Outcomes of transcatheter mitral valve repair for secondary mitral regurgitation by severity of left ventricular dysfunction

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This paper also includes supplementary data published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01265

KEYWORDS

- depressed left ventricular function
- mitral regurgitation
- mitral valve repair

Abstract

Background: In the COAPT trial, transcatheter mitral valve repair with the MitraClip plus maximally tolerated guideline-directed medical therapy (GDMT) improved clinical outcomes compared with GDMT alone in symptomatic patients with heart failure (HF) and 3+ or 4+ secondary mitral regurgitation (SMR) due to left ventricular (LV) dysfunction.

Aims: In this COAPT substudy, we sought to evaluate two-year outcomes in HF patients with reduced LV ejection fraction (HFrEF; LVEF ≤40%) versus preserved LVEF (HFpEF; LVEF >40%) and in those with severe (LVEF ≤30%) versus moderate (LVEF >30%) LV dysfunction.

Methods: The principal effectiveness outcome was the two-year rate of death from any cause or HF hospitalisations (HFH). Subgroup analysis with interaction testing was performed according to baseline LVEF; 472 patients (82.1%) had HFrEF (mean LVEF 28.0%±6.2%; range 12% to 40%) and 103 (17.9%) had HFpEF (mean LVEF 46.6%±4.9%; range 41% to 65%), while 292 (50.7%) had severely depressed LVEF (LVEF ≤30%; mean LVEF 23.9%±3.8%) and 283 (49.3%) had moderately depressed LVEF (LVEF >30%; mean LVEF 39.0%±6.8%).

Results: The two-year rate of death or HFH was 56.7% in patients with HFrEF and 53.4% with HFpEF (HR 1.16, 95% CI: 0.86-1.57, p=0.32). MitraClip reduced the two-year rate of death or HFH in patients with HFrEF (HR 0.50, 95% CI: 0.39-0.65) and HFpEF (HR 0.60, 95% CI: 0.35-1.05), p_{int}=0.55. MitraClip was consistently effective in reducing the individual endpoints of mortality and HFH, improving MR severity, quality of life, and six-minute walk distance in patients with HFrEF, HFpEF, LVEF ≤30%, and LVEF >30%.

Conclusions: In the COAPT trial, among patients with HF and 3+ or 4+ SMR who remained symptomatic despite maximally tolerated GDMT, the MitraClip was consistently effective in improving survival and health status in patients with severe and moderate LV dysfunction and those with preserved LVEF.

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SUBMITTED ON 02/11/2020 - REVISION RECEIVED ON 1st 06/01/2021 / 2nd 04/02/2021 - ACCEPTED ON 05/02/2021

Abbreviations

GDMT	guideline-directed medical therapy
HFH	heart failure hospitalisation
HFmrEF	heart failure with mid-range ejection fraction
HFpEF	heart failure with preserved ejection fraction
HFrEF	heart failure with reduced ejection fraction
LVEF	left ventricular ejection fraction
QOL	quality of life
6MWD	6-minute walk distance
SMR	secondary mitral regurgitation
TMVr	transcatheter mitral valve repair

Introduction

The mitral valve is a dynamic and complex structure[1,2]. In patients with heart failure (HF), geometric displacement of the papillary muscles and chordae may result in leaflet tethering and lack of coaptation of the mitral leaflets, with secondary (or functional) mitral regurgitation (SMR)[3]. In SMR, disruption of mitral valve function is caused principally by the underlying left ventricular (LV) dilatation rather than structural derangements in the mitral valve complex per se[4]. As a result, guideline-directed medical therapy (GDMT) for LV dysfunction is the foundation of the management of SMR[5,6]. Substantial SMR is associated with decreased quality of life (QOL), increased rates of hospitalisation for HF, and diminished survival[7,8]. GDMT and cardiac resynchronisation therapy in selected patients have been shown to reduce the severity of SMR and provide symptomatic relief[7].

With the advent of transcatheter mitral valve repair (TMVr), treatment options for SMR have expanded[9-11]. Two landmark randomised trials have recently evaluated the role of transcatheter leaflet approximation with the MitraClip™ (Abbott, Santa Clara, CA, USA) in HF patients with SMR. In the COAPT trial, TMVr with the MitraClip markedly improved two-year survival and health status compared with maximally tolerated GDMT alone in symptomatic patients with HF and moderate-to-severe (3+) or severe (4+) SMR due to LV dysfunction[3,12]. In contrast, in the MITRA-FR trial there were no significant differences at one year or two years in any of these endpoints[1,13]. Important differences in baseline patient characteristics, background therapies, and treatments may explain the discrepant outcomes of these trials[5,6,12]. Of note, although the mean LV ejection fractions (LVEF) were similar between the two studies, COAPT enrolled a substantial proportion of patients with HF and systolic dysfunction in the range often termed "preserved" EF (HFpEF; LVEF >40%), whereas enrolment in MITRA-FR was restricted to patients with HF and reduced EF (HFrEF; LVEF ≤40%). In the present study we sought to examine the outcomes from the COAPT trial according to LVEF to determine the extent to which the severity of LV dysfunction may impact on the potential benefits of TMVr in patients with HF and severe SMR.

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Methods

TRIAL DESIGN

The rationale for and design of the COAPT trial have been published previously[14]. COAPT was a randomised, multicentre, controlled, parallel group, open-label trial of TMVr with the MitraClip in patients with HF and moderate-to-severe or severe SMR confirmed by an echocardiographic core laboratory. The protocol was planned according to the criteria dictated by the Mitral Valve Academic Research Consortium[7,15]. The study was approved by the institutional review board at each site, and each enrolled patient signed informed consent.

RANDOMISATION AND STUDY GROUPS

Patients with ischaemic or non-ischaemic cardiomyopathy with LVEF of 20% to 50% and moderate-to-severe (3+) or severe (4+) SMR who remained symptomatic despite maximally tolerated GDMT were eligible for enrolment. Detailed inclusion and exclusion criteria have been reported previously[3,14]. Details regarding randomisation, device implantation, and study procedures have been published previously[14]. Follow-up was performed at 1 week and 1, 6, 12, 18, and 24 months (the time of the primary endpoint) and is ongoing up to 5 years. Follow-up assessments included periodic echocardiography, six-minute walk distance (6MWD), and QOL measures, including the New York Heart Association (NYHA) functional class and Kansas City Cardiomyopathy Questionnaire (KCCQ). MitraClip treatment was not allowed in the control group until at or beyond the two-year follow-up time point.

OBJECTIVES AND ENDPOINTS

In the present study we sought to compare two-year outcomes of patients enrolled in the COAPT trial according to baseline LVEF. The principal endpoints for the COAPT trial have been described previously[14]. The primary effectiveness endpoint for the present study was the two-year composite rate of all-cause mortality or hospitalisations for HF, as adjudicated by an independent events committee after review of original source documents. We evaluated clinical and health status outcomes in patients with HFrEF (LVEF ≤40%) versus HFpEF (LVEF >40%) as well as in those with severe LV dysfunction (LVEF ≤30%) versus moderate LV dysfunction (LVEF >30%) at the time of enrolment. Of note, site-assessed LVEF was used as the criterion to qualify the patient for randomisation. For the present analysis, LVEF as assessed by the echocardiographic core laboratory on the baseline pre-randomisation transthoracic echocardiogram was used for LVEF stratification. As such, some patients were enrolled with an LVEF <20% or >50%.

STATISTICAL ANALYSIS

Categorical variables were compared with Fisher's exact test, and continuous variables were compared with t-tests unless the data were not normally distributed, in which case the Wilcoxon rank-sum test was used. The times to the first occurrence of death or HF hospitalisation (HFH) were estimated using the Kaplan-Meier method and were compared with the log-rank test. Multivariable analysis was performed using Cox regression with LVEF forced into the model. Formal interaction testing was performed to

determine whether there were differences in the hazard ratios of patients randomised to the device versus control groups according to LVEF subgroup. A spline analysis was also performed to evaluate the continuous relationship between baseline LVEF, randomisation arm, and the two-year rates and relative hazard of death or HFH. Changes in KCCQ and 6MWD from baseline to later intervals were performed by analysis of covariance, adjusting for baseline differences. All analyses were performed on an intention-to-treat basis. A two-sided p-value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, USA).

Results

PATIENTS AND LVEF

From December 2012 to June 2017, 614 patients at 78 centres in the USA and Canada were enrolled in the trial. Baseline echocardiograms suitable for LVEF analysis by the echocardiographic core laboratory were available in 575 patients (94%), representing the current study population. By core laboratory analysis, the mean LVEF in the entire study population was 31.3%±9.3% **(Figure 1)**; 472 patients (82.1%) had HFrEF (mean LVEF 28.0%±6.2%; range 12% to 40%) and 103 (17.9%) had HFpEF (mean LVEF 46.6%±4.9%; range 41% to 65%). LVEF was <20% and >50% in 32 and 13 patients, respectively. LVEF was severely depressed (LVEF ≤30%; mean LVEF 23.9%±3.8%) in 292 patients (50.7%) and moderately depressed (LVEF >30%; mean LVEF 39.0%±6.8%) in 283 (49.3%). Differences in baseline characteristics and medication use between patients with HFrEF versus HFpEF are shown in **Supplementary Table 1** and **Supplementary Table 2**, while differences between patients with LVEF ≤30% versus >30% are shown in **Supplementary Table 3** and **Supplementary Table 4**.

OUTCOMES ACCORDING TO LVEF

The composite endpoint of death or HFH occurred in 56.7% of patients with HFrEF and 53.4% with HFpEF (HR 1.16, 95% CI: 0.86-1.57, p=0.32) **(Figure 2A)**. By multivariable analysis, LVEF (as a continuous variable) was not an independent predictor of the composite rate of death or HFH (adjusted HR per 5% increase in LVEF 0.99, 95% CI: 0.97-1.00, p=0.07) **(Table 1)**. Similarly, there were no significant differences in the two-year individual rates of death or HFH **(Figure 2B, Figure 2C)** or improvement in KCCQ or 6MWD over time between HFrEF and HFpEF **(Supplementary Table 5)**. The composite endpoint of death or HFH occurred in 61.3% of patients with LVEF ≤30% and in 50.6% with LVEF >30% (HR 1.3, 95% CI: 1.04, 1.62, p=0.02) **(Supplementary Figure 1A)**. The individual endpoint of HFH occurred in 52.5% of patients with LVEF ≤30% and in 38.8% with LVEF >30% (HR 1.48, 95% CI: 1.14, 1.91, p=0.003) **(Supplementary Figure 1B)**. There was no significant difference in the two-year rate of death or improvement in KCCQ or 6MWD over time between patients with LVEF ≤30% versus >30% **(Supplementary Table 6, Supplementary Figure 1C)**.

