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Failure of acute procedural success predicts adverse outcome after percutaneous edge-to-edge mitral valve repair with MitraClip

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KEYWORDS

- failure of acute procedural success
- heart failure
- MitraClip
- mitral regurgitation
- outcome predictors
- percutaneous mitral valve repair

Abstract

Aims: MitraClip implantation is evolving as a potential alternative treatment to conventional surgery in high-risk patients with significant mitral regurgitation (MR). However, outcome predictors are under-investigated. The aim of this study was to identify predictors of midterm mortality and heart failure rehospitalisation after percutaneous mitral valve repair with MitraClip.

Methods and results: A total of 150 consecutive patients were followed for a median of 463 days. Survival analyses were performed for baseline characteristics, risk scores and failure of acute procedural success (APS) defined as persisting MR grade 3+ or 4+. Univariate significant risk stratifiers were tested in multivariate analyses using a Cox proportional hazards model. Overall survival was 96% at 30 days, 79.5% at 12 months, and 62% at two years. Multivariate analysis identified APS failure (HR 2.13, p=0.02), NYHA Class IV at baseline (HR 2.11, p=0.01) and STS score ≥12 (HR 2.20, p<0.0001) as significant independent predictors of all-cause mortality, and APS failure (HR 2.31, p=0.01) and NYHA Class IV at baseline (HR 1.89, p=0.03) as significant independent predictors of heart failure rehospitalisation. Furthermore, a post-procedural significant decrease in hospitalisation rate could only be observed after successful interventions (0.89±1.07 per year before vs. 0.54±0.96 after implantation, p=0.01). Patients with severely dilated and overloaded ventricles who did not meet EVEREST II eligibility criteria were at higher risk of APS failure.

Conclusions: The failure of acute procedural success proved to have the most important impact on outcome after MitraClip implantation.

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Introduction

Mitral regurgitation (MR) is the second most common form of valvular heart disease requiring treatment in Europe[1]. Clinical outcome under medical management and after surgery is different in organic and functional disease and varies according to patients' age, degree of MR, and severity of symptoms[2], but in particular patients with functional MR have a poor prognosis, and increasing severity is associated with worse outcome[3]. Given the high prevalence of MR in the elderly population at high surgical risk due to relevant comorbidities, it is not surprising that surgery is denied in nearly 50% of patients with severe symptomatic MR, with impaired LVEF, older age, and comorbidity as the most striking characteristics of patients who are not operated[4].

The percutaneous edge-to-edge mitral valve repair with MitraClip® (Abbott Vascular, Santa Clara, CA, USA) is based on the surgical technique first described by Alfieri[5]. This novel procedure was initially performed in the EVEREST trials in selected patients amenable to surgery with predominantly degenerative mitral valve disease[6,7]. However, patients who are currently treated with MitraClip in daily clinical practice are mostly at very high or prohibitive surgical risk with predominantly functional disease due to dilative or ischaemic cardiomyopathy[8]. Clinical midterm outcome following MitraClip implantation is, as yet, not well documented, and valid outcome predictors for overall survival and heart failure rehospitalisation have not yet been identified. In the present study, we therefore aimed to identify risk factors with prognostic impact on midterm survival and heart failure rehospitalisation in a single-centre cohort of consecutive "real-world" patients treated with MitraClip.

Methods

STUDY DESIGN

We report on the first 150 consecutive patients with moderate to severe MR treated with MitraClip at the University Medical Centre of Göttingen between April 2009 and June 2012. This prospective observational study was reviewed and approved by the ethics committee of the University Medical Centre Göttingen, and written informed consent was obtained from all patients.

PRE-INTERVENTIONAL EVALUATION

The indication and technique for treatment of MR was discussed in an interdisciplinary Heart Team in accordance with current guidelines[9,10]. All patients underwent intensive pre-interventional screening including transthoracic and transoesophageal echocardiography. Surgical risk was assessed by current scoring systems like the logistic EuroSCORE I and the Society of Thoracic Surgeons (STS) mortality risk calculation. Exclusion criteria for MitraClip implantation were a mitral valve area <2.0 cm^2 by planimetry[6] and acute endocarditis. The exclusion criteria for the EVEREST II trial[7] were evaluated for each patient in order to characterise the patient population, but did not represent a treatment contraindication in the present study.

PROCEDURE

The MitraClip implantation was performed as previously described[6] in a hybrid operating room under general anaesthesia and guided by two-dimensional and three-dimensional TEE and fluoroscopy. All procedures were performed by the same interventional cardiologists (W.S. and M.H.) and a team of two experienced echocardiographers (M.P. and K.R.).

ECHOCARDIOGRAPHY

Echocardiographic measurements were performed before the MitraClip implantation, during and directly after the procedure, at discharge, and during follow-up (at six months and 12 months) according to current recommendations. The severity of MR was graded as proposed in the EVEREST I trial[6] in accordance with the American Society of Echocardiography[11], and post-procedural grading was performed according to Foster et al[12]. The definition of acute procedural success (APS) was adopted from the EVEREST II trial[9] and was defined as a residual MR grade of 2+ or less measured at the time of hospital discharge after MitraClip implantation. To exclude the influence of general anaesthesia, we explicitly did not count the direct postoperative MR grade. Measurement of left ventricular volumes and ejection fraction was performed by using the biplane Simpson's method.

FOLLOW-UP

At six and 12 months, we performed transthoracic echocardiography, a clinical examination, a six-minute walk test and a structured interview including the Minnesota Living with Heart Failure Questionnaire (MLWHF QoL), and assessed the serum N-terminal pro-brain natriuretic peptide (NT-proBNP) levels. In some patients who refused to undertake a surveillance visit (mainly due to the long distance of our clinic from their places of residence), the follow-up was restricted to a telephone interview, but medical documents and echocardiographic recordings were acquired from resident cardiologists whenever possible. Before completion of the manuscript, all patients were followed by telephone contact again in January and February 2013 to investigate the incidence of major adverse events and of death. Also, the number of heart failure hospitalisations one year before and one year after MitraClip implantation was investigated and all relevant medical documents acquired to examine possible alterations in hospitalisation rates.

STUDY ENDPOINTS

All-cause mortality was defined as the primary clinical endpoint of the study. As the secondary endpoint, heart failure hospitalisation was chosen and was defined as hospitalisation due to clinical signs of worsening congestive heart failure with objective symptoms including pulmonary congestion, worsening oedema, hypoperfusion or documented volume overload leading to administration of diuretic and/ or inotropic therapy, or institution of mechanical support (i.e., assist devices).

