Aus der Medizinischen Klinik mit Schwerpunkt Kardiologie der
Medizinischen Fakultät Charité – Universitätsmedizin Berlin

DISSERTATION

Mitral valve surgery and interventional MitraClip therapy for functional mitral regurgitation in patients with severely reduced left ventricular function

Mitralklappenchirurgie und perkutane MitraClip-Implantation zur Therapie der funktionellen Mitralklappeninsuffizienz bei Patienten mit hochgradig eingeschränkter linksventrikulärer Pumpfunktion

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ABSTRACT (deutsch)

Die funktionelle Mitralklappeninsuffizienz (FMR) stellt einen unabhängigen Risikofaktor für die Zunahme einer Herzinsuffizienz dar. Neben operativem Mitralklappenersatz oder -rekonstruktion (sMVR) steht die perkutane „Edge-to-Edge“-Rekonstruktion mit MitraClip (pMVR) als minimalinvasive Technik als Therapieoption zur Verfügung. Das Ziel dieser Arbeit ist es, die Ergebnisse von sMVR und pMVR bei Patienten mit Herzinsuffizienz und hochgradig reduzierter linksventrikulärer Ejektionsfraktion (LVEF ≤30%) zu vergleichen.

In der ersten Studie werden die klinischen Verläufe von sMVR und pMVR verglichen. 132 Patienten mit LVEF ≤30% und stattgehabter sMVR (n=47) oder pMVR (n=85) bei FMR wurden identifiziert. Nach Propensity-Score-Matching bezüglich Alter, logistischem EuroSCORE und linksventrikulärem endsystolischem Volumen zeigte pMVR eine geringere perioperative Mortalitäts- und Komplikationsrate, aber auch eine höhere Rest-Mitralklappeninsuffizienz als die sMVR. Gemäß stratifizierter multivariater Cox-Modell-Analyse war die Schwere der Restinsuffizienz ein unabhängiger Risikofaktor für Herztod und erneuten Krankenhausaufenthalt wegen Herzinsuffizienz im Verlauf von 1 Jahr. Stratifizierte multivariate Cox-Regressionsanalyse nach 3 Jahren identifizierte pMVR als Risikofaktor für kardialen Tod und erneuten Krankenhausaufenthalt wegen Herzinsuffizienz. Außerdem stellte eine erhöhte Rest-Mitralklappeninsuffizienz einen Risikofaktor für Herztod dar.

In der zweiten Studie wurde die Auswirkung der präoperativen Schwere einer co-existenten funktionellen Trikuspidalklappeninsuffizienz (FTR) auf das frühe Ergebnis nach pMVR mit FMR bei LVEF ≤30% untersucht. Von Januar 2013 bis Dezember 2017 unterzogen sich 80 Patienten mit LVEF ≤30% und FMR einer pMVR. Das Überleben bis 3 Jahre betrug 58%. Cox-Regressionsanalyse zur 1-Jahres-Überlebensrate zeigte eine Auswirkung der Schwere der FTR, der präoperativen Klasse nach der New York Heart Association und der peripheren Arterienerkrankung. Eine Kaplan-Meier-Analyse ergab, dass die Herztod-Rate innerhalb 1 Jahr in der Gruppe mit mittelschwerer bis schwerer FTR höher war als in der ohne oder mit milder FTR. Nach dieser Studie konnten 77% der Fälle mittelschwerer bis schwerer FTR vor dem

MitraClip-Eingriff nicht signifikant reduziert werden. Ein mittelschwerer bis schwerer Grad der FTR nach dem MitraClip-Verfahren war mit einer geringeren Überlebensrate assoziiert.

Insgesamt führte die MitraClip-Therapie bei Patienten mit FMR und LVEF ≤30% zu geringeren perioperativen Komplikationen und einer geringeren Mortalität als sMVR. Operativ behandelte Patienten, die das perioperative Stadium überlebten, hatten jedoch eine geringere Restinsuffizienz und weniger erneute Krankenhausaufenthalte wegen Herzinsuffizienz bis 1 Jahr sowie eine geringere Herzmortalität bis 3 Jahre als Patienten, die eine pMVR erhielten. Bei Patienten mit LVEF ≤30%, die gegen FMR mit MitraClip behandelt wurden, war eine postoperative mittelschwere bis schwere FTR ein unabhängiger Prädiktor für Herztod innerhalb von 1 Jahr. Zur Verbesserung des Überlebens sollte in der Frühphase nach der MitraClip-Therapie eine zusätzliche Therapie der Rest-FTR erwogen werden.

ABSTRACT (English)

Functional mitral valve regurgitation (FMR) is an independent risk factor of progressive heart failure. Besides surgical mitral valve replacement or repair (sMVR), percutaneous edge-to-edge repair using MitraClip (pMVR) has emerged as an alternative, minimally invasive therapeutic option. The aim of this work is to compare the results of sMVR and pMVR in patients with heart failure and severely reduced left-ventricular ejection fraction (LVEF ≦30%).

The first study compares the clinical outcomes of sMVR and pMVR. A total of 132 patients with LVEF ≦30% submitted to sMVR (n=47) or pMVR (n=85) for FMR were identified. Using propensity score matching by age, logistic EuroSCORE, and LV end-systolic volume, pMVR showed lower perioperative mortality and rate of complications, yet increased residual MR grade as compared to sMVR. According to stratified multivariate Cox model analysis, residual MR severity was an independent risk factor for cardiac death and re-hospitalization for heart failure at 1-year follow-up. Stratified multivariable Cox regression analysis at 3 years identified pMVR as risk factor for cardiac death and re-hospitalization for heart failure. Also, an elevated grade of residual mitral regurgitation acted as a risk factor for cardiac death.

In the second study, the impact of pre-interventional severity of functional tricuspid regurgitation (FTR) on early outcome after pMVR for FMR in patients with LVEF ≦30% was

investigated. From January 2013 to December 2017, 80 patients with LVEF ≦30% and FMR underwent pMVR. The 3-year actuarial survival was 58%. Cox regression analysis of 1-year survival demonstrated a negative impact of FTR severity, preoperative New York Heart Association class and peripheral artery disease. Kaplan-Meier analysis showed that 1 year-cardiac death was higher in the moderate-to-severe FTR group compared to none-to-mild ($p=0.048$). In this study, 77% of moderate-to-severe FTR pre-MitraClip could not be significantly reduced. Post-MitraClip, moderate-to-severe FTR grade was related to lower survival.

In conclusion, in patients with FMR and LVEF ≤30%, MitraClip therapy resulted in lower perioperative complications and mortality than sMVR. However, surgically treated patients who survived the perioperative stage had less residual mitral regurgitation and experienced lower rates of re-hospitalization for heart failure at 1 year and lower cardiac mortality at 1 and 3 years of follow-up than patients undergoing pMVR. In patients with LVEF ≦30% treated with MitraClip for FMR, post-procedural moderate-to-severe FTR was an independent predictor of cardiac death within 1 year. To improve survival, additional therapy to residual FTR should be considered in early phase after MitraClip therapy.

CHAPTER 1 – INTRODUCTION

1.1 **Background**

Functional mitral regurgitation (FMR) is frequently observed in patients with ischemic and non-ischemic cardiomyopathy, and is associated with poor clinical outcome in patients with heart failure with reduced ejection fraction (HFrEF) due to dilative left ventricular remodeling.[1,2] While FMR is regarded by many as a marker rather than a driver of poor outcome in these patients, non-pharmacological treatment of FMR is frequently considered by the treating physicians of these patients.[3] Although surgical mitral valve repair or replacement (sMVR) is regarded as the gold standard for therapy, in clinical practice about 50% of patients with severe FMR are not referred for surgery due to perceived high surgical risk.[4–6] Frequently, these are elderly patients (age >80 years) with relevant comorbidities and severely reduced left ventricular function (LVEF <30%).[7,8] Since 2013, percutaneous edge-to-edge transcatheter mitral valve repair (pMVR) with the MitraClip system (Abbott Vascular, Menlo Park, CA) for FMR in patients with high risk of perioperative mortality and comorbidities is available and has become increasingly favored over sMVR, representing a less invasive beating-heart interventional technique.[9–13] In addition, while the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study did not find a significant benefit of sMVR over optimal medical therapy, another recent randomized trial ("Cardiovascular outcomes assessment of the MitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation"; COAPT trial) suggested that pMVR is superior to medical therapy with regard to survival and recurrent hospitalization for heart failure.[14,15] In the eyes of many readers, these results further support the use of pMVR with MitraClip in this population, despite the fact that both American and European guidelines only see a low level of evidence (class IIb) to support any procedure for correcting mitral regurgitation in patients with functional, not primary mitral regurgitation.[16,17] However, there have been no published randomized studies comparing pMVR and sMVR on subjects with functional MR.[18] Therefore, current guidelines do not strongly recommend percutaneous repair for FMR.

1.2 **Mitral valve regurgitation: Functional vs. primary**

MR is classified as primary if regurgitation is primarily caused by a structural or degenerative abnormality of the valve components, including the leaflets, chordae tendineae, papillary

muscles, annulus, or a combination of those.[19] On the other hand, FMR (or secondary MR) is a disease process characterized by dysfunction of structurally normal mitral valve leaflets due to tethering and/ or incomplete coaptation in dilated left ventricles with or without annular dilation.[20] This condition is seen in patients with left ventricular (LV) remodeling due to ischemic or non-ischemic cardiomyopathy. Because FMR is associated with normal valve components, it commonly is categorized as a disease of the ventricle. Since FMR is only one manifestation of a greater disease process in these patients, addressing the valve problem is not a causal approach and is not curative. However, FMR is associated with impaired outcome, as reflected by increased mortality rates and hospitalizations for heart failure.[1,2] Therefore, there is an ongoing debate if FMR should be specifically treated in these patients in order to reduce additional volume load to the left ventricle. As such, the optimal treatment regimen is much less clear for FMR than for primary MR, and there is a significant interest in identifying the optimal treatment strategy for patients with FMR.

1.3 Therapeutic options for functional MR

The goals of therapy in patients with FMR are to improve symptoms and quality of life, to reduce HF hospitalizations, and to potentially improve survival. To date, the most effective therapies for FMR are aimed at treating the underlying LV dysfunction, including guideline-directed medical therapy (GDMT) for HF and device-based cardiac resynchronisation therapy (CRT) when appropriate.[21-23] Surgical options for FMR include surgical MV repair and replacement, implantation of mechanical LV assist devices, and orthotopic herat transplantation. Although FMR can technically be corrected by MV surgery, surgical MR repair or replacement have never clearly been demonstrated to alter the natural history of the primary disease (progression to terminal heart failure) or to improve survival.[24-26] Moreover, whether the response to surgery is different in FMR due to ischemic vs. non-ischemic cardiomyopathy has not been established. Recently, less invasive transcatheter technologies have been developed to treat FMR.[27] These devices are designed to mimic surgical approaches, and can be classified as edge-to-edge repair, direct or indirect annuloplasty, chordal plication or replacement, complete MV replacement, or other approaches. Of those, trans-catheter edge-to-edge repair using the MitraClip™ device has found the most widespread use so far and is the only approach with relevant data on outcome so far.

1.4 The MitraClip device

MitraClip™ (Abbott, Abbott Park, Il., US) has been used in over 80 000 patients with MR worldwide (more than 60% in FMR) and has found wide-spread acceptance as an important treatment option with a growing body of clinical and real-world experience.[28] The MitraClip procedure is performed with a steerable guide catheter (SGC) and a clip delivery system (CDS). The guiding catheter is advanced to the right atrium from a right femoral venous puncture site. The procedure consists of six setps: 1) transseptal approach and puncture; 2) introduction of the SGC into the left atrium; 3) navigation with the CDS into the left atrium to place the MitraClip above the mitral valve; 4) crossing the valve and advancing the CDS into the left ventricle; 5) grasping the leaflets and assessment of the quality of the grasping; and 6) final mitral regurgitation assessment.[29] A recent study reviewed a total of 63 463 consecutive echocardiographic studies performed in 19 European centers found that FMR has emerged as a leading cause of MR (~30% of severe or moderate MR). 87% of these patients with FMR were not eligible for surgical treatment due to unacceptable high risk (LVEF <30%, and/or age>80 years old), and 70% of the patients had suitable mitral anatomy for MitraClip.[30] The authors of both articles concluded that there clearly are significant "unmet needs" in these patients, and that MitraClip therapy might be an important treatment option. Nonetheless, ESC/EACTS guideline updated in 2017 recommended only gave a Class IIb (level of evidence C) recommendation for the use of a percutaneous edge-to-edge procedure in symptomatic severe FMR, arguing that there was no systematic data on outcome in MitraClip therapy.[17] More recently, two prospective multi-center trials were carried out to close this gap and investigate the impact of MitraClip therapy on the outcome of patients with FMR.[14,15]

1.5 The MITRA-FR trial

In this French study, 307 patients with systolic heart failure (LVEF 15-40%) and severe FMR (effective regurgitation orifice area (EROA) > 20 mm^2 or regurgitant volume >30 mL/beat) were randomly assigned to mitral valve repair with the MitraClip device plus optimal medical treatment or optimal medical treatment alone.[14] Heart failure was of ischemic origin in 59% and CRT was used in 27%. Baseline medical treatment was similar in both groups, although changes in medication were not monitored during follow-up. MitraClip repair achieved a reduction of MR to grade 2+ or less according to ESC/EACTS guidelines in 92% of patients at the time of

hospital discharge, but had no impact on the primary endpoint of all-cause mortality or heart failure re-hospitalization at 1-year follow-up [54.6 vs. 51.3%, odds ratio (OR) 1.16; 95% CI 0.73-1.84; P=0.53]. Rates of all-cause mortality [24.3% vs.22.4%, hazard ratio (HR) 1.11; 95% CI 0.69-1.77], and heart failure re-hospitalization [48.7% vs. 47.4%, HR 1.13; 95%CI 0.81-1.56] were also similar in the two groups. Estimates of secondary outcomes were imprecise due to incomplete follow-up data.[14,17]

1.6 The COAPT trial

This US trial randomly assigned 614 patients with symptomatic systolic heart failure (LVEF 20-50%) and moderate-to-severe FMR to MitraClip repair plus optimal medical treatment or to optimal medical treatment alone. Heart failure was of ischemic origin in 61% and CRT was used in 36%.[15]

MitraClip repair (mean 1.7±0.7 clips) was successful in 98% of patients, with a reduction in peri-procedural MR to ≦grade 2 + in 95% that was maintained in survivors at 2-year follow up. Importantly, the procedure was safe with freedom from device-related complications in 97% at 1 year. MitraClip therapy was associated with a substantial reduction in the primary endpoint [hospitalization for heart failure 35.8% vs. 67.9% per patient-year: HR 0.53. 95%CI 0.40-0.70; p<0.001; number needed to treat (NNT) 3.1, 95%CI 1.9-7.9] and every 1 of 10 pre-specified, statistically powered secondary endpoints [including 2-year all cause mortality (29.1% vs. 46.1%: HR 0.62, 95%CI 0.46-0.82; P<0.001;NNT 5.9, 95% CI 3.9-11.7] and the composite of death and heart failure rehospitalization [45.7% vs.67.9%:HR 0.57, 95% CI 0.45-0.71; P<0.001; NNT 4.5, 95%, CI 3.3-7.2)].

