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MitraClip in secondary mitral regurgitation as a bridge to heart transplantation: 1-year outcomes from the International MitraBridge Registry

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BACKGROUND: Patients awaiting heart transplantation (HTx) often need bridging therapies to reduce worsening and progression of underlying disease. Limited data are available regarding the use of the MitraClip procedure in secondary mitral regurgitation for this clinical condition.
METHODS: We evaluated an international, multicenter (17 centers) registry including 119 patients (median age: 58 years) with moderate-to-severe or severe secondary mitral regurgitation and advanced heart failure (HF) (median left ventricular ejection fraction: 26%) treated with MitraClip as a bridge strategy according to 1 of the following criteria: (1) patients active on HTx list (in list group) ($n = 31$); (2) patients suitable for HTx but awaiting clinical decision (bridge to decision group) ($n = 54$); or (3) patients not yet suitable for HTx because of potentially reversible relative contraindications (bridge to candidacy group) ($n = 34$).
RESULTS: Procedural success was achieved in 87.5% of cases, and 30-day survival was 100%. At 1 year, Kaplan−Meier estimates of freedom from the composite primary end-point (death, urgent HTx or left ventricular assist device implantation, first rehospitalization for HF) was 64%. At the time of last available follow-up (median: 532 days), 15% of patients underwent elective transplant, 15.5% remained or could be included in the HTx waiting list, and 23.5% had no more indication to HTx because of clinical improvement.
CONCLUSIONS: MitraClip procedure as a bridge strategy to HTx in patients with advanced HF with significant mitral regurgitation was safe, and two thirds of patients remained free from adverse events at 1 year. These findings should be considered exploratory and hypothesis-generating to guide further study for percutaneous intervention in high-risk patients with advanced HF.
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Heart transplantation (HTx) is an effective therapeutic option for patients with advanced chronic heart failure (HF). However, increasing numbers of patients with refractory chronic HF and decreased availability of organs have resulted in expanded waiting lists and prolonged waiting times for patients listed for HTx.[1] More than 60% of patients are transplanted in high-urgency status[2] (Interagency Registry for Mechanically Assisted Circulatory Support [INTERMACS] profile 1 and 2), leaving little chance for patients listed for less urgent transplantation (INTERMACS profile 3−7); notably, the mortality rate on the Eurotransplant waiting list in 2019 was 13% at 1 year and 19% up to 3 years.[1] Despite pharmacological measures, several bridging therapies, including mechanical circulatory support, have been implemented during the waiting period to improve the general condition of patients by helping reverse worsening end-organ function[3] and preventing sustained ventricular arrhythmias.[4] Currently, limited data are available regarding the use of MitraClip in patients with significant mitral regurgitation (MR) and advanced HF waiting for heart transplantation.[5−10] The aim of this multicenter registry is to report on the safety and efficacy of the percutaneous MitraClip procedure as a bridge strategy to HTx in a larger number of patients with advanced HF and concomitant moderate-to-severe or severe secondary MR.

Methods

Registry study design

MitraBridge is a multicenter observational registry, including all consecutive patients with chronic advanced HF (defined as New York Heart Association [NYHA] III or IV and/or left ventricular ejection fraction [LVEF] ≤ 30% and according to the recently updated definitions proposed by the Heart Failure Association of the European Society of Cardiology[3]) and concomitant moderate-to-severe or severe secondary (or functional) MR being potential candidates for HTx. The registry was initiated in June 2018 without the support of any external funding and has been designed to collect data from centers with experience in transcatheter MitraClip treatment (Abbott Vascular, Santa Clara, CA). A total of 17 centers from Europe and Canada contributed to the registry. Baseline and follow-up data (the latter according to study centers' availability) were collected through the use of a prospectively maintained database. The inclusion of patients in this study was approved at each institution by a local ethical committee or per local practice for the collection of prospective data. This study is registered with ClinicalTrials.gov (NCT04293575).

Patient selection and definitions

All potential candidates for HTx treated with MitraClip in the context of a pre-specified bridge strategy were classified according to 1 of the following clinical conditions present at the time of MitraClip procedure:

1. patients active on an HTx list (in list group) with a low likelihood to receive an organ rapidly (e.g., for blood group) and/or progressive unstable clinical conditions;
2. patients with new unexpected clinical worsening and/or new history of acute HF decompensation, who were otherwise suitable for HTx (according to local heart team evaluation) but were still waiting for final clinical decision (bridge to decision [BTD] group); or
3. patients who could not be yet be listed for HTx (bridge to candidacy [BTC] group) because of concomitant, potentially reversible contraindications, such as severe pulmonary hypertension, elevated pulmonary vascular resistance, unsatisfactory response to vasodilator challenge or other causes resulting in a prohibitive periprocedural risk (e.g., pre-transplant body mass index

>35 kg/m^2, severe renal dysfunction with creatinine clearance <30 ml/min), and other reasons (current alcohol, tobacco, or drug abuse; poor social support; non-residents) (Figure 1). All patients were considered as high-risk surgical candidates because of advanced HF. Only patients with mitral valve anatomy suitable for percutaneous mitral valve repair using the MitraClip device were included. No exclusion criteria were applied according to baseline patient INTERMACS profiles. Grading of the severity of MR was assessed using a combination of semi-quantitative and quantitative assessment, as described by the American Society of Echocardiography guidelines and the European Association of Echocardiography guidelines.[11,12]

