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

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Abstract

Objectives: To investigate the predictors and clinical impact of left ventricular reverse remodeling (LVRR) after MitraClip (MC) therapy for degenerative (DMR) and functional mitral regurgitation (FMR).

Background: MC therapy induces LVRR in patients with mitral regurgitation (MR) at high-risk for surgery. However, specific data on predictors of LVRR therapy are limited.

Methods: This study included 164 patients treated by MC implantation with complete clinical and echocardiographic evaluation at baseline, 6 months, and 12 months. LVRR was defined as a decrease of ≥10% of the left ventricular end-diastolic diameter after 12 months and was found in 49% of the patients.

Results: LVRR was associated with significantly reduced event rate 2 years after MC procedure. In the total cohort, multivariate regression analysis determined severe recurrent/residual MR after 12 months (p = .010, odds ratio [OR] = 0.26), male gender (p = .050, OR = 0.49) and left ventricular ejection fraction (LVEF) <20% (p = .046, OR = 0.24) as predictors of absence of LVRR. In the subgroup analysis according to etiology of MR, multivariate regression analysis revealed severe recurrent/residual MR after 12 months (p = .04, OR = 0.184) to inversely predict LVRR only in the DMR subgroup. In FMR, residual severe tricuspid regurgitation (TR) inversely predicts LVRR (p = .032, OR = 0.361).

Conclusions: LVRR occurs in half of the patients after MC and is associated with reduced MACCE rates at follow-up. Combined information on residual/recurrent MR, baseline LVEF and gender predict LVRR after MC procedure. While residual/recurrent MR is the independent predictor for the absence of LVRR in DMR, in FMR only severe residual TR independently predict LVRR.

Mirjam Keßler and Sinisa Markovic contributed equally to this study.

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INTRODUCTION

Over the past years, MitraClip (MC) therapy has emerged as a treatment option for both degenerative (DMR) and functional mitral regurgitation (FMR) in high-risk patients. Reduction of mitral regurgitation (MR) grade by MC has been shown to induce left ventricular reverse remodeling (LVRR),\(^1\)–\(^6\) known to be associated with survival benefit after various medical therapies including cardiac resynchronization therapy (CRT) and surgical valve repair.\(^7\)–\(^10\) FMR and DMR present distinct pathophysiology, thus it is unclear whether a similar magnitude of reverse remodeling and hemodynamic response can be expected after successful MC therapy. Furthermore, data on predictors and prognostic role of LVRR after MC therapies are limited.\(^1\)\(^,\)\(^11\)\(^,\)\(^12\)

This study investigates the extent and the predictors of LVRR after MC therapy having the ability to separately assess the entities of FMR and DMR, and the impact of reverse ventricular remodeling after MC therapy on clinical outcome.

METHODS

For this study, we analyzed 374 consecutive patients receiving MC implantation between January 2010 and December 2016 at our center. One hundred sixty-four patients (44%) completed a full clinical and echocardiographic follow-up at 6 months as well as 12 months and hence were included in further analysis. Of note, no relevant differences in baseline characteristics existed between the included and excluded patients (supplemental Table I). The study was ethically approved by the ethics committee of the University of Ulm and complied with the Declaration of Helsinki (NCT03104660).

All patients included in the present study were symptomatic in terms of heart failure (New York Heart Association [NYHA] functional class >II) despite guideline-directed medical therapy and CRT.

All patients underwent diagnostic work-up prior to the MC as previously described.\(^13\) Device success was defined as clip implantation with a reduction of the MR of more than two degrees.\(^14\) During long-term follow-up, the occurrence of mortality, heart failure rehospitalization, reintervention, and major adverse cardiac and cerebrovascular events (MACCE, composite endpoint of rehospitalization due to heart failure, neurological events or bleeding, further reintervention on the mitral valve, need for left ventricular assist device [LVAD], and mortality) were analyzed. Severity of MR was classified in four degrees according to the EVEREST criteria for MR quantification.\(^4\)

All included patients had severe MR (i.e., grade III/IV) except for two patients with dynamic high-grade MR. Echocardiographic characteristics at baseline and follow-up (including grade of tricuspid regurgitation [TR], grade of MR, and cardiac dimensions) were available for all study patients. The left ventricle (LV) end-diastolic and end-systolic diameters were measured by transthoracic echocardiography in the long axis parasternal view. Left ventricular ejection fraction (LVEF) was measured using the biplane Simpson's method. The change in left ventricular end-diastolic diameter (LVEDD) was calculated as follows: (LVEDD baseline – LVEDD 12 months)/LVEDD baseline × 100. LVRR has been defined in accordance to previous studies, which identified a cut-off value of 10% reduction in left ventricular end-diastolic volume (LVEDV) or in LVEDD for prediction of long-term all-cause and cardiovascular

