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Original article

Long-term survival after MitraClip® therapy in patients with severe mitral regurgitation and severe congestive heart failure: A comparison among survivals predicted by heart failure models

Thomas Schau (MD)[a,1,*], Akihiro Isotani (MD)[a,1], Michael Neuss (MD)[a], Maren Schöpp (MD)[a], Martin Seifert (MD)[a], Christin Höpfner (MD)[a], Daniel Burkhoff (MD, PhD)[b], Christian Butter (MD)[a]

[a] *Heart Center Brandenburg in Bernau, Bernau, Germany*
[b] *Columbia University, New York, NY, USA*

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ABSTRACT

Background: The aim of the study was to investigate mortality following transcatheter mitral valve repair with the MitraClip System (MC) (Abbott Vascular, Santa Clara, CA, USA) in patients with mitral regurgitation and moderate-to-severe symptomatic heart failure in comparison to mortality predicted by the Seattle Heart Failure Model (SHFM) and the heart failure calculator of the meta-analysis global group in chronic heart failure (MAGGIC).

Methods and results: This retrospective study included 194 consecutive patients, who received a MC implantation between 2009 and 2013 at our institution. The observed mortality was compared with that predicted by the SHFM and the MAGGIC after 1 year: 24% observed, 18% by SHFM ($p = 0.185$) and 20.9% by MAGGIC ($p = 0.542$). At 2 years: 32% observed vs. 33% by SHFM ($p = 0.919$). The subgroup of patients with end-stage heart failure and N-terminal pro-B-type natriuretic peptide (NTproBNP) >10,000 pg/ml ($n = 41$) had significantly worse mortality after 1 year (49%) than predicted by SHFM (24%, $p = 0.034$) and MAGGIC (24.8%, $p = 0.041$).

Conclusion: In the overall patient cohort defined by 3+ to 4+ mitral valve regurgitation with New York Heart Association III and IV symptomatic heart failure, mortality following MC is consistent with that predicted by SHFM and MAGGIC for patients that are not at high risk. However, the subset of patients with severe heart failure defined by NTproBNP >10,000 pg/ml had worse than predicted mortality and may not benefit from MC therapy, mainly due to a high 30-day mortality.

Introduction

Percutaneous edge-to-edge mitral valve repair using the MitraClip (MC) device (Abbott Vascular, Santa Clara, CA, USA) has evolved as a new tool for the treatment of severe mitral valve regurgitation (MR). This technique has been evaluated in patients at low and high risk for surgery [1–4]. The EVEREST II study demonstrated superior safety compared to surgical mitral valve repair with inferior clinical efficacy but similar clinical outcomes in patients with low- or moderate-risk surgical profiles [2]. However, patients with advanced age, multiple comorbidities, and heart failure are currently the first to be considered for nonsurgical techniques. A few studies have already looked into feasibility and safety in patients with high surgical risks during short-term follow-up [5–8]. First results of patients not amenable to cardiac surgery suggest an improvement in symptoms and echocardiographic parameters [9–12]. Moreover, the long-term outcome after MC implantation compared to conservative medical therapy is not known in patients with severe heart failure and severe MR.

The purpose of the present retrospective study was therefore to evaluate survival following MC by comparing observed mortality to that predicted by the well-established, previously validated, and widely referenced Seattle Heart Failure Survival Model (SHFM) [13,14] and the recently published heart failure risk calculator from the meta-analysis global group in chronic heart failure (MAGGIC) [15].

* Corresponding author at: Heart Center Brandenburg in Bernau, Ladeburger Straße 17, 16321 Bernau, Germany. Tel.: +49 3338 694 610; fax: +49 3338 694 644.
E-mail address: t.schau@immanuel.de (T. Schau).
[1] These authors contributed equally to this publication (share first authorship).

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Methods

Study population

From March 2009 through May 2013, 194 consecutive patients were scheduled to be treated with MC implantation at our institution. All included patients had a EURO-score >20 or other severe comorbidities which increased the surgical risks dramatically [for example chronic obstructive pulmonary disease (COPD) with permanent oxygen supplementation, prior radiation to thorax due to malignancy, etc.]. All patients were evaluated by a multidisciplinary team consisting of a heart failure specialist, an interventional cardiologist, an echocardiographer, a cardiac surgeon, and an anesthesiologist.

All patients had symptomatic, severe >2+ MR despite optimal medical therapy, which included cardiac resynchronization therapy (CRT) when QRS duration was greater than 150 ms. The main exclusion criteria were severe clinical comorbidities that limited expected life expectancy below 6 months (e.g. end-stage cancer). Patients were also excluded if the morphology of the mitral valve made MC implantation technically impossible or unlikely according to the EVEREST criteria (i.e. short or calcified posterior leaflet without possibility of leaflet grasping or beginning mitral stenosis).

