

Clinical outcomes through 12 months in patients with degenerative mitral regurgitation treated with the MitraClip® device in the ACCESS-EU Phase I trial[†]

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Abstract

OBJECTIVES: Percutaneous treatment with the MitraClip device represents an alternative option for selected patients with degenerative mitral regurgitation (DMR) considered ineligible for surgery due to contraindications or high surgical risk by an inter-disciplinary heart team. We describe 12-month outcomes following treatment with the MitraClip device in DMR patients.

METHODS: The MitraClip Therapy Economic and Clinical Outcomes Study Europe (ACCESS-EU) Study has completed the enrolment of 567 patients as of April 2011, 117 of whom were DMR. Baseline demographics, procedural and acute safety results at 30 days and survival at 12 months were evaluated in the DMR subset. Effectiveness results, defined by a reduction in MR, and improvement in clinical outcomes based on changes in New York Heart Association (NYHA) functional Class, 6-min walk test (6MWT) and quality-of-life data were also assessed. Furthermore, DMR patients were stratified into high- and low-risk subgroups (logistic European System of Cardiac Operative Risk Evaluation I (logEuroSCORE I $\geq 20\%$ or $< 20\%$, respectively) and differentially evaluated.

RESULTS: One hundred and seventeen DMR patients underwent the MitraClip procedure with a 94.9% rate (111 of 117) of successful clip implantation. Baseline characteristics and comorbidities included NYHA Class III/IV (74%), left ventricular ejection fraction (LVEF) $< 40\%$ (9%), prior cardiac surgery (24%) and prior myocardial infarction (MI) (22%). Mean logEuroSCORE I was $15.5 \pm 13.3\%$. Mortalities at 30 days and 12 months were 6.0 and 17.1%, respectively. At 12 months, 74.6% (53 of 71) of patients in follow-up achieved MR \leq grade 2+ and 80.8% (63 of 78) were in NYHA functional class I/II. Both Minnesota Living with Heart Failure questionnaire (MLHFQ) scores and 6MWT distance improved significantly at 12 months compared with baseline ($P = 0.03$ and $P < 0.0001$, respectively).

CONCLUSIONS: The MitraClip procedure resulted in significant reductions in MR and improvements in clinical outcomes at 12 months in selected patients with severe DMR. MitraClip therapy may serve as a complementary non-surgical therapeutic option for DMR patients who are considered at high risk or ineligible for surgery by an inter-disciplinary dedicated heart team. Interventional treatment should be indicated following the discussion of patients in an inter-disciplinary conference of cardiologists and cardiac surgeons as suggested by current international guidelines.

Keywords: Degenerative mitral regurgitation • MitraClip • Percutaneous

INTRODUCTION

Reconstructive mitral valve surgery (mitral valve repair, MVR) is the current gold standard for treatment of severe mitral regurgitation of

any given aetiology according to current international guidelines [1, 2]. In patients with degenerative mitral regurgitation (DMR), surgery can be performed with low perioperative morbidity and acute mortality rates as low as 0.6% [3]. The long-term durability of modern repair techniques is excellent, with re-established life expectancy compared with an age-matched control population [4, 5]. Recently, minimally invasive surgical techniques have gained clinical

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importance and have decreased surgical trauma and further enhanced postoperative recovery [6–8]. Considering these results, elective MVR may be indicated even in the asymptomatic patient with severe MR [9].

It is a clinical reality however that a large proportion of patients with severe MR are considered ineligible for surgery due to contraindications or perceived high surgical risk [10]. For these patients, transcatheter-based MVR using the MitraClip device has proven a viable alternative. Although less effective at reducing MR compared with MVR [11], successful MitraClip therapy has been shown to effectively improve functional and clinical outcome in inoperable or high-risk patients [12–14].

This report includes the baseline through 12-month clinical data collected in the ACCESS-EU Phase I postapproval study in a patient subset with DMR.

METHODS

The ACCESS-EU Phase I postapproval study was designed to gain information regarding the use of the MitraClip system in the European Union with respect to health economics and clinical care, and to provide further evidence of the safety and effectiveness of the MitraClip system in a real-world setting. Patient enrolment began in October 2008 and was completed in April 2011.

MitraClip procedure

The MitraClip system is a catheter-based device designed to treat MR on the beating-heart. The procedure is best performed in a hybrid cath-lab or operating suite under echocardiographic and fluoroscopic guidance and general anaesthesia, as previously described [11]. The MitraClip device is a polyester-covered cobalt-chromium clip which is inserted via the femoral vein and advanced into the left atrium following trans-septal puncture. The clip is opened, positioned above the regurgitant jet and advanced into the left ventricle. With the MitraClip device centred above the origin of the regurgitant jet, the free edges of both mitral leaflets are grasped and closed to coapt the mitral leaflets across the regurgitant orifice. Adequacy of MR reduction can be assessed under physiological haemodynamic conditions and clip repositioning or placement of additional clips performed if necessary. Transthoracic echocardiograms were performed at participating sites at baseline and 12 months after MitraClip treatment, according to protocol.

Patient screening, enrolment, treatment and follow-up

Patients were assigned to MitraClip according to local institutional practice in consideration of current CE-mark-approved labeling and the MitraClip system Instructions for Use. Eligible patients included those with symptomatic MR or asymptomatic moderate-to-severe (3+) or severe (4+) mitral regurgitation. Transthoracic and transoesophageal echocardiograms studies were performed by the sites at baseline to assess patient eligibility.

