

Hospitalization of Symptomatic Patients With Heart Failure and Moderate to Severe Functional Mitral Regurgitation Treated With MitraClip



Insights From RESHAPE-HF2

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ABBREVIATIONS AND ACRONYMS

ACM = all-cause mortality
BNP = B-type natriuretic peptide
CV = cardiovascular
EROA = effective regurgitant orifice area
FMR = functional mitral regurgitation
GDMT = guideline-directed medical therapy
HF = heart failure
KCCQ = Kansas City Cardiomyopathy Questionnaire
LVEF = left ventricular ejection fraction
MR = mitral regurgitation
M-TEER = mitral transcatheter edge-to-edge repair
NT-proBNP = N-terminal pro-B-type natriuretic peptide

ABSTRACT

BACKGROUND For patients with functional mitral regurgitation (FMR) and symptomatic heart failure (HF), randomized trials of mitral transcatheter edge-to-edge repair (M-TEER) have produced conflicting results.

OBJECTIVES This study sought to assess the impact of M-TEER on hospitalization rates, and explore the effects of M-TEER on patients who did or did not have a history of recent HF hospitalizations before undergoing M-TEER.

METHODS RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation) included patients with symptomatic HF and moderate to severe FMR (mean effective regurgitant orifice area 0.25 cm²; 14% >0.40 cm², 23% <0.20 cm²) and showed that M-TEER reduced recurrent HF hospitalizations with and without the addition of cardiovascular (CV) death and improved quality of life. We now report the results of prespecified analyses on hospitalization rates and for the subgroup of patients (n = 333) with a HF hospitalization in the 12 months before randomization.

RESULTS At 24 months, the time to first event of CV death or HF hospitalization (HR: 0.65; 95% CI: 0.49-0.85; *P* = 0.002), the rate of recurrent CV hospitalizations (rate ratio [RR]: 0.75; 95% CI: 0.57-0.99; *P* = 0.046), the composite rate of recurrent CV hospitalizations and all-cause mortality (RR: 0.74; 95% CI: 0.57-0.95; *P* = 0.017), and of recurrent CV death and CV hospitalizations (RR: 0.76; 95% CI: 0.58-0.99; *P* = 0.040), were all lower in the M-TEER group. The RR of recurrent hospitalizations for any cause was 0.82 (95% CI: 0.63-1.07; *P* = 0.15) for patients in the M-TEER group vs control group patients. Patients randomized to M-TEER lost fewer days due to death or HF hospitalization (13.9% [95% CI: 13.0%-14.8%] vs 17.4% [95% CI: 16.4%-18.4%] of follow-up time; *P* < 0.0001, and 1,067 vs 1,776 total days lost; *P* < 0.0001). Patients randomized to M-TEER also had better NYHA functional class at 30 days and at 6, 12, and 24 months of follow-up (*P* < 0.0001). A history of HF hospitalizations before randomization was associated with worse outcomes and greater benefit with M-TEER on the rate of the composite of recurrent HF hospitalizations and CV death (*P*_{interaction} = 0.03) and of recurrent HF hospitalizations within 24 months (*P*_{interaction} = 0.06).

CONCLUSIONS These results indicate that a broader application of M-TEER in addition to optimal guideline-directed medical therapy should be considered among patients with symptomatic HF and moderate to severe FMR, particularly in those with a history of a recent hospitalization for HF. (JACC. 2024;84:2347-2363) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/>).

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Functional mitral regurgitation (FMR) is frequent in heart failure (HF), exacerbates HF symptoms and worsen patient outcomes.¹⁻³ For patients with symptomatic HF and severe FMR, mitral transcatheter edge-to-edge repair (M-TEER) has emerged as a therapeutic option, however, with conflicting results.⁴⁻⁶ In these patients, the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trial showed no effect of M-TEER compared with medical therapy alone on all-cause mortality or hospitalization for HF,⁴ whereas the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) demonstrated significant reduction in the rate of hospitalization for HF and in all-cause mortality in patients who underwent M-TEER.⁵ The most recent RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: 2nd Trial in Patients with Clinically Significant Functional Mitral Regurgitation) trial, which recruited symptomatic HF patients with less severe FMR (mean effective regurgitant orifice area [EROA] of 0.25 cm², only 14% of patients had EROA >0.40 cm², and almost a quarter of patients had EROA <0.20 cm²) have shown that M-TEER reduces the composite of cardiovascular (CV) death and HF hospitalizations, and enhances quality of life, as assessed by the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the NYHA functional class.⁶

Hospitalization, which often complicates the natural history of HF, is a major driver of HF economic burden, and is associated with higher mortality and morbidity and poor quality of life, is now considered an important therapeutic target.^{7,8} Despite this, there are still limited data on the effect of M-TEER on hospitalization rates from randomized clinical trials.⁹ It is unclear whether the treatment effect of M-TEER is influenced by the presence or absence of prior HF hospitalizations. Therefore, in this prespecified analysis of RESHAPE-HF2, we aim to assess the impact of M-TEER on hospitalization rates (with and without consideration of mortality) in symptomatic patients with HF and moderate to severe FMR, and additionally explore the effects of M-TEER on patients who did or did not have a history of recent HF hospitalizations before undergoing M-TEER.

SEE PAGES 2364, 2369, 2372 AND 2376

METHODS

STUDY DESIGN. We present here results for prespecified additional outcomes and on a prespecified subgroup for the RESHAPE-HF2 trial. The design and

methods of the RESHAPE-HF2 trial have been described in detail in prior publications.¹⁰⁻¹² The trial was a prospective, randomized, investigator-initiated, multicenter study conducted on symptomatic patients with HF and moderate to severe FMR, despite optimal guideline-directed therapy, in whom isolated mitral valve surgery was not recommended. The trial was registered under the ClinicalTrials.gov [NCT02444338](https://clinicaltrials.gov/ct2/show/study/NCT02444338) (Reshape-HF2, sponsor: University Medicine Göttingen, May 12, 2015) and previously also under the ClinicalTrials.gov [NCT01772108](https://clinicaltrials.gov/ct2/show/study/NCT01772108) (A Randomized Study of the MitraClip Device in Heart Failure Patients With Clinically Significant Functional Mitral Regurgitation [RESHAPE-HF], sponsor: Abbott, January 17, 2013).

STUDY PATIENTS. A total of 505 participants were recruited from 30 sites across 9 countries and were randomly assigned in a 1:1 ratio to either the device group receiving M-TEER in addition to medical therapy or the control group receiving medical therapy alone. The participants were eligible, if they had signs and symptoms of HF despite adhering to guideline-recommended medical therapy, 3+ or 4+ FMR, a left ventricular ejection fraction (LVEF) between 20% and 50% (initially 15% to 35% for NYHA functional class II patients and 15% to 45% for NYHA functional class III/IV patients), and recent HF hospitalization or elevated plasma concentrations of natriuretic peptide (B-type natriuretic peptide [BNP] ≥ 300 pg/mL or N-terminal pro-B-type natriuretic peptide [NT-proBNP] $\geq 1,000$ pg/mL) within the past 90 days, and were not recommended for mitral surgery. Patients diagnosed with mitral regurgitation (MR) caused by degenerative disease of the mitral valve apparatus, as determined by transesophageal echocardiography or transthoracic echocardiography, were excluded. Patients who had undergone any percutaneous CV intervention, carotid surgery, cardiovascular surgery, or atrial fibrillation ablation within 90 days leading up to the randomization process were also excluded ([Supplemental Table 1](#)). Severity of FMR was defined according to the criteria of European Association of Echocardiography.¹³ Patients were considered for randomization only when their HF was considered optimally managed by site investigators, and echocardiography core laboratory had confirmed their eligibility. The trial received approval by Institutional Review Boards or ethics committees at each participating site, and all subjects provided written informed consent.

STUDY ASSESSMENTS. Patients assigned to the device group were scheduled to receive M-TEER within 14 days of randomization. Follow-up visits occurred upon discharge (only for the device group), after

30 days, 180 days, and 365 days, and then yearly. Patients underwent a comprehensive assessment of their clinical status, which included a physical examination, monitoring of vital signs, review of HF medications, evaluation of NYHA functional class, analysis of a 12-lead electrocardiogram, measurement of NT-proBNP levels, and assessments using echocardiography. In-person visits with a HF specialist investigator were held to ensure optimal HF treatment. Additionally, quality-of-life assessments using the KCCQ and EuroQoL-5D (EQ-5D) were performed. Various laboratory tests, including a full blood count with differentials, liver panel, albumin, serum creatinine/estimated glomerular ejection fraction, and cardiac biomarkers, were conducted. Adverse events such as all-cause mortality (ACM) were recorded throughout the entire duration of the trial to assess the safety and effectiveness of M-TEER. Data on total number of hospital admissions were not collected beyond 24 months.

