

# 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

Stefan D. Anker<sup>1,2,3\*</sup>, Tim Friede<sup>4,5</sup>, Ralph Stephan von Bardeleben<sup>6</sup>, Javed Butler<sup>7,8</sup>, Muhammad Shahzeb Khan<sup>9</sup>, Monika Diek<sup>1,2,3</sup>, Jutta Heinrich<sup>10</sup>, Martin Geyer<sup>6</sup>, Marius Placzek<sup>4,5</sup>, Roberto Ferrari<sup>11</sup>, William T. Abraham<sup>12</sup>, Ottavio Alfieri<sup>13</sup>, Angelo Auricchio<sup>14</sup>, Antoni Bayes-Genis<sup>15</sup>, John G.F. Cleland<sup>16</sup>, Gerasimos Filippatos<sup>17</sup>, Finn Gustafsson<sup>18</sup>, Wilhelm Haverkamp<sup>1</sup>, Malte Kelm<sup>19,20</sup>, Karl-Heinz Kuck<sup>21</sup>, Ulf Landmesser<sup>22,23,24</sup>, Aldo P. Maggioni<sup>25</sup>, Marco Metra<sup>26</sup>, Vlasis Ninios<sup>27</sup>, Mark C. Petrie<sup>16</sup>, Tienush Rassaf<sup>28</sup>, Frank Ruschitzka<sup>29,30</sup>, Ulrich Schäfer<sup>31</sup>, P. Christian Schulze<sup>32</sup>, Konstantinos Spargias<sup>33</sup>, Alec Vahanian<sup>34</sup>, Jose Luis Zamorano<sup>35,36</sup>, Andreas Zeiher<sup>37,38</sup>, Mahir Karakas<sup>39,40</sup>, Friedrich Koehler<sup>24,41,42</sup>, Mitja Lainscak<sup>43,44</sup>, Alper Öner<sup>45</sup>, Nikolaos Mezilis<sup>46</sup>, Efstratios K Theofilogiannakos<sup>46</sup>, Ilias Ninios<sup>27</sup>, Michael Chrissoheris<sup>33</sup>, Panagiota Kourkouveli<sup>33</sup>, Konstantinos Papadopoulos<sup>27,33</sup>, Grzegorz Smolka<sup>47</sup>, Wojciech Wojakowski<sup>47</sup>, Krzysztof Reczuch<sup>48</sup>, Fausto J. Pinto<sup>49</sup>, Krzysztof Zmudka<sup>50</sup>, Zbigniew Kalarus<sup>51</sup>, Marianna Adamo<sup>26</sup>, Evelyn Santiago-Vacas<sup>15</sup>, Tobias Friedrich Ruf<sup>6</sup>, Michael Gross<sup>52</sup>, Joern Tongers<sup>53</sup>, Gerd Hasenfuß<sup>2,3</sup>, Wolfgang Schillinger<sup>2,54</sup>, and Piotr Ponikowski<sup>49</sup>