The ACCESS-EU study was approved by the institutional review board at each participating site, and all patients provided written informed consent prior to their participation in the study. The

echocardiographic and clinical assessments were performed as per routine practice at the institutions at baseline, discharge, 6 months and 1 year after enrolment. The 6-min walk test (6MWT) and Minnesota Living with Heart Failure questionnaire (MLHFQ) were administered at baseline, 6 and 12 months. Peri- and post-procedural adverse events (AEs) were site-reported only without prospective definition of event types and without adjudication by a clinical events committee. Of 117 initially enrolled patients, 20 expired within 12 months, 9 withdrew consent and 7 missed their 12-month visit, resulting in 81 completed 12-month visits.

Statistical considerations

Results were analysed for the entire DMR cohort and additionally stratified in a *post hoc* manner into subgroups of patients at high or low surgical risk according to logEuroSCORE I $\geq 20\%$ or $< 20\%$, respectively. Baseline and demographical qualitative variables were expressed as percentages, and quantitative variables were expressed as mean (SD) or median (25th–75th interquartile range). Serial paired data are shown for surviving patients only. MR severity and NYHA Functional Class were compared between baseline and 12-months using Bowker's test. 'The null hypothesis ($H_0: P_{ij} = P_{ji}$) states that the marginal probabilities for each outcome, (i.e. improvement and worsening) are the same. Rejection of the null hypothesis is evidence of lack of symmetry ($H_1: P_{ij} \neq P_{ji}$), and a resulting statistically significant *P*-value indicates patients improved category following baseline'. Changes in 6MWT and MLHFQ between baseline and 12 months were analysed using paired *t*-tests. Survival rates to 12 months were presented as Kaplan–Meier curves. Differences were considered statistically significant at the 0.05 level. The data were analysed with SAS statistical software version 9.1.3 (SAS Institute, Inc., Cary, NC, USA).

RESULTS

Enrolment

Between October 2008 and April 2011, a total of 567 patients with significant mitral regurgitation were enrolled at 14 European sites and received the MitraClip device. Of these 567 patients, 117 (20.6%) were determined to have DMR.

Baseline characteristics

Table 1 shows baseline demographics and comorbidities for DMR patients. The overall DMR cohort was elderly (75.6 ± 12.1 years), with 61.5% of patients being over 75 years of age and 49.6% of male gender. The majority of ACCESS-EU Phase I DMR patients presented multiple comorbidities at baseline including congestive heart failure (62.4%), coronary artery disease (41.0%), atrial fibrillation (58.8%), hypertension (75.0%), cardiomyopathy (22.6%) and moderate-to-severe renal disease (25.6%). Approximately, one quarter (24%) of the patients had previous cardiovascular surgery including coronary artery bypass grafting (17.1%), and 27.6% of patients underwent percutaneous coronary intervention prior to enrolment in the ACCESS-EU study. The vast majority of patients (96.6%) in the DMR cohort had a mitral regurgitation grade 3+ or 4+ at baseline and most (73.9%) were symptomatic with New York

Table 1: Baseline demographics and comorbidities

Characteristic ^a	DMR patients (N = 117)	High-risk DMR patients (N = 33)	Low-risk DMR patients (N = 84)	P-value
Age (years)				
Mean \pm SD (N)	75.6 \pm 12.1 (117)	81.2 \pm 5.2 (33)	73.4 \pm 13.3 (84)	0.001
Patients over 75 years of age	61.5% (72/117)	87.9% (29/33)	51.2% (43/84)	0.0003
Gender				0.68
Female	50.4% (59/117)	54.5% (18/33)	48.8% (41/84)	
Male	49.6% (58/117)	45.5% (15/33)	51.2% (43/84)	
Comorbidities				
Congestive heart failure	62.4% (73/117)	90.9% (30/33)	51.2% (43/84)	<0.0001
Coronary artery disease	41.0% (48/117)	57.6% (19/33)	34.5% (29/84)	0.036
Myocardial infarction	21.6% (25/116)	31.3% (10/32)	17.9% (15/84)	0.13
Atrial fibrillation	58.8% (67/114)	77.4% (24/31)	51.8% (43/83)	0.018
Cerebrovascular disease	10.3% (12/117)	18.2% (6/33)	7.1% (6/84)	0.095
Cardiomyopathy	22.6% (26/115)	28.1% (9/32)	20.5% (17/83)	0.46
Hypertension	75.0% (87/116)	78.8% (26/33)	73.5% (61/83)	0.64
Diabetes	14.5% (17/117)	18.2% (6/33)	13.1% (11/84)	0.56
Moderate-to-severe renal disease	25.6% (30/117)	51.5% (17/33)	15.5% (13/84)	0.0001
Peptic ulcer disease	2.6% (3/117)	3.0% (1/33)	2.4% (2/84)	>0.99
Cardiogenic shock	2.6% (3/116)	0%	3.6% (3/84)	0.56
Chronic pulmonary disease	14.7% (17/116)	24.2% (8/33)	10.8% (9/83)	0.083
Previous cardiac surgery	23.9% (28/117)	54.5% (18/33)	11.9% (10/84)	<0.0001
Previous percutaneous intervention	27.6% (32/116)	27.3% (9/33)	27.7% (23/83)	>0.99
Cardiac rhythm device implant (%) (n/N)				
Cardiac resynchronisation therapy	1.7% (2/115)	3.0% (1/33)	1.2% (1/82)	0.49
Implantable cardiac defibrillator	3.5% (4/115)	3.0% (1/33)	3.7% (3/82)	>0.99
Pacemaker	12.2% (14/115)	33.3% (11/33)	3.7% (3/82)	0.0001
No device	82.6% (95/115)	60.6% (20/33)	91.5% (75/82)	0.0002
Logistic EuroSCORE (mean \pm SD (N))	15.5 \pm 13.3 (117)	33.1 \pm 11.5 (33)	8.6 \pm 5.1 (84)	<0.0001
LV ejection fraction (%) (n/N)				0.08
10–20%	3.4% (4/117)	0%	4.8% (4/84)	
20–30%	0.9% (1/117)	0%	1.2% (1/84)	
30–40%	5.1% (6/117)	12.1% (4/33)	2.4% (2/84)	
>40%	90.6% (106/117)	87.9% (29/33)	91.7% (77/84)	
NYHA functional Class, % (n/N)				0.0013
I	5.2% (6/115)	0%	7.3% (6/82)	
II	20.9% (24/115)	3.0% (1/33)	28.0% (23/82)	
III	67.0% (77/115)	84.8% (28/33)	59.8% (49/82)	
IV	7.0% (8/115)	12.1% (4/33)	4.9% (4/82)	
MR, % (n/N)				0.89
2+: Moderate	3.4% (4/117)	6.1% (2/33)	2.4% (2/84)	
3+: Moderate-to-severe	37.6% (44/117)	36.4% (12/33)	38.1% (32/84)	
4+: Severe	59.0% (69/117)	57.6% (19/33)	59.5% (50/84)	
LV Internal dimensions, systole (cm) (mean \pm SD (N))	3.5 \pm 0.9 (94)	4.0 \pm 1.0 (26)	3.3 \pm 0.8 (68)	0.0007

