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ORIGINAL RESEARCH

HEART FAILURE

Evaluating Mitral TEER in the Management of Moderate Secondary Mitral Regurgitation Among Heart Failure Patients

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ABSTRACT

BACKGROUND Moderate secondary mitral regurgitation (SMR) represents a subgroup of heart failure (HF) patients with treatment restricted to medical therapy. Outcomes in patients with moderate SMR treated with mitral transcatheter edge-to-edge repair (M-TEER) are less well known.

OBJECTIVES The aim of this study was to assess the safety and effectiveness of M-TEER in subjects with moderate SMR using the EXPANDed studies.

METHODS One-year outcomes in subjects from the EXPANDed studies (EXPAND [A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices] and EXPAND G4 [A Post-Market Study Assessment of the Safety and Performance of the MitraClip G4 System] MitraClip studies) with baseline moderate SMR (2+), per echocardiographic core laboratory (ECL) assessment, were compared with subjects with baseline severe SMR (≥3+).

RESULTS There were 335 subjects with moderate SMR and 525 with severe SMR at baseline per ECL review. Baseline characteristics were similar between the 2 subgroups. After treatment with M-TEER, significant MR reduction was achieved in both groups. Significant left ventricular (LV) reverse remodeling was observed through 1 year, with a >20 mL decrease in LV end-diastolic and end-systolic volumes on average in the moderate SMR group. Significant 1-year improvements in NYHA functional class (>78% NYHA functional class I or II) and quality of life (>20 points on the Kansas City Cardiomyopathy Questionnaire–Overall Summary) were observed in subjects with moderate SMR. Similarly, low rates of major adverse events, all-cause mortality, and HF hospitalizations were observed between the 2 subgroups through 1 year.

CONCLUSIONS In the EXPANDed studies, subjects with moderate SMR treated with M-TEER had improvements similar to subjects with severe SMR in quality of life and positive LV remodeling at 1 year. Future studies are needed to evaluate if M-TEER would be beneficial for HF patients with moderate SMR. (JACC Heart Fail. 2025;13:213–225)
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ABBREVIATIONS AND ACRONYMS

ACEI = angiotensin-converting enzyme inhibitor

ARB = angiotensin II receptor blocker

ECL = echocardiographic core laboratory

GDMT = guideline-directed medical therapy

HFH = heart failure hospitalization

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

LVESV = left ventricular end-systolic volume

M-TEER = mitral transcatheter edge-to-edge repair

MR = mitral regurgitation

MV = mitral valve

PMR = primary mitral regurgitation

SMR = secondary mitral regurgitation

TEER = transcatheter edge-to-edge repair

Secondary mitral regurgitation (SMR) has a wide spectrum of disease in heart failure (HF) patients with phenotypes characterized by mitral regurgitation (MR) severity, left ventricular (LV) dysfunction and dilation, and diminished quality of life. Increasing MR severity, such as moderate (2+) and severe (≥3+) SMR, is associated with a poor prognosis,[1] including symptomatic reduction in quality of life, adverse LV remodeling, and a higher risk of morbidity, including heart failure hospitalizations (HFHs). Heterogeneity of SMR is well documented; multiple phenotypes capturing LV function, size, and symptoms have been used to try to develop effective treatment options.[2] At present, the available data suggest that a beneficial response to treatment of SMR with mitral transcatheter edge-to-edge repair (M-TEER) may be related to factors that include response to guideline-directed medical therapy (GDMT) and pre-existing LV dysfunction and dilatation, all of which may be used to identify patients in various stages of the disease.

Evaluation of MR severity is complex and relies on assessing patients in a resting state, although MR is well known to be dynamic and subject to change during exercise. The ASE (American Society of Echocardiography) grading system uses quantitative assessments of MR, including effective regurgitant orifice area, regurgitant volume, and regurgitant fraction, to classify MR severity into 5 grades: grade 0 (none/trace), grade 1+ (mild), grade 2+ (moderate), grade 3+ (moderate to severe), and grade 4+ (severe).[3] Moderate MR at rest may reflect a spectrum of disease that is truly moderate or which increases with volume overload or exercise to be more hemodynamically significant and in some cases severe.[4] Patients with moderate SMR can exhibit a range of LV dilation as well. Previous studies have shown enlarged LV sizes in patients with moderate SMR,[5,6] which can vary within the different stages of HF.[2] Although long-term outcomes such as mortality increase with increasing severities of SMR,[1] mortality rates have been shown to be similar between moderate and severe SMR when treated with GDMT alone and lower when treated with M-TEER.[7] Patients with moderate SMR may have poor quality of life, enlarged left ventricles, and a high mortality and HFH risk when treated with GDMT alone.[5-7] Mortality and morbidity of patients with both LV dysfunction and SMR remain high despite treatment with currently accepted standard medical therapy.[8]

Surgical mitral valve (MV) repair has been previously evaluated for the treatment of moderate ischemic MR at the time of revascularization; however, surgical repair did not have a significant impact on LV remodeling and was associated with an increased early risk of neurologic events.[9] GDMT, in combination with other interventions such as M-TEER, may provide an optimal treatment option for patients with moderate 2+ SMR, particularly in those with LV dysfunction and progressing HF symptoms.

Currently, data on outcomes of treatment with M-TEER in patients with moderate SMR are limited, and much of the existing research has not been conducted in a contemporary setting with M-TEER. The aim of the current study was to evaluate the outcomes of the MitraClip system (Abbott) for the treatment of patients with echocardiographic core laboratory (ECL)-assessed moderate (2+) SMR from the EXPANDed studies.

METHODS

STUDY DESIGN. The EXPANDed data set combines data from the contemporary postmarketing studies EXPAND (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip® Devices; NCT03502811) and EXPAND G4 (A Post-Market Study

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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Assessment of the Safety and Performance of the MitraClip G4 System; NCT04177394). Details on both studies have been published previously.[10-12] In brief, the EXPANDed studies are global postmarketing studies conducted to evaluate the safety and effectiveness of the third-generation (MitraClip NTR/XTR System in EXPAND; 1,041 subjects) and fourth-generation (MitraClip G4 System in EXPAND G4; 1,164 subjects) MitraClip systems.

From 2018 to 2022, a total of 2,205 subjects with symptomatic primary mitral regurgitation (PMR) or SMR were enrolled across 91 centers in the United States, Europe, Canada, Israel, Saudi Arabia, and Japan. Subjects were enrolled and commercially treated according to the associated study protocol, designed to be all-comers per the regional indications for use, and subject selection was based on site-reported assessment of MR severity and evaluation by a heart team. All subjects had a site-evaluated indication for treatment of site-assessed severe MR with M-TEER. No independent review of optimal GDMT was performed. Clinical data at baseline, discharge, 30 days, and 1 year after the MitraClip procedure were collected. Transthoracic and transesophageal echocardiograms were retrospectively evaluated by an independent ECL.

The EXPANDed studies were sponsored by Abbott and conducted per the latest Good Clinical Practice standards of the Declaration of Helsinki; they were approved by local ethics committees and applicable competent authorities of participating countries.

