



Predictors of mortality in ischaemic versus non-ischaemic functional mitral regurgitation after successful transcatheter mitral valve repair using MitraClip: results from two high-volume centres

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Abstract

Introduction Transcatheter edge-to-edge mitral valve repair using the MitraClip has been widely performed in surgical high-risk patients with reduced left ventricular systolic function and severe functional mitral regurgitation (FMR). Ischaemic heart disease is the leading aetiology of heart disease worldwide. We aimed to assess the clinical implications of ischaemic aetiology in patients with severe FMR who underwent MitraClip implantation.

Methods and results From two high-volume centres in Germany, we retrospectively compared the clinical outcomes and clinical predictors of all-cause mortality after MitraClip implantation in patients with ischaemic (I-FMR) and non-ischaemic FMR (NI-FMR). In the overall FMR cohort ($n=575$), there were 336 (58%) patients with I-FMR and 239 (42%) with NI-FMR. There was no significant difference in survival between the two groups (log-rank $p=0.78$). In a multivariable Cox regression analysis of all-cause mortality, different predictors were observed for either group. In I-FMR patients, decreasing tricuspid annular systolic excursion [adjusted hazard ratio (HR_{adj}) 1.06, 95% confidence interval (95% CI) 1.01–1.14 / 1 mm, $p=0.028$] and increasing logistic EuroSCORE (HR_{adj} 1.02, 95% CI 1.00–1.03, $p=0.037$) were independent predictors, whereas in NI-FMR patients, NT-pro BNP (HR_{adj} 1.05, 95% CI 1.02–1.08, $p=0.001$) and age (HR_{adj} 1.06, 95% CI 1.01–1.11, $p=0.013$) were independently predictive of mortality.

Conclusions Despite the similar survival between ischaemic and non-ischaemic FMR, different predictors of all-cause mortality were demonstrated. Further clinical studies are mandated to focus on each FMR subgroup with stratification by ischaemic origin.

Keywords Transcatheter edge-to-edge mitral valve repair · MitraClip · Functional mitral regurgitation · Ischaemic functional mitral regurgitation · Non-ischaemic functional mitral regurgitation

Abbreviations

CABG	Coronary artery bypass grafting	LV	Left ventricle/ventricular
CAD	Coronary artery disease	logES	logistic EuroSCORE
eGFR	Estimated glomerular filtration rate	MR	Mitral regurgitation
FMR	Functional mitral regurgitation	NT-proBNP	N-terminal pro-brain natriuretic peptide
HF	Heart failure	NYHA	New York Heart Association
IQR	Interquartile range	RV	Right ventricle/ventricular
		TAPSE	Tricuspid annular plane systolic excursion

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Introduction

Transcatheter mitral valve repair using the MitraClip® system (Abbott, Menlo Park, CA, USA) has been used widely in clinical settings, especially in surgical high-risk patients with severe mitral regurgitation (MR) [1–4]. Functional mitral regurgitation (FMR) is an aetiology

arising mainly from left ventricular (LV) dysfunction and has been the primary focus of previously published studies [5–11] and several ongoing large prospective studies [12] [RESHAPE-HF 2 (NCT02444338), MATTERHORN (NCT02371512), COAPT (NCT01626079), and MITRA-FR (NCT01920698)].

Ischaemic heart disease is the leading aetiology of heart disease globally. The prevalence of ischaemic aetiology was reported to be 48–57% in patients with FMR who underwent MitraClip treatment [10, 13–15]. In daily practice, although concomitant ischaemic FMR reportedly aggravates the symptoms of heart failure (HF) in patients with ischaemic cardiomyopathy [16, 17], mitral valve surgery has been avoided in a substantial portion of patients because of the high risk of perioperative mortality [18].

MitraClip implantation is an effective therapy for patients with severe ischaemic as well as non-ischaemic FMR [10]. However, the clinical background and the comorbidities appear to be different in these cohorts, and further investigation is required to elucidate the clinical impact of ischaemic origin on therapeutic strategies for individual patients with severe FMR. Therefore, we conducted a large cohort, retrospective study at two high-volume centres in Germany to assess the clinical differences and outcomes of the MitraClip implantation in patients with ischaemic FMR vs. patients with non-ischaemic FMR.

Methods

Definitions of ischaemic and non-ischaemic FMR

Ischaemic FMR is the consequence of LV dysfunction following an ischaemic event, without relevant structural abnormalities of the mitral valve (MV) apparatus, in which there are two different mechanisms, such as regional LV dysfunction with asymmetric tethering of MV leaflet and global LV dilatation with increased sphericity [19]. Asymmetric tethering is characterized by dislocation of the centromedial papillary muscle and its chordae, resulting in more tethered posteromedial scallop (P3) than anterolateral one (P1), typically seen in patients after inferior myocardial infarct. In addition, given global LV dysfunction based on post-infarct remodelling, increased LV sphericity causes dislocation of both papillary muscles and consequent symmetric tethering followed by malcoaptation of MV leaflets. The latter mechanism plays a main role in post-anterior infarct MR and non-ischaemic FMR due to non-ischaemic DCM [20–22]. Coronary artery disease (CAD) was considered present in patients with documented significant stenosis (> 75%) in at least one coronary artery. CAD patients with LV dysfunction and FMR without significantly degenerative mitral leaflets

were defined as having ischaemic FMR. In contrast, non-ischaemic FMR is caused by global LV systolic dysfunction and/or mitral annular dilatation due to other cardiac diseases rather than CAD, such as non-ischaemic DCM and long-standing atrial fibrillation. Some non-ischaemic DCM patients had also significant coronary stenosis which was unlikely to cause global LV dysfunction, classified as non-ischaemic FMR group. ($n = 11$).

