JACC: CARDIOVASCULAR INTERVENTIONS VOL. 17, NO. 7, 2024

ORIGINAL RESEARCH

STRUCTURAL

Mitral Valve Transcatheter Edge-to-Edge Repair

1-Year Outcomes From the MiCLASP Study

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ABSTRACT

BACKGROUND Mitral transcatheter edge-to-edge repair (M-TEER) is a guideline-recommended treatment option for patients with severe symptomatic mitral regurgitation (MR). Outcomes with the PASCAL system in a post-market setting have not been established.

OBJECTIVES The authors report 30-day and 1-year outcomes from the MiCLASP (Transcatheter Repair of Mitral Regurgitation with Edwards PASCAL Transcatheter Valve Repair System) European post-market clinical follow-up study.

METHODS Patients with symptomatic, clinically significant MR were prospectively enrolled. The primary safety endpoint was clinical events committee–adjudicated 30-day composite major adverse event rate and the primary effectiveness endpoint was echocardiographic core laboratory–assessed MR severity at discharge compared with baseline. Clinical, echocardiographic, functional, and quality-of-life outcomes were assessed at 1 year.

RESULTS A total of 544 patients were enrolled (59% functional MR, 30% degenerative MR). The 30-day composite major adverse event rate was 6.8%. MR reduction was significant from baseline to discharge and sustained at 1 year with 98% of patients achieving MR ≤2+ and 82.6% MR ≤1+ (all $P < 0.001$ vs baseline). One-year Kaplan-Meier estimate for survival was 87.3%, and freedom from heart failure hospitalization was 84.3%. Significant functional and quality-of-life improvements were observed at 1 year, including 71.6% in NYHA functional class I/II, 14.4-point increase in Kansas City Cardiomyopathy Questionnaire score, and 24.2-m improvement in 6-minute walk distance (all $P < 0.001$ vs baseline).

CONCLUSIONS One-year outcomes of this large cohort from the MiCLASP study demonstrate continued safety and effectiveness of M-TEER with the PASCAL system in a post-market setting. Results demonstrate high survival and freedom from heart failure hospitalization, significant and sustained MR reduction, and improvements in symptoms, functional capacity, and quality of life. (J Am Coll Cardiol Intv 2024;17:890-903) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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ISSN 1936-8798 https://doi.org/10.1016/j.jcin.2024.02.022

Severe mitral regurgitation (MR) is the most common form of valvular heart disease and is associated with reduced survival, increased incidence of heart failure hospitalization, and substantial impairments in quality of life, irrespective of underlying pathology. [1] Current European and American guidelines on valvular heart disease reinforce the role of mitral valve transcatheter edge-to-edge repair (M-TEER) as a favorable therapeutic option in symptomatic patients with degenerative (DMR) or functional mitral regurgitation (FMR) who are at high or prohibitive surgical risk or contraindicated for surgery.[2,3] Despite the profound clinical implications of untreated MR, only a minority of patients are offered surgical or interventional treatment for mitral valve disease owing to high surgical risk, under referral and anatomical limitations posed by currently available therapies[4-6]

Among interventional approaches, the PASCAL transcatheter valve repair system (Edwards Lifesciences) has emerged as an important M-TEER option for the treatment of MR. The safety and efficacy of the system was demonstrated in the CLASP (Edwards PASCAL TrAnScatheter Mitral Valve RePair System) and CLASP IID (Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical Trial) studies leading to approval in Europe and the United States, respectively.[7-9] Single-center and multicenter real-world experiences have corroborated these findings.[10,11]

MiCLASP (Transcatheter Repair of Mitral Regurgitation with Edwards PASCAL Transcatheter Valve Repair System) is an ongoing, European, prospective, multicenter, post-market clinical follow-up (PMCF) study, designed to assess the safety and effectiveness of this system in the treatment of clinically significant MR in a broad patient population including those with challenging mitral valve anatomies. We report 30-day and 1-year outcomes from the MiCLASP study.

METHODS

STUDY DESIGN AND PATIENTS. The MiCLASP study is a European, prospective, multicenter, single-arm, PMCF study initiated with the PASCAL transcatheter valve repair system, and after full enrollment of 500 patients, the study was extended to include the newer PASCAL Precision system (collectively referred to as the "PASCAL system"). The study was initiated with an eligibility criterion of site-assessed MR ≥2+ commensurate with device labelling; and at the time of introduction of the newer system, the eligibility criterion was revised to site-assessed MR ≥3+ in accordance with updated device labelling. All patients were deemed to be candidates for M-TEER by the local multidisciplinary heart team consisting of a heart failure specialist, interventional cardiologist, cardiac surgeon, and an imaging specialist. Patients were enrolled in the study based on site assessment including transthoracic echocardiography, transesophageal echocardiography, and clinical presentation. Echocardiograms were subsequently evaluated by the echocardiographic core lab.

Key exclusion criteria were transesophageal echocardiography contraindicated or screening transesophageal echocardiography unsuccessful; mitral valve area <4.0 cm^2; echocardiographic evidence of an intracardiac mass, thrombus, or vegetation; left ventricular (LV) end-diastolic diameter >8.0 cm as measured using transthoracic echocardiography

ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

CEC = clinical events committee

DMR = degenerative mitral regurgitation

EQ5D = EuroQoL-5 Dimension

FMR = functional mitral regurgitation

KCCQ = Kansas City Cardiomyopathy Questionnaire

LV = left ventricle/ventricular

MAE = major adverse event(s)

MI = myocardial infarction

MR = mitral regurgitation

M-TEER = mitral valve transcatheter edge-to-edge repair

PMCF = post-market clinical follow-up

POD = postoperative day

SLDA = single-leaflet device attachment

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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.

Manuscript received October 10, 2023; revised manuscript received February 19, 2024, accepted February 21, 2024.

within 60 days before the intervention; contraindication to transseptal catheterization; severe aortic, tricuspid and/or pulmonic valve stenosis and/or regurgitation; presence of an occluded or thrombosed inferior vena cava filter that would interfere with the delivery catheter or presence of ipsilateral deep vein thrombosis; history of bleeding diathesis or coagulopathy or patient who refuses blood donation; or concurrent medical condition with life expectancy of <12 months.

The MiCLASP study was conducted in compliance with the ethical principles set forth by the 1964 Declaration of Helsinki and its later amendments, International Conference on Harmonisation Good Clinical Practice principles, and ISO 14155:2011. The research protocol was approved by the locally appointed ethics committees and respective health authorities of each participating country. Written informed consent was provided by all patients. An independent clinical events committee (CEC) adjudicated all major adverse events (MAEs) except for device embolizations, which were adjudicated by the echocardiographic core laboratory. Study assessments were performed at baseline, discharge, 30 days, 6 months, and 1 year. The MiCLASP study is sponsored by Edwards Lifesciences and is registered on ClinicalTrials.gov (Transcatheter Repair of Mitral Regurgitation With Edwards PASCAL Transcatheter Valve Repair System: A European Prospective, Multicenter Post Market Clinical Follow-Up (PMCF) Study; NCT04430075).

STUDY ENDPOINTS. The primary safety endpoint was a composite of the following MAEs at 30 days: cardiovascular mortality, stroke, myocardial infarction (MI), mitral valve reintervention, major access site and vascular complications, major cardiac structural complications, device embolization, renal complications requiring unplanned dialysis or renal replacement therapy, and severe bleeding (major, extensive, life-threatening, or fatal bleeding, as defined by the Mitral Valve Academic Research Consortium).[12]

The primary effectiveness endpoint was MR severity at discharge compared with baseline as assessed by the echocardiography core laboratory. Secondary effectiveness endpoints included EuroQoL-5 Dimension (EQ5D), Kansas City Cardiomyopathy Questionnaire (KCCQ), 6-minute walk distance (6MWD), and NYHA functional class at 30 days, 6 months, and 1 year.

Device success was defined as device deployed as intended and delivery system successfully retrieved as intended at the time of patient exit from the cardiac catheterization laboratory. Procedural success was defined as device success without the need for surgical or percutaneous intervention before hospital discharge and with evidence of MR grade ≤2+ at discharge for patients with baseline MR grade >2+; or MR grade ≤1+ at discharge for patients with baseline MR grade 2+. Clinical success was defined as procedural success without MAEs at 30 days.

