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2-Year Outcomes for Transcatheter Repair in Patients With Mitral Regurgitation From the CLASP Study

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ABSTRACT

OBJECTIVES The study reports 2-year outcomes from the multicenter, prospective, single-arm CLASP study with functional mitral regurgitation (FMR) and degenerative MR (DMR) analysis.

BACKGROUND Transcatheter repair is a favorable option to treat MR. Long-term prognostic impact of the PASCAL transcatheter valve repair system in patients with clinically significant MR remains to be established.

METHODS Patients had clinically significant MR ≥3+ as evaluated by the echocardiographic core laboratory and were deemed candidates for transcatheter repair by the heart team. Assessments were performed by clinical events committee to 1 year (site-reported thereafter) and core laboratory to 2 years.

RESULTS A total of 124 patients (69% FMR, 31% DMR) were enrolled with a mean age of 75 years, 56% were male, 60% were New York Heart Association functional class III to IVa, and 100% had MR ≥3+. At 2 years, Kaplan-Meier estimates showed 80% survival (72% FMR, 94% DMR) and 84% freedom from heart failure (HF) hospitalization (78% FMR, 97% DMR), with 85% reduction in annualized HF hospitalization rate (81% FMR, 98% DMR). MR ≤1+ was achieved in 78% of patients (84% FMR, 71% DMR) and MR ≤2+ was achieved in 97% (95% FMR, 100% DMR) (all $p < 0.001$). Left ventricular end-diastolic volume decreased by 33 ml ($p < 0.001$); 93% of patients were in New York Heart Association functional class I to II ($p < 0.001$).

CONCLUSIONS The PASCAL repair system demonstrated sustained favorable outcomes at 2 years in FMR and DMR patients. Results showed high survival and freedom from HF rehospitalization rates with a significantly reduced annualized HF hospitalization rate. Durable MR reduction was achieved with evidence of left ventricular reverse remodeling and significant improvement in functional status. The CLASP IID/IIF randomized pivotal trial is ongoing.
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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

CEC = clinical events committee

DMR = degenerative mitral regurgitation

FMR = functional mitral regurgitation

HF = heart failure

LV = left ventricular

LVEDV = left ventricular end-diastolic volume

LVEF = left ventricular ejection fraction

MAE = major adverse event

MI = myocardial infarction

MR = mitral regurgitation

NYHA = New York Heart Association

Mitral regurgitation (MR) is one of the most prevalent valvular heart diseases worldwide (1,2). Left untreated, MR leads to increased hospitalizations and significant morbidity and mortality (3). However, owing to high operative risk or missed referrals, only 15% of patients diagnosed with moderate-severe MR undergo surgery (4). MR is a heterogeneous disease with varying treatment options. Surgical intervention is the gold standard for degenerative MR (DMR), whereas patients with functional MR (FMR) are frequently medically managed (5). Transcatheter mitral valve repair has emerged as an important option in patient care for treating MR with a need for longer term data (5–9).

The CLASP (Edwards PASCAL TrAnScatheter Mitral Valve RePair System) study assessed the safety and feasibility of the PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, California). Previously, results from 109 patients were reported and showed 96% of patients achieved MR ≤2+ at 30 days and 100% at 1 year (10). Furthermore, in 62 patients with 1-year follow-up, the authors reported 92% survival and 88% freedom from heart failure (HF) rehospitalization at 1 year (10). Herein, we report outcomes to 2 years and analysis by FMR and DMR etiologies.

METHODS

PATIENT SELECTION. Key inclusion criteria were clinically significant MR ≥3+ as confirmed by the echocardiographic core laboratory and New York Heart Association (NYHA) functional class II-ambulatory IV despite medical therapy. Patients were deemed candidates for transcatheter mitral valve repair by the local multidisciplinary heart team, which included HF specialists, interventional cardiologists, cardiac surgeons, and imaging specialists. Other eligibility criteria included presence of a noncommissural primary regurgitant jet with absence of a clinically significant secondary jet and left ventricular (LV) ejection fraction ≤20%. Key exclusion criteria were mitral valve area <4 cm^2; severe tricuspid regurgitation; previous mitral valve surgery or transcatheter procedure; LV end-diastolic diameter >8 cm; and untreated significant coronary artery diseases, unstable angina, or myocardial infarction (MI) (9,10).

STUDY CONDUCT. Patient eligibility was evaluated by a multidisciplinary central eligibility committee after initial screening by investigators. An echocardiographic core laboratory assessed all echocardiograms, and an independent clinical events committee (CEC) adjudicated major adverse events to 1 year. All respective local ethics committees and health authorities of participating countries approved the study, and all patients provided written informed consent. The study was sponsored by Edwards Lifesciences, registered in ClinicalTrials.gov (NCT03170349), and was conducted in conformance with the Declaration of Helsinki, Good Clinical Practice principles, and ISO 14155:2011.

THE PASCAL TRANSCATHETER VALVE REPAIR SYSTEM AND PROCEDURE. The PASCAL repair system is a differentiated transcatheter leaflet repair therapy to treat a regurgitant mitral valve using a percutaneous transseptal approach. The PASCAL implant consists of 2 clasps with retention elements, 2 paddles, and a central spacer. The clasps and retention elements gently grasp the mitral leaflets, the paddles facilitate coaptation, and the spacer fills the regurgitant orifice area to minimize MR. The broad contoured paddles are designed to maximize leaflet coaptation while minimizing stress on native leaflets. To optimize MR outcomes, the clasps can be operated simultaneously or independently, which allows staged leaflet capture and adjustment of leaflet insertion. The features of the PASCAL repair system have been previously described (9,10). The PASCAL Ace implant is a recent addition to the PASCAL repair system platform and features narrower contoured paddles (6-mm wide compared with 10 mm in the original PASCAL implant) with a modified clasp design to engage relatively more leaflet for a small implant (Supplemental Figure 1).

