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ORIGINAL ARTICLE

One-year results following PASCAL-based or MitraClip-based mitral valve transcatheter edge-to-edge repair

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Abstract

Aims Mitral valve transcatheter edge-to-edge repair (TEER) has been established as a suitable alternative to mitral valve surgery in patients with severe mitral regurgitation (MR) and high surgical risk. The PASCAL system represents a novel device, potentially augmenting the toolkit for TEER. The aim of this study was to assess and compare short and 1 year safety and efficacy of the PASCAL and MitraClip systems for TEER.

Methods and results Procedural, short, and 1 year outcomes of a 1:2 propensity-matched cohort including 41 PASCAL and 82 MitraClip cases were investigated. Matching was based on clinical, laboratory, echocardiographic, and functional characteristics. The primary endpoints assessed were procedural success [as defined by the Mitral Valve Academy Research Consortium (MVARC)], residual MR, functional class, and a composite endpoint comprising death, heart failure hospitalization, and mitral valve re-intervention. We found for the PASCAL and the matched MitraClip cohort no significant differences in MVARC defined technical (90.2% vs. 95.1%, $P = 0.44$), device (90.2% vs. 89.0%, $P = 1.0$), or procedural (87.8% vs. 80.5%, $P = 0.45$) success rates. Accordingly, the overall MR reduction and improvement in New York Heart Association (NYHA) class were comparable (1 year follow-up: MR ≤ 2 95% vs. 93.6%, $P = 1.0$; NYHA ≤ 2 57.1% vs. 66.7%, $P = 0.59$). The composite outcome revealed no statistically significant difference between both devices (1 year follow-up: 31.7% vs. 37.8%, $P = 0.55$). Interestingly, we found at both short and 1 year follow-up a significantly higher rate of patients with none or trace MR in the PASCAL-treated cohort (short follow-up: 17.9% vs. 0%, $P = 0.0081$; 1 year follow-up: 25% vs. 0%, $P = 0.0016$). Conversely, the rate of aborted device implantations due to an elevated transmitral gradient was higher in PASCAL interventions (9.8% vs. 1.2%, $P = 0.04$).

Conclusions Transcatheter edge-to-edge repair using the PASCAL or MitraClip device results in favourable and comparable outcomes regarding safety, efficacy, and clinical improvement after 1 year.

Keywords PASCAL; MitraClip; Mitral regurgitation; Transcatheter mitral valve edge-to-edge repair; TEER

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Introduction

Untreated severe mitral regurgitation (MR) results in cardiac remodelling involving left ventricular and left atrial enlargement, pulmonary hypertension, and heart failure (HF) due to chronic volume overload.[1] This contributes to significant morbidity and results in increased mortality, irrespective of the underlying MR pathology.[2–4] Considering the ageing population, prevalence of severe MR in patients with multiple co-morbidities and high or prohibitive surgical risk is rapidly increasing.[5,6] Mitral valve transcatheter edge-to-edge repair (TEER) for treatment of MR has been established as a suitable alternative to mitral valve (MV) surgery for those patients.[7] In this context, the MitraClip device (Abbott Vascular Devices, Santa Clara, CA, USA) is the most frequently applied technique with more than 100 000 patients treated worldwide.[8] Just

recently, guideline recommendations for TEER have been upgraded to Class IIa for degenerative as well as functional MR.[9,10]

In February 2019, the PASCAL TEER system (Edwards Lifesciences, Irvine, CA, USA) received CE approval for treatment of severe functional and degenerative MR, respectively. This system also employs an edge-to-edge approach but differs in device construction, steering and grasping function.[11–13] To date, only limited information regarding the use of this novel TEER device has been reported and especially midterm and long-term real-world data are scarce.[11–18] Thus, in the present study, we investigated PASCAL therapy in comparison with MitraClip therapy in a propensity-matched analysis regarding feasibility, safety, and efficacy.

Methods

Patient population

All patients undergoing primary TEER with third-generation MitraClip (NTR/XTR) from March 2018 to March 2020 as well as the first patients implanted with a PASCAL device until March 2020 were analysed in this retrospective study. Within this time frame, a total of 145 patients underwent TEER with the MitraClip system and 41 patients with the PASCAL mitral repair system in our centre. Indication for leaflet repair was performed according to the recommendation of the institutional interdisciplinary heart team. TEER was recommended in patients deemed at high risk for surgery. The choice of device was at the discretion of the operator. All patients were informed about specific risks and alternatives of TEER and gave informed written consent to the procedure. The study was performed in accordance with the local ethics committee (S-299/2015) and conducted in conformity with the *Declaration of Helsinki* principles.

MitraClip and PASCAL: device properties and device implantation

Both the MitraClip and PASCAL systems are based on an edge-to-edge approach for leaflet repair, and the implantation procedures have been described in detail previously.[8,11] All interventions were performed under general anaesthesia with transesophageal echo and fluoroscopic guiding. The femoral vein puncture site was routinely closed using the Perclose ProGlide System (Abbott Vascular Devices). Upon completion of the intervention, patients were extubated and transferred to our intermediate care unit for a post-interventional observation period of at least 6 h. All patients received anticoagulation for a minimum of 4 weeks after intervention, as described previously.[19]

Echocardiographic assessment

All patients eligible for TEER received baseline echocardiographic and haemodynamic evaluation.[20] The assessment followed an integrative approach according to current recommendations. MR was graded in none or trace, mild (1), moderate (2), and severe (3).[20,21] MR aetiology was primarily classified in functional, degenerative, and mixed. Patients with mixed aetiology were further evaluated for leading aetiology and classified accordingly.

Study endpoints

The procedural endpoints were defined according to the Mitral Valve Academy Research Consortium.[22] However, device success and procedural success were measured at time of discharge. The composite endpoint combined death, HF hospitalization, and MV re-intervention. Clinical and echocardiographic endpoints were New York Heart Association (NYHA) class at follow-up and residual MR grade at discharge and follow-up.

Follow-up

Follow-up appointments were frequently performed by the referring specialist in private practice. We therefore requested follow-up data from all patients not undergoing in-house follow-up. The follow-up appointments were divided into two time frames: a short follow-up between 30 days and 4 months and a long follow-up between 6 and 18 months after device implantation.

Statistical analysis and propensity score matching

Statistical analyses were performed using RStudio software Version 4.0.3 (RStudio, PBC, Boston, MA, USA).[23,24] Patients receiving a PASCAL device were matched 1:2 with patients receiving a MitraClip using the MatchIt package.[25] Matching was based on patient characteristics gathered at baseline comprising age, gender, NYHA class, left ventricular ejection fraction (LVEF), MR aetiology, flail width, flail gap, posterior leaflet length, coaptation length and depth, MV mean pressure gradient (MPG), vena contracta, medical history (diabetes, hypertension, and coronary artery disease), and laboratory findings [high-sensitive cardiac troponin T (hsTnT), N-terminal pro-BNP, and creatinine]. Six missing values were imputed with the help of an expectation–maximization with bootstrapping algorithm using the Amelia II package.[26] Propensity score-based matching was performed using the *k*-nearest neighbour algorithm.

