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STRUCTURAL

Elevated Mitral Valve Pressure Gradient After MitraClip Implantation Deteriorates Long-Term Outcome in Patients With Severe Mitral Regurgitation and Severe Heart Failure

Michael Neuss, MD, Thomas Schau, MD, Akihiro Isotani, MD, Markus Pilz, Maren Schöpp, MD, Christian Butter, MD

ABSTRACT

OBJECTIVES This single-center study was performed to analyze the effect of an increased transvalvular gradient after the MitraClip (MC) (Abbott Laboratories, Abbott Park, Illinois) procedure on patient outcome during follow-up.

BACKGROUND Percutaneous transcatheter repair of the mitral valve with the MC device has been established as a novel technique for patients with severe mitral regurgitation and high surgical risk. This study investigated the influence of an increased pressure gradient after MC implantation on the long-term outcome of patients.

METHODS A total of 268 patients were enrolled, who received MC implantation between April 2009 and July 2014 in our institution (75 ± 9 years of age, 68% men, weight 76 ± 15 kg, median N-terminal pro-B-type natriuretic peptide 3,696 [interquartile range: 1,989 to 7,711] pg/ml, left ventricular ejection fraction 39 ± 16%, log European System for Cardiac Operative Risk Evaluation score 20% [interquartile range: 12% to 33%]). Pressure in the left atrium and left ventricle were measured during the procedure using fluid-filled catheters. The pressure gradients over the mitral valve were determined simultaneously invasively and echocardiographically directly after MC deployment. A Kaplan-Meier analysis was performed and correlated with the pressure gradients. We used a combined primary endpoint: all-cause-mortality, left ventricular assist device, mitral valve replacement, and redo procedure.

RESULTS The Kaplan-Meier-analysis showed a significantly poorer long-term-outcome in the case of an invasively determined mitral valve pressure gradient (MVPG) in excess of 5 mm Hg at implantation for the combined endpoint ($p = 0.001$) and for all-cause mortality ($p = 0.018$). For the echocardiographically determined MVPG the cutoff value was 4.4 mm Hg. Propensity score matching was used to balance baseline differences between the groups. In a Cox model the increased residual MVPG >5 mm Hg was a significant outcome predictor in univariate and multivariate analysis (hazard ratio: 2.3; 95% confidence interval: 1.4 to 3.8; $p = 0.002$, multivariate after adjustment for N-terminal pro-B-type natriuretic peptide, age, and remaining mitral regurgitation).

CONCLUSIONS It is recommended that the quality of the implantation result be analyzed carefully and repositioning of the MC be considered in the case of an elevated pressure gradient over the mitral valve. (J Am Coll Cardiol Intv 2017;10:931-9)

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ABBREVIATIONS AND ACRONYMS

CI = confidence interval

HR = hazard ratio

MC = MitraClip

MR = mitral regurgitation

MVOA = mitral valve opening area

MVPG = mitral valve pressure gradient

MS = mitral stenosis

NT-proBNP = N-terminal pro-B-type natriuretic peptide

MitraClip (MC) (Abbott Laboratories, Abbott Park, Illinois) is a new percutaneous transcatheter therapy of mitral valve (MV) repair for patients with severe mitral regurgitation (MR). Safety and feasibility of the therapy in comparison to standard surgical treatment was established in the EVEREST (Endovascular Valve Edge-to-Edge Repair Study) II trial. This trial demonstrated also similar mortality in comparison to surgery during 5 years of follow-up (1,2). Compared to the EVEREST II trial, patients treated in Europe on average had a higher surgical risk, more frequently functional than degenerative MR, and valve morphology considered unsuitable for treatment within the EVEREST II trial (3–7). Some publications and registries suggest improvement of clinical and echocardiographic parameters in such patients not amenable to cardiac surgery (8,9).

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First papers report that the long-term outcome of patients may depend on the grade of the remaining MR (10). The relevance of a remaining transvalvular gradient over the MV after the procedure on the long-term outcome is completely uncertain. It was the aim of this study to investigate how the MV pressure gradient (MVPG) influences the long-term outcome of patients after MC implantation.

