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ORIGINAL RESEARCH

# One-Year Outcomes According to Mitral Regurgitation Etiology Following Transcatheter Edge-to-Edge Repair With the PASCAL System: Results From a Multicenter Registry

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**BACKGROUND:** We previously reported procedural and 30-day outcomes of a German early multicenter experience with the PASCAL system for severe mitral regurgitation (MR). This study reports 1-year outcomes of mitral valve transcatheter edge-to-edge repair with the PASCAL system according to MR etiology in a large all-comer cohort.

**METHODS AND RESULTS:** Clinical and echocardiographic outcomes up to 1-year were investigated according to MR etiology (degenerative [DMR], functional [FMR], or mixed [MMR]) in the first 282 patients with symptomatic MR 3+/4+ treated with the PASCAL implant at 9 centers in 2019. A total of 282 patients were included (33% DMR, 50% FMR, 17% MMR). At discharge, MR reduction to ≤1+/2+ was achieved in 58%/87% of DMR, in 75%/97% of FMR, and in 78%/98% of patients with MMR ($P$=0.004). MR reduction to ≤1+/2+ was sustained at 30 days (50%/83% DMR, 67%/97% FMR, 74%/100% MMR) and at 1 year (53%/78% DMR, 75%/97% FMR, 67%/91% MMR) with significant differences between etiologies. DMR patients with residual MR 3+/4+ at 1-year had at least complex valve morphology in 91.7%. Valve-related reintervention was performed in 7.4% DMR, 0.7% FMR, and 0.0% MMR ($P$=0.010). At 1-year, New York Heart Association Functional Class was significantly improved irrespective of MR etiology ($P$<0.001).

**CONCLUSIONS:** In this large all-comer cohort, mitral valve transcatheter edge-to-edge repair with the PASCAL system was associated with an acute and sustained MR reduction at 1-year in all causes. However, in patients with DMR, MR reduction was less pronounced, reflecting the high incidence of complex or very complex anatomies being referred for mitral valve transcatheter edge-to-edge repair.

**Key Words:** mitral regurgitation ■ mitral regurgitation cause ■ mitral valve transcatheter edge-to-edge repair ■ PASCAL

See Editorial by Zahr and Chadderdon

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## CLINICAL PERSPECTIVE

### What Is New?

- The PASCAL system demonstrates acute and sustained MR reduction across all MR etiology in a real-world population over the course of 1-year.
- MR reduction is most pronounced in patients with FMR and less pronounced in patients with DMR.

### What Are the Clinical Implications?

- Favorable results, particularly in patients with functional MR, can be achieved with the PASCAL system.
- Patients treated for DMR should be carefully evaluated with regard to appropriate device selection.
- The impact of the introduction of the PASCAL Ace system on clinical outcomes remains to be elucidated.

### Nonstandard Abbreviations and Acronyms

| | |
|---|---|
| **DMR** | degenerative mitral regurgitation |
| **FMR** | function mitral regurgitation |
| **MMR** | mixed mitral regurgitation |
| **MR** | mitral regurgitation |
| **M-TEER** | mitral valve transcatheter edge-to-edge repair |
| **NYHA-FC** | New York Heart Association Functional Class |
| **SLDA** | single-leaflet device attachment |

Mitral regurgitation (MR) is the most prevalent valvular heart disease with poor prognosis, if left untreated. Despite its impact on death, morbidity, and quality of life, only 15% of patients are referred for mitral valve surgery because of presumed high surgical risk.[1–3] As a consequence, mitral valve transcatheter edge-to-edge repair (M-TEER) has emerged as an important alternative for patients unsuitable for surgery. Current guidelines granted a class IIb recommendation for patients with degenerative mitral regurgitation (DMR) and a class IIa recommendation for patients with functional mitral regurgitation (FMR) who meet certain criteria.[4] Achieving an optimal MR reduction in patients undergoing M-TEER has been shown to be a determining aspect of lower mortality and heart failure hospitalization rates.[5,6]

The morphologic variability of MR requires a tailored approach to individually address the respective pathology and the introduction of the PASCAL system (Edwards Lifesciences, Irvine, CA) has broadened the armamentarium of M-TEER. However, available data on the PASCAL system were mainly derived from early approval trials including an anatomically and clinically highly selected patient cohort. This limited database may lead to uncertainties regarding the application and the selection of the appropriate device, especially in complex cases.[7–10]

We previously reported procedural and 30-day outcomes of a large postapproval patient cohort treated at 10 high-volume centers.[11] Thereby, technical success was 96%, and the degree of MR was significantly reduced with MR at discharge being ≤2+ in 93.5% and ≤1+ in 70%.[11] Herein, we present 1-year outcomes according to MR etiology.

## METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request.

### Study Population and Data Collection

This study reports 1-year results of the first 282 consecutive patients treated commercially with the PASCAL P10 repair system for symptomatic moderate-to-severe or severe MR between February and December 2019 at 9 tertiary care centers in Germany. One center of the original cohort was unable to provide follow-up data (N=27) and had to be excluded from the analysis. As previously reported, each center had extensive experience with M-TEER and performed at least 12 procedures within this registry.[11] All patients were considered high surgical risk or inoperable by the local interdisciplinary heart team. There were no prespecified inclusion or exclusion criteria. However, the first 4 patients treated at each center were selected in collaboration with the manufacturer.[11] The selection of all further patients and the decision to use the PASCAL system over other percutaneous options was at the discretion of the local physicians. Most centers treated all patients, with 2 centers initially restricting treatment to those with noncomplex anatomies and 3 also accepting patients with particularly complex pathologies, including those deemed unsuitable for MitraClip implantation. Retrospective data collection was approved by the respective local ethics committee, and the requirement for informed consent from subjects was waived. The anonymized data were analyzed centrally.