Patients

This study had a two-centre design, representing a collaboration between the Asklepios Klinik St. Georg (Hamburg, Germany) and the Brandenburg Heart Centre (Bernau, Germany). Of 934 consecutive patients who underwent MitraClip implantation between September 2009 and June 2016 at either centre (557 patients from Hamburg and 387 from Bernau), 575 patients with FMR were enrolled in this study. We excluded patients with degenerative MR ($n = 307$); patients who underwent previous MV procedures ($n = 21$); patients who had undetermined aetiology of FMR because of lacking clinical data ($n = 20$); and patients who had incomplete information regarding procedural results ($n = 11$) (Fig. 1). The follow-up data were acquired from medical records, including clinical manifestation, past history, transthoracic echocardiography, and blood examination. We investigated baseline patient characteristics and echocardiographic findings as well as survival rates to elucidate the differences between patients with and without ischaemic FMR aetiology. All cases were discussed with the local heart team.

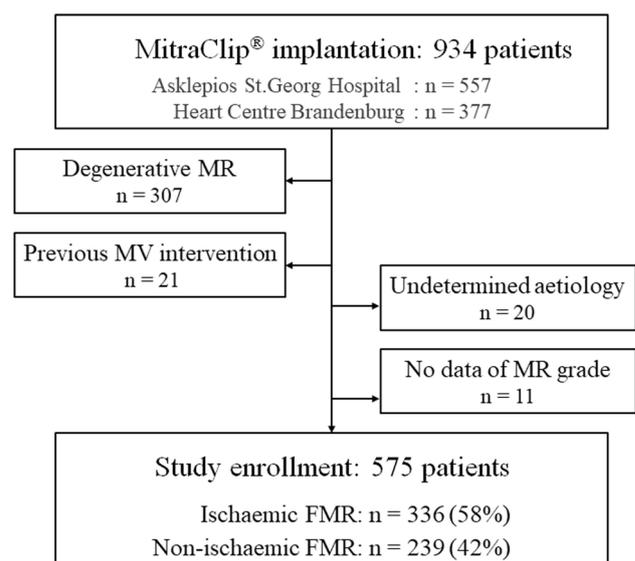


Fig. 1 Patient flow chart

The MitraClip procedure and the diagnosis of MR severity

The details of the MitraClip device and procedure were published in previous reports [1, 23]. The diagnosis of FMR was made based on echocardiographic findings, according to the recent European Society of Cardiology/European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease [24]. The severity of MR was classified as 1+ (mild), 2+ (moderate), 3+ (moderate-to-severe), and 4+ (severe). The indication for the MitraClip procedure was symptomatic HF (New York Heart Association (NYHA) class II–IV) related to moderate-to-severe or severe FMR despite optimized medical therapy, in the presence of high surgical risk according to the consensus of the institutional heart team. Procedural success was defined as a residual MR grade of $\leq 2+$ which was assessed by the transthoracic echocardiography at discharge.

Statistics

Continuous variables are expressed as mean \pm standard deviation or as median and interquartile range (IQR; first-to-third quartile), where appropriate. These were compared using unpaired Student's *t* test if normally distributed or Mann–Whitney *U* test if not normally distributed. Categorical variables were expressed as counts (percentages), which were compared using Chi-square test or Fisher's exact test (if the number of at least one cell < 5). We used a Cox proportional hazards model to identify clinical predictors of all-cause mortality. In multivariable analysis, the model was adjusted by age, estimated glomerular filtration rate (eGFR), logES, NYHA class IV dyspnoea, N-terminal pro-brain natriuretic peptide (NT-pro BNP), and tricuspid annular plane systolic excursion (TAPSE). Survival analysis was conducted using the Kaplan–Meier method. The differences in survival between subgroups were assessed with the log-rank test. A *p* value of < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS® software, version 24 (IBM Corporation, New York, NY, United States).

Results

There were 336 patients (58%) with ischaemic FMR and 239 (42%) with non-ischaemic FMR in the overall cohort (Fig. 1). The median follow-up was 409 (IQR 106–798) days. The follow-up rates were 83% at 1 year and 73% at 2 years.

Baseline characteristics

The baseline patient characteristics of patients with successful MitraClip implantation are shown in Table 1. In the ischaemic FMR group, there were fewer female patients (25% vs. 40%, $p < 0.001$); a lower prevalence of atrial fibrillation (61% vs. 70%, $p = 0.023$); a lower prevalence of cardiac resynchronization therapy (20 vs. 29%, $p = 0.017$); a higher prevalence of hyperlipidaemia (75 vs. 38%, $p < 0.0001$), and a higher prevalence of chronic obstructive pulmonary disease (23 vs. 15%, $p = 0.023$) than in the non-ischaemic FMR group. All patients with ischaemic FMR had a history of CAD, and 93% of patients had received coronary revascularisation [percutaneous coronary intervention (74%) and coronary artery bypass grafting (CABG) (46%)]. All other patients without coronary revascularization (7%) had prior myocardial infarction. The logistic EuroSCORE (logES) was significantly higher in the ischaemic FMR group (25.3 ± 18.3 vs. 17.0 ± 12.9 , $p < 0.0001$). There were no significant differences in age, body mass index, eGFR, and NT-proBNP, or in the prevalence of peripheral artery disease, and implantable cardioverter defibrillator, between the two groups. M-mode parameters of the LV were similar, but TAPSE was significantly lower in the ischaemic FMR group (15.4 ± 4.5 vs. 16.6 ± 4.7 mm, $p = 0.004$).

Procedural results of MitraClip implantation

The distributions of the number of clips implanted in the two patient groups are shown in Fig. 2. Note that no clip could be implanted in three patients. The distributions of FMR severity at baseline and discharge are shown in Fig. 3. With FMR grade $> 2+$ at discharge in 26 patients (7.7%) with ischaemic FMR and 17 patients (7.1%) with non-ischaemic FMR ($p = 0.78$), procedural success was achieved in 310 patients (92.3%) and 222 patients (92.9%), respectively. The median length of hospital stay after MitraClip was 6 (IQR 4–9) days in the ischaemic FMR group and 5 (IQR 4–8) days in the non-ischaemic FMR group ($p = 0.13$). There were 8 in-hospital deaths (2.4%), 17 deaths (5.1%) at 30 days, and 111 deaths (33.0%) during follow-up in the ischaemic FMR group; corresponding numbers and rates were 9 (3.8%), 17 (7.1%), and 65 (27.2%) in the non-ischaemic FMR group ($p = 0.33$, $p = 0.22$, and 0.14, respectively).

