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STRUCTURAL

Randomized Comparison of Transcatheter Edge-to-Edge Repair for Degenerative Mitral Regurgitation in Prohibitive Surgical Risk Patients

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ABSTRACT

BACKGROUND Severe symptomatic degenerative mitral regurgitation (DMR) has a poor prognosis in the absence of treatment, and new transcatheter options are emerging.

OBJECTIVES The CLASP IID (Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial) randomized trial (NCT03706833) is the first to evaluate the safety and effectiveness of the PASCAL system compared with the MitraClip system in patients with significant symptomatic DMR. This report presents the primary safety and effectiveness endpoints for the trial.

METHODS Patients with 3+ or 4+ DMR at prohibitive surgical risk were assessed by a central screening committee and randomized 2:1 (PASCAL:MitraClip). Study oversight also included an echocardiography core laboratory and a clinical events committee. The primary safety endpoint was the composite major adverse event rate at 30 days. The primary effectiveness endpoint was the proportion of patients with mitral regurgitation (MR) ≤2+ at 6 months.

RESULTS A prespecified interim analysis in 180 patients demonstrated noninferiority of the PASCAL system vs the MitraClip system for the primary safety and effectiveness endpoints of major adverse event rate (3.4% vs 4.8%) and MR ≤2+ (96.5% vs 96.8%), respectively. Functional and quality-of-life outcomes significantly improved in both groups ($P < 0.05$). The proportion of patients with MR ≤1+ was durable in the PASCAL group from discharge to 6 months (PASCAL, 87.2% and 83.7% [$P = 0.317$ vs discharge]; MitraClip, 88.5% and 71.2% [$P = 0.003$ vs discharge]).

CONCLUSIONS The CLASP IID trial demonstrated safety and effectiveness of the PASCAL system and met noninferiority endpoints, expanding transcatheter treatment options for prohibitive surgical risk patients with significant symptomatic DMR. (J Am Coll Cardiol Intv 2022;15:2523–2536) © 2022 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

DMR = degenerative mitral regurgitation

HFH = heart failure hospitalization

MAE = major adverse event(s)

MR = mitral regurgitation

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

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Mitral regurgitation (MR) is a highly prevalent valvular disease in the United States and Europe and presents a significant health care burden.[1,2] Untreated severe MR is associated with poor prognosis, including reduced survival, increased heart failure hospitalization (HFH), and impaired functional and quality-of-life outcomes.[3-5] For patients with degenerative MR (DMR), medical therapy has a limited role. In the current guidelines, surgical mitral valve repair is a Class I recommendation with proven efficacy and a well-established safety profile for patients with DMR who are symptomatic and/or have impaired left ventricular systolic function.[6,7] However, patients remain undertreated because of high operative risk, underreferral,[8] and aversion to surgery.[9]

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Mitral valve transcatheter edge-to-edge repair (M-TEER) is a safe and effective option for patients with DMR at prohibitive surgical risk.[6] Since the initial M-TEER trials[10-12] with the early MitraClip system (Abbott Vascular), design iterations have been introduced,[13] while limitations[14] such as inadequate MR reduction,[15,16] leaflet injury,[15,17] and mitral stenosis[18] remain.

The PASCAL transcatheter valve repair system (Edwards Lifesciences) with its differentiated design was assessed in the multicenter, single-arm CLASP (Edwards PASCAL Transcatheter Mitral Valve Repair System) study. It demonstrated high procedural success, low complications, durable MR reduction, and high survival at 2 years in patients with clinically significant MR.[19-21]

The CLASP IID (Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial) randomized trial directly compares the safety and effectiveness of the PASCAL system and the MitraClip system in patients with significant symptomatic DMR at prohibitive surgical risk. Outcomes from the single-arm roll-in cohort representing early experience were previously reported and demonstrated 100% implantation success and significant MR reduction.[22] Herein, we report the primary safety and effectiveness endpoints of the CLASP IID randomized trial.

METHODS

STUDY DESIGN. The CLASP IID trial is a prospective, multicenter, multinational, randomized controlled trial comparing the safety and effectiveness of the PASCAL system and the MitraClip system in patients with significant symptomatic DMR at prohibitive surgical risk. The study hypotheses were that the PASCAL system is not inferior to the MitraClip system with respect to: 1) safety on the basis of the proportion of patients with major adverse events (MAE) at 30 days; and 2) effectiveness on the basis of the proportion of patients with MR ≤2+ at 6 months.