An independent echocardiographic core laboratory (Cardiovascular Core Lab at Morristown Medical Centre, Morristown, New Jersey) assessed all transthoracic echocardiography at baseline and follow-up according to pre-established protocols and included the following: MR severity, LV end-diastolic volume, LV end-systolic volume, mitral valve effective orifice area, mitral regurgitant volume, LV ejection fraction, stroke volume, left atrial volume, and tricuspid regurgitation severity. MR severity was evaluated by 2-dimensional Doppler echocardiography according to the American Society of Echocardiography guidelines as none or trace (0), mild (1+), mild to moderate (2+), moderate to severe (3+), and severe (4+).[12-15] Mitral annular calcification was qualitatively assessed using transthoracic echocardiographic short-axis views at the base and graded as mild, moderate, or severe based on its circumferential extent of up to one-third, two-thirds, or more than two-thirds of the mitral annular circumference, respectively (Supplemental Figure 1).[16]

STATISTICAL ANALYSIS. All analyses were performed on the intent-to-treat population. Continuous variables were assessed as mean ± SD or median (Q1-Q3) as appropriate, and comparison between 2 time points was performed using paired Student's *t*-test. Categorical variables were summarized using counts and percentages. The Wilcoxon signed rank test was used to compare categorical variables between 2 time points. An alpha level of 0.05 was used for all 2-sided significance tests. Deltas were calculated for paired analyses. Survival curves were constructed using Kaplan-Meier analysis, and the Greenwood formula was used to calculate standard error.[17] Pre- and postprocedure HF hospitalization rates were calculated using a Poisson regression model, with days of postprocedure follow-up as an offset; statistical significance was obtained using the Wald chi-square test from the model. Statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

BASELINE CHARACTERISTICS. A total of 544 patients were enrolled at 30 sites in 9 European countries. Mean age was 77.1 years, and 59% were male

TABLE 1 Baseline Characteristics

	Overall (N = 544)	FMR[a] (n = 322)	DMR[b] (n = 163)
Age, y	77.1 ± 9.29 (544)	75.6 ± 10.09 (322)	79.9 ± 6.2 (163)
Male	59.0 (321)	59.3 (191)	57.1 (93)
NYHA functional class III/IV	76.6 (415)	77.8 (249)	70.6 (115)
STS score for mitral valve repair, %	5.1 ± 4.18 (544)	5.4 ± 4.5 (322)	4.2 ± 3.09 (163)
EuroSCORE II, %	7.2 ± 7.07 (543)	8.2 ± 7.67 (321)	5.1 ± 5.13 (163)
Mitral annular calcification	45.6 (239)	42.1 (135)	49.7 (81)
Mild	39.9 (209)	37.7 (121)	41.7 (68)
Moderate	5.5 (29)	4.4 (14)	8.0 (13)
Severe	0.2 (1)	0.0 (0)	0.0 (0)
Mitral valve complexity[c]	18.4 (100)	18.0 (58)	19.0 (31)
EROA, cm^2	0.35 ± 0.151 (233)	0.32 ± 0.127 (146)	0.40 ± 0.168 (75)
Regurgitant volume, mL	52.4 ± 21.50 (232)	47.6 ± 18.20 (146)	59.8 ± 23.78 (74)
Vena contracta width, A-P, mm	5.9 ± 3.0 (414)	5.9 ± 3.5 (270)	6.0 ± 1.8 (125)
TR severity ≥3+, moderate-severe	11.4 (56)	5.1 (4)	10.5 (16)
Comorbidities			
Hypertension	85.1 (463)	85.4 (275)	85.9 (140)
Pulmonary hypertension, ≥30 mm Hg	61.5 (333)	61.4 (196)	58.3 (95)
Cardiomyopathy	26.7 (145)	40.1 (129)	4.3 (7)
Myocardial infarction	19.7 (107)	26.1 (84)	8.6 (14)
Percutaneous coronary intervention/stent	39.2 (213)	44.4 (143)	29.4 (48)
Prior TIA or stroke	10.7 (58)	13.04 (42)	6.7 (11)
Atrial fibrillation	64.3 (350)	64.6 (208)	62.6 (102)
Dyslipidemia or hyperlipidemia	50.9 (277)	52.5 (169)	47.2 (77)
Heart failure hospitalizations within the last year	51.8 (282)	52.8 (170)	50.3 (82)
AV block >1st degree or ventricular block	25.0 (136)	27.6 (89)	19.6 (32)
Diabetes	23.5 (128)	28.3 (91)	12.9 (21)
Renal insufficiency or failure, ≥stage II	53.5 (291)	59.6 (192)	40.5 (66)

Values are % (n) or mean ± SD (n). [a]Includes 87 patients with mitral regurgitation (MR) classified as pure annular dilatation. [b]Includes 2 patients with MR classified as rheumatic etiology. [c]Includes commissural jets, 2 or more significant jets, mitral valve area <4 cm^2, grasping area calcification, minimal tissue for leaflet attachment, and severely degenerative leaflets.

A-P = anterior-posterior; AV = atrioventricular; DMR = degenerative mitral regurgitation; EROA = effective regurgitant orifice area; eGFR = estimated glomerular filtration rate; FMR = functional mitral regurgitation; STS = Society of Thoracic Surgeons; TIA = transient ischemic attack; TR = tricuspid regurgitation.

with 76.6% of patients in NYHA functional class III/IV. Hypertension, atrial fibrillation, dyslipidemia or hyperlipidemia, heart failure, and renal insufficiency or failure were present in a majority of patients. MR etiology was 59.2% FMR, 30% DMR, 3.1% mixed, and in 7.7%, the etiology could not be unequivocally determined by the echocardiographic core laboratory. Per eligibility criteria, all enrolled patients had MR ≥2+ as assessed by the sites based on collective evaluation of transthoracic echocardiography, transesophageal echocardiography, and clinical findings. The echocardiographic core laboratory assessment of MR severity at baseline was retrospective and based on evaluation of transthoracic echocardiography images using American Society of Echocardiography guidelines, resulting in 93.2% with MR grade ≥2+. A total of 18.4% (n = 100) patients were deemed to have complex mitral valve anatomy by the echocardiographic core laboratory including commissural primary jet in 66%, 2 or more significant jets in 20%, mitral valve area <4 cm^2 in 3%, calcified landing zone in 10%, minimal leaflet tissue for implant attachment in 8% and severely degenerative leaflets in 2%. Baseline characteristics are described in **Table 1**. Baseline characteristics of patients who did not complete 1-year follow-up visits are listed in Supplemental Table 1. Patients with missed 1-year visit had a significantly higher rate of heart failure hospitalization within the past 12 months, as well as significantly higher vena contracta width and lower body mass index.

At the time of analysis, 30-day follow-up was available in 91.9% of eligible patients, and 1-year follow-up, in 85.9% of eligible patients (**Figure 1**).

PROCEDURAL OUTCOMES. M-TEER device implantation was successful in 97.1% of patients. Of the 16 patients with unsuccessful implantation, 6 resulted from inability to adequately grasp leaflets to allow for optimal MR reduction (1 underwent surgical mitral valve replacement), 5 patients had high gradient after leaflet grasping (1 underwent transcatheter

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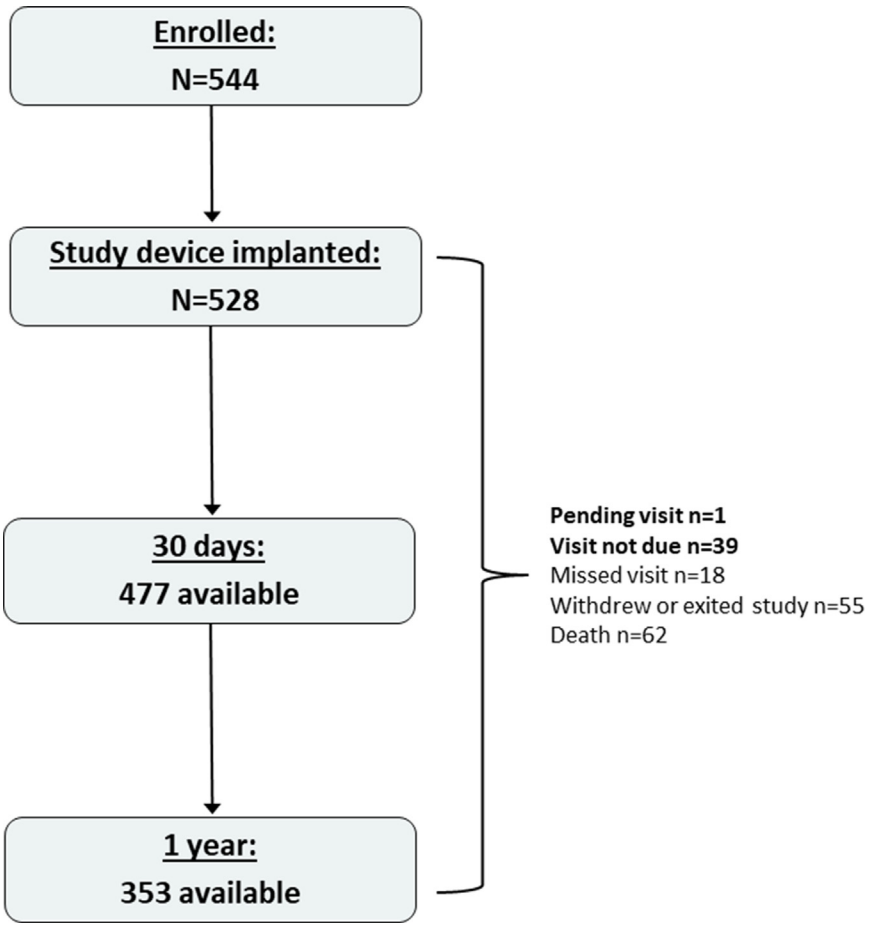
APRIL 8, 2024:890-903