Percutaneous access to the left atrium is obtained using a transvenous, transseptal approach. The PASCAL repair procedure is guided by transesophageal echocardiography with systematic intraprocedural assessment of residual MR and transmitral gradient (9,10). The low-profile 22-F guide sheath and

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Baseline Characteristics

	Overall (N = 124)	FMR (n = 85)	DMR (n = 39)
Age, yrs	74.9 ± 11.2	72.2 ± 11.6	80.7 ± 7.4
Male	55.6 (69)	55.3 (47)	56.4 (22)
NYHA functional class III-IVa	60.2 (74)	64.7 (55)	50.0 (19)
NT-proBNP, pg/ml	4,148.7 ± 6,430.8 (36)	5,122.3 ± 7,271.9 (26)	1,617.2 ± 2,018.9 (10)
eGFR, ml/min/1.73 m^2	58.6 ± 20.8 (113)	58.6 ± 21.5 (78)	58.7 ± 19.3 (35)
Mitral annular calcification ≤ mild (TTE)	96.0 (119)	97.6 (83)	92.3 (36)
Vena contracta width, A-P (TTE), mm	6.3 ± 1.4 (108)	6.2 ± 1.4 (76)	6.6 ± 1.5 (32)
Jet width, commissural (TEE), mm,	13.4 ± 3.8 (102)	13.7 ± 3.6 (72)	12.5 ± 4.1 (30)
Tricuspid regurgitation ≥ mild-moderate (TTE)	28.5 (35)	32.1 (27)	20.5 (8)
Comorbidities			
Hypertension	66.9 (83)	63.5 (54)	74.4 (29)
Pulmonary hypertension (>35mm Hg)	19.4 (24)	16.5 (14)	25.6 (10)
Cardiomyopathy	51.8 (58)	66.2 (49)	23.7 (9)
Previous myocardial infarction	36.3 (45)	41.2 (35)	25.6 (10)
Prior TIA or stroke	15.3 (19)	18.8 (16)	7.7 (3)
Aortic valve disease*	37.1 (43)	36.7 (29)	37.8 (14)
Pulmonic valve disease†	35.5 (44)	38.8 (33)	28.2 (11)
Tricuspid valve disease‡	58.1 (72)	63.5 (54)	46.2 (18)
Coronary artery disease	41.9 (52)	52.9 (45)	17.9 (7)
Heart failure	53.2 (66)	56.5 (48)	46.2 (18)
Atrial fibrillation	53.4 (63)	57.0 (45)	46.2 (18)
AV block ≥ first degree	23.4 (29)	23.5 (20)	23.1 (9)
Diabetes	29.0 (36)	31.8 (27)	23.1 (9)
Renal disease	24.2 (30)	24.7 (21)	23.1 (9)
Chronic lung disease	5.6 (7)	7.1 (6)	2.6 (1)

Values are % (n) or mean ± SD (n). *Aortic valve disease includes regurgitation and stenosis. †Pulmonic valve disease includes rheumatic, syncope, and thromboembolic. ‡Tricuspid valve disease includes ventricular septal defect.

A-P = anterior-posterior; AV = atrioventricular; DMR = degenerative mitral regurgitation; eGFR = estimated glomerular filtration rate; FMR = functional mitral regurgitation; NT-proBNP = N-terminal pro-B-type natriuretic peptide; NYHA = New York Heart Association; TEE = transesophageal echocardiography; TIA = transient ischemic attack; TTE = transthoracic echocardiography.

steerable catheter enable control of implant positioning and trajectory, while the implant catheter enables control of actuation, orientation, and release of the implant. The ability to independently steer these catheters allows maneuverability in 3 different planes. If implant repositioning is desired, the PASCAL repair system allows for implant elongation for low-profile and atraumatic maneuvering within the subvalvular anatomy.

STUDY ENDPOINTS. The CLASP study endpoints have been previously described (9,10). The primary performance endpoints included procedural and clinical success. Procedural success was defined as at least 1 device deployed with successful retrieval of the delivery system at the time of the patient's exit from the cardiac catheterization laboratory, and evidence of MR reduction ≤2+ at discharge without need for surgical or percutaneous intervention. Clinical success was defined as procedural success plus evidence of MR reduction to ≤2+ with absence of major adverse events (MAEs) at 30 days. The primary safety endpoint was a 30-day MAE rate defined as the composite of cardiovascular mortality, stroke, MI, new need for renal replacement therapy, severe bleeding (major, extensive, life-threatening, or fatal bleeding, as defined by the Mitral Valve Academic Research Consortium) (11), and reintervention for study device-related complications. All MAEs were adjudicated by an independent CEC to 1 year and site-reported thereafter in accordance with the protocol.

Secondary endpoints included NYHA functional class, 6-min walk distance (6MWD), and quality-of-life scores as measured by Kansas City Cardiomyopathy Questionnaire and EQ-5D (EuroQoL-5 Dimension). Clinical and echocardiographic assessments were conducted at 30 days, 1 year, and 2 years. 6MWD and quality-of-life assessments were performed to 1 year in accordance with the protocol.