<sup>1</sup>Department of Cardiology (CVK) of German Heart Center Charité; Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) Partner Site Berlin, Charité Universitätsmedizin, Berlin, Germany; <sup>2</sup>Department of Cardiology and Pneumology, University Medical Centre Göttingen, Georg August University of Göttingen, Göttingen, Germany; <sup>3</sup>German Centre for Cardiovascular Research (DZHK), Partner Site Göttingen, Göttingen, Germany; <sup>4</sup>Department of Medical Statistics, University Medical Center Göttingen, Göttingen, Germany; <sup>5</sup>German Centre for Cardiovascular Research (DZHK), partner site Göttingen, Göttingen, Germany; <sup>6</sup>Department of Cardiology, University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; <sup>7</sup>Department of Medicine, University of Mississippi Medical Center, Jackson, MS, USA; <sup>8</sup>Baylor Scott and White Research Institute, Dallas, TX, USA; <sup>9</sup>Division of Cardiology, Duke University School of Medicine, Durham, NC, USA; <sup>10</sup>Clinical Trial Unit, University Medical Center Göttingen, Göttingen, Germany; <sup>11</sup>Department of Translational Medicine, University of Ferrara, Ferrara, Italy; <sup>12</sup>Division of Cardiovascular Medicine, The Ohio State University, Columbus, OH, USA; <sup>13</sup>Cardiac Surgery Unit, IRCCS San Raffaele Scientific Institute, Milan, Italy; <sup>14</sup>Department of Cardiology, Cardiocentro Ticino Institute-EOC, Lugano, Switzerland; <sup>15</sup>Heart Institute, Hospital Universitari Germans Trias i Pujol, Barcelona, Spain; <sup>16</sup>School of Cardiovascular and Metabolic Health, University of Glasgow, British Heart Foundation Glasgow Cardiovascular Research Centre, Glasgow, UK; <sup>17</sup>Department of Cardiology, Attikon University Hospital, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece; <sup>18</sup>Department of Cardiology, Copenhagen University Hospital – Rigshospitalet, Copenhagen, Denmark; <sup>19</sup>Department of Cardiology, Pulmonology and Vascular Medicine, University Hospital Düsseldorf, Medical Faculty of the Heinrich Heine University Düsseldorf, Düsseldorf, Germany; <sup>20</sup>CARID, Cardiovascular Research Institute, Medical Faculty and University Hospital Düsseldorf, Heinrich-Heine University, Düsseldorf, Germany; <sup>21</sup>Department of Rhythmology, University Heart Center Lübeck, University Hospital Schleswig-Holstein, Lübeck, Germany;

\*Corresponding author. Department of Cardiology (CVK) of German Heart Center Charité, Charité Universitätsmedizin Berlin, Augustenburger Platz 1, D-13353 Berlin, Germany. Email: s.anker@cachexia.de

© 2024 The Authors. *European Journal of Heart Failure* published by John Wiley & Sons Ltd on behalf of European Society of Cardiology. This is an open access article under the terms of the [Creative Commons Attribution-NonCommercial-NoDerivs](https://creativecommons.org/licenses/by-nc-nd/4.0/) License, which permits use and distribution in any medium, provided the original work is properly cited, the use is non-commercial and no modifications or adaptations are made.

