Extended long-term follow-up of consecutive patients after percutaneous mitral valve repair

Percutaneous mitral valve repair with the MitraClip™ system

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Summary

OBJECTIVES: We performed extended follow-up for longer than 1 year in consecutive patients undergoing percutaneous mitral valve repair (PMVR) with the MitraClip™ system.

BACKGROUND: PMVR with the MitraClip™ system has become a valid alternative to surgery for patients with severe mitral regurgitation, anatomical suitability and high surgical risk, but data on long-term outcomes more than 1 year after the procedure are scarce.

METHODS: We included 148 consecutive patients with symptomatic moderate–severe (3+) or severe (4+) mitral regurgitation, who underwent PMVR at the University Heart Centre Zurich between March 2009 and February 2014. Clinical endpoints on follow-up included all-cause death, mitral valve surgery/reoperation, hospitalisation for congestive heart failure, and heart transplantation.

RESULTS: Mitral regurgitation aetiology was functional in 57%, degenerative in 37%, and mixed in 6%. EuroSCORE I was 26 ± 14 and STS risk score for mortality was 8 ± 11%. Median follow-up was 1.9 years (interquartile range 0.8–2.7). Acute procedural success (defined as successful clip implantation with residual mitral regurgitation grade ≤2+) was achieved in 94% of patients. At 6 months' follow-up, 67% of patients had a persistent good result with mitral regurgitation grade 1–2+. Event rates of the combined endpoint were 31% at 1 year and 53% at 2 years, and mortality was 18% at 1 year and 32% at 2 years. Baseline NYHA class and mitral regurgitation severity at discharge were independent predictors of the combined endpoint.

CONCLUSIONS: PMVR with the MitraClip™ system allows durable reduction of mitral regurgitation severity and improvement in patients' symptoms and functional status. Event rates, however, remain remarkably high despite successful treatment, reflecting the advanced age and high comorbidity status of our population.

Key words: interventional cardiology; valvular disease; mitral valve regurgitation; MitraClip



Introduction

Mitral regurgitation is the most common cardiac valve pathology. The prevalence of moderate to severe mitral regurgitation in a general population aged 75 years and older is approximately 10% [1, 2] and its presence generally contributes to an impaired prognosis for the patients [3–8]. Surgical mitral valve repair (particularly in degenerative mitral regurgitation) is widely established based on excellent long-term outcomes and effective reduction of mitral regurgitation [9]. In functional mitral regurgitation, isolated mitral valve surgery is less well established owing to poorer surgical results and the lack of evidence for a benefit of surgery over medical therapy [10]. This is related to the fact that in functional mitral regurgitation, the valvular incompetence may appear secondary to changes in left ventricular size and geometry, and thereby contribute to a variable extent to the underlying pathophysiology of congestive heart failure. Moreover, many patients with severe mitral regurgitation are denied surgery as a result of their high surgical risk because of age, poor left ventricular function, or other comorbidities [11].

Percutaneous mitral valve repair (PMVR) using the MitraClip™ system (Abbott Vascular, Abbott Park, Illinois, USA) has become a valid alternative to surgery for mitral regurgitation patients with anatomical suitability who are at high surgical risk. Conceptually, this technique is based on the surgical method developed by Alfieri, which consists of edge-to-edge approximation of the middle scallops of the mitral valve leaflets by means of percutaneous delivery of a mitral clip, thereby creating a double-orifice mitral valve [12]. Safety, feasibility, high procedural success rates and short- to mid-term durability of PMVR have been proven in several clinical registries [13–18] and one randomised clinical trial [14]. However, to date most registries investigating outcome after PMVR are limited to only 1 year of follow-up [19–23]. Although the EVEREST II trial had a 4-year follow-up, the registry was limited to surgical candidates only [24], who differ significantly in their baseline risk from current MitraClip™ candidates in Europe and the United States.