TABLE 2 CEC-Adjudicated Events to 1 Year

	Overall (N = 124)		FMR (n = 85)		DMR (n = 39)	
	30 Days	1 Year	30 Days	1 Year	30 Days	1 Year
MAE						
Cardiovascular mortality	0.8 (1)	5.6 (7)	1.2 (1)	8.2 (7)	0	0
Stroke	0.8 (1)	1.6 (2)	1.2 (1)	2.4 (2)	0	0
Myocardial infarction	0	1.6 (2)	0	1.2 (1)	0	2.6 (1)
New need for renal replacement therapy	0.8 (1)	0.8 (1)	1.2 (1)	1.2 (1)	0	0
Severe bleeding*	7.3 (9)	11.3 (14)	9.4 (8)	15.3 (13)	2.6 (1)	2.6 (1)
Reintervention for study device-related complications	0.8 (1)	1.6 (2)	1.2 (1)	2.4 (2)	0	0
Composite MAE rate	8.1 (10)	18.5 (23)	10.6 (9)	24.7 (21)	2.6 (1)	5.1 (2)
Other events						
All-cause mortality	0.8 (1)	8.1 (10)	1.2 (1)	10.6 (9)	0	2.6 (1)
Heart failure rehospitalization	2.4 (3)	12.1 (15)	3.5 (3)	17.6 (15)	0	0

Values are % (n). *Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium.
CEC = clinical events committee; MAE = major adverse event; other abbreviations as in Table 1.

ECHOCARDIOGRAPHIC ASSESSMENT. All patients underwent transthoracic echocardiography and transesophageal echocardiography prior to enrollment to assess anatomic feasibility and aid in procedural planning. All screening, baseline, and follow-up echocardiograms were analyzed by an independent core laboratory (Cardiovascular Core Lab at Morristown Medical Center, Morristown, New Jersey) according to pre-established protocols and American Society of Echocardiography guidelines (9-14).

STATISTICAL METHODS. Continuous variables are presented as median (interquartile range) or mean ± SD comparing baseline and specific timepoints using paired Student's *t*-test. Categorical data are expressed as a percentage and compared using the Wilcoxon signed rank test. Transvalvular gradients were analyzed using analysis of variance. Statistical significance was set at $p < 0.05$ as 2-tailed tests at a confidence level of 95%. Deltas were calculated using paired analyses.

Time-to-event variables were analyzed using Kaplan-Meier survival analysis, and the exponential Greenwood method was used to calculate standard error (15). The duration of follow-up is presented as median (interquartile range). Pre-procedure and post-procedure HF hospitalization rates were analyzed with a Poisson regression model using length of post-procedure follow-up days as an offset; statistical significance was computed with the Wald chi-square statistic from the model. All statistical analyses were performed using SAS Software version 9.4 (SAS Institute, Cary, North Carolina).

RESULTS

Between June 2017 and July 2020, 124 patients were treated with the PASCAL repair system at 14 sites in 5 countries. All patients were followed for at least 30 days with a median follow-up of 1.9 (interquartile range: 1.1 to 2.3) years and a maximum of 3.2 years (Supplemental Figure 2). At the time of analysis, patient follow-up is ongoing, with 10 patients pending 1-year follow-up and 32 pending 2-year follow-up. The echocardiographic core laboratory further assessed patients with mixed etiology and categorized as predominantly FMR or DMR, resulting in a total of 69% (n = 85) patients with FMR and 31% (n = 39) patients with DMR for analysis.

BASELINE CHARACTERISTICS. Mean patient age was 75 years, 56% were male, and 60% were in NYHA functional class III to IVa. Comorbidities included cardiomyopathy (52%), tricuspid valve disease (58%), coronary artery disease (42%), HF (53%), and atrial fibrillation (53%). FMR patients had elevated N-terminal pro-B-type natriuretic peptide (5,122 pg/ml) and higher prevalence of HF (57%), cardiomyopathy (66%), prior MI (41%), prior transient ischemic attack or stroke (19%), tricuspid valve disease (64%), coronary artery disease (53%), and atrial fibrillation (57%). DMR patients were older (mean age 81 years) and had overall lower risk factors other than hypertension (74%) and pulmonary hypertension >35 mm Hg (26%). Baseline characteristics are shown in Table 1.

PROCEDURAL OUTCOMES. Successful implantation was achieved in 96% of patients. Five patients did not

receive an implant due to inability to adequately grasp leaflets (n = 3), unsuitable venous access (n = 1), or single-leaflet device attachment, which was converted to surgical mitral valve replacement (n = 1).

Procedural success was achieved in 94% of patients (94% FMR, 95% DMR). The median number of devices implanted was 1 (2 FMR, 1 DMR), with 53% of patients receiving only 1 implant. Other procedural measures are summarized in Supplemental Table 1.

CLINICAL OUTCOMES. Clinical success was achieved in 87% of patients (84% FMR, 92% DMR).

Events are summarized in **Tables 2 and 3**. The CEC-adjudicated composite MAE rate at 30 days was 8.1% (10.6% FMR, 2.6% DMR), with 1 (0.8%) cardiovascular death, 1 (0.8%) stroke, no MI, 1 (0.8%) new need for renal replacement therapy, 9 (7.3%) severe bleeds, and 1 (0.8%) surgical reintervention. Of these events, 3 were adjudicated to be device-related: stroke (n = 1), severe bleed (n = 1), and surgical reintervention (n = 1).

At 1 year, the CEC-adjudicated composite MAE rate was 18.5% (24.7% FMR, 5.1% DMR) including 5.6% cardiovascular mortality (all in FMR patients). Late MAEs between 30 days and 1 year included 6 cardiovascular deaths, 1 stroke, and 2 MIs. All these events were adjudicated to be unrelated to study device or procedure. One device-related surgical reintervention occurred due to an single-leaflet device attachment and device embolization.

At 2 years, the site-reported composite MAE rate was 16.9% (20.0% FMR, 10.3% DMR) including 8.9% cardiovascular mortality (predominantly in FMR patients). Between 1 and 2 years, MAEs included 4 cardiovascular deaths, 2 strokes, 1 MI, and 1 new reintervention.

