed as number (percentage), median (IQR), or mean ± SD.
TR, Tricuspid regurgitation.
*Defined according to Mitral Valve Academic Research Consortium criteria.
[†]Measurements available in 139 of 167 patients at 12-month TTE.
[‡]Measurements available in 140 of 167 patients at 12-month TTE. Valid percentages are given.
[§]Measurements available in 126 of 167 patients at 12-month TTE.

was lower in the RVdFMR cohort than the RVpFMR cohort (hazard ratio, 0.61; 95% CI, 0.37–1.01; P = .05). This tendency was absent after correcting for baseline LVEF (Supplemental Tables 6 and 7).

DISCUSSION

The main findings of this multicenter study on the relationship between FMR proportionality at baseline and impact of TEER are as follows: (1) the implementation of the proportionality framework was challenging in our clinical context; (2) patients with dFMR experienced more MR reduction early after clipping, but not at 1-year follow-up; (3) 35% of patients (similar for dFMR and pFMR) with available 12-month TTE experienced FMR worsening despite initial improvement; (4) overall, 16% of patients (similar for dFMR and pFMR) were nonresponders, with no FMR reduction at 12 months; and (5) there was no difference in mortality or HF hospitalization between proportionality groups after 2 years of follow-up.

In this multicenter registry, echocardiographic and clinical data were used to study the conceptual framework of MR proportionality in patients with HF and FMR. A substantial proportion of the initial
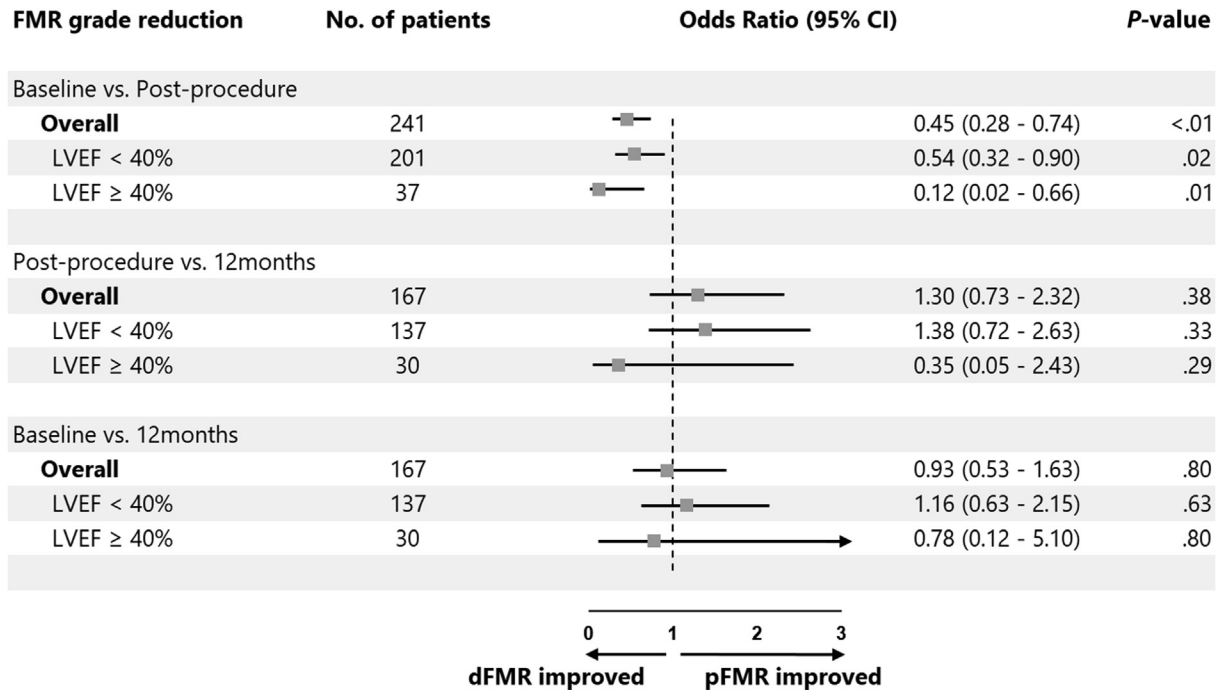
FMR grade reduction	No. of patients		Odds Ratio (95% CI)	P-value
Baseline vs. Post-procedure				
Overall	241		0.45 (0.28 - 0.74)	<.01
LVEF < 40%	201		0.54 (0.32 - 0.90)	.02
LVEF ≥ 40%	37		0.12 (0.02 - 0.66)	.01
Post-procedure vs. 12months				
Overall	167		1.30 (0.73 - 2.32)	.38
LVEF < 40%	137		1.38 (0.72 - 2.63)	.33
LVEF ≥ 40%	30		0.35 (0.05 - 2.43)	.29
Baseline vs. 12months				
Overall	167		0.93 (0.53 - 1.63)	.80
LVEF < 40%	137		1.16 (0.63 - 2.15)	.63
LVEF ≥ 40%	30		0.78 (0.12 - 5.10)	.80