1.7 Differences between MitraFR and COAPT trial

Percutaneous mitral valve repair using the MitraClip device has been proposed for correcting FMR. The COAPT trial confers a survival benefit compared with optimal medical therapy.[15] On the contrary, the MITRA-FR trial did not demonstrate a survival benefit.[14] The differences in outcomes from these two trials may be due to different MR characteristics in the patients enrolled to the study, as explained by Graburn et al., who introduced the novel concept of proportionate vs. disproportionate MR.[31] Of note, the COAPT trial enrolled a subset of patients who had smaller LV end-diastolic volumes and less advanced LV disease compared with

MITRA-FR patients.[14,15] The disturbing differences in the results of these two landmark randomized trials underscore the importance of careful patient selection for this intervention.

1.8 Hemodynamic consequences of MR repair in severe LV dysfunction

In cardiovascular surgery, LVEF is regarded as one of the main determinants of surgical risk, since hearts with reduced myocardial contractility have limited capacity in coping with ischemic injury (from cardiac bypass) and acute hemodynamic challenges.[32,33] In MR, LVEF represents the sum of forward stroke volume (FSV) and regurgitation volume (MRV). When MR is corrected, MRV is eliminated and LVEF is acutely reduced. For example, in a patient with severe MR, a reduced LVEF of 30% includes typically an FSV of 65 ml:

$$(FSV+MRV)/(FSV+MRV+ESV) = LVEF$$
$$(65+45)/(65+45+255)=0.3*$$

After full MR repair, LVEF will be reduced to 20% because the LV end-systolic volume (ESV) is unchanged in the acute post-procedural phase (until 1-6 months):

$$FSV/(FSV+ESV) = LVEF$$
$$65/(65+255)=0.2**$$

In other words, pre-procedural LVEF in patients with MR underestimates the true extent of LV dysfunction, which is unmasked after MR is corrected. Note that this apparent “remodeling process” after mitral correction is independent of the type of repair.

**0.3 = LVEF of 30%; ** 0.2 = LVEF of 20%*

1.9 Differences between MitraClip and surgery for functional MR

FMR in patients with HFrEF is often associated with functional tricuspid regurgitation (FTR), atrial fibrillation, or ischemic disease. In sMVR, concomitant procedures can be performed to address these conditions including tricuspid valve surgery, maze procedures, and coronary artery bypass grafting (CABG). In contrast, pMVR – as a concept of minimal invasive therapy –

consists of an isolated intervention on the mitral valve regardless of concomitant abnormalities.

1.10 Open questions

In the absence of conclusive evidence from randomized controlled trials, sMVR and pMVR have naturally been the subject of a contentious debate to determine which modality is superior in symptomatic patients with HFrEF and FMR.[18] In our first study, we sought to compare the clinical outcomes (freedom from re-hospitalization and cardiac death) after sMVR vs. pMVR in symptomatic patients with FMR and severe left-ventricular dysfunction (LVEF ≦30%). In order to further step into the mechanisms behind the clinical outcome of patients with HFrEF and FMR, we investigated the role of tricuspid regurgitation in these patients in a second study.

CHAPTER 2 – MATERIALS AND METHODS

2.1 Study design

This single-center study was approved by the Institutional Review Board of Sana Heart Center in Cottbus (Germany) and complied with the declaration of Helsinki. Hospital records were screened by the author to retrospectively identify patients with moderate to severe FMR and severely reduced LVEF (≤30%) who were treated in our hospital between January 2013 and December 2017 with pMVR or sMRV. The author reviewed the clinical course of all patients retrospectively based on patients' charts as available from clinical routine preoperatively, postoperatively in the intensive care unit, and at discharge. Information about the follow-up status was collected by the author from hospital charts or – if unavailable – from the treating general physicians or from the patients themselves by phone and facsimile.

2.2 MitraClip therapy

Prior to MitraClip implantation, all patients underwent coronary angiography to exclude relevant coronary artery disease necessitating revascularisation. All interventional procedures with MitraClips were carried out by experienced interventional cardiologists. All clips (arm length 9 mm) were implanted according to standard practices under general anesthesia with transesophageal echocardiographic and fluoroscopic guidance. Maximum residual MR grade 2 at a mean blood pressure of ≥60 mmHg was regarded as an acceptable procedural result;

additional clips were placed until this requirement was met. The author reviewed all procedural reports and collected data on the interventional procedures for statistical analysis.

2.3 Surgical methods

All procedures were performed by experienced board-certified cardiovascular surgeons via median sternotomy or right thoracotomy (RT). sMVR with concomitant procedures including aortic valve replacement (AVR), TVR, CABG, pulmonary vein ablation and other procedures (ASD-closure and resection of left atrial appendage) were performed by full sternotomy, if possible. With sternotomy, cardiopulmonary bypass (CPB) was established through direct cannulation of ascending aorta and right atrium vein, or SVC/IVC in cases requiring TVR and ASD closure. In the right-thoracotomy approach, skin- incision in the fourth intercostal space was performed after establishing CPB through femoral artery and vein cannulation. Access to mitral valve was gained either via a direct left atrial or transseptal incision depending on the need for TVR and ASD closure. Standard MV replacement and MV annuloplasty with semi-rigid CG ring were performed on the arrested heart under normal temperature (36℃). Intraoperative transesophageal echocardiography was performed to verify that there was no MR in MV replacement and residual MR grade 0-1 in MV repair. All patients were treated with warfarin as anticoagulation therapy for 3 postoperative months. The author reviewed all sugical reports and collected data on the surgical procedures for statistical analysis.

2.4 Echocardiography

Transthoracic echocardiography (TTE) data were available for all patients preoperatively. All patients had TEE during MitraClip implantation and at discharge. The TTE examinations were performed by 2 experienced cardiologists, and all evaluations were carried out according to standard techniques recommended by the American Society of Echocardiography.[34] The author collected the results of all echocardiographic studies from the clinical reports. In addition, he reviewed all echocardiograms to systematically assess right ventricular function and TR from the apical four-chamber view. The severity of TR assessed by Doppler echocardiography was classified as none/trivial (0), mild (1), moderate (2), moderate-severe (3), or severe (4).

2.5 Statistical evaluation

Statistical analysis was performed by the author and revised by two biostatisticians (Dipl.-Math. Andrea Stroux, Institute of Biometry and Clinical Epidemiology, Charité – Universitätsmedizin Berlin and Yousuke Sasaki, Medical Statistical Section, Satista, Co., Ltd in Japan). Results are expressed as mean ± standard deviation (SD) or as median + 25th to 75th percentile interquartile range for continuous variables, and frequency and percentage for categorical variables. Univariable comparisons were performed with Student's unpaired t-test for continuous normally distributed data. The Mann-Whitney U test was used for comparisons of non-parametric continuous data and Fisher's exact test for categorical data. Survival and freedom from cardiac events were derived using the Kaplan-Meier method; comparisons were made using the log-rank test. ***In the first study,*** patient characteristics of the pMVR and sMVR groups were compared, and propensity score (PS) analysis was performed to adjust for the 3 major aspects where significant differences were detected. Patients undergoing MitraClip therapy were matched on a one-on-one basis to patients undergoing surgical treatment on the basis of propensity scores by use of nearest-neighbour matching without replacement with a matching tolerance (caliper) of 0.25 and an absolute standardized difference of ≦10%. Rates of freedom from re-hospitalization for heart failure and cardiac death in the matched cohort were generated using the Kaplan-Meier method, and comparisons were made using the stratified log-rank test. To estimate the independent effects for re-hospitalization for heart failure and cardiac death, multivariable Cox proportional-hazards regression analysis, also stratified on the matched pairs, was subsequently applied to the matched population to identify any independent predictor of mortality. Covariates were included via stepwise regression analysis using a probability for stepwise entry of 0.05. ***In the second study,*** the association between post-interventional TR severity and occurrence rate of 1-year cardiovascular event (cardiac death) was evaluated with Cox regression analysis, and the results were expressed as hazard ratios (HRs) with 95% confidence intervals (95% CIs). Candidate covariates were chosen based on previous medical knowledge. P-value <0.05 was considered statistically significant, and all reported P-values are two-sided. Statistical analysis was performed using SPSS for windows version 22.0 (IBM Japan, Tokyo, Japan).

CHAPTER 3 – RESULTS

First study:

3.1 Comparison of survival and re-hospitalization in sMVR vs. pMVR groups

A total of 132 patients with moderate to severe FMR and preoperative LVEF≦30% were retrospectively identified and included in the study. Of 132 patients, 47 patients (36%) underwent sMVR (n=28/47, 60% ischemic, n=19/47, 40% non-ischemic) and 85 patients (64%) underwent pMVR (n=41/85, 48% ischemic; n=44/85, 52% nonischemic) in our center.

3.2 Baseline characteristics and perioperative outcomes in the PS-matched cohort

Based on the results of the logistic regression analysis, significant differences in characteristics of sMVR and pMVR groups were found for age, logisticEuroSCORE, and LVESV.[35] Accordingly, PS matching was performed for age, logistic EuroSCORE, and LVESV (absolute standardized difference 1%, 5%, and 4%, respectively), resulting in 30 matching pairs of pMVR and sMVR subjects. In sMVR, simple MV repair/ replacement was performed in 8 patients (27%), while 22 patients underwent additional procedures (CABG, n=14; TVP, n= 7; ablation, n=5). In pMVR, a mean of 2.1±0.73 clips was used with an acute success rate of 93%. Postoperative MR grade at discharge was reduced to a mean of 0.20±0.50 in sMVR, compared to a mean of 1.33±0.88 in pMVR ($p<0.0001$). In the PS-matched cohort, one pMVR patient with ischemic cardiomyopathy who had entered the MitraClip procedure in prior cardiogenic shock subsequently died of low output syndrome. In contrast, 4 sMVR patients died post-operatively (cardiogenic shock, n=2; right heart failure, n=1; septic shock, n=1) at a mean of 6.5±3.3 days despite the use of ECMO therapy in 3. In pMVR, 25 patients (83%) could be extubated in the hybrid operation hall and no patients had major perioperative events such as stroke, cardiac tamponade, or clip-related complications. ICU stay and hospital stay were shorter in the pMVR group ($p<0.001$). The rate of discharge to home was higher in pMVR than in sMVR ($p=<0.001$). Differences in in-hospital mortality ($p=0.36$) or 30 day-mortality ($p=0.67$) between the two groups did not reach statistical significance.

3.3 Predictors for re-hospitalization for heart failure and cardiac death at mid-term follow up

In the PS-matched cohort, re-hospitalization for heart failure and cardiac death were not

significantly different in sMVR vs. pMVR groups (stratified log-rank test: p=0.28 and p=0.15, respectively). The rates of freedom from re-hospitalization for heart failure and cardiac death were the same at 4 months. Within 4 months after pMVR, 3 patients died of heart failure, of which 1 patient was associated with residual MR grade 4 and the other 2 had MR grade ≤2. At 1 year, the rates of freedom from re-hospitalization for heart failure in sMVR and pMVR were 90% (95CI 0.79-1.00) and 73.3% (95CI 0.58-0.89%), respectively (p=0.19), and the rate of cardiac death in sMVR and pMVR were 90% (95CI 0.79-1.00) and 73.3% (95CI 0.58-0.89), respectively (p= 0.094). When comparing only the patients who survived the peri-operative phase in the matched cohort (n=26 in sMVR vs. n=26 in pMVR), the rates of freedom from re-hospitalization and cardiac death were significantly higher in the sMVR group than in the pMVR group (p=0.009 and p=0.009, respectively) at 1-year follow-up. This advantage of the sMVR group remained statistically significant at 3 years of follow-up for freedom from cardiac death (p=0.043), but not for freedom from re-hospitalization for heart failure (stratified log-rank test; p=0.12). NYHA grade in survivors at 1 year follow-up was not significantly different with 2.2±0.59 in sMVR vs. 2.2±0.79 in pMVR patients, respectively (p=0.89).

At stratified multivariable Cox regression analysis at 1-year follow-up, postoperative MR severity represented an independent risk factor for re-hospitalization (HR 3.07; 95%CI 1.5-6.3, p=0.0022) and cardiac death (HR 2.8; 95%CI 1.4-5.5, p=0.0025) across all matched patients. Stratified multivariable Cox regression analysis at 3 years identified pMVR (vs. sMVR) as risk factor for cardiac death (HR 0.19; 95%CI 0.040-0.86, p=0.048) and for re-hospitalization for heart failure (HR 0.28; 95%CI 0.077-0.99, p=0.048). Also, an elevated grade of residual TR acted as a risk factor for cardiac death (HR 2.69; 95%CI 1.14-0.99, p=0.048).

Second study:

3.4 The impact of tricuspidal regurgitation on survival in patients with LV dysfunction

85 patients with moderate-to-severe FMR and HFrEF (≦30%) were treated with pMVR in our hospital between January 2013 and December 2017. Patients with acute emergency treatment, redo-pMVR, organic mitral or TV disease, and those who were lost to follow-up (n=2) were excluded. Moreover, 3 patients (3.5%) with unsuccessful pMVR (defined as postoperative MR grade of 3 or more) were also excluded for the purpose of surveying the accurate impact of pMVR, resulting in 80 patients (age 72±8.7 years, 60% male) with end-stage cardiomyopathy

(non-ischemic n=41; ischaemic n=39), who underwent MitraClip therapy. LVEF showed a mean of 22%±5.3%. Preoperative echocardiography showed LVEF≦15% in 13 patients (16%). Baseline TR had a mean grade of 1.63±0.75.

3.5 Predictors of early cardiac death

Kaplan-Meier estimates for overall survival at 3 years were 57.4%. Survival rate at 1-year follow-up was 72.5%. All these 22 patients died of cardiac death within 1 year, although pMVR was successful. Multivariate Cox regression analysis for 1-year survival identified preoperative TR grade (HR, 1.765; 95% CI, 1.007-3.093, p=0.047), preoperative New York Heart Association (NYHA) grade (HR, 2.811; 95%CI, 1.222-6.469, p=0.015), and peripheral artery disease (PAD) (HR, 5.376; 95%CI, 1.642-17.6, p=0.0054) as independent predictors at 1-year survival. Other variables including ischemic vs. non-ischemic origin, preoperative LVEF, and other parameters of echocardiography were not found as predictors.

3.6 The clinical impact of pre-procedural TR severity

In the Kaplan-Meier analysis, the rates of freedom from cardiac death was significantly higher for preprocedual none-to-mild TR group at 1-year follow-up (p=0.048). Between the 2 groups, there were significant differences in re-hospitalisation due to heart failure (p=0.021) and the trend towards higher cardiac death (p=0.077). A total of 5 patients required left ventricular assist device (LVAD) implantation (n=2) or mitral valve replacement (n=3) due to clip failure at 1-year follow-up, but this was not significantly different between the 2 groups. NYHA grade of survivors at 1 year was not statistically different.

