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Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip System

A dissertation presented to the medical faculty of the
Ulm University
In fulfillment of the requirements for the degree of
Doctor in Medicine

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Born in Piatra-Neamt, Romania

2020

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Thesis defense: 24 June 2021

Teile dieser Dissertation wurden bereits in dem folgenden Fachartikel veröffentlicht:

Nicoleta Nita, Dominik Scharnbeck, Leonhard-Moritz Schneider, Julia Seeger, Jochen Wöhrle, Wolfgang Rottbauer, Mirjam Keßler, Sinisa Markovic „Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system “, Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

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Abbreviations

ACE	Angiotensin-converting enzyme
CE	European Conformity
CRT	Cardiac Resynchronization Therapy
DMR	degenerative mitral regurgitation
ECG	electrocardiography
EF	ejection fraction
EuroSCORE II	European System for Cardiac Operative Risk Evaluation Score
FMR	functional mitral regurgitation
FSV	forward stroke volume
HF	heart failure
LA	left atrium
LV	left ventricle
LVEF	left ventricle ejection fraction
LVEDD	left ventricle end-diastolic diameter
LVESD	left ventricle end-systolic diameter
LVEDV	left ventricle end-diastolic volume
LVESV	left ventricle end-systolic volume
LVRR	left ventricular reverse remodeling
MACCE	major adverse cardiac and cerebrovascular events
MI	myocardial infarction
MR	mitral regurgitation
MV	mitral valve

NYHA	New York Heart Association
OR	odds ratio
ROC	Receiver operating characteristic
STS	Society of Thoracic Surgeons
TR	tricuspid regurgitation

1. Introduction

1.1 Burden of mitral regurgitation

Mitral regurgitation (MR) represents a significant source of heart failure and death in the Western world [90, 111]. The impact of prolonged volume overload on cardiac function extends beyond impaired hemodynamics to complex ventricular adverse remodeling, pulmonary hypertension, electrical instability and eventually terminal heart failure [36, 90, 111]. Mitral regurgitation is the most frequent valvular disease in the United States with an estimated prevalence of 1.7% in the adult population [73, 111], and is the second most common form of valvular disorder requiring invasive treatment in Europe reaching a prevalence of 2% [71, 72, 153].

The global epidemiology of valvular heart disease has changed markedly in the past decades [16]. Even though prevalence of rheumatic cardiac disease significantly decreased in the Western world [38, 111], recent epidemiological community studies have underlined the increasing burden of mitral regurgitation, being impactful for outcome and seriously undertreated [34, 111]. The OxVALVE Population Cohort Study (OxVALVE-PCS), a large ongoing prospective cohort study which performed systematic echocardiographic scanning in elderly patients, emphasized the growing epidemic of MR aligned with major economic impact on the healthcare system [30].

Improved life expectancy allowed expression of degenerative changes, consecutively resulting in increased prevalence of age-related valvular diseases. Thus, degenerative disease is today the most frequent cause of MR in the Western world [47]. Nevertheless, advanced heart failure management associated with prolonged survival translated in rising burden of secondary MR in the context of regional or global left ventricular (LV) remodeling [34]. A more combative treatment strategy of coronary disease, which is currently responsible for 20% of MR, is expected to decrease the high prevalence of functional mitral regurgitation (FMR) in the Western world [23].

The exact global prevalence of severe mitral regurgitation in the general population is unknown, however, it was estimated to exceed five million worldwide [14, 35, 111]. As a result of degenerative pathophysiology, the prevalence of MR increases progressively with age afflicting more than 10% in the elderly population aged ≥75 years [73].

Volha et al. [34] performed quantitative assessment of MR in a large community study and reported, in contrast to previous surgical series [6], similar prevalence of MR in both sexes, reflecting the large burden of MR in women which was previously underestimated [34].

Mitral regurgitation is defined as abnormal backflow from the left ventricle to the left atrium during systole [35]. Any damage of the mitral valve (MV) apparatus that impairs leaflet coaptation will result in some degree of mitral regurgitation [31]. MR is commonly classified as primary or secondary [144]. Primary or degenerative mitral regurgitation (DMR) derives from intrinsic lesions of the mitral valve, resulting in left ventricular volume overload. Secondary or functional MR prevails in patients with ischemic or non-ischemic cardiomyopathy and is caused by atrial or ventricular remodeling without intrinsic leaflet pathology [91]. LV remodeling can be global, where the major determinant is LV dilatation causing tethering and valve malcoaptation due to increased sphericity index [81, 131], or localized, involving mainly the posterior papillary muscle - bearing LV walls [162]. Mixed pathology implying degenerative valvular changes and leaflet coaptation failure related to left ventricular dilatation may be found.

Regardless of the etiology, severe mitral regurgitation bears a poor prognosis [9]. Without proper treatment, this valvular disorder has an annual mortality rate of 6% per year or up to 60% at 5 years in patients with heart failure (HF), as revealed by the Euro Heart Survey on valvular heart disease [106]. Rossi et al. reported that functional MR in patients with HF and left ventricular ejection fraction (LVEF) < 35% doubled the risk of HF hospitalization and all-cause mortality [128]. Recently, the large Olmsted County Community study [34], analyzing single-valvular MR, showed that mitral regurgitation, even isolated, bears excessive mortality in all subgroups of patients: with FMR or DMR, with high or low left ventricular ejection fraction, with moderate or severe regurgitation, with or without comorbidities. The proportion of patients alive at 5 years was 53% (vs. expected 78% in the rest of the community) and at 10 years 30% (vs. expected 63%). Likewise, the proportion of patients with heart failure at 5 years was 64% and 76% at 10 years [34]. The poor prognosis of MR has been repeatedly related to extensive adverse LV remodeling and pulmonary hypertension following chronic volume overload [20, 108].

High prevalence and excess mortality are both compelling reasons to develop comprehensive strategies in order to improve outcome of mitral regurgitation [34].

1.2 Therapeutic strategies for mitral regurgitation

According to current European and American guidelines, surgical mitral valve repair or replacement represents the first-line therapy in patients with symptomatic degenerative MR or asymptomatic degenerative MR with impaired LV function, pulmonary hypertension or atrial fibrillation [9, 109, 152]. Prompt valve repair restores life expectancy in these patients, underlining the importance of early detection and timely treatment [9]. Importantly, medical therapy doesn't delay the need for surgical intervention in DMR [109, 149].

With regard to secondary MR, surgical approach has rather restrictive indications due to high recurrence rates, as well as high perioperative mortality risk of more than 14% if the LV function is impaired [56], without robust evidence of survival benefit compared with medical therapy [106]. Therefore, the 2017 European Society of Cardiology/European Association for Cardiothoracic Surgery guidelines indicate surgery for isolated severe FMR in HF patients with only a class IIb level of evidence C designation, unless other cardiac operations are planned [11]. Accordingly, the 2017 American Heart Association guidelines for the management of patients with valvular disease recommend surgical approach with only a class IIb level of evidence B designation [109].

Optimal medical therapy and cardiac resynchronization therapy improve HF symptoms and may reduce the severity of mitral regurgitation, being standard of care management in patients with FMR [143, 144]. However, these high-risk patients have limited therapeutic options, most of them receiving only conservative medical treatment [109].

1.2.1 Undertreatment of mitral regurgitation

Despite high prevalence and excessive mortality of MR, increasing data suggest significant rates of undertreatment, not only in patients with extensive comorbidities or high surgical risk status. Prior studies estimated that only 50% of the patients with severe MR and indication for surgery actually receive surgical treatment [15, 54, 106]. Beyond elevated surgical risk, other factors such as patient refusal of invasive care or economic restraints in the healthcare delivery system have been found responsible for this important therapeutic gap [53].

Newly published results from a community cohort study conducted by M. E. Sarano revealed substantial undertreatment of MR, not only for secondary MR, but also for primary MR, with only 30% of patients with degenerative etiology receiving surgical repair even in a clinical setting with all facilities and expertise available [34]. In addition, as stated by Glover and colleagues [53], according to the Society of Thoracic Surgeons database from 2012, solely 5.6% of patients receiving surgical MV treatment presented high surgical risk, underlining again the high rates of undertreatment of MR.

1.2.2 Percutaneous mitral valve repair with the MitraClip system

Percutaneous mitral valve repair was developed to respond this unmet need for treatment in a selected high-surgical-risk population with both degenerative and functional MR. Before the emerge of transcatheter valve therapies, these patients could only receive heart failure treatment including resynchronization therapy and coronary revascularization when appropriate [109].

Presently, the only percutaneous device with CE (European Conformity) market approval is the MitraClip system (Abbott Vascular, Abbott Park, IL). Since its debut in 2009, over 80.000 patients (as of March 2019, according to Abbott Laboratories data) have been treated with the MitraClip device, many of them enrolled in prospective clinical trials. This device mimics the surgical concept of Ottavio Alfieri who developed the edge-to-edge repair in the 1990s, which reduces the regurgitant jet by grasping the MV leaflets with one or more clips, creating a double orifice valve [40, 137, 144].

The feasibility, safety and efficacy of the percutaneous mitral valve repair with MitraClip was proved in the Endovascular Valve Edge-to-Edge Study (EVEREST I) [43]. The EVEREST II Trial randomized standard-risk patients to surgery or percutaneous repair and demonstrated that MitraClip therapy was less effective in reducing the severity of mitral regurgitation, but safer than surgery [40]. More important, similar mid-term outcomes have been reported after surgery and transcatheter approach [40].

Although in the EVEREST Trials the majority of patients had degenerative MR, data from post approval registries such as TRAMI registry or ACCESS-Europe registry revealed significant differences in the real-world application of the MitraClip device compared to the EVEREST II trial: the functional etiology predominated and patients tended to have higher surgical risk. Initial concerns have been raised that high morbidity of the treated patients might outweigh the potential clinical benefit after the procedure [53]. Subsequently, a growing body of evidence from post approval studies demonstrated that MitraClip therapy promoted significant clinical benefit in this high-risk population. Among others, in patients in whom Cardiac Resynchronization Therapy (CRT) failed to improve clinical status and severity of MR, MitraClip therapy showed promising results. The Percutaneous Mitral Valve Repair in Cardiac Resynchronization Therapy (PERMIT-CARE) feasibility study [5] included CRT non-responders with moderate-to-severe FMR; MitraClip implantation led to

considerable reduction of MR aligned with prompt improvement in New York Heart Association (NYHA) functional class which sustained within the ensuing 3–12 months in most patients. Moreover, relevant decrease in left ventricular dimensions were reported at six and 12 months follow-up [5].

The only FDA-approved indication for MitraClip refers to primary degenerative MR with prohibitive risk for surgery and fulfillment of the echocardiographic criteria of eligibility. The new European guidelines recommend MitraClip therapy for high surgical risk, symptomatic patients with secondary MR under maximal HF medical therapy (class 2b recommendation) [11]. However, recently published results from the randomized COAPT trial may significantly change current guidelines [143]. This trial compared percutaneous edge-to-edge repair with MitraClip device along with guideline-directed medical therapy to medical therapy alone in patients with heart failure and more than moderate functional MR, and demonstrated not only improved quality of life and reduced hospitalization rates, but also improved survival in the group treated with MitraClip device. The authors reported an absolute risk reduction in all-cause mortality of 17% in patients receiving MitraClip device, which means a number needed to treat of 6 to prevent one death over two years. The results of the randomized RESHAPE-HF trial are awaited to replicate the promising findings of the COAPT trial.