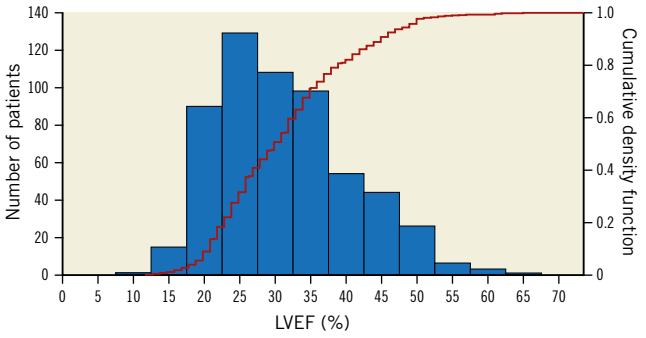

Figure 1. *Histogram of left ventricular ejection fractions of patients enrolled in the COAPT trial. The left y-axis is the number of patients for each 5 percent increment of left ventricular ejection fraction (LVEF). The superimposed curve and corresponding right y-axis represent the cumulative frequency distribution of LVEF.*

Table 1. Multivariable model for the two-year composite rate of death or hospitalisation for heart failure.

	Hazard ratio (95% confidence interval)	*p*-value
Left ventricular ejection fraction (per 5% increase)	0.99 (0.97-1.00)	0.07
MitraClip (versus guideline-directed medical therapy alone)	0.54 (0.42-0.71)	<0.0001
Age (per 5 years)	0.99 (0.91-1.07)	0.75
Male sex	1.12 (0.81-1.53)	0.49
Diabetes	1.08 (0.81-1.43)	0.61
Hypertension	0.94 (0.67-1.32)	0.73
Hypercholesterolaemia	1.18 (0.90-1.56)	0.23
Previous myocardial infarction	1.16 (0.83-1.62)	0.39
Previous percutaneous coronary intervention	1.11 (0.80-1.54)	0.53
Previous stroke or transient ischaemic attack	0.74 (0.52-1.05)	0.10
Peripheral vascular disease	1.17 (0.83-1.63)	0.37
Chronic obstructive lung disease	1.08 (0.79-1.48)	0.61
History of atrial fibrillation or flutter	1.48 (1.12-1.94)	0.005
Body mass index (per 5 kg/m^2)	0.97 (0.84-1.11)	0.62
Creatinine clearance (per 5 mL/min)	0.98 (0.95-1.01)	0.16
Anaemia	1.24 (0.92-1.66)	0.16
Ischaemic cardiomyopathy (versus non-ischaemic)	0.83 (0.56-1.21)	0.33
New York Heart Association Class IV	1.32 (0.86-2.05)	0.21
Heart failure hospitalisation within the previous year	0.93 (0.72-1.22)	0.61
KCCQ score (per 5 points)	0.98 (0.95-1.01)	0.16
6-minute walk distance (per 50 metres)	0.93 (0.87-0.99)	0.03
Mitral regurgitation 4+ (versus 3+)	1.13 (0.85-1.49)	0.40
Left ventricular end-diastolic dimension (per 1 cm)	1.18 (0.94-1.48)	0.16
Right ventricular systolic pressure (per 5 mmHg)	1.07 (1.02-1.13)	0.005
Tricuspid regurgitation severity ≥3+ (versus ≤2+)	0.99 (0.23-4.19)	0.99

KCCQ: Kansas City Cardiomyopathy Questionnaire

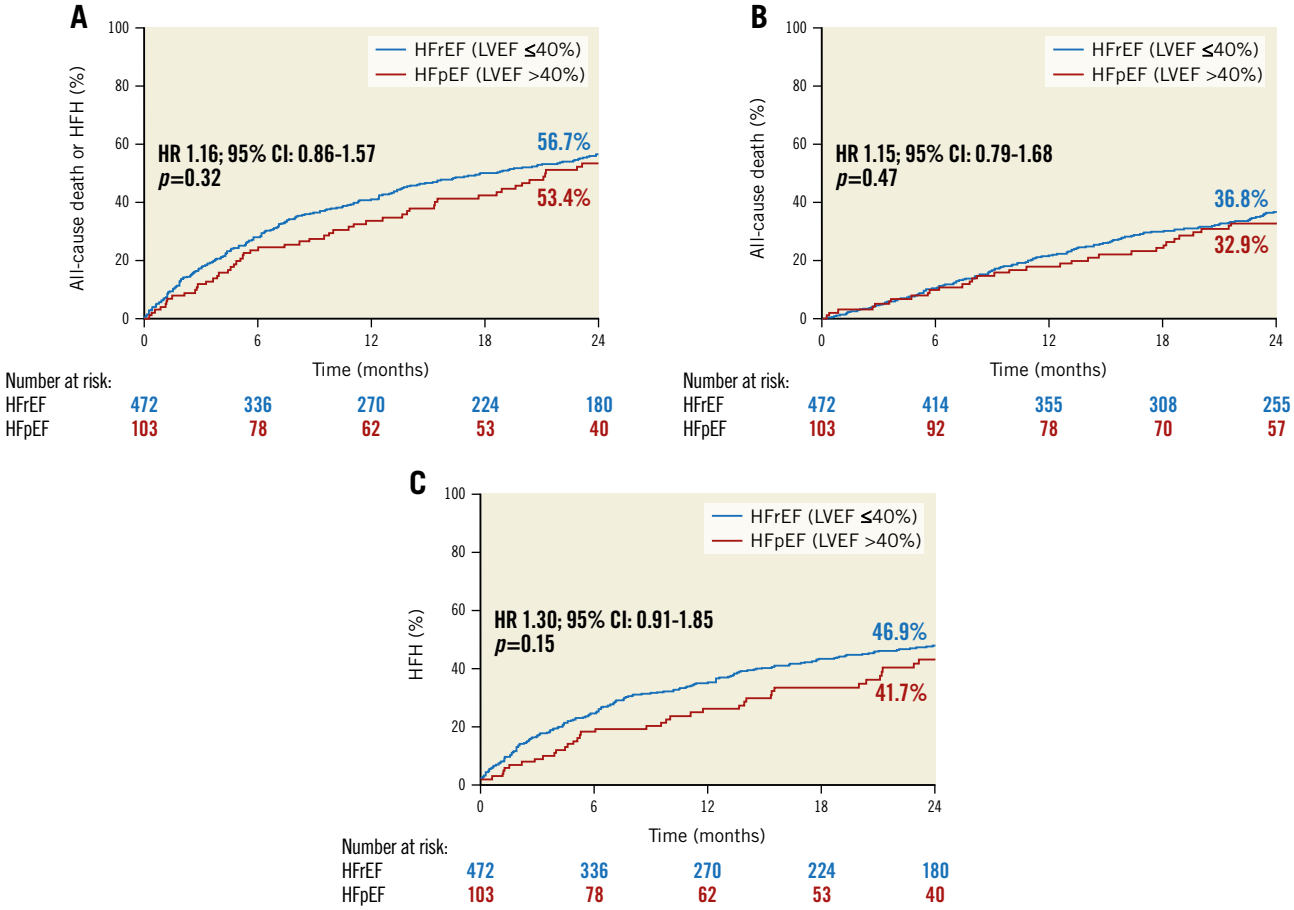

Figure 2. *Kaplan-Meier time-to-first-event curves in patients with HFrEF versus HFpEF. A) Death or heart failure hospitalisation (HFH). B) Death. C) HFH. CI: confidence interval; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio*

IMPACT OF MITRACLIP TREATMENT ACCORDING TO LVEF

Among the 472 HFrEF patients, 231 were randomised to MitraClip plus GDMT and 241 to GDMT alone. Among the 103 HFpEF patients, 50 were randomised to MitraClip plus GDMT and 53 to GDMT alone. The baseline characteristics in both subgroups were well matched between the device and control arms **(Supplementary Table 7, Supplementary Table 8)**. Compared with GDMT alone, MitraClip consistently reduced the two-year rate of death or HFH in patients with HFrEF (HR 0.50, 95% CI: 0.38-0.68) and HFpEF (HR 0.58, 95% CI: 0.34-1.01); p_{int}=0.63 **(Figure 3, Supplementary Table 9)**. The MitraClip was also consistently effective both in patients with HFrEF and in those with HFpEF in reducing the individual endpoints of mortality and HFH, and improving MR severity, QOL, and 6MWD **(Figure 3, Supplementary Table 9)**. Similar outcomes were observed in patients with LVEF ≤30% and >30% **(Supplementary Table 10, Supplementary Figure 2)**. By spline analysis, the benefits of MitraClip in reducing death or HFH at two years were consistent across the range of LVEF enrolled **(Figure 4)**; however, given small numbers at the margins the spline curves show uncertainty regarding the benefits of MitraClip in patients with the lowest (≤20%) and highest (>50%) LVEFs. The utility of the MitraClip in these groups requires further evaluation in future studies.

Discussion

SMR is in most cases a disease of the LV myocardium[6]. Patients with LV dysfunction who develop SMR of any magnitude of severity have a worse prognosis than those without MR[16,17]. MR reduces the resistance to LV ejection (afterload); as such, the LVEF in patients with severe MR underestimates the degree of LV systolic dysfunction[18]. SMR is a strong predictor of death even in patients with less severe HF[19].

Whereas guidelines recommend early surgical intervention for severe primary MR[6,8,20], the optimal timing of intervention for severe SMR is less clear[21]; surgical treatment for SMR has not been shown to improve prognosis[22]. Until recently, patients with HF and SMR were treated principally with medications targeted to the underlying LV myocardial dysfunction[5,23]. Recently, two multicentre randomised trials assessed the role of TMVr with the MitraClip in patients with HF and SMR. The MITRA-FR trial randomised patients with SMR with LVEF of 15% to 40% to GDMT plus TMVr versus GDMT alone[1]. At one-year follow-up, there was