Study end-points

The primary end-point was the 1-year composite adverse events rate of all-cause death, urgent HTx or left ventricular assist device (LVAD) implantation, and first rehospitalization for HF. As secondary end-point, we included the rate of first rehospitalization for HF within the first year after MitraClip procedure. Moreover, we described the clinical status of patients at the time of last available follow-up to report the rates of patients entering (or remaining) in the waiting list, having no more indication to HTx because of significant echocardiographic and/or clinical improvements during the entire observational period, and going for elective HTx. Mitral Valve Academic Research Consortium criteria were used to define procedural success and composite events.[13] After the procedure, patients were prospectively evaluated at 1 month and 1 year and then according to the time frame elapsed from the index procedure to data lock for present analysis. For patients who underwent LVAD implantation, the follow-up time was stopped at the date of mechanical device placement.

Statistical analysis

Results are presented as mean ± SD for continuous variables normally distributed (tested by the Shapiro-Wilk normality test), as median (25th and 75th percentiles) for continuous variables without normal distribution, and as percentages for categorical data. One-way analysis of variance and Student's unpaired *t*-test were used to compare normally distributed continuous variables. For non-normally distributed continuous variables, the Kruskal-Wallis test and Wilcoxon rank-sum test were used to compare data between 3 or 2 groups, respectively. Chi-square and Fisher exact tests were used to compare categorical variables. Survival was reported using the Kaplan−Meier method, and comparisons were performed using the log-rank test. A two-tailed p-value < 0.05 was considered statistically significant. Univariate analysis of predictors of the primary end-point was performed with Cox proportional hazards regression. All variables with a p-value < 0.10 and those considered clinically relevant (age and estimated glomerular filtration rate) were inserted in a multivariate Cox regression model to assess the hazard ratio (HR) and 95% confidence interval (CI) of the relationship between predictors and primary end-point. The convention of limiting the number of independent variables to 1 for every 10 events was followed.[14] The statistical analysis, the Kaplan−Meier mortality curves, and the graphs were performed with the use of Stata version 14 (StataCorp LLC, College Station, TX) and GraphPad Prism software version 6 (GraphPad, Inc, San Diego, CA).

Results

Study population and demographics

In the MitraBridge registry, 119 patients with moderate-to-severe or severe secondary MR and advanced HF across 17 centers (in Italy, Switzerland, the Netherlands, Spain, and Canada) have been included. The median age of the treated population was 58 years (25th−75th percentile: 51−63 years), with 59% of patients ≤60 years old. Before MitraClip procedure, all patients were on guideline-directed medical therapy as tolerated (Table 1). Hospitalization for HF within the previous 6 months was reported in 61.5% of cases, with 36% of patients treated during rehospitalization with inotropic agents for circulatory support. Median N-terminal pro−B-type natriuretic peptide level at baseline was

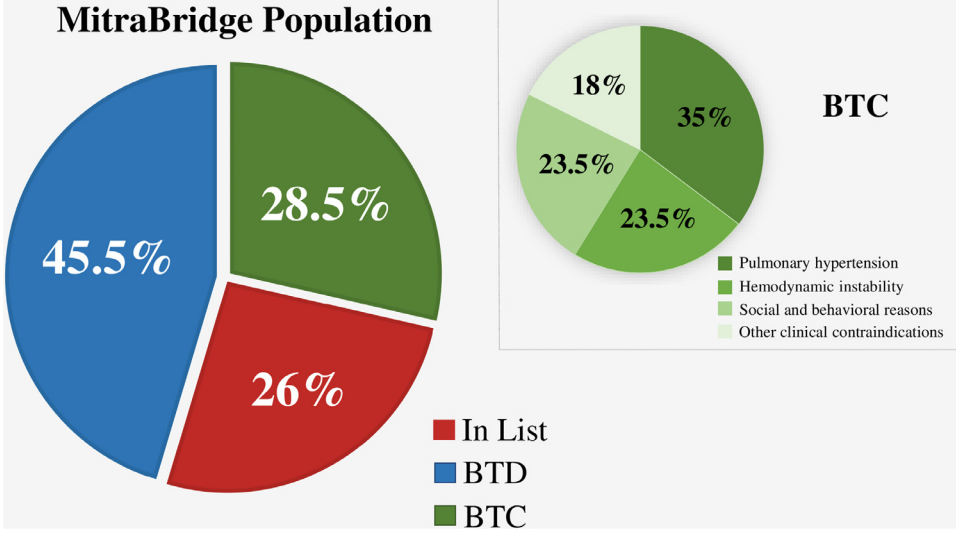


Figure 1 Clinical status according to heart transplantation list at the time of MitraClip procedure.
BTC, bridge to candidacy; BTD, bridge to decision.

