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ARTICLE

Baseline echocardiographic characteristics of patients enrolled in the randomized investigation of MitraClip device in heart failure (RESHAPE HF-2) trial: comparison with COAPT and Mitra-FR

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Abstract

Background: The RESHAPE-HF2 trial is aimed at evaluating the efficacy of the MitraClip device for the treatment of clinically significant functional mitral regurgitation (FMR) in patients with heart failure (HF). This report describes the baseline echocardiographic characteristics of patients enrolled in the RESHAPE-HF2 trial compared to those enrolled in the COAPT and MITRA-FR trials.

Methods: The RESHAPE-HF2 study is a prospective, randomized, multicenter trial involving patients with symptomatic HF, a left ventricular ejection fraction (LVEF) between 20% and 50%, and moderate-to-severe or severe FMR who are ineligible for isolated mitral valve surgery, despite receiving guideline-directed therapy. Patients were randomized 1:1 to either receive the MitraClip or be placed in a control group without the intervention.

Results: For the 505 patients randomized (mean age 70 years, 20% female, mean body mass index 26.8 kg/m^2), the mean LVEF in the cohort was 31±8%. The mean regurgitant volume was 37±12 mL, while mean proximal iso-velocity surface area (PISA) radius was 0.72 cm. Less than half of the patients (44%) had MR severity grade 4+. The mean effective regurgitant orifice area (EROA) among patients in RESHAPE-HF2 (0.25 cm^2) was lower compared to patients in MITRA-FR (0.31 cm^2) and in COAPT (0.40 cm^2) trials. Regurgitant volumes in RESHAPE-HF2 were 18% lower than in than in MITRA-FR (45 mL) but 38% higher than in COAPT (27 mL). The mean LV end-diastolic volumes values in the RESHAPE-HF2, COAPT, and MITRA-FR trials were 211 mL, 193 mL, and 250 mL, respectively. Patients in RESHAPE-HF2 (41 mmHg) had a comparatively lower right ventricular systolic pressure than patients in MITRA-FR (54 mmHg) and in COAPT (44 mmHg). Patients in RESHAPE-HF2, MITRA-FR, and COAPT had a similar LVEF of around 31%.

Conclusions: The baseline echocardiographic characteristics of patients in the RESHAPE-HF2 trial differ from patients in the MITRA-FR and COAPT trials. Patients enrolled in RESHAPE-HF2 had moderate-to-severe FMR, characterized by a smaller PISA radius, a lesser proportion of MR severity grade of 4+, and lower mean EROA and regurgitant volumes compared to patients in COAPT and MITRA-FR trials. LVEF was largely similar across all trials. RESHAPE-HF2 is testing TEER in a third distinct cohort of patients who have less severe FMR compared to patients in COAPT trial but have high left atrial volumes. The RESHAPE-HF2 population is also echocardiographically different from the MITRA-FR cohort.

Key words: heart failure, functional mitral regurgitation, MitraClip, echocardiography, clinical trial.

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Introduction

Heart failure (HF) affects around 6 million individuals in the United States and 10 million across Europe.[1,2] Functional mitral regurgitation (FMR) frequently coexists with HF, affecting one in five patients and substantially impacts overall survival.[3] While guideline-directed medical therapy and cardiac resynchronization therapy (CRT) can lessen the severity of FMR, survival rates remain low for patients with HF and chronic FMR who are unresponsive to therapy.[4-6] The MitraClip device used in the transcatheter edge-to-edge repair (TEER) procedure has emerged as a promising treatment option in this cohort.[7] Prior studies, such as 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), have evaluated the effectiveness of MitraClip in HF patients with primarily severe FMR.[8,9] The MITRA-FR trial did not demonstrate a reduction in the composite endpoint of HF hospitalizations or cardiovascular mortality (54.6% *vs.* 51.3%, p=0.53) in the MitraClip arm, while the COAPT trial reported a reduction in HF hospitalizations (35.8% *vs.* 67.9%) and all-cause mortality (29.1% *vs.* 46.1%) among patients receiving MitraClip intervention *vs.* control.