ANALYSIS POPULATION. Subjects in EXPANDed with an SMR etiology assessment and evaluable MR grade at baseline as evaluated by the ECL were included in the analysis; subjects with PMR or mixed etiology were excluded from this analysis. Subjects with SMR were categorized into 2 groups: 1) moderate SMR: subjects with a baseline MR grade of moderate (2+); and 2) severe SMR: subjects with a baseline MR grade of moderate to severe (3+) or severe (4+) (MR ≥3+).

STUDY DEFINITIONS. All echocardiographic measures reported in this analysis were assessed by an independent ECL. MR severity and etiology for all EXPANDed subjects were assessed by the MedStar Health Research Institute per the ASE guidelines.[3,13] LV parameters were assessed by the Medical Research Development S.L. in EXPAND and the MedStar Health Research Institute in EXPAND G4. Additional details of echocardiographic assessments have been described previously.[10-12]

Clinical outcomes included functional status (assessed according to the NYHA functional class), quality of life (assessed according to the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score [KCCQ-OSS]), all-cause mortality, and HFHs through 1 year. Safety outcomes, including major adverse events, were defined as a composite of all-cause mortality, myocardial infarction, stroke, and MV surgical reintervention. Major adverse events were site reported through 1 year and adjudicated by an independent clinical evaluations committee through 30 days in EXPAND. Leaflet adverse events were assessed by the ECL (MedStar Health Research Institute) in both studies and included single-leaflet device attachment events.

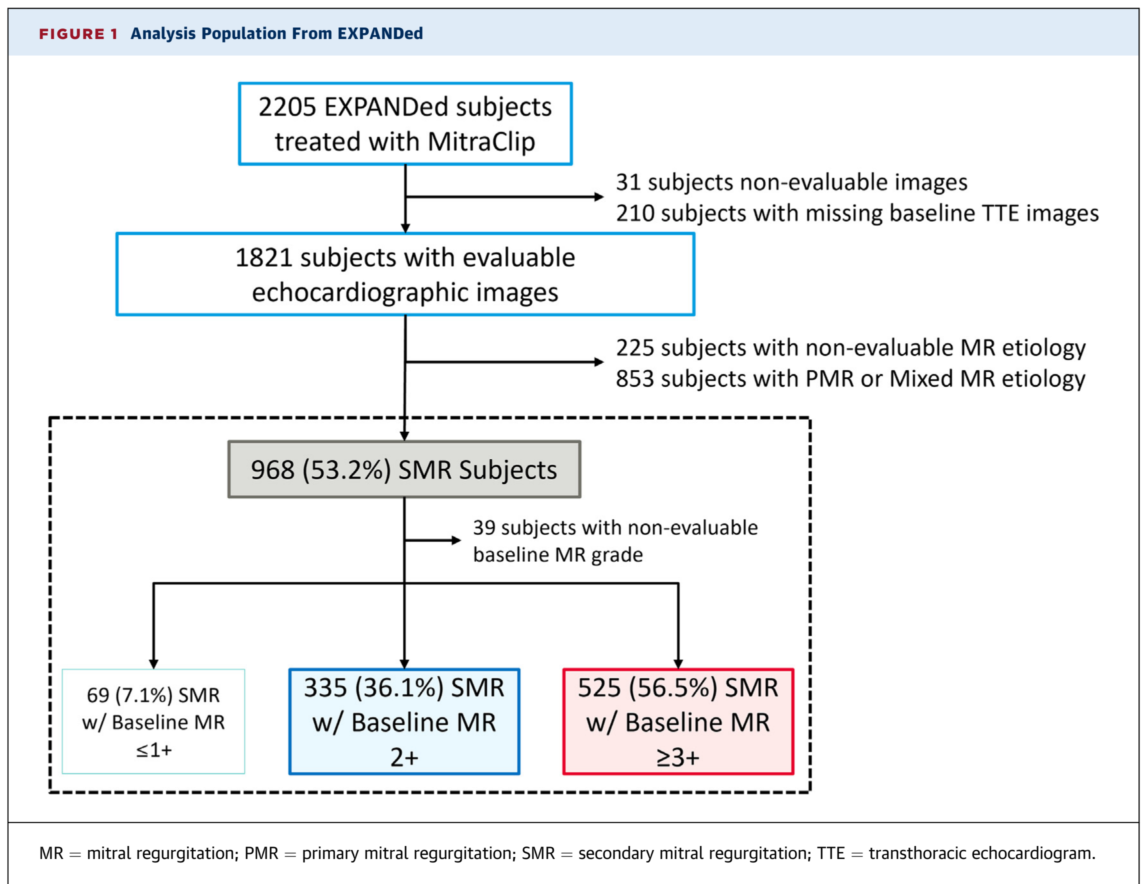
STATISTICAL ANALYSIS. Categorical variables are reported as percentages of available data and were compared by using the Fisher exact or chi-square test. Bowker's test was used for paired nominal data. Continuous variables are reported as mean ± SD unless otherwise specified and were compared by using analysis of variance or the Kruskal-Wallis test for nonparametric data. Student's *t*-test was used for paired continuous data. LV remodeling and KCCQ-OSS were analyzed for subjects with complete baseline, 30-day, and 1-year data. Major adverse events and device-related complications 1 year after the index procedure were reported in subjects who had adverse events or did not withdraw from the study prior to the lower limit of the visit window. The Kaplan-Meier method was used to estimate all-cause mortality at 1 year, with *P* values from log-rank tests reported between subgroups. Subjects were censored at their last known event-free date. Fine and Gray cumulative incidence through 1 year for HFH was performed with death as a competing risk event. Two-sided alpha values of $P < 0.05$ were considered statistically significant. Statistical analyses were performed by using SAS version 9.4 (SAS Institute, Inc).

RESULTS

STUDY POPULATION. Of the 2,205 subjects in the EXPANDed studies, 968 subjects had SMR (53.2%) per ECL assessment. Registry inclusion criteria have been previously described and required the presence of site-assessed MR per regional indications for use. Retrospective ECL evaluation of included subjects identified 335 (36.1%) subjects with SMR and a baseline MR grade of 2+ and 525 (56.5%) subjects with SMR and a baseline MR grade of ≥3+. Additional details of the study population are shown in Figure 1.

Baseline characteristics were similar between subjects with MR 2+ and subjects with MR ≥3+ (Table 1). Subjects in both MR severity subgroups had an average age of 75 ± 10 years and a Society of Thoracic Surgeons replacement score of 8.9%. Atrial

FIGURE 1 Analysis Population From EXPANDed



MR = mitral regurgitation; PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation; TTE = transthoracic echocardiogram.

fibrillation was noted in 60% of subjects, and subjects with MR 2+ had a lower proportion of prior myocardial infarction (26.3% MR 2+ vs 34.7% MR ≥3+; P = 0.01). HFH within 1 year of the MitraClip procedure occurred in >50% of subjects in both groups, with more subjects having a history of HFH in those with more severe MR (51.9% MR 2+ vs 59.0% MR ≥3+; P = 0.05). LV dysfunction was present in both groups with a similar mean left ventricular ejection fraction (LVEF): 39.6% in the MR 2+ subgroup and 39.3% in the MR ≥3+ subgroup. LV dilatation was present in both groups at baseline, with increased diastolic and systolic LV volumes. MR severity parameters, such as effective regurgitant orifice area, regurgitant fraction, and regurgitant volume, were lower in the MR 2+ subgroup than in the MR ≥3+ subgroup, as expected based on ASE guidelines.

