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ORIGINAL RESEARCH

Transcatheter Edge-to-Edge Repair in Secondary Mitral Regurgitation With Extended Non–COAPT-Like Features

From the EXPANDed Studies

Gilbert H.L. Tang, MD, MSc, MBA,[a] Matthew J. Price, MD,[b] Wolfgang Rottbauer, MD,[c] Paul D. Mahoney, MD,[d] Jorg Hausleiter, MD,[e] Philip W. Raake, MD,[f] William A. Rollefson, MD,[g] Philipp Lurz, MD,[h] Paolo Denti, MD,[i] Bassem K. Chehab, MD,[j] Melody Dong, PhD,[k] Rong Huang, MS,[k] Federico M. Asch, MD,[l] Jose Luis Zamorano, MD,[m] Ralph Stephan von Bardeleben, MD,[h] Francesco Maisano, MD,[n] Saibal Kar, MD,[o] Evelio Rodriguez, MD[p]

ABSTRACT

BACKGROUND Mitral transcatheter edge-to-edge repair (MTEER) is approved for patients with secondary mitral regurgitation (SMR) and heart failure based on COAPT (The Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy) eligibility criteria. Outcomes in patients beyond COAPT criteria with more advanced heart disease remain unclear.

OBJECTIVES This study aimed to assess the outcomes of MTEER in SMR patients beyond COAPT trial criteria from the global, post-market EXPANDed studies.

METHODS Analyses were performed with the EXPANDed data set, including 2,205 patients treated with the 3rd/4th-generation MitraClip MTEER System. Non–COAPT-like patients were classified by baseline ≥3+ SMR and at least 1 of the following: left ventricular ejection fraction <20%, left ventricular end-systolic diameter >70 mm, or systolic pulmonary artery pressure >70 mm Hg. Echocardiographic outcomes were assessed by an echocardiographic core laboratory.

RESULTS Of the 967 SMR patients in EXPANDed, 197 were categorized as COAPT-like and 81 as non–COAPT-like. Both groups were elderly (74.4 ± 10.1 vs 73.6 ± 10.2 years) with a high prevalence of prior heart failure hospitalizations (HFH; 63% and 64%, respectively). Non–COAPT-like patients had larger left ventricular end-diastolic volumes (183 mL COAPT-like, 220 non–COAPT-like) and effective regurgitant orifice areas (0.33 cm^2; 0.36). One-year mortality and HFH rates were similar between groups and comparable or lower to those in the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation) and COAPT trials. HFH was reduced by 56% in COAPT-like and 74% in non–COAPT-like patients from pre- to post-MTEER. At 1 year, both groups achieved significant MR reduction (90% MR ≤1+ COAPT-like and non–COAPT-like).

CONCLUSIONS In the EXPANDed studies, non–COAPT-like patients experienced significant improvements in MR, HFH, and quality-of-life at 1 year, comparable with those observed in COAPT-like patients. These findings suggest that MTEER may be an effective therapeutic option in appropriately selected patients outside COAPT eligibility. (The MitraClip EXPAND Study of the Next Generation of MitraClip Devices [EXPAND]; NCT03502811) (MitraClip EXPAND G4 Study [EXPAND G4]; NCT04177394) (JACC Heart Fail. 2025;13:102565) © 2025 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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ABBREVIATIONS AND ACRONYMS

ECL = echocardiographic core laboratory

EROA = effective regurgitant orifice area

GDMT = guideline-directed medical therapy

HF = heart failure

HFH = heart failure hospitalization

KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score

LV = left ventricle

LVEF = left ventricular ejection fraction

LVESD = left ventricular end-systolic diameter

MR = mitral regurgitation

MTEER = mitral transcatheter edge-to-edge repair

SLDA = single-leaflet device attachment

SMR = secondary mitral regurgitation

sPAP = systolic pulmonary artery pressure

Secondary mitral regurgitation (SMR) presents a significant challenge in heart failure (HF) management.[1,2] Based on findings from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy) trial, current HF and valvular disease guidelines recommend mitral transcatheter edge-to-edge repair (MTEER) with the MitraClip System (Abbott Structural Heart) in patients with severe SMR and a left ventricular ejection fraction (LVEF) between 20% and 50%, left ventricular end-systolic diameter (LVESD) ≤70 mm, and a systolic pulmonary artery pressure (sPAP) ≤70 mm Hg.[3-5]

However, emerging clinical experience outside of this trial suggests that MTEER may benefit patients beyond the strict COAPT eligibility criteria.[6-8] The RESHAPE-HF2 (Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients with Clinically Significant Functional Mitral Regurgitation) randomized controlled trial demonstrated that patients with SMR and lower effective regurgitant orifice areas (EROAs) who received MTEER and guideline-directed medical therapy (GDMT) had a lower rate of heart failure hospitalization (HFH) compared with those who received GDMT alone.[9,10] These findings contrast with the MITRA-FR (Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation) trial, which showed no difference in outcomes between patients who underwent MitraClip MTEER vs GDMT alone.[11] However, the SMR patient populations in COAPT, RESHAPE-HF2, and MITRA-FR differed substantially in terms of comorbidities, left ventricular (LV) size, and mitral regurgitation (MR) severity, reflecting the broad spectrum of HF patients. The extent to which the benefits of MTEER extend beyond population defined by the COAPT trial remains uncertain.

The EXPANDed studies (EXPAND [The MitraClip EXPAND Study of the Next Generation of MitraClip Devices; NCT03502811] and EXPAND G4 [MitraClip EXPAND G4 Study; NCT04177394) were initiated to evaluate real-world clinical experience and outcomes associated with the use of the latest generation MitraClip Systems.[12,13] Data from these studies provide a unique opportunity to assess treatment effectiveness in a broader patient population representing a different spectrum of SMR patients than previously studied in controlled trials.[14] The analysis herein aimed to evaluate outcomes in patients treated with the MitraClip System who fall outside traditional COAPT criteria, particularly those with more advanced heart disease characteristics.

METHODS

STUDY DESIGN. The EXPANDed data set is a patient-level, pooled cohort combining 2 global, postmarket studies—EXPAND and EXPAND G4—designed to evaluate the real-world safety and effectiveness of the MitraClip systems. The studies were conducted across 91 sites in 12 countries spanning the United States, Canada, Europe, Saudi Arabia, Israel, and Japan. Patients were enrolled and commercially treated according to the associated study protocols, which were designed to be all-comers per the regional indications for use, with patient selection based on site-reported assessments and evaluations by a heart team. No independent review of optimal GDMT was performed. Full details on the studies have been reported previously.[12,13] Enrollment periods were 2018-2019 for EXPAND (n = 1,041) and 2020-2022 for EXPAND G4 (n = 1,164). The EXPANDed studies were sponsored by Abbott, conducted per the latest Good Clinical Practice

From the [a]Department of Cardiovascular Surgery, Mount Sinai Health System, New York, New York, USA; [b]Scripps Clinic, La Jolla, California, USA; [c]Ulm University Heart Center, Ulm, Germany; [d]University of Pittsburgh Medical Center Heart and Vascular Institute, Pittsburgh, Pennsylvania, USA; [e]Medizinische Klinik und Poliklinik I, Klinikum der Universität München, Munich, Germany; [f]Department of Cardiology, Respiratory Medicine and Intensive Care, University Hospital Augsburg, Augsburg, Germany; [g]Arkansas Heart Hospital, Little Rock, Arkansas, USA; [h]University Medical Center of the Johannes Gutenberg-University Mainz, Mainz, Germany; [i]Cardiac Surgery Department, San Raffaele University, Hospital, Milan, Italy; [j]Ascension Via Christi, Wichita, Kansas, USA; [k]Abbott Structural Heart, Santa Clara, California, USA; [l]Cardiovascular Core Laboratories, MedStar Health Research Institute, Washington, District of Columbia, USA; [m]Ramón y Cajal University Hospital, Madrid, Spain; [n]IRCCS Ospedale San Raffaele, Milan, Italy; [o]Los Robles Regional, Thousand Oaks, California, USA; and the [p]Ascension Saint Thomas, Nashville, Tennessee, USA.