Survival rates (Kaplan-Meier analysis) were 91.2% at 1 year (88.3% FMR, 97.3% DMR) and 80.3% at 2 years (72.3% FMR, 94.3% DMR) (**Central Illustration**). The CEC-adjudicated rate of freedom from HF rehospitalization (Kaplan-Meier analysis) was 87.0% at 1 year (80.9% FMR, 100% DMR) (Supplemental Figure 3). The site-reported rate of freedom from HF rehospitalization (Kaplan-Meier analysis) was 84.3% at 2 years (77.5% FMR, 97.3% DMR) (**Central Illustration**).

The CEC-adjudicated annualized HF hospitalization rate decreased from 1.16 pre-procedure to 0.20 post-procedure ($p < 0.001$) at 1 year, an 82% reduction (78% FMR, 100% DMR). The 2-year site-reported reduction in annualized HF hospitalization rate was 85% (81% FMR, 98% DMR) (**Figure 1**).

ECHOCARDIOGRAPHIC RESULTS. Echocardiographic data were available at 30 days for 119 patients (81 FMR, 38 DMR), 1 year for 85 patients (53 FMR, 32 DMR), and 2 years for 36 patients (19 FMR, 17 DMR) with follow-up ongoing.

TABLE 3 Site-Reported Events to 2 Years

	Overall (N = 124)	FMR (n = 85)	DMR (n = 39)
MAE			
Cardiovascular mortality	8.9 (11)	11.8 (10)	2.6 (1)
Stroke	3.2 (4)	3.5 (3)	2.6 (1)
Myocardial infarction	2.4 (3)	1.2 (1)	5.1 (2)
New need for renal replacement therapy	0.8 (1)	1.2 (1)	0
Severe bleeding*	7.3 (9)	8.2 (7)	5.1 (2)
Reintervention for study device related complications	2.4 (3)	3.5 (3)	0
Composite MAE rate	16.9 (21)	20.0 (17)	10.3 (4)
Other events			
All-cause mortality	15.3 (19)	20.0 (17)	5.1 (2)
Heart failure rehospitalization	13.7 (17)	18.8 (16)	2.6 (1)

Values are % (n). *Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium.

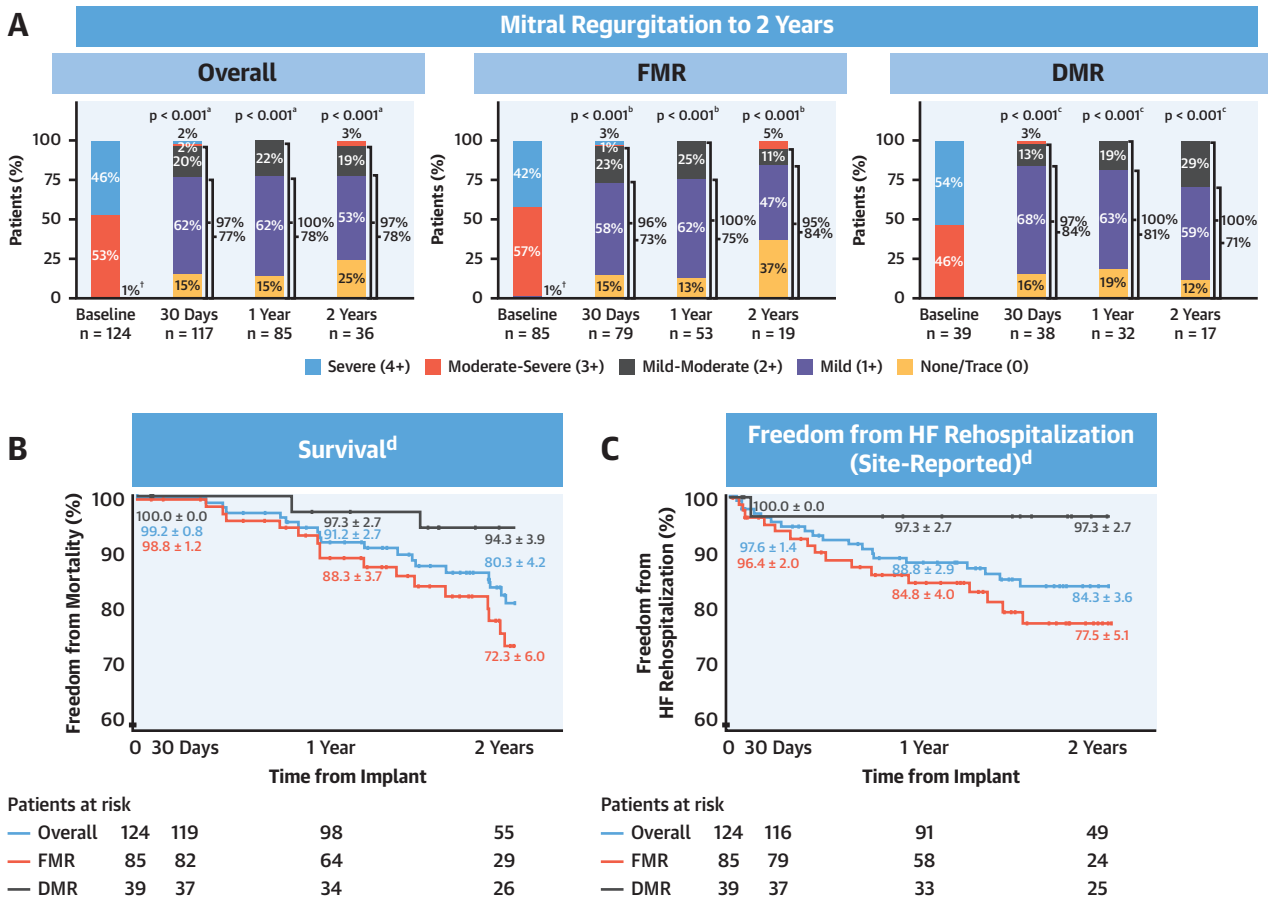
Abbreviations as in **Tables 1 and 2**.