STATISTICAL ANALYSIS

Statistical analysis was performed with the Statistical Computing Software R (version 2.15.1; http://www.r-project.org) or with GraphPad Prism (version 4.0). Continuous variables are presented as

median and interquartile range, and were compared using the Mann-Whitney U test. Categorical variables are presented as absolute numbers and percentage, and were compared by Pearson's chi-square test. A value of $p<0.05$ was considered statistically significant.

Survival analysis was performed on time to event data (i.e., time to first heart failure hospitalisation or time to death of any cause) using the R package survival. Survival data were visualised by Kaplan-Meier plots, and significance was calculated by the log rank test (for two group comparisons). For multivariate models, the Cox proportional hazards model was used. Survival and rehospitalisation analyses were performed for baseline characteristics, risk scores and failure of procedural success. Risk stratifiers that were found to be significant in univariate analyses were tested in multivariate analyses. The influence of different risk scores (logistic EuroSCORE I, STS score) and the presence of EVEREST II exclusion criteria as a risk stratifier were assessed using ANOVA analysis. In this model, STS score and EuroSCORE were used as continuous variables. A multivariate Cox model (coxph) was fitted using forward variable selection and model comparisons in different orders.

Results

BASELINE CHARACTERISTICS

The patient cohort was characterised by advanced age (mean, 74.4±9.3 years) and significant comorbidities leading to a high surgical risk expressed by a high logistic EuroSCORE I (mean, 28.6±17.9%) and a high STS score (mean, 10.5±8.7%) **(Table 1)**. The aetiology of MR was predominantly functional (in 66%), and 45% of the total patient cohort suffered from a severely reduced left ventricular ejection fraction (LVEF) of ≤30%. Of note, only 33% of patients would have met the EVEREST II eligibility criteria[7]. Furthermore, our patients showed severe symptoms of congestive heart failure, with 87% presenting in New York Heart Association (NYHA) Classes III and IV, 45% suffering from clinical signs of right heart failure, and 15% even being dependent on inotropic support.

Table 1. Baseline characteristics.

		All patients (N=150)	APS (N=128)	Failure of APS (N=22)	*p*
Mean±SD					
Age, years		74.4±9.3	74.7±9.3	72.5±9.5	0.32
Calculated surgical risk	logistic EuroSCORE I, %	28.6±17.9	28.2±17.3	30.8±21.7	0.94
	STS score, %	10.5±8.7	10.3±8.0	11.4±12.2	0.56
n (%)					
Female gender		53 (35%)	46 (36%)	7 (32%)	0.71
NYHA functional Class III		94 (63%)	82 (64%)	12 (55%)	0.39
NYHA functional Class IV		36 (24%)	28 (22%)	8 (36%)	0.14
Aetiology of MR	organic	52 (35%)	46 (36%)	6 (27%)	0.43
	functional	98 (65%)	82 (64%)	16 (73%)	0.43
LVEF ≤30%		68 (45%)	55 (43%)	13 (59%)	0.16
CRT-D		38 (25%)	31 (24%)	7 (32%)	0.45
Coronary artery disease		93 (62%)	80 (63%)	13 (59%)	0.76
Previous cardiac surgery		54 (36%)	44 (34%)	10 (45%)	0.32
Pulmonary hypertension (>50 mmHg)		94 (63%)	76 (59%)	18 (82%)	0.04*
Right heart failure (clinical)		68 (45%)	59 (46%)	9 (41%)	0.65
Atrial fibrillation		99 (66%)	84(66%)	15 (68%)	0.97
Peripheral artery disease		20 (13%)	15 (12%)	5 (23%)	0.16
Previous stroke		12 (8%)	12 (9%)	0	0.13
Chronic renal failure	GFR* <30 mL/min/1.73 m^2	23 (15%)	18 (14%)	5 (23%)	0.30
	GFR* <60 mL/min/1.73 m^2	101 (67%)	83 (65%)	18 (82%)	0.12
COPD		33 (22%)	30 (23%)	3 (14%)	0.31
Diabetes mellitus		47 (31%)	43 (34%)	4 (18%)	0.15
Inotropic support		22 (15%)	19 (15%)	3 (14%)	0.40
Eligibility for EVEREST II		49 (33%)	47 (37%)	2 (9%)	0.01*

*calculated with MDRD formula (Levey); APS: acute procedural success; COPD: chronic obstructive pulmonary disease; CRT-D: cardiac resynchronisation therapy - defibrillator; GFR: glomerular filtration rate; LVEF; left ventricular ejection fraction; MR: mitral regurgitation; NYHA: New York Heart Association; STS: Society of Thoracic Surgeons

PROCEDURAL AND IN-HOSPITAL OUTCOME

The procedure itself was relatively safe, and no peri-interventional mortality was observed. The in-hospital mortality was 5.3%. Four patients died after a complicated in-hospital course with primary bleeding complications and consecutive further events on days 33, 34, 24 and 12 (see also below). The causes of death in the remaining four cases were therapy-resistant ventricular fibrillation (day 10) in one patient and septic shock (days 6, 11 and 5) in three patients (one of whom had already received MitraClip implantation as last-resort therapy in a very bad clinical condition with acute respiratory distress syndrome and massive dependence on inotropic support).

Complications occurring in the first 30 days post procedure or until first hospital discharge after MitraClip implantation (if the postoperative length of stay was longer than 30 days) are demonstrated in **Table 2**. Peri-interventional myocardial infarction, need for mechanical assistance or immediate surgery did not occur. However, 23 patients (15%) experienced procedure-related complications. Relevant bleeding complications (classified as GUSTO severe) were observed postoperatively in seven cases (4.7%) and were often associated with the need for therapeutic anticoagulation due to mechanical prosthetic valves (n=2) or atrial fibrillation (n=2) leading to diffuse bleeding (in three patients) or retroperitoneal haematoma (in one patient). The bleeding led to further complications like prolonged ventilation (>24 hr) with development of pneumonia, acute renal failure or development of ischaemic stroke in the latter four patients who died due to septic shock in the end on days 33, 34, 24 and 12. The remaining bleeding complications were groin haematoma with need for transfusion in one patient (who experienced no further complications), pericardial tamponade (which was successfully treated by pericardiocentesis) in one patient who had undergone left atrial appendage occlusion at the same time as MitraClip implantation, and intracranial bleeding on day 8 after the procedure in one patient (who showed a good neurological recovery without relevant residua).