1.3 Cardiac remodeling

1.3.1 Concepts of adverse ventricular remodeling

The term "cardiac remodeling" as equivalent to adverse ventricular remodeling was first used in experimental myocardial infarction (MI) models to describe increase in the ventricular size and replacement of infarcted tissue with scar tissue [7, 65]. Recognition of cardiac remodeling in the current context emerged from the work of Janice Pfeffer, who first demonstrated a strong correlation between survival and ventricular dilation using a rat model of MI [119]. Subsequently, studies on Angiotensin-converting enzyme (ACE) inhibitors demonstrated for the first time drug-related reverse ventricular remodeling with reduced ventricular dimensions along with survival benefit in infarcted rats [121]. Research data of Pfeffer et al. laid the first stone for human studies that have eventually proved the complexity of remodeling process, its major impact on prognosis and nevertheless the unexpected reversal potential [150].

Any kind of myocardial insult from ischemic damage to pressure or volume overload can promote adverse ventricular remodeling [82, 115, 116]. A consensus paper from an international forum defined cardiac remodeling as molecular, cellular and interstitial disturbances which translate into deterioration of size, shape and function of the heart following cardiac injury [28]. This international forum also established the need for remodeling targeted therapeutic interventions, based on study data available in the emerging era of ACE inhibitors. Subsequently, a growing body of studies have substantiated the strong correlation between maladaptive remodeling and survival [82, 85, 155].

Ventricular remodeling understood as maladaptive or adverse ventricular remodeling, irrespective of the underlying insult, has been considered the substrate for heart failure and repeatedly associated with reduced survival [7, 50, 158]. Previous studies showed that even moderate ventricular dilation promotes poor prognosis with increased all-cause mortality in HF patients following myocardial infarction [28, 62, 119, 158]. Several patterns of remodeling have been distinguished: volume overload induced, pressure overload induced and post infarction, along with significant differences in terms of geometry changes, wall stress profile and molecular modulation of cardiomyocytes and extracellular matrix [22, 61].

1.3.2 Adverse cardiac remodeling in mitral regurgitation

Cardiac remodeling in response to chronic volume overload in MR is significantly different from pressure overload induced remodeling and refers to a complex interplay of specific mechanical, neurohormonal and genetic factors reflected by typical alterations in geometry and function of the heart, eventually threatening the overall hemodynamics. The molecular biology of these remodeling patterns has been examined in detail by Toisher et al. and will not be further discussed [148].

In the course of chronic mitral regurgitation, the systolic regurgitant backflow through the mitral valve causes a reduction in forward stroke volume (FSV) into the aorta and an increase in left atrium (LA) blood volume which result in an increase of left ventricular preload, the so-called "volume overloaded state" [21]. The first changes in the early remodeling phase relate to damage in the extracellular matrix [70], thus allowing cardiac chambers to accommodate increased volume load through enhanced ventricular compliance and chamber enlargement [104]. Significant infiltration with inflammatory mast cells and extracellular collagen depletion have been observed in experimental models in the early stages of remodeling [70].

Enhanced diastolic wall stress and excessive diastolic stretch of cardiomyocytes activate specific cellular signaling resulting in ventricular eccentric hypertrophy in an attempt to sustain an adequate forward stroke volume [21]. These initial changes lead to the typical hemodynamic pattern in MR with enhanced diastolic function and relatively preserved systolic function [21].
Although asymptomatic in the early stages, volume overload is inevitably a progressive process evolving to cardiomyocyte apoptosis, common to all forms of heart failure. In the course of disease evolution, the distorted ventricular geometry extends to mitral annular dilation and papillary muscle displacement further aggravating leaflet coaptation.

Adverse cardiac remodeling in functional mitral regurgitation relates to a complex pathophysiology, given that a dysfunctional left ventricle predates the mitral regurgitation [35, 127]. Most experimental and clinical studies investigated volume overload induced remodeling in previous healthy hearts, thus significantly lesser information is available on this topic in secondary MR compared to primary MR [127].

Secondary MR arise from decreased LV closing forces and mitral annular dilatation in response to regional or global LV remodeling [12, 126, 127]. The resultant volume overload renders additional diastolic wall stress and entertains at a neurohormonal and molecular level the preexisting loop of pathological remodeling, leading to further LV dysfunction [107, 140, 151]. In other words, as previously stated [19], MR promotes the process causing its genesis, perpetuating a vicious cycle.

Understanding the pathophysiology of volume overload induced cardiac remodeling is pivotal for prognosis assessment and guidance of therapy in mitral regurgitation in order to prevent or delay the onset of heart failure [104].

1.3.3 Reverse ventricular remodeling

Since adverse ventricular remodeling is the fundamental substrate of progressive heart failure and poor prognosis, preventing or reversing cardiac dilatation in patients with mitral regurgitation represents, as in HF, an imperative therapeutic target [122]. The concept of reverse remodeling was established in the beginning era of ACE inhibitors to describe improved ventricular geometry and reduction in LV volumes and dimensions observed in heart failure patients [156]. Prior studies on heart failure rouse awareness for reverse ventricular remodeling by reporting that outcomes were closely related not only with LVEF but rather with changes in LV volumes and dimensions [57, 83, 87, 160].

There is a growing body of evidence supporting the benefits of pharmacological agents, CRT or valve surgery used to induce reverse remodeling in dilated hearts. Reverse remodeling was reported in approximately one-third of patients with cardiomyopathy, with estimates ranging from 26% to 46% [26, 105].

Trials on both ACE inhibitors (SOLVD studies) and angiotensin II receptor blockers (the Elite Studies) demonstrated a beneficial pharmacological effect on ventricular remodeling by promoting regression in cardiac dilation [84, 120, 132]. Increased adrenergic activity has been strongly associated with adverse ventricular remodeling. Thus prior trials reported even more pronounced reverse remodeling following beta-blocker therapy compared to ACE inhibitors therapy [67, 132].

CRT has been also acknowledged to induce reverse remodeling, as shown in the randomized REVERSE and MADIT Trials, which demonstrated significant reduction in left ventricular volumes and dimensions during follow-up [10, 55]. Nevertheless, surgical repair in degenerative and functional mitral regurgitation has been proven to reverse the remodeling process [130, 157]. Among other studies, the randomized multicentric Acorn trial assessed long-term ventricular changes in patients with secondary mitral regurgitation, showing significant improvement in ventricular geometry and function after surgical mitral valve repair. Similar results were demonstrated by Fattouch et al. after surgical mitral annuloplasty in ischemic mitral regurgitation [1, 39]. With regard to MitraClip Therapy, reports on left ventricular reverse remodeling are heterogeneous [59, 63, 133, 134].

The reverse remodeling response, quantified as reduction of left ventricular (LV) volumes and dimensions, has important prognostic significance as shown in pharmacological and CRT studies of heart failure or in trials after surgical or percutaneous valve repair. Patients who develop reverse remodeling have a proven survival benefit [83, 84, 124, 161].

Among many pharmacological studies, Hoshikawa et al. [67] evaluated the impact of reverse remodeling on survival. This study showed that decrease in LV end-systolic dimension at follow-up was an independent predictor of cardiac mortality or heart transplantation in patients with dilatated cardiomyopathy. According to this study, patients with progressive ventricular dilation died during the follow-up of 5 years, while patients who presented some reversal in ventricular dilation survived. Analogously, Matsumura et al. [98] investigated the impact of reverse remodeling on long-term prognosis in heart failure. The authors reported that regression of cardiac dilatation, defined as decrease of LV end-diastolic dimension ≤ 55 mm, was associated with significant survival benefit after 12 years of follow-up.

The results of these small scaled studies have been expanded in larger randomized trials. Kramer and colleagues reported in a metanalysis of 30 randomized trials including almost 70000 patients with left ventricular dysfunction, a strong association between reverse remodeling and reduced mortality after pharmacological and device therapy. Mortality significantly decreased by 50% in patients who experienced reverse cardiac remodeling compared with those who did not [87].

1.4 Research questions

We hypothesized that sustained MR reduction after MitraClip therapy would be associated with significant left ventricular reverse remodeling and sought to identify clinical and echocardiographic characteristics that predict left ventricular reverse remodeling. Given that degenerative and functional mitral regurgitation represent two different disease entities, it is uncertain whether successful MitraClip therapy would induce similar extent of reverse ventricular remodeling in both etiologies. Therefore, we sought to determine potential differences regarding the magnitude and the predictors of left ventricular reverse remodeling in degenerative mitral regurgitation compared to functional mitral regurgitation.

Reverse cardiac remodeling has been repeatedly related to survival benefit after various treatments in heart failure, including medical therapy, CRT and valvular interventions, playing therefore a crucial role in the process of risk stratification and therapeutic guidance. However, the prognostic implications of reverse ventricular remodeling after percutaneous edge-to-edge repair have been scarcely evaluated so far. The secondary objective of this study was to evaluate the impact of MitraClip-induced left ventricular reverse remodeling on clinical outcome after 2 years of follow-up in a “real-world cohort” with reduced left ventricular ejection fraction and extensive ventricular dilatation.

2. Materials and methods

2.1 Study population and design

In the present study consecutive high surgical risk patients with severe mitral regurgitation receiving MitraClip implantation between January 2010 and December 2016 in our high-volume institution were analyzed. Data obtained at discharge and follow-up was collected into an observational prospective registry. A total of 374 patients with severe symptomatic functional MR and degenerative MR underwent the procedure after previous assessment in our heart team consisting of cardiologists and heart surgeons and in accordance with current guidelines recommendations on valvular heart disease [11, 152].

From this population, 164 patients (44%) underwent an extensive clinical and echocardiographic work-up and were enclosed in further analysis. The echocardiographic follow-up required for inclusion was set at 6 months and 12 months after the procedure.
210 patients have been excluded from the analysis for the following reasons: lost to follow-up, unsuccessful procedure, missing LVEDD measurements for LVRR assessment at baseline or during follow-up and occurrence of a major event during the first 12 months (i.e. death, heart transplantation, LV assist device implantation).

All patients suffered from severe mitral regurgitation (i.e. grade III or IV) documented by echocardiography, and presented symptoms of heart failure (New York Heart Association functional class > II) despite optimal pharmacotherapy. Surgical risk was calculated in accordance to the European System for Cardiac Operative Risk Evaluation Score (EuroSCORE II, http://www.euroscore.org/calc.html) and Society of Thoracic Surgeons (STS, http://riskcalc.sts.org/ stswebriskcalc/#/calculate) model for mortality.

The study was ethically approved by the ethics committee of the University of Ulm and complied with the Declaration of Helsinki (NCT03104660).

2.2 Device and MitraClip Implantation

Before intervention, diagnostic evaluation with laboratory testing, electrocardiography (ECG), transthoracic and transesophageal echocardiography as well as clinical assessment including medical history with current medication and NYHA classification was performed for all patients. Prior to MitraClip implantation, invasive hemodynamic measurement with right and left and right catheterization was performed. The MitraClip System (Abbot) has been previously described in details [42]. Briefly, it is a catheter based device implanted in beating heart which affords percutaneous repair by approximating the free edges of the anterior and posterior mitral leaflets forming a double orifice [40, 137].

The intervention was performed under general anesthesia in a hybrid catheterization laboratory, as previously described [43]. Device implantation was conducted under fluoroscopic and echocardiographic guidance via venous access through transatrial route. Peri-procedural transesophageal echocardiography was performed by cardiologists specialized in invasive imaging, consistent with current recommendations of the European Society of Cardiology [88]. Live real-time 3-D echocardiography was performed to improve the imagistic guidance during the procedure. Depending on residual MR and on complexity of the underlying MR pathophysiology, in selected cases, more than one clip was needed to achieve optimal results. Patients received oral anticoagulation and acetylsalicylic acid for 4 weeks after the procedure or indefinite anticoagulation if indicated.

Device success was defined using the Mitral Valve Academic Research Consortium (MVARC) criteria as effective reduction in MR of more than two degrees without mitral stenosis, absence of procedural mortality, stroke, unplanned surgical or interventional procedure, proper delivery and positioning as well as proper performance of the device without functional or structural failure [142, 144].