Univariate and multivariate logistic regression models were calculated with the MASS package.[27] Multivariate regression models were evaluated using the Hosmer and Lemeshow goodness-of-fit test. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Two-sided *P*-value of <0.05 was defined for statistical significance. Logistic regression results were reported with OR and a 95% CI. Cox hazard model calculation, endpoint analysis, log-rank tests, and Kaplan–Meier plots were performed using the survminer package.[28] Unless stated otherwise, non-normal distributed values are reported as median ± inter-quartile range. Non-parametric values were compared using Wilcoxon rank-sum tests. Count data reported in the patient characteristics table were compared using Fisher's exact test. Unadjusted *P*-values were reported in the patient characteristics table. Adjusted *P*-levels were calculated using Holm–Bonferroni as this robust method does not assume independence. Plots were created using ggplot2 and ggpubr.[29,30]

Results

Baseline patient characteristics

The median age was 77.5 (29–95) years in the MitraClip group and 74.4 (31–90) years in the PASCAL group; 55% and 59% of the patients were male. All patients had a baseline MR grade of 3. The leading MR aetiology was functional in 77 (62.6%) patients and degenerative in 46 (37.4%) patients. Most patients were in NYHA Functional Class III or IV (87.8% in both groups). The patient population had a high prevalence of co-morbidities, including severely reduced LVEF, severe tricuspid regurgitation, elevated systolic pulmonary pressure, severe renal failure, and chronic lung disease, resulting in a high EuroSCORE II in both groups (median of 6.55% for MitraClip and 5.1% for PASCAL, *P* = ns). A significant fraction of 9% of all included patients was acute in cardiogenic shock or respiratory failure prior to TEER. Baseline characteristics differed only in two clinical aspects with significantly more patients presenting with previous cardiac surgery in the MitraClip group and significantly more patients suffering from malignancies in the PASCAL group. In addition, regarding echocardiographic parameters, the PASCAL group had a slightly larger MV area and mitral annulus AP diameter. Baseline characteristics are described in *Table 1*.

Procedural outcomes

No significant difference in the number of devices implanted per patient was evident, with a vast majority of patients being treated with one device [75.6% of the patients in the MitraClip group (62/82) and 78.1% in the PASCAL group (32/41)]. Two devices were implanted in 17.1% (14/82) of the MitraClip patients and 9.8% (4/41) of the PASCAL patients, and three devices were implanted only in 3.7% (3/82) of the patients in the MitraClip group and 2.4% (1/41) of the patients in the PASCAL group. The procedural and in-hospital outcomes are summarized in *Table 2*.

Technical success was achieved in 95.1% (78/82) of the MitraClip patients and 90.2% (37/41) of the PASCAL patients. In the MitraClip group, three implantations were aborted without device implantation: one due to failure to grasp, one due to an elevated MPG after device closure, and one due to a cardiac anatomy impeding safe transeptal puncture. One procedural death occurred during a bridge-to-transplant rescue procedure in an advanced HF patient not suitable for left ventricular assist device (LVAD) (EuroSCORE II 34.9%). In the PASCAL group, four implantations were aborted without device implantation (9.8%). This was due to an elevated MPG after device closure in three patients, including a bailout procedure in a non-operable case. The fourth aborted procedure was due to a remaining severe MR with concurrent MPG of 5 mmHg after leaflet grasping.

Statistically, there was no significant difference in technical success between both systems (*P* = 0.4388). However, the need to abort the implantation due to elevated MPG was significantly more frequent in the PASCAL group (*P* = 0.0419).

In one PASCAL case, periinterventional haemodynamic instability with concurrent ST-segment elevations in inferior leads occurred, suggestive for air embolization. Immediate coronary angiography excluded coronary occlusion or stenosis, and the patient stabilized within a few minutes. No sequelae for the patient resulted from this.

Device success at the time of hospital discharge was achieved in 89.0% (73/82) of the MitraClip intention-to-treat group and 90.2% (37/41) of the PASCAL intention-to-treat group. The MitraClip device failure group (9/82) comprises four patients with technical failure, two patients in whom MPG was $\geq$5 mmHg at hospital discharge, and three patients wherein MitraClip failed to reduce MR by at least one grade, including a patient with partial leaflet detachment. In the PASCAL group, device failure (4/41) was due to technical failure in the four patients mentioned earlier. There was no significant difference between MitraClip and PASCAL for device success at hospital discharge (*P* = 1).

Univariate and multivariate logistic regression identified baseline MPG as an independent predictor for technical failure (*P* = 0.016) and device failure (*P* = 0.013). The TEER system, the leading MR aetiology, and the coaptation length of the MV did not significantly impact technical or device success.

Outcomes at discharge

Echocardiographic outcomes

In 75/82 patients (91.5%) of the MitraClip intention-to-treat group, TEER successfully reduced MR by at least one grade,