FIGURE 1 Patient Disposition and Flow



mitral valve replacement with Tendyne [Abbott Cardiovascular], 1 surgical mitral valve replacement, and 1 repair with MitraClip [Abbott Cardiovascular]), 1 patient with poor imaging, and 4 patients with complex anatomy. The mean number of devices implanted per patient was 1.4, with 62.9% of patients receiving only 1 implant. The median procedure time (skin incision to closure) was 84.5 minutes (60.0-115.0 minutes), and length of hospital stay was 3.5 days (2.0-5.0 days) with 92.6% of patients discharged home. Procedural outcomes are summarized in Table 2.

CLINICAL OUTCOMES. The CEC-adjudicated composite MAE rate at 30 days was 6.8%, comprising cardiovascular mortality (1.1%), stroke (0.9%), MI (0.2%), mitral valve reinterventions (1.3%), major cardiac structural complications (0.4%), device embolization (0.2%), renal complications requiring dialysis (1.1%), severe bleeding (4%), and major access site and vascular complications (1.1%) (Table 3).

Of the 6 cardiovascular deaths, 1 was adjudicated as device-related. This was a DMR patient who received a third device that resulted in a single-leaflet device attachment (SLDA) and subsequent embolization to the left common iliac artery; this patient died due to heart and multiorgan failure despite medical therapy. The other 5 cardiovascular deaths were adjudicated to be procedure-related: 1 cardiorenal syndrome, 1 cardiogenic shock accompanied by acute kidney failure, 1 hemorrhagic shock resulting from hemothorax, 1 cardiorespiratory arrest, and 1 MI due to delayed treatment. Five patients experienced ischemic strokes, all adjudicated as procedure-related. There were 7 mitral valve reinterventions at 30 days, of which 3 were device-related and attributed to SLDAs: 2 patients had successful surgical mitral valve reinterventions, and 1 patient received an additional PASCAL implant. The other 4 reinterventions were in patients with aborted procedures: 1 M-TEER with MitraClip, 1 transcatheter mitral valve

TABLE 2 Procedural Outcomes

	Overall (N = 544)	FMR (n = 322)	DMR (n = 163)
Successful implantation	97.1 (528/544)	97.2 (313/322)	96.9 (158/163)
Number of devices implanted	1.4 ± 0.5 (528)	1.4 ± 0.5 (313)	1.4 ± 0.5 (158)
Device success[a]	94.8 (718/757)	94.8 (422/445)	95.2 (220/231)
Procedural success[b]			
Core laboratory MR = 2+ at baseline	89.8 (115/128)	91.4 (85/93)	81.5 (22/27)
Core laboratory MR >2+ at baseline	93.1 (295/317)	95.2 (178/187)	92.1 (105/114)
Clinical success[c]			
Core laboratory MR = 2+ at baseline	84.7 (105/124)	89.1 (82/89)	70.4 (19/27)
Core laboratory MR >2+ at baseline	86.5 (270/312)	91.4 (170/186)	82.9 (92/111)
Procedure time, skin incision to closure, min	84.5 (60.0-115.0)	85.0 (61.0-117.0)	83.5 (59.0-113.0)
Device deployment time, min[d]	47.0 (29.5-71.0)	47.0 (29.0-70.0)	46.0 (31.0-75.0)
ICU stay, d	1.9 ± 2.4 (109)	1.8 ± 2.18 (64)	2.3 ± 3.11 (32)
Length of hospital stay, d[e]	3.5 (2.0-5.0)	3.0 (2.0-5.0)	4.0 (2.0-5.0)
Patients discharged home	92.6 (500/540)	93.8 (301/321)	91.9 (148/161)

Values are % (n/N), mean ± SD (n), or median (Q1-Q3). [a]Device is deployed as intended and delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory (per device analysis). [b]Device success with evidence of MR ≤1+ (for patients with baseline MR grade = 2+) or MR ≤2+ (for patients with baseline MR grade >2+) at discharge and without the need for a surgical or percutaneous intervention before hospital discharge, denominator calculated based on number of patients for whom all 3 data fields were reported as yes or at least 1 data field was reported as no. [c]Procedural success with evidence of MR ≤1+ at discharge (for patients with baseline MR grade = 2+) or MR ≤2+ (for patients with baseline MR grade >2+) and without major adverse events at 30 days, denominator calculated based on number of patients for whom all 3 data fields were reported as yes or at least 1 data field was reported as no. [d]Transseptal puncture to final implant release. [e]Study procedure date to hospital discharge date.

ICU = intensive care unit; other abbreviations as in Table 1.

replacement with a Tendyne valve, and 2 surgical mitral valve replacements.

The 1-year composite MAE rate was 16.4% (16.8% FMR, 15.3% DMR) (Table 3). Five mitral valve reinterventions occurred between 30 days and 1 year with 3 adjudicated to be device-related: 1 patient with persistent 3+ MR postprocedure had a reintervention attempted with MitraClip (postoperative day [POD] 42) that was aborted after multiple unsuccessful attempts to reduce MR, with patient death on POD 43; 1 SLDA (POD 33) followed by surgical mitral valve replacement; and 1 partial leaflet tear (POD 50) treated with a MitraClip device. The echocardiographic core laboratory-assessed 1-year SLDA rate was 1.7% (n = 9) with 8 occurring within 30 days and 1 at POD 33. Of the 9, there was 1 cardiovascular mortality and 4 reinterventions described in the preceding text, and in the remaining 4 patients, the MR grade remained ≤mild-moderate with no further intervention.

The 1-year Kaplan-Meier estimate for survival was 87.3% (86.6% FMR, 89.1% DMR), and freedom from heart failure hospitalization was 84.3% (81.9% FMR, 89.6% DMR) (Central Illustration). The Kaplan-Meier estimate for freedom from all-cause mortality and heart failure hospitalization was 76.4% (73.5% FMR, 82.5% DMR) (Supplemental Figure 2). The CEC-adjudicated annualized heart failure hospitalization rate decreased from 0.79 preprocedure to 0.24 1-year postprocedure ($P < 0.001$), a 68.9% reduction (62.9% FMR, 82.7% DMR; all $P < 0.001$) (Figure 2).

ECHOCARDIOGRAPHIC OUTCOMES. Significant MR reduction from baseline to 30 days was observed with 97.3% patients achieving MR ≤2+ (98.4% FMR, 96.5% DMR) and 78.6% achieving MR ≤1+ (80.4% FMR, 76.1% DMR) ($P < 0.001$). At 1 year, 97.9% patients achieved MR ≤2+ (98.3% FMR, 98.8% DMR) and 82.6% achieved MR ≤1+ (82.6% FMR, 82.1% DMR) ($P < 0.001$ vs baseline) (Central Illustration). In patients with complex MV anatomy, significant MR reduction from baseline to 1 year was observed, with 79.6 % achieving MR ≤1+, and 93.9 % achieving MR ≤2+ ($P < 0.001$) (Supplemental Figure 3). Similar outcomes were observed in paired analysis.

