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ORIGINAL ARTICLE

Safety and efficacy of MitraClip in acutely ill (NYHA Class IV) patients with mitral regurgitation: Results from the global EXPAND study

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Abstract

Aim Patients with severe mitral regurgitation (MR) and acute heart failure (HF) have refractory symptoms without adequate response to medical therapy. The objective of this analysis was to assess the impact of the MitraClip device in acutely ill HF patients, characterized by NYHA Class IV at baseline, in a real-world, contemporary setting.

Methods and results EXPAND was a prospective, multicenter, international study enrolling patients with MR who consented to receive the MitraClip System at 57 sites globally. The study outcomes included acute procedural success (APS), quality of life, heart failure hospitalizations (HFH), and all-cause mortality. The study population comprised 1,041 patients, with 118 patients having baseline NYHA Class IV, and 922 having baseline NYHA Class I/II/III. NYHA Class IV patients had a significantly higher rate of baseline co-morbidities and secondary MR aetiology compared with NYHA Class I/II/III patients. APS was achieved in 92.4% of NYHA Class IV patients and significant improvement in MR grade to ≤Mild (1+) in 90.7% of subjects at 30 days and 92.9% at 1 year was observed. 1-year-mortality was higher in the NYHA Class IV subjects compared with the NYHA Class I/II/III subjects (29.2% vs. 17.7%, $P < 0.01$). Significant improvement in functional capacity assessed by NYHA Functional Class and Quality of Life assessed through KCCQ score was observed. At 1 year, 72.6% of NYHA Class IV subjects improved to NYHA Class I/II and ΔKCCQ was 31.2 (24.1, 38.3) compared with baseline.

Conclusion In the prospective, real-world EXPAND study, MitraClip in patients with severe MR and NYHA Class IV was found to be safe and effective in treating MR, and significantly improving QoL and long-term clinical outcomes.

Keywords Mitral regurgitation; Mitral valve repair; Class IV heart failure

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Introduction

Heart failure (HF) is a major health problem that is characterized by the worsening of symptoms and clinical deterioration.[1] Due to the increase in life expectancy and the evolution of therapy, a higher proportion of patients reach a more advanced stage of disease.[2,3] The New York Heart Association (NYHA) Functional Class is based on the burden of HF symptoms and is known to be a marker of hospitalization, disease progression, and mortality in patients with chronic HF.[4] Patients with NYHA Class IV have refractory symptoms without an adequate response to the optimal

medical therapy and are poorly represented in clinical trials. Treatment of these patients is often more challenging due to co-morbidities, and possible side effects like hypotension, hyperkalemia, and renal failure.[5,6] Severe MR is a common complication in patients with ischaemic and other cardiomyopathies and is often associated with high morbidity and mortality.

One-fifth of patients with advanced HF have hemodynamically significant MR of at least moderate to severe.[7] Mitral valve surgery in these patients is often avoided due to frailty and as a result, they are treated conservatively. Transcatheter mitral valve repair (TMVr) with the MitraClip™ device (Abbott, Abbott Park, IL, USA) has evolved as a therapeutic alternative for patients with significant MR, of both degenerative and functional origin, and whose surgical risk is considered high or prohibitive.[8] TMVr showed an improvement in symptoms and quality of life (QoL) while significantly reducing heart failure hospitalizations (HFH) and mortality in patients with functional MR.[9–12] MitraClip intervention in acutely ill HF patients with severe MR has been shown to be safe and effective,[13,14] but such studies have been limited in size. Data from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) trial suggested that improved outcomes after MitraClip implantation was consistent in subjects belonging to all NYHA functional classes. However, MITRA-FR-like subjects may not benefit from intervention due to advanced HF. The current analysis assesses the impact of the MitraClip device in acutely ill HF subjects, characterized by baseline NYHA Class IV, in a real-world, contemporary setting.

Methods

Study design

EXPAND was a prospective, multicenter, single-arm, international, post-market, real-world, observational study. The trial was approved by the institutional review committee at each site, and all subjects provided written informed consent and were eligible to receive the MitraClip™ per the currently approved indications for use in their respective geographies. 1,041 consecutive subjects consented to receive the MitraClip NTR/XTR system at 57 sites in North America, Europe, and the Middle East from April 2018 to March 2019. Study physicians at each site recorded relevant clinical and demographic information on pre-specified forms for consecutive participants. Subjects received MitraClip per standard of care and clinical and echocardiographic echo-core-laboratory assessed follow-up occurred at baseline, discharge, 30-day, and 12 months. The outcome measures included MR severity, procedural outcomes, all-cause mortality, HFH, QoL assessed using the Kansas City Cardiomyopathy Questionnaire (KCCQ), and functional capacity assessed using NYHA class. The primary endpoint was MR Severity ≤2 + at 30-day follow-up. MR severity was assessed per ASE guidelines consistent with the methodology of prior MitraClip trials.[15] Acute Procedural Success (APS) was defined as the successful implantation of the MitraClip™ device with a resulting MR severity of 2 + or less on the discharge Echocardiogram per Echo Core Lab assessment. Subjects who died or underwent mitral valve surgery before discharge were considered to be an APS failure. NYHA Class IV was defined by the inability to perform any physical activity without symptoms of HF or as having symptoms of HF at rest.[16] One subject was excluded from the present analysis due to the absence of a baseline NYHA functional class. All echocardiographic data was assessed by an independent core laboratory (MedStar Health Research Institute, Washington DC, USA).

