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Long-term outcome, survival and predictors of mortality after MitraClip therapy: Results from the German Transcatheter Mitral Valve Interventions (TRAMI) registry☆

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ABSTRACT

Background: MitraClip therapy is increasingly used in patients deemed inoperable to treat severe mitral regurgitation (MR), but long-tern data is scarce.
Aims: The multicentre, industry-independent German Transcatheter Mitral Valve Interventions (TRAMI) registry comprises the largest prospectively enrolled cohort of patients treated by MitraClip therapy. The current analysis is focusing on long-term mortality rates, cardiac rehospitalization and reintervention.
Methods and results: Long-term follow-up (median time 1037 days) in the TRAMI registry was available for 722 patients treated at 20 German centres. Improvements in New York Heart Association (NYHA) functional class (I/II long-term: 65% vs. 1-year follow-up: 63.3%) and self-rated health-status (EuroQuol visual analogue scale [EQ VAS] long-term: 60 [50–70] vs. 1-year follow-up: 60 [50; 70]) were pertained over time.
Estimated mortality rates by Kaplan-Meier method were 19.7% for 1-year, 31.9% for 2-year and 53.1% for 4-year follow-up without differences found for MR aetiology. Multivariable Cox-regression analysis identified previous aortic valve implantation (hazard ratio [HR] = 2.21; $p < 0.0001$), NYHA class IV (HR = 1.78; $p < 0.001$), prior cardiac decompensation (HR = 1.63; $p < 0.001$), creatinine > 1.5 mg/dl (HR = 1.63; $p < 0.0001$) and left ventricular ejection fraction < 30% (HR = 1.60; $p < 0.001$) as most predictive for long-term mortality.

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; DMR, degenerative mitral regurgitation; EVEREST II, Endovascular Valve Edge-to-Edge Repair; EQ VAS, EuroQuol visual analogue scale; FMR, functional mitral regurgitation; IHF, Stiftung Institut für Herzinfarktforschung, Ludwigshafen; LV, left ventricle; LVEF, left ventricular ejection fraction; MDRD, modification of diet in real disease; MR, mitral regurgitation; MV, mitral valve; NT-proBNP, N-terminal pro brain natriuretic peptide; PAD, peripheral artery disease; PAP sys, systolic pulmonary artery pressure; RCT, randomized controlled trial; STS, Society of Thoracic Surgeons; TRAMI, Transcatheter Mitral Valve Interventions.

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Conclusions: Long-term outcome in the TRAMI registry confirmed lasting clinical improvements and low intervention rates. Long-term mortality was strongly influenced by cardiac and non-cardiac co-morbidities and was found comparable for both MR aetiologies.

1. Introduction

Recently, the 5-year results of Endovascular Valve Edge-to-Edge Repair II Study (EVEREST II) have been published, demonstrating lasting durability and comparable overall mortality rates in patients treated by MitraClip (Abbott Vascular, Menlo Park, California) in contrast to open-heart surgery [1]. Translating these results into daily routine remains challenging since characteristics of patients characteristics enrolled into EVEREST II differ tremendously compared to real-life cohorts, especially in terms of patient age, co-morbidities, left ventricular (LV) function and mitral regurgitation (MR) aetiology [2–4].

The industry-independent, post-market Transcatheter Mitral Valve Interventions (TRAMI) registry, exclusively enrolled patients suffering from relevant MR considered inoperable and represents the largest real-life cohort. The 1-year follow-up has indicated significant clinical improvements and identified procedural failure as the strongest predictor of 1-year mortality [5].

Yet, except for EVEREST II, reliable data from randomized controlled trials (RCT) is lacking and long-term outcomes of patients undergoing MitraClip implantation are scarce. So far, larger European multicentre cohorts like the ACCESS-EU or the Pilot European Sentinel registries have only published 1-year results [4,6].

This study analyses long-term outcome after MitraClip implantation in the TRAMI registry, focusing on mortality rates and predictors of mortality and combined endpoints including cardiac rehospitalization and reintervention rates.

2. Methods

2.1. Transcatheter Mitral Valve Interventions registry

Established in 2010, the aim of the industry-independent TRAMI registry was to assess safety and patient outcomes after catheter-based mitral valve (MV) interventions. Further details about the registry and initial results have been published earlier [7].

The present analysis includes only prospectively enrolled patients treated by MitraClip implantation between 08/2010 until 07/2013. Out of 21 treatment centres and n = 828 patients, the following analysis included 799 patients prospectively enrolled (one centre had to be excluded due to incomplete follow-up information [n = 29]). Long-term follow-up data (median 1037 days [911; 1214]) was available for 722 patients. There were 44 drop-outs (5.6%) and 14 patients lost to follow-up (1.8%).

The "Stiftung Institut für Herzinfarktforschung" (IHF), a German research facility for myocardial infarction and other aspects of cardiovascular diseases, located in Ludwigshafen is responsible for patient follow-up by telephone interview after 30 days 1, 3 and 5 years. All patients provided written informed consent prior to intervention.