3.7 Post-procedural TR grade influencing survival

Post-procedural moderate-to-severe FTR grade was noted in 38 patients (47.5%). The low TR grade in the none-to-mild pre-MitraClip TR group was preserved post-MitraClip (0.92±0.28 vs 1.03±0.45, p=0.103), whereas TR grade of the moderate-severe group significantly improved (2.23±0.42 vs 1.93±0.62, p=0.0034). Overall, TR grade was reduced in 16 patients (20%), preserved in 56 (70%), and increased in 8 (10%). Pre-procedural moderate-to-severe TR grade was decreased to mild TR grade in 10 patients (23%), but no improvement of TR grade was in 34 patients (77%) at post-procedure. In the Kaplan-Meier analysis, the rates of freedom from

all-cause death were significantly higher for post-procedural none-to-mild FTR group at 1 and 3 years of follow-up (p=0.0007 and p=0.0020, respectively). Moreover, in 34 patients with preoperative moderate-to-severe TR grade, all-cause survival rate was significantly higher in the 15 patients with postoperatively improved TR grade than in the 19 patients with non-improved TR grade at 1 and 3 years of follow-up (p=0.031 and p=0.012, respectively). Meanwhile, pre-procedural none-to-mild TR grade was increased to moderate to severe TR grade in 4 patients (11.1%). Only one patient of these 4 patients was died of heart failure during follow-up.

CHAPTER 4 – DISCUSSION

4.1 Main findings

In the first study, we compared the clinical outcomes of two different therapeutic approaches in symptomatic patients with severely reduced ejection fraction and functional MR: sMVR, which allows for full repair/ replacement and concomitant surgical procedures yet requires cardiac arrest, and pMVR using edge-to-edge repair, a less comprehensive approach performed on a beating heart.

There are two main findings in that study. First, in a cohort of HFrEF patients with treated FMR, perioperative mortality is higher in patients with sMVR than pMVR. However, when surviving the peri-operative stage, sMVR is significantly associated with longer freedom from re-hospitalization (p=0.048) and cardiac death (p=0.030) during 3 years of follow-up as compared to pMVR. Second, residual MR (which is primarily found in pMVR) is associated with cardiac death and re-hospitalization due to heart failure at 1-year follow-up (p<0.01).

In the second study, *pre-procedural* moderate-to-severe FTR grade was an independent predictor for cardiac death at 1 year in HFrEF patients, even if MitraClip therapy was successful with regard to the reduction of FMR. Furthermore, *residual* moderate-to-severe FTR grade was also a predictor for cardiac death at 1 year and all-cause mortality at mid-term follow-up in patients. Residual moderate-to-severe FTR grade was significantly associated with early mortality.

As expected, pMVR was found to be safer than surgery regarding peri-procedural risk. With an acute success rate of 97.6% (defined as postoperative MR grade ≦2), the functional results of pMVR in our cohort were better than those recently reported in the MITRA-FR and COAPT trials.[14,15] Perioperative mortality in the PS-matched pMVR group was only 3.3%, based on one

death in a patient presenting with preoperative cardiogenic shock. More than 90% of pMVR patients were stable on medical heart failure therapy and could be discharged home, even if LVEF was poor. On the other hand, several patients in the sMVR group needed short-term circulatory support including ECMO and IABP. In the PS-matched analysis, perioperative mortality in the sMVR group reached 13% as opposed to 3.3% in the pMVR group, even if the difference was not statistically significant (p=0.36).

The picture changed once the peri-operative stage was over. 4 months after the procedure, the same number of patients had died from cardiac death in both groups (13%). At 1 year of follow-up, mortality and rate of re-hospitalization for heart failure was significantly higher in the MitraClip group than in the surgical group, with the difference in mortality remaining significant until 3 years of follow-up despite the relatively low number of cases available for analysis at this time point. Thus, for those patients who survive the perioperative stage, a surgical approach to treating FMR in HFrEF seems to be superior to percutaneous edge-to-edge repair.

In our study, the severity of residual MR was lower in the sMVR group (p<0.001), and sMVR patients exhibited more reduced post-operative LV function than pMVR patients. Accordingly, more patients in the PS-matched cohort died of cardiogenic shock in the days after sMVR than after pMVR. During 1 year of follow-up, only one patient undergoing pMVR needed mitral valve surgery due to recurrence of severe MR with mitral ring dilatation, indicating that the durability of the procedural result might be comparable in pMVR and sMVR. However, residual MR (as assessed immediately after the procedure) had a strong impact on cardiac death and re-hospitalization for heart failure. Due to the nature of the MitraClip procedure, pMVR rarely achieved full resolution of MR, while sMVR frequently did.[18] Accordingly, the hazard ratios for cardiac death (HR 0.33, 95%CI: 0.089-1.2, p=0.095) and re-hospitalization for heart failure (HR 0.33, 95%CI: 0.090-1.2, p=0.10) at 1-year follow-up were lower after sMVR compared with pMVR. Thus, HFrEF patients with FMR whose left ventricles were able to tolerate the immediate effects of full resolution of MR on the long run seemed to benefit more from sMVR than from pMVR.

Interestingly, residual TR was also an independent risk factor for cardiac death in our study (HR: 2.69, 95%CI: 1.1-6.4, p=0.024), pointing at the important role of the right ventricle in advanced stages of heart failure.

Some authors have suggested that moderate-to-severe FTR in patients undergoing MV surgery alone is strongly related to lower survival at mid-term follow-up.[36] Generally, the residual MR grade after pMVR is greater than that after MV surgery. Therefore, residual FTR severity is difficult to be reduced and seems to have more significant influence on cardiac death. In HFrEF patients with post-procedural moderate-to-severe TR, attempts to treat FTR need to be discussed, even if pMVR is successful. Interestingly, 77% of patients with pre-procedural moderate-to-severe FTR had no improvement of FTR postoperatively, and more than 40% died within 1 year because of heart failure. Echocardiographic variables of both groups were similar, except for TR severity. As suggested in our study, pre-procedural FTR severity seems to be an important predictor for poor survival.

Since recent studies have suggested that transcatheter tricuspid edge-to-edge repair can reduce the severity of FTR, future studies should investigate if this approach can improve survival in patients with residual moderate-to-severe FTR after pMVR in patients with HFrEF.[37] We suggest that patients with moderate to severe pre-procedual FTR should be observed carefully after MitraClip procedure, and that interventional treatment of FTR should be considered if there is no improvement of FTR in the early phase.

4.2 Limitations

In our studies there are various limitations. They are non-randomized retrospective, single-center observational studies with a limited number of patients. Due to this design, the higher risk patients would be selected naturally for non-open surgery, therefore, the intrinsic risk of patients receiving pMVR would potentially be higher. In addition, differences in frailty could be a factor rejecting patients to open surgery, but it might not be fully reflected in the PS matched analysis, which in turn might potentially affect the outcome of patients after pMVR. Moreover, our TTE data were evaluated by experienced cardiologists, but not adjudicated by an external core lab. Thus, conclusions from our study should be taken with caution until confirmed by prospective and randomized clinical trials such as the currently ongoing MATTERHORN trial (NCT 02371512).

4.3 Future research

At the moment, late survival is better in sMVR than pMVR and seems to be related to residual TR. To improve the outcome in pMVR, future studies are necessary to determine the value of additional transcatheter tricuspid edge-to-edge repair in patients with residual moderate-to-severe FTR in the early phase after pMVR.

CONCLUSION

MitraClip therapy resulted in lower perioperative complications and mortality than surgical therapy but yielded less reduction in FMR. In contrast, surgically treated patients who survived the perioperative stage had less residual MR and experienced lower rates of re-hospitalization for heart failure at 1 year as well as lower cardiac mortality at 1 year and 3 years of follow-up than patients undergoing pMVR. In addition, residual FTR in this cohort was a major predictor of cardiac death at 1-year follow-up.

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EIDESSTATTLCHE VERSICHERUNG

„Ich, Takayuki Gyoten, versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema *„Mitral valve surgery and interventional MitraClip therapy for functional mitral regurgitation in patients with severely reduced left ventricular function – Mitralklappenchirurgie und perkutane MitraClip-Implantation zur Therapie der funktionellen Mitralklappeninsuffizienz bei Patienten mit hochgradig eingeschränkter linksventrikulärer Pumpfunktion“* selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe. Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren beruhen, sind als solche in korrekter Zitierung (siehe „Uniform Requirements for Manuscripts (URM)“ des ICMJE -www.icmje.org) kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) entsprechen den URM (s.o) und werden von mir verantwortet. Meine Anteile an den ausgewählten Publikationen entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Betreuer/in, angegeben sind. Sämtliche Publikationen, die aus dieser Dissertation hervorgegangen sind und bei denen ich Autor bin, entsprechen den URM (s.o) und werden von mir verantwortet. Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§156,161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum: 25.08.2020 Unterschrift: Takayuki Gyoten

ANTEILSERKLÄRUNG AN DEN BETEILIGTEN PUBLIKATIONEN

Takayuki Gyoten hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1

Gyoten T, Schenk S, Rochor K, Herwig V, Harnath A, Grimmig O, Just S, Fritzsche D, Messroghli D. Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction. ESC Heart Fail. 2020 May 23.
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Beitrag in der Publikation 1:
Takayui Gyoten entwickelte aus seiner Vorerfahrung als angehender Herzchirurg heraus selbständig die Fragestellung der Arbeit. Studienkonzept und -protokolle wurden gemeinsam mit den beiden Betreuern (Daniel Messroghli und Dirk Fritzsche) der Studie ausgearbeitet. Takayuki Gyoten führte die retrospektive Sammlung aller Daten aus Arztbriefen und klinischen Berichten durch, kontaktierte teilweise Hausärzte und Patienten und nahm – soweit notwendig – die Nachauswertung der Bilddaten vor, unter Anleitung und Kontrolle durch die beiden Betreuer. Die Erstellung aller Tabellen und Abbildungen sowie die gesamte Datenanalyse erfolgten durch Takayuki Gyoten unter Anleitung und Kontrolle durch die beiden Betreuer sowie durch einen Statistiker. Takayuki Gyoten schrieb die initialen Versionen der Publikationen sowie des Manteltextes sowie die finalen Versionen nach Revision durch die Co-Autoren bzw. Betreuer.

Publikation 2

Gyoten T, Messroghli D, Schenk S, Rochor K, Grimmig O, Just S, Fritzsche D. Impact of preinterventional tricuspid regurgitation on outcome of MitraClip therapy in patients with severely reduced ejection fraction. Open Heart. 2020 Mar 15;7(1):e001203.
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Beitrag in der Publikation 2 :
Takayui Gyoten entwickelte selbständig die Fragestellung der Arbeit. Studienkonzept

und -protokolle wurden gemeinsam mit den beiden Betreuern (Daniel Messroghli und Dirk Fritzsche) der Studie ausgearbeitet. Takayuki Gyoten führte die retrospektive Sammlung aller Daten aus Arztbriefen und klinischen Berichten durch, kontaktierte teilweise Hausärzte und Patienten und nahm – soweit notwendig – die Nachauswertung der Bilddaten vor, unter Anleitung und Kontrolle durch die beiden Betreuer. Die Erstellung aller Tabellen und Abbildungen sowie die gesamte Datenanalyse erfolgten durch Takayuki Gyoten unter Anleitung und Kontrolle durch die beiden Betreuer sowie durch einen Statistiker. Takayuki Gyoten schrieb die initialen Versionen der Publikationen sowie des Manteltextes sowie die finalen Versionen nach Revision durch die Co-Autoren bzw. Betreuer.

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Unterschrift, Datum und Stempel des betreuenden Hochschullehrers

Takayuki Gyoten

AUSZUG AUS DER JOURNAL SUMMARY LIST

(ISI-Web-Liste-Kategorie-Cardiac and Cardiovascular Systems)

Journal Data Filtered By: **Selected JCR Year: 2018** Selected Editions: SCIE,SSCI Selected Categories: **"CARDIAC and CARDIOVASCULAR SYSTEMS"** Selected Category Scheme: WoS

Gesamtanzahl: 136 Journale

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
1	EUROPEAN HEART JOURNAL	57,358	23.239	0.125920
2	CIRCULATION	166,484	23.054	0.211290
3	JOURNAL OF THE AMERICAN COLLEGE OF CARDIOLOGY	100,986	18.639	0.193290
4	Nature Reviews Cardiology	6,301	17.420	0.018820
5	CIRCULATION RESEARCH	52,988	15.862	0.072290
6	EUROPEAN JOURNAL OF HEART FAILURE	13,107	13.965	0.027620
7	JAMA Cardiology	3,280	11.866	0.019320
8	JACC-Cardiovascular Imaging	8,801	10.975	0.026160
9	JACC-Cardiovascular Interventions	11,555	9.544	0.033640
10	JACC-Heart Failure	3,537	8.910	0.016830
11	JOURNAL OF HEART AND LUNG TRANSPLANTATION	12,436	8.578	0.027310
12	CARDIOVASCULAR RESEARCH	21,828	7.014	0.021500
13	European Heart Journal-Cardiovascular Pharmacotherapy	442	6.723	0.001430
14	Circulation-Heart Failure	6,900	6.526	0.022830
15	BASIC RESEARCH IN CARDIOLOGY	4,137	6.470	0.005590
16	PROGRESS IN CARDIOVASCULAR DISEASES	4,055	6.162	0.008860
17	JOURNAL OF THE AMERICAN SOCIETY OF ECHOCARDIOGRAPHY	10,478	6.111	0.016060
18	EUROPACE	10,908	6.100	0.025320
19	Circulation-Cardiovascular Interventions	5,289	6.060	0.016640

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
20	Cardiovascular Diabetology	5,392	5.948	0.011550
21	Circulation-Cardiovascular Imaging	5,456	5.813	0.018480
22	European Journal of Preventive Cardiology	4,782	5.640	0.013370
23	CANADIAN JOURNAL OF CARDIOLOGY	6,710	5.592	0.018500
24	JOURNAL OF THORACIC AND CARDIOVASCULAR SURGERY	29,599	5.261	0.036950
25	European Heart Journal-Cardiovascular Imaging	5,498	5.260	0.021650
26	HEART RHYTHM	12,344	5.225	0.029030
27	REVISTA ESPANOLA DE CARDIOLOGIA	3,566	5.126	0.004640
28	HEART	18,063	5.082	0.030620
29	JOURNAL OF CARDIOVASCULAR MAGNETIC RESONANCE	5,113	5.070	0.014020
30	JOURNAL OF MOLECULAR AND CELLULAR CARDIOLOGY	14,143	5.055	0.020450
31	Circulation-Arrhythmia and Electrophysiology	6,432	4.968	0.017840
32	Clinical Research in Cardiology	3,022	4.907	0.006760
33	Circulation-Cardiovascular Genetics	3,441	4.864	0.010500
34	Journal of the American Heart Association	13,230	4.660	0.060340
35	TRENDS IN CARDIOVASCULAR MEDICINE	2,667	4.462	0.003930
36	Circulation-Cardiovascular Quality and Outcomes	4,531	4.378	0.014350
37	ATHEROSCLEROSIS	23,442	4.255	0.033500
38	CARDIOVASCULAR DRUGS AND THERAPY	2,109	4.181	0.003140
39	JOURNAL OF NUCLEAR CARDIOLOGY	3,711	4.112	0.004480

