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RESEARCH ARTICLE

Percutaneous repair of moderate-to-severe or severe functional mitral regurgitation in patients with symptomatic heart failure: Baseline characteristics of patients in the RESHAPE-HF2 trial and comparison to COAPT and MITRA-FR trials

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Aim

The RESHAPE-HF2 trial is designed to assess the efficacy and safety of the MitraClip device system for the treatment of clinically important functional mitral regurgitation (FMR) in patients with heart failure (HF). This report describes the baseline characteristics of patients enrolled in the RESHAPE-HF2 trial compared to those enrolled in the COAPT and MITRA-FR trials.

Methods and results

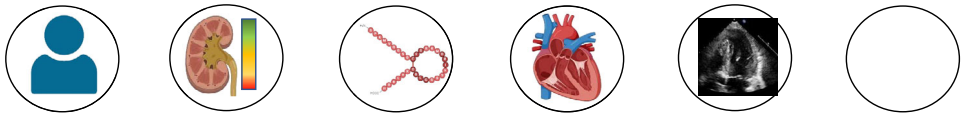
The RESHAPE-HF2 study is an investigator-initiated, prospective, randomized, multicentre trial including patients with symptomatic HF, a left ventricular ejection fraction (LVEF) between 20% and 50% with moderate-to-severe or severe FMR, for whom isolated mitral valve surgery was not recommended. Patients were randomized 1:1 to a strategy of delivering or withholding MitraClip. Of 506 patients randomized, the mean age of the patients was 70 ± 10 years, and 99 of them (20%) were women. The median EuroSCORE II was 5.3 (2.8–9.0) and median plasma N-terminal pro-B-type natriuretic peptide (NT-proBNP) was 2745 (1407–5385) pg/ml. Most patients were prescribed beta-blockers (96%), diuretics (96%), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers/angiotensin receptor–neprilysin inhibitors (82%) and mineralocorticoid receptor antagonists (82%). The use of sodium–glucose cotransporter 2 inhibitors was rare (7%). Cardiac resynchronization therapy (CRT) devices had been previously implanted in 29% of patients. Mean LVEF, left ventricular end-diastolic volume and effective regurgitant orifice area (EROA) were 31 ± 8%, 211 ± 76 ml and 0.25 ± 0.08 cm^2, respectively, whereas 44% of patients had mitral regurgitation severity of grade 4+. Compared to patients enrolled in COAPT and MITRA-FR, those enrolled in RESHAPE-HF2 were less likely to have mitral regurgitation grade 4+ and, on average, HAD lower EROA, and plasma NT-proBNP and higher estimated glomerular filtration rate, but otherwise had similar age, comorbidities, CRT therapy and LVEF.

Conclusion

Patients enrolled in RESHAPE-HF2 represent a third distinct population where MitraClip was tested in, that is one mainly comprising of patients with moderate-to-severe FMR instead of only severe FMR, as enrolled in the COAPT and MITRA-FR trials. The results of RESHAPE-HF2 will provide crucial insights regarding broader application of the transcatheter edge-to-edge repair procedure in clinical practice.

Graphical Abstract

Patients in RESHAPE-HF2 form a third distinct population tested with MitraClip, primarily comprising those with moderate-to-severe FMR, unlike the COAPT and MITRA-FR trials, which recruited patients with severe FMR



	Age (years)	eGFR (ml/min/1.73 m²)	NT-proBNP (pg/ml)	LVEF (%)	Mean EROA (cm²)	6MWD (m)
RESHAPE-HF2	70	56 ± 21	Mean: 4185 Median: 2745	31 ± 8	0.25	Mean: 292 Median: 300
COAPT	72	49 ± 26	Mean: 5558	31 ± 9	0.40	Median: 240
MITRA-FR	70	50 ± 20	Median: ≈3400	33 ± 6	0.31	Mean: 310

Baseline characteristics of patients in the RESHAPE-HF2 trial compared to the COAPT and MITRA-FR trials. 6MWD, 6-min walk distance; eGFR, estimated glomerular filtration rate; EROA, effective regurgitant orifice area; FMR, functional mitral regurgitation; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