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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standards of the Declaration of Helsinki, and were approved by local ethics committees and applicable competent authorities of participating countries. All patients provided written informed consent.

The studies' sponsor was involved in the design and conduct of the study, in the collection, analysis, and interpretation of the data, and in the preparation, review, or approval of the manuscript.

ANALYSIS POPULATION. Of the 2,205 patients enrolled and treated with the 3rd- or 4th-generation MitraClip Systems, 967 patients had echocardiographic core laboratory-assessed SMR. To understand the outcomes of MitraClip MTEER beyond the COAPT criteria, 2 subgroups of SMR patients were defined—COAPT-like and non-COAPT-like—based on key COAPT criteria and HF guidelines. COAPT-like patients met all the following criteria: severe (≥3+) MR, LVEF ≥20% and ≤50%, LVESD ≤70 mm, and sPAP ≤70 mm Hg. Non-COAPT-like patients met the following criteria: at least moderate-to-severe (≥3+) MR and at least 1 of the following: LVEF <20%, LVESD >70 mm, and/or a sPAP >70 mm Hg. Patients with missing or nonevaluable baseline MR, LVEF, LVESD, or sPAP measurements were excluded from the analysis.

CLINICAL OUTCOMES AND ECHOCARDIOGRAPHIC ASSESSMENT. Procedural outcomes included clip use, device time, and acute procedural success, defined as MR reduction to ≤2+ without death or mitral valve replacement surgery. Safety outcomes included major adverse events, defined as the composite of death, myocardial infarction, stroke, need for surgical mitral valve replacement, single-leaflet device attachment (SLDA), leaflet damage, and device embolization. Additional clinical outcomes included 1-year all-cause mortality and HFH, as well as functional status (NYHA functional class) and quality of life (Kansas City Cardiomyopathy Questionnaire-Overall Summary Score [KCCQ-OSS]).

All echocardiograms (transthoracic and transesophageal) obtained at baseline, discharge, 30 days, and 1 year were evaluated by an echocardiographic core laboratory (ECL). Echocardiograms were assessed by 2 independent ECLs, as described previously.[12,13,15] Clinical events were assessed by an independent clinical events committee for EXPAND and site-reported for EXPAND G4. Leaflet adverse events, including SLDA, device embolization, and leaflet damage, were assessed by the ECL (MedStar Health Research Institute) in both studies. ECL grading for MR severity was previously reported;[12,15,16] the ECL also assessed LV and mitral annular remodeling.

TABLE 1 Baseline Characteristics by Study and Definition

	COAPT-Like (n = 197)	Non-COAPT-Like (n = 81)	*P* Value
Age, y	74.4 ± 10.1 (197)	73.6 ± 10.2 (81)	0.55
Female	75 (38.1)	27 (33.3)	0.46
STS replacement score, %	9.17 ± 8.30 (128)	7.78 ± 7.88 (47)	0.26
STS repair score, %	7.07 ± 7.36 (138)	5.57 ± 6.40 (59)	0.11
Atrial fibrillation	116 (58.9)	46 (57.5)	0.89
Prior myocardial infarction	73 (38.2)	26 (32.5)	0.37
Renal failure	76 (39.0)	33 (40.7)	0.78
Permanent pacemaker	68 (34.9)	28 (34.6)	0.96
Prior HFH within 1 y	115 (62.5)	49 (63.6)	0.86
BNP, pg/mL	952 (507-2,076) (64)	647 (375-1,647) (16)	0.18
NT-proBNP, pg/mL	4,012 (1,693-7,997) (80)	4,494 (3,208-7,822) (45)	0.36
NYHA functional class III/IV	145 (74.4)	62 (76.5)	0.70
KCCQ-OSS	45.7 ± 24.4 (182)	46.4 ± 23.8 (77)	0.84
Baseline TR ≥3+	34 (17.8)	12 (15.8)	0.69
LVEF, %	34 ± 8 (197)	34 ± 16 (81)	0.09
LVEF <20%	0 (0)	24 (29.6)	N/A
LVESV, mL	122 ± 51 (197)	152 ± 91 (81)	0.03
LVEDV, mL	183 ± 66 (197)	220 ± 105 (81)	0.02
LVESD, cm	5.2 ± 0.9 (197)	5.7 ± 1.5 (81)	0.01
LVESD >70 mm	0 (0)	23 (28.4)	N/A
LVEDD, cm	6.1 ± 0.8 (197)	6.7 ± 1.3 (81)	0.005
LVEDD, cm	6.1 ± 0.6 (197)	6.7 ± 1.3 (81)	0.005
sPAP, mm Hg	48.1 ± 12.7 (197)	65.7 ± 22.3 (76)	<0.0001
sPAP >70 mm Hg	0 (0)	43 (53.1)	N/A
EROA, cm^2	0.33 ± 0.10 (164)	0.36 ± 0.12 (59)	0.05
Regurgitant fraction, %	26 ± 30 (83)	12 ± 23 (28)	0.03

Values are mean ± SD (n), n (%), or median (Q1-Q3) (n), unless otherwise indicated. *P* value indicates significance between COAPT-like and non-COAPT-like.

BNP = B-type natriuretic peptide; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy; EROA = effective regurgitant orifice area; HF = heart failure; HFH = heart failure hospitalization; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; LVEF = left ventricular ejection fraction; LVEDD = left ventricular end-diastolic dimension; LVEDV = left ventricular end-diastolic volume; LVESD = left ventricular end-systolic dimension; LVESV = left ventricular end-systolic volume; N/A = not applicable; NT-proBNP = N-terminal pro-B-type natriuretic peptide; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons; TR = tricuspid regurgitation.