Table 1 Patient characteristics

	MitraClip Intention to treat $N = 82$	PASCAL Intention to treat $N = 41$	*P*-value
Age (years)	77.51 (IQR 18.87)	74.37 (IQR 18.09)	0.4542
Sex (male)	54.88% (45 of 82)	58.53% (24 of 41)	0.8474
NYHA Class III or IV	87.8% (72 of 82)	87.8% (36 of 41)	1.0000
logEuroSCORE (%)	17.1 (IQR 21.88)	14.74 (IQR 18.92)	0.3396
EuroSCORE II (%)	6.55 (IQR 9.84)	5.1 (IQR 4.76)	0.0502
Co-morbidities			
Cardiogenic shock or respiratory insufficiency at the hospital stay	8.54% (7 of 82)	9.76% (4 of 41)	1.0000
Diabetes mellitus	30.49% (25 of 82)	31.7% (13 of 41)	1.0000
Arterial hypertension	82.92% (68 of 82)	80.49% (33 of 41)	0.8045
Significant CAD	51.22% (42 of 82)	53.66% (22 of 41)	0.8496
ICD	30.49% (25 of 82)	26.83% (11 of 41)	0.8338
CRT	17.07% (14 of 82)	14.63% (6 of 41)	0.8011
Previous cardiac surgery	30.49% (25 of 82)	9.76% (4 of 41)	0.0126
Atrial fibrillation	69.51% (57 of 82)	65.85% (27 of 41)	0.6863
Previous cerebrovascular accident	14.63% (12 of 82)	12.2% (5 of 41)	0.7887
Peripheral artery disease	20.73% (17 of 82)	12.2% (5 of 41)	0.3213
Chronic lung disease	59.76% (49 of 82)	53.66% (22 of 41)	0.5645
Obstructive sleep apnoea	6.1% (5 of 82)	4.88% (2 of 41)	1.0000
Chronic renal failure (creatinine >1.3 mg/dL)	32.93% (27 of 82)	39.02% (16 of 41)	0.5503
GFR < 30 mL/min/1.73 m^2	13.41% (11 of 82)	12.2% (5 of 41)	1.0000
Malignancies	17.07% (14 of 82)	34.15% (14 of 41)	0.0414
MR aetiology			
Functional MR	60.98% (50 of 82)	65.85% (27 of 41)	0.6939
Degenerative MR	39.02% (32 of 82)	34.15% (14 of 41)	0.6939
Echocardiographic parameters			
Mean vena contracta width (mm)	11.13 (IQR 3.66)	11.13 (IQR 4.43)	0.6925
Flail width (mm)	3.3 (IQR 1.8)	3.1 (IQR 2)	0.8237
Flail gap (mm)	2.25 (IQR 3.55)	2.6 (IQR 1.7)	0.5795
PML length (mm)	14.4 (IQR 3.68)	14.7 (IQR 4.5)	0.2575
Coaptation length (mm)	3.4 (IQR 1.1)	3.3 (IQR 1.3)	0.6270
Coaptation depth (mm)	7.5 (IQR 4.85)	7.9 (IQR 3.2)	0.5248
Mitral annulus AP diameter (mm)	34.5 (IQR 5.33)	36.1 (IQR 6.3)	0.0224
Mitral annulus ML diameter (mm)	36.7 (IQR 7.33)	37.5 (IQR 4.5)	0.1896
Mitral valve area (cm^2)	5 (IQR 2.75)	5.8 (IQR 2.3)	0.0378
PPG (mmHg)	4.4 (IQR 2.44)	3.99 (IQR 2.98)	0.6764
MPG (mmHg)	1.11 (IQR 0.84)	1.21 (IQR 0.89)	0.3343
LVEF (%)	40 (IQR 28)	38 (IQR 33)	0.7325
LVEF under 20%	17.07% (14 of 82)	17.07% (7 of 41)	1.0000
LVESD (mm)	43.5 (IQR 18)	44 (IQR 21)	0.9743
LVEDD (mm)	56 (IQR 14.25)	55 (IQR 16)	0.9700
LA diameter (mm)	51.5 (IQR 8)	50 (IQR 9)	0.9080
Severe TR	12.2% (10 of 82)	14.63% (6 of 41)	0.7783
PASP (mmHg)	49 (IQR 18.25)	53 (IQR 18.5)	0.2491
Laboratory parameters			
hsTnT (pg/mL)	32 (IQR 44.75)	35 (IQR 33)	0.4638
NT-proBNP (ng/L)	5575 (IQR 9269)	4351 (IQR 9654.5)	0.6239
Creatinine (mg/dL)	1.12 (IQR 0.56)	1.15 (IQR 0.54)	0.8742

AP, anteroposterior; CAD, coronary artery disease; CRT, cardiac resynchronization therapy; GFR, glomerular filtration rate; hsTnT, high-sensitive troponin T; ICD, implantable cardioverter defibrillator; IQR, inter-quartile range; LA, left atrial; LVEDD, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVESD, left ventricular end-systolic diameter; ML, mediolateral; MPG, mean pressure gradient; MR, mitral regurgitation; NT-pro-BNP, N-terminal prohormone brain natriuretic peptide; NYHA, New York Heart Association; PASP, pulmonary arterial systolic pressure; PML, posterior mitral leaflet; PPG, peak pressure gradient; TR, tricuspid regurgitation. Values are % (*n*) or median (IQR).

compared with 37/41 (90.2%) patients in the PASCAL intention-to-treat group. In the patients with successful device implantation, failure to reduce MR ≥ 1 degree occurred in four patients with MitraClip implantation but none of the PASCAL implantations. This difference was not statistically significant ($P = 0.3048$). After implantation of ≥1 MitraClip device, 94.9% (75/79) of the patients had an MR grade ≤2 and 68.4% (54/79) grade ≤1. The implantation of ≥1 PASCAL device reduced MR to ≤2 in all patients (37/37), and an MR reduction to ≤1 was achieved in 62.2% (23/37).

Safety and procedural outcomes

Five out of 82 patients (6.1%) in the MitraClip group died before hospital discharge. This includes the aforementioned procedural death and another comparable rescue intervention (patient EuroSCORE II 25.9%). The three other cases

Table 2 Procedural and in-hospital outcomes

	MitraClip Intention to treat $n = 82$	PASCAL Intention to treat $n = 41$	*P*-value
Technical success[a]	95.12% (78 of 82)	90.24% (37 of 41)	0.4388
Failure to grasp	1.22% (1 of 82)	0% (0 of 41)	1.0000
Elevated MV gradient during intervention	1.22% (1 of 82)	9.76% (4 of 41)	0.0419
Incompatible fossa ovalis anatomy	1.22% (1 of 82)	0% (0 of 41)	1.0000
Procedural mortality	1.22% (1 of 82)	0% (0 of 41)	1.0000
Conversion to surgery	0% (0 of 82)	0% (0 of 41)	1.0000
Device success[b]	89.02% (73 of 82)	90.24% (37 of 41)	1.0000
Failure to reduce MR at least 1 grade	8.54% (7 of 82)	9.76% (4 of 41)	1.0000
MR at discharge ≤2	91.46% (75 of 82)	90.24% (37 of 41)	1.0000
MR at discharge ≤1	65.85% (54 of 82)	56.1% (23 of 41)	0.3265
Device detachment[c]	1.22% (1 of 82)	0% (0 of 41)	1.0000
Procedural success[b]	80.49% (66 of 82)	87.8% (36 of 41)	0.4465
In-hospital mortality	6.1% (5 of 82)	0% (0 of 41)	0.1682
Cerebrovascular accident	2.44% (2 of 82)	0% (0 of 41)	0.5519
Severe bleeding[d]	2.44% (2 of 82)	0% (0 of 41)	0.5519
Vascular access complications[e]	0% (0 of 82)	0% (0 of 41)	1.0000
Cardiac structural damage	0% (0 of 82)	0% (0 of 41)	1.0000
Pericardial effusion	0% (0 of 82)	0% (0 of 41)	1.0000
Air embolism	0% (0 of 82)	2.44% (1 of 41)	0.3333
Myocardial infarction	0% (0 of 82)	0% (0 of 41)	1.0000
Severe hypotension and acute heart or respiratory failure[f]	4.88% (4 of 82)	2.44% (1 of 41)	0.6639
Endocarditis	0% (0 of 82)	0% (0 of 41)	1.0000
Valve-related complication requiring re-intervention	0% (0 of 82)	0% (0 of 41)	1.0000
Other safety outcomes			
Thrombus at atrial septum	0% (0 of 82)	2.44% (1 of 41)	0.3333

i.v., intravenous; MR, mitral regurgitation; MV, mitral valve; MVARC, Mitral Valve Academic Research Consortium.
Values are % (*n* of total) or median (inter-quartile range). Each safety outcome is included in the consequent MVARC endpoint.[22]
[a]According to the endpoint definition provided by the Mitral Valve Academic Research Consortium (MVARC) measured at exit from catheterization laboratory.[22]
[b]According to the MVARC endpoint definition[22] but measured at hospital discharge.
[c]Partial, anterior, device detachment.
[d]Major, extensive, life-threatening, or fatal bleeding according to the Primary Bleeding Scale by the MVARC.[22]
[e]Major vascular access site complications according to MVARC definition.[22]
[f]Severe hypotension and heart or respiratory failure requiring i.v. pressors, invasive heart failure treatments, or intubation for at least 48 h according to MVARC definition.[22]

comprise a major bleeding-associated prolonged hospitalization resulting in limitation of therapy, a death due to respiratory failure and cardiogenic shock in severe COPD, and one death due to sepsis.

