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NEW RESEARCH PAPER

STRUCTURAL

Contemporary Outcomes Following Transcatheter Edge-to-Edge Repair

1-Year Results From the EXPAND Study

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ABSTRACT

BACKGROUND The third-generation MitraClip NTR/XTR transcatheter edge-to-edge repair system was introduced to assist in leaflet grasping with the longer clip arms of MitraClip XTR and to improve ease of use with the modified delivery catheter.

OBJECTIVES The EXPAND study evaluated contemporary real-world outcomes in subjects with mitral regurgitation (MR) treated with the third-generation MitraClip NTR/XTR transcatheter edge-to-edge repair system.

METHODS EXPAND is a prospective, multicenter, international, single-arm study that enrolled patients with primary MR and secondary MR at 57 centers. Follow-up was conducted through 12 months. Echocardiograms were analyzed by an echocardiographic core laboratories. Study outcomes included: MR severity, functional capacity measured by New York Heart Association functional class, quality of life measured by Kansas City Cardiomyopathy Questionnaire, heart failure hospitalizations, all-cause mortality.

RESULTS 1,041 patients were enrolled from April 2018 through March 2019, of which 50.5% had primary or mixed etiology. Implant success was 98.9%; 1.5 ± 0.6 clips were implanted per subject. Significant MR reduction from baseline (≥MR 3+: 56.0%) to 30 days (≤MR 1+:88.8%) was maintained through 1 year (MR ≤1+: 89.2%). A total of 84.5% and 93.0% of subjects in primary MR and secondary MR, respectively, had ≤1+ MR at 1 year. Significant improvements were observed in clinical outcomes (New York Heart Association functional class I/II in 80.3%, +21.6 improvement in Kansas City Cardiomyopathy Questionnaire score) at 1 year. All-cause mortality and heart failure hospitalizations at 1 year were 14.9% and 18.9%, respectively, which was significantly lower than previous studies.

CONCLUSIONS The study demonstrates treatment with the third-generation system resulted in substantial reduction of MR in a contemporary real-world practice, compared with the results of earlier EVEREST and COAPT trials.(The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices [EXPAND]; NCT03502811)
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ABBREVIATIONS AND ACRONYMS

ASE = American Society of Echocardiography

ECL = echocardiographic core laboratory

HFH = heart failure hospitalizations

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle/ventricular

MI = myocardial infarction

MR = mitral regurgitation

MV = mitral valve

NYHA = New York Heart Association

PMR = primary (degenerative) mitral regurgitation

QoL = quality of life

SLDA = single leaflet device attachment

SMR = secondary (functional) mitral regurgitation

TEE = transesophageal echocardiography

TEER = transcatheter edge-to-edge repair

TTE = transthoracic echocardiography

Over the last 16 years, MitraClip (Abbott) has been implanted in over 150,000 patients worldwide and studied in multiple premarket and postmarket studies.[1-9] The criteria for mitral regurgitation (MR) patient selection, particularly for primary MR (PMR), were established early during the EVEREST II study (Endovascular Valve Edge-to-Edge Repair Study), consisting of a primary jet in the A2/P2 region with relatively narrow prolapse or flail segments, no calcification in the clip landing zone, and a large valve area. As the therapy has matured, its potential use in broader mitral valve (MV) anatomies has gained interest. The GRASP (Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation) registry found that the safety and clinical outcomes of patients who met the EVEREST criteria were similar to those who did not meet it.[10] In another study reported by Lesevic et al,[11] acute procedural success was similar in patients that did and did not fulfill the EVEREST criteria, whereas at a mean follow-up of 3.5 years, recurrent MR ≥3+ was more frequent in non-EVEREST patients (28% vs 45%; $P = 0.066$). Reinterventions for recurrent MR were more frequent in non-EVEREST vs EVEREST patients, including second transcatheter edge-to-edge repair (TEER) interventions (2% vs 13%; $P = 0.085$) and MV surgeries (9% vs 28%; $P = 0.047$). Flail width was an independent predictor for reintervention, whereas flail gap ≥10 mm displayed a strong trend.

In alignment with these observations, modifications to the system were made, which included introduction of the third-generation XTR implant with longer arms and an improved delivery system (**Figure 1**). It was hypothesized that these changes would allow a tailored therapy for broader MV pathologies than that delineated by the restrictive EVEREST criteria, in a more precise and predictable way.

The EXPAND study (The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices) was initiated to evaluate contemporary real-world clinical outcomes in subjects treated with the third-generation system. The objective of this analysis is to report 1-year outcomes associated with MitraClip NTR/XTR systems from the EXPAND study.

METHODS

STUDY DESIGN. The EXPAND study was a prospective, multicenter, single-arm, international, postmarket, observational study conducted in the United States, Europe, and the Middle East to evaluate real-world contemporary outcomes with the third-generation NTR or XTR. A minimum of 1,000 consented subjects with symptomatic moderate-to-severe and severe (3+/4+) MR (assessed by sites) were planned to enroll at 60 sites. Centers were required to have experience with previous generations and performed ≥3 cases with the NTR/XTR systems before enrollment in EXPAND. The trial was approved by the institutional review committee at each site, and all subjects provided written informed consent and were eligible to receive TEER per the current approved indications for use. Enrolled patients were treated per standard of care and followed-up from baseline through discharge, 30 days, and 12 months. Key outcomes included MR severity, procedural outcomes, adverse events, survival, heart failure hospitalization (HFH), quality of life (QoL) per Kansas City Cardiomyopathy Questionnaire (KCCQ), and functional capacity using New York Heart Association (NYHA) functional class. The study data were adjudicated by 3 separate committees:

1. Clinical Events committee adjudicated major adverse events through 30 days, that is, all-cause mortality, myocardial infarction (MI), stroke, and nonelective cardiovascular surgery related to device-related complications. Adverse events through 1 year were based on site reports.
2. Echo core laboratory (ECL) retrospectively assessed echocardiographic measures including MR etiology, MR severity, detailed baseline MV anatomical characterization, left ventricle (LV) measurements.
3. Independent physician committee including the chair of the ECL reviewed and adjudicated single leaflet device attachment (SLDA) and leaflet damage events.[12]

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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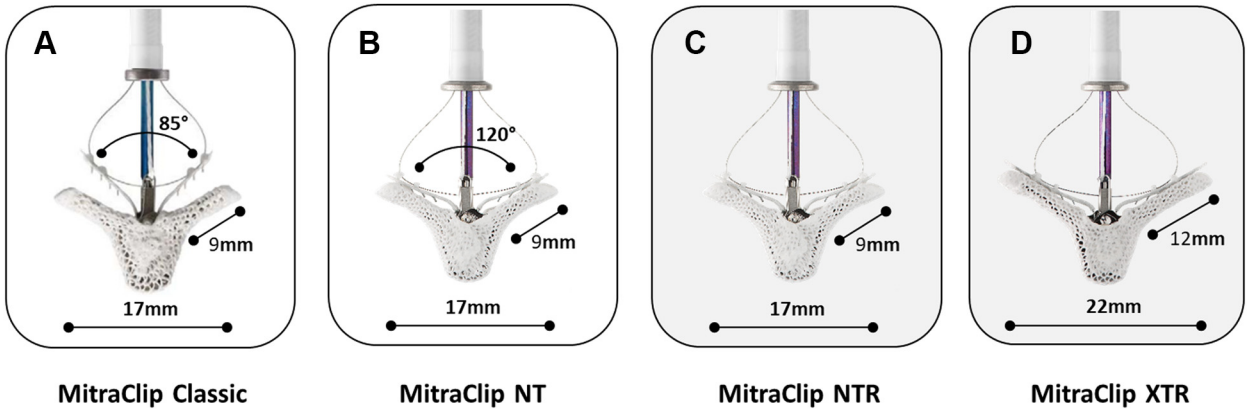
FIGURE 1 MitraClip Implant Evolution



MitraClip implant evolution from first-generation Classic **(A)** to second-generation NT, which increased the gripper drop angle from 85° to 120°, allowing a more efficient leaflet capture on the first attempt **(B)**; to the third-generation NTR and XTR. The NTR **(C)** is identical size-wise to NT with an improved delivery system, increasing precision and predictability during steering **(C)**. The XTR has longer clip arms for easier grasp and better reach, with improved delivery system **(D)**. Historical trials (EVEREST II [Endovascular Valve Edge-to-Edge Repair Study], COAPT [Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation]) used the Classic, whereas EXPAND (The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices) studied the third-generation NTR/XTR system.