STATISTICAL ANALYSIS. Statistical methods used both descriptive and inferential analyses. Imputation for missing data was not performed. Continuous variables were presented as mean ± SD or median (Q1-Q3), as appropriate, and were compared using an analysis of variance or the Kruskal-Wallis test for nonparametric data. Student's *t*-test was used for paired continuous data. LV echocardiographic parameters and KCCQ-OSS were analyzed for patients with complete baseline, 30-day, and 1-year data. Categorical variables were presented as percentages of available data and were compared using the Fisher exact or chi-square test. Bowker's test was used for paired nominal data. Pre- vs post-MTEER annualized HFH rates were compared using the chi-squared test. Major adverse events and device-related complications 1 year after the index procedure were reported in patients who had adverse events or did not withdraw from the study prior to the lower limit of the

TABLE 2 Procedural Outcomes

	COAPT-Like (n = 197)	Non-COAPT-Like (n = 81)	*P* Value
Procedure time, min	79 (57-101) (197)	83 (57-112) (81)	0.14
Device time, min	40 (26-60) (195)	40 (24-70) (79)	0.17
Acute procedural success	95.9 (188/196)	91.3 (73/80)	0.14
Number of clips implanted (per patient)	1 (1-2) (197)	1 (1-2) (81)	0.59

Values are median (Q1-Q3) (n) or % (n/N), unless otherwise indicated. Acute procedural success defined as reduction of mitral regurgitation to ≤2+ at discharge or 30 days without mitral valve replacement or death. *P* value indicates significance between COAPT-like and non-COAPT-like.
Abbreviations as in Table 1.

visit window. The Kaplan-Meier method was used to estimate all-cause mortality and HFH at 1 year with log-rank tests for group comparisons; patients were censored at their last known event-free date. Cox proportional hazards regression models were used to assess covariates associated with all-cause mortality and HFH at 1 year. All models were adjusted. HRs with 95% CIs were reported for each covariate. A 2-sided values of $P < 0.05$ was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute Inc).

RESULTS

ANALYSIS POPULATION. A total of 967 patients in EXPANDed had ECL-assessed SMR. Of the 967 SMR patients in the study, 403 were excluded due to an ECL-assessed MR ≤2+ (results of which were recently reported by Asgar et al[14]), 39 were excluded due to missing or nonevaluable MR, and 247 were excluded due to LVEF, LVESD, or sPAP measurements outside the defined range of the analysis population or missing or nonevaluable data for these variables. After these exclusions, 197 patients were categorized as COAPT-like and 81 patients categorized as non-COAPT-like (Table 1). For the 3 criteria aside from MR ≥3+ defining non-COAPT-like, LVEF <20% was present in 24 patients (30%), LVESD >70 mm in 23 patients (28%), and sPAP >70 mm Hg in 43 patients (53%). Most patients who were categorized as non-COAPT-like met 1 criterion (n = 72) (88.9%), whereas the remaining met 2 criteria (n = 9) (11.1%). Both groups were elderly with a similarly high prevalence of a HFH 1 year before the procedure (63% COAPT-like vs 64% non-COAPT-like; $P = 0.86$). Although baseline characteristics were generally similar between COAPT-like and non-COAPT-like patients, expected differences in cardiac parameters were observed: non-COAPT-like patients had significantly larger LVs and smaller EROAs compared with the COAPT-like group ($P < 0.05$).

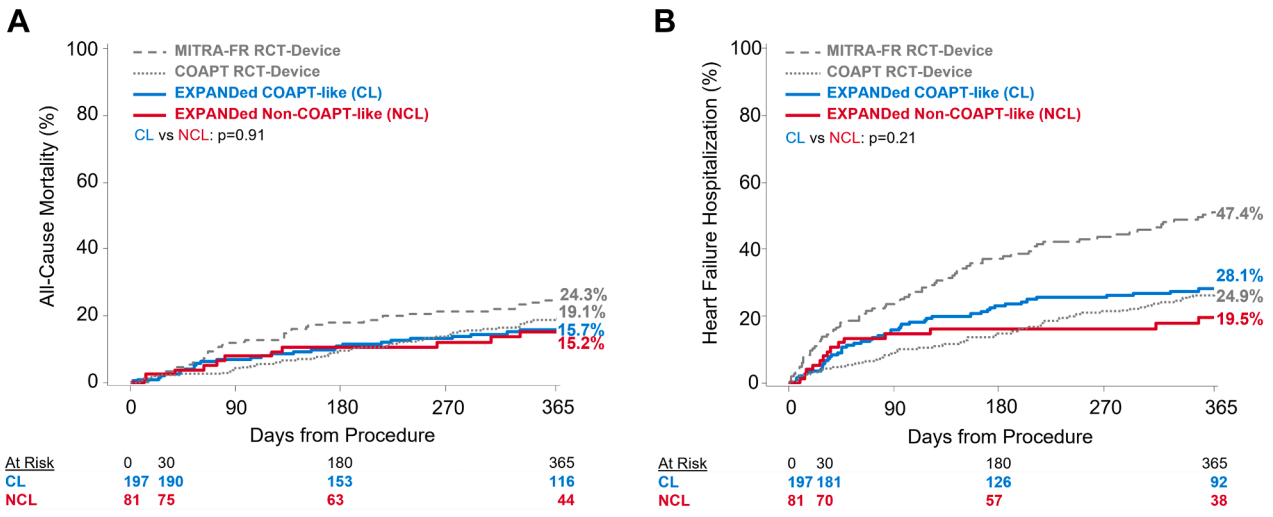
PROCEDURAL OUTCOMES. Procedural outcomes were similarly safe and effective in the 2 groups (Table 2). Acute procedural success rates were consistently high and similar in both groups, with 96% in the COAPT-like group and 91.3% in the non-COAPT-like group ($P = 0.14$). Most patients received 1 clip regardless of subgroup. Device time was similar and low at a median of 40 minutes in both groups.

CLINICAL AND SAFETY OUTCOMES THROUGH 1 YEAR. The 1-year all-cause mortality rates were comparable between groups: 15.7% for COAPT-like and 15.2% for non-COAPT-like groups ($P = 0.91$) (Figure 1A). HFH rates at 1 year were 28.1% and 19.5% for COAPT-like and non-COAPT-like groups, respectively ($P = 0.21$) (Figure 1B). After adjustment of 30-day use of any HF medications, aldosterone antagonists, or diuretics, which were significantly different between COAPT-like and non-COAPT-like patients, 1-year all-cause mortality ($P = 0.38$) and HFH ($P = 0.21$) rates remained comparable between groups (Supplemental Table 1). There was a significant reduction in cumulative annualized HFH rate 1 year before the MTEER procedure compared with 1 year after M-TEER with a 56% reduction in HFH in the COAPT-like group and a 74% reduction in HFH in the non-COAPT-like group (Figure 2). Results from a multivariate analysis for associations of the 3 non-COAPT-like criteria (excluding baseline MR ≥3+) (ie, LVEF, LVESD, and sPAP) with 1-year all-cause mortality or HFH showed that LVEF, LVESD, and sPAP were not significantly associated with the 1-year hazards of all-cause mortality or HFH (Supplemental Table 2).

Functional status improved significantly, with 79% of COAPT-like and 80% of non-COAPT-like patients achieving NYHA functional class I/II at 1 year (Figure 3, paired data shown in Supplemental Figure 1). Both groups demonstrated significant improvement in quality of life, with higher KCCQ-OSSs at 1 year (COAPT-like: $\Delta = +22$; $P < 0.0001$ 1 year vs baseline; non-COAPT-like: $\Delta = +16$; $P = 0.004$ 1 year vs baseline) (Figure 4). Medication use remained stable from baseline to 30 days in the non-COAPT-like group with >97.3% on any HF medication at 30 days, and decreased slightly in the COAPT-like group with >88.9% of COAPT-like on any HF medication at 30 days (Table 3).

Major adverse events remained low through both 30 days and 1 year, with no significant differences between groups ($P > 0.05$) (Table 4). SLDA rates were low (<3%). There were no instances of device embolization through 1 year. Leaflet damage events were rare, occurring in only 1 patient within the first 30 days postprocedure in the non-COAPT-like group.