Patients underwent transthoracic and transesophageal echocardiography to quantify MR and left ventricular (LV) size and to judge morphologic suitability for MC implantation. The transthoracic and transesophageal echocardiograms were obtained using commercially available ultrasound diagnostic systems (Vivid 7 and Vivid E9, GE Medical Systems, Milwaukee, WI, USA and Philips IE 33, Royal Philips Electronics, Amsterdam, The Netherlands) by experienced echocardiographers. The LV end-diastolic diameter (LVEDD) was measured by transthoracic echocardiography in the long axis parasternal view. The LV end-diastolic volume (LVEDV) was quantified in the standard apical four chamber view using Simpson's method.

MC implantation procedure

The endovascular edge-to-edge mitral valve repair procedure has been described in detail previously [1,2]. All procedures were performed using the 24 Fr CDS01 or CDS02 MitraClip device. All clips were implanted under general anesthesia and fluoroscopic and transesophageal echocardiographic guidance. Hemostasis of the femoral vein access site was achieved by Z-suture and compression of the vein for 12 h. Patients were transferred to our intermediate care or, if necessary, intensive care unit after the procedure (for ≤24 h) for post-procedure observation.

Follow-up data

Most patients had regular follow-up visits at our outpatient clinic. In a few cases (n = 10), clinic visits were not possible due to long distance between home and hospital, the health status, or some other personal reasons. In these few cases patient data were collected via telephone calls to patients, their relatives, and/or their family physicians/cardiologists.

Prediction of survival by Seattle Heart Failure Model

The SHFM is a score used to predict the probability of survival in patients with heart failure [13,14]. It is a well-validated scoring system that relies on a combination of the following clinical parameters: age, gender, New York Heart Association (NYHA) class, LV ejection fraction (EF), coronary artery disease, systolic blood pressure, medications, laboratory tests of sodium, cholesterol, hemoglobin, lymphocytes, and uric acid. These parameters were available from the patients' records. Lymphocytes and uric acid were not determined in each case. For missing individual values of lymphocytes, the mean value of the overall population was used. Regarding the uric acid, the missing values were replaced by the upper limit (417 μmol/l) of the normal range (202–417 μmol/l), which was the mean value of heart failure patients in unpublished studies in our hospital. This method of assigning missing patient data has been described previously [13]. The daily diuretic dose was calculated in equivalents of daily furosemide dosage (mg/day) to account for different diuretic agents. The SHFM score was calculated for each patient on the date of the MC implantation. A predicted survival curve was then calculated for the cohort from the mean SHFM score of all patients. This curve was then compared with the actual survival observed in the study cohort.

Prediction of survival by the meta-analysis global group in chronic heart failure score

The recently published MAGGIC score [15] relies on a combination of the following clinical parameters: age, gender, body mass index, NYHA class, LVEF, systolic blood pressure, laboratory test of serum creatinine, co-morbidities such as COPD, diabetes mellitus, smoking, and medications. These parameters were all available from the patients' records. The predicted 1-year survival was calculated for every patient. The median predicted 1-year survival was compared with the observed survival.

Subgroup analyses

Analyses were performed to investigate potential risks in the following subgroups of interest: patients with extremely high values of N-terminal pro-B-type natriuretic peptide (NTproBNP; >10,000 pg/ml), functional (FMR) vs. degenerative (DMR) MR, LVEDD, and LVEDV. The optimal cut-off for NTproBNP was found as the point with the most significant log rank test-split in a former publication [12]. ROC analysis was also used to determine cut-off values for heart size based on LVEDD and LVEDV values that most discretely separated outcome among groups. These ROC analyses yielded cut-off values of 70 mm for LVEDD and 260 ml for LVEDV. These subgroup analyses were chosen because none of these grouping factors are included in the SHFM or the MAGGIC. An additional subgroup analysis stratified patients for different predicted initial risks, specifically a lower SHFM score vs. higher ared to the median value of the entire cohort.

Statistical analysis

The primary endpoint of this study was a comparison between observed all-cause mortality and that predicted by the SHFM and MAGGIC scores using Kaplan–Meier analysis. We performed an intention-to-treat analysis; therefore, the patients with unsuccessful MC implantation were included because they received general anesthesia. Observed and predicted survivals were compared at the 1- and 2-year time-point after MC implantation using 2 × 2 matrix and X^2-test.

Continuous variables are expressed as mean ± SD when normal distribution was confirmed or otherwise as median plus interquartile range (IQR). Categorical variables are presented as absolute numbers and percentages. Normality was assessed with Shapiro–Wilk test. Comparisons among groups were made using Wilcoxon, X^2-test or Fisher's exact test as appropriate. The open-source software 'R' version 2.15.1 (R Foundation for Statistical Computing, Vienna, Austria) was applied for all statistical tests.