dFMR improved   pFMR improved

Figure 1 Change in FMR after TEER according to proportionality.
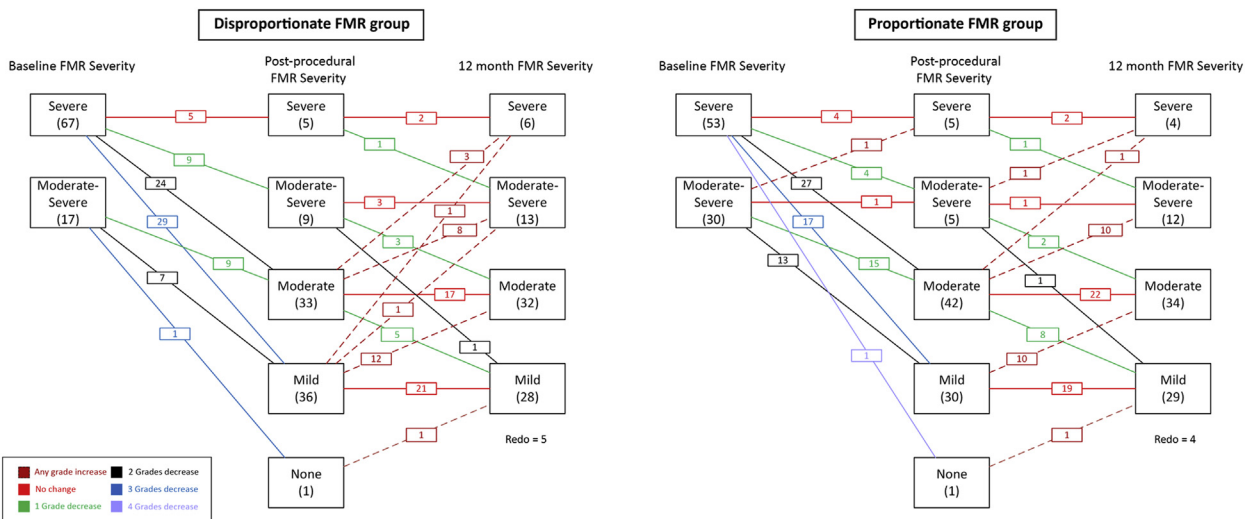

Figure 2 Change in FMR severity during follow-up. Severity of FMR at baseline, postprocedure, and 12-month follow-up assessed by TTE for the dFMR and pFMR groups. Patient numbers are in *brackets* or boxes.

cohort (15%) had to be excluded because quantitative echocardiographic measurements were incompletely recorded to allow FMR proportionality determination. Clearly, daily clinical practice seemed to rely more on qualitative rather than quantitative parameters to quantify MR severity.[15]

Several methods to determine FMR proportionality have been proposed.[12,16] One method relied on LVEDV, LVEF, and RF (with gray areas) to generate individual EROA reference values that served as the cutoff for determining proportionality.[12] This approach immediately incorporated LV function but was limited by an increased number of variables with intrinsic measurement errors and thus larger margins of uncertainty. The other method proposed the EROA/

LVEDV ratio to determine proportionality, in which patients were dichotomized (dFMR vs pFMR) on the basis of the median value of this ratio.[16] A limitation of this method was that it did not incorporate LV function when assessing proportionality. Furthermore, no formal cutoff value for EROA/LVEDV ratio exists, and by using the median as a cutoff, distinction between dFMR and pFMR relies increasingly on group composition. In our study, we chose to use the EROA/LVEDV ratio, as it accommodated the distinct reality of echocardiographic variability in our clinical context (which contrasts with a highly controlled and selected randomized trial environment). Different cutoffs were tested, and the median EROA/LVEDV ratio, providing an equal distribution, was selected to identify dFMR and pFMR. Our