Keywords Mitral regurgitation • MitraClip • Transcatheter edge-to-edge repair

Introduction

By 2030, 4 million patients are expected to have diagnosed functional mitral regurgitation (FMR) in the United States alone.[1,2] One in every five patients with heart failure (HF) may have moderate-to-severe FMR which is associated with substantial morbidity and mortality.[3–5] Cardiac resynchronization therapy (CRT), and guideline-recommended pharmacological therapy for HF including beta-blockers, sodium–glucose cotransporter 2 (SGLT2) inhibitors, angiotensin receptor–neprilysin inhibition (ARNI), and mineralocorticoid receptor antagonist (MRA) can all help to reduce FMR by reverse left ventricular (LV) remodelling, but many patients continue to have FMR.[6,7] Surgery for FMR is usually not recommended, unless it is treated together with other pathologies that require surgical approach such as coronary artery bypass surgery or aortic valve replacement.[8,9] For this subgroup of patients, transcatheter edge-to-edge repair (TEER) for FMR has emerged as an attractive option.

The previously published trials MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) and COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) demonstrated discordant results.[10,11] In the MITRA-FR trial, no significant difference was observed between the MitraClip arm and the control group regarding the primary composite endpoint of mortality or HF hospitalizations at 1-year follow-up (54.6% vs. 51.3%, $p = 0.53$), whereas in the COAPT trial, patients randomized to MitraClip demonstrated significantly reduced annual rates of HF hospitalization (35.8% vs. 67.9%), and all-cause mortality at 2-year follow-up (29.1% vs. 46.1%). There are many reasons that have been proposed to explain such conflicting results, that included the different baseline HF severity, the baseline LV dimensions, baseline mitral regurgitation (MR) severity measured by effective regurgitant orifice area (EROA) or regurgitant volume, a concomitant right ventricular dysfunction and the degree of optimization of standard HF medical treatment before MitraClip.[12–15] Thus, there remains ambiguity regarding which patients may benefit from TEER.

The RESHAPE-HF2 trial (Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation) aims to provide conclusive evidence regarding the safety and effectiveness of the MitraClip in patients with HF and FMR. Moreover, it aims to extend the evidence for TEER to patients with less severe FMR. Since the conflicting results from MITRA-FR and COAPT studies may have been attributed to the different baseline characteristics of the patients enrolled, it is important to assess the baseline characteristics of patients enrolled in RESHAPE-HF2. Therefore, the aim of this report is to describe the baseline characteristics of the RESHAPE-HF2 cohort

and compare them with the characteristics of the patients enrolled in the COAPT and MITRA-FR trials.

Methods

Study design

RESHAPE-HF2 (NCT02444338) is a prospective, randomized, multicentre study designed to assess the safety and effectiveness of the MitraClip device for the treatment of clinically significant FMR in patients with HF and New York Heart Association (NYHA) functional class II–IV symptoms, despite optimal guideline-directed therapy and in whom isolated mitral valve surgery is not the recommended treatment. The design paper has been previously published and it is briefly summarized below.[16] The data presented in this manuscript are based on a baseline data export (of blinded data) performed on 25 March 2024. Very minor differences may develop between now and final database lock for selected data points, but they are not expected to cause any material change for any of the population averages reported here. The legal sponsor of the study is Universitätsmedizin Göttingen (Germany) and financial support for the trial is provided by Abbott Laboratories based on an unrestricted grant to Universitätsmedizin Göttingen. The conduct of the trial is approved by the appropriate Ethics Committee of the respective sites.

Study patients

Patients eligible for enrolment were required to have signs and symptoms of HF despite optimal medical therapy, moderate-to-severe or severe FMR, LV ejection fraction (LVEF) between ≥20% and ≤50% (initially 15–35% for NYHA class II patients, and 15–45% for NYHA class III/IV patients), HF hospitalization or elevated natriuretic peptide concentrations (B-type natriuretic peptide [BNP] ≥300 pg/ml or N-terminal proBNP [NT-proBNP] ≥1000 pg/ml) within 90 days prior to enrolment, CRT device according to indications, and in whom isolated mitral valve surgery was not the recommended treatment. Patients with primary MR due to degenerative disease of the mitral valve apparatus (degenerative MR), as determined by transesophageal echocardiography (TEE) or, if applicable, transthoracic echocardiography (TTE) were excluded. Similarly, patients with any percutaneous coronary intervention, carotid surgery, cardiovascular surgery or atrial fibrillation ablation within 90 days prior to randomization were also excluded.