METHODS

STUDY POPULATION. This retrospective study included 268 consecutive patients with severe MR who underwent MC implantation between March 2009 and April 2014 in our heart center. A patient flow chart is given in **Figure 1**. All patients were evaluated by an interdisciplinary heart team for MC implantation and referred to interventional treatment due to high surgical risk (mostly European System for Cardiac Operative Risk Evaluation score >20% or other severe comorbidities). Patients had symptomatic heart failure (New York Heart Association functional class III or IV) despite established optimal medical therapy. All patients gave written consent. This retrospective study was performed according to ethical guidelines of our institution.

PROCEDURES. The MC implantation procedure has been described previously (1,2). All procedures were performed using the 24-F CDS01 or CDS02 MC device (Abbott Vascular, Santa Clara, California) following the standard instruction for use.

ECHOCARDIOGRAPHIC MEASUREMENT. Transthoracic and transesophageal echocardiography were performed by experienced sonographers using commercially available ultrasound systems (Vivid 7 and Vivid E9, GE Medical Systems, Milwaukee, Wisconsin; and Philips IE 33, Royal Philips Electronics, Amsterdam, the Netherlands). The echocardiographic loops recorded during the procedure were retrospectively read and analyzed for this study by an experienced board-certified echocardiographer independently of the implantation procedure and the treatment process of the patients.

Initial MR was graded comprehensively using semi-quantitative methods measuring the color Doppler regurgitation area, assessment of vena contracta width, and the quantitative method of the proximal isovelocity surface area according to the guideline of the American Society of Echocardiography using 4 MR grades (11). After the intervention, MR severity was assessed with the technique previously reported (12). The MR was determined 1 or 2 days after the implantation procedure before discharge by transthoracic echocardiography. Mitral stenosis (MS) was evaluated by recording the transmitral mean pressure gradient calculated from the continuous Doppler waveform in transesophageal echocardiography during the implantation procedure simultaneously to invasive MVPG measurement directly after clip deployment (13).

MV orifice area (MVOA) was traced at the level of the leaflet tip in maximum opening during diastole using transgastric view or in orthogonal flexi-slices of midtransesophageal 3-dimensional views, if available. Because 3-dimensional transesophageal echocardiography was provided by GE Medical Systems only at the end of 2012, we decided to use mainly 2-dimensional echocardiography and to confirm these data by 3-dimensional echocardiography, if available.

INVASIVE MEASUREMENT OF TRANSMITRAL PRESSURE GRADIENT. For the invasive measurement of the transmitral pressure gradient a 5-F pigtail-catheter (Merit Medical Systems, South Jordan, Utah) was placed in the apex of the left ventricle through a 6-F sheath in the left radial artery and the left ventricular pressure was measured using a pressure transducer (Medex, Smiths Medical, Ashford, United Kingdom). In the first patients the left atrial pressure was determined by connecting the MC steerable guide catheter to a fluid filled pressure line that was connected to a pressure transducer. In some patients the left atrial pressure could not be reliably measured using this approach. Data from these patients were not used for data analysis (**Figure 1**). Later during our study a 4-F pigtail catheter was introduced into the left atrium in parallel to the MC steerable guide

catheter. After the transseptal puncture a 0.025-inch and a 0.035-inch guidewire were introduced through a single sheath. The 0.025-inch wire was used for advancing a 4-F pigtail catheter and the 0.035-inch wire for advancing the steerable guide catheter using a single venous and transseptal puncture.

All pressure recordings were done simultaneously. The pressure curves were registered directly after clip deployment simultaneously to the echocardiographic scan. There were no adverse events related to the pressure recordings. The pressure data were retrospectively read and analyzed independently of the implantation procedure and the treatment process of patients using Mac-Lab IT Hemodynamic Recording System, version 6.8.1 (GE Medical Systems). The MVPG values of 5 heart cycles were averaged for the invasive pressure measurements.

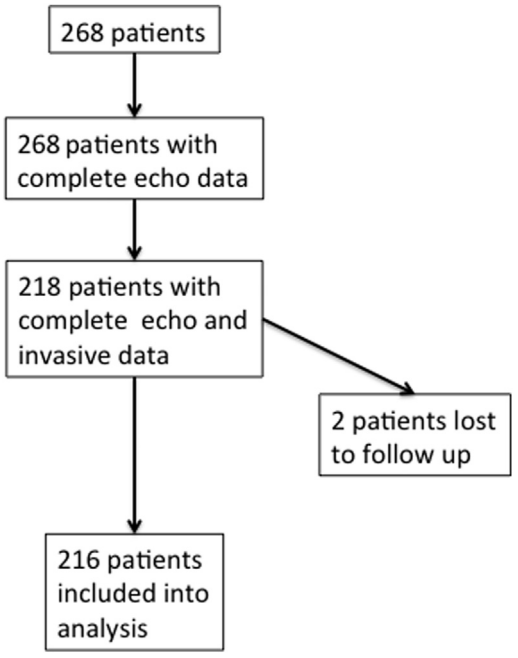
Invasive measurements were not performed in every case. Probing of the left ventricle was not possible in the case of an implanted mechanical aortic valve (n = 3). During the first MC cases invasive measurements of left ventricular pressure were not always used.