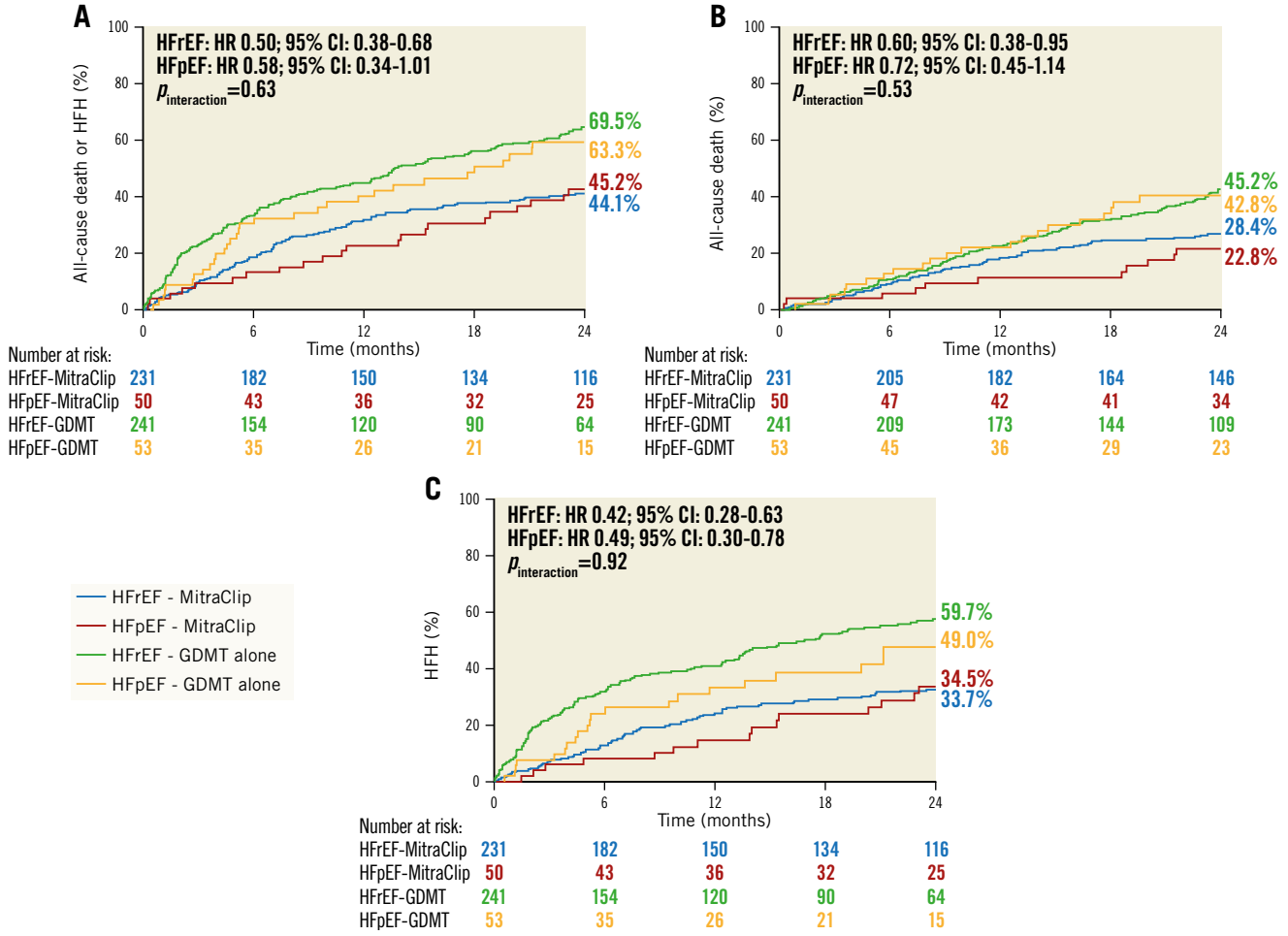

Figure 3. *Kaplan-Meier time-to-first-event curves in patients randomised to MitraClip plus GDMT versus GDMT alone and with HFrEF versus HFpEF. A) Death or heart failure hospitalisation (HFH). B) Death. C) HFH. CI: confidence interval; GDMT: guideline-directed medical therapy; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio*

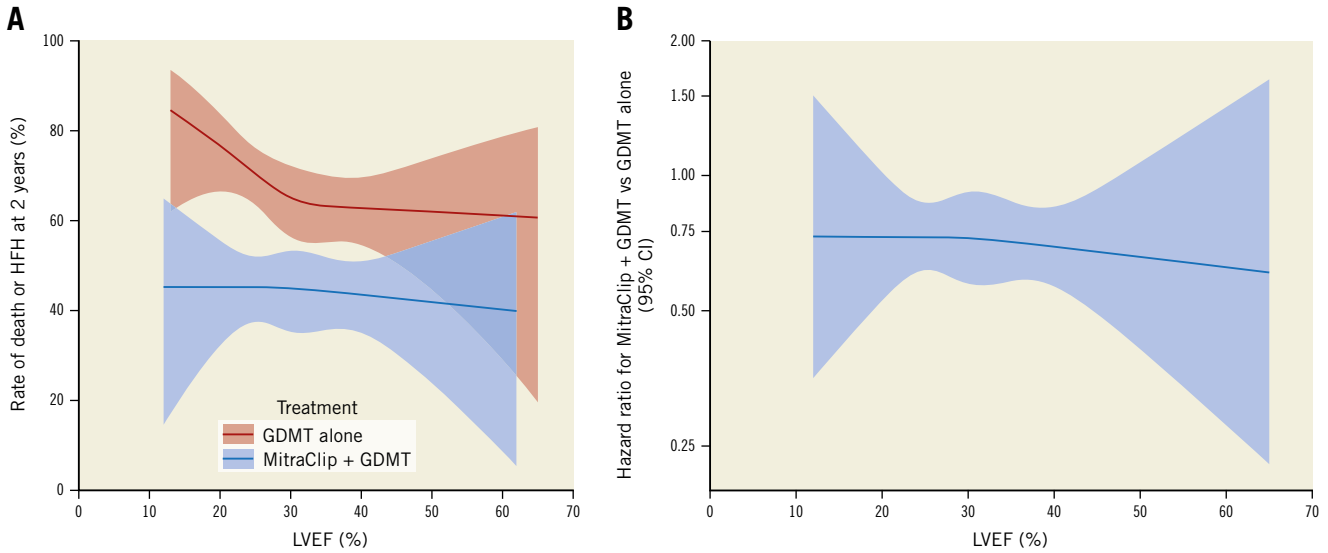

Figure 4. *Spline analysis. A) Rate of death or heart failure hospitalisation (HFH) at two years according to baseline left ventricular ejection fraction (LVEF) in patients randomised to MitraClip plus guideline-directed medical therapy (GDMT) and GDMT alone. B) Hazard ratio for death or HFH at two years in patients treated with MitraClip plus GDMT versus GDMT alone according to baseline LVEF. CI: confidence interval*

no significant difference between the two treatments for all-cause death (HR 1.11, 95% CI: 0.69-1.77) or HFH (HR 1.13, 95% CI: 0.81-1.56). The COAPT trial randomised patients with SMR with LVEF of 20% to 50% to GDMT plus TMVr versus GDMT alone[3]. At two-year follow-up, all HFHs were markedly lower in the MitraClip group compared with control (HR 0.53, 95% CI: 0.40-0.70; p<0.001). Death occurred in 29.1% of patients treated with TMVr compared with 46.1% treated with GDMT alone (HR 0.62, 95% CI: 0.46-0.82, p<0.001). While numerous differences between these trials may underlie their discordant findings, one common view has centred around the severity of MR relative to the degree of LV dysfunction. Patients in COAPT had more severe SMR compared with MITRA-FR (mean effective regurgitant orifice area 0.41 cm^2 versus 0.31 cm^2), yet smaller LV end-diastolic volumes[4-6,13,21], signifying a greater proportion of patients with "disproportionately" severe MR in COAPT[1,2].

Whereas LV dilatation was less pronounced in COAPT compared with MITRA-FR, the mean population LVEF was similar in the two studies (31.3% and 33.1%, respectively). In COAPT the benefits of MitraClip in terms of MR reduction, functional improvement, and freedom from death and HFH were consistent in those patients with a markedly depressed LVEF (≤30%) and less severely depressed LVEF (>30%) (mean LVEF in the two groups 23.9% and 39.0%, respectively). Moreover, nearly one in five COAPT patients had HFpEF (LVEF >40%), although most fell within the span of so-called HF with mid-range EF (HFmrEF), consistent with mildly reduced LV systolic function[24]. Data from the Acute Decompensated Heart Failure Syndromes (ATTEND) registry showed that even mild MR is associated with an increased risk of adverse outcomes in patients with HFpEF, while moderate to severe MR is associated with adverse outcomes in HFrEF[25]. The MitraClip consistently improved outcomes in this subgroup as well, which perhaps is not surprising given that HFmrEF patients have often responded to pharmacotherapies concordantly with HFrEF rather than HFpEF patients. In addition, given the afterload-reducing effect of severe MR, the severity of underlying LV systolic dysfunction in patients in COAPT with baseline LVEF of 40%-50% more likely resembles that of patients with LVEF <40% without MR. Thus, while the present study is reassuring that symptomatic patients with HF, LVEF ≤50%, and 3+ or 4+ MR will have an improved prognosis after MitraClip compared with GDMT alone, further studies are required to examine the outcomes of TMVr in a true HFpEF population, those with LVEF >50% (or >60%). In patients with truly normal LV function, the mechanism of SMR may more frequently be left atrial dysfunction with primary mitral annular dilatation often due to atrial fibrillation (so-called "atrial" functional MR)[25,26] rather than classic SMR due to LV dilatation with mitral leaflet tethering. Atrial functional MR as a result of atrial fibrillation or HFpEF-induced left atrial remodelling and subsequent annular dilatation, when present, is associated with a worse prognosis[26]. As patients with pure atrial MR were excluded from COAPT, whether such cases respond equally well to the MitraClip is unknown (although we cannot exclude the possibility that atrial SMR was the predominant mechanism in a few patients with a high baseline LVEF).

Limitations

The principal limitations of the present study apply to the COAPT trial in general. Namely, the present results apply to patients who remained symptomatic despite maximally tolerated GDMT, in whom truly severe MR was present according to American Society of Echocardiography criteria[27] but without severe LV dilatation or marked pulmonary hypertension or severe right ventricular failure. In addition, echocardiography may be inaccurate in measuring LVEF because of foreshortening, poor endocardial border detection, and geometric assumptions that must be applied[27]. The challenges in echocardiographic LVEF measurements are evidenced in the variations in LVEF measured by the sites and the echocardiographic core laboratory; by core laboratory assessment, 45 patients were enrolled with an LVEF <20% or >50%, outside the protocol limits. Cardiac magnetic resonance imaging, which may be a superior gold standard to measure LV volumes and LVEF, was not performed in the present study[28]. Finally, several of the subgroups evaluated in this study were small, and subgroup analysis is inherently underpowered. Our findings should therefore be considered hypothesis generating.

Conclusions

Among patients with HF and moderate-to-severe (3+) and severe (4+) SMR due to LV dysfunction, the MitraClip was consistently effective in improving prognosis and health status across the range of LVEF enrolled in the COAPT trial (intended LVEF 20%-50%, actual LVEF 12%-65%).

Impact on daily practice

The findings of this COAPT substudy provide critical guidance for the treatment of a range of heart failure patients with symptomatic significant secondary mitral regurgitation. MitraClip on top of guideline-directed medical therapy (GDMT) consistently and effectively reduces the mortality and heart failure hospitalisation and improves the healthcare status of patients with severe and moderate left ventricular dysfunction compared to GDMT alone.

Funding

The COAPT trial was sponsored by Abbott (Santa Clara, CA, USA).