Clinical outcomes assessed at 12 and 24 months after the procedure included mortality, heart failure rehospitalization, reintervention, major adverse cardiac and cerebrovascular events (*MACCE,* composite endpoint of stroke or cerebral bleeding, heart failure related rehospitalization, reintervention on the mitral valve, implantation of left ventricular assist device and cardiac death).

2.3 Echocardiographic evaluation

Patients underwent transthoracic and transesophageal echocardiography to evaluate severity and etiology of MR, left atrial and ventricular dimensions and function.

Severity of mitral regurgitation was graded according to the criteria of the EVEREST trials [43] by the use of an integrative approach (e.g. quantitative measurements: regurgitant volume, regurgitant fraction, EROA and qualitative criteria with color Doppler). Patients receiving MitraClip therapy presented moderate-to-severe (grade 3) or severe (grade 4) MR. The etiology was established by interventional echographers in MitraClip Team. Patients with leaflet malcoaptation caused by left ventricular dilation, annular dilation and leaflet tethering in the setting of impaired systolic LV function were classified as functional MR. Patients with primary leaflet lesions in terms of mitral valve leaflet prolapse, flail leaflet, clefts, chordal and papillary muscle rupture and fibroelastic deficiency were classified as primary MR. Measurements of the left ventricle end-diastolic diameter (LVEDD) and left ventricle end-systolic diameter (LVESD) were provided by transthoracic echocardiography in the long axis parasternal view. LVEF was calculated with biplane Simpson's method.

Studies of HF determined a cut-off value of 10% decrease in LVEDV/LVEDD with high sensitivity and specificity for prediction of cardiovascular mortality and HF hospitalizations after medical and device therapy [163]. According to previous studies [8, 52, 79, 103], we defined reverse ventricular remodeling as a decrease of $\geq$ 10% in the LV end-diastolic diameter 12 months after MitraClip therapy [110].

2.4 Statistical Analyses

The study population was dichotomized into two groups of interest according to the presence (LVRR group, n=81) vs. absence of reverse ventricular remodeling (no-LVRR group, n=83). In addition, separate analyses were performed for patients with functional MR (FMR group, n= 111) and patients with degenerative MR (DMR group, n=53).

The normal distribution of continuous variables was determined with the Shapiro–Wilk test. Continuous parameters following a normal distribution are presented as mean ± standard deviation and were compared using the *t*-test; variables not following a normal distribution were reported as median and interquartile range and were compared with the Mann–Whitney test.

Categorical variables are expressed as counts and percentages and were compared by Chi-square test. All results having a p-value of <0.05 were considered statistically significant.

For the identification of independent predictors of LVRR, univariate analysis was performed. All clinical and echocardiographic variables with a p-value <0.10 were consequently included in the multivariate logistic regression analysis using a backward stepwise algorithm. End- diastolic and end-systolic LV diameter at baseline and at follow-up have been associated with high variance inflation factors (7.6 and 6.6) and therefore were excluded from the multivariate regression model. Finally, the multivariate model included gender, severely reduced LVEF (below 20%), NYHA class at baseline, severe mitral regurgitation at 12 months and severe tricuspid regurgitation (TR) at 12 months [110].

Similar analyses were performed for the two subgroups according to the etiology of MR: functional MR (n=111) and degenerative MR (n=53). Multiple stepwise regression analyses were performed with stepwise inclusion of the following variables from the univariate analysis: severely reduced LVEF (below 20%), number of implanted clips, NYHA class at baseline, severe recurrent or residual tricuspid regurgitation at 12 months and severe recurrent mitral regurgitation after 12 months. The event rate at one and two years was estimated using the Kaplan–Meier method, and curves (LVRR vs. no-LVRR) were compared with the log-rank test [110].

All statistical analyses were calculated with the Statistica software version 7.1 (Stat Soft, Inc., Tulsa, Oklahoma, USA) and SPSS, version 20.0 (SPSS Inc., Chicago, IL, USA).

3. Results

From the total cohort of 374 patients receiving percutaneous treatment with MitraClip system for severe MR between January 2010 and December 2016, 210 subjects were excluded from the analysis for the ensuing reasons: 75 were lost to follow-up, 6 patients had an unsuccessful procedure; 50 subjects died and 8 underwent LV assist device implantation (6) or cardiac transplantation (2) within 12 months after the procedure; 71 patients had missing LVEDD measurements for LVRR assessment at baseline or during follow-up [110]. However, no significant differences in baseline features could be noted between the study patients and the excluded patients, as shown in Table 1 [110].

3.1 Reverse remodeling in the total cohort

The study population had a mean age of 76.9±8.6 years; 67.7% were male and 67.7% had functional mitral regurgitation. Mean LVEF was 43.5±16.8%. 49.4% of the study cohort (81 patients) experienced left ventricular reverse remodeling, defined as decrease of ≥10% of LVEDD at 12 months follow-up after the MitraClip procedure.

Baseline features of the LVRR group (n=81) compared to the no-LVRR group (n=83) are reported in Table 2 and Table 3 [110]. No significant differences were found between the two groups regarding grade or MR, NYHA functional class, baseline LVEF, comorbidities or STS Score. Within the LVRR group, 65.4% of the patients had functional MR and 34.6% presented degenerative MR. A similar distribution was observed within the no-LVRR group: functional MR was present in 69.9% of patients, degenerative MR in 30.1% of the patients. For interventional edge-to-edge therapy, in the no-LVRR group 1.3±0.5 and in the LVRR group 1.2±0.4 MitraClip devices were implanted. LVEDD at baseline was significantly higher in the LVRR group (65.1±10.8 mm) compared to the no-LVRR group (61.2±10.9 mm, p=0.025). Baseline LVEF in the total cohort was 43.5±16.8 %. Even though baseline LVEF in the LVRR group (44.5±16.3%) was similar compared to the no-LVRR group (42.5±17.2%, p=0.49), the proportion of patients having LVEF < 20% was higher in the no-LVRR group (10.8%) compared to the LVRR group (3.7%, p=0.07) [110].

Table 1 Baseline characteristics in the total population with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**Excluded patients**	**Study patients**	**P-Value**
Number of patients	374	210	164	
Male, N (%)	228 (61.0)	117 (55.7)	111 (67.7)	0.02
Age> 75 years	270 (72.2)	151(71.9)	119 (72.6)	0.88
Logistic Euro SCORE	8.7±7.8	8.6±7.3	8.9±8.3	0.94
non ischemic cardiomyopathy	63 (16.8)	34 (16.2)	29 (17.7)	0.70
atrial fibrillation/flutter	252 (67.4)	147 (70.0)	105 (64.0)	0.22
NT-pro BNP (pg/ml)	5736.9±6604	6176.9±6752	5161.3±6391	0.06
Troponin T(ng/ml)	39.1±38	39.1±37	39.1±40	0.47
chronic obstructive pulmonary disease	49 (13.1)	29 (13.8)	20 (12.2)	0.64
CRT	36 (9.6)	19 (9.1)	17 (10.4)	0.67
Glomerular filtration rate< 60 ml/min	206 (55.1)	122 (58.1)	84 (51.2)	0.18
NYHA functional class	3.1±0.7	3.2±0.7	3.1±0.7	0.15
functional etiology	237 (63.4)	135 (64.3)	102 (62.2)	0.67
degenerative etiology	137 (36.6)	75 (35.7)	62 (37.8)	0.67

Values are mean ± standard deviation, or number (%). NYHA, New York Heart Association; NT-pro BNP, N-terminal pro-B-type natriuretic peptide; CRT, cardiac resynchronization therapy; P-values by Student's t-test and Chi2 test. Table from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

Table 2 Baseline characteristics of the study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**no-LVRR**	**LVRR**	**P-Value**
Number of patients	164	83	81	
Male, N (%)	111 (67.7)	62 (74.7)	49 (60.5)	0.051
Age in Years	76.9±8.6	75.6±10.2	78.2±6.4	0.16
NYHA functional class	3.1±0.7	3.1±0.7	3.0±0.8	0.91
EuroSCORE II	8.9±8.3	9.0±8.8	8.7±7.9	0.85
STS Score of mortality	3.7±3.9	3.3±2.8	4.2±4.7	0.22
Diabetes mellitus	43 (26.2)	25 (30.1)	18 (22.2)	0.25
non ischemic cardiomyopathy	29 (17.7)	15 (18.1)	14 (17.3)	0.89
atrial fibrillation/flutter	105 (64.0)	58 (69.9)	47 (58.0)	0.11
NT-pro BNP (pg/ml)	5173.3±6418	5126.9±6230	5207.4±6605	0.56
Troponin T(ng/l)	39.2±40	39.7±42	38.7±38	0.81
chronic obstructive pulmonary disease	20 (12.2)	10 (12.0)	10 (12.4)	0.95
CRT	17 (10.4)	8 (9.6)	9 (11.1)	0.76
Glomerular filtration rate <60mL/min	84 (51.2)	43 (51.8)	41 (50.6)	0.88
LBBB	51 (31.1)	26 (31.3)	25 (30.9)	0.95
Etiology of mitral valve regurgitation				
functional	111 (67.7)	58 (69.9)	53 (65.4)	0.54
degenerative	53 (32.3)	25 (30.1)	28 (34.6)	0.54

Values are mean ± standard deviation, or number (%). NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRT, cardiac resynchronization therapy; LBBB, Left Bundle Branch Block; P-values by Student's t-test and Chi2 test. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

Table 3 Baseline echocardiographic parameters in the total study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**no-LVRR**	**LVRR**	**P-Value**
LVEDD (mm)	63.1±11.0	61.2±10.9	65.1±10.8	0.025
LVESD (mm)	47.4±13.1	46.2±13.1	48.6±13.2	0.17
LA diameter (mm)	56.0±8.2	56.5±8.6	55.5±7.7	0.66
Left ventricular ejection fraction (%)	43.5±16.8	42.5±17.2	44.5±16.3	0.49
LVEF < 40%	75 (45.7)	40 (48.2)	35 (43.2)	0.52
LVEF < 20%	12 (7.3)	9 (10.8)	3 (3.7)	0.07
Severe mitral regurgitation (grade III/IV)	162 (98.8)	82 (98.8)	80 (98.8)	0.99
Severe tricuspid regurgitation	78 (47.6)	38 (45.8)	40 (49.4)	0.64
Maximal tricuspid Gradient	47.9±13.7	47.2±13.8	48.7±13.6	0.89

Values are mean ± standard deviation, or number (%). LVEDD, left ventricular end-diastolic diameter; FU, follow-up; LVESD, left ventricular end-systolic diameter; LA, left atrial; P-values by Student's t-test and Chi2 test.

3.1.1 Echocardiographic results

At 12 months follow-up LVEDD decreased in the LVRR group from 65.1±10.8 mm to 52.9±9.0 mm ($p<0.001$), whereas it remained stable in the no-LVRR group ($p=0.23$). Likewise, LVESD was constant in the no-LVRR group ($p=0.17$), whereas it significantly decreased in the LVRR group from 48.6±13.2 mm to 38.8±10.8 mm ($p<0.001$). Opposed to left ventricular dimensions, decrease of left atrial dimensions has been observed both in the LVRR group ($p=0.03$) and in the no-LVRR group ($p=0.01$). LVEF at 12 months follow-up improved from 44.5±16.3% to 46.5±16.0% in the LVRR group ($p=0.14$), whereas it remained stable in the no-LVRR group (42.5±17.2% at baseline vs. 42.9±17.8% at follow-up, $p=0.76$) [110].

Mitral regurgitation degree at baseline did not differ between the two groups, 98.8% of patients having severe MR in each group, $p=0.99$. Immediate postprocedural results showed similar reduction of MR severity in the no-LVRR group (severe MR grade III/IV in 7.2%) compared to LVRR group (severe MR grade III/IV in 2.5%, $p=0.15$). Yet, at 12 months after the MitraClip procedure patients without LVRR presented significantly more frequent severe MR (20.5%) compared to the LVRR group (7.4%, $p=0.01$) [110].