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Therefore, the purpose of the current study was to perform extended follow-up for longer than 1 year in consecutive high-risk patients treated for mitral regurgitation with PMVR with the MitraClip™ system at the University Heart Centre Zurich, Switzerland.

Methods

Patients

We consecutively included in the analysis 148 patients undergoing PMVR using the MitraClip™ System at the University Heart Centre Zurich between March 2009 and February 2014. All patients suffered from symptomatic moderate-to-severe (3+) or severe (4+) functional or degenerative mitral regurgitation. Indications were discussed by an interdisciplinary heart team consisting of interventional cardiologists, echocardiographers, cardiac anaesthetists and cardiac surgeons, and were assigned to MitraClip™ according to local institutional practice in consideration of the European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines on the management of valvular heart disease [9]. The study protocol was approved by the local institutional review board (KEK ZH NR 2010-0466), and all patients gave written informed consent to participating except in the event of death. In this case written informed consent was waived by the local institutional review board owing to the retrospective clinical nature of the study (KEK-ZH NR 2015-0251).

MitraClip™ procedure

As previously described, percutaneous MitraClip™ implantation was performed in a hybrid catheter laboratory under general anaesthesia with transoesophageal and fluoroscopic guidance [14]. Following trans-septal puncture, the MitraClip™ (a polyester-covered cobalt-chromium clip) was advanced through a 24-French catheter-based delivery system into the left atrium. The clip was opened, directed towards the mitral valve and positioned above the regurgitant jet in the left ventricle. Thereafter, the free edges of both mitral leaflets were grasped and closed to coapt the mitral leaflets across the regurgitant orifice. The reduction in severity of mitral regurgitation was assessed after each MitraClip™ implantation on the basis of visual assessment of colour Doppler echocardiography of the regurgitant jet and haemodynamic assessment from pulmonary capillary wedge pressure (PCWP). A mean transmitral gradient >5 mm Hg was considered a contraindication for further clip implantation. If the transmitral gradient was low, the need for further clip implantation was judged from the severity of mitral regurgitation on echocardiography and haemodynamic assessment, the overall reduction of mitral regurgitation, and the anatomical location and feasibility. Acute procedural success was defined as successful implantation of one or more clips with reduction of the mitral regurgitation to less than 2+.

Follow-up and endpoints

Clinical and echocardiographic assessments were recommended at baseline, discharge, at 1, 3, and 6 months, and on a yearly basis after enrolment. Echocardiographic follow-up was performed either at the University Heart Centre Zurich or at referral hospitals and general cardiologists. Severity of mitral regurgitation was graded according to recommendations of the American Society of Echocardiography [25]. Left ventricular ejection fraction (LVEF) and left ventricular volumes were measured by means of the biplane Simpson's method [26]. In the case of an event, hospital charts were reviewed, or the cardiologist or primary care physician was contacted.

Clinical endpoints comprised of all-cause mortality, mitral valve surgery due to failure of PMVR or reoperation, hospitalisation for congestive heart failure (CHF), heart transplantation and the composite of all four endpoints.

Statistical analysis

Data are presented as mean (standard deviation) or frequency as appropriate. Time-to-event after the index procedure was estimated with the Kaplan-Meier method and log-rank tests were applied to compare event rates for the combined endpoint between groups (mitral regurgitation grade 1–2+ vs 3–4+; degenerative vs functional mitral regurgitation). By use of multivariate Cox regression analysis, the effect of New York Heart Association (NYHA) functional class at baseline, mitral regurgitation severity at discharge, age, LVEF at baseline, functional mitral regurgitation, left ventricular end-diastolic volume (LVEDV) at baseline, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) on the combined outcome and on mortality was assessed. A two-sided p-value ≤0.05 was considered statistically significant. Statistical analyses were performed with IBM SPSS statistics version 22.

