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RESEARCH ARTICLE

Transcatheter edge-to-edge repair for secondary mitral regurgitation with third-generation devices in heart failure patients – results from the Global EXPAND Post-Market study

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Aims Mitral valve transcatheter edge-to-edge repair is a guideline-recommended treatment option for patients with secondary mitral regurgitation (SMR). The purpose of this analysis was to report contemporary real-world outcomes in SMR patients treated with third-generation MitraClip systems.

Methods and results EXPAND is a prospective, multicentre, international, single-arm study with 1041 patients treated for mitral regurgitation (MR) with MitraClip NTR/XTR, with 30-day and 1-year follow-up. All echocardiograms were analysed by an independent echocardiographic core lab. Study outcomes included procedural outcomes, durability of MR reduction, and major adverse events including all-cause mortality and heart failure hospitalizations (HFH). A subgroup of 413 symptomatic patients (age 74.7 ± 10.1 years, 58% male) with severe SMR were included. MR reduction to MR ≤ 1+ and MR ≤ 2+ was achieved in 93.0% and 98.5% of patients, respectively, which was sustained at 1-year follow-up. All-cause mortality was 17.7% at 1-year- follow-up, and the combined endpoint of all-cause mortality or first HFH occurred in 34% of patients. This combined endpoint was significantly less frequently observed in MR ≤ 1+ patients (Kaplan–Maier estimates: 29.7% vs. 69.6% for MR ≤ 1+ vs. MR ≥ 2+; $p < 0.0001$). New York Heart Association (NYHA) functional class improved significantly from baseline (NYHA ≤ II: 17%) to 1-year follow-up (NYHA ≤ II: 78%) ($p < 0.0001$). While MR reduction was comparable between NTR-only vs. XTR-only treated patients, less XTR clips were required for achieving MR reduction.

Conclusions Under real-world conditions, optimal sustained MR reduction to MR ≤ 1+ was achieved in a high percentage of patients with third-generation MitraClip, which translated into symptomatic improvement and low event rates. These results appear to be comparable with recent randomized clinical trials.

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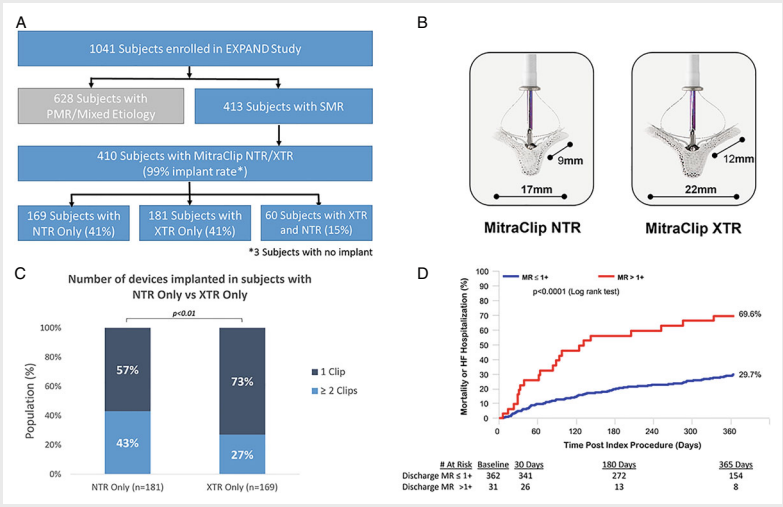
Graphical Abstract



(*A*) Subject consort diagram. (*B*) Illustrations showing MitraClip NTR, which is identical to the original MitraClip NT/classic clip, and MitraClip XTR, which has longer clip arms for easier grasp and better reach. (*C*) Number of devices implanted with NTR only and XTR only showing more single clip use when XTR is used. (*D*) Combined all-cause mortality and heart failure (HF) hospitalization through 1-year follow-up for the EXPAND SMR population as stratified by discharge residual mitral regurgitation (MR) >1+ and ≤1+ as assessed by echocardiography core lab; event rates are Kaplan–Meier time to first event estimates. PMR, primary mitral regurgitation; SMR, secondary mitral regurgitation.

Keywords MitraClip • Mitral valve transcatheter edge-to-edge repair • Transcatheter mitral valve repair • Mitral regurgitation • Secondary mitral regurgitation • Heart failure

Introduction

Mitral regurgitation (MR) is a major cause for valvular heart failure, causes substantial morbidity and mortality,[1,2] and in contrast to aortic valve disease, is significantly undertreated.[3] In particular secondary MR (SMR) poses a therapeutic challenge due to the underlying atrioventricular dysfunction which leads to progressive, mutual deterioration of left ventricular (LV) and valve function.[4,5] Recent advances in medical and transcatheter therapies are significantly enhancing our treatment options for SMR.[6,7] Eminently, the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation (COAPT) trial has shown that mitral valve transcatheter edge-to-edge repair (M-TEER) with the second generation of the MitraClip system improves prognosis and quality of life in heart failure patients with reduced LV ejection fraction (LVEF) and SMR.[8] Current technical development in the field of M-TEER aims at refining device design and expanding device sizes to further reduce MR and optimize procedural outcome in challenging mitral valve (MV) anatomies. These advances could translate into amelioration of heart failure symptoms and potentially improved prognosis in SMR patients, who would otherwise be denied M-TEER due to anatomic difficulties. Initial single-centre reports not explicitly distinguishing primary MR and SMR patients have indicated that different clip sizes are effective for MR reduction, with one study showing that larger clips could potentially cause more frequently leaflet injury.[9] The present investigation aimed to evaluate the real-world experience with two different sizes of the third generation of MitraClip devices in patients with SMR from the Global EXPAND study with centrally adjudicated clinical and echocardiographic outcomes.