The patients were recruited in the sites listed in online Supplementary Appendix. All patients were randomized in a 1:1 ratio between the device and control group, with the patients in the device arm scheduled to undergo MitraClip implantation within 14 days of randomization. The trial has three primary endpoints: (1) composite rate of total (i.e. first and recurrent) HF hospitalizations and cardiovascular death during 24 months of follow-up; (2) the rate of total (i.e. first and recurrent) HF hospitalizations within 24 months; (3) the change from baseline to 12 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score.

Baseline data

All patients were evaluated by the site team consisting of a HF specialist, an interventional cardiologist, an echocardiographer, and a cardiothoracic surgeon to ensure that all patients were on optimal guideline-directed therapy (for the team members see also Appendix S2). All patients were scheduled to undergo both TTE and TEE studies before enrolment. All patients had a detailed baseline visit which consisted of medical and social history based on chart review and patient self-report. The following variables were collected at the baseline visit: history of prior myocardial infarction, stroke, chronic obstructive pulmonary disease, hypertension, dyslipidaemia, atrial fibrillation, type 2 diabetes, chronic kidney disease, and prior hospitalization for HF. All HF medications were recorded at baseline. Physical examination and laboratory data included heart rate, systolic and diastolic blood pressure, height, weight, complete blood count, NT-proBNP concentrations and basal metabolic panel including estimated glomerular filtration rate (eGFR). Health status assessment was performed using the 23-question KCCQ. Baseline surgical risk was calculated using EuroSCORE. Data from TTE and TEE prior to randomization were also included with special focus on LVEF, LV end-systolic and end-diastolic volumes, severity of FMR, EROA and regurgitant volumes.

Comparison with COAPT and MITRA-FR trials

Baseline demographic and clinical characteristics from RESHAPE-HF2 were compared with those from MITRA-FR and COAPT trials. Echocardiographic characteristics such as LVEF, LV end-systolic and end-diastolic volumes, severity of FMR, and EROA were also compared between patients enrolled in RESHAPE-HF2, MITRA-FR and COAPT trials.

Results

Baseline demographic and clinical characteristics

Between March 2015 and October 2023, 621 patients were screened in nine countries and 506 were enrolled. The mean age of the cohort was 70 ± 10 years, and 99 (20%) were female. The median EuroSCORE II was 5.3 (2.8–9.0). Almost half of the patients had a history of hypertension (53%) and previous myocardial infarction (55%). A total of 177 patients (35%) had a non-ischaemic cardiomyopathy, whereas 29% of patients had prior CRT device. The majority of patients were on beta-blockers (96%), diuretics (96%) and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker/ARNI (82%). Utilization of MRA was in 82% of patients while SGLT2 inhibitors were rarely used (7%). The mean eGFR was 56 ± 21 ml/min/1.73 m^2, and mean NT-proBNP concentrations were 4185 ± 4340 pg/ml (median [interquartile range]) 2745 ([1407–5385] pg/ml). The mean KCCQ overall summary score was 46 ± 24.

Baseline echocardiographic characteristics

The mean LVEF of the cohort was 31 ± 8%. The mean LV end-systolic and diastolic volume were 147 ± 65 and 211 ± 76 ml, respectively. Less than half of the patients had MR severity classification by the echocardiography core laboratory of grade