3,612.5 pg/ml (25th−75th percentile: 2,182.5−7,043.5 pg/ml). At the time of MitraClip procedure, 31 patients (26%) were on the active HTx list (in list group), 21 of them with progressive deterioration of clinical status, needing 1 or more rehospitalizations for HF in the 6 months before the procedure, and 10 patients with a stable clinical condition but a low likelihood to receive an organ shortly because of heart size (4 patients) and blood group type (6 patients). A total of 54 patients (45.5%) were still waiting for final clinical decision (BTD group). Finally, 34 patients (28.5%) could not be yet be listed (BTC group) because of concomitant severe pulmonary hypertension and/or elevated pulmonary vascular resistance ($n = 12$), severe hemodynamic instability ($n = 8$; 2 patients with recurrent sustained

Table 1 Baseline Clinical Characteristics

Clinical characteristics	Overall($n = 119$)	In list($n = 31$)	BTD($n = 54$)	BTC($n = 34$)	p-value
Age, years	58 (51−63)	53 (43−61)	60 (55−64)	58.5 (43−63)	0.0016
Age ≤60 years	70 (59)	23 (74)	28 (52)	19 (56)	0.121
Male sex	91 (76.5)	25 (81)	41 (76)	25 (73.5)	0.790
BMI, kg/m^2	25 (23.4−28.4)	25.3 (23.4−28.4)	24.7 (23.4−28.4)	25.4 (22.5−28.7)	0.963
Hypertension	51 (43)	10 (32)	27 (50)	14 (41)	0.274
Diabetes	32 (27)	4 (13)	15 (28)	13 (38)	0.070
Hypercholesterolemia	62 (52)	17 (55)	28 (52)	17 (50)	0.926
eGFR, ml/min	67.1 (54−90)	71.7 (61.3−94.5)	59.5 (48.2−77.4)	76.4 (57−100)	0.052
eGFR ≤60 ml/min	43 (36)	6 (19)	27 (50)	10 (29.5)	0.011
Atrial fibrillation	42 (35)	17 (55)	14 (26)	11 (32.5)	0.025
COPD	10 (8.5)	1 (3)	5 (9)	4 (12)	0.388
NYHA class III−IV	113 (95)	27 (87)	53 (98)	33 (97)	0.065
Ischemic MR	57 (48)	12 (39)	28 (52)	17 (50)	0.485
INTERMACS profiles					0.288
1−2	4 (3.5)	0 (0)	3 (5.5)	1 (3)	
3−4	44 (37)	12 (39)	18 (33.5)	14 (41)	
5−6	52 (43.5)	16 (51.5)	20 (37)	16 (47)	
7	19 (16)	3 (9.5)	13 (24)	3 (9)	
EuroSCORE II, %	3.5 (2.6−6.2)	3.2 (2.2−7.1)	3.8 (3−7.5)	3.3 (2.3−4.8)	0.173
Past medical history					
Previous AMI	55 (46)	11 (35.5)	27 (50)	17 (50)	0.378
Previous PCI	46 (38.5)	11 (35.5)	21 (39)	14 (41)	0.894
Previous CABG	12 (10)	2 (6.5)	6 (11)	4 (12)	0.734
Previous stroke	9 (7.5)	2 (6.5)	6 (11)	1 (3)	0.356
HF hospitalization within previous 6 months	73 (61.5)	21 (68)	32 (59)	20 (59)	0.696
GDMT at baseline					
ACE-I/ARB	85 (71.5)	25 (81)	33 (61)	27 (79.5)	0.075
ARNI	18 (15)	6 (19)	11 (20.5)	1 (3)	0.063
Beta-blocker	106 (89)	31 (100)	45 (83.5)	30 (88)	0.060
Ivabradine	20 (17)	4 (13)	11 (20.5)	5 (14.5)	0.626
K sparing diuretics	102 (85.5)	27 (87)	45 (83.5)	30 (88)	0.779
Loop diuretics	113 (95)	29 (93.5)	51 (94.5)	33 (97)	0.771
ICD	91 (76.5)	28 (90.5)	33 (61)	30 (88)	0.002
CRT	45 (38)	13 (42)	23 (42.5)	9 (26.5)	0.271
Procedural outcomes					
Procedural success	104 (87.5)	28 (90.5)	50 (92.5)	26 (76.5)	0.072
N° clips					0.164
0	2 (1.5)	2 (6.5)	0 (0)	0 (0)	
1	38 (32)	8 (26)	20 (37)	10 (29.5)	
2	64 (54)	15 (48.5)	30 (55.5)	19 (56)	
>3	15 (12.5)	6 (19)	4 (7.5)	5 (14.5)	

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitors; AMI, acute myocardial infarction; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor neprilysin inhibitor; BMI, body mass index; BTC, bridge to candidacy; BTD, bridge to decision; CABG, coronary artery bypass grafting; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; GDMT, guideline-directed medical therapy; HF, heart failure; ICD, implantable cardioverter defibrillator; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; MR, mitral regurgitation; NYHA, New York Heart Association; PCI, percutaneous coronary intervention.

