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ORIGINAL RESEARCH ARTICLE

MitraClip implantation followed by insertion of a left ventricular assist device in patients with advanced heart failure

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Abstract

Aims Mitral valve regurgitation (MR) is common in patients with advanced heart failure (HF). Percutaneous mitral valve repair (PMVR) via MitraClip (MC) has emerged as a feasible treatment strategy for these high-risk patients. However, as HF often further progresses, there is a frequent need for left ventricular assist device (LVAD) implantation in these patients. We aimed to investigate whether prior MC implantation affects the subsequent LVAD implantation and outcome.

Methods and results Thirty-seven patients with advanced HF and significant MR who underwent LVAD implantation were retrospectively analysed. Follow-up data were collected at 1 year after LVAD implantation. Primary endpoint was all-cause mortality. Secondary endpoint included peri-operative parameters and clinical development depicted as *New York Heart Association* (NYHA) class and *Interagency Registry for Mechanically Assisted Circulatory Support* (INTERMACS) level. Seventeen patients initially received a MC device (MC group), resulting in a significant reduction in MR grade. After MC, NYHA class and INTERMACS level further worsened, leading to subsequent LVAD implantation after a median time of 475 days in the MC group. At LVAD implantation, overall characteristics were comparable with those of the patients undergoing LVAD implantation without prior MC placement (no-MC group). Procedural data revealed a higher incidence of right ventricular (RV) failure needing mechanical RV assistance and a longer need for nitric oxide ventilation in the MC group after LVAD implantation. One-year survival was slightly better in the no-MC group compared with the MC group [41% (n = 7/17) vs. 65% (n = 13/20); P = 0.15], albeit event-free survival was comparable between both groups, MC and no-MC.

Conclusions LVAD implantation after MC is feasible and safe. However, in patients with advanced HF and severe MR, PMVR may only delay a needed LVAD implantation and thereby lead to poorer peri-operative RV function and impaired outcome. Arguably, these patients might benefit from the timely management of advanced HF by the means of early LVAD implantation or heart transplantation.

Keywords Advanced heart failure; Ventricular assist devices; Mechanical circulatory support; Percutaneous mitral valve repair; MitraClip

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Introduction

Heart failure (HF) is one of the leading causes of death worldwide despite advancements in HF treatments and vast implementation of guideline-directed therapies.[1,2] Secondary (functional) mitral valve regurgitation (MR) is a common finding in >50% of the patients with severely impaired left ventricular (LV) ejection fraction resulting from tethering and

annular dilatation due to LV dysfunction. Significant MR is associated with a poor prognosis.[3–5] With the progression of the underlying disease to advanced stages, medical therapy and cardiac resynchronization therapy may not lead to sufficient stabilization of those patients.[6,7] Edge-to-edge percutaneous mitral valve repair (PMVR) via MitraClip (MC; Abbott Vascular, North Chicago, Illinois, USA) implantation has emerged as a therapeutic option for patients with severe MR and prohibitive surgical risk.[8–12] Of particular high risk for surgery are patients with advanced stages of HF.[7,13,14] It is expected that in this patient group the PMVR could lead to improved haemodynamics and clinical symptoms.[15,16] However, even after successful MC placement, the underlying cardiomyopathy can progress further. In such cases, cardiac transplantation or the use of mechanical circulatory support (MCS) devices, most frequently LV assist devices (LVADs), are indicated.[1,2,17,18] To date, only limited data regarding implantation of LVADs in patients with prior MC exist,[19,20] leaving a gap in evidence on how an initial therapy with MC affects the later management of these patients who become candidates for LVAD therapy or heart transplantation. The present study reviews a single-centre experience comparing patients with advanced HF and consecutive functional MR who were supported with an LVAD with and without prior MC implantation.

Methods

The study conforms with the principles outlined in the Declaration of Helsinki.[13] The study was performed in a retrospective approach.

Patient population

From January 2013 to June 2018, a total of 119 patients received a permanent MCS device at our institution, either as LVAD or biventricular assist device (BiVAD). Patients undergoing BiVAD implantation were excluded (n = 36). Of the remaining patients, only patients with moderate-to-severe or severe MR were included in the study, resulting in a study population of 37 patients. Implanted devices were HeartWare HVAD (Medtronic), Thoratec HeartMate3 (Abbott), and CircuLite Synergy micropump (CircuLite Inc., now Medtronic). Included were patients who were implanted as bridge to transplantation (BTT) and patients undergoing destination therapy (DT). Patients who were already listed for heart transplantation or in the process of being listed were categorized as BTT. Patients with contraindications for heart transplant or who refused heart transplantation were categorized as DT. For study inclusion, the minimum age at implantation was 18 years. All patients met the following inclusion criteria: (i) severe or moderate-to-severe MR, (ii) dyspnoea *New York Heart Association* (NYHA) Class II to IV, and (iii) highly impaired LV ejection fraction. Seventeen patients underwent PMVR by MC, and 20 patients received the LVAD implantation without prior PMVR.