Survival of patients after successful MitraClip implantation

From the overall cohort, 310 patients who underwent successful MitraClip implantation (MR grade $\leq 2+$ at discharge) in ischaemic FMR and 222 in non-ischaemic FMR were evaluated in survival analysis. These patients were followed for a median of 410 (IQR 107–798) days. The Kaplan–Meier

Table 1 Baseline patient characteristics in patients with acute procedural success

	Ischaemic FMR	Non-ischaemic FMR	<i>p</i> value
No. of patients	310	222	
Age, years	74.0±9.0	73.0±9.7	0.27
Female gender	77 (25)	88 (40)	<0.001
Body mass index, kg/m ²	26.4±4.3	26.0±4.5	0.16
log. EuroSCORE, %	25.3±18.3	17.0±12.9	<0.0001
log. EuroSCORE≥20%	142/276 (51)	62/193 (32)	<0.0001
Heart surgery	149/305 (49)	23/218 (11)	<0.0001
CAD	310/310 (100)	9/220 (4)	<0.0001
PCI	226/306 (74)	8/219 (4)	<0.0001
CABG	143/309 (46)	0/219 (0)	<0.0001
MI	163/305 (53)	6/214 (3)	<0.0001
Hypertension	231/309 (75)	135/220 (61)	0.001
Hyperlipidaemia	139/186 (75)	48/128 (38)	<0.0001
Diabetes	157/309 (51)	98/222 (44)	0.13
eGFR, ml/min/1.73m ²	51.8±22.2	52.0±21.2	0.92
eGFR<30 ml/min/1.73m ²	51/293 (17)	29/210 (14)	0.28
Atrial fibrillation	187/308 (61)	156/222 (70)	0.023
PAD	34/186 (18)	16/128 (13)	0.17
COPD	72/309 (23)	34/222 (15)	0.023
ICD	135/310 (44)	90/222 (41)	0.49
CRT	63/310 (20)	65/222 (29)	0.017
NYHA functional class			0.90
< III	22/280 (8)	15/211 (7)	
III	186/280 (66)	144/211 (68)	
IV	72/280 (26)	52/211 (25)	
NT-proBNP, 10 ³ pg/ml	4.4 [2.5–9.0] (<i>n</i> =245)	4.7 [2.2–9.7] (<i>n</i> =175)	0.73
LVEF, %	31.4±12.0 (<i>n</i> =299)	33.2±14.9 (<i>n</i> =217)	0.63
LVEDD, mm	63.5±9.2 (<i>n</i> =291)	63.4±11.2 (<i>n</i> =208)	0.69
LA diameter, mm	45.0±5.2 (<i>n</i> =94)	47.0±7.6 (<i>n</i> =77)	0.058
TR grade			0.54
0 or 1+	91/227 (40)	60/162 (37)	
≥2+	136/227 (60)	102/162 (63)	
TRPG, mmHg	43.5±15.0 (<i>n</i> =206)	42.7±12.7 (<i>n</i> =132)	0.97
TAPSE, mm	15.4±4.5 (<i>n</i> =288)	16.6±4.7 (<i>n</i> =214)	0.004
TAPSE<17 mm	163/265 (62)	103/199 (52)	0.036

Values are counts (percentage), mean±standard deviation, or median [first-to-third quartile]

CABG, coronary artery bypass grafting; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CRT, cardiac resynchronization therapy; eGFR, estimated glomerular filtration rate; ICD, implantable cardioverter defibrillator; I-FMR, ischaemic functional mitral regurgitation; LA, left atrial; LVEF, left ventricular ejection fraction; LVEDD, left ventricular end-diastolic diameter; MI, myocardial infarction; MR, mitral regurgitation; NI-FMR, non-ischaemic functional mitral regurgitation; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PAD, peripheral arterial disease; PAH, pulmonary artery hypertension; PCI, percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; TRPG, tricuspid regurgitation pressure gradient

curves of cumulative survival are shown in Fig. 4. There was no significant difference in survival (log-rank *p*=0.78). The estimated survival rates at 1 year and 2 years were 76% (95% CI 71–81%) and 66% (95% CI 60–73%) in the ischaemic FMR group, and 82% (95% CI 77–89%) and 69% (95% CI 61–77%) in the non-ischaemic FMR group, respectively.

In a univariate Cox proportional hazards regression analysis of all patients, logES, age, history of CABG, diabetes, eGFR, atrial fibrillation, NYHA class IV, NT-pro BNP, and TAPSE were significant predictors of all-cause mortality (Table 2). In a multivariable analysis of all

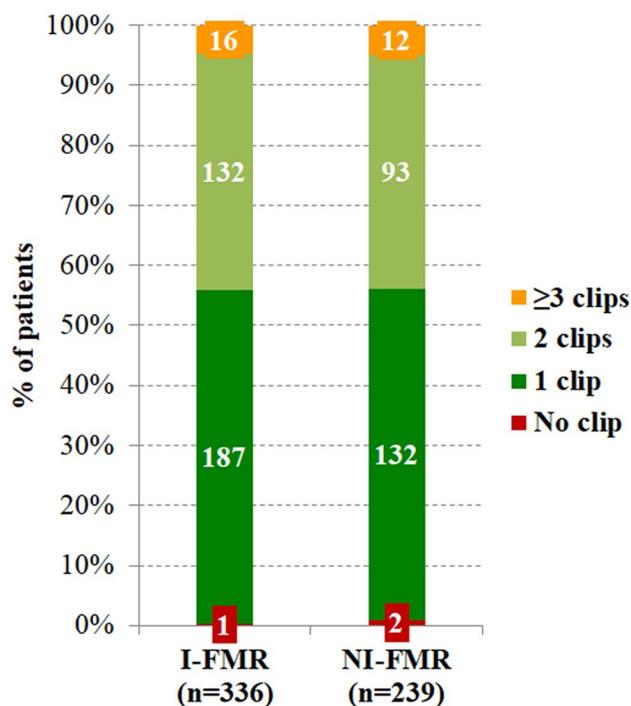


Fig. 2 Distributions of clips implanted in the two study groups. Numbers in column segments denote numbers of patients. *I-FMR* ischaemic functional mitral regurgitation, *NI-FMR* non-ischaemic functional mitral regurgitation