FIGURE 1 Flow diagram of patient selection and follow-up
TABLE 1  Baseline characteristics of the entire study cohort

| No LVRR | LVRR | p-value |
|---------|------|---------|
| Number of patients | 83 | 81 | .68 |
| Male, N (%) | 62 (74.7) | 49 (60.5) | .051 |
| Age in years | 75.6 ± 10.2 | 78.2 ± 6.4 | .16 |
| EuroSCORE II | 9.0 ± 8.8 | 8.7 ± 7.9 | .85 |
| STS Score of mortality | 3.3 ± 2.8 | 4.2 ± 4.7 | .22 |
| Prior HF admission | 1.19 ± 1.1 | 0.94 ± 1.1 | .12 |
| Diabetes mellitus | 25 (30.1) | 18 (22.2) | .25 |
| Chronic obstructive pulmonary disease | 10 (12.0) | 10 (12.4) | .95 |
| Chronic renal failure (glomerular filtration rate < 60 ml/min) | 43 (51.8) | 41 (50.6) | .88 |
| Atrial fibrillation/flutter | 58 (69.9) | 47 (58.0) | .11 |
| Nonischemic cardiomyopathy | 15 (18.1) | 14 (17.3) | .89 |
| NYHA functional class | | | |
| I | 3 (3.6) | 5 (6.17) | .44 |
| II | 8 (9.6) | 7 (8.6) | .82 |
| III | 51 (61.5) | 48 (59.3) | .77 |
| IV | 21 (25.3) | 21 (25.9) | .93 |
| NT-pro BNP (pg/ml) | 5126.9 ± 6230 | 5207.4 ± 6605 | .56 |
| Troponin T(ng/l) | 39.7 ± 42 | 38.7 ± 38 | .81 |
| CRT-D | 8 (9.6) | 9 (11.1) | .76 |
| LBBB | 26 (31.3) | 25 (30.9) | .95 |

Note: Values are mean ± SD, or number (%).
Abbreviations: CRT, cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; LVRR, left ventricular reverse remodeling; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; p-values by Student’s t-test and chi-square test; STS, Society of Thoracic Surgeons.

3  | STATISTICAL ANALYSES

Analyses were performed in following subgroups: patients with left ventricular reverse remodeling (LVRR group, n = 81) versus without left ventricular reverse remodeling (no-LVRR group, n = 83). All statistical analyses were calculated with the Statistica software version 7.1 (Stat Soft, Inc., Tulsa, OK) and SPSS, version 20.0 (SPSS Inc., Chicago, IL). Categorical variables are expressed as counts and percentages and are compared by chi-square test. Continuous parameters are presented as the mean ± SD and are compared with t-test or Mann-Whitney test for unpaired comparisons. Differences were considered statistically significant when p < .05.

To identify predictors of LVRR, univariate analysis was performed for the cohort of 164 patients for all potential influential (significant p < .05, and probable p < .10) clinical and echocardiographic variables. In multivariate logistic regression analysis, a backward stepwise algorithm was applied to all potential influential parameters (p < .10) from univariate logistic regression analysis. Furthermore, we tested multicollinearity for all influential parameters using the variance inflation factor. Greatest variance inflation factors were calculated for the LVEDD at baseline and at follow-up (7.6 and 6.6, respectively). Hence, LV diameter was not included in multivariate regression analysis due to clinical relation and collinearity with the primary point of interest. Variables that were included in the multivariate model were gender, severe MR at 12 months, severe TR at 12 months, severely reduced LVEF (below 20%), and NYHA class at baseline.

In addition, an analogous approach was followed for the two different MR etiologies: FMR (n = 111) and DMR (n = 53). Influential variables of univariate analysis that were included in the multivariate model were number for implanted clips, severely reduced LVEF (below 20%), NYHA class at baseline, severe TR at 12 months and severe (residual/recurrent) MR after 12 months. Time-to-event analyses for 12 and 24 months’ follow-up were performed with the use of Kaplan–Meier estimates and were compared with the log-rank test. Kaplan–Meier survival curves were generated for time-to-event outcomes.

4  | RESULTS

Of the 374 patients undergoing percutaneous mitral valve repair with the MC system, 50 died within 12 months of the procedure, other 160 patients have been excluded from the analysis due to missing LVEDD measurements for LVRR calculation or other major events (heart transplantation, LVAD implantation), as shown in Figure 1.

The prespecified remodeling endpoint in this study was defined as a decrease of ≥10% of LVEDD after 12-months follow-up after MC. LVRR was observed in 81 patients (49.4%).