All patients were informed about specific risks and alternative treatments and they gave informed written consent.

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Results

Patient baseline characteristics and parameters used in the SHFM and MAGGIC scores are presented in Table 1. The data (all patients NYHA class III or IV, median NTproBNP 3452 pg/ml) indicate that most patients had severe heart failure.

Demographic data of the subgroup of patients with NTproBNP levels >10,000 pg/ml showed significantly lower LVEFs (mean 27% vs. 44%), a greater proportion with NYHA class IV symptoms (60% vs. 36%), lower systolic blood pressure (108 mmHg vs. 117 mmHg), a lower body weight (70 kg vs. 79 kg), a higher log. EUROscore I (28% vs. 21%), a lower serum hemoglobin (10.1 g/dl vs. 10.9 g/dl) and were receiving higher daily doses of diuretics (60 mg vs. 40 mg furosemide equivalent).

More than 2/3 of patients had FMR. Organic DMR was found in 43 (27%) cases. Patients with NTproBNP >10,000 pg/ml had significantly higher rates of FMR (90% vs. 68%). The proportion of patients with FMR is comparable with populations included in prior studies [9–11].

Of the 194 patients who underwent an implantation procedure, the MC was implanted and successful in reducing MR grade to ≤2+ at discharge in 181 patients. The distribution of MR grade at the time of hospital discharge was: 1+, $n = 53$ and 2+, $n = 128$. These results were achieved with one ($n = 144$), two ($n = 34$), or three ($n = 3$) MCs. Regarding durability of MR reduction, follow-up echocardiograms showed significant reduction in MR after 1 and 2 years. Partial leaflet detachment was observed in eight cases. Redo procedures were performed in 7 cases at a median of 98 (IQR: 16–302) days. MV replacement was necessary in 10 patients at a period of median 125 (IQR: 21–334) days. Five patients received LV assist device at a median time of 431 (IQR: 318–463) days.

Of the 181 patients with successful implantation (MR ≤2+ at discharge) there were a total of 57 deaths over a median (range) follow-up time of 376 (128–834) days. Fourteen patients (7%) died during the first 30 days following the procedure, nine of whom succumbed to pump failure and five of whom died with multiorgan failure due to comorbid conditions. Older and very sick patients had an increased risk of early peri-procedural death. Significant predictors of 30-day mortality were NTproBNP >10,000 pg/ml (HR 7.2, 95%CI: 2.4–21.5, $p < 0.001$), MAGGIC score >30 (HR 5.3, 95%CI: 1.8–15.3, $p = 0.002$), age >77 years (HR 4.5, 95%CI: 1.4–14.4, $p = 0.011$), log. EURO-score I >30 (HR 3.5, 95%CI: 1.2–10.1, $p = 0.018$), and SHFM score >1.8 (HR 3.5, 95%CI: 1.2–10.1, $p = 0.018$) in univariate analysis. In multivariate analysis, NTproBNP >10,000 pg/ml (HR 7.8, 95%CI: 2.6–23.5, $p < 0.001$) and age >77 years (HR 5.0, 95%CI: 1.6–16, $p = 0.007$) were most predictive in an optimized model. As best as can be determined in this retrospective analysis, all deaths occurring at later times (as summarized in Fig. 1) were due to heart failure (pump failure).

Table 1
Demographic baseline parameters.