Statistical analysis

Analyses were performed by comparing subjects of baseline NYHA Class IV group with subjects of baseline NYHA Class ≤III. Subject characteristics were reported according to variable properties. Categorical variables were reported as n (%), and differences between subgroups were tested, when appropriate, using the chi-square test or Fischer's exact test. Continuous variables were reported according to their distribution. Those with a normal distribution were reported as mean (± standard deviation), and the differences between subgroups were tested using the student's T-test. Those without a normal distribution were reported as median (interquartile range), and the differences between subgroups were tested using the Mann-Whittney U test. Survival curves for time-to-event were constructed on the basis of all available follow-up data using Kaplan–Meier estimates and comparisons between subjects with baseline NYHA Class IV and baseline NYHA ≤Class III were performed using the log-rank test. Cox regression analysis was performed to identify the predictors for all-cause mortality through 1 year. Hazard ratios (HRs) and 95% confidence intervals (CIs) were calculated using Cox regression models. The independent association between baseline NYHA functional class and the risk for death at 1 year was further evaluated in multivariate Cox regression models. The multivariable model was created using stepwise model selection. Model selection criteria: variables were entered into the model at the $P < 0.25$ and were eligible for staying in the model at $P < 0.05$. Statistical analyses were performed using SPSS version 25.0. (IBM Corp. Released 2017. IBM SPSS Statistics for Windows, Version 25.0. Armonk, NY: IBM Corp.) and a P-value <0.05 was regarded as statistically significant.

Results

Of the 1,041 subjects who underwent a MitraClip procedure in the EXPAND study, 118 subjects had a baseline NYHA Class IV, 922 had a baseline NYHA Class of I/II/III, and 1 did not have a recorded baseline NYHA class (*Figure 1*). Baseline characteristics of the subjects with NYHA Class IV compared with the rest of the cohort are shown in *Table 1*. NYHA Class IV subjects were younger compared with subjects with NYHA Class I–III (74.7 vs. 77.6, $P = 0.008$), but had higher EuroScore II (8.04 vs. 4.87, $P = 0.002$), bleeding (19.5% vs. 10.4, $P = 0.004$), HFH rates in the previous year (70.1% vs. 50.6%, $P = 0.0003$), and other significant co-morbidities including prior cerebrovascular events, myocardial infarction, arrhythmia, renal failure, diabetes mellitus, and chronic lung disease. The baseline characteristics for subjects with NYHA Class IV stratified by MR Aetiology are shown in *Table 2*. Subjects with NYHA Class IV had higher rates of secondary MR aetiology

Figure 1 Study population. Distribution of subjects with NYHA Class IV and NYHA Class I/II/III in the EXPAND study.