Conflict of interest statement

F.M. Asch reports institutional research contracts for work as core lab director, with Edwards, Medtronic, BSC, LivaNova, Neovasc, Ancora, and MVRx. N.J. Weissman is associate director of an academic echocardiography core laboratory (MedStar Health Research Institute) with institutional contracts with Abbott, Neovasc, Ancora, Mitralign, Medtronic, Boston Scientific, Edwards Lifesciences, Biotronik, and LivaNova. S. Kar reports consulting fees/advisory board - Boston Scientific, consulting fees/

stock equity - Valcare, consulting fees - W.L. Gore and Medtronic. D.S. Lim reports research grant support from Abbott, Edwards, Medtronic and Gore, being a consultant to Abbott, Edwards, Keystone Heart, Pipeline, Siemens, Valgen, and Venus, being on the advisory board of Ancora and Venus, and having equity in 510 Kardiac and Venus. B.K. Whisenant reports being a consultant to Edwards Lifesciences, Boston Scientific, Gore, and Neochord. P.A. Grayburn reports consulting fees from Abbott Vascular, Edwards Lifesciences, W.L. Gore, Medtronic and 4C Medical, and grant support from Abbott Vascular, Boston Scientific, Cardiovalve, Edwards Lifesciences, W.L. Gore, Medtronic, and Neochord. M.J. Rinaldi reports being on the advisory board of Abbott, Boston Scientific, Cordis and 4C Medical, teaching courses for Abbott and Edwards, consulting for Abbott, Boston, Edwards and Cordis, and research support/grant from Boston Scientific. S.K. Sharma reports being on the speakers bureau of Abbott Vascular, Boston Scientific, and Cardiovascular Systems, Inc. S.R. Kapadia reports stock options in NaviGate Cardiac Structures, Inc. V. Rajagopal reports being a consultant to Abbott Vascular, being on the steering committee of TRILUMINATE (Abbott), being on the screening committee of Intrepid (Medtronic), and being founder/CEO of Opus Medical Therapies. I.J. Sarembock reports being on the advisory board of and consultant to Boston Scientific. G.H.L. Tang reports personal fees from Abbott Structural Heart, Medtronic, and W.L. Gore & Associates. J.A. Lindenfeld reports grants from and being a consultant to AstraZeneca, grants from Sensible Medical and VoluMetrix, and being a consultant to Abbott, Boehringer Ingelheim, CVRx, Edwards Lifesciences, Impulse Dynamics, and V-Wave. W.T. Abraham reports consulting fees from Boehringer Ingelheim, Respicardia, Sensible Medical, CVRx, and Impulse Dynamics, and salary support from V-Wave Medical, all for work done in the field of heart failure. M.J. Mack reports grants from Abbott. G.W. Stone reports speaker or other honoraria from Cook, Terumo, Qool Therapeutics and Orchestra Biomed, being a consultant to Valfix, TherOx, Vascular Dynamics, Robocath, HeartFlow, Gore, Ablative Solutions, Miracor, Neovasc, V-Wave, Abiomed, Ancora, MAIA Pharmaceuticals, Vectorious, Reva, Matrizyme and Cardiomech, and equity/options from Ancora, Qool Therapeutics, Cagent, Applied Therapeutics, Biostar family of funds, SpectraWave, Orchestra Biomed, Aria, Cardiac Success, MedFocus family of funds, and Valfix. The other authors have no conflicts of interest to declare.

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Supplementary data

Supplementary Figure 1. Kaplan-Meier time-to-first-event curves in patients with severe versus moderate left ventricular dysfunction.

Supplementary Figure 2. Kaplan-Meier time-to-first-event curves in patients randomised to MitraClip plus GDMT versus GDMT alone, and with severe versus moderate left ventricular dysfunction.

Supplementary Table 1. Baseline characteristics of patients with HFrEF versus HFpEF.

Supplementary Table 2. Medication use at baseline and at 30-day follow-up in patients with HFrEF versus HFpEF.

Supplementary Table 3. Baseline characteristics of patients with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

Supplementary Table 4. Medication use at baseline and at 30-day follow-up in patients. with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

Supplementary Table 5. Change in health status and exercise capacity over time in patients with HFrEF versus HFpEF.

Supplementary Table 6. Change in health status and exercise capacity over time in patients with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

Supplementary Table 7. Baseline characteristics of device versus control group patients in the HFrEF (LVEF ≤40%) cohort.

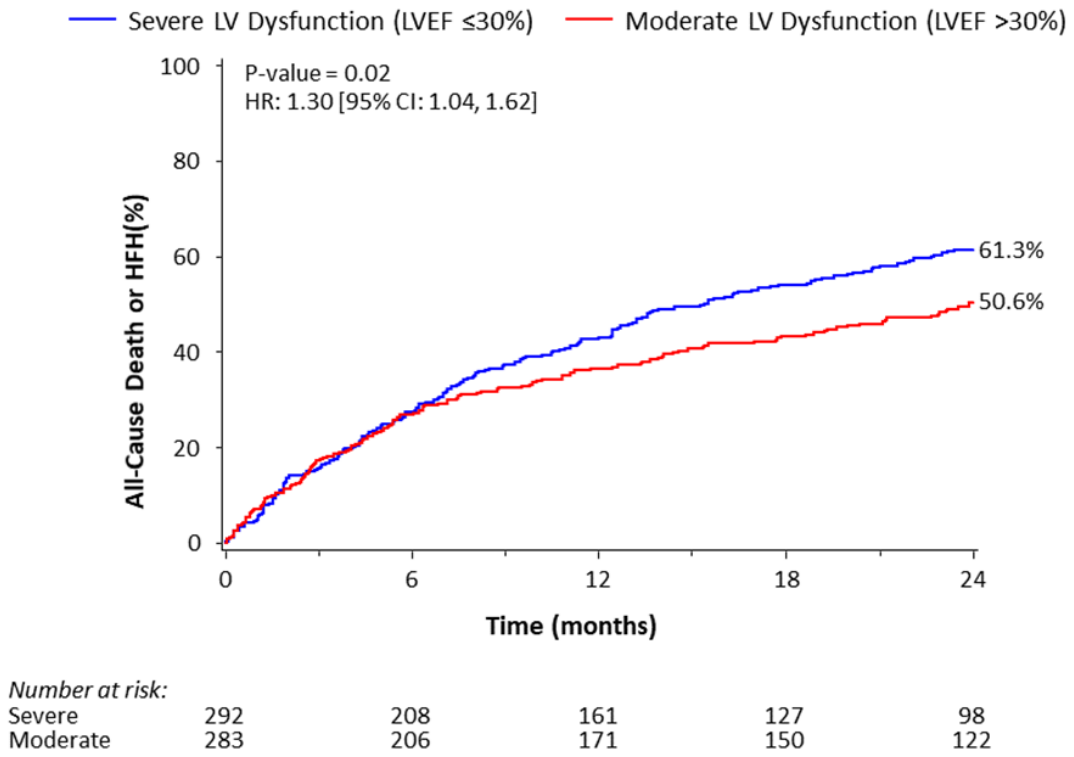
Supplementary Table 8. Baseline characteristics of device versus control group patients in the HFpEF (LVEF >40%) cohort.

Supplementary Table 9. Outcomes according to left ventricular ejection fraction and randomisation.

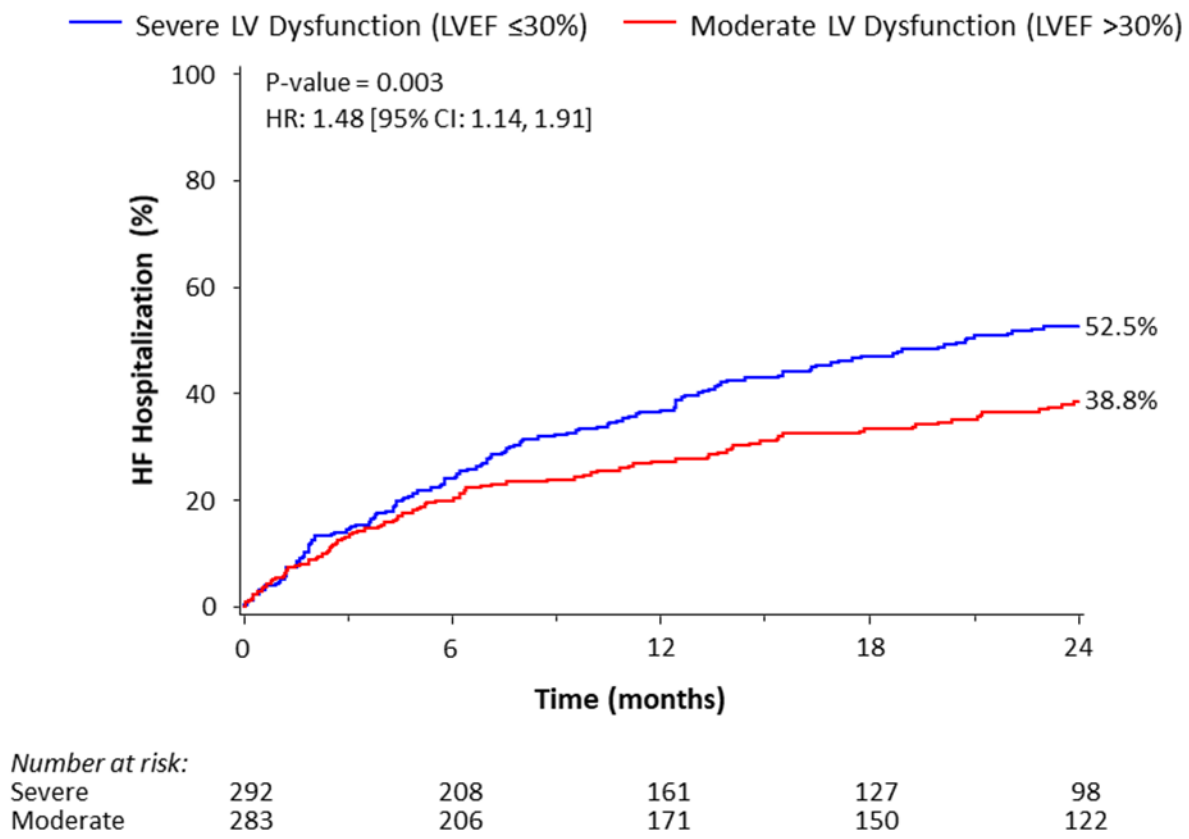
Supplementary Table 10. Outcomes according to LVEF and randomisation.

The supplementary data are published online at: https://eurointervention.pcronline.com/doi/10.4244/EIJ-D-20-01265

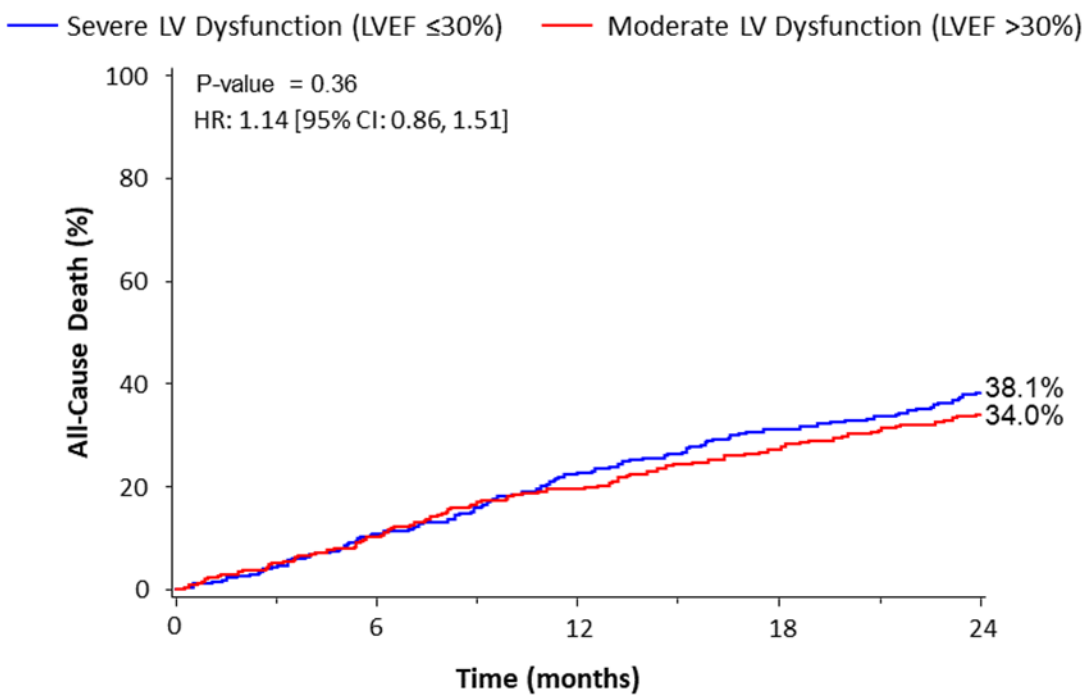
Supplementary data



A) Death or heart failure hospitalisation (HFH).