Parameter		All patients	NTproBNP ≤10,000 pg/ml	NTproBNP >10,000 pg/ml	p	MC implantation failure
n (%)		194 (100%)	153 (79%)	41 (21%)		13
♂/♀	*n* (%)	124 (64%)/70 (36%)	99 (64%)/54 (36%)	25 (60%)/16 (40%)	0.800	7 (54%)/6 (46%)
Age	Years	74 ± 10	74 ± 9	74 ± 10	0.691	77 ± 5
Age >80 years	*n* (%)	51 (26%)	42 (27%)	9 (21%)		3 (23%)
LVEF mean	%	40 ± 17	44 ± 16	27 ± 13	<0.001	45 ± 13
LVEF ≤35%	*n* (%)	75 (39%)	46 (30%)	29 (71%)		1 (8%)
Systolic RR	mmHg	115 ± 16	117 ± 14	108 ± 22	0.011	110 ± 12
Body weight	kg	77 ± 15	79 ± 15	70 ± 14	0.001	81 ± 15
NYHA						
Class 3	*n* (%)	114 (59%)	98 (64%)	16 (40%)	0.007	3 (23%)
Class 4	*n* (%)	80 (41%)	55 (36%)	25 (60%)		10 (77%)
MR grad 3+	*n* (%)	74 (38%)	62 (40%)	12 (29%)	0.256	1 (8%)
MR grad 4+	*n* (%)	120 (62%)	91 (60%)	29 (71%)		12 (92%)
DMR	*n* (%)	53 (27%)	49 (32%)	4 (10%)	0.008	5 (38%)
FMR	*n* (%)	141 (73%)	104 (68%)	37 (90%)		8 (62%)
LVEDD	mm	60 ± 10	59 ± 10	63 ± 10	0.038	59 ± 10
LVEDV	ml	158 ± 79	151 ± 76	182 ± 84	0.047	124 ± 47
CRTD	*n* (%)	39 (20%)	29 (19%)	10 (24%)	0.581	0
CRTP	*n* (%)	2 (1%)	1 (1%)	1 (2%)		0
ICD	*n* (%)	28 (14%)	20 (13%)	8 (19%)	0.428	1 (8%)
LVAD	*n* (%)	3 (2%)	1 (1%)	2 (4%)		0
CAD	*n* (%)	123 (63%)	95 (62%)	28 (68%)	0.520	7 (54%)
Diabetes mellitus	*n* (%)	66 (34%)	54 (35%)	12 (29%)	0.591	5 (38%)
Log. EUROscore I	%	23 ± 17	21 ± 15	30 ± 19	0.008	31 ± 24
Serum sodium	mmol/l	136 ± 4	137 ± 4	135 ± 5	0.151	133 ± 5
Total cholesterol	mg/dl	162 ± 47	164 ± 48	156 ± 42	0.358	136 ± 40
Hemoglobin	g/dl	10.5 (9.2–11.8)	10.6 (9.5–11.9)	9.8 (8.9–10.8)	0.001	10.5 (9.7–11.3)
NTproBNP	pg/ml	3452 (1941–7711)	2756 (1788–4588)	15,520 (11,850–29,240)	<0.001	4334 (3584–10,950)
Serum creatinine	μmol/l	130 ± 62	127 ± 65	141 ± 45	0.128	145 ± 41
Diuretic furosemide equivalent dose	mg/day	50 (30–80)	40 (30–80)	80 (40–120)	<0.001	60 (40–100)
ACE inhibitor	*n* (%)	128 (66%)	102 (67%)	26 (63%)	0.838	9 (69%)
ARB	*n* (%)	50 (26%)	43 (28%)	7 (17%)	0.218	3 (23%)
MR antagonist	*n* (%)	79 (41%)	56 (37%)	23 (56%)	0.038	5 (38%)
Beta blocker	*n* (%)	170 (88%)	131 (86%)	37 (90%)	0.608	12 (92%)
Allopurinol	*n* (%)	48 (25%)	34 (22%)	14 (34%)	0.171	3 (23%)
Statin	*n* (%)	125 (64%)	99 (65%)	26 (63%)	1.000	6 (46%)
SHFM score		1.58 (1.09–2.12)	1.45 (1.02–1.93)	1.91 (1.52–2.69)	<0.001	1.89 (1.60–2.43)*
MAGGIC score		28 (24–30)	27 (24–30)	30 (28–34)	<0.001	28 (24–30)

DMR, degenerative mitral regurgitation; FMR, functional mitral regurgitation; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; CRTD, cardiac resynchronization therapy defibrillator; CRTP, cardiac resynchronization therapy pacemaker; ICD, intracardiac defibrillator; LVAD, left ventricular assist device; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; MR, mineralocorticoid receptor.
* Single parameter with significance $p = 0.033$, all other parameters: $p > 0.05$.

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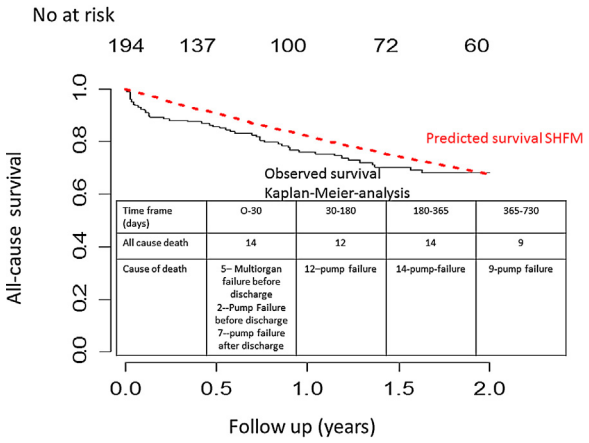

Fig. 1. Observed survival (based on all-cause mortality) following MitraClip (MC) vs. survival predicted by the Seattle Heart Failure Model (SHFM). The curves diverge early due to the peri-procedural mortality, but the difference is not statistically significant. The curves join after 2 years. The table differentiates the number and cause of death for different time periods in the first 2 years after MC implantation.