Table 4 Clinical outcomes within 2-year follow-up

	Total group (N = 241)	dFMR (n = 123)	pFMR (n = 118)	Hazard ratio (95% CI)	P
All-cause mortality*	66 (30.4)	35 (32.2)	31 (28.7)		
Any HF hospitalization*	76 (37.3)	38 (37.4)	38 (37.3)	0.94 (0.68–1.30)	.69
All-cause mortality or HF hospitalization	107 (48.2)	55 (48.8)	52 (47.6)	—	.66[†]
LVAD implantation	3 (1.7)	3 (3.4)	—	—	—
Heart transplantation	3 (1.6)	2 (1.9)	1 (1.2)	—	—
Mortality or LVAD implantation or heart transplantation[‡]	70 (32.5)	38 (34.7)	32 (30.2)	1.00 (0.85–1.19)	.97
Redo TEER or mitral surgery	16 (8.2)	8 (7.8)	8 (8.5)	0.97 (0.37–2.61)	.96
NYHA functional class improvement (at least one class) at 1-y follow-up[§]	126 (71.2)	68 (77.3)	58 (65.2)	—	.08[¶]

Values are numbers (Kaplan-Meier estimates of event rate at 2-year follow-up) except as indicated.
LVAD, LV assist device; *NYHA*, New York Heart Association.
*Stratified by age.
[†]The analysis was performed using the win ratio approach, of which details are provided in Supplemental Table 3.
[‡]Stratified according to baseline characteristic: previous stroke or transient ischemic attack (yes or no).
[§]Values are numbers (proportions of nonmissing population).
[¶]The analysis was performed using the χ^2 test.

median compared favorably with the previously suggested Gorlin equation–derived cutoff (0.14), which in turn was derived from a set of assumptions.[6] Importantly, clinical and FMR outcome data remained the same when corrected for LVEF. Notably, EROA, used in all methods, has inherent limitations (e.g., the simplified assumption of a circular mitral orifice and constant values throughout the cardiac cycle).[17-19] These caveats are even more pronounced after TEER.

EROA as a parameter for FMR disregards left atrial–LV pressure differences and therefore serves as a surrogate for RegVol.[20] In this study, we therefore repeated the main analyses also for FMR (dis)proportionality on the basis of RegVol/LVEDV and found similar outcomes when taking LVEF into account. It is important to note that echocardiographically obtained RegVol also has its limitations. Of note, RegVol is often derived from EROA and the velocity-time integral, which retains the limitations associated with EROA and adds potential measurement error of the velocity-time integral. Conceivably, further research of FMR proportionality may benefit from standardized, more precise and reproducible FMR quantification methods, as could be achieved with cardiac magnetic resonance imaging. Additionally, cardiac magnetic resonance imaging adds tissue characterization and enables assessment of underlying FMR mechanisms.[21,22] As such, Gaasch and Meyer[20,23] proposed cardiac magnetic resonance–derived RegVol/LVEDV ratio at baseline to predict clinical outcome.

Our findings suggested that patients with dFMR seemed more responsive to TEER with greater (initial) MR reduction compared with those with pFMR, independent of LVEF. Conceivably, the smaller LV (and mitral annulus) dimensions in dFMR may be associated with better mitral leaflet coaptation and thus easier leaflet grasping and clipping. At 12 months, any FMR reduction was present in 84% of patients and was similar in the dFMR and pFMR cohorts. This could partially be explained by survival bias. Importantly, the patient-level analysis (baseline vs postprocedural and postprocedural vs 12-month TTE) revealed that more than one third of the patients experienced FMR deterioration after initial improvement. This finding raises some concern for

TEER durability. Previously, de Bonis *et al.*[24] also reported favorable initial procedural results (MR ≤ 1+) but a decay toward MR ≥ 2+ after 1 year (paired data) that continued throughout 4 years of follow-up. Although evidence for mechanisms behind delayed FMR deterioration is limited, several anatomic predictors, including LVEDV, may play a key role.[25,26]

This sobering reality contrasts with the excellent 1- and 2-year echocardiographic data from the COAPT trial showing maintained MR reduction over time, although patient-level FMR follow-up has not been published to date. Several studies have reported discharge and 12-month FMR grade but did not perform pairwise comparisons of postprocedural versus 12-month FMR grade,[27-30] precluding reliable insights on durable effects of TEER on FMR reduction. Also, in MITRA-FR, transthoracic echocardiography follow-up was limited, impairing evaluation of TEER durability.[4] A recent report of the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation registry investigated the impact of FMR proportionality on post-TEER outcomes and demonstrated FMR grade ≤ 2+ in 92% versus 96% of dFMR and pFMR groups, respectively.[30] Distributions of FMR grades at discharge and 1-year follow-up (median, 447 days) remained similar and suggested stable MR reduction comparable with the COAPT trial. Importantly, follow-up transthoracic echocardiographic data were available in only 531 of 1,016 patients, time of assessment differed, and comparisons were made at a between-group level. This is a relevant difference from the present registry, in which FMR reduction was investigated at a patient level and FMR change (with magnitude of change) was incorporated in the primary end point. Patient-level comparison is more accurate than distribution comparisons within cohorts, especially in the case of substantial missing (echocardiographic follow-up) data. Clearly more patient-level analyses in larger study samples are needed to determine the durability of TEER's effect on FMR. Furthermore, long-term data are required to evaluate the association of delayed FMR deterioration with clinical outcomes.