## Echocardiographic Assessment

MR severity was graded at baseline, discharge, and 30-day and 1-year follow-up using a multiparametric approach according to current guidelines with the grades none/trace (no MR), mild (1+), mild to moderate (2+), moderate to severe (3+), and severe (4+).[12] To monitor data quality, 3 experts from 3 different centers reviewed discharge echocardiograms from a randomly selected cohort and found excellent interrater agreement, as previously reported.[13] Classification of MR etiology into DMR, FMR, and mixed mitral regurgitation (MMR) was performed by the respective centers.

## PASCAL System and Implantation Procedure

The implantation technique of the PASCAL system as well as the design of the system were described in detail previously.[8,14] All procedures were performed with the original PASCAL implant.

## End Points and Follow-Up

All clinical and echocardiographic results were assessed by local investigators experienced in echocardiography. Follow-up visits were scheduled at 30-days and 1-year and included clinical and echocardiographic assessment. In case of a patient's inability to come to the intervention center for follow-up, telephone follow-up was performed as part of the clinical routine. End points were defined according to the Mitral Valve Academic Research Consortium (MVARC) consensus unless otherwise indicated.[15] Performance end points were technical success, device success at 30-days and 1-year as defined by the MVARC (successful device implantation, MR ≤2+, mean gradient <5 mm Hg and freedom from death, stroke, unplanned surgical or interventional procedures, and device failure) as well as MR severity at discharge, 30-days, and 1-year.[15] Safety end point was the rate of major adverse events at 30-days including all-cause death, stroke, cardiac structural complication, acute kidney injury requiring new renal replacement therapy, and severe bleeding (major, extensive, life-threatening, or fatal bleeding).[15] Clinical end points at 1 year included all-cause death, rehospitalization for heart failure, valve-related reintervention (surgical or percutaneous), and New York Heart Association Functional Class (NYHA-FC). As has been shown previously, the inclusion and exclusion criteria of the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients With Functional Mitral Regurgitation) trial predict outcome in patients with FMR.[16–18] Accordingly, we categorized FMR patients (total n=141) as COAPT-eligible if all of the following adapted COAPT inclusion/exclusion criteria were met: FMR grade ≥3+ according to guidelines of the American Society of Echocardiography, NYHA-FC ≥II, left ventricular ejection fraction ≥20%, left ventricular end-systolic diameter ≤70 mm, tricuspid regurgitation grade <3+, estimated pulmonary artery systolic pressure ≤70 mm Hg, and mitral valve orifice area >4 $cm^2$.[16–19]

## Statistical Analysis

Continuous variables are presented as mean±SD or median (interquartile range), as appropriate. Distribution of continuous variables was assessed with the Kolmogorov–Smirnov test. Categorical variables are reported as frequencies and percentages (n [%]). Comparisons between groups were performed using Fisher's exact tests for categorical variables, Student's *t* test or Mann–Whitney *U* test for unpaired continuous variables, and the paired Student's *t* test or Wilcoxon rank-sum test for paired variables, depending on data distribution. Thirty-day- and 1-year mortality rates were estimated by Kaplan–Meier analysis (log-rank test). Two-sided *P* values <0.05 were considered statistically significant. Statistical data analyses were performed using IBM SPSS Statistics version 28.0 (IBM, Armonk, NY).

# RESULTS

## Patient Population and Baseline Characteristics

A total of 92 patients with DMR (32.6%), 141 patients with FMR (50.0%), and 49 patients with MMR (17.4%) underwent M-TEER with the PASCAL system; no patient had concomitant tricuspid valve intervention. Baseline characteristics are summarized in Table 1. At 81±7 years and 78±7 years, respectively, patients with DMR and patients with MMR were the oldest, whereas patients with FMR were the youngest, at 74±11 years (*P*<0.001 across etiologies). In addition, patients with DMR/MMR were more often women than patients with FMR (*P*=0.010 across etiologies). The predicted perioperative risk calculated with the European System for Cardiac Operative Risk Evaluation II (EuroSCORE II) was higher in patients with FMR (4.3±3.3%) and patients with MMR (6.1±5.1%) than in patients with DMR (6.4±5.0%) (*P*=0.014 across etiolgies). At baseline, most patients were in NYHA-FC III/IV (82% DMR, 85% FMR, 95% MMR; *P*=0.072).