STATISTICAL ANALYSIS. Continuous variables are expressed as the mean ± SD when normal distribution is present or as median (interquartile range) otherwise. Categorical variables are presented as absolute numbers and percentages. Survival data were analyzed with a primary combined endpoint (all-cause mortality, unsuccessful implantation, MV surgery, left ventricular assist device implantation, and redo procedure) using Kaplan-Meier analysis. Factors were proved as event predictors for the combined endpoint using univariate and multivariate analysis (Cox proportional hazards). The multivariate analysis was performed with those parameters, that showed significance ($p < 0.05$) in univariate analysis. A linear regression analysis, intraclass correlation, and Bland-Altman plot were used to describe the correlation between different metric parameters. Odds ratios were calculated from logistic regression, if appropriate. These statistical analyses were performed using R version 2.13.0 (R Foundation for Statistical Computing, Vienna, Austria) or SPSS version 22.0 (IBM, Armonk, New York). To test for the influence of covariates we applied propensity score matching using *psmatch2* in Stata version 14.0 (StataCorp, College Station, Texas).

RESULTS

DEMOGRAPHIC DATA OF PATIENTS WITH PROCEDURE-RELATED MS. Our patients are a typical MC cohort comparable to other patients in other publications (see demographic data in **Table 1**) (4,5). The highly elevated N-terminal pro-B-type natriuretic peptide (NT-proBNP) confirms the presence of severe heart failure or New York Heart Association functional class III or IV in all patients. Seventy percent of patients had functional MR. We encountered few periprocedural complications that are listed in **Table 2**.

FIGURE 1 Patient Flow Chart



Only patients with both invasive and echo data were included in the final data analysis. Two patients were lost to follow-up.

Twenty-five percent of patients had an increased MVPG >5 mm Hg after MC implantation (**Table 1**). After correction for baseline imbalances between groups with respect to reduced estimated glomerular filtration rate, tricuspid regurgitation, and right ventricular function as measured by tricuspid annular plane systolic excursion, the difference between the groups is not significant. The number of clips implanted per patient is slightly higher in the patients with MS after the procedure (1.50 ± 0.72 vs. 1.29 ± 0.54; p = 0.022). All other recorded parameters were not significantly different between the 2 groups before the procedure.

MV opening area (MVOA) before the procedure could be an important anatomic predictor of post-interventional MS. A MVOA of <4.0 cm^2 before the procedure was present in 12% (29 of 251 patients) and

TABLE 1 Demographic and Procedural Data of Patients With Normal MVPG and Increased MVPG > 5 mm Hg After MC Implantation

	MVPG ≤5 mm Hg After MC	MVPG >5 mm Hg After MC	p Value
n	150 (75)	50 (25)	
Age, yrs	77 ± 10	76 ± 10	0.55
Female/male	48 (33)/96 (67)	19 (40)/28 (60)	0.328
Weight, kg	75 ± 15	77 ± 24	0.528
Height, cm	169 ± 9	168 ± 7	0.641
BMI, kg/m^2	25 ± 4	26 ± 4	0.149
BSA, kg*m	1.84 (1.72–2.00)	1.9 (1.79–2.01)	0.195
EuroSCORE I, %	22 (11–27)	22 (13–31)	0.977
EuroSCORE II, %	10 (4–13)	10 (4–15)	0,495
NYHA functional class, %			
I	5 (3.3)	0	0.250
II	105 (70)	40 (83)	
II	40 (26.7)	8 (17)	
NT-proBNP, pg/ml	6,100 (1,845–6,486)	6,950 (2,068–9,375)	0.485
LVEF, %	39 ± 17	37 ± 15	0.604
eGFR, ml/min	53 (38–66)	47 (33–57)	0.105
MVOA, cm^2	5.8 (4.7–7.3)	6.1 (5.4–6.9)	0.609
DMR/FMR	52 (35)/98 (65)	15 (30)/35 (70)	0.416
DMR without rupture	34 (65)	7	
DMR with rupture	18 (35)	5	
VC width, mm	6.75 ± 1.56	6.6 ± 1.43	0.542
EROA, cm^2	0.46 ± 0.14	0.38 ± 0.12	0.056
PISA, cm	0.77 ± 0.14	0.71 ± 0.17	0.029
Regurgitant volume, ml	71.52 ± 9.18	65.27 ± 19.7	0.086
Clips implanted	1.29 ± 0.54	1.50 ± 0.72	0.022
CAD	100 (71)	32 (72)	1.000
COPD	28 (19)	16 (32)	0.170
Previous cardiac surgery	35 (23)	12 (30)	0.629