At 30 days, 97% of patients achieved MR ≤2+ and 77% MR ≤1+ ($p < 0.001$ vs. baseline). MR reduction was sustained at 2 years with 97% of patients with MR ≤2+ and 78% MR ≤1+ ($p < 0.001$). In FMR patients, 95% of patients achieved MR ≤2+ and 84% MR ≤1+ at 2 years ($p < 0.001$). In DMR patients, 100% achieved MR ≤2+ and 71% MR ≤1+ at 2 years ($p < 0.001$). Results are shown in the **Central Illustration**.

Mean transvalvular gradients were stable over time with 4.0 mm Hg at discharge, 3.9 mm Hg at 30 days, 3.9 mm Hg at 1 year, and 4.1 mm Hg at 2 years ($p = 0.661$ vs. discharge) (Supplemental Figure 4). In FMR patients, mean gradients were 4.1 mm Hg at discharge, 4.0 mm Hg at 30 days, 4.2 mm Hg at 1 year, and 4.8 mm Hg at 2 years ($p = 0.765$ vs. discharge). In DMR patients, mean gradients were 3.9 mm Hg at discharge, 3.6 mm Hg at 30 days, 3.4 mm Hg at 1 year, and 3.4 mm Hg at 2 years ($p = 0.315$ vs. discharge). The change from discharge to 2 years was not significant in overall, FMR, and DMR groups.

Significant reductions in all echocardiographic MR indices were observed at 30 days and were sustained at 1 year and 2 years (**Table 4,** Supplemental Tables 2 and 3). LV end-diastolic diameter decreased by 2.7 mm at 30 days ($p < 0.001$ vs. baseline), which was sustained at 1 year (3.9 mm; $p < 0.001$) and 2 years (2.7 mm; $p = 0.002$); LV end-diastolic volume (LVEDV) (**Figure 2**) decreased by 11 ml at 30 days ($p < 0.001$) and continued to decrease at 1 year (25 ml; $p < 0.001$) and 2 years (33 ml; $p < 0.001$). Significant and sustained improvements were also observed at 30 days, 1 year, and 2 years in both FMR and DMR groups.

CENTRAL ILLUSTRATION **2-Year MR Reduction, Survival, and HF Rehospitalizations in the CLASP Study**



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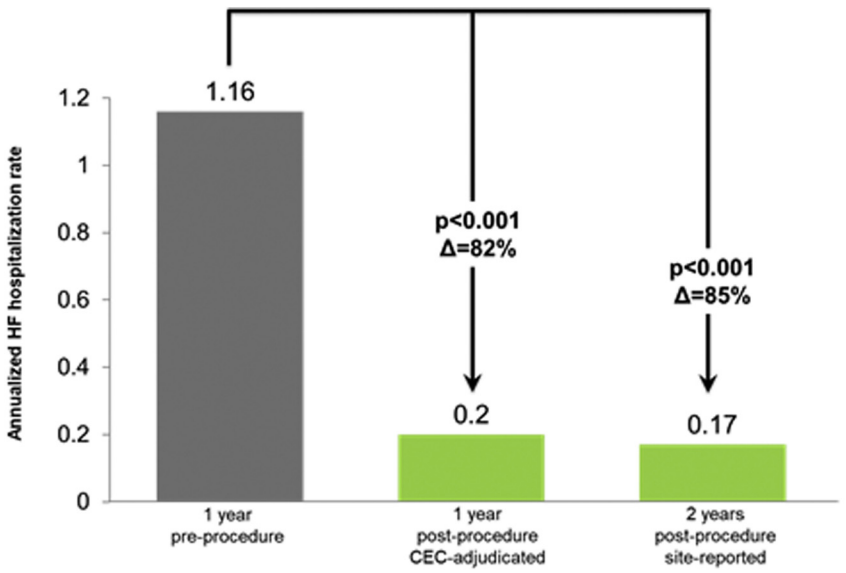
Graphs show unpaired data. The p value was calculated from paired analysis using the Wilcoxon signed rank test. [a]Baseline versus 30 days (n = 117), 1 year (n = 85), and 2 years (n = 36). [b]Baseline versus 30 days (n = 79), 1 year (n = 53), and 2 years (n = 19). [c]Baseline versus 30 days (n = 38), 1 year (n = 32), and 2 years (n = 17). [†]One patient had mitral regurgitation (MR) 1+ by transthoracic echocardiography and 3+ by transesophageal echocardiography. [d]Kaplan-Meier analysis time to first event ± SE. DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; HF = heart failure.

In the overall group, LV ejection fraction (LVEF) remained stable, from 43.8% at baseline to 43.1% ($p = 0.013$ vs. baseline) at 30 days, at 1 year (45.4%; $p = 0.163$), and at 2 years (47.2%; $p = 0.382$). In FMR patients, an LVEF of 36.7% at baseline remained stable at 36.3% ($p = 0.143$) at 30 days and at 1 year (39.0%; $p = 0.365$). At 2 years in FMR patients, LVEF recovered to 39.5% with an absolute improvement of 4.7% compared with baseline in paired analysis ($p = 0.016$). In DMR patients, LVEF of 59.3% at baseline was maintained at 30 days (57.6%; $p = 0.030$), 1 year (56.1%; $p < 0.001$), and 2 years (55.8%; $p = 0.027$).