Analogously, severe tricuspid regurgitation (TR) at baseline was equally distributed in both groups (49.4% in the LVRR group vs. 45.8% in the no-LVRR group, $p=0.64$). The baseline maximal tricuspid pressure gradient in the no-LVRR group was 47.2±13.8 mmHg, similar to 48.7±13.6 mmHg in the LVRR group ($p=0.89$). During 12-months follow-up, TR grade significantly decreased in both groups ($p<0.001$ in the LVRR group and $p<0.009$ in the no-LVRR group), however a trend towards a lower frequency of severe TR was noted in the LVRR vs. no-LVRR group (19.8% vs. 32.5%, $p=0.06$).
All echocardiographic parameters during follow-up are summarized in Table 4.

Table 4 Echocardiographic parameters during follow-up in the total study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016

		Total	no-LVRR	LVRR	P-Value
LVEF (%)	6 months	43.4±16.6	42.6±17.6	44.2±15.6	0.51
	12 months	44.7±17.0	42.9±17.8	46.5±16.0	0.16
LVEDD (mm)	6 months	59.3±11.5	61.2±12.0	57.5±10.9	0.09
	12 months	57.5±11.1	61.9±11.1	52.9±9.0	<0.001
LVESD (mm)	6 months	45.1±13.9	47.0±14.8	43.2±12.8	0.13
	12 months	43.1±13.1	47.4±14.2	38.8±10.8	<0.001
Severe mitral regurgitation (grade III/IV)	Postprocedural	8 (4.9)	6 (7.2)	2 (2.5)	0.15
	6 months	28 (17.1)	20 (24.1)	8 (9.9)	0.01
	12 months	23 (14.0)	17 (20.5)	6 (7.4)	0.01
Severe tricuspid regurgitation	6 months	51 (31.1)	31 (37.4)	20 (24.7)	0.08
	12 months	43 (26.2)	27 (32.5)	16 (19.8)	0.06
LA diameter (mm)	6 months	54.3±8.7	54.9±8.6	53.7±8.8	0.27
	12 months	54.0±8.9	54.5±8.9	53.5±8.9	0.52

Values are mean ± standard deviation, or number (%). LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrial; P-values by Student's t-test and Chi2 test.

3.2 Predictors of LVRR in the overall population

In search of predictors for the non-occurrence of LVRR, multivariate logistic regression analysis was performed. In the total cohort, male gender (OR 0.499), severe recurrent mitral regurgitation after 12 months (OR 0.262) and poor baseline left ventricular function (baseline LVEF below 20%, OR 0.244) were identified as independent predictors for lack of LVRR after adjustment for severe TR at 12-months follow-up, as shown in Table 5 [110].

Table 5 Multivariate regression analysis for predictors of reverse remodeling in the total study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016

Variables	**Odds Ratio**	**95% CI**	**P-Value**
Male gender	0.499	0.248-1.00	0.050
Baseline LVEF < 20%	0.244	0.061-0.972	0.046
Recurrent severe MR at 12-month follow-up	0.262	0.094-0.729	0.010
Residual severe TR at 12-month follow-up	0.481	0.227-1.017	0.06

CI, confidence interval; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

3.3 Reverse remodeling in FMR versus DMR

A main purpose of this study was to determine differences between DMR and FMR regarding the magnitude and predictors for reverse ventricular remodeling. The study population was therefore divided into two different cohorts according to etiology in order to analyze reverse remodeling in each group of patients.

Table 6 shows demographic, clinical and echocardiographic variables at baseline according to the cause of MR. As expected, patients with FMR tended to have lower LVEF and larger LV dimensions than patients with DMR. Patients with FMR had higher surgical risk (Logistic EuroScore 9.7±8.7) compared to DMR patients (Logistic Euroscore 7.1±7.2 p=0.04). In patients with functional MR baseline Troponin T and NT pro-BNP values were significantly higher compared to degenerative MR (p= 0.04 and p=0.01 respectively). Patients with DMR were older (79.8±5.0 years) compared to patients with FMR (75.5±9.6 years, p=0.004). No significant differences in terms of comorbidities (hypertension, diabetes mellitus, atrial fibrillation, renal failure) between FMR and DMR were observed.

Table 6 Baseline characteristics in FMR versus DMR subgroups of patients treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**FMR**	**DMR**	**P-Value**
Number of patients	164	111	53	
Male, N (%)	111 (67.7)	80 (72.1)	31 (58.5)	0.08
Age in years	76.9±8.6	75.5±9.6	79.8±5.0	0.004
Hypertension	138 (84.1)	93 (83.8)	45 (84.9)	0.85
Diabetes mellitus II	43 (26.2)	33 (29.7)	10 (18.9)	0.13
Logistic Euro SCORE	8.9±8.3	9.7±8.7	7.1±7.2	0.04
atrial fibrillation/flutter	105 (64.0)	67 (60.4)	38 (71.7)	0.15
NT-pro BNP (pg/ml)	5173.3±6418	5927.6±6940	3348.3±4527	0.01
Troponin T	39.2±40.1	43.4±43.5	28.0±27.0	0.04
chronic obstructive pulmonary disease	20 (12.2)	14 (12.6)	6 (11.3)	0.81
Glomerular filtration rate <60mL/min	84 (51.2)	60 (54.1)	24 (45.3)	0.29
NYHA functional class	3.1±0.7	3.0±0.7	3.2±0.7	0.18
LVEF (%), at baseline	43.5±16.8	36.5± 14.8	58.1±10.0	<0.001
LVEDD at baseline	63.1 ±11.0	66.0±11.4	57.2±7.1	<0.001
LVESD at baseline	47.4±13.1	51.9±13.4	37.9±5.2	<0.001
LA Diameter at baseline	56.0±8.2	55.7±7.0	56.6±10.2	0.78
severe MR grade III/IV at baseline	162 (98.8)	109 (98.2)	53 (100)	0.21

Values are mean ± standard deviation, or number (%). DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; NYHA, New York Heart Association; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRT, cardiac resynchronization therapy; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrial; MR, mitral regurgitation; P-values by Student's t-test and Chi2 test.

3.3.1 Reverse remodeling in the FMR Cohort

48% of the patients with functional etiology showed reverse remodeling at 12-months follow-up. The baseline characteristics of the FMR population and differences between the LVRR group and no-LVRR group are detailed in Table 7 [110]. There were no significant differences in NYHA functional class, severity of MR, severity of TR, baseline LVEF, STS-Score, EuroSCORE or comorbidities between the LVRR and no-LVRR groups in the FMR population. Similar proportion of patients with FMR received CRT prior MitraClip implantation in the LVRR (17.0%) and no-LVRR (12.1%) subgroups, p=0.46.

Table 7 Baseline characteristics in FMR cohort treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**no-LVRR**	**LVRR**	**P-Value**
Number of patients	111	58	53	
Male, N (%)	80 (72.1)	45 (77.6)	35 (66.0)	0.17
Age in Years	75.5±9.6	73.8±11.5	77.3±6.6	0.13
NYHA class	3.1±0.7	3.0±0.7	3.1±0.7	0.52
Logistic Euro SCORE	9.7±8.7	10.2±10.1	9.2±7.0	0.86
STS Score of mortality	3.7±4.3	2.9±2.6	4.6±5.5	0.12
Diabetes mellitus	33 (29.7)	19 (32.8)	14 (26.4)	0.46
Diuretics	88 (79.3)	47 (81.0)	41 (77.4)	0.63
Hypertension	93 (83.8)	45 (77.6)	48 (90.6)	0.06
non ischemic cardiomyopathy	29 (26.1)	15 (25.9)	14 (26.4)	0.94
atrial fibrillation/flutter	67 (64.0)	38 (65.5)	29 (54.7)	0.24
NT-pro BNP (pg/ml)	5927.6±6940	5557.6±6531	6287.8±7386	0.97
Troponin T (nl/l)	43.4±43.5	43.0±44.5	43.8±42.9	0.92
chronic obstructive pulmonary disease	14 (12.6)	8 (13.8)	6 (11.3)	0.69
CRT	16 (14.4)	7 (12.1)	9 (17.0)	0.46
Glomerular filtration rate <60mL/min)	60 (54.1)	31 (53.5)	29 (54.7)	0.89
LBBB	42 (37.8)	20 (34.5)	22 (41.5)	0.44

Values are mean ± standard deviation, or number (%). NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRT, cardiac resynchronization therapy; LBBB, Left Bundle Branch Block; P-values by Student's t-test and Chi2 test. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

Twelve months after MitraClip implantation LVEF improved from 37.2±14.2% to 39.0±13.1% in the LVRR group (p=0.14) and remained stable (35.8±15.3% to 35.6±15.3%, p=0.76) in the no-LVRR group. In the first year after MitraClip implantation LVEDD decreased in the LVRR group from 68.2±11.2 mm to 54.8±9.6 mm (p<0.001), whereas it increased in the no-LVRR group from 63.9±11.4 mm to 65.1±11.0 mm. Left atrial dimensions decreased both in the LVRR group as well as in the no-LVRR group. Recurrent or residual high-grade MR at 12 months follow-up was more frequent in the no-LVRR subgroup (12.1%) compared to the LVRR subgroup (5.7%), however the difference was not statistically significant (p=0.23). By contrast, residual severe tricuspid regurgitation at follow-up was significant more frequent in the no-LVRR group compared to the LVRR group (34.5% vs. 17%, p=0.03), as shown in Table 8 [110].

Table 8 Echocardiographic parameters at baseline and during follow-up in the FMR cohort treated with MitraClip, University Clinic Ulm, 2010-2016

		Total	**no-LVRR**	**LVRR**	**P-Value**
Left ventricular ejection fraction (%)	baseline	36.5±14.8	35.8±15.3	37.2±14.2	0.69
	6 months	35.7±13.6	35.1±15.2	36.2±12.0	0.36
	12 months	37.3±14.3	35.6±15.3	39.0±13.1	0.11
LVEDD (mm)	baseline	66.0±11.4	63.9±11.4	68.2±11.2	0.06
	6 months	62.5±12.2	65.2±11.9	60.0±11.9	0.05
	12 months	60.2±11.6	65.1±11.0	54.8±9.6	<0.001
LVESD (mm)	baseline	51.9±13.4	50.5±13.3	53.5±13.5	0.21
	6 months	50.1±13.9	52.9±14.0	47.4±13.4	0.05
	12 months	47.7±13.4	52.7±13.3	42.3±11.3	<0.001
Severe mitral regurgitation (grade III/IV)	Baseline	109 (98.2)	57 (98.3)	52 (98.1)	0.94
	postprocedural	5 (4.5)	4(6.9)	1 (1.9)	0.20
	6 months	16 (14.4)	11 (19.1)	5 (9.4)	0.15
	12 months	10 (9.0)	7(12.1)	3 (5.7)	0.23
Severe tricuspid regurgitation	baseline	49 (44.1)	25 (43.1)	24(45.3)	0.81
	6 months	35 (31.5)	21 (36.2)	14 (26.4)	0.26
	12 months	29 (26.1)	20(34.5)	9 (17.0)	0.03
LA diameter (mm)	baseline	55.7±7.0	56.0±6.3	55.4±7.9	0.71
	6 months	54.2±7.8	54.6±7.0	53.8±8.6	0.44
	12 months	54.0±8.9	54.0±7.5	53.2±8.2	0.57

Values are mean ± standard deviation, or number (%). LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrial; P-values by Student's t-test and Chi2 test. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

3.3.2 Predictors of reverse ventricular remodeling in FMR

Multivariate logistic analysis was performed in order to identify predictors for reverse remodeling in the FMR population. Only severe residual TR was identified as independent predictor for the non-occurrence of LVRR (p=0.032, OR 0.361) after adjustment for gender, number of implanted clips, severely reduced LVEF (beyond 20%) and NYHA class at baseline, as shown in Table 9 [110].