Methods

Study design and patients

The Global EXPAND study (NCT03502811) is a post-market, prospective, observational, multicentre study of the commercially available third-generation MitraClip NTR and XTR M-TEER system. The EXPAND study was conducted in accordance with the principles of the Declaration of Helsinki, Good Clinical Practice, and regional clinical study guidelines. The study was approved by each local institutional review board and the health authorities of the participating centres. A minimum of 1000 consecutive consented subjects with symptomatic moderate-to-severe and severe primary MR or SMR (as assessed by the sites) were planned to be enrolled at up to 60 sites. Patients were enrolled in the study if they met the inclusion criteria: symptomatic severe MR and were eligible for M-TEER by the local investigator and Heart Team according to the approved MitraClip

indication for use in their country. All patients provided written informed consent prior to study enrolment.

Transcatheter edge-to-edge repair procedure

The procedure was performed under general anaesthesia. Each MitraClip was introduced via transfemoral venous access, through the interatrial septum into the left atrium and implanted into the MV by leaflet grasping to achieve MR reduction. The MitraClip NTR has a 9 mm arm length and 5 mm width, and the MitraClip XTR a 12 mm arm length and 5 mm width. The MitraClip XTR is equipped with six frictional elements instead of the previously four of the NTR. Clip selection guidelines generated by expert physicians on the EXPAND Steering Committee for this study recommended at least 6 mm of leaflet length for use of NTR and at least 9 mm of leaflet length for use of XTR (online supplementary *Table*). Other reasons for determining implant size selection for the first clip was mainly dependent on site assessment of anatomy, MR severity, MR aetiology and valve area.

Study endpoints and data adjudication

The primary endpoint was assessment of safety as a composite of major adverse events (MAEs) at 30 days, including all-cause death, myocardial infarction, stroke, or non-elective cardiovascular surgery for device-related complications. A Clinical Events Committee (CEC) centrally adjudicated all reported MAEs up to 30 days. Single leaflet device detachment (SLDA) and leaflet damage/injury reported up to 1 year were adjudicated by an independent physician committee.[10] Adverse events through 1 year were based on site reporting. Key performance measures include MR reduction to grade ≤2+ and grade ≤1+ at 30 days and 1-year follow-up. These endpoints were descriptively compared to outcomes from the landmark COAPT and Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation (MITRA-FR) trials.[8,11] MR severity and aetiology, and other echocardiographic parameters, at baseline and follow-up were assessed by an independent echocardiography core lab (ECL), in accordance with the chamber quantification and evaluation of valvular regurgitation guidelines.[12] Additional performance measures included acute procedural success defined as successful device implantation with resulting MR ≤2+ at discharge, and acute device success defined as successful device implantation without device-related complications such as device embolization, SLDA, bleeding, or perforation at discharge. Clinical and echocardiogram outcomes, improvement in New York Heart Association (NYHA) functional class and quality of life as assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ) score through 1 year are also reported in this study.

Statistical analysis

Continuous variables were presented as mean ± standard deviation (SD) or median with interquartile range (IQR). Categorical variables were presented as number and relative percentages. Paired analysis was performed using Student's *t*-test or Bowker's test as appropriate. Kaplan–Meier curves with log-rank test were used for all-cause death, first heart failure hospitalization (HFH), and combined all-cause death and first HFH analysis. The rate of HFH in the year before M-TEER and post procedure was compared with the Poisson regression model. Statistical analyses were performed using SAS version 9.4 (SAS Institute., Cary, NC, USA), and a *p*-value of <0.05 was considered statistically significant.

Results

Population and baseline characteristics

The EXPAND study enrolled a total of 1041 patients from 57 centres (22 sites in the USA; 35 in Europe) who underwent M-TEER. A total of 413 (US: 28%, Europe: 72%) patients were identified by the ECL to have SMR, and further analyses and results are based on these 413 patients. The mean age was 74.7 ± 10.1 years; 58% were men; mean EuroSCORE II was 9.8 ± 9.4 and STS repair score was 7.2 ± 7.3; chronic lung disease was present in 25% of patients, diabetes in 30%, and chronic renal failure in 47% (*Table 1*). The

Table 1 Baseline patient characteristics (*n* = 413)

Age, years	74.7 ± 10.1
Male sex	58.4% (241/413)
Body mass index, kg/m^2	26.04 ± 4.87 (411)
EuroSCORE II	9.83 ± 9.36 (234)
STS replacement score	8.83 ± 7.47 (261)
STS repair score	7.20 ± 7.34 (283)
Cardiac arrhythmia	68.8% (282/410)
Prior cardiac surgeries	34.9% (144/413)
Prior percutaneous coronary intervention	45.5% (184/403)
Permanent pacemaker	20.7% (85/410)
CRT	10.2% (42/410)
Previous ICD	37.0% (152/411)
Prior heart failure hospitalization within 1 year	64.8% (248/383)
Chronic lung disease	25.2% (100/397)
Diabetes	29.5% (120/407)
Renal failure	47.1% (192/408)
On dialysis/dialysis-dependent	4.7% (19/189)
Prior valve procedure	11.5% (47/410)
Prior MV procedure	27.7% (13/47)
MV repair – surgical	15.4% (2/13)
Mitral annuloplasty ring – surgical	7.7% (1/13)
MV transcatheter intervention	84.6% (11/13)
Prior AV procedure	70.2% (33/47)
Prior TV procedure	2.1% (1/47)
Medication data	
Beta-blockers	88.6% (366/413)
ACE inhibitors	37.8% (156/413)
Angiotensin receptor blockers	22.3% (92/413)
Mineralocorticoid receptor antagonist	36.6% (151/413)
Diuretic (any type)	85.7% (354/413)
Angiotensin receptor–neprilysin inhibitor	11.6% (48/413)
Functional class and QOL	
NYHA class ≤II	16.9% (70/413)
NYHA class ≤III	83.1% (343/413)
KCCQ score	43.7 ± 23.7 (389)