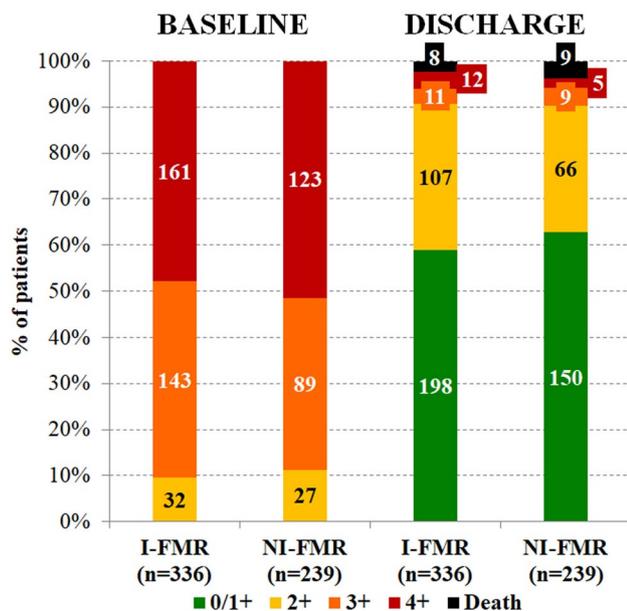


Fig. 3 Distributions of FMR severity at baseline and at discharge in the two study groups. Numbers in column segments denote numbers of patients. *I-FMR* ischaemic functional mitral regurgitation, *NI-FMR* non-ischaemic functional mitral regurgitation

patients, NT-proBNP, age, and TAPSE remained statistically

significant in the model, whereas the ischaemic origin of FMR when forced into the model did not impact on survival (Table 3).

Survival analysis with stratification by ischaemic vs. non-ischaemic FMR

Different predictors of mortality were observed in the two groups. In the univariate analysis for the ischaemic FMR group, logES, age, history of CABG, history of heart surgery, diabetes, eGFR, NT-proBNP, and TAPSE were identified as clinical predictors of all-cause mortality; in the non-ischaemic FMR group, age, NYHA class IV dyspnoea, and NT-proBNP were associated with mortality (Table 2). In the multivariable analysis, logES and TAPSE were independently predictive of mortality in the ischaemic FMR group, indicating a 2% increase in the likelihood of death with every 1% increase in logES, and a 6% increase in the likelihood of death with every 1 mm decrease in TAPSE (Table 3). NT-pro BNP and age were independently predictive of death in the non-ischaemic FMR group, with an increase in NT-pro BNP by 1000 pg/ml associated with a 5% increase in the likelihood of death, and a 1-year increase in age associated with a 6% increase in likelihood of death (Table 3).

Discussion

In this study of 310 patients with ischaemic FMR and 222 patients with non-ischaemic FMR having undergone successful MitraClip implantation, we found that survival was not different between the two patient groups, but that the baseline characteristics and the predictors of mortality were different. We recruited patients with moderate-to-severe or severe FMR who presented with symptomatic heart failure and reduced LV function and were at high risk for cardiac surgery. These patients were in advanced stages of HF and were considered clinically challenging. The main mechanisms of impaired mitral leaflet coaptation were thought to be different in both groups. Nevertheless, the procedural results of MitraClip implantation were the same in both groups. MitraClip implantation enables operators to directly manipulate the mitral leaflets in the beating heart under echocardiographic guidance, and to modify treatment by reattempting to grasp the mitral leaflets, and to perform an additional implantation of MitraClip if procedural results appear unfavourable. These procedural advantages may have resulted in the similar success and survival rates after MitraClip implantation in both groups. Moreover, in terms of the entire clinical spectrum of HF patients with reduced EF, HF progression might have been similar in both groups, in which I-FMR demonstrated no predictive impact on survival after MC implantation.

Fig. 4 Kaplan–Meier survival curves of 310 successfully treated patients with ischaemic functional mitral regurgitation (FMR) and 222 successfully treated patients with non-ischaemic FMR