## Procedural and Intrahospital Outcomes

Procedural and intrahospital outcomes are detailed in Table 2. Comparably high technical success was observed in all etiologies (96% DMR, 97% FMR, 98% MMR). In 2 patients with DMR, 3 patients with FMR, and 1 patient with MMR, the procedure was aborted

**Table 1. Baseline Characteristics.**

| | DMR | FMR | MMR | |
|---|---|---|---|---|
| | N=92 | N=141 | N=49 | *P* value |
| Age, y | 80.6±7.1 | 73.8±11.2 | 77.7±7.4 | <0.001* |
| Sex, female | 48 (52.2) | 48 (34.0) | 25 (51.0) | 0.010* |
| NTproBNP, pg/mL (n=194) | 1551 (791–2884) | 2890 (1271–5335) | 3823 (2197–8541) | <0.001* |
| BNP, pg/mL (n=32) | 1971 (1350–2505) | 607 (264–1439) | 809 (589–1028) | 0.070 |
| NYHA-FC III/IV | 75 (81.5) | 120 (85.1) | 46 (93.9) | 0.125 |
| Mitral regurgitation | | | | 0.002* |
| 3+ | 25 (27.2) | 57 (40.4) | 28 (57.1) | |
| 4+ | 67 (72.8) | 84 (59.6) | 21 (42.9) | |
| EuroSCORE II, % | 4.3±3.3 | 6.1±5.1 | 6.4±5.0 | 0.014* |
| Comorbidities | | | | |
| Arterial hypertension | 80 (87.0) | 128 (90.8) | 43 (87.8) | 0.602 |
| Diabetes | 19 (20.7) | 41 (29.1) | 11 (22.4) | 0.334 |
| Coronary artery disease | 43 (46.7) | 81 (57.4) | 30 (61.2) | 0.169 |
| Previous myocardial infarction | 5 (5.4) | 35 (24.8) | 3 (6.1) | <0.001* |
| Previous cardiac surgery | 17 (18.5) | 25 (17.7) | 15 (30.6) | 0.161 |
| ICD/CRT | 5 (5.4) | 43 (30.5) | 12 (24.5) | <0.001* |
| Atrial fibrillation | 63 (68.5) | 101 (71.6) | 36 (73.5) | 0.811 |
| Chronic lung disease | 15 (16.3) | 30 (21.3) | 12 (24.5) | 0.448 |
| Renal disease, GFR <60 mL/min | 50 (54.3) | 91 (64.5) | 29 (59.2) | 0.285 |
| On dialysis | 1 (1.1) | 2 (1.4) | 1 (2.0) | >0.999 |
| GFR, mL/min | 57±19 | 52±22 | 56±25 | 0.081 |

Values are mean±SD, median (interquartile range), or n (%). BNP indicates brain natriuretic peptide; CRT, cardiac resynchronization therapy; DMR, degenerative mitral regurgitation; EuroSCORE II, European System for Cardiac Operative Risk Evaluation II; FMR, functional mitral regurgitation; GFR, glomerular filtration rate; ICD, implantable cardioverterdefibrillator; MMR, mixed mitral regurgitation; NTproBNP, N-terminal pro-B-type natriuretic peptide; and NYHA-FC, New York Heart Association Functional Class.

*$P<0.05$.

without PASCAL implantation, and the number of implanted PASCAL devices did not differ across etiologies. Intraprocedural single-leaflet device attachment (SLDA) occurred in 2 patients with DMR (2.2%) and 1 patient with FMR (0.7%); SLDA did not occur in any patient with MMR. At discharge, the degree of MR was significantly reduced, with MR ≤2+ in 86.7% of patients with DMR, 97.2% of patients with FMR, and 98.0% of

**Table 2. Procedural Outcomes.**

| | DMR | FMR | MMR | |
|---|---|---|---|---|
| | N=92 | N=141 | N=49 | *P* value |
| Technical success | 88 (95.7) | 137 (97.2) | 48 (98.0) | 0.817 |
| Intraprocedural SLDA | 2 (2.2) | 1 (0.7) | 0 (0.0) | 0.583 |
| Procedure aborted | 2 (2.2) | 3 (2.1) | 1 (2.0) | >0.999 |
| Procedural death | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Conversion to surgery | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Cardiac structural damage | 0 (0.0) | 0 (0.0) | 0 (0.0) | |
| Devices implanted | | | | 0.947 |
| 0 | 2 (2.2) | 3 (2.1) | 1 (2.0) | |
| 1 | 68 (73.9) | 101 (71.6) | 39 (79.6) | |
| 2 | 22 (23.9) | 36 (25.5) | 9 (18.4) | |
| 3 | 0 (0.0) | 1 (0.7) | 0 (0.0) | |
| Procedure time, min | 95±40 | 90±48 | 88±50 | 0.182 |

Values are n (%). DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; MMR, mixed mitral regurgitation; and SLDA, single-leaflet device attachment.

patients with MMR (*P*=0.004 across etiologies) and ≤1+ in 57.8% of patients with DMR, 75.2% of patients with FMR, and 77.6% of patients with MMR patients (*P*=0.010 across etiologies).

## Clinical Outcomes at 30 Days and 1 Year

Clinical outcomes at 30 days and 1 year are detailed in Table 3. At 30 days, there were no differences in the cumulative incidence of major adverse events with respect to etiologiy. Among 233 patients with complete data to assess the respective end point, device success at 30-days was achieved in 67.1%, 90.8%, and 83.8% of patients with DMR, patients with FMR, and patients with MMR, respectively (*P*<0.001 across etiologies). The significantly lower rate of device success at 30 days in the DMR group was driven by a higher proportion of patients with (1) residual MR 3+/4+, (2) mean gradient ≥5 mm Hg, and (3) SLDA compared with patients with FMR and MMR, respectively (Figure 1).