<sup>22</sup>Department of Cardiology, Angiology and Intensive Care Medicine, Deutsches Herzzentrum der Charité, Campus Benjamin Franklin, Berlin, Germany; <sup>23</sup>Berlin Institute of Health, Berlin, Germany; <sup>24</sup>DZHK (German Centre for Cardiovascular Research), Partner Site Berlin, Berlin, Germany; <sup>25</sup>ANMCO Research Center, Heart Care Foundation, Florence, Italy; <sup>26</sup>Institute of Cardiology, ASST Spedali Civili and Department of Medical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; <sup>27</sup>European Interbalkan Medical Center, Thessaloniki, Greece; <sup>28</sup>West German Heart and Vascular Center, Department of Cardiology and Vascular Medicine, University Hospital Essen, University Duisburg-Essen, Essen, Germany; <sup>29</sup>Department of Cardiology, University Heart Center, University Hospital Zurich and University of Zurich, Zurich, Switzerland; <sup>30</sup>Center for Translational and Experimental Cardiology (CTEC), Department of Cardiology, University Hospital Zurich, University of Zurich, Zurich, Switzerland; <sup>31</sup>Heart and Vascular Centre, Bad Bevensen, Germany; <sup>32</sup>Department of Internal Medicine I, Cardiology, University Hospital Jena, Jena, Germany; <sup>33</sup>Department of Transcatheter Heart Valves, HYGEIA Hospital, Athens, Greece; <sup>34</sup>UFR Medecine, Université de Paris-Cité, site Bichat, GH Bichat, Paris, France; <sup>35</sup>Department of Cardiology, Hospital Universitario Ramón y Cajal, Madrid, Spain; <sup>36</sup>CIBERCV, Instituto de Salud Carlos III (ISCIII), Madrid, Spain; <sup>37</sup>Institute for Cardiovascular Regeneration, Goethe University Frankfurt, Frankfurt am Main, Germany; <sup>38</sup>German Center of Cardiovascular Research (DZHK), Partner Site Rhein-Main, Frankfurt am Main, Germany; <sup>39</sup>Department of Intensive Care Medicine, University Medical Center Hamburg-Eppendorf, Hamburg, Germany; <sup>40</sup>German Centre for Cardiovascular Research (DZHK), Partner Site Hamburg/Kiel/Lübeck, Hamburg, Germany; <sup>41</sup>Deutsches Herzzentrum der Charité (DHZC), Department of Cardiology, Angiology and Intensive Care Medicine, Campus Charité Mitte, Berlin, Germany; <sup>42</sup>Center for Cardiovascular Telemedicine, Charité - Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin and Humboldt-Universität zu Berlin, Berlin, Germany; <sup>43</sup>Division of Cardiology, General Hospital Murska Sobota, Murska Sobota, Slovenia; <sup>44</sup>Faculty of Medicine, University of Ljubljana, Ljubljana, Slovenia; <sup>45</sup>Department of Cardiology, Rostock University Medical Centre, Rostock, Germany; <sup>46</sup>Department of Cardiology, St Luke's Hospital, Thessaloniki, Greece; <sup>47</sup>Division of Cardiology and Structural Heart Diseases, Medical University of Silesia, Katowice, Poland; <sup>48</sup>Institute of Heart Diseases, Medical University and University Hospital, Wrocław, Poland; <sup>49</sup>Centro Academico de Medicina de Lisboa, CCUL@RISE, Faculdade de Medicina da Universidade de Lisboa, Lisbon, Portugal; <sup>50</sup>Clinic of Interventional Cardiology, John Paul II Hospital, Kraków, Poland; <sup>51</sup>Department of Cardiology, Congenital Heart Diseases and Electrotherapy, Medical University of Silesia, Katowice, Poland; <sup>52</sup>Department of Medicine, Heart and Vascular Center, Division of Cardiology and Vascular Medicine, Johanniter Hospital Stendal, Stendal, Germany; <sup>53</sup>Mid-German Heart Center, Department of Cardiology, Angiology and Intensive Care Medicine, University Hospital Halle/Saale, Halle, Germany; and <sup>54</sup>Heart Center, Department of Cardiology, Georg-August-University Göttingen, Göttingen, Germany

Received 11 April 2024; revised 24 April 2024; accepted 30 April 2024; online publish-ahead-of-print 7 June 2024

## 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

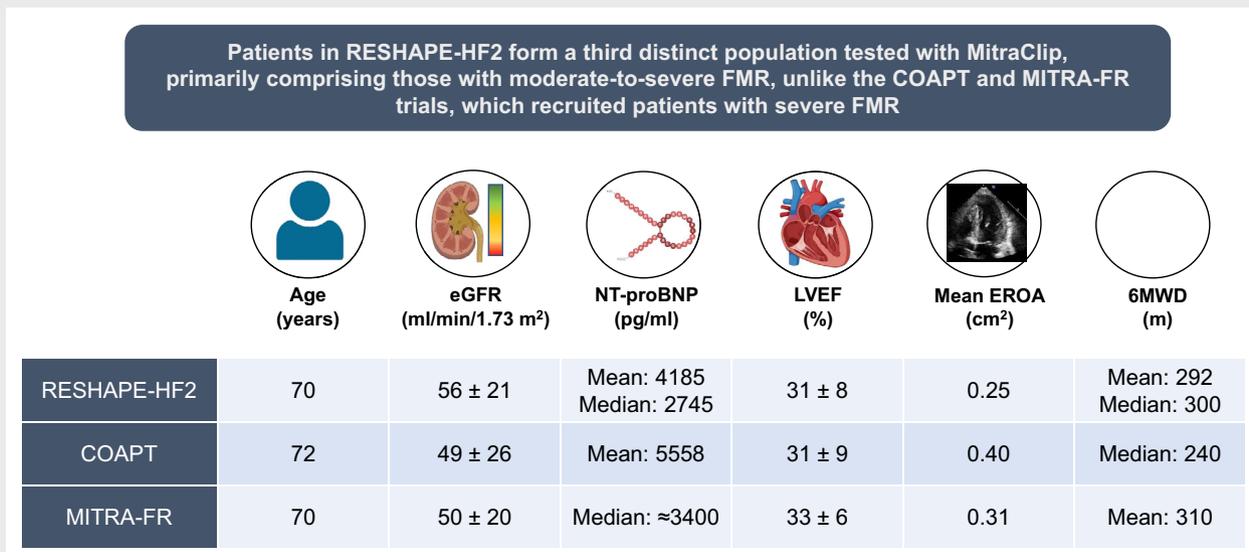
The RESHAPE-HF2 study is an investigator-initiated, prospective, randomized, multicentre trial including patients with symptomatic HF, a left ventricular ejection fraction (LVEF) between 20% and 50% with moderate-to-severe or severe FMR, for whom isolated mitral valve surgery was not recommended. Patients were randomized 1:1 to a strategy of delivering or withholding MitraClip. Of 506 patients randomized, the mean age of the patients was  $70 \pm 10$  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  $31 \pm 8\%$ ,  $211 \pm 76$  ml and  $0.25 \pm 0.08$  cm<sup>2</sup>, 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