STUDY OUTCOMES. RESHAPE-HF had 3 primary endpoints, that is, recurrent events of hospitalizations for HF with and without consideration of CV death events during 24 months of follow-up as well as quality of life as reflected in the KCCQ overall summary score,⁶ analyzed using the Hochberg procedure.¹⁴ Outcomes of interest in the present study were to determine the proportion of patients with all-cause, CV-related hospitalizations, HF-related hospitalizations; the composite of recurrent CV hospitalizations and ACM, recurrent CV death, and CV hospitalizations, and time to first event of CV death or HF hospitalization; each hospitalization event was considered fatal if death occurred during that index hospitalization or nonfatal if the patient was discharged alive. Nonprotocol M-TEER implantations after baseline were considered as HF hospitalizations during adjudication.

In addition, at each scheduled study visit, the improvement/deterioration in NYHA functional class compared with baseline was evaluated. The percentage of patients in NYHA functional class I/II at 30 days and 6, 12, and 24 months of follow-up was also determined. Patients who had NYHA functional class data available were included in the respective analyses. No imputation was used. A central adjudication committee adjudicated all hospitalization events.

STATISTICAL ANALYSIS. The statistical analyses were conducted based on the intention-to-treat principle, which includes outcomes up to 2 years after randomization. The mean \pm SD were used to present normally distributed data, whereas the median (Q1-Q3) were used for non-normally distributed

data. The categorical variables were summarized using proportions. Comparisons between device and control groups were reported using either Student's *t*-tests, a Wilcoxon rank sum test, a chi-square test, or a Fisher exact test, depending on the type of outcome. Time-to-event analyses were performed using the Cox-proportional hazards model and HRs with 95% CIs were reported. Sensitivity analyses were performed using the Fine-Gray model (post hoc). To estimate event rates, the Kaplan-Meier approach was utilized when all-cause mortality was part of the composite endpoint, otherwise the Aalen-Johansen estimator was employed to account for the competing event, that is, death or non-CV death. For recurrent event analyses, the LWYY model was used. Here, rate ratios (RRs) with 95% CIs were reported. The study also examined independent variables that predict hospitalizations for all causes and specific causes using multivariable Cox regression models. All reported *P* values are 2-sided, and a *P* value <0.05 was statistically significant. The statistical analyses were conducted using R version 4.3.1 (R Foundation for Statistical Computing).

RESULTS

In RESHAPE-HF2, we recruited HF patients with a mean age of 70 ± 10 years vs 69 ± 11 years in the device group vs the control group, respectively. In the device group ($n = 255$), 22% were women, the median LVEF was 32%, the median left ventricular end-diastolic volume was 200 mL, the median EROA was 0.23 cm^2 , and the median regurgitant volume was 35.4 mL, with 44% of patients being classified to have MR severity grade 4+ by the echocardiography core laboratory. The median KCCQ overall summary score was 42 points. In the control group ($n = 250$), 17% were women, the median LVEF was 31%, the median left ventricular end-diastolic volume was 206 mL, the median EROA was 0.23 cm^2 , and the median regurgitant volume was 35.6 mL, with 45% of patients being classified to have MR severity grade 4+ by the echocardiography core laboratory. The median KCCQ overall summary score was 44 for patients in the control group.

Among the 505 patients enrolled in the RESHAPE-HF2 trial, 333 (65.9%) had a prior HF hospitalization in the 12 months before randomization. Patients with prior HF hospitalization had lower KCCQ scores at baseline and were more likely to have NYHA functional class III and IV symptoms. Otherwise, the 2 groups were largely similar (Supplemental Table 2). Among the 505 patients enrolled in the RESHAPE-HF2 trial, 173 patients (34.3%) had at least 1 HF

TABLE 1 Baseline Characteristics According to History of HHF Within 12 Months Before Randomization in the Device Group and the Control Group

	Device Arm			Control Arm		
	HF Hospitalization (n = 165)	No HF Hospitalization (n = 85)	P Value	HF Hospitalization (n = 168)	No HF Hospitalization (n = 87)	P Value
Age, y	69.3 ± 10.5	71.3 ± 10.24	0.13	69.1 ± 11.1	69.9 ± 9.9	0.70
Male	126 (76.36)	69 (81.18)	0.38	139 (82.74)	72 (82.76)	>0.99
Diabetes	57 (34.55)	34 (40.00)	0.40	63 (37.50)	22 (25.29)	0.050
Hypertension	96 (58.18)	45 (52.94)	0.43	89 (52.98)	38 (43.68)	0.16
Previous MI	99 (60.00)	45 (52.94)	0.28	88 (52.38)	47 (54.02)	0.80
Previous PCI	80 (48.48)	38 (44.71)	0.57	82 (48.81)	43 (49.43)	0.93
Previous CABG	42 (25.45)	27 (31.76)	0.29	42 (25.00)	22 (25.29)	0.96
Previous stroke or TIA	20 (12.12)	9 (10.59)	0.72	23 (13.69)	7 (8.05)	0.18
Peripheral vascular disease	26 (15.76)	12 (14.12)	0.73	18 (10.71)	9 (10.34)	0.93
COPD	21 (12.73)	13 (15.29)	0.58	27 (16.07)	10 (11.49)	0.32
History of atrial fibrillation or flutter	73 (44.24)	45 (52.94)	0.19	86 (51.19)	39 (44.83)	0.34
Body mass index, kg/m ²	26.79 ± 4.39	27.26 ± 4.15	0.24	27.07 ± 4.28	26.05 ± 4.28	0.06
Median EuroSCORE II	5.51 (2.86-8.70)	4.84 (2.41-10.36)	0.60	4.69 (2.59-8.94)	6.05 (3.19-9.36)	0.21
Nonischemic cause of cardiomyopathy	55 (33.33)	33 (38.82)	0.39	59 (35.12)	29 (33.33)	0.78
NYHA functional class II	38 (23.03)	21 (24.71)	0.015	39 (23.21)	26 (29.89)	0.22
NYHA functional class III	92 (55.76)	58 (68.24)		102 (60.71)	51 (58.62)	
NYHA functional class IV	35 (21.21)	6 (7.06)		27 (16.07)	9 (10.34)	
Previous CRT	46 (28.05)	31 (36.47)	0.17	44 (26.19)	24 (27.59)	0.81
Previous ICD	51 (31.10)	24 (28.24)	0.64	66 (39.29)	37 (42.53)	0.62
NT-proBNP, pg/mL	3,152 (1,579-5,328)	2,537 (1,717-4,149)	0.50	2,717 (1,128-5,587)	3,025 (1,723-5,429)	0.19
BNP, pg/mL	524 (228-885)	564 (428-1,039)	0.14	414 (193-893)	399 (309-746)	0.61
6-min walk test distance, m	297 (223-376)	302 (212-394)	0.66	305 (206-376)	312 (196-380)	0.87
KCCQ overall summary score	39.1 (25.0-58.8)	49.0 (32.6-68.8)	0.011	42.4 (22.7-64.0)	51.2 (29.9-66.8)	0.09
Assessed at the echocardiographic core laboratory						
Left ventricular ejection fraction, %	31.5 (25.7-37.0)	32.8 (25.8-36.6)	0.83	30.8 (25.3-37.2)	30.6 (25.0-35.4)	0.60
Left ventricular end-systolic dimension, cm	5.90 (5.30-6.50)	5.80 (5.30-6.65)	0.96	5.80 (5.20-6.48)	6.00 (5.45-6.40)	0.13
Left ventricular end-diastolic dimension, cm	6.90 (6.29-7.55)	6.90 (6.30-7.53)	0.76	6.80 (6.30-7.50)	6.90 (6.55-7.40)	0.42
Left ventricular end-systolic volume, mL	139 (100-173)	137 (96-181)	0.94	138 (104-179)	144 (98-174)	0.97
Left ventricular end-diastolic volume, mL	203 (152-247)	187 (158-254)	0.97	205 (159-255)	210 (156-249)	0.84
Mitral regurgitation severity 3+	92 (55.76)	49 (57.65)	0.78	97 (57.74)	44 (50.57)	0.28
Mitral regurgitation severity 4+	73 (44.24)	36 (42.35)		71 (42.26)	43 (49.43)	
Effective regurgitant orifice area, cm ²	0.23 (0.20-0.30)	0.24 (0.20-0.30)	0.54	0.23 (0.19-0.27)	0.24 (0.20-0.33)	0.06
Regurgitant volume, mL	34.55 (28.63-43.83)	37.00 (29.00-43.70)	0.44	34.50 (27.50-41.20)	36.95 (29.38-46.43)	0.022
Right ventricular systolic pressure, mm Hg	40.0 (30.0-53.5)	40.0 (32.0-49.4)	0.82	40.0 (35.0-50.0)	40.0 (32.2-49.5)	0.37

Values are mean ± SD, n (%), or median (Q1-Q3).