In the PASCAL group, no patient died during hospital stay. The difference in in-hospital mortality was statistically not significant ($P = 0.1682$). The adverse events until hospital discharge are summarized in *Table 2*.

The procedural success rate was 80.5% ($n = 66$) in the MitraClip group and 87.8% ($n = 36$) in the PASCAL group. This difference was not statistically significant ($P = 0.4465$).

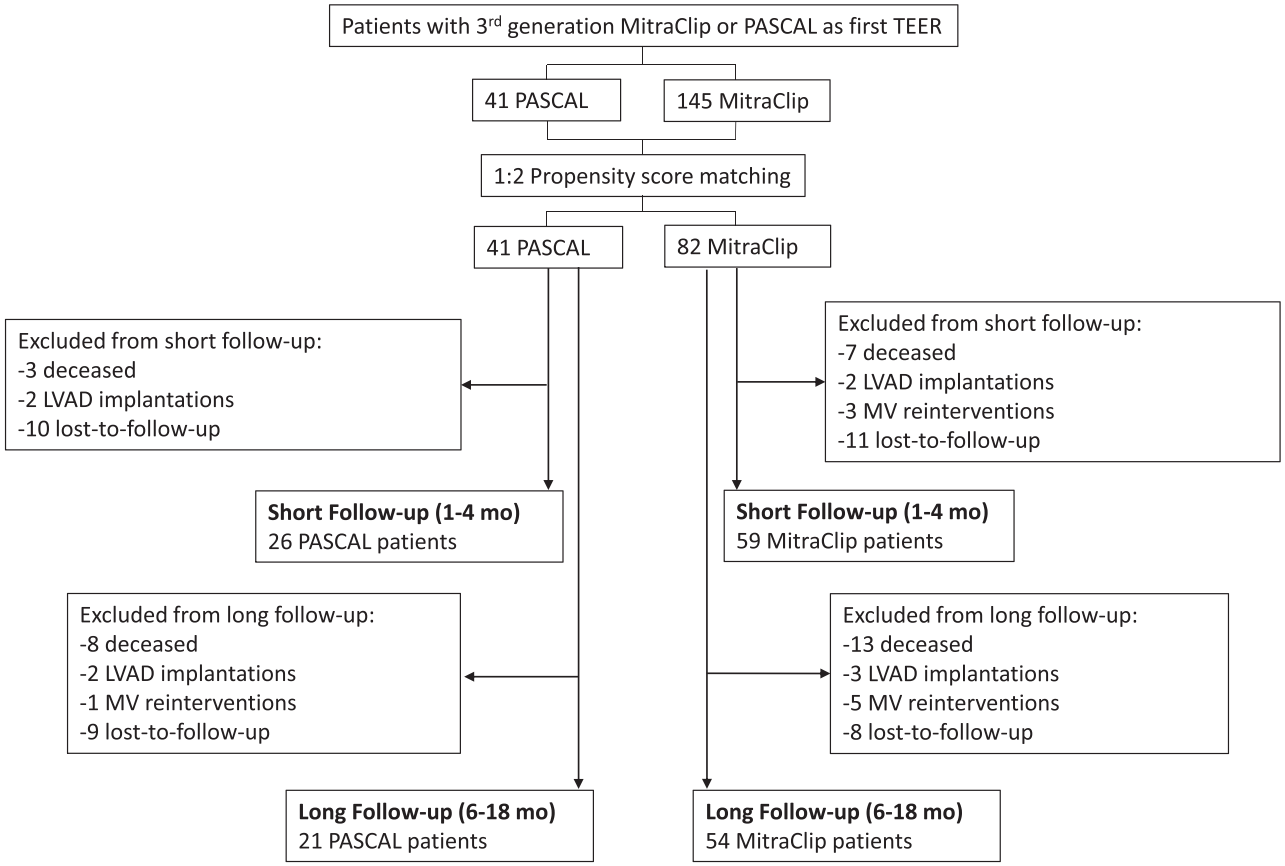
Outcomes at follow-up

The median of time from TEER to first follow-up was 50 days for the MitraClip group and 58 days for the PASCAL group. The second follow-up took place, in median, 360.5 days after intervention for the MitraClip patients and 359 days for the PASCAL patients. Patient flow is depicted in *Figure 1*.

Seventy-one (86.6%) of the patients in the MitraClip group have data for the first follow-up time frame. Seven patients (8.5%) died before first follow-up visit, including the five intra-hospital deaths described. In addition, two patients died during follow-up, one due to a presumably embolic stroke from MV endocarditis 52 days after implantation and the other due to surgical complications after heart transplantation 41 days after MitraClip implantation. In three patients, an MV re-intervention was performed (two cases of TEER using MitraClip and one case of surgical MV replacement) within 4 months following MitraClip implantation attempt ($n = 2$) or successful MitraClip implantation ($n = 1$). Two patients received an LVAD at 36 and 69 days after TEER.

Of the remaining 70 patients in the MitraClip group, 59 (84.3%) completed a primary follow-up appointment in this period; 11.9% were in NYHA Class I, 49.2% in NYHA Class II, 32.2% in NYHA Class III, and 6.8% (4/59) in NYHA Class IV (*Figure 2*). Fifty-seven patients were evaluated with echocardiography; 57.9% had a first-grade MR, 31.6% had a second-grade MR, and 10.5% (6/57) had a third-grade MR (*Figure 2*).

Figure 1 Study patient flow chart. Patients who underwent transcatheter mitral valve (MV) edge-to-edge repair (TEER) due to severe mitral regurgitation between March 2018 and March 2020 were included in this retrospective analysis. Following propensity score matching in a 1:2 ratio (PASCAL/MitraClip), 123 patients were included in the analysis. LVAD, left ventricular assist device; mo, months.



Thirty-one patients (75.6%) in the PASCAL group have data for the first 4 months; 3/41 patients (7.3%) died before completing the first follow-up visit. One patient, in whom the PASCAL implantation was aborted because of elevated MPG, refused surgical MV reconstruction and died of cardiogenic shock 64 days after TEER attempt. The other two patients died of cancer 29 and 42 days after TEER. There were no MV re-interventions within the first 4 months after PASCAL implantation. Two patients received an LVAD at 21 and 26 days after TEER. Twenty-six of the remaining 36 patients (72.2%) had a follow-up appointment in this period; 15.4% were in NYHA Class I, 34.6% in NYHA Class II, 42.3% in NYHA Class III, and 7.7% in NYHA Class IV (2/26) (*Figure 2*); 15.4% (4/26) had no residual MR, 34.6% had a first-grade MR, 42.3% had a second-grade MR, and 7.7% had a third-grade MR (*Figure 3*).