A total of 6.5% of patients with DMR, 0.7% of patients with FMR, and no patients with MMR had SLDA (*P*=0.017 across etiologies), and no SLDA was observed beyond 30-days. Valve-related reintervention after the index procedure was performed in 6 patients with DMR (7.4%) and 1 patient with FMR (0.7%), but was not required in any patient with MMR (*P*=0.010 across etiologies). Reinterventions were performed due to persistent MR after an aborted index procedure (n=2), SLDA (n=2) or persistent severe MR despite PASCAL implantation (n=3). Interventions were Cardioband implantation (n=1) or surgical mitral valve replacement (n=6). Additional percutaneous treatment attempts (PASCAL/MitraClip) before mitral valve replacement were performed in 2 patients. There was 1 patient with FMR with a device-related endocarditis at 1 year. Details of all 7 cases with valve-related reintervention are presented in Table S1.

At 1-year (median follow-up time, 365 [210–414] days), device success was achieved in 51.5% of patients with DMR (n=35/68), 75.5% of patients with FMR (n=80/106), and 50.0% of patients with MMR (n=19/38) patients (*P*<0.001 across etiologies). Different aspects have driven this end point in the respective etiology. In patients with DMR, this end point was driven by persistent MR 3+/4+ (n=12/68, 17.6%), mean gradient ≥5 mm Hg (n=9/68, 13.2%), and reinterventions (n=7/68, 10.3%). In patients with FMR and MMR, this end point was driven primarily by death (n=14/106, 13.2%; and n=9/38 23.7%, respectively; Figure 1). Kaplan–Meier estimated the 1-year mortality rate and freedom from heart failure rehospitalization was 9.0% (DMR), 10.7% (FMR), and 23.5% (MMR) and 91.3% (DMR), 86.7% (FMR), and 79.2% (MMR), respectively (Figure 2). Patients with FMR were grouped into COAPT-eligible and -ineligible patients as described previously.[16] We

**Table 3. Follow-Up Outcome**

| | DMR | FMR | MMR | |
|---|---|---|---|---|
| | N=92 | N=141 | N=49 | *P* value |
| 30-d outcome | | | | |
| All-cause death | 2 (2.3) | 2 (1.5) | 1 (2.2) | 0.186 |
| Severe bleeding | 2 (2.2) | 4 (2.8) | 1 (2.0) | >0.999 |
| Cerebrovascular event | 1 (1.1) | 0 (0.0) | 0 (0.0) | 0.500 |
| Renal failure requiring dialysis | 1 (1.1) | 1 (0.7) | 0 (0.0) | >0.999 |
| Reintervention for device failure | 1 (1.1) | 0 (0.0) | 0 (0.0) | 0.500 |
| Composite MAE rate | 4 (4.3) | 6 (4.3) | 2 (4.1) | >0.999 |
| Device success (n=233) | 51 (67.1) | 109 (90.8) | 31 (83.8) | <0.001* |
| Mean gradient ≥5 mm Hg | 11 (16.7) | 2 (1.8) | 4 (11.8) | <0.001* |
| 1-y outcome | | | | |
| All-cause death | 7 (9.0) | 14 (10.7) | 9 (23.5) | 0.067 |
| Heart failure rehospitalization | 4 (8.7) | 13 (13.3) | 5 (20.8) | 0.327 |
| Single-leaflet device attachment | 6 (6.5) | 1 (0.7) | 0 (0.0) | 0.017* |
| Reintervention for device failure | 6 (7.4) | 1 (0.7) | 0 (0.0) | 0.010* |
| Percutaneous | 1 (1.2) | 0 (0.0) | 0 (0.0) | |
| Surgical mitral valve repair | 5 (6.2) | 1 (0.7) | 0 (0.0) | |
| Endocarditis | 0 (0.0) | 1 (1.4) | 0 (0.0) | >0.999 |
| Device success (n=212) | 35 (51.5) | 80 (75.5) | 19 (50.0) | <0.001* |
| Mean gradient ≥5 mm Hg | 8 (15.4) | 4 (4.5) | 7 (23.3) | 0.007* |

Values are n (%). DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; MMR, mixed mitral regurgitation; and MAE, major adverse event.

*$P<0.05$.