After providing written informed consent and meeting initial eligibility criteria, patients were evaluated by their local heart team for surgical risk and eligibility for M-TEER. In accordance with Mitral Valve Academic Research Consortium, the heart team consisted of a multidisciplinary team of a heart failure or valve cardiologist, an interventional cardiologist skilled in the relevant access and device implantation procedures, a mitral valve cardiac surgeon, and an imaging specialist. To be included in the study, all patients were required to be identified as at prohibitive risk for mitral valve surgery (repair or replacement) per the local heart team. Some patients had multiple reasons for prohibitive risk, and the primary reasons were reported. Frailty was assessed by in-person cardiac surgeon consultation using the CSHA (Canadian Study of Health and Aging) Frailty Scale. Eligible patients were evaluated by the central screening committee on the basis of echocardiograms

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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.

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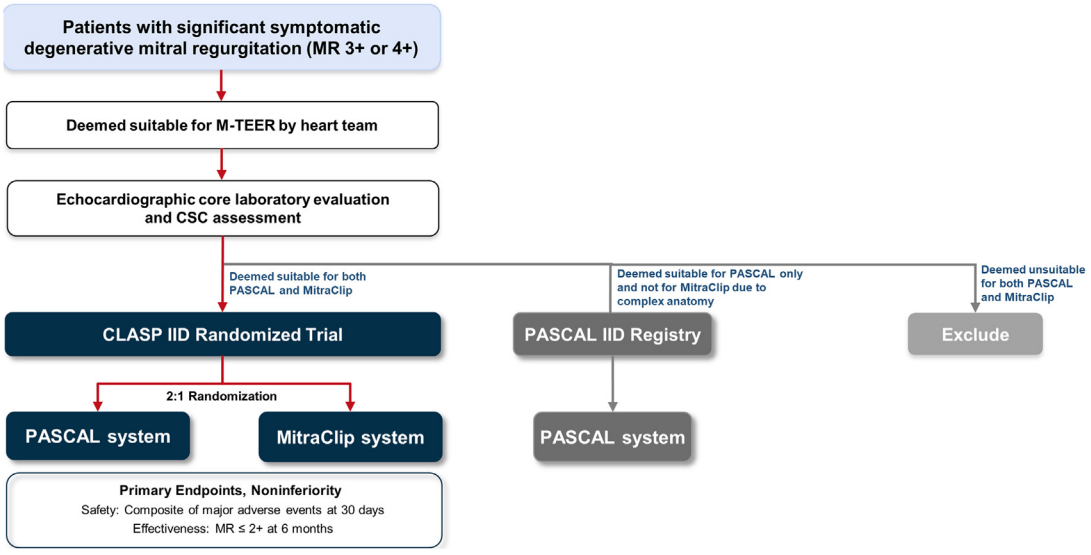
FIGURE 1 The CLASP IID Trial Design



Flowchart illustrating the trial design. CLASP IID = Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial; CSC = central screening committee; MR = mitral regurgitation; M-TEER = mitral valve transcatheter edge-to-edge repair.