Heart Association (NYHA) Functional class III or IV. Mean logEuroSCORE I for the entire DMR cohort was 15.5 \pm 13.3%. Stratification into high- and low-risk patients revealed important demographic differences culminating in mean logEuroSCORE I of 33.1 \pm 11.5 and 8.6 \pm 5.1% for the two cohorts, respectively.

MitraClip procedure

In the ACCESS-EU DMR cohort, ≤ 2 MitraClip devices were successfully implanted in 94.9% of patients (111 of 117). In one high-surgical-risk patient, three MitraClip devices were required to adequately reduce MR. Two patients required mitral valve surgery on the day of the index procedure and 1 was treated by repeat MitraClip on Day 7 after initial clipping due to single leaflet device attachment discovered post-procedurally. In 3 other patients, single leaflet device attachment was noted during the index procedure.

In general, low-risk patients were more likely to receive > 1 MitraClip device compared with high-surgical-risk patients (40.5% (34 of 84) vs 21.2% (7 of 33), $P = 0.055$).

Procedure time, contrast volume and fluoroscopy duration data are presented in Table 2. The average procedure time was 24.0 min shorter for high-risk patients compared with low-risk patients ($P = 0.1$). This may be due in part to a larger proportion of low-risk patients receiving > 1 MitraClip (Table 2).

Clinical and echocardiographic outcome to 30 days

Overall, the mean duration of stay in the intensive care unit, cardiac care unit or postanaesthesia care unit following the MitraClip procedure was 2.4 \pm 3.1 days, with a median of 1 (range 0–20) day. No significant difference was observed in the median acute care between high-risk and low-risk DMR patients (2.4 \pm 3.8

Table 2: Procedure time, contrast volume and fluoroscopy duration

Mean \pm SD (N) median (min, max)	DMR patients (N = 117) ^a	High-risk DMR patients (N = 33)	Low-risk DMR patients (N = 84)
Procedure time ^b (min)	113.5 \pm 65.1 (90) 100.0 (15.0, 390.0)	98.1 \pm 55.3 (32) 90.0 (25.0, 255.0)	122.0 \pm 68.9 (58) 101.5 (15.0, 390.0)
Contrast volume (ml)	16.1 \pm 43.3 (115) 0.0 (0.0, 280.0)	12.2 \pm 22.4 (33) 0.5 (0.0, 100.0)	17.7 \pm 49.3 (82) 0.0 (0.0, 280.0)
Patients with no contrast	60.0% (69/115)	45.5% (15/33)	65.9% (54/82)
Fluoroscopy duration (min)	27.8 \pm 16.9 (83) 22.0 (5.0, 83.0)	23.2 \pm 12.8 (32) 18.5 (5.0, 53.0)	30.7 \pm 18.5 (51) 26.0 (8.0, 83.0)

^aSample sizes or denominators smaller than 117 reflect missing data.

^bProcedure time is defined as the time from trans-septal puncture until removal of the guide catheter.