Values are n (%), mean ± SD, or median (interquartile range).

BMI = body mass index; BSA = body surface area; CAD = coronary artery disease; COPD = chronic obstructive pulmonary disease; DMR = degenerative mitral regurgitation; eGFR = estimated glomerular filtration rate; EROA = effective regurgitant orifice area; EuroSCORE = European System for Cardiac Operative Risk Evaluation score; FMR = functional mitral regurgitation; LVEF = left ventricular ejection fraction; MC = MitraClip; MVOA = mitral valve opening area; MVPG = mitral valve pressure gradient; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; PISA = proximal isovelocity surface area; VC = vena contracta.

these patients had a significantly higher initial MVPG compared to those with a larger MVOA (5.0 mm Hg vs. 3.4 mm Hg; p < 0.001). An MVOA ≤4.0 cm^2 before the procedure predicted the development of MS (MVPG >5 mm Hg) after the procedure (odds ratio: 3.41; p = 0.003). Fourteen of 29 patients (48%) with an MVOA ≤4.0 cm^2 had MS after procedure, whereas only 21% of patients with a larger mitral orifice developed MS (p = 0.017).

There was a significant linear correlation between MVOA and MVPG after MC implantation in a linear regression analysis. The following linear regression equation was determined: MVPG = 4.4 - (0.21 · MVOA) (r^2 = 0.31; p = 0.008).

TABLE 2 Procedural Complications in the Entire Cohort

Pericardial tamponade	1 (0.5)
Retroperitoneal hematoma	2 (1.0)
Requiring transfusion	2 (1.0)
Requiring operation and transfusion	1 (0.5)
Femoral arteriovenous fistula	2 (1.0)
Requiring operation	1 (0.5)
Pneumothorax after insertion of central venous line	1 (0.5)
Anemia requiring transfusion, bleeding unclear	1 (0.5)
Partial clip detachment before discharge	2 (1.0)

Values are n (%).

CORRELATION BETWEEN ECHOCARDIOGRAPHIC AND INVASIVE MEASUREMENTS OF MVPG. The intraclass correlation between the echocardiographically and invasively determined MVPG is moderate (Pearson-correlation coefficient, r = 0.539) (Figure 2). In the Bland-Altman plot the mean difference between echocardiographic and invasive measurements is 0.6. Additionally, the limits of agreement (-2.2 and 3.6) may be relevant and show some difference, which may be caused by changed inflow pattern after MC implantation with double or more orifices.

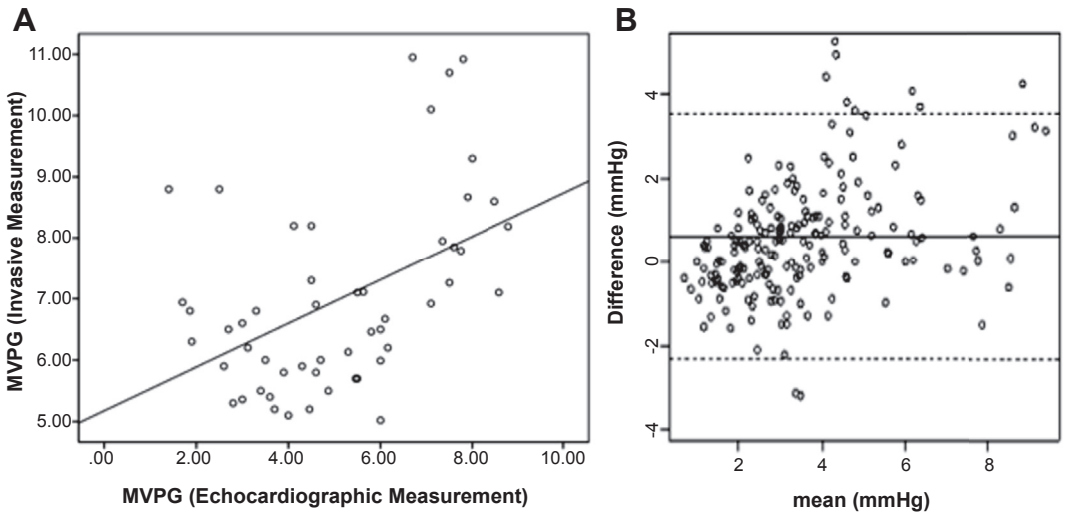
LONG-TERM OUTCOME. The Kaplan-Meier-analyses of the entire cohort and some subgroups are shown in Figures 2A to 2D. The combined endpoint was mainly determined by all-cause mortality, which was 22% after 1 year and 30% after 2 years (Figure 2A). Few patients received a surgical MV replacement, an implantation of a left ventricular assist device, or a redo procedure during follow-up (<5% after 2 years).