Table 9 Multivariate regression analysis for predictors of reverse remodeling in FMR patients treated with MitraClip, University Clinic Ulm, 2010-2016

Variables	**Odds Ratio**	**95% CI**	**P-Value**
Male gender	0.497	0.203-1.218	0.3
Baseline LVEF < 20%	0.256	0.062-1.058	0.08
Recurrent severe MR at 12-month follow-up	0.297	0.067-1.313	0.08
Residual severe TR at 12-month follow-up	0.361	0.142-0.916	0.03

CI, confidence interval; FMR, functional mitral regurgitation; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR tricuspid regurgitation. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

3.3.3 Reverse remodeling in the DMR Cohort

Similar to FMR, the population with degenerative MR was separately analyzed with regard to reverse remodeling after MitraClip therapy. 53% of the patients with degenerative etiology developed reverse remodeling at 12-months follow-up. As shown in Table 10 [110], no significant differences in the baseline characteristics between the LVRR group and no-LVRR group in the DMR population could be noted.

Table 10 Baseline characteristics in DMR cohort treated with MitraClip, University Clinic Ulm, 2010-2016

	Total	**no-LVRR**	**LVRR**	**P-Value**
Number of patients	53	25	28	
Male, N (%)	31 (58.5)	17 (68.0)	14 (50.0)	0.18
Age in Years	79.8±5.0	79.6±4.4	79.9±5.6	0.84
Diabetes mellitus	10 (18.9)	6 (24.0)	4 (14.3)	036
Hypertension	45 (84.9)	22 (88.0)	23 (82.1)	0.55
NYHA class	3.2±0.7	3.3±0.6	3.0±0.8	0.25
Logistic Euro SCORE	7.1±7.1	6.4±3.4	7.7±9.4	0.56
STS Score of mortality	3.6±2.9	3.7±3.2	3.6±2.6	0.91
atrial fibrillation/flutter	38 (71.7)	20 (80.0)	18 (64.3)	0.20
NT-pro BNP (pg/ml)	3348.3±4527	3135.1±4364	3422.5±4676	0.96
Troponin T(ng/l)	28.0±27.1	19.9±5.7	30.5±30.4	0.73
chronic obstructive pulmonary disease	6 (11.3)	2 (8.0)	4 (14.3)	0.47
CRT	1 (1.9)	1 (4.1)	0 (0.0)	0.28
Glomerular filtration rate <60mL/min	24 (45.3)	12 (48.0)	12 (42.9)	0.70

Values are mean ± standard deviation, or number (%). DMR, degenerative mitral regurgitation; NYHA, New York Heart Association; STS, Society of Thoracic Surgeons; NT-proBNP, N-terminal pro-B-type natriuretic peptide; CRT, cardiac resynchronization therapy; P-values by Student's t-test and Chi2 test. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

In the first year after MitraClip implantation LVEDD decreased in the LVRR group from 59.1±7.2 mm to 49.5±6.6 mm ($p<0.001$), whereas it remained stable in the no-LVRR group (55.1±6.4 mm to 54.6±7.1 mm).

Even though severe mitral regurgitation was equally distributed at baseline between LVRR and no-LVRR groups and MitraClip was successful implanted in both groups, recurrent high grade MR after 12 months was significantly more frequent in the no-LVRR group compared to the LVRR group: severe MR was present in 40.1% in the no-LVRR group, compared to 10.7% in the LVRR group (p=0.01), as noted in Table 11 [110]. Different results have been observed with the tricuspid valve in the DMR population: at 12 months follow-up no significant difference could be demonstrated between LVRR group and no-LVRR group regarding severe residual TR (28% vs. 25%, p=0.8) [110].

Table 11 Echocardiographic parameters at baseline and during follow-up in the DMR cohort treated with MitraClip, University Clinic Ulm, 2010-2016

		Total	**no-LVRR**	**LVRR**	**P-Value**
Left ventricular ejection fraction (%)	Baseline	58.1±10.0	58.0±9.9	58.1±10.3	0.86
	6 months	58.7±10.1	58.2±11.1	59.2±9.3	0.61
	12 months	60.2±10.4	59.7±10.6	60.5±10.4	0.58
LVEDD (mm)	baseline	57.2±7.1	55.1±6.4	59.1±7.2	0.06
	6 months	53.0±6.6	53.0±6.9	52.9±6.5	0.79
	12 months	51.9±7.2	54.6±7.1	49.5±6.6	0.01
LVESD (mm)	baseline	37.9±5.2	36.4±4.2	39.4±5.5	0.05
	6 months	35.1±6.4	34.8±6.5	35.3±6.4	0.82
	12 months	33.5±5.9	35.2±6.5	32.0±4.9	0.09
Severe mitral regurgitation (grade III/IV)	baseline	53 (100.0)	25 (100)	28 (100)	0.94
	postprocedural	3 (5.7)	2 (8.0)	1 (3.6)	0.48
	6 months	12 (22.6)	9 (36.0)	3 (10.7)	0.02
	12 months	13 (24.5)	10 (40.1)	3 (10.7)	0.01
Severe tricuspid regurgitation	baseline	29 (54.7)	13 (52.0)	16 (57.1)	0.70
	6 months	16 (30.2)	10 (40.0)	6 (21.4)	0.14
	12 months	14 (24.6)	7(28.0)	7 (25.0)	0.80
LA diameter (mm)	baseline	56.6±10.2	57.6±12.6	55.8±7.6	0.77
	6 months	54.5±10.3	55.6±11.5	53.6±9.2	0.41
	12 months	54.9±10.8	55.7±11.6	54.2±10.2	0.70

Values are mean ± standard deviation, or number (%). DMR, degenerative mitral regurgitation; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LA, left atrial; P-values by Student's t-test and Chi2 test. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

3.3.4 Predictors of reverse ventricular remodeling in DMR

Multivariate logistic analysis for patients with DMR was performed to identify predictors for reverse ventricular remodeling. In contrast to FMR, where only residual high-grade TR was identified as an independent predictor for absence of reverse remodeling, in the subgroup of patients with degenerative etiology of MR, only recurrent severe MR at 12 months follow-up was identified as an independent predictor of the non-occurrence of LVRR (p=0.031, OR 0.201, CI 95% = 0.047 to 0.867), as noted in Table 12 [110].

Table 12 Multivariate regression analysis for predictors of reverse remodeling in DMR cohort treated with MitraClip, University Clinic Ulm, 2010-2016

Variables	**Odds Ratio**	**95% CI**	**P-Value**
Male gender	0.592	0.181-1.936	0.39
Recurrent severe MR at 12-month follow-up	0.201	0.047-0.867	0.031
Residual severe TR at 12-month follow-up	0.899	0.239-3.385	0.87

CI, confidence interval; DMR, degenerative mitral regurgitation; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspid regurgitation. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

3.4 Clinical outcome during 12- and 24-months follow-up

An important purpose of the present study was to evaluate the impact of reverse remodeling on clinical outcome after MitraClip therapy.

In the total cohort, baseline NYHA functional class was comparable between the LVRR group (3.0±0.8) and no-LVRR group (3.1±0.7), p=0.91.

At 12 months follow-up symptoms improved significantly in both groups: NYHA class decreased to 2.1±0.8 in the no-LVRR group (p<0.001) and to 2.0±0.8 in the LVRR group (p<0.001, Figure 1 [110]).

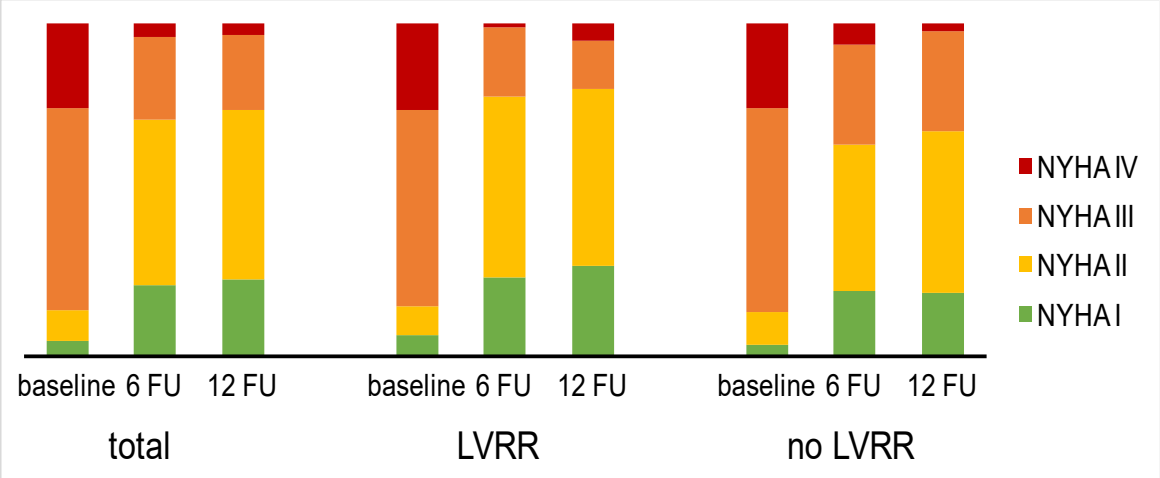

Figure 1. New York Heart Association (NYHA) class at baseline, 6 months and 12 months follow-up in total cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016, in patients with left ventricular reverse remodeling (LVRR) and without LVRR. During 12-month follow-up NYHA class decreased to a greater degree in the LVRR group compared to no- LVRR group (reduction to 2.1±0.8 in the no-LVRR group (p<0.001) and 2.0±0.8 in the LVRR group (p<0.001)). Figure from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

Patients in the LVRR group showed a trend towards lower rehospitalization rates in the first year and lower rehospitalization and mortality rates in the second year after MitraClip therapy. LVRR patients presented significantly reduced MACCE rates (35.8%) compared to the no-LVRR patients (50.6%) after 24 months follow-up (p=0.049, Table 13, Figure 2 [110]).

Table 13 Kaplan-Meier estimates of 1- and 2-years clinical outcome in the study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016 in patients with and without LVRR

	1-year follow-up		P-Value	2-year follow-up		P-Value
	No LVRR	**LVRR**		**No LVRR**	**LVRR**	
Mortality	0.0%	0.0%	--	11.2%	8.6%	0.47
MACCE	33.7%	22.2%	0.10	50.6%	35.8%	0.049
Reintervention	0.0%	0.0%	--	4.4%	1.4%	0.29
Rehospitalization due to heart failure	22.9%	17.3%	0.36	32.5%	23.5%	0.20

Values are numbers (%). LVRR, left ventricular reverse remodeling; MACCE, major adverse cardiac and cerebrovascular events. Table adapted from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

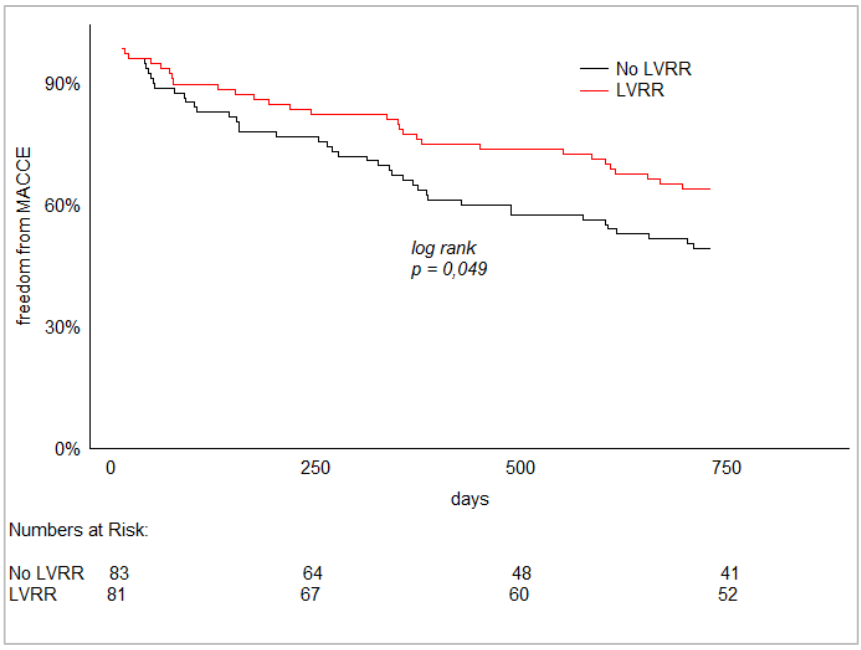

Figure 2. Kaplan–Meier analysis of rates of major adverse cardiac and cerebrovascular events (*MACCE*) two years after MitraClip implantation according to left ventricular reverse remodeling (LVRR) in the study cohort with mitral regurgitation treated with MitraClip, University Clinic Ulm, 2010-2016. Figure from Nita et al., Predictors of left ventricular reverse remodeling after percutaneous therapy for mitral regurgitation with the MitraClip system. Catheterization and Cardiovascular Interventions, 2020, 96: 687-697.