Pre-interventional workup

Pre-interventional workup was conducted before MC intervention in the MC patients as well as before LVAD implantation in both groups. This included medical history, clinical assessment, determining NYHA class, and *Interagency Registry for Mechanically Assisted Circulatory Support* (INTERMACS) level and a 6 minute walk test (6-MWT). Further, complete laboratory workup including high-sensitivity troponin T, N-terminal pro-brain natriuretic peptide (NT pro-BNP), and serum creatinine was performed in all patients. MR and mitral valve morphology were determined by transthoracic and transoesophageal echocardiographies. MR was graded according to current guidelines[21,22] in a semi-quantitative manner with colour Doppler and assessment of the width of the vena contracta. Moreover, severity of MR was quantified in each patient by invasive measurements in the cathlab using LV angiogram, pulmonary artery (PA) pressure, and v-wave.[23] Additionally, to classify advanced HF and assess for LVAD implantation, right heart catheterizations via a femoral venous approach were performed to determine cardiac index, PA pressures, pulmonary capillary wedge (PCW) pressure, PA resistance, and mixed venous oxygen saturation (SvO_2).[24] All shown data were taken from the latest available visit for each patient before MC implantation and LVAD implantation. The medical decision for MC implantation as well as for LVAD implantation was provided by cardiologists and cardiac surgeons in the heart team. All patients were informed about specific risks and alternatives of each therapy, as well as the options for continued medical treatment, and all patients gave informed written consent for the procedure. At one year after LVAD implantation, all available data included in the above-mentioned workup were collected for the remaining patients.

Statistical analysis

Quantitative data are presented as mean ± standard error of mean or as median and interquartile ranges (25–75), depending on the distribution of the data. For qualitative parameters, absolute and relative frequencies are presented. Comparisons between the two groups were performed with the Mann–Whitney U-test for quantitative variables. Qualitative patient characteristics were compared using the χ^2 test for categorical variables. To estimate the effects of prior MC implantation on patients' all-cause mortality and event-free survival, Kaplan–Meier survival curves were created. The

log-rank test was used to compare survival curves. All analyses were exploratory, and a two-tailed *P*-value of ≤0.05 was taken as a cut-off for statistical significance.

Results

Study population and baseline data prior to any intervention

This study comprises a total of 37 patients who received an LVAD between 2013 and 2018 at the University Hospital Heidelberg. Prior to LVAD implantation, 17 patients underwent PMVR (MC procedure; MC group). Twenty patients with moderate-to-severe or severe MR underwent LVAD implantation without prior mitral valve intervention (no-MC group). *Tables 1* and *S1* show the baseline characteristics of both groups, the MC group and no-MC group, before any of the interventions, MC or LVAD implantation, was performed. There were no significant differences regarding gender, underlying disease, or co-morbidities in both groups (*Table S1*). In the no-MC group, patients tended to a higher degree of functional impairment documented by higher NYHA class, poorer INTERMACS level, and lower walking distance in 6-MWT than did the MC group. However, overall both cohorts consisted of advanced HF patients with >80% NYHA level III–IV and a highly reduced functional capacity with 6-MWT results below 400 m (*Table 1*). All patients who were analysed underwent invasive haemodynamic assessment before any intervention. Severe haemodynamic impairment was documented by elevated right atrial (RA) pressure, mean PA pressure, and PCW pressure. Values were highly pathological in all patients and overall comparable in both groups. Moreover, cardiac index, and SvO_2 were markedly reduced in all patients with slightly worse values in the no-MC group (cardiac index 1.91 vs. 1.54 L/min/m^2; *P* = 0.048; SvO_2 55% vs. 43%; *P* = 0.070; *Table 1*). Although all patients had at least moderate MR, patients who underwent a MC procedure first revealed more severe regurgitation with over 80% severe MR as opposed to only 35% severe MR patients in the no-MC group. Taken together, before any intervention, patients in the MC group displayed a higher degree of MR, justifying the preferred MC procedure in this patient cohort. Vice versa, in the no-MC group, HF was slightly more advanced, explaining the decision for LVAD implantation instead of PMVR in that patient cohort. However, as documented by severely impaired functional as well as echocardiography and haemodynamic parameters, both patient cohorts comprised a true advanced HF population and within both groups, the MC and no-MC group, an immediate LVAD implantation would have been reasonable according to current recommendations.[17]