Data are presented as absolute numbers and percentages (for categorical variables) and median value and 25th and 75th percentiles (for continuous variables).

ventricular tachycardia, 5 patients with persistent unstable hemodynamic condition requiring mechanical circulatory support and/or infusion of vasoactive drugs, and 1 patient with repeatedly unsuccessful weaning from mechanical ventilation), other clinical causes making the peri-procedural risk prohibitive ($n = 6$; 1 patient with pre-transplant body mass index >30 kg/m^2, 1 patient with severe renal dysfunction, 2 patients with diabetes complicated by severe vasculopathy, and 2 patients with new-onset neoplasia awaiting prognostic definition and treatment), or social and behavioral reasons ($n = 8$; 5 patients for current alcohol or tobacco abuse, 2 patients because they were non-residents, and 1 for poor social support) (Figure 1). According to INTERMACS classification, most patients were in profile 3 to 4 (37%) and 5 to 6 (43.5%), whereas 4 (3.5%) patients were in profile 1 to 2, requiring mechanical and pharmacological circulatory supports (Table 1).

Echocardiography and right heart catheterization at baseline

All included patients had secondary MR owing to left ventricular dysfunction and remodeling. Median LVEF was 26% (25th−75th percentile: 20%−32%), and 71.5% of patients ($n = 85$) had an LVEF ≤30%. Median left ventricular end diastolic volume index (LVEDVi) and median left atrial volume index were 122.5 ml/m^2 (25th−75th percentile: 104.5−150.5 ml/m^2) and 59 ml/m^2 (25th−75th percentile: 38−78.5 ml/m^2), respectively, showing advanced left heart chambers remodeling. According to each study center's echocardiographic practice, a quantitative assessment of MR severity using the proximal isovelocity surface area radius method was available in 24.5% of patients ($n = 29$), with no statistical difference between the 3 groups: median effective regurgitant orifice area (EROA) and median regurgitant volume (RVol) were 30 mm^2 (25th−75th percentile: 25−40.5 mm^2, p-value = 0.563) and 41 ml/beat (25th−75th percentile: 30−55 ml/beat, p-value = 0.932), respectively. Right ventricle dysfunction (defined as tricuspid annular plane systolic excursion <17 mm) was observed in 28.5% of patients (overall tricuspid annular plane systolic excursion: 17 ± 4 mm). Median systolic pulmonary artery pressure (sPAP) was 48.5 mm Hg (25th−75th percentile: 40 −60 mm Hg) and 46% of patients had sPAP ≥50 mm Hg (Table 2). Pre-procedural right heart catheterization data were available for more than half of patients (65.5%), and they had homogeneous distribution within the study population (Table 2). Post-capillary pulmonary hypertension was the main pattern.

MitraClip peri-procedural results

No deaths occurred during the MitraClip procedure. Procedural success was achieved in 87.5% of cases, with a higher success in those on the HTx list (90.5%) and BTD groups (92.5%) than in BTC group (76.5%; $p = 0.072$). Two patients could not be implanted because of inadequate clip positioning and the unfavorable device trajectory in a giant left atrium, respectively (Table 1). The rate of 30-day mortality was 0%.

Clinical outcome

The clinical follow-up was available for 116 patients (97.5%), within an overall median follow-up time of 532 days (25th−75th percentile: 188−986 days). After the MitraClip procedure, 13 patients (11%) died (median time: 610 days; 25th−75th percentile: 230−1,089 days): cardiac death occurred in 9 (69%) patients, mainly HF (67%) and sudden death (33%); 4 patients died because of non-cardiovascular causes (31%); 1 patient died of septic shock; 1 patient died of cancer; and 2 died because of unknown causes. Urgent HTx was necessary in 7 patients (6%). LVAD implantation was performed in 21 patients (18%) (median time: 483 days, 25th−75th percentile: 66−743 days) because of MitraClip bridge therapy failure with progressive clinical worsening: 19 patients received LVAD as bridge therapy, whereas 2 patients, who belonged to the BTC group because of new-onset neoplasia and poor social support, finally received LVAD as destination therapy.

Elective HTx was successfully performed in 17 patients (15%) at a median time of 477 days (25th−75th percentile: 181−602 days) after the MitraClip procedure; all patients were stable on oral medications and able to wait at home. Of these, 8 patients were on the HTx list before MitraClip implantation, 5 patients belonged to the BTD group, and 4 patients were in the BTC group (Figure 2). Clinical information after the transplant was available in 9 of 17 cases, with a median follow-up time of 628 days (25th−75th percentile: 279−899 days). Three patients died because of acute heart transplantation adverse events (2 HTx rejections and 1 from infectious complications) and 1 patient died secondary to septic shock 305 days after the transplant; in the other 5 cases, patients were still alive with optimal hemodynamic and functional status (NYHA class I or II).