Due to the large volume of echocardiographic images collected across all time points, 2 ECLs performed the assessments. Consistently with previous studies, MR severity and etiology assessments were performed by MedStar Health Research Institute, Washington, DC, USA.[1-3] A multiparametric algorithm adapted from the criteria recommended by the American Society of Echocardiography (ASE) guidelines was used for MR severity assessments.[13] Baseline detailed MV and LV anatomical characterization were performed by Medical Research Development S.L., Madrid, Spain.

MV anatomy was determined to be complex by the ECL if at least 1 of the following features were observed on baseline transesophageal echocardiography (TEE):

1. PMR jet outside of A2-P2 coaptation zone
2. More than 1 significant MR jet
3. An extremely wide MR jet (requires multiple implants)
4. MV orifice area <4 cm^2
5. Calcification in the intended landing zone of the implant
6. Minimal leaflet tissue for attachment (coaptation length <2 mm)
7. Severely degenerative leaflets or wide flail gaps (>10 mm) or widths (>15 mm)

The MR etiology was determined by the ECL as either PMR, secondary (SMR), or mixed (if both were present, and neither was the dominant mechanism).

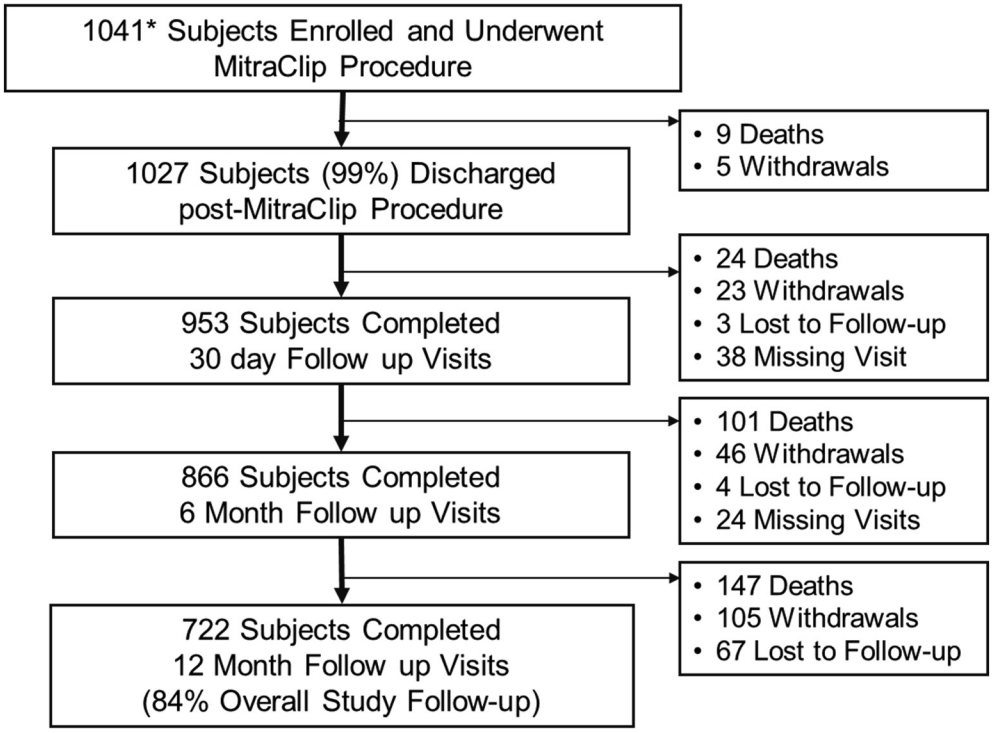
Acute procedural success was defined as successful implantation of the device with resulting MR severity of ≤2+ on discharge echocardiogram (30-day echocardiogram was used if discharge echocardiogram was unavailable or uninterpretable). Subjects who died or underwent MV surgery before discharge were considered acute procedural failures.

STATISTICAL ANALYSIS. Fisher exact test was used to compare categorical variables and Bowker test for paired nominal data. Continuous variables were compared using *t*-tests, or Wilcoxon rank sum test if data were not normally distributed. Changes in KCCQ scores and LV volumes from baseline to later intervals were performed by covariance analysis, adjusting for baseline differences. All analyses were by intention-to-treat. A 2-sided *P* value of <0.05 was considered statistically significant. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

STUDY POPULATION. From April 5, 2018, through March 29, 2019, the EXPAND study enrolled 1,041 subjects subsequently undergoing TEER.

FIGURE 2 Patient Consort Diagram



*A total of 1,045 subjects consented in the study; 4 subjects were withdrawn from the study before the index procedure; 1,030 subjects were implanted with MitraClip NTR/XTR.

Despite challenges due to the COVID-19 pandemic, 722 subjects completed 12-month follow-up visits, resulting in 84% overall study follow-up (Figure 2). Median duration of study follow-up was 12.0 months (IQR: 11.0-13.1 months).

BASELINE CHARACTERISTICS. Baseline demographics and comorbidities are shown in Table 1. Average age was 77.3 ± 9.7 years, and 54.9% were male. The Society for Thoracic Surgery predicted mortality risk (STS-PROM) for repair and replacement were 6.3% ± 6.3% and 8.0% ± 6.4%, respectively, and the EuroSCORE II was 8.1 ± 8.0. The most predominant comorbidities were hypertension (82.9%), atrial fibrillation (59.3%), and renal failure (36.1%). Approximately one-half of the subjects experienced a HFH visit in the prior 12 months (53.7%). A total of 28.2% of subjects had prior cardiac surgeries, 35.7% prior cardiac interventions, and 78.6% NYHA functional class III/IV symptoms. Table 2 summarizes ECL-adjudicated baseline echocardiographic characteristics. Although the sites reported all-subjects' baseline MR severity of 3+/4+ based on a collective assessment of clinical findings, transthoracic echocardiography (TTE), and TEE, ECL-assessed severity of MR was based on TTE images only. Accordingly, 56% of subjects had 3+/4+, and 44% had ≤2+ MR grade per ASE guidelines; whereas 92% had MR grade ≥3+ per EU guidelines.[14] A total of 18% of subjects (n = 158) were deemed to have a complex MV anatomy by the ECL. The reasons for MV complexity included primary jet outside of A2-P2 in 10.9%, wide jet in 30.1%, significant secondary jet in 25.3%, small valve in 4.5%, calcification in the landing zone in 33.3%, minimal leaflet tissue in 10.3%, and severely degenerative leaflets in 48.1%. Imaging for echocardiographic assessment of MR etiology was available in 835 subjects. In 206 subjects, baseline echocardiographic images were either missing or not evaluable. Nearly one-half of the subjects (50.5%) had

primary or mixed etiology of their MV disease, and the remaining one-half (49.5%) were deemed SMR by ECL. Baseline characteristics for both PMR and SMR groups are detailed in Tables 1 and 2.