Table 1 Comparison of baseline characteristics across trials

	RESHAPE-HF2 ($n = 506$)	COAPT ($n = 614$)	MITRA-FR ($n = 304$)
Age (years)			
Mean ± SD	70 ± 10	72[a]	70[a]
Median [IQR]	71 [63–78]		
Women	99 (19.6)	221 (36.0)	77 (25.3)
Diabetes	176 (34.8)	229 (37.3)	89 (29.3)
Hypertension	269 (53.2)	494 (80.5)	NR
Previous MI	279 (55.1)	316 (51.5)	127 (41.8)
Previous PCI	244 (48.2)[b]	283 (46.1)	135 (44.4)
Previous CABG	133 (26.3)	247 (40.2)	NR
Previous stroke or TIA	59 (11.7)	105 (17.1)	NR
Peripheral vascular disease	65 (12.8)	109 (17.8)	NR
COPD	72 (14.2)	143 (23.2)	NR
History of atrial fibrillation or flutter	243 (48.0)	339 (55.2)	97 (31.9)
Body mass index (kg/m^2)	26.8 ± 4.3	27[a]	NR
EuroSCORE II[c]	5.3 [2.8–9.0]	NR	MC: 6.6 [3.5–11.9] UC: 5.9 [3.4–10.4]
Non-ischaemic cause of cardiomyopathy	177 (35.0)	241 (39.3)	180 (59.2)
NYHA class			
II	125 (24.8)	239 (39.1)	100 (32.9)
III	303 (59.9)	322 (52.5)	178 (58.6)
IV	77 (15.2)	51 (8.3)	26 (8.5)
HHF within previous 1 year	333 (65.8)	351 (57.2)	304 (100)
Previous CRT	147 (29.1)	224 (36.5)	81 (26.6)
Previous ICD	178 (35.2)	192 (31.3)	105 (34.5)
6-min walk distance (m)			
Mean ± SD	292 ± 107	240 [146–331]	310 ± 126 ($n = 223$)[a]
Median [IQR]	300 [207–378] ($n = 491$)		
KCCQ overall summary score	46 ± 24	52.4 ± 23.0	NR

Data are provided as mean ± SD, median [IQR], or *n* (%).
CABG, coronary artery bypass graft; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; HHF, hospitalization for heart failure; ICD, implantable cardioverter-defibrillator; IQR, interquartile range; KCCQ, Kansas City Cardiomyopathy Questionnaire; MC, MitraClip group; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; SD, standard deviation; TIA, transient ischaemic attack; UC, usual care group.
[a]For selected variables, when data were only available for patients with device therapy or usual care separately, overall medians were estimated.
[b]Represents for RESHAPE-HF2 the combined number of patients with a prior stent and/or PCI therapy.
[c]For 109 patients, EuroSCORE I was assessed.

4+ (44%). Only 33 patients (9%) in RESHAPE-HF2 had an EROA >40 mm^2.

Comparison of patient characteristics across trials

Table 1 compares the baseline demographic and clinical characteristics of patients enrolled in RESHAPE-HF2, COAPT and MITRA-FR trials. The mean age of the patients enrolled in all three trials was ~70 years. Previous CRT and defibrillator implantation were roughly in one third of the population in all three trials. The proportion of women (36% vs. 20%), of patients with history of hypertension (80% vs. 53%) and coronary artery bypass graft surgery (40.2 vs. 26.3%) was higher in the COAPT trial compared to RESHAPE-HF2. Compared to the COAPT (39%) and MITRA-FR (59%) trials, less patients had non-ischaemic cardiomyopathy in the RESHAPE-HF2 trial (35%).

Comparison of laboratory values and medication use across trials

Table 2 compares the baseline laboratory values and medication use among patients enrolled in RESHAPE-HF2, COAPT and MITRA-FR trials. MRA (82% vs. 50% vs. 55%), and beta-blocker use was higher among patients in RESHAPE-HF2 compared to COAPT and MITRA-FR trials (96% vs. 90% vs. 90%). Patients in RESHAPE-HF2 had higher eGFR (56 ± 21 ml/min/1.73 m^2) compared to COAPT and MITRA-FR (~50 ml/min/1.73 m^2). Plasma BNP and NT-proBNP concentrations were lower among patients enrolled in RESHAPE-HF2.