MR reduction was associated with significant improvements in all echocardiographic MR indices (Table 4). Changes from baseline to 1 year included reductions in LV end-diastolic volume (−27.3 mL; $P < 0.001$), LV end-systolic volume (−13.2 mL; $P < 0.001$) (Figure 3), LV end-diastolic diameter (−3.8 mm; $P < 0.001$), and LV end-systolic diameter (−2.8 mm; $P < 0.001$). LV ejection fraction remained stable ($P = 0.08$), with a significant increase in stroke volume (+3.3 mL; $P < 0.05$). There was a significant reduction in pulmonary artery systolic pressure (−4.2 mm Hg; $P < 0.001$). Similar significant and sustained improvements were demonstrated in the FMR and DMR populations at 1 year (Supplemental Tables 2 and 3).

In the overall population, the mean transmitral valve gradient increased from 2.1 mm Hg at baseline

TABLE 3 CEC Adjudicated Events at 30 Days and 1 Year

	Overall (N = 544)		FMR (n = 322)		DMR (n = 163)	
	30 d	1 y	30 d	1 y	30 d	1 y
Major adverse events						
Cardiovascular mortality	1.1 (6)	8.3 (45)	0.6 (2)	9.0 (29)	1.2 (2)	6.1 (10)
Stroke	0.9 (5)	2.9 (16)	0.6 (2)	2.5 (8)	1.8 (3)	4.3 (7)
Myocardial infarction	0.2 (1)	0.6 (3)	0 (0)	0.6 (2)	0 (0)	0.0 (0)
Mitral valve reintervention	1.3 (7)	2.2 (12)	0.6 (2)	1.2 (4)	2.5 (4)	3.1 (5)
Major cardiac structural complications[a]	0.4 (2)	0.4 (2)	0.3 (1)	0.3 (1)	0.6 (1)	0.6 (1)
Device embolization	0.2 (1)	0.2 (1)	0 (0)	0.0 (0)	0.6 (1)	0.6 (1)
Renal complications requiring unplanned dialysis or renal replacement therapy	1.1 (6)	2.8 (15)	0.9 (3)	3.4 (11)	1.8 (3)	2.5 (4)
Severe bleeding[b]	4.0 (22)	6.4 (35)	2.5 (8)	6.2 (20)	7.4 (12)	7.4 (12)
Major access site and vascular complications	1.1 (6)	1.1 (6)	0.6 (2)	0.6 (2)	2.5 (4)	2.5 (4)
Composite MAE rate	6.8 (37)	16.4 (89)	4.3 (14)	16.8 (54)	11.0 (18)	15.3 (25)
Other events						
All-cause mortality	1.3 (7)	11.0 (60)	0.9 (3)	11.8 (38)	1.2 (2)	9.2 (15)
Heart failure rehospitalization	2.0 (11)	13.4 (73)	2.5 (8)	15.5 (50)	1.2 (2)	9.2 (15)
SLDA	1.5 (8)	1.7 (9)	0.9 (3)	0.9 (3)	3.1 (5)	3.7 (6)

Values are % (n). [a]Due to access-related issues. [b]Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium.
CEC = clinical events committee; MAE = major adverse event(s); SLDA = single leaflet device attachment; other abbreviations as in Table 1.

to 3.3 mm Hg at discharge and remained stable at 3.3 mm Hg through 1 year ($P = 0.950$ vs discharge). Similar trends were seen in the FMR and DMR populations (Supplemental Figure 4).

FUNCTIONAL AND QUALITY-OF-LIFE OUTCOMES. Significant and sustained improvements in clinical, functional, and quality-of-life outcomes were observed at 1 year compared with baseline. At 1 year, 71.6% of patients were in NYHA functional class I or II (68.1% FMR, 79.4% DMR) ($P < 0.001$) (Figure 4). The mean KCCQ overall summary score increased by 14.4 ± 23.1 points (13.5 ± 22.1 FMR, 17.9 ± 24.3 DMR; all $P < 0.001$) and the mean EQ5D overall health score improved by 7.2 ± 20.8 points (6.9 ± 21.1 FMR, 10.2 ± 18.7 DMR; all $P < 0.001$) (Figure 5). There was significant improvement in the mean 6MWD with an increase of 24.2 ± 96.3 m (17.5 ± 94.0 m FMR, 51.0 ± 89.2 m DMR; all $P < 0.05$) (Figure 5). Similar outcomes were observed in paired analysis.

DISCUSSION

MiCLASP is the first prospective study evaluating the safety and efficacy of M-TEER with the PASCAL system in a European post-market setting with adjudication by a CEC and echocardiographic core laboratory. This first report of outcomes from the MiCLASP study demonstrates that introduction of the device in a post-market setting, including to new operators, was safe and resulted in favorable echocardiographic changes. At 30 days and 1 year, both FMR and DMR patients demonstrated: 1) favorable safety showing low all-cause mortality and MAE rates; 2) significant MR reduction accompanied with stable transmitral gradients and evidence of LV remodeling; and 3) significantly improved clinical, functional and quality-of-life measures.

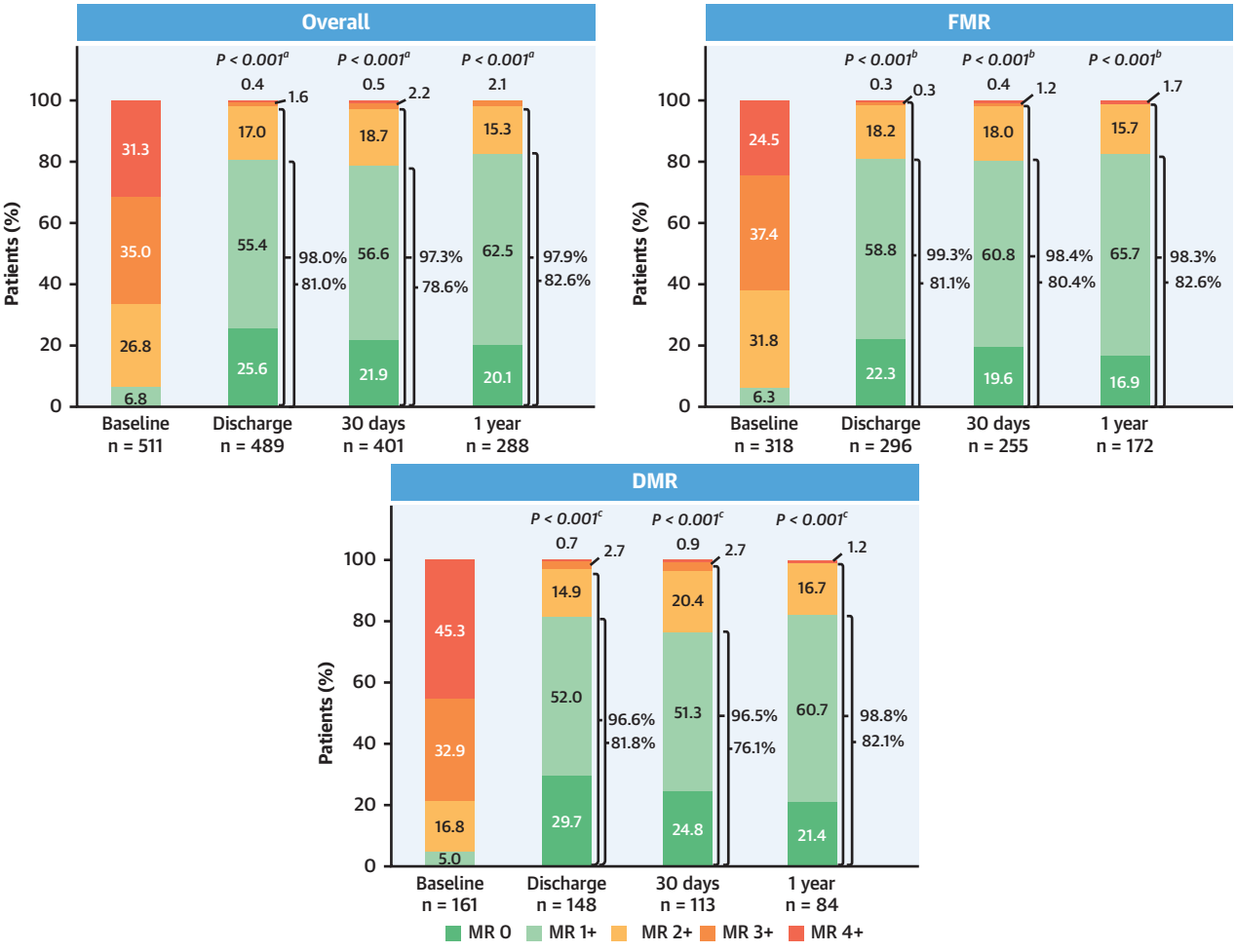
Successful implantation of the device was achieved in 97.1% of patients, with a high proportion of patients (62.9%) requiring implantation of only 1 device. The median procedure time of 84.5 minutes was lower than that reported in the earlier CLASP study (109 minutes) and comparable to the recent CLASP IID (88 minutes) and EXPAND (A Contemporary, Prospective Study Evaluating Real-world Experience of Performance and Safety for the Next Generation of MitraClip Devices) (80 minutes) studies, as well as other real-world reports for PASCAL and MitraClip system procedures performed by experienced operators.[7,11,14,18-21]