One of the potential reasons for the disconcordant results of MITRA-FR and COAPT has been reported to be the concept of proportionate or disproportionate FMR. It has been suggested that larger effective regurgitant orifice area (EROA) or regurgitant volume relative to LV dimensions maybe predictive of patients who benefit from TEER, such as patient population in COAPT trial. Other echocardiographic characteristics such as tricuspid regurgitation and right ventricle systolic pressure have also been proposed to be important predictors of TEER success. Thus, it is important to assess the baseline echocardiographic characteristics of the patients enrolled in RESHAPE-HF2 [A Randomized Study of the MitraClip Device in Heart Failure Patients with Clinically Significant Functional Mitral Regurgitation (NCT02444338)] trial which evaluates safety and efficacy of MitraClip in patients with HF and moderate-to-severe FMR. This report outlines the baseline echocardiographic characteristics of patients enrolled in RESHAPE-HF2 and compares them with patients enrolled in the COAPT and MITRA-FR trials.

Materials and Methods

Study design

The RESHAPE-HF2 (NCT02444338) is a prospective, randomized, parallel-controlled, multicenter study designed to assess the safety and efficacy of the MitraClip device in the management of clinically significant FMR in patients with chronic HF and New York Heart Association (NYHA) functional class II-IV symptoms despite treatment with guideline directed therapy and in whom isolated mitral valve surgery is not advised as a treatment option. The design has been previously published and is briefly summarized below.[10]

Study patients

Eligible patients included those exhibiting signs and symptoms of HF (NYHA class II-IV despite optimal therapy), have moderate-to-severe or severe FMR, have LVEF between ≥20% and ≤50% (initially 15-35% for NYHA class II patients, and 15-45% for NYHA III/IV patients), HF hospitalization or raised natriuretic peptides (BNP ≥300 pg/mL or NT-proBNP ≥1000 pg/mL) within the preceding 90 days, have undergone cardiac resynchronization therapy, if eligible, and in whom isolated mitral valve surgery is not advised for treatment. Patients with primary mitral regurgitation due to degenerative diseases of the mitral valve apparatus (Degenerative MR), as determined by transesophageal echocardiography (TEE) or, if applicable, transthoracic echocardiography (TTE) were ineligible. Similarly, patients who underwent percutaneous cardiovascular intervention, carotid surgery, cardiovascular surgery, or atrial fibrillation ablation within 90 days before randomization were also ineligible. Patients were randomized in a 1:1 ratio between the intervention and control groups, wherein participants in the intervention group were scheduled to undergo the MitraClip procedure within 14 days following randomization. The trial includes three primary outcomes: i) composite rate of total (first and recurrent) HF hospitalizations and cardiovascular death during 24 months of follow-up; ii) the rate of total (*i.e.,* first and recurrent) HF hospitalizations within 24 months; iii) the change from baseline to 12 months in the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score.

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.

Baseline data

All patients underwent evaluation by the site heart team consisting of a HF specialist, an interventional cardiologist, an echocardiographer, and a cardiothoracic surgeon to ensure that all patients are on optimally guideline directed therapy. All patients were required to have both TTE and TEE echocardiographic studies done prior to study enrollment. All patients underwent a detailed baseline visit, including a thorough review of medical and social history obtained by chart review and patient self-report. During the baseline visit, the following data was collected: history of previous myocardial infarction, stroke, chronic obstructive pulmonary disease, hypertension, dyslipidemia, atrial fibrillation, type 2 diabetes, chronic kidney disease, and hospitalization for HF. At the baseline visit, all medications for HF were documented. Physical examination and laboratory data included heart rate, systolic and diastolic blood pressure, height, weight, complete blood count, NT-proBNP and basal metabolic panel including estimated glomerular filtration rate. The health status assessment utilized the 23-question KCCQ. The baseline surgical risk was determined by calculating the Euro Score. Data from TTE and TEE conducted prior to randomization were extracted, particularly for left ventricular ejection fraction (LVEF), LV end systolic and end diastolic parameters, severity of FMR, effective regurgitant orifice area (EROA), and regurgitant volumes.

As endorsed by MVARC recommendations, all echocardiographic datasets were assessed by an independent echocardiographic core laboratory prior to inclusion in the study. Both baseline TEE and TTE of all screening individuals were transmitted via a file transfer-platform in DICOM standard to an independent central university center institution (Echo Corelab / ECL) in an pseudonymized fashion for detailed analysis of MR severity as well as all other echocardiographic parameters for this manuscript. Evaluation on echocardiographic eligibility was confirmed by the ECL before randomization in device or control group.