Table 2. In-hospital (at least 30 days) safety outcome data*.

n (%)	All patients (N=150)	APS (N=128)	Failure of APS (N=22)	*p*
Death	8 (5.3%)	6 (4.7%)	2 (9.1%)	0.40
Early rehospitalisation due to heart failure	7 (4.7%)	4 (3.1%)	3 (13.6%)	0.03*
Severe bleeding (GUSTO)#	7 (4.7%)	4 (3.1%)	3 (13.6%)	0.03*
Myocardial infarction	0	0	0	–
Stroke (ischaemic/bleeding)	2 (1.3%)	1 (0.8%)	1 (4.5%)	0.16
Cardiac surgery	0	0	0	–
Mechanical support	0	0	0	–
Pericardial tamponade	1 (0.7%)	1 (0.8%)	0	0.68
Ventilation > 24 hr	6 (4.0%)	3 (2.3%)	3 (13.6%)	0.01*
Phlebothrombosis	2 (1.3%)	2 (1.6%)	0	0.56
Acute renal failure with indication for renal replacement therapy	2 (1.3%)	2 (1.6%)	0	0.56
Clip detachment (all partial)	4 (2.6%)	2 (1.6%)	2 (9.1%)	0.04*
intraprocedural	3 (2.0%)	2 (1.6%)	1 (4.5%)	0.3
postprocedural	1 (0.7%)	0	1 (4.5%)	0.02*
Patients with event	23 (15%)	15 (12%)	8 (36%)	0.003*

* complications occurring during the first 30 days post procedure or until first hospital discharge after MitraClip implantation if the postoperative length of stay was longer than 30 days; # intracranial bleeding or bleeding that caused substantial haemodynamic compromise requiring treatment

On average, 1.5±0.6 clips per patient were implanted (0 clips in one case, one clip in 79 cases, two clips in 65 cases, three clips in five cases). Acute procedural success was achieved in 128 patients (85%). No complete clip detachment with embolisation occurred. However, four patients (2.6%) experienced a partial clip detachment from one leaflet which was successfully treated with two additional clips during the same procedure in two cases. One further patient underwent operative mitral valve replacement on day 49, and the fourth patient was scheduled for surgery but died from severe pneumonia before the operation. Before hospital discharge, 18 patients had a residual MR grade 3+ and four patients a residual MR grade 4+. These 22 individuals are summarised as "patients with failure of APS" in the following section.

SIX-MONTH OUTCOMES (MATCHED DATA FOR STATISTICAL ANALYSES)

At six months post procedure, 22 patients had already died. All 128 remaining patients could be contacted via telephone, and 112 of them consented to undergo a follow-up visit including clinical examination and transthoracic echocardiography (106 at our clinic, six visiting their resident cardiologists). 79% had an MR grade ≤2, and 65% corresponded to NYHA functional Classes I/II.

Among the 22 patients with failure of APS, four had undergone a second mitral valve intervention (surgical mitral valve replacements, n=3; second MitraClip procedure, n=1) and seven had already died before the time of the six-month follow-up. Concerning the 128 individuals with initial APS, 15 deaths and no reinterventions occurred in the first six months. However, an echocardiographic deterioration of the acute procedural result with recurrence of MR grade 3+ or 4+ was present in 14 patients at six-month follow-up (MR 3+, n=12; MR 4+, n=2) **(Figure 1)**.

TWELVE-MONTH OUTCOMES (MATCHED DATA FOR STATISTICAL ANALYSES)

Of the 131 patients who had completed 12 months post procedure at the time of manuscript preparation, 31 had already died. All 100 remaining patients were contactable by telephone, and 92 of them had already undergone a follow-up visit including echocardiography (83 at our clinic, nine at their resident cardiologist). In the eight patients who refused to undergo a surveillance visit, the follow-up was restricted to a telephone interview. Of the 92 patients with available echocardiographic data, 85% had an MR grade ≤2, and 67% were in NYHA functional Classes I/II.

Regarding the APS failure cohort, one further surgical mitral valve replacement and four further deaths occurred between six and 12-month follow-up. Among patients with initial APS, five further patients died before 12-month follow-up, two underwent a second MitraClip procedure, one received a left ventricular assist device and one underwent heart transplantation **(Figure 1)**.

EVENTS OCCURRING BEYOND 12-MONTH FOLLOW-UP

Concerning the APS failure cohort, two further patients died and one received a left ventricular assist device. No further mitral valve interventions were carried out. At the time of the last telephone follow-up in Jan/Feb 2013, nine patients (41%) were still alive in this group (n=1 in NYHA Class I, n=4 in NYHA Class II, n=4 in NYHA Class III).

Regarding the 128 patients with initial acute procedural success, 18 further deaths occurred after the 12-month follow-up, three surgical mitral valve replacements were carried out due to a deterioration of the initial procedural result, and three patients underwent heart transplantation. At the time of follow-up in Jan/Feb 2013, 90 patients (70%) were still alive in this group. Of the survivors, 24% (n=22) pertained to NYHA Class I, 46% (n=41) to NYHA Class II, 27% (n=24) to NYHA Class III and 3% (n=3) to NYHA Class IV.

IMPACT OF RECURRENT HIGH-GRADE MR DURING FOLLOW-UP

As already reported, an echocardiographic deterioration of the acute procedural result with recurrence of MR grade 3+ or 4+ was present in 14 patients after initial successful MitraClip implantation (organic MR, n=3; functional MR, n=11) at six-month follow-up. Among these individuals, four deaths (29%) occurred during follow-up, two patients underwent a second MitraClip procedure, one patient a surgical mitral valve replacement, and two patients underwent heart transplantation.

ANALYSIS OF ALL-CAUSE MORTALITY DURING FOLLOW-UP

Median follow-up was 463 days. Overall survival was 96% at 30 days, 85% at six months, 80% at 12 months, and 62% at two years. Altogether, 51 patients (34%) had died at the time of recent follow-up. The eight in-hospital deaths have already been reported. Causes