2.2. Assessment of functional, laboratory and echocardiographic parameters

Quality of life assessment was realized by the EQ-5D-3L, a commonly used health-related evaluation tool comprising two parts. First, mobility, self-care, usual activities, pain/discomfort and anxiety/depression are descriptively assessed. Then, the self-rated EQ visual analogue scale (EQ VAS) ranging from "best imaginable health state", labelled 100 to "worst imaginable health state", labelled 0 is used. In addition, New York Heart Association (NYHA) classification and the 6-minute walking distance were recorded. Creatinine, glomerular filtration rate (Modification of diet in real disease [MDRD]), and N-terminal pro brain natriuretic peptide (NT-proBNP) were measured. Transthoracic echocardiographic parameters were evaluated according to current guideline recommendations [8] and institutional practice of the treatment centre.

2.3. Definitions and endpoints

Procedural failure was recorded if one of the following criteria was reached: failure of clip placement, severe residual MR, conversion to surgery or operator-reported failure. Primary outcome was all-cause mortality. Additionally, combined outcomes of death or cardiac rehospitalization as well as death or reintervention (additional MitraClip procedure or MV surgery including both reconstruction and replacement) were analysed.

2.4. Statistics

Statistical analyses were performed at the IHF, Ludwigshafen. Categorical variables were presented by absolute numbers and percentages and compared by X^2 or Fisher's test. Continuous variables were expressed as mean with standard deviation or median

Table 1
Baseline characteristics.

	TRAMI registry (n = 799)
Age, years	75.3 ± 8.6
Female gender	314/799 (39.3%)
Body mass index, kg/m^2 (n = 770)	26.6 ± 12.4
Risk stratification	
Frailty	181/795 (22.8%)
Logistic EuroSCORE, % (n = 721)	23.7 ± 16.0
Society of Thoracic Surgeons Score, % (n = 156)	8.5 ± 7.5
Cardiovascular risk factors	
Hypertension	524/672 (78.0%)
Diabetes mellitus	214/767 (31.4%)
Hyperlipidaemia	342/665 (51.4%)
Nicotine abuse	108/665 (16.2%)
Leading cardiac disease	
Coronary artery disease	453/577 (78.5%)
Dilatative cardiomyopathy	71/578 (12.3%)
History of myocardial infarction	214/770 (27.8%)
History of cardiac decompensation	436/769 (56.8%)
Cardiogenic shock	29/769 (3.8%)
Atrial fibrillation	340/773 (44.0%)
Pacemaker	102/772 (13.2%)
Implantable cardioverter defibrillator	118/772 (15.3%)
Cardiac resynchronization therapy	82/772 (10.6%)
Prior cardiothoracic surgery	345/773 (44.6%)
Co-morbidities	
Chronic kidney disease	325/762 (42.7%)
Peripheral artery disease	105/765 (13.7%)
Chronic obstructive pulmonary disease	168/766 (21.9%)
Prior stroke	79/766 (10.3%)
Anaemia	21/799 (2.6%)
Malignancy	71/762 (9.3%)
Pulmonary hypertension	366/765 (47.8%)
PAP sys = pulmonary artery systolic pressure, mm Hg (n = 643)	44.9 ± 14.7
Echocardiographic parameters	
Mitral regurgitation grade	
Mild	1/751 (0.1%)
Moderate	44/751 (5.9%)
Severe	705/751 (93.9%)
LV ejection fraction	
>50%	248/749 (33.1%)
30–50%	266/749 (35.5%)
<30%	235/749 (33.1%)
LV enddiastolic diameter, mm [IQR]	58 [52; 67]
LV endsystolic diameter, mm [IQR]	45 [36; 55]
Functional mitral regurgitation	495/714 (69.3%)
Clinical presentation	
NYHA	
I/II	84/775 (10.8%)
III/IV	691/775 (89.2%)
6-minute walking distance, m [IQR]	200 (120; 312)
EuroQuol visual analogue scale [IQR]	50.0 [40.0; 60.0]
Laboratory parameters	
Creatinine, mg/dl [IQR]	1.3 [1.0; 1.7]
Glomerular filtration rate (MDRD), ml/min [IQR]	51.3 [36.7; 69.7]
NT-proBNP, pg/ml [IQR]	3505 [1585; 6926]

Abbreviations: IQR, interquartile range; LV, left ventricle; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide.