Clinical course between MitraClip and left ventricular assist device implantation

Success rates of the MC procedure according to MVARC (*Mitral Valve Academic Research Consortium*)[25] were 100% (technical success), 94.1% (device success), and 82.4% (procedural success). Patients were treated in 12 cases with one clip, in four cases with two clips, and in one case with three clips. MR was at most moderate after successful MC therapy

Table 1 Baseline characteristics prior to any intervention

		MC group *n* = 17	No-MC group *n* = 20	*P*-value
Functional parameters				
NYHA class	I	0	0	0.080
	II	3 (18%)	0	
	III	9 (53%)	9 (45%)	
	IV	5 (29%)	11 (55%)	
INTERMACS level	1	0	0	**0.025**
	2	0	4 (20%)	
	3	2 (11.8%)	2 (10%)	
	4	2 (11.8%)	2 (10%)	
	5	2 (11.8%)	8 (40%)	
	6	6 (35.3%)	4 (20%)	
	7	5 (29.4%)	0	
6-MWT (m)		378 [308; 449]	250 [218; 359]	**0.049**
Laboratory parameters				
Creatinine (mg/dL)		1.14 [0.97; 1.51]	1.15 [0.96; 1.51]	1.000
Bilirubin (mg/dL)		0.9 [0.55; 1.9]	1.0 [0.8; 2.0]	0.525
hsTnT (pg/mL)		30 [19; 50]	49.0 [18.0; 103.0]	0.362
NT pro-BNP (ng/L)		9464 [3624; 11 249]	11 318 [5043; 25 417]	0.135
Echocardiography				
LV ejection fraction (%)		15 [11.0; 22.5]	15 [11; 20]	0.672
LVEDD (mm)		71 [67; 77]	66.5 [59.5; 72.0]	0.186
LVESD (mm)		65 [60; 70]	58 [54; 65]	0.108
RV (mm)		36.5 [32.0; 42.0]	39 [31; 44]	0.770
MR	1	0	0	**0.001**
	2	2 (11.8%)	13 (65%)	
	3	14 (82.4%)	7 (35%)	
	4	1 (5.9%)	0	
Invasive haemodynamics				
Cardiac index (L/min/m^2)		1.91 [1.69; 2.13]	1.54 [1.3; 1.9]	**0.048**
SvO_2 (%)		55 [46; 64]	43 [40; 52]	0.070
PCW pressure (mmHg)		27 [23; 32]	29 [26; 32]	0.560
Mean PA pressure (mmHg)		38.5 [31.5; 45.0]	35 [30; 42]	0.655

6-MWT, 6 minute walk test; hsTnT, high-sensitivity troponin T; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT, pro-BNP N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCW, post-capillary wedge; RV, right ventricular; SvO_2 mixed venous oxygen saturation.
Comparison between patients implanted with a MitraClip (MC) before insertion of a left ventricular assist device (MC group) and patients who did not receive an MC (no-MC group). Data are given as median [25th–75th percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney *U*-test for quantitative variables and χ^2 test for qualitative variables. Bold text represents *P*-values < 0.05.

in all cases (data not shown). The median time from MC implantation to LVAD implantation was 475 days (108; 777), and at this time point, MR remained improved highly significant (*Table 2*), demonstrating that the initial MC procedure was effective and that the effects were persistent. After MC implantation and prior to LVAD placement, all patients (MC group; n = 17) were reassessed regarding functional as well as echocardiographic and invasive parameters (*Table* 2). Although functional capacity as measured by 6-MWT showed no significant difference after MC procedure and before LVAD implantation (378 vs. 385 m; P = 0.9), further progress of HF was documented by a decrease in INTERMACS levels prior to LVAD surgery as opposed to prior to MC intervention (P = 0.01) and a worsened NYHA stage (*Table* 2). Albeit echocardiographic assessment showed no difference in LV end-diastolic diameter (LVEDD) or LV end-systolic diameter (LVESD), right ventricular (RV) diameters were significantly higher prior LVAD implantation. In addition, laboratory workup prior to LVAD implantation revealed an increase in creatinine (1.14 vs. 1.41 mg/dL; P = 0.05) as well as significant increase in NT pro-BNP levels (9464 vs. 21 720 ng/L; P = 0.003) between MC and LVAD implantation, all documenting a further progress of the underlying disease.