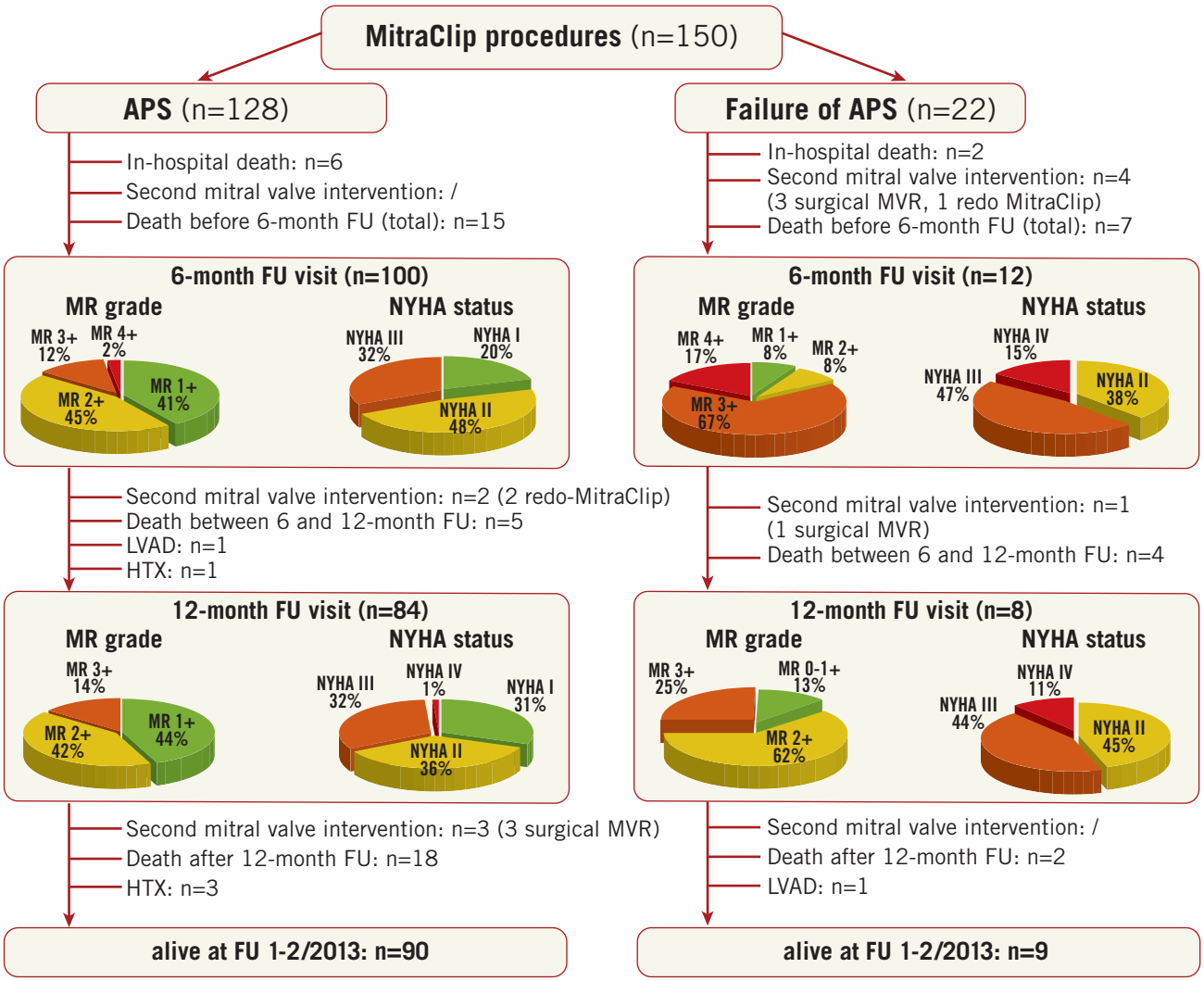


Figure 1. *Flow chart demonstrating clinical course and follow-up events of our MitraClip cohort of 150 consecutive patients depending on presence or absence of acute procedural success. APS: acute procedural success; FU: follow-up; HTX: heart transplantation; LVAD: left ventricular assist device; MR: mitral regurgitation*

of death occurring after first discharge (n=43) were the following: heart failure and/or documented ventricular arrhythmia (n=19), sudden death (n=7), death due to perioperative complications after conventional mitral valve surgery (n=2), acute renal failure (n=3), pneumonia (n=3), cancer (n=2), pleural empyoema (n=1), septic shock due to ileus (n=1), intracranial bleeding (n=1), expected death at home (or in nursing home) in bad clinical condition without further classifiable cause (n=3), unknown (n=1).

Furthermore, we performed survival analyses to test the potential of different baseline parameters, risk scores and the presence of failure of acute procedural success to predict mortality. Univariate analyses identified NYHA functional Class IV at baseline, glomerular filtration rate (GFR) <60 mL/min/1.73 m^2, logistic EuroSCORE I ≥20%, STS score ≥12%, presence of exclusion criteria for EVEREST II and failure of acute procedural success (APS) as significant predictors of mortality **(Table 3A)**. Importantly, established risk factors for elevated mortality in conventional surgery like age, female gender, previous cardiac surgery, reduced LV ejection fraction, peripheral vascular disease, and chronic lung disease did not predict mortality in our MitraClip patient cohort.

Risk factors that were found to be significant in univariate analyses were tested in multivariate analyses using a Cox proportional hazards model. Heart failure symptoms according to NYHA functional Class IV (p=0.01) and APS failure (p=0.02) proved to be significant also in multivariate analyses, whereas GFR <60 mL/min/1.73 m^2 failed to be significant (p=0.08) **(Table 3B)**.

Similarly, the independent predictive value of an STS score ≥12 could be confirmed by ANOVA analysis using forward variable selection, whereas logistic EuroSCORE I and EVEREST II exclusion criteria did not yield any additional significance. In a combined ANOVA analysis of all significant parameters, failure of APS and STS score ≥12 still had significant impact on mortality prediction, whereas NYHA functional Class IV did not, in the presence of the STS score.

Table 3A. Univariate analyses of risk factors.