Comparison with COAPT and MITRA-FR Trials

Baseline echocardiographic characteristics from RESHAPE-HF2 were compared with those of other trials investigating efficacy of MitraClip in patients with chronic HF and FMR, such as MITRA-FR and COAPT trials. Echocardiographic characteristics such as LVEF, LV end-systolic and end-diastolic dimensions (LVESD and LVEDD, respectively), LV end-systolic and end-diastolic volumes (LVESV and LVEDV, respectively), peak E velocity, left-atrial (LA) volume, right ventricular systolic pressure (RVSP), tricuspid regurgitation (TR) severity, proximal isovelocity surface area (PISA) radius, severity of FMR, EROA, regurgitant volumes, and vena contracta diameter were compared between patients enrolled in RESHAPE-HF2, MITRA-FR and COAPT trials.

Results

Baseline echocardiographic characteristics

Between March 2015 and October 2023, 621 patients across 9 countries were screened, and a total of 505 were randomized (mean age 70 years, 20% female, mean body mass index 26.8 kg/m^2). The mean LVEF in the cohort was 31±8%. Mean LV end-systolic and end-diastolic volumes were 147±65 mL and 211±76 mL, respectively. The mean EROA was 0.25 cm^2. The mean regurgitant volume was 37±12 mL, while mean PISA radius was 0.72 cm. Less than half of the patients (44%) had MR severity grade 4+. TR severity grade 3+ was observed in 37 patients (7.3%).

Comparison of echocardiographic characteristics across trials

Patients in RESHAPE-HF2, MITRA-FR, and COAPT had a similar LVEF of around 31% (Table 1). The mean LVESD and LVEDD values were larger in patients enrolled in RESHAPE-HF2 (5.9 cm and 7.0 cm, respectively) than in patients in COAPT (5.3 cm and 6.2 cm, respectively), but similar to MITRA-FR. The mean LVESV values in the RESHAPE-HF2 and COAPT trials were 147 mL and 134 mL, respectively. In Mitra-FR it was higher (169 mL). The mean LVEDV values in the RESHAPE-HF2, COAPT, and MITRA-FR trials were 211 mL, 193 mL, and 250 mL, respectively. Peak E velocity was 109 cm/s in RESHAPE-HF2, and 110 cm/s in the

COAPT trial population. Patients enrolled in RESHAPE-HF2 had higher LA volumes (124 mL *vs.* 91 mL) compared to patients in the COAPT trial.

The mean PISA radius among patients in RESHAPE-HF2 (0.72 cm) was lower than in patients in COAPT (0.89 cm) (Table 1). The mean EROA among patients in RESHAPE-HF2 (0.25 cm^2) was lower compared to patients in MITRA-FR (0.31 cm^2) and in COAPT (0.40 cm^2) trials. Regurgitant volumes were also lower in RESHAPE-HF2 (37 mL *vs.* 45 mL) than in MITRA-FR, but higher than in COAPT (27 mL). However, RESHAPE-HF2 had a higher mean vena contracta diameter (0.82 cm) compared to COAPT (0.58 cm).

Patients in RESHAPE-HF2 (41 mmHg) had a lower RVSP than patients in MITRA-FR (54 mmHg) and in COAPT (44 mmHg)

Table 1. Comparison of baseline left ventricular function and mitral regurgitation among patients enrolled in RESHAPE-HF2, COAPT, and MITRA-FR trials.