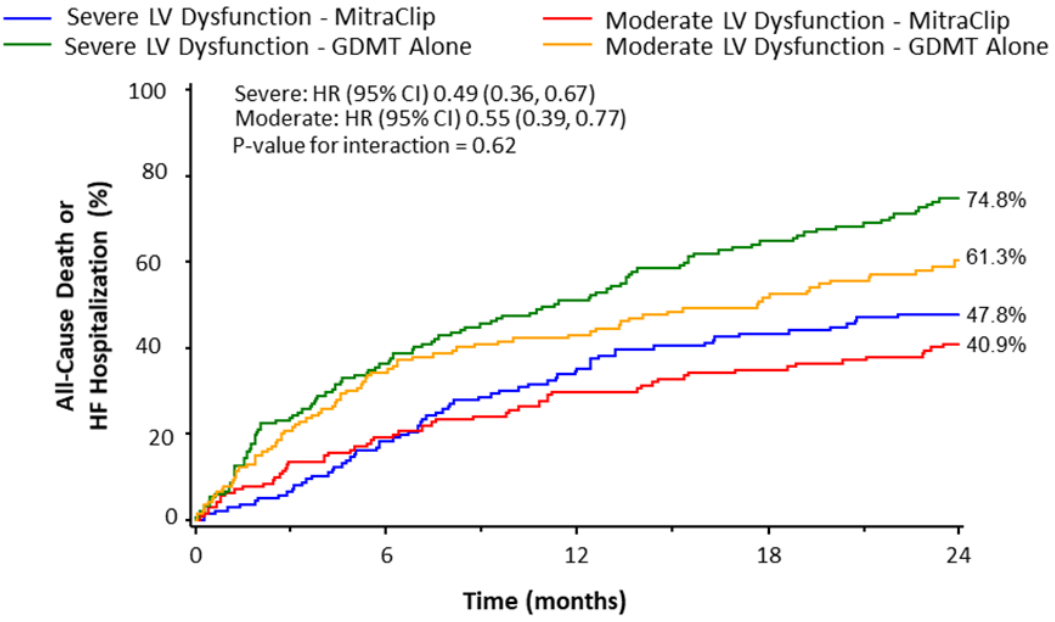
B) Heart failure hospitalisation (HFH).



C) Death.

Supplementary Figure 1. Kaplan-Meier time-to-first-event curves in patients with severe versus moderate left ventricular dysfunction. A) Death or heart failure hospitalisation (HFH); B) HFH; C) death.

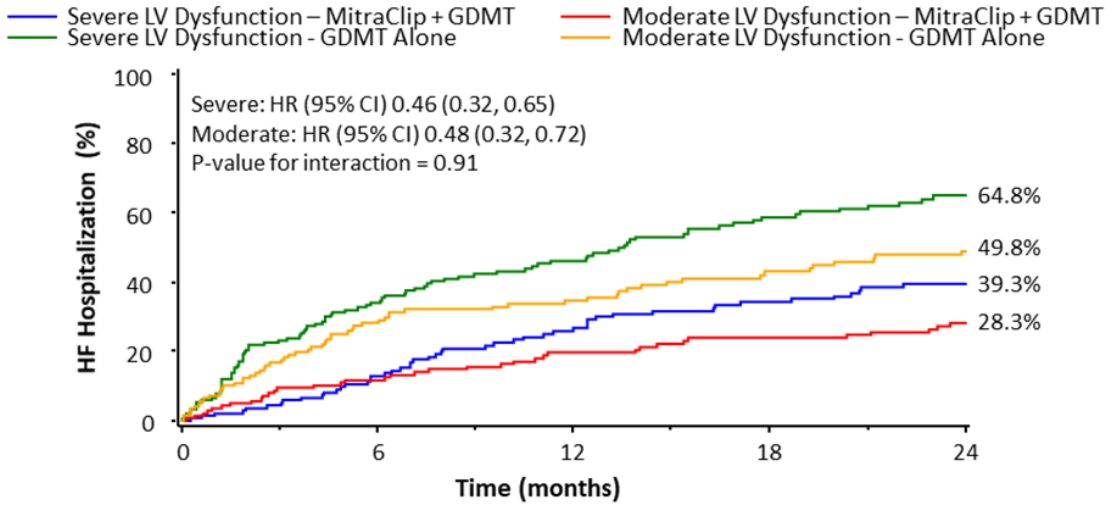
CI: confidence interval; HR: hazard ratio; LV: left ventricular; LVEF: left ventricular ejection fraction



Number at risk:

Severe-MitraClip	139	111	89	77	65
Moderate-MitraClip	142	114	97	89	76
Severe-GDMT Alone	153	97	72	50	33
Moderate-GDMT Alone	141	92	74	61	46

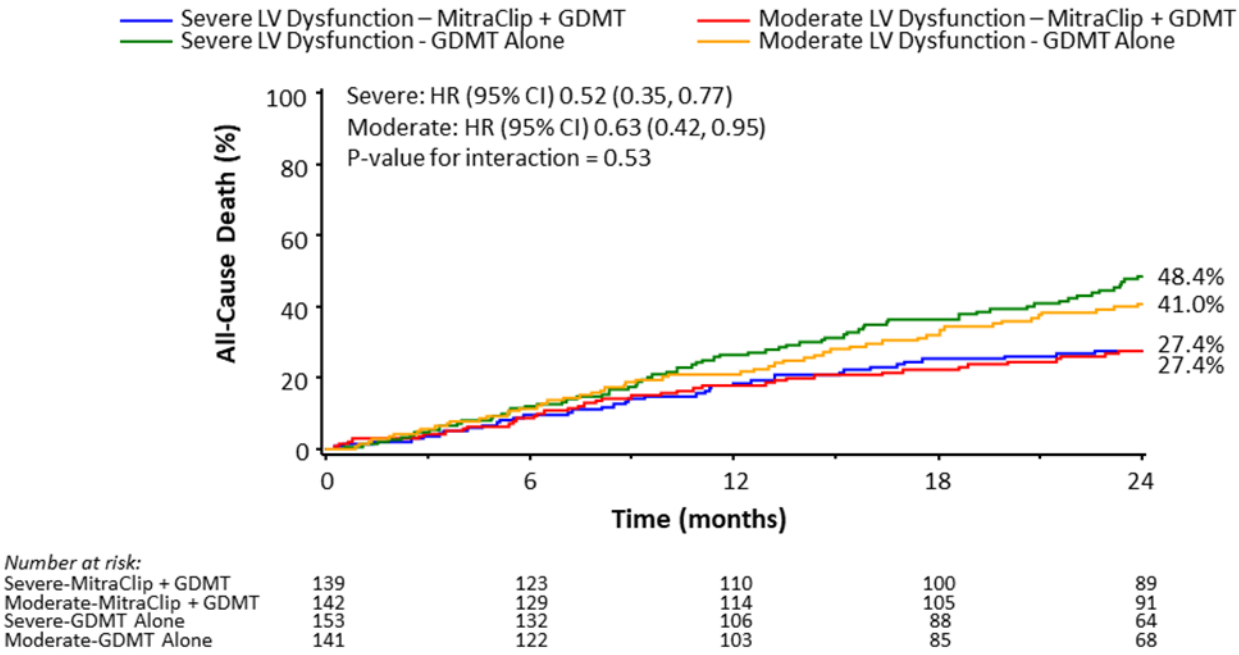
A) Death or heart failure hospitalisation (HFH).



Number at risk:

Severe-MitraClip + GDMT	139	111	89	77	65
Moderate-MitraClip + GDMT	142	114	97	89	76
Severe-GDMT Alone	153	97	72	50	33
Moderate-GDMT Alone	141	92	74	61	46

B) Heart failure hospitalisation (HFH).



C) Death.

Supplementary Figure 2. Kaplan-Meier time-to-first-event curves in patients randomised to MitraClip plus GDMT versus GDMT alone, and with severe versus moderate left ventricular dysfunction.
A) Death or heart failure hospitalisation (HFH); B) HFH; C) death.

CI: confidence interval; GDMT: guideline-directed medical therapy; HR: hazard ratio

Supplementary Table 1. Baseline characteristics of patients with HFrEF versus HFpEF.

	HFrEF (n=472)	HFpEF (n=103)	*p*-value
Age, years	71.4±11.4	75.1±9.9	0.002
Male sex	61.2% (63/103)	64.0% (368/575)	0.51
Diabetes	34.5% (163/472)	47.6% (49/103)	0.01
Hypertension	78.2% (369/472)	86.4% (89/103)	0.06
Hypercholesterolaemia	51.3% (242/472)	62.1% (64/103)	0.045
Previous myocardial infarction	49.2% (232/472)	59.2% (61/103)	0.06
Previous percutaneous coronary intervention	45.3% (214/472)	51.5% (53/103)	0.26
Previous stroke or TIA	15.7% (74/472)	20.4% (21/103)	0.24
Peripheral vascular disease	16.3% (77/472)	27.2% (28/103)	0.01
Chronic obstructive lung disease	21.4% (101/472)	28.2% (29/103)	0.14
History of atrial fibrillation or flutter	53.0% (250/472)	63.1% (65/103)	0.06
Body mass index, kg/m^2	27.7±5.5	27.0±6.0	0.18
Creatinine clearance, mL/min	41.7±21.7	49.8±27.1	0.0008
Anaemia	22.2% (105/472)	30.1% (31/103)	0.09
Ischaemic cardiomyopathy (versus non-ischaemic)	58.5% (276/472)	70.9% (73/103)	0.02
NYHA Class I or II	39.0% (184/472)	34.3% (35/102)	0.38
NYHA Class III	51.3% (242/472)	61.8% (63/102)	0.054
NYHA Class IV	9.7% (46/472)	3.9% (4/102)	0.059
HFH within the previous year	56.4% (266/472)	61.2% (63/103)	0.37
Previous CRT implant	40.0% (189/472)	19.4% (20/103)	<0.0001
Previous defibrillator implant	69.1% (326/472)	33.0% (34/103)	<0.0001
B-type natriuretic peptide level, pg/mL	721.6 (734.0)	1,044.3 (1,178.0)	0.01
N-terminal pro–B-type natriuretic peptide level, pg/mL	4,995.1 (5,548.8)	5,722.8 (7,823.2)	0.65
KCCQ score	52.9±23.0	49.2±22.9	0.14
6-minute walk distance, metres	244.7±125.0	222.6±112.6	0.10
Echo core lab measures			
MR severity 4+ (versus ≤3+)	48.5% (229/472)	44.7% (46/103)	0.48
LVESD, cm	5.5±0.8	4.4±0.7	<0.0001
LVEDD, cm	6.3±0.7	5.7±0.7	<0.0001
Left ventricular ejection fraction, %	28.0±6.2	46.6±4.9	<0.0001
RVSP, mmHg	44.0±13.6	45.1±12.5	0.48
TR severity ≥3+ (versus ≤2+)	0.9% (4/463)	1.0% (1/102)	0.91

Values are mean±standard deviation or % (n/N).