BNP = B-type natriuretic peptide; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; HF = heart failure; HHF = hospitalization for heart failure; ICD = implantable cardioverter-defibrillator; KCCQ = Kansas City Cardiomyopathy Questionnaire; MI = myocardial infarction; NT-proBNP = N-terminal B-type natriuretic peptide; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

hospitalization during follow-up. The median duration of follow-up in the overall cohort, device group, and control group was 24.0 months (Q1-Q3: 12.0-25.0 months), 23.6 months (Q1-Q3: 10.4-24.9 months), and 24.2 months (Q1-Q3: 15.7-25.0 months), respectively. There were 38 M-TEER procedures performed among 37 patients in the control arm before 2 years (Supplemental Figure 1). Baseline characteristics differed based on HF hospitalization events during follow-up (Tables 1 and 2). Patients who experienced HF hospitalization after randomization had more severe MR and tricuspid regurgitation, higher NT-proBNP levels and EuroSCORE than those who were not hospitalized. Of

the 244 cases where M-TEER was performed, echocardiography data at the end of the procedure were available in 243 patients (98%). Mitral regurgitation grade was 1+ or lower in 181 patients (74.5%), 2+ in 43 patients (17.7%), 3+ in 10 patients (4.1%), and 4+ in 9 patients (3.7%). Of the 243 patients in this analysis, 137 patients had MR 3+ at baseline, and 106 had MR 4+ at baseline (Supplemental Figure 2).

M-TEER AND HOSPITALIZATIONS. At 24 months, the device group showed significant improvements across several hospitalization outcomes compared with the control group (Tables 3 and 4). The rates of the first event of HF hospitalizations (HR: 0.57;

TABLE 2 Baseline Characteristics for Patients With or Without at Least 1 HHF During Follow-Up

	At Least 1 HF Hospitalization During Follow-Up (n = 173)	No HF Hospitalization During Follow-Up (n = 332)	P Value
Age, y	70.0 ± 11.1	69.5 ± 10.3	0.32
Male	143 (82.66)	263 (79.22)	0.36
Diabetes	74 (42.77)	102 (30.72)	0.007
Hypertension	98 (56.65)	170 (51.20)	0.24
Previous MI	82 (47.40)	197 (59.34)	0.010
Previous PCI	82 (47.40)	161 (48.49)	0.82
Previous CABG	43 (24.86)	90 (27.11)	0.58
Previous stroke or TIA	20 (11.56)	39 (11.75)	0.95
Peripheral vascular disease	28 (16.18)	37 (11.14)	0.11
COPD	28 (16.18)	43 (12.95)	0.32
History of atrial fibrillation or flutter	86 (49.71)	157 (47.29)	0.60
Body mass index, kg/m ²	27.04 ± 4.45	26.73 ± 4.23	0.42
Median EuroSCORE II	5.32 (2.79-8.62)	5.34 (2.71-9.10)	>0.9
Nonischemic cause of cardiomyopathy	70 (40.46)	106 (31.93)	0.06
NYHA functional class II	32 (18.50)	92 (27.71)	0.031
NYHA functional class III	118 (68.21)	185 (55.72)	
NYHA functional class IV	23 (13.29)	54 (16.27)	
HHF within previous 1 y	127 (73.41)	206 (62.05)	0.011
Previous CRT	53 (30.64)	92 (27.79)	0.50
Previous ICD	61 (35.26)	117 (35.35)	>0.9
NT-proBNP, pg/mL	3,445 (2,013-6,114)	2,293 (1,254-4,676)	0.001
BNP, pg/mL	569 (312-1,051)	454 (221-884)	0.29
6-min walk test distance, m	287 (185.8-367.5)	310 (231-394)	0.012
KCCQ overall summary score	38.0 (21.4-57.0)	47.9 (29.7-68.9)	<0.001
Assessed at the echocardiographic core laboratory			
Left ventricular ejection fraction, %	30.90 (24.70-36.50)	31.47 (26.05-37.00)	0.32
Left ventricular end-systolic dimension, cm	5.90 (5.30-6.50)	5.85 (5.30-6.50)	0.87
Left ventricular end-diastolic dimension, cm	6.85 (6.40-7.50)	6.90 (6.30-7.50)	0.96
Left ventricular end-systolic volume, mL	144.00 (109.00-174.00)	133.00 (98.75-174.00)	0.18
Left ventricular end-diastolic volume, mL	209.00 (167.00-256.00)	201.50 (153.00-249.00)	0.28
Mitral regurgitation severity 3+	92 (53.18)	190 (57.23)	0.38
Mitral regurgitation severity 4+	81 (46.82)	142 (42.77)	
Effective regurgitant orifice area, cm ²	0.24 (0.20-0.30)	0.23 (0.20-0.28)	0.10
Regurgitant volume, mL	35.50 (28.85-42.70)	35.60 (28.20-43.25)	0.57
Right ventricular systolic pressure, mm Hg	40.00 (35.00-53.00)	40.00 (30.00-50.00)	0.023

Values are mean ± SD, n (%), or median (Q1-Q3).
Abbreviations as in [Table 1](#).

95% CI: 0.42-0.77; $P < 0.001$) ([Supplemental Figure 3A](#)), and of first CV hospitalizations (HR: 0.74; 95% CI: 0.56-0.98; $P = 0.036$) ([Supplemental Figure 3B](#)), were significantly lower in the device group compared with the control group. Also the rates of recurrent CV hospitalizations (RR: 0.75; 95% CI: 0.57-0.99; $P = 0.046$) ([Figure 1](#)), and recurrent HF hospitalizations (RR: 0.59; 95% CI: 0.42-0.82; $P = 0.002$) were significantly lower in the device group compared with the control group. First hospitalizations due to any cause (HR: 0.79; 95% CI: 0.61-1.02; $P = 0.07$) and the rates of recurrent all-cause hospitalizations (RR: 0.82; 95% CI: 0.63-1.07; $P = 0.15$) were numerically lower in the device group,

but the differences were not statistically significant ([Figure 2](#)). M-TEER also lowered the total number of days patients were hospitalized for HF (1,067 vs 1,776 days; $P < 0.0001$) in comparison to the control group. The distribution of the number of hospitalizations across the 2 randomized groups is also shown in [Supplemental Table 3](#).

M-TEER AND COMPOSITE OUTCOMES. At 24 months, the device group showed significant improvements across several composite CV outcomes compared with the control group ([Tables 3 and 4](#)). The rates of the first event of the composite of ACM or CV hospitalizations (HR: 0.78; 95% CI: 0.60-1.00; $P = 0.046$), ACM or HF hospitalizations (HR: 0.65; 95% CI: 0.50-0.85;

TABLE 3 Hospitalizations and Deaths (Time-to-First-Event Analyses)

	Control Arm (N = 250)			Device Arm (N = 255)			HR (95% CI) ^b	P Value
	No. of Events	Events per 100 pt-y	2-y Event Probability (95% CI) ^a	No. of Events	Events per 100 pt-y	2-y Event Probability (95% CI) ^a		
Time to first CV hospitalization or all-cause mortality	133	49	0.56 (0.50-0.63)	116	36	0.50 (0.44-0.57)	0.78 (0.60-1.00)	0.046
Time to first HF hospitalization or all-cause mortality	127	45	0.54 (0.48-0.61)	97	28	0.42 (0.36-0.48)	0.65 (0.50-0.85)	0.002
Time to first event of any hospitalization or all-cause mortality	138	52	0.58 (0.52-0.65)	126	42	0.54 (0.48-0.61)	0.83 (0.65-1.05)	0.13
Time to first CV hospitalization or CV death	127	47	0.53 (0.47-0.60)	110	35	0.47 (0.41-0.54)	0.77 (0.60-1.00)	0.05
Time to first HF-hospitalization or CV death	120	42	0.50 (0.44-0.57)	90	26	0.39 (0.33-0.45)	0.65 (0.49-0.85)	0.002
Time to first HF hospitalization	105	37	0.44 (0.38-0.51)	68	20	0.29 (0.24-0.35)	0.57 (0.42-0.77)	<0.001
Time to first CV hospitalization	112	41	0.47 (0.41-0.54)	92	29	0.39 (0.34-0.46)	0.74 (0.56-0.98)	0.036
Time to first hospitalization for any reason	122	46	0.51 (0.45-0.58)	105	35	0.45 (0.39-0.52)	0.79 (0.61-1.02)	0.07

^aFor composite endpoints including all-cause mortality 2-year event probabilities are given by the Kaplan-Meier estimates at 24 months; for endpoints not including all-cause mortality, the Aalen-Johansen estimates at 24 months are reported (modeling all-cause death or noncardiovascular [non-CV] death as competing event). ^bCox proportional hazard model adjusting for country and etiology (ischemic vs nonischemic etiology of heart failure).

pt-y = patient-years; other abbreviations as in Table 1.