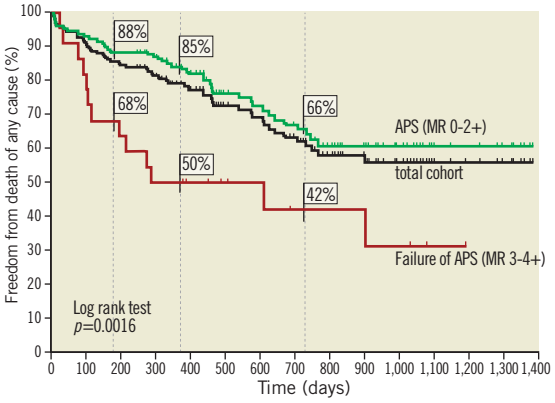
		All-cause mortality		Heart failure hospitalisation	
		Hazard ratio*	*p* [log rank]	Hazard ratio*	*p* [log rank]
Risk factor present	Age ≥70 years	1.17 [0.6-2.3]	0.64	0.77 [0.5-1.3]	0.35
	Female gender	1.14 [0.7-2.0]	0.65	1.19 [0.7-1.9]	0.49
Aetiology of MR	Degenerative MR	1.15 [0.7-2.0]	0.63	0.67 [0.4-1.1]	0.13
	Functional MR	0.81 [0.5-1.4]	0.46	1.36 [0.8-2.3]	0.24
Cardiac comorbidity	DCM	0.93 [0.5-1.7]	0.83	1.70 [1.0-2.8]	0.03*
	ICM	1.05 [0.6-1.8]	0.86	0.76 [0.5-1.2]	0.26
	LVEF <30%	1.35 [0.8-2.3]	0.29	1.80 [1.1-2.9]	0.01*
	LVEDD ≥59 mm (=median)	1.09 [0.6-1.9]	0.78	1.28 [0.8-2.1]	0.32
	LVESD ≥45 mm	0.80 [0.5-1.4]	0.44	1.17 [0.7-1.9]	0.53
	LVESD ≥55 mm	1.60 [0.9-2.9]	0.11	1.90 [1.1-3.1]	0.01*
	LVEDV ≥145 ml (=median)	0.81 [0.5-1.4]	0.47	1.19 [0.7-1.9]	0.47
	LVESV ≥81 ml (=median)	0.96 [0.6-1.7]	0.90	1.43 [0.9-2.3]	0.14
	MR grade 4+ at baseline	1.28 [0.7-2.3]	0.40	0.83 [0.5-1.3]	0.45
	NYHA IV at baseline	2.4 [1.4-4.3]	0.002*	1.82 [1.1-3.1]	0.03*
	Inotropes at baseline	1.67 [0.8-3.3]	0.14	1.74 [0.9-3.2]	0.07
	Right heart failure at baseline	1.68 [1.0-2.9]	0.06	0.91 [0.6-1.5]	0.72
	Tricuspid regurgitation	1.43 [0.8-2.5]	0.20	0.77 [0.5-1.3]	0.28
	pHTN (PAsP >50 mmHg)	1.38 [0.8-2.5]	0.28	0.98 [0.6-1.6]	0.95
	Atrial fibrillation	1.51 [0.8-2.8]	0.19	1.22 [0.7-2.0]	0.44
	Coronary artery disease	0.98 [0.6-1.7]	0.93	1.01 [0.6-1.6]	0.97
	Prior PCI	2.05 [0.7-5.7]	0.16	1.59 [0.6-4.4]	0.37
	Previous cardiac surgery	1.48 [0.9-2.6]	0.17	0.97 [0.6-1.6]	0.90
	CRT-D	0.93 [0.5-1.7]	0.81	1.48 [0.9-2.5]	0.13
Non-cardiac comorbidity	Previous stroke	0.47 [0.1-1.9]	0.29	0.88 [0.4-2.2]	0.79
	Peripheral vascular disease	1.28 [0.6-2.6]	0.50	0.65 [0.3-1.4]	0.27
	GFR <30 mL/min/1.73 m²	1.84 [0.9-3.6]	0.07	0.67 [0.3-1.5]	0.32
	GFR <60 mL/min/1.73 m²	2.05 [1.1-4.0]	0.03*	1.46 [0.9-2.5]	0.16
	COPD	1.46 [0.8-2.7]	0.24	0.83 [0.5-1.6]	0.57
	Diabetes mellitus	1.08 [0.6-1.9]	0.80	1.05 [0.6-1.8]	0.86
Risk score, stratifier	Log. EuroSCORE I ≥20%	2.02 [1.1-3.9]	0.03*	1.05 [0.6-1.7]	0.83
	STS score ≥12%	2.20 [1.3-3.8]	0.004*	1.4 [0.9-2.3]	0.19
	Outside of EVEREST II	2.45 [1.2-5.0]	0.01*	1.62 [1.0-2.7]	0.07
	Failure of procedural success	2.66 [1.4-5.0]	0.002*	3.07 [1.7-5.5]	<0.001*

Table 3B. Multivariate analyses of univariate significant risk factors.

		All-cause mortality		Heart failure hospitalisation	
		Hazard ratio*	*p* [log coxph]	Hazard ratio*	*p* [log coxph]
Comorbidity	DCM			1.61 [0.9-2.8]	0.09
	LVEF <30%			1.50 [0.8-2.8]	0.21
	LVESD ≥55 mm			0.96 [0.5-1.9]	0.91
	NYHA IV	2.11 [1.2-3.8]	0.01*	1.89 [1.1-3.4]	0.03*
	GFR <60 mL/min/1.73 m²	1.82 [0.9-3.6]	0.08		
Risk score, stratifier	Log. EuroSCORE I ≥20%	/ (ANOVA)	0.28		
	STS score ≥12%	/ (ANOVA)	<0.0001*		
	Outside of EVEREST II	/ (ANOVA)	0.08		
	Failure of procedural success	2.13 [1.2-4.1]	0.02*	2.31 [1.2-4.4]	0.01*

* 95% CI indicated in brackets. COPD: chronic obstructive pulmonary disease; CRT-D: cardiac resynchronisation therapy – defibrillator; DCM: dilative cardiomyopathy; GFR: glomerular filtration rate, calculated with MDRD formula (Levey); ICM: ischaemic cardiomyopathy; LVEF: left ventricular ejection fraction; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; pHTN: pulmonary hypertension; PAsP: pulmonary artery systolic pressure; PCI: percutaneous coronary intervention

In conclusion, failure of acute procedural success and STS score of ≥12 could be identified as highly significant independent predictors of all-cause mortality by different statistical models. A Kaplan-Meier curve demonstrating the impact of APS failure on survival is demonstrated in **Figure 2**.



Number at risk	150	127	87	60	38	23	9
APS achieved	128	113	78	54	34	20	0
Failure of APS	22	14	9	6	4	3	0

Figure 2. *Survival dependent on acute procedural success. Kaplan-Meier curve demonstrating the impact of acute procedural success (APS) on freedom from death of any cause (survival proportions at 6 months, 1 year and 2 years are indicated for patients with and without APS).*

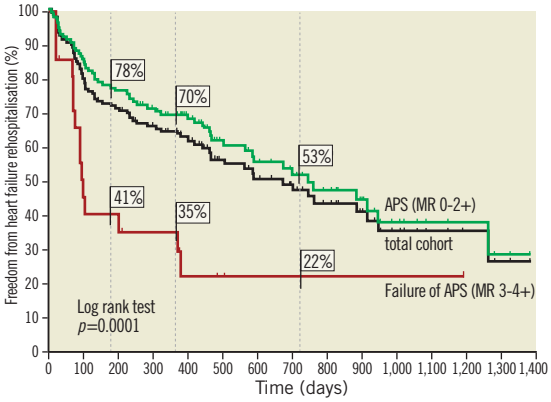
ANALYSIS OF HEART FAILURE REHOSPITALISATION DURING FOLLOW-UP

In the whole cohort, freedom from heart failure rehospitalisation was 95% at 30 days, 73% at six months, 65% at 12 months, and 47% at two years.