Table 2 Worsening of heart failure between MitraClip and left ventricular assist device implantation

		Before MC n = 17	Before LVAD n = 17	P-value
Functional parameters				
NYHA class	I	0	0	**0.043**
	II	3 (17.6%)	0	
	III	9 (52.9%)	7 (41.2%)	
	IV	5 (29.4%)	10 (58.5%)	
INTERMACS level	1	0	0	**0.012**
	2	0	0	
	3	2 (11.8%)	5 (29.4%)	
	4	2 (11.8%)	2 (11.8%)	
	5	2 (11.8%)	7 (41.2%)	
	6	6 (35.3%)	3 (17.6%)	
	7	5 (29.4%)	0	
6-MWT (m)		378 [308; 449]	385 [311; 439.5]	0.981
Laboratory parameters				
Creatinine (mg/dL)		1.14 [0.97; 1.51]	1.43 [1.11; 1.8]	0.050
Bilirubin (mg/dL)		0.9 [0.55; 1.9]	0.9 [0.7; 1.3]	0.910
hsTnT (pg/mL)		30 [19; 50]	22 [17; 64]	0.858
NT pro-BNP (ng/L)		9464 [3624; 11 249]	21 720 [11 354; 27 955]	**0.003**
Echocardiography				
LV ejection fraction (%)		15 [11; 22.5]	10 [10; 15]	**0.022**
LVESD (mm)		65 [60; 70]	67.5 [62.5; 72.0]	0.635
RV (mm)		36.5 [32.0; 42.0]	43.0 [40.0; 45.5]	**0.021**
MR	1	0	7 (41.2%)	**<0.001**
	2	2 (11.8%)	6 (35.3%)	
	3	14 (82.4%)	4 (23.5%)	
	4	1 (5.9%)	0	
Invasive haemodynamics				
Cardiac index (L/min/m^2)		1.91 [1.69; 2.13]	1.80 [1.60; 2.01]	0.395
SvO_2 (%)		55 [46; 64]	48 [44; 54]	0.179
PCW pressure (mmHg)		27 [23; 32]	25 [21; 28]	0.394
Mean PA pressure (mmHg)		38.5 [31.5; 45.0]	35.0 [31.0; 40.0]	0.740

6-MWT, 6 minute walk test; hsTnT, high-sensitivity troponin T; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCW, post-capillary wedge; RV, right ventricular; SvO_2, mixed venous oxygen saturation.
Comparison of parameters before MitraClip (MC) procedure and after MC, before left ventricular assist device (LVAD) implantation. Data are given as median [25th–75th percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney U-test for quantitative variables and χ^2 test for qualitative variables. Bold text represents P-values < 0.05.

Outcomes after left ventricular assist device implantation with or without prior MitraClip procedure

At time of LVAD implantation, both patient cohorts, the MC and no-MC groups, were comparable in terms of age at implantation (median age 59.7 vs. 55.7 years; P = 0.3), NYHA class, and INTERMACS levels, as well as laboratory parameters (*Table 3*). As expected from the sufficient technical, device, and procedural success rates of the MC procedure, the degree of MR was significantly lower in the MC group (*Table 3*). Slight differences only occurred in 6-MWT and cardiac index (lower in the no-MC group) as well as in LVEDD and LVESD (higher in the MC group; *Table 3*), indicating that the stage of HF was comparably advanced in both groups, MC and no-MC, at the time of LVAD implantation. Device types implanted are listed in *Table 4* along with peri-operative and post-operative data, most of them comparable between the MC and no-MC groups. There were no significant differences noted regarding implanted device type, implant strategy (BTT or DT), duration of surgery or post-operative ICU (intensive care unit), or in-hospital days (*Table 4*). Further, major post-operative complications as defined by INTERMACS,[26] and duration of inotropic support were without a significant difference between the MC and no-MC groups. Remarkably, there was a trend towards higher incidence of post-operative RV failure as defined by EUROMACS (*European Registry for Patients with Mechanical Circulatory Support*)[27,28] in the MC group (P = 0.077), along with a more frequent need for RV support[28,29] and a significantly higher duration of nitric oxygen (NO) ventilation in the MC group (*Table 4*), pointing to a higher peri-operative tension on the RV in the MC group compared with the no-MC group. Functional as well as laboratory and echocardiography parameters did not display differences between the MC and no-MC groups at one year after LVAD implantation (*Table 5*). However, one year survival was slightly better in the cohort, who did not receive an MC earlier on, compared with the

Table 3 Baseline characteristics before left ventricular assist device implantation