Results

Patient characteristics

Between March 2009 and February 2014, a total of 148 patients were included and received PMVR with the MitraClip™ System at the University Heart Centre Zurich. Sixty-one percent of the patients were male and

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Table 1: Baseline characteristics.

	Study population (n = 148)
Age (yrs)	75 ± 11
Gender (male), n (%)	90 (61)
Body mass index (kg/m^2)	25 ± 5
Hypertension, n (%)	102 (69)
Hyperlipidaemia, n (%)	63 (43)
Diabetes mellitus, n (%)	27 (18)
Coronary artery disease, n (%)	67 (45)
Previous myocardial infarction	37 (25)
Previous percutaneous cornary intervention	44 (30)
Previous coronary artery bypass graft	23 (16)
Previous valve surgery, n (%)	15 (10)
Previous vascular/aortic surgery, n (%)	5 (3)
Atrial fibrillation, n (%)	96 (65)
Previous pacemaker or implantable cardioverter-defibrillator implantation, n (%)	37 (25)
Cardiac resynchronisation therapy	22 (15)
Previous cerebrovascular infarction, n (%)	14 (9)
Chronic obstructive pulmonary disease, n (%)	22 (15)
Renal failure, n (%)	85 (58)
Cancer of any type, n (%)	18 (12)
NYHA functional Class, n (%)	
I/II	27 (18)
III	103 (70)
IV	18 (12)
STS score for mortality	8 ± 11
EuroSCORE I	26 ± 14
Baseline LVEF, %	45 ± 18
LVEDV, ml	174 ± 104
Mitral regurgitation severity, n (%)	
Moderate to severe	31 (21)
Severe	117 (79)
Mitral regurgitation aetiology, n (%)	
Functional	84 (57)
Degenerative	54 (36)
Mixed	10 (7)

Values are mean ± SD or n (%).
LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; STS score = The Society of Thoracic Surgeons risk score

patient age was 75 ± 11 years. All 148 patients had mitral regurgitation grade 3+ or 4+ and the majority of patients were symptomatic with NYHA functional class III or IV. Fifty-seven percent of patients were determined to have functional mitral regurgitation, in 37% of patients the aetiology was degenerative, and 6% of patients had mixed aetiology. LVEF was 45 ± 18, in 40% of patients LVEF was <35. Mean surgical risk as assessed with EuroSCORE I was 26 ± 14% and the STS score for mortality was 8 ± 11. Many patients presented multiple comorbidities, which are listed together with the remainder of baseline characteristics in table 1.

Procedural information

Acute procedural success was achieved in 139 (94%) patients. In 36 patients (24%) a single clip was implanted, in 88 patients (60%) two clips and in 21 patients (14%) three clips were required to adequately reduce mitral regurgitation. In the remaining three patients (2%), four clips were implanted. However, in two of these three patients mitral regurgitation grade 4+ persisted after PMVR and they were referred for mitral valve surgery. The severity grade was reduced to 1+ in 66% of patients and to 2+ in 28% of patients. There was no immediate conversion to surgery and no intraprocedural death occurred.

Clinical and echocardiographic outcome

At 6 months, functional status was available for 131 patients (89%); echocardiographic data was available for 92 patients (62%) at 6 months and for 28 patients (19%) at 12 months of follow-up. At 6 months after PMVR, 75% of patients were in NYHA functional class I or II ($p < 0.001$ compared with baseline), whereas 25% of patients remained in NYHA functional class III or IV (fig. 1). At 6 months' follow-up, 67% of patients had a persistent good result with mitral regurgitation grade 1–2+. (fig. 2).