In the MitraClip group, there are follow-up data for the second follow-up for 74 patients (90.2%); 13/82 patients (15.9%) died within the first 18 months; 7 deaths have been described earlier, the cause of death is unknown for six patients. Five patients had undergone MV re-intervention, three were detailed earlier, and two received MV replacement 6 months after MitraClip implantation due to recurrence of severe MR. Three patients had received an LVAD at this time point, two were described earlier and the third patient was implanted with an LVAD 133 days after TEER. In one patient, initial intervention was aborted. In a novel approach after 49 days, MitraClip implantation was successful. The patient died of unknown causes 1 year later. Thus, a total of 20 patients in the MitraClip group were excluded from the final analysis.

Of the remaining 62 patients, 54 (87.1%) completed a follow-up appointment in the period between 6 and 18 months: 9.3% (5/54) were in NYHA Class I, 55.6% (30/54) were in NYHA Class II, 29.6% (16/54) were in NYHA Class III, and 5.6% (3/54) were in NYHA Class IV (*Figure 2*). The MR grade was documented in 49 patients. All patients had residual MR: 55.1% (27/49) first-grade MR, 38.8% (19/49) second-grade MR, and 6.1% (3/49) third-grade MR (*Figure 3*).

Thirty-two patients in the PASCAL group (78.1%) have data for the second follow-up; 8/41 patients (19.5%) had died

Figure 2 New York Heart Association (NYHA) functional class and follow-up rate after transcatheter mitral valve (MV) edge-to-edge repair with either the PASCAL or MitraClip device. (A) Summary of NYHA functional class changes, death, and follow-up rates from baseline [baseline value before implantation (Pre)] to early follow-up [1–4 months after implantation (1.FU)] and late follow-up [6–18 months after implantation (2.FU)] in intention-to-treat analysis with PASCAL or MitraClip for severe mitral regurgitation. (B) NYHA functional class changes from baseline (Pre) to early follow-up (1.FU) and late follow-up (2.FU) in intention-to-treat analysis with PASCAL or MitraClip for severe mitral regurgitation. VAD, ventricular assist device.

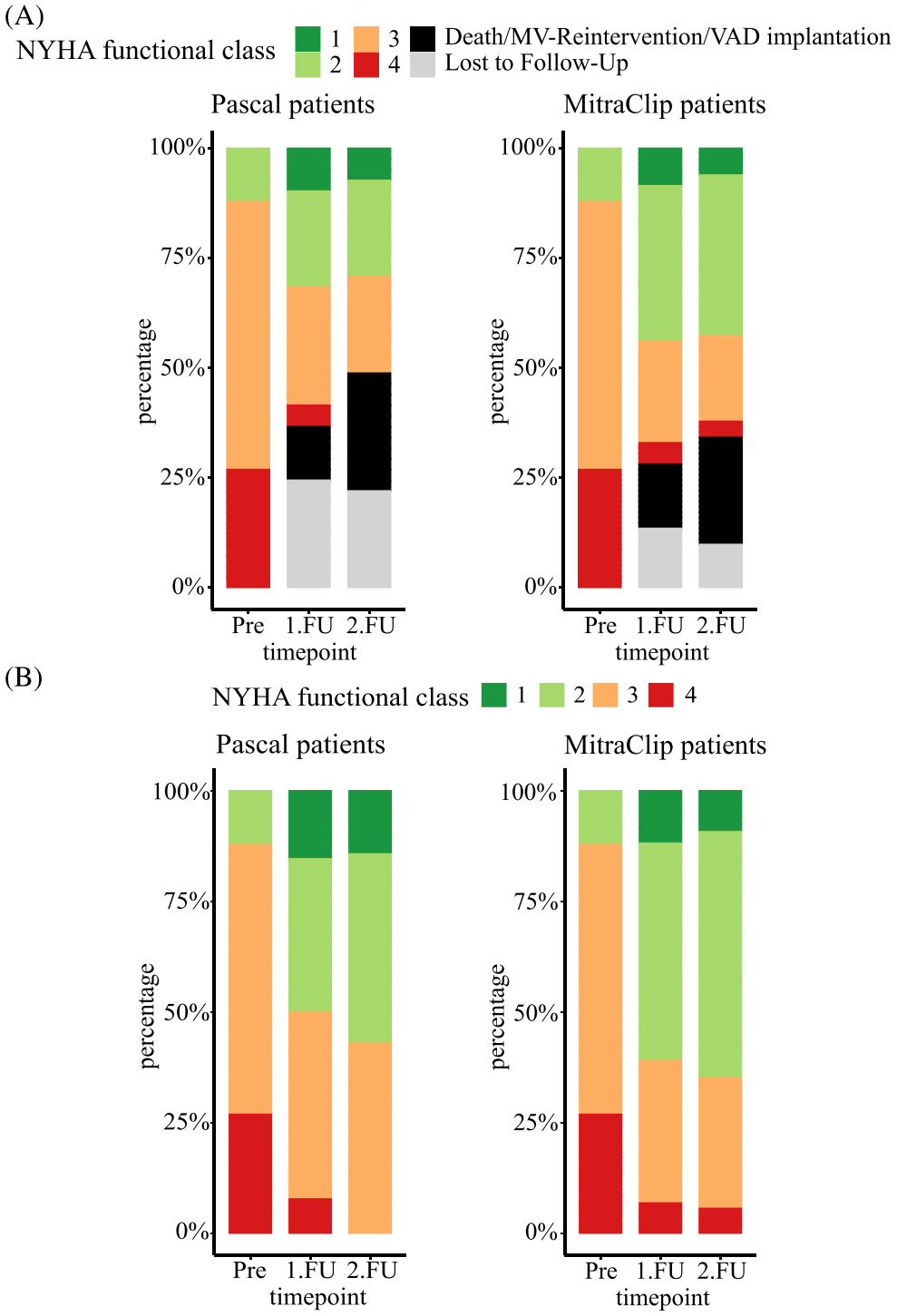
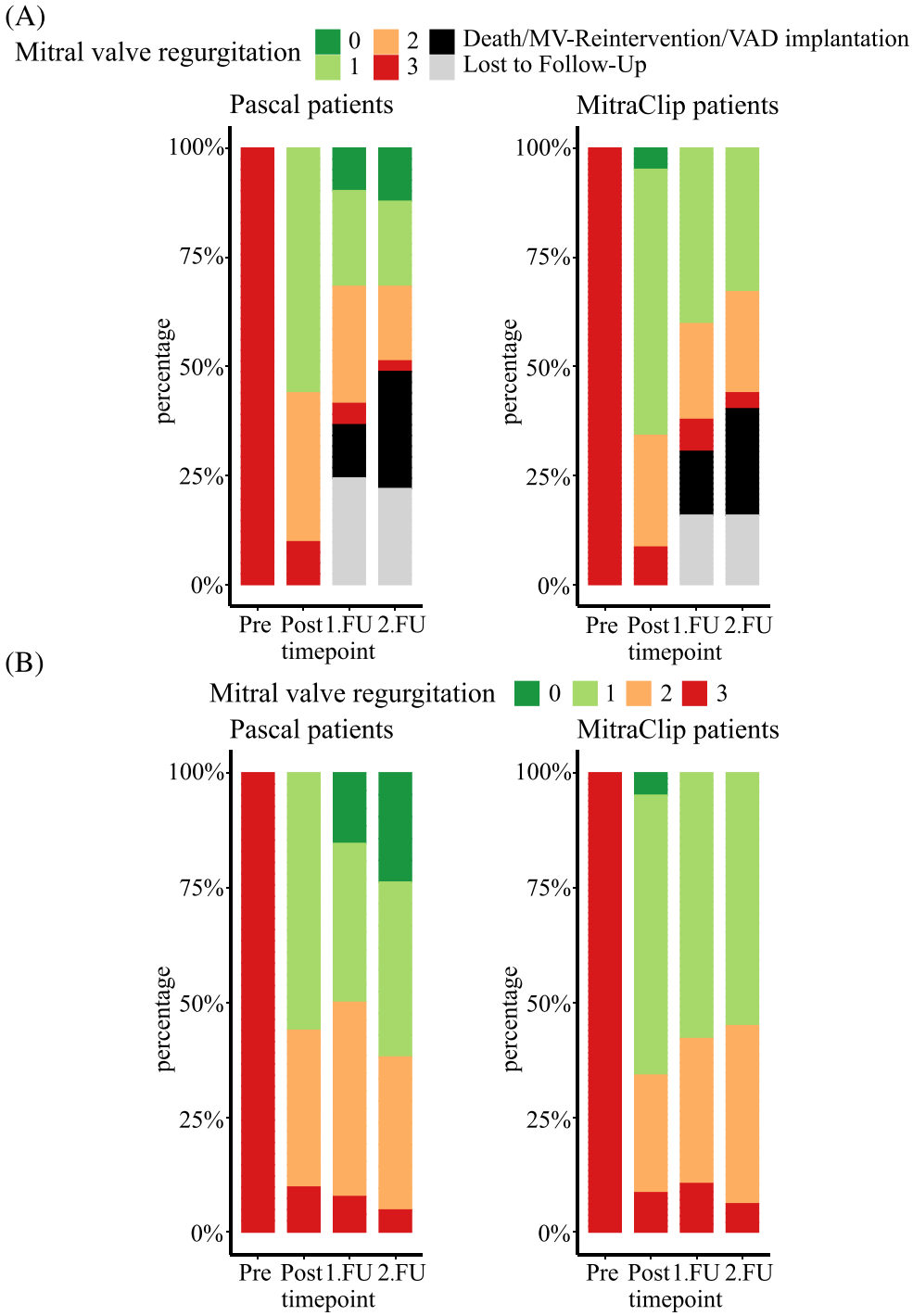