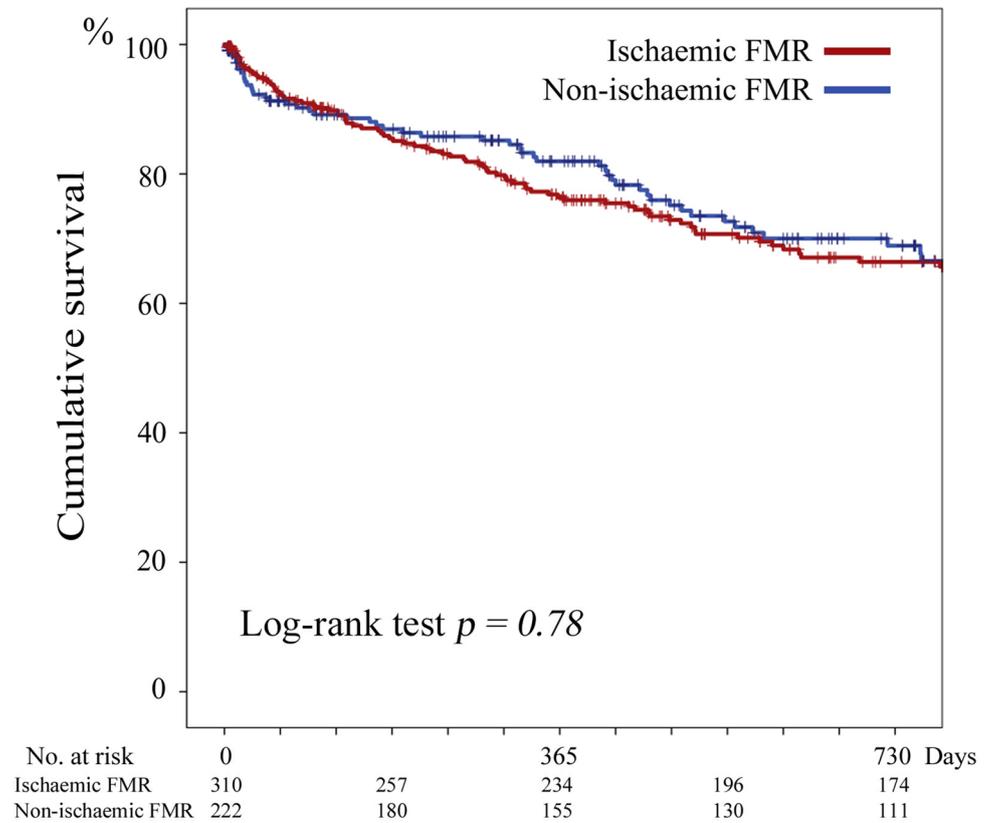


Table 2 Univariable analysis of predictors of mortality in patients with acute procedural success

Covariates	All patients (n = 532)		Ischaemic FMR (n = 310)		Non-ischaemic FMR (n = 222)	
	HR [95% CI]	p value	HR [95% CI]	p value	HR [95% CI]	p value
Ischaemic origin of FMR	1.05 [0.76–1.45]	0.78				
log. EuroSCORE	1.02 [1.01–1.03]	<0.0001	1.02 [1.01–1.03]	<0.001	1.02 [1.00–1.04]	0.087
Age	1.03 [1.01–1.05]	<0.001	1.03 [1.01–1.06]	0.014	1.04 [1.01–1.07]	0.021
Female gender	0.96 [0.68–1.36]	0.81	0.72 [0.42–1.21]	0.22	1.33 [0.80–2.21]	0.27
Body mass index	0.98 [0.94–1.02]	0.36	0.99 [0.94–1.05]	0.76	0.97 [0.91–1.03]	0.29
Myocardial infarction	0.87 [0.62–1.24]	0.45	0.86 [0.57–1.30]	0.46		
PCI	0.90 [0.65–1.25]	0.54	0.87 [0.56–1.37]	0.56		
CABG	1.48 [1.06–2.06]	0.022	1.66 [1.10–2.50]	0.017		
Heart surgery	1.33 [0.96–1.84]	0.091	1.59 [1.05–2.41]	0.028	0.82 [0.35–1.91]	0.64
Hypertension	1.21 [0.85–1.72]	0.30	1.46 [0.87–2.45]	0.15	0.96 [0.57–1.61]	0.88
Diabetes	1.62 [1.18–2.23]	0.003	1.95 [1.28–2.97]	0.002	1.20 [0.72–1.99]	0.49
eGFR	0.98 [0.98–0.99]	0.0001	0.98 [0.97–0.99]	0.001	0.99 [0.97–1.00]	0.059
Atrial fibrillation	1.56 [1.10–2.22]	0.013	1.52 [0.98–2.36]	0.059	1.69 [0.92–3.13]	0.093
NYHA class IV	1.48 [1.04–2.10]	0.028	1.13 [0.71–1.81]	0.60	2.26 [1.33–3.86]	0.003
NT-proBNP—10 ³ pg/ml increase	1.02 [1.02–1.03]	<0.0001	1.02 [1.00–1.03]	0.009	1.06 [1.03–1.08]	<0.0001
LVEF	1.00 [0.99–1.01]	0.90	0.99 [0.98–1.01]	0.53	1.01 [0.99–1.03]	0.38
LVEDD	0.99 [0.97–1.01]	0.29	1.00 [0.98–1.02]	0.85	0.98 [0.96–1.01]	0.18
TAPSE—1 mm decrease	1.05 [1.01–1.10]	0.011	1.06 [1.01–1.12]	0.012	1.03 [0.97–1.10]	0.32

CABG, coronary artery bypass grafting; CI, confidence interval; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation; HR, hazard ratio; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro-brain natriuretic peptide; NYHA, New York Heart Association; PCI, percutaneous coronary intervention; TAPSE, tricuspid annular plane systolic excursion

Table 3 Multivariable analysis of predictors of mortality in patients with acute procedural success

	All patients			Ischaemic FMR			Non-ischaemic FMR		
	Adjusted HR	95% CI	<i>p</i> value	Adjusted HR	95% CI	<i>p</i> value	Adjusted HR	95% CI	<i>p</i> value
Ischaemic origin	0.72	0.47–1.12	0.15						
NT-proBNP—10 ³ pg/ml increase	1.01	1.00–1.03	0.023	1.01	0.99–1.02	0.34	1.05	1.02–1.08	0.001
Age	1.03	1.00–1.06	0.038	1.01	0.97–1.05	0.54	1.06	1.01–1.11	0.013
TAPSE—1 mm decrease	1.05	1.00–1.10	0.044	1.06	1.01–1.14	0.028	1.03	0.96–1.10	0.36
eGFR	0.99	0.98–1.00	0.050	0.99	0.97–1.00	0.16	1.00	0.98–1.01	0.56
log _e EuroSCORE	1.01	1.00–1.02	0.21	1.02	1.00–1.03	0.037	1.00	0.97–1.02	0.72
NYHA class IV	1.04	0.65–1.65	0.88	0.82	0.42–1.58	0.55	1.53	0.76–3.08	0.23
LVEF	1.00	0.98–1.02	0.92						

CI, confidence interval; eGFR, estimated glomerular filtration rate; FMR, functional mitral regurgitation; HR, hazard ratio NT-proBNP, N-terminal pro B-type natriuretic peptide; TAPSE, tricuspid annular plane systolic excursion