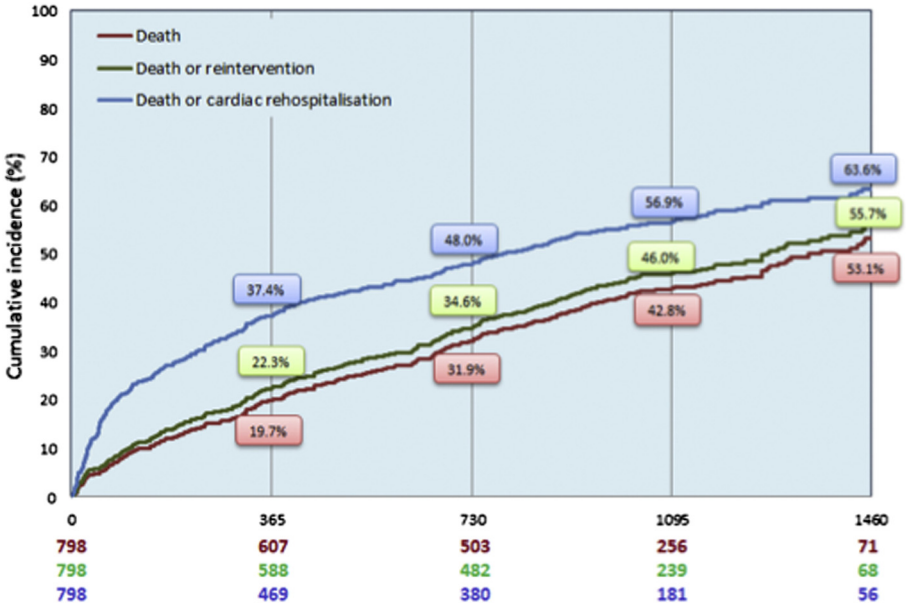

Fig. 1. Kaplan-Meier estimates for death and the composite endpoints of death or mitral valve reintervention as well as death or cardiac rehospitalization.

with interquartile range and compared by Mann-Whitney-Wilcoxon test. The cumulative mortality rates as well as composite endpoints for [1] death, [2] death or MV reintervention and [3] death or cardiac rehospitalization were estimated by Kaplan-Meier method. In addition, a 12-month landmark analysis was calculated.

Multivariable Cox regression were performed to analyse the influence of relevant variables on long-term mortality including the covariates "age > 75 years", "gender" and all baseline measures at $p < 0.1$, and treatment centre as random effect. Systolic pulmonary artery pressure (PAP sys), NT-proBNP and anaemia were omitted due to high numbers of missing values. Furthermore, the logistic EuroSCORE and the STS Score were excluded to avoid redundancy. Further analysis on long-term mortality included multivariate Cox regression for survivors ≥1 year post intervention and for cardiac and non-cardiac death separately.

All tests were two-tailed and p-values < 0.05 were considered significant. SAS statistical package version 9.3 (Cary, North Carolina, USA) was used for the computations.

3. Results

3.1. Baseline characteristics, procedural and in-hospital outcomes

Out of 799 patients enrolled (75.3 ± 8.6 years, male gender: 60.7%, EuroSCORE 23.7% ± 16.0, STS score 8.5% ± 7.5), FMR was the dominating aetiology (n = 495/714, 69.3%, Table 1).

Overall, there was a high burden of co-morbidities including relevant cardiac (coronary artery disease [78.5%], history of myocardial infarction [27.8%] or previous cardiac surgery [44.6%]) and non-cardiac (chronic kidney disease [CKD, 42.7%], diabetes mellitus [31.4%], chronic obstructive pulmonary disease [COPD, 21.9%] and peripheral artery disease [PAD, 13.7%]) diseases. Severe MR was present in 93.9% and severely impaired left ventricular ejection fraction (LVEF < 30%) in 33.1%. Successful treatment was achieved in 96.5% (Online Table 1). A mean number of 1.4 ± 0.6 MitraClips were implanted (mean procedure time 103.2 ± 54.1 min). Intraprocedural complications were rare (0.6%). Severe bleeding/transfusion was the most frequent complication intra-hospital (7.5%). Acute and early MV reinterventions both surgical and percutaneous were infrequent (1.3%) and mainly necessary due to partial clip detachment (0.6%).

3.2. Functional outcomes

Concerning quality of life, significant improvements in the EQ-5D-3L were found for the categories 'anxiety/depression' (no depression/

Table 2
MACCE and non-MACCE long-term outcomes.