		MC group $n = 17$	No-MC group $n = 20$	*P*-value
Functional parameters				
NYHA	I	0	0	0.815
	II	0	0	
	III	7 (41.2%)	9 (45%)	
	IV	10 (58.5%)	11 (55%)	
INTERMACS	1	0	0	0.259
	2	0	4 (20%)	
	3	5 (29.4%)	2 (10%)	
	4	2 (11.8%)	2 (10%)	
	5	7 (41.2%)	8 (40%)	
	6	3 (17.6%)	4 (20%)	
	7	0	0	
6-MWT		385 [311; 440]	250 [218; 359]	**0.030**
Laboratory parameters				
Creatinine (mg/dL)		1.43 [1.11; 1.80]	1.15 [0.96; 1.51]	0.053
Bilirubin (total) (mg/dL)		0.9 [0.7; 1.3]	1.0 [0.8; 2.0]	0.482
hsTnT (pg/mL)		22 [17.0; 64.0]	49.0 [18.0; 103.0]	0.222
NT pro-BNP (ng/L)		21 720 [11 354; 27 955]	11 318 [5043; 25 417]	0.117
Echocardiography				
LV ejection fraction (%)		10 [10; 15]	15 [11; 20]	**0.023**
LVEDD (mm)		73.0 [68.0; 81.0]	66.5 [59.5; 72.0]	**0.025**
LVESD (mm)		67.5 [62.5; 72.0]	58.0 [54.0; 65.0]	0.063
RV (mm)		43 [40; 45]	39 [30; 42]	**0.025**
MR	1	7 (41.2%)	0	**0.030**
	2	6 (35.3%)	13 (65%)	
	3	4 (23.5%)	7 (35%)	
	4	0	0	
Invasive haemodynamics				
Cardiac index (L/min/m^2)		1.80 [1.60; 2.01]	1.54 [1.3; 1.9]	**0.046**
SvO_2 (%)		48 [44; 54]	43 [40; 52]	0.163
PCW pressure (mmHg)		25 [21; 28]	29 [26; 32]	0.083
Mean PA pressure (mmHg)		35 [31; 40]	35 [30; 42]	0.937

6-MWT, 6 minute walk test; hsTnT, high-sensitivity troponin T; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCW, post-capillary wedge; RV, right ventricular; SvO_2, mixed venous oxygen saturation.
Comparison of parameters of both groups, MC (MitraClip) group and no-MC group, immediately before left ventricular assist device (LVAD) implantation. Data are given as median [25th–75th percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney *U*-test for quantitative variables and χ^2 test for qualitative variables. Bold text represents *P*-values < 0.05.

Table 4 Peri-operative parameters (left ventricular assist device implantation)

		MC group $n = 17$	No-MC group $n = 20$	*P*-value
Age at implantation (years)		59.7 [54.7; 61.9]	55.7 [46.8; 63.7]	0.259
Device type	HMIII	5 (29.4%)	3 (15%)	0.278
	HVAD	11 (64.7%)	17 (85%)	
	Circulite	1 (5.9%)	0	
Implant strategy	BTT	14 (82.3%)	17 (85%)	0.828
	DT	3 (17.7%)	3 (15%)	
Duration of surgery (min)		290 [221; 339]	267.5 [225; 295]	0.670
Off-pump time (min)		154 [106; 178]	132.5 [107; 159]	0.563
Post-operative hospital days		58 [45; 115]	68 [53; 88]	0.751
Post-operative ICU days		22.5 [5; 40]	9 [5; 14]	0.237
Duration of inotropic support (days)		15.5 [9; 44]	13 [11; 20]	0.435
RV failure		14 (82.35%)	11 (55%)	0.077
Need for RV support (RVAD)		8 (47.06%)	5 (25%)	0.161
Duration of NO ventilation (h)		90 [34; 169]	22 [20; 39]	**0.013**
Major post-operative complications		12 (70.6%)	15 (75%)	0.763

BTT, bridge to transplantation; DT, destination therapy; ICU, intensive care unit; NO, nitric oxide; RV, right ventricle; RVAD, right ventricular assist device.
Peri-operative parameters related to left ventricular assist device (LVAD) implantation in both groups, MC (MitraClip) group and no-MC group. Data are given as median [25th–75th percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney *U*-test for quantitative variables and χ^2 test for qualitative variables. Bold text represents *P*-values < 0.05. Major post-operative complications are defined as LVAD thrombosis, major bleeding, stroke, infection, or death. HMIII HeartMate III (Thoratec, Abbott), HVAD (Heartware, Medtronic), and Circulite (Abbott).