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; AV, aortic valve; CRT, cardiac resynchronization therapy; ICD, implantable cardioverter defibrillator; KCCQ, Kansas City Cardiomyopathy Questionnaire; MV, mitral valve; NYHA, New York Heart Association; QOL, quality of life; STS, Society of Thoracic Surgeons; TV, tricuspid valve.

majority of patients were in NYHA class III (69%) and IV (14%), with an impaired KCCQ score of 44 ± 24. A high proportion of patients were reported to be taking heart failure medications (*Table 1* and online supplementary *Table S2*): 88.6% (366/413) on beta-blockers, 37.8% (156/413) on angiotensin-converting enzyme inhibitors, 22.3% (92/413) on angiotensin receptor blockers, 36.6% (151/413) on mineralocorticoid receptor antagonists, and 85.7% (354/413) on diuretics (any type). An angiotensin receptor–neprilysin inhibitor was taken in 11.6% (48/413). A total of 37% (152/411) of patients had a previous implantable cardioverter defibrillator and 10.2% (42/410) reported to have cardiac resynchronization therapy.

Echocardiographic baseline characteristics

The ECL assessed that 92% of SMR patients had 3+ or 4+ MR as per European Society of Cardiology/European Association for Cardio-Thoracic Surgery (ESC/EACTS) guidelines[13]; 48.3% of SMR patients had 3+ or 4+ MR as per American Society of Echocardiography guidelines[12] (*Table 2*). Mean LVEF was 39.4 ± 13.5%, LV end-diastolic volume (LVEDV) was 181 ± 80 ml and LVEDV index was 97.5 ± 41.6 ml/m^2. Mean vena contracta and effective regurgitant orifice area (EROA) were 0.53 ± 0.13 cm and 0.30 ± 0.12 cm^2, respectively. At least moderate (≥2+) tricuspid regurgitation (TR) was present in 42% of patients. Echocardiographic systolic pulmonary artery pressure (Echo-SPAP) was 54 ± 15 mmHg.

Procedural characteristics

The implant rate was 99% (410/413 patients). Acute procedural success was achieved in 97% (399/410) of patients (*Table 3*). Mean procedure time was 86.8 ± 46.7 min. The XTR clip was exclusively implanted in 169 (41%) patients, NTR exclusively in 181 (44%) patients, while 60 (14.6%) patients received both XTR and NTR clips. In XTR-treated patients, 73% received one clip and 27% received two or more clips (*Graphical Abstract*). In patients treated with NTR device, 57% received one clip and 43% received two or more clips. Proportion of patients treated with one versus two clips was higher in XTR-treated patients than in NTR ($p < 0.01$). In 29.9% of cases, the leaflet length was the major criteria for selecting the first device size. XTR was selected as the first clip implanted in 56% (229/410) of subjects, whereas NTR was the first clip implanted in 44% (182/410). At discharge, 99% (389 of 393 patients with discharge assessment) had MR ≤2+, and 92% (362/393) had MR ≤1+.

Table 2 Baseline echocardiographic characteristics

MR parameters	
MR grades (ESC/EACTS guidelines)[a]	
2+: Moderate	7.5% (24/404)
3+: Moderate-to-severe	27.4% (113/404)
4+: Severe	64.8% (267/404)
Vena contracta, cm	0.53 ± 0.13 (297)
EROA (PISA), cm^2	0.30 ± 0.12 (298)
Regurgitant volume, ml	44.8 ± 19.4 (298)
MV and LV parameters	
MVA[b], cm^2	3.93 ± 1.16 (290)
MVA < 4 cm^2	56.2% (163/290)
MVA ≥ 4 cm^2	43.8% (127/290)
MPG, mmHg	2.11 ± 1.13 (286)
MPG ≤ 5 mmHg	96.9% (277/286)
MPG > 5 mmHg	3.1% (9/286)
LVEF, %	39.4 ± 13.5 (377)
Left ventricular end-systolic dimension, cm	4.98 ± 1.14 (393)
Left ventricular end-diastolic dimension, cm	6.07 ± 0.94 (396)
Left ventricular end-systolic volume, ml	115.6 ± 69.0 (378)
Left ventricular end-diastolic volume, ml	181.2 ± 80.4 (377)
Mean pulmonary artery pressure, mmHg	24.9 ± 9.2 (375)
Systolic pulmonary artery pressure, mmHg	54.4 ± 14.9(363)
Anterior posterior systolic diameter, cm	3.08 ± 0.48 (395)
Anterior posterior diastolic diameter, cm	3.40 ± 0.49 (396)
Lateral medial systolic diameter, cm	3.03 ± 0.46 (383)
Lateral medial diastolic diameter, cm	3.31 ± 0.49 (381)
Coaptation depth	
Mean, cm	0.76 ± 0.27 (373)
Coaptation depth ≤1.10 cm	89.0% (332/373)
Coaptation depth >1.10 cm	11.0% (41/373)
Coaptation length	
Mean, cm	0.35 ± 0.16 (341)
Coaptation length ≤0.2 cm	9.7% (33/341)
Coaptation length >0.2 cm	90.3% (308/341)
Tricuspid regurgitation	
None	6.8% (25/368)
Mild	51.1% (188/368)
Moderate	22.6% (83/368)
Severe	13.6% (50/368)
Massive	6.0% (22/368)

EACTS, European Association for Cardio-Thoracic Surgery; ECL, echocardiography core lab; ESC, European Society of Cardiology; EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; MR, mitral regurgitation; MV, mitral valve; MVA, mitral valve area; PISA, proximal isovelocity surface area.