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.<sup>1,2</sup> One in every five patients with heart failure (HF) may have moderate-to-severe FMR which is associated with substantial morbidity and mortality.<sup>3–5</sup> 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.<sup>6,7</sup> 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.<sup>8,9</sup> 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.<sup>10,11</sup> 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.<sup>12–15</sup> 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.<sup>16</sup> 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  $\geq 20\%$  and  $\leq 50\%$  (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]  $\geq 300$  pg/ml or N-terminal proBNP [NT-proBNP]  $\geq 1000$  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  $70 \pm 10$  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-ischaeamic 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  $56 \pm 21$  ml/min/1.73 m<sup>2</sup>, and mean NT-proBNP concentrations were  $4185 \pm 4340$  pg/ml (median [interquartile range]) 2745 ([1407–5385] pg/ml). The mean KCCQ overall summary score was  $46 \pm 24$ .

### Baseline echocardiographic characteristics

The mean LVEF of the cohort was  $31 \pm 8\%$ . The mean LV end-systolic and diastolic volume were  $147 \pm 65$  and  $211 \pm 76$  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 <sup>a</sup>	70 <sup>a</sup>
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) <sup>b</sup>	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 <sup>2</sup> )	26.8 ± 4.3	27 <sup>a</sup>	NR
EuroSCORE II <sup>c</sup>	5.3 [2.8–9.0]	NR	MC: 6.6 [3.5–11.9] UC: 5.9 [3.4–10.4]
Non-isaemic 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) <sup>a</sup>
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.

<sup>a</sup>For selected variables, when data were only available for patients with device therapy or usual care separately, overall medians were estimated.

<sup>b</sup>Represents for RESHAPE-HF2 the combined number of patients with a prior stent and/or PCI therapy.

<sup>c</sup>For 109 patients, EuroSCORE I was assessed.

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

## 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-isaemic 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<sup>2</sup>) compared to COAPT and MITRA-FR (~50 ml/min/1.73 m<sup>2</sup>). 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 <sup>a</sup>	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 <sup>a</sup>	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 <sup>a</sup>	33 ± 6 <sup>a</sup>
eGFR (ml/min/1.73 m <sup>2</sup> )	56 ± 21 (n = 498)	49 ± 26 <sup>a</sup>	50 ± 20 <sup>a</sup>
Heart rate (bpm)	73 ± 12	74 ± 12 <sup>a</sup>	73 ± 13 <sup>a</sup>
Systolic blood pressure (mmHg)	113 ± 16	111 ± 17 <sup>a</sup>	109 ± 16 <sup>a</sup>
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.

<sup>a</sup>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<sup>2</sup>) was lower than in patients in MITRA-FR (0.31 cm<sup>2</sup>) and COAPT (0.40 cm<sup>2</sup>). A considerably lower proportion of patients had EROA >0.40 cm<sup>2</sup> 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.<sup>17,18</sup> 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.<sup>19,20</sup> 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 ( $56 \pm 21$  ml/min/1.73 m<sup>2</sup>) compared to patients in COAPT and MITRA-FR who had eGFR  $\sim 50$  ml/min/1.73 m<sup>2</sup>.