Table 3: 30-day site-reported safety outcomes

30-day site-reported safety outcomes	DMR patients (n = 117)	High-risk DMR patients (N = 33)	Low-risk DMR patients (N = 84)
Death	6.0% (7/117)	9.1% (3/33)	4.8% (4/84)
Stroke	0.9% (1/117)	0%	1.2% (1/84)
Myocardial infarction	0.9% (1/117)	3.0% (1/33)	0%
Renal failure	2.6% (3/117)	3.0% (1/33)	2.4% (2/84)
Need for resuscitation	0.9% (1/117)	3.0% (1/33)	0%
Cardiac tamponade	0.9% (1/117)	3.0% (1/33)	0%
Bleeding complications	3.4% (4/117)	6.1% (2/33)	2.4% (2/84)
Repeat MitraClip	0.9% (1/117)	0%	1.2% (1/84)
Mitral valve surgery	1.7% (2/117)	0%	2.4% (2/84)
Total adverse events	17.9% (21/117)	27.3% (9/33)	14.3% (12/84)

Adverse events (AEs) as reported by participating sites; No formal comparisons of the rates of site-reported AEs were performed between the high-risk and low-risk DMR groups. These events occurred at a low rate. The study was not powered to detect differences in these low rate events between high-risk and low-risk DMR patients.

days for high risk vs 2.4 ± 2.8 days for low risk). However, the mean post-procedural hospital stay was slightly longer for high-surgical-risk patients when compared with low-surgical-risk patients (7.2 ± 4.3 days for high risk vs 6.5 ± 5.4 days for low risk). Also, a significantly larger proportion of low-risk patients were discharged home with or without home health care than of high-risk patients (83.1 and 71.9%, respectively).

One hundred and six patients were implanted with a MitraClip device and information on the severity of their MR was available at baseline and discharge; 88.7% (94 of 106) achieved an MR reduction to grade $\leq 2+$ at discharge, and 56.6% (60 of 106) achieved an MR reduction to grade $\leq 1+$ at discharge ($P < 0.0001$). The proportion of low-surgical-risk patients achieving an MR reduction to grade $\leq 1+$ was insignificantly higher (59.7%, 46 of 77) compared with high-surgical-risk patients (48.3%, 14 of 29, $P = 0.38$).

Site-reported adverse events to 30 days

Table 3 shows selected site-reported AEs within 30 days of the MitraClip procedure in the ACCESS-EU DMR cohort. Overall incidence of AE was 17.9% (21/117), 27.3% (9/33) and 14.3% (12/84) for high- and low-risk subgroups, respectively. This included 3 patients requiring valve reintervention (mitral valve surgery in 2 cases on the day of the index procedure, and repeat MitraClip in

1 case 7 days after the index procedure). Thirty-day mortality was 6.0% (7 of 117) with 9.1% (3 of 33) and 4.8% (4 of 84) for high- and low-risk subgroups, respectively. Causes of death were classified as cardiac in 42.9% (3 of 7) of cases as determined by the sites.

Clinical and echocardiographic outcome to 12 months

For 71 patients, echocardiographic data were available at 12 months of follow-up (Fig. 1). Overall rate of freedom from site-assessed MR $>$ grade 2+ was 74.6% (53 of 71). There were no statistically significant differences in high-risk, compared with low-risk, patients (80.0% (16 of 20) and 72.5% (37 of 51), $P = 0.76$). The majority of patients experienced improvement in heart failure symptoms and functional capacity. There was a median improvement in NYHA functional classes of one class in the total cohort ($P < 0.0001$) with 68% (53 of 78) of patients improving by at least one NYHA functional class. Two- or three-class improvement was observed in 20.5% (16 of 78) of patients. In the high-risk and low-risk patients, 57% (12 of 21) and 72% (41 of 57) of patients improved by at least one NYHA functional class, respectively. ($P = 0.06$, and $P < 0.0001$, respectively). Twenty-four percent (5 of 21) of high-risk and 19% (11/57) of low-risk patients experienced a two-class improvement or better in NYHA functional class. At 12 months, 80.8% (63 of 78)

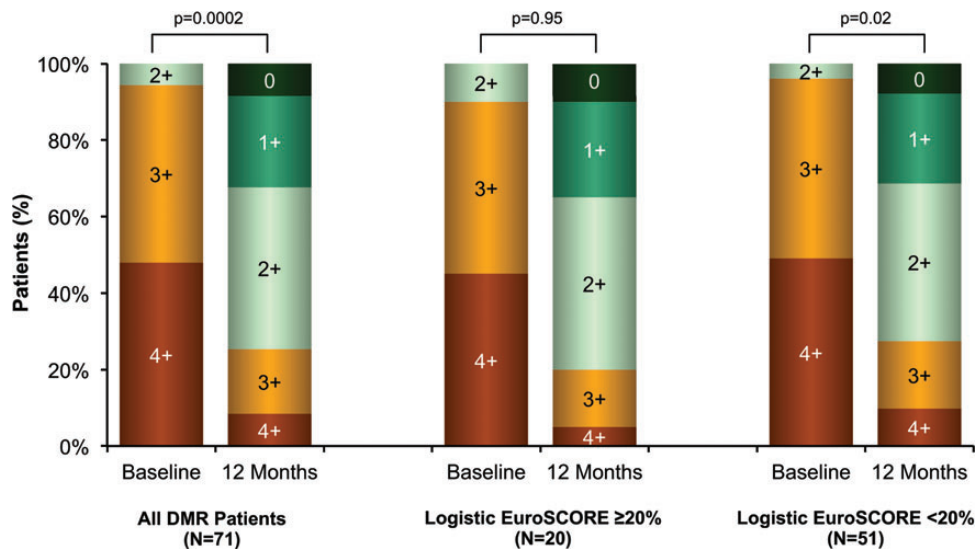


Figure 1: Mitral regurgitation at baseline and 12 months (paired data).