Observed and SHFM-predicted survival curves for the overall cohort are shown in Fig. 1. Due to early peri-procedural deaths of 14 patients (7%) the observed all-cause mortality was slightly, but not significantly, higher than predicted at the end of 1 year (24% vs. 18%, $p = 0.185$). However, observed and SHFM-predicted mortality rates were nearly identical after 2 years (32% vs. 33%, $p = 0.919$). Similarly, the 1-year mortality predicted from the MAGGIC score was 20.9%, which was similar to that predicted by SHFM and did not differ from the observed 24% ($p = 0.542$, Table 2).

Results of specific subgroup analyses are summarized in Table 2 and Fig. 2. For patients with NTproBNP <10,000 pg/ml, observed and SHFM-predicted survivals were not significantly different (Fig. 2a). However, for patients with NTproBNP >10,000 pg/ml, observed survival was significantly less than predicted by SHFM ($p = 0.035$ and 0.034 after 1 and 2 years, respectively) and by MAGGIC ($p = 0.041$ after 1 year).

Patients with age >77 years had a significantly poorer outcome compared to younger patients (Fig. 2b). For patients ≤77 years, observed and SHFM-predicted survivals were not significantly different. However, for older patients >77 years, observed survival was not significantly less than predicted by either SHFM ($p = 0.189$ and 0.981 after 1 and 2 years, respectively) or by MAGGIC ($p = 0.183$ after 1 year).