The baseline characteristics of the study patients and the differences between the LVRR group and no-LVRR group are detailed in Table 1. The two cohorts were comparable in terms of baseline LVEF, NYHA functional class, severity of MR, EuroSCORE II, or relevant comorbidities. Etiology of MR was equally distributed in the LVRR and no-LVRR groups (p = .54): functional MR was evident in 69.9% of patients in the no-LVRR group, compared with 65.4% in the LVRR group. Likewise, in the no-LVRR group, DMR was present in 30.1% and in 34.6% in the LVRR group. Baseline LVRR between the two groups was not different (42.5 ± 17.2% in the no-LVRR group compared with 44.5 ± 16.3% in the LVRR group, p = .49). However, the proportion of patients with LVEF <20% was more frequent in the no-LVRR group at baseline (44.5 ± 16.3% in the LVRR group, p = .07).

Analogously, Table 2 displays baseline demographic and clinical characteristics separately for DMR and FMR subgroups. Patients with FMR present higher surgical risk compared with patients with DMR. Similar to the total cohort, no significant differences in terms of comorbidities could be observed between LVRR group and no-LVRR group within the FMR population or DMR cohort. Regarding procedural data, no differences were noted between the LVRR group and no-LVRR group in the number of clips implanted or MR reduction in both DMR population and FMR population (Table 3).
### TABLE 2  Baseline characteristics of DMR and FMR

|                          | Degenerative MR | Functional MR | p-value |
|--------------------------|-----------------|---------------|---------|
|                          | No-LVRR         | LVRR          |         |
| Number of patients       | 25 (30.1)       | 28 (34.6)     | .18     |
| Male, N (%)              | 17 (68.0)       | 14 (50.0)     | .18     |
| Age in years             | 79.6 ± 4.4      | 79.9 ± 5.6    | .84     |
| EuroSCORE II             | 6.4 ± 3.4       | 7.7 ± 9.4     | .56     |
| STS score of mortality   | 3.7 ± 3.2       | 3.6 ± 2.6     | .91     |
| Prior HF admission       | 1.2 ± 1.0       | 0.7 ± 0.8     | .05     |
| Diabetes mellitus        | 6 (24.0)        | 4 (14.3)      | .36     |
| Chronic obstructive pulmonary disease | 2 (8.0) | 4 (14.3) | .47 |
| Chronic renal failure (glomerular filtration rate < 60 ml/min) | 12 (48.0) | 12 (42.9) | .70 |
| Atrial fibrillation/flutter | 20 (80.0) | 18 (64.3) | .20 |
| Nonischemic cardiomyopathy | 0 (0.0) | 0 (0.0) | 1.00 |
| NYHA functional class    |                 |               |        |
| I                        | 0 (0.0)         | 2 (7.1)       | .11     |
| II                       | 1 (4.00)        | 3 (10.7)      | .34     |
| III                      | 15 (60.0)       | 15 (53.6)     | .64     |
| IV                       | 9 (36.0)        | 8 (28.6)      | .56     |
| NT-pro BNP (pg/ml)       | 3135.1 ± 4364   | 3422.5 ± 4676 | .96     |
| Troponin T(ng/l)         | 19.9 ± 5.7      | 30.5 ± 30.4   | .73     |
| CRT-D                    | 1 (4.1)         | 0 (0.0)       | .28     |
| LBBB                     | 6 (24.0)        | 3 (10.7)      | .19     |

Note: Values are mean ± SD, or number (%).
Abbreviations: CRT, cardiac resynchronization therapy; HF, heart failure; LBBB, left bundle branch block; LVRR- left ventricular reverse remodeling; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; p-values by Student’s t test and chi-square test. STS, Society of Thoracic Surgeons.

### TABLE 3  Procedural data

|                          | Degenerative MR | Functional MR | p-value |
|--------------------------|-----------------|---------------|---------|
|                          | No LVRR         | LVRR          |         |
| Number of patients       | 25 28           | 58 53         | .87     |
| Emergent procedure, N (%)| 3 (12.0)        | 15 (25.9)     | .36     |
| Time in hospital before clip (days) | 3.1 ± 3.9 | 4.1 ± 3.7 | .18 |
| Time in hospital after procedure (days) | 7.5 ± 3.4 | 6.3 ± 2.5 | .21 |
| Fluoroscopy time (min)   | 34.4 ± 16.4     | 34.3 ± 18.0   | .67     |
| Length of ICU stay post-MC (days) | 0.8 ± 1.2 | 0.4 ± 0.9 | .44 |
| Number of clips implanted | 1.3 ± 0.45      | 1.3 ± 0.5     | .79     |
| activated clotting time peak | 268.2 ± 54.1 | 277.5 ± 41.8 | .48 |
| Grade of MR after procedure | 1.5 ± 0.8      | 1.4 ± 0.6     | .76     |
| Partial clip detachment  | 0 0             | 1.0           | 1.7     |
| Transmitral mean gradient after procedure | 4.3 ± 1.7 | 4.5 ± 1.6 | .82 |
| Severe MR after procedure | 0 0             | 1.0           | 0 0     | 1.0 |