	RESHAPE-HF2 (n=505)	COAPT (n=614)	MITRA-FR (n=304)
Left ventricular ejection fraction (%)	31.4±8.0	MitraClip: 31.3±9.1 Control: 31.3±9.6	MitraClip: 33.3±6.5 Control: 32.9±6.7
Left ventricular end-systolic dimension (cm)	5.9±1.0 *N-Miss=5*	MitraClip: 5.3±0.9 Control: 5.3±0.9	5.8
Left ventricular end-diastolic dimension (cm)	7.0±1.0 *N-Miss=5*	MitraClip: 6.2±0.7 Control: 6.2±0.8	6.9
Left ventricular end-systolic volume (mL)	147.3±65.0	MitraClip: 135±56 Control: 134±60	169
Left ventricular end-diastolic volume (mL)	211.4±75.8	MitraClip: 194±69 Control: 191±73	250 (75)
LA volume (mL)	123.6±53.9 *N-Miss=3*	MitraClip: 91.7±36.3 Control: 91.0±44.8	NR
Peak E (cm/s)	108.7±28.0 *N-Miss=7*	MitraClip: 110.6±28.7 Control: 109.4±24.9	NR
Left ventricular end-systolic dimension index (cm/m^2)	3.2±0.5 *N-Miss=9*	2.8±0.5	3.2±0.5
Left ventricular end-diastolic dimension index (cm/m^2)	3.7±0.6 *N-Miss=9*	3.3±0.4	3.8±0.5
Left ventricular end-systolic volume index (mL/m^2)	78±33 *N-Miss=4*	71.1±29.1	92±30
Left ventricular end-diastolic volume index (mL/m^2)	111±38 *N-Miss=4*	101±34	MitraClip: 136±37 Control: 134±33
PISA radius (cm)	0.72±0.11 *N-Miss=12*	MitraClip: 0.89±0.17 Control: 0.88±0.18	NR
MR Severity 3+	282 (55.8)	320 (52.2)	NR
MR Severity 4+	223 (44.2)	293 (47.8)	NR
Effective regurgitant orifice area (cm^2)	0.25±0.08 *N-Miss=27*	MitraClip: 0.41±0.15 Control: 0.40±0.15	MitraClip: 0.31±0.1 Control: 0.31±0.11
Moderate EROA (20-29 mm^2), %	53	14	52
Moderate to Severe EROA (30-39 mm^2), %	17	46	32
Severe EROA (≥40 mm^2), %	7	41	16
EROA/LVESD (mm^2/mm)	0.43±0.15 *N-Miss=30*	NR	0.54±0.19
EROA/LVEDD (mm^2/mm)	0.37±0.12 *N-Miss=30*	NR	0.45±0.16
EROA/LVESV (mm^2/mL)	0.20±0.10 *N-Miss=27*	NR	0.20±0.09
EROA/LVEDV (mm^2/mL)	0.13±0.05 *N-Miss=27*	NR	0.13±0.05
Regurgitant volume (mL)	37±12 *N-Miss=27*	26.8±16.2	MitraClip: 45±13 Control: 45±14
Vena contracta diameter (cm)	0.82±0.43 *N-Miss=2*	0.58±0.12	NR
Mitral valve orifice area (cm^2)	5.3±0.9 *N-Miss=8*	5.2±1.2	NR
Regurgitant fraction (%)	44.0±8.9 *N-Miss=67*	36.4±14.5	0.49±0.1
Regurgitant fraction LVEF	0.14±0.04 *N-Miss=67*	0.11±0.3	0.16±0.5

LA, left atrial; PISA, proximal isovelocity surface area; MR, mitral regurgitation; EROA, effective regurgitant orifice area; NR, data not reported; LVESD, left ventricular end-systolic dimension; LVEDD, left ventricular end-diastolic dimension; LVESV, left ventricular end-systolic volume; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; N-Miss, number of missing assessments.

(Table 2). RESHAPE-HF2 (54.3%) had a lower proportion of patients with TR severity grade 1+ than in COAPT (79.6%) and MITRA-FR (81%). However, RESHAPE-HF2 had a greater proportion of patients with TR severity grade 2+ (35.2% *vs.* 15.0%) and grade 3+ (7.3% *vs*. 0.8%) than in the COAPT trial.

Discussion

The RESHAPE-HF2 trial, a multicenter, randomized, parallel-controlled study, aims to evaluate the efficacy of MitraClip in conjunction with optimal standard treatment for patients with moderate-to-severe FMR and NYHA class II-IV HF in comparison to the use of optimal standard treatment alone. Our study shows that the baseline echocardiographic characteristics of the RESHAPE-HF2 trial are somewhat different from those of the earlier MITRA-FR and COAPT trials. First, in RESHAPE-HF2, a higher number of patients had TR severity grades of 2+ and 3+ compared to MITRA-FR and COAPT trials. Second, patients in RESHAPE-HF2 had less severe FMR, as evidenced by a smaller PISA radius, a lower percentage of patients with MR grade 4+ severity, a lower mean EROA, and a lower regurgitant volume. Third, LVEF was largely similar across all trials with patients in MITRA-FR having the highest LV volumes. These findings suggest that the patients enrolled in the RESHAPE-HF2 trial represent a distinct cohort of patients for evaluating MitraClip, where patients have moderate-to-severe FMR unlike the MITRA-FR and COAPT trials, which were limited to patients with mainly severe FMR (Figure 1).