	All patients (n = 780)	FMR (n = 484)	DMR (n = 211)	p-Value[a]
Follow-up time, days [IQR]	1037 [911; 1214]	1071 [924, 1230]	984 [747, 1160]	<0.01
MACCE				
Overall mortality	338/740 (45.7%)	209/470 (44.5%)	92/193 (47.7%)	0.45
Myocardial infarction	8/259 (3.1%)	3/166 (1.8%)	4/70 (5.7%)	0.11
Stroke	9/259 (3.5%)	5/167 (3.0%)	2/70 (2.9%)	0.95
Non-MACCE				
Transitory ischemic attack	22/262 (8.4%)	9/168 (5.4%)	9/70 (12.9%)	<0.05
Bleeding complications	38/277 (13.7%)	25/176 (14.2%)	9/76 (11.8%)	0.61
Survived resuscitation	9/262 (3.4%)	8/168 (4.8%)	1/70 (1.4%)	0.22
Mitral reintervention	32/273 (11.7%)	20/171 (11.7%)	9/77 (11.7%)	1.00
- surgery	10/32 (31.3%)	6/20 (30.0%)	3/9 (33.3%)	0.86
- endovascular	18/32 (56.3%)	10/20 (50.0%)	5/9 (55.6%)	0.78
Rehospitalization	375/479 (78.3%)	246/308 (79.9%)	90/121 (74.4%)	0.21
- for decompensation	68/375 (18.1%)	48/246 (19.5%)	17/90 (18.9%)	0.90
- for other cardiac reason	106/375 (28.3%)	67/246 (27.2%)	24/90 (26.7%)	0.92
- for non-cardiac reason	162/375 (43.2%)	108/246 (43.9%)	40/90 (44.4%)	0.93

Abbreviations: DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; IQR, interquartile range; MACCE, major adverse cardiovascular and cerebrovascular events (death, myocardial infarction, stroke).
[a] *t*-Test for DMR vs. FMR.

anxiety: 49.1% [baseline] vs. 72.6% [long-term follow-up]; p < 0.0001) and for 'pain/discomfort' (no pain/discomfort: 37.0% [baseline] vs. 55.3% [long-term follow-up]; p = 0.046, data not shown). Compared to 1-year follow-up, significantly less people reported to be completely independent concerning ´self-care´ (1-year follow-up: 74.7% vs. long-term follow-up: 66.1%; p < 0.0001). Significant and lasting improvements in NYHA functional class were registered (NYHA I/II in 65.0% [long-term follow-up] vs. 64.9% [1-year follow-up] vs. 10.8% [baseline], data not shown) and for the EQ VAS (baseline: 50 [IQR 40; 60] vs. long-term follow-up: 60 [IQR 50; 70]; p < 0.001 and vs. 1-year: 60 [IQR 50; 70]; p < 0.0001, data not shown).

3.3. Long-term mortality

Mortality rates, estimated by Kaplan-Meier method, were as follows: 19.7% (1-year), 31.9% (2-year), 42.8% (3-year) and 53.1% (4-year) (Fig. 1). Stratification for MR aetiology did not show significant differences for long-term survival (registered death in FMR: 44.5% compared to 47.7% in DMR; p = 0.45) (Table 2). Causes of death reported were sudden/unexpected death (11.5%), cardiovascular (12.1%), non-cardiovascular (19.5%) and unknown reason (57.0%). Besides age, female gender, PAP and LV diameter, there was no significant difference regarding other baseline characteristics between patients who died with known reason compared to unknown cause of death (Online Table 2).

Out of 588 patients surviving ≥1 year, a total of 186 (31.6%) died. Mortality was the dominating adverse event beyond 1-year follow-up, while cardiac rehospitalization and re-intervention were of minor importance for long-term patient outcome (12-month landmark analysis, Fig. 2). In comparison to those who died within 1 year, patients surviving ≥1 year were younger (74.9 ± 8.5 years vs. 77.0 ± 7.5 years, p < 0.01), had a lower logistic EuroSCORE (19.0 vs. 24.0, p < 0.001), presented with a significant smaller burden of co-morbidities concerning CKD (p < 0.0001), PAD (p < 0.001), COPD (p < 0.05) and exhibited increased functional capacities (6-MWD 200 m vs. 175 m, p < 0.01, Table 3).

3.4. MACCE and non-MACCE long-term outcomes

Cumulatively, the rate of myocardial infarction, transient ischemic attack and stroke was 3.1%, 8.4% and 3.5%, respectively (Table 2) and the overall post-hospital MACCE-rate was 57.9%. Regarding MR aetiology patients with DMR had higher level of transitory ischemic attack compared to FMR patients (p < 0.05). Rehospitalization rate was 78.3%, thereof 18.1% for cardiac decompensation, 28.3% for other cardiac reasons, while the majority was non-cardiac (43.2%) or for unknown reasons (10.4%). Mortality and rehospitalization rates, estimated by Kaplan-Meier method, were as follows: 37.4% (1-year), 48.0% (2-year), 56.9% (3-year) and 63.6% (4-year) (Fig. 1). During long-term follow-up, mitral valve reinterventions were necessary in 11.7% (surgery n = 10/32 and additional MitraClip n = 18/32 patients) and there was no significant difference between MR aetiologies (Table 2).