XTR AND NTR CLIP UTILIZATION. Recommendations on anatomical considerations for clip size selection, as determined by the EXPAND steering committee, were provided to EXPAND operators for guidance (Supplemental Figure 1). XTR was used more frequently than NTR (45.0% vs 40.4%), followed by patients treated with both XTR and NTR (14.7%) (Figure 3). At least 1 XTR clip was used for treatment of 64.2% PMR patients, whereas 59% of SMR patients were treated with at least 1 NTR clip. The average number of clips implanted per patient was 1.5 ± 0.1 (median: 1.0; IQR: 1.0-2.0). Table 3 shows pre-procedure mitral inflow gradients were not different between patients treated with XTR and NTR (2.3 ± 1.3 mm Hg for XTR, and 2.2 ± 1.2 mm Hg for NTR; $P = 0.76$). The XTR, despite its longer arms, was not associated with increased MV gradient postprocedure at 30 days compared with NTR with standard arm length (3.5 ± 1.6 mm Hg vs 3.9 ± 3.5 mm Hg; $P = 0.06$). Table 3 shows clip usage by baseline anatomical characteristics. Anatomical complexity was similar between clip sizes although subjects treated with XTR had larger prolapse gaps, larger flail gaps, larger annular and ventricular dimensions, greater baseline MR grade, and larger coaptation depth compared with subjects with NTR.

PROCEDURAL OUTCOMES. Procedural outcomes are shown in Table 4. Implantation success rate was 98.9% (1,030/1,041), and the acute procedural success rate was 95.8% (985/1,028), with a median procedure time of 80 minutes and median device time of 46 minutes. Inadequate MV anatomy (5 cases), high mitral gradient (4 cases), and pericardial effusions (2 cases) resulted in attempted procedures without clip implantation. Average hospital stay length was 5 days and varied between the United States and outside the United States (mean: 6 days; IQR: 4-10 days). This hospital stay difference was primarily related to differing practice pathways in the 2 regions and not due to procedure or patient complexity.

1-YEAR OUTCOMES. Significant MR reduction from baseline to 30 days (MR grade ≤1+ and ≤2+ in 88.8% and 97.8% of subjects, respectively) was maintained through 1 year in surviving patients with evaluable echocardiograms: MR grade ≤1+ and ≤2+ in 89.2% and 97.5%, respectively, at 1 year (Figure 4). A total of 84.5% and 93% of subjects in PMR and SMR,

TABLE 1 Baseline Characteristics

	EXPAND (n = 1,041)	Primary MR (n = 422)	Secondary MR (n = 413)
Age, y	77.3 ± 9.7	79.5 ± 9.4	74.7 ± 10.1
Male	54.9 (571)	52.1 (220)	58.4 (241)
Body mass index, kg/m^2	25.9 ± 5.1	25.2 ± 4.8	26.0 ± 4.9
STS repair score	6.3 ± 6.3	5.5 ± 5.4	7.2 ± 7.3
STS replacement score	8.0 ± 6.4	7.3 ± 5.6	8.8 ± 7.5
EuroSCORE II	8.1 ± 8.0	5.9 ± 5.6	9.8 ± 9.4
NYHA functional class			
I/II	21.4 (223)	26.4 (111)	16.9 (70)
III/IV	78.6 (817)	73.6 (310)	83.1 (343)
Atrial fibrillation	59.3 (614)	56.0 (235)	60.2 (247)
Renal failure	36.1 (374)	28.2 (119)	47.1 (192)
Diabetes	25.4 (261)	19.2 (261)	29.5 (120)
Dyslipidemia	57.2 (582)	52.5 (219)	61.4 (245)
Hypertension	82.9 (859)	79.5 (334)	84.1 (345)
Prior HF hospitalization within 1 y	53.7 (502)	43.2 (164)	64.8 (248)
Prior cardiac surgeries	28.2 (294)	20.6 (87)	34.9 (144)
Prior PCI	35.7 (365)	25.0 (104)	45.4 (183)
Prior myocardial infarction	24.2 (246)	13.6 (46)	35.8 (145)

Values are mean ± SD or % (n). Categorical data are presented as the proportion of subjects where data were provided. Missing data were excluded.

EXPAND = The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices; HF = heart failure; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons.

TABLE 2 ECL-Assessed Baseline Echocardiographic Parameters

	EXPAND (n = 1,041)	Primary MR (n = 422)	Secondary MR (n = 413)
Etiology primary MR[a]	50.5 (422)	100.0 (422)	0.0 (0)
MR severity			
Grades 3+ or 4+	56.0 (509)	66.4 (279)	52.1 (213)
Grades ≤2+[b]	44.0 (400)	33.6 (141)	47.9 (196)
EROA, cm^2	0.35 ± 0.18	0.40 ± 0.21	0.30 ± 0.12
Baseline TR of 3+ or 4+	21.5 (174)	22.8 (84)	19.6 (77)
LVEF, %	51.4 ± 16.0	61.8 ± 9.9	39.4 ± 13.5
LVESV, mL	78.8 ± 61.3	48.0 ± 30.5	115.1 ± 68.8
LVEDV, mL	148.1 ± 87.2	121.0 ± 48.7	180.4 ± 80.0
LVESVi, mL/m^2	42.5 ± 32.8	26.0 ± 15.8	62.4 ± 36.7
LVEDVi, mL/m^2	80.1 ± 36.7	66.0 ± 23.4	97.9 ± 41.9
Mitral valve complexity[c]	18.2 (156)	28.3 (115)	10.1 (40)

Values are % (n) or mean ± SD. Categorical data are presented as the proportion of subjects where data were provided. Missing data were excluded. [a]Adequate echo imaging for mitral regurgitation (MR) etiology assessment was available in 835 subjects, whereas baselines images were missing or not evaluable by the echocardiographic core laboratory (ECL) among the remaining 206 subjects. [b]These subjects were assessed as baseline MR severity 3+/4+ by the sites. [c]Mitral valve complexity was adjudicated by ECL per wide jet, primary jet outside of A2-P2, more than 1 significant jet, small valve, calcified landing zone, severely degenerative leaflets with large flail/prolapse, and minimum leaflet tissue for attachment.

EROA = effective regurgitant orifice area; EXPAND = The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; TR = tricuspid regurgitation.