MitraClip procedural characteristics were similar in both subgroups with an average number of 1.4 ± 0.6 clips implanted per subject. Additional procedural outcomes are shown in Supplemental Table 1; there were no discernable differences between the subgroups.

ECHOCARDIOGRAPHIC OUTCOMES. Subjects in both the MR 2+ and MR ≥3+ subgroups achieved significant reduction in MR at 30 days that was sustained 1-year post-MitraClip procedure (**Figure 2**) with MR ≤1+ at 1 year in 96.8% of baseline MR 2+ subjects and 92.4% of baseline MR ≥3+ subjects; similar outcomes were noted in a paired analysis (Supplemental Figure 1). Changes in LVEF, left ventricular end-diastolic volume (LVEDV), and left ventricular end-systolic volume (LVESV) are shown in **Figure 3**. In the MR 2+ subgroup, LVEF significantly increased from baseline (40%) to 1 year (43%; P = 0.04). In the MR ≥3+ group, LVEF remained consistent. For all subjects, LVEDV and LVESV were significantly reduced from baseline to 1 year and from 30 days to 1 year. In the MR 2+ subgroup, there was a 25 mL (IQR: 16-33 mL) decrease in LVEDV and a 20 mL (IQR: 12-28 mL) decrease in LVESV from baseline to 1 year. In the MR ≥3+ subgroup, there was a significant decrease in LVEDV and LVESV from baseline to 1 year but to a smaller extent (19 mL [IQR: 10-27 mL] decrease in LVEDV and 8 mL [IQR: 0-16 mL] decrease in LVESV). LVESV reduction from baseline to 1 year was significantly greater in the MR 2+ subgroup than IN the MR ≥3+ subgroup (P = 0.04).

TABLE 1 Baseline Characteristics

	SMR Baseline MR 2+ (n = 335)	SMR Baseline MR ≥3+ (n = 525)	*P* Value
Age, y	74.8 ± 10.0 (335)	75.3 ± 9.5 (525)	0.49
Female	43.6 (146)	40.4 (212)	0.35
STS replacement score, %	8.9 ± 7.5 (186)	8.9 ± 7.9 (288)	0.64
Atrial fibrillation	60.4 (201)	60.0 (314)	0.94
Prior MV procedure	3.3 (11)	1.9 (10)	0.26
Prior myocardial infarction	26.3 (86)	34.7 (179)	0.011
Renal failure	39.7 (131)	40.2 (210)	0.89
Pacemaker	27.5 (92)	32.8 (171)	0.10
CRT	4.2 (14)	5.0 (26)	0.58
Prior CABG	69.1 (76)	67.5 (114)	0.77
Prior cardiac surgeries	32.8 (110)	32.2 (169)	0.84
Chronic lung disease	20.2 (67)	24.3 (124)	0.17
COPD	72.3 (47)	77.4 (96)	0.44
Prior HFH within 1 year	51.9 (162)	59.0 (288)	0.049
Moderate to severe or severe TR	11.9 (35)	15.2 (74)	0.19
NYHA functional class III/IV	81.2 (272)	75.5 (395)	0.052
KCCQ-OSS	44.4 ± 22.9 (322)	47.6 ± 24.4 (497)	0.058
APDAD, cm	3.4 ± 0.5 (285)	3.5 ± 0.5 (476)	0.11
LVEF, %	39.6 ± 14.4 (256)	39.3 ± 13.9 (406)	0.85
HFpEF (LVEF ≥50%)	25.1 (64)	25.6 (104)	0.88
HFmrEF (LVEF ≥40% and <50%)	20.0 (51)	19.5 (79)	0.86
HFrEF (LVEF <40%)	54.9 (140)	54.9 (223)	0.99
LVESV, mL	105.4 ± 63.4 (256)	110.8 ± 64.5 (406)	0.21
LVESVi, mL/m^2	56.9 ± 33.8 (256)	60.1 ± 33.7 (406)	0.24
LVEDV, mL	164.6 ± 72.2 (256)	174.8 ± 77.1 (405)	0.086
LVEDVi, mL/m^2	88.7 ± 37.6 (256)	95.0 ± 39.2 (405)	0.044
EROA, cm^2	0.2 ± 0.1 (201)	0.3 ± 0.1 (405)	<0.001
Regurgitant fraction, %	20.1 ± 24.9 (107)	26.3 ± 30.7 (163)	0.028
Regurgitant volume, mL	32.6 ± 12.5 (200)	50.5 ± 17.3 (404)	<0.001
Systolic pulmonary artery pressure, mm Hg	46.4 ± 13.7 (260)	49.4 ± 16.5 (438)	0.03

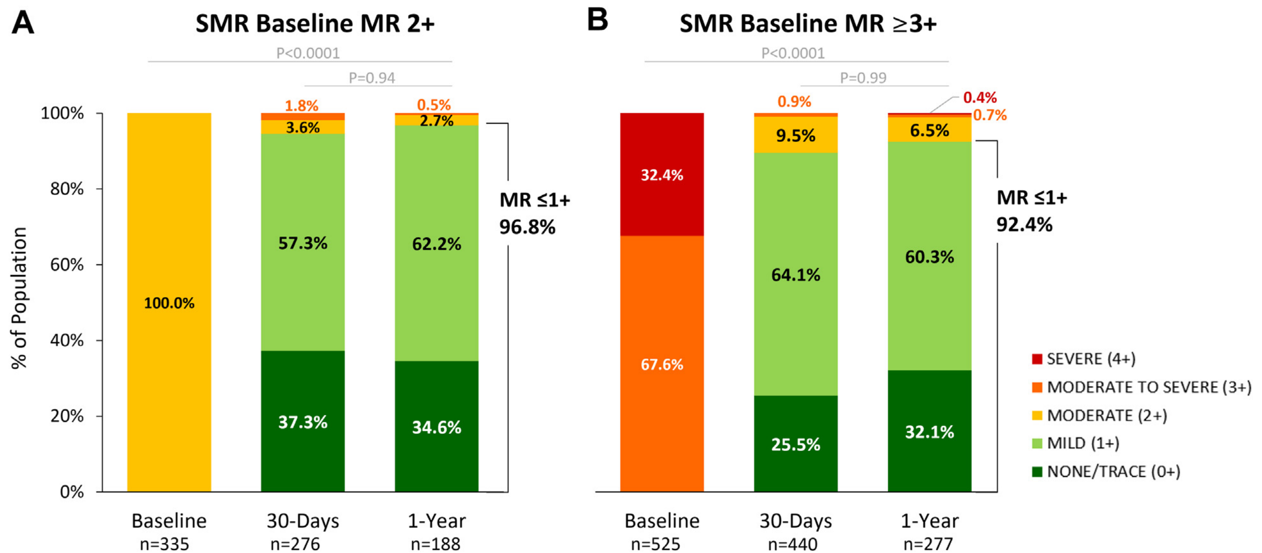
Values are mean ± SD (n) or n (%), unless otherwise indicated.