FIGURE 1 Kaplan-Meier Estimates of All-Cause Mortality and HFH



Kaplan-Meier 1-year estimates for all-cause mortality (A) and HFH (B) were similar between the CL and NCL groups, and similar or lower to the COAPT and MITRA-FR RCT device arms, respectively. *P* values represent significance according to a log-rank comparison between CL and NCL Kaplan-Meier estimates. CL = COAPT-like; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy; HFH = heart failure hospitalization; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; NCL = non-COAPT-like; RCT = randomized controlled trial.

ECHOCARDIOGRAPHIC OUTCOMES THROUGH 1 YEAR

At 1-year follow-up, significant MR reduction to ≤1+ was achieved in 90% of both COAPT-like patients and non-COAPT-like patients ($P < 0.0001$ baseline vs 1 year COAPT-like and non-COAPT-like; $P = 0.99$ COAPT-like vs non-COAPT-like at 1 year) (**Figure 5**, paired data shown in Supplemental Figure 2). This MR reduction was durable, with no significant differences in MR ≤1+ between 30 days and 1 year in either group. Both groups showed significant reductions in LV end-diastolic volume at 1 year; LV end-diastolic dimensions reduced significantly in the COAPT-like group but not the non-COAPT-like group. The improvements in cardiac volumes were maintained through 1 year with larger reductions in volumes from 30 days to 1 year (**Table 5**).

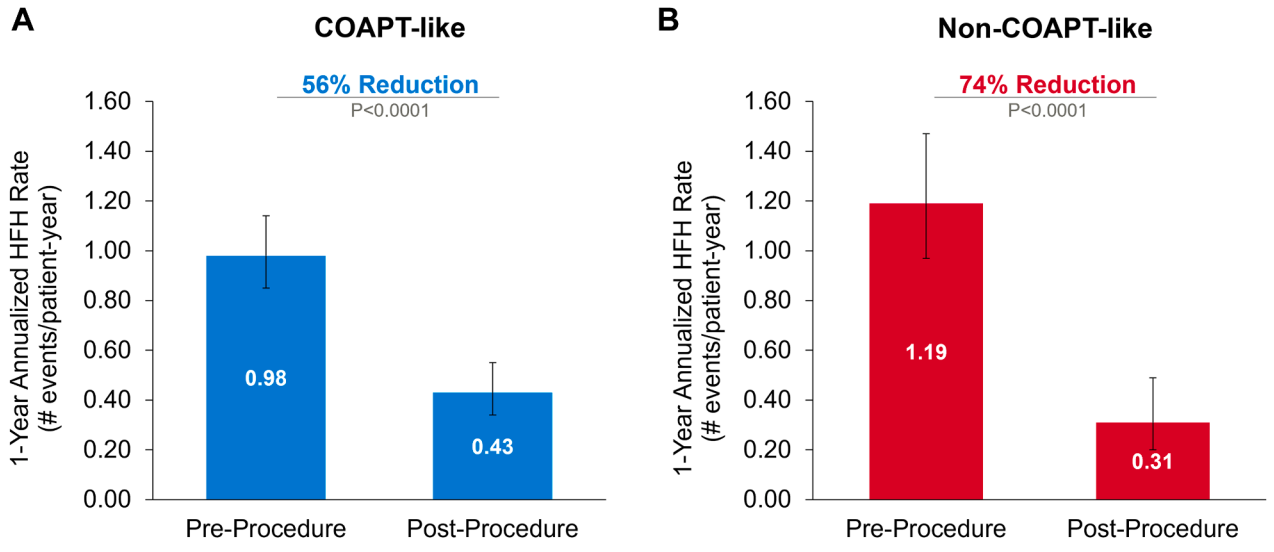
DISCUSSION

Our analysis of patients outside the COAPT trial's inclusion and exclusion criteria with advanced heart disease characteristics in the EXPANDed studies had the following key findings: 1) non-COAPT-like patients, defined by lower LVEF, larger LV sizes, or elevated pulmonary pressures, had similar rates of procedural success and clinical outcomes with the MitraClip System, compared with patients who were COAPT-like; 2) the non-COAPT-like patients had similar quality of life improvement to those seen in COAPT-like patients; and 3) sustained and significant MR reductions were observed in both COAPT-like patients and non-COAPT-like through 1 year.

These findings suggest that carefully selected patients with advanced heart disease characteristics may benefit from the MitraClip therapy, even if they fall outside of traditional trial eligibility criteria and current guideline recommendations.

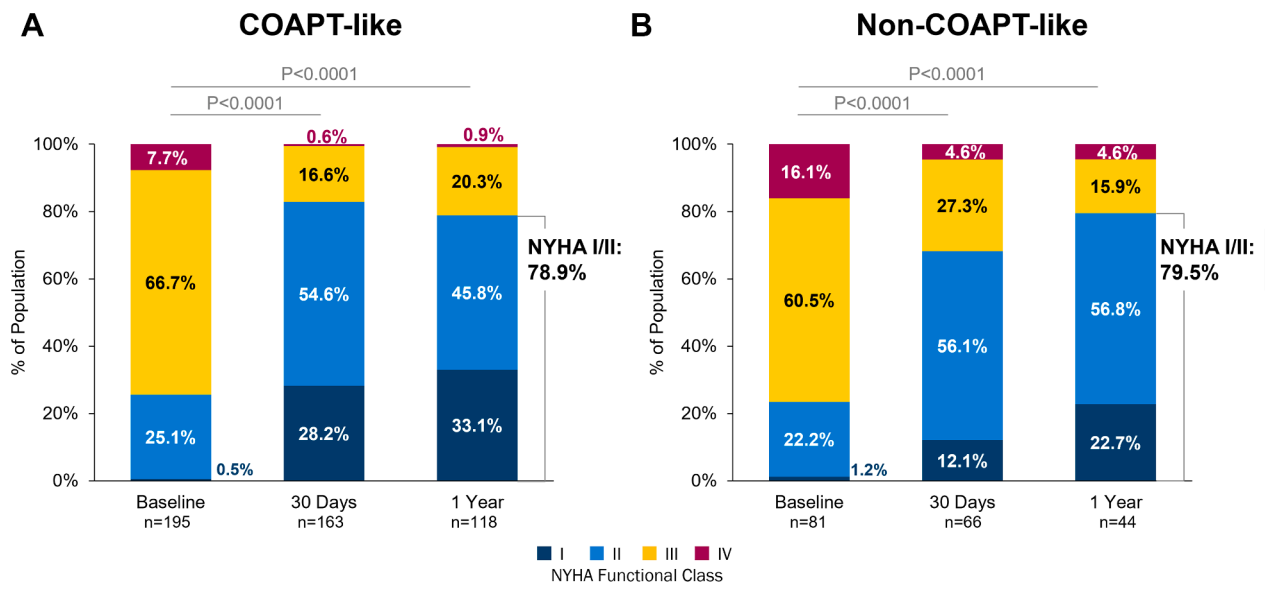
MTEER WAS SAFE AND EFFECTIVE IN PATIENTS WITH SMR OUTSIDE OF COAPT ELIGIBILITY FROM EXPANDed. Current valve guidelines on MTEER are largely based on the COAPT eligibility criteria and supported by differences seen in the patient population between the MITRA-FR and COAPT trials. However, real-world experience and technological advancements of MTEER have broadened the scope of MTEER use in SMR. Patients in the current EXPANDed subgroups represent a different spectrum of SMR patients than those previously evaluated in the COAPT, MITRA-FR, and RESHAPE-HF2 trials. In EXPANDed, COAPT-like patients were older, more symptomatic (eg, larger proportion in NYHA functional class III/IV and lower KCCQ-OSSs), and had smaller LVs than COAPT and MITRA-FR subjects. EXPANDed non-COAPT-like patients were older with larger LV volumes but smaller EROAs compared with