$P = 0.002$), ACM or all-cause hospitalizations (HR: 0.83; 95% CI: 0.65-1.05; $P = 0.13$), CV death or CV hospitalizations (HR: 0.77; 95% CI: 0.60-1.00; $P = 0.050$), and CV death or HF hospitalizations (HR: 0.65; 95% CI: 0.49-0.85; $P = 0.002$) were significantly lower in the device group compared with the control group. The rate of recurrent events of the composite of ACM or CV hospitalizations (RR: 0.74; 95% CI: 0.57-0.95; $P = 0.017$), CV death or CV hospitalizations (RR: 0.76; 95% CI: 0.58-0.99; $P = 0.040$), ACM or HF hospitalizations (RR: 0.62; 95% CI: 0.47-0.82; $P < 0.001$),

and CV death or HF hospitalizations (RR: 0.64; 95% CI: 0.48-0.85; $P = 0.002$) were significantly lower in the device group, compared with the control group.

Further, patients in the device group lost fewer days due to death or any hospitalization (13.9% [95% CI: 13.0%-14.8%] vs 17.4% [95% CI: 16.4%-18.4%] of follow-up time; $P < 0.0001$), in comparison to the control group (Figure 3).

SENSITIVITY ANALYSES. Sensitivity analyses for time-to-first-event outcomes using the Fine-Gray

TABLE 4 Hospitalizations and Deaths (Recurrent-Events Analyses)

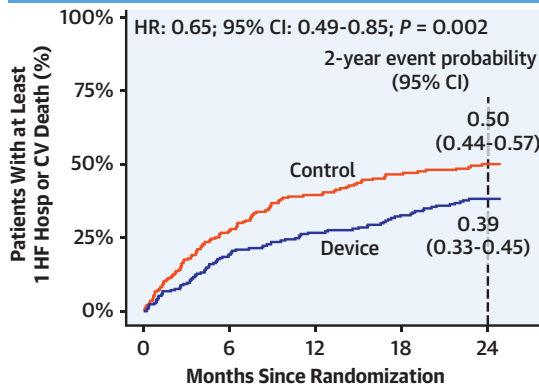
Hospitalization Type	Control Arm (n = 250)		Device Arm (n = 255)		RR (95% CI)	P Value
	No. of Events	Events per 100 pt-y	No. of Events	Events per 100 pt-y		
Recurrent hospitalizations for any reason	233	61	199	49	0.82 (0.63-1.07)	0.15
Fatal hospitalizations for any reason	21	5.5	16	3.9	0.73 (0.38-1.40)	0.34
Nonfatal hospitalizations for any reason	212	56	183	45	0.83 (0.63-1.10)	0.19
Recurrent CV hospitalizations	204	53	159	39	0.75 (0.57-0.99)	0.046
Fatal CV hospitalization	14	3.7	13	3.2	0.87 (0.41-1.86) ^a	0.72
Nonfatal CV hospitalization	190	50	146	36	0.74 (0.56-0.99)	0.040
Recurrent HF hospitalizations	178	47	110	27	0.59 (0.42-0.82)	0.002
Fatal HF hospitalization	12	3.1	9	2.2	0.71 (0.30-1.67) ^a	0.43
Nonfatal HF hospitalization	166	43	101	25	0.58 (0.42-0.82)	0.002
Recurrent events of CV hospitalizations and all-cause death	271	71	210	51	0.74 (0.57-0.95)	0.017
Recurrent events of CV hospitalizations and CV death	251	66	200	49	0.76 (0.58-0.99)	0.040
Recurrent events of HF hospitalizations and all-cause death	245	64	161	39	0.62 (0.47-0.82)	<0.001

^aStatistical model not adjusted for country and etiology (ischemic vs nonischemic etiology of heart failure) due to small number of events.

RR = rate ratio; other abbreviations as in Tables 1 and 3.

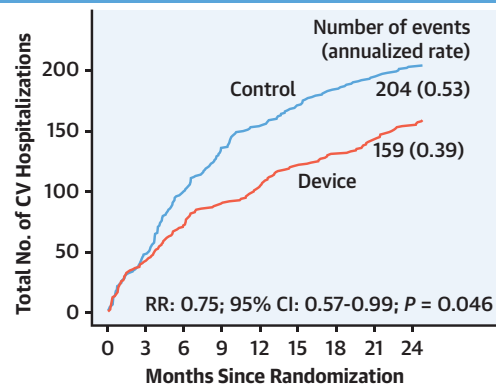
FIGURE 1 Event Rates in the Device vs Control Arm

A First HF Hospitalization or CV Death



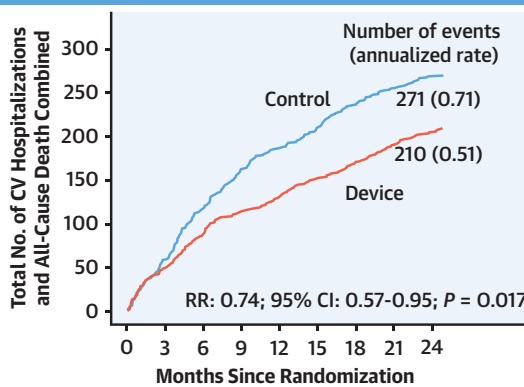
No. at Risk	0	3	6	9	12	15	18	21	24
Device	250	189	159	140	103				
Control	255	171	125	104	63				

B CV Hospitalization



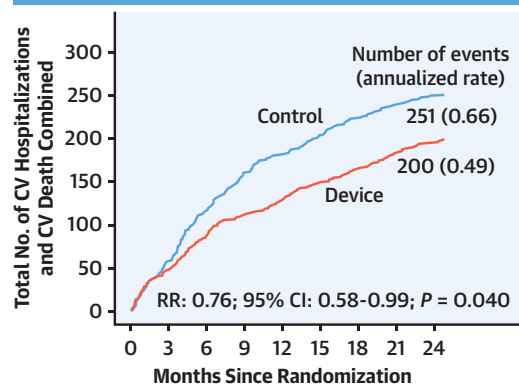
No. at Risk	0	3	6	9	12	15	18	21	24
Control	255	240	223	204	189	179	165	155	146
Device	250	241	222	207	197	191	179	170	163

C CV Hospitalization + All-Cause Death



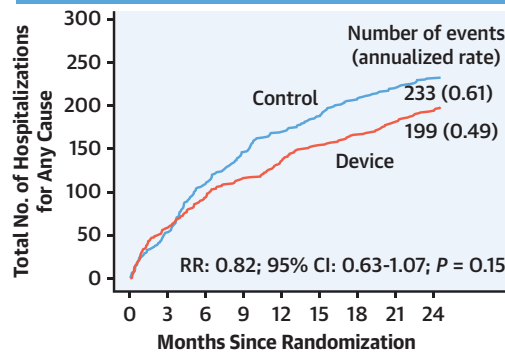
No. at Risk	0	3	6	9	12	15	18	21	24
Control	255	240	223	204	189	179	165	155	146
Device	250	241	222	207	197	191	179	170	163