MC cohort, albeit with no statistical significance [one year survival rate 41% (n = 7/17) vs. 65% (n = 13/20); P = 0.15]. Actuarial survival for the entire cohort, compared with those who received PMVR before LVAD implantation vs. patients in the no-MC group, is presented as Kaplan–Meier curves in *Figure 1*. Although a slightly better outcome for the latter cohort is depicted, no statistical significance was reached in the log-rank test (P = 0.119). In addition, *Figure 2* shows event-free survival at 1 year after LVAD implantation comparing both groups, event-free survival being defined as free from LVAD thrombosis, major bleeding, stroke, and infection. Here, no significant difference was demonstrated.

Discussion

Our study confirms previously published data[19,20] that LVAD implantation is feasible and safe in patients with previously positioned MC device. Furthermore, our data represent the first comparison of previous PMVR vs. immediate LVAD implantation in an advanced HF cohort requiring MCS. Although conclusions are limited due to a small number of patients in the present study, its retrospective design, and potential selection bias, our data point to an inferior outcome, when patients are previously treated with MC before LVAD. Although the reasons for this observation remain unknown, one could speculate that these are related to a delay

Table 5 One-year outcomes after left ventricular assist device implantation

		MC group $n = 7$	No-MC group $n = 12$	*P*-value
Functional parameters				
NYHA class	I	1 (14.2%)	0	0.365
	II	3 (42.9%)	8 (66.7%)	
	III	3 (42.9%)	3 (25%)	
	IV	0	1 (8.3%)	
INTERMACS level	1	0	0	0.864
	2	0	0	
	3	0	0	
	4	0	0	
	5	0	0	
	6	2 (28.6%)	3 (25%)	
	7	5 (71.4%)	9 (75%)	
6-MWT		418.5 [372; 465]	559 [559; 559]	0.221
Laboratory parameters				
Creatinine (mg/dL)		1.25 [1.06; 1.57]	1.01 [0.79; 1.13]	0.051
Bilirubin (total) (mg/dL)		0.6 [0.5; 0.6]	0.5 [0.4; 0.7]	0.469
hsTnT (pg/mL)		34.5 [9; 50]	20.5 [14; 34]	0.278
NT pro-BNP (ng/L)		1132 [726; 3794]	1384 [745; 1755]	0.828
Echocardiography				
LV ejection fraction (%)		15 [10; 15]	15 [15; 25]	0.074
LVEDD (mm)		73 [67; 78]	60 [54; 70]	0.125
LVESD (mm)		67.5 [55; 72]	46 [45; 66]	0.099
RV (mm)		40 [37; 44.5]	34 [32; 40]	0.147
MR	0	1 (16.66%)	3 (30%)	0.602
	1	2 (33.33%)	3 (30%)	
	2	3 (50%)	4 (40%)	
	3	0	0	

6-MWT, 6 minute walk test; hsTnT, high-sensitivity troponin T; INTERMACS, Interagency Registry for Mechanically Assisted Circulatory Support; LV, left ventricular; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; MR, mitral regurgitation; NT pro-BNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PA, pulmonary artery; PCW, post-capillary wedge; RV, right ventricular; SvO_2, mixed venous oxygen saturation.
Comparison of parameters of both groups, MC (MitraClip) group and no-MC group, at one year after left ventricular assist device (LVAD) implantation. Data are given as median [25th–75th percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney *U*-test for quantitative variables and χ^2 test for qualitative variables. Bold text represents *P*-values < 0.05.

of the adequate treatment strategy in term of MCS or by directly MC-related factors.

Mitral valve repair in advanced heart failure patients

The usefulness of PMVR in advanced HF has been a matter of debate since many years, and this discussion has been fired recently, as two large randomized trials provided apparently conflicting results.[30–32] While the COAPT (*Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation*) trial clearly demonstrated a survival benefit in HF patients, the MITRA-FR (*Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation*) trial showed no benefit in outcome for at least those patients receiving MC with an LVEDD $>$ 70 mm, representing a severe HF cohort with advanced ventricular remodelling. Although the reasons for the positive results in COAPT vs. negative results in MITRA-FR are certainly complex,[32] we have learned that patients with very advanced HF and ventricular remodelling may be less eligible for PMVR than patients in earlier stages of the disease. In this regard, mean LVEDD was 71 mm before MC in our patients, pointing to a very sick

Figure 1 One-year survival after left ventricular assist device (LVAD) implantation. Kaplan–Meier survival curve of estimated all-cause mortality at one year after LVAD comparing patients who previously received an MitraClip (MC) (MC group) with patients with moderate-to-severe mitral regurgitation without previous MC implantation (no-MC group). Patients receiving heart transplantation or device explantation within the first year were censored (vertical bars). *P*-value is given for log-rank test.