Univariate analyses were able to confirm a significant impact on heart failure hospitalisation for dilative cardiomyopathy (DCM), left ventricular ejection fraction (LVEF) <30%, left ventricular end-systolic diameter (LVESD) ≥55 mm, NYHA functional Class IV at baseline and failure of acute procedural success **(Table 3A)**. NYHA functional Class IV at baseline and failure of APS proved to be significant also in multivariate analysis (p=0.03 and p=0.01), whereas DCM, LVEF ≤30% and LVESD ≥55 mm were not significant independent predictors (p=0.09, p=0.21 and p=0.91). ANOVA analysis revealed that only APS failure remained a significant predictor of heart failure hospitalisation independent of the order in which the parameters were fitted into the model (**Figure 3**, corresponding Kaplan-Meier curve).

HOSPITALISATION RATE BEFORE AND AFTER MITRACLIP IMPLANTATION

We compared the heart failure hospitalisation rate during one year before and one year after the procedure in all patients who had been discharged alive after MitraClip implantation and who had completed 12 months post procedure (n=129 persons). In patients with successful procedures (n=109), a significant decrease in heart



Number at risk	150	99	64	34	21	10	4
APS achieved	128	91	61	33	20	9	4
Failure of APS	22	8	3	1	1	1	0

Figure 3. *Freedom from heart failure rehospitalisation dependent on acute procedural success. Kaplan-Meier curve demonstrating the impact of acute procedural success (APS) on freedom from heart failure rehospitalisation (survival proportions at 6 months, 1 year and 2 years are indicated for patients with and without APS).*

failure hospitalisations was observed (0.89±1.07 pre-procedure vs. 0.54±0.96 post-procedure, p=0.01), whereas no change was present in patients with APS failure (n=20, 1.45±1.79 vs. 1.30±2.43, p=0.76) **(Figure 4)**.

PREDICTORS OF ACUTE PROCEDURAL FAILURE

In order to characterise patients with acute procedural failure further, we considered baseline characteristics, echocardiographic parameters and peri-interventional features. Patients with unsuccessful procedures presented more frequently with pulmonary hypertension (defined as pulmonary artery systolic pressure of >50 mmHg, p=0.04) and met the EVEREST II eligibility criteria less frequently

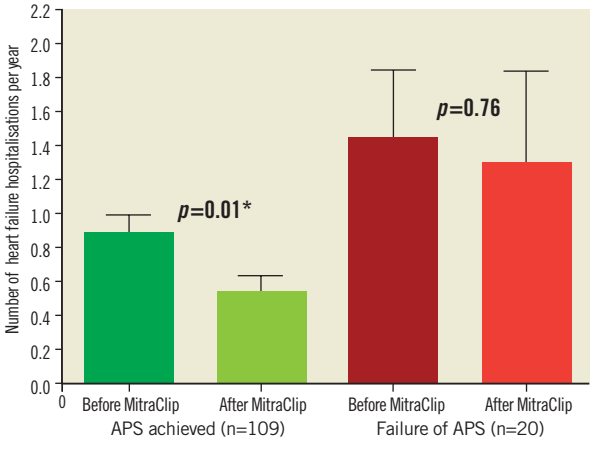


Figure 4. *Comparison of heart failure hospitalisation rates before and after MitraClip. Number of heart failure hospitalisations during 12 months before and 12 months after MitraClip implantation depending on presence or absence of acute procedural success. Bars indicate mean and standard error.*

(p=0.01) **(Table 1)**. However, remaining baseline characteristics as well as calculated surgical risk expressed by logistic EuroSCORE I and STS score did not differ. Regarding echocardiographic measurements, the patient cohort with APS failure was characterised by significantly higher left ventricular volumes and left ventricular end-diastolic diameters as well as a significantly higher prevalence of MR grade 4+ at baseline **(Table 4)**, whereas the distribution of MR aetiologies was comparable. Furthermore, total procedure time (median, 132 [105-220] vs. 93 [65-127] min, p<0.0001) and radiation time (median, 34.9 [25.3-63] vs. 21 [15-31] min, p<0.0001) were significantly higher in unsuccessful procedures, and patients were more likely to experience procedural complications like severe bleeding (p=0.03), need for prolonged ventilation (p=0.01), and partial clip detachment (p=0.04) **(Table 2)**. The distribution of one-clip, two-clip or three-clip procedures did not differ significantly.

Table 4. Baseline echocardiographic measurements.

n (%)	All patients (N=150)	APS (N=128)	Failure of APS (N=22)	*p*
Aetiology of MR				
organic	51 (34%)	46 (36%)	6 (27%)	0.43
functional	99 (66%)	82 (64%)	16 (73%)	0.43
– ICM	62 (62.6%)	53 (64.6%)	9 (52.9%)	0.36
– DCM	37 (37.3%)	29 (35.4%)	8 (47.1%)	0.36
Severity of MR				
Grade 2+	2 (1.3%)	2 (1.6%)	0	0.56
Grade 3+	54 (36%)	51 (39.8%)	3 (13.6%)	0.02*
Grade 4+	94 (62.7%)	75 (58.6%)	19 (86.4%)	0.01*
PAsP >50 mmHg	94 (63%)	76 (59%)	18 (82%)	0.04*
Median (25^{th}-75^{th} percentile)				
LVEF, %	35 (25-51)	36.5 (25-51.5)	30 (18-47.5)	0.12
LVEDD, mm	59 (51-68)	58 (50-67)	65 (56-73.5)	0.037*
LVESD, mm	45 (37-57)	44.5 (37-56)	54 (37-61)	0.22
LVEDV, ml	145 (98-225)	144 (92-221)	191 (135-257)	0.038*
LVESV, ml	81 (42-155)	80 (39-144)	115 (69-211)	0.047*

LVEF: left ventricular ejection fraction; LVEDD: left ventricular end-diastolic diameter; LVESD: left ventricular end-systolic diameter; LVEDV: left ventricular end-diastolic volume; LVESV: left ventricular end-systolic volume; MR: mitral regurgitation; PAsP: pulmonary artery systolic pressure

Discussion

First of all, our observational study provides an insight into the use of MitraClip therapy and its midterm outcomes in daily clinical practice, reporting on a cohort characterised by a median LVEF of 35% and a prevalence of functional MR of 66%. Similar patient characteristics are observed, for example, in the German transcatheter mitral valve interventions (TRAMI) registry[8] suggesting that MitraClip therapy is evolving as a new therapeutic option for heart failure patients with significant MR, possibly even as a bridge to transplant (four of our patients underwent heart transplantation one to three years after MitraClip implantation; **Figure 1**).