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.<sup>21–25</sup> 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<sup>2</sup> was lower in RESHAPE-HF2 whereas the COAPT trial recruited patients with severe MR (mean EROA  $0.41 \pm 0.15$  cm<sup>2</sup>) with only a minority of patients (14%) having an EROA  $<0.30$  cm<sup>2</sup>. 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.<sup>26</sup>

## 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.

## Acknowledgement

Open Access funding enabled and organized by Projekt DEAL.

## References

- Nkomo VT, Gardin JM, Skelton TN, Gottdiener JS, Scott CG, Enriquez-Sarano M. Burden of valvular heart diseases: A population-based study. *Lancet* 2006;**368**:1005–1011. [https://doi.org/10.1016/S0140-6736\(06\)69208-8](https://doi.org/10.1016/S0140-6736(06)69208-8)
- Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics 2016 update: A report from the American Heart Association. *Circulation* 2016;**133**:e38–e360. <https://doi.org/10.1161/CIR.0000000000000350>
- Levine RA, Schwammenthal E. Ischemic mitral regurgitation on the threshold of a solution: From paradoxes to unifying concepts. *Circulation* 2005;**112**:745–758. <https://doi.org/10.1161/CIRCULATIONAHA.104.486720>
- Rossi A, Dini FL, Faggiano P, Agricola E, Ciccoira M, Frattini S, et al. Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 2011;**97**:1675–1680. <https://doi.org/10.1136/hrt.2011.225789>
- Vajapey R, Kwon D. Guide to functional mitral regurgitation: A contemporary review. *Cardiovasc Diagn Ther* 2021;**11**:781–792. <https://doi.org/10.21037/cdt-20-277>
- Stone GW, Vahanian AS, Adams DH, Abraham WT, Borer JS, Bax JJ, et al.; Mitral Valve Academic Research Consortium (MVARC). Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: Part 1: Clinical trial design principles: A consensus document from the Mitral Valve Academic Research Consortium. *J Am Coll Cardiol* 2015;**66**:278–307. <https://doi.org/10.1016/j.jacc.2015.05.046>
- Barnes C, Sharma H, Gamble J, Dawkins S. Management of secondary mitral regurgitation: From drugs to devices. *Heart*. <https://doi.org/10.1136/heartjnl-2022-322001>. Published online ahead of print 22/08/23.
- Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP III, Fleisher LA, et al. 2017 AHA/ACC Focused update of the 2014 AHA/ACC Guideline for the management of patients with valvular heart disease: A report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *J Am Coll Cardiol* 2017;**70**:252–289. <https://doi.org/10.1016/j.jacc.2017.03.011>
- Baumgartner H, Falk V, Bax JJ, de Bonis M, Hamm C, Holm PJ, et al.; ESC Scientific Document Group. 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 2017;**38**:2739–2791. <https://doi.org/10.1093/eurheartj/ehx391>
- Obadia JF, Messika-Zeitoun D, Leurent G, Lung B, Bonnet G, Piriou N, et al.; MITRA-FR Investigators. Percutaneous repair or medical treatment for secondary mitral regurgitation. *N Engl J Med* 2018;**379**:2297–2306. <https://doi.org/10.1056/NEJMoa1805374>
- Stone GW, Lindenfeld J, Abraham WT, Kar S, Lim DS, Mishell JM, et al.; COAPT Investigators. Transcatheter mitral-valve repair in patients with heart failure. *N Engl J Med* 2018;**379**:2307–2318. <https://doi.org/10.1056/NEJMoa1806640>
- Nappi F, Nenna A, Sing SSA, Timofeeva I, Mihos C, Gentile F, et al. Mitral regurgitation: Lessons learned from COAPT and MITRA-FR. *J Thorac Dis* 2020;**12**:2936–2944. <https://doi.org/10.21037/jtd.2020.01.67>