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
40	AMERICAN JOURNAL OF PHYSIOLOGY-HEART AND CIRCULATORY PHYSIOLOGY	27,828	4.048	0.022820
41	AMERICAN HEART JOURNAL	20,811	4.023	0.026780
42	EuroIntervention	6,097	4.018	0.016840
43	HEART FAILURE REVIEWS	2,598	4.015	0.005300
44	ANNALS OF THORACIC SURGERY	36,145	3.919	0.040630
45	JOURNAL OF CARDIAC FAILURE	5,339	3.857	0.009350
46	EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY	17,156	3.847	0.026410
47	European Heart Journal-Acute Cardiovascular Care	1,466	3.734	0.005330
48	INTERNATIONAL JOURNAL OF CARDIOLOGY	30,479	3.471	0.080570
49	ESC Heart Failure	680	3.407	0.002020
50	NUTRITION METABOLISM AND CARDIOVASCULAR DISEASES	5,821	3.340	0.010180
51	CURRENT PROBLEMS IN CARDIOLOGY	574	3.333	0.000700
52	Journal of Cardiovascular Computed Tomography	1,711	3.316	0.004430
53	Global Heart	881	3.238	0.003800
54	RESPIRATORY MEDICINE	11,846	3.237	0.015840
55	CIRCULATION JOURNAL	9,904	3.025	0.016510
56	JOURNAL OF THROMBOSIS AND THROMBOLYSIS	2,789	2.941	0.005860
57	JOURNAL OF CARDIOVASCULAR ELECTROPHYSIOLOGY	7,508	2.910	0.010700
58	Annals of Cardiothoracic Surgery	1,528	2.895	0.004950
59	AMERICAN JOURNAL OF CARDIOLOGY	37,275	2.843	0.044530

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
60	Journal of Cardiovascular Translational Research	1,458	2.756	0.003220
61	Cardiovascular Toxicology	1,209	2.630	0.001720
62	American Journal of Cardiovascular Drugs	1,005	2.578	0.001830
63	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY AND THERAPEUTICS	1,239	2.570	0.002540
64	CATHETERIZATION AND CARDIOVASCULAR INTERVENTIONS	9,366	2.551	0.016550
65	Journal of Cardiovascular Nursing	1,997	2.510	0.003080
66	European Journal of Cardiovascular Nursing	1,648	2.497	0.002480
67	CLINICAL CARDIOLOGY	4,234	2.455	0.006620
68	Current Cardiology Reports	1,859	2.395	0.005470
69	JOURNAL OF CARDIOVASCULAR PHARMACOLOGY	5,522	2.371	0.004680
70	Archives of Cardiovascular Diseases	1,496	2.355	0.003590
71	Cardiovascular Therapeutics	1,353	2.315	0.002190
72	Journal of Cardiology	2,991	2.289	0.006360
73	Hellenic Journal of Cardiology	850	2.269	0.000840
74	International Heart Journal	1,791	2.226	0.002530
75	CardioRenal Medicine	517	2.214	0.001230
76	Cardiology Research and Practice	847	2.140	0.001360
77	JOURNAL OF INTERVENTIONAL CARDIOLOGY	1,406	2.106	0.002590
78	Heart Lung and Circulation	2,503	2.078	0.006030
79	Pulmonary Circulation	1,407	2.075	0.004170
80	CARDIOLOGY CLINICS	1,075	2.061	0.001630

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
81	Cardiovascular Ultrasound	1,022	2.043	0.001740
82	Congenital Heart Disease	1,534	2.036	0.003760
83	Cardiovascular Diagnosis and Therapy	763	2.006	0.002480
84	CURRENT OPINION IN CARDIOLOGY	2,056	1.979	0.003750
85	Netherlands Heart Journal	1,196	1.972	0.001920
86	BMC Cardiovascular Disorders	3,243	1.947	0.008320
87	Interactive Cardiovascular and Thoracic Surgery	5,544	1.931	0.010010
88	CARDIOVASCULAR AND INTERVENTIONAL RADIOLOGY	5,219	1.928	0.007850
89	Heart Failure Clinics	903	1.895	0.001840
90	JOURNAL OF CARDIOTHORACIC AND VASCULAR ANESTHESIA	5,098	1.882	0.006650
91	INTERNATIONAL JOURNAL OF CARDIOVASCULAR IMAGING	2,949	1.860	0.006790
92	HEART & LUNG	2,445	1.840	0.003060
93	Cardiovascular Engineering and Technology	447	1.776	0.000870
94	CARDIOVASCULAR PATHOLOGY	1,830	1.765	0.003290
95	Journal of Geriatric Cardiology	917	1.763	0.002450
96	Cardiology Journal	1,144	1.743	0.001920
97	Korean Circulation Journal	1,117	1.694	0.002180
98	Arquivos Brasileiros de Cardiologia	2,999	1.679	0.003300
99	Acta Cardiologica Sinica	517	1.676	0.000850
100	Kardiologia Polska	1,532	1.674	0.002140
101	HEART AND VESSELS	2,093	1.620	0.003690

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
102	Journal of Cardiopulmonary Rehabilitation and Prevention	1,728	1.568	0.001830
103	CARDIOLOGY	2,415	1.561	0.002710
104	CORONARY ARTERY DISEASE	1,709	1.554	0.002300
105	Cardiology in Review	1,061	1.552	0.001440
106	JOURNAL OF INTERVENTIONAL CARDIAC ELECTROPHYSIOLOGY	1,594	1.534	0.003270
107	Annals of Thoracic Medicine	676	1.512	0.001210
108	Journal of Cardiothoracic Surgery	1,975	1.470	0.004400
109	Journal of Cardiovascular Medicine	1,668	1.427	0.002800
110	PEDIATRIC CARDIOLOGY	4,245	1.413	0.007420
111	Cardiovascular Journal of Africa	899	1.410	0.001980
112	JOURNAL OF INVASIVE CARDIOLOGY	1,896	1.363	0.002880
113	PACE-PACING AND CLINICAL ELECTROPHYSIOLOGY	5,550	1.340	0.005750
114	EUROPEAN HEART JOURNAL SUPPLEMENTS	434	1.321	0.000540
115	ECHOCARDIOGRAPHY-A JOURNAL OF CARDIOVASCULAR ULTRASOUND AND ALLIED TECHNIQUES	3,021	1.287	0.005200
116	SCANDINAVIAN CARDIOVASCULAR JOURNAL	759	1.286	0.001250
117	ANNALS OF NONINVASIVE ELECTROCARDIOLOGY	1,267	1.235	0.001870
118	General Thoracic and Cardiovascular Surgery	1,235	1.219	0.002500
119	JOURNAL OF ELECTROCARDIOLOGY	2,763	1.166	0.003520
120	Postepy w Kardiologii Interwencyjnej	263	1.160	0.000600
121	THORACIC AND CARDIOVASCULAR SURGEON	1,805	1.152	0.002460

Rank	Full Journal Title	Total Cites	Journal Impact Factor	Eigenfactor Score
122	Anatolian Journal of Cardiology	1,080	1.112	0.001720
123	Annals of Thoracic and Cardiovascular Surgery	1,154	1.109	0.001510
124	JOURNAL OF CARDIOVASCULAR SURGERY	1,835	1.062	0.002580
125	HERZ	1,060	0.995	0.001630
126	ACTA CARDIOLOGICA	998	0.951	0.001190
127	PERFUSION-UK	1,304	0.950	0.001810
128	CARDIOLOGY IN THE YOUNG	2,346	0.943	0.004120
129	Brazilian Journal of Cardiovascular Surgery	740	0.796	0.000960
130	Revista Portuguesa de Cardiologia	824	0.785	0.000950
131	MINERVA CARDIOANGIOLOGICA	371	0.781	0.000510
132	TEXAS HEART INSTITUTE JOURNAL	1,771	0.758	0.001820
133	Reviews in Cardiovascular Medicine	262	0.610	0.000400
134	HEART SURGERY FORUM	534	0.564	0.000430
135	KARDIOLOGIYA	604	0.377	0.000230
136	Circulation-Genomic and Precision Medicine	114	Not Available	0.000000

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ORIGINAL RESEARCH ARTICLE

Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction

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Abstract

Aims The aim of this study was to compare the outcomes of surgical mitral valve repair or replacement (sMVR) and percutaneous edge-to-edge repair using MitraClip (pMVR) in patients with severe left ventricular dysfunction affected by functional mitral regurgitation (FMR).

Methods and results We retrospectively identified 132 patients with left ventricular ejection fraction (LVEF) ≦ 30% submitted to sMVR (n = 47) or pMVR (n = 85) for FMR at our centre from January 2013 to December 2017. To adjust for baseline imbalances, we used a propensity score matching by age, logistic EuroSCORE, and left ventricular end-systolic volume. After being matched, MitraClip therapy showed lower perioperative mortality and rate of complications yet increased residual mitral regurgitation (MR) grade than did surgery (0.2 ± 0.50 in sMVR vs. 1.3 ± 0.88 in pMVR, $P < 0.0001$). According to stratified multivariate Cox model analysis, residual MR severity was an independent risk factor for cardiac death [hazard ratio (HR), 2.81; 95% confidence interval [CI], 1.44–5.48, $P = 0.0025$] and re-hospitalization for heart failure (HR, 3.07; 95% CI, 1.50–6.29, $P = 0.0022$) at 1 year follow-up. Stratified multivariable Cox regression analysis at 3 years identified pMVR as risk factor for cardiac death (HR, 0.19; 95% CI, 0.040–0.86, $P = 0.031$) and re-hospitalization for heart failure (HR, 0.28; 95% CI, 0.077–0.99, $P = 0.048$).

Conclusions In patients with FMR and LVEF ≤ 30%, MitraClip therapy resulted in lower perioperative complications and mortality than sMVR. However, surgically treated patients who survived the perioperative stage had less residual MR and experienced lower rates of re-hospitalization for heart failure at 1 year and lower cardiac mortality at 1 and 3 years of follow-up than did patients undergoing pMVR.

Keywords Heart failure; Left ventricular dysfunction; Functional mitral regurgitation; MitraClip; Mitral valve surgery

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Introduction

Functional mitral regurgitation (FMR) is frequently observed in patients with ischaemic and non-ischaemic cardiomyopathy and is associated with poor clinical outcome in patients with heart failure (HF) with reduced ejection fraction (HFrEF) due to dilative left ventricular remodelling.[1,2] While FMR is regarded by many as a marker rather than a driver of poor outcome in these patients, non-pharmacological treatment of FMR is frequently considered by the treating physicians of these patients.[3] Although surgical mitral valve repair or replacement (sMVR) is regarded as the gold standard for

therapy, in clinical practice, about 50% of patients with severe FMR are not referred for surgery owing to perceived high surgical risk.[4–6] Frequently, these are elderly patients (age $>$ 80 years) with relevant co-morbidities and severely reduced left ventricular ejection function (LVEF $<$ 30%).[7,8] Since 2013, percutaneous edge-to-edge transcatheter mitral valve repair (pMVR) with the MitraClip system (Abbott Vascular, Menlo Park, CA) for FMR in patients with high risk of perioperative mortality and co-morbidities is available and has become increasingly favoured over sMVR, representing a less invasive beating-heart interventional technique.[9–13] In addition, while the MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) study did not find a significant benefit of sMVR over optical medical therapy, another recent randomized trial ['Cardiovascular outcomes assessment of the MitraClip percutaneous therapy for heart failure patients with functional mitral regurgitation' (COAPT) trial] suggested that pMVR is superior to medical therapy with regard to survival and recurrent hospitalization for HF.[14] In the eyes of many readers, these results further support the use of pMVR with MitraClip in this population, despite the fact that both American and European guidelines only see a low level of evidence (class IIb) to support any procedure for correcting mitral regurgitation in patients with functional, not primary mitral regurgitation.[15,16]

FMR in patients with HFrEF is often associated with functional tricuspid regurgitation, atrial fibrillation, or ischaemic disease. In sMVR, concomitant procedures can be performed to address these conditions including tricuspid valve surgery, maze procedures, and coronary artery bypass grafting (CABG). Meanwhile, pMVR—as a concept of minimal invasive therapy—consists of an isolated intervention on the mitral valve regardless of concomitant abnormalities. In the absence of conclusive evidence from randomized controlled trials, these two strategies have naturally been the subject of a contentious debate to determine which modality is superior in symptomatic patients with HFrEF and FMR.[17] In our study, we sought to compare the clinical outcomes (freedom from re-hospitalization and cardiac death) after sMVR vs. pMVR in symptomatic patients with FMR and severe left ventricular dysfunction (LVEF $\leqq$ 30%).

Methods

Study design and follow-up

This single-centre study was approved by the Institutional Review Board of Sana Heart Center in Cottbus (Germany). Hospital records were screened to retrospectively identify patients with moderate to severe FMR and severely reduced LVEF (≤30%) who were treated in our hospital between January 2013 and December 2017 with pMVR or sMVR. Treatment was performed electively (with elective admission) or urgently (during a non-elective admission for HF). Patients with acute emergency treatment, endocarditis, mitral valve stenosis, sMVR after MitraClip implantation, or redo-sMVR were excluded. The clinical course of all patients was retrospectively reviewed based on patients' charts as assessed in clinical routine preoperatively, post-operatively in the intensive care unit, and at discharge. Follow-up data of clinical status and transthoracic echocardiography were obtained from the patients' general practitioners or private cardiologists by telephone and fax communication and were complete in 91% of patients. The clinical follow-up was closed on 31 December 2018, when the last enrolled patient had completed 1 year of follow-up. Endpoints of the study were first re-hospitalization for HF or cardiovascular death. Re-hospitalization for HF was defined as new-onset or worsening signs and symptoms of HF that require urgent therapy and result in hospitalization.

Surgical procedures

All procedures were performed by experienced board-certified cardiovascular surgeons via median sternotomy or right thoracotomy. sMVR with concomitant procedures including aortic valve replacement, tricuspid valve repair (TVR), CABG, pulmonary vein ablation and other procedures [atrial septal defect (ASD) closure and resection of left atrial appendage] were performed by full sternotomy, if possible. With sternotomy, cardiopulmonary bypass (CPB) was established through direct cannulation of ascending aorta and right atrium vein, or superior vena cava/inferior vena cava in cases requiring TVR and ASD closure. In the right-thoracotomy approach, skin incision in the fourth intercostal space was performed after establishing CPB through femoral artery and vein cannulation. Access to mitral valve was gained either via a direct left atrial or transseptal incision depending on the need for TVR and ASD closure. Standard MV replacement and MV annuloplasty with semi-rigid Colvin–Galloway ring were performed on the arrested heart under normal temperature (36°C). Intraoperative transesophageal echocardiography (TEE) was performed to verify that there was no mitral regurgitation (MR) in MV replacement and residual MR grade 0–1 in MV repair. All patients were treated with warfarin as anticoagulation therapy for three post-operative months.