Table 5 Study findings in the context of COAPT, MITRA-FR, and EuroSMR

	dFMR (n = 123)	COAPT device group[3,29] (n = 302)	EuroSMR dFMR[30] (n = 505)	pFMR (n = 118)	MITRA-FR device group[4,36] (n = 152)	EuroSMR pFMR[30] (n = 209)
Clinical characteristics						
Age, y	73 (66–79)	71.7 ± 11.8	75 ± 10	72 (66–77)	70.1 ± 10.1	72 ± 10
Ischemic cardiomyopathy	63	61	51	75	63	52
STS-PROM, %	2.4 (1.4–5.4)	7.8 ± 5.5	—	3.4 (1.7–6.3)	—	—
Creatinine clearance, mL/min	47 ± 19	51 ± 29	47 ± 22	42 ± 18	49 ± 20	49 ± 22
Cardiac resynchronization therapy	18	38	14	23	31	25
Baseline HF medication						
Renin-angiotensin system antagonist	68	72	66	74	73	70
β-blocker	77	91	75	84	88	75
Mineralocorticoid antagonist	55	51	37	54	57	42
Any diuretic	90	89	—	92	99	—
Baseline echocardiographic assessment						
LVEF, %	32 (27–39)	31 ± 9	40 ± 13	27 (22–33)	33 ± 7	33 ± 11
LVEDV, mL	176 (135–220)	194.4 ± 69.2	142.0 ± 55.4	243 (201–300)	252*	200.4 ± 69.6
EROA, mm^2	34 (25–41)	41 ± 15	38 ± 17	23 (19–29)	31 ± 10	27 ± 9
RegVol, mL	48 (35–57)	(?)	54 ± 23	37 (28–44)	45 ± 13	39 ± 16
Procedural characteristics						
Average number of clips implanted	1.6 ± 0.6	1.7 ± 0.7[†]	—	1.6 ± 0.6	1.6[†]	—
Discharge MR greater than moderate (3+ or 4+)	15.6	7.4[‡]	8.0	14.7	8.1	4.0
Clinical endpoints						
All-cause death at 2 y (Kaplan-Meier estimates)	32.2	29.1	31	28.7	33.9	34
HF hospitalization at 2 y (rate per 100 patient-years)	42.0	35.8	—	49.5	55.9	—

Data are expressed as median (IQR), mean ± SD, or percentages. For further details please refer Supplemental Table 8.
STS-PROM, Society of Thoracic Surgeons Predicted Risk of Mortality.
*The original article reported indexed LVEDV of 136 mL/m^2. This was estimated to be an LVEDV of 252 mL by Grayburn *et al*.[5]
[†]Mean from total of the attempted patients.
[‡]Assessed 30 days after index procedure. Of note, given differences in study design and reporting, comparison of these variables should be performed with caution.

The proportion of echocardiographic nonresponders at 1 year in our study (16%) was comparable with that in previous retrospective studies of TEER in FMR[27,31] but was higher than reported in COAPT and MITRA-FR (Table 5). Higher rates of nonresponse might be partially explained by patient selection (i.e., optimized therapy, anatomic parameters) in the randomized trials. Nonresponders were characterized by LBBB, nonischemic cardiomyopathy, and less severe FMR at baseline (Supplemental Tables 1A and 1B).