[a]MR severity assessed by ECL based on 2017 ESC/EACTS guidelines.[13] Retrospective assessment of baseline MR by ECL according to the American Society of Echocardiography guidelines[12] was MR 1+: 9.2% (38/412), MR 2+: 42.5% (175/412), MR 3+: 33.0% (136/412), MR 4+: 15.3% (63/412).

[b]MVA was assessed per pressure half-time estimation.

Echocardiographic and clinical outcomes

Safety and performance evaluation

The safety endpoint of 30-day MAEs occurred in 3.6% (15/412). There were 11 cardiovascular deaths, one subject had ischaemic stroke and four patients underwent non-elective cardiovascular surgery for device-related complications, including for SLDA of NTR clip ($n = 1$), iatrogenic atrial septum defects that required closure ($n = 2$) and MV replacement ($n = 4$) (online supplementary *Table S3*). SLDA was confirmed in eight patients (1.9%), three with XTR and five with NTR: two reported during the procedure, three reported at discharge, and three reported at 30-day follow-up. Only one SLDA event resulted in a MAE as described, and the other cases were resolved with additional clip placement in an

Table 3 Procedure data and patient discharge status

MitraClip (n = 413)			
Acute procedural success			97.3% (399/410)
Implant rate			99.3% (410/413)
Acute device success			98.1% (405/413)
Device time, min			54.5 ± 39.9 (413)
Procedure time, min			86.8 ± 46.7 (413)
Fluoroscopy time, min			19.7 ± 12.0 (413)
Median (Q1, Q3)			16.7 (11.4, 25.0)
Length of stay in hospital for index procedure, days			7.8 ± 7.3 (413)
Post-procedure PACU/CCU/ICU duration, h			46.3 ± 64.7 (299)
MitraClip usage	**1 Clip**	**2 Clips**	**3 Clips**
XTR Only (41.2%, 169/410)	30.0% (123/410)	11.0% (45/410)	0.2% (1/410)
NTR only (44.1%, 181/410)	25.4% (104/410)	17.3% (71/410)	1.5% (6/410)
XTR and NTR (14.6%, 60/410)	0.0% (0/410)	10.5% (43/60)	4.1% (17/410)
Total usage	55.4% (227/410)	38.8% (159/410)	5.9% (24/410)

CCU, cardiac care unit; ICU, intensive care unit; PACU, post-anaesthesia care unit.

additional procedure to achieve residual MR ≤2+. Reduction to MR ≤2+ at 30 days was accomplished in 331 of 336 (98.5%) patients with echocardiographic follow-up. At 1-year follow-up, 99.6% (225/226) of the SMR patients had maintained MR ≤2+. In 93% of patients, MR grade was reduced to MR ≤1+ and sustained up to 1-year follow-up compared to baseline ($p < 0.001$) (online supplementary *Table S2*).

Clinical outcomes at 1-year follow-up

At 1 year, all-cause mortality was 17.7% (n = 68), and 26.0% of patients had HFH (*Figure 1A,B*). One year prior to M-TEER, 64.8% (248/383) of patients had HFH, with an annualized HFH rate reduction of 65% from 1.08 HFH/year before M-TEER to 0.38 after M-TEER ($p < 0.001$) (online supplementary *Figure Appendix S1*). The combined event rate of all-cause death or first HFH occurred in 133 (34.1%) patients at 1 year (*Figure 1C*). These event rates are comparable to the results from the COAPT trial and lower than in the MITRA-FR trial (online supplementary *Table S2*). Reduction to MR ≤1+ at discharge was associated with improved survival and freedom from first HFH at 1 year (*Figure 2*, *Graphical Abstract*). Patients with an EROA <0.3 versus ≥0.3 cm^2 had comparable mortality and HFH rates after M-TEER (online supplementary *Figure*).

The NYHA class improved in the majority of patients at 30 days (76% in NYHA class ≤ II, $p < 0.001$) and 12 months (78% in NYHA class ≤ II) compared to baseline ($p < 0.001$). The KCCQ score improved by a mean of 19 points at 30 days ($p < 0.001$) and 22 points at 12 months ($p < 0.001$) after M-TEER in surviving patients with follow-up. There was a decrease in beta-blocker use which was paralleled by an increase in mineralocorticoid receptor antagonist and angiotensin receptor–neprilysin inhibitor use (*Table 4*).

Procedure-related events at 1-year follow-up

Device- and procedure-related adverse events through 1-year follow-up occurred in 43 patients (10.4%). There were no reports of new leaflet-related adverse events at 1-year follow-up. Six patients underwent MV replacement (1.4%), and six patients needed repeat MV reintervention (online supplementary *Table S4*).

Echocardiographic outcomes at 1-year follow-up

A total of 285 of the 413 subjects completed 12-month follow-up visit with ECL assessment. At 1-year follow-up, MV area decreased by 28% (<0.001) and mean MV gradient increased from 2.0 ± 1.0 at baseline to 3.4 ± 3.2 mmHg after M-TEER ($p < 0.001$) (*Table 5*). Systolic anterior-posterior and lateral-medial MV diameters decreased by 5% and 8% ($p < 0.001$). LVEDV and LVESV progressively decreased by 11% and 12%, respectively (both $p < 0.001$), while LVEF remained at 40%. Mean pulmonary artery pressure decreased by 3.9 ± 1.2 mmHg ($p < 0.001$). The number of patients with at least moderate TR (≥2+) decreased significantly to 24% ($p < 0.001$).