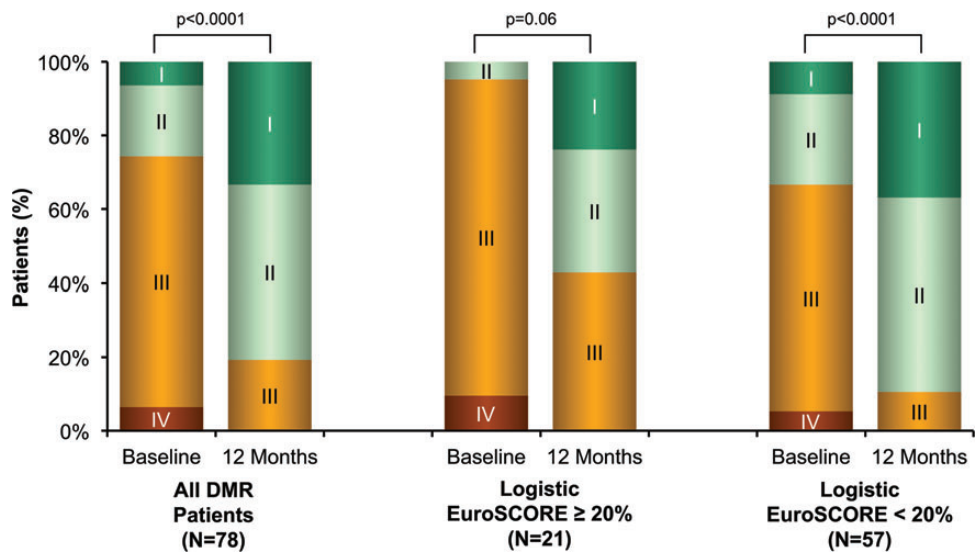


Figure 2: New York Heart Association Functional Class at baseline and 12 months (paired data).

of patients in the total cohort and 57.1% (12 of 21) and 89.5% (51 of 57) high-risk and low-risk patients, respectively, remained in NYHA functional classes I and II (Fig. 2). Results of both 6MWT and MLHFQ improved significantly at 12 months compared with baseline. Patients improved by a mean of 77.4 metres in 6MWT ($P < 0.0001$) and by a mean of 13.3 units in MLHFQ ($P = 0.03$; Fig. 3).

Site-reported adverse events to 12 months

The overall incidence of AE in the entire cohort was 41.0% (48 of 117). This included 13 patients undergoing repeat valve intervention: mitral valve surgery in 9 cases at a median of 128 days (range 0–300 days) after the index procedure and repeat MitraClip placement in 4 patients at 7, 83, 182 and 198 days after the index procedure. Further AE are detailed in Table 4. Mortality at 12 months was 17.1% (20 of 117) for the entire cohort and 24.2% (8 of 33)

and 14.3% (12 of 84) for high-risk and low-risk subgroups, respectively (P (log rank) = 0.51, Fig. 4). Causes of death were classified as cardiac in 45% (9 of 20) cases as determined by the sites.

DISCUSSION

According to the Annual Report of the German Society for Thoracic and Cardiovascular Surgery, mortality after isolated MVR was 1.8% in 2011 in a wide spectrum of patients with MR of all aetiologies [15]. However, demographically degenerative disease is known to be the most frequent cause of severe MR in western societies. Similarly, favourable outcomes are reported throughout the literature [16, 17], even in elderly patients [18] or in large patient samples such as in the Society of Thoracic Surgeons database where mortality after elective isolated MVR is reported at 1.2% [3]. These results of modern mitral valve surgery have to be the benchmark against which any new technique has to be