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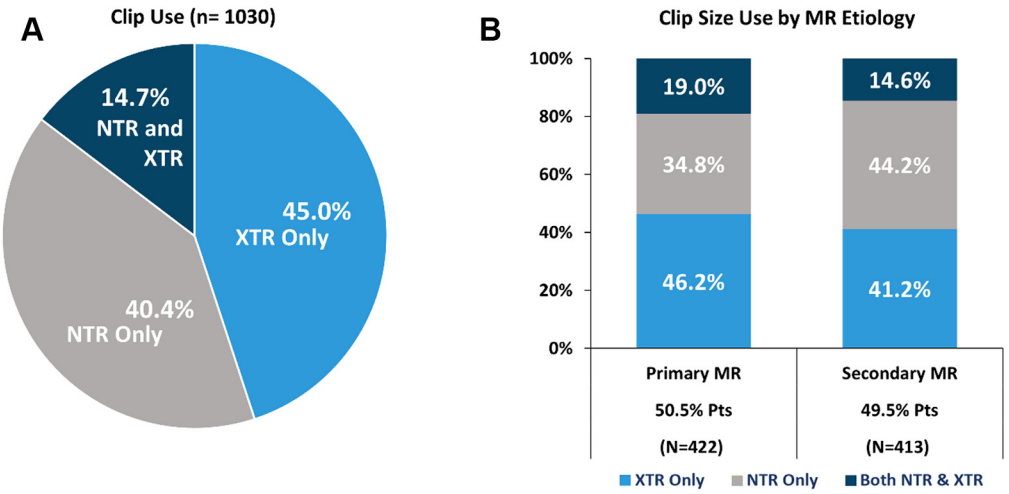
FIGURE 3 Clip Usage in EXPAND



Summary of study subjects treated with 1 of 3 clip combinations (NTR-only: 1 or more NTR clip(s), XTR-only: 1 or more XTR clip(s), NTR and XTR: both NTR and XTR clips) with a successful implant **(A)**, and by mitral regurgitation (MR) etiology **(B)**. EXPAND = The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices.

respectively, had MR grade ≤1+ at 1 year. For those subjects where ECL assessed MR as 3+/4+ at baseline, MR grade ≤1+ and ≤2+ was achieved in 83.5% and 96.0%, respectively, in surviving patients with evaluable echocardiograms at 1 year (**Central Illustration**). Clip use was tailored to patients' individual anatomy. XTR applied more often to patients with larger gaps, larger MVs, and larger ventricles compared with NTR (**Table 3**). Despite differences in anatomies treated, MR reduction was significant, durable, and comparable between clip sizes. In PMR patients, XTR achieved more favorable MR reduction (at least 2 grades) in patients with more severe baseline MR, large prolapse gaps, and complex MR anatomies (Supplemental Figure 2). In SMR patients, there was no advantage of clip selection strategy to improve MR reduction. MR reduction was associated with significant reduction in LV volumes (end-diastolic volume reduction and end-systolic volume reduction from baseline through 1 year) (**Figure 5**). Importantly, there was a small but definite reduction in annular dimensions through 1 year (**Table 5**).

As expected, there were improvements in NYHA functional class and QoL (**Figure 6**). A total of 80.3% of surviving patients at 1 year were in functional class I/II, in comparison to only 21.5% at baseline ($P < 0.0001$). KCCQ overall summary scores improved significantly for the entire population. There was a similar improvement in QoL in both the PMR and SMR groups: +21.3-point improvement in PMR (51.6 ± 24.7 at baseline to 72.9 ± 24.7 at 1 year; $P < 0.0001$) and +22.0-point improvement in SMR (46.4 ± 24.1 at baseline to 68.5 ± 22.1 at 1 year; $P < 0.0001$).

HFH rate at 1 year was 18.9% for the overall population (**Figure 7A**). HFH rate was less frequent in PMR than SMR patients. Annualized HFH rate was 80% (745 HFH events per 934 patient-years) at 1 year before TEER vs 28% (251 HFH events per 887 patient-years) at 1-year post-TEER (relative risk [RR]: 0.37; $P < 0.001$). The reduction in the annualized HFH rate was consistent across both PMR (58% at 1 year before TEER vs 18% at 1-year post-TEER; RR: 0.33; $P < 0.001$) and SMR (108% at 1 year before TEER vs 38% at 1 year post-TEER; RR: 0.36; $P < 0.001$). All-cause mortality at 1 year (**Figure 7B**) was 14.9% in the overall population, with a higher mortality rate in the SMR group. Other important clinical event rates at 1 year included: MI in 1.2%, stroke in 1.7%, MV stenosis in 0.5%, and need for MV replacement surgery in 1.9% of patients (**Table 6**). An independent physician committee adjudicated all SLDA and leaflet injury events, and determined 4 subjects (0.4%) had a leaflet injury and 18 (1.7%) had an SLDA through 1-year follow-up. Among the 18 SLDA events, 10 were associated with

XTR use. The comprehensive assessment of the independent physician committee showed the following[12]:

1. Overall incidence of leaflet adverse events (leaflet detachment and injury) was low (2.0%) and occurred in 9 cases with NTR and 12 cases XTR;
2. Events seemed to be related to multiple grasping attempts, but not to MV complexity, and occurred both in PMR and SMR;
3. Leaflet injury was rare, occurred at implant time, and resulted in severe MR and surgical reintervention;
4. SLDA events occurred during implantation (n = 2), predischarge (n = 7), or at 30-day follow-up (n = 7) and were resolved with ≤2+ MR with subsequent deployment of additional implant in 75% of cases.

TABLE 3 Clip Usage by ECL-Assessed Mitral Valve Gradient and Baseline Anatomical Characteristics

	XTR Only (n = 463)	NTR Only (n = 416)	*P* Value
Preprocedure mitral gradient, mm Hg	2.26 ± 1.27 (298)	2.23 ± 1.22 (274)	0.755
Postprocedure (30-day) mitral gradient, mm Hg	3.49 ± 1.64 (353)	3.89 ± 3.52 (327)	0.059
Baseline MR severity			
1+	9.2 (37/401)	10.6 (38/360)	0.539
2+	31.9 (128/401)	40.0 (144/360)	0.020
3+	30.7 (123/401)	33.9 (122/360)	0.343
4+	27.7 (111/401)	15.6 (56/360)	<0.0001
EROA, cm^2	0.37 ± 0.22	0.31 ± 0.12	<0.0001
LVEF, %	51.2 ± 16.4	51.4 ± 15.7	0.884
LVEDV, mL	153.4 ± 74.4	141.6 ± 69.8	0.031
LVEDVi, mL/m^2	82.7 ± 37.6	77.5 ± 36.7	0.069
APSAD, mm	30.1 ± 5.1	29.1 ± 4.9	0.007
CCSAD, mm	29.9 ± 4.6	29.0 ± 5.0	0.019
Mitral valve complexity	18.5 (70/378)	16.4 (55/335)	0.462
Primary MR			
Leaflet prolapse	58.9 (83/141)	41.1 (58/141)	
A2 pseudoprolapse	44.1 (26/59)	55.9 (33/59)	
P2 prolapse	73.0 (54/74)	27.0 (20/74)	
Leaflet flail	64.4 (76/118)	35.6 (42/118)	
A2 flail	54.6 (12/22)	45.4 (10/22)	
P2 flail	69.0 (58/84)	31.0 (26/84)	
Prolapse gap, mm	4.2 ± 2.3	3.1 ± 1.6	0.006
Flail gap, mm	5.9 ± 3.1	4.5 ± 2.2	0.007
Secondary MR			
Leaflet tethering, n = 242	49.6 (120/242)	50.4 (122/242)	
Tethering location			
A2	49.2 (59/120)	50.8 (61/120)	
P2	48.7 (115/236)	51.3 (121/236)	
P3	61.8 (21/34)	38.2 (13/34)	
Coaptation depth, mm	7.9 ± 2.6	7.1 ± 2.7	0.005
Coaptation length, mm	3.5 ± 1.5	3.4 ± 1.6	0.413
Tenting area, cm^2	1.60 ± 0.68	1.46 ± 0.71	0.07

Values are mean ± SD (N), % (n/N), or mean ± SD.

APSAD = anterior-posterior systolic annular dimension; CCSAD = commissure-to-commissure systolic anterior dimension; LVEDVi = left ventricular end-diastolic volume index; other abbreviations as in Table 2.