Clinical endpoints and predictors of outcome

Median clinical follow-up of the study population was 1.9 years (interquartile range 0.8–2.7). Overall, the composite endpoint of all-cause mortality, mitral valve surgery due to PMVR failure, hospitalisation for congestive heart failure and heart transplantation occurred in 84 (57%) patients. Fifty-two (35%) patients died (average annual mortality 15%/year) and 45 (30%) patients suffered congestive heart failure events during follow-up. Ten (7%) patients had to be referred for mitral valve surgery because of failure of PMVR. Heart transplantation was performed in four (3%) patients during follow-up. Table 2 summarises the endpoints and their respective cumulative 1- and 2-year event rates, and figure 3 shows Kaplan-Meier estimates for event-free survival. Comparison of PMVR procedures performed between 2009–2011 and 2012–2014 did not reveal a significant difference in the occurrence of the combined endpoint (fig. 4). However, mitral regurgitation grade at discharge was significantly higher in

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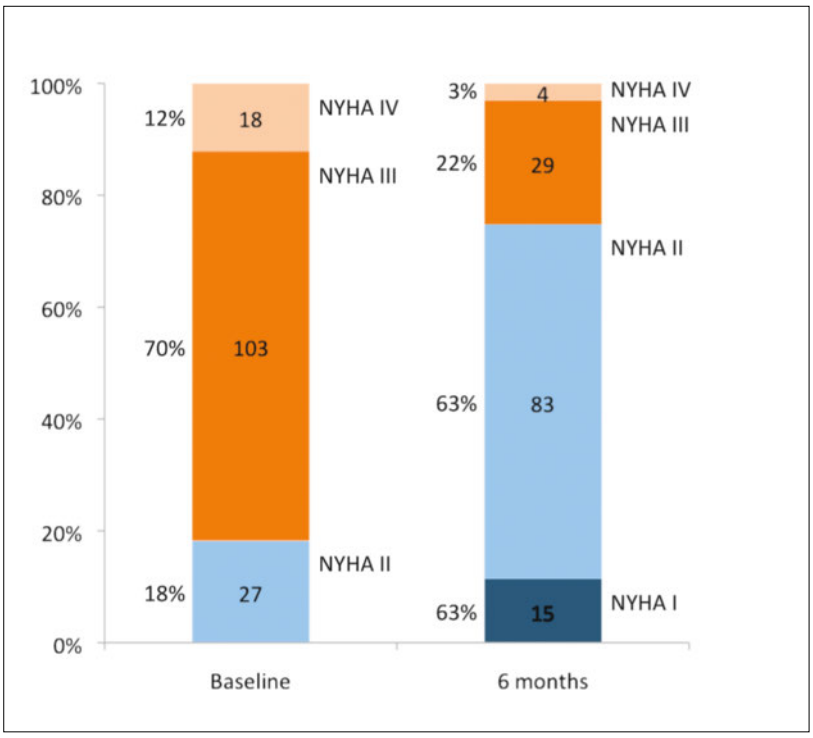


Figure 1: NYHA functional class at baseline and follow-up. Values are %.

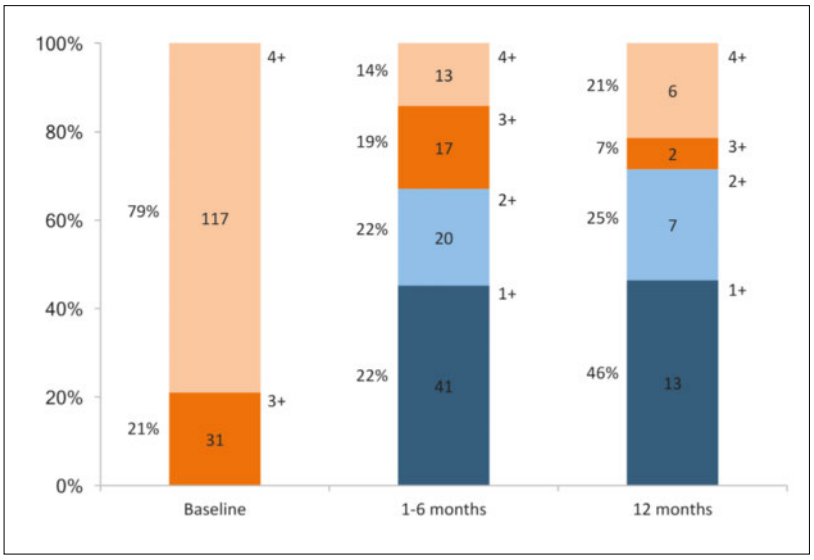


Figure 2: Mitral regurgitation at baseline, 1–6 and 12 months. Values are %.