The results of the multivariable analysis in the ischaemic FMR cohort suggest that their comorbidities played critical roles for survival, even though the MitraClip procedure may have ameliorated their HF condition in addition to coronary revascularization and optimized medical treatment. Interestingly, the predictive impacts of NT-proBNP, eGFR, and age were absent. It is also statistically plausible that the logES might be behaving as a substitute variable, since age, LV function, NYHA class, and renal dysfunction are part of the score. Indeed, in the present study cohort, age ($r=0.41$), NT-proBNP ($r=0.26$), and eGFR ($r=-0.27$) showed mild-to-moderate correlation with the logES. Furthermore, right ventricular (RV) systolic function was recognized as an independent predictor of all-cause mortality, in which TAPSE was significantly lower than in patients with non-ischaemic FMR ($p=0.003$). RV dysfunction occurs in patients with severe FMR and advanced HF, suggesting worse outcomes after MitraClip implantation [8, 25–27]. In those with proximal right coronary artery disease, the RV function can be directly impaired as a result of RV branch ischaemia [28], and inferior MI associates with higher grade of ischaemic MR than anterior MI [29]. Inferior MI and circumflex-related infarction are associated with papillary muscle infarction [30]. However, any culprit coronary vessels and other parameters of RV function were not investigated in the present study. Further studies are needed to clarify these issues.

Despite relevant differences in baseline characteristics, the survival rates were similar in both groups, in which unmeasured confounders in non-ischaemic FMR might have balanced out the differences affecting survival, e.g. long history of non-ischaemic cardiac disease and subsequent physical deconditioning. Indeed, in the non-ischaemic FMR cohort, we observed no difference in the logES between those with and without death during the follow-up (18.2 ± 13.3 vs. 16.4 ± 12.7 , $p=0.39$), suggesting that their comorbidities played no role in predicting mortality after

successful MitraClip implantation. Thus, it should be noted that no other determinants, e.g. malignant disease, liver cirrhosis, and frailty, were taken into account to estimate the mortality in the logES model.

Similar to the results in the overall cohort, in the non-ischaemic FMR cohort, NT-proBNP and age influenced survival after successful MitraClip implantation, while the marker of RV function was not predictive of death. In general, most cardiomyopathies begin from the left side of the heart, and the RV may be involved only in advanced stages of HF. Theoretically, TAPSE reflects not only systolic function but also RV preload, and markers of RV dysfunction improved after the MitraClip implantation [22, 31]. It is possible that TAPSE might have been modified by volume retention in decompensated FMR patients before MitraClip implantation, and did not reflect the baseline HF progress. Although a different LV loading status can be presumed between the groups, further study is needed to elucidate this issue.

Recently, some investigators reported the clinical implications of ischaemic aetiology in an FMR cohort [10, 14, 32]. Similar procedural outcomes and survival between both groups have already been reported in the study from the Pilot Sentinel registry of the European Society of Cardiology [10]. Moreover, patients with ischaemic FMR have presented more comorbidities and higher EuroSCOREs than those with non-ischaemic FMR, in line with our study [10, 14, 32].

Limitations

We are aware of several study limitations. First, though this registry included a large cohort of FMR patients who underwent transcatheter mitral valve repair using the MitraClip, the number of participating institutions was limited, and both were from the same country. Therefore, it might not be possible to generalise these findings. Second, there was

unavoidable selection bias in the investigation of the nature of ischaemic FMR. All patients had severe FMR and HF symptoms, and we excluded patients who had previously undergone invasive mitral valve treatment. Thus, patients with significant MR requiring surgical treatment at the time of CABG surgery were not included in this study. This means that almost all severe FMRs developed during the chronic phase after the index ischaemic event in the ischaemic FMR cohort with previous CABG. Third, the morphological differences in the mitral valve apparatus between the two groups were not determined in this study. Although the definition of I-FMR by echocardiography still remains challenging, future studies are mandated to pursue the definitions using MV tethering and LV sphericity. Finally, we did not assess other follow-up data including symptoms, physical capacity, and echocardiography.

Conclusions

We conducted this registry study of transcatheter mitral valve repair using the MitraClip at two centres in Germany. In the present study, we confirmed previous findings of different patient characteristics but similar survival in ischaemic and non-ischaemic FMR. From the survival analysis, we found different predictors for survival after successful MitraClip implantation between patients with ischaemic FMR and with non-ischaemic FMR. These differences were determined to originate from different background characteristics between ischaemic FMR, representing multi-comorbidities, and non-ischaemic FMR as a result of left-sided HF progression. Further clinical studies are needed on each subgroup, stratified according to FMR origin.

Impact on daily practice

Symptomatic heart failure patients with reduced ejection fraction and ischaemic FMR have been targeted as the largest cohort among MitraClip candidates. They have more comorbidities than the patients with FMR of non-ischaemic origin. Importantly, although the results of MitraClip treatment and survival are similar in both groups, we must be aware of the heterogeneity in their backgrounds and survival predictors after the successful procedure. Thus, TAPSE and logES are useful to predict survival only in the ischaemic FMR cohort, while other parameters, such as NT-proBNP and age, should be taken into account in the non-ischaemic FMR cohort. Ischaemic origin in FMR patients should be addressed in future studies, to elucidate the essential differences between two origins of FMR in morphological analyses of the mitral valve apparatus and in the therapeutic strategy of MitraClip implantation.

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Compliance with ethical standards

Conflict of interest Dr. Kuck has received research funding from Abbott Vascular. Dr. Frerker, Dr. Butter, and Dr. Neuss have received lecture honoraria and travel grants from Abbott Laboratories, Abbott Park (Illinois, USA). All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

Ethical approval All patients provided written informed consent and the study protocol conformed to the ethical guidelines of the 1964 Declaration of Helsinki and its later amendments.