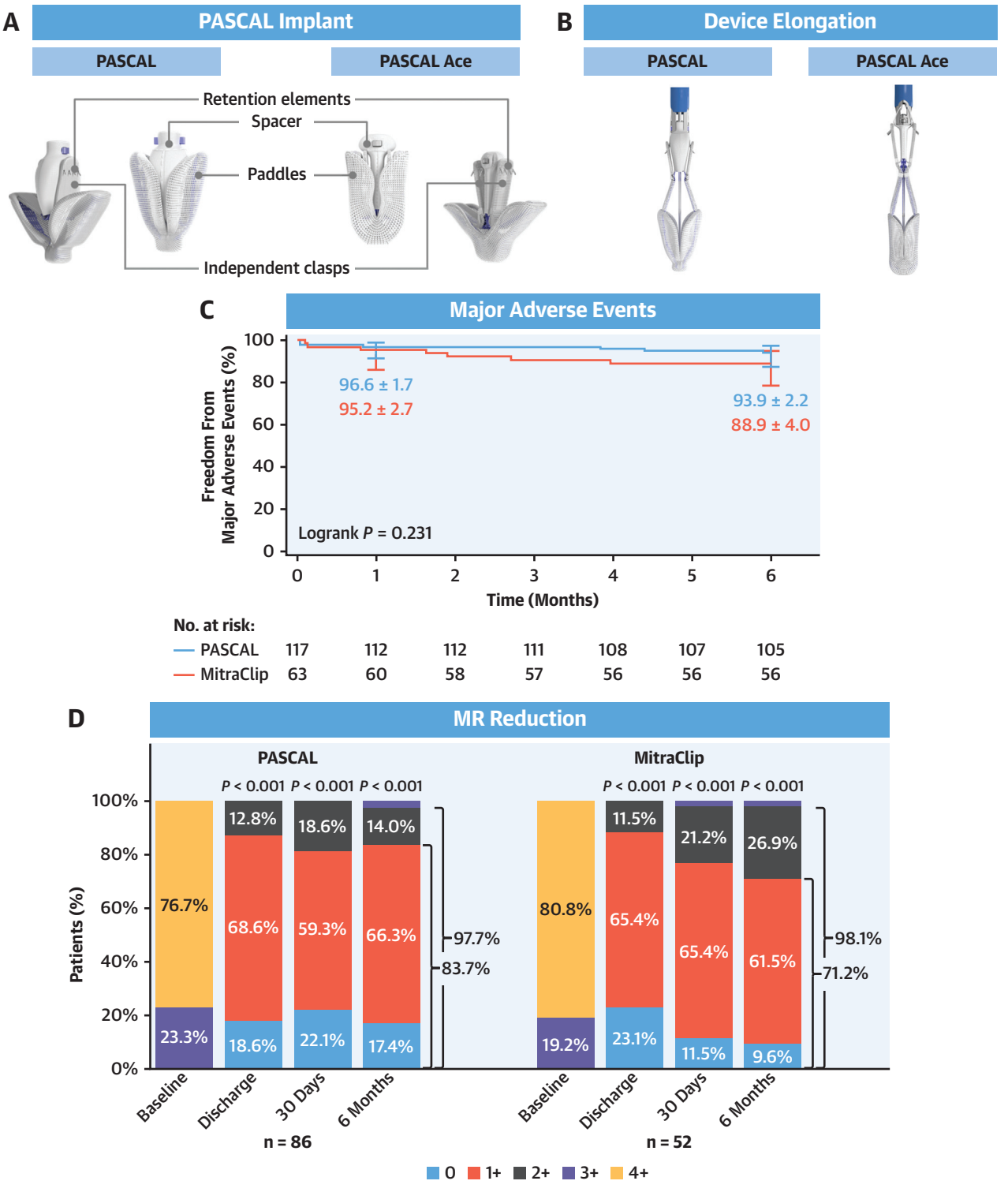
assessed by the echocardiography core laboratory (Cardiovascular Core Lab, Atlantic Health System Morristown Medical Center) to determine anatomical suitability for treatment with each device. Patients confirmed to be anatomically eligible for both devices were randomized 2:1 (PASCAL:MitraClip) and underwent treatment per assignment. Assessments are performed at baseline, during hospital stay, at discharge or 7 days postprocedure (whichever was earlier), and during follow-up at 30 days, 6 months, 1 year, and annually for 5 years. Patients suitable for the PASCAL system and not for the MitraClip system based on anatomical characteristics in the special patient populations section of the MitraClip instructions for use (IFU)[23] were considered for the PASCAL IID registry (**Figure 1**).

PATIENT SELECTION. Key inclusion criteria were age ≥18 years, grade 3+ or 4+ DMR by transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE) as assessed by the echocardiography core laboratory, M-TEER candidate suitable for both the PASCAL system and the MitraClip system, and deemed at prohibitive surgical risk by the local heart team including a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in treating mitral valve disease. Prohibitive risk determination was based on the MitraClip instructions for use.[23] Exclusion criteria included contraindication to TEE or unsuccessful screening TEE and mitral valve anatomy that might preclude proper access, use, and/or deployment of either device. A complete list of inclusion and exclusion criteria is provided in Supplemental Table 1.