FUNCTIONAL AND QUALITY-OF-LIFE OUTCOMES. In the overall group, 88% of patients were in NYHA functional class I to II at 30 days ($p < 0.001$ vs. baseline), which was sustained at 1 year (89%; $p < 0.001$) and at 2 years (93%; $p < 0.001$) as shown in **Figure 3**. Mean 6MWD (Supplemental Figure 5) increased by 25 m at 30 days ($p < 0.001$), sustained at 1 year (34 m; $p < 0.001$). Average Kansas City Cardiomyopathy Questionnaire score (Supplemental Figure 6) improved by 16 points at 30 days ($p < 0.001$), sustained at 1 year (16 points; $p < 0.001$). Average EQ-5D score (Supplemental Figure 7) improved by 12 points at 30 days ($p < 0.001$), which was maintained at 1 year (10 points; $p < 0.001$). Improvements in functional outcomes, exercise capacity, and quality of life were similar in the FMR and DMR groups.

FIGURE 1 **Annualized Rate of HF Hospitalization**



	1 year pre-procedure	1 year post-procedure CEC-adjudicated		2 years post-procedure site-reported	
	Patient years (#events)	Patient years (#events)	Relative RR % [95% CI] p-value	Patient years (#events)	Relative RR % [95% CI] p-value
Overall	124 (144)	112 (23)	82.4 [72.6, 88.6] p<0.001	190 (33)	85.0 [78.1, 89.7] p<0.001
FMR	85 (117)	76 (23)	77.9 [65.5, 85.9] p<0.001	122 (32)	81.0 [71.9, 87.1] p<0.001
DMR	39 (27)	37 (0)	100 [NA, NA] NA	67 (1)	97.9 [84.2, 99.7] p<0.001

CEC = clinical events committee; CI = confidence interval; DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; HF = heart failure; NA = not applicable; RR = reduction rate.

DISCUSSION

The 2-year outcomes of the CLASP study reveal 3 key findings. First, results show high survival with remarkable reduction in annualized rate of HF hospitalization. Second, MR reduction was durable and accompanied with evidence of positive LV remodeling. Third, patients experienced sustained improved functional status, exercise capacity, and quality of life. These results were pertinent to both FMR and DMR groups.

Given that randomized comparisons are forthcoming and comparing studies is difficult due to potential differences in patients, operator experience, follow-up completion, availability of echocardiographic data, and other factors, any comparisons discussed are for illustrative purposes. In the FMR group of the CLASP study, the 2-year survival and freedom from HF rehospitalization rates were 72% and 78%, respectively, comparable to 71% survival and 64% freedom from HF rehospitalization from the COAPT (Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation) study (7). In the DMR group, the 2-year survival and freedom from HF rehospitalization rates were 94% and 97%, respectively, compared with 94% and 83% in the EVEREST (Endovascular Valve Edge-to-Edge REpair Study) study (16). More impressively, in the CLASP study, the annualized rate of HF hospitalization fell by 85%, which was greater than the 65% reported in the EXPAND (A Contemporary, Prospective

TABLE 4 Echocardiographic Outcomes to 2 Years: Overall

	Baseline (n = 124)	30 Days (n = 123)	Delta p Value	1 Year (n = 96)	Δ p Value	2 Years (n = 48)	Δ p Value
LV end-diastolic diameter, mm	61.8 ± 8.0 (123)	59.0 ± 8.6 (118)	-2.7 ± 3.7 (117) p < 0.001	57.2 ± 8.3 (84)	-3.9 ± 4.4 (83) p < 0.001	56.8 ± 7.9 (36)	-2.7 ± 4.7 (36) p = 0.002
LV end-systolic diameter, mm	49.5 ± 11.7 (122)	48.1 ± 12.0 (117)	-1.2 ± 4.5 (115) p = 0.004	45.1 ± 11.2 (84)	-3.0 ± 5.5 (82) p < 0.001	44.3 ± 11.1 (36)	-2.4 ± 5.9 (36) p = 0.020
LV end-diastolic volume, ml	181.2 ± 60.8 (108)	169.1 ± 65.5 (101)	-10.8 ± 29.3 (91) p = 0.001	152.4 ± 54.5 (73)	-25.0 ± 34.0 (67) p < 0.001	136.7 ± 45.4 (34)	-33.2 ± 30.1 (30) p < 0.001
LV end-systolic volume, ml	108.7 ± 55.1 (108)	103.3 ± 57.1 (101)	-4.3 ± 19.7 (91) p = 0.038	90.2 ± 48.0 (73)	-13.3 ± 26.2 (67) p < 0.001	75.5 ± 40.2 (34)	-17.9 ± 19.6 (30) p < 0.001
Ejection fraction, %	43.8 ± 14.5 (124)	43.1 ± 13.8 (119)	-1.0 ± 4.5 (119) p = 0.013	45.4 ± 12.9 (85)	-0.9 ± 5.6 (85) p = 0.163	47.2 ± 12.4 (36)	1.1 ± 7.4 (36) p = 0.382
PISA EROA, cm^2*	0.38 ± 0.15 (101)	0.17 ± 0.21 (25)	-0.24 ± 0.22 (24) p < 0.001	0.18 ± 0.06 (10)	-0.22 ± 0.20 (9) p = 0.010	0.22 ± 0.01 (2)	-0.15 ± 0.08 (2) p = NA
Mean gradient, mm Hg	2.2 ± 0.9 (107)	3.9 ± 1.7 (117)	1.5 ± 1.5 (101) p < 0.001	3.9 ± 1.8 (85)	1.6 ± 1.6 (73) p < 0.001	4.1 ± 1.7 (36)	1.5 ± 1.5 (31) p < 0.001
Regurgitant volume, ml*	57.3 ± 19.7 (99)	25.2 ± 18.7 (25)	-38.2 ± 23.8 (23) p < 0.001	30.1 ± 10.1 (10)	-31.2 ± 17.6 (9) p = 0.001	36.0 ± 3.6 (2)	-21.4 ± 20.7 (2) p = NA
Vena contracta width, mm	6.3 ± 1.4 (108)	4.4 ± 1.2 (51)	-2.2 ± 2.1 (45) p < 0.001	4.2 ± 1.3 (43)	-2.3 ± 1.9 (38) p < 0.001	4.2 ± 1.5 (17)	-2.7 ± 1.0 (15) p < 0.001
PASP, mm Hg	46.4 ± 12.6 (112)	42.3 ± 11.3 (99)	-4.1 ± 12.0 (95) p = 0.001	40.2 ± 11.7 (70)	-5.8 ± 13.1 (68) p = 0.001	33.4 ± 9.7 (31)	-9.2 ± 13.6 (29) p = 0.001
Tricuspid regurgitation severity, 1-grade reduction	NA	29.3 (34/116)	NA p = 0.008	34.5 (29/84)	NA p = 0.008	25.0 (9/36)	NA p = 0.606