DISCUSSION

This study represents the first contemporary report of an ECL-assessed and central events committee-adjudicated 1-year outcomes in subjects with both PMR and SMR treated with the third-generation NTR/XTR system in real-world practice. In contrast to previous postmarket registries lacking centralized data adjudication,[5-7] the EXPAND study ensured robustness of results by enrolling patients across global regions and using an independent clinical adjudication committee to adjudicate clinical events, a centralized ECL, and an independent expert panel to adjudicate leaflet adverse events. In this respect, EXPAND provides a large, contemporary dataset to evaluate real-world outcomes of TEER.

Results suggest the introduction of additional clip size and improvements in the delivery system in the hands of experienced operators in a contemporary setting contributed to a greater reduction in MR and improved clinical outcomes at 1 year across a broader range of MV anatomies compared with previous studies. The 1-year mortality rate of 14.9% in this study was lower than historical trials with a similar high-risk study population, 22.8% in the EVEREST II High Risk Registry.[16] The analysis results by etiology is an important aspect of this study. In SMR groups, the MR reduction and clinical outcomes were similar to historical trials. One-year mortality for SMR in EXPAND (17.7%) was comparable to COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) (18.8%) (Figure 8). On the other hand, in PMR patients, there was a greater reduction of MR compared with historical studies (EVEREST II) (Central Illustration). PMR patients had substantially lower all-cause mortality at 1 year in the EXPAND study (12.5%) compared with EVEREST II high-risk patients (23.8%) (Figure 8). These encouraging results, which were more pronounced in the PMR group, have prompted a new contemporary clinical trial comparing TEER to surgical repair.

In order to allow for meaningful comparisons, the same ECL and MR assessment methodology was

TABLE 4 Procedural Outcomes

	EXPAND	EVEREST II REALISM[3]	TVT Registry[9]	ACCESS-EU[7]
Implantation rate	98.9 (1,030/1,041) (98.1%-99.5%)	94.2 (592/628)	N/A	99.6 (565/567)
Acute procedural success	95.9 (983/1,026) (94.4%-97.0%)	84.1 (528/628)	91.8 (2,709/2,952) Site-reported	91 (514/565) Site-reported
Fluoroscopy time, min	17.2 [11.1-27.0]	33.0 [0-265]	N/A	25 [0-152]
Procedure time, min	80.0 [54.0-115.0]	126.0 [29-448]	N/A	100.0 [15-390]
Length of stay in hospital for index procedure, days	1.0 [1.0-4.0] (U.S. only)	2.0 [N/A-N/A]	2.0 [1.0-5.0]	6.0 [N/A- N/A]

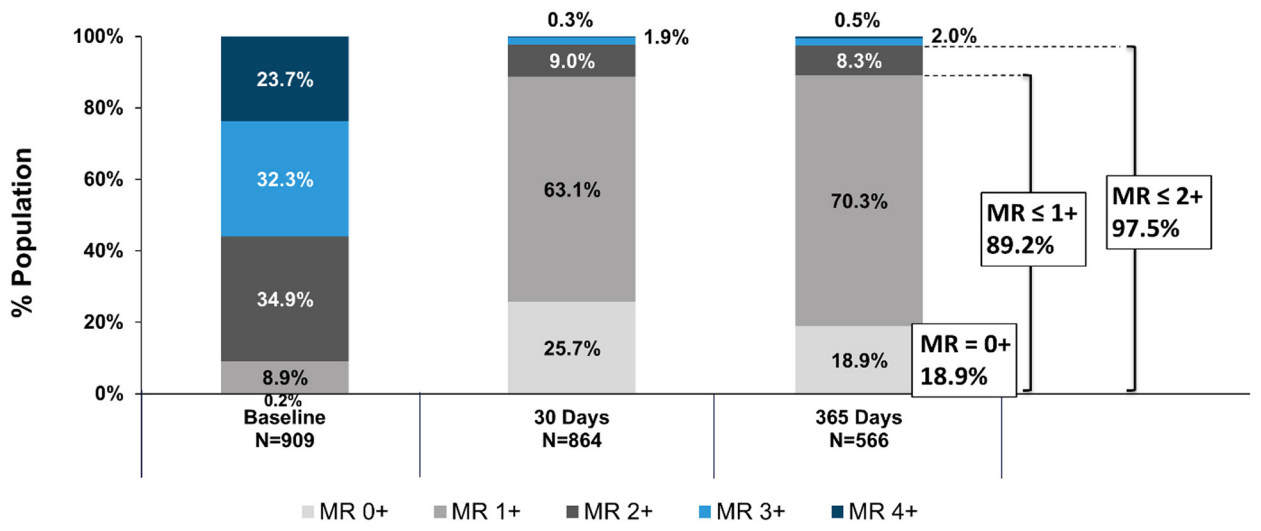
Values are % (n/N) (95% CI) or median [IQR]. Acute procedural success was defined as successful implantation with resulting MR severity of ≤2+ on discharge echocardiogram (30-day echocardiogram was used if discharge is unavailable or uninterpretable). Subjects who died or underwent mitral valve surgery before discharge were considered as an acute procedural success failure. MR severity for acute procedural success assessment was adjudicated by echocardiographic core laboratory. Note: Data are not from head-to-head studies. Data differences depicted between these trials may not be directly comparable, statistically significant, or clinically meaningful due to differences in trial protocols, endpoints, and/or patient populations. Data are provided for informational purposes only.

ACCESS-EU = ACCESS-Europe: A Two-Phase Observational Study of the MitraClip System in Europe; EXPAND = The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices; EVEREST II REALISM = Real World Expanded Multicenter Study of the MitraClip® System; TVT Registry = STS-ACC Transcatheter Valve Therapy Registry.

utilized in EXPAND as in earlier EVEREST and COAPT trials. We reported MR results for the overall population as well as subjects with baseline MR ≥3+. We observed 83.5% of subjects had MR ≤1+ at 1 year, which is numerically higher than the previous ECL-adjudicated studies (Central Illustration).[2,3,5] These results highlight the advancement in TEER therapy over the past 16 years. In fact, TEER may be comparable to contemporary surgical repair in achieving sustainable MR reduction, considering a recent study reported approximately 80% of patients who underwent MV surgery alone had MR of ≤1+ at 1 year.[15]

Contemporary procedural outcomes with the third-generation system significantly improved since the EVEREST II and REALISM (Real World Expanded

FIGURE 4 Change in MR From Baseline Through 1-Year Follow-Up



Significant mitral regurgitation (MR) reduction from baseline through 1 year was maintained; trace MR was achieved in 18.9%, MR ≤1+ in 89.2% and MR ≤2+ in 97.5% at 1-year follow-up.