A total of 27 patients (23.5%) no longer had an indication for HTx because of significant clinical improvement: 5 of these patients belonged to the in list group (delisted for clinical improvement), the other 22 to the BTD ($n = 12$) and BTC ($n = 10$) groups. All of them had residual MR grade ≤2 and experienced significant reduction of NYHA functional class at follow-up; particularly, no patient was in NYHA functional class IV, and an improvement of at least 1 NYHA class was observed in 24 patients (89%). Hospitalization for HF in the 6 months before the MitraClip procedure occurred in 14 patients (52%), whereas in the 6 months after the procedure, only 1 (4%) patient has been rehospitalized ($p < 0.001$). The median LVEDVi and sPAP changed from 116 ml/m^2 (25th−75th percentile: 84−126 ml/m^2) to 107.5 ml/m^2 (25th−75th percentile: 80−126.5 ml/m^2; $p = 0.605$) and from 45 mm Hg (25th−75th percentile: 36−55 mm Hg) to 32 mm Hg (25th−75th percentile: 29−45 mm Hg; $p = 0.02$), respectively; values of LVEF remained stable, from 29% (25th−75th percentile: 25% −34%) to 29% (25th−75th percentile: 23%−36%; $p = 0.776$).

Table 2 Echocardiographic and Right Heart Catheterization Characteristics

Echocardiographic characteristics	Overall($n=119$)	In list($n=31$)	BTD($n=54$)	BTC($n=34$)	p-value
Mitral regurgitation					0.985
Moderate to severe (3+)	15 (12.5)	4 (13)	7 (13)	4 (12)	
Severe (4+)	104 (87.5)	27 (87)	47 (87)	30 (88)	
LVEF, %	26 (20–32)	24 (20–31)	24 (20–30)	28.5 (25–34)	0.076
LVEF ≤30%	85 (71.5)	23 (74)	41 (76)	21 (62)	0.332
LVEDVi, ml/m^2	122.5 (104.5–150.5)	121.5 (106–156)	126.5 (102–151)	118 (100–143)	0.634
LVESVi, ml/m^2	86 (71.5–112)	87.5 (82.5–109)	94 (72.5–121)	83 (60.5–103)	0.275
LVEDD, mm	71 ± 10	71.5 ± 8.5	71 ± 10	70.5 ± 11	0.912
LVESD, mm	61.5 ± 10.5	65 ± 10	62 ± 10	59 ± 11	0.146
LAVi, ml/m^2[a]	59 (38–78.5)	61.5 (23–77.5)	57 (38–79)	64 (51–79.5)	0.707
sPAP, mm Hg	48.5 (40–60)	55 (45–70)	45 (38–55)	48.5 (40–60)	0.029
sPAP ≥ 50 mm Hg	55 (46)	21 (68)	19 (35)	15 (44)	0.021
Tricuspid regurgitation > 2[a]	22 (18.5)	5 (16)	8 (15)	9 (26.5)	0.595
TAPSE, mm[a]	17 ± 4	17 ± 4	17.5 ± 4.5	17.5 ± 3.5	0.761
Basal RVD, mm[a]	37.5 ± 10	42 ± 9	40 ± 8	29 ± 9.5	<0.001
RH catheterization characteristics[b]	**Overall($n=78$)**	**In list($n=23$)**	**BTD($n=33$)**	**BTC($n=22$)**	**p-value**
Cardiac index, liter/min/m^2	1.9 (1.6–2.3)	1.9 (1.4–2.2)	2 (1.7–2.4)	1.9 (1.7–2.4)	0.505
Cardiac index <2 liter/min/m^2	47 (60)	16 (70)	18 (54.5)	13 (59)	0.524
Wedge pressure, mm Hg	26 ± 10	27 ± 7.5	27 ± 11.5	23 ± 9	0.248
Systolic PAP, mm Hg	52 ± 16	53 ± 12.7	48 ± 13.7	55.5 ± 21	0.373
Diastolic PAP, mm Hg	25 ± 7.8	27.5 ± 5	24 ± 7	24.2 ± 10	0.350
Mean PAP, mm Hg	34.5 ± 10	36 ± 7	32.5 ± 9	35 ± 13	0.631
Mean PAP ≥40 mm Hg	16 (20.5)	6 (26)	4 (12)	6 (27)	0.569
PVR, WU	3.06 ± 2.7	2.6 ± 1.2	2.1 ± 2.4	3.9 ± 3.5	0.234
PVRi, WU m^2	5.73 ± 5.5	4.8 ± 2.2	4 ± 4.6	7.4 ± 7.3	0.265
TPG >12 mm Hg	8 (10)	2 (8.5)	2 (6)	4 (18)	0.605

Abbreviations: BTC, bridge to candidacy; BTD, bridge to decision; LAVi, left atrial volume index; LVEDD, left ventricular end diastolic diameter; LVEDVi, left ventricular end diastolic volume index; LVEF, left ventricular ejection fraction; LVESD, left ventricular end systolic diameter; LVESVi, left ventricular end systolic volume index; PAP, pulmonary artery pressure; PVR, pulmonary vascular resistance; PVRi, pulmonary vascular resistance index; RH, right heart; RVD, right ventricular diameter; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary gradient; WU, Wood unit.