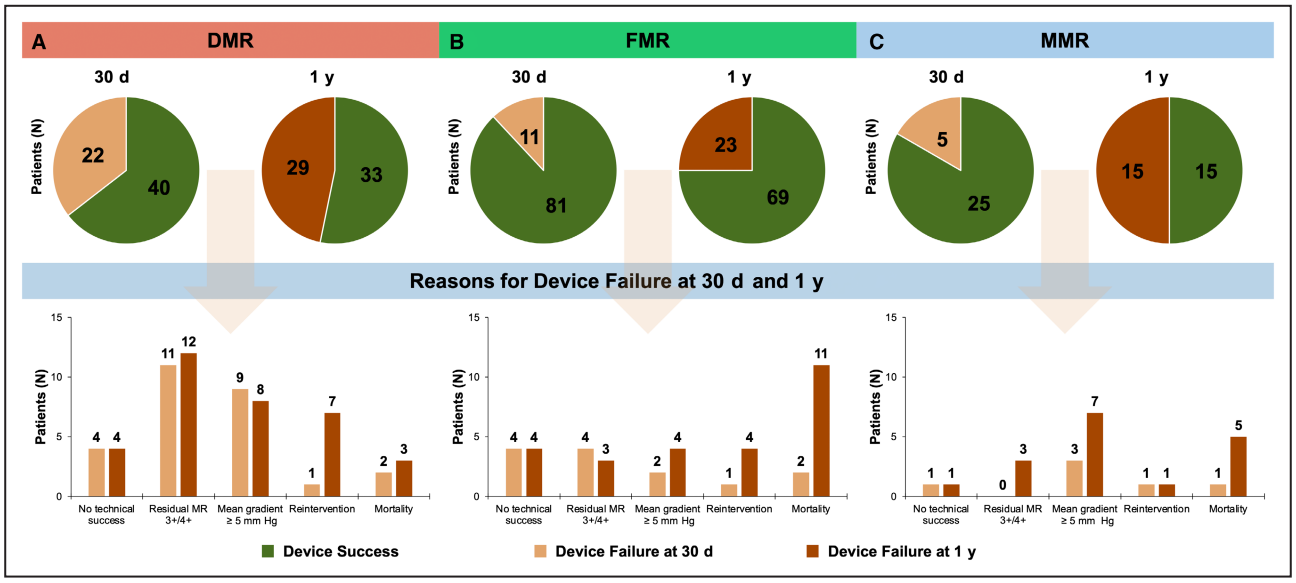


**Figure 1. Paired device success at 30 days and 1 year.**
Device success at 30-days and 1-year was achieved in DMR: 64.5% and 53.2% (A); FMR: 88.0% and 75.0% (B); and MMR: 83.3% and 50.0% (C) (n=15/30). Reinterventions for iatrogenic atrial septal defect and for mitral valve dysfunction were included. DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; MMR, mixed mitral regurgitation; and MR, mitral regurgitation.

identified 84 COAPT-eligible and 57 COAPT-ineligible patients with FMR, who were ineligible because of left ventricular ejection fraction <20% (n=12), left ventricular end-systolic diameter >70 mm (n=7), tricuspid regurgitation grade >2+, estimated pulmonary artery systolic pressure >70 mm Hg (n=5), and mitral valve orifice area <4 $cm^2$ (n=16). At 1-year, no difference in mortality rate was observed between COAPT-eligible and COAPT-ineligible patients (9.5% and 10.5%, respectively; log-rank test *P*=0.810). However, significantly more COAPT-ineligible than COAPT-eligible patients (4.8% versus 15.8%) were hospitalized for heart failure within 1-year (log-rank test *P*=0.039).

NYHA-FC was available in 282, 246, and 196 patients at baseline and 30-day and 1-year follow-up, respectively. At baseline, all patients were in NYHA-FC II to IV, with no difference between etiologies (*P*=0.072). At 30 days, NYHA-FC was significantly improved in all causes with 70.8% in NYHA-FC I/II (*P*<0.001 for each cause compared with baseline, and *P*=0.496 across etiologies). At 1 year, NYHA-FC was persistently improved, with 64.8% of patients in NYHA-FC I/II

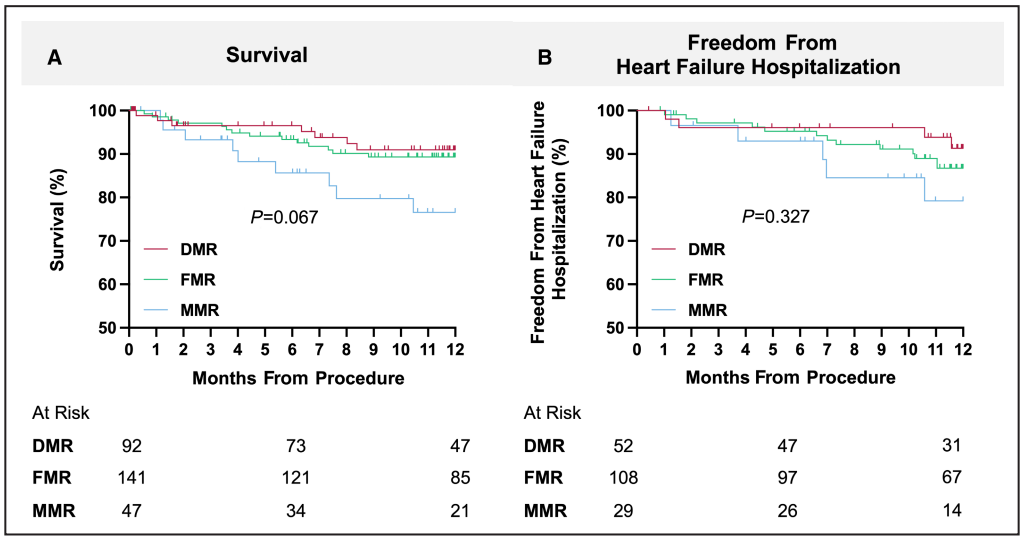


**Figure 2. Kaplan–Meier estimates of survival and freedom from heart failure hospitalization at 1 year.**
Kaplan–Meier survival (**A**) and freedom from heart failure hospitalization (**B**). DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; and MMR, mixed mitral regurgitation.

(*P*<0.001 for each etiology compared with baseline, and *P*=0.385 across etiologies; Figure 3).

## Echocardiographic Outcomes at 30 Days and 1 Year

Echocardiographic follow-up at 30-days and 1-year was obtained in 76% (DMR, N=70/92), 82% (FMR, N=115/141), and 71% (MMR, N=35/49) of patients and in 60% (DMR, N=55/92), 69% (FMR, N=97/141), and 65% (MMR, N=32/49) of patients, respectively.