THE PASCAL SYSTEM AND IMPLANTATION PROCEDURE. The PASCAL system comprises a 22-F guide sheath, a steerable catheter, and an implant catheter with a preattached implant. The system is available with 2 implant options, the original PASCAL implant and the narrow PASCAL Ace implant, which was introduced during the trial, and both implant options are collectively referred to as the PASCAL implant (**Central Illustration A and B**). The PASCAL system and implantation procedure have been previously described[19–22] and are outlined in Supplemental Methods Section 1. The MitraClip system and implantation procedure have been previously described.[10,13,23,24]

STUDY CONDUCT AND OVERSIGHT. The study is registered at ClinicalTrials.gov (NCT03706833) and was sponsored by Edwards Lifesciences. The study protocol was designed in accordance with the Mitral Valve Academic Research Consortium[25,26] and approved by the investigational review board or

CENTRAL ILLUSTRATION **The CLASP IID Randomized Trial Key Outcomes at 6 Months**



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(A) PASCAL implant design. **(B)** Elongation feature of the PASCAL implant. **(C)** Kaplan-Meier estimates for freedom from major adverse events (MAE) (Kaplan-Meier estimate ± SE). **Error bars** represent 95% CI. MAE include cardiovascular mortality, stroke, myocardial infarction, need for new renal replacement therapy, severe bleeding, and nonelective mitral valve reintervention (either percutaneous or surgical). **(D)** Mitral regurgitation severity assessed by echocardiography core laboratory using transthoracic echocardiography. The graph shows paired analysis, and *P* values were calculated using the Wilcoxon signed rank test. CLASP IID = Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial.

ethics committee at each participating center. All patients provided written informed consent, and the study conformed to the Declaration of Helsinki, Good Clinical Practice principles and ISO 14155:2011. A multidisciplinary central screening committee reviewed and approved randomization of each patient. An independent echocardiography core laboratory evaluated echocardiograms and a clinical events committee adjudicated prespecified adverse events. An independent data and safety monitoring board monitored the safety of the trial. The sponsor participated in site selection, trial management, and data analysis. All sites were required to have prior experience with the MitraClip system. The principal investigators had unrestricted access to the data and attest to the accuracy and completeness of data in this paper. The principal investigators drafted, reviewed, and revised the manuscript. Trial organization, leadership, participating sites, and key personnel are listed in Supplemental Tables 2 and 3.

STUDY ENDPOINTS. The primary safety endpoint was the composite MAE rate at 30 days, comprising cardiovascular mortality, stroke, myocardial infarction, new need for renal replacement therapy, severe bleeding, and nonelective mitral valve reintervention (either percutaneous or surgical). The primary effectiveness endpoint was the proportion of patients with MR ≤2+ at 6 months as assessed by the echocardiography core laboratory. Noninferiority of the PASCAL system compared with the MitraClip system was assessed for primary safety and effectiveness endpoints. Additional outcomes included all-cause mortality, HFH, New York Heart Association functional class, 6-minute walk distance, and quality of life by Kansas City Cardiomyopathy Questionnaire and EuroQol 5 Dimension 5 Level score.

ECHOCARDIOGRAPHIC ASSESSMENTS. Image acquisition was performed in accordance with the echocardiography core laboratory-recommended protocol. All echocardiograms obtained during screening, baseline, discharge, and follow-up were assessed by the core laboratory according to preestablished protocols based on American Society of Echocardiography guidelines, and MR severity was graded on a scale of 0 to 4+ (Supplemental Table 4).[27,28] TTE or TEE was used for baseline qualification, procedural planning, and intraprocedural imaging, and TTE was used for follow-up assessments.

STATISTICAL ANALYSIS. Up to 300 enrolled patients (PASCAL, n = 200; MitraClip, n = 100) were planned, assuming 5% attrition at 30 days, yielding a predicted sample size of 285 randomized patients for comparison (PASCAL, n = 190; MitraClip, n = 95). A Bayesian adaptive design provided a predictive model for primary endpoint analysis prior to reaching the full sample size. Interim analyses were planned for 180, 210, and 240 patients, and the interim sample size was deemed sufficient for primary endpoint analysis if the predictive probability for trial success exceeded 96.5% in 180 patients, 95.0% in 210 patients, or 95.0% in 240 patients. Primary safety and effectiveness endpoints were assessed against prespecified noninferiority margins of 15% and 18%, respectively. The power and sample size calculation and statistical methodology are provided in Supplemental Methods Section 2.