Comparison of echocardiographic characteristics across trials

Patients enrolled in the RESHAPE-HF2 trial had the lowest proportion of MR severity of grade 4+. The mean EROA among patients in

Table 2 Comparison of additional clinical data and baseline medications across trials

	RESHAPE-HF2 ($n = 506$)	COAPT ($n = 614$)	MITRA-FR ($n = 304$)
NT-proBNP (pg/ml)			
Mean ± SD	4185 ± 4340	5558[a]	MC: 3407 [1948–6790]
Median [IQR]	2745 [1407–5385] ($n = 384$)		UC: 3292 [1937–6343] ($n = 147$)
BNP (pg/ml)			
Mean ± SD	787 ± 871	1016[a]	MC: 765 [417–1281]
Median [IQR]	455 [260–999] ($n = 123$)		UC: 835 [496–1258] ($n = 126$)
Left ventricular ejection fraction (%)	31 ± 8	31 ± 9[a]	33 ± 6[a]
eGFR (ml/min/1.73 m^2)	56 ± 21 ($n = 498$)	49 ± 26[a]	50 ± 20[a]
Heart rate (bpm)	73 ± 12	74 ± 12[a]	73 ± 13[a]
Systolic blood pressure (mmHg)	113 ± 16	111 ± 17[a]	109 ± 16[a]
Beta-blocker	484 (95.8)	555 (90.3)	272 (89.5)
ACEI or ARB or ARNI	414 (82.1)	412 (67.1)	NR
ACEI or ARB	375 (74.3)	NR	224 (73.7)
ACEI	283 (56.0)	253 (41.2)	NR
ARB	97 (19.2)	138 (22.4)	NR
ARNI	69 (13.7)	22 (3.6%)	31 (10.2)
MRA	416 (82.4)	308 (50.2)	166 (54.6)
SGLT2 inhibitors	36 (7.1)	NR	NR
Hydralazine	2 (0.4)	105 (17.1)	NR
Nitrates	20 (4.0)	44 (7.2)	NR
Diuretics	484 (95.8)	547 (89.1)	300 (98.7)
Aspirin	93 (18.4)	376 (61.2)	NR
Oral anticoagulant	260 (51.4)	265 (43.2)	186 (61.2)
Statin	187 (37.0)	378 (61.2)	NR

Data are provided as mean ± SD, median [IQR], or *n* (%).
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor–neprilysin inhibitor; BNP, B-type natriuretic peptide; eGFR, estimated glomerular filtration rate; IQR, interquartile range; MC, MitraClip group; MRA, mineralocorticoid receptor antagonist; NR, not reported; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SD, standard deviation; SGLT2, sodium–glucose cotransporter 2; UC, usual care group.
[a]For selected variables, when data were only available for patients with device therapy or usual care separately, overall means were estimated.

RESHAPE-HF2 (0.25 cm^2) was lower than in patients in MITRA-FR (0.31 cm^2) and COAPT (0.40 cm^2). A considerably lower proportion of patients had EROA >0.40 cm^2 in RESHAPE-HF2 compared to COAPT (9% vs. 41%). LVEF was largely similar among all three trials around 31%. Mean LV end-diastolic volume values in RESHAPE-HF2, COAPT and MITRA-FR trials were 211, 194 and 252 ml, respectively.

Discussion

RESHAPE-HF2 is a randomized controlled trial evaluating the efficacy of the MitraClip device in the treatment of clinically significant FMR in patients with symptomatic HF despite optimal therapy. It represents the most contemporary cohort of patients for MitraClip and aims to extend the evidence for TEER to patients with less severe FMR. Baseline characteristics of patients enrolled in the RESHAPE-HF2 trial are similar to the ones of the patients enrolled in COAPT and MITRA-FR in terms of age, comorbidities, CRT and LVEF. However, there are some important differences. First, patients enrolled in RESHAPE-HF2 may have been less sick compared to patients enrolled in COAPT and MITRA-FR as evidenced by lower NT-proBNP concentrations and higher eGFR values. Second, FMR severity in RESHAPE-HF2 was lower compared to previously published trials as seen by lower EROA values, and lower proportion of patients with MR grade 4+ severity. We also observed a higher proportion of patients on HF guideline-directed medical therapy in RESHAPE-HF2 than in the other two studies. These results suggest that the patients enrolled in RESHAPE-HF2 may represent a third distinct population where MitraClip was tested in, i.e. one that is mostly consisting of moderate-to-severe FMR instead of severe FMR only, as recruited in COAPT and MITRA-FR trials.