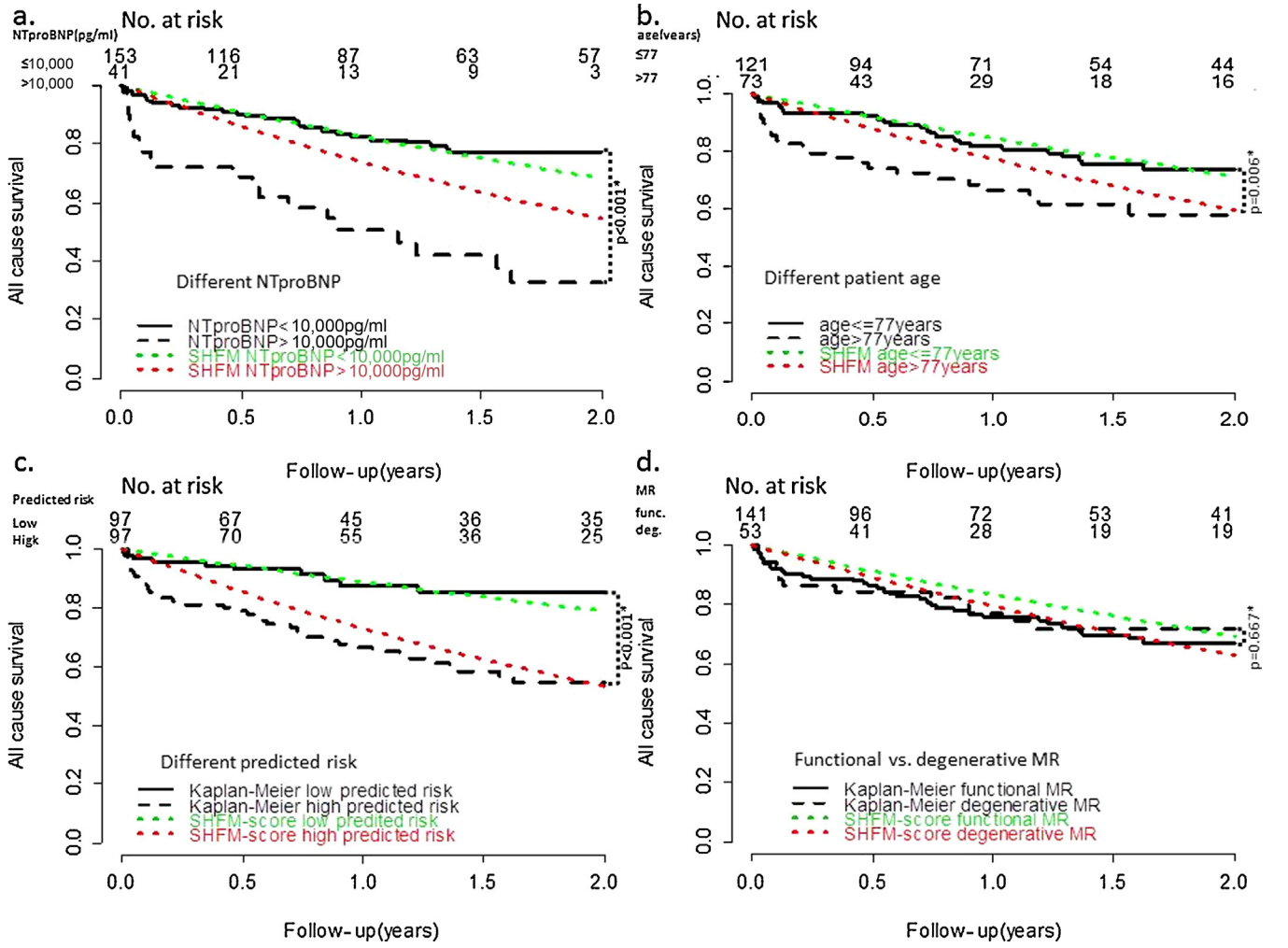

Fig. 2. Observed vs. Seattle Heart Failure Model (SHFM)-predicted survival curves for: (a) N-terminal pro-B-type natriuretic peptide (NTproBNP) levels greater than or less than 10,000 pg/ml. (b) Patients age older or younger than 77 years. (c) SHFM above or below median value. (d) Functional vs. degenerative mitral valve regurgitation (MR). The observed outcome was nearly identical for both MR types ($p = 0.667$) and comparable to predicted outcome by SHFM. *p-Values of log-rank test between both different Kaplan–Meier curves.

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Table 2
Observed vs. SHFM-predicted all-cause mortality in overall cohort and subgroups of interest.

	N	Observed all-cause mortality	Predicted all-cause mortality			
			SHFM		MAGGIC	
			Median (IQR)	p^*	Median (IQR)	p^*
All patients of complete cohort						
After 1 year (%)	194	24 (17–30)	18 (11–29)	0.185	20.9 (14.7–24.8)	0.542
After 2 years (%)	194	32 (24–39)	33 (21–49)	0.919		
Subgroup analysis						
NTproBNP ≤10,000 pg/ml						
After 1 year (%)	153	17 (10–24)	16 (11–24)	0.935	19.1 (14.7–24.8)	0.742
After 2 years (%)	153	24 (16–32)	29 (20–43)	0.389		
NTproBNP >10,000 pg/ml						
After 1 year (%)	41	49 (28–64)	24 (17–45)	0.034	24.8 (20.9–36.9)	0.041
After 2 years (%)	41	67 (43–81)	42 (31–70)	0.035		
Age ≤77 years						
After 1 year (%)	121	18 (10–25)	15 (10–23)	0.726	17.5 (13.4–22.7)	1.000
After 2 years (%)	121	26 (16–35)	29 (19–41)	1.000		
Age >77 years						
After 1 year (%)	73	34 (20–45)	23 (15–30)	0.189	22.7 (20.9–29.2)	0.183
After 2 years (%)	73	42 (36–54)	40 (29–50)	0.981		
Predicted risk low (<SHFM median)						
After 1 year (%)	97	12 (6–20)	12 (9–17)	1.000	16 (12.2–20.9)	0.548
After 2 years (%)	97	17 (7–26)	23 (17–30)	0.384		
Predicted risk high (>SHFM median)						
After 1 year (%)	97	33 (22–43)	27 (22–40)	0.447	22.7 (19.1–29.2)	0.147
After 2 years (%)	97	47 (34–47)	47 (39–65)	1.000		
Functional MR						
Overall cohort						
After 1 year (%)	141	24 (16–31)	17 (10–27)	0.191	20.9 (14.7–24.8)	0.630
After 2 years (%)	141	35 (24–43)	31 (20–46)	0.557		
NTproBNP ≤10,000 pg/ml						
After 1 year (%)	104	17 (9–25)	15 (9–24)	0.838	19.1 (14.7–24.8)	0.828
After 2 years (%)	104	25 (15–35)	27 (18–40)	0.864		
Degenerative MR						
Complete cohort						
After 1 year (%)	53	26 (12–37)	21 (14–29)	0.705	20.9 (16.0–24.8)	0.696
After 2 years (%)	53	33 (16–46)	34 (25–49)	1.000		
NTproBNP ≤10,000 pg/ml						
After 1 year (%)	49	21 (8–32)	19 (13–29)	1.000	19.1 (14.7–24.8)	1.000
After 2 years (%)	49	26 (9–40)	37 (28–51)	0.340		
LVEDD ≤70 mm						
After 1 year (%)	154	24 (16–31)	18 (12–26)	0.340	20.9 (14.7–24.8)	0.757
After 2 years (%)	154	32 (23–41)	32 (22–45)	0.662		
LVEDD >70 mm						
After 1 year (%)	28	31 (10–47)	17 (9–28)	0.361	20.9 (13.4–24.8)	0.577
After 2 years (%)	28	47 (13–55)	31 (19–49)	0.340		
LVEDV ≤260 ml						
After 1 year (%)	163	24 (17–31)	17 (12–28)	0.153	19.1 (14.7–24.8)	0.347
After 2 years (%)	163	33 (24–41)	32 (22–48)	0.941		
LVEDD >260 ml						
After 1 year (%)	19	40 (11–59)	17 (9–26)	0.226	20.9 (17.5–36.9)	0.354
After 2 years (%)	19	47 (16–67)	32 (17–46)	0.539		

LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation.
* *p*-Value: X^2-test between Kaplan–Meyer analysis and predicted survival by SHFM.