APDAD = anteroposterior diastolic annular diameter; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; CRT = cardiac resynchronization therapy; CRT-D = cardiac resynchronization therapy-defibrillator; EROA = effective regurgitant orifice area; HFH = heart failure hospitalization; HFpEF = heart failure with preserved ejection fraction; HFmrEF = heart failure with mildly reduced ejection fraction; HFrEF = heart failure reduced ejection fraction; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; LVEDV = left ventricular end-diastolic volume; LVEDVi = left ventricular end-diastolic volume index; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; LVESVi = left ventricular end-systolic volume index; MR = mitral regurgitation; MV = mitral valve; SMR = secondary mitral regurgitation; STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation.

A summary of the left ventricular volumes is shown in Table 2. Large reductions in LV volumes were observed predominantly in subjects with MR 2+ and an LVEF ≤35% at baseline. These subjects had a large LVEDV (205 mL [IQR: 167-252 mL]) and LVESV (151 mL [IQR: 115-181 mL]) at baseline and had an average 37 mL (IQR: 22-52 mL) decrease in LVEDV and 39 mL (IQR: 24-54 mL) decrease in LVESV at 1 year (Supplemental Figure 2).

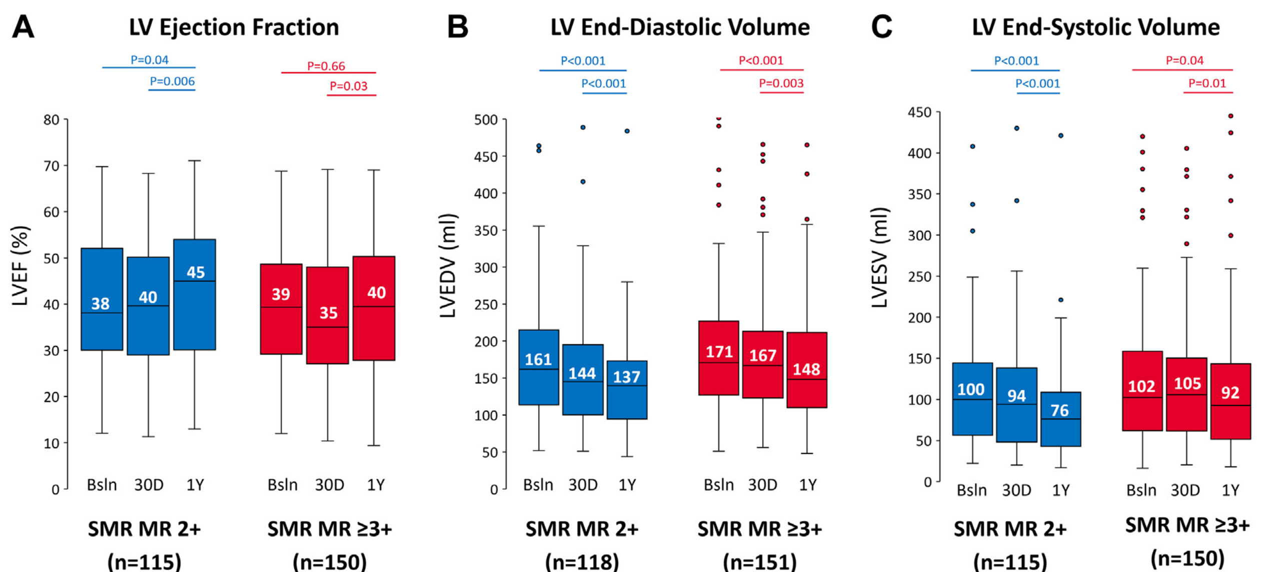
CLINICAL AND SAFETY OUTCOMES. The use of HF medications was similar between MR 2+ and MR ≥3+ subjects at baseline and 30 days; 23% to 29% of subjects were taking angiotensin-converting enzyme (ACEIs), angiotensin II receptor blockers (ARBs), and aldosterone antagonists at baseline (Table 3). At 30 days, there was a slight decrease in the proportion of subjects using beta-blockers, ACEIs, ARBs, and vasodilators for both subgroups. Improvement in NYHA functional class was significant in both MR 2+ and MR ≥3+ subgroups, with 79.2% and 77.8% in NYHA functional class I or II at 1 year, respectively (Figure 4A); similar results were shown in a paired analysis (Supplemental Figure 3). Similarly, there were significant and large improvements in quality of life with a >20-point mean improvement in KCCQ-OSS from baseline to 1 year in both MR 2+ and MR ≥3+ subjects (Figure 4B). Kaplan-Meier estimates of all-cause mortality (Figure 5A) and HFH (Figure 5B) showed similar 1-year rates, with 15.2% in MR 2+ subjects and 16.0% in MR ≥3+ subjects for all-cause mortality and 21.9% in MR 2+ subjects and 23.7% in MR ≥3+ subjects for HFH. The Fine and

FIGURE 2 Reduction in MR Severity After M-TEER in Subjects With SMR and Baseline MR 2+ or Baseline MR ≥3+



A sustained, significant reduction in echocardiographic core laboratory-assessed MR severity at 1 year was observed in subjects with SMR and baseline MR 2+ (A) as well as in subjects with SMR and baseline MR ≥3+ (B). Data shown for all subjects with available data. *P* values represent paired significance by Bowker's test. M-TEER = mitral transcatheter edge-to-edge repair; other abbreviations as in Figure 1.

FIGURE 3 Significant Left Ventricular Remodeling in Subjects With SMR and Baseline MR 2+ Through 1 Year



Left ventricular ejection fraction (LVEF) (A) significantly increased from baseline and 30 days to 1 year in subjects with SMR baseline MR 2+ while left ventricular end-diastolic volume (LVEDV) (B) and left ventricular end-systolic volume (LVESV) (C) significantly decreased in these subjects after M-TEER. Data shown as boxplots of the median and IQR with the whiskers representing 1.5 × IQR, paired, for subjects with evaluable data at all presented time points. Significance according to paired Student's *t*-test. 1Y = 1 year; 30D = 30 day; Bsln = baseline; other abbreviations as in Figures 1 and 2.

TABLE 2 LV Remodeling Changes

	SMR MR 2+	SMR MR ≥3+
LVEF, %	(n = 115)	(n = 150)
Baseline	38 (30-52)	39.4 (29.1-49.5)
30 d	40 (29-50)	35.2 (26.0-49.0)
1 y	45 (30-54)	39.8 (26.1-51.0)
Δ 1 y—baseline	3 (0 to 5)	-0.4 (-2.4 to 1.5)
LVEDV, mL	(n = 118)	(n = 151)
Baseline	161 (108-213)	171 (127-227)
30 d	144 (100-195)	167 (123-213)
1 y	138 (95-173)	148 to (110-212)
Δ 1 y—baseline	-25 (-33 to -16)	-19 (-27 to -10)
LVESV, mL	(n = 115)	(n = 150)
Baseline	100 (57-144)	102 (62-158)
30 d	94 (48-138)	105 (62-150)
1 y	76 (43-109)	92 (51-143)
Δ 1 y—baseline	-20 (-28 to -12)	-8 (-16 to 0)

Baseline, 30 days, and 1 year left ventricular (LV) parameter; values are median (IQR). Change in LV parameters defined as 1 year minus baseline; values are mean (95% CI). All data from paired patients at all 3 time points.