The residual MR after MC implantation has a large impact on the long-term outcome (Figure 2B). Small remaining MR grade ≤1+ has the best long-term outcome. The outcome of MR grade 2+ is slightly poorer. Residual MR grade >2+ predicts higher mortality rates, which increases further with higher MR grades.

Procedure-related MS with an invasively measured MVPG >5 mm Hg predicted a significantly poorer long-term outcome (Figures 3A and 3B). For the invasively determined MVPG the cutoff value of 5 mm Hg was found by repetitive log-rank testing as minimum p value. The all-cause mortality as secondary endpoint was also poorer in the case of post-procedural MVPG >5 mm Hg (p = 0.018).

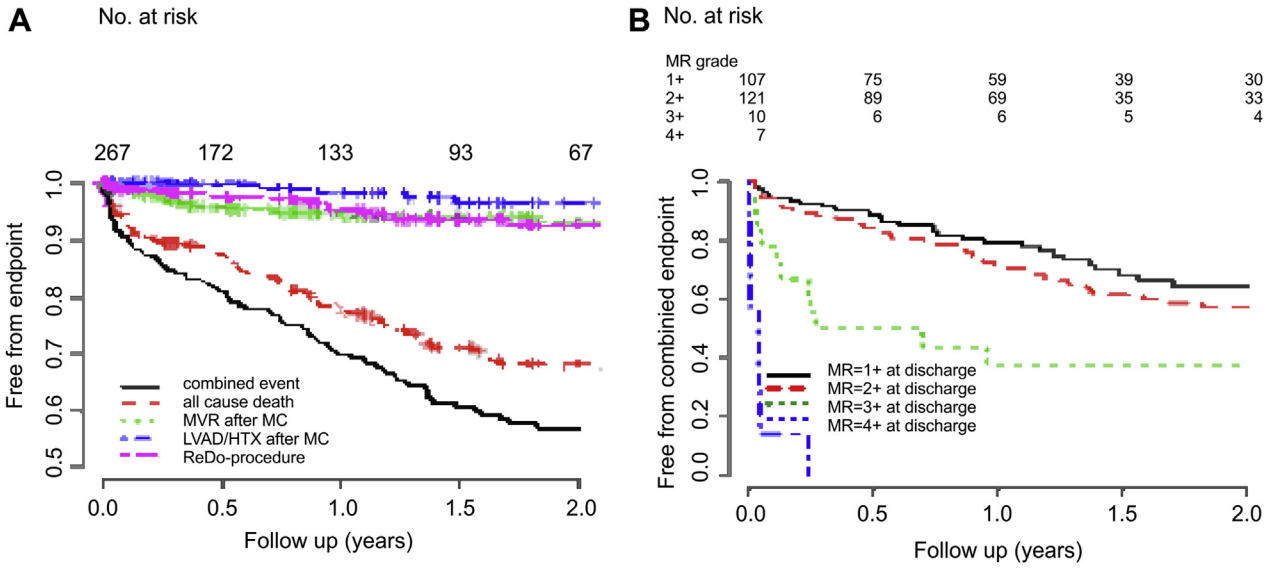
For the echocardiographically determined MVPG a cutoff value of 4.4 mm Hg was determined by repetitive log-rank testing (Figure 3D). Patients with a higher post-procedural MVPG had a significantly poorer long-term outcome (p = 0.018). The all cause survival showed also a trend toward a poorer