Note: Values are mean ± SD, or number (%). p-values by Student’s t-test and chi-square test.
Abbreviations: ICU, intermediate care unit; LVRR- left ventricular reverse remodeling; MC, MitraClip; MR, mitral regurgitation.
In the first year after MC implantation, LVEF improved from 44.5 ± 16.3% to 46.5 ± 16.0% in the LVRR group (p = .14), compared with 42.5 ± 17.2% to 42.9 ± 17.8% in the no-LVRR group (p = .76, Figure 2). In contrast to left ventricular dimensions, left atrial dimensions decreased both in the LVRR group (p = .03) and in the no-LVRR group (p = .01, Figure 2).

High-grade MR (grade III/IV) was equally distributed in both groups at baseline (98.8% in both groups, p = .99) and was reduced after the MC implantation in both groups to a comparable magnitude (severe MR III/IV 7.2% in the no-LVRR group vs. 2.5% in the LVRR group, p = .15). Hence, in the year after MC severe MR was significantly more frequent in the no-LVRR group, compared with the LVRR group: High-grade MR was present in 7.4% in the LVRR group, compared with 20.5% in the no-LVRR group (p = .01, Figure 3). Similar observations were made with the tricuspid valve, where high-grade TR was present in comparable proportions in both groups at baseline (49.4% in the LVRR group, 45.8% in the no-LVRR group, p = .64). During follow-up grade of TR decreased significantly both in the LVRR group (p < .001) and in the no-LVRR group (p = .009), but reduction was more frequent in the LVRR group (19.8 vs. 32.5%, p = .06, Figure 3).

Forty-eight percent of the patients with FMR and 53% of the patients with degenerative etiology developed reverse remodeling at 12-months follow-up. Table 4 summarizes all echocardiographic data at baseline during follow-up separately for DMR and FMR patients.

During 12-months follow-up NYHA class decreased significantly to 2.1 ± 0.8 in the no-LVRR group (p < .001) and 2.0 ± 0.8 in the LVRR group (p < .001 Figure 4). Analogously, in the subgroup analysis according to etiology, NYHA class improved in patients with reverse remodeling to 1.8 ± 0.8 in the FMR group and to 2.2 ± 0.6 in the DMR group (Figure 4). Patients in the LVRR group had numerically lower rehospitalization rates in the first year and lower rehospitalization and mortality rates in the second year, resulting in a significantly reduced MACCE rate in the LVRR group compared to the no-LVRR group in the 24-months follow-up (p = .049, Table 5, Figure 5).
Data of multivariate logistic regression analysis is noted in Table 6. Among the variables assessed, in the total population of 164 patients, multivariate analysis identified male gender (OR = 0.499), severe MR after 12 months (OR = 0.262), and poor baseline left ventricular function (baseline LVEF <20%, OR = 0.244) as independent predictors for the nonoccurrence of LVRR after adjustment for severe TR at 12-months follow-up. In the subgroup of patients with DMR, only severe MR at 12-months follow-up was identified as a predictor of the nonoccurrence of LVRR (p = .025, OR = 0.184, CI 95%: 0.042–0.812). By contrast, in patients with FMR, only severe residual TR was identified as independent predictor for nonoccurrence of LVRR (p = .032, OR = 0.361) after adjustment for gender, number of implanted clips, severely reduced LVEF (beyond 20%) and NYHA class at baseline.

5 | DISCUSSION

This study demonstrates that recurrent/residual MR after 12 months of follow-up, poor baseline LVEF and male gender inversely predict LVRR after MC therapy.

LVRR after MC therapy occurred in 49% of the patients. Even though prior publications used the 6-months period to assess for LVRR, we included in the final analysis only patients who completed...
both 6- and 12-months follow-up in order to evaluate whether the LVRR persisted during longer follow-up. Indeed, a decrease in left ventricular dimensions became already evident after 6 months and further improved after 12 months, underlining the consistency of the study findings. Patients in the LVRR group developed similar reduction of LVEDD and left ventricular end-systolic diameter (LVESD). Moreover, these LV changes were congruent with improvement in LA dimensions. On the contrary, there was only a slight trend toward LVEF improvement, neither the LVRR group, nor the no-LVRR group experienced statistically significant changes in LVEF: 44.5 ± 16.3% to 46.5 ± 16.0%. Although the LVRR group showed a slight trend toward LVEF improvement, neither the LVRR group, nor the no-LVRR group experienced statistically significant changes in LVEDD and left ventricular end-systolic diameter (LVESD). Moreover, these LV changes were congruent with improvement in LA dimensions. The reduction of regurgitation volume leads to a decrease of left ventricular volume overload with reduction of LV dilatation, aligned with measurable reverse remodeling. The hypothesis of volume overload is further confirmed by the changes of regurgitation of both atrioventricular valves that we observed after percutaneous mitral valve repair in our cohort. Rate of severe MR during 12-months follow-up was significantly more frequent in the no-LVRR cohort despite comparable immediate post-procedural results. Similarly, severe TR during 12-months follow-up was more frequent in the no-LVRR cohort (32.5% vs. 19.8%).