At 30-days, MR reduction to ≤1+ or ≤2+ was achieved in 50.0% and 82.9% of patients with DMR, 67.0% and 96.5% of patients with FMR, and 74.3% and 100% of patients with MMR, respectively (*P*=0.024 and *P*<0.001 for MR ≤1+ or MR ≤2+ across etiologies, respectively). At 1-year, MR reduction to ≤1+ or ≤2+ was achieved in 52.7% and 78.2% of patients with DMR, 75.0% and 96.9% of patients with FMR, and 68.8% and 90.6% of patients with MMR, respectively (*P*=0.021 and *P*<0.001 for MR ≤1+ or MR ≤2+ across etiologies, respectively). Details are provided in Figure 3. Moreover, Table S2 provides anatomic details of patients with DMR with residual MR 3+/4+ at 1-year follow-up. Paired echocardiographic data were available for 57% (N=52/92) of patients with DMR and revealed MR ≤1/2+ in 65.4%/94.2%, 50.0%/88.5%, and 50.0%/76.9% at discharge, 30days, and 1-year, respectively. Paired analysis could be performed in 60% (N=84/141) of patients with FMR and demonstrated MR ≤1/2+ in 76.2%/98.8% at discharge and in 65.5%/96.4% at 30-days and in 72.6%/96.6% at 1-year. For 53% (N=26/49) of the patients with MMR paired echocardiographic data was available and found an MR reduction to ≤1/2+ in 80.8%/100%, 73.1%/100%, and 69.2%/88% at discharge, 30-days, and 1-year, respectively. Details on paired echocardiographic outcomes are given in Tables S3 through S5 and in Figure 3.