Abbreviations as in Table 1.

Gray method for estimating HFH rates with mortality as a competing risk showed similar results (Supplemental Figure 4).

All-cause mortality and HFH through 1 year according to baseline MR severity is shown in Supplemental Figure 5. The 1-year cumulative HFH rate before M-TEER was significantly greater than the 1-year cumulative HFH rate after M-TEER in both groups (before: 0.78 per patient-year MR 2+ and 0.95 per patient-year MR ≥3+; after: 0.30 per patient-year and 0.39 per patient-year; $P < 0.001$) (Figure 6).

Major adverse event rates were low for both subgroups (Table 4), and similar 1-year rates of myocardial infarction, stroke, single leaflet device attachment were reported in the MR 2+ and MR ≥3+ subgroups. The rates of MV replacement surgery at 1 year in the MR 2+ (0.6%) and MR ≥3+ (3.0%) subgroups were low.

TABLE 3 Medications Usage at Baseline and 30 Days

	Baseline		30 d	
	SMR MR 2+ (n = 335)	SMR MR ≥3+ (n = 525)	SMR MR 2+ (n = 316)	SMR MR ≥3+ (n = 499)
Beta-blockers	84.8 (284)	82.3 (432)	79.4 (251)	77.0 (384)
ACEIs	27.8 (93)	26.9 (141)	23.7 (75)	23.4 (117)
Angiotensin receptor blockers	23.9 (80)	22.9 (120)	18.0 (57)	21.6 (108)
Vasodilators	10.1 (34)	10.5 (55)	8.5 (27)	9.2 (46)
Aldosterone antagonists	28.7 (96)	31.2 (164)	32.3 (102)	29.3 (146)
Diuretic agents	84.8 (284)	84.4 (443)	82.3 (260)	83.4 (416)

Values are n (%).

ACEI = angiotensin-converting enzyme inhibitor; other abbreviations as in Table 1.

DISCUSSION

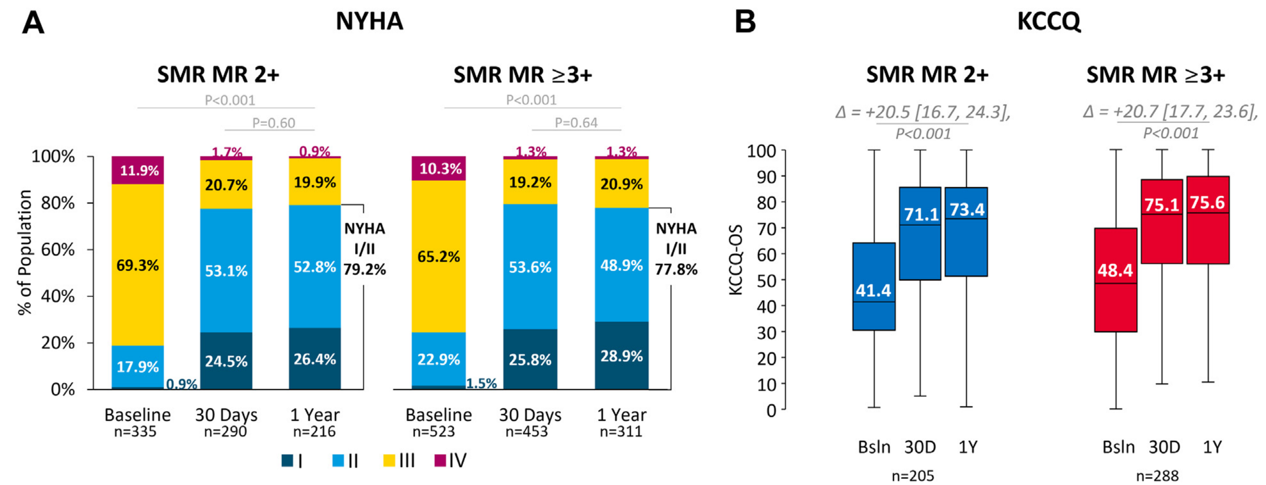
This study of contemporary postmarketing patients shows that in symptomatic patients with ECL-adjudicated moderate SMR, treatment with MitraClip resulted in significant MR reduction, sustained improvement in LV remodeling, and sustained improvement in quality of life (Central Illustration).

MR severity has been historically challenging to define, with controversy surrounding whether PMR and SMR should have different cutoffs for severity. The ASE guidelines favor a quantitative approach, focusing on identifying patients with clearly mild or severe MR and then classifying the remaining patients as moderate (MR grade 2+ and 3+) irrespective of etiology. Moderate MR, grade 2+, is defined as an effective regurgitant orifice area of 0.2 to 0.3 cm^2, regurgitant volume of 30 to 44 mL, and regurgitant fraction of 30% to 39%.[3] Current HF guidelines recommend GDMT alone for patients with HF and moderate MR,[14] although these patients may still have a poor quality of life, dilated left ventricle, and high mortality with increased risk of HFH.[5-8]

Despite these concerns and limitations, surgical repair for moderate ischemic SMR was not found to be beneficial for patients and was associated with increased risk of neurologic events. Specifically, treatment of moderate SMR with surgical repair at the time of bypass grafting in patients with ischemic heart disease did not have an impact on LV remodeling, survival, or reduction in HFH in the CTSN (Cardiothoracic Surgical Trials Network) study.[9] Interestingly, patients in this study had LVEF similar to those in the EXPANDed study (LVEF 39.3% and 39.6%) but were less symptomatic, with only 36.7% NYHA functional class III/IV compared with 81.2% in EXPANDed. Conversely, LV volumes were similar at baseline in those treated with surgical repair compared with the patients with moderate MR treated with MitraClip in this study (LVESV index 59.6 ± 25.7 mL/m^2 compared with 56.9 ± 33.8 mL/m^2);[9] however, patients receiving MitraClip, unlike those with surgical repair, had evidence of significant LV remodeling with decreased systolic and diastolic volumes at 1 year.

The findings from our current and prior studies raise the question of whether HF patients with SMR who may benefit from M-TEER can be classified based on MR severity alone. What is more likely is that such patients exist on a spectrum of phenotypes of HF with SMR. The subjects in EXPANDed with moderate SMR