3.5. Predictors of long-term mortality

Multivariable Cox regression identified prior cardiac decompensation (HR = 1.67; p = 0.02), previous aortic valve intervention (HR = 1.87; p = 0.046), creatinine ≥ 1.5 mg/dl (HR = 1.80; p = 0.006), PAD (HR = 1.65; p = 0.049), severe tricuspid regurgitation (HR = 1.87; p = 0.01) and LVEF < 30% (HR = 1.61; p = 0.02) predictive for long-term cardiac mortality (Table 4). Predictor for long-term non-cardiac death was only COPD (HR = 2.24; p = 0.02). Multivariable Cox regression identified previous aortic valve intervention as the strongest independent predictor for long-term mortality (HR = 2.21; p < 0.0001) (Fig. 3). A multivariable Cox regression analysis for mortality, including exclusively patients with ≥1-year survival, confirmed the vast majority of predictors already identified for the entire cohort (Table 5) with two important exceptions: PAD lost its significance (HR = 0.93; 95%-CI: 0.57–1.52; p = 0.77), whereas chronic liver disease was significantly associated with mortality (HR = 2.58; 95%-CI: 1.40–4.77; p = 0.002).

4. Discussion

The TRAMI registry represents the largest cohort of real-world patients treated by MitraClip implantation. This study reports the long-term results of the prospective section with the following findings:

(1) relevant functional improvements and low MV reintervention rates were pertained over the entire follow-up period while estimated mortality rates exceed >50% at 4-year follow-up.
(2) the strongest predictor for long-term mortality proofed to be previous aortic valve implantation (followed by NYHA class IV, prior cardiac decompensation, chronic renal disease and LVEF < 30%), opposing predictors for 1-year mortality (with procedural failure as dominating variable).
(3) as found for MACCE and non-MACCE long-term outcomes, mortality rates were comparable for both MR aetiologies, supposedly because long-term outcome is strongly dependent on the burden of co-morbidities.

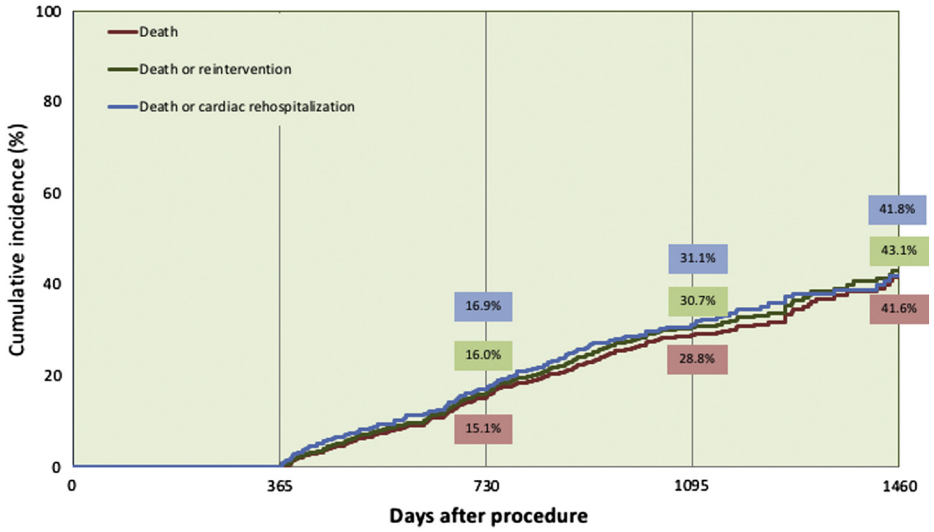

Fig. 2. Kaplan-Meier curve for death and the composite endpoints of death or mitral valve reintervention as well as death or cardiac rehospitalization 12-month landmark analysis.

Table 3
Baseline characteristics, stratified by 1-year survival.