CLINICAL OUTCOMES

As we were able to demonstrate in our study and as consistently documented in previous studies for follow-up periods of around 12 months, MitraClip therapy is able to reduce MR severity, to reverse ventricular remodelling, and to improve clinical symptoms in a high proportion of patients with significant MR and high or prohibitive risk of conventional surgery[13-16]. To our knowledge, our study is the first that was able additionally to demonstrate a significant decrease in heart failure hospitalisations after successful MitraClip implantations.

However, all previously published studies report on patients with failure of acute procedural success, commonly defined as MR grade >2+ at discharge. In the EVEREST I trial[6] 26% of patients met this criterion, in the EVEREST II trial[7] 23%, in the EVEREST II High Risk Cohort[16] 20.5%, in the PERMIT-CARE study[13] approximately 20%, in the Swiss registry[17] 15% and in the Hamburg single-centre cohort[15] 8%. Regarding our own series, 15% of patients experienced APS failure, which is well in line with the previous reports.

PREDICTORS OF ALL-CAUSE MORTALITY AND HEART FAILURE REHOSPITALISATION

In our study, we were able to identify the failure of acute procedural success, an STS score of ≥12 and NYHA Class IV at baseline as independent predictors of all-cause mortality, and APS failure and NYHA Class IV at baseline alone as independent predictors of heart failure hospitalisation during follow-up, emphasising the adverse impact of procedural failure. Further risk predictors that have recently been reported to have significant independent impact on survival and rehospitalisation were a logistic EuroSCORE I of ≥20%[18] and the degree of residual MR[14]. However, in our own patient cohort a logistic EuroSCORE I of ≥20% was a significant predictor of all-cause mortality only in univariate analysis but lost its significant impact in multivariate ANOVA analysis as soon as the STS score was inserted into the model. Concerning the degree of post-interventional MR, only the presence of MR 3+ and 4+ (defined as failure of APS) was associated with significantly increased mortality and morbidity during follow-up, whereas no significant differences could be observed in survival curves of patients with MR 0-1+ and 2+ at discharge (p=0.6). Very recently, Sürder et al[17] also identified failure of APS and discharge MR grade as univariate significant predictors of survival among the first 100 consecutive patients in the Swiss registry.

Importantly, the presence of established risk factors for adverse outcome after conventional surgery like age, female gender, previous cardiac surgery, atrial fibrillation, peripheral vascular disease, diabetes and chronic lung disease[10] had no impact on outcome in our study as well as in a previous report[14], and should therefore not be a reason for rejection of a patient for MitraClip implantation.

PREDICTION OF PROCEDURAL FAILURE

Patients with severely dilated and overloaded ventricles who did not meet EVEREST II eligibility criteria, that is to say patients with worse clinical baseline conditions, were at higher risk of procedural failure. The resulting question whether the procedural failure is the

primary cause of worse outcomes or whether it might also be an indicator of worse baseline status cannot be answered on the basis of our observational study.

A clinical summary of the 22 cases with APS failure is presented in **Online Table 1**. The majority of unsuccessful procedures took place in our first 50 MitraClip cases. This has recently been suggested, for the most part, to reflect the impact of the learning curve[19]. However, APS failure still occurred beyond this initial experience. This indicates that procedural success is influenced by additional factors not related to learning. Many patients with APS failure in our series exhibited anatomical valve morphologies or ventricular dysfunction that met EVEREST II exclusion criteria. The main (coherent) reasons for EVEREST II ineligibility in the APS failure group were a severely reduced left ventricular ejection fraction (≤25%, n=9), severe left ventricular dilation (LVESD >55 mm, n=10), and coaptation depths of >11 mm (n=9)[6], resulting in significant volume overload and pulmonary hypertension (patients # 10, 17, 27, 29, 36, 40, 46, 57, 85, 115, 123, 126). These patients with functional MR were predominantly at high surgical risk and *per se* not good surgical candidates, because current guidelines give no surgical recommendation for patients with secondary MR and LVEF ≤30% without the option for revascularisation[10]. In patients with degenerative mitral valve disease and APS failure, the EVEREST II ineligibility resulted mainly from anatomical causes like flail gap ≥10 mm (#50), flail width ≥15 mm (#61), bileaflet prolapse (#96), or prior surgical mitral valve repair with an annuloplasty ring (#23). Renal failure would have excluded three further patients (#8, 22, 86) from the EVEREST II trial. Some of our patients with APS failure would in principle have been surgical candidates, but reasons like metastasised cancer (patient #50), repeated previous cardiac operations (#61), or patient's wish (#96) led to a referral for MitraClip implantation.

IMPACT OF RECURRENT HIGH-GRADE MR DURING FOLLOW-UP

Recurrence of MR grade 3+ or 4+ at six-month follow-up was associated with elevated mortality during further follow-up (29% in this subgroup compared to 19% in patients with MR ≤2). The late procedural failure was speculatively attributed to a progression of the underlying cardiomyopathy with alterations of LV geometry in most cases - which might also have influenced mortality in addition to MR itself worsening. No late clip detachments were observed.

STUDY LIMITATIONS

This analysis represents a single-centre experience, which could be regarded as a limitation of the study. However, the complete analysis of consecutive patients without any exclusion is never realised in registries which additionally often lack a good follow-up which could create an analytical bias. For example, in the German transcatheter mitral valve interventions (TRAMI) registry, a substantial number of patients were enrolled retrospectively which allowed no follow-up beyond discharge after MitraClip implantation. In our study, no patient was completely lost to follow-up. However, a significant proportion of patients had already died at six or 12 months, which may have caused an optimistic selection bias concerning these measurements.

Haemodynamic parameters measured during MitraClip implantation that have recently been shown to predict midterm outcome (mean pulmonary capillary wedge pressure and mean pulmonary artery pressure[20]) were not included in the present analysis. Implantation success was assessed by Doppler echocardiographic parameters that are known to be potentially challenging and associated with inter-observer variability after MitraClip implantation.

Furthermore, this purely observational study was not designed to address pathophysiological issues (particularly with regard to differences between functional and degenerative MR). This should be done by future multicentre studies.