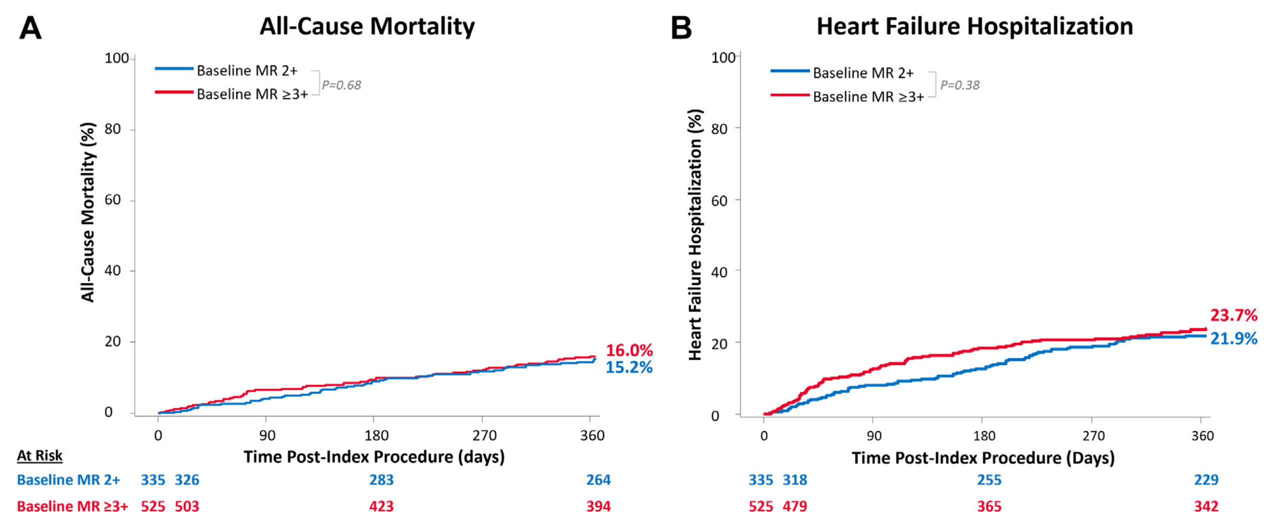
FIGURE 4 Significant Improvements in Functional Class and Quality of Life Assessment for Subjects With SMR and Baseline MR 2+ or Baseline MR ≥3



(A) Significant increase in the proportion of subjects with NYHA functional class I or II were observed in both subgroups from baseline to 1 year, and no significant differences was observed between 30 days and 1 year, suggesting sustainment of this acute increase at 30 days through 1 year. (B) Similarly, a significant increase in mean Kansas City Cardiomyopathy Questionnaire–Overall Summary Score (KCCQ-OSS) was found for both subgroups between baseline and 1 year. Boxplots of the median and IQR with whiskers representing 1.5 × IQR and change from baseline to 1 year represented as mean (95% CI); paired data shown. For NYHA functional class, data shown for all subjects with available data. *P* values represent paired significance by Bowker's test for NYHA functional class and a paired Student's *t*-test for KCCQ-OSS. Abbreviations as in Figures 1 and 3.

had baseline characteristics similar to those with severe SMR, including comorbidities and baseline KCCQ-OSS and NYHA functional class. A phenotype of significant SMR may include characteristics such as LV function, NYHA functional class, LV dimensions, and MR severity. These phenotypes have been represented in previous SMR trials. For example, severe LV dilation and dysfunction with severe MR are representative of patients in the MITRA-FR (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) trials, which showed limited benefit of M-TEER

FIGURE 5 Kaplan-Meier All-Cause Mortality and Heart-Failure Hospitalization Through 1 Year



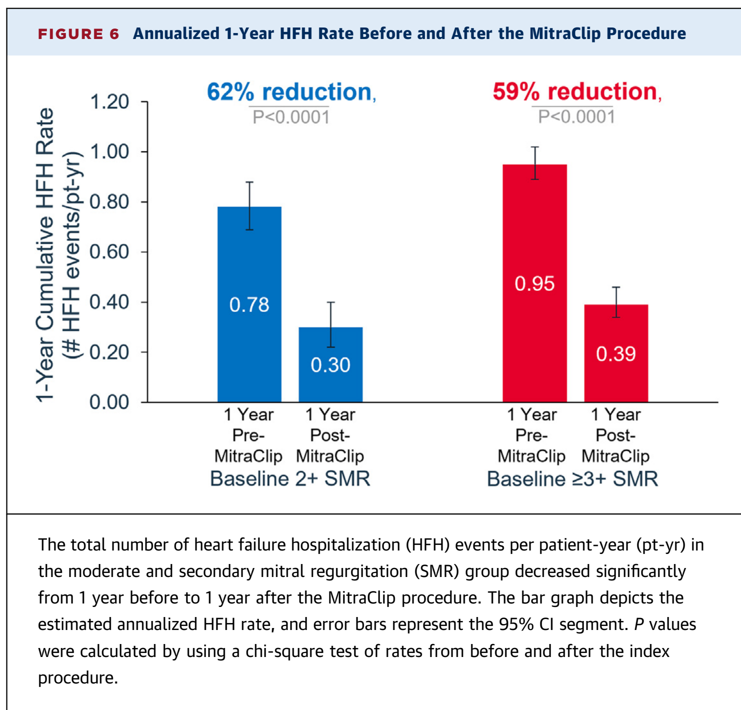
Estimates for all-cause mortality (A) and heart-failure hospitalization (B) were similar between subgroups through 1 year. *P* values represent significance according to log-rank tests. Abbreviation as in Figure 1.

compared with GDMT alone.[15] Conversely, the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial showed benefit of M-TEER compared with GDMT and represented a phenotype with severe SMR and less LV dilation than those in the MITRA-FR trial.[16] In the EXPANDed cohort, patients with moderate and severe SMR had similar LV dilation, LV dysfunction, and NYHA functional class slightly less severe than subjects in the COAPT trial. Patients with moderate SMR in the EXPANDed cohort had reductions in MR severity and rates of all-cause mortality and HFH similar to subjects with severe MR (≥3+). These findings suggest a similar treatment benefit of M-TEER in patients with moderate MR, who share a similar phenotype of decreased LV function, advanced NYHA functional class, and dilated ventricles.

The overarching goal of the treatment of SMR in HF is to improve mortality, morbidity, quality of life, and LV remodeling. Patients with moderate SMR often have dysfunctional and enlarged left ventricles,[5,6] which are associated with poor long-term outcomes. In EXPANDed, treatment of moderate SMR with M-TEER resulted in LV reverse remodeling with substantial 1-year reduction in the LVEDV and LVESV of 25 mL and 20 mL, respectively, largely driven by subjects with low ejection fractions (≤35%). This volume reduction was more than that observed in the MR ≥3+ subgroup. In addition, these positive changes in LV dimension were observed in the absence of optimized GDMT. Many subjects decreased their medication usage by 30 days and/or were not confirmed to be optimized at baseline. These observed improvements in LV size in subjects with MR 2+ suggest that early treatment with M-TEER may positively affect cardiac remodeling. Previous studies have recognized the association between advanced LV dysfunction and size with an inability to remodel favorably, as shown with the differences in the COAPT and MITRA-FR populations.[17] However, additional studies are necessary to understand general remodeling outcomes after M-TEER and how treatment timing, alongside medication usage, may best optimize positive results.