early patients (p = 0.045); in contrast, acute procedural success was not different between the two groups (p = 0.45). On multivariate regression analysis, baseline NYHA functional class (hazard ratio [HR] 2.12, 95% confidence interval [CI] 1.03–1.84; p = 0.004) and mitral regurgitation severity at discharge (HR 1.38, 95% CI 1.38–3.50; p = 0.03) emerged as independent predictors of the combined endpoint (table 3, fig. 5). Interestingly, age, LVEF at baseline, aetiology of mitral regurgitation (functional vs degenerative) (fig. 5), and LVEDV at baseline were not predictors of combined clinical outcome.

Discussion

Most registries investigating outcome after PMVR are limited to only 1 year of follow-up [19–23]. Although the EVEREST II trial had a 4-year follow-up, the population studied differs significantly from European cohorts [24]. This latter trial enrolled predominantly younger patients with degenerative mitral regurgitation, preserved left ventricular function and low surgical risk, and therefore a large group of patients who might potentially benefit from the procedure were excluded. With the first patient included in March 2009 (5 years' follow-up) and a median follow-up of 1.9 years, the aim of the present study was to extend the period of observation beyond 1 year and record events occurring during longer-term follow-up.

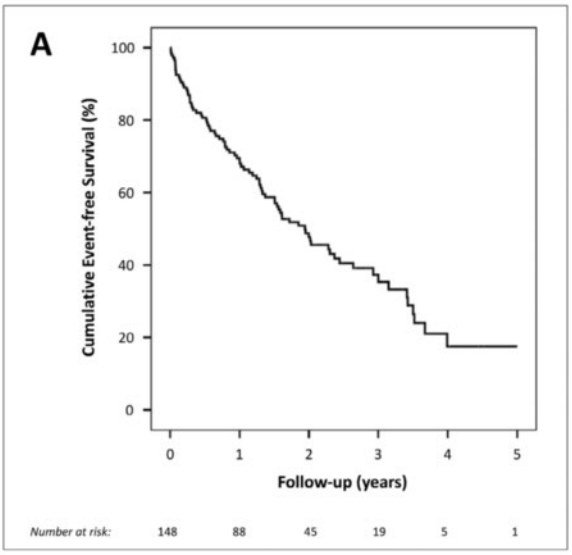
Compared with the EVEREST II population, patients enrolled in our registry were considerably older, had poorer ejection fraction, more comorbidities, a higher proportion of functional mitral regurgitation, and were at high surgical risk, and were therefore more alike to patients entered into European MitraClip registries. In line with these registries, we demonstrated a high acute procedural success rate of 94% with a sustainable improvement in mitral regurgitation at 6 months (67% of patients had severity grade 1–2+ at 6-month follow-up). Moreover, our patients experienced significant improvement in heart failure symptoms with a significant reduction of NYHA functional class at 6 months' follow-up in 75% of patients. However, despite efficient mitral regurgitation reduction and symptomatic improvement, event rates remain remarkably high (fig. 3), reflecting the advanced age and high comorbidity status of PMVR populations. The 1-year mortality rate of 18% in our cohort is comparable to the mortality reported in ACCESS-Europe (17%) [19]