4. Discussion

During the past decade, percutaneous mitral valve repair has rapidly emerged as a versatile interventional alternative treatment of both degenerative and functional mitral regurgitation and revolutionized care of selected, high-risk and otherwise severely undertreated patients [110]. The MitraClip system is the most widely used catheter-based treatment for mitral regurgitation (MR), being safe and effective, and leading to significant improvement in heart failure symptoms, quality of life and even survival [40, 143].

Left ventricular reverse remodeling (LVRR) has been consistently associated with survival benefit after various treatments, including medical therapy, CRT and valvular interventions, playing therefore a fundamental role in the prognostic evaluation and improvement of support strategies. Reduction of MR grade by transcatheter techniques has been shown to induce left ventricular reverse remodeling, however predictors and clinical impact of cardiac reverse remodeling after MitraClip implantation have not been extensively explored [110]. The present study was designed to analyze these important topics separately for functional and degenerative mitral regurgitation.

This study showed significant improvement in clinical outcome up to 2 years follow-up in patients who experienced reverse ventricular remodeling after MitraClip therapy. We found that recurrent severe mitral regurgitation, poor baseline left ventricular ejection fraction (LVEF < 20%) and male gender predict absence of LVRR following MitraClip implantation. To our knowledge this is the first study to identify different predictors for reverse remodeling according to the etiology of mitral regurgitation. While recurrent MR remains the only independent predictor for no-LVRR in degenerative mitral regurgitation (DMR), in functional mitral regurgitation (FMR) only severe residual tricuspid regurgitation (TR) independently predicts absence of LVRR.

4.1 Clinical response to MitraClip Therapy

Acute reduction of regurgitant volume aligned with enhancement in cardiac output and decrease in left atrial pressure have been associated with prompt amelioration in symptoms following percutaneous edge-to-edge therapy [48, 66, 97, 136].

In accordance with large randomized studies (COAPT, EVEREST and ACCESS-EU) [42, 96, 143], this investigation confirmed the massive impact of MitraClip therapy upon clinical status in both patients with FMR and DMR. Improved left ventricular hemodynamics followed by cardiac reverse remodeling translated in significant alleviation of symptoms at follow-up in all patient subgroups, revealed by notable NYHA functional class improvement. Clinical amelioration six months after MitraClip therapy persisted during further follow-up at 12 months, supporting consistency of the study findings.

However, as shown by others, not the clinical improvement but development of left ventricular reverse remodeling predicts long-term survival in patients with dilated hearts after medical or device therapy. Among previous studies analyzing this topic, Cheuk-Man Yu et al. [163] showed in a series of 141 patients with heart failure and severe cardiac dilatation treated with CRT, that improvement in clinical status after CRT was not an independent determinant of long-term clinical outcome. By contrast, multivariable analysis identified LV reverse remodeling as the most important predictor of long-term survival [163].

4.2 Left ventricular reverse remodeling after MitraClip therapy in the total cohort

In the present study, the impact of MitraClip therapy on LVRR after a follow-up period of 12 months was evaluated. 49% of the study patients experienced left ventricular reverse remodeling, defined as reduction of left ventricular end-diastolic diameter (LVEDD) of more than 10% at 12 months after the procedure. Patients with FMR developed reverse ventricular remodeling to the same extent as patients with DMR.

First studies in the beginning era of device therapy, especially CRT, arbitrarily defined LV reverse remodeling as a reduction of more than 15% in LV end-systolic/diastolic volumes and dimensions 3 to 6 months postprocedural in heart failure patients [141, 164]. Yet it was unclear whether this arbitrarily defined cut-off value of 15% was clinically significant [163]. Further studies researched the impact of LV reverse remodeling on outcomes as well as the extent of reverse remodeling needed to improve symptoms in patients with heart failure. Yu et al. identified a lower cut-off value of 10% reduction in LVESV derived from the ROC (Receiver Operating Characteristic) curves of mortality with high specificity and sensitivity to predict long-term cardiovascular death [163].

Postprocedural reduction of volume overload along with reduced wall stress eventually translated in improved left ventricular overall hemodynamics. The documented macroscopic changes in this study, such as significant reductions in LVEDD and LVESD even in severely dilated hearts prove an impressive cardiac plasticity in response to volume unloading after MitraClip therapy. Reverse left ventricular remodeling was initially observed after 6 months and further improved after 12 months of follow-up. Similar to ACORN trial [1], where baseline LV end-diastolic diameter exceeded 6.0 cm, in the present study extensive reversal of ventricular dilatation was observed when the baseline end-diastolic diameters were larger. The authors of the ACORN trial demonstrated sustained reductions in LV end-systolic and end-diastolic dimensions up to 5 years after mitral annuloplasty.

Reports on left ventricular reverse remodeling after MitraClip therapy are heterogeneous [59, 63, 133, 134]. Initial studies on reverse remodeling after surgical repair of MR reported "a point of no return" in the course of the maladaptive changes, stressing the prompt surgical repair in asymptomatic patients with severe MR, when the LV end-systolic dimension exceeds 40 mm or when LV ejection fraction falls below 60% [14, 45]. Given that most patients receiving percutaneous repair presented impaired LV function and severely altered ventricular geometry before the procedure [96], reverse remodeling seemed unlikely to develop after MitraClip procedure. Surprisingly, increasing data demonstrated not only clinical benefit but also relevant unloading effects with improved ventricular geometry and reduced left ventricular and left atrial dimensions after the procedure [40, 45, 58, 59, 133, 159].

Reverse ventricular remodeling after correction of MR using a percutaneous approach was first reported by Foster et al. on 64 of 107 patients enrolled in the EVEREST I feasibility and safety trial and the roll-in phase of the EVEREST II pivotal trial [45]. Successfully treated patients showed significant decline in LV volumes and dimensions 12 months after the procedure [45]. The EVEREST trials substudies showed a 10% decrease in left ventricle end-diastolic volume (LVEDV) for 58% of patients with functional MR and, on average, 14% for 55% of patients with degenerative MR [45, 59]. Similar extent of reverse remodeling was observed following surgical mitral annuloplasty in ischemic mitral regurgitation [39]. However, these remodeling results could not be easily extrapolated to the "real-world" population with severely reduced LVEF and considerable left chamber dilatation [96]. Subsequent studies including high-risk patients reported however encouraging results on this topic [96].

The EVEREST II trial included a prospective registry of "real-world" high-surgical-risk patients treated by MitraClip, the ongoing EVEREST II REALISM Continued Access Study High-Risk arm, with more than 600 patients from 2009 to date. Glower et al. reported the 12-month echocardiographic outcomes of 351 patients included in these registries: the LV end-diastolic volume reduced from 161±56 ml to 143±53 ml ($p<0.001$) and LV end-systolic volume from 87±47 ml to 79±44 ml ($p<0.001$) [53]. Similar results were shown at 1-year follow-up in the Access-EU post-market registry [96]. Our findings are consistent with most previous remodeling studies after percutaneous mitral valve repair [53, 59, 103, 129, 134]. We do acknowledge that assessment of LVEDD by two-dimensional echocardiography in our study might not accurately reflect LV hemodynamics after the procedure. However, a reverse remodeling prevalence rate of 50% in a population with severely damaged ventricular geometry and impaired LVEF is encouraging for the MitraClip therapy, promising not only improved clinical status but also better prognosis [18].

4.3 Changes in left ventricular ejection fraction after MitraClip therapy

Interestingly, despite significant reduction in the end-diastolic and end-systolic dimensions and clinical benefit at follow-up, the present study showed only a modest improvement in the global EF for the entire cohort (44.5±16.3% to 46.5±16.0%, $p=0.14$). LVEF after surgical and percutaneous repair in mitral regurgitation has been a controversial topic, given the well-

known limits of global EF to measure the myocardial function in MR and the multitude of confounding factors that contribute to the LV performance after the procedure [18].

Prior studies have reported different results regarding LVEF outcome after repair of mitral regurgitation [4, 17, 53]. The afterload mismatch effect may be indicative for absence or delay in LVEF recovery after the procedure [18]. Postinterventional redirection of regurgitant volume produce an acute increase in end-systolic LV wall stress which may reveal - due to partial ventricular emptying into the low pressure left atrium - a previous not evident impaired myocardial contractility. Thus, surgical repair of MR may lead to an initial reduction of 10-15% in LVEF [29]. Drop effects of LVEF after MitraClip therapy have been shown in approximately 30% of the patients, yet to a lesser degree in comparison to surgery (absolute reduction of LVEF 3-8%) [41, 86, 89, 133]. This initial postprocedural reduction in ejection fraction might be confusing when assessing the process of reverse remodeling. Moreover it has been postulated that prompt recovery of ejection fraction after the procedure could influence the extent of reverse LV remodeling [89]. Though, as shown by others [45, 89], this initial unfavorable effect of increase in end-systolic wall stress is mostly outweighed by the end-diastolic volume unloading, supposing sufficient contractile reserve is provided. So, this hypothesis of afterload mismatch might explain the lack of LVEF improvement only in patients with very poor baseline LVEF, in whom however no or little reverse remodeling is expected.

The restraints of LVEF in the assessment of myocardial performance in patients with mitral regurgitation, especially in heterogeneous populations are acknowledged, however the present study showed modest, statistically not significant improvements in LVEF for both patients with DMR (58.1±10.0% to 60.2±10.4%, p=0.18) and FMR (36.5±14.8% to 37.3±14.3%, p=0.11) after MitraClip therapy. Since the majority of patients with DMR in this study had normal baseline LVEF, the post procedural LVEF improvement becomes relevant mostly for the FMR cohort with impaired baseline LVEF.

The Acorn trial [1] included patients with secondary MR, where the majority had non-ischemic cardiomyopathy and demonstrated notable and sustained improvements in LVEF at 12 months after mitral valve annuloplasty. Among other previous series including patients with secondary MR, Brown et al. [17] demonstrated, in contrast to ACORN results, in a cohort with secondary non-ischemic cardiomyopathy undergoing mitral valve annuloplasty

only a slight, statistically not relevant, improvement in LVEF (from 26±8% to 29±11% at 2-year follow-up).

With regard to percutaneous mitral valve repair, conflicting results in terms of LVEF improvement during follow-up have been reported [4, 53]. A sub-analysis of the Getting Reduction of Mitral Insufficiency by Percutaneous Clip Implantation (GRASP) registry reported significant improvement of the LVEF 12-months post-MitraClip in patients with secondary MR (from 40.72±11.62% to 46.23±9.03%) [4]. In contrast, The Real World Expanded Multicenter Study of the MitraClip System (REALISM) study including 379 patients with secondary MR showed stable LVEF at 12 months follow-up after MitraClip (44±11% at baseline vs. 44±11% at follow-up) [59]. These conflicting findings regarding postprocedural LVEF improvement might be explained through the disparities in population characteristics especially in terms of comorbidities and cardiovascular profile risk.