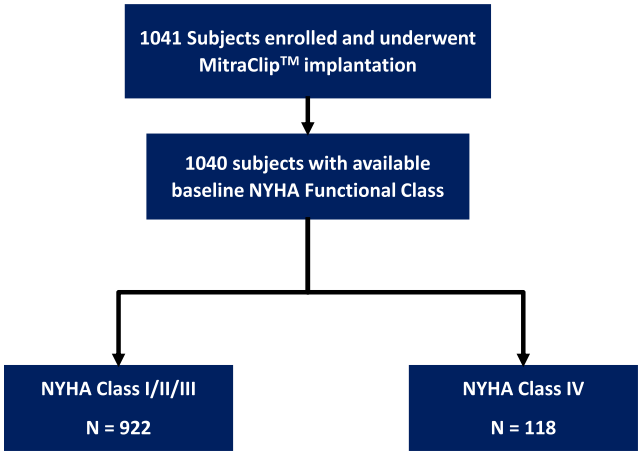


Table 1 Baseline characteristics

Demographics, co-morbidities, medical history	Baseline NYHA Class I/II/III ($N = 922$)	Baseline NYHA Class IV ($N = 118$)	*P*-value
Age (years)	77.6 (629)	74.7 (154)	0.01
Body mass index (kg/m^2)	25.79 (920)	26.72 (117)	0.07
EuroSCORE II	7.51 (466)	11.15 (73)	0.002
STS repair score	6.05 (651)	8.12 (83)	0.02
Prior CVA (%)	8.7 (79/905)	21.1 (24/114)	<0.0001
Prior myocardial infarction (%)	22.9 (205/897)	35.0 (41/117)	0.004
Cardiac arrhythmia (%)	63.8 (585/917)	74.6 (88/118)	0.02
Previous ICD (%)	17.6 (161/915)	27.4 (32/117)	0.01
Prior HFH within 1 year (%)	51.6 (426/826)	70.1 (75/107)	0.0003
Currently smoking (%)	4.9 (43/886)	15.0 (17/113)	<0.0001
Cachexia (%)	2.0 (18/915)	5.2 (6/116)	0.04
Diabetes (%)	24.5 (224/913)	32.2 (37/115)	0.08
Renal failure (%)	34.7 (318/916)	47.5 (56/118)	0.007
Dialysis dependent (%)	8.6 (27/314)	16.4 (9/55)	0.07
Chronic lung disease (%)	20.6 (184/895)	37.1 (43/116)	<0.0001
COPD (%)	75.8 (135/178)	79.1 (34/43)	0.65
Home oxygen (%)	18.0 (32/178)	35.9 (14/39)	0.01
Pulmonary artery pressure, mean (mmHg)	25.57 ± 10.04 (746)	25.85 ± 9.35 (98)	0.78
Pulmonary artery pressure, systolic (mmHg)	55.00 ± 15.89 (716)	56.47 ± 15.48 (99)	0.39
Severe pulmonary hypertension	46/925 (5.0%)	8/119 (6.7%)	0.38
NT-pro BNP (pg/mL)	5,915 ± 9,405 (342)	8,415 ± 8313 (48)	0.06
Peripheral arterial disease (%)	12.2 (107/876)	23.2 (26/112)	0.001
Prior bleeding (%)	10.4 (92/888)	19.5 (22/113)	0.004
Prior mitral valve procedure (%)	5.4 (50/918)	3.4 (4/118)	0.51
Prior aortic valve procedure (%)	9.6 (88/918)	5.9 (7/118)	0.24

Abbreviations: CVA, cerebro-vascular accidents; ICD, implantable cardioverter-defibrillators; HFH, heart failure hospitalization; COPD, chronic obstructive pulmonary disease.

Table 2 Baseline characteristics by MR aetiology

Demographics, co-morbidities, medical history	Subjects with DMR and NYHA Class IV	Subjects with SMR and NYHA Class IV	*P*-value
Age (years)	79.0 ± 10.4 (38)	71.4 ± 11.1 (56)	0.001
Body mass index (kg/m^2)	25.98 ± 4.61 (38)	25.98 ± 4.61 (38)	0.78
EuroSCORE II	8.50 ± 6.90 (23)	13.13 ± 10.44 (36)	0.05
Hypertension (%)	92.1% (35/38)	74.5% (41/55)	0.03
Cardiac arrhythmia (%)	84.2% (32/38)	69.6% (39/56)	0.11
Prior cardiac surgeries (%)	15.8% (6/38)	35.7% (20/56)	0.03
Prior cardiac interventions (%)	23.7% (9/38)	44.6% (25/56)	0.04
Previous ICD (%)	10.8% (4/37)	39.3% (22/56)	0.003
Prior HFH within 1 year (%)	55.9% (19/34)	81.1% (43/53)	0.01
Currently smoking (%)	5.6% (2/36)	22.6% (12/53)	0.02
Diabetes (%)	29.7% (11/37)	31.5% (17/54)	0.86
Renal failure (%)	42.1% (16/38)	46.4% (26/56)	0.68
Chronic lung disease (%)	29.7% (11/37)	45.5% (25/55)	0.13
Peripheral arterial disease (%)	17.1% (6/35)	32.1% (17/53)	0.12

Table 3 Echocardiography parameters

Echo measures	Baseline NYHA Class I/II/III (N = 922)	Baseline NYHA Class IV (N = 118)	*P*-value
EROA, cm^2	0.44 (324)	0.55 (31)	0.09
LVEF, %	52.01 (742)	46.79 (94)	0.003
LVESD, cm	4.14 (775)	4.54 (104)	0.005
LVEDD, cm	5.56 (780)	5.82 (104)	0.02
LVESV,mL	76.32 (743)	99.23 (94)	0.006
LVESVi, mL/m^2	41.18 (742)	53.65 (93)	0.007
LVEDV, mL	145.38 (742)	170.69 (94)	0.01
LVEDVi, mL/m^2	78.70 (741)	91.95 (93)	0.01
PMR (%)	55.3 (430/778)	41.0 (43/105)	0.006
SMR (%)	43.8 (341/778)	58.1 (61/105)	0.006

Abbreviations: EROA, effective regurgitant orifice area; LVEF, left ventricular ejection fraction; LVESD/LVEDD, left ventricular end systolic/diastolic dimension; LVESV/LVEDV, left ventricular end systolic/diastolic volume; LVESVi/LVEDVi, left ventricular end systolic/diastolic volume index; PMR, primary mitral regurgitation, SMR, secondary mitral regurgitation.

(58.1% vs. 43.8%, P = 0. 006), lower ejection fractions, (46.8% vs. 52%, P = 0.003), and significantly more dilated left ventricles at baseline (*Table 3*).

Immediate procedural success was high in all subjects but was slightly lower among subjects with NYHA Class IV (92.4% vs. 96.3%, P = 0.08). The duration of hospital stay after the index procedure was significantly higher in the NYHA Class IV group. Other procedural outcomes were similar between the study groups as shown in Supplementary *Table* S1.