Interventional procedures

All interventional procedures with MitraClips were by one experienced interventional cardiologist. All clips (arm length 9 mm) were implanted according to standard practices under

general anaesthesia with TEE and fluoroscopic guidance. Maximum residual MR grade 2 at a mean blood pressure of ≥ 60 mmHg was regarded as an acceptable procedural result; additional clips were placed until this requirement was met.

Choice of treatment strategy in clinical routine

Patients were regarded as potential candidates for pMVR if they met basic criteria for intervention from the German Cardiac Society.[18] The local heart team (consisting of a cardiologist, a cardiac surgeon, a perfusionist, and a cardio-anaesthetist) discussed the individual therapeutic approach based on age, surgical risk as estimated by logistic EuroSCORE, cardiac and extra-cardiac co-morbidities, and mitral valve morphology as assessed by TEE.

Statistical analysis

Results are expressed as mean ± standard deviation (SD) or as median + 25th to 75th percentile interquartile range for continuous variables, and frequency and percentage for categorical variables. Univariable comparisons were performed with Student's unpaired *t*-test for continuous normally distributed data. The Mann–Whitney *U* test was used for comparisons of non-parametric continuous data and Fisher's exact test for categorical data. Survival and freedom from cardiac events were derived using the Kaplan–Meier method; comparisons were made using the log-rank test. Patient characteristics of the pMVR and sMVR groups were compared, and propensity score (PS) analysis was performed to adjust for the three major aspects where significant differences were detected. Patients undergoing MitraClip therapy were matched on a one-on-one basis to patients undergoing surgical treatment on the basis of PSs by use of nearest-neighbour matching without replacement with a matching tolerance (calliper) of 0.25 and an absolute standardized difference of ≦10%. Rates of freedom from re-hospitalization for HF and cardiac death in the matched cohort were generated using the Kaplan–Meier method, and comparisons were made using the stratified log-rank test. To estimate the independent effects for re-hospitalization for HF and cardiac death, multivariable Cox proportional-hazards regression analysis, also stratified on the matched pairs, was subsequently applied to the matched population to identify any independent predictor of mortality. Covariates were included via stepwise regression analysis using a probability for stepwise entry of 0.05. Candidate covariates were chosen based on previous medical knowledge. *P*-value < 0.05 was considered statistically significant, and all reported *P*-values are two-sided. Statistical analysis was performed using SPSS for windows version 22.0 (IBM Japan, Tokyo, Japan).

Results

Baseline characteristics and perioperative outcomes in the full cohort

A total of 132 patients with moderate to severe FMR and preoperative LVEF ≦ 30% were retrospectively identified and included in the study. Of 132 patients, 47 patients (36%) underwent sMVR (*n* = 28/47, 60% ischemic; *n* = 19/47, 40% non-ischemic) and 85 patients (64%) underwent pMVR (*n* = 41/85, 48% ischemic; *n* = 44/85, 52% non-ischaemic) in our centre. All patients underwent coronary angiography prior to MVR to assess coronary artery state. Demographic and clinical features are shown in *Table 1*.

Patients in the pMVR group were older (*P* = 0.043) and had a higher predicted surgical risk by logistic EuroSCORE (*P* = 0.038) than are sMVR patients. The prevalence of implanted cardioverter defibrillator (ICD) or cardiac resynchronization therapy device therapy, previous cardiac surgery, percutaneous coronary artery intervention, and use of spironolactone were significantly higher in the pMVR than in the sMVR group (*Table 1*). Preoperative echocardiography revealed lower LVEF ($P < 0.001$) and higher LV volumes [$P < 0.001$ for LV end-diastolic volume and $P < 0.001$ for left ventricular end-systolic volume LV end-systolic volume (LVESV)] and reduced right ventricular function (*P* = 0.012 for tricuspid annular plane systolic excursion) in the pMVR group. *Table 2* shows preoperative echocardiography data of both groups in more detail.

In the sMVR group (35% urgent), post-operative MR grade was ≦2 in all patients. In the pMVR group (1.1% urgent), 85 patients had an average of 2.1 ± 0.75 clips with post-interventional MR grade ≦ 2 in 97.6%. Post-operative MR grade at discharge was reduced to a mean ± SD of 0.17 ± 0.44 in sMVR as compared with 1.4 ± 0.69 in pMVR ($P < 0.001$). Intensive care unit (ICU) stay and hospital stay were shorter in the pMVR group ($P < 0.001$); 47% (*n* = 22/47) of sMVR patients were discharged to home as compared with 86% (73/85) in pMVR ($P < 0.001$). There was a trend towards higher in-hospital mortality (*P* = 0.0966) and 30 day mortality (*P* = 0.132) in sMVR that did not reach statistical significance.

Propensity score matching

To minimize potential effects of selection bias and to decrease variability of both groups, a second series of analyses were performed on selected pMVR and sMVR patients with corresponding clinical and echocardiography characteristics on the basis of PS matching.

Table 1 Baseline characteristics of the full cohort and PS-matched cohort; *n* (%) if not otherwise specified

Full cohort	Total $n = 132$	sMVR $n = 47$	pMVR $n = 85$	*P*-value
Age, mean ± SD (years)	70 ± 9.0	68 ± 9.6	72 ± 8.5	0.0429
Age ≧ 80 years old	17 (13%)	3 (6%)	14 (16%)	0.112
Male gender	91 (69%)	28 (60%)	63 (74%)	0.116
Body mass index, mean ± SD (kg/m^2)	26 ± 4.9	27 ± 5.5	26 ± 4.6	0.655
COLD	22 (17%)	7 (15%)	15 (18%)	0.809
Arterial hypertension	118 (89%)	41 (87%)	77 (91%)	0.566
Chronic renal disease	48 (36%)	12 (26%)	36 (42%)	0.0611
Diabetes mellitus	51 (39%)	14 (30%)	37 (44%)	0.138
Logistic EuroSCORE, mean ± SD	31 ± 21	25.0 ± 22	33.5 ± 20	0.0377
EuroSCORE, mean ± SD	16 ± 13	15 ± 13	16 ± 14	0.853
Ischaemic cardiomyopathy	69 (52%)	28 (60%)	41(48%)	0.275
Dilated cardiomyopathy	63 (48%)	19 (40%)	44 (52%)	0.275
Atrial fibrillation	77 (58%)	26 (55%)	51 (60%)	0.713
Previous CRT	43 (33%)	6 (13%)	37 (44%)	<0.001
Previous ICD	46 (35%)	3 (6%)	43 (51%)	<0.001
Previous cardiac surgery	31 (23%)	5 (11%)	26 (31%)	0.0102
Previous percutaneous coronary intervention	45 (34%)	9 (19%)	36 (42%)	0.0121
NYHA functional class, mean ± SD	3.2 ± 0.46	3.2 ± 0.46	3.2 ± 0.46	0.683
NYHA II	2 (2%)	1 (2%)	1 (1%)	
NYHA III	97 (73%)	35 (74%)	62 (73%)	
NYHA IV	33 (25%)	11 (23%)	22 (26%)	
Medication				
ACE inhibitor/ARB	94 (71%)	31 (66%)	63 (74%)	0.856
Beta-blocker	113 (86%)	40 (85%)	73 (86%)	1
Mineralocorticoid receptor antagonist	81 (61%)	17 (36%)	64 (75%)	<0.01
Loop diuretics	118 (89%)	37 (79%)	81(95%)	0.00592
Digitoxin	27 (20%)	6 (13%)	21(25%)	0.119
PS-matched cohort	**Total $n = 60$**	**SMVR $n = 30$**	**PMVR $n = 30$**	***P*-value**
Age, mean ± SD (years)	71 ± 8.3	71 ± 8.5	71 ± 8.2	0.963
Age ≧ 80 years old	6 (10%)	3 (10%)	3 (10%)	1
Male gender	38 (63%)	17(61%)	21(70%)	0.422
Body mass index, mean ± SD (kg/m^2)	27 ± 4.4	26 ± 3.7	28 ± 4.9	0.122
COLD	10 (17%)	5 (17%)	5 (17%)	1
Arterial hypertension	56 (93%)	27 (90%)	29 (97%)	0.612
Chronic renal disease	23 (38%)	9 (30%)	14 (47%)	0.288
Diabetes mellitus	22 (37%)	7 (23%)	15 (50%)	0.06
Logistic EuroSCORE, mean ± SD	30 ± 20	30 ± 24	29 ± 16	0.859
EuroSCORE, mean ± SD	14 ± 13	17 ± 15	11 ± 9.8	0.104
Ischaemic cardiomyopathy	31 (52%)	16 (53%)	15 (50%)	1
Dilated cardiomyopathy	29 (48%)	14 (47%)	15 (50%)	1
Atrial fibrillation	33 (55%)	20 (67%)	13 (43%)	0.119
Previous CRT	16 (27%)	6 (20%)	10 (33%)	0.382
Previous ICD	17 (28%)	1 (3.3%)	16 (53%)	<0.001
Previous cardiac surgery	9 (15%)	4 (13%)	5 (17%)	1
Previous percutaneous coronary intervention	16 (27%)	6 (20%)	10 (3.3%)	0.0292
NYHA functional class, mean ± SD	3.2 ± 0.46	3.2 ± 0.48	3.1 ± 0.43	0.577
NYHA II	2 (3%)	1 (3.3%)	1 (3.3%)	
NYHA III	46 (77%)	22 (73%)	24 (80%)	
NYHA IV	12 (20%)	7 (23%)	5 (17%)	
Medication				
ACE inhibitor/ARB	47 (78%)	19 (63%)	28 (93%)	0.0102
Beta-blocker	53 (88%)	26 (87%)	27 (90%)	1
Mineralocorticoid receptor antagonist	30 (50%)	10 (33%)	20 (66%)	0.0194
Loop diuretics	51 (85%)	24 (80%)	27 (90%)	0.472
Digitoxin	10 (17%)	5 (17%)	5 (17%)	1

ARB, angiotensin receptor blocker; COLD, chronic obstructive lung disease; CRT, cardiac resynchronization therapy; ICD, implanted cardioverter defibrillator.

Table 2 Baseline results of transthoracic echocardiography in the full cohort and the PS-matched cohort; *n* (%) if not otherwise specified

Full cohort	sMVR *n* = 47	pMVR *n* = 85	*P*-value
LVEF mean ± SD (%)	26 ± 5.2	22 ± 5.3	<0.001
MR grade, mean ± SD	3 ± 0.44	3 ± 0.35	0.76
MR grade 2	5 (11%)	5 (6%)	
MR grade 3	38 (81%)	75 (88%)	
MR grade 4	4 (8%)	5 (6%)	
TR grade, mean ± SD	1.6 ± 0.93	1.7 ± 0.75	0.478
TR grade 0	5 (11%)	3 (3.5%)	
TR grade 1	20 (42%)	34 (40%)	
TR grade 2	13 (28%)	37 (43.5%)	
TR grade 3	9 (19%)	11 (13%)	
RVESP, mean ± SD (mmHg)	49 ± 3.1	54 ± 15	0.0731
LVDd, mean ± SD (mm)	70 ± 7.3	73 ± 6.4	0.0674
LVDs, mean ± SD (mm)	63 ± 8.4	66 ± 7.2	0.0974
RVDd, mean ± SD (mm)	40 ± 6.0	39 ± 6.3	0.876
RVDs, mean ± SD (mm)	32 ± 5.7	34 ± 6.2	0.275
LA, mean ± SD (mm)	53 ± 6.5	53 ± 8.4	0.797
TAPSE, mean ± SD (mm)	17 ± 4.2	14 ± 4.6	0.00206
LVEDV, mean ± SD (mL)	197 ± 71	243 ± 68	0.00056
LVESV, mean ± SD (mL)	133 ± 58	182 ± 64	0.00004
LVSV, mean ± SD (mL)	64 ± 30	61 ± 28	0.604
PS-matched cohort	**sMVR *n* = 30**	**pMVR *n* = 30**	***P*-value**
LVEF mean ± SD (%)	25 ± 5.8	22 ± 5.2	0.05
MR grade, mean ± SD	3.0 ± 0.32	3.0 ± 0.32	1
MR grade 2	1 (3.3%)	1 (3.3%)	
MR grade 3	27 (90%)	27 (90%)	
MR grade 4	2 (6.7%)	2 (6.7%)	
TR grade, mean ± SD	1.6 ± 1.0	1.5 ± 0.73	0.549
TR grade 0	3 (10%)	2 (6.7%)	
TR grade 1	13 (43%)	14 (47%)	
TR grade 2	7 (23%)	12 (40%)	
TR grade 3	7 (23%)	2 (6.7%)	
RVESP, mean ± SD (mmHg)	46 ± 12	48 ± 18	0.389
LVDd, mean ± SD (mm)	72 ± 8.0	71 ± 5.2	0.28
LVDs, mean ± SD (mm)	66 ± 9.0	63 ± 6.0	0.165
RVDd, mean ± SD (mm)	41 ± 6.2	39 ± 7.2	0.196
RVDs, mean ± SD (mm)	34 ± 5.6	33 ± 7.4	0.755
LA, mean ± SD (mm)	53 ± 7.4	50 ± 5.7	0.14
TAPSE, mean ± SD (mm)	16 ± 4.8	14 ± 4.2	0.0503
LVEDV, mean ± SD (mL)	217 ± 71	215 ± 58	0.923
LVESV, mean ± SD (mL)	149 ± 61	151 ± 50	0.882
LVSV, mean ± SD (mL)	68 ± 30	64 ± 27	0.611

EDV, end-diastolic volume; ESV, end-systolic volume; LA, left atrium; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; RVDd, right ventricular diastolic diameter; RVDs, right ventricular systolic diameter; RVESP, right ventricular end-systolic pressure; SV, systolic volume; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation.

Baseline characteristics and perioperative outcomes in the propensity score-matched cohort

Based on the results of the logistic regression analysis, significant differences in characteristics of sMVR and pMVR groups were found for age, logistic EuroSCORE, and LVESV.[19] Accordingly, PS matching was performed for age, logistic EuroSCORE, and LVESV (absolute standardized difference 1%, 5%, and 4%, respectively), resulting in 30 matching pairs of pMVR and sMVR subjects. In the PS-matched cohort, only ICD implantation, history of PCI, systolic pulmonary hypertension, and preoperative use of renin–angiotensin–aldosterone system-directed medication remained different (*Table 1*). Results of echocardiography in the matched cohort are shown in *Table 2*. In sMVR, simple MV repair/replacement was performed in eight patients (27%), while 22 patients underwent additional procedures (CABG, *n* = 14; tricuspid valvuloplasty, *n* = 7; ablation, *n* = 5). In pMVR, a mean of 2.1 ± 0.73 clips was used with an acute success rate of 93%. Post-operative MR grade at discharge was reduced to a mean of 0.20 ± 0.50 in sMVR, compared with a mean of 1.33 ± 0.88 in pMVR ($P < 0.0001$, *Table 3*). In the PS-matched cohort, one pMVR patient with ischaemic cardiomyopathy who had entered the MitraClip procedure in prior cardiogenic shock subsequently died of low output syndrome. In contrast, four sMVR patients died post-operatively (cardiogenic shock, *n* = 2; right HF, *n* = 1; septic shock, *n* = 1) at a mean of 6.5 ± 3.3 days despite the use of extracorporeal membrane oxygenation (ECMO) therapy in three (*Table 4*). In pMVR, 25 patients (83%) could be extubated in the hybrid operation hall, and no patients had major perioperative events such as stroke, cardiac tamponade, or clip-related complications. ICU stay and hospital stay were shorter in the pMVR group ($P < 0.001$). The rate of discharge to home was higher in pMVR than in sMVR ($P \leq 0.001$). Differences in in-hospital mortality ($P = 0.36$) or 30 day mortality ($P = 0.67$) between the two groups did not reach statistical significance (Table *S1*).