LBBB has been suggested to be a codeterminant of FMR through dys-synchrony.[32,33] Limited sample size prohibited any landmark analysis of clinical outcomes, but previous studies showed that TEER nonresponse is associated with increased mortality,[27] which stresses the importance of achieving and maintaining a durable FMR reduction. Clinical outcomes in our study were similar for both proportionality cohorts and remained the same when corrected for LV function. Post hoc analyses of both MITRA-FR and COAPT also failed to

demonstrate any effect of FMR proportionality on the clinical impact of TEER.[34,35] Of note, patient characteristics were different from the two large randomized FMR trials and the EuroSMR registry (Table 5).[3,4,29,30,36] Our dFMR cohort had similar LV dimensions as the COAPT device arm (which arguably included predominantly dFMR). Conversely, the dFMR cohort in our study showed less severe FMR, increased residual FMR after clipping, and more HF hospitalizations, while mortality was similar (Table 5). The unparalleled COAPT results may reflect the overall highly selected patient population (using an external screening committee), enrolling only 39% of all screened patients with a potential focus on patients who were not as advanced in their HF lifecycle (i.e., before the point of no return) and with FMR phenotype more amenable to clipping, stricter adherence to guideline-directed medical therapy including cardiac resynchronization therapy, and the inclusion of predominantly dFMR. Still, guideline-directed medical therapy in our study typically reflected what can be expected in a real-world context.[37,38]

Conversely, the relatively high HF hospitalization rate in our pFMR cohort reinforces the lesson learned from MITRA-FR that TEER may underperform in patients with extensively dilated left ventricles and poor LVEFs (Table 5).[30] Of note, per the original proportionality framework, the cutoff for dFMR shifts upward at higher LVEF.[5] An interesting post hoc analysis of the MITRA-FR trial looked at patients who met the echocardiographic inclusion criteria of the COAPT trial. Overall, this "COAPT-eligible" subgroup of MITRA-FR patients still had more dilated LV dimensions and lower EROAs but had improved clinical outcome, albeit with still no difference between the device and control arms.[39] Similarly, a post hoc analysis of COAPT investigated patients who would correspond with the MITRA-FR patients on the basis of the median EROA and LVEDV index values (58 of 548) and found no improved clinical outcomes with TEER over medical therapy alone.[40]

Limitations

Apart from the inherent limitations associated with the retrospective, multicenter design of this study, such as reporting and selection bias, we also acknowledge the following limitations. First, all transthoracic echocardiographic analyses were performed and reported by the participating centers, increasing the likelihood of interobserver variability. There was no independent echocardiography core laboratory. Second, 15% of the overall cohort was excluded because of incomplete echocardiographic studies at baseline, precluding the determination of FMR proportionality. Third, transthoracic echocardiographic follow-up was incomplete at 1 year. Fourth, sample size and proportionality cutoffs may have resulted in type II error. Finally, because of a limited number of events and notable baseline differences, we could not correct for all parameters in the survival analysis. However, the most relevant parameters, including correction for study site, could be incorporated. Our findings contribute to the ongoing debate, provide new insights, and demand further investigation in larger (preferably prospective) study samples.

CONCLUSION

TEER resulted in more pronounced early FMR reduction in patients with dFMR compared with those with pFMR. Yet after initial improvement, FMR deteriorated in a substantial number of patients, calling into question the durability of MR reductions with TEER in selected patients. The proportionality framework may not identify durable TEER responders.

SUPPLEMENTARY DATA

Supplementary data related to this article can be found at https://doi.org/10.1016/j.echo.2021.08.002.

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Supplemental Table 1A MR on TTE 12 months after TEER compared with baseline

	MR improvement (n = 140)	No MR improvement (including redo) (n = 27)	P
Baseline demographics			
Age, y	72 (66–77)	70 (65–77)	.61
Gender, male	99 (70.7)	19 (70.4)	.97
Hypertension	74 (52.9)	18 (66.7)	.20
Diabetes mellitus	39 (27.9)	6 (22.2)	.55
Stroke/TIA	21 (15.0)	2 (7.4)	.30
Peripheral vascular disease	17 (12.1)	5 (18.5)	.37
COPD	19 (13.6)	4 (14.8)	.77
Previous myocardial infarction	86 (61.4)	10 (37.0)	.02
Ischemic cardiomyopathy	102 (72.9)	14 (51.9)	.03
Previous non–mitral valve surgery	5 (3.6)	2 (7.4)	.32
Previous TAVI	2 (1.4)	—	—
Atrial fibrillation	78 (55.7)	17 (63.0)	.49
Cardiac resynchronization therapy	23 (16.4)	7 (25.9)	.24
Implantable cardioverter-defibrillator	61 (43.6)	13 (48.1)	.66
eGFR ≤ 35 mL/min	42 (30.0)	8 (29.6)	.95
Creatinine clearance, mL/min	46.5 ± 17.3	46.9 ± 22.5	.93
NT-proBNP at baseline*	1,464 (402–4,481)	564 (285–2,721)	.31
NYHA functional class			.01
II	14 (10.0)	7 (25.9)	
III	91 (65.0)	19 (70.4)	
IV	35 (25.0)	1 (3.7)	
STS-PROM[†]	2.4 (1.5–4.7)	3.5 (2.1–5.7)	.27
Conduction parameters[†]			
QRS duration, msec	126 (106–164)	143 (121–172)	.09
LBBB[‡]	59 (42.8)	18 (69.2)	.01
HF medications			
Renin-angiotensin system antagonist	100 (71.4)	22 (81.5)	.28
β-blocker	116 (82.9)	18 (66.7)	.05
Neprilysin inhibitor	10 (7.1)	—	.37
Mineralocorticoid receptor antagonist	76 (54.3)	12 (44.4)	.34
Any diuretic	132 (94.3)	22 (81.5)	.02