In surviving NYHA Class IV subjects, clinical follow-up was available at 30 days in 95/103 (92.2%), and at 1 year in 62/81 (76.5%) subjects. Similarly, in surviving NYHA Class I/II/III subjects, clinical follow-up was available at 30 days in 843/899 (93.8%), and at 1 year in 659/802 (82.2%).

Significant improvement in MR grade was achieved and maintained through 1-year for all subjects irrespective of baseline NYHA Functional Class (*Figure 2*). NYHA Class IV subjects showed a significant improvement in MR grade to None/Trace (0) or Mild (1+) in 90.7% of subjects at 30 days and 92.9% of subjects at 1 year. Additionally, left ventricular end-diastolic volumes significantly decreased from baseline to 1 year (Degenerative MR (DMR) subjects: 127.7 ± 44.4 mL to 100.8 ± 35.3 mL, P = 0.02; Secondary MR (SMR) subjects: 193.0 ± 94.8 mL to 172.1 ± 86.1 mL, P = 0.001) (*Table 4*).

The MitraClip device resulted in a marked improvement in NYHA Functional Class and KCCQ Score at 1 year as shown in *Figure 3*. 72.6% of NYHA Class IV subjects were of NYHA Class I/II at 1 year ($P < 0.0001$, compared with baseline). Among subjects with baseline NYHA Class IV, the change in KCCQ from baseline to 1 year was +31.18 (24.06, 38.30) ($P < 0.0001$). Interestingly, NYHA Class IV subjects had numerically higher QoL improvement than Class III or less (+31.2 vs. +20.7) at 1 year, potentially attributed to the lower KCCQ score at baseline.

In-hospital mortality and 30-day mortality was 0.8% and 7.7% in the NYHA Class IV group and 0.0% and 1.6% in the NYHA Class I/II/III group, respectively. At 1 year, mortality and HFH were higher in NYHA Class IV subjects compared with NYHA Class I/II/III subjects as shown in *Figure 4* (Mortality: 32.4% vs. 12.7%, $P < 0.0001$; HFH: 29.2% vs. 17.7%, $P < 0.002$). A similar pattern was observed in NYHA Class IV and NYHA Class I/II/III subjects with primary and secondary MR, although, the impact of MR aetiology was higher in HFH rates than on mortality (*Figure 5*).

Predictors of all-cause mortality or HFH at 1 year are presented in *Table 5*. Outcomes of mortality or HFH at 1-year were significantly associated with discharge MR grade and left ventricular end-systolic volume ($P < 0.001$), and to a relatively lesser extent were associated with car-

Figure 2 Change in MR grade by baseline NYHA class. Significant improvement in MR grade was achieved and maintained through 1 year follow-up for all subjects, irrespective of the baseline NYHA class.