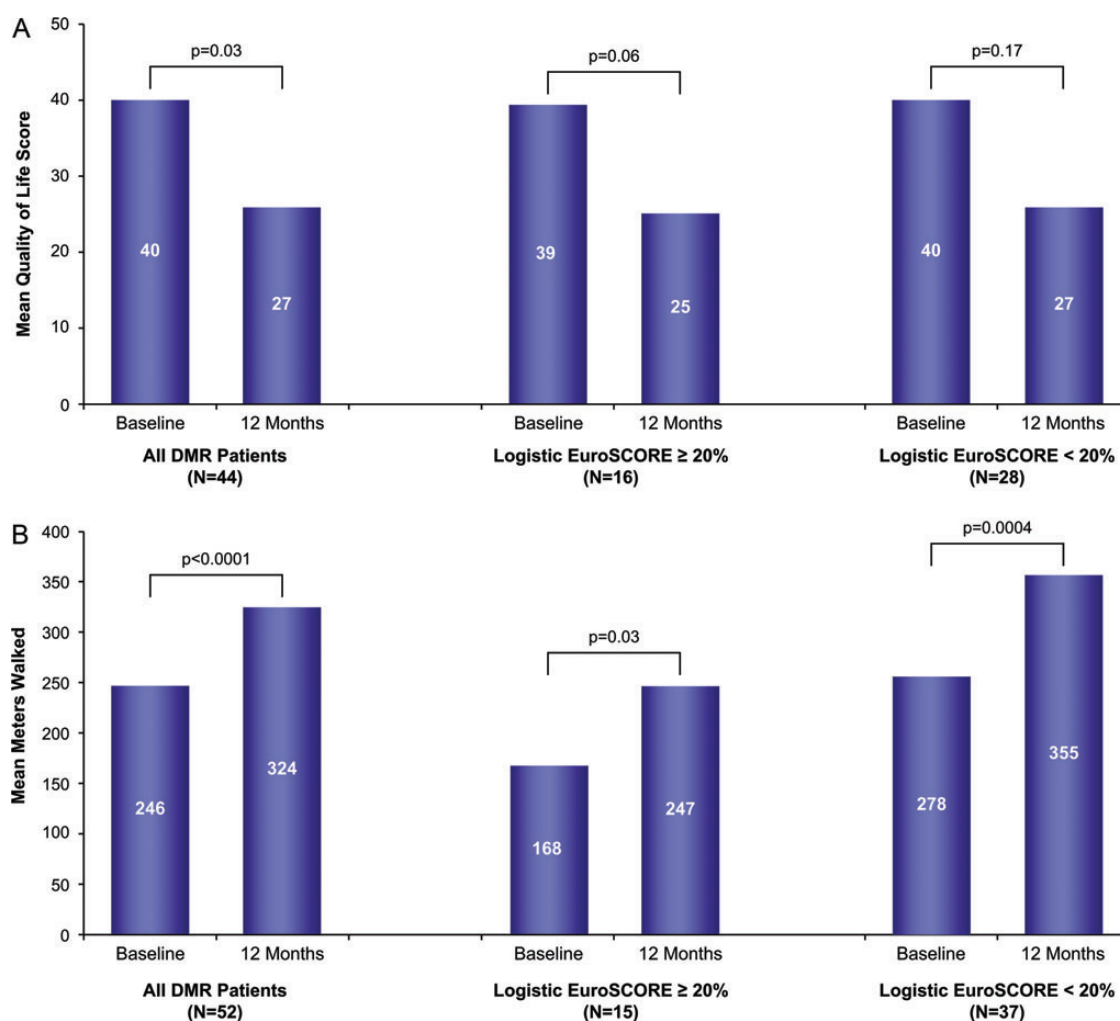


Figure 3: Results of Minnesota Living with Heart Failure questionnaire (A) and 6-min walk test (B) (paired data).

judged, even though it has to be acknowledged that MitraClip therapy is a relatively young treatment that as of yet has not become a routine procedure at most centres, as opposed to surgical MVR with long-term experience in specialized centres. In the light of these excellent results after MVR, international guidelines have recently recommended the restriction of percutaneous MitraClip therapy to patients ineligible for surgery due to excessively high surgical risk or contraindications to surgery. Additionally, the interdisciplinary assessment of patients and indications for the respective treatment option is strongly encouraged [2].

In the present report, the overall risk profile was characterized by a mean logEuroSCORE I of $15.5 \pm 13.3\%$. Stratification into high- and low-risk yielded subgroups with mean logEuroSCORE I of $33.1 \pm 11.5\%$ and $8.6 \pm 5.1\%$. While the former group truly qualifies as high risk, the latter likely represents a group of patients rather at intermediate risk from a surgical perspective, even though logEuroSCORE I may not have captured actual risk in each individual patient. As this was a post-market registry, there were no explicit inclusion or exclusion criteria other than the presence of severe MR and eligibility for MitraClip therapy as judged by the investigators, taking into account the patients' clinical status and medical history. Therefore, the discrimination of patients who are truly inoperable as opposed to those who are at high risk for surgery was not possible in this study.

Regarding acute echocardiographic outcome with reduction of MR to grade $\leq 2+$ in 88.7% of all patients at discharge, results were favourable compared with the recent EVEREST II trial, where this rate was reported at 77% [10]. Comparability to other reports after MitraClip therapy is difficult, as most patient populations comprise patients with mixed or pure functional MR only [19, 20]. For the low-risk patient cohort, freedom from MR $\leq 2+$ was 89.6%, which is unsatisfactory from a surgical point of view, especially since this rate approaches near-perfect values for MVR at specialized centres [21] and since it is unequivocally known from both surgical [22] and interventional series [23] that residual MR adversely affects patient survival. Also, 30-day mortality was not negligible at 4.8% in this subgroup of patients, therefore surgical MVR remains the standard of care in patients at low to intermediate risk due to superior outcomes and proven long-term durability.

In the high-risk subgroup of patients in this report, 30-day mortality was 9.1%. Again, comparability to previous reports is hampered by different aetiologies. In the EVEREST II trial that comprised 74% of patients with DMR, 30-day mortality was 1% in the device group. However, patients were markedly younger and had a much lower prevalence of risk factors such as coronary artery disease, previous myocardial infarction, atrial fibrillation or diabetes [10]. Furthermore, logEuroSCORE I was not specified in EVEREST II. In the high-risk registry of the EVEREST II trial [13],

Table 4: Twelve-months site-reported safety outcomes

12-months site-reported safety outcomes	DMR patients (n = 117)	High-risk DMR patients (n = 33)	Low-risk DMR patients (n = 84)
Death	17.1% (20/117)	24.2% (8/33)	14.3% (12/84)
Stroke	0.9% (1/117)	0%	1.2% (1/84)
Myocardial infarction	0.9% (1/117)	3.0% (1/33)	0%
Renal failure	6.0% (7/117)	12.1% (4/33)	3.6% (3/84)
Need for resuscitation	0.9% (1/117)	3.0% (1/33)	0%
Cardiac tamponade	0.9% (1/117)	3.0% (1/33)	0%
Bleeding complications	3.4% (4/117)	6.1% (2/33)	2.4% (2/84)
Repeat MitraClip	3.4% (4/117)	3.0% (1/33)	3.6% (3/84)
Mitral valve surgery	7.7% (9/117)	3.0% (1/33)	9.5% (8/84)
Total adverse events	41.0% (48/117)	57.6% (19/33)	34.5% (29/84)

Adverse events (AEs) as reported by participating sites; No formal comparisons of the rates of site-reported AEs were performed between the high-risk and low-risk DMR groups. These events occurred at a low rate. The study was not powered to detect differences in these low rate events between high-risk and low-risk DMR patients.