CENTRAL ILLUSTRATION **Mitral Regurgitation Severity in EXPAND and Other Edge-to-Edge Repair Trials**

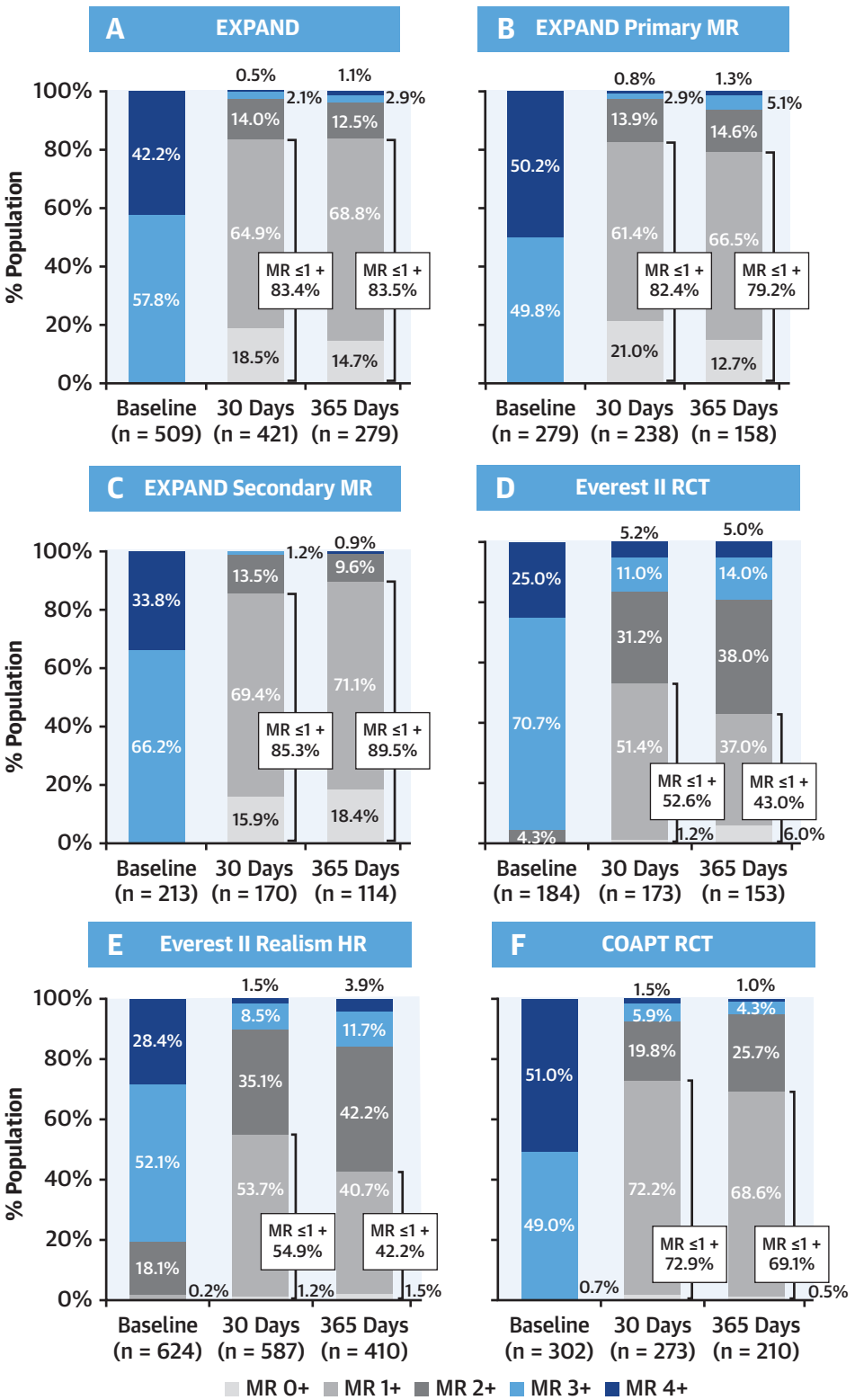


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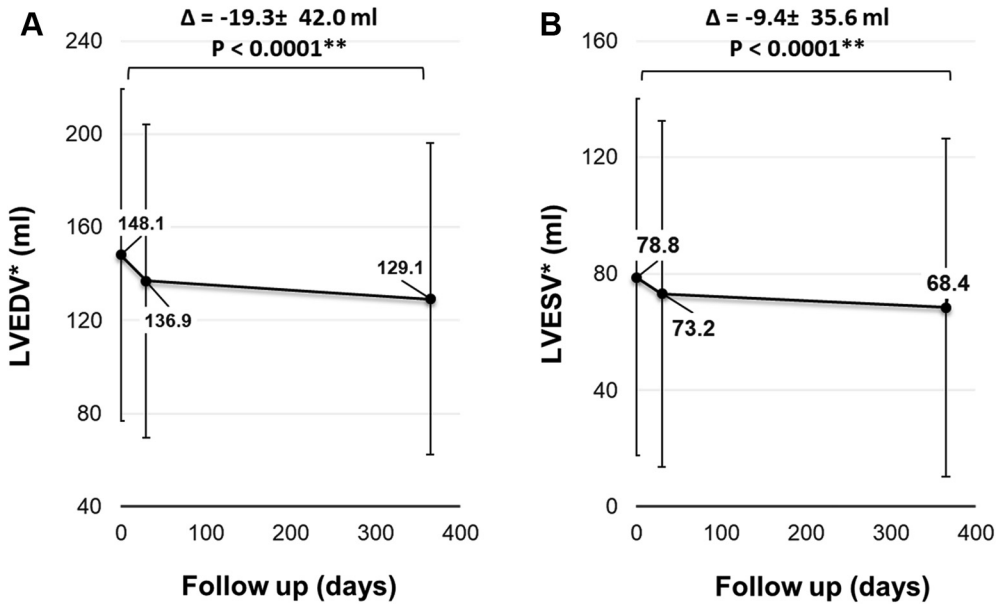
FIGURE 5 Left Ventricle Remodeling Postprocedure



Diastolic **(A)** and systolic **(B)** volumes reduced consistently and significantly from baseline through 1 year. **Data points** on the graphs represent mean value, and **error bars** correspond to ±SD at each follow-up time point. **P* values are the pairwise comparison between left ventricular end-diastolic volume (LVEDV) at baseline and 1 year (n = 445) and left ventricular end-systolic volume (LVESV) at baseline and 30 days (n = 445).

Multicenter Study of the MitraClip® System) studies. The successful implantation rate increased from 94.2% to 98.9%.[2,3] The acute procedural success was also improved from 84.1% in EVEREST II REALISM HR, 91.8% in TVT (STS-ACC Transcatheter Valve Therapy Registry), 91% in ACCESS-EU (ACCESS-Europe: A Two-Phase Observational Study of MitraClip System in Europe) to 95.9% in EXPAND.[3,7,9] Procedural efficiency improved with shorter procedural time (median of 126 minutes in EVEREST II REALISM HR and 100 minutes in ACCESS-EU to 80 minutes in EXPAND) (Table 4).