13. Grayburn PA, Chandrashekar YS. Functional mitral regurgitation: More questions than answers. *JACC Cardiovasc Imaging* 2021;**14**:711–714. <https://doi.org/10.1016/j.jcmg.2021.03.001>
14. Grayburn PA, Sannino A, Packer M. Proportionate and disproportionate functional mitral regurgitation: A new conceptual framework that reconciles the results of the MITRA-FR and COAPT trials. *JACC Cardiovasc Imaging* 2019;**12**:353–362. <https://doi.org/10.1016/j.jcmg.2018.11.006>
15. Pibarot P, Delgado V, Bax JJ. MITRA-FR vs. COAPT: Lessons from two trials with diametrically opposed results. *Eur Heart J Cardiovasc Imaging* 2019;**20**:620–624. <https://doi.org/10.1093/ehjci/jez073>
16. Anker SD, Friede T, von Bardeleben RS, Butler J, Fatima K, Diek M, et al. Randomised investigation of MitraClip device in heart failure: Design and rationale of the RESHAPE-HF2 trial. *Eur J Heart Fail* 2024;**26**:984–993. <https://doi.org/10.1002/ehf.3247>
17. Levine RA, Hagège AA, Judge DP, Padala M, Dal-Bianco JP, Aikawa E, et al.; Leducq Mitral Transatlantic Network. Mitral valve disease – morphology and mechanisms. *Nat Rev Cardiol* 2015;**12**:689–710. <https://doi.org/10.1038/nrcardio.2015.161>
18. Varma PK, Krishna N, Jose RL, Madkaiker AN. Ischemic mitral regurgitation. *Ann Card Anaesth* 2017;**20**:432–439. [https://doi.org/10.4103/aca.ACA\\_58\\_17](https://doi.org/10.4103/aca.ACA_58_17)
19. Tsutsui H, Albert NM, Coats AJS, Anker SD, Bayes-Genis A, Butler J, et al. Natriuretic peptides: Role in the diagnosis and management of heart failure: A scientific statement from the Heart Failure Association of the European Society of Cardiology, Heart Failure Society of America and Japanese Heart Failure Society. *Eur J Heart Fail* 2023;**25**:616–631. <https://doi.org/10.1002/ehf.2848>
20. Mueller C, McDonald K, de Boer RA, Maisel A, Cleland JGF, Kozhuharov N, et al.; Heart Failure Association of the European Society of Cardiology. Heart Failure Association of the European Society of Cardiology practical guidance on the use of natriuretic peptide concentrations. *Eur J Heart Fail* 2019;**21**:715–731. <https://doi.org/10.1002/ehf.1494>
21. Kang DH, Park SJ, Shin SH, Hong GR, Lee S, Kim MS, et al. Angiotensin receptor neprilysin inhibitor for functional mitral regurgitation. *Circulation* 2019;**139**:1354–1365. <https://doi.org/10.1161/CIRCULATIONAHA.118.037077>
22. Rosano GMC, Farkas J. Evolving targets for heart failure: The journey so far. *Global Cardiol* 2023;**1**:3–6. <https://doi.org/10.4081/cardio.2023.6>
23. Siddiqi TJ, Butler J, Coats AJ, Verma S, Friede T, Filippatos G, et al. SGLT2 inhibitors and risk reduction for mortality in high-risk patients: A meta-analysis of randomized controlled trials. *Global Cardiol* 2023;**1**:55–60. <https://doi.org/10.4081/cardio.2023.2>
24. Capomolla S, Febo O, Gnemmi M, Riccardi G, Opasich C, Caporotondi A, et al. Beta-blockade therapy in chronic heart failure: Diastolic function and mitral regurgitation improvement by carvedilol. *Am Heart J* 2000;**139**:596–608. [https://doi.org/10.1016/s0002-8703\(00\)90036-x](https://doi.org/10.1016/s0002-8703(00)90036-x)
25. Seneviratne B, Moore GA, West PD. Effect of captopril on functional mitral regurgitation in dilated heart failure: A randomised double blind placebo controlled trial. *Br Heart J* 1994;**72**:63–68. <https://doi.org/10.1136/hrt.72.1.63>
26. Rosano GMC. Clinical trial design, endpoints and regulatory considerations in heart failure. *Global Cardiol*. <https://doi.org/10.4081/cardio.2024.18>. Published online ahead of print 28/03/24.