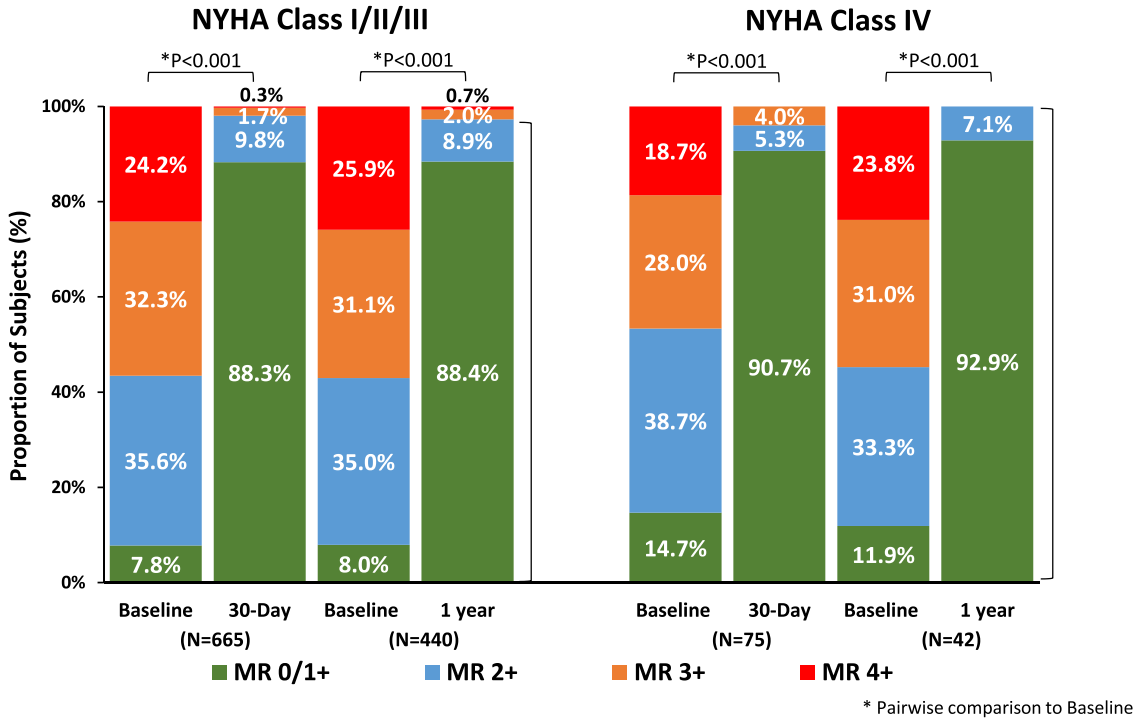


Table 4 Left ventricular measurements from baseline to 1 year

	NYHA Class IV			NYHA Class I/II/III		
Parameter	Baseline	1 year	*P*-value	Baseline	1 year	*P*-value
Primary MR aetiology						
LVEF, %	64.8 ± 8.4 (13)	57.0 ± 11.5 (13)	0.007	63.5 ± 8.0 (176)	62.1 ± 8.1 (176)	0.02
LVESD, cm	3.7 ± 0.8 (15)	3.8 ± 0.9 (15)	0.6	3.4 ± 0.7 (184)	3.4 ± 0.8 (184)	0.99
LVEDD, cm	5.4 ± 0.8 (15)	5.2 ± 0.7 (15)	0.05	5.1 ± 0.6 (186)	5.0 ± 0.7 (186)	0.0001
LVESV, mL	46.0 ± 22.4 (13)	44.7 ± 22.9 (13)	0.8	44.0 ± 22.2 (176)	39.6 ± 18.2 (176)	0.0001
LVEDV, mL	127.7 ± 44.4 (13)	100.8 ± 35.3 (13)	0.02	118.1 ± 43.0 (176)	103.4 ± 37.3 (176)	<0.0001
APSAD, cm	2.9 ± 0.4 (14)	2.8 ± 0.5 (14)	0.3	2.9 ± 0.5 (185)	2.7 ± 0.4 (185)	<0.0001
APDAD, cm	3.2 ± 0.4 (14)	3.3 ± 0.5 (14)	0.4	3.2 ± 0.5 (187)	3.1 ± 0.5 (187)	0.002
Secondary MR aetiology						
LVEF, %	35.5 ± 10.0 (18)	34.9 ± 14.4 (18)	0.8	40.6 ± 13.8 (189)	41.9 ± 13.9 (189)	0.2
LVESD, cm	5.2 ± 1.3 (21)	5.1 ± 1.5 (21)	0.7	5.0 ± 1.1 (195)	4.9 ± 1.2 (195)	0.2
LVEDD, cm	6.2 ± 1.2 (21)	6.1 ± 1.3 (21)	0.4	6.1 ± 0.9 (198)	5.9 ± 1.1 (198)	0.001
LVESV, mL	128.2 ± 73.3 (18)	120.3 ± 80.3 (18)	0.2	116.2 ± 73.0 (189)	99.7 ± 71.0 (189)	<0.0001
LVEDV, mL	193.0 ± 94.8 (18)	172.1 ± 86.1 (18)	0.001	184.8 ± 83.3 (189)	159.9 ± 80.1 (189)	<0.0001
APSAD, cm	3.0 ± 0.4 (21)	2.9 ± 0.5 (21)	0.4	3.1 ± 0.5 (194)	3.0 ± 0.5 (194)	0.0003
APDAD, cm	3.3 ± 0.4 (21)	3.2 ± 0.5 (21)	0.2	3.4 ± 0.5 (195)	3.3 ± 0.5 (195)	0.002

diac arrhythmias (P = 0.027) and baseline NYHA class (P = 0.053).

Discussion

Real-world outcomes with MitraClip in subjects with severe MR and NYHA Class IV HF are limited. The prospective, multi-centre, core-lab adjudicated, real-world EXPAND study included both primary and secondary MR subjects treated with MitraClip NTR and XTR Systems. The results suggest that the MitraClip procedure results in significant and durable MR reduction, and substantial clinical benefit based on significant improvement in QoL and symptoms for subjects with severe MR and NYHA Class IV HF. Baseline NYHA Class IV was associated with adverse outcomes; however, after adjusting for

Figure 3 NYHA class and KCCQ changes at 1 year.