FIGURE 2 Annualized 1-Year HFH Rate



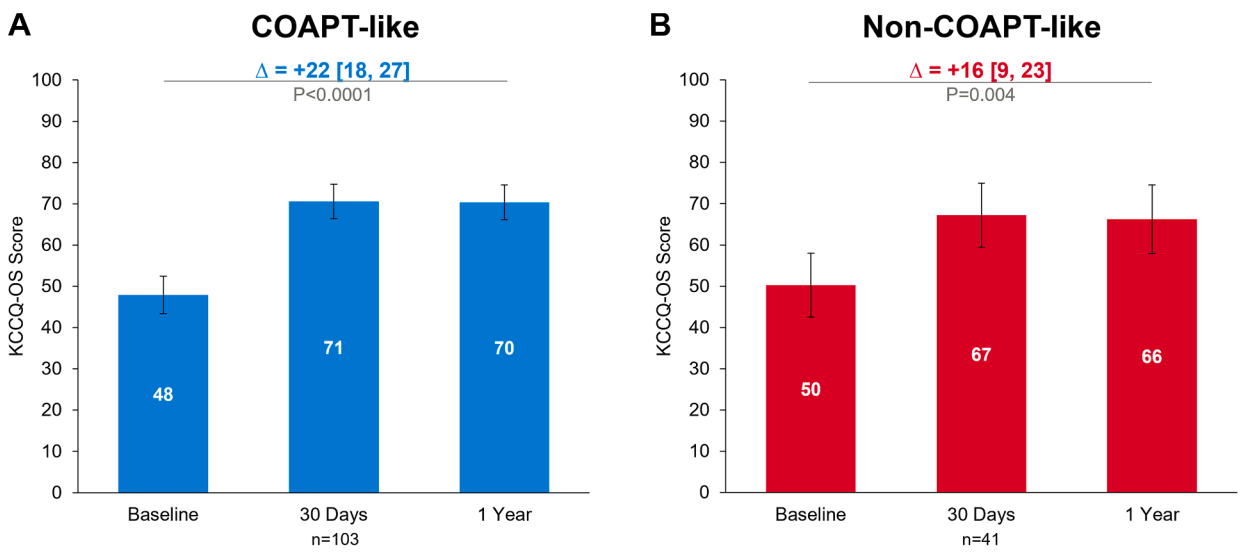
The annualized rate of HFH, defined as total number of HFH events per patient-year, in the CL (A) and NCL (B) groups decreased significantly from 1 year before to 1 year after the MitraClip procedure. The bar graphs depict the annualized HFH rate, and error bars represent the 95% CI segment. *P* values from chi-square test of rates from before and after the index procedure. Abbreviations as in Figure 1.

FIGURE 3 Change in Functional Status



Distribution of NYHA functional classes in CL (A) and NCL (B) groups at baseline, 30 days, and 1 year of follow-up. Both groups had significant improvements to NYHA functional class I/II. Compared with the CL group, improvement to NYHA functional class I/II in the NCL group was higher at 30 days ($P = 0.01$ based on chi-square test), but similar at 1 year ($P = 0.9$ based on chi-square test). *P* values represent paired significance based on Bowker's test. Abbreviations as in Figure 1.

FIGURE 4 Quality-of-Life Improvement



Mean KCCQ-OSS in CL (A) (n = 103) and NCL (B) (n = 41) groups in a paired cohort at baseline, 30 days, and 1 year, with error bars representing 95% CIs. Significant improvement in KCCQ-OSS in both cohorts represented as mean (95% CI), with *P* values representing paired significance between baseline and 1 year based on Student's *t*-test. The improvement in KCCQ-OSS at 1 year was similar between CL and NCL (*P* = 0.15 by pooled Student's *t*-test). KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; other abbreviations as in Figure 1.

COAPT subjects, had smaller LV volumes but larger EROAs compared with MITRA-FR subjects, and were older with similar symptoms, similar larger LV volumes, but larger EROAs compared with RESHAPE-HF2 subjects (Central Illustration). In EXPANDed, more than 97% of patients in the COAPT-like or non-COAPT-like group were on HF medications at baseline, reflecting real-world treatment of SMR.

Despite falling outside guideline-based and COAPT criteria, non-COAPT-like patients had significant symptomatic improvement and similar or lower mortality and HFH rates compared with COAPT-like patients (Table 6). A multivariate analysis did not reveal significant associations of baseline LVEF, LVESD, or sPAP with mortality or HFH for the EXPANDed COAPT-like and non-COAPT-like populations. The mortality and HFH rates in the COAPT-like and non-COAPT-like groups in EXPANDed were lower than the rates reported in MITRA-FR and similar to the rates reported in COAPT, further supporting the potential role of MTEER in selected SMR patients with more advanced heart disease

TABLE 3 Medication Use at Baseline and 30 Days

	Baseline			30 Days		
	COAPT-Like (n = 197)	Non-COAPT-Like (n = 81)	*P* Value	COAPT-Like (n = 189)	Non-COAPT-Like (n = 73)	*P* Value
Any HF medication	192 (97.5)	79 (97.5)	0.99	168 (88.9)	71 (97.3)	0.03
Beta-blockers	164 (83.2)	71 (87.7)	0.36	150 (79.4)	61 (83.6)	0.44
ACEI	50 (25.4)	24 (29.6)	0.47	39 (20.6)	22 (30.1)	0.10
Angiotensin receptor blockers	38 (19.3)	17 (21.0)	0.75	30 (15.9)	16 (21.9)	0.25
Vasodilators	28 (14.2)	6 (7.4)	0.12	22 (11.6)	5 (6.8)	0.25
Aldosterone antagonists	64 (32.5)	35 (43.2)	0.09	50 (26.5)	31 (42.5)	0.01
Diuretic agents	165 (83.8)	71 (87.7)	0.41	151 (79.9)	69 (94.5)	0.004

Values are n (%), unless otherwise indicated. *P* value indicates statistical differences between COAPT-like and non-COAPT-like at baseline and at 30 days.
ACEI = angiotensin-converting enzyme inhibitor; other abbreviations as in Table 1.