Figure 3 Mitral regurgitation (MR) grade and follow-up rate after transcatheter mitral valve (MV) edge-to-edge repair with either the PASCAL or MitraClip device. (A) Summary of MR changes, death, and follow-up rates from baseline [baseline value before implantation (Pre)] to early follow-up [1–4 months after implantation (1.FU)] and late follow-up [6–18 months after implantation (2.FU)] in intention-to-treat analysis with PASCAL or MitraClip for severe MR. (B) Net MR changes from baseline (Pre) to early (1.FU) and late follow-up (2.FU) in intention-to-treat analysis with PASCAL or MitraClip for severe MR. NYHA, New York Heart Association; Post, value after implantation before hospital discharge; VAD, ventricular assist device.



within 18 months, three were described earlier and the other five causes of death remained unknown. One patient underwent re-TEER with implantation of a second PASCAL device. Two patients had received an LVAD implantation, as mentioned earlier. Of the remaining 30 patients, 21 (70%) completed a follow-up appointment in this time frame;

Table 3 Outcomes at follow-up

	MitraClip	PASCAL	*P*-value
First follow-up			
Days until first follow-up	50 (IQR 23)	58 (IQR 44.5)	0.0533
Combined endpoint[a]	23.17% (19 of 82)	14.63% (6 of 41)	0.3447
Mortality	8.54% (7 of 82)	7.32% (3 of 41)	1.0000
Hospitalization due to heart failure	15.85% (13 of 82)	9.76% (4 of 41)	0.4188
Mitral valve re-intervention	3.66% (3 of 82)	0% (0 of 41)	0.5501
Ventricular assist device implantation	2.44% (2 of 82)	4.88% (2 of 41)	0.6001
NYHA class ≤2 at first FU	61.02% (36 of 59)	50% (13 of 26)	0.3538
Absolute reduction of NYHA class, at least 1 grade	52.54% (31 of 59)	46.15% (12 of 26)	0.6426
Absolute reduction of NYHA class, at least 2 grades	13.56% (8 of 59)	11.54% (3 of 26)	1.0000
MR 0 at first FU	0% (0 of 57)	15.38% (4 of 26)	**0.0081**
MR ≤ 1 at first FU	57.89% (33 of 57)	50% (13 of 26)	0.6347
MR ≤ 2 at first FU	89.47% (51 of 57)	92.31% (24 of 26)	1.0000
Absolute reduction of MR, at least 1 grade	89.47% (51 of 57)	92.31% (24 of 26)	1.0000
Absolute reduction of MR, at least 2 grades	56.14% (32 of 57)	46.15% (12 of 26)	0.4795
Last follow-up			
Days until last follow-up	360.5 (IQR 97.5)	359 (IQR 141)	0.6538
Combined endpoint[a]	42.68% (35 of 82)	34.15% (14 of 41)	0.4361
Mortality	15.85% (13 of 82)	19.51% (8 of 41)	0.6189
Hospitalization due to heart failure	30.49% (25 of 82)	14.63% (6 of 41)	0.0774
Mitral valve re-intervention	6.1% (5 of 82)	2.44% (1 of 41)	0.6625
Ventricular assist device implantation	3.66% (3 of 82)	4.88% (2 of 41)	1.0000
NYHA class ≤2 at last FU	64.82% (35 of 54)	57.14% (12 of 21)	0.5998
Absolute reduction of NYHA class, at least 1 grade	59.26% (32 of 54)	57.14% (12 of 21)	1.0000
Absolute reduction of NYHA class, at least 2 grades	18.52% (10 of 54)	19.05% (4 of 21)	1.0000
MR 0 at last FU	0% (0 of 49)	23.81% (5 of 21)	**0.0017**
MR ≤ 1 at last FU	55.1% (27 of 49)	61.9% (13 of 21)	0.7926
MR ≤ 2 at last FU	93.88% (46 of 49)	95.24% (20 of 21)	1.0000
Absolute reduction of MR, at least 1 grade	91.84% (45 of 49)	95.24% (20 of 21)	1.0000
Absolute reduction of MR, at least 2 grades	55.1% (27 of 49)	57.14% (12 of 21)	1.0000

FU, follow-up; IQR, inter-quartile range; MR, mitral regurgitation; NYHA, New York Heart Association.
Values are % (*n* of total) or median (IQR). Bold emphasis indicates statistically significant differences (all *P*-values <0.05).
[a]The combined endpoint comprises death, hospitalization due to heart failure, and mitral valve re-intervention.