Patients treated with NTR versus XTR device

The summary of baseline echo parameters of patients treated with NTR-only versus XTR-only clips are shown in *Table 6*. Baseline MR parameters were comparable between groups: vena contracta (0.53 cm for both, $p = 0.86$), EROA (0.29 vs. 0.30 cm^2, $p = 0.54$), regurgitant volume (46 vs. 44 ml, $p = 0.38$) and proximal isovelocity surface area (PISA) radius (0.70 vs. 0.72 cm, $p = 0.27$) for NTR-only vs. XTR-only. LVEF was lower in the XTR-only group (NTR-only vs. XTR-only: 41% vs. 38%, $p = 0.027$), while LV volumes and dimensions were larger in the XTR-only group (LVEDV NTR-only vs. XTR-only: 169.5 vs. 190.3 ml, $p = 0.023$; LVESV: 106.1 vs. 123.8 ml, $p = 0.022$; LVESD: 4.83 vs. 5.09 cm, $p = 0.043$).

While differences in clip usage were observed for LV size and function, clip use differed also for certain MV anatomical considerations. Larger coaptation depth (0.71 vs. 0.79 cm for NTR vs. XTR, $p = 0.005$) and tenting area (1.46 vs. 1.60 cm^2 for NTR vs. XTR, $p = 0.07$) showed the trend for usage of XTR in MV with more severe tenting. Mean MV area was 3.90 vs. 3.96 cm^2 for NTR-only versus XTR-only groups ($p = 0.73$) with a similar proportion of patients having a MV area ≥4 cm^2 in both groups (41% with NTR vs. 46% with XTR, $p = 0.39$). Mean MV gradient was 2.1 mmHg with NTR versus 2.1 mmHg with XTR ($p = 0.78$). MV annular dimensions were not different between groups. Baseline TR with at least moderate degree (≥2+) was also not significantly different between groups (NTR vs. XTR: 40.6% vs. 40.8%, $p = 0.9$).

No significant difference was seen in clinical outcomes at 1-year follow-up based on clip size used. Reduction to MR ≤ 2+ at 30 days was accomplished in 99.3% of NTR-only patients and 97.8% of XTR-only patients with echocardiographic follow-up. At 1-year follow-up, 100% NTR-only patients and 99.2% XTR-only patients had maintained MR ≤ 2+. In 98.1% of NTR-only patients and 88.5% of XTR-only patients, MR grade was reduced to MR ≤ 1+ at 1-year follow-up. All-cause mortality rate was 19.2%

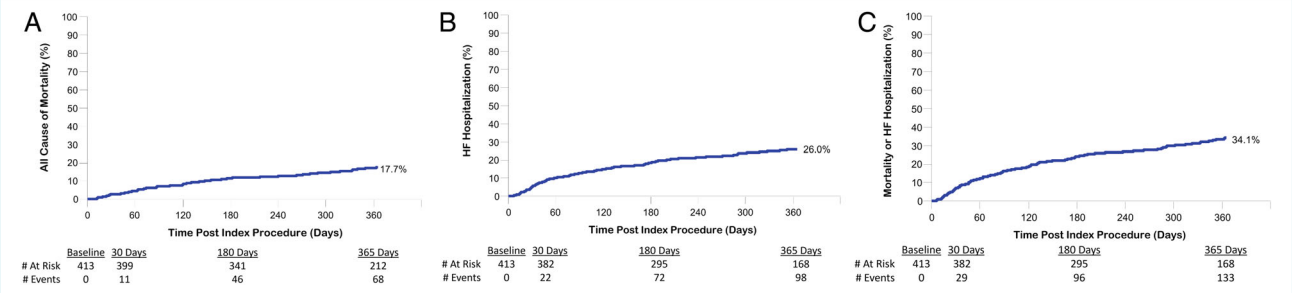


Figure 1 Clinical outcome after mitral valve transcatheter edge-to-edge repair. All-cause mortality (*A*), heart failure (HF) hospitalization (*B*), and combined all-cause mortality and HF hospitalization (*C*) through 1-year follow-up for the EXPAND secondary mitral regurgitation population. Event rates are Kaplan–Meier time to first event estimates.

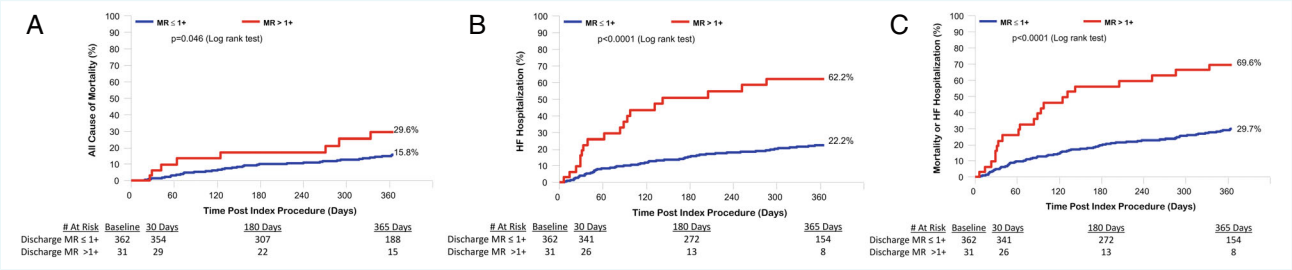


Figure 2 Clinical outcome after mitral valve transcatheter edge-to-edge repair according to echocardiography core lab assessed discharge mitral regurgitation (MR). All-cause mortality (*A*), heart failure (HF) hospitalization (*B*), and combined all-cause mortality and HF hospitalization (*C*) through 1-year follow-up for the EXPAND secondary MR population as stratified by discharge residual MR >1+ and ≤1+ as assessed by the echocardiography core lab. Event rates are Kaplan–Meier time to first event estimates.