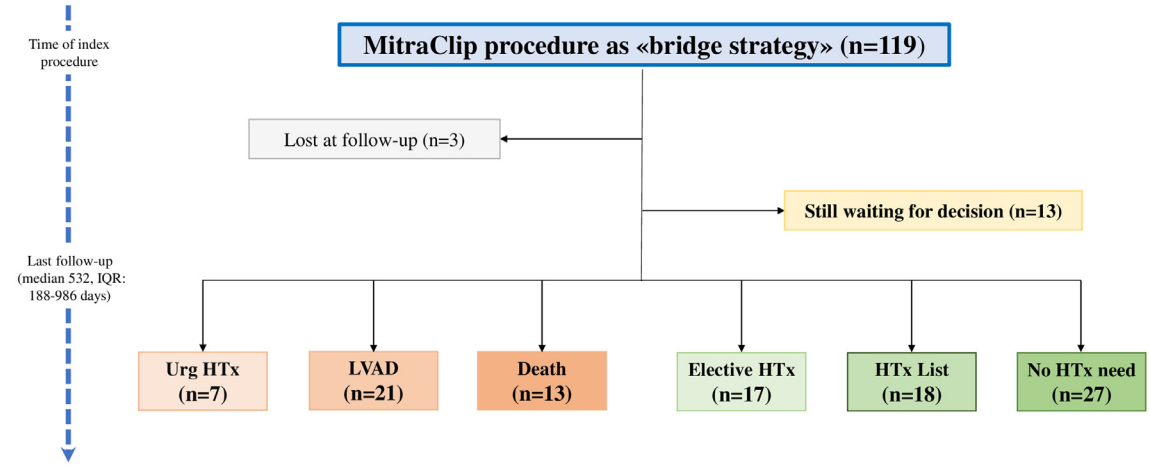
Data are presented as absolute numbers and percentages (for categorical variables) and mean value ± SD or median value and 25th and 75th percentiles (for continuous variables).

[a]Data for these parameters were not available for all patients.

[b]RH catheterization data were available for 78 (65.5%) patients.

Finally, whereas 10 patients (8.5%) remained in list for HTx, 8 patients (7%), previously belonging to the BTD ($n=4$) and BTC ($n=4$) groups, moved to the active HTx list. For BTC group patients, 3 of them, who had been previously excluded from the HTx list because of severe pulmonary hypertension with elevated right atrial pressure, became eligible for HTx owing to reduction of arterial pulmonary pressure; for the other patient, who had been temporarily excluded from the HTx list because of new-onset breast cancer, the MitraClip procedure allowed her to maintain a stable clinical condition until the eligibility for HTx was reconfirmed after neoplasia treatment. For all 4 patients in the BTD group, an end-stage HF condition needing HTx was confirmed, and MitraClip treatment guaranteed them to be eligible for elective transplant without new HF rehospitalization. Clinical conditions at the time of last available follow-up, stratified according to pre-defined baseline criteria, are presented in Figure 2. Regarding the 2 patients unable to successfully have the procedure (both belonging to the in list group), both were rehospitalized for acute HF after the index procedure; one of them underwent urgent HTx after 152 days, whereas the other one is awaiting HTx.

The 1-year Kaplan–Meier estimates of freedom from composite of all-cause of death, urgent HTx or LVAD implantation, and first rehospitalization for HF (primary end-point) was 64% (Figure 3a). Within the first year of follow-up, 35 rehospitalizations for HF (30%), 5 all-cause deaths (4.5%), 7 urgent HTxs (6%), and 6 LVAD implantations (5%) occurred. The 1-year Kaplan–Meier estimates of freedom from secondary end-point (rehospitalization for HF) was 67% (Figure 3b) with no statistically significant difference among the 3 population groups (Figure 3C). Particularly, a far lower rate of rehospitalization in the 6 months after the intervention compared with the previous 6 months (24.5% vs 61.5%) was observed.



Baseline groups						
In List (%)	5 (16)	0 (0)	2 (6.5)	8 (26)	10 (32)	5 (16)
BTD (%)	1 (2)	16 (29.5)	8 (15)	5 (9)	4 (7.5)	12 (22)
BTC (%)	1 (3)	5 (15)	3 (9)	4 (12)	4 (12)	10 (29.5)

Figure 2 Follow-up status stratified according to pre-defined baseline criteria. Stratified data according to pre-defined baseline criteria are presented as absolute numbers and percentages. BTC, bridge to candidacy; BTD, bridge to decision; HTx, heart transplantation; IQR, interquartile range; LVAD, left ventricular assist device; Urg, urgent.

At multivariable Cox regression analysis, post-procedural MR grade >2 (HR: 3.2; 95% CI: 1.4−7.3; *p*-value = 0.006), hospitalization for HF within 6 months before the procedure (HR: 2.9; 95% CI: 1.3−6.6, *p*-value = 0.009), and baseline INTERMACS profile 1 to 4 (HR: 2.7; 95% CI: 1.3−5.6; *p*-value = 0.008) were confirmed as independent predictors of the primary composite end-point (Table 3).