FIGURE 2 **Intraclass Correlation and Bland-Altman Plot Between MVPG Measured in Echocardiography and Invasively**



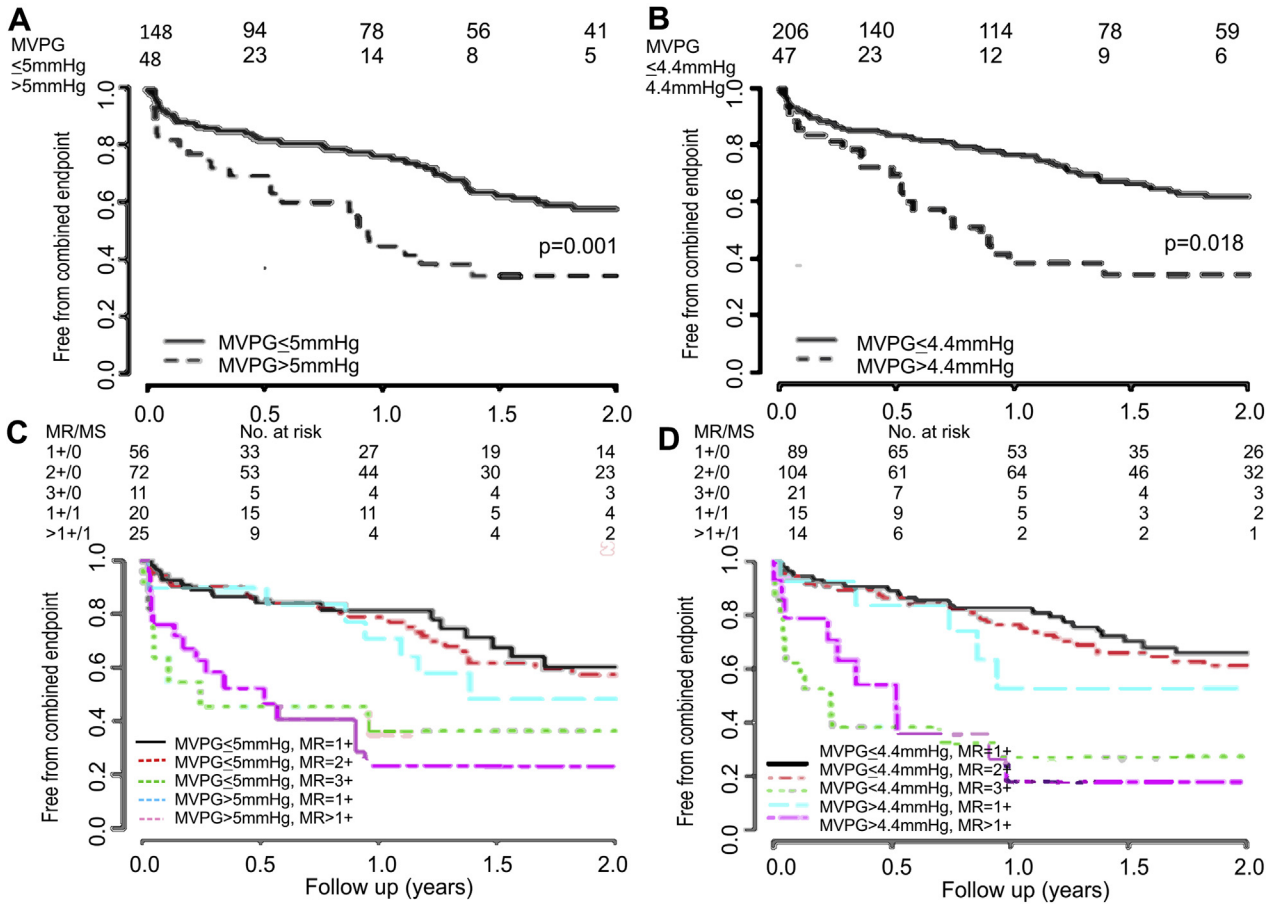
(A) The graph shows a significant intraclass correlation between the echocardiographically and invasively determined mitral valve pressure gradient (MVPG). **(B)** The Bland-Altman plot shows a significant interaction between echocardiographically and invasively determined pressure gradient.