The patients enrolled in RESHAPE-HF2, MITRA-FR and COAPT had very comparable LVEF (ca. 31%). COAPT patients had lowest LVESD and LVEDD compared to both RESHAPE-HF2 and MITRA-FR patients with similar values. MITRA-FR patients had highest LVESV and LVEDD compared to both RESHAPE-HF2 and COAPT patients with by and large similar values for these parameters. MITRA-FR appeared to have more severe LV dysfunction compared to both the RESHAPE-HF2 and COAPT trial patients. It is important to note that COAPT trial excluded patients with very severe LV dilation whereas MITRA-FR had no such limit. Also, MITRA-FR enrolled patients with LVEF 15-40% while COAPT (like RESHAPE-HF2) enrolled patients with LVEF 20-50%. Studies have shown that in HF patients with FMR, significant LV dilation and dysfunction are linked to persistent MR, limited reversal of LV remodeling, and a poor prognosis.[11-15]

We also show that RESHAPE-HF2 included patients primarily with moderate-to-severe FMR, in contrast to the predominantly severe FMR cases in the previous two trials. This is evidenced by a smaller PISA radius, indicating lower MR severity, as well as a smaller proportion of patients with MR severity grade 4+. Additionally, the mean EROA value was lowest in RESHAPE-HF2 patients (0.25 cm^2), followed by MITRA-FR (0.31 cm^2), and highest in COAPT (0.40 cm^2). Notably, RESHAPE-HF2 had more patients with moderate (EROA: 20-29 mm^2) and moderate-to-severe MR (EROA: 30-39 mm^2), compared to prior trials which had more patients with severe MR (EROA ≥40 mm^2). Regurgitant volumes in RESHAPE-HF2 (37 mL) were 18% lower than in than in MITRA-FR (45 mL) but 38% higher than in COAPT (27

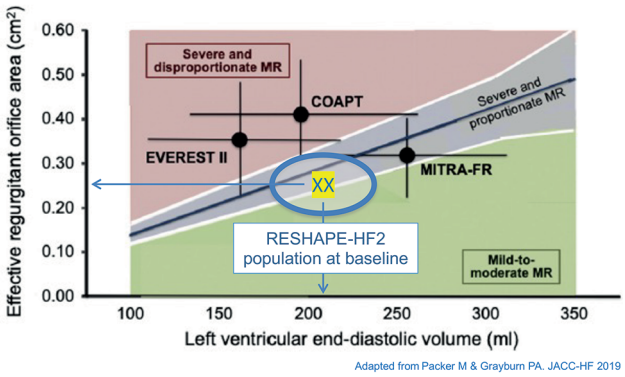

Figure 1. Relationship between left ventricular end-diastolic volume and effective regurgitant orifice area in several trials testing TEER (MitraClip), including Reshape-HF2.

Table 2. Comparison of baseline right ventricular function and tricuspid regurgitation among patients enrolled in RESHAPE-HF2, COAPT, and MITRA-FR trials.

	RESHAPE-HF2 (n=505)	COAPT (n=614)	MITRA-FR (n=304)
RV systolic pressure (mmHg)	41.4±12.7 *N-Miss=87*	44.3±13.7	54±14
TR severity: none / 0, n (%)	4 (0.8)	12 (1.9)	NR
TR severity: mild / 1+, n (%)	274 (54.3)	489 (79.6)	228 (81.4)
TR severity: moderate / 2+, n (%)	178 (35.2)	92 (15.0)	NR
TR severity: moderate to severe / 3+, n (%)	37 (7.3)	5 (0.8)	52 (18.6)
TR severity: severe / 4+, n (%)	NR	1 (0.2)	NR
Not evaluable	12 (2.4)	NR	NR
Tricuspid annulus diameter (systole), cm	2.77±0.57 *N-Miss=1*	NR	NR
Tricuspid annulus diameter (diastole), cm	3.29±0.59 *N-Miss=1*	NR	NR

RV, right ventricle; TR, tricuspid regurgitation; NR, not reported.

mL). Of note, RESHAPE-HF2 patients had 36% higher LA volumes compared to patients in the COAPT trial. This may be relevant as the origin of FMR in some of the patients included in RESHAPE-HF2.

It has been suggested that MITRA-FR was neutral because patients enrolled in that trial had proportionate MR in terms of LVEDV and EROA i.e. patients most likely cause of HF was underlying cardiomyopathy and FMR was possibly a bystander and proportional to the degree of HF. However, patients in COAPT trial had disproportionate MR i.e. EROA was significantly larger compared to LVEDV indicating that FMR was the main determinant of poor outcomes. RESHAPE-HF2 will test TEER in a third distinct cohort of patients who have less severe FMR compared to patients in COAPT trial.

We also show that a larger proportion of RESHAPE-HF2 patients had TR severity grades 2+ and 3+ in comparison to previous trials. RV function can significantly influence morbidity and mortality in patients with HF and FMR.[16] Hence, the presence of concurrent RV dysfunction in patients enrolled in RESHAPE-HF2 is important to note as it provides a diverse cohort which was not commonly seen in previous trials.