The mean age of the patients enrolled in all three trials was approximately 70 years old, with almost one third of patients having a prior CRT or cardioverter-defibrillator implantation, and half of the patients having a history of prior myocardial infarction. The mean LVEF of the patients enrolled in all three trials was around 31%. Clinically important FMR can happen in the setting of global LV dysfunction or regional wall motional abnormalities, and therefore can occur in both non-ischaemic and ischaemic cardiomyopathies.[17,18] The majority of the patients enrolled in MITRA-FR had non-ischaemic cardiomyopathy (59%) compared to patients enrolled in COAPT (39%) and RESHAPE-HF2 (35%).

Our results suggest that the patients enrolled in RESHAPE-HF2 are less sick compared to patients enrolled in COAPT and MITRA-FR. Natriuretic peptides are often used for prognosis in HF and correlate with LV end-diastolic pressure.[19,20] The BNP and NT-proBNP concentrations were much higher in the COAPT study compared to MITRA-FR and RESHAPE-HF2, suggesting that the patients enrolled in COAPT had higher LV end-diastolic pressure and congestion. Patients in RESHAPE-HF2 had higher eGFR (56 ± 21 ml/min/1.73 m^2) compared to patients in COAPT and MITRA-FR who had eGFR ~50 ml/min/1.73 m^2.

Heart failure guideline-directed medical therapy can significantly reduce the severity of FMR by reverse LV remodelling. Multiple studies have shown that treatment with neuro-hormonal antagonists and beta-blockers significantly reduce morbidity and mortality in patients with FMR and HF, and lead to reduction of FMR.[21–25] A higher proportion of patients were on guideline-directed medical therapy in the RESHAPE-HF2 trial compared to COAPT and MITRA-FR. Notably, four out of five patients were on MRA in RESHAPE-HF2 compared to only half of the patients in COAPT and MITRA-FR. Similarly, the use of ARNI and beta-blockers was also higher in RESHAPE-HF2. Also this may suggest that patients enrolled in the RESHAPE-HF2 trial were somewhat less sick, which resulted in an overall better tolerance of optimized HF therapy.

Most importantly, FMR severity of patients enrolled in RESHAPE-HF2 was lower compared to COAPT and MITRA-FR, although LVEF was similar. The proportion of patients who had MR severity 4+ and EROA >0.40 cm^2 was lower in RESHAPE-HF2 whereas the COAPT trial recruited patients with severe MR (mean EROA 0.41 ± 0.15 cm^2) with only a minority of patients (14%) having an EROA <0.30 cm^2. It is important to highlight that numerical head-to-head comparison of FMR grade severity across trials is limited owing to the different definitions used by each trial for FMR severity, and due to some missingness of EROA data in each trial. Largely, MITRA-FR enrolled patients who had the highest LV dimensions. Patients who received MitraClip in the MITRA-FR trial had a mean LV end-diastolic volume of 252 ml compared to a mean of 192 ml in COAPT and 214 ml in RESHAPE-HF2. This suggests that the patients enrolled in COAPT and MITRA-FR were two distinct patient cohorts with the MITRA-FR cohort having greatest LV volumes and less severe MR, and patients in COAPT having more severe MR with lower LV volumes. We believe that the patients enrolled in RESHAPE-HF2 represent a third unique cohort of patients who had mostly moderate-to-severe FMR instead of severe FMR seen in the COAPT trial, but not with as large LV volumes and high BNP concentrations as observed in MITRA-FR.

In conclusion, baseline characteristics of patients enrolled in the RESHAPE-HF2 trial are similar to the ones of the patients enrolled in the COAPT and MITRA-FR trials in terms of age, comorbidities, CRT and LVEF. However, patients enrolled in RESHAPE-HF2 are somewhat less sick compared to COAPT and MITRA-FR as evidenced by lower concentrations of natriuretic peptides, higher eGFR values, and a lower severity of FMR as seen by lower EROA values and lower proportion of patients with MR grade 4+. These results suggest that the patients enrolled in RESHAPE-HF2 may represent a third distinct cohort of patients where TEER was tested in, who had mostly moderate-to-severe FMR instead of severe FMR. They will be analysed using an innovative endpoint concept with several meaningful outcomes.[26]

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Conflict of interest: Online supplementary Appendix *S1*.

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