	Death within 1 year (n = 152)	Survival ≥ 1 year (n = 608)	p-Value
Age, years	77.0 ± 7.5	74.9 ± 8.5	<0.01
Female gender	57/152 (37.5%)	238/608 (39.1%)	0.71
Body mass index, kg/m^2	24.9 [22.4, 28.1]	25.7 [23.4, 28.4]	0.05
Risk stratification			
Frailty	41/151 (27.2%)	125/605 (20.7%)	0.08
Logistic EuroSCORE, %	24.0 [14.0, 39.0]	19.0 [12.0, 30.0]	<0.001
Society of Thoracic Surgeons Score, %	10.0 [6.0, 14.0]	5.0 [3.0, 10.0]	<0.01
Cardiovascular risk factors			
Hypertension	99/120 (82.5%)	401/522 (76.8%)	0.18
Diabetes mellitus	48/146 (32.9%)	183/584 (31.3%)	0.72
Hyperlipidemia	61/117 (52.1%)	267/519 (51.4%)	0.89
Nicotine abuse	22/117 (18.8%)	80/519 (15.4%)	0.37
Cardiac medical history			
Coronary artery disease	80/109 (81.7%)	343/443 (77.4%)	0.34
Dilatative cardiomyopathy	13/109 (11.9%)	56/444 (12.6%)	0.85
Myocardial infarction	44/146 (30.1%)	158/586 (27.0%)	0.44
Cardiac decompensation	95/146 (65.1%)	317/585 (54.2%)	<0.05
Cardiogenic shock	1/146 (0.7%)	27/585 (4.6%)	<0.05
Atrial fibrillation	75/148 (50.0%)	250/587 (42.6%)	0.10
Implantable cardiac pacing device	66/148 (44.6%)	229/586 (39.1%)	0.22
Prior cardiothoracic surgery	75/147 (51.0%)	259/588 (44.0%)	0.13
Co-morbidities			
Chronic kidney disease	84/143 (58.7%)	223/582 (38.3%)	<0.0001
Peripheral artery disease	36/145 (24.8%)	67/583 (11.5%)	<0.0001
Chronic obstructive pulmonary disease	44/146 (30.1%)	118/583 (20.2%)	<0.05
Prior Stroke	14/145 (9.7%)	62/584 (10.6%)	0.73
Anaemia	9/152 (5.9%)	12/608 (2.0%)	<0.01
Malignancy	1/143 (8.4%)	57/582 (9.8%)	0.61
Chronic liver disease	9/144 (6.3%)	27/582 (4.6%)	0.43
Pulmonary hypertension	77/145 (53.1%)	273/583 (46.8%)	0.18
Pulmonary artery systolic pressure, mm Hg	48.1 ± 14.3	43.9 ± 14.8	<0.01
Echocardiographic parameters			
Mitral regurgitation grade			0.77
Moderate	8/142 (5.6%)	34/573 (5.9%)	
Severe	134/142 (94.4%)	537/573 (93.7%)	
LV ejection fraction			0.13
>50%	40/141 (28.4%)	178/570 (31.2%)	
30–50%	44/141 (31.2%)	209/570 (36.7%)	
<30%	57/141 (40.4%)	183/570 (32.1%)	
LV enddiastolic diameter, mm [IQR]	59.5 [52.5, 69.0]	58.5 [51.0, 67.0]	0.59
LV endsystolic diameter, mm [IQR]	49.0 [38.0, 59.0]	45.0 [36.0, 55.0]	0.11
Functional mitral regurgitation	93/137 (67.9%)	387/544 (71.1%)	0.46
Clinical presentation			
NYHA III/IV	136/147 (92.5%)	520/590 (88.1%)	0.13
6-minute walking distance, m [IQR]	175 [100, 260]	200 [140, 330]	<0.01
EuroQuol visual analogue scale [IQR]	45 [30, 60]	50 [40, 60]	<0.01
Laboratory parameters			
Creatinine, mg/dl [IQR]	1.5 [1.1, 2.0]	1.3 [1.0, 1.7]	<0.0001
Glomerular filtration rate (MDRD), ml/min [IQR]	42.4 [32.0, 61.7]	53.3 [38.6, 71.6]	<0.0001
NT-proBNP, pg/ml [IQR]	5134 [2695, 11,596]	3213 [1398, 6171]	<0.0001

Abbreviations: IQR, interquartile range; LV, left ventricle; MDRD, modification of diet in renal disease; NYHA, New York Heart Association; NT-proBNP, N-terminal pro brain natriuretic peptide.

Table 4
Multivariable predictors of cardiac and non-cardiac mortality.

	Hazard ratio	95%-CI	p-Value
Predictors for cardiac death			
Female gender	0.55	0.33–0.90	0.02
Prior cardiac decompensation	1.67	1.08–2.58	0.02
Previous aortic valve intervention	1.87	1.01–3.44	0.046
Creatinine ≥ 1.5 mg/dl	1.80	1.18–2.72	0.006
Peripheral artery disease	1.65	1.00–2.72	0.049
Severe tricuspid regurgitation	1.87	1.16–3.02	0.01
Left ventricular ejection fraction < 30%	1.61	1.07–2.43	0.02
Predictors for non-cardiac death			
Chronic obstructive lung disease	2.24	1.13–4.41	0.02

Abbreviations: HR, hazard ratio; LCL, lower confidence limit; UCL, upper confidence limit; NYHA, New York Heart Association; COPD, chronic obstructive pulmonary disease; SM, pacemaker; ICD, implantable cardioverter defibrillator; CRT, cardiac resynchronisation therapy; CI, confidence interval.

To date, only one multicentre RCT, the EVEREST II trial, is available to evaluate treatment by MitraClip implantation.

Out of the larger real-world registries, this is the first study to report on long-term outcomes. Procedural success rates reported range between 97.0% [TRAMI] and 91.0% [ACCESS-EU] compared to 77.0% [EVEREST II]. Mitral valve reinterventions were low in all registries (1.5% [TRAMI], 2.8% [ACCESS-EU] compared to 15.2% [EVEREST II]).

For long-term follow-up, 5-year results of EVEREST II indicated a low rate of MV reinterventions or worsening of MR beyond 1-year follow-up without significant differences compared to MV surgery. Accordingly, MV reinterventions were infrequent in the TRAMI cohort and very infrequent beyond 1-year.