Our findings are consistent with previous studies which reported absence or modest increase of the global ejection fraction (EF) despite significant decrease in cardiac dimensions and improved ventricular hemodynamics [63, 134]. This suggests that mainly the reduction of end-systolic and end-diastolic wall stress along with decrease in left atrial pressure drive the clinical benefits after MitraClip therapy [110].

Takeda et al. showed in patients with secondary MR who underwent cardiac multi-detector row computed tomography prior to and 2 months after mitral annuloplasty, a 11% decrease in global LV end-systolic wall stress along with significant LV reverse remodeling (21% reduction of LV end-systolic volume and 13% reduction in LV end-diastolic volume) and increased forward ejection fraction. The authors reported only a slight improvement in LV end-systolic wall stress corrected for LV end-systolic volume (a load-independent parameter of myocardial contractility). This fact shows that enhancement in LV performance corroborates mostly with reduction in volume overload (ventricular preload) and systolic wall stress (afterload) rather than with intrinsic myocardial contractile recovery [146].

In conclusion, conventional LVEF measurement alone should not be considered a reliable reflector of cardiac performance in patients with MR undergoing percutaneous repair. Recent data promoted other echocardiographic tools, such as LV outflow tract stroke volume or global LV longitudinal strain for the assessment of LV myocardial function and hemodynamic procedural effects [80].

4.4 Predictors of reverse remodeling in the total cohort

The main purpose of this study was to identify predictors for absence of LVRR after percutaneous edge-to-edge mitral valve repair. 51% of the study cohort did not experience LVRR. Patients in the no-LVRR group were predominantly male, presenting with severely reduced left ventricular function and severe tricuspid and (recurrent) mitral regurgitation at 6 and 12-months follow-up after MitraClip implantation. Furthermore, NYHA functional class during 12-months follow-up was worse in the no-LVRR cohort compared to the LVRR group. In the total cohort, recurrent severe MR, male gender and severely reduced left ventricular function (LVEF < 20%) were identified as independent predictors for absence of LVRR within 12 months after the MitraClip procedure.

Recurrent mitral regurgitation was identified as an independent predictor for lack of reverse ventricular remodeling in the total cohort in the present study. Prior work emphasized that the extent of reverse remodeling directly depends on the degree of MR reduction after surgical or percutaneous mitral valve repair [59, 117]. Suri et al. [145] analyzed 924 patients who received surgical repair for DMR at the Mayo Clinic. 95% of the treated patients had MR reduced to none or mild associated with significant reduction of LV end-diastolic diameter from 60 mm to 51 mm at 1-year follow-up. Similar results have been reported by Shafii et al. in 2778 patients surgically treated at the Cleveland Clinic [135]. In this cohort, where MR was considerable reduced to less than mild, LV end-diastolic diameter significantly decreased from 57 mm to 49 mm. Both these studies demonstrated significant LV reverse remodeling when MR was considerable reduced to none or mild.

Grayburn and colleagues reported in a large study including patients treated percutaneous with MitraClip (801 pts.) or surgically (80), that reduction of LV volumes and dimensions at end-diastole and end-systole strongly correlates with residual or recurrent high-grade MR at 12 months follow-up ($p<0.0001$) [59]. Overall, greater remodeling was observed with greater MR reduction. Grayburn et al. documented an absolute decrease of 0.2 cm in LV diameter at end-diastole in the first year in the group with severe recurrent MR (with 5.6±0.7cm at baseline and 5.4±0.7cm at 12 month follow-up) compared to 0.4 cm in the MR≤1 group (5.5±0.7cm at baseline and 5.1±0.7cm at 12 months follow- up). The authors demonstrated that reduction of LV volume overload achieved by MR reduction by MitraClip is directly affiliated with LVRR. Moreover, even modest reduction of MR severity to moderate degree promoted cardiac reverse remodeling [59]. Our study data are consistent

with these findings: in the total population, patients with severe recurrent MR during the first year after MitraClip presented a 3.4-fold higher risk for absence of LVRR.

Multivariate analysis identified poor baseline LVEF as an independent predictor for lack of reverse ventricular remodeling in the total cohort. To date, few studies reported inconsistent effects of MitraClip on reverse remodeling in patients with severely reduced LVEF. Schrage and colleagues [134] found in 130 patients successfully treated with MitraClip, different hemodynamic responses according to the baseline LVEF. Only in patients with mid-ranged or preserved EF, reverse remodeling with reduced LV dilatation and increased contractility was found. In contrast, patients with reduced EF (<40%) showed no reverse remodeling and no improvement in LV performance [134]. Pleger et al. reported in a retrospective study including patients with a mean EF of 33% significant reduction in the LVEDD 12 months after the procedure [125]. In the randomized ACORN trial [1], which included patients with mean LVEF of 23.9±8.9%, relevant LVRR after surgical repair was reported. In the study of Grayburn et al. [59], the average LVEF in functional mitral regurgitation patients was 43±12%. Reverse remodeling was reported in patients treated either surgical or with MitraClip therapy. However, patients with LVEF < 20% and severely dilated ventricles (LVEDD > 6 cm) were excluded from the trial [59].

In the present study, LVRR was notably less frequent in patients with severely reduced LVEF (<20%). Multivariate regression analysis substantiated left ventricular EF < 20% as an independent predictor for absence of LVRR (p=0.04). It has been postulated that patients with severe pre-existing LV dysfunction don't provide enough contractile reserve to compensate for the initial effect of afterload mismatch seen after mitral valve repair. This would be most probably the reason for the absence of reverse remodeling or even adverse remodeling seen in some patients with poor LVEF [76]. In these groups, the genuine severity of the underlying ventricular dysfunction is unmasked early after the intervention being associated with high rehospitalization rates after the procedure [18]. Enriquez-Sarano et al. demonstrated that early post-operative LV dysfunction was associated with more than doubled risk of cardiovascular mortality in patients surgically treated for severe symptomatic MR [37]. Reduced survival has been observed also after non-valvular interventions, such as CRT, in patients with poor baseline who developed adverse remodeling postprocedural [139].

Finally, we identified female gender as an independent predictor for reverse ventricular remodeling in the total cohort after percutaneous edge-to-edge repair. To our knowledge this is the first study to report gender-related differences in reverse remodeling after MitraClip therapy. Greater propensity of women to reverse remodeling has been repeatedly observed in heart failure studies including epidemiological [64] and placebo-controlled clinical trials [2, 51, 138]. Irrespective of the underlying etiology of HF, female sex has been associated with survival benefit, mostly attributed to better remodeling response after medical or device therapy, especially in heart failure patients receiving CRT [93, 154]. Among other studies, the MADIT-CRT trial identified female gender as a strong and independent predictor of super-response (defined as an absolute LVEF increase of 18±3%) to CRT plus defibrillator [68]. Pharmacological studies also reported that women display a more prominent response to drug therapy [33, 75, 113, 138], as demonstrated for eplerenon [77]. It has been speculated that estrogens may interfere with drug metabolism, however there is no solid data supporting this statement.

Aimo and colleagues [3] showed in a large cohort of 927 patients with chronic systolic heart failure under HF treatment that female sex strongly predicted reverse remodeling (OR: 1.54; 95%, CI: 1.11 to 2.14; p=0.011) in all categories of patients: those with ischemic or non-ischemic cardiomyopathy, with moderate or severely impaired LVEF. The underlying pathophysiological processes responsible for a better remodeling response in female patients are still uncertain. Experimental and clinical studies have evaluated sex related myocardial changes following volume overload, pressure overload and myocardial infarction. Kararigas and colleagues studied pressure overload effects in aortic stenosis and reported significant more cardiac fibrosis and inflammation in male patients compared to female patients [78]. Accordingly, Petrov et al. reported that women experienced significant more reverse ventricular remodeling defined as regression of cardiac hypertrophy as well as decrease in LV diameters compared to male patients after aortic valve replacement [118]. Experimental studies demonstrated that female hearts tolerate volume overload better than male hearts [24, 32]. To date, gender related trends in reverse cardiac remodeling in mitral regurgitation have been scarcely analyzed in human studies. However, the present study reports greater propensity of women to reverse remodeling after MitraClip implantation [110].

Many hypotheses have been proposed to explain these gender related differences. A considerable interference with vascular and cardiac cells has been attributed to estrogens, as reviewed by Piro et al. [123]. Experimental series pointed out the fundamental role of estrogen receptors in the pathophysiology of cardiac remodeling in heart failure [95]. Cardiomyocytes and cardiac fibroblasts express estrogen receptors. Immunofluorescence studies demonstrated that activation and up-regulation of these receptors through genomic and non-genomic signaling pathways can reverse the process of adverse remodeling before the myocardium becomes irreversibly damaged, even in post-menopausal women [112, 123]. Moreover, Grohe et al. distinguished between ovarian synthesis of estrogens and intramyocardial synthesis, which remains stable after menopause, when most women present with HF [60].

The favorable effects of estrogens have been related to their inhibitory effects on mast cell-mediated extracellular matrix degradation [24]. Moreover, estrogens increase the active form of B-cell lymphoma 2 protein, known for inhibiting apoptosis [32]. While estrogens have been linked to cardiac recovery, androgens have been shown to induce myocardial inflammation, fibrosis, hypertrophy and even apoptosis [49, 92, 165].

Regardless of the underlying cause for these gender related differences, the documented predilection of women to develop reverse ventricular remodeling in our study should be considered in the process of risk stratification and follow-up strategies after MitraClip therapy [3, 110].

4.5 Left ventricular reverse remodeling in FMR compared to DMR

A main purpose of this study was to determine differences between primary MR (or DMR) and secondary MR (or FMR) in terms of magnitude and predictors of reverse ventricular remodeling after percutaneous mitral valve repair with the MitraClip system.

DMR and FMR present significant differences concerning pathophysiology, clinical characteristics, response to interventional or surgical therapies and clinical outcomes. With regard to baseline characteristics, the present study showed, as expected, higher cardiovascular risk profile in patients affected by FMR compared with those with DMR. Furthermore, the echocardiographic assessment showed, as expected, according to the underlying pathophysiology, significantly lower LVEF and higher LV dimensions in patients with FMR. The EVEREST II Trials reported on acute, mid and long-term outcome including data regarding reversal of cardiac dilation in patients with DMR and FMR treated with MitraClip, however the trial wasn't powered to evaluate etiology related differences, given that the majority of patients presented degenerative etiology [40].

Regarding reverse remodeling after MitraClip implantation, even more scarce data reporting on etiology related differences is available. The present study was intended to evaluate such differences concerning the extent and predictors of reverse ventricular remodeling in DMR and FMR after the procedure. Degenerative MR is caused by MV apparatus intrinsic lesions. It is logical to assume that recovery of mitral competence with mitral valve repair leading to relief of volume overload stress should consecutively translate into reverse ventricular remodeling in DMR patients. By contrast, MR reduction in secondary (functional) MR might result in only moderate reverse cardiac remodeling due to the underlying ventricular pathology which predated and promoted the MR [110, 147]. The results of the Asia-Pacific trial [147] were consistent with this assumption: patients with DMR experienced significantly greater decrease in left ventricular end-diastolic diameter ($p=0.002$) and end-systolic diameter ($p=0.017$) after MitraClip therapy compared to patients with FMR. In our study, patients with FMR developed similar magnitude of reverse ventricular remodeling compared to patients with DMR (47.8% vs. 52.8%, $p=0.54$). Grayburn et al. reported similar results in a cohort of 881 patients treated either with MitraClip or surgically [59].