In 51% of the cases, no LVRR was detectable. In the total cohort, we identified recurrent/residual MR, male gender, and severely reduced left ventricular ejection function as independent predictors for absence of LVRR within 12 months after MC procedure.

5.1 LVRR and severe recurrent MR

The relationship between LVRR and the extent of reduction in MR has been shown previously. Grayburn and colleagues demonstrated in 881 patients either treated interventionally by MC (801 patients) or surgically (80 patients), that reduction of end-diastolic LV volumes was paralleled with lower grade of residual MR at 12 months. Our study supports these results: severe MR during the

| TABLE 4 | Echocardiographic parameters at baseline and during 12-months follow-up |
|---------|-----------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|         | Degenerative MR | Functional MR    |                 |                 |                 |                 |
|         | No LVRR         | LVRR             | No LVRR         | LVRR             |                 |                 |
| LVEF (%)| Baseline        | 58.0 ± 9.9       | 58.1 ± 10.3     | .86              | 35.8 ± 15.3     | 37.2 ± 14.2     | .69 |
|         | 6-months FU     | 58.2 ± 11.1      | 59.2 ± 9.3      | .61              | 35.1 ± 15.2     | 36.2 ± 12.0     | .36 |
|         | 12-months FU    | 59.7 ± 10.6      | 60.5 ± 10.4     | .58              | 35.1 ± 15.2     | 36.2 ± 12.0     | .36 |
| LVEDD (mm) | Baseline       | 55.1 ± 6.4       | 59.1 ± 7.2      | .06              | 63.9 ± 11.4     | 68.2 ± 11.2     | .06 |
|          | 6-months FU     | 53.0 ± 6.9       | 52.9 ± 6.5      | .79              | 65.2 ± 11.9     | 60.0 ± 11.9     | .05 |
|          | 12-months FU    | 54.6 ± 7.1       | 49.5 ± 6.6      | .01              | 65.1 ± 11.0     | 54.8 ± 9.6      | <.001 |
| LVESD (mm) | Baseline       | 36.4 ± 4.2       | 39.4 ± 5.5      | .05              | 50.5 ± 13.3     | 53.5 ± 13.5     | .21 |
|          | 6-months FU     | 34.8 ± 6.5       | 35.3 ± 6.4      | .82              | 52.9 ± 14.0     | 47.4 ± 13.4     | .05 |
|          | 12-months FU    | 35.2 ± 6.5       | 32.0 ± 4.9      | .09              | 52.7 ± 13.3     | 42.3 ± 11.3     | <.001 |
| Severe MR (Grade III/IV) | Baseline | 25 (100)         | 28 (100)        | 1.0              | 57 (98.3)       | 52 (98.1)       | .94 |
|          | 6-months FU     | 9 (36.0)         | 3 (10.7)        | .02              | 11 (19.1)       | 5 (9.4)         | .15 |
|          | 12-months FU    | 10 (40.1)        | 3 (10.7)        | .01              | 7 (12.1)        | 3 (5.7)         | .23 |
| Severe TR (Grade III/IV) | Baseline | 13 (52.0)        | 16 (57.1)       | .70              | 25 (43.1)       | 24 (45.3)       | .81 |
|          | 6-months FU     | 10 (40.0)        | 6 (21.4)        | .14              | 21 (36.2)       | 14 (26.4)       | .26 |
|          | 12-months FU    | 7 (28.0)         | 7 (25.0)        | .80              | 20 (34.5)       | 9 (17.0)        | .03 |
| LA diameter (mm) | Baseline | 7 (28.0)         | 7 (25.0)        | .80              | 56.0 ± 6.3      | 55.4 ± 7.9      | .71 |
|          | 6-months FU     | 55.6 ± 11.5      | 53.6 ± 9.2      | .41              | 54.6 ± 7.0      | 53.8 ± 8.6      | .44 |
|          | 12-months FU    | 55.7 ± 11.6      | 54.2 ± 10.2     | .70              | 54.0 ± 7.5      | 53.2 ± 8.2      | .57 |

Note: Values are mean ± standard deviation, or number (%). p-values by Student’s t-test and chi-square test. Abbreviations: LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVESD, left ventricular end-systolic diameter; LVRR- left ventricular reverse remodeling.
first year after MC increases the risk for absence of LVRR by 3.4-fold in the total cohort.