Comparison of early and midterm outcomes for re-hospitalization and cardiac death

For the full cohort, median follow-up was 24 months for sMVR [inter-quartile range (IQR) 13–42 months, range 0–65 months] and 23 months for pMVR (IQR 8.4–34 months, range 0.17–70 months). In sMVR, there were no cases of endocarditis, early degeneration of the implanted valve prosthesis, or severe valvular dysfunction requiring redo-surgery during the follow-up period. In pMVR, three patients required surgical revision due to recurrent severe MR with partial clip detachment, and four patients needed second-intervention clip implantations for recurrent severe MR. On Kaplan–Meier analysis of the un-matched cohort, the rates of freedom from re-hospitalization for HF and cardiac death were significantly higher for sMVR at 3 years of follow-up ($P = 0.0013$ and $P = 0.0037$, respectively) (Figure *1*).

In the PS-matched cohort, re-hospitalization for HF and cardiac death was not significantly different in sMVR vs. pMVR groups (stratified log-rank test: $P = 0.28$ and $P = 0.15$, respectively) (*Figure 2*). The rates of freedom from re-hospitalization for HF and cardiac death were the same

Table 3 Procedural characteristics of PS-matched cohort; *n* (%) if not otherwise specified

	sMVR	pMVR	
	n = 30	*n* = 30	*P*-value
Urgent	12 (40%)	1 (3%)	0.00105
Elective	18 (60%)	29 (97%)	0.00105
Isolated MV replacement or repair	8 (27%)	—	—
MV replacement + additional procedures	22 (73%)	—	—
MV repair	8 (27%)	—	—
Redo-surgery	4 (13%)	—	—
Sternotomy	24 (80%)	—	—
RT approach	6 (20%)	—	—
ACC, mean ± SD (min)	62 ± 23	—	—
ECC, mean ± SD (min)	107 ± 36	—	—
MitraClip, mean ± SD	—	2.1 ± 0.78	—
Procedural success rate (MR □ 2 grade)	30 (100%)	28 (93%)	0.492
Concomitant procedures			
AVR	4 (13%)	—	—
TVR	7 (23%)	—	—
CABG	13 (43%)	—	—
LA ablation	5 (17%)	—	—
LAA closure	4 (13%)	—	—

ACC, aortic cross clamping; AVR, aortic valve replacement; CABG, cardiopulmonary bypass grafting; ECC, extracorporeal circulation; LAA, left atrial appendage; MV, mitral valve; RT, right thoracotomy; TVR, tricuspid valve repair.

Table 4 Cases of perioperative death in PS-matched cohort (pMVR *n* = 1, sMVR *n* = 4)

	Nr.	Age (years)/ gender	DCM/ ICM	LVEF	Technical approach	Mode of death	Survival (days)	log EuroSCORE
pMVR	1	64/male	ICM	10%	1 clip	Low output syndrome, cardiogenic shock	8	43.6
sMVR	1	74/male	ICM	23%	redo-MVR + CABGx3 IABP + ECMO	Low output syndrome, cardiogenic shock	4	37.2
	2	78/male	DCM	20%	MVR + TVR	Septic shock	11	43.5
	3	66/male	DCM	10%	MVR + TVR + AVR IABP + ECMO	Low output syndrome, cardiogenic shock	4	33.0
	4	78/male	ICM	21%	MVR + TVR ECMO	Right heart failure	7	84.5

AVR, aortic valve replacement; CABG, coronary artery bypass grafting; DCM, dilated cardiomyopathy; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pumping; ICM, ischaemic cardiomyopathy; MVR, mitral valve replacement; TVR, tricuspid valve repair.

at 4 months. Within 4 months after pMVR, three patients died of HF, of which one patient was associated with residual MR grade 4 and the other two had MR grade ≤ 2. At 1 year, the rates of freedom from re-hospitalization for HF in sMVR and pMVR were 90% (95% CI, 0.79–1.00) and 73.3% (95% CI, 0.58–0.89%), respectively ($P = 0.19$); and the rates of cardiac death in sMVR and pMVR were 90% (95% CI, 0.79–1.00) and 73.3% (95% CI, 0.58–0.89), respectively ($P = 0.094$). When comparing only the patients who survived the perioperative phase in the matched cohort ($n = 26$ in sMVR vs. $n = 26$ in pMVR), the rates of freedom from re-hospitalization and cardiac death were significantly higher in the sMVR group than in the pMVR group ($P = 0.009$ and $P = 0.009$, respectively) at 1 year follow-up. This advantage of the sMVR group remained statistically significant at 3 years of follow-up for freedom from cardiac death ($P = 0.043$), but not for freedom from re-hospitalization for HF (stratified log-rank test; $P = 0.12$) (*Figure S1*). New York Heart Association grade in survivors at 1 year follow-up was not significantly different with 2.2 ± 0.59 in sMVR vs. 2.2 ± 0.79 in pMVR patients ($P = 0.89$).

At stratified multivariable Cox regression analysis at 1 year follow-up, post-operative MR severity represented an independent risk factor for re-hospitalization [hazard ratio (HR), 3.07; 95% CI, 1.5–6.3, $P = 0.0022$] and cardiac death (HR, 2.8; 95% CI, 1.4–5.5, $P = 0.0025$) across all matched patients (Table *S2*). Stratified multivariable Cox regression analysis at 3 years identified pMVR (vs. sMVR) as risk factor for cardiac death (HR, 0.19; 95% CI, 0.040–0.86, $P = 0.048$) and for re-hospitalization for HF (HR, 0.28; 95% CI, 0.077–0.99, $P = 0.048$). Also, an elevated grade of residual tricuspid valve regurgitation (TR) acted as a risk factor for cardiac death (HR, 2.69; 95% CI, 1.14–0.99, $P = 0.048$) (Table *S3*).

Figure 1 Clinical outcome of full cohort. Kaplan–Meier curves for freedom from re-hospitalization (A) and freedom from cardiac death (B) for sMVR (red line) vs. pMVR (black line), showing better outcome for sMVR at 3 years (log-rank $P = 0.0013$ and $P = 0.0037$, respectively). sMVR, surgical mitral valve repair or replacement; pMVR, percutaneous edge-to-edge repair using MitraClip.

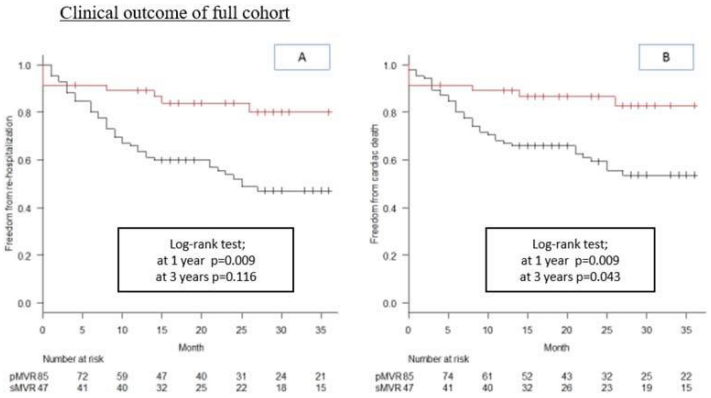
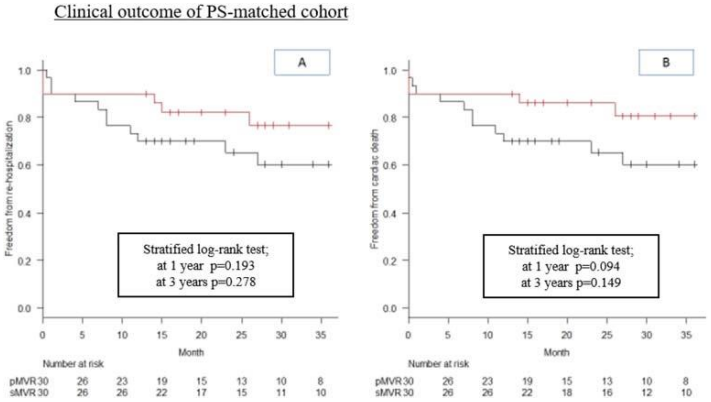


Figure 2 Clinical outcome of PS-matched cohort. Kaplan–Meier curves for freedom from re-hospitalization (A) and freedom from cardiac death (B) for sMVR (red line) vs. pMVR (black line), showing better outcome regarding both events for sMVR at 1 year (stratified log-rank test $P = 0.193$ and $P = 0.094$, respectively) and 3 years (stratified log-rank test $P = 0.278$ and $P = 0.149$, respectively). pMVR, percutaneous edge-to-edge repair using MitraClip; PS, propensity score; sMVR, surgical mitral valve repair or replacement.



Discussion

In this study, we compared the clinical outcomes of two different therapeutic approaches in symptomatic patients with severely reduced ejection fraction and functional MR: sMVR, which allows for full repair/replacement and concomitant surgical procedures yet requires cardiac arrest, and pMVR using edge-to-edge repair, a less comprehensive approach performed on a beating heart.

There are two main findings of the current study. First, in a cohort of HFrEF patients with treated FMR, perioperative mortality is higher in patients with sMVR than pMVR, yet when surviving the perioperative stage, sMVR is significantly associated with longer freedom from re-hospitalization

(P = 0.048) and cardiac death (P = 0.030) during 3 years of follow-up as compared with pMVR. Second, residual MR is associated with cardiac death and re-hospitalization due to HF at 1 year follow-up ($P < 0.01$); in pMVR, residual MR grade was an independent risk factor for re-hospitalization for HF and cardiac death.

Outcome in surgical mitral valve replacement or repair and percutaneous edge-to-edge transcatheter mitral valve repair

As expected, pMVR was found to be safer than surgery regarding peri-procedural risk. With an acute success rate of 97.6% (defined as post-operative MR grade $\leqq$ 2), the functional results of pMVR in our cohort were better than those recently reported in the MITRA-FR and COAPT trials.[14,20] Perioperative mortality in the PS-matched pMVR group was only 3.3%, based on one death in a patient presenting with preoperative cardiogenic shock. More than 90% of pMVR patients were stable on medical HF therapy and could be discharged home, even if LVEF was poor. In contrast to sMVR, there were no such complications as respiratory failure with need for re-intubation, bleeding requiring blood transfusion, or stroke. On the other hand, several patients in the sMVR group needed short-term circulatory support including ECMO and intra-aortic balloon pump. Other sMVR patients had to undergo redo-thoracotomy owing to severe perioperative bleeding, which was associated with prolonged post-operative ICU stay. In the PS-matched analysis, perioperative mortality in the sMVR group reached 13% as opposed to 3.3% in the pMVR group, even if the difference was not statistically significant (P = 0.36).

The picture changed once the perioperative stage was over. Four months after the procedure, the same number of patients had died from cardiac death in both groups (13%). At 1 year of follow-up, mortality and rate of re-hospitalization for HF were significantly higher in the MitraClip group than in the surgical group, with the difference in mortality remaining significant until 3 years of follow-up despite the relatively low number of cases available for analysis at this time point. Thus, for those patients who survive the perioperative stage, a surgical approach to treating FMR in HFrEF seems to be superior to percutaneous edge-to-edge repair.

Our results indicate that the reason for the favourable midterm/long_x2010;term outcome of short-term sMVR survivors might be related to the more effective reduction in mitral valve regurgitation in sMVR. There were only four sMVR patients with residual MR $>$ grade 0 (vs. 26 pMVR), and none of these four were free from re-hospitalization and cardiac death. In pMVR, residual MR grade was an independent risk factor for cardiac death and re-hospitalization for HF at 1 year follow-up. According to Notomi et al., post-operative LVEF is reduced early (1 to 6 months) after correction for mitral regurgitation in severely reduced LVEF, when the MR volume is fully eliminated or at least significantly reduced.[21] In our study, the severity of residual MR was lower in the sMVR group ($P < 0.001$), and sMVR patients exhibited more reduced post-operative LV function than pMVR patients. Accordingly, more patients in the PS-matched cohort died of cardiogenic shock in the days after sMVR than after pMVR. During 1 year of follow-up, only one patient undergoing pMVR needed mitral valve surgery owing to recurrence of severe MR with mitral ring dilatation, indicating that the durability of the procedural result might be comparable in pMVR and sMVR. However, residual MR (as assessed immediately after the procedure) had a strong impact on cardiac death and re-hospitalization for HF. Owing to the nature of the MitraClip procedure, pMVR rarely achieved full resolution of MR, while sMVR frequently did.[17] Accordingly, the HRs for cardiac death (HR, 0.33; 95% CI, 0.089–1.2, P = 0.095) and re-hospitalization for HF (HR, 0.33; 95% CI, 0.090–1.2, P = 0.10) at 1 year follow-up were lower after sMVR compared with pMVR. Thus, HFrEF patients with FMR whose left ventricles were able to tolerate the immediate effects of full resolution of MR on the long run seemed to benefit more from sMVR than from pMVR.

Interestingly, residual TR was also an independent risk factor for cardiac death in our study (HR, 2.69; 95% CI, 1.1–6.4, P = 0.024), pointing at the important role of the right ventricle in advanced stages of HF. According to previous studies, up to 19% of patients with severe FMR have moderate to severe TR associated with a poor clinical course of HF.[22,23] At the moment, interventional strategies for the treatment of FMR address the mitral valve only, whereas sMVR is frequently combined with TVR when TR is present. While TR is seen by many as a consequence rather than a cause of poor RV function, its correction might still be worthwhile in a situation where an optimization of LV haemodynamics is attempted by MVR. Our results support the hypothesis that combined interventions for MR and TR or early interventions for residual TR should be performed in cases where TR is moderate or severe.[24]

According to a recent article analysing the results of COAPT and MITRA-FR, the degree of LV dilatation may indicate if patients will benefit from pMVR or not.[25] Our Transthoracic echocardiography (TTE) parameters representing LV dilatation (LVEF, LV end-diastolic diameter, and LVESV) in sMVR were comparable with those in MITRA-FR, but survival at 3 years of follow-up in our sMVR patients (81%) was superior to MitraClip patients in both COAPT and MITRA-FR. Our results may support that sMVR is superior to pMVR in patients with HFrEF and dilated left ventricle.[25]

Study limitations

In our study, there are various limitations. This is a non-randomized retrospective, single-centre observational study with

a limited number of patients. Owing to this design, the higher risk patients would be selected naturally for non-open surgery; therefore, the intrinsic risk of patients receiving pMVR would potentially be higher. In addition, differences in frailty could be a factor rejecting patients to open surgery, but it might not be reflected in the PS-matched analysis, which in turn might potentially affect the outcome of patients after pMVR. Moreover, our TTE data were evaluated by experienced cardiologists, but not adjudicated by an external core lab. Thus, conclusions from our study should be taken with caution until confirmed by prospective and randomized clinical trials such as the currently ongoing MATTERHORN trial (NCT 02371512).