Treating FMR is part of the concept of phenotype focused therapy of patients with heart failure.[17-19] Evidence based medical HF therapy can significantly reduce the severity of FMR because it triggers reverse LV remodeling – several studies have shown that.[20-24] The MitraClip therapy can do so as well, which is a secondary endpoint of the RESHAPE-HF2 trial,[10] where the proportion of patients with grade 1+ at 12 months will be assessed as part of the secondary endpoints. This analysis is part of the overall innovative endpoints concept with several meaningful outcomes all tested in RESHAPE-HF2.[10,25]

Conclusions

In conclusion, the baseline echocardiographic characteristics of patients in the RESHAPE-HF2 trial differ somewhat from patients in the MITRA-FR and COAPT trials. Patients enrolled in RESHAPE-HF2 had moderate-to-severe FMR, characterized by a smaller PISA radius, a lesser proportion of MR severity grade of 4+, and lower mean EROA and regurgitant volumes compared to patients in COAPT and MITRA-FR trials. LVEF was largely similar across all trials. RESHAPE-HF2 is testing TEER in a third distinct cohort of patients who have less severe FMR compared to patients in COAPT trial, but have high left atrial volumes. The RESHAPE-HF2 population is also echocardiographically different from the MITRA-FR cohort. This is in line with the overall clinical characteristics of the RESHAPE-HF2 population that shows somewhat less clinical severity that the COAPT and MITRA-FR trial populations.[26]

Conflict of interest

RSvB reports EchoCoreLab IIT grant from UMG Göttingen, consulting fees from Abbott Vascular, Jenscare, Edwards Lifesciences, Medtronic, honoraria from Abbott Vascular, Jenavalve, Jenscare, Edwards Lifesciences, Medtronic, Philips, Siemens, and is Trial Committee member of Medtronic and Heart Valve Society (unpaid), EU SHD Coalition (unpaid).

MSK reports participation on a Data Safety Monitoring Board or Advisory Board from Bayer.

TF reports payments to institution from Abbott, grants from Deutsche Forschungsgemeinschaft (DFG), Federal Joint Committee (G-BA) and European Commission; consulting fees from Actimed, Bayer, BMS, CSLBehring, Daiichi Sankyo, Galapagos, Immunic, KyowaKirin, LivaNova, Minoryx, Novartis, RECARDIO, Relaxera, Roche, Servier, Viatris, and Vifor, payments from Fresenius Kabi and PINK gegen Brustkrebs, is Trial Data Monitoring Committee member of Aslan, Bayer, BiosenseWebster, Enanta, Galapagos, IQVIA, Novartis, PPD, Recordati, Roche, VICO Therapeutics and is Trial Steering Committee member of SCLBehring.

JB reports consulting fees from Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, Cardiorem, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronics, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Pfize, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll, and honoraria from Novartis, Boehringer Ingelheim-Lilly, Astra Zeneca, Impulse Dynamics, Vifor.

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AA reports consulting fees from Boston Scientific, Medtronic, Microport CRM, Philips, Xspline and Abbott, and honoraria from Boston Scientific, Medtronic, Microport CRM, Philips, Xspline.

ABG has lectured and/or participated in advisory boards for Abbott, AstraZeneca, Bayer, Boehringer-Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, Vifor

JGFC reports grants from Bristol Myers Squibb, CSL-Vifor, British Heart Foundation and Pharmacosmos, consulting fees from Pharmacosmos, CSL-Vifor and Biopeutics and honoraria from Pharmacosmos.

GF reports honoraria from Bayer, Boehringer Ingelheim, Servier and Novartis and participation in the trial committee board of Bayer, Medtronic, Boehringer Ingelheim, Vifor, Amgen, Servier, Impulse Dynamics, Cardior and NovoNordisk andand in the boards of the Heart Failure Association and JACC Heart Failure.

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GS reports proctoring activities for Abbott Vascular.
WW reports consulting fees and/or honoraria from Abbott Vascular, Medtronic and Edwards Lifesciences.
KR reports honoraria for lectures from Abbott.
FJP reports consulting fees and/or honoraria from Boehringher Ingelheim, Daichi Sankyo, Novartis, Servier, Vifor and Zydus and participation in the Advisory Board for Medtronic, Novartis, Servier, Vifor.
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All other authors report no conflict of interest.

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