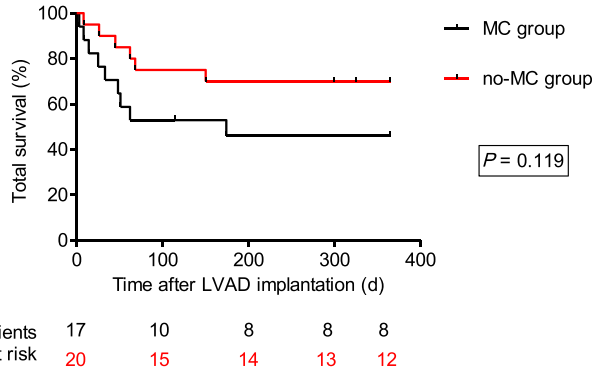
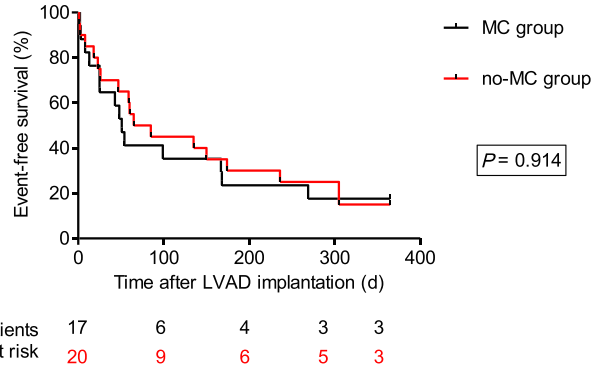


Figure 2 Event-free survival after left ventricular assist device (LVAD) implantation. Kaplan–Meier survival curve of event-free survival at one year after LVAD comparing patients who previously received an MitraClip (MC) (MC group) with patients with moderate-to-severe mitral regurgitation without previous MC implantation (no-MC group). Event-free survival defined as free from LVAD thrombosis, major bleeding, stroke, and infection. Patients receiving heart transplantation or device explantation within the first year were censored (vertical bars). *P*-value is given for log-rank test.



cohort of patients with exceptionally poor outcomes and probably in many centres those patients would have been rejected for PMVR in contemporary practice. However, at our centre, we have conduced MC procedures in advanced HF patients over the last decade with respectable success,[7,16,33] documenting that PMVR is even feasible in patients with heavily dilated LV, when patients are carefully selected and the operator is experienced.

Do we need to address mitral regurgitation in left ventricular assist device patients?

While the COAPT trial showed that MC placement in patients with advanced HF and severe MR results in a lower all-cause mortality at 2 years,[30] in that study, only three out of 298 patients underwent a LVAD implantation during the follow-up period. To date, no further data regarding outcome or safety in this small sub-cohort of MC patients were reported. With the natural progression of the underlying cardiomyopathy, it is expected that a larger number of patients will receive an LVAD implant after previous MC procedure. However, as reported in an INTERMACS registry analysis in 2018, patients who received a combined LVAD surgery with mitral valve replacement or repair showed no significant difference regarding outcome compared with those who did not undergo a simultaneous mitral valve procedure.[34] This observation raises the question whether MR needs to be addressed at all in patients with MCS, or if we can neglect MR when we aim on other treatment strategies, as MCS or heart transplantation. It is well known that baseline severe and moderate-to-severe MR is an important risk factor after LVAD implantation with one year survival between 63% and 55%,[35,36] comparable with what we observe in our present study. However, whether MR is a treatment target in these patients remains unclear.