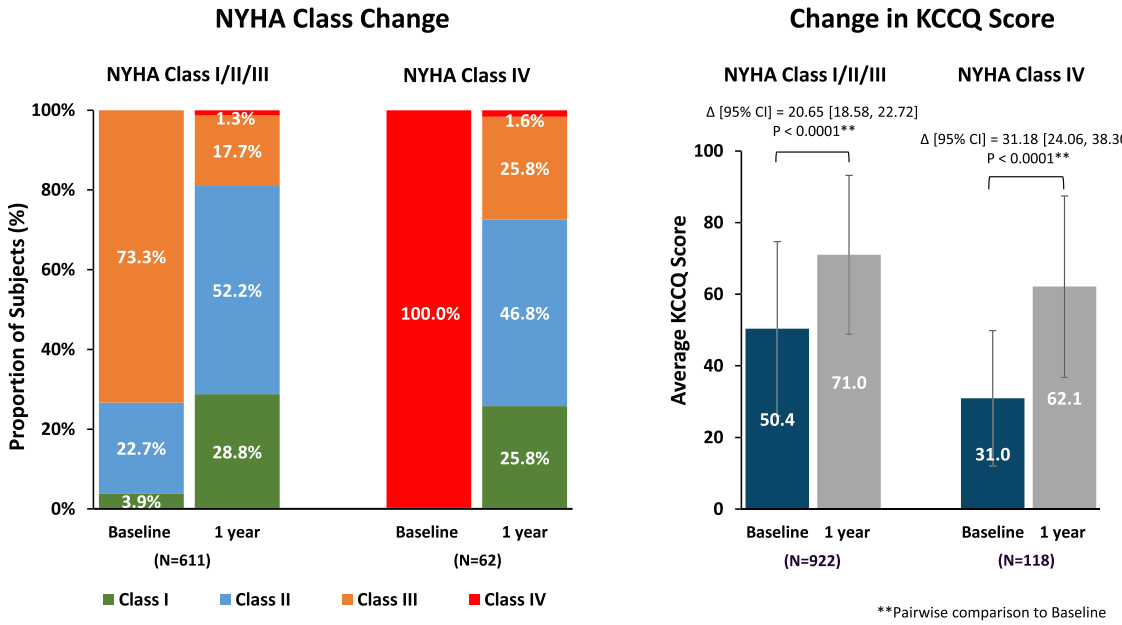
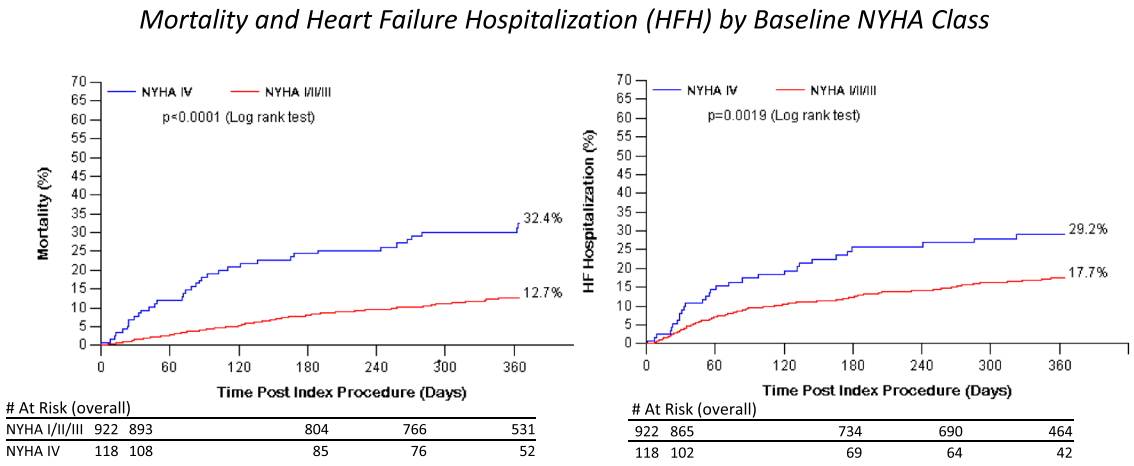


Figure 4 Clinical outcomes at 1 year. Mortality and heart failure hospitalization (HFH) by baseline NYHA class.



other factors, the efficacy of treatment with MitraClip (discharge MR), is more strongly correlated with clinical outcomes than the baseline NYHA class. However, one-year mortality and HFH rates were not neglectable in these acutely ill, NYHA Class IV subjects. Baseline NYHA class is known to be a marker of hospitalization, disease progression, and mortality in a wide spectrum of ambulatory subjects with chronic HF.[17]

NYHA Class IV includes subjects who were admitted with acute decompensated HF or ambulatory subjects with advanced symptoms due to end-stage chronic HF. Data from the ARIC (Atherosclerosis Risk in Communities) study suggest that patients with acute decompensated HF had a considerable burden of moderate or severe MR, which was independently associated with mortality 1 year after hospitalization.[18] Despite improved outcomes with the emerging mechanical circulatory support technologies, the management of this population is complex, and many patients are not suitable candidates for such therapy whereas others often need bridging therapies to reduce the worsening and progression of HF. Although severe MR is associated with

Figure 5 Clinical outcomes at 1 year by aetiology. Mortality and heart failure hospitalization (HFH) by baseline NYHA class and MR aetiology.