14.3% (3/21) reported being in NYHA Class I, 42.9% (9/21) in NYHA Class II, and another 42.9% in NYHA Class III. No patient reported symptoms for Functional Class IV (*Figure 2*). Echocardiography data for MR are available in 21 patients: 23.8% (5/21) had no residual MR, 38.1% (8/21) had a first-grade MR, 33.3% (7/21) had a second-grade MR, and 4.8% (1/21) had a third-grade MR (*Figure 3*). The follow-up outcomes, including MR and NYHA class, are summarized in *Table 3*.

The Cox hazard model for the composite endpoint (death, HF hospitalization, and MV re-intervention) revealed baseline hsTnT level above 50 pg/mL ($P = 0.0016$ for technical success and $P < 0.001$ for device success), technical failure at implantation ($P = 0.0025$; log-rank test $P = 0.0016$), and device failure at hospital discharge ($P = 0.0098$; log-rank test = 0.0059) as independent predictors, analysing all patients irrespective of the implanted device. Neither sex, age, EuroSCORE II, nor the TEER system itself was found statistically significant (*Figure 4*).

Propensity-matched device comparison

There were no significant differences between devices, regarding neither the composite endpoint comprising death, HF hospitalization, or MV re-intervention ($P = 0.35$, *Figure 5A*) nor the individual endpoints: death ($P = 0.61$, *Figure 5B*), HF hospitalization ($P = 0.089$, *Figure 5C*), or MV re-intervention ($P = 0.31$). Furthermore, there was no significant difference regarding stroke in both groups ($P = 0.11$).

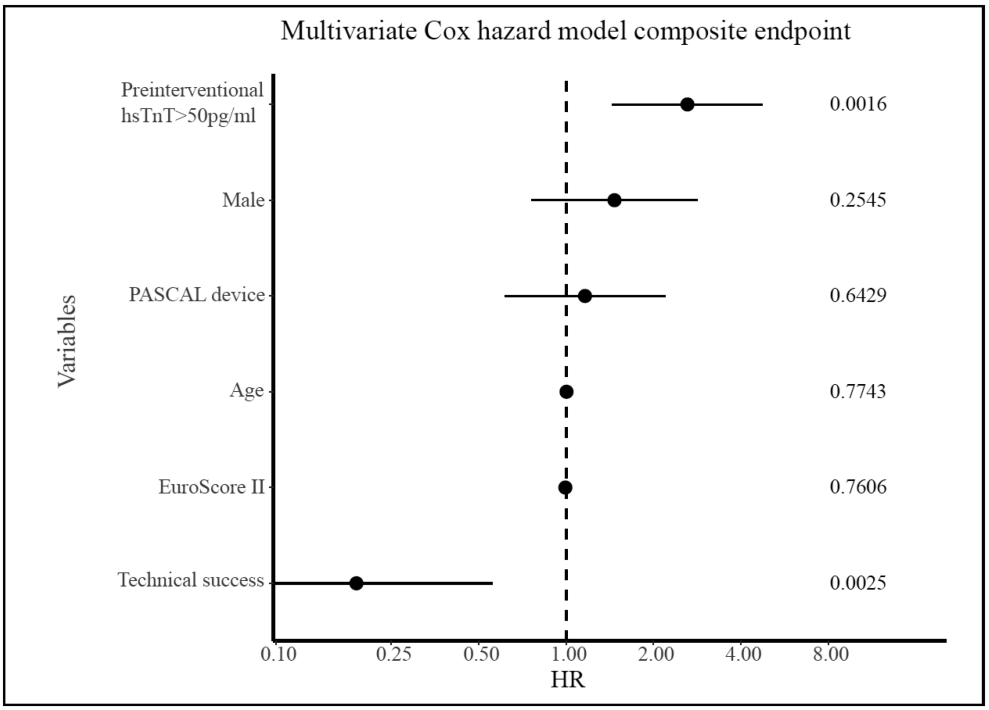
While at follow-up no statistical difference regarding mild, moderate, or severe MR grades was apparent, the number of patients with no or trace residual MR was significantly higher among patients in the PASCAL intention-to-treat group at either follow-up time point (1.follow-up: $P = 0.0081$; 2.follow-up: $P = 0.0017$).

There was no difference in the degree of absolute MR reduction detectable between MitraClip-treated and PASCAL-treated groups. A detailed outcome description at follow-up is presented in *Table 3*.

Discussion

Feasibility of TEER using the PASCAL device in patients presenting with high or prohibitive surgical risk has been suggested by the CLASP trial and several mostly single-centre reports with limited patient numbers and largely short follow-up periods.[13–17,31] In this study, we

Figure 4 Variables influencing Cox hazard model for the composite endpoint. *P*-values are depicted at the right border. EuroSCORE II, European System for Cardiac Operative Risk Evaluation; HR, hazard ratio; hsTnT, high-sensitive cardiac troponin T.



analysed procedural, short-term, and 1 year outcome of patients undergoing TEER using the PASCAL system and compared data with patients treated with the MitraClip device in a propensity-matched analysis. To the best of our knowledge, this study provides the longest real-world follow-up data on TEER using the PASCAL system with matched comparison with the MitraClip device.

The main findings of our study comprise technical feasibility, procedural safety, and clinical efficacy of PASCAL implantation in high-risk patients with symptomatic severe MR, irrespective of the underlying MV pathology. Successful TEER significantly reduced MR at discharge, independently of the device used. This is well in line with previous data by Gerçek *et al*.[32] This resulted in sustained midterm MR reduction with significantly more patients presenting without residual MR at 1 year follow-up compared with matched MitraClip-treated patients. Moreover, persistent improvement in patients' functional status could be achieved in both groups, and a combined clinical endpoint (death, HF hospitalization, and/or MV re-intervention) revealed no relevant differences between the two devices at short-term and 1 year follow-up.