Regarding long-term functional outcome, improvements reported at 1-year follow-up were pertained (NYHA I/II: 65.0% at long-term follow-up compared to 63.3% at 1-year follow-up). Yet, it has to be assumed that the results are significantly influenced by survivorship bias. This might be especially true for the assessment of EQ-5D-3L. Overall, MitraClip therapy represents a feasible and safe treatment option to

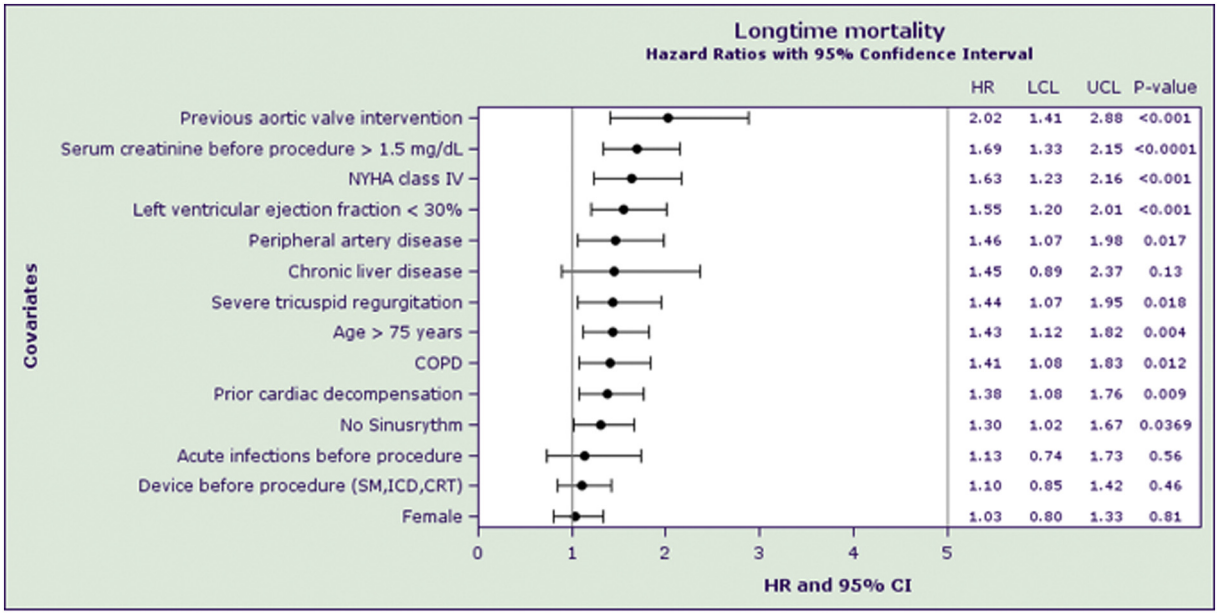

Fig. 3. Predictors for long-term mortality (Cox-Regression, multivariable adjustment).

achieve long-lasting symptomatic alleviation in symptomatic patients with relevant MR deemed inoperable.

The current analysis reports substantial mortality rates of 53.1% for 4-year follow-up. Providing a proper explanation for the increased mortality rates remains challenging due to the inhomogeneous patient collective and a high number of unknown reasons for death. Real-world data from a U.S. registry report a comparable 1-year mortality rates of 25.8% in DMR-patients [9]. In large parts, reduced survival rates can be explained by the accompanying co-morbidities. In TRAMI, numerous co-morbidities were independently associated with long-term mortality. Most of these co-variates are known to impact long-term outcome like CKD, PAD, atrial fibrillation and COPD. Since TRAMI enrolled elderly, multi-morbid patients, it seems convincing that all these factors are prognosis-limiting. In addition, other cardiac pathologies, like impaired LV function, severe tricuspid regurgitation or previous aortic valve intervention are associated with increased mortality. The fact that NYHA IV and prior cardiac decompensation are predictive for long-term outcomes, seems to indicate that patients should not be treated to late in the course of the disease.

In comparison, predictors associated with 1-year mortality in TRAMI comprised procedural failure as strongest factor (HR = 4.36) [5].

Table 5
Predictors for mortality stratified by 1-year survival.

	Survivors ≥ 1 year post intervention (n = 608)		
	Hazard ratio	95%-CI	p-Value
Age > 75 years	1.49	1.07–2.06	0.02
Female gender	1.05	0.75–1.48	0.78
New York Heart Association class IV	1.63	1.09–2.44	0.02
Prior cardiac decompensation	1.46	1.06–2.03	0.02
No sinus rhythm	1.33	0.95–1.86	0.10
Implantable cardiac pacing device	1.18	0.84–1.66	0.33
Previous aortic valve intervention	1.84	1.05–3.22	0.03
Creatinine ≥ 1.5 mg/dl	1.80	1.30–2.49	0.0004
Peripheral artery disease	0.93	0.57–1.52	0.77
Chronic obstructive lung disease	1.48	1.02–2.13	0.04
Chronic liver disease	2.58	1.40–4.77	0.002
Severe tricuspid regurgitation	1.19	0.76–1.88	0.45
Left ventricular ejection fraction < 30%	1.60	1.14–2.25	0.007
Acute infections before procedure	0.71	0.36–1.40	0.32

Abbreviations: CI, confidence interval.