TABLE 4 Major Adverse Events

	Through 30 Days			Through 1 Year		
	COAPT-Like (n = 197)	Non-COAPT-Like (n = 81)	*P* Value	COAPT-Like (n = 197)	Non-COAPT-Like (n = 81)	*P* Value
Death	5 (2.5)	2 (2.6)	0.99	28 (14.7)	11 (14.3)	0.89
Myocardial infarction	0 (0.0)	0 (0.0)	N/A	2 (1.0)	1 (1.3)	0.99
Stroke	0 (0.0)	0 (0.0)	N/A	1 (0.5)	0 (0.0)	0.99
Mitral valve replacement	3 (1.5)	2 (2.6)	0.63	6 (3.1)	3 (3.9)	0.72
Single-leaflet device attachment	1 (0.5)	2 (2.6)	0.20	1 (0.5)	2 (2.6)	0.20
Device embolization	0 (0.0)	0 (0.0)	N/A	0 (0.0)	0 (0.0)	N/A
Leaflet damage	0 (0.0)	1 (1.3)	0.28	0 (0.0)	1 (1.3)	0.30

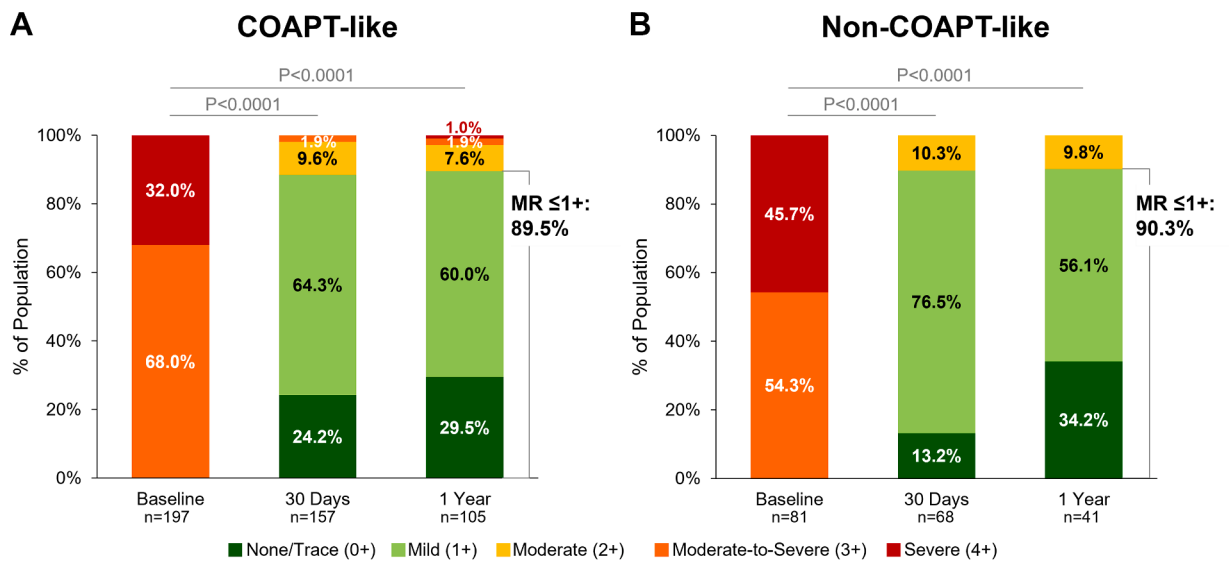
Values are n (%), unless otherwise indicated. *P* value indicates statistical differences between COAPT-like and Non-COAPT-like at 30 d and 1 y.
Abbreviations as in Table 1.

characteristics.[3,11,17] The sustained MR reduction and functional improvement in both COAPT-like and non-COAPT-like groups were similar to or better than those observed in the COAPT, RESHAPE-HF2, and MITRA-FR trials (**Central Illustration**).[3,9,11] These outcomes challenge the notion that strict adherence to COAPT criteria is necessary for successful MTEER outcomes.

Furthermore, quality-of-life improvement was substantial, particularly in the non-COAPT-like group—an elderly, highly symptomatic population. The significant improvement in KCCQ-OSSs in both groups from EXPANDed were greater than COAPT and similar to RESHAPE-HF2 outcomes,[3,9] reinforcing the value of MTEER in improving quality of life regardless of baseline ventricular function and dimensions.[18]

ADDITIONAL FACTORS TO CONSIDER FOR MTEER IN PATIENT CANDIDACY OUTSIDE OF COAPT CRITERIA. A more holistic approach to patient selection may improve prognostic accuracy and treatment outcomes of MTEER. Advanced heart disease

FIGURE 5 Reduction in MR



Distribution of MR grades in CL (A) and NCL (B) groups at baseline, 30 days, and 1 year of follow-up. Sustained and significant reduction in ECL-assessed MR severity to ≤1+ at 1 year was observed in both groups. The 30-day and 1-year proportion of MR ≤1+ were similar between CL and NCL groups ($P = 0.80$ based on chi-square test; $P = 0.99$ based on Fisher exact test). Displayed *P* values represent paired significance by Bowker's test. ECL = echocardiographic core laboratory; MR = mitral regurgitation; other abbreviations as in Figure 1.

TABLE 5 Left Ventricular Reverse Remodeling Changes

	COAPT-Like	Non-COAPT-Like	*P* Value Between COAPT-Like and Non-COAPT-Like
LVEF, %	n = 76	n = 35	
Baseline	37 (29-43)	34 (19-49)	
30 d	32 (26-39)	31 (19-43)	
1 y	35 (26-45)	34 (20-48)	
Δ 30 d − baseline	−2 (−4 to +1); *P* = 0.13	−2 (−5 to +1); *P* = 0.16	0.84
Δ 1 y − baseline	0 (−2 to +3); *P* = 0.76	−1 (−5 to +4); *P* = 0.73	0.64
LVESV, mL	n = 76	n = 35	
Baseline	121 (93-157)	130 (77-217)	
30 d	117 (84-154)	145 (81-241)	
1 y	104 (70-145)	116 (64-244)	
Δ 30 d − baseline	−3 (−14 to +9); *P* = 0.65	+1 (−10 to +12); *P* = 0.83	0.63
Δ 1 y − baseline	−10 (−24 to +4); *P* = 0.16	−6 (−20 to +8); *P* = 0.37	0.70
LVEDV, mL	n = 76	n = 35	
Baseline	183 (150-228)	191 (152-288)	
30 d	171 (133-215)	197 (144-286)	
1 y	162 (126-215)	181 (137-287)	
Δ 30 d − baseline	−10 (−23 to + 3); *P* = 0.14	−11 (−25 to +3); *P* = 0.12	0.89
Δ 1 y − baseline	−18 (−33 to −3); *P* = 0.02	−18 (−33 to −3); *P* = 0.017	0.97
LVESD, cm	n = 85	n = 37	
Baseline	5.3 (4.5-5.9)	5.7 (4.3-6.9)	
30 d	5.1 (4.5-5.8)	5.5 (4.1-6.7)	
1 y	5.1 (4.4-5.8)	5.3 (4.1-6.8)	
Δ 30 d − baseline	−0.1 (−0.2 to +0.1); *P* = 0.42	−0.1 (−0.3 to +0.1); *P* = 0.16	0.56
Δ 1 y − baseline	−0.1 (−0.3 to +0.1); *P* = 0.32	−0.2 (−0.5 to 0); *P* = 0.09	0.47
LVEDD, cm	n = 92	n = 38	
Baseline	6.5 (5.6-6.7)	6.5 (5.6-7.7)	
30 d	6.0 (5.5-6.4)	6.4 (5.5-7.2)	
1 y	6.1 (5.3-6.5)	6.4 (5.3-7.4)	
Δ 30 d − baseline	−0.2 (−0.4 to −0.1); *P* = 0.002	−0.1 (−0.3 to 0); *P* = 0.10	0.47
Δ 1 y − baseline	−0.2 (−0.4 to −0.1); *P* = 0.002	−0.1 (−0.4 to +0.1); *P* = 0.25	0.43
APDAD, cm	n = 92	n = 38	
Baseline	3.5 (3.1-3.8)	3.4 (3.1-4.1)	
30 d	3.2 (2.9-3.5)	3.4 (2.9-3.7)	
1 y	3.4 (3.1-3.7)	3.4 (3.1-3.9)	
Δ 30 d − baseline	−0.3 (−0.5 to −0.2); *P* < 0.001	−0.2 (−0.4 to 0); *P* = 0.08	0.16
Δ 1 y − baseline	−0.1 (−0.2 to 0); *P* = 0.13	0 (−0.3 to +0.2); *P* = 0.76	0.56