Values are mean ± SD (n) or % (n/n). The p values were calculated using Student's *t*-test or the Wilcoxon signed rank test compared with baseline. *Limited sample size due to difficulty in measuring small regurgitant volumes.

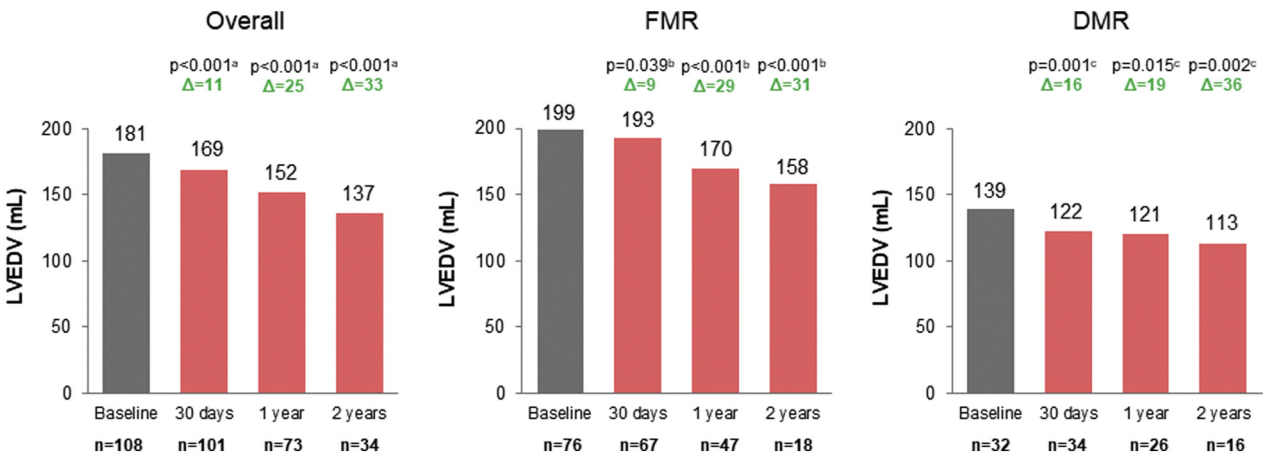
EROA = effective regurgitant orifice area; LV = left ventricular; NA = not applicable or not significant due to small sample size or not relevant; PASP = pulmonary artery systolic pressure; PISA = proximal isovelocity surface area; other abbreviations as in Table 1.

Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) study (17). Moreover, this rate reduced by 81% in the FMR group, compared with 36% in the EXPAND study and 46% in the COAPT study (7,17). Similarly, the rate in the DMR group decreased by 98%, in contrast to 33% and 73% from the EXPAND and EVEREST II studies, respectively (17,18).

Favorable survival and reduced hospitalization accompanied sustained MR reduction and positive LV remodeling in this study. These durable results hinge on minimizing residual MR (19–23). In the FMR group of our study, 100% and 95% of patients achieved MR ≤2+ at 1 year and 2 years, respectively, comparable to 95% and 99% reported in the COAPT study (7). In the DMR group of the CLASP study, 100% of patients achieved MR ≤2+ at both 1 year and 2 years, which compares favorably to 94% from the EXPAND study at 1 year (17). Additionally, in the CLASP study, the transmitral mean gradient was stable at 4.1 mm Hg at 2 years. In the FMR group, there was an insignificant change in mean gradient from 4.0 mm Hg at 30 days to 4.8 mm Hg at 2 years. Even though 7 patients had mean gradient ≥5.0 mm Hg, MR was sustained at ≤2+ without any deterioration in functional outcomes. These results were achieved with relatively few devices (median 1 implant per patient), despite being the first use of the PASCAL repair system by many operators, and may point to advantages in procedural efficiency with the frequent need for only 1 PASCAL implant and potentially shorter procedural time.

Reduction in MR severity decreases LV preload by reducing LVEDV and contributes to LV reverse remodeling (24). This phenomenon was observed in the CLASP study. The FMR group of our study demonstrated a significant 1-year and 2-year decrease in LVEDV of 29 ml and 31 ml, respectively, based on limited available paired data for 43 patients from baseline to 1 year, and 16 patients from baseline to 2 years. These results compare favorably to the 1-ml decrease in LVEDV reported at 1 year in the COAPT study and are similar to the decreases reported from single-center studies (7,25–27). The DMR group of the CLASP study demonstrated a significant 1-year and 2-year reduction in LVEDV of 19 ml and 36 ml, respectively, based on limited available paired data for 24 patients from baseline to 1 year, and 14 patients from baseline to 2 years compared with a 10-ml 1-year reduction reported by the Sentinel registry and 25 ml reported in the EVEREST II study (6,28).