FIGURE 3 **Kaplan-Meier Survival Analysis of the Long-Term Outcome After MC Implantation**



(A) The graph shows the long-term outcome after MitraClip (MC) (Abbott Laboratories) implantation according to a combined endpoint **(black line)**, all-cause death **(red line)**, mitral valve replacement (MVR) **(green line)**, left ventricular assist device (LVAD) or heart transplantation (HTX) **(blue line)**, and redo procedure **(purple line)** for the entire patient cohort treated. **(B)** The graph shows the long-term outcome after MC implantation as a function of residual mitral regurgitation (MR) after the procedure. The higher the degree of residual mitral regurgitation is, the worse the prognosis is.

FIGURE 4 Kaplan-Meier Survival Analysis for the Long-Term Outcome After MC Implantation According to Mitral Stenosis and Residual MR After the Procedure



(A, B) The graph shows the freedom of the combined endpoint as a function of the **(A)** invasively and **(B)** echocardiographically determined transvalvular pressure gradient. **(C, D)** The graph shows the freedom of the combined endpoint according to different extents of mitral stenosis (MS) and MR after the procedure. The highest event rate was observed in combinations of MS and MR. Other abbreviations as in Figures 2 and 3.

outcome, but marginally failed the significance test ($p = 0.062$). The sample size of the echocardiographically determined MVPG was larger because invasive measurements were not performed in every case.

The described difference of cutoff values between invasive and echocardiographic measurement is in agreement with the difference shown in the Bland-Altman plot (Figure 4B), which was 0.6 mm Hg.

Because we had different results regarding remaining residual MR and procedure-related MS after MC implantation, the impact of different combinations between residual MR and MS on the long-term outcome was evaluated in the present study. The Kaplan-Meier curves for different MR grade and different MS are shown in Figures 3C and 3D. Small MR grade (≤1+) without MS had the best long-term outcome. MR grade 2+ had a slightly poorer outcome. The outcome with MS and only small MR grade (≤1+) was worse. Higher MR grades (>2+) had the poorest long-term outcomes, especially concomitant with MS. Results of invasively and echocardiographically determined procedure-related MS were comparable, although the sample size of echocardiographic measurements were larger. The events are listed in Table 3, which confirmed that the combined endpoint was mainly reached by the all-cause mortality.

The proportional hazards in a Cox model are calculated for the combined endpoint in Table 4. In univariate analysis NT-proBNP >8,000 pg/ml, >74 years of age and the implantation results of

MVPG >5 mm Hg and MR grade >2+ were event predictors for the combined endpoint. In multivariate analysis the procedure-related MS with MVPG >5 mm Hg (invasive measurement) was a significant event predictor for the combined endpoint (hazard ratio [HR]: 2.3; 95% confidence interval [CI]: 1.4 to 3.8; $p < 0.002$) adjusted for MR grade >2+ at discharge (HR: 3.7; 95% CI: 1.8 to 7.7; $p < 0.001$) and NT-proBNP >8.000pg/ml (HR: 1.8; 95% CI: 1.1 to 2.9; $p = 0.23$).

TABLE 3 Events of the Combined Endpoint for Different MR Grade and Different MVPG Groups

	MR Grade				
	1+ (n = 56)	2+ (n = 72)	3+ (n = 11)	1+ (n = 20)	>1+ (n = 23)
MVPG	≤5	≤5	≤5	>5	>5
Death	11 (20)	24 (33)	4 (36)	5 (25)	12 (52)
MVR	2 (4)	2 (3)	2 (18)	2 (10)	2 (8)
LVAD	2 (4)	0	1 (9)	1 (5)	0 (0)

Values are n (%).

LVAD = left ventricular assist device; MR = mitral regurgitation; MVPG = mitral valve pressure gradient; MVR = mitral valve replacement.

DISCUSSION

Our results demonstrate that a post-procedural MS after MC implantation has a negative impact on the long-term outcome of patients. A cutoff value was found at 5 mm Hg for invasively and 4.4 mm Hg for echocardiographically determined MVPG.

In the EVEREST II or other trials, MS was not defined as a failed procedure and therefore few data are available (1,7,14). The frequency of MS at discharge was previously reported to occur in 31% to 35% of patients (10,15-17) and is comparable to the data of the present study (25%).

Baseline MVOA ≤4.0 cm^2 was found as a significant predictor of MS after MC implantation. Interestingly, patients with 2 or more clips had significantly elevated MVPG and more frequently MS after the procedure, which differs from the report of Biaggi et al. (13). Because baseline MVPG was different (2.2 mm Hg vs. 1.0 mm Hg) between our report and the Biaggi et al. (13) report, patients' background and baseline MV condition might have been different.