Values are median (Q1-Q3) in a paired analysis at the baseline, 30-d, and 1-y timepoints. Δ between timepoints presented as mean (95% CI); *P* value indicating significant change between timepoints. *P* value between COAPT-like and non-COAPT-like groups indicate significance between groups in the change in parameter between timepoints using a pooled Student's *t*-test or Welch *t*-test.

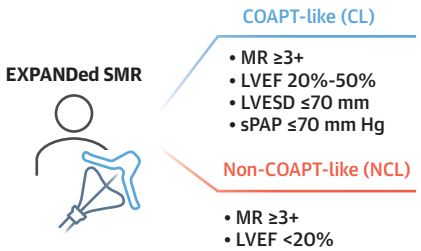
APDAD = anterior posterior diastolic annular dimension; other abbreviations as in Table 1.

can be characterized by parameters not included in guidelines, such as right ventricular/pulmonary artery uncoupling, tricuspid regurgitation, or other comorbidities, which may drive a bigger disparity in prognostic outcomes.[19-21] Although our non-COAPT-like definition focused on LVEF <20%, LVESD >70 mm, and sPAP >70 mm Hg, these may not be the only parameters to consider when selecting patients for MTEER. Other registries have reported that patients outside the COAPT criteria, inclusive but not limited to the guideline parameters, had higher 1-year HFH rates compared with those within the COAPT criteria after MTEER.[7,8] In EXPANDed, 1-year HFH rates were not statistically different between COAPT-like and non-COAPT-like patients, suggesting that the benefits of MTEER may extend beyond the parameters set in the guidelines. However, medical use rates in EXPANDed reflect

CENTRAL ILLUSTRATION **Transcatheter Edge-to-Edge Repair in NCL Patients With SMR: From the EXPANDed Studies**

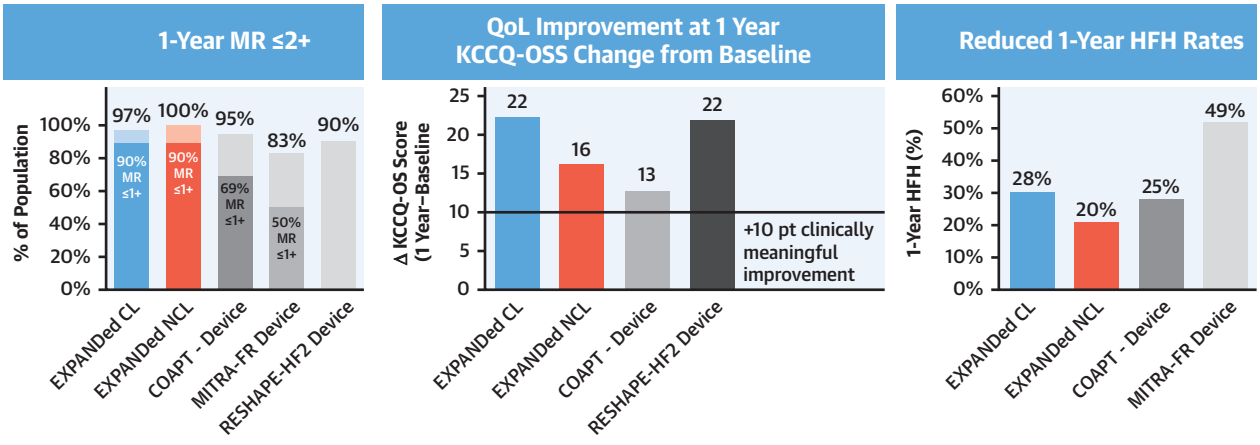
Patients With SMR Outside of COAPT Eligibility Criteria in EXPANDed

Patients With SMR from EXPANDed Treated With Mitral Transcatheter Edge-to-Edge Repair



	EXPANDed CL (N = 197)	EXPANDed NCL (N = 81)	COAPT Device (N = 302)	MITRA-FR Device (N = 152)	RESHAPE-HF2 Device (N = 250)
Age, y	74 ± 10	74 ± 10	72 ± 12	70 ± 10	70 ± 10
NYHA functional class III/IV	74.4%	76.5%	57.0%	63.1%	76.4%
LVEF, %	34 ± 8	34 ± 16	31 ± 9	33 ± 7	32 [26-37]
LVESD, cm	5.2 ± 0.9	5.7 ± 1.5	5.3 ± 0.9	–	–
sPAP, mm Hg	48 ± 13	66 ± 22	–	–	–
LVEDV, mL	183 ± 66	220 ± 105	194 ± 69	252*	200 [153-249]
EROA, cm^2	0.33 ± 0.10	0.36 ± 0.12	0.41 ± 0.15	0.31 ± 0.10	0.23 [0.20-0.30]

Improvements in Mitral Regurgitation Grade, QoL, and HFH



Tang GHL, et al. JACC Heart Fail. 2025;13(9):102565.

In the EXPANDed studies, patients with SMR treated with the MitraClip System were categorized as CL or NCL according to the key eligibility criteria from the COAPT trial and current valvular and HF guidelines. At baseline, CL and NCL patients were older than those enrolled in previous MitraClip RCTs (COAPT, MITRA-FR, and RESHAPE-HF2). NCL patients had symptom severity similar to those in RESHAPE-HF2, larger LVEDV like patients in MITRA-FR, and smaller EROAs compared with those in COAPT. Despite these differences, CL and NCL achieved significant MR reduction to ≤2+, substantial improvement in KCCQ-OSS (greater than or similar to COAPT and RESHAPE-HF2), and 1-year HFH rates (Kaplan-Meier 1-year estimates) similar to those reported in COAPT. *LVEDV in MITRA-FR estimated from Grayburn et al.[23] Proportion of MR ≤1+ at 1 year in MITRA-FR estimated from Obadia et al.[11] CL = COAPT-like; COAPT = Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy; EROAs = effective regurgitant orifice areas; EXPANDed = EXPAND [The MitraClip EXPAND Study of the Next Generation of MitraClip Devices] and EXPAND G4 [MitraClip EXPAND G4 Study]; HF = heart failure; HFH = heart failure hospitalization; KCCQ-OSS = Kansas City Cardiomyopathy Questionnaire-Overall Summary Score; LVEDV = left ventricular end-diastolic volumes; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic dimension; MITRA-FR = Multicentre Study of Percutaneous Mitral Valve Repair MitraClip Device in Patients with Severe Secondary Mitral Regurgitation; NCL = non-COAPT-like; QoL = quality of life; RCT = randomized controlled trial; RESHAPE-HF2 = Randomized Investigation of the MitraClip Device in Heart Failure: Second Trial in Patients with Clinically Significant Functional Mitral Regurgitation; SMR = secondary mitral regurgitation; sPAP = systolic pulmonary artery pressure.