Data are median (IQR), number (percentage), or mean ± SD.
COPD, Chronic obstructive pulmonary disease; *eGFR*, estimated glomerular filtration rate; *NT-proBNP*, N-terminal pro–brain natriuretic peptide; *NYHA*, New York Heart Association; *STS-PROM*, Society of Thoracic Surgeons Predicted Risk of Mortality; *TAVI*, transcatheter aortic valve replacement; *TIA*, transient ischemic attack.
*Data were available in 138 patients.
[†]Data were available in 164 patients.
[‡]This includes patients with permanent LV pacing.

Supplemental Table 1B MR on TTE 12 months after TEER compared with baseline

Baseline transthoracic echocardiographic parameter	MR improvement (n = 140)	No MR improvement (including redo) (n = 27)	P
LVEF, %	30 (25–36)	30 (23–35)	.32
LVESV, mL	140 (108–189)	145 (100–220)	.63
LVEDV, mL	213 (166–263)	227 (167–270)	.77
LVEDD, cm	64.3 ± 9.5	66.1 ± 11.2	.38
LVESD, cm	54 (48–60)	59 (50–66)	.06
LA dimension index, mm/m^2	27.1 ± 4.2	27.0 ± 3.8	.91
MR grade			.05
Moderate to severe	36 (25.7)	12 (44.4)	
Severe	104 (74.3)	15 (55.6)	
EROA, mm^2	27 (21–36)	29 (21–39)	.53
MR VTI, cm	155.1 ± 30.9	144.3 ± 36.6	.12
Mitral RegVol, mL	40 (32–54)	42 (32–51)	.73
dFMR (%)	70 (50.0)	14 (51.9)	.86

Data are expressed as median (IQR), mean ± SD, or number (percentage).
LA, Left atrial; *LVEDD,* LV end-diastolic diameter; *LVESD,* LV end-systolic diameter; *LVESV,* LV end-systolic volume; *TR,* tricuspid regurgitation; *VTI,* velocity-time integral.

Supplemental Table 1C MR on TTE 12 months after TEER compared with baseline

Procedural parameter	MR improvement (n = 140)	No MR improvement (including redo) (n = 27)	P
Number of clips ≥ 2	79 (56.4)	14 (51.9)	.66
Mean mitral gradient after TEER, mm Hg	3 (2–4)	3 (2–4)	.96

Data are expressed as number (percentage) or median (IQR).

Supplemental Table 2 Cross-table of FMR change between baseline and first reported versus first reported and 1 year after TEER

	FMR severity	Compared with first reported TTE		Total number of patients
		Equal or improvement at 1 y	Deterioration at 1 y	
Compared with baseline TTE	First reported: no improvement	7	4	11
	First reported: any improvement	102	54	156
	Total number of patients	109	58	167

Values are numbers of patients per group.

Supplemental Table 3 Unmatched win ratio analysis with proportionality EROA/LVEDV ratio derived

Death in dFMR first	3,274
Death in pFMR first	2,751
HF hospitalization in dFMR first	1,751
HF hospitalization in pFMR first	1,883
Total number of pairs	14.514
Win ratio (95% CI)	0.92 (0.64–1.33)
Analysis	
*Z*score	−0.43
P	.66

Supplemental Table 4 Clinical outcomes within 2-year follow-up: corrected LVEF* with proportionality EROA/LVEDV ratio derived

	Total group (N = 241)	dFMR (n = 123)	pFMR (n = 118)	Hazard ratio (95% CI)	P
All-cause mortality	66 (30.4)	35 (28.5)	31 (26.3)	1.09 (0.64–1.85)	.75
Any HF hospitalization	76 (37.3)	38 (30.9)	38 (32.2)	1.05 (0.65–1.71)	.84
Mortality or LVAD implantation or heart transplantation	107 (48.2)	38 (30.9)	32 (27.1)	1.17 (0.70–1.94)	.55

Values are numbers (Kaplan-Meier estimates of event rate). Hazard ratios were calculated with pFMR as the reference group.
LVAD, LV assist device.
*Also included in the model were age, gender, ischemic cardiomyopathy, and stroke or transient ischemic attack.