Conclusions

Treatment of significant MR with MitraClip is efficacious and results in significant clinical improvements in a high proportion of patients after six and 12 months. In our patient cohort, the failure of acute procedural success emerged as the strongest independent predictor of midterm outcome concerning both all-cause mortality and heart failure hospitalisation during follow-up. Therefore, every effort should be undertaken to avoid APS failure. First of all, this includes a thorough discussion of the different treatment options and their risks in the Heart Team. The only randomised trial comparing MitraClip implantation and surgical MVR in patients with predominantly degenerative MR (EVEREST II[7]) demonstrated a superior efficacy of conventional surgery in terms of MR reduction and freedom of repeat interventions, whereas MitraClip therapy was associated with superior safety. This fact should be taken into account particularly in patients with degenerative mitral valve disease in whom conventional surgery as the gold standard for treatment[10] is still an option.

However, the number of elderly patients with severe functional MR and relevant comorbidities who are not good surgical candidates is expected to increase further in the future due to an ageing population and improved medical therapy. In patients who are considered ineligible for surgery, eligibility for MitraClip therapy should be carefully evaluated according to anatomical considerations. As we can confirm after analysis of our own data, the EVEREST II exclusion criteria are a useful guideline for patient selection at the beginning of MitraClip implantations in new centres, whereas patients with difficult anatomical conditions should be postponed until approximately 50 procedures have been performed. Despite this, a majority of patients with successful procedures in our series also did not meet the EVEREST II eligibility criteria, indicating that we need to carry out prospective studies to define new anatomical criteria that allow a better prediction of APS. Nevertheless, the occurrence of procedural failure with the described adverse impact will not be completely avoidable even in highly experienced centres. Patients with unsuccessful procedures require particularly close attention in post-interventional care. Corrective percutaneous or surgical interventions should be considered and discussed early.

Conflict of interest statement

M. Puls, M. Hünlich, K. Rüter, R. Seipelt and W. Schillinger have received travel expenses from Abbott Vascular. W. Schillinger has also received lecture fees from Abbott Vascular. The other authors have no conflicts of interest to declare.

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Online data supplement

Online Table 1. Summary of cases with failure of acute procedural success.

OnlineTable 1. Summary of cases with failure of acute procedural success.

Pat. #	Sex	Age (years)	log Euro SCORE I (%)	STS score (%)	Aetiology of MR	EF (%)	LVESD (mm)	LVEDD (mm)	EVEREST II eligibility	# of clips	Potential reason for failure	Reintervention on day	Death on day	Reason for death
#8	M	72	29	9	Degenerative/ prolapse AML	60	54	68	No (previous AVR, renal failure)	1	Post-procedural partial clip detachment	/	33	Septic shock after complicated in-hospital course
#10	M	80	52	10	Functional/ICM	15	73	77	No (EF, LVESD, coaptation depth 14 mm)	0	Placement of clip not successful (LVESD, coaptation depth)	/	214	Sudden death
#17	M	60	17	4	Functional/DCM	20	65	71	No (EF, LVESD)	2	LVESD	/	/	
#22	F	85	66	55	Functional/ICM	38	41	59	No (renal failure)	1	1 clip probably not sufficient	/	24	Septic shock after complicated in-hospital course
#23	F	79	32	20	Degenerative/ AML flail, prior mitral valve repair	60	23	44	No (prior surgical MVR with annuloplasty ring)	1	prior surgical MVR with annuloplasty ring	287 (operative mitral valve replacement)	287	Direct postoperative pump failure
#27	F	74	27	5	Functional/DCM	20	61	69	No (EF, LVESD, coapt. depth 12 mm)	2	LVESD, coaptation depth	81 (operative mitral valve replacement)	900	Heart failure
#29	M	75	81	24	Functional/ICM	20	70	79	No (EF, LVESD, coapt. depth 12 mm)	2	LVESD, coaptation depth	/	114	Heart failure
#36	F	57	12	2	Functional/DCM	25	50	60	No (EF)	2	Leaflets more degenerated than expected	79 (operative mitral valve replacement)	/	
#40	M	51	14	21	Functional/DCM	13	64	76	No (EF, LVESD, coapt. depth 15 mm)	2	LVESD, coaptation depth	969 (LVAD)	/	
#46	M	69	24	3	Functional/DCM	20	58	72	No (EF, LVESD, coapt. depth 16 mm)	2	LVESD, coaptation depth	/	87	Heart failure
#47	M	78	31	5	Functional/ICM	30	46	60	Yes	1	1 clip probably not sufficient	45 (second MitraClip procedure)	195	Urosepsis, acute renal failure
#50	M	66	11	3	Degenerative/flail PML	30	58	75	No (LVESD, flail gap 10 mm)	2	Flail gap	/	99	Heart failure (concomitant metastasised larynx cancer)
#57	M	59	58	20	Functional/ICM	30	54	70	No (coapt. depth 12 mm)	3	LVESD, coaptation depth	/	273	Heart failure
#61	M	70	8	5	Degenerative/flail AML	60	39	65	No (flail width 20 mm)	1	Intraprocedural partial clip detachment	49 (operative mitral valve replacement)	101	Septic shock after re-operation for prosthetic mitral valve endocarditis
#85	M	78	14	5	Functional/DCM	15	68	74	No (EF, LVESD, coapt. depth 16 mm)	2	LVESD, coaptation depth	/	/	
#86	F	83	22	17	Degenerative	65	32	44	No (previous AVR, renal failure)	1	1 clip probably not sufficient	/	610	Heart failure
#91	M	82	23	8	Functional/ICM	40	33	57	No (previous AVR)	1	1 clip probably not sufficient	/	/	
#96	F	77	18	7	Degenerative/ bileaflet prolapse	35	33	49	No (bileaflet prolapse)	2	Bileaflet prolapse, A3 segment involved	/	/	
#103	M	80	17	4	Functional/ICM	50	34	54	Yes	1	1 clip probably not sufficient	/	/	
#115	M	79	64	25	Functional/ICM	16	55	60	No (EF, LVESD)	2	Chordal rupture during placement of second clip into a medial residual jet	/	92	Sudden death
#123	M	54	4	3	Functional/DCM	35	52	66	No (coapt. depth 12)	2	First clip to medial			
#126	M	71	54	14	Functional/ICM	30	60	77	No (LVESD, coapt. depth 15)	2	LVESD, coaptation depth	/	/	

AML: anterior mitral leaflet; AVR: aortic valve replacement; DCM: dilative cardiomyopathy; EF: ejection fraction; ICM: ischaemic cardiomyopathy; LVESD: left ventricular end-systolic diameter; MVR: mitral valve repair; PML: posterior mitral leaflet