The 30-day all-cause mortality (1.3%), stroke (0.9%), mitral valve reintervention (1.3%), and SLDA (1.5%) rates in our study were low and similar to reports from the CLASP and CLASP IID studies, and those recently reported in the MitraClip EXPAND G4 study (A Post-Market Study Assessment of the Safety and Performance of the MitraClip G4 System) (1.3% all-cause death, 0.5% stroke, 0.9% mitral valve reintervention, and 1.1% SLDA).[9,20,21] This trend was maintained at 1 year in the MiCLASP study with continued low rates for all-cause mortality (11%), stroke (2.9%), MI (0.6%), and mitral valve reintervention (2.2%), comparable to the 1-year outcomes from the EXPAND study (14.9% mortality, 1.7% stroke, 1.2% MI, and 1.9% mitral valve

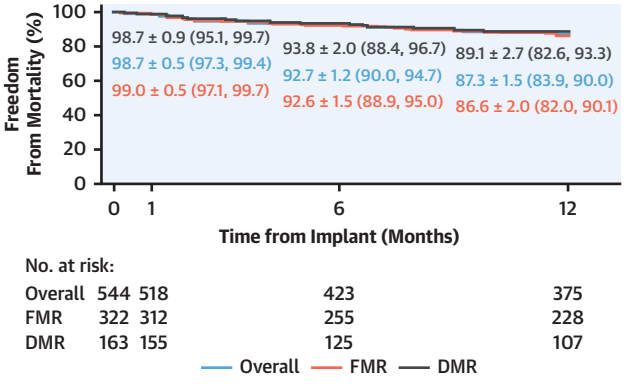
CENTRAL ILLUSTRATION MiCLASP Study 1-Year Outcomes

Transcatheter Repair of Mitral Regurgitation With PASCAL System From the MiCLASP Study at 1 Year

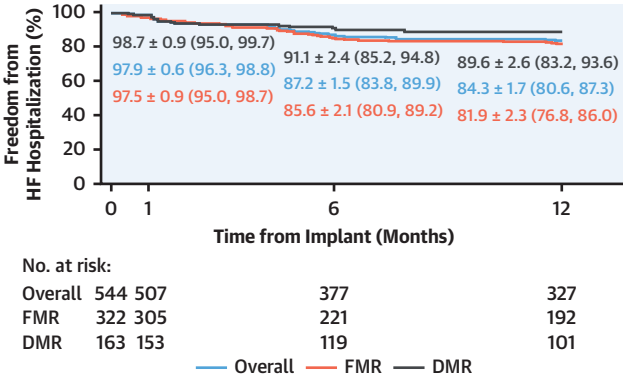
A Mitral Regurgitation by Core Laboratory



B Survival



C Freedom From Heart Failure Hospitalization



1-year outcomes from the prospective MiCLASP study demonstrate safety and effectiveness of the PASCAL system in a post-market setting

- 98% of patients with MR ≤2+ and 83% with MR ≤1+
- 87% survival and 84% freedom from HF hospitalization
- Significant improvements in KCCQ (14 points) and 6MWD (24 meters)

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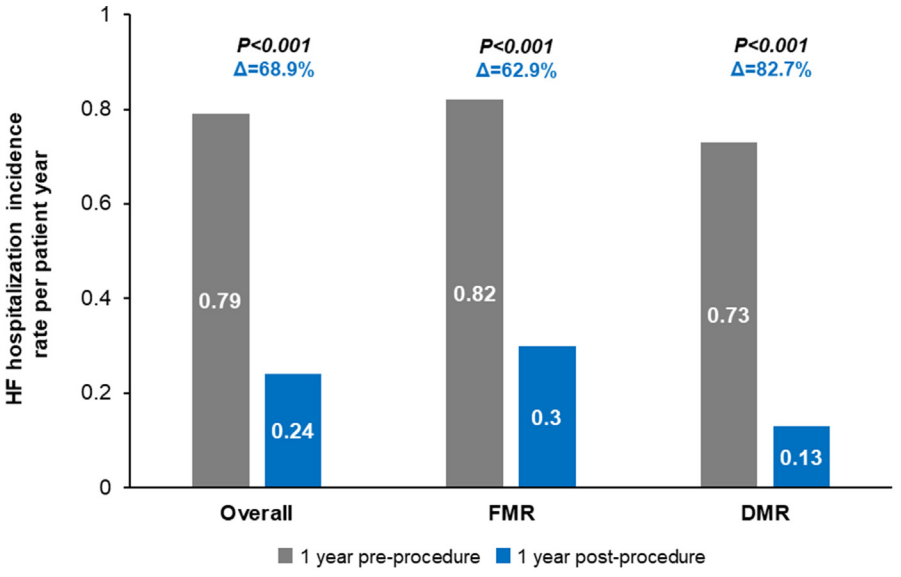
FIGURE 2 Annualized Rate of HF Hospitalization



	1 year pre-procedure	1 year post-procedure CEC-adjudicated	
	Patient years (# events)	Patient years (# events)	Relative reduction % [95% CI] p-value
Overall	517 (407)	544 (105)	68.9 [61.5, 74.9] p<0.001
FMR	306 (250)	322 (79)	62.9 [52.2, 71.2] p<0.001
DMR	154 (113)	163 (16)	82.7 [70.7, 89.7] p<0.001

Preprocedure hospitalization is site reported; postprocedure hospitalization is clinical events committee (CEC) adjudicated.
DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; HF = heart failure.

replacement) and previously published outcomes for M-TEER.[7-9,19,22,23] The 1-year rates of SLDA (1.7%) and device-related major cardiac structural complications (0.4%) in the MiCLASP study remained low in a post-market setting and are comparable to previously published data for this M-TEER system and alternative leaflet repair therapies.[11,22] The higher incidence of SLDA observed in the DMR group may be attributed to greater residual leaflet mobility, complex lesions, and higher prevalence of leaflet calcification associated with this etiology. Features of this M-TEER system such as maneuverability, subvalvular elongation, and flexible nitinol design may have contributed to the safe device profile.

At 30 days, 97.3% of patients in our study achieved MR ≤2+ and 78.6% MR ≤1+ which was sustained to 1

CENTRAL ILLUSTRATION Continued

Graphs show unpaired data. *P* value calculated from paired analysis using Wilcoxon signed rank test. (A) Mitral regurgitation by core laboratory. [a]Baseline vs discharge (n = 468; mitral regurgitation [MR] ≤1+ = 80.6%; MR ≤2+ = 97.9%), 30 days (n = 383; MR ≤1+ = 78.1%; MR ≤2+ = 97.1%), and 1 year (n = 272; MR ≤1+ = 82.4%; MR ≤2+ = 97.8%), [b]baseline vs discharge (n = 292; MR ≤1+ = 80.8%; MR ≤2+ = 99.3%), 30 days (n = 252; MR ≤1+ = 80.2%; MR ≤2+ = 98.4%) and 1 year (n = 170; MR ≤1+ = 82.4%; MR ≤2+ = 98.2%), [c]baseline vs discharge (n = 146; MR ≤1+ = 81.5%; MR ≤2+ = 96.6%), 30 days (n = 112; MR ≤1+ = 75.9%; MR ≤2+ = 96.4%) and 1 year (n = 84; MR ≤1+ = 82.1%; MR ≤2+ = 98.8%). (B) and (C) Kaplan-Meier estimates of freedom from mortality and heart failure hospitalization. Graphs show Kaplan-Meier analysis time to first event ± SE (95% CI). 6MWD = 6-minute walk distance; DMR = degenerative mitral regurgitation; FMR = functional mitral regurgitation; KCCQ = Kansas City Cardiomyopathy Questionnaire; MiCLASP = Transcatheter Repair of Mitral Regurgitation with Edwards PASCAL Transcatheter Valve Repair System.