versus 16.6% ($p = 0.54$) and HFH rate was 23.0% versus 28.1% ($p = 0.29$) in the NTR-only versus XTR-only clip use groups (online supplementary *Table S5*). Regardless of clip size used, a similar improvement was seen in NYHA functional class at 1-year follow-up (NYHA class ≤ II, NTR vs. XTR: 80.7% vs. 75.7%, $p = 0.64$) as well as quality of life (ΔKCCQ score, 20.5 ± 26.2 vs. 23.2 ± 25.6, $p = 0.42$). Use of either clip size resulted in significant reduction in anterior-posterior systolic and diastolic dimensions (APsys and APdia) from baseline to 1-year follow-up: (ΔAPsys: NTR: -0.17 ± 0.59 cm, $p = 0.005$; XTR: -0.13 ± 0.57 cm, $p = 0.014$; and ΔAPdia: NTR: -0.14 ± 0.64 cm, $p = 0.04$; XTR: -0.14 ± 0.57 cm, $p = 0.0071$). Reduction in LV volume at 1-year follow-up was comparable despite the differences in LV volume and dimensions at baseline: (ΔLVEDV; NTR: -25.2 ± 63.1 ml; XTR: -23.7 ± 43.9 ml, $p = 0.56$; and ΔLVESV: NTR: -17.6 ± 59.1 ml; XTR: -14.4 ± 39.7 ml, $p = 0.31$).

Discussion

This is the first and largest study to assess outcomes and echocardiographic characteristics in SMR patients treated with two different MitraClip sizes in a prospective trial with core-lab reviewed data. The EXPAND trial confirmed the safety and efficacy of both MitraClip sizes in patients with SMR. Clinical outcome including all-cause mortality and HFH were comparable in patients treated with either NTR or XTR device. Patients treated with NTR versus XTR devices differed primarily in left heart anatomy. The left ventricle was more dilated and LV function was more impaired in XTR-treated patients. Patients treated with the XTR clip had relatively larger coaptation depths and tenting, however, the observed difference in tenting area was not statistically significant.

Recently, M-TEER has become the guideline-recommended interventional therapy for patients with severe SMR and impaired LVEF <50% on top of guideline-directed medical therapy in the US. In Europe, M-TEER is also indicated as a class IIa guideline-recommended treatment for patients similar to the COAPT population and not eligible for surgery.[14] Since the majority of patients with SMR have LVEF <50% and/or are at high surgical risk, M-TEER has become a major pillar of valvular heart failure therapy for this vulnerable patient group in both the US and Europe. Notably, the decision to favour M-TEER is based on the positive outcome of M-TEER in the COAPT trial and the unsatisfactory outcome of surgical MV repair for this indication, with substantial MR recurrence even in low-risk patients in the latter case. With the projected further expansion in use of M-TEER comes the encounter of challenging anatomies in an expanding patient population, for which a single MitraClip size might not have been enough to achieve effective MR reduction. Therefore, availability of multiple device sizes offers a tailored approach for the treatment

Table 4 New York Heart Association functional class, Kansas City Cardiomyopathy Questionnaire score and medication baseline through 1 year

	Baseline	30 days	1 year
NYHA functional class			
I	1.2% (5/413)	17.1% (58/339)	22.5% (61/271)
II	15.7% (65/413)	59.0% (200/339)	55.4% (150/271)
III	69.5% (287/413)	21.5% (73/339)	19.2% (52/271)
IV	13.6% (56/413)	2.4% (8/339)	3.0% (8/271)
NYHA ≤II	16.9% (70/413)	76.1% (258/339)[a]	77.9% (211/271)[a]
NYHA ≤III	83.1% (343/413)	23.9% (81/339)	22.1% (60/271)
KCCQ score			
All available	43.7 ± 23.7 (389)	64.1 ± 23.9 (342)	68.3 ± 22.1 (258)
Paired baseline vs. 30 days	44.8 ± 23.4 (334)	64.2 ± 23.8 (334)	NA
Difference		19.5 ± 24.9 (334)[b]	
Paired baseline vs. 1 year	46.4 ± 24.1 (252)	NA	68.5 ± 22.1 (252)
Difference		22.0 ± 25.8 (252)[b]	
Medication data			
Beta-blockers	88.6% (366/413)		80.8% (227/281)
Mineralocorticoid receptor antagonist	36.6% (151/413)		44.5% (125/281)
Diuretic (any type)	85.7% (354/413)		87.5% (246/281)
Any ACE inhibitors, angiotensin receptor blockers, or angiotensin receptor–neprilysin inhibitor	71.7% (296/413)		74.0% (208/281)
ACE inhibitors	37.8% (156/413)		32.0% (90/281)
Angiotensin receptor blockers	22.3% (92/413)		20.3% (57/281)
Angiotensin receptor–neprilysin inhibitor	11.6% (48/413)		21.7% (61/281)

ACE, angiotensin-converting enzyme; KCCQ, Kansas City Cardiomyopathy Questionnaire; NA, not available; NYHA, New York Heart Association.
[a]Significant improvement in NYHA from Baseline to 30-days and baseline to 1-year, (Bowker's Test), p-value of <0.0001 for each comparison.
[b]Significant improvement in KCCQ score from baseline to 30 days and baseline to 1 year, $p < 0.0001$ for both comparisons.