The relevant impact of remaining MR and the worse outcome with increasing MR was recently published (7,16) and can be confirmed with the data of the present study.

In daily routines it is a common problem for the interventional team to accept a higher MVPG for better MR reduction during a MC implantation procedure. Our results give some guidance for this frequent problem. In accordance with our results we do not accept an elevated MVPG >5 mm Hg because according to our data the long-term outcome of procedure-related MS is poorer than MR grade ≤2+. MC are no longer deployed in our institution in such cases. In cases of doubt test clipping was performed without clip deployment and patients were hemodynamically challenged using an elevation of heart rate or cardiac output using a combination of atropine and orciprenaline or dobutamine. In our hands we see more options for the medical treatment of MR than for the medical treatment of MS and try to avoid the deployment of clips if a procedure-related MS would be the result. In rare cases we removed clips before deployment to avoid the creation of MS. Due to different cutoff values for invasively (5.0 mm Hg) and echocardiographically (4.4 mm Hg) determined transmitral pressure gradients we believe that both techniques are relevant and should be performed to monitor the implantation.

The relevance of MS in the present study is in accordance with the literature. A recently published study reported the impact of remaining MV area after mitral valvotomy in cases of severe rheumatic MS (17). Little is known about the relevance of MS after surgical MV repair. Patients with higher MV gradients had worse quality of life after mitral annuloplasty (18). Recently published reports suggest that MV repair for rheumatic MR is associated with a significant rate of valve failure and reoperation (19). Bertrand et al. (20) recently stressed the relevance of effective MV area after restrictive MV annuloplasty for secondary MR for the long-term outcome. However, the relevance of MS in conjunction with MC has to our knowledge never been described before.

STUDY LIMITATIONS. This is a single-center study with a limited number of patients. An initial learning curve might have affected the results and biased the

TABLE 4 Outcome Prediction for the Combined Endpoint of Clinical and Functional Parameters After MC Implantation (Cox Proportional Hazards Model)

	Univariate Analysis		Multivariate Analysis, Optimized Model	
	HR (95% CI)	p Value	HR (95% CI)	p Value
NT-proBNP >8,000 pg/ml	1.8 (1.2–2.8)	0.006	1.8 (1.1–2.9)	0.023
>74 yrs of age	1.6 (1.1–2.5)	0.021		
Post-MC implantation				
MVPG >5 mm Hg	2.1 (1.3–3.4)	0.003	2.3 (1.4–3.8)	0.002
MR grade >2+ at discharge	4.3 (2.5–7.5)	<0.001	3.7 (1.8–7.7)	<0.001

CI = confidence interval; HR = hazard ratio; MR = mitral regurgitation; other abbreviations as in Table 1.

patient selection. Due to the retrospective design, the data sets are not completely available for all patients.

CONCLUSIONS

Increased MVPG deteriorates the long-term outcome after MC therapy and is a significant event predictor for poorer long-term outcome and increased all-cause mortality. A procedure-related MS has a poor prognosis. It is therefore recommended to check the quality of the implantation result carefully and to consider repositioning of the MC in case of a slightly elevated pressure gradient over the MV. Patients with procedure-related MS should be followed frequently and cardiac surgery should be discussed on a nonurgent basis.

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ADDRESS FOR CORRESPONDENCE: Dr. Michael Neuss, Heart Center Brandenburg in Bernau, Ladeburger Straße 17, 16321 Bernau, Germany. E-mail: m.neuss@immanuel.de.

PERSPECTIVES

WHAT IS KNOWN? The treatment with the MC device is a safe and efficient way of treating patients with symptomatic MR and high surgical risk. In terms of residual MR the results are inferior to surgical mitral repair.

WHAT IS NEW? In this single-center analysis we report on the follow-up of 218 patients treated with the MC device. Transvalvular mitral gradient was measured invasively and echocardiographically after deployment of the clip. A transvalvular gradient of >4.4 mm Hg in echo or >5.0 mm Hg invasively predicted a significantly worse outcome during follow-up.

WHAT IS NEXT? Data from registries and randomized studies should be analyzed whether the adverse effect of an increased transvalvular gradient can be confirmed in larger patient groups. Until further data are available, increased transvalvular gradients should be avoided.

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