LVRR and poor LVEF

There are limited data showing divergent effects of MC on left ventricular reverse remodeling in patients with reduced LVEF. Grayburn and colleagues demonstrated in a subgroup of patients with FMR diastolic reverse remodeling when MR severity was reduced to grade 2 or less by MC therapy. Mean LVEF in this cohort was 43 ± 12%, patients with LVEF <20% were excluded. Pleger et al. presented in a cohort of 41 patients (mean LVEF 33%) that a reduction in the LVEDD was evident 12 months after MC procedure. In the randomized Acorn Trial, the authors observed LVRR after reduction of MR by surgery. Mean LVEF in this trial was 23.9 ± 8.9%. In our cohort, mean LVEF was 43.5 ± 16.8%. Given that etiology of MR was equally distributed in the LVRR and no-LVRR groups (FMR was evident in 69.9% of patients in the no-LVRR group, compared to 65.4% in the LVRR group \( p = .54 \)), the overall LVEF between the two groups was not different (42.5 ± 17.2% in the no-LVRR group compared with 44.5 ± 16.3% in the LVRR group, \( p = .49 \)). However, the proportion of patients with LVEF <20% was more frequent in the no-LVRR group (10.8%) compared with the LVRR group (3.7%, \( p = .07 \)). Hence, multivariate regression analysis identified left ventricular EF < 20% as independent predictor for absence of LVRR in the total cohort.

TABLE 5 Kaplan–Meier estimates of 1- and 2-year clinical outcome in patients with and without LVRR

| % Mortality | 1-year outcome (%) | 2-year outcome (%) |
|-------------|-------------------|-------------------|
| No LVRR     | LVRR              | No LVRR           | LVRR              |
| 0.0         | 0.0               | 11.2              | 8.6               |
| p-value     |                   |                   | .47               |
| MACCE       | 33.7              | 22.2              | 50.6              | 35.8             |
|             |                   |                   | .10               | .049             |
| Reintervention | 0.0              | 0.0               | 4.4               | 1.4              |
|             |                   |                   |                   | .29               |
| Rehospitalization due to heart failure | 22.9 | 17.3 | 32.5 | 23.5 |
|             |                   |                   | .36               | .20               |

Abbreviations: LVRR- left ventricular reverse remodeling; MACCE, major adverse cardiac and cerebrovascular events.
5.3 LVRR and gender

Female sex has been shown to be a strong and independent predictor of outcome and reverse remodeling in chronic systolic heart failure.9 The mechanism by which female patients experience a better hemodynamic response is yet unclear and deserves further investigation. An analysis by Kararigas22 revealed that pressure overload in patients with aortic stenosis induced increased fibrosis and inflammation in male hearts, while the female heart suppresses fibrosis-related and inflammatory processes. Hence, female patients undergoing aortic valve replacement show decreased LV diameters in early first weeks after surgery more frequently than male patients.23 Gender specific effects on reverse remodeling in volume overload models have been less frequently studied so far. In our study, male gender independently predicts absence of LVRR (OR = 0.499, \( p = .044 \)) after MC in the total cohort including both patients with FMR and DMR. Likewise, Adamo et al. recently reported female sex as an independent predictor of reverse remodeling in a cohort of patients only with FMR after MC therapy.12

5.4 LVRR in DMR versus FMR

To the best of our knowledge, this is the first study that separately evaluates the predictors of left ventricular reverse remodeling for DMR versus FMR in patients treated with MC therapy.

One could assume that reduction of the regurgitation in primary (degenerative) MR as the genuine (valvular) pathology should have a greater effect on LVRR than in FMR. This hypothesis has been supported by the Asia-Pacific registry,24 where DMR cohort showed a significantly greater reduction in left ventricular end-diastolic diameter after MC procedure compared to FMR cohort. In our study, LVRR was not different between DMR and FMR subgroups. Despite comparable postprocedural results in both etiologies and despite comparable rates of recurrent MR to those published in the literature,25,26 recurrent/residual MR up to 12 months follow-up was more frequent in the DMR group than in the FMR group in our study (24.5 vs. 9.0%). This is surprising, particularly since recurrence of MR is a main concern of FMR due to progressive LV dysfunction.24 In a recent meta-analysis