6MWD: 6-minute walk distance; CRT: cardiac resynchronisation therapy; HFH: heart failure hospitalisation; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; MR: mitral regurgitation; NYHA: New York Heart Association; RVSP: right ventricular systolic pressure; TIA: transient ischaemic attack; TR: tricuspid regurgitation

Supplementary Table 2. Medication use at baseline and at 30-day follow-up in patients with HFrEF versus HFpEF.

	HFrEF (n=472)	HFpEF (n=103)	*p*-value
Baseline			
ACEi, ARB, or ARNi	67.4% (318/472)	61.2% (63/103)	0.23
ACEi/ARB	64.2% (303/472)	58.3% (60/103)	0.26
ACEi	41.5% (196/472)	38.8% (40/103)	0.62
ARB	22.9% (108/472)	19.4% (20/103)	0.44
ARNi	3.2% (15/472)	2.9% (3/103)	0.89
Aldosterone antagonist	54.0% (255/472)	32.0% (33/103)	<0.0001
Beta-blockers	91.7% (433/472)	82.5% (85/103)	0.005
Nitrate	5.9% (28/472)	9.7% (10/103)	0.16
Hydralazine	16.3% (77/472)	21.4% (22/103)	0.22
Nitrate plus hydralazine	4.7% (22/472)	7.8% (8/103)	0.20
Diuretic	88.3% (417/472)	93.2% (96/103)	0.15
Chronic oral anticoagulant, any	41.1% (194/472)	49.5% (51/103)	0.12
Warfarin	27.1% (128/472)	36.9% (38/103)	0.05
Direct acting oral anticoagulant	14.2% (67/472)	12.6% (13/103)	0.68
Aspirin	61.0% (288/472)	60.2% (62/103)	0.88
$P2Y_{12}$ receptor inhibitor, any	22.5% (106/472)	27.2% (28/103)	0.30
Clopidogrel	19.7% (93/472)	24.3% (25/103)	0.30
Prasugrel	1.5% (7/472)	1.9% (2/103)	0.73
Ticagrelor	1.3% (6/472)	1.0% (1/103)	0.80
Prasugrel or ticagrelor	2.8% (13/472)	2.9% (3/103)	0.93
Statin	58.9% (278/472)	69.9% (72/103)	0.04
30 days			
ACEi, ARB, or ARNi	66.5% (307/462)	61.6% (61/99)	0.36
ACEi/ARB	61.9% (286/462)	58.6% (58/99)	0.54
ACEi	39.2% (181/462)	37.4% (37/99)	0.74
ARB	22.7% (105/462)	22.2% (22/99)	0.91
ARNi	5.6% (26/462)	5.1% (5/99)	0.82
Aldosterone antagonist	53.7% (248/462)	30.3% (30/99)	<0.0001
Beta-blockers	92.2% (426/462)	85.9% (85/99)	0.04
Nitrate	6.5% (30/462)	10.1% (10/99)	0.21
Hydralazine	15.8% (73/462)	23.2% (23/99)	0.07
Nitrate plus hydralazine	5.2% (24/462)	7.1% (7/99)	0.46
Diuretic	89.0% (411/462)	92.9% (92/99)	0.24
Chronic oral anticoagulant, any	42.6% (197/462)	52.5% (52/99)	0.07
Warfarin	28.1% (130/462)	37.4% (37/99)	0.07
Direct acting oral anticoagulant	14.9% (69/462)	15.2% (15/99)	0.96
Aspirin	65.8% (304/462)	63.6% (63/99)	0.68
$P2Y_{12}$ receptor inhibitor, any	27.5% (127/462)	29.3% (29/99)	0.72
Clopidogrel	24.7% (114/462)	25.3% (25/99)	0.90
Prasugrel	1.5% (7/462)	3.0% (3/99)	0.30
Ticagrelor	1.3% (6/462)	1.0% (1/99)	0.81
Prasugrel or ticagrelor	2.8% (13/462)	4.0% (4/99)	0.52

Statin	59.1% (273/462)	68.7% (68/99)	0.08

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNi: angiotensin receptor-neprilysin inhibitors; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; LVEF: left ventricular ejection fraction

Supplementary Table 3. Baseline characteristics of patients with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

	LVEF ≤30% (n=292)	LVEF >30% (n=283)	*p*-value
Age, years	71.2 (11.6)	73.0 (10.8)	0.06
Male sex	64.0% (187/292)	64.0% (181/283)	0.98
Diabetes	34.9% (102/292)	38.9% (110/283)	0.33
Hypertension	75.3% (220/292)	84.1% (238/283)	0.009
Hypercholesterolaemia	47.9% (140/292)	58.7% (166/283)	0.01
Previous myocardial infarction	45.5% (133/292)	56.5% (160/283)	0.008
Previous percutaneous coronary intervention	43.5% (127/292)	49.5% (140/283)	0.15
Previous stroke or TIA	15.4% (45/292)	17.7% (50/283)	0.47
Peripheral vascular disease	13.4% (39/292)	23.3% (66/283)	0.002
Chronic obstructive lung disease	18.8% (55/292)	26.5% (75/283)	0.03
History of atrial fibrillation or flutter	52.1% (152/292)	57.6% (163/283)	0.18
Body mass index, kg/m^2	26.6 (5.5)	27.5 (6.4)	0.08
Creatinine clearance, mL/min	51.4 (26.8)	48.0 (27.4)	0.14
Anaemia	22.3% (65/292)	25.1% (71/283)	0.42
Ischaemic cardiomyopathy (versus non-ischaemic)	54.5% (159/292)	67.1% (190/283)	0.002
NYHA Class I	0.0% (0/292)	0.4% (1/282)	0.31
NYHA Class II	38.0% (111/292)	37.9% (107/282)	0.99
NYHA Class III	52.4% (153/292)	53.9% (152/282)	0.72
NYHA Class IV	9.6% (28/292)	7.8% (22/282)	0.45
HFH within the previous year	56.2% (164/292)	58.3% (165/283)	0.60
Previous CRT implant	43.8% (128/292)	28.6% (81/283)	0.0001
Previous defibrillator implant	74.7% (218/292)	50.2% (142/283)	<0.0001
B-type natriuretic peptide level, pg/ml	1,268.3 (1,401.4)	820.3 (847.2)	0.0002
N-terminal pro–B-type natriuretic peptide level, pg/mL	6,523.3 (9,391.9)	4,769.3 (5,307.7)	0.17
KCCQ score	52.6 (23.7)	51.9 (22.4)	0.71
6-minute walk distance, metres	241.8 (130.6)	239.6 (115.1)	0.83
Echo core lab measures			
MR severity 4+ (versus 3+)	48.3% (141/292)	47.3% (134/283)	0.82
LVESD, cm	5.7 (0.7)	4.9 (0.8)	<0.0001
LVEDD, cm	6.4 (0.7)	6.0 (0.7)	<0.0001
Left ventricular ejection fraction, %	23.9 (3.8)	39.0 (6.8)	<0.0001
RVSP, mmHg	44.4 (13.4)	44.0 (13.4)	0.77
TR severity ≥3+ (versus ≤2+)	0.7% (2/285)	1.1% (3/280)	0.64

Values are mean±standard deviation or % (n/N). CRT: cardiac resynchronisation therapy; HFH: heart failure hospitalisation; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; MR: mitral regurgitation; NYHA: New York Heart Association; RVSP: right ventricular systolic pressure; TIA: transient ischaemic attack; TR: tricuspid regurgitation

Supplementary Table 4. Medication use at baseline and at 30-day follow-up in patients with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

	LVEF ≤30% (n=292)	LVEF >30% (n=283)	*p*-value
Baseline			
ACEi, ARB, or ARNi	67.5% (197/292)	65.0% (184/283)	0.53
ACEi/ARB	63.0% (184/292)	63.3% (179/283)	0.95
ACEi	42.1% (123/292)	39.9% (113/283)	0.59
ARB	21.2% (62/292)	23.3% (66/283)	0.55
ARNi	4.5% (13/292)	1.8% (5/283)	0.06
Aldosterone antagonist	56.5% (165/292)	43.5% (123/283)	0.002
Beta-blockers	90.8% (265/292)	89.4% (253/283)	0.59
Nitrate	5.8% (17/292)	7.4% (21/283)	0.44
Hydralazine	15.1% (44/292)	19.4% (55/283)	0.17
Nitrate plus hydralazine	4.8% (14/292)	5.7% (16/283)	0.64
Diuretic	88.0% (257/292)	90.5% (256/283)	0.34
Chronic oral anticoagulant, any	39.7% (116/292)	45.6% (129/283)	0.16
Warfarin	24.7% (72/292)	33.2% (94/283)	0.02
Direct acting oral anticoagulant	15.1% (44/292)	12.7% (36/283)	0.42
Aspirin	58.9% (172/292)	62.9% (178/283)	0.33
$P2Y_{12}$ receptor inhibitor, any	22.6% (66/292)	24.0% (68/283)	0.69
Clopidogrel	19.9% (58/292)	21.2% (60/283)	0.69
Prasugrel	1.4% (4/292)	1.8% (5/283)	0.70
Ticagrelor	1.4% (4/292)	1.1% (3/283)	0.73
Prasugrel or ticagrelor	2.7% (8/292)	2.8% (8/283)	0.95
Statin	54.1% (158/292)	67.8% (192/283)	0.0007
30 days			
ACEi, ARB, or ARNi	67.1% (192/286)	64.0% (176/275)	0.43
ACEi/ARB	61.2% (175/286)	61.5% (169/275)	0.95
ACEi	40.2% (115/286)	37.5% (103/275)	0.50
ARB	21.0% (60/286)	24.4% (67/275)	0.34
ARNi	7.3% (21/286)	3.6% (10/275)	0.06
Aldosterone antagonist	56.6% (162/286)	42.2% (116/275)	0.0006
Beta-blockers	90.6% (259/286)	91.6% (252/275)	0.65
Nitrate	5.2% (15/286)	9.1% (25/275)	0.08
Hydralazine	14.7% (42/286)	19.6% (54/275)	0.12
Nitrate plus hydralazine	4.2% (12/286)	6.9% (19/275)	0.16
Diuretic	88.5% (253/286)	90.9% (250/275)	0.34
Chronic oral anticoagulant, any	41.6% (119/286)	47.3% (130/275)	0.18
Warfarin	25.5% (73/286)	34.2% (94/275)	0.02
Direct acting oral anticoagulant	16.8% (48/286)	13.1% (36/275)	0.22
Aspirin	62.2% (178/286)	68.7% (189/275)	0.11
$P2Y_{12}$ receptor inhibitor, any	25.5% (73/286)	30.2% (83/275)	0.22
Clopidogrel	22.7% (65/286)	26.9% (74/275)	0.25
Prasugrel	1.4% (4/286)	2.2% (6/275)	0.48

Ticagrelor	1.4% (4/286)	1.1% (3/275)	0.74
Prasugrel or ticagrelor	2.8% (8/286)	3.3% (9/275)	0.74
Statin	54.5% (156/286)	67.3% (185/275)	0.002

ACEi: angiotensin-converting enzyme inhibitors; ARB: angiotensin II receptor blockers; ARNi: angiotensin receptor-neprilysin inhibitors; LVEF: left ventricular ejection fraction

Supplementary Table 5. Change in health status and exercise capacity over time in patients with HFrEF versus HFpEF.