SMR subjects in EXPANDed represent the commercial application of medication use per standard of care. Unlike the COAPT randomized controlled trial, optimized GDMT was not thoroughly reviewed by an independent committee in EXPANDed. In EXPANDed, a smaller proportion of patients were taking beta-blockers, ACEIs, ARBs, aldosterone antagonists, and diuretic agents compared with more rigorously controlled studies such as COAPT.[16] This usage of HF medications was lowered slightly at 30 days, although the reasons are unclear. This is similar to other contemporary studies, which have shown low use of optimal GDMT.[18,19] Patient tolerability and adherence to medical treatment plans have been cited as barriers to achieving optimal GDMT,[18] which may be applicable to the subjects in this study. However, adherence to GDMT was not collected in our study. Despite less usage of maximal GDMT, subjects in EXPANDed with moderate SMR still had a large improvement in quality of life and functional class. The average 20-point improvement in KCCQ-OSS in subjects with moderate and severe SMR showed clinical benefit when treated with M-TEER that was maintained from 30 days to 1 year. This was a larger

FIGURE 6 Annualized 1-Year HFH Rate Before and After the MitraClip Procedure



The total number of heart failure hospitalization (HFH) events per patient-year (pt-yr) in the moderate and secondary mitral regurgitation (SMR) group decreased significantly from 1 year before to 1 year after the MitraClip procedure. The bar graph depicts the estimated annualized HFH rate, and error bars represent the 95% CI segment. *P* values were calculated by using a chi-square test of rates from before and after the index procedure.

TABLE 4 Major Adverse Events Through 1 Year

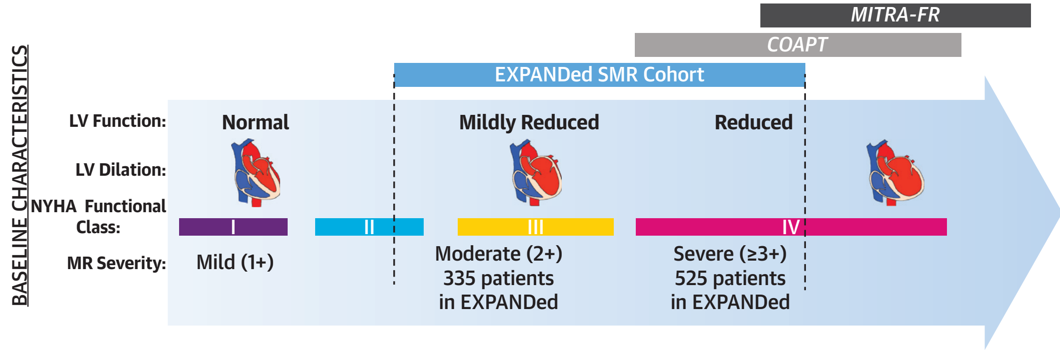
	Through 30 d		Through 1 y	
	SMR Baseline MR 2+ (n = 335)	SMR Baseline MR ≥3+ (n = 525)	SMR Baseline MR 2+ (n = 335)	SMR Baseline MR ≥3+ (n = 525)
All-cause mortality[a]	1.5 (5)	2.3 (12)	15.2 (47)	16.0 (76)
Myocardial infarction	0.0 (0)	0.0 (0)	1.2 (4)	1.7 (9)
Stroke	0.6 (2)	0.4 (2)	1.2 (4)	1.1 (6)
Mitral valve replacement surgery	0.3 (1)	1.5 (8)	0.6 (2)	3.0 (16)
SLDA	0.3 (1)	1.1 (6)	0.3 (1)	1.5 (8)

Values are n (%). [a]Kaplan-Meier estimate.
SLDA = single leaflet device attachment; other abbreviations as in Table 1.

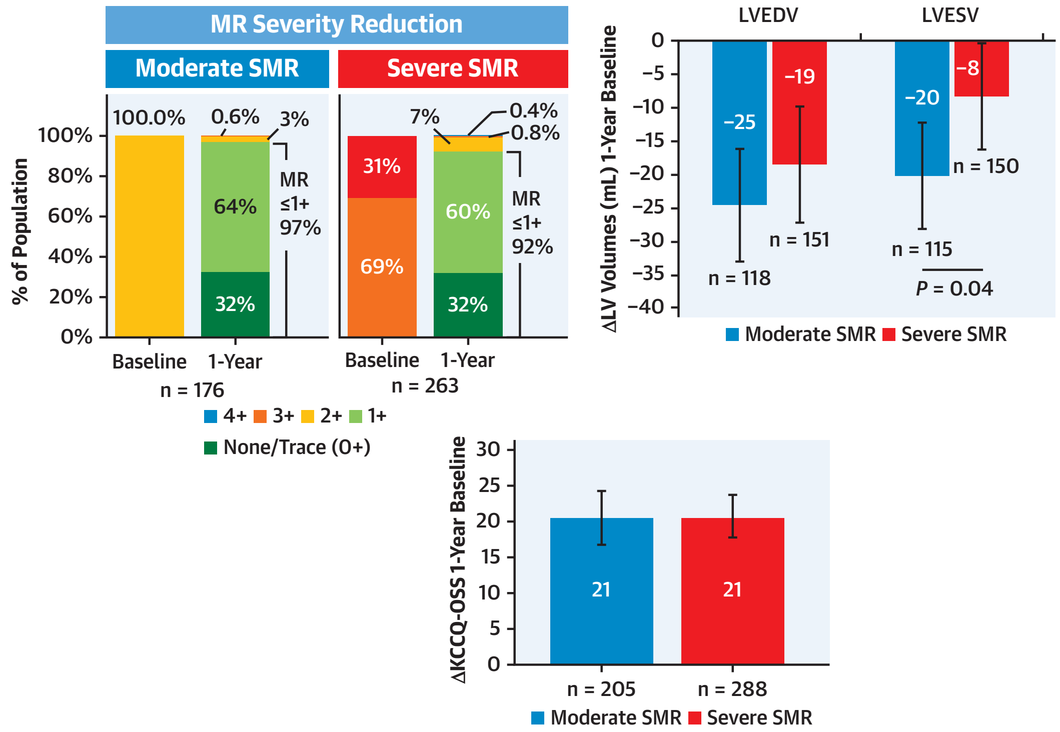
CENTRAL ILLUSTRATION 1-Year Outcomes in Subjects With Moderate Secondary Mitral Regurgitation Treated With the MitraClip System

In Symptomatic Patients With Moderate Secondary MR, Treatment With the MitraClip System Resulted in MR Reduction, LV Remodeling, and Improvement in Quality of Life

Phenotypes of SMR With HF



1-Year Outcomes With M-TEER in Moderate and Severe SMR in EXPANDed



Asgar AW, et al. JACC Heart Fail. 2025;13(2):213-225.