4.6 Predictors of LVRR in patients with DMR

In the present study recurrent MR up to 12 months follow-up was more frequent in the DMR group compared to the FMR group (24.5% vs. 9.0%, p=0.007), despite similar postprocedural results in both subgroups (residual severe MR 4.5% for FMR vs. 5.7% in DMR, p=0.75). These results are interesting, since one would expect that a severely altered ventricular geometry in patients with FMR would mainly drive MR recurrence after the procedure [110]. Previous surgical series reported high rates of recurrent severe MR (grade 3 and 4) postoperative in 14%–66% patients with FMR at follow-up, mostly attributed to progressive LV dysfunction [56, 69, 102, 147]. Thus, we underline the low rates of recurrent MR found in the FMR cohort after MitraClip therapy in our study (9% at 12 months follow-up). These results suggest that low rates of recurrent MR achieved by percutaneous valve repair in FMR could break the MR-LV dilation vicious circle, thus explaining similar extents of reverse remodeling comparing to DMR patients [59].

By contrast, surgical series demonstrated that postoperative results sustained during long-term follow-up in patients with DMR, with low rates of recurrent severe MR [44]. Though, our DMR cohort experienced recurrent severe MR significantly more frequent compared to FMR cohort. Although rates of recurrent MR (III/IV) in this study in both cohorts were comparable to those published in literature [69, 94], the detected higher MR recurrence rate in the DMR group is eminent. These results could be partially explained through the extensive degenerative changes with severely calcified MV lesions in our elderly cohort with DMR. In accordance, Chiarito et al. reported in a metanalysis of randomized and observational studies of 2615 patients undergoing MitraClip implantation, similar rates of recurrent MR at 12-months follow-up in DMR and FMR cohorts (p=0.40) [25]. Interestingly, the authors showed that patients with degenerative MR needed mitral valve re-intervention significantly more frequent compared with patients having functional MR (10% vs. 4%, p=0.04). However, in the present study, multivariate analysis revealed that recurrent mitral regurgitation was the only predictor for lack of reverse remodeling in the DMR subgroup.

4.7 Predictors of LVRR in patients with FMR

For the FMR cohort, multivariate analysis identified only severe residual tricuspid regurgitation as a predictor for absence of LVRR. Baseline severe tricuspid regurgitation has been shown to be a major determinant for all-cause mortality in patients undergoing MitraClip implantation [114]. In our study, severe TR decreased from 47.6% to 26.2% at 12 months follow-up (p=0.00001) in the entire cohort, similar to other trials [46, 114].

To date, the relationship between recurrent/residual TR and left ventricular reverse remodeling after percutaneous mitral valve repair with the MitraClip system has not been investigated. In the present study, residual TR at 12 months was more frequent in the no-LVRR group compared to LVRR group in the total cohort. This distribution was even more obvious in the FMR cohort with 34.5% residual TR in the no-LVRR group vs. 17.0% in the LVRR group (p=0.03).

Surgical series have reported that successful left-sided surgery performed for patients affected by degenerative [101] or rheumatic mitral valve disease [74] lessens the severity of functional TR. In contrast, surgical studies on patients with FMR [13, 99] demonstrated that severe TR may aggravate during mid-term follow-up regardless of successful mitral valve repair. Accordingly, in the present study severe residual TR was more frequent in the FMR group compared to the DMR group and had a major impact on reverse ventricular remodeling. Patients with reduced LVEF tend to develop biventricular failure, hence TR in these patients is not only a consequence of chronic MR but rather an effect of the underlying cardiac dilatation [13]. Previous work showed that patients undergoing surgical repair for FMR don’t experience significant relief of HF symptoms and present higher mortality rates in case of co-existent untreated moderate to severe TR [114, 117].

To our knowledge this is the first study reporting residual TR at 12 months follow-up as an independent predictor for absence of left ventricular reverse remodeling in patients with FMR. Given that almost 50% of patients undergoing surgical MV repair with untreated TR develop progressive tricuspid valve dysfunction aligned with poor prognosis [100], the European guidelines indicate tricuspid valve repair during left-heart surgery in the presence of severe TR (class I; level of evidence C) [152]. Simultaneous percutaneous repair of severe MR and TR is not currently established in the clinical practice. Further studies are warranted in this field [114].

However, the present study suggests that a more combative approach towards residual TR should be promoted. Residual or recurrent TR should be prompt diagnosed and treated in FMR patients in order to maintain the benefits achieved with isolated MitraClip implantation [110].

In conclusion, correction of primary degenerative MR as genuine intrinsic pathology has a direct impact on LVRR. In contrast, repair of secondary MR might bring a considerable relief of volume and pressure overload and yet reverse ventricular remodeling depends on other factors and correlate best with severe residual TR.

4.8 Impact of reverse ventricular remodeling on clinical outcome

To date, there is limited data regarding the prevalence of LVRR and its clinical impact in symptomatic patients with MR percutaneously treated with the MitraClip system [25, 27, 94]. The present study offers a large cohort investigating the clinical implication of LVRR after MitraClip implantation. Patients who experienced reverse remodeling in our study showed lower rehospitalization rates in the first year and a lower rehospitalization and mortality rates in the second year. Overall, these outcomes translated in a significantly reduced MACCE rates in the LVRR group compared to the no-LVRR group after 2 years of follow-up (p=0.049) [110].

4.9 Study Limitations

From the initial total cohort of 374 patients treated with the MitraClip system between January 2010 and December 2016, a significant proportion (56%) has been excluded from further analysis, mostly due to insufficient echocardiographic data during follow-up at 6 and 12 months. This however reflects the nature of our institution as a referral center. Both included and excluded patient groups shared similar baseline characteristics and periprocedural results, however a selection bias cannot be excluded.

Almost 50% of the study patients developed left ventricular reverse remodeling following edge-to-edge MV repair, a prevalence rate consistent with most previous studies on this topic [53, 59, 103, 129, 134], irrespective of the parameter applied to define LVRR. We do admit that the echocardiographic parameter selected to define LVRR might influence the

prevalence rate of LV reverse remodeling. Our LVRR definition implying ≥10% decrease of LVEDD has been used in other studies [8, 52, 79, 103] and is a practical and well-established approach in the daily clinical setting. However, we do acknowledge that assessment of LVRR by two-dimensional echocardiography might not accurately reflect LV hemodynamics after the procedure [110].

In summary, knowledge about LVRR predictors and their related prognostic role is pivotal for risk stratification and guidance of therapy in patients with severe MR treated with MitraClip therapy. The present study gives further insights regarding the predictors of LVRR after the percutaneous edge-to-edge procedure and underlines the major impact of reverse ventricular remodeling on clinical outcome. LVRR occurs in nearly half of the patients treated by MitraClip for mitral regurgitation and is associated with lower rehospitalization and mortality rates 2 years after the procedure. Recurrent severe mitral regurgitation after 12 months, poor baseline LVEF < 20% and male gender are independent predictors for absence of LVRR after MitraClip therapy in the total cohort. Different predictors for reverse ventricular remodeling have been determined according to MR etiology. In patients with DMR, recurrent severe mitral regurgitation was the only independent predictor for the absence of LVRR, whereas in patients with FMR only severe residual tricuspid regurgitation after 12 months inversely predicts LVRR after MitraClip therapy.

5. Summary

Percutaneous edge-to-edge repair with MitraClip (MC) system has revolutionized care of high-risk, otherwise severely undertreated patients with both degenerative and functional mitral regurgitation (MR). Left ventricular reverse remodeling (LVRR) has been consistently linked to survival benefit after various treatments including medical, device therapy or surgical valve repair. Transcatheter techniques have been shown to induce left ventricular reverse remodeling in patients with severe MR, yet specific data on predictors of LVRR and their prognostic impact after MitraClip therapy are limited. Since degenerative mitral regurgitation (DMR) and functional mitral regurgitation (FMR) constitute two different disease entities, the present study was specifically designed to explore differences between DMR and FMR regarding reverse remodeling.

This retrospective study analyzed 164 patients successfully treated by MC implantation from January 2010 to December 2016 undergoing clinical and echocardiographic evaluation at baseline, 6 months and 12 months follow-up. LVRR was defined as decrease of ≥10% of the left ventricular end-diastolic diameter at 12 months follow-up. Patients were dichotomized according to the absence (no-LVRR group, n=83) and presence of LVRR (LVRR group, n=81) and were analyzed regarding their baseline characteristics as well as their clinical and echocardiographic outcome to identify predictors of LVRR and determine its impact on clinical outcome.

Echocardiography revealed significant LVRR in 49% of the patients. Patients with FMR developed reverse ventricular remodeling to the same extent as patients with DMR (47.7% vs 52.8%). In the overall population MC implantation resulted in significant symptomatic improvement of New York Heart Association (NYHA) functional class and MR reduction (3.0±0.2 to 1.5±0.6, $p<0.001$). Despite clinical amelioration and significant reduction in the end-diastolic and end-systolic dimensions at follow-up, only a modest improvement in the global left ventricular ejection fraction (LVEF) was observed: 44.5±16.3% to 46.5±16.0%, p=0.14. Recurrent MR was evident in 14.0% of the total cohort 12 months after the MC procedure (20.5% in no-LVRR vs. 7.4% in LVRR group, p=0.01). Recurrent MR up to 12 months follow-up was more frequent in the DMR group compared to the FMR group (24.5% vs 9.0%, p=0.007), despite comparable postprocedural results in both etiologies (residual severe MR 4.5% for FMR vs. 5.7% in DMR, p=0.75). In the total cohort, multivariate logistic regression analysis identified severe recurrent MR after 12 months (p=0.01, odds ratio 0.26,

confidence interval= 0.094 - 0.72), male gender (p=0.05, odds ratio 0.49, confidence interval= 0.24 - 1.0) and LVEF <20% (p=0.046, odds ratio 0.24, confidence interval= 0.061 - 0.97) as independent predictors of absence of LVRR. In the subgroup analysis according to the etiology, multivariate logistic regression analysis identified severe recurrent MR after 12 months (p=0.03, odds ratio 0.2, confidence interval= 0.047 - 0.867) as independent predictor for the non-occurrence of LVRR only in the DMR subgroup. In FMR, only residual severe tricuspid regurgitation (TR) inversely predicts LVRR (p=0.03, odds ratio 0.361, confidence interval= 0.142 - 0.916).
Patients who experienced reverse ventricular remodeling showed lower rehospitalization rates in the first year and lower rehospitalization and mortality rates in the second year, leading to significantly reduced MACCE rates in the LVRR group compared to the no-LVRR group at 2 years follow-up (p=0.049).

In conclusion, reverse ventricular remodeling occurred in nearly half of the patients treated by MitraClip and was associated with significant improvement in clinical outcome up to 2 years of follow-up. Recurrent severe MR after 12 months, poor baseline LVEF and male gender are independent predictors for absence of LVRR after MitraClip therapy in the total cohort. In patients with DMR, recurrent severe mitral regurgitation was the only independent predictor for the absence of LVRR, whereas in patients with FMR only severe residual TR after 12 months inversely predicts LVRR after MitraClip therapy. A better understanding of reverse remodeling predictors is essential for the process of risk stratification and decision making about potential need for care escalation in patients receiving percutaneous mitral valve repair. Poor ejection fraction has been proven to be an independent predictor for non-occurrence of LVRR, underlining the importance of prompt interventional treatment before myocardial dysfunction becomes irreversible. Nevertheless, the present study suggests that a more combative approach towards residual tricuspid regurgitation should be promoted in FMR patients in order to maintain the benefits achieved with isolated MitraClip implantation and to improve outcome in this high-risk population.

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Acknowledgements

Die Danksagung wurde aus Gründen des Datenschutzes entfernt.

Curriculum Vitae

Der Lebenslauf wurde aus Gründen des Datenschutzes entfernt.

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