	HFrEF (n=472)	HFpEF (n=103)	*p*-value
Kansas City Cardiomyopathy Questionnaire			
No. of patients with paired measures at 6 months	377	79	
Baseline score[1]	54.5±23.0	51.2±21.8	0.23
6-month score[1]	66.9±23.7	61.9±25.3	0.11
Difference from baseline to 6-month score[1]	12.4±25.5	10.7±22.7	0.57
Difference between groups in baseline to 6-month score[2]	3.4 (-1.8 to 8.7)		0.20
No. of patients with paired measures at 12 months	308	71	
Baseline score[1]	55.2±22.8	52.9±22.3	0.44
12-month score[1]	66.7±23.6	65.5±25.1	0.71
Difference from baseline to 12-month score[1]	11.5±26.2	12.6±23.3	0.73
Difference between groups in baseline to 12-month score[2]	0.3 (-5.4 to 6.0)		0.93
No. of patients with paired measures at 24 months	238	54	
Baseline score[1]	54.1±23.1	54.0±22.3	0.99
24-month score[1]	64.8±25.3	66.0±24.1	0.75
Difference from baseline to 24-month score[1]	10.8±27.7	12.0±25.0	0.75
Difference between groups in baseline to 24-month score[2]	-1.2 (-8.1 to 5.8)		0.74
6-minute walk distance			
No. of patients with paired measures at 6 months	336	70	-
Baseline score[1]	263.6±122.3	238.4±116.2	0.10
6-month score[1]	281.2±127.2	246.7±128.6	0.043
Difference from baseline to 6-month score[1]	17.6±104.3	8.3±80.7	0.41
Difference between groups in baseline to 6-month score[2]	16.6 (-7.8 to 41.1)		0.18
No. of patients with paired measures at 12 months	274	58	-
Baseline score[1]	272.8±124.0	249.3±113.4	0.16
12-month score[1]	299.8±127.1	250.7±117.9	0.006
Difference from baseline to 12-month score[1]	27.0±112.3	1.4±96.3	0.08
Difference between groups in baseline to 12-month score[2]	34.4 (6.0 to 62.9)		0.018
No. of patients with paired measures at 24 months	194	41	-
Baseline score[1]	281.9±121.4	249.9±116.6	0.12
24-month score[1]	290.7±138.8	250.5±128.9	0.08
Difference from baseline to 24-month score[1]	8.8±124.0	0.6±101.9	0.66
Difference between groups in baseline to 24-month score[2]	19.5 (-19.0 to 57.9)		0.32

[1]Data are presented as mean±standard deviation and were compared by the Student's t-test. [2]Differences with 95% confidence intervals were estimated using baseline-adjusted analysis of covariance. 6MWD: 6-minute walk distance; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire

Supplementary Table 6. Change in health status and exercise capacity over time in patients with severe (LVEF ≤30%) versus moderate (LVEF >30%) left ventricular dysfunction.

	LVEF ≤30% (n=292)	LVEF >30% (n=283)	*p*-value
Kansas City Cardiomyopathy Questionnaire			
No. of patients with paired measures at 6 months	234	222	
Baseline score[1]	53.8±23.7	54.0±21.9	0.92
6-month score[1]	65.6±24.5	66.4±23.6	0.71
Difference from baseline to 6-month score[1]	11.8±26.8	12.4±23.0	0.79
Difference between groups in baseline to 6-month score[2]	-0.7 (-4.7 to 3.3)		0.72
No. of patients with paired measures at 12 months	188	191	
Baseline score[1]	54.9±23.3	54.6±22.1	0.91
12-month score[1]	66.6±23.7	66.3±24.1	0.89
Difference from baseline to 12-month score[1]	11.8±27.1	11.7±24.3	0.98
Difference between groups in baseline to 12-month score[2]	0.2 (-4.2 to 4.7)		0.92
No. of patients with paired measures at 24 months	139	153	
Baseline score[1]	53.8±24.0	54.3±22.0	0.84
24-month score[1]	66.6±25.0	63.7±25.1	0.32
Difference from baseline to 24-month score[1]	12.8±29.1	9.3±25.3	0.28
Difference between groups in baseline to 24-month score[2]	3.1 (-2.2 to 8.5)		0.25
6-minute walk distance			
No. of patients with paired measures at 6 months	206	200	
Baseline score[1]	257.9±127.9	260.7±114.8	0.82
6-month score[1]	275.9±130.1	274.5±126.1	0.91
Difference from baseline to 6-month score[1]	18.0±109.8	13.9±90.3	0.68
Difference between groups in baseline to 6-month score[2]	3.4 (-15.1 to 21.8)		0.72
No. of patients with paired measures at 12 months	166	166	
Baseline score[1]	268.8±130.8	268.6±113.7	0.99
12-month score[1]	297.7±130.7	284.9±122.8	0.36
Difference from baseline to 12-month score[1]	28.9±113.8	16.2±105.9	0.30
Difference between groups in baseline to 12-month score[2]	12.7 (-9.0 to 34.4)		0.25
No. of patients with paired measures at 24 months	112	123	
Baseline score[1]	282.9±125.6	270.3±116.7	0.43
24-month score[1]	297.7±143.5	271.0±131.5	0.14
Difference from baseline to 24-month score[1]	14.8±120.9	0.6±119.8	0.37
Difference between groups in baseline to 24-month score[2]	18.6 (-10.5 to 47.6)		0.21

[1]Data are presented as mean±standard deviation and were compared by the Student's t-test. [2]Differences with 95% confidence intervals were estimated using baseline-adjusted analysis of covariance.

6MWD: 6-minute walk distance; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; KCCQ: Kansas City Cardiomyopathy Questionnaire

Supplementary Table 7. Baseline characteristics of device versus control group patients in the HFrEF (LVEF ≤40%) cohort.

	Device (n=231)	Control (n=241)	*p*-value
Age, years	70.6 (12.3)	72.1 (10.4)	0.15
Male sex	67.1% (155/231)	62.2% (150/241)	0.27
Diabetes	30.7% (71/231)	38.2% (92/241)	0.09
Hypertension	79.2% (183/231)	77.2% (186/241)	0.59
Hypercholesterolaemia	52.4% (121/231)	50.2% (121/241)	0.64
Previous myocardial infarction	48.9% (113/231)	49.4% (119/241)	0.92
Previous percutaneous coronary intervention	42.0% (97/231)	48.5% (117/241)	0.15
Previous stroke or TIA	17.7% (41/231)	13.7% (33/241)	0.23
Peripheral vascular disease	13.4% (31/231)	19.1% (46/241)	0.10
Chronic obstructive lung disease	22.1% (51/231)	20.7% (50/241)	0.72
History of atrial fibrillation or flutter	55.4% (128/231)	50.6% (122/241)	0.30
Body mass index, kg/m^2	26.8 (6.0)	26.9 (6.1)	0.87
Creatinine clearance, mL/min	53.0 (30.3)	50.1 (25.3)	0.28
Anaemia	22.1% (51/231)	22.4% (54/241)	0.93
Ischaemic cardiomyopathy (versus non-ischaemic)	59.7% (138/231)	57.3% (138/241)	0.58
NYHA Class I or II	41.6% (96/231)	36.5% (88/241)	0.26
NYHA Class III	51.5% (119/231)	51.0% (123/241)	0.92
NYHA Class IV	6.9% (16/231)	12.4% (30/241)	0.04
HFH within the previous year	58.4% (135/231)	54.4% (131/241)	0.37
Previous CRT implant	42.4% (98/231)	37.8% (91/241)	0.30
Previous defibrillator implant	70.1% (162/231)	68.0% (164/241)	0.63
B-type natriuretic peptide level, pg/mL	1,094.5 (1,144.6)	1,137.6 (1,341.0)	0.76
N-terminal pro–B-type natriuretic peptide level, pg/mL	5,433.4 (7,286.4)	6,170.3 (8,814.7)	0.61
KCCQ score	53.1 (23.4)	52.7 (22.7)	0.86
6-minute walk distance, metres	249.5 (123.0)	240.1 (126.9)	0.42
Echo core lab measures			
MR severity 4+ (versus ≤3+)	51.5% (119/231)	45.6% (110/241)	0.20
LVESD, cm	5.5 (0.8)	5.5 (0.8)	0.62
LVEDD, cm	6.3 (0.7)	6.3 (0.7)	0.63
Left ventricular ejection fraction, %	28.2 (6.3)	27.8 (6.2)	0.54
RVSP, mmHg	43.7 (13.1)	44.3 (14.0)	0.62
TR severity ≥3+ (versus ≤2+)	0.4% (1/228)	1.3% (3/235)	0.33

Values are mean±standard deviation or % (n/N).

CRT: cardiac resynchronisation therapy; HFH: heart failure hospitalisation; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; MR: mitral regurgitation; NYHA: New York Heart Association; RVSP: right ventricular systolic pressure; TIA: transient ischaemic attack; TR: tricuspid regurgitation

Supplementary Table 8. Baseline characteristics of device versus control group patients in the HFpEF (LVEF >40%) cohort.