Discussion

This is a multicenter, international registry reporting data in patients with advanced HF with significant secondary MR and the MitraClip procedure as a bridge to transplant strategy. The main findings demonstrate the following: (1) the selected use of MitraClip as a bridge strategy to HTx was safe (87.5% procedural success and no death at 30 days)

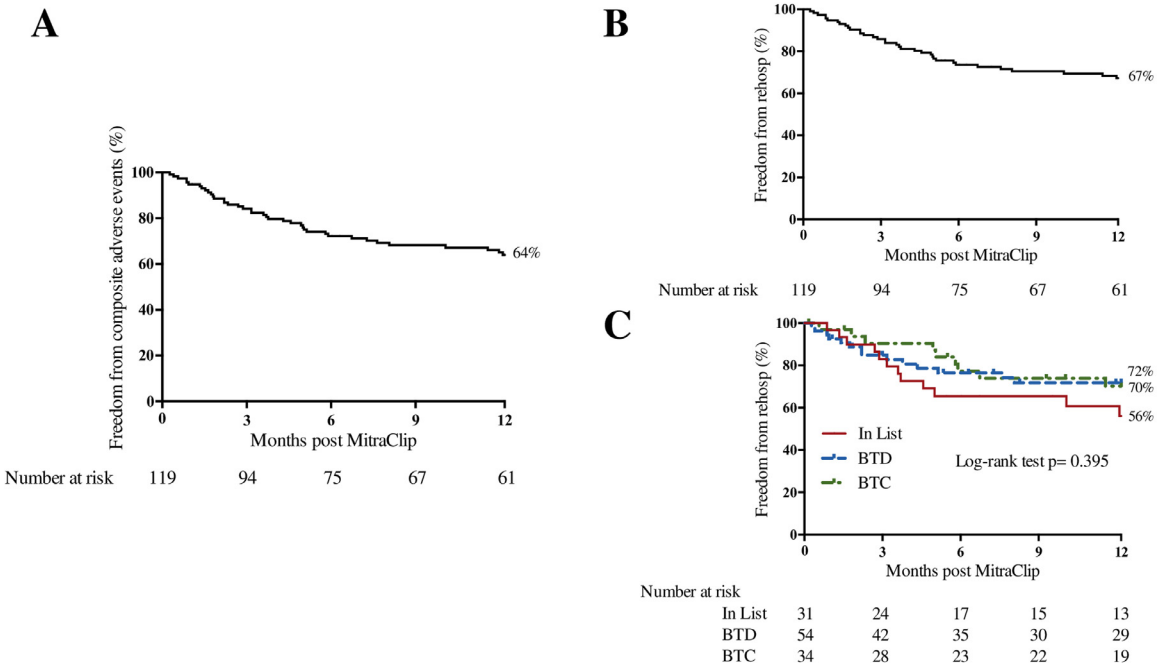


Figure 3 Kaplan−Meier curves. (a) Primary composite end-point (all-cause death, urgent HTx or LVAD implantation, first rehosp for HF) at 1 year in the overall population. (b) Secondary end-point (first rehosp for HF) at 1 year in the overall population and (c) stratified by baseline clinical status. BTC, bridge to candidacy; BTD, bridge to decision; HF, heart failure; LVAD, left ventricular assist device; rehosp, rehospitalization.

Table 3 Predictors of Univariate and Multivariate Cox Regression Analysis

Predictor	Univariate		Multivariate	
	HR (95% CI)	p-value	HR (95% CI)	p-value
Age	1 (0.97−1.03)	0.777	1.03 (0.99−1.07)	0.124
eGFR	0.9 (0.98−1)	0.296	1 (0.98−1.01)	0.753
Previous rehosp. within 6 months	3.2 (1.4−6.9)	0.003	2.9 (1.3−6.6)	0.009
Procedural failure	2.5 (1.2−5.3)	0.015	—	—
Residual MR >2	3.1 (1.5−6.4)	0.002	3.2 (1.4−7.3)	0.006
INTERMACS 1−4	3.4 (1.8−6.6)	<0.001	2.7 (1.3−5.6)	0.008
LVEF	0.95 (0.9−0.99)	0.033	—	—
LVESVi	1.01 (1−1.02)	0.030	—	—
Inotropic agents	1.9 (1−3.8)	0.037	—	—
NYHA Class 4	2.5 (1.3−4.6)	0.005	—	—

Abbreviations: eGFR, estimated glomerular filtration rate; HR, hazard ratio; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LVEF, left ventricular ejection fraction; LVESVi, left ventricular end systolic volume index; MR, mitral regurgitation; NYHA, New York Heart Association; rehosp, rehospitalization.

and effective; (2) two thirds of patients remain free of development of composite adverse events at 1 year (primary end-point); (3) 15.5% became eligible for transplant; and (4) nearly a quarter could be removed from consideration for HTx because of clinical improvement.