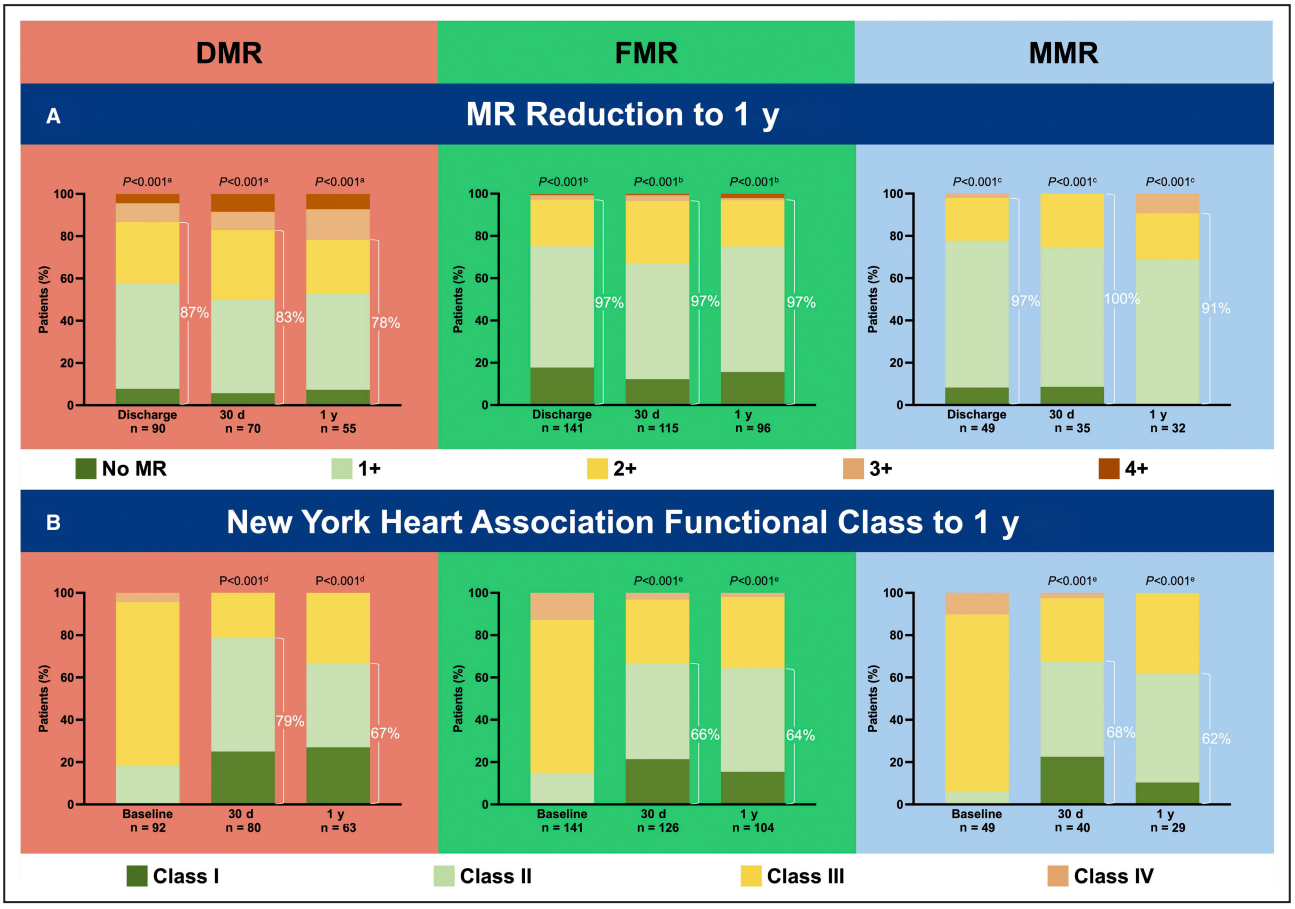


**Figure 3. Echocardiographic and functional outcomes according to mitral regurgitation cause up to 1-year for the PASCAL mitral transcatheter edge-to-edge repair system.**
**A**, Unpaired MR reduction. Paired MR reduction[a–c] was available at 30-days and 1-year in N=70 and N=55 (DMR), N=115 and N=96 (FMR), and N=35 and N=32 (MMR) patients, respectively. **B**, Unpaired NYHA-FC. Paired NYHA-FC[d–f] was available at 30-days and 1-year in N=80 and N=63 (DMR), N=126, and N=104 (FMR), and N=40 and N=29 (MMR) patients, respectively. All paired analyses were performed vs baseline. DMR indicates degenerative mitral regurgitation; FMR, functional mitral regurgitation; MMR, mixed mitral regurgitation; MR, mitral regurgitation; and NYHA-FC, New York Heart Association Functional Class.

## DISCUSSION

We report outcomes according to MR etiology up to 1-year of the to-date largest real-world experience with the PASCAL M-TEER system. The observed population consisted of 282 patients, with 33% DMR, 50% FMR, and 17% MMR, thus being representative for current M-TEER populations.[7] The main findings of our study are as follows: (1) procedural success was comparably high, irrespective of MR etiology; (2) acute MR reduction to a degree ≤1/2+ was achieved more frequently in FMR and MMR compared with DMR; (3) MR reduction was highly sustained in FMR and MMR but to a lesser extent in DMR; (4) functional capacity was significantly improved in all patients, regardless of MR etiology, with >60% presenting in NYHA-FC I/II at 1-year.

The present study reports the results of a largely unselected real-world population including consecutive patients treated at an early phase of experience with the PASCAL M-TEER system. This is in relevant contrast to other recent studies on the PASCAL devices that included both anatomically and clinically highly selected patients. The CLASP approval trial enrolled 109 patients with symptomatic MR, including 73 with FMR.[7] Patients with advanced left ventricular disease (left ventricular ejection fraction ≤20%; left ventricular end-diastolic diameter >80 mm), small mitral valve area, or relevant tricuspid regurgitation were excluded. Furthermore, patients had to pass a central eligibility committee for inclusion.[7] Despite these differences with respect to eligibility criteria, the 1-year results of our cohort were still comparable with those of the CLASP study with regard to death (10.5% in CLASP versus 10.6%), heart failure–related rehospitalization (18.4% in CLASP versus 11.6%), and valve-related reintervention (2.6% in CLASP versus 0.7%).[7] Also, in FMR the extent of MR reduction was comparable (MR ≤1/2+ at 1 year 79%/100% versus 75%/97%), demonstrating the ability of experienced operators to achieve durable MR reduction in FMR also in unselected patients.

The EXPAND study, a multicenter postmarket registry of the third-generation MitraClip, reported contemporary outcomes of 413 patients with symptomatic FMR. The EXPAND study included patients eligible for M-TEER according to the MitraClip indication approved in the respective country and hence did not include patients with exceptionally complex pathologies.[20] The results of the EXPAND study compare well with our results regarding MR reduction and durability of MR reduction up to 1-year. Of relevance is the comparatively high rate of SLDA (1.9%) observed in the FMR group of the EXPAND study. Although this rate is lower than the early experience with various MitraClip devices, it is still higher than the SLDA rate of 0.7% we observed with the PASCAL device.[20–22] It may be speculated that the novel features of the PASCAL system such as the central spacer and the shaped paddles may be beneficial in FMR patients in which the mitral leaflets often experience tethering and therefore more tension.[21,23] Moreover, the possibility of independent leaflet grasping may have provided an advantage over the third-generation MitraClip system, allowing more stable positioning of the device.[24]

In contrast with the durable outcomes with the PASCAL system in FMR, we observed a deterioration of the primary procedural result in DMR from MR ≤1/2+ in 58%/87% at discharge to 53%/78% at 1-year. This was even more pronounced in paired echo analysis of 55 patients with DMR (MR ≤1/2+ at discharge in 65%/94% versus 50%77% at 1-year). While the acute results of MR reduction to ≤2+ are in line with the literature, our 1-year results are appreciably less encouraging than in the CLASP and CLASP IID study.[7,10,25] In the CLASP study, MR reduction to ≤2+ was sustained in all, and to ≤1+ in 86%, 21 available patients with DMR at 1-year.[7] Similar results were achieved in the CLASP IID trial with an MR ≤1/2+ at 6 -months in 84%/98%.[10] Notably, compared with our study, which focused exclusively on the PASCAL P10 implant, in the CLASP IID trial, a total of 32.7% (24.1% alone and 8.6% in combination with the P10) of patients were treated with the more recently introduced PASCAL Ace.[10] From an interventional perspective, the P10 implant and the Ace implant may exhibit advantages and disadvantages in different scenarios. The PASCAL P10 is a large implant with a medial-lateral dimension of 10 mm compared with 6 mm of the PASCAL Ace implant, and the central spacer of the P10 is wider at 5 mm compared with 2 mm of the Ace. With its narrower dimensions, the PASCAL Ace may be more suitable for the treatment of complex anatomies such as commissurally located pathologies, smaller mitral valve orifice areas, and multiscallop prolapse involvement, as more implants may be required in the latter scenario. On the other side, the PASCAL P10 with its wide central spacer provides filling of the regurgitant orifice and is thought to reduce stress on the leaflets, benefits that may be beneficial in patients with FMR. Finally, the PASCAL P10 casts a spherical shadow that can make echocardiographic visualization of the pathology more challenging.