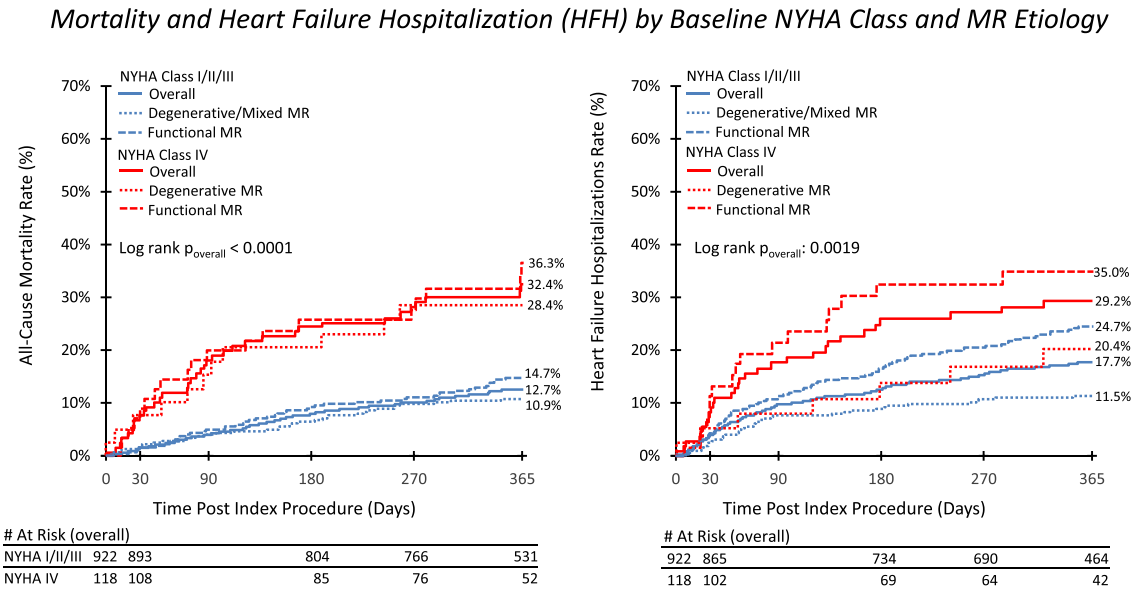


Table 5 Predictors of mortality or HFH at 1 year

	Univariable[a]		Multivariable[b]	
	Hazard ratio (95% CI)	*P*-value	Hazard ratio (95% CI)	*P*-value
NYHA IV vs. I/II/III	2.3 (1.7,3.1)	<0.001	1.7 (1.0,2.8)	0.05
Aetiology (DMR vs. FMR)	0.6 (0.4,0.8)	<0.001		
Discharge MR (≤1+ vs. ≥2+)	0.4 (0.3,0.6)	<0.001	0.4 (0.2,0.6)	<0.001
Left ventricular end systolic volume (mL)	1.0 (1.0,1.0)	<0.001	1.0 (1.0,1.0)	<0.001
STS repair	1.0 (1.0,1.0)	<0.001		
Implantable cardioverter- defibrillators	1.8 (1.4,2.4)	<0.001		
Renal failure	1.6 (1.2,2.0)	<0.001		
Cardiac arrhythmia	1.6 (1.2,2.0)	0.001	1.6 (1.1,2.4)	0.03
Cachexia	2.3 (1.3,4.1)	0.004		
Prior cardiac surgeries	1.4 (1.1,1.8)	0.005		
Diabetes	1.4 (1.1,1.9)	0.006		
Peripheral arterial disease	1.5 (1.1,2.0)	0.01		
Prior Myocardial Infarction	1.4 (1.0,1.8)	0.02		
Pulmonary artery pressure (systolic) (mmHg)	1.0 (1.0,1.0)	0.03		
Hypertension	1.4 (1.0,2.0)	0.04		
Prior cerebrovascular accidents	1.4 (1.0,2.0)	0.08		
Prior bleeding	1.3 (0.9,1.9)	0.1		
Chronic lung disease	1.2 (0.9,1.6)	0.2		
Age	1.0 (1.0,1.0)	0.2		

[a]Other metrics analysed in the univariate model included left ventricular end systolic/diastolic volume and diastolic dimension, septal lateral MV annulus dimension, MV area, mean mitral gradient, complex anatomy, MR jet velocity and VTI, MV peak E velocity, left ventricular ejection fraction, vena contracta, effective regurgitant orifice area, PISA radius, aliasing velocity, and regurgitant volume, pacemaker, prior transient ischaemic attack, dyslipidaemia, cancer, cirrhosis, prior valve procedure, prior cardiac interventions, and body mass index.
[b]The multivariable model was created using stepwise model selection. Model selection criteria: variables were entered into the model at $P < 0.25$ and were eligible for remaining in the model at $P < 0.05$.

poor prognoses in the HF population, it might also be a target for intervention in patients with chronic HF, as well as in patients with acute decompensated HF.

Beradini et al. evaluated 75 patients with secondary MR grade ≥3+ and end-stage HF treated with TMVr and showed improved symptoms and reduced re-hospitalization and pro-BNP levels at 6 months.[19] Godino et al. recently showed that the MitraClip procedure might serve as a bridge strategy to heart transplant in patients with advanced HF, and that two-thirds of patients remained free from adverse events at 1 year.[20] Recent subgroup analysis from the COAPT trial showed the prognostic utility of the NYHA functional class

in patients with HF, and the consistent benefit of MitraClip across patients with better or worse NYHA class. The mortality and HFH rates of NYHA Class IV patients in the MitraClip arm were 33.3% and 31%, respectively, which is similar to our findings and significantly lower compared with the outcomes with medical therapy alone.[21] Importantly, the EXPAND study had an all-comers population that included patients with primary MR, as well as non-ambulatory NYHA Class IV patients that were not included in the COAPT trial.