These exploratory results are promising and support the further study of MitraClip as an alternative strategy in selected compromised patients with advanced HF before transplant. Patients with advanced HF comprise an estimated 1% to 10% of the overall HF population, and the prevalence is increasing because of the growing number of patients with HF and their better treatment and survival.[15−17] This is a clinical area where conventional treatments (i.e., guideline-directed drugs, percutaneous devices, conventional surgery) are often insufficient in reducing a patient's symptoms, and advanced (e.g., cardiac transplantation, mechanical cardiac support) or palliative therapies (e.g., inotropic infusions, ultrafiltration or peritoneal dialysis to control volume, or end-of-life comfort care) are needed.[3] However, in situations where a patient's clinical condition deteriorates or end-organ function is compromised, short-term therapies may be needed until mechanical cardiac support can be implanted or while the patient is waiting on the transplant list. The possible role of MitraClip as a bridge to transplant has already been reported in some case reports and limited case series.[5−10] The MitraBridge registry results can be considered as a proof of concept in a larger and more geographically diverse cohort of patients demonstrating the effective role of MitraClip as a bridge strategy to HTx in patients with advanced HF who are on the waiting list or at that moment not eligible or at high risk for HTx. In the MitraBridge population, the MitraClip procedure was followed by a sustained reduction of pulmonary hypertension in 34% of patients (defined as a reduction in sPAP by at least 10 mm Hg of baseline), allowing some of them to become eligible for HTx. Moreover, about 60.5% of patients were at least 1 NYHA functional class lower than baseline, in line with previous results on functional MR populations.[18] These findings may be a consequence of the increase in antegrade cardiac output and the decrease of left ventricle filling pressure following mechanical reduction of MR.[19] In this series, all-cause mortality rate at 1 year was 4.5% and was lower compared with the 13% 1-year mortality rate reported by the Eurotransplant waiting list in 2019.[1]

In the near future, it would be desirable to have further data from observational studies regarding acute percutaneous MR repair in patients with cardiogenic shock and end-organ damage.[20] These data would allow us to evaluate whether percutaneous mitral valve interventions (with MitraClip and other mitral valve repair systems) could stabilize patients' hemodynamics and end-organ perfusion, allowing subsequent evaluation of patients' candidacy for HTx.

INTERMACS profiles could help to identify potential candidates for MitraClip in a bridge strategy. These profiles are commonly used as descriptors of disease severity in patients receiving mechanical circulatory support, and lately their utility in risk assessment and triaging of ambulatory patients with advanced HF was shown.[21] Most of the patients treated in this series were in INTERMACS profile ≥3. INTERMACS profiles 1 (critical cardiogenic shock) and 2 (progressive decline despite inotropic support) identify patients that may be treated with either paracorporeal or percutaneous short-term ventricular assist devices as a BTD.[3] Although INTERMACS profiles alone are insufficient to evaluate an individual patient for urgent HTx or mechanical cardiac support, based on these preliminary data, selected INTERMACS profile ≥3 can be evaluated for MitraClip bridge strategy in patients with advanced HF and concomitant significant secondary MR.

Finally, about 80% of patients included in the MitraBridge registry would have been formally ineligible for the MitraClip procedure based on the COAPT trial criteria.[22] Conversely, MitraBridge patients are more similar to those from the Mitra-FR trial[23] because of extremely dilated left ventricles (median LVEDVi: 122.5 ml/m^2) and proportionate[24] functional MR, according to available EROA (30 mm^2) and RVol (41 ml/beat) values. Nevertheless, a higher success in reducing HF rehospitalizations was observed (rates of HF rehospitalizations at 1 year: MitraBridge 30%

vs Mitra-FR 48.7%), likely because of the clinical potential of MitraClip treatment when applied on top of guideline-directed medical therapy in a much younger population.

These findings can be helpful in improving indications, patient selection, and decision-making criteria for MitraClip use in patients with advanced HF and concomitant significant MR waiting for HTx.[25,26] In particular, patients with indication to BTD or to candidacy, who currently have few therapeutic options besides medical therapy alone, could benefit the most from this strategy.

Study limitations

This study has several limitations. First, it is an observational study without a control group. Second, this is a real-world registry reporting the clinical practice in different centers and countries; therefore, echocardiographic and clinical outcomes have been reported by the different sites and investigators without core lab adjudication. In addition, the semi-quantitative MR grading evaluation for most patients (75.5%) represents an important methodological limitation. This reflects practice 2 years ago, well before the results of the COAPT trial,[22] which highlighted the importance of quantitative MR grading and pushed toward a greater clinical application of EROA and RVol. Third, the sample size remains relatively small. Fourth, a significant confounder in the comparison between hospitalization for HF before and after index procedure can exist, as those patients who underwent MitraClip would likely have closer medical follow-up after the procedure compared with the pre-procedure time. Finally, we want to underline the fact that this study is in a specific set of patients with advanced HF and concomitant significant MR, who have been chosen to undergo MitraClip procedure because of the favorable anatomical and clinical characteristics. Therefore, careful patient selection for this treatment strategy is of paramount importance, and the results should be interpreted with some caution. The conclusions should be considered exploratory, as generating hypotheses, and need to be confirmed in the future in a larger cohort of patients.

Conclusions

In this cohort of patients with advanced HF with significant secondary MR who were either listed for transplantation, awaiting listing for transplantation, or in a decision toward candidacy for transplantation, the selected use of MitraClip as a bridge strategy to HTx was safe, with two thirds of patients free from adverse events at 1 year. These findings will serve to guide further study for MitraClip use in this high-risk population, which is needed to confirm this exploratory experience.

Disclosure statement

Dr Rodrigo Estévez-Loureiro reports receiving grants and personal fees from Abbott during the conduct of the study. The remaining authors have no conflicts of interest to declare.

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