Continuous variables are summarized as number of observations, mean ± SD, or median (interquartile range/IQR) and 95% CI on the basis of *t* distribution. *P* values for continuous variables were calculated using Student's *t*-test. Paired analysis comprised data for the same patient for specified time points. An analysis of covariance model with baseline values and planned treatment as covariates was used to compare mean changes between time points and groups. The McNemar test was used to assess binary repeated measures. Categorical variables are summarized as patient count, percentage, and 95% exact CI and were compared using the Wilcoxon signed rank test. Kaplan-Meier estimates were used to analyze time-to-event variables, and SE was calculated using the exponential Greenwood method, with log-rank *P* value calculated for intergroup comparisons. As appropriate, differences between treatment groups are summarized as mean difference and 95% CI or percentage difference and 95% exact CI. Unless noted otherwise, patients with missing data were excluded from the denominator. To adjust for potential impact of the COVID-19 pandemic on follow-up visit compliance, the analysis window for the 6-month transthoracic echocardiographic data for the primary effectiveness endpoint was defined as day 23 to day 270 after the index procedure. Statistical analyses were performed with SAS version 9.4 or higher (SAS Institute). All analyses were performed for the modified intent-to-treat population defined in Supplemental Methods Section 2.

RESULTS

Patients were enrolled at 43 sites in the United States, Canada, and Europe between November 2018 and December 2021. Bayesian analysis for 180 randomized patients (PASCAL, n = 117; MitraClip, n = 63) met the

FIGURE 2 Patient Disposition and Flow for the CLASP IID Randomized Trial

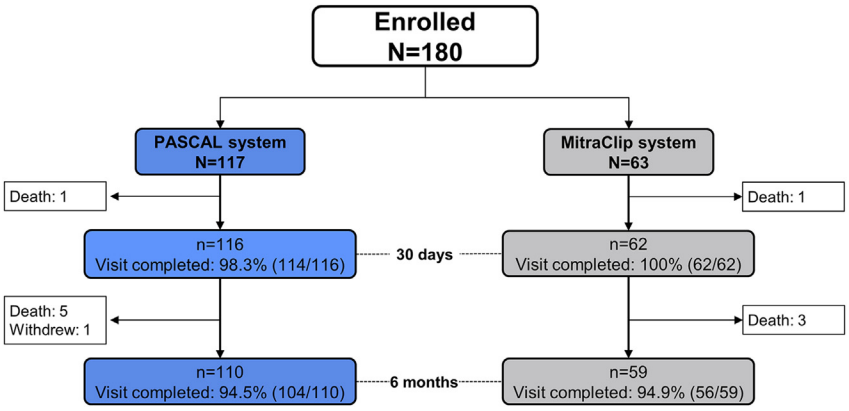


Illustration of patient enrollment, randomization, and follow-up, with visit windows of 30 ± 7 days and 6 months ± 30 days. For follow-up visits affected by the COVID-19 pandemic, the visit windows were adjusted to 30 days −7/+14 days and 6 months −30/+90 days.
CLASP IID = Edwards PASCAL Transcatheter Valve Repair System Pivotal Clinical Trial.

predictive probability for trial success. All patients had the study procedure and device attempted and were included in the modified intent-to-treat population. At 30 days, follow-up was complete for 98.3% and 100.0% patients in the PASCAL and MitraClip groups, respectively. At 6 months, follow-up was 94.5% for the PASCAL group and 94.9% for the MitraClip group. Patient disposition and study flow are shown in Figure 2.

BASELINE CHARACTERISTICS. Patient characteristics are listed in Table 1. Overall, the treatment groups were well matched ($P > 0.05$ for all), with a notable difference approaching significance in prior aortic valve surgery or intervention (12% for the PASCAL group, 3.2% for the MitraClip group; $P = 0.056$). Frailty was the most common reason for prohibitive risk (84.6% for the PASCAL group, 90.5% for the MitraClip group) (Supplemental Table 5).

PROCEDURAL OUTCOMES. All patients received devices except for 1 aborted procedure in the PASCAL group because of inability to grasp the posterior leaflet. In the PASCAL group, 67.2% patients received the PASCAL implant, 24.1% received the PASCAL Ace implant, and 8.6% received a combination. In the MitraClip group, 39.3% patients received NT, NTR, or XTR implants and 60.7% received the newer (G4) NT, NTW, XT, or XTW implants. The mean number of devices implanted per patient was similar for both groups (1.5 with PASCAL, 1.6 with MitraClip; $P = 0.215$). The median procedure time was 88.0 minutes for the PASCAL group and 79.0 minutes for the MitraClip group ($P = 0.023$), and the median device times were 60.0 minutes and 41.0 minutes, respectively ($P < 0.001$) (Table 2). A learning curve analysis revealed a trend in reduced procedure time (mean 107.7 to 98.2 minutes) and device time (mean 77.9 to 69.6 minutes) with experience from 1 to >3 PASCAL procedures (Supplemental Figure 1).

PRIMARY ENDPOINTS. Primary safety endpoint. The primary safety endpoint was met