FIGURE 2 **Mean LVEDV to 2 Years**

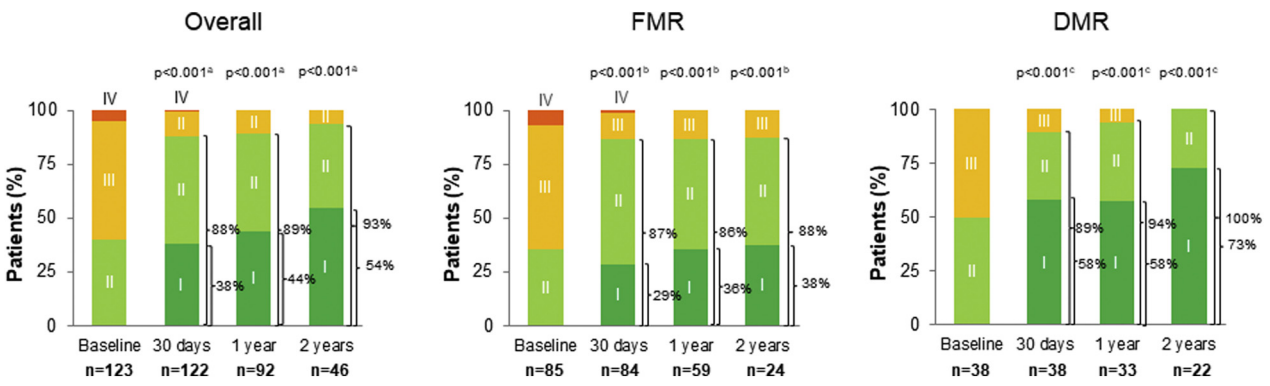


Graphs show unpaired data. Δ and p value presented for paired analysis; the p value was calculated using Student's *t*-test. [a]Baseline versus 30 days (n = 91), 1 year (n = 67), and 2 years (n = 30). [b]Baseline versus 30 days (n = 62), 1 year (n = 43), and 2 years (n = 16). [c]Baseline versus 30 days (n = 29), 1 year (n = 24), and 2 years (n = 14). LVEDV = left ventricular end-diastolic volume; other abbreviations as in Figure 1.

Nevertheless, positive LV remodeling leads to improved LV function (18,24,28-35). In the FMR group of the CLASP study, patients showed stable LVEF at 30 days and 1 year, followed by signs of recovery at 2 years with improvement from baseline reaching statistical significance based on limited available paired data for 19 patients. This contrasts with the 6.0% reduction in LVEF in the COAPT study at 2 years (35). The absolute improvement of 4.7% compared with baseline was similar to 4.6% improvement reported in chronic HF patients treated with cardiac resynchronization therapy (33). In the DMR group of the CLASP study, the change in LVEF was consistent with the EVEREST study in a patient group of 73% DMR (34).

Furthermore, tricuspid regurgitation is concomitantly prevalent in patients with MR (36). Pulmonary artery systolic pressure and corresponding tricuspid regurgitation grades show significant reductions post-transcatheter mitral valve repair (37-41). In our

FIGURE 3 **New York Heart Association Functional Class to 2 Years**



Graphs show unpaired data. The p value was calculated from paired analysis using the Wilcoxon signed rank test. [a]Baseline versus 30 days (n = 121), 1 year (n = 91), and 2 years (n = 46). [b]Baseline versus 30 days (n = 84), 1 year (n = 59), and 2 years (n = 24). [c]Baseline versus 30 days (n = 37), 1 year (n = 32), and 2 years (n = 22). Abbreviations as in Figure 1.

study, pulmonary artery systolic pressure showed a sustained significant reduction from baseline to 2 years based on limited available paired data for 29 patients. While patients with ≥ severe tricuspid regurgitation were excluded, 35 patients had ≥ mild-moderate tricuspid regurgitation at baseline, and a 1-grade reduction in tricuspid regurgitation was observed in 29% of patients at 30 days, 35% at 1 year, and 25% at 2 years.

These results suggest that the PASCAL repair therapy may have a stabilizing or minimizing effect on the functional decline of the FMR population with continued guideline-directed medical therapy. The CLASP study was not designed to evaluate this concept. However, this is hypothesis generating and requires further investigation. Regardless, the findings are encouraging for this difficult group of patients.

STUDY LIMITATIONS. The CLASP study has limitations that should be considered when interpreting the data. As a single-arm study, the absence of a control group may have contributed to a Hawthorne effect. The study follow-up is ongoing, and not all patients had reached 2-year follow-up at the time of analysis. CEC adjudication of events, assessment of 6MWD, and quality-of-life measures were limited to 1 year based on the protocol. The sample sizes of some quantitative echocardiographic measurements were limited by the number of patients available for follow-up, the impact of the COVID-19 (coronavirus disease 2019) pandemic on follow-up visits and ability to conduct echocardiographic evaluations, and the technical difficulty of measuring small regurgitant volumes.

CONCLUSIONS

In the CLASP study, the PASCAL transcatheter valve repair system demonstrated sustained favorable outcomes at 2 years in patients with clinically significant MR. Results showed high rates of 2-year survival and freedom from HF rehospitalization with significant reduction in annualized HF hospitalization rate. Durable and sustained MR reduction was achieved with evidence of LV reverse remodeling and significant improvement in functional status. The pivotal CLASP IID/IIF randomized trial is ongoing.

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PERSPECTIVES

WHAT IS KNOWN? Patients with symptomatic, clinically significant MR are at an increased risk of mortality if left untreated. Transcatheter therapies offer an important option for these patients.

WHAT IS NEW? At 2 years, the PASCAL repair system demonstrated high survival, reduced HF hospitalization, sustained MR reduction to MR ≤2+ in 97% and ≤1+ in 78% of patients with evidence of LV reverse remodeling, and significant clinical improvement.

WHAT IS NEXT? The CLASP IID/IIF randomized pivotal trial is underway.

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KEY WORDS CLASP study, degenerative mitral regurgitation, functional mitral regurgitation, mitral regurgitation, mitral repair, PASCAL

APPENDIX For supplemental tables and figures, please see the online version of this paper.