Patients were next grouped according to SHFM score, with a high-risk group having SHFM greater than the group's median value (a score of 1.584) (Fig. 2c). The observed Kaplan–Meier survival curves were significantly lower in the group with high SHFM scores, but for each group, observed and predicted curves did not differ significantly. Similarly, observed and MAGGIC-predicted 1-year mortality did not differ in these subgroups.

Survival curves were similar for patients with FMR and DMR and, for both subgroups, observed and SHFM-predicted survival curves did not differ from each other, and observed and MAGGIC-predicted 1-year mortalities did not differ. This was true for the entire cohort (Fig. 2d) and even more so for the subgroup with NTproBNP <10,000 pg/ml.

Two additional subgroup analyses assessed the impact on heart size (indexed by either LVEDD or LVEDV) on outcome (Table 2). ROC analysis was used to determine cut-off values that most discretely separated outcome among groups; these values were 70 ml for LVEDD and 260 ml for LVEDV. Enlarged left ventricles with LVEDV >260 ml and LVEDD >70 mm showed slightly poorer outcome, but the difference was not significant. Regarding comparison of observed vs. predicted survival, these were reasonably similar for patients with small hearts. However, in patients with larger hearts, observed survival showed a trend toward worse outcome than predicted by SHFM or MAGGIC. The difference was not significant, probably because of the small sample size.

Outcome in patients who failed MC implantation

Thirteen patients failed MC implantation. The demographic data of these patients showed a trend to more severe heart failure stage with significant higher SHFM score ($p = 0.033$, see Table 1). All other parameters showed no significance probably due to small sample size ($p > 0.05$). Summarizing patients who failed MC

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Table 3
Clinical improvements of heart failure symptoms at patients' follow-up after one and two years (median follow-up time: 376 (128–834) days).

Parameter	Pre-MC		Follow-up after 1 year			Follow-up after 2 years		
	Median (IQR)/mean ± std	*n*	Median (IQR)/mean ± std	*n*	*p*	Median (IQR)/mean ± std	*n*	*p*
NYHA class	3 (3–4)	103	2 (2–3)	103	<0.001	2 (2–3)	52	<0.001
LVEF (%)	41 ± 17	99	45 ± 17	99	<0.001	44 ± 18	52	<0.001
NTproBNP (pg/ml)	3103 (1853–6915)	94	2160 (1212–3883)	94	<0.001	1535 (783–3101)	47	0.030
MR grad								
1+, *n* (%)	0	99	36 (35%)	99	<0.001	19 (37%)	52	<0.001
2+, *n* (%)	0		54 (55%)			29 (55%)		
3+, *n* (%)	41 (41%)		9 (10%)			4 (8%)		
4+, *n* (%)	58 (59%)		0			0		

NYHA class, New York heart association class; LVEF, left ventricular ejection fraction; MR, mitral regurgitation.

implantation shows that they may have more progressed heart failure state.

Seven patients who died before hospital discharge were included in this group. Five of these deaths were due to multiorgan failure and comorbidities, the other two due to pump failure. In six cases, MC was not placeable due to obtaining mitral stenosis in two cases or anatomical abnormalities in the other cases. One of these patients received conventional surgical MV replacement and is still alive. In two other patients conventional surgery was planned, but patients died due to severe congestive heart failure before surgery was performed. Three patients refused conventional surgery; one of them is still alive, the other patients died.

Long-term efficacy

The surviving patients showed significant functional benefit of MC therapy and improvement in symptoms. The LVEF, NYHA status, and NTproBNP improved significantly after 1 and 2 years (Table 3).

Discussion

We demonstrated that rates of mortality in a group of patients with severe heart failure and severe MR following successful treatment with a MC was indistinguishable from that predicted by SHFM and MAGGIC risk scores at 1 year, and from that predicted by the SHFM at 2 years. The interpretation of these findings rests on the strength of the evidence that severe MR increases mortality in heart failure and an understanding of the degree to which MR is factored into each of these two risk scores.

With regard to the first point, there are only a few studies that provide a definitive answer on the degree to which MR impacts on mortality. Cleland et al. depicted the large impact of MR on survival of CRT patients in Care-HF [16]. Another recent study showed that in patients with inferior infarctions, the severity of MR correlates with the risk of mortality and cardiovascular morbidity [17]. Enriquez-Sarano and Sundt reviewed several studies and concluded that patients with either organic or functional MR are at increased risk of mortality [18].