Conclusions

In a single-centre retrospective analysis of patients with FMR and severely reduced LVEF, MitraClip therapy resulted in lower perioperative complications and mortality than surgical therapy but yielded less reduction in FMR. In contrast, surgically treated patients who survived the perioperative stage had less residual MR and experienced lower rates of re-hospitalization for HF at 1 year as well as lower cardiac mortality at 1 and 3 years of follow-up than patients undergoing pMVR.

Conflict of interest

None declared.

Supporting information

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

Figure S1. Outcome of perioperative survivors (excluding cases with peri-operative death) of PS-matched cohort.
Table S1. Perioperative course of PS-matched cohort; n (%) if not otherwise specified. There were no cases of myocardial infarction or AV blockage. ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; AV, atrioventricular; ICU, intensive care unit; LVEF, left ventricular ejection fraction; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation.
Table S2. Cox regression model analysis at 1-year follow-up. DCM, dilated cardiomyopathy.
Table S3. Cox regression model analysis in 3 years follow-up. DCM, dilated cardiomyopathy.

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Impact of preinterventional tricuspid regurgitation on outcome of MitraClip therapy in patients with severely reduced ejection fraction

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ABSTRACT

Aim To evaluate the impact of preinterventional moderate-to-severe functional tricuspid regurgitation (FTR) on early outcome after percutaneous edge-to-edge mitral valve repair (pMVR) with MitraClip procedures for functional mitral regurgitation (FMR) in patients with heart failure with reduced ejection fraction (HFrEF).

Methods and results From January 2013 to December 2017, 80 patients with HFrEF (ejection fraction 22%±5.3%) and FMR (grade 3.0±0.36) underwent successful pMVR. The 3-year actuarial survival was 58%. However, 73% (n=22) of non-survivors died of cardiac failure within 1 year. Patients were categorised into none-to-mild (n=36) and moderate-to-severe (n=44) postinterventional FTR groups according to pre-MitraClip tricuspid regurgitation grade. Cox regression analysis on 1-year survival demonstrated an impact of FTR severity (HR=1.8, 95% CI 1.01% to 3.09%, p=0.047), preoperative New York Heart Association class (HR=2.8, 95% CI 1.2% to 6.5%, p=0.015) and peripheral artery disease (HR=5.4, 95% CI 1.6 to 18, p=0.0054). Kaplan-Meier analysis showed that 1-year cardiac death was higher in the moderate-to-severe FTR group (p=0.048). In our study, 77% of pre-MitraClip moderate-to-severe FTR cannot be significantly reduced. Post-MitraClip moderate-to-severe FTR grade was related to lower survival (p<0.001).

Conclusion In patients with HFrEF treated with MitraClip for FMR, moderate-to-severe FTR was an independent predictor of cardiac death within 1 year. To improve survival, additional therapy to residual FTR should be considered in early phase after MitraClip therapy.

Key questions

What is already known about this subject?

- Functional tricuspid regurgitation (FTR) is a common finding in the presence of functional mitral valve regurgitation, and untreated moderate-to-severe FTR is known as a predictor of poor survival.

What does this study add?

- In patients with heart failure with reduced ejection fraction undergoing percutaneous edge-to-edge mitral valve repair (pMVR), postinterventional moderate-to-severe tricuspid regurgitation (TR) grade was an independent predictor of cardiac death within 1 year.
- 77% of pre-MitraClip moderate-to-severe FTR cannot be significantly reduced.

How might this impact on clinical practice?

- Residual moderate-to-severe TR might require dedicated additional procedures (an additional TR intervention) even if pMVR was successful.

INTRODUCTION

Functional tricuspid regurgitation (FTR) is a common finding in the presence of functional mitral valve regurgitation (FMR).[1–3] In case of moderate-to-severe FTR, tricuspid valve (TV) repair is usually performed simultaneously when patients undergo mitral valve surgery. In the modern era, isolated percutaneous edge-to-edge transcatheter mitral valve repair (pMVR) with the MitraClip system (Abbott Vascular, Menlo Park, California) for FMR in patients with a high risk of perioperative mortality and comorbidities is available and has become increasingly favoured over sMVR (surgical mitral valve repair), representing a less invasive beating-heart interventional technique.[4–7] According to a recent randomised study, early clinical results of pMVR were acceptable in patients with heart failure with reduced ejection fraction (HFrEF).[8] Concomitant FTR ameliorates by itself in some patients treated for FMR, but remains significant in others. Simultaneous TV edge-to-edge repair (transcatheter mitral plus tricuspid valve edge-to-edge repair) in addition to pMVR has been described but is not routinely performed in clinical practice.[9] In general, untreated moderate-to-severe FTR is known as a predictor of poor survival, yet the prognostic role of FTR severity after pMVR has not yet been investigated. Therefore, the present retrospective study aimed to evaluate the impact of FTR severity in the

early phase after pMVR in patients with HFrEF and symptomatic FMR.

METHODS

Patient selection

Since the start of our MitraClip programme in 2013, individual treatment selection has been based on a multimodal decision-making process based on age, evaluation of surgical risk by logistic EuroSCORE, as well as adjunctive risk evaluation (liver dysfunction, during chemotherapy for malignancy and frailty). In addition, preoperative echocardiography played a critical role in patient selection for MitraClip implantation according to the German Cardiac Society (DGK) criteria.[10] In selected cases, patients were enrolled in the programme despite extremely poor left ventricular (LV) function (ejection fraction <15%).

Echocardiography

Transthoracic echocardiography (TTE) data were available for all patients preoperatively. All patients had TEE (Transesophageal echocariography) during MitraClip implantation and at discharge. The TTE examinations were performed by two experienced cardiologists, and all evaluations were carried out according to standard techniques recommended by the American Society of Echocardiography.[11] Assessment of right ventricular (RV) function was performed from the apical four-chamber view. The severity of tricuspid regurgitation (TR) assessed by Doppler echocardiography was classified as none/trivial (0), mild (1), moderate (2), moderate-severe (3) or severe (4). Pulmonary artery pressure was also measured by TTE.

pMVR with MitraClip procedure

Prior to MitraClip implantation, all patients underwent coronary angiography to exclude relevant coronary artery disease necessitating revascularisation. All MitraClip procedures were performed by one experienced interventional cardiologist. All clips (arm length of 9 mm) were implanted according to standard practices under general anaesthesia with TEE and fluoroscopic guidance. Additional clips were placed until the residual mitral valve regurgitation (MR) corresponded to a maximum grade of 2 at a mean blood pressure of 60 mm Hg.

Postoperative course, endpoint and follow-up

All patients who were treated in our hospital between January 2013 and December 2017 were enrolled. After pMVR, all patients were admitted to the intensive care unit (ICU), before they were further moved to the cardiology ward. The clinical follow-up was closed on 31 December 2018, when the last enrolled patient had completed 1 year of follow-up. The median follow-up was 24 months (IQR: 11–34 months; range: 0.17–70 months). Follow-up data of clinical status were obtained from patients' general practitioners or private cardiologists by phone calls and facsimile, and were completed in 98% of patients. The primary endpoints of the study were 1-year and 3-year survival.

Statistical analysis

Results are expressed as mean±SD or as median +25th–75th percentile IQR for continuous variables, and frequency and percentage for categorical variables. Univariable comparisons were performed with Student's unpaired t-test for continuous normally distributed data. The Mann-Whitney U test was used for comparisons of non-parametric continuous data and Fisher's exact test for categorical data. Data for survival and freedom from cardiac events and all-cause death were derived using the Kaplan-Meier method; comparisons were made using the log-rank test. The association between postinterventional TR severity and occurrence rate of 1-year cardiovascular event (cardiac death) was evaluated with Cox regression analysis, and the results were expressed as HR with 95% CI. Candidate covariates were chosen based on previous medical knowledge; then, a backward stepwise selection was performed. Differences were considered statistically significant at $p<0.05$. Statistical analysis was performed using SPSS for Windows V.22.0.

RESULTS

Study cohort and characteristics

Eighty-five patients with moderate-to-severe FMR and HFrEF (≤30%) were treated with pMVR in our hospital between January 2013 and December 2017. Patients with acute emergency treatment, redo-pMVR, organic mitral or TV disease and those who were lost to follow-up (n=2) were excluded. Moreover, three (3.5%) patients with unsuccessful pMVR (defined as postoperative MR grade of 3 or more) were also excluded for the purpose of surveying the accurate impact of pMVR, resulting in 80 patients (age 72±8.7 years, 60% male) with end-stage cardiomyopathy (non-ischaemic n=41; ischaemic n=39) who underwent MitraClip therapy. Left ventricular ejection fraction (LVEF) showed a mean of 22%±5.3%. Preoperative echocardiography showed LVEF ≤15% in 13 (16%) patients. Baseline TR had a mean grade of 1.63±0.75. The characteristics of baseline and preoperative echocardiography are shown in tables 1 and 2.

Predictors of early cardiac death

The Kaplan-Meier estimate for overall survival at 3 years was 57.4%. Survival rate at 1-year follow-up was 72.5%. All these 22 patients died of cardiac death within 1 year, although pMVR was successful (figure 1). Multivariate Cox regression analysis for 1-year survival identified preoperative TR grade (HR=1.765, 95% CI 1.007 to 3.093, p=0.047), preoperative New York Heart Association (NYHA) grade (HR=2.811, 95% CI 1.222 to 6.469, p=0.015) and peripheral artery disease (HR=5.376, 95% CI 1.642 to 17.6, p=0.0054) as independent predictors at 1-year survival (table 3). Other variables including ischaemic versus non-ischaemic origin, preoperative

Table 1 Baseline characteristics of the full cohort

Variables	Total (N=80)
Age, mean±SD (years)	72±8.7
Male gender	60 (75)
Body mass index, mean±SD (kg/m^2)	26±4.7
Diabetes mellitus	34 (43)
Arterial hypertension	72 (90)
COLD	14 (18)
PAD	9 (11)
Stroke	16 (20)
Chronic renal disease	33 (41)
Ischaemic cardiomyopathy	39 (49)
Dilated cardiomyopathy	41 (51)
Previous percutaneous coronary intervention	34 (43)
Percutaneous coronary intervention within 3 months	12 (15)
Previous cardiac surgery	25 (31)
Previous CRT	33 (41)
Previous ICD	42 (53)
NYHA functional class, mean±SD	3.3±0.46
Atrial fibrillation	49 (61)
Logistic EuroSCORE, mean±SD	34±20
EuroSCORE, mean±SD	16±13
Medication	
ACE inhibitor/ARB	64 (80)
Beta-blocker	68 (85)
Mineralocorticoid receptor antagonist	59 (74)
Loop diuretics	76 (95)
Digitoxin	21 (26)

n (%) if not otherwise specified.
ARB, angiotensin receptor blocker; COLD, chronic obstructive lung disease; CRT, cardiac resynchronisation therapy; ICD, implanted cardioverter defibrillator; NYHA, New York Heart Association; PAD, peripheral artery disease.

LVEF, and other parameters of echocardiography were not found as predictors.

Preprocedural characteristics and periprocedural results according to TR grade

According to preoperative TR severity, this cohort was divided into none-to-mild FTR group (36 patients, 45%) and moderate-to-severe FTR group (44 patients, 55%) (TR grade: 0.92±0.28 vs 2.2±0.42, p<0.001). When comparing these two groups, there were no significant differences in preoperative characteristics and echocardiography, including the parameters of RV dimension, pulmonary artery hypertension and tricuspid annular plane systolic excursion. The details of the baseline characteristics of the two groups are shown in table 4. In-hospital death occurred in two (2.5%) patients, regardless of extracorporeal membrane oxygenation and intra-aortic balloon pump, because of postoperative cardiogenic shock state,

Table 2 Baseline results of transthoracic echocardiography in the full cohort

Variables	Total (N=80)
LVEF (%)	22±5.3
MR grade	3.0±0.36
LVDd (mm)	73±6.4
LVDs (mm)	66±7.1
LA (mm)	54±8.4
LVEDV (mL)	242±69
LVESV (mL)	182±64
EDVI (mL/m^2)	129±39
ESVI (mL/m^2)	97±35
TR grade	1.63±0.75
RVDd (mm)	39±6.4
RVDs (mm)	34±6.2
Systolic pulmonary artery (mm Hg)	54±15
TAPSE (mm)	14±4.65
RVESP (mm Hg)	44±15

Results expressed as mean±SD.
EDVI, end-diastolic volume index; ESVI, end-systolic volume index; LA, left atrium; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; MR, mitral valve regurgitation; RVDd, right ventricular diastolic diameter; RVDs, right ventricular systolic diameter; RVESP, right ventricular end-systolic pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid valve regurgitation.

although postoperative MR severity was reduced to an MR grade of 1. Of these, one patient with a TR grade of 1 had a preoperative high value of logistic EuroSCORE of 44% with LVEF of 10% and died after 8 days. The other

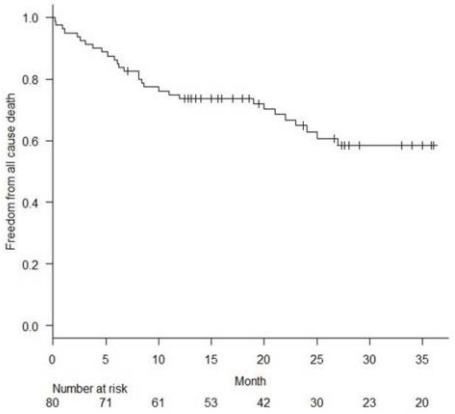

Figure 1 Clinical outcome of the full cohort. Kaplan-Meier curves for freedom from all-cause death estimated at 72.5% at 1 year and 57.4% at 3 years.

Table 3 Cox regression model analysis for cardiac death at 1-year follow-up

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Preoperative TR grade	1.72 (0.98 to 3.00)	0.058	1.77 (1.01 to 3.09)	0.047
NYHA grade	2.54 (1.08 to 5.94)	0.032	2.81 (1.22 to 6.47)	0.015
PAD	3.11 (1.13 to 8.53)	0.028	5.376 (1.64 to 17.6)	0.0054
Preoperative LVEF	0.94 (0.86 to 1.02)	0.148		
LogEuroSCORE	1.01 (0.99 to 1.04)	0.176		

LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PAD, peripheral artery disease; TR, tricuspid valve regurgitation.

patient with a TR grade of 2 had high surgical risk of 30% with LVEF of 17% and died after 5 days.