Mitral valve repair in left ventricular assist device patients

In patients with significant MR who receive an LVAD as end-stage HF therapy, only a small number undergo concomitant or prior mitral valve procedures (e.g. interventional or surgical repair or replacement).[19,34] In some cases, a MC device can be implanted as an alternative in patients who are also candidates for LVAD implantation to prevent or delay the surgery.[30] In these patients with advanced HF, it remains unclear whether a prior MC implantation has any benefit as a bridge to LVAD. We have recently published that PMVR can be successfully used as a 'bridge to transplant' strategy in patients awaiting heart transplantation.[33] However, this is a situation where the aspired treatment strategy is not immediately available, making a 'bridge to' strategy necessary. Our present data are the first to compare the strategy of PMVR and subsequent LVAD insertion in an advanced HF population with immediate LVAD implantation. Previously published series only focused on feasibility and results in MC/LVAD without control group: in a recently published small case series report from Ammirati and colleagues,[19] the clinical course of six patients undergoing LVAD implantation with previously implanted MC device is described. LVAD implantation took place after a median of 282 days. This observational study described no complications related to the MC device and a reduction of MR severity from moderate to mild regurgitation after LVAD implantation in all patients, concluding that the implantation of an LVAD appears safe in patients with previously positioned MC, with no requirement for further mitral valve surgery. No long-term follow-up was conducted leaving in unclear, whether the management of these patients has benefited due to prior MC placement. Likewise, Dogan *et al*. reported a case series of six patients with severe HF, receiving a LVAD implantation after undergoing an MC procedure.[20] Although there was a successful reduction of the MR in all patients with clear improvement of their clinical symptoms, none to only little improvement regarding invasive haemodynamic (cardiac index and PCW pressure) and echocardiographic (LVEDD and ejection fraction) parameters were noted. This subsequently led to the need of LVAD implantation in these six patients. All these data concur with the findings of our present study, that in an advanced HF cohort, HF progresses despite MC implantation.

Higher peri-operative risk in MitraClip patients undergoing left ventricular assist device implantation?

What are possible explanations for RV failure, prolonged need for NO ventilation, and more frequent right ventricular assist device support after LVAD implantation in MC patients in our study? This finding may simply reflect the significant MR burden that these patients had at baseline prior to any treatment that had impacted on the afterload of the RV. But one could as well speculate that a reduced mitral valve area after MC could result in an iatrogenic stenosis,[37] leading to restriction of the blood flow into the LV and thereby decreasing the ability of the LVAD to reduce PA pressures and RV tension. Although no statistical significance was reached in this study, it coincides with previous findings that in patients suffering from end-stage systolic HF with the need for MCS or heart transplantation, the prior implantation of an MC device leads to no haemodynamic improvement with unpreventable progression of the underlying disease and subsequent need for LVAD implantation. Although INTERMACS levels, 6-MWT, and invasive haemodynamics (cardiac index, SvO_2, PCW pressure, and mean PA pressure) were

considerably worse in the no-MC group when compared with the MC group before MC placement, the patients in the MC cohort were already eligible for LVAD implantation.[17] The optimal timing for LVAD implantation is still under scientific debate, and HF physicians should have an everyday discussion with the individual patients about this in the clinical daily routine. Our data may add on the idea of 'the earlier the better', because in these patients, the initial implantation of an MC device seems to only delay the LVAD surgery with no significant benefit regarding objective parameters. The loss of this valuable time seems to lead to poor pre-operative conditions and hence impaired outcome as opposed to patients who immediately undergo LVAD implantation.

Limitations

Our study has many limitations, ranging from the small number of patients, the single-centre design, and the retrospective approach. The latter generates a selection bias whereby only patients that eventually had LVAD implantation and prior MC procedure or moderate-to-severe or severe MR at the time of evaluation were included in the study. Hence, the validity of the results is limited by the selection of the patients for the MC and no-MC groups, respectively.

Conclusions

Functional MR is a common finding in patients with advanced HF. In these patients, LVAD implantation seems feasible and safe after prior MC placement. However, the protracted MCS and hence delayed treatment of the limiting HF seems to be associated with a poorer outcome in these patients. The present data underlines that there is a dire need to clarify the benefit of mitral valve procedures in end-stage HF patients vs. the timely management of the underlying disease by means of early LVAD implantation or heart transplantation. Nevertheless, as the small number of patients in total and the retrospective nature of the study unfortunately does not allow for safe conclusions, our data should be seen as hypothesis generating and therefore may stimulate further research efforts.

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Conflict of interest

M.M.K. received research grants from Abbott (Thoratec) and travel grants (for international conferences) from Medtronic (HeartWare). B.S. and A.R. received travel grants (for international conferences) and consultancy fees from Berlin Heart and Abbott. P.W.R. received speaker honoraria from Abbott (Thoratec). The other authors report no conflict of interest regarding the content herein.

Supporting information

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

Table S1. Gender, underlying disease and comorbidities. Baseline characteristics of patients included in the study, compared between patients implanted with a MitraClip (MC) before insertion of a left ventricular assist device (MC group) and patients who did not receive a MC (no-MC group). Data are given as median [25–75 percentile] or absolute number (%). Comparisons between the two groups were performed with the Mann–Whitney U-test for quantitative variables and chi-square test for qualitative variables. Bold text represents *p*-values <0.05. *ICD implanted cardioverter/defibrillator.*

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