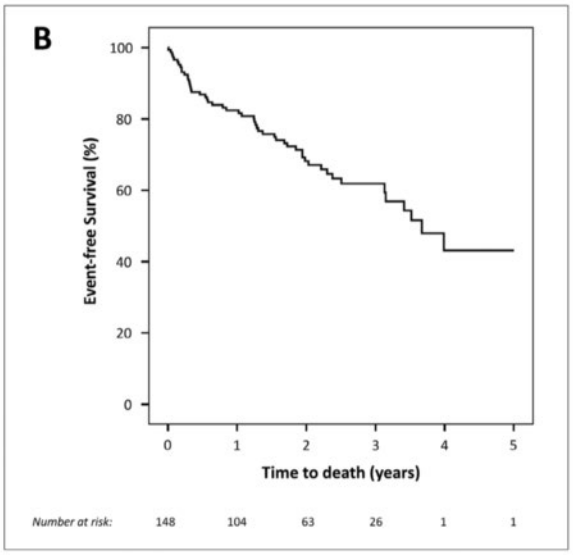
Table 2: Clinical endpoints.

	1 year	Cumulative 2 year	Overall
Combined endpoint	43 (31)	68 (53)	84 (57)
All-cause mortality	25 (18)	41 (32)	52 (35)
Hospitalisations for CHF	19 (15)	36 (33)	45 (30)
MR surgery	7 (5)	8 (6)	10 (7)
Heart transplantation	2 (2)	4 (4)	4 (4)

Values are n (%).
CHF = congestive heart failure; MR = Mitral regurgitation.

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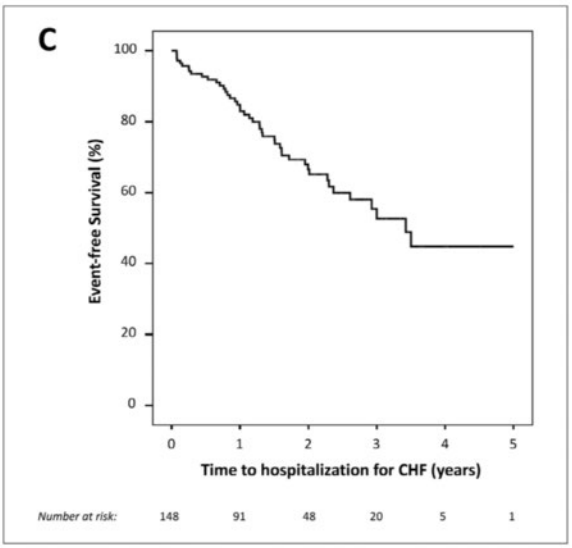


Figure 3: Kaplan-Meier curves: (A) freedom from combined endpoint; (B) overall survival; (C) freedom from hospitalisations due to congestive heart failure (CHF).

and in TRAMI (20%) [21]. Similarly, the rate of hospitalisations for congestive heart failure in our study (15%) was comparable to the European Sentinel Registry (23%) [20], the TRAMI registry [14%) [21], and the EVEREST II high-risk-patients (16%) [23]. Finally, surgery for mitral valve dysfunction 1 year after PMVR was performed only in 5% of patients (20% in EVEREST II, 6% in ACCESS-EU) [19, 24]. Interestingly, there was no significant difference between PMVR procedures performed before 2012 and procedures performed thereafter in terms of the combined clinical outcome. Although a learning curve associated with better procedural outcome can be expected, the overall high event rate in our aged and comorbid real-world population may mask the effect of a learning curve on clinical outcome.

In view of the high event rates observed in our patients, the central question as to whether PMVR provides any prognostic benefit over optimal medical therapy alone in this aged population with predominantly functional mitral regurgitation remains. A conclusive answer awaits publication of larger randomised controlled trials comparing both strategies, some indirect evidence is found in observational studies: Glower and colleagues reported a 48% lower incidence of hospitalisations for congestive heart failure in the year after PMVR compared with the year prior to the intervention [27]. Whitlow and colleagues compared outcomes in the EVEREST II high-risk registry with the outcomes of a medically treated comparator group with severe mitral regurgitation, and found a 20% reduction in all-cause mortality with PMVR [23]. Our