Supplemental Table 5 Change in FMR after TEER according to proportionality on the basis of RegVol/LVEDV ratio

FMR grade reduction	Number of patients	Or (95% CI)	P
Baseline vs postprocedure*	241	0.39 (0.23–0.64)	<.001
Postprocedure vs 12 mo[†]	167	1.31 (0.73–2.34)	.36
Baseline vs 12 mo*	167	0.78 (0.44–1.38)	.40

*Corrected for year of procedure and study site.
[†]Corrected for study site only. Addition of year of procedure led to nonconverging of the model. pFMR was the reference group.

Supplemental Table 6 Clinical outcomes within 2-year follow-up with proportionality on the basis of RegVol/LVEDV ratio

	Total group (N = 241)	dFMR (n = 120)	pFMR (n = 121)	Hazard ratio (95% CI)	P
All-cause mortality*	66 (30.4)	28 (27.2)	38 (33.4)	0.61 (0.37–1.01)	.05
Any HF hospitalization*	76 (37.3)	35 (36.8)	41 (37.9)	0.85 (0.55–1.18)	.45
All-cause mortality or HF hospitalization	107 (48.2)	48 (45.9)	59 (50.4)	—	.23[†]
Mortality or LVAD implantation or heart transplantation[‡]	70 (32.5)	30 (29.3)	40 (35.5)	0.64 (0.41–1.02)	.06
Redo MitraClip or mitral surgery	16 (8.2)	7 (7.5)	9 (8.9)	0.79 (0.30–2.13)	.65

Values are numbers (Kaplan-Meier estimates of event rate at 2-year follow-up).
LVAD, LV assist device.
*Stratified by age.
[†]The analysis was performed using the win ratio approach.
[‡]Stratified according to baseline characteristic: previous stroke or transient ischemic attack (yes or no).

Supplemental Table 7 Clinical outcomes within 2-year follow-up: corrected LVEF* with proportionality RegVol/LVEDV ratio derived

	Total group (N = 241)	dFMR (n = 120)	pFMR (n = 121)	Hazard ratio (95% CI)	P
All-cause mortality	66 (30.4)	28 (27.2)	38 (33.4)	0.73 (0.42–1.28)	.27
Any HF hospitalization	76 (37.3)	35 (36.8)	41 (37.9)	0.98 (0.59–1.63)	.94
Mortality or LVAD implantation or heart transplantation	107 (48.2)	30 (29.3)	40 (35.5)	0.77 (0.45–1.31)	.33

Values are numbers (Kaplan-Meier estimates of event rate). Hazard ratios were calculated with pFMR as the reference group.
*LVAD*, LV assist device.
*Also included in the model were age, gender, ischemic cardiomyopathy, and stroke or transient ischemic attack.

Supplemental Table 8 Study findings in the context of COAPT, MITRA-FR, and EuroSMR