In the EXPANDed studies, the mitral regurgitation (MR) severity of subjects with secondary mitral regurgitation (SMR) was independently assessed by an echocardiographic core laboratory. Patients with moderate and severe SMR cover a spectrum of heart failure characterized by left ventricular (LV) function, LV dilatation, and symptoms that are represented in the EXPANDed studies, COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) randomized controlled trial, and MITRA-FR (Percutaneous Repair With the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) randomized controlled trial. Although the baseline characteristics of subjects with moderate or severe MR were similar, large and significant reduction in MR severity, LV volumes, and substantial improvement in quality of life (assessed by using the Kansas City Cardiomyopathy Questionnaire-Overall Summary Score [KCCQ-OSS]) were observed at 1-year after the mitral transcatheter edge-to-edge repair procedure showing a potential benefit of treating patients with moderate SMR with this procedure. HF = heart failure; LVEDV = left ventricular end-diastolic volume; LVESV = left ventricular end-systolic volume; M-TEER = mitral transcatheter edge-to-edge repair.

improvement than what had been shown in the COAPT trial (Δ = +17.0 points at 1 year)[16] and more than double the 10-point increase considered to be moderate to large, clinically relevant, and impactful for patients.[20] Moreover, improvement in functional class to >78% in NYHA functional class I or II at 1 year emphasizes the benefits to both patient subgroups. These improvements, coupled with the LV reverse remodeling, show that the observed clinical benefits are not just a placebo effect but a true benefit to the patient, as has been shown in previous studies with large quality of life gains.[21]

Mortality and HFH rates increase with increasing severity of SMR,[1,5] with similarly increasing high rates of mortality between MR 2+ and MR ≥3+ when treated with GDMT alone.[10,22] This suggests that patients with moderate SMR or those with severe SMR are both at similar risk of mortality and HFH. After treatment with M-TEER, the 1-year rates of all-cause mortality and HFH were similar between the moderate and severe SMR groups in EXPANDed, with no significant differences in the Kaplan-Meier curves and similar clinical outcomes and safety. All-cause mortality rates in EXPANDed (15.2% and 16.0% in moderate and severe SMR) were lower than the MitraClip arms of the COAPT (18.8%) and MITRA-FR (24.3%) studies;[15,16] these findings may reflect the important differences in baseline characteristics, including higher baseline LVEF, less LV dilatation, and/or less MR at baseline with superior MR reduction using newer generation devices. However, usage of GDMT was not optimized at baseline in this patient population, and a recent study has shown reduction in MR and clinical benefit when patients are optimized with sacubitril/valsartan and sodium-glucose cotransporter 2 inhibitors.[23,24] Although this study did not include a control arm, which limits comparability with medical treatment alone, these outcomes provide an opportunity to understand the impact of M-TEER in HF patients with moderate SMR receiving GDMT in clinical practice.

STUDY LIMITATIONS. Enrollment into the EXPANDed studies was conducted per site evaluation of MR, which considers a comprehensive assessment and includes regional differences in echocardiographic guidelines. All MR severity grading reported in this analysis was conducted by the ECL to standardize gradings across all subjects and all time points in the global EXPANDed studies. However, assessment by the ECL was performed on the transthoracic echocardiogram at one point in time at baseline and follow-up and may not capture the dynamic range of MR. In addition, the EXPANDed studies are postmarketing, observational studies and therefore lack a control arm by design. Monitoring use of GDMT in this study was limited to the proportion of patients taking HF medication, and dosages/changes in titration were not collected. The EXPANDed studies were conducted before the generalized use of the newer HF agents, including sacubitril/valsartan and sodium-glucose cotransporter 2 inhibitors, which are now considered to be first-line agents for the treatment of HF. In such patients, M-TEER would be considered in those with significant MR despite GDMT, including these agents. Although this analysis cannot provide a direct comparison vs other treatment options, 1-year outcomes in patients with moderate 2+ MR treated with MitraClip show a clinical benefit in LV reverse remodeling and quality of life. Additional randomized controlled trials are needed to fully understand the benefit of M-TEER in the moderate SMR population.

CONCLUSIONS

In the postmarketing EXPANDed studies, subjects with moderate SMR had a patient profile similar to those with severe SMR. Treatment of moderate SMR with M-TEER showed substantial clinical benefit with sustained MR reduction, LV reverse remodeling, large improvements in quality of life, and functional capacity. One-year all-cause mortality and HFH rates after MitraClip were similar between moderate and severe (≥3+) SMR. These outcomes suggest an opportunity to treat patients with moderate SMR with M-TEER and a need for future trials to study the best treatment options in combination with GDMT for this population with moderate SMR.

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member of the steering committee of the EXPAND G4 study for Abbott and Encourage AF study for Daiichi Sankyo. Dr Morse is a consultant for Edwards LifeSciences. Dr Denti has received speaker honoraria from Abbott and Edwards LifeSciences; and has been a consultant to InnovHeart, Artiness, and Pi-Cardia. Dr Mahoney is a consultant and proctor for Medtronic, Edwards LifeSciences, and Boston Scientific; is a consultant for Abbott; and has been awarded research grants from Edwards LifeSciences, Medtronic Abbott, and Boston Scientific. Dr Rinaldi has been awarded honoraria and/or consulting fees from Abbott, Boston Scientific, and Edwards LifeSciences. Dr Asch's work as an academic core laboratory director is performed through institutional research grants (MedStar Health) with Abbott, Boston Scientific, Medtronic, Edwards LifeSciences, Neovasc, Ancora Heart, LivaNova, MVRx, InnovHeart, Polares Medical, and Aria CV. Dr Zamorano has received speaker honoraria from Pfizer, Amgen, and Daiichi Sankyo; and research grants from Abbott and Edwards LifeSciences. Dr Dong and Ms Huang are employees of Abbott Structural Heart. Dr Lindenfeld has been a consultant for Abbott, Alleviant, AstraZeneca, Biotronik, Boston Scientific, CVRx, Edwards LifeSciences, Merck, Medtronic, V-Wave, Vascular Dynamics, WhiteSwell, and Vectorious; and receives research funding from AstraZeneca. Dr Maisano has received grants and/or institutional research support from Abbott, Medtronic, Edwards LifeSciences, Biotronik, Boston Scientific, NVT, and Terumo; has received honoraria and consulting fees (personal and institutional) from Abbott, Medtronic, Edwards LifeSciences, Xeltis, and Cardiovalve; has received royalty income and intellectual property rights from Edwards LifeSciences; and is a shareholder (including stock options) of CardioGard, Magenta, SwissVortex, Transseptal Solutions, Occlufit, 4Tech, and Perifect. Dr von Bardeleben has performed nonpaid trial activities for Abbott, Edwards LifeSciences, Medtronic, and the University of Göttingen (IIT); and serves as an advisory board or speaker bureau member for Abbott Cardiovascular Edwards LifeSciences, Medtronic, and NeoChord. Dr Kar has received grants and institutional research support from Abbott, Boston Scientific, and Edwards LifeSciences; has received consulting fees/honoraria from Abbott, Boston Scientific, W.L. Gore, and Medtronic; served as a steering committee member of the TRILUMINATE study (Abbott) and as national principal investigator of the EXPAND study and the REPAIR MR study for Abbott. Dr Rodriguez has been awarded grants and support for research from Abbott, Edwards LifeSciences, Boston Scientific, AtriCure, and CardioMech; and has received honoraria or consulting fees from Abbott, Edwards LifeSciences, Philips, Teleflex, and CardioMech.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: This paper highlights the benefits seen in a contemporary, postmarketing population of patients with moderate SMR treated with M-TEER using the MitraClip device and illustrates the clinical similarities between these patients and those with severe MR.

COMPETENCY IN MEDICAL KNOWLEDGE: In real-world practice, symptomatic patients with moderate SMR are already being treated with M-TEER with clinical improvement and low rates of adverse events.

TRANSLATIONAL OUTLOOK: Given the clinical spectrum of patients with moderate SMR, more research is required to clearly define the phenotype of patients with SMR who can benefit from M-TEER in addition to medical therapy.

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KEY WORDS MitraClip, mitral valve repair, moderate mitral regurgitation, secondary mitral regurgitation, transcatheter edge-to-edge repair

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