Table 5 Echocardiographic outcomes at 1-year follow-up

Left ventricular parameters	Baseline	1 year	*p*-value
MVA, cm^2	3.9 ± 1.1 (121)	2.8 ± 1.0 (121)	<0.0001
MPG, mmHg	2.0 ± 1.0 (134)	3.4 ± 3.2 (134)	<0.0001
LVEF, %	40.2 ± 13.6 (207)	41.3 ± 14.0 (207)	0.19
Left ventricular end-systolic dimension, cm	4.97 ± 1.10 (216)	4.89 ± 1.26 (216)	0.16
Left ventricular end-diastolic dimension, cm	6.12 ± 0.92 (219)	5.94 ± 1.07 (219)	0.0007
Left ventricular end-systolic volume, ml	117.2 ± 72.9 (207)	101.5 ± 71.8 (207)	<0.0001
Left ventricular end-diastolic volume, ml	185.5 ± 84.1 (207)	161.0 ± 80.5 (207)	<0.0001
Mean pulmonary artery pressure, mmHg	24.2 ± 8.2 (182)	20.3 ± 7.0 (182)	<0.0001
Anterior posterior systolic diameter, cm	3.09 ± 0.49 (215)	2.94 ± 0.48 (215)	0.0002
Anterior posterior diastolic diameter, cm	3.39 ± 0.51 (216)	3.25 ± 0.51 (216)	0.0008
Lateral medial systolic diameter, cm	3.02 ± 0.49 (206)	2.77 ± 0.46 (206)	<0.0001
Lateral medial diastolic diameter, cm	3.31 ± 0.52 (203)	3.12 ± 0.52 (203)	<0.0001
Tricuspid regurgitation			
None	4.9% (9/183)	18.0% (33/183)	
Mild	55.8% (101/183)	59.0% (107/183)	
Moderate	20.9% (38/183)	15.0% (28/183)	<0.0001[a]
Severe	11.0% (20/183)	6.6% (12/183)	
Massive	7.2% (13/183)	1.6% (3/183)	

Paired analysis shown.
LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; MVA, mitral valve area.
[a]Bowker's test for comparison of tricuspid regurgitation ≥ 2+ vs. < 2+.

Table 6 Baseline echocardiographic characteristics of subjects treated with NTR-only versus XTR-only clip types

Baseline echo characteristics	NTR-only (n = 181)	XTR-only (n = 169)	p-value
MR (ESC/EACTS guidelines)[a]			
None	0.0% (0/176)	0.0% (0/168)	1.00
Mild	0.0% (0/176)	0.0% (0/168)	1.00
Moderate	6.3% (11/176)	6.5% (11/168)	0.91
Moderate-to-severe	31.3% (55/176)	25.0% (42/168)	0.20
Severe	62.5% (110/176)	67.9% (114/168)	0.30
Vena contracta, cm	0.53 ± 0.13 (121)	0.53 ± 0.13 (127)	0.86
EROA, cm^2	0.29 ± 0.10 (128)	0.30 ± 0.13 (126)	0.54
Regurgitant volume, ml	45.5 ± 18.5 (128)	43.3 ± 20.4 (126)	0.38
PISA radius, cm	0.70 ± 0.17 (155)	0.72 ± 0.19 (139)	0.27
MVA, cm^2	3.90 ± 1.18 (126)	3.96 ± 1.15 (120)	0.67
MVA ≥4 cm^2	40.5% (51/126)	45.8% (55/120)	0.40
MPG, mmHg	2.1 ± 1.2 (120)	2.1 ± 1.1 (121)	0.78
Mean pulmonary artery pressure, mmHg	26.0 ± 9.5 (165)	24.4 ± 9.2 (154)	0.12
Coaptation depth, cm	0.71 ± 0.27 (161)	0.79 ± 0.26 (155)	0.005
Coaptation depth >1.1 cm	9.3% (15/161)	13.5% (22/156)	0.64
Coaptation length, cm	0.34 ± 0.16 (150)	0.35 ± 0.15 (142)	0.41
Coaptation length <0.2 cm	11.3% (17/150)	7.7% (11/142)	0.30
Tenting area, cm^2	1.46 ± 0.71 (169)	1.60 ± 0.68 (157)	0.07
LVEF, %	41.1 ± 14.2 (159)	37.7 ± 12.8 (160)	0.027
Left ventricular end-systolic dimension, cm	4.83 ± 1.09 (173)	5.09 ± 1.19 (162)	0.043
Left ventricular end-diastolic dimension, cm	5.97 ± 0.90 (173)	6.11 ± 0.98 (164)	0.17
Left ventricular end-systolic volume, ml	106.1 ± 68.2 (160)	123.8 ± 70.2 (160)	0.022
Left ventricular end-diastolic volume, ml	169.5 ± 78.6 (159)	190.3 ± 84.0 (160)	0.023
Left ventricular end-systolic volume index, ml/m^2	58.0 ± 36.8 (160)	66.4 ± 37.0 (159)	0.044
Left ventricular end-diastolic volume index, ml/m^2	92.9 ± 42.0 (159)	102.1 ± 42.8 (159)	0.055
Anterior posterior systolic annular dimension, cm	3.11 ± 0.47 (168)	3.07 ± 0.47 (166)	0.38
Anterior posterior diastolic annular dimension, cm	3.42 ± 0.49 (169)	3.38 ± 0.49 (166)	0.45
Tricuspid regurgitation			
None	6.9% (11/160)	7.2% (11/152)	0.90
Mild	52.5% (84/160)	52.0% (79/152)	0.93
Moderate	17.5% (28/160)	24.3% (37/152)	0.14
Severe	15.0% (24/160)	12.5% (19/152)	0.52
Massive	8.1% (13/160)	3.9% (6/152)	0.12
Baseline TR > moderate	23.1% (37/160)	16.4% (25/152)	0.14

Paired analysis shown, categorical using Chi-square test; continuous using t-test.
EACTS, European Association for Cardio-Thoracic Surgery; EROA, effective regurgitant orifice area; ESC, European Society of Cardiology; LVEF, left ventricular ejection fraction; MPG, mean pressure gradient; MR, mitral regurgitation; MVA, mitral valve area; PISA, proximal isovelocity surface area; TR, tricuspid regurgitation.
[a]MR severity assessed by echocardiography core lab based on 2017 ESC/EACTS guidelines.[13]

of MR as part of the comprehensive personalized heart failure therapy.