Although most of the factors associated with long-term mortality do match those for 1-year mortality, procedural failure was not found to be predictive in neither uni- nor multivariable analysis. Presumably, there are two main factors to explain this finding: first, the low number of procedural failure (n = 28) in contrast to the high number of death registered (n = 338) and second, the high number of cardiac and non-cardiac co-morbidities. In EVEREST II, a 6-month landmark analysis indicated identical outcomes for freedom from MV surgery or reoperation and an overall comparable survival rate [1]. Accordingly, reintervention rates in TRAMI were low. It seems that 1-year outcomes are strongly influenced by the procedural result, whereas long-term mortality beyond 1-year is determined by concomitant cardiac and non-cardiac diseases [5].

While CKD, NYHA class IV and LVEF < 30% are unsurprisingly associated with inferior long-term survival, it might be unexpected that the strongest predictor for long-term mortality proofed to be previous aortic valve implantation. Severe aortic stenosis is leading to LV remodelling with progressive hypertrophy and LV dilatation as maladaptive consequence [10,11]. Mitral regurgitation represents an independent predictor for decreased survival in patients undergoing aortic valve replacement [12]. Thus, the impact on long-term mortality might be explained by maladaptive remodelling of the LV formerly burdened with volume-overload caused by MR and pressure-overload caused by aortic stenosis.

There are substantial differences in patients suffering from DMR in contrast to FMR. Yet, studies reporting mid- and long-term outcomes of patients undergoing MitraClip implantation are often not substratified for MR aetiology. The EVEREST II trial itself comprised 73.0% DMR-patients and is underpowered to identify differences regarding the impact of MR aetiology.

Metanalysis has indicated comparable outcomes out to 1-year follow-up and concludes that MitraClip therapy is a reasonable option for both FMR und DMR [13]. To our best knowledge, this is the first study to report long-term outcomes separately analysed for MR aetiology. Despite the overall good safety profile, there are no differences found for the number of implanted clips, reintervention or mortality rates.

The fact that long-term mortality does not differ between MR aetiologies, might further strengthen the hypothesis that long-term outcome in these elderly, multimorbid patients is in majority driven by the co-morbidities. To that respect, ongoing RCTs like the Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for

Heart Failure Patients With Functional Mitral Regurgitation (COAPT, NCT01626079) and Percutaneous MV Repair Mitra-Clip Device in Patients With Severe Secondary Mitral Regurgitation (MITRA-FR, NCT01920698) will help to assess if prognostic improvements can be achieved by MitraClip therapy.

4.1. Limitations

In the post-market TRAMI registry, enrolment was available for all sites, thus leading to an inhomogeneous patient population reflecting a large range of non-consecutive enrolment. Importantly, unknown cause of death had to be reported in a large proportion of deceased patients limiting the prognostic assessment of MitraClip therapy. Despite the subanalysis provided, all multivariable Cox regression models performed for the identification of variables associated with long-term mortality have to be interpreted cautiously. Additionally, important factors determining long-term outcomes like PAP sys and NT-proBNP levels had to be excluded for the multivariable Cox regression analysis. There is an overall high prevalence of missing information for different baseline parameters that might have additionally affected the results of the multivariable model.

Echocardiographic measures are only available as reported by the treating centre and were not core-lab evaluated, thus minor or at least inhomogeneous quality has to be presumed. Follow-up data was collected by telephone interview only and no echocardiographic follow-up data is available limiting evaluation on the durability of results and LV remodelling. Additionally, no laboratory values are available for follow-up.

4.2. Conclusions

Long-term outcomes in the TRAMI registry confirm stable functional outcomes and low reintervention rates after MitraClip therapy. High long-term mortality rates (53.1% for 4-year follow-up) seem to reflect the impact of numerous and relevant co-morbidities in this elderly, frail cohort. Consequently, predictors of long-term mortality comprised multiple cardiac and non-cardiac co-morbidities, while long-term mortality rates were comparable for FMR vs. DMR and MR aetiology itself was not associated with long-term mortality.

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Conflict of interest

Authors US and WS are members of the advisory board of Abbott, whereas PB and HI have received proctor fees from Abbott. Furthermore, research grants (RSvB, EL), consulting fees (HS), speakers honoria (US, RSvB, HS, BP, CB, WS, EL) and travel expenses (DK, US, HS, EL) were disbursed by Abbott. All other authors report no conflicts of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2018.08.023.

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