D CV Hospitalization + CV Death



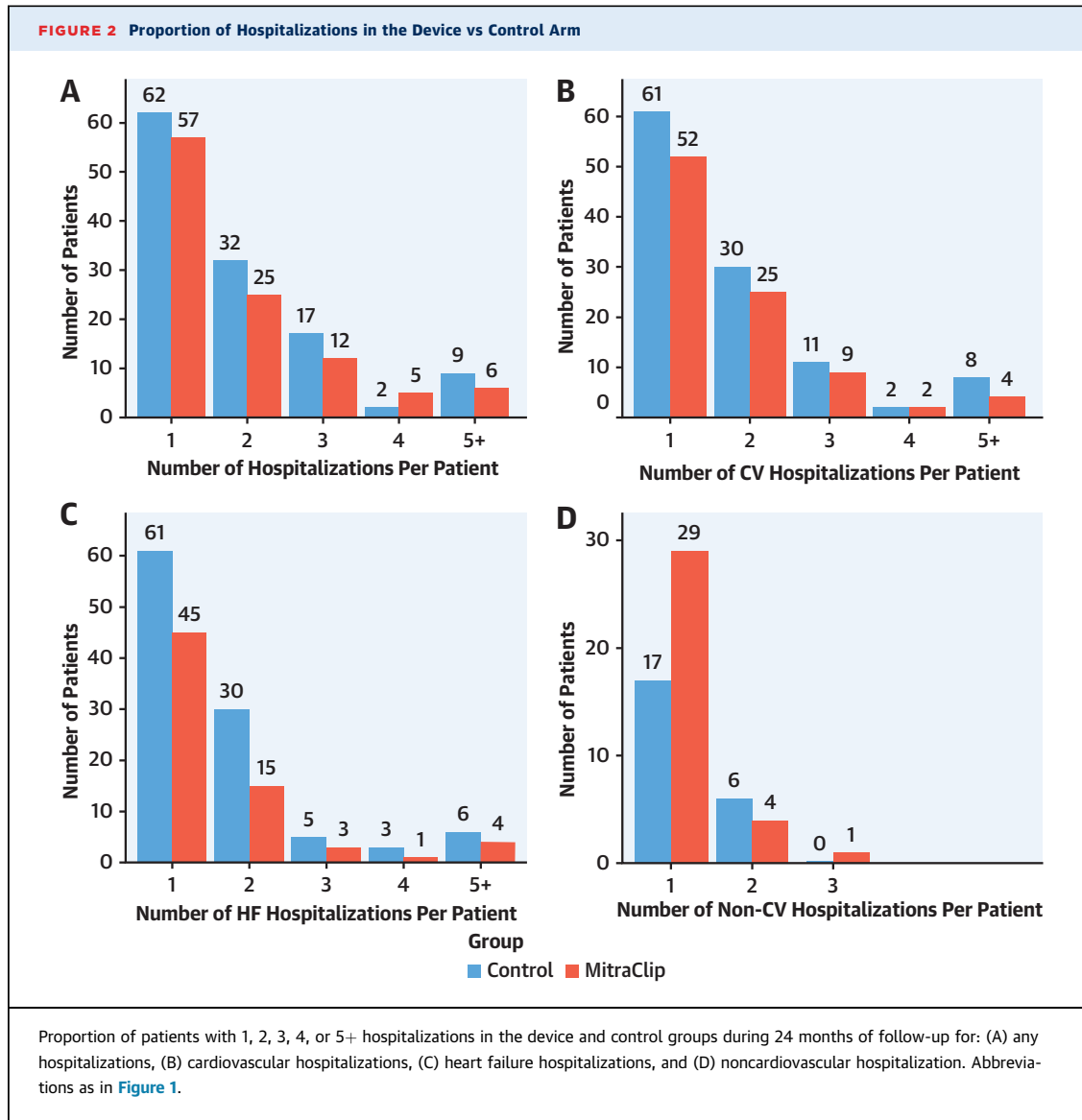
No. at Risk	0	3	6	9	12	15	18	21	24
Control	255	240	223	204	189	179	165	155	146
Device	250	241	222	207	197	191	179	170	163

E Hospitalization for Any Cause



No. at Risk	0	3	6	9	12	15	18	21	24
Control	255	240	223	204	189	179	165	155	146
Device	250	241	222	207	197	191	179	170	163

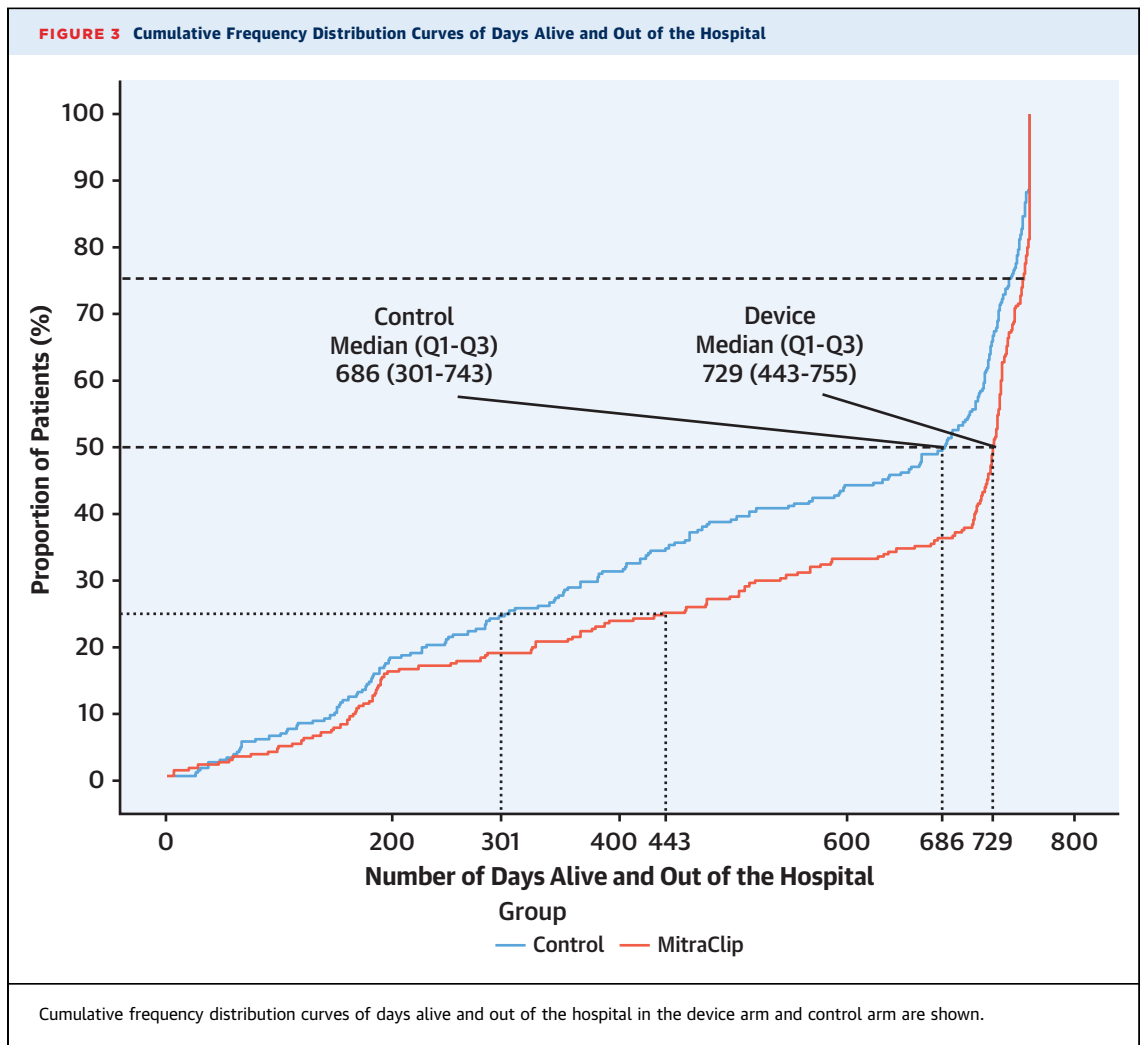
Graphical display of the event rates during 24 months of follow-up for patients in the device and control groups for: (A) First heart failure hospitalization (HF Hosp) or cardiovascular (CV) death. (B) Recurrent events of cardiovascular hospitalization. (C) Recurrent events of cardiovascular hospitalization or death for any reason. (D) Recurrent events of cardiovascular hospitalization or death for cardiovascular reason. (E) Recurrent events of hospitalization for any cause. RR = rate ratio.



model (vs the Cox proportional hazard model as prespecified), and for recurrent events using the Joint-Frailty model (vs LWYY model as prespecified) are now shown in Supplemental Tables 4 and 5, respectively. From these tables, it can be seen that the sensitivity analyses support our findings from the prespecified analytical models.