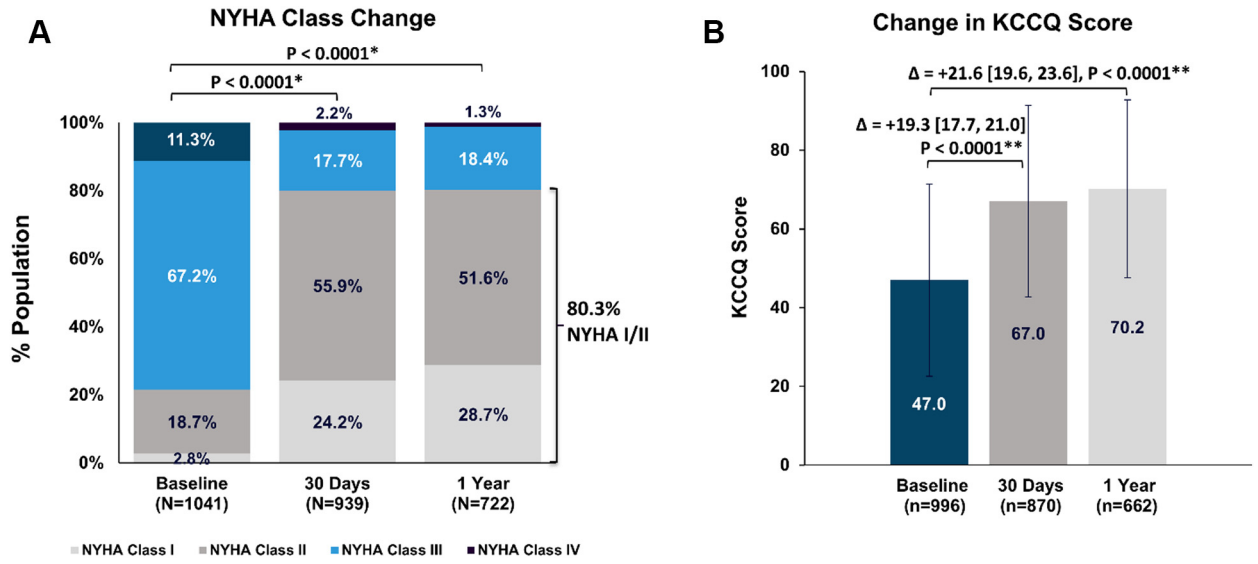
Collectively, the improvement in procedural and 1-year outcomes is likely a result of combination of factors, including increased operator experience since the original EVEREST trial, technological device improvements (more precise and predictable delivery and new clip size introduced with the third-generation), improvements in adjunctive imaging capabilities (eg, multiplanar TEE imaging), and the heart team approach (where surgeons, interventional cardiologists, and echocardiographers collaborate for better patient selection and treatment delivery).

Although previous EVEREST and REALISM studies included only noncomplex MV anatomies, EXPAND was an all-comer, real-world postmarket study and enrolled MR patients per local approved indications for use. Echocardiographic findings from EXPAND suggest nearly 1 in 5 patients treated with the third-generation clips had complex MV anatomies. The XTR clip with longer clip arms was widely adopted as the clip size of choice, particularly for PMR patients

CENTRAL ILLUSTRATION Continued

Echocardiographic core laboratory–adjudicated mitral regurgitation (MR) severity assessments across baseline, 30-day, and 1-year follow-up for EXPAND all subjects **(A)**, PMR **(B)**, and SMR **(C)**, with echocardiographic core laboratory–adjudicated baseline MR ≥moderate-to-severe (3+). MR reduction to ≤1+ at 1-year was achieved in 79.2% in primary MR, 89.5% in secondary MR subjects, and 83.5% of subjects overall in EXPAND (The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices), which is higher than that reported in historical trials: EVEREST II (Endovascular Valve Edge-to-Edge Repair Study)[1] **(D)**, EVEREST II REALISM HR[3] **(E)**, and COAPT RCT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation)[5] **(F)**.

FIGURE 6 Change in Quality of Life and Functional Capacity From Baseline Through 1 Year



Quality of life and functional capacity improvements using New York Heart Association (NYHA) functional class **(A)**, and Kansas City Cardiomyopathy Questionnaire (KCCQ) **(B)**. In **B, bars** represent mean KCCQ score, and **error bars** correspond to ±SD at each time point. **P* value calculated from Bowker test for comparing baseline to 30-day and to 1-year NYHA functional class. ***P* value calculated using paired *t*-test comparison between baseline to 30-day and 1-year KCCQ scores.

with larger prolapse and flail gaps, and larger annular and ventricular dimensions, and for SMR patients with significant leaflet tethering. Despite the use of the XTR clip with longer arms, there was no increase in adverse events nor postprocedural MV gradients. These results suggest that the third-generation system with 2 arm lengths has allowed operators to tailor the treatment strategy for the appropriate pathology and to safely treat a broader range of MV anatomies than previous EVEREST criteria.

TABLE 5 Left Ventricle and Mitral Valve Dimensions Through 1 Year

	Baseline	1 Year	*P* Value
LVESD, mm	41.6 ± 11.9 (474)	41.3 ± 12.7 (474)	0.3545
LVEDD, mm	56.0 ± 9.2 (480)	54.6 ± 10.1 (480)	<0.0001
APSAD, mm	29.7 ± 5.0 (469)	28.1 ± 4.7 (469)	<0.0001
APDAD, mm	32.9 ± 5.2 (472)	31.5 ± 5.1 (472)	<0.0001
CCSAD, mm	29.6 ± 5.0 (442)	27.0 ± 4.8 (442)	<0.0001
CCDAD, mm	32.3 ± 5.2 (442)	30.4 ± 5.3 (442)	<0.0001

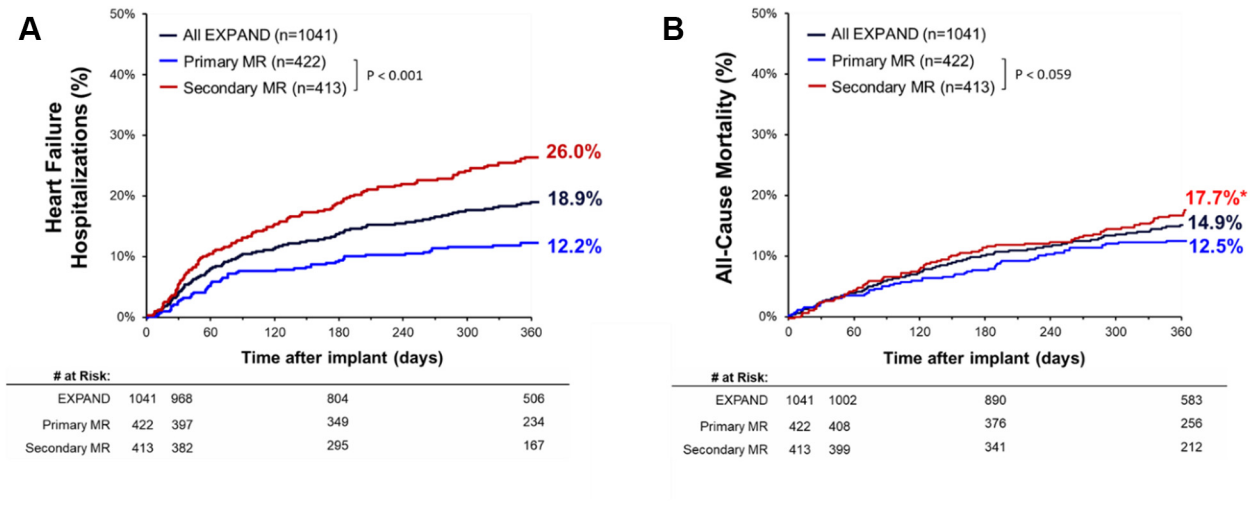
Values are mean ± SD (N). *P* values refer to pairwise comparison between baseline and 1 year for each parameter presented.

APDAD = anterior-posterior diastolic annular dimension; CCDAD = commissure-to-commissure diastolic anterior dimension; other abbreviations as in Tables 2 and 3.

The acute and sustained procedural success translated into significant reduction in MR and is associated with improvements in functional class and QoL, consistent reverse LV remodeling, and reduced hospitalization rates at 1 year. The stability of the MV annulus at 1 year may be an explanation of the low rate of recurrent MR in both PMR and SMR groups. Results confirm LV and MV annular dimensions were stable through 1-year follow-up visits, which supports the unique mechanism of action of the therapy that approximates MV leaflets forming a double orifice, consistently reduces LV dimensions, and stabilizes the MV annulus in the absence of a surgical ring.