TABLE 4 Echocardiographic Outcomes by Core Laboratory Through 1 Year (Overall)

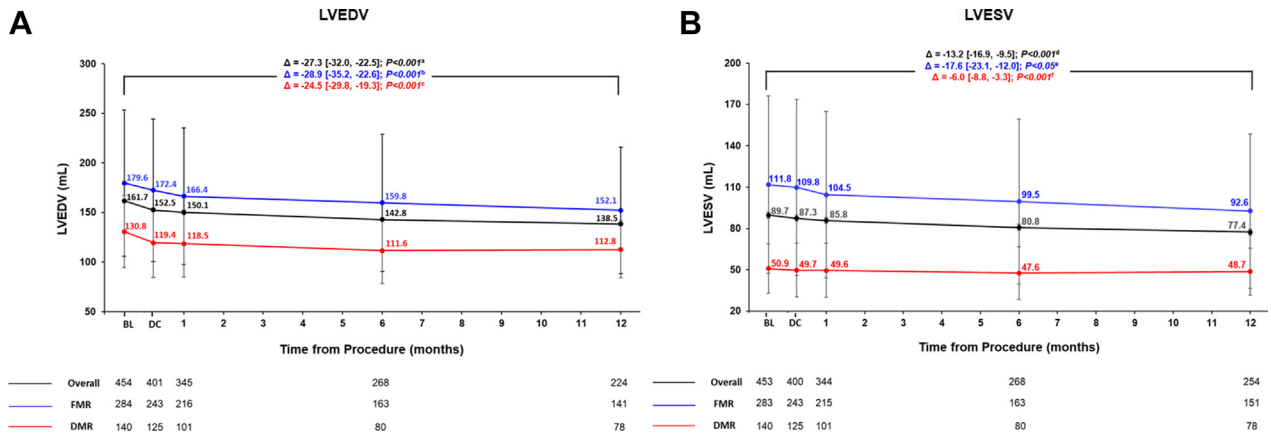
	Baseline	Discharge	Δ Discharge - Baseline *P* Value	30 d	Δ 30 d - Baseline *P* Value	1 y	Δ 1 y - Baseline *P* Value
LVEDD, mm	60.2 ± 9.0 (468)	58.1 ± 9.3 (443)	−1.9 ± 2.8 (401) *P* < 0.001	57.9 ± 9.2 (366)	−2.6 ± 3.6 (326) *P* < 0.001	56.7 ± 8.6 (267)	−3.8 ± 4.4 (237) *P* < 0.001
LVESD, mm	46.4 ± 12.5 (447)	45.4 ± 12.77 (413)	−1.0 ± 4.4 (365) *P* < 0.001	44.9 ± 12.2 (352)	−1.9 ± 5.5 (307) *P* < 0.001	43.9 ± 11.1 (257)	−2.8 ± 6.0 (222) *P* < 0.001
LVEDV, mL	161.7 ± 67.7 (454)	152.5 ± 66.4 (401)	−10.1 ± 20.1 (360) *P* < 0.001	150.1 ± 63.0 (345)	−15.4 ± 26.8 (308) *P* < 0.001	138.5 ± 57.5 (254)	−27.3 ± 36.0 (224) *P* < 0.001
LVESV, mL	89.7 ± 59.9 (453)	87.3 ± 59.37 (400)	−3.6 ± 15.4 (360) *P* < 0.001	85.8 ± 56.3 (344)	−7.3 ± 19.50 (306) *P* < 0.001	77.4 ± 51.3 (254)	−13.2 ± 28.1 (223) *P* < 0.001
LVEF, %	48.2 ± 14.9 (515)	47.5 ± 14.66 (485)	−0.84 ± 4.8 (473) *P* < 0.001	47.2 ± 14.3 (401)	−0.37 ± 5.5 (386) *P* = 0.190	47.4 ± 13.6 (288)	−0.77 ± 7.2 (274) *P* = 0.080
Stroke volume, mL	55.1 ± 18.3 (333)	58.1 ± 18.5 (312)	3.8 ± 12.4 (238) *P* < 0.001	60.0 ± 18.6 (297)	5.2 ± 15.9 (207) *P* < 0.001	59.3 ± 17.6 (219)	3.3 ± 17.4 (156) *P* = 0.019
LA volume, mL	129.9 ± 68.9 (494)	124.5 ± 63.8 (475)	−5.0 ± 24.5 (445) *P* < 0.001	120.3 ± 65.7 (391)	−8.0 ± 24.9 (366) *P* < 0.001	111.9 ± 52.0 (272)	−13.1 ± 25.7 (256) *P* < 0.001
Transmitral mean gradient, mm Hg	2.1 ± 0.9 (370)	3.3 ± 1.53 (478)	1.3 ± 1.4 (335) *P* < 0.001	3.3 ± 1.4 (380)	1.5 ± 1.4 (258) *P* < 0.001	3.3 ± 1.7 (282)	1.3 ± 1.5 (196) *P* < 0.001
PASP, mm Hg	44.0 ± 13.2 (408)	39.2 ± 10.1 (361)	−4.8 ± 10.6 (312) *P* < 0.001	38.5 ± 11.7 (316)	−4.6 ± 13.4 (265) *P* < 0.001	39.0 ± 11.3 (225)	−4.2 ± 12.6 (187) *P* < 0.001

Values are mean ± SD (n). Paired data were used for the calculation of deltas, and *P* values (using paired Student's *t*-test) were compared with baseline.

LA = left atrial; LV = left ventricular; LVEDD = left ventricular end-diastolic diameter; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESD = left ventricular end-systolic diameter; LVESV = left ventricular end-systolic volume; PASP = pulmonary artery systolic pressure.

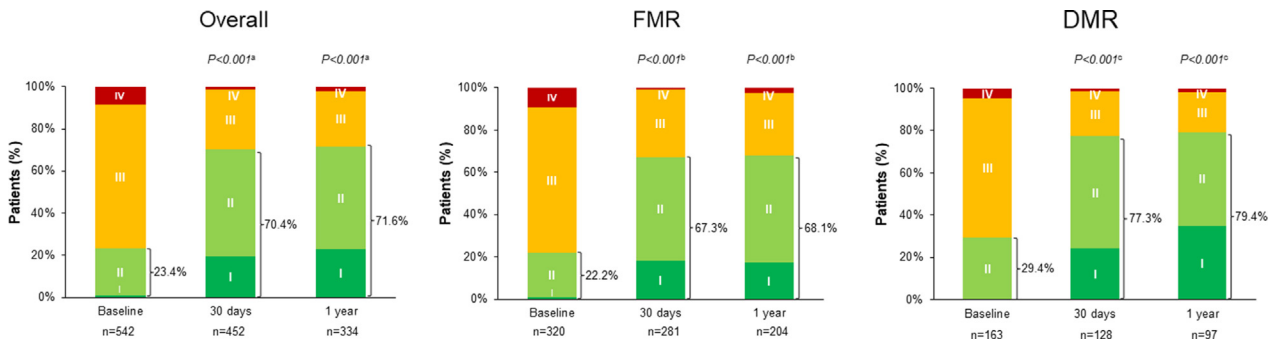
year with 97.9% patients with MR ≤2+ and 82.6% with MR ≤1+, as adjudicated by the echocardiographic core laboratory. These outcomes are consistent with prior reports for this device and those reported by EXPAND G4 (MR ≤2 achieved in 98% and ≤1+ in 91% patients at 30 days; MR ≤2 achieved in 98.5% and ≤1+ in 92.6% patients at 1 year) and EXPAND (MR ≤2 achieved in 97.5% and ≤1+ in 89.2% patients at 1 year) studies, which treated a patient population with a baseline MR profile similar to the MiCLASP study.[19-21,24,25] Importantly, patients with complex anatomy achieved significant and sustained

FIGURE 3 LV Reverse Remodeling at 1 Year



Graphs show unpaired data. Error bars represent ± SD. One-year Δ and *P* value presented for paired analysis using Student's *t*-test, baseline vs 1 year. (A) [a]Overall (N = 224; mean baseline left ventricular end-diastolic volume [LVEDV] = 164.9; mean 1-year LVEDV = 137.6), [b]FMR (n = 141; mean baseline LVEDV = 180.7; mean 1-year LVEDV = 151.8), and [c]DMR (n = 69; mean baseline LVEDV = 136.3; mean 1-year LVEDV = 111.7). (B) [d]Overall (N = 223; mean baseline left ventricular end-systolic volume [LVESV] = 89.9; mean 1-year LVESV = 76.7), [e]FMR (n = 140; mean baseline LVESV = 110.0; mean 1-year LVESV = 92.5), and [f]DMR (n = 69; mean baseline LVESV = 54.2; mean 1-year LVESV = 48.1). BL = baseline; DC = discharge; other abbreviations as in Figure 2.