Besides MR reduction to ≤1/2+, CLASP observed appreciably lower rates of death (4.2% in CLASP versus 9.0%) and heart failure rehospitalization (0.0% in CLASP versus 8.7%) at 1-year, indicating a substantially higher morbidity burden in all-comers populations compared with the selected study populations. However, the higher rate of heart failure rehospitalization may also be influenced by the worse procedural outcome. The differences to our study with regard to durability of M-TEER are most likely due to the strict anatomic selection criteria of CLASP/CLASP IID. On average, only 1.4 patients/center per year were

actually randomized into CLASP IID, hence not representing the vast majority of patients with DMR.[10] Moreover, the patients in our study were the first patients treated with the PASCAL implant and thus early in the learning curve with a new device. Finally, the alleged advantages of the PASCAL system in terms of steerability and independent leaflet capture have led to the inclusion of particular complex anatomies considered unsuitable for MitraClip treatment. The observed poorer acute and less sustainable MR reduction in DMR emphasizes the high relevance of real-world data, as unselected patients have poorer outcomes, at least in the long term.[26] An anatomic reanalysis of patients with DMR with residual MR 3+/4+ (Table S2) revealed a high proportion of anatomies considered complex or very complex such as Barlow disease, noncentral pathology, or small mitral valve area.[23] Most recently, the CLASP IID registry, investigating the PASCAL system in DMR with anatomically complex mitral valve anatomy, demonstrated MR reduction to ≤2+ in 92.4% and ≤1+ in 56.1% (paired analysis) at 6 months, being more comparable with our results than the results of the randomized trial. The CLASP IID registry included patients that were not eligible for randomization within the CLASP IID randomized trial due to anatomic criteria outside of the traditional instructions for use criteria of the MitraClip system.[9] It should be noted that these criteria have been surpassed in daily clinical practice in experienced centers for years and even the complex cases included in the CLASP IID registry are most likely not representative for the prevalence of complex DMR anatomies in the real world.[23,26]

In the DMR subgroup of the EXPAND study, death and heart failure rehospitalization were comparable to our study. It is worth noting that the DMR subgroup of the EXPAND study included patients with DMR and MMR. At 1 year, MR reduction to ≤2+ was observed appreciably more often in the EXPAND study (93.8% in EXPAND versus 78.2% in our study). Of interest, although all patients in the DMR/MMR subgroup of the EXPAND trial had a site-reported MR severity of ≥3+ at baseline, remarkable 33.6% of these patients were downgraded to MR ≤2+ after reanalysis by an echocardiography core lab.[27] Furthermore, SLDA were substantially less frequent in the DMR/MMR (2.4%) subpopulation than in our population (6.5%), which could be due to the early stage of the learning curve with a new device or due to the distinct features of the devices. However, it seems more likely that the aforementioned differences in MR reduction and SLDA reflect the fact that the EXPAND study included only patients who were eligible for the MitraClip within the currently approved indications in their respective geographies. Also, pooling DMR and MMR in EXPAND, rather than reporting these causes separately, may have had an impact on reported MR reduction and SLDA, as outcomes of MMR patients are generally more comparable to FMR patients, as we also observed.[27]

Summarized, in daily clinical practice, mitral anatomies and patient characteristics seem to be more diverse and complex compared with trial populations with strict eligibility criteria.[7,10,28] In this context, outcomes in terms of MR reduction, death, heart failure rehospitalization, and valve-related reintervention appear to be substantially less favorable for DMR. The current results reflect the high prevalence of complex degenerative anatomies and the clinical need for treatment, often due to a lack of alternatives in patients with prohibitive surgical risk. In patients with FMR/MMR, however, an excellent and sustained MR reduction could be achieved despite the lack of any selection criteria. Therefore, the efficacy of MR reduction in FMR/MMR in the context of PASCAL treatment appears to be less dependent on rigorous patient selection as in patients with DMR.

## Study Limitations

The present study is of observational nature and has several limitations. Designed as a registry, all echocardiographic and clinical data are site reported and lack independent adjudication by an event committee. However, MR grading has been adjudicated in a selected number of patients by an expert panel that found excellent agreement with the site-reported MR grading.[13] Furthermore, sample size was limited for 30-day as well as 1-year echocardiographic and functional assessment since all centers have large referral areas and many patients deny returning for follow-up assessment. In addition, our work focused exclusively on the performance of the P10 device while the smaller PASCAL Ace has been introduced into clinical practice. Finally, the results of efficacy and safety must be regarded in the context of the early phase of the learning curve with a new device, as reported previously.[11]

# CONCLUSIONS

In this large all-comer cohort, M-TEER with the PASCAL system was associated with an acute MR reduction to ≤2+ in 86.7% of patients with DMR, in 97.2% of patients with FMR, and in 98.0% of patients with MMR ($P$=0.004). At 1 year, MR reduction to ≤2+ was sustained in all etiologies, although in patients with DMR, MR reduction was less pronounced, reflecting the high incidence of complex or very complex anatomies being referred for M-TEER.

## ARTICLE INFORMATION

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## Supplemental Material

Tables S1–S5

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