STUDY STRENGTHS AND LIMITATIONS. It is both a strength and a limitation of the study that patient eligibility was based on site interpretation of MR severity rather than prospective review and approval by core lab following multiparametric ASE guidelines. Patients were enrolled based on sites' analysis of clinical findings, TTE, and TEE. A considerable number of patients were deemed by ECL to have moderate MR at baseline for several reasons. The ECL assessment of severity was based on the retrospective TTE only. It is well known that MR in patients with eccentric MR jets, especially arising from the commissures, can be underestimated by TTE and better

FIGURE 7 Heart Failure Hospitalizations and All-Cause Mortality Through 1 Year



Heart failure hospitalizations **(A)** and all-cause mortality **(B)** through 1-year follow-up for the EXPAND population, primary MR, and secondary MR groups. Event rates are Kaplan-Meier time-to-first event estimates. Abbreviations as in Figure 3.

visualized and quantified by TEE. For SMR, ECL reported only 52% of patients with MR ≥3+ vs 92% reported per EU guidelines, both at baseline. Many of the European investigators used the EU guidelines, which use different parameters for defining MR severity. Finally, the degree of MR can be dynamic, and the baseline images submitted to the ECL may reflect the severity at just 1 time point. These facts highlight the challenges in quantitative assessment of MR severity in current clinical practice and emphasize the importance of a central ECL for clinical trials to prevent interobserver variability. We accounted for the discordance by excluding EXPAND patients with MR ≤1+ at baseline when comparing MR severity assessments across baseline, 30 days, and 1 year to historical trials (**Central Illustration**).

Despite the discordance seen in baseline MR severity between sites and the ECL, clinical benefit was seen across the study population. We further analyzed the outcomes of patients with MR 2+ at baseline (Supplemental Table 1). In these patients, MR ≤1+ was achieved and maintained through 1-year follow-up in 95.8%, and the mortality incidence, MI, stroke, SLDA, clip embolization events at 30 days (1.6%-0%, 1.3%-0.3, 0%, respectively) were similar to baseline MR 3+/4+ patients.

These findings prove that treatment of a patient should be based on a comprehensive analysis of clinical findings and imaging results rather than a single echocardiographic parameter.

It is worthwhile to note that the real-world nature of the EXPAND study also resulted in variability in the completeness of follow-up visits, primarily due to the COVID-19 pandemic, and the quality of echocardiographic acquisitions; hence, certain measurements were not available for all patients.

TABLE 6 1-Year Adverse Events

	EXPAND (n = 1,041)	PMR (n = 422)	SMR (n = 413)
All-cause mortality	14.9 (147)	12.5 (51)	17.7 (68)
MI	1.2 (12)	0.7 (3)	1.5 (6)
Stroke	1.7 (18)	2.4 (10)	1.2 (5)
SLDA	1.7 (18)	2.4 (10)	1.9 (8)
Leaflet injury	0.4 (4)	0.5 (2)	0.5 (2)
MV stenosis	0.5 (5)	0.7 (3)	0.5 (2)
MV replacement surgery	1.9 (20)	2.1 (9)	1.5 (6)

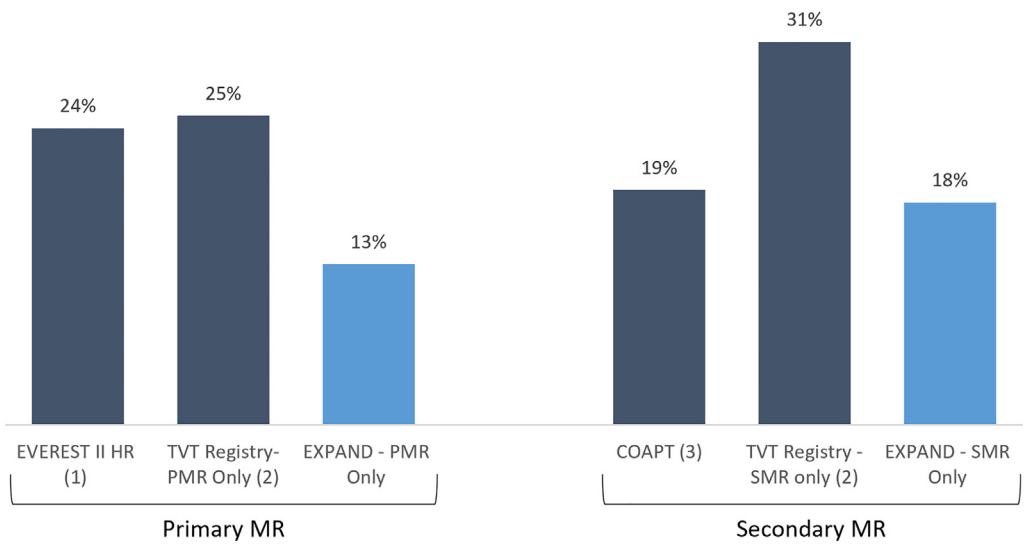
Values are % (n). Incidence rate and event count (in parenthesis) of site-reported adverse events through 1 year are shown. Single leaflet device attachment (SLDA) and leaflet injury events were adjudicated by an independent physician committee based on procedural and follow-up images, and clinical and surgical reports.

EXPAND = The MitraClip® EXPAND Study of the Next Generation of MitraClip® Devices; MI = myocardial infarction; MV = mitral valve; PMR = primary mitral regurgitation; SMR = secondary mitral regurgitation.

CONCLUSIONS

Overall, this study confirms that the third generation TEER in a contemporary setting leads to a greater reduction of MR, which resulted in significantly

FIGURE 8 1-Year All-Cause Mortality Rates Across Trials by Etiology



One-year mortality rate, particularly for primary mitral regurgitation (PMR), has been significantly lower in the contemporary settings than previously reported in approval studies or postmarket registries. (1) = Glower et al 2014,[16] (2) = Sorajja et al 2017,[9] and (3) = Stone et al 2018.[5] SMR = secondary mitral regurgitation; other abbreviations as in Figure 1.

improved outcomes in patients with a broad range of MV pathologies.

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PERSPECTIVES

WHAT IS KNOWN? TEER of PMR and SMR has been guided by the recommended patient selection established in historical trials with earlier generations of TEER devices (ie, EVEREST and COAPT). It was hypothesized that introduction of 2 different size clips along with improvements of delivery system would allow a more tailored therapy based on different MV pathologies that are much broader than that delineated by the restrictive criteria.

WHAT IS NEW? This study represents the first contemporary report of an ECL and central events committee adjudicated 1-year outcomes in subjects with both PMR and SMR treated with the third-generation NTR and XTR systems. Results suggest that introduction of additional clip size, XTR, and improvements in the delivery system in the hands of experienced operators in a contemporary setting resulted in greater MR reduction at 1 year across a broader range of MV anatomies, without an increase in adverse events. Clinical improvement was observed in both SMR and PMR subjects. Lower all-cause mortality rates associated with greater MR reduction was observed particularly in PMR subjects compared with historical controls.

WHAT IS NEXT? The encouraging results of this study has prompted a new prospective randomized clinical trial (MitraClip REPAIR MR study NCT04198870), comparing MitraClip TEER to contemporary surgical repair for moderate surgical risk degenerative MR patients. This single-arm postmarket study format will be used to evaluate future generation TEER devices in a broader population of patients that are often not included in randomized clinical trials.

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KEY WORDS MitraClip, mitral regurgitation, mitral valve repair, transcatheter edge-to-edge repair (TEER)

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