FIGURE 4 NYHA Functional Status at 1 Year



Graphs show unpaired data. *P* value calculated from paired analysis using Wilcoxon signed rank test. [a]Baseline vs 30 days (n = 451; NYHA functional class I/II = 70.3%) and 1 year (n = 333; NYHA functional class I/II = 71.5%), [b]baseline vs 30 days (n = 280; NYHA functional class I/II = 67.1%) and 1 year (n = 203; NYHA functional class I/II = 68%), and [c]baseline vs 30 days (n = 128; NYHA functional class I/II = 77.3%) and 1 year (n = 97; NYHA functional class I/II = 79.4%). Abbreviations as in Figure 2.

MR reduction, confirming prior reports of successful treatment with this device in a population historically considered unsuitable for M-TEER. The MR reduction was accompanied with reverse cardiac remodeling in our study patients.

The 1-year MiCLASP results demonstrate that successful MR reduction was achievable with a low number of devices while maintaining gradients well below 5 mm Hg, despite being the first use of this M-TEER system by many operators. The profound impact on MR reduction experienced by the patients in our study translated into early clinical benefits as demonstrated by the significant improvements observed in functional and quality-of-life measures. At 1 year, 71.6% of patients were in NYHA functional class ≤II as compared with only 23.4% at baseline. DMR patients had lower risk scores and healthier baseline indices compared with FMR patients, which may have contributed to the numerically higher 6MWD, KCCQ, and EQ5D outcomes in the DMR group. Nevertheless, significant improvements in clinical and quality-of-life outcomes were demonstrated in both groups, which combined with the significant reduction in HF hospitalization rates at 1 year indicate the favorable effects of MR reduction on quality of life. Prior reports have linked improvements in KCCQ with a lower subsequent risk of mortality and heart failure hospitalization in patients with functional MR.[26-28]

The 1-year outcomes of the MiCLASP study show favorable results for this M-TEER system in a broad patient population. Ongoing follow-up will further elucidate the efficacy and durability of M-TEER with the system in the treatment of different MR etiologies.

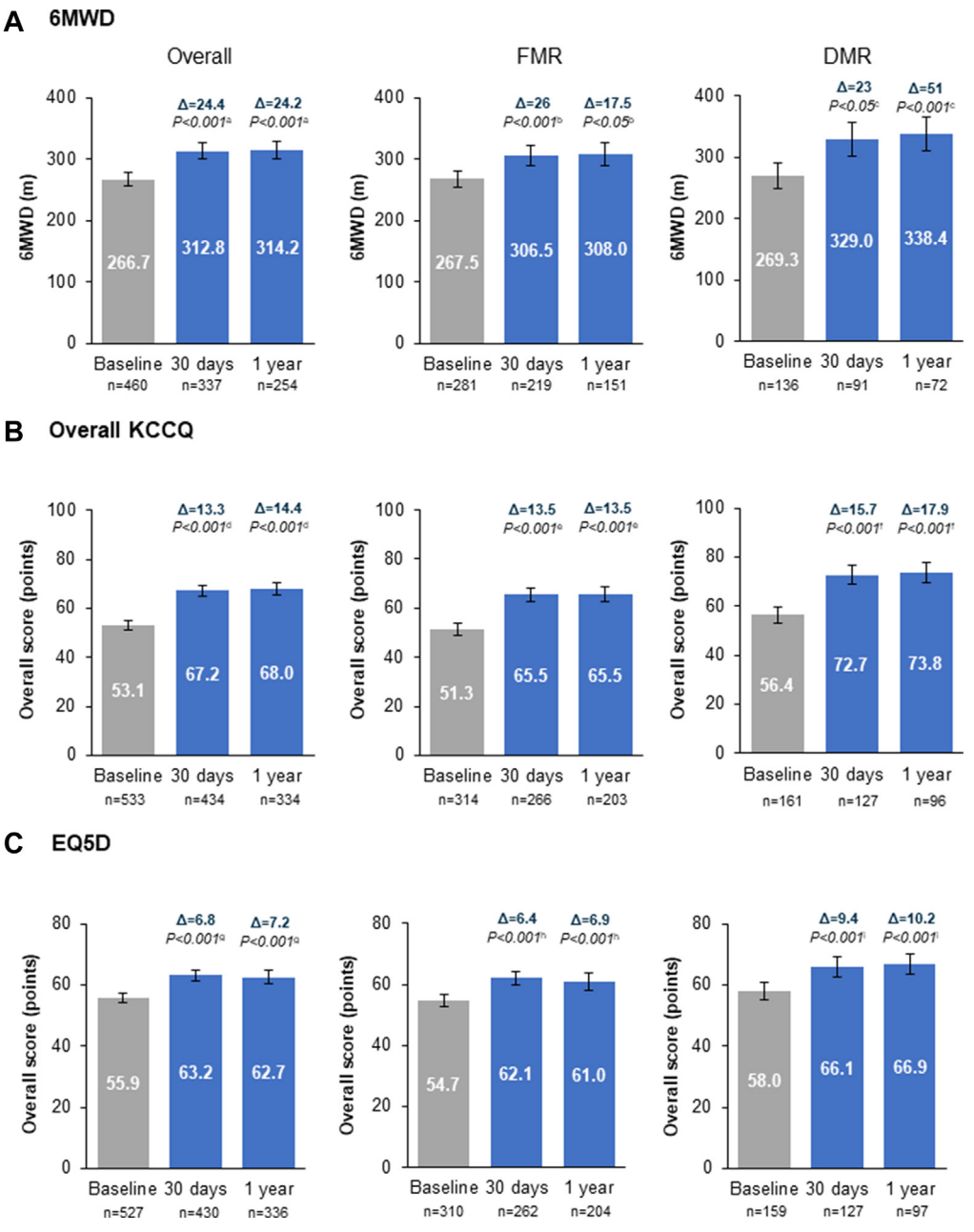
STUDY LIMITATIONS. The MiCLASP study is a single-arm PMCF study without a control group. Patient eligibility and enrollment were based on site assessment of baseline MR severity using EU guidelines, and core laboratory assessments were performed after patient enrollment using American Society of Echocardiography guidelines, resulting in some discrepancy in grading of baseline MR. The core laboratory could not evaluate baseline MR and MR etiology in some patients due to poor quality of imaging or missing echocardiograms. The COVID-19 pandemic contributed to variability in patient follow-up visits and incomplete echocardiographic assessments at some timepoints. Thirty-nine patients enrolled at study extension with the PASCAL Precision system are pending 1-year follow-up due to the visit window not yet open. Missed visits and study withdrawals and exits limit the availability of patient-reported outcome measures.

CONCLUSIONS

In this first report of 30-day and 1-year outcomes from the MiCLASP study, the safety and effectiveness of the PASCAL system in a post-market setting was demonstrated in a large cohort of FMR and DMR patients with symptomatic, clinically significant MR. High survival and sustained MR reduction was achieved at 1 year with evidence of LV reverse remodeling and significant improvements in symptoms, functional capacity, and quality of life.