Nonprotocol M-TEER procedures were identified through serious adverse event reporting, which was restricted to 24 months. We observed 38 M-TEER procedures in 37 patients (14%) in the control group. The cumulative incidence (modeling for the competing risk of death) was 14% and 15% at 12 and

24 months, respectively. The median time from randomization to M-TEER crossover in the control group is 121 days (Q1-Q3: 47-197 days). We observed 8 TEER procedures in 8 patients in the device group (ie, in 3% of that population, a repeat intervention was performed, which represents cumulative incidence probabilities of 3% at both 12 and 24 months). The impact of crossovers on the trial results can go in opposite directions, that is, they can inflate or decrease the observed treatment difference. Hence, regarding unplanned M-TEER, we performed 2 sensitivity analyses: 1) anyone in the control group with a M-TEER procedure is censored 1 day after the



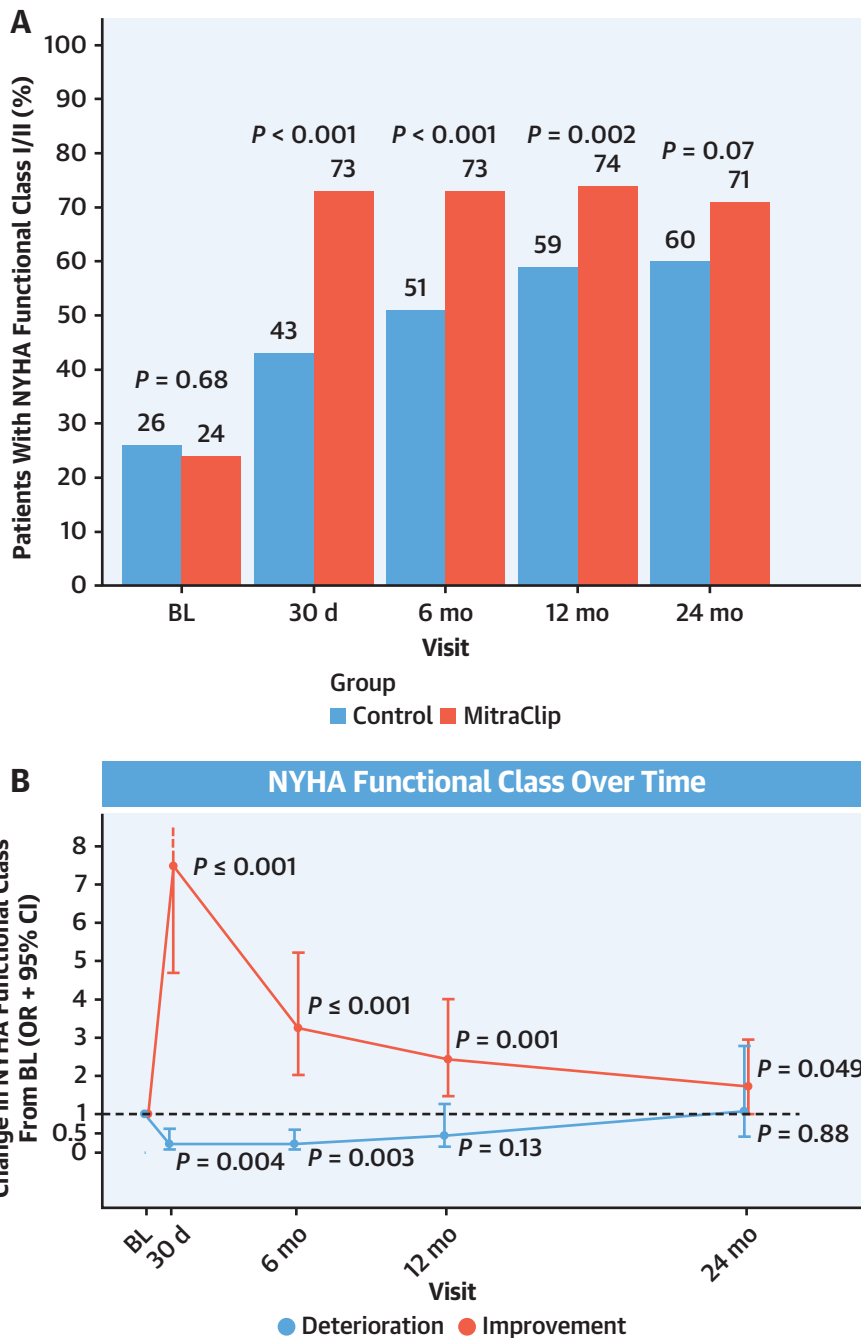
M-TEER (ie, ignoring further follow-up time); and 2) any M-TEER procedure after baseline in either treatment arm is ignored as an HF event. The results for these sensitivity analyses for the 2 events based primary endpoints of the trial are given in [Supplemental Table 6](#). The results support the results of the prespecified primary analyses.

NYHA FUNCTIONAL CLASS AND KCCQ. The impact of M-TEER on being in NYHA functional class I or II (as assessed in 1 of the secondary endpoints of the trial only for the 12-month visit) were evident at each planned visit throughout the 24 months of follow-up ([Figure 4A](#)). NYHA functional class data were available at 30 days, 6 months, 12 months, and 24 months for 456, 412, 360, and 294 patients, respectively. At planned study assessments, patients in the M-TEER

group had better symptomatic status as assessed by NYHA functional class with a much higher likelihood of improvement throughout the study and a lower likelihood of deterioration in the first 6 months ([Figure 4B](#)). The mean increase from baseline to 12 months in the KCCQ overall summary score was 21.6 ± 26.9 in the device group vs 8.0 ± 24.5 in the control group (least-squares mean difference: $+10.9$; 95% CI: 6.8-15.0; $P < 0.001$).

PATIENTS WITH VS WITHOUT A HISTORY OF HF HOSPITALIZATION 12 MONTHS BEFORE RANDOMIZATION. There were no differences in baseline characteristics for patients with or without a prior HF hospitalization within 12 months of randomization between these subgroups in the device and control arms ([Table 1](#)). Patient characteristics of patients with