There were no cases of postoperative cardiac tamponade or new pacemaker implantation. There was no significant difference in postoperative MR severity (p=0.37) between the two groups. However, there was a trend towards higher number of implanted clips in the moderate-to-severe TR group (2.23±0.71 vs 1.92±0.69, respectively; p=0.053). In addition, extubation rate in the hybrid room (p=0.28), duration of ICU stay (p=0.39) and total hospital stay (p=0.24) were not significantly different between the two groups. The discharge rate to home was similar at 89% in both groups. Intraprocedural results and periprocedural outcomes are presented in table 5.

Clinical impact of preprocedural TR severity

In the Kaplan-Meier analysis, the rates of freedom from cardiac death were significantly higher for preprocedural none-to-mild TR group at 1-year follow-up (p=0.048) (online supplementary figure 1). Clinical outcomes at 1-year follow-up are shown in table 6. Between the two groups, there were significant differences in rehospitalisation due to heart failure (p=0.021) and trend towards higher cardiac death (p=0.077). A total of five patients required LV assist device implantation (n=2) or mitral valve replacement (n=3) due to clip failure at 1-year follow-up, but this was not significantly different between the two groups. NYHA grade of survivors at 1 year was not statistically different.

Postprocedural TR grade influencing survival

Postprocedural moderate-to-severe FTR grade was noted in 38 (47.5%) patients. The low TR grade in the none-to-mild pre-MitraClip TR group was preserved post-MitraClip (0.92±0.28 vs 1.03±0.45, p=0.103), whereas the TR grade of the moderate-severe group significantly improved (2.23±0.42 vs 1.93±0.62, p=0.0034). Online supplementary figure 2A,B shows the alteration of TR grade before and after MitraClip therapy. Overall, TR grade was reduced in 16 (20%) patients, preserved in 56 (70%) and increased in 8 (10%). Preprocedural moderate-to-severe TR grade was decreased to mild TR grade in 10 (23%) patients, but no improvement in TR grade in 34 (77%) patients postprocedure. In the Kaplan-Meier analysis, the rates of freedom from all-cause death were significantly higher for postprocedural none-to-mild FTR group at 1 and 3 years of follow-up (p=0.0007 and p=0.0020, respectively) (online supplementary figure 3).

Table 4 Preprocedural characteristics and echocardiography between none/mild and moderate/severe TR grade

	None/mild TR, n=36	Moderate/severe TR, n=44	P value
Age, mean±SD (years)	70±8.3	73±8.8	0.08
Male gender	25	35	0.31
PAD	3	6	0.50
Chronic renal disease	15	18	1
Diabetes mellitus	16	18	0.82
Dilated cardiomyopathy	18	23	1
Ischaemic cardiomyopathy	18	21	1
NYHA functional class, mean±SD	3.3±0.45	3.2±0.48	0.63
Previous CRT	16	17	0.65
Previous ICD	18	24	0.82
Logistic EuroSCORE, mean±SD	32±21	36±19	0.45
Echocardiography			
LVEF, mean±SD (%)	23±5.1	22±5.5	0.56
MR grade, mean±SD	2.9±0.33	3.0±0.37	0.21
TR grade, mean±SD	0.92±0.28	2.2±0.42	<0.001
LVDd, mean±SD (mm)	73±7.2	73±5.7	0.98
LVDs, mean±SD (mm)	65±8.0	66±6.3	0.43
LA, mean±SD (mm)	52±6.9	55±9.3	0.12
EDVI, mean±SD (mL/m^2)	131±41	127±37	0.60
ESVI, mean±SD (mL/m^2)	97±36	96±35	0.88
RVDd, mean±SD (mm)	39±6.4	40±6.5	0.41
RVDs, mean±SD (mm)	33±6.2	34±6.2	0.27
Systolic pulmonary artery (mm Hg)	54±17	55±14	0.73
TAPSE, mean±SD (mm)	15±4.8	14±4.5	0.40
RVESP, mean±SD (mm Hg)	52±17	56±14	0.21

CRT, cardiac resynchronisation therapy; EDVI, end-diastolic volume index; ESVI, end-systolic volume index; ICD, implanted cardioverter defibrillator; LA, left atrium; LEVF, left ventricular ejection fraction; LVDd, left ventricular diastolic diameter; LVDs, left ventricular systolic diameter; MR, mitral valve regurgitation; NYHA, New York Heart Association; PAD, peripheral artery disease; RVDd, right ventricular diastolic diameter; RVDs, right ventricular systolic diameter; RVESP, right ventricular end-systolic pressure; TAPSE, tricuspid annual plane systolic excursion; TR, tricuspid regurgitation.

Table 5 Perioperative course

	None/mild TR, n=36	Moderate/severe, TR n=44	P value
In-hospital death	1 (2.8)	1 (2.3)	1
Postoperative MR grade, mean±SD	1.25±0.55	1.36±0.57	0.37
Postoperative TR grade, mean±SD	1.03±0.45	1.93±0.62	<0.0001
MitraClip, mean±SD	1.92±0.69	2.23±0.71	0.053
Hybrid extubation	34 (94)	38 (86)	0.28
ECMO	1 (2.8)	0 (0)	1
IABP	1 (2.8)	1 (2.3)	1
Tamponade	0 (0)	0 (0)	1
ICU stay, mean±SD (days)	1.22±1.2	1.55±2.0	0.39
Hospital stay, mean±SD (days)	5.3±2.2	6.2±3.8	0.24
Discharge			
To home	32 (89)	39 (89)	1
To rehabilitation	0 (0)	4 (9.1)	0.12
To stroke unit	0 (0)	0 (0)	1
Cardiology	3 (8.3)	0 (0)	0.090

n (%) if not otherwise specified.
There were no cases of myocardial infarction or AV blockage.
AV, atrioventricular; ECMO, extracorporeal membrane oxygenation; IABP, intra-aortic balloon pump; ICU, intensive care unit; MR, mitral valve regurgitation; TR, tricuspid valve regurgitation.

Moreover, in 34 patients with preoperative moderate-to-severe TR grade, all-cause survival rate was significantly higher in the 15 patients with postoperatively improved TR grade than in the 19 patients with non-improved TR grade at 1 and 3 years of follow-up (p=0.031 and p=0.012, respectively). Meanwhile, preprocedural none-to-mild TR grade was increased to moderate-to-severe TR grade in four patients (11.1%) (online supplementary figure 2A). One of these four patients died of heart failure during follow-up.

Table 6 Clinical outcomes during 1-year follow-up

	None/mild TR, n=36	Moderate/severe TR, n=44	P value
In-hospitalisation for heart failure	8 (22)	21 (48)	0.021
Cardiac death	6 (17)	16 (36)	0.077
Second MitraClip	1 (2.8)	2 (4.5)	1
Surgical mitral valve revision	1 (2.8)	2 (4.5)	1
LVAD implantation	0 (0)	2 (4.5)	0.50
NYHA grade of survivors	2.5±0.88 (n=28)	2.37±0.69 (n=27)	0.55

LVAD, left ventricular assist device; NYHA, New York Heart Association; TR, tricuspid regurgitation.

Table 7 Cox regression model analysis for cardiac death at 1-year follow-up in ICM and DCM groups

	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
ICM				
Postprocedural TR grade	1.75 (0.6999 to 4.378)	0.2313		
NYHA grade	1.56 (0.4277 to 5.702)	0.4999		
LogEuroSCORE	1.008 (0.9723 to 1.046)	0.6576		
DCM				
Postprocedural TR grade	2.611 (1.287 to 5.295)	0.0078	2.611 (1.287 to 5.295)	0.0078
NYHA grade	3.579 (1.193 to 10.74)	0.0229		
LogEuroSCORE	1.025 (0.9999 to 1.051)	0.0505		

DCM, dilated cardiomyopathy; ICM, ischaemic cardiomyopathy; NYHA, New York Heart Association; TR, tricuspid regurgitation.

Clinical impact of postoperative moderate-to-severe TR in ischaemic versus non-ischaemic cardiomyopathy

Survival rate for all-cause death between the ischaemic and non-ischaemic groups, regardless of residual TR severity, was not significantly different (online supplementary figure 4A,B). Multivariate Cox regression analysis identified postprocedural TR grade as an independent predictor of 1-year survival in the non-ischaemic group, but not in the ischaemic group (table 7). In the Kaplan-Meier analysis, survival rate for all-cause death at 1 and 3 years of follow-up was not significantly different between patients with ischaemia with postoperative none-to-mild TR and those with postoperative moderate-to-severe TR (p=0.125 and 0.0748, respectively), but it was significantly different among the non-ischaemic patients (p=0.00426 and p=0.00433, respectively) (online supplementary figure 4C,D).

DISCUSSION

We studied the impact of FTR in patients with HFrEF (LVEF ≤30%) with high surgical risk undergoing pMVR.

The main findings of the current study are as follows. First, the periprocedural mortality (2.5%) is acceptable and not affected by FTR severity in patients with HFrEF. Second, preprocedural moderate-to-severe FTR grade is an independent predictor of cardiac death at 1 year in patients with HFrEF, even if the MitraClip therapy is successful with regard to the reduction of FMR. Third, residual moderate-to-severe FTR grade is a predictor of cardiac death at 1 year and all-cause mortality at midterm follow-up in patients with non-ischaemic, but not in ischaemic cardiomyopathy.

Residual moderate-to-severe FTR grade was significantly associated with early mortality. In our cohort, only

23% of cases with preoperative moderate-to-severe FTR grade could be reduced to mild FTR by pMVR, leaving 77% of patients at high risk of early mortality. As pMVR alone is not able to relieve FTR effectively in these patients, an additional intervention reducing FTR might be necessary in order to address left-sided and right-sided heart disease individually.

FTR is caused by TV annular dilation[12] and is often related to increased tethering of tricuspid leaflets due to RV enlargement owing to pulmonary hypertension.[13 14] A reported echocardiographic study emphasised that moderate-to-severe TR can increase the mortality rate regardless of pulmonary hypertension or low ejection fraction.[15] According to the literature, dilation of the right ventricle correlates with poor prognosis in patients with severe LV dysfunction.[16] In our two groups, none of the echocardiographic variables assessed were significantly different except for TR severity (table 2). Although there is no information about TV annulus diameter, we considered that these two groups might be different in terms of the preoperative TV annulus diameter influencing the FTR severity. However, it should be noted that the function of the right ventricle cannot be easily quantified by echocardiography due to its complex geometry. Recent studies have described that severe FTR or pulmonary hypertension may increase mortality after MitraClip procedure.[17 18] In our cohort with severely reduced LV systolic function, mild-to-severe preinterventional FTR was a predictor of mortality after MitraClip therapy, but not pulmonary hypertension. Postcapillary pulmonary hypertension as an immediate consequence of MR usually decreases after the procedure, whereas TR, reflecting sustained RV volume and pressure overload, seems to represent a structural defect in itself when present. The relation between efficiency of MitraClip and pulmonary artery pressure over time needs to be further studied.

Although our study was performed at a single centre, our outcomes reflect real-world practice, at least for high-volume centres in Germany. Our patients had severe LV dysfunction (mean LVEF of 22%±5.3%), as reflected by a high risk for surgical mortality (mean logEuroSCORE 34%±20%). Our clinical outcomes compared well with a previous large cohort study.[8]

In our cohort, 55% of patients had preoperative moderate-to-severe TR grade, yet the difference in preoperative TR severity did not have any influence on perioperative mortality (table 5) or duration of ICU stay (1.22±1.2 vs 1.55±2.0 days, p=0.39). The proportions of patients with none-to-mild FTR and those with moderate-to-severe FTR who were discharged home were 88.9% and 88.6%, respectively (p=ns), showing that pMVR can be safely performed in patients with HFrEF and high surgical risk.

Some authors have suggested that moderate-to-severe FTR in patients undergoing mitral valve surgery alone is strongly related to lower survival at midterm follow-up.[19] Generally, the residual MR grade after pMVR is greater than that after mitral valve surgery. Therefore, residual FTR severity is difficult to be reduced and seems to have more significant influence on cardiac death. In patients with HFrEF with postprocedural moderate-to-severe TR, attempts to treat FTR need to be discussed, even if pMVR is successful. Interestingly, 77% of patients with preprocedural moderate-to-severe FTR showed no improvement in FTR postoperatively and more than 40% died within 1 year because of heart failure. Echocardiographic variables of our two groups were similar, except for TR severity (table 4). As suggested in our study, preprocedural FTR severity seems to be an important predictor of poor survival.

Interestingly, early survival was not related to residual TR grade in patients with ischaemic cardiomyopathy (ICM), but was in patients with dilated cardiomyopathy (DCM). Most published reports concluded that survival both in patients with DCM and in patients with ICM is similar at midterm follow-up, which is in line with the findings of our study.[20] However, this was not differentiated by residual TR severity so far. We hypothesise that high-grade residual TR in DCM represents a risk factor in itself and should be considered a therapeutic target in order to improve survival in patients with DCM.

As recent studies have suggested that transcatheter tricuspid edge-to-edge repair (TTVR) can reduce the severity of FTR,[21] future studies should investigate if TTVR can improve survival in patients with residual moderate-to-severe FTR after pMVR in patients with HFrEF. We suggest that patients with moderate-to-severe preprocedural FTR should be observed carefully after MitraClip procedure. If FTR does not improve, additional interventional therapy should be considered early.

Limitations

This observational study was conducted at a single centre. Although patients were selected from a real-world clinical setting, the patient population was relatively small and the follow-up duration was relatively short. There were no CMR (Cardiovascular magnetic resonance) data available which would have allowed for more advanced analysis of RV function. In our study, preoperative NYHA grade was identified as an independent predictor of 1-year survival. However, preoperative NYHA grade might not entirely represent heart failure because of severe frailty in this cohort.

CONCLUSION

MitraClip therapy in patients with HFrEF was safe, regardless of preoperative FTR severity. However, preoperative FTR was not significantly improved. In our study, preoperative FTR was a major predictor of cardiac death at 1-year follow-up. Future studies are necessary to determine the value of additional TTVR in patients with residual moderate-to-severe FTR in the early phase after pMVR.

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Data availability statement Data are available in a public, open access repository. Data are available upon reasonable request. All data relevant to the study are included in the article or uploaded as supplementary information. Upon receiving approval from the Institutional Review Board of the Sana Heart Center, we retrospectively reviewed the records of consecutive patients who, between January 2013 and January 2018, had undergone medication therapy alone, repeat MitraClip therapy, or surgical revision for persistent or recurrent MR after percutaneous MitraClip therapy.

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CURRICULUM VITAE

Lebenslauf

Mein Lebenslauf wird aus datenschutzrechtichen Gründen in der elektronischen Version meiner Arbeit nicht veröffentlicht.

VOLLSTÄNDIGE PUBLIKATIONSLISTE

Publikationen

Gyoten T, Schenk S, Rochor K, Herwig V, Harnath A, Grimmig O, Just S, Fritzsche D, Messroghli D. Outcome comparison of mitral valve surgery and MitraClip therapy in patients with severely reduced left ventricular dysfunction. ESC Heart Fail. 2020 May 23;7(4):1781-90. IF: 3.407

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Vortrag

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