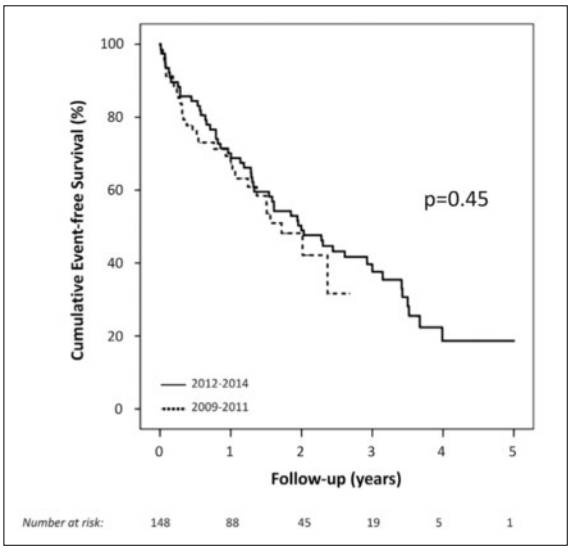


Figure 4: Event-free survival from combined endpoint according to procedure date.

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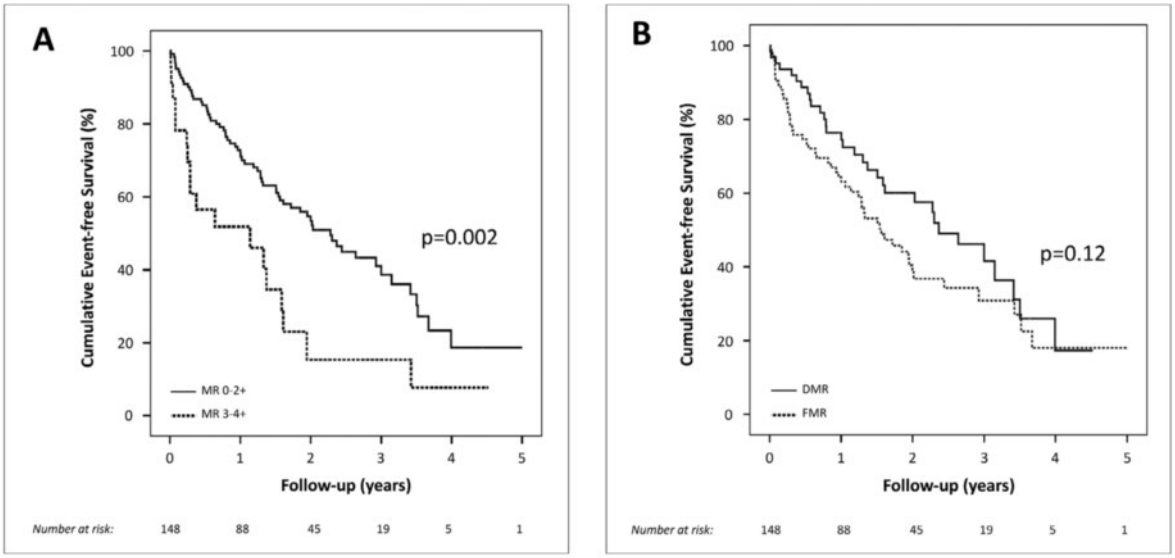


Figure 5: Event-free survival from combined endpont according to mitral regurgitation grade at discharge (A) and aetiology (B). DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation.

Table 3: Multivariate logistic regression analysis of the combined endpoint.