- Median or mean RegVol in the COAPT trial was not published in the main report. Median values of RegVol reported by Asch et al.[29] are hampered by missing data.
- The average number of clips is derived from total of the attempted patients: for COAPT, $n = 293$; and for MITRA-FR, $n = 144$. In the MITRA-FR report, the number of clips is presented as a nominal variable. In the highest category (three or more clips), the exact number of clips was not specified. For the 13 patients in this category, we assumed that three clips per patient were implanted (total number of clips = 266).
- HF hospitalization at 2 years: data for COAPT were calculated from data presented in the supplementary material of the main report, in which 160 hospitalizations for HF occurred in 446.5 patient-years of follow-up in the device group (intention-to-treat analysis).
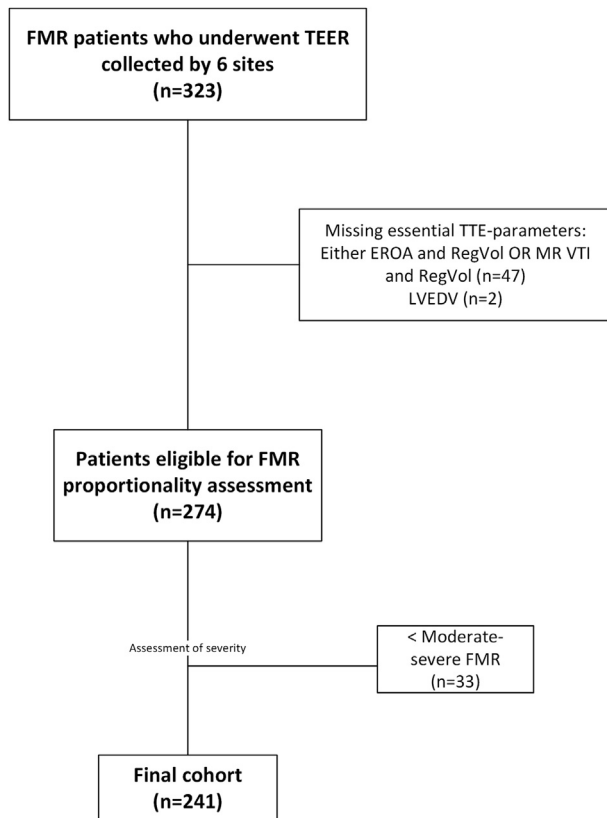
Supplemental Figure 1 Flowchart of patient inclusion. The registry included 323 patients treated with TEER at six centers from 2011 to 2019. The final cohort comprised 241 patients. *VTI*, Velocity-time integral.
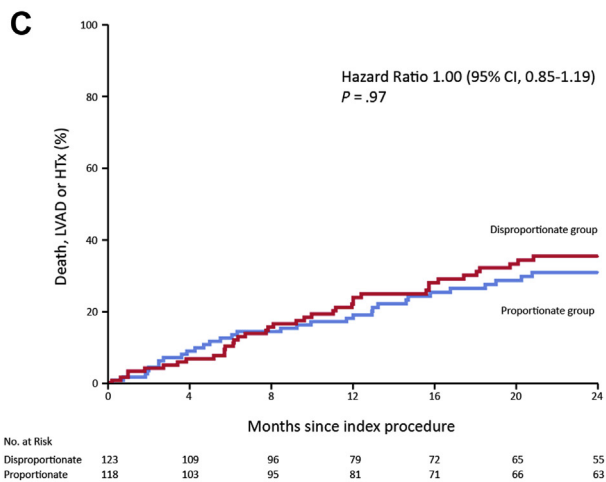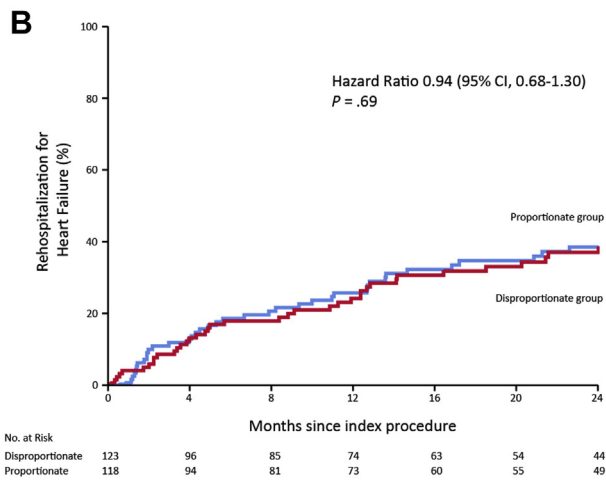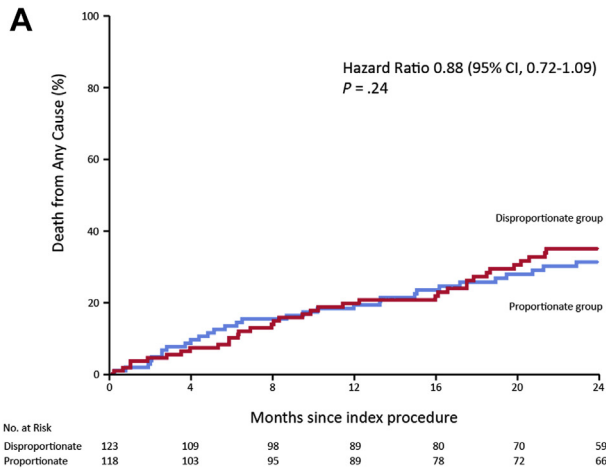
Supplemental Figure 2 Clinical outcomes within 2 years of follow-up. Time-to-event curves for **(A)** all-cause mortality, **(B)** HF hospitalization after index procedure, **(C)** composite of all-cause mortality, LV assist device (LVAD) implantation, or heart transplantation (HTx) in the dFMR *(red line)* and pFMR *(blue line)* groups.