References

1. Feldman T, Wasserman HS, Herrmann HC, Gray W, Block PC, Whitlow P, St Goar F, Rodriguez L, Silvestry F, Schwartz A, Sanborn TA, Condado JA, Foster E (2005) Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. *J Am Coll Cardiol* 46:2134–2140
2. Feldman T, Kar S, Rinaldi M, Fail P, Hermiller J, Smalling R, Whitlow PL, Gray W, Low R, Herrmann HC, Lim S, Foster E, Glower D (2009) Everest Investigators. Percutaneous mitral repair with the MitraClip system: safety and midterm durability in the initial EVEREST (Endovascular Valve Edge-to-Edge REpair Study) cohort. *J Am Coll Cardiol* 54:686–694
3. Maisano F, Franzen O, Baldus S, Schäfer U, Hausleiter J, Butter C, Ussia GP, Sievert H, Richardt G, Widder JD, Moccetti T, Schillinger W (2013) Percutaneous mitral valve interventions in the real world: early and 1-year results from the ACCESS-EU, a prospective, multicenter, nonrandomized post-approval study of the MitraClip therapy in Europe. *J Am Coll Cardiol* 62:1052–1061
4. Baldus S, Schillinger W, Franzen O, Bekerredjian R, Sievert H, Schofer J, Kuck KH, Konorza T, Mollmann H, Hehrlein C, Ouarak T, Senges J, Meinertz T, German Transcatheter Mitral Valve Interventions (TRAMI) investigators (2012) MitraClip therapy in daily clinical practice: initial results from the German transcatheter mitral valve interventions (TRAMI) registry. *Eur J Heart Fail* 14:1050–1055
5. Rossi A, Dini FL, Faggiano P, Agricola E, Ciccoira M, Frattini S, Simioniu A, Gullace M, Ghio S, Enriquez-Sarano M, Temporelli PL (2011) Independent prognostic value of functional mitral regurgitation in patients with heart failure. A quantitative analysis of 1256 patients with ischaemic and non-ischaemic dilated cardiomyopathy. *Heart* 97:1675–1680
6. Taramasso M, Maisano F, Latib A, Denti P, Buzzatti N, Cioni M, La Canna G, Colombo A, Alfieri O (2014) Clinical outcomes of MitraClip for the treatment of functional mitral regurgitation. *EuroIntervention* 10:746–752
7. Kaneko H, Suzuki S, Uejima T, Kano H, Matsuno S, Takai H, Oikawa Y, Yajima J, Aizawa T, Yamashita T (2014) Functional mitral regurgitation and left ventricular systolic dysfunction in the recent era of cardiovascular clinical practice, an observational cohort study. *Hypertens Res* 37:1082–1087
8. Kaneko H, Neuss M, Weissenborn J, Butter C (2016) Prognostic significance of right ventricular dysfunction in patients with functional mitral regurgitation undergoing MitraClip. *Am J Cardiol* 118:1717–1722
9. Kajimoto K, Sato N, Takano T, investigators of the Acute Decompensated Heart Failure Syndromes (ATTEND) registry (2016)