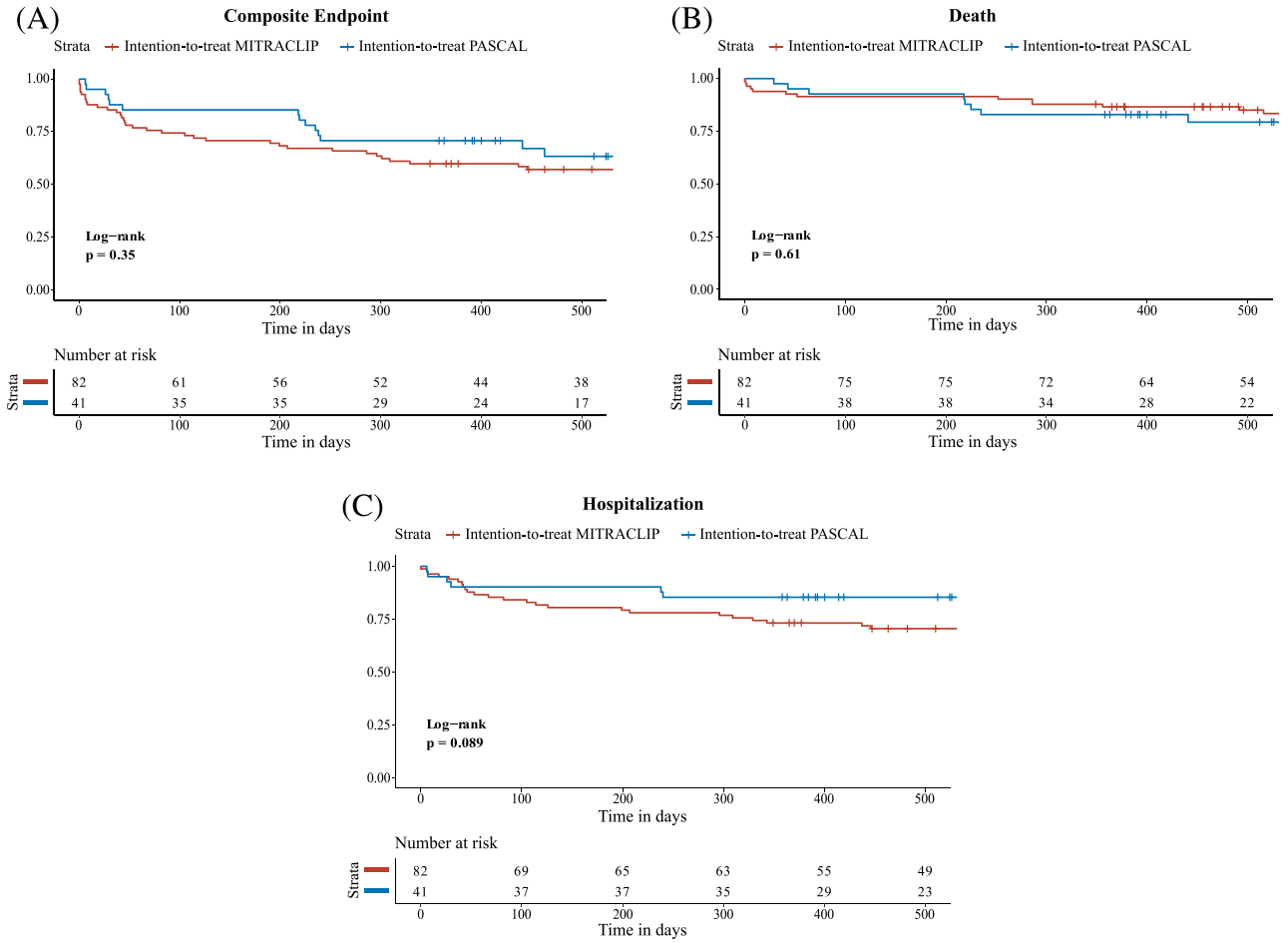
Technical and device success rates were similarly high, irrespective of the applied TEER device with no statistical difference comparing MitraClip and PASCAL groups. Success rates are mainly in line with previously published studies and differences well attributable to the advanced state of disease in this cohort.[8,11–18,31,33,34]

Interestingly, aborted implantations due to elevated MPG were significantly more frequent in the PASCAL group ($P = 0.0419$), although MV area was significantly larger in this patient cohort ($P = 0.0378$) and baseline MPG did not differ between groups. This might represent a limitation of the broader PASCAL implant compared with the slenderer NTR and XTR. However, this limitation could potentially be addressed with the meanwhile available PASCAL Ace device. Finally, the employed TEER system did not significantly impact technical or device success according to univariate and multivariate logistic regression.

In this propensity-matched cohorts, we encountered overall 5 (6%) intra-hospital deaths in the MitraClip group, while none of the PASCAL-implanted patients died in hospital. This difference, however, was not statistically significant, and fatalities occurred in cases with advanced disease evidenced by a highly elevated EuroSCORE II, which was beyond 25% in three of the five cases. Consequently, this cannot be safely attributed to the TEER device.

Analysis of patients with at least one implanted device revealed no statistically significant difference between groups, while an MR reduction to ≤ 2 could be achieved in 94.9% of

Figure 5 Kaplan–Meier curves for (A) the composite endpoint, (B) survival, and (C) rehospitalization due to heart failure for MitraClip vs. PASCAL.



MitraClip patients and all PASCAL-treated patients. Accordingly, these only minor differences did not result in a significant difference in procedural success rate, which was numerically lower in MitraClip patients mainly due to the aforementioned in-hospital deaths.

The numbers of patients in the intention-to-treat analysis experiencing a major adverse event during follow-up were low [11% (9/82) for MitraClip and 5% (2/41) for PASCAL] and comparable with previous studies.[13,15] There was no statistical difference between treatment groups (P = 0.3334).

Clinical improvement was comparable and sustained until 1 year follow-up in both device groups according to NYHA functional class.

Interestingly, at 1 year follow-up, significantly more patients presented without residual MR in the PASCAL group (5/21 vs. 0/49, P = 0.0017). This is particularly promising as residual MR following TEER has been shown to have a prognostic impact.[35–37] Improved MR reduction might be attributable to several unique features of the PASCAL device including a central spacer filling the regurgitant orifice area, capability of independent leaflet grasping, and the flexible nitinol construction with broader-shaped paddles aiming at reducing leaflet stress.

Limitations of the study

The data were retrieved from a single centre in a retrospective approach. In addition, the lack of an external core lab adjudicating the events may bias data interpretation. Furthermore, in this study, third-generation MitraClip XTR and NTR was compared with the PASCAL device. Meanwhile, in the context of accelerated product improvement, fourth-generation MitraClip has been FDA approved and CE certified, and the PASCAL Ace device has been introduced.

Conclusions

In high-risk patients with severe MR undergoing MV TEER with the MitraClip or PASCAL device, procedural safety, efficacy, and clinical improvement after 1 year are comparable.

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Conflict of interest

N.A.G., P.S., and P.W.J.R. are investigators in the RESHAPE-HF 1, RESHAPE-HF 2, and the CLASP IID/IIF trial. P.W.J.R. has received speaker honoraria from Abbott Cardiovascular. N.F., P.S., and P.W.J.R. received speaker honoraria from Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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