ACKNOWLEDGMENTS The authors would like to thank all the patients, sites, and study principal investigators who participated in the MiCLASP study. In

FIGURE 5 **Functional and Quality of Life Outcomes at 1 Year**



Graphs show unpaired data. Error bars represent 95% CI. Δ and *P* value calculated from paired analysis using Student's *t*-test. (A) [a]Baseline vs 30 days (n = 312; mean baseline 6-minute walk distance [6MWD] = 289.6 m; mean 30-day 6MWD = 314.0 m) and 1 year (n = 224; mean baseline 6MWD = 290.9 m; mean 1-year 6MWD = 315.1 m), [b]baseline vs 30 days (n = 206; mean baseline 6MWD = 283.0 m; mean 30-day 6MWD = 309.0 m) and 1 year (n = 140; mean baseline 6MWD = 292.4 m; mean 1-year 6MWD = 309.8 m), [c]baseline vs 30 days (n = 83; mean baseline 6MWD = 304.2 m; mean 30-day 6MWD = 327.2 m) and 1 year (n = 59; mean baseline 6MWD = 290.4 m; mean 1-year 6MWD = 341.3 m). (B) [d]Baseline vs 30 days (n = 429; mean baseline Kansas City Cardiomyopathy Questionnaire [KCCQ] = 54.2; mean 30-day KCCQ = 67.5) and 1 year (n = 327; mean baseline KCCQ = 54.0; mean 1-year KCCQ = 68.3), [e]baseline vs 30 days (n = 261; mean baseline KCCQ = 52.3; mean 30-day KCCQ = 65.9) and 1 year (n = 197; mean baseline KCCQ = 52.3; mean 1-year KCCQ = 65.9), [f]baseline vs 30 days (n = 127; mean baseline KCCQ = 57.0; mean 30-day KCCQ = 72.7) and 1 year (n = 96; mean baseline KCCQ = 55.9; mean 1-year KCCQ = 73.8). (C) [g]Baseline vs 30 days (n = 423; mean baseline EuroQol 5 Dimensions Health Questionnaire [EQ-5D-5L] = 56.5; mean 30-day EQ-5D-5L = 63.3) and 1 year (n = 326; mean baseline EQ-5D-5L = 55.7; mean 1-year EQ-5D-5L = 62.9), [h]baseline vs 30 days (n = 257; mean baseline EQ-5D-5L = 55.8; mean 30-day EQ-5D-5L = 62.2) and 1 year (n = 197; mean baseline EQ-5D-5L = 54.3; mean 1-year EQ-5D-5L = 61.2), [i]baseline vs 30 days (n = 125; mean baseline EQ-5D-5L = 56.8; mean 30-day EQ-5D-5L = 66.3) and 1 year (n = 95; mean baseline EQ-5D-5L = 56.9; mean 1 year EQ-5D-5L = 67.1). Abbreviations as in Figure 2.

JACC: CARDIOVASCULAR INTERVENTIONS VOL. 17, NO. 7, 2024
APRIL 8, 2024:890–903

addition, they would like to thank Edwards Lifesciences TMTT members for their support of this publication; Maithili Shrivastava, PhD, Shiyu (Vanessa) Wang, MS, Allison Weiser, MPH, Suzanne Gilmore, MPIA, and Ted Feldman, MD.

FUNDING SUPPORT AND AUTHOR DISCLOSURES

This work was supported by Edwards Lifesciences. Prof Lurz has received institutional fees and research grants from Abbott Vascular, Edwards Lifesciences, Medtronic, ReCor, and Occlutech. Dr Schmitz has received speaker fees and proctor honorarium from Edwards Lifesciences and Abbott. Dr Geisler has received personal fees (lecture honoraria) and institutional research grants from Edwards Lifesciences. Dr Hausleiter is a consultant and receives speaker fees and institutional research support from Edwards Lifesciences. Prof Eitel has received research grants from Abbott Vascular and speaker fees from Abbott, Edwards Lifesciences, and Boston Scientific. Dr Rudolph has received research grants from Edwards Lifesciences, Abbott, and Boston Scientific. Dr Lubos has received grants from Abbott and personal fees from Abbott, Abiomed, AstraZeneca, Bayer, Edwards Lifesciences, New Valve Technology, and Novartis. Dr von Bardeleben is a principal investigator for Abbott, DZHK, Edwards Lifesciences, JensCare, Medtronic, NeoChord, and the University of Göttingen IIT; and serves as an advisor, proctor, or speaker for Abbott, Edwards Lifesciences, JenaValve, JensCare, Medtronic, NeoChord, Philips, and Siemens. Dr Berti has received honoraria from and is a consultant for Proctor & Gamble, Abbott, and Boston Scientific. Dr De Marco has received honoraria and consultation fees from Edwards Lifesciences. Dr Linke has received grants from Novartis and Edwards Lifesciences; personal fees from Abbott, Abiomed, AstraZeneca, Bayer, Boehringer Ingelheim, Boston Scientific, Edwards Lifesciences, Medtronic, Novartis, Sanofi Genzyme, and Pfizer; and other fees from Picardia, Filterlex, and Transverse Medical outside the submitted work. Dr Hengstenberg has received institutional research grants from Edwards Lifesciences, Boston Scientific, Abbott, and Medtronic; and serves as a proctor for Edwards Lifesciences and Boston Scientific. Dr Baldus has received a research grant from Abbott; and lecture fees from Abbott and Edwards Lifesciences. Dr Spargias has received honoraria or consultation fees from Edwards Lifesciences, Abbott Vascular, and Medtronic. Dr Denti is a consultant for InnovHeart, Approxima, Picardia, and HRV; and receives speaker fees from Edwards Lifesciences and Abbott. Prof Nickenig has received research funding from the Deutsche Forschungsgemeinschaft, the German Federal Ministry of Education and Research, the EU, Abbott, AGA Medical, AstraZeneca, Bayer, Berlin Chemie, Biosensus, Biotronic, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St. Jude Medical; and has received honoraria for lectures or advisory boards from Abbott, AGA Medical, AstraZeneca, Bayer, Berlin, Cardiovalve, Berlin Chemie, Biosensus, Biotronic, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Edwards Lifesciences, Medtronic, Novartis, Pfizer, Sanofi, and St. Jude Medical. Prof Möllmann has receives speaker/proctor fees from Abbott, Boston Scientific, Edwards Lifesciences, Medtronic, and SMT. Prof Rottbauer is a consultant for and receives speaker honoraria from Edwards Lifesciences. Dr Praz received travel expenses from Edwards Lifesciences, Abbott Vascular, Polares Medical, Medira, and Siemens Healthineers. Dr Butter has received lecture fees from Edwards Lifesciences and Abbott; and educational grants from Boston Scientific. Dr Van Mieghem has received research grants from Abbott Vascular, Boston Scientific, Medtronic, Edwards Lifesciences, Daiichi-Sankyo, AstraZeneca, and Teleflex; and scientific advisory fees from Anteris, JenaValve, Abbott Vascular, Boston Scientific, Medtronic, Amgen, Daiichi-Sankyo, Siemens, Pie Medical, and Teleflex. Dr Sherif is a consultant for and receives speaker honoraria from Edwards Lifesciences. Dr Swaans is a proctor/lecturer for Abbott Vascular, Boston Scientific, Bioventrix, Cardiac Dimensions, Edwards Lifesciences, GE Healthcare, Medtronic, and Philips Healthcare. Dr Witkowski is an advisory board member and has received honoraria from Abbott and Edwards Lifesciences. Dr Buch participates in the Abbott structural heart advisory group; and has received honoraria from Abbott. Prof Seidler has received honoraria for lectures, advisory boards, or travel grants from Abbott Vascular, AstraZeneca, Boehringer Ingelheim, Bristol Myers Squibb, Corvia, Cytokinetics, Edwards Lifesciences, Medtronic, Myocardia, Novartis, Pfizer, and Teleflex. Dr Eißmann has received honoraria or consultation fees from Edwards Lifesciences and Abbott Vascular. Dr Marcoff serves as a member of the echocardiography core laboratory for Edwards Lifesciences and Abbott for which he receives no direct compensation. Dr Koulogiannis is a consultant and advisory board member for Edwards Lifesciences; and a speaker for Abbott. Dr Rassaf has received research funding from the Deutsche Forschungsgemeinschaft and Abbott; and receives honoraria for lectures or advisory boards from AstraZeneca, Bayer, Berlin Chemie, Bristol Myers Squibb, Boehringer Ingelheim, Daiichi-Sankyo, Medtronic, Novartis, and Pfizer. Dr Luedike received research grants and honoraria for consulting and lectures from Edwards Lifesciences, Novartis, and Pfizer. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Mitral regurgitation is the most common valvular disorder worldwide and when untreated is associated with considerable morbidity and mortality. Mitral transcatheter edge-to-edge repair is an effective option for the treatment of these patients.

WHAT IS NEW? Outcomes from the MiCLASP study affirm the safety and efficacy of the PASCAL system in treatment of symptomatic MR in a post-market setting. At 1 year, patients treated with this M-TEER system demonstrated high survival, reduced HF hospitalization, and sustained MR reduction to MR ≤2+ in 98% and ≤1+ in 82.6% of patients as adjudicated by a CEC and echocardiographic core laboratory, respectively. Patients experienced significant and sustained clinical improvements.

WHAT IS NEXT? Longer term patient follow-up will be assessed annually to 5 years.

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KEY WORDS MiCLASP, mitral regurgitation, M-TEER, PASCAL, post-market

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