- Functional mitral regurgitation at discharge and outcomes in patients hospitalized for acute decompensated heart failure with a preserved or reduced ejection fraction. *Eur J Heart Fail* 18:1051–1059
10. Pighi M, Estevez-Loureiro R, Maisano F, Ussia GP, Dall'Arca G, Franzen O, Laroche C, Settergren M, Winter R, Nickenig G, Gilard M, Di Mario C, Transcatheter Valve Treatment (TCVT) Sentinel Registry Investigators of the EURObservational Research Programme (EORP) of the European Society of Cardiology (2017) Immediate and 12-month outcomes of ischemic versus nonischemic functional mitral regurgitation in patients treated with Mitraclip (from the 2011 to 2012 pilot sentinel registry of percutaneous edge-to-edge mitral valve repair of the European Society of Cardiology). *Am J Cardiol* 119:630–637
 11. Michler RE, Smith PK, Parides MK, Ailawadi G, Thourani V, Moskowitz AJ, Acker MA, Hung JW, Chang HL, Perrault LP, Gillinov AM, Argenziano M, Bagiella E, Overbey JR, Moquete EG, Gupta LN, Miller MA, Taddei-Peters WC, Jeffries N, Weisel RD, Rose EA, Gammie JS, DeRose JJ Jr, Puskas JD, Dagenais F, Burks SG, El-Hamamsy I, Milano CA, Atluri P, Voisine P, O'Gara PT, Gelijns AC, for the CTSN (2016) Two-year outcomes of surgical treatment of moderate ischemic mitral regurgitation. *N Engl J Med* 374:1932–1941
 12. Feldman T, Mehta A, Guerrero M, Levisay JP, Salinger MH (2016) MitraClip therapy for mitral regurgitation: secondary mitral regurgitation. *Interv Cardiol Clin* 5:83–91
 13. Schäfer U, Maisano F, Butter C, Franzen O, Baldus S, Hausleiter J, Ussia GP, Sievert H, Geist V, Widder JD, Moccetti T, Schillinger W (2016) Impact of preprocedural left ventricular ejection fraction on 1-year outcomes after MitraClip implantation (from the ACCESS-EU phase I, a prospective, multicenter, nonrandomized postapproval study of the MitraClip therapy in Europe). *Am J Cardiol* 118:873–880
 14. Capodanno D, Adamo M, Barbanti M, Giannini C, Laudisa ML, Cannata S, Curello S, Imme S, Maffeo D, Bedogni F, Petronio AS, Etori F, Tamburino C, Grasso C, Grasp-It Investigators (2015) Predictors of clinical outcomes after edge-to-edge percutaneous mitral valve repair. *Am Heart J* 170:187–195
 15. Matsumoto T, Nakamura M, Yeow WL, Hussaini A, Ram V, Makar M, Gurudevan SV, Trento A, Siegel RJ, Kar S (2014) Impact of pulmonary hypertension on outcomes in patients with functional mitral regurgitation undergoing percutaneous edge-to-edge repair. *Am J Cardiol* 114:1735–1739
 16. Ellis SG, Whitlow PL, Raymond RE, Schneider JP (2002) Impact of mitral regurgitation on long-term survival after percutaneous coronary intervention. *Am J Cardiol* 89:315–318
 17. Deja MA, Grayburn PA, Sun B, Rao V, She L, Krejca M, Jain AR, Leng Chua Y, Daly R, Senni M, Mokrzycki K, Menicanti L, Oh JK, Michler R, Wrobel K, Lamy A, Velazquez EJ, Lee KL, Jones RH (2012) Influence of mitral regurgitation repair on survival in the surgical treatment for ischemic heart failure trial. *Circulation* 125:2639–2648
 18. Mirabel M, Iung B, Baron G, Messika-Zeitoun D, Detaint D, Vanoverschelde JL, Butchart EG, Ravaud P, Vahanian A (2007) What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery? *Eur Heart J* 28:1358–1365
 19. Zoghbi WA, Adams D, Bonow RO, Enriquez-Sarano M, Foster E, Grayburn PA, Hahn RT, Han Y, Hung J, Lang RM, Little SH, Shah DJ, Shernan S, Thavendiranathan P, Thomas JD, Weissman NJ (2017) Recommendations for noninvasive evaluation of native valvular regurgitation: a report from the American society of echocardiography developed in collaboration with the society for cardiovascular magnetic resonance. *J Am Soc Echocardiogr* 30:303–371
 20. Di Donato M, Dabic P, Castelvecchio S, Santambrogio C, Brankovic J, Collarini L, Joussef T, Frigiola A, Buckberg G, Menicanti L, Group R (2006) Left ventricular geometry in normal and post-anterior myocardial infarction patients: sphericity index and 'new' conicity index comparisons. *Eur J Cardiothorac Surg* 29(Suppl 1):S225–S230
 21. Nagasaki M, Nishimura S, Ohtaki E, Kasegawa H, Matsumura T, Nagayama M, Koyanagi T, Tohbaru T, Misu K, Asano R, Sumiyoshi T, Hosoda S (2006) The echocardiographic determinants of functional mitral regurgitation differ in ischemic and non-ischemic cardiomyopathy. *Int J Cardiol* 108:171–176
 22. Juliani PS, Das-Neves-Pereira JC, Monteiro R, Correia AT, Moreira LFP, Jatene FB (2018) Left ventricular chamber geometry in cardiomyopathies: insights from a computerized anatomical study. *ESC Heart Fail* 5:355–364
 23. Feldman T, Foster E, Glower DD, Kar S, Rinaldi MJ, Fail PS, Smalling RW, Siegel R, Rose GA, Engeron E, Loghin C, Trento A, Skipper ER, Fudge T, Letsou GV, Massaro JM, Mauri L (2011) Everest II Investigators. Percutaneous repair or surgery for mitral regurgitation. *N Engl J Med* 364:1395–1406
 24. Baumgartner H, Falk V, Bax JJ, De Bonis M, Hamm C, Holm PJ, Iung B, Lancellotti P, Lansac E, Muñoz DR, Rosenhek R, Sjogren J, Tornos Mas P, Vahanian A, Walther T, Wendler O, Windecker S, Zamorano JL, ESC Scientific Document Group (2017) 2017 ESC/EACTS Guidelines for the management of valvular heart disease. *Eur Heart J* 38:2739–2791
 25. Neuss M, Schau T, Schoepp M, Seifert M, Holschermann F, Meyhofer J, Butter C (2013) Patient selection criteria and midterm clinical outcome for MitraClip therapy in patients with severe mitral regurgitation and severe congestive heart failure. *Eur J Heart Fail* 15:786–795
 26. Godino C, Salerno A, Cera M, Agricola E, Fragasso G, Rosa I, Oppizzi M, Monello A, Scotti A, Magni V, Montorfano M, Cappelletti A, Margonato A, Colombo A (2016) Impact and evolution of right ventricular dysfunction after successful MitraClip implantation in patients with functional mitral regurgitation. *Int J Cardiol Heart Vasc* 11:90–98
 27. Giannini C, Fiorelli F, Colombo A, De Carlo M, Weisz SH, Agricola E, Godino C, Castriota F, Golino P, Petronio AS (2016) Right ventricular evaluation to improve survival outcome in patients with severe functional mitral regurgitation and advanced heart failure undergoing MitraClip therapy. *Int J Cardiol* 223:574–580
 28. Park SJ, Park JH, Lee HS, Kim MS, Park YK, Park Y, Kim YJ, Lee JH, Choi SW, Jeong JO, Kwon IS, Seong IW (2015) Impaired RV global longitudinal strain is associated with poor long-term clinical outcomes in patients with acute inferior STEMI. *JACC Cardiovasc Imaging* 8:161–169
 29. Mentias A, Raza MQ, Barakat AF, Hill E, Youssef D, Krishnaswamy A, Desai MY, Griffin B, Ellis S, Menon V, Tuzcu EM, Kapadia SR (2017) Prognostic significance of ischemic mitral regurgitation on outcomes in acute ST-elevation myocardial infarction managed by primary percutaneous coronary intervention. *Am J Cardiol* 119:20–26
 30. Bouma W, Willemsen HM, Lexis CP, Prakken NH, Lipsic E, van Veldhuisen DJ, Mariani MA, van der Harst P, van der Horst IC (2016) Chronic ischemic mitral regurgitation and papillary muscle infarction detected by late gadolinium-enhanced cardiac magnetic resonance imaging in patients with ST-segment elevation myocardial infarction. *Clin Res Cardiol* 105:981–991
 31. Giannini C, Petronio AS, De Carlo M, Guarracino F, Conte L, Fiorelli F, Pieroni A, Di Bello V (2014) Integrated reverse left and right ventricular remodelling after MitraClip implantation in functional mitral regurgitation: an echocardiographic study. *Eur Heart J Cardiovasc Imaging* 15:95–103
 32. Schwencke C, Bijuklic K, Ouarrak T, Lubos E, Schillinger W, Plicht B, Eggebrecht H, Baldus S, Schymik G, Boekstegers P, Hoffmann R, Senges J, Schofer J (2017) Impact of cardiac comorbidities on early and 1-year outcome after percutaneous mitral valve interventions: data from the German transcatheter mitral valve interventions (TRAMI) registry. *Clin Res Cardiol* 106:249–258