As such, the EXPAND trial results show that procedural MR reduction was extremely effective and associated with improved survival and freedom from first HFH after 1 year, with reduction to grade ≤ 1+ in 93% of patients sustained through 1-year follow-up. This percentage of patients with sustained reduction of MR ≤ 1+ is higher than both COAPT and MITRA-FR trial results.[8,11] Additionally, 97.3% of patients having received at least one device and achieved reduction to MR ≤ 2+ at discharge, a rate that was maintained at 30 days (98.5%) and 1-year follow-up (99.2%). This rate of MR reduction is remarkable, since the randomized MITRA-FR trial showed that <85% of patients had MR ≤ 2+ after 12 months, 95% in COAPT and >95% in the European Registry of Transcatheter Repair for Secondary Mitral Regurgitation (EuroSMR). As shown in COAPT and the EuroSMR registry, effective MR reduction with lowest possible residual MR is key to improve outcomes after M-TEER.[15,16]

Notably, the estimated 1-year mortality rate of EXPAND with 17.7% is comparable to COAPT (19%), MITRA-FR (24%) and EuroSMR registry (20%). The potentially lower mortality compared to MITRA-FR (24%) could be due to the procedural results in EXPAND and further emphasizes that MR reduction is strongly associated with mortality outcomes (*Graphical Abstract*). A contributor to this outcome could be the significant MR reduction in EXPAND, potentially achieved by individual device selection of either NTR or XTR clips. The option for device size selection based on individual patient anatomy was not available yet in COAPT,

MITRA-FR, or EuroSMR. Nevertheless, other contributors to mortality such as baseline characteristics and patient selection could have influenced outcomes of all studies.

Of relevance for the application of different clip sizes could be the reported association of usage of a larger device with more SLDAs and leaflet tears.[9] Leaflet adverse events within EXPAND have been further analysed by an expert panel.[10] Reassuringly, only two peri-procedural SLDA were reported, with further six SLDA through 30 days and no other leaflet related adverse events through 1 year. This 1.9% rate of SLDA is lower than the very early experience with different MitraClip devices reported before.[9,17] This could be due to the aetiology of SMR. In SMR, the prevalence of fragile and degenerative leaflets or extensive mitral annulus calcifications should be low. As such, the study by Doldi *et al.*[9] pointed at a potential effect in primary MR, not in SMR. Leaflet injury and SLDAs seem to be rather acute events, as both studies did not report any delayed SLDAs after 30 days.[9,17] The documented leaflet injuries and SLDAs occurred in a very early application phase after the XTR clip was available. Therefore, a steep learning curve could have contributed to the lower incidence of SLDAs in our subsequent study.

The majority of participating cardiac valve centres in this study had prior experience in characterizing SMR by comprehensive echocardiographic protocols and thus optimally treating SMR patients with M-TEER procedure. Therefore, these results might not be representative of the learning curve of centres starting their M-TEER programme. The growing operator experience over the years in addition to improved pre- and periprocedural imaging and careful patient selection are likely to have contributed to the procedural results in this trial. Another limitation of this study is the echocardiographic follow-up rate of 69%, which could have influenced the interpretation of results, however this follow-up rate is comparable to the COAPT trial. Lastly, definitions of severe SMR differ between both past and current European and US guidelines. This needs to be reflected if trial results are interpreted. The selection criteria for NTR and XTR implantation are still under investigation. The criteria recommended here by the EXPAND Steering Committee are based on expert knowledge. However, a recent echocardiographic analysis confirmed that the NTR clip is more suitable for smaller MV areas.[18] This supports the recommendation in this study to use the NTR clip if MV area is below 4 cm^2.

As expected, EXPAND results demonstrate that third-generation clip designs are effective treatment options in experienced heart valve centres for treatment of a variety of patient anatomies. Both the XTR clip and the NTR clip were implanted in comparable numbers of patients. Also, the combination of both clip designs was feasible in a substantial number of patients. Notably, if patients were treated with the NTR clip, almost 40% of them received ≥2 clips in contrast to only 27% of the XTR-treated patients receiving ≥2 clips. As shown by the echocardiographic differences between NTR- and XTR-treated patients, the implantation of larger clips in larger ventricular anatomies could overcome the potential challenges to achieve optimal SMR reduction with the smaller size first-generation clips. Currently, fourth-generation devices have been developed with wider clip arms and independent leaflet grasping, which are now in use for MR patients, but broad 1-year clinical data have not been gathered yet. This is in contrast to the large patient number presented here in this study.

This analysis represents ECL-assessed echocardiographic and clinical events committee-assessed clinical outcomes in patients with SMR treated with the third-generation MitraClip (NTR/XTR) system. Results from this real-world contemporary setting confirm that repair with either the NTR or XTR MitraClip alone or in combination is associated with a favourable safety profile and good clinical outcomes. The real-world efficacy of SMR treatment with MitraClip NTR/XTR was shown by MR reduction to grade ≤2+ in 99.6% of patients and reduction to grade ≤1+ in 93% of patients that sustained through 1-year follow-up. Moreover, these results show that continuous improvements in treatment of MR with M-TEER have been achieved since the introduction of the first-generation MitraClip. In experienced heart valve centres, NTR and XTR MitraClip devices extend the options for the heart team to achieve optimal procedural results in different SMR anatomies to assure prognostic benefit.

Supplementary Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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