real-world GDMT practice,[7,22] and variability in HF medication use between COAPT-like and non-COAPT-like patients was observed at 30 days. The lower medication usage in COAPT-like patients after MTEER may be reflected in the subsequent numerically higher 1-year HFH rates in the COAPT-like patients compared with non-COAPT-like patients. Although the differences in outcomes between groups were not statistically significant after adjusting for medication use, medication

TABLE 6 Baseline Characteristics and Outcomes Across Studies

	EXPANDed COAPT-Like (n = 197)	EXPANDed Non-COAPT-Like (n = 81)	COAPT (Device Group)[1] (n = 302)	MITRA-FR (Device Group)[11] (n = 152)	RESHAPE-HF2 (Device Group)[9] (n = 250)	TVT Registry (COAPT-Ineligible)[12] (n = 2,954)
Baseline characteristics						
Age, y	74 ± 10	74 ± 10	72 ± 12	70 ± 10	70 ± 10	75 ± 11
LVEF, %	34 ± 8 (197)	34 ± 16 (81)	31 ± 9 (302)	33 ± 7 (152)	32 (26-37)	35 ± 16
LVESD, cm	5.2 ± 0.9 (197)	5.7 ± 1.5 (81)	5.3 ± 0.9 (302)	–	–	–
LVEDD, cm	6.1 ± 0.8 (197)	6.7 ± 1.3 (81)	6.2 ± 0.7 (302)	–	–	–
LVESV, mL	122 ± 51 (197)	152 ± 91 (81)	136 ± 56 (302)	–	–	–
LVEDV, mL	183 ± 66 (197)	220 ± 105 (81)	194 ± 69 (302)	252[a]	200 (153-249)	–
sPAP, mm Hg	48.1 ± 12.7 (197)	65.7 ± 22.3 (76)	–	–	–	–
EROA, cm^2	0.33 ± 0.10 (164)	0.36 ± 0.12 (59)	0.41 ± 0.15 (302)	0.31 ± 0.10 (152)	0.23 (0.20-0.30)	–
Prior HFH	115 (62.5)	49 (63.6)	176 (58.3)	152 (100)	165 (66.0)	1,978 (74.1)
NYHA functional class III/IV	145 (74.4)	62 (76.5)	172 (57.0)	96 (63.1)	191 (76.4)	2,660 (90.6)
KCCQ-OSS	45.7 ± 24.4 (182)	46.4 ± 23.8 (77)	54.2 ± 22.7 (2,336)	–	42.2 (28.3-62.0)	34.6 ± 23.0 (1,409)
1-yr outcomes						
MR ≤1+	89.5 (94/105)	90.3 (37/41)	145 (69.1)	50%[b]	–	–
MR ≤2+	97.1 (102/105)	100.0 (41/41)	199 (94.8)	83%	90.4%	90.9%
NYHA functional class I/II, %	78.9	79.5	72.2	–	74.5	–
KCCQ-OSS Improvement	+22 (18-27)	+16 (9-23)	+12.5 ± 1.8	–	21.6 ± 26.9	–
All-cause mortality, %[c]	15.7	15.2	19.1	24.3	–	35.2
HFH, %[c]	28.1	19.5	24.9	48.7	–	20.3

Values are mean ± SD, mean ± SD (n), median (IQR) (n), n (%), or % (n/N). [a]LVEDV from MITRA-FR reported from Grayburn et al.[23] [b]Estimated from Obadia et al.[11] [c]Kaplan-Meier estimates of 1-y all-cause mortality and HFH rates.

TVT = transcatheter valve therapy; other abbreviations as in Table 1.

management remains a critical component in HF care. Further research with larger studies is needed to better understand how medication use may interact with MTEER outcomes in non-COAPT-like patients. The discordance in reported HFH rates from this EXPANDed analysis compared with prior studies highlights the importance of GDMT and suggests that better patient selection and refinement in clinical and echocardiographic parameters, beyond those used in the recent randomized controlled trials, would be useful to identify the optimal patient population with SMR and advanced heart disease who would benefit from MTEER.

STUDY LIMITATIONS. Enrollment into the EXPANDed studies was conducted per site evaluation of MR, LV parameters, and other comorbidities, which considers a comprehensive assessment and includes regional differences in echocardiographic guidelines. All echocardiographic parameters reported in this analysis were conducted by the ECL to standardize gradings across all patients and all timepoints in the global EXPANDed studies. Additionally, the EXPANDed studies were designed as postmarket, observational studies and, therefore, lack a control arm or blinding. Monitoring use of GDMT in this study was limited to the proportion of patients taking HF medication, and medication titration was not collected. The greater number of non-COAPT-like patients on any HF on any HF medication(s) at 30 days may have confounded to the low mortality and HFH rates within EXPANDed compared with prior studies. Finally, because this analysis was performed post hoc, the number of patients in the analysis subgroups are limited due to data availability for the subgroup definitions mainly from patients with moderate or less MR at baseline, which may introduce a selection bias in this analysis population. Heterogeneity in the subgroups reflects the spectrum of HF in SMR patients and supports the need to assess other comorbidities and parameters that may have a more significant impact on outcomes than the COAPT criteria outlined in the guidelines. Larger, prospective studies are needed to validate these results and assess long-term outcomes.

CONCLUSIONS

Real-world data from the EXPANDed studies demonstrate that MTEER with the MitraClip System provides significant clinical benefits in selected SMR

patients with advanced heart disease characteristics who fall outside traditional COAPT criteria and guideline recommendations. Procedural success, MR reduction, and improvements in functional status and quality of life were comparable between COAPT-like and non-COAPT-like patients, with no significant differences in mortality or HFH at 1 year. These findings support the consideration of MTEER in a broader patient population and challenge the notion that strict adherence to the COAPT criteria is necessary for favorable outcomes. Expanding eligibility criteria for MTEER may be reasonable in carefully selected patients, offering a new therapeutic avenue for this group with more advanced heart disease characteristics.

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ADDRESS FOR CORRESPONDENCE: Dr Gilbert H.L. Tang, Department of Cardiovascular Surgery, Mount Sinai Health System, 1190 Fifth Avenue, Box 1028, New York, New York 10029, USA. E-mail: gilbert.tang@mountsinai.org. X handle: @GilbertTangMD.

PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Selected patients with advanced heart disease characteristics who fall outside the strict eligibility criteria of the landmark COAPT trial and current guidelines are increasingly being treated with MTEER. Real-world data from the EXPANDed studies demonstrate that these patients can experience clinical benefits—including MR reduction, improved functional status, and quality of life—comparable with those observed in COAPT-like and guideline-recommended SMR populations.

TRANSLATIONAL OUTLOOK: Expanding MTEER eligibility beyond current guideline criteria and beyond the COAPT criteria may be reasonable in selected patients with SMR. More research is required to clearly define the advanced HF patients who may benefit from MTEER.

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