The clinical benefit of TMVr in non-ambulatory NYHA Class IV patients with refractory HF in the setting of cardiogenic shock that required salvage intervention was demonstrated in several small studies. The IRREMI registry evaluated patients with recent MI who developed acute MR and showed that TMVr is safe and effective, in patients with cardiogenic shock or with low ejection fraction.[22,23] Furthermore, TMVr was associated with lower in-hospital and 1-year mortality compared with conservative treatment or surgery.[24] Our data highlights the potential utility of the MitraClip TMVr technology in this acutely ill patient population including both primary and secondary MR subjects with otherwise limited treatment options. Interestingly the type of MR (primary or secondary) had a limited impact on mortality, but a significant impact on HFH after MitraClip. This finding might be related to the highly beneficial impact of MitraClip in NYHA IV patients with primary MR and preserved LV function. The lack of impact of MR aetiology on mortality might be related to other co-morbidities in this high-risk population. For example, the average age of patients with primary MR was around 80 years old, which may explain the improvement in HFH but not mortality in this group. This finding should be elaborated on in future TEER studies.

Among NYHA class IV patients, almost 80% had chronic obstructive pulmonary disease (COPD) and more than one-third required home oxygen. Importantly, the clinical symptoms and signs of advanced HF and chronic lung disease frequently overlap. Furthermore, the evaluation of cardiac and pulmonary function might be misleading. Although most NYHA Class IV patients had elevated BNP and their HF symptoms improved after MitraClip, it is plausible that at least part of their symptoms are attributed to lung disease rather than to HF. Therefore, proper management of concurrent COPD and HF is required.

Limitations

Although the EXPAND post-market study is the largest registry that evaluated the impact of TMVr among patients with NYHA Class IV, our results should be considered hypothesis-generating, and should be validated through additional clinical evidence, including randomized clinical trials, robust real-world evidence, etc., to determine the optimal treatment in this population. Second, subject allocation to each NYHA class may be biased due to clinical factors that affected physician decision-making. Third, the NYHA Functional Class assessment is a subjective assessment of patient symptoms and depends on physician interpretation. The heterogeneous NYHA Class IV group includes the elderly population with preserved LV function as well as the younger population with depressed LV function. Therefore, clinicians must carefully weigh the risks and benefits of each therapy to develop an optimal treatment strategy. There might also be advanced HF subjects similar to the MITRA-FR population who may not benefit from intervention. Fourth, the dyspnoea symptoms of the subjects may have been related to several factors, and not exclusively heart failure. Lastly, it should be acknowledged that TMVr procedures in the EXPAND study were performed at centers with experienced operators who can manage technically challenging cases due to the clinical condition of acutely ill patients.

Conclusion

Results from the EXPAND study demonstrate that TMVr is a safe and effective strategy to reduce MR and improve clinical outcomes in acutely ill HF patients with NYHA Class IV.

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Conflict of interest

Dr. Shuvy is a proctor and consultant for Abbott and Edwards Lifesciences. Dr. von Bardeleben has served in unpaid trial activities for Abbott, Edwards Lifesciences, University of Göttingen (IIT), and advisory or speaker bureau for Abbott Cardiovascular, Bioventrix, Boston Scientific, Cardiac Dimensions, Edwards Lifesciences, Neochord. Dr. Grasso serves as a proctor for Abbott, Boston Scientific, and has received fees as a speaker from Edwards Lifesciences. Dr. Raake has received speaker honoraria from Abbott. Prof. Lurz has served as a consultant, received institutional fees and research grants from Abbott, Edwards Lifesciences, Medtronic, ReCor, and Occlutech. Dr. Zamorano has received speaker honoraria from Pfizer, Amgen, and Daichii, and research grants from Abbott and Edwards Lifesciences. Dr. Asch has no personal disclosures. His work as the director of an Academic Core laboratory is through institutional research grants (MedStar Health) with Abbott, Boston Scientific, Medtronic, Edwards Lifesciences, Neovasc, Ancora Heart, Livanova, MVRx, InnovHeart, Polares medical, and Aria CV. Dr. Kar has received grants and institutional research support from Abbott, Boston Scientific, and Edwards Lifesciences, and consulting fees/honoraria from Abbott, Boston Scientific, W.L. Gore and Medtronic. Prof. Maisano has received a grant and/or institutional research support from Abbott, Medtronic, Edwards Lifesciences, Biotronik, Boston Scientific Corporation, NVT, Terumo. He received consulting fees, honoraria personal and institutional from Abbott, Medtronic, Edwards Lifesciences, Xeltis, Cardiovalve. He has received royalty income/IP rights from Edwards Lifesciences. He is a shareholder (including share options) of Cardiogard, Magenta, SwissVortex, Transseptal Solutions, Occlufit, 4Tech, Perifect. Dr. Lurz is a consultant for Abbott Vascular, ReCor, Edwards Lifesciences, and Medtronic. He has received institutional research grants from Abbott Vascular, ReCor, and Edwards Lifesciences.

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Supporting information

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

Table S1. Procedural Outcomes.

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