FIGURE 4 NYHA Functional Class at All Time Points During the Trial

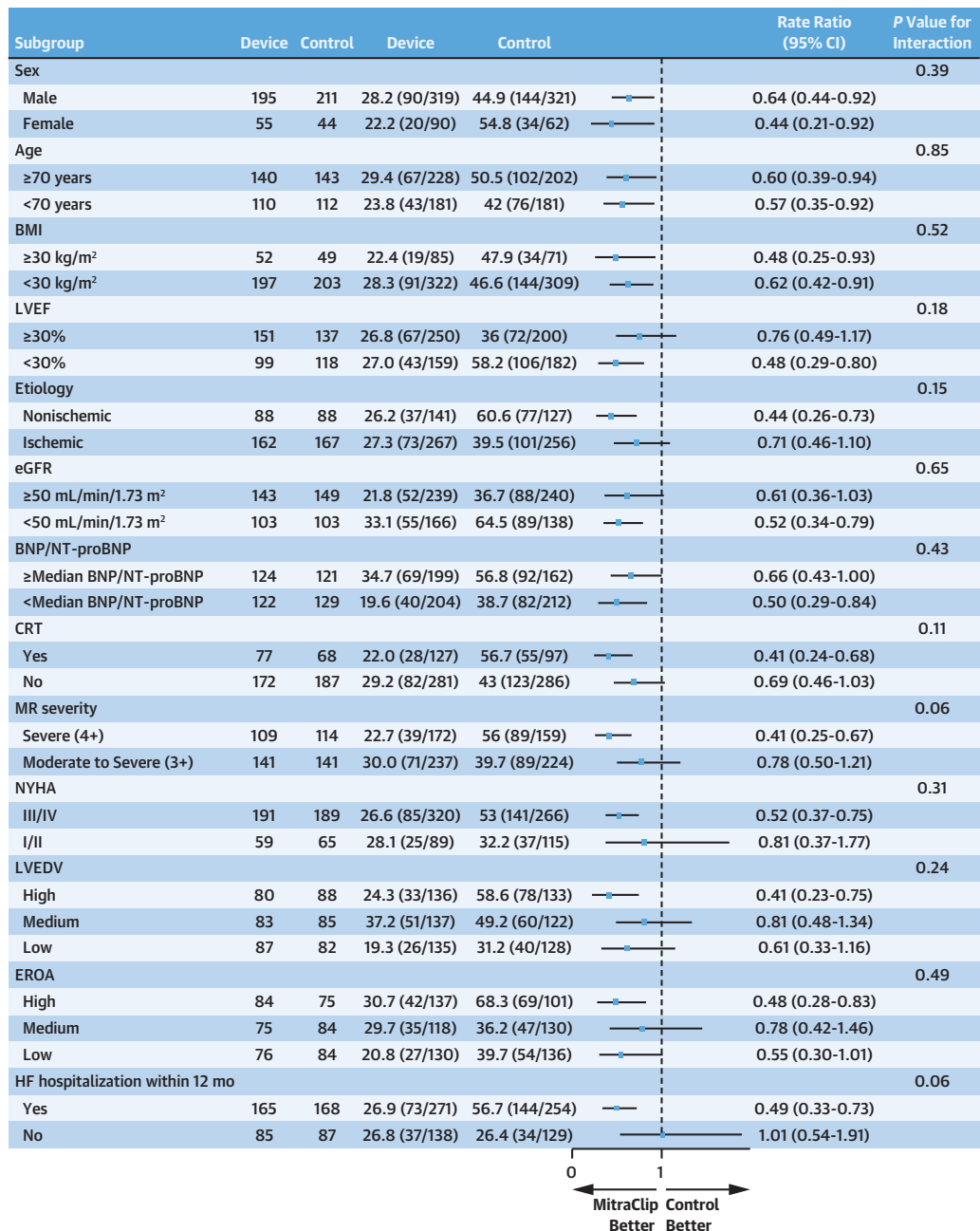


Analyses are presented (A) for the frequency of patients in NYHA functional class I/II (as per secondary endpoint), and (B) analyzing ORs for deteriorations and improvements in NYHA functional class from baseline to respective time points between treatment groups over time. P values in A were calculated at each time point using a chi-square test. BL = baseline.

or without at least 1 HF hospitalization event during follow-up show that patients with a subsequent event have higher NT-proBNP and lower KCCQ OSS values at baseline (Table 2). Patients with

a prior HF hospitalization within 12 months of randomization obtained greater benefit from device treatment on the composite rate of total HF hospitalizations and CV death within 24 months (RR:

FIGURE 5 Prespecified Subgroup Analyses



Forest plot of prespecified subgroup analyses for the second primary endpoint of RESHAPE-HF2, that is, the rate of recurrent HF hospitalizations within 24 months. For left ventricular end-diastolic volume (LVEDV), the following cutpoints for tertiles were used for analyses: low tertile: ≤170 mL; medium tertile: >170 to ≤227 mL; high tertile: >227 mL. For effective regurgitant orifice area (EROA), the following cutpoints for tertiles were used for analyses: low tertile: ≤0.21 cm²; medium tertile: >0.21 to ≤0.27 cm²; high tertile: >0.27 cm². BMI = body mass index; BNP = B-type natriuretic peptide; CRT = cardiac resynchronization therapy; eGFR = estimated glomerular ejection fraction; LVEF = left ventricular ejection fraction; MR = mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide.

TABLE 5 Predictors of Hospitalization

	All Hospitalizations		CV Hospitalizations		Hospitalization for HF		Non-CV Hospitalizations	
	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value	HR (95% CI)	P Value
Device vs control	0.74 (0.54-1.01)	0.06	0.71 (0.51-0.99)	0.040	0.59 (0.41-0.85)	0.004	1.46 (0.75-2.84)	0.26
MR severity, 4+ vs 3+	0.96 (0.69-1.34)	0.81	1.02 (0.72-1.44)	0.90	0.92 (0.63-1.34)	0.66	0.68 (0.33-1.43)	0.30
NT-proBNP, per 500 pg/mL	1.01 (1.00-1.03)	0.14	1.02 (1.00-1.04)	0.12	1.02 (1.00-1.04)	0.07	1.03 (1.00-1.07)	0.09
Baseline KCCQ, per 10 points	0.90 (0.83-0.98)	0.016	0.87 (0.80-0.95)	0.001	0.86 (0.79-0.95)	0.002	0.94 (0.79-1.12)	0.50
History of Afib, yes vs no	0.97 (0.71-1.35)	0.87	1.04 (0.74-1.46)	0.81	0.93 (0.64-1.34)	0.69	0.94 (0.47-1.86)	0.86
Baseline 6MWD, per 10 m	0.98 (0.96-1.00)	0.06	0.99 (0.97-1.01)	0.35	0.99 (0.97-1.01)	0.52	0.99 (0.95-1.03)	0.48
Age, per 10 y	1.07 (0.89-1.27)	0.49	1.09 (0.91-1.32)	0.35	1.15 (0.94-1.41)	0.18	1.23 (0.82-1.85)	0.31
Previous CRT, yes vs no	0.80 (0.56-1.14)	0.21	0.84 (0.58-1.22)	0.35	0.77 (0.51-1.17)	0.22	0.77 (0.36-1.66)	0.50
EuroSCORE II	1.02 (1.00-1.04)	0.16	1.01 (0.98-1.03)	0.66	1.01 (0.98-1.04)	0.50	1.00 (0.95-1.05)	0.84
HF hospitalization within 12 mo before randomization, yes vs no	1.48 (1.05-2.11)	0.024	1.57 (1.09-2.28)	0.013	1.65 (1.10-2.47)	0.013	0.61 (0.31-1.22)	0.166

Cox proportional hazards model adjusting for country and etiology (ischemic vs nonischemic etiology of heart failure), and including all listed predictors. 6MWD = 6-minute walk distance; Afib = atrial fibrillation; MR = mitral regurgitation; other abbreviations as in Table 1.

0.53; 95% CI: 0.37-0.75) compared with patients without a prior hospitalization within 12 months of randomization (RR: 1.05; 95% CI: 0.62-1.79; $P_{interaction} = 0.03$), and on the rate of recurrent HF hospitalizations for within 24 months (RR: 0.49; 95% CI: 0.33-0.73 vs RR: 1.01; 95% CI: 0.54-1.91; $P_{interaction} = 0.06$).

SUBGROUP ANALYSES. The lower rates of HF hospitalization in the device group, compared with the control group, were observed across all prespecified subgroups (Figure 5).

PREDICTORS OF HOSPITALIZATION. After adjusting for multiple variables, M-TEER was associated with a significantly lower risk of CV-related and HF-related hospitalizations compared with the control group (Table 5). Patients with a lower baseline KCCQ and with a HF hospitalization within 12 months before randomization had significantly higher rates of all-cause, CV-related, and HF-related hospitalizations at 24 months (Table 5). Results were essentially identical when instead of the variable MR severity 4+ vs 3+, the EROA was included in all analyses (Supplemental Table 7).

DISCUSSION

In this analysis of the RESHAPE-HF2 trial, we highlight several key findings for M-TEER in patients with HF and moderate to severe FMR, particularly those with a history of recent hospitalization for HF at randomization. M-TEER was associated with a reduction in HF hospitalization rates and in reductions of composite rates of CV or all-cause death

and recurrent HF or CV hospitalizations. M-TEER led to fewer days spent in hospital due to HF and an improvement in NYHA functional class throughout the trial duration of 24 months in comparison to control. It is important to highlight that the mean EROA in the cohort was 0.25, indicating that the majority of the enrolled population had moderate FMR. Therefore, these results suggest a role of M-TEER in addition to guideline-directed medical therapy (GDMT) in managing patients with HF and moderate to severe FMR, particularly those with a history of recent hospitalization for HF at baseline.

Patients with recent HF hospitalizations at baseline are at higher risk of future events, as the occurrence of HF hospitalizations in the trial correlated with higher mortality across both treatment groups. Similar findings were observed in previous studies. In a subgroup analysis of the COAPT trial, patients with a recent history of HF hospitalization at baseline who experienced all-cause, HF-related, and CV-related hospitalizations faced a consistently higher risk of 2-year mortality in both device and control groups.¹⁵ Additionally, analysis of data from 3,242 symptomatic patients with FMR from the National Readmission Database indicated significantly higher mortality in patients who received M-TEER and were subsequently rehospitalized.¹⁶ A similar trend was noted in a study from the U.S. Department of Defense network that included 51,286 patients with a first event of HF hospitalization, where repeat HF hospitalizations were associated with increased mortality and correlated with the frequency of hospitalizations.¹⁷ Despite this, M-TEER reduced the rates of

recurrent CV and of HF hospitalizations among patients who had a higher initial risk due to recent HF hospitalizations. This is consistent with prior studies, where M-TEER reduced recurrent hospitalizations in patients with severe HF and FMR, hence confirming its benefit for this patient subgroup.^{18,19} Of note, it was observed in RESHAPE-HF2 that patients with FMR severity 4+ also derived somewhat more benefit ($P_{\text{interaction}} = 0.07$) from M-TEER for the primary endpoint of the composite CV death and recurrent HF hospitalizations.⁶

Additionally, patients in the M-TEER group experienced fewer days lost to death or hospitalization. Fewer hospitalizations and better survival translate into less disruption to daily life, lower medical costs, and a better overall quality of life for these patients.²⁰⁻²² Subsequently, lower recurrent hospitalizations after M-TEER, as observed earlier, reduce economic burden that hospitalizations impose on the health care system in the United States.²³ Therefore, these benefits suggest that a broader application of M-TEER in patients with prior HF hospitalizations should be considered.