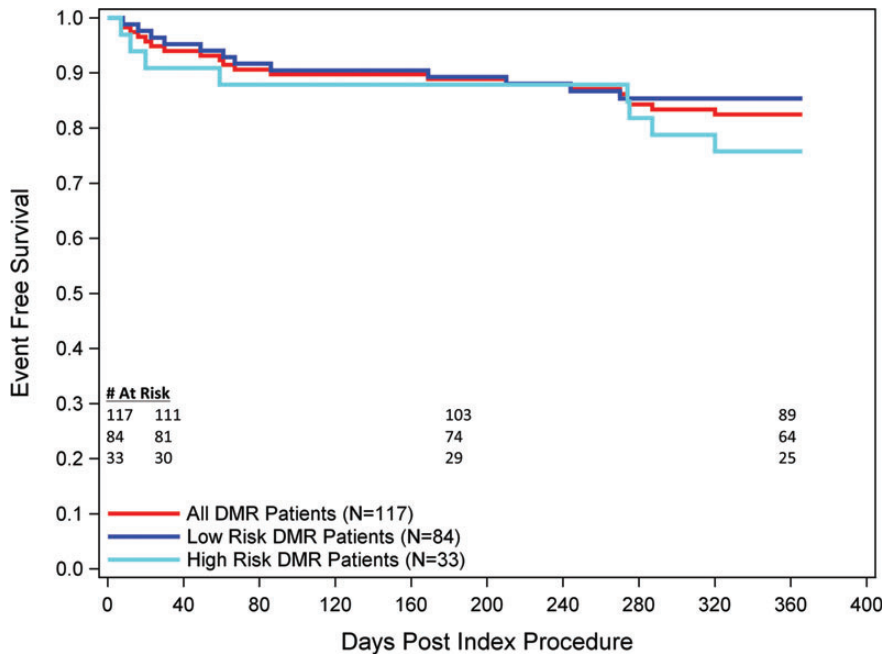


Figure 4: Kaplan-Meier survival estimates. Numbers of events for all/low-risk/high-risk patients at baseline, 30 days, 6 months, 12 months were 0/0/0, 7/4/3, 13/9/4, 20/12/8, respectively.

where 30-day mortality was 7.7%, a Society of Thoracic Surgeons (STS) score of $18.2 \pm 8.0\%$ suggests a risk profile comparable with the high-risk cohort of the present study. However, here, MR was degenerative in 41% of patients only. In reports on the real-world use of the MitraClip in high-risk patients, acute mortality rates range from 2.5 to 4.8% [11, 18, 24].

For want of comparable MitraClip series, results in the low-risk subgroup of the present report with 14.3% mortality at 12 months have to be held against current surgical series. Even though direct comparability is impossible due to differences in patient risk profiles and even though logEuroSCORE I in this patient subgroup may not reflect true risk, these results have to be viewed critically. However, logEuroSCORE I was not calibrated to assess risk in patients with valvular heart disease, and it seems likely that these were patients in whom true risk was not adequately captured by this scoring system. When selecting patients for a MitraClip

procedure who are (at least formally, as measured by logEuroSCORE I) low to intermediate risk, indication for treatment should be guided by inter-disciplinary assessment within a heart team consisting of cardiologists and cardiac surgeons as suggested by others [11] and as is recommended for high-risk patients. Regarding mortality up to 12 months of follow-up, results from the high-risk subgroup of this study seem acceptable at 24.2% compared with other MitraClip series ranging from 6 to 24.4%, depending on risk profiles of the respective study populations [11–14].

Even though echocardiographic results appear suboptimal from a surgical standpoint, there was significant clinical benefit in the overall patient population as well as in both separate subgroups regarding NYHA functional class, and improvement in 6MWT and Minnesota Living with Heart Failure questionnaires. This observation is well supported in the literature, with similar effects in

various types of clinical settings [10, 11, 19] and strongly supports the notion that MitraClip therapy is indicated in patients deemed inoperable or at high surgical risk to reduce symptoms and enhance quality of life. Furthermore, it is well known from the surgical literature that severity of MR has a graded impact on patient survival and that even reduction of MR from severe to moderate can be expected to yield a survival benefit [25]. Durability of MR reduction as well as clinical benefit warrant further monitoring of patients after MitraClip therapy during longer follow-up.

CONCLUSIONS

Primarily for DMR patients who are inoperable or at exceedingly high risk for surgical MVR, MitraClip therapy represents an attractive and less-invasive treatment option. The majority of patients thus treated benefit significantly regarding the severity of MR as well as clinically, regarding NYHA functional class and improvements in physical capacities and quality of life. Interventional treatment should be indicated following the discussion of patients in an inter-disciplinary conference of cardiologists and cardiac surgeons as suggested by current international guidelines.