| Table 6 | Multivariate regression analysis for predictors of reverse remodeling [Color table can be viewed at wileyonlinelibrary.com] |
|----------|------------------------------------------------------------------------------|
| Variables | Beta | Odds ratio | 95% CI | p-value |
| **Total cohort** | | | | |
| Male gender | −0.696 | 0.499 | 0.248–1.00 | .050 |
| Baseline LVEF <20% | −1.409 | 0.244 | 0.061–0.972 | .046 |
| Recurrent/Residual severe MR at 12-month follow-up | −1.341 | 0.262 | 0.094–0.729 | .010 |
| Residual severe TR at 12-month follow-up | −0.733 | 0.481 | 0.227–1.017 | .06 |
| **Degenerative MR** | | | | |
| Male gender | −0.525 | 0.592 | 0.181–1.936 | .39 |
| Recurrent/Residual severe MR at 12-month follow-up | −1.605 | 0.201 | 0.047–0.867 | .031 |
| Residual severe TR at 12-month follow-up | −0.107 | 0.899 | 0.239–3.385 | .87 |
| **Functional MR** | | | | |
| Male gender | −0.699 | 0.497 | 0.203–1.218 | .3 |
| Baseline LVEF <20% | −1.361 | 0.256 | 0.062–1.058 | .08 |
| Recurrent/Residual severe MR at 12-month follow-up | −1.216 | 0.297 | 0.067–1.313 | .08 |
| Residual severe TR at 12-month follow-up | −0.102 | 0.361 | 0.142–0.916 | .036 |

Abbreviations: CI, confidence interval; LVEF, left ventricular ejection fraction; MR, mitral regurgitation; TR, tricuspidal regurgitation.
of 2,615 patients treated with the MC, the reported percentage of patients with MR grade ≤2 at 1-year follow-up was comparable between the two cohorts (58 vs. 54%). Nevertheless, there was a significantly lower rate of mitral valve reintervention in patients with FMR compared with those with DMR (4 vs. 10%). If we compare LVRR in the two cohorts in our study after excluding severe recurrent/residual MR, the difference between DMR and FMR cohort becomes more evident (62.5 vs. 49.5%). Hence, multivariate analysis revealed that recurrent/residual MR was a predictor for absence of LVRR only in the DMR subgroup. Our results are in line with recently published study results of cohort of patients with FMR, where LVRR occurred independently of recurrent/residual MR. Severe recurrent MR should be promptly diagnosed after MC therapy performed for DMR to identify patients possibly benefitting from reintervention of MR to avoid adverse clinical outcome.

An analysis of a cohort of 146 patients from the GRASP registry showed an improvement in LVEF coupled with reduction in LV volumes regardless of baseline TR severity. However, the correlation between residual TR and LVRR was not investigated. In our total cohort, LVRR was more frequent in the subgroup without severe residual TR (53.7%), compared with 37.2% in the subgroup with severe TR after 12-months follow-up. And this difference was more evident in the FMR subgroup. Hence, in FMR cohort only severe residual TR was found to be a predictor for absence of LVRR. Twelve-month echocardiographic screening for severe residual/recurrent TR after MC therapy in patients with FMR represents a valuable tool to predict absence of LVRR and therefore poor prognosis. Timely therapy of severe TR should be considered as an important target to improve clinical outcome in these patients.

### 5.5 LVRR and clinical impact

Reverse ventricular remodeling after surgical and interventional treatment of mitral valve is associated with better survival and decreased rate of heart failure rehospitalization. Our study confirms these results and underlines the relation between improved outcome and reverse remodeling: Patients in the LVRR group had numerically lower rehospitalization rates in the first year and a lower rehospitalization and mortality rates in the second year, resulting in a significantly reduced MACCE rate compared with the no-LVRR group during 24-months follow-up (50.6 vs. 35.8%).

### 6 LIMITATIONS

A substantial proportion of patients who underwent MC implantation at our institution were not included in the analysis because of the lack of a complete echocardiographic follow-up both at 6- and at 12-months follow-up. Although baseline characteristics were similar between the study population and the excluded patients, a selection bias cannot be ruled out.

The prevalence of LVRR was in accordance with most previous studies regardless what exact definitions were applied for LVRR. However, the prevalence of reverse remodeling after percutaneous mitral valve repair may depend on the definition of reverse remodeling. Many combinations of various echocardiographic parameters have been introduced to determine favorable structural response in patients following medical therapies. Our definition with 10% decrease of LVEDD is a pragmatic approach being applied in others studies and can be easily used, in a daily routine. However, taking only this dimension-based parameter into account, probably does not sufficiently reflect LV hemodynamics after the percutaneous edge-to-edge procedure.

### 7 CONCLUSIONS

LVRR occurs in nearly half of the patients treated by MC for MR. Recurrent/residual severe MR after 12 months, poor baseline LVEF and male gender were independent predictors for absence of LVRR after MC therapy. In patients with DMR, only recurrent/residual severe MR inversely predicts LVRR after MC therapy. In contrast, in FMR severe residual TR after 12 months inversely predicts LVRR after MC therapy.