	Device (n=50)	Control (n=53)	*p*-value
Age, years	75.8 (8.5)	74.5 (11.1)	0.50
Male sex	62.0% (31/50)	60.4% (32/53)	0.87
Diabetes	52.0% (26/50)	43.4% (23/53)	0.38
Hypertension	82.0% (41/50)	90.6% (48/53)	0.20
Hypercholesterolaemia	64.0% (32/50)	60.4% (32/53)	0.70
Previous myocardial infarction	62.0% (31/50)	56.6% (30/53)	0.58
Previous percutaneous coronary intervention	56.0% (28/50)	47.2% (25/53)	0.37
Previous stroke or TIA	22.0% (11/50)	18.9% (10/53)	0.69
Peripheral vascular disease	36.0% (18/50)	18.9% (10/53)	0.051
Chronic obstructive lung disease	64.0% (32/50)	60.4% (32/53)	0.70
History of atrial fibrillation or flutter	62.0% (31/50)	64.2% (34/53)	0.82
Body mass index, kg/m^2	27.8 (5.6)	27.7 (5.6)	0.98
Creatinine clearance, mL/min	41.4 (17.9)	41.9 (24.9)	0.91
Anaemia	26.0% (13/50)	34.0% (18/53)	0.38
Ischaemic cardiomyopathy (versus non-ischaemic)	70.0% (35/50)	71.7% (38/53)	0.85
NYHA Class I	2.0% (1/50)	0.0% (0/52)	0.31
NYHA Class II	38.0% (19/50)	28.8% (15/52)	0.33
NYHA Class III	56.0% (28/50)	67.3% (35/52)	0.24
NYHA Class IV	4.0% (2/50)	3.8% (2/52)	0.97
HFH within the previous year	58.0% (29/50)	64.2% (34/53)	0.52
Previous CRT implant	22.0% (11/50)	17.0% (9/53)	0.52
Previous defibrillator implant	36.0% (18/50)	30.2% (16/53)	0.53
B-type natriuretic peptide level, pg/ml	813.3 (937.0)	637.4 (476.9)	0.32
N-terminal pro–B-type natriuretic peptide level, pg/mL	4,463.5 (3,518.8)	5,579.9 (7,344.3)	0.66
KCCQ score	53.0 (21.2)	45.4 (24.1)	0.09
6-minute walk distance, metres	233.7 (116.9)	211.7 (108.2)	0.33
Echo core lab measures			
MR severity 4+ (versus 3+)	50.0% (25/50)	39.6% (21/53)	0.29
LVESD, cm	4.5 (0.7)	4.4 (0.8)	0.6
LVEDD, cm	5.7 (0.6)	5.6 (0.7)	0.67
Left ventricular ejection fraction, %	46.0 (4.5)	47.2 (5.2)	0.20
RVSP, mmHg	43.5 (12.3)	46.5 (12.7)	0.25
TR severity ≥3+ (versus ≤2+)	0.0% (0/50)	1.9% (1/52)	0.32

Values are mean±standard deviation or % (n/N).

CRT: cardiac resynchronisation therapy; HFH: heart failure hospitalisation; KCCQ: Kansas City Cardiomyopathy Questionnaire; LVEDD: left ventricular end-diastolic dimension; LVESD: left ventricular end-systolic dimension; MR: mitral regurgitation; NYHA: New York Heart Association; RVSP: right ventricular systolic pressure; TIA: transient ischaemic attack; TR: tricuspid regurgitation

Supplementary Table 9. Outcomes according to left ventricular ejection fraction and randomisation.

	HFrEF (n=472)			HFpEF (n=103)			
	MitraClip plus GDMT (n=231)	**GDMT alone (n=241)**	**Estimate (95% CI)**	**MitraClip plus GDMT (n=50)**	**GDMT alone (n=53)**	**Estimate [95% CI]**	$p_{interaction}$
2-year rates[1]	Kaplan–Meier rate (n events)		HR (95% CI)	Kaplan–Meier rate (n events)		HR (95% CI)	
Death or HFH	44.1% (100)	69.5% (163)	0.50 (0.38 to 0.68)	45.2% (22)	63.3% (31)	0.58 (0.34 to 1.01)	0.63
Death	28.4% (64)	45.2% (102)	0.59 (0.43 to 0.81)	22.8% (11)	42.8% (21)	0.45 (0.22 to 0.93)	0.49
HFH	33.7% (70)	59.7% (132)	0.44 (0.33 to 0.59)	34.5% (15)	49.0% (21)	0.59 (0.31 to 1.15)	0.42
MR severity ≤2+[2]	% (n/N)		OR (95% CI)	% (n/N)		OR (95% CI)	
At 30 days	93.9% (200/213)	33.8% (67/198)	30.1 (16.0 to 56.7)	88.6% (39/44)	33.3% (14/42)	15.6 (5.0 to 48.3)	0.32
At 6 months	95.1% (175/184)	38.0% (65/171)	31.7 (15.16 to 66.3)	87.5% (35/40)	38.2% (13/34)	11.3 (3.5 to 36.2)	0.14
At 1 year	95.1% (154/162)	49.3% (66/134)	19.8 (9.02 to 43.6)	94.3% (33/35)	40.7% (11/27)	24.0 (4.8 to 121.3)	0.84
At 2 years	99.2% (123/124)	47.9% (45/94)	—	100.0% (28/28)	35.0% (7/20)	—	—
Change in KCCQ from baseline to:	Mean±Standard Deviation		Difference (95% CI)[3]	Mean±Standard Deviation		Difference (95% CI)[3]	
30 days	18.0±22.8	1.0±18.1	17.0 (13.5 to 20.6)	13.3±22.3	4.7±19.3	11.1 (3.4 to 18.8)	0.17
6 months	19.9±25.3	4.4±23.2	14.7 (10.5 to 18.8)	12.8±23.1	8.4±22.2	9.8 (0.7 to 19.0)	0.34
1 year	17.9±26.3	4.2±24.3	12.6 (7.8 to 17.3)	14.5±21.9	10.0±25.2	8.0 (-2.1 to 18.0)	0.42
2 years	16.9±27.2	3.0±26.4	11.9 (6.1 to 17.7)	18.2±21.4	3.0±27.5	18.8 (6.5 to 31.1)	0.32
Change in 6MWD from baseline to:	Mean±Standard Deviation		Difference (95% CI)[3]	Mean±Standard Deviation		Difference (95% CI)[3]	
30 days	37.1±108.9	-2.7±86.4	42.2 (24.9 to 59.6)	18.3±84.5	8.8±79.5	20.1 (-19.7 to 59.9)	0.32
6 months	34.0±101.1	-0.9±104.9	34.3 (14.3 to 54.3)	2.5±81.8	16.4±79.8	-3.6 (-48.2 to 40.9)	0.13
1 year	45.0±99.5	6.2±122.6	37.8 (14.3 to 61.3)	-7.7±100.1	12.7±92.0	-7.4 (-58.7 to 43.9)	0.12
2 years	18.5±109.3	-3.9±140.7	18.6 (-13.7 to 50.9)	-15.8±78.5	23.8±127.0	-22.0 (-92.9 to 48.9)	0.31

[1]Data are presented as Kaplan-Meier estimated event rates (number of patients with events). Estimates are hazard ratios with 95% confidence intervals from Cox proportional hazards regression models. [2]Data are presented as proportion (frequency/patients). Estimates are odds ratios with 95% confidence intervals from logistic regression models. [3]Differences were baseline-adjusted in analysis of covariance models.

Supplementary Table 10. Outcomes according to LVEF and randomisation.

	LVEF ≤30% (n=292)			LVEF >30% (n=283)			
	MitraClip plus GDMT (n=139)	**GDMT alone (n=153)**	**Estimate (95% CI)**	**MitraClip plus GDMT (n=142)**	**GDMT alone (n=141)**	**Estimate (95% CI)**	$p_{interaction}$
2-year rates[1]	Kaplan-Meier rate (n events)		HR (95% CI)	Kaplan-Meier rate (n events)		HR (95% CI)	
Death or HFH	47.8% (65)	74.8% (111)	0.49 (0.36 to 0.67)	40.9% (57)	61.3% (83)	0.55 (0.39 to 0.77)	0.62
Death	27.4% (37)	48.4% (69)	0.52 (0.35 to 0.78)	27.4% (38)	41.0% (54)	0.63 (0.41 to 0.95)	0.53
HFH	39.3% (49)	64.8% (91)	0.46 (0.32 to 0.65)	28.3% (36)	49.8% (62)	0.47 (0.31 to 0.71)	0.92
MR severity ≤2+[2]	% (n/N)		OR (95% CI)	% (n/N)		OR (95% CI)	
At 30 days	92.9% (118/127)	35.7% (46/129)	23.66 (10.98 to 50.97)	93.1% (121/130)	31.5% (35/111)	29.19 (13.29 to 64.11)	0.71
At 6 months	94.6% (105/111)	36.1% (39/108)	30.95 (12.44 to 77.01)	92.9% (105/113)	40.2% (39/97)	19.52 (8.55 to 44.56)	0.46
At 1 year	93.8% (90/96)	50.0% (41/82)	15.00 (5.90 to 38.13)	96.0% (97/101)	45.6% (36/79)	28.97 (9.70 to 86.46)	0.37
At 2 years	98.6% (70/71)	47.3% (26/55)	78.08 (10.12 to 602.66)	100.0% (81/81)	44.1% (26/59)	—	—
Change in KCCQ from baseline to:	Mean±Standard Deviation		Difference (95% CI)[3]	Mean±Standard Deviation		Difference (95% CI)[3]	
30 days	19.8±23.3	0.1±17.8	19.4 (14.9 to 23.8)	14.7±21.9	3.4±18.9	12.5 (7.9 to 17.1)	0.04
6 months	20.8±26.1	2.6±24.4	16.4 (11.1 to 21.7)	16.5±23.9	7.8±21.1	11.0 (5.5 to 16.4)	0.16
1 year	18.1±27.1	4.6±25.4	12.0 (5.9 to 18.1)	16.4±23.9	5.8±23.6	11.4 (5.3 to 17.5)	0.89
2 years	17.2±29.7	7.5±7.8	8.1 (0.6 to 15.6)	17.1±22.9	-1.4±24.6	18.1 (10.8 to 25.3)	0.06
Change in 6MWD from baseline to:	Mean±Standard Deviation		Difference (95% CI)[3]	Mean±Standard Deviation		Difference (95% CI)[3]	
30 days	37.9±119.8	0.1±75.5	40.8 (18.7 to 62.9)	30.0±88.6	-2.2±95.8	36.3 (13.3 to 59.4)	0.78
6 months	32.7±110.1	1.8±107.8	30.9 (5.2 to 56.6)	23.6±85.8	1.7±94.6	23.8 (-2.4 to 50.0)	0.70
1 year	48.9±102.7	5.2±122.2	43.3 (12.8-73.8)	22.2±98.8	9.4±113.8	15.8 (-14.7 to 46.2)	0.21
2 years	13.2±104.4	16.7±139.8	-3.1 (-45.4 to 39.2)	11.6±106.2	-14.8±136.3	26.0 (-14.8 to 66.7)	0.33

[1]Data are presented as Kaplan-Meier estimated event rates (number of patients with events). Estimates are hazard ratios with 95% confidence intervals from Cox proportional hazards regression models. [2]Data are presented as proportion (frequency/patients). Estimates are odds ratios with 95% confidence intervals from logistic regression models. [3]Differences were baseline-adjusted in analysis of covariance models.

CI: confidence interval; GDMT: guideline-directed medical therapy; HFH: heart failure hospitalisation; HFpEF: heart failure with preserved ejection fraction; HFrEF: heart failure with reduced ejection fraction; HR: hazard ratio; KCCQ: Kansas City Cardiomyopathy Questionnaire; MR: mitral regurgitation; OR: odds ratio