The SHFM score was derived from analysis of one study population [19] and validated in five additional study populations [20–24] of heart failure patients. Patients with severe MR were included in some of the underlying studies (ELITE2, $n = 2987$ [20]; Val-HeFT, $n = 5010$ [21]; IN-CHF, $n = 872$ [24]; UW, $n = 148$ [23]) and excluded in other studies (PRAISE, $n = 1125$ [19]; RENAISSANCE, $n = 925$ [22]). The proportion of severe MR in each cohort is not reported in detail. The inclusion and exclusion criteria suggest that, at most, only a small number of patients with severe MR may have been included in the SHFM database. Accordingly, MR is not an input parameter for the SHFM score. However, according to the current consensus, patients with MR should have a significantly worse prognosis.

The MAGGIC score is based on 39,372 patients from 30 studies: six were randomized controlled trials (24,041 patients) and 24 were registries (15,331 patients). Similar to SHFM, the proportion of patients with severe MR is not reported in detail. Nevertheless, MAGGIC also predicted 1-year survival for our overall cohort of patients in whom MR was treated by MC.

Based on the premise that SHFM and MAGGIC are validated in groups of patients without a predominance of severe MR and that severe MR confers an increased risk of mortality, the results of the present study suggest that in addition to symptomatic improvement of heart failure symptoms as previously described [12], MC implantation appears to confirm survival that is equivalent to that of the general heart failure population. That is, after MC implantation, the expected worse survival appears to match survival of heart failure patients with conventional medical therapy without severe MR. This might be cautiously interpreted as a survival benefit conferred by the MC therapy.

However, as for MV annuloplasty, which provides symptomatic improvement without proven impact on mortality [25–27], a randomized prospective trial is necessary for definitive proof. Due to the spreading use of MC therapy such studies are difficult to implement. Two studies have been started. The RESHAPE study has recently terminated prematurely due to sluggish enrollment in countries where MC therapy is already clinically established and moved to countries where this therapy is still under investigation. The enrollment of the still ongoing COAPT trial seems to be slow.

Subgroup analysis showed that the outcome after MC implantation depends more on the severity of neurohumoral activation than on parameters of the LV size or function (Fig. 2). NTproBNP may contain additional information regarding severity of disease beyond that contained in either the SHFM of MAGGIC scores. The dramatically worse prognosis in patients with end-stage heart failure and NTproBNP >10,000 pg/ml compared to predicted prognosis suggests that MC may not improve survival in all cases. The outcome of these patients with severe neurohumoral activation was poorer than predicted by the SHFM and MAGGIC. The main reason was a high 30-day mortality. In some of these patients an immediate deterioration of LV function became obvious after clip implantation, indicating further aggravation of afterload mismatch in terminal heart failure. Stabilization and improvement of LV function was achievable on the intensive care unit in some patients, in other cases the patients died some days after MC implantation due to progressive heart failure. Because of comorbid conditions, implantation of an assist device was not an option in these patients. Especially older patients with the combination of dramatically increased NTproBNP, high Euroscore, and high SHFM and MAGGIC scores had a high risk of early 30-day mortality after MC (Table 3). The indication for MC

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implantation in these patients with NTproBNP >10,000 pg/ml should be considered on an individual basis, taking into account the stage of heart failure, the patient's clinical condition, and existing comorbidities.

Limitations

This was a single center study with a retrospective design and a limited number of patients. The results might have been influenced by an initial learning curve with this newly developed interventional technique. The main limitation, already discussed above, is that it is uncertain to what degree the presence of severe MR would impact on survival predicted by the MAGGIC and SHFM scores.

Some recently published articles reviewed several critical aspects of the MAGGIC and the SHFM scores. Alba et al. found that SHFM may perform only modestly, because there may be some differences between the derivation and validation data sets [28]. The MAGGIC score may lack some external validation, as recently reviewed by Braunwald [29].

Only prospective randomized controlled trials can definitely answer the comparison between MC and medical therapy for severe MR in heart failure patients. The results of such randomized trials are years away from being available, if ever finished. Therefore we believe that our comparison of data between survival data and established and widely used heart failure models may at least give some interesting valuable information despite the honestly above-mentioned limitations. For the population as a whole, at the very worst, the current findings of our study indicate that MC does not worsen survival overall.

Conclusion

The interventional implantation of MC is a new treatment for severe MR with significant improvement of symptoms in many reported cases, but may adjust long-term survival compared to the predicted survival of the SHFM and MAGGIC scores especially in the group of patients without severe neurohumoral activation. Especially end-stage heart failure patients with NTproBNP value >10,000 pg/ml do not appear to benefit from the MC therapy, mainly due to a high 30-day mortality. The treatment of these end-stage heart failure patients should therefore be based on individualized decision-making considering existing comorbidities. The validation of our retrospectively determined results by randomized trials may take a long time after modification of the RESHAPE study and the sluggish enrollment in the COAPT study. In the meantime our results using established and proven heart failure models may give some guidance for the continuously increased use of MC therapy.

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