### CONFLICT OF INTEREST

The authors declare no potential conflict of interest.

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### REFERENCES

1. Grayburn PA, Foster E, Sangli C, et al. Relationship between the magnitude of reduction in mitral regurgitation severity and left ventricular and left atrial reverse remodeling after MitraClip therapy. Circulation. 2013;128(15):1667-1674.
2. Herbrand T, Eschenhagen S, Zeus T, et al. Acute reverse annular remodeling during MitraClip therapy predicts improved clinical outcome in heart failure patients: a 3D echocardiography study. Eur J Med Res. 2017;22(1):33.
3. Schrage B, Kalbacher D, Schwarzl M, et al. Distinct hemodynamic changes after interventional mitral valve edge-to-edge repair in different phenotypes of heart failure: an integrated hemodynamic analysis. J Am Heart Assoc. 2018;7(6):e007963.
4. Feldman T, Wasserman HS, Hermann HC, et al. Percutaneous mitral valve repair using the edge-to-edge technique: six-month results of the EVEREST Phase I Clinical Trial. J Am Coll Cardiol. 2005;46(11):2134-2140.
5. Giannini C, Petronio AS, De Carlo M, et al. Integrated reverse left and right ventricular remodelling after MitraClip implantation in functional mitral regurgitation: an echocardiographic study. Eur Heart J Cardiovasc Imaging. 2014;15(1):95-103.
6. Rudolph V, Knup M, Franzen O, et al. Echocardiographic and clinical outcomes of MitraClip therapy in patients not amenable to surgery. J Am Coll Cardiol. 2011;58(21):2190-2195.
7. Konstam MA, Patten RD, Thomas I, et al. Effects of losartan and captopril on left ventricular volumes in elderly patients with heart failure: results of the ELITE ventricular function substudy. Am Heart J. 2000;139(6):1081-1087.
8. Cioffi G, Stefenni C, Tarantini L, Opaścich. Prevalence, predictors, and prognostic implications of improvement in left ventricular systolic function and clinical status in patients >70 years of age with recently diagnosed systolic heart failure. Am J Cardiol. 2003;92(2):166-172.

9. Verhaert D, Grimm RA, Puntawangkoon C, et al. Long-term reverse remodeling with cardiac resynchronization therapy: results of extended echocardiographic follow-up. J Am Coll Cardiol. 2010;55(17):1788-1795.

10. Gold MR, Daubert C, Abraham WT, et al. The effect of reverse remodelling on long-term survival in mildly symptomatic patients with heart failure receiving cardiac resynchronization therapy: results of the REVERSE study. Heart Rhythm. 2015;12(3):524-530.

11. Scandura S, Uslia GP, Capranzano P, et al. Left cardiac chambers reverse remodeling after percutaneous mitral valve repair with the MitraClip system. J Am Soc Echocardiogr. 2012;25(10):1099-1105.

12. Adamo M, Godino C, Giannini C, et al. Left ventricular reverse remodelling predicts long-term outcomes in patients with functional mitral regurgitation undergoing MitraClip therapy: results from a multicentre registry. Eur J Heart Fail. 2019;21(2):182-192.

13. Stone GW, Adams DH, Abraham WT, et al. Clinical trial design principles and endpoint definitions for transcatheter mitral valve repair and replacement: part 2: endpoint definitions: a consensus document from the Mitral Valve Academic Research Consortium. J Am Coll Cardiol. 2015;66(3):308-321.

14. Kawai K, Takaoka H, Hata K, Yokota Y, Yokoyama M. Prevalence, predictors, and prognosis of reversal of maladaptive remodeling with intensive medical therapy in idiopathic dilated cardiomyopathy. Am J Cardiol. 1999;84(6):671-676.

15. Banno A, Kohsaka S, Inohara T, et al. Early vs. late reverse ventricular remodeling in patients with cardiomyopathy. J Cardiol. 2016;68(1):57-63.

16. Witkowski TG, Thomas JD, Debonnaire PJ, et al. Global longitudinal strain predicts left ventricular dysfunction after mitral valve repair. Eur Heart J Cardiovasc Imaging. 2013;14(1):69-76.

17. Kim MS, Kim YJ, Kim HK, et al. Evaluation of left ventricular short- and long-axis function in severe mitral regurgitation using 2-dimensional strain echocardiography. Am Heart J. 2009;157(2):345-351.

18. Pavasini R, Ruggerini S, Grapsa J, et al. Role of the tricuspid regurgitation after mitraclep and transcatheter aortic valve implantation: a systematic review and meta-analysis. Eur Heart J Cardiovasc Imaging. 2013;14(1):50-56.

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