Patients in the M-TEER group spent fewer days in the hospital, spending approximately 2 months fewer than patients in the control group. These findings are consistent with the COAPT trial, where patients with baseline clinical instability also showed a benefit of 2 months of additional life free from hospitalization.¹⁵ Adding to the improved prognosis, patients in the M-TEER group consistently demonstrated lower NYHA functional class over the 24-month period, compared with patients in the control group. We would like to emphasize that these benefits were seen in addition to optimal GDMT. This is important as there are phenotype variations in FMR that may respond differently to GDMT vs M-TEER, which could have led to different results seen in MITRA-FR.²⁴

M-TEER, in addition to a reduction of the events of worsening HF requiring hospital admission, also significantly enhanced NYHA functional class consistently throughout the entire 24-month follow-up period and in the first 6 months also reduced the risk of deterioration in NYHA functional class (Figure 4B), resulting in a higher proportion of patients in NYHA functional class I and II throughout the study (Figure 4A). Of note, these effects were already present early at the first post-discharge follow-up visit at 30 days. These findings are clinically relevant for patients with moderate to severe FMR who, despite optimal medical management, remain highly symptomatic and often tend to experience exacerbations in HF signs/symptoms. Thus,

maintaining clinical stability over time in this population remains a therapeutic target. These benefits to the overall prognosis and survival without HF hospitalization events after M-TEER support its increased adoption in the management of patients with HF and FMR, particularly in those with greater initial risk. However, this may include even those with a more severe risk. For instance, the RESHAPE-HF2 trial included fewer patients with NYHA functional class IV, yet M-TEER benefits may also extend to those patients with a more severe baseline risk. For example, in an analysis from the EXPAND (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) study, 118 patients with NYHA functional class IV and acute decompensated HF with clinical instability at baseline showed greater improvements in KCCQ and NYHA functional class after M-TEER than patients with NYHA functional class III or lower.²⁵ Moreover, ACM or HF hospitalization at 12 months had no significant association with baseline NYHA functional class.

STUDY LIMITATIONS. First, although our analysis adjusts for known confounders and was a randomized, controlled trial, residual factors such as adherence to HF medications, concurrent HF therapies, or variations in the severity of the disease could influence the observed results, albeit likely only to a small degree if at all. Second, the follow-up duration of 24 months in our study may be too short to assess the long-term impacts of M-TEER. Third, as the study was open-label, improvements in patient-reported outcomes may be exaggerated in the absence of a sham control. Fourth, the study was not adequately powered to assess smaller group differences such as all-cause mortality. Lastly, it is important to highlight that FMR is a complex disease that requires careful considerations on various aspects, and the role of the heart team is vital to ensure a tailored approach for each patient.

CONCLUSIONS

These results indicate that a broader application of M-TEER in addition to optimal GDMT should be considered among patients with symptomatic HF and moderate to severe FMR, particularly in those with a history of a recent hospitalization for HF. Patients assigned to M-TEER had better symptom status throughout the study, and they had lower rates of CV-related and HF-related hospitalizations at 24 months.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

Prof Ponikowski has received a grant from Vifor Pharma; has received consulting fees and/or honoraria from Boehringer Ingelheim, AstraZeneca, Vifor Pharma, Servier, Novartis, Berlin Chemie, Bayer, Abbott Vascular, Novo Nordisk, Pharmacosmos, Moderna, Pfizer, and Abbott Vascular; and has received fees for trial committee work from Boehringer Ingelheim, Vifor Pharma, Novo Nordisk, Pharmacosmos, and Moderna. Dr Friede has received payments to his institution from Abbott; has received grants from Deutsche Forschungsgemeinschaft (DFG), Federal Joint Committee (G-BA), and European Commission; has received consulting fees from Actimed, Bayer, BMS, CSL Behring, Daiichi-Sankyo, Galapagos, Immunic, KyowaKirin, LivaNova, Minoryx, Novartis, RECARDIO, Relaxera, Roche, Servier, Viatrix, and Vifor; has received payments from Fresenius Kabi and PINK gegen Brustkrebs; is a trial data monitoring committee member for Aslan, Bayer, Biosense Webster, Enanta, Galapagos, IQVIA, Novartis, PPD, Recordati, Roche, and VICO Therapeutics; and is a trial steering committee member for CSL Behring. Dr von Bardeleben has received an EchoCoreLab IIT grant from Clinical Trial Unit of UMG Göttingen; has received consulting fees from Abbott Vascular, Jensecare, Edwards Lifesciences, and Medtronic; has received honoraria from Abbott Vascular, Jenavalve, Jensecare, Edwards Lifesciences, Medtronic, Philips, Siemens; and is a trial committee member for Medtronic and Heart Valve Society (unpaid), and EU SHD Coalition (unpaid). Dr Butler has received consulting fees from Abbott, American Regent, Amgen, Applied Therapeutic, AskBio, Astellas, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Bristol Myers Squibb, Cardiac Dimension, Cardiocell, Cardior, Cardiore, CSL Bearing, CVRx, Cytokinetics, Daxor, Edwards Lifesciences, Element Science, Faraday, Foundry, G3P, Innolife, Impulse Dynamics, Imbria, Inventiva, Ionis, Lexicon, Lilly, LivaNova, Janssen, Medtronic, Merck, Occlutech, Owkin, Novartis, Novo Nordisk, Pfizer, Pharmacosmos, Pharmain, Pfizer, Prolaio, Regeneron, Renibus, Roche, Salamandra, Sanofi, SC Pharma, Secretome, Sequana, SQ Innovation, Tenex, Tricog, Ultromics, Vifor, and Zoll; and has received honoraria from Novartis, Boehringer Ingelheim-Lilly, AstraZeneca, Impulse Dynamics, and Vifor. Dr Khan has participated in a data safety monitoring board or advisory board for Bayer. Dr Ferrari has received honoraria and support for attending meetings from Servier, Merck Serono, Bayer, Lupin, and Sunpharma. Dr Abraham has received payments from Abbott; has received grants from National Institutes of Health 1 UG3 / UH3 HL140144-01; has received consulting fees from Zoll Respicardia; has received honoraria from Impulse Dynamics, Edwards Lifesciences, and Abbott; and is an advisory board member for Sensible Medical, WhiteSwell, AquaPass, Cordio Medical, and Boehringer Ingelheim. Dr Auricchio has received consulting fees and honoraria from Boston Scientific, Medtronic, Microport CRM, Philips, Xspline, and Abbott. Dr Bayes-Genis has lectured and/or participated in advisory boards for Abbott, AstraZeneca, Bayer, Boehringer Ingelheim, Medtronic, Novartis, Novo Nordisk, Roche Diagnostics, and Vifor. Dr Cleland has received grants from Bristol Myers Squibb, CSL-Vifor, British Heart Foundation, and Pharmacosmos; has received consulting fees from Pharmacosmos, CSL-Vifor, and Biopetetics; and has received honoraria from Pharmacosmos. Dr Filippatos has received honoraria from Bayer, Boehringer Ingelheim, Servier, and Novartis; has served on the trial committee boards for Bayer, Medtronic, Boehringer Ingelheim, Vifor, Amgen, Servier, Impulse Dynamics, Cardior, and Novo Nordisk; and has served on the boards of the Heart Failure Association and *JACC Heart Failure*. Dr Gustafsson has received consulting fees and/or honoraria from Abbott, Bayer, Pfizer, and AstraZeneca; has participated on the trial committee board of AdJuCor; and has served on the board of the Heart Failure Association. Dr Haverkamp has received consulting fees and/or honoraria from Bayer and AstraZeneca. Dr Kelm has received grants or contracts from Microvision Medical Holding B.V., Edwards Lifesciences, Mars Scientific Advisory Council, Abiomed Europe GmbH, B. Braun Melsungen AG, DFG SFB 1116, EU Horizon 2020, and Daiichi-Sankyo

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APPENDIX For supplemental figures and tables, please see the online version of this paper.