	Hazard ratio	95% CI	p-value
Age (y)	1.02	0.99–1.04	0.21
NYHA class at baseline	2.12	1.28–3.50	0.004
LVEF at baseline (%)	0.99	0.97–1.02	0.51
LVEDV (ml)	1.00	1.00–1.01	0.085
MR at discharge	1.38	1.03–1.84	0.03
Functional MR	0.69	0.34–1.40	0.31
NT-proBNP (ng/l)	1.00	1.00–1.00	0.28

CI = confidence interval; LVEDV = left ventricular enddiastolic volume; LVEF = left ventricular ejection fraction; MR = Mitral regurgitation; NT-Pro BNP = N-terminal Pro-B-type natriuretic peptide; NYHA = New York Heart Association

study precludes any direct comparison with optimal medical therapy of severe mitral regurgitation. However, our 2-year survival rate of approximately 70% compares favourably with reported historical outcomes in medically treated patients with mitral regurgitation in the range of 55–60% [4, 6]. Nevertheless, high event rates in our real-life cohort further emphasise the importance of preprocedural assessment and thorough discussion of patients' individual risk and long-term prognosis to improve future patient selection for PMVR.

In our patients, baseline NYHA class and severity of mitral regurgitation at discharge were independent predictors of clinical outcome in line with previous publications [21, 28], with an increase in the rates of death, congestive heart failure hospitalisations, mitral valve surgery and heart transplantation. The latter emphasises the need to obtain a near-perfect procedural result with additional clips if needed to avoid residual significant mitral regurgitation. Interestingly, neither age, ejection fraction, nor aetiology emerged as an independent predictor of outcome. The latter may appear somewhat surprising, since functional mitral regurgitation is a condition that is generally associated with dilated and/or remodelled left ventricles and poorer ejection fraction. On the other hand, patients with functional mitral regurgitation undergoing PMVR are considerably younger than patients with a degenerative aetiology, which may counteract the effect of function mitral regurgitation on survival statistics. Nonetheless, our results are in line with the Pilot European Sentinel Study, which reported similar all-cause mortality after PMVR in both degenerative and functional types [20]. It is likely that patients with functional mitral regurgitation may suffer a higher incidence of congestive heart failure hospitalisations after PMVR compared with degenerative mitral regurgitation patients. However, our study was too small for a meaningful comparison of this endpoint between the two aetiologies.

Study limitations

We acknowledge the following limitations of our study. The sample size (n = 148) is limited. Furthermore, despite our attempt to extend the follow-up as long as possible (the first patient was enrolled in 2009), the overall follow-up is limited with only a median of 1.9 years. This limited follow-up is not due to patients lost

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to follow-up but simply due to the high mortality of enrolled patients, which prevents longer periods of observation. Furthermore, the echocardiographic data were not assessed by a core laboratory and many echocardiographic examinations were performed by referral centres and general cardiologists. Therefore, echocardiographic data are not standardised and follow-up data are incomplete. Clinical events were not adjudicated by an independent committee and were site-reported. Furthermore, more objective data on functional capacity (e.g. VO_2max, 6-minute walking distance) are lacking. Finally, and as mentioned before, there is no prospective comparison with a medical arm, which would be needed to investigate the efficacy of the MitraClip™ procedure compared with established conservative treatment strategies.

Conclusions

In conclusion, our data confirm that PMVR with the MitraClip™ system allows durable reduction of mitral regurgitation severity and improvement in patients' symptoms and functional status. Although comparable to other real world registries, event rates in our cohort are remarkably high despite successful PMVR therapy and reflect the high comorbidity status and advanced age of the population. NYHA functional status and residual mitral regurgitation after PMVR are the most important independent predictors of outcome after PMVR.

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Disclosure statement
Prof. Maisano has received consulting fees from Abbott Vascular, Medtronic, ValtechCardio, and St. Jude Medical; is a founder of 4Tech; and has received royalties from Edwards Lifesciences. No other potential conflict of interest relevant to this article was reported.

Author contributions
Dres Gaemperli and Attinger-Toller have equally contributed to this manuscript (shared first coauthorship).
Prof. Corti's current employer is Heart Clinic Hirslanden, Zurich, Switzerland

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The full list of references is included in the online version of the article at www.cardiovascmed.ch



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