Limitations

Patients were not randomly assigned to receive MitraClip therapy. Outcomes of surgical and medical treatment comparator groups have not been reported to date. The process of patient selection as well as determination of the aetiology of MR were not guided by a detailed study protocol with inclusion/exclusion criteria but was rather conducted following standard local clinical practice. Thus, the eligibility of patients for MitraClip therapy may have been judged differently among participating sites. Furthermore, there were no clinical events committee definitions for important parameters such as clinical end-points (e.g. procedural success) or major adverse events. Furthermore, on-site monitoring of clinical data was limited to annual visits during the conduct of the study.

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APPENDIX. CONFERENCE DISCUSSION

Dr H. Treede (Hamburg, Germany): Although we all know that the logistic EuroSCORE is probably not a good measure for mitral valve patients, still I was surprised about the fairly high mortality in this very low-risk patient group of 4.8% at 30 days and even increasing to 10.8% after six months. The question is whether the mortality in those patients dying in that specific patient group in the long run was related to the ineffective reduction of MR? So have these been the patients that did not profit from the MitraClip implantation?

Dr Maisano: This is a multicentre registry and the adjudication of events has been site-adjudicated. So, quite honestly, it is difficult today to really go back in all cases and review the picture that you are talking about. We have been very surprised at seeing such high mortality in this so-called low-risk population, but obviously we are facing something which is probably not predicted by the logistic EuroSCORE; there is some degree of uncertainty due to the logistic EuroSCORE.

And I have two things to support this point, because, as you know, we have been probably two of the most active implanters, and I think both of us have never done a MitraClip in patients at low risk for surgery. There are multiple situations in which you would not do MitraClip procedures, such as the presence of COPD or other conditions, which can be very much associated with a poor outcome.

The other important comment on the data that is supporting the problematic use of logistic EuroSCORE in this population is that for the first time in all our studies we have not seen any impact on baseline logistic EuroSCORE at six-month outcome, and this is the first cohort in which I have seen this kind of outcome. This means that, unfortunately, the logistic EuroSCORE should probably not be used to evaluate risk in mitral valve patients.

Dr Treede: The second question concerns the patients who did not profit from implant of a MitraClip and then underwent post-MitraClip surgery: can you comment on how the implantation of the clip influenced such a good strategy in these patients and if they were possibly replaced or repaired?

Dr Maisano: As you know, in most of these patients there were some failures and most of the failures have been replaced, and I think this is also mainly due to the high-risk population. As surgeons probably facing high-risk patients, we don't want to have the chance of another failure, so we go for a replacement. There have also been some successful post-MitraClip, second MitraClip procedures, and actually I think in this cohort there have been four of those, three of them successful. So there have been quite a number of patients with failures.

This is not a great outcome study. I would say that this is really demonstrating a learning curve. I strongly believe the learning curve in DMR is longer than in

FMR, and we are learning new techniques, new approaches to improve the outcomes. And obviously based on the data we have in this study, you should probably not suggest MitraClip for DMR. On the other hand, we all know as implanters that the outcomes are improving on a day-by-day basis because of more knowledge. So I really believe that starting from here we need to come up with a properly designed study for DMR.

Dr JJ. Thiis (Copenhagen, Denmark): When we don't want to operate on patients, we refer them to MitraClip because of the risk, but it seems to me that the risk with MitraClip is very high. Which patients do you really turn down for a MitraClip, if any?

Dr Maisano: Well, that is an interesting question, and I think this is coming out in most of the transcatheter valve procedures. Again, this is the first time of reporting this data, so there has not been enough time to evaluate and discuss outcomes in a critical way, but I think we are dealing here with the actual issue of ability. There might be too many futile procedures in this Registry: remember, this is a real-world registry, and most of the initial procedures have been done in very sick patients, because, at least in the beginning, this procedure has been considered a last resort to offer to patients who had no other alternatives. This has also been the experience in TAVI. And what we see here is the first Registry in the mitral space, which is probably telling us that we need to be more selective.

Now, to address the question of who I would turn down. Today we should turn down patients who have no anatomical chances of being repaired and, quite honestly, in the Registry many of those patients had been treated just in an attempt to identify the limits of this technology. Number two, I will not indicate the procedure in patients who have no one-year survival, predicted by an underlying disease which is associated with mitral regurgitation. So we really need to learn who are the patients in whom we should refrain from doing any procedure.

Dr P. Punjabi (London, UK): I congratulate you on trying to extend the indications to degenerative MR. One of the criticisms of functional MR has been the absence of an annuloplasty ring, and we have been through quite a lot of that. Do you think, especially in the degenerative group, even though a good repair or reduction in the MR right at the time, but at six-month follow-up the absence of an annuloplasty ring in this particular group may contribute to an unusual mortality or even a recurrence rate?

Dr Maisano: Obviously, the additional annuloplasty is expected to improve outcomes of single device therapy in transcatheter valve procedures. We can only elaborate on this in a theoretical fashion. But quite honestly, the numbers are too small to get any predictive factor based on haemodynamic performance. So I am not really convinced that these patients died because of residual MR. I think there were actually other reasons, maybe crossovers and other reasons, baseline conditions, that had more influence on the one-year outcome. Again, this is an initial study and you need to understand that we are trying to determine whether there is a role in DMR for the MitraClip, and never forget that DMR has been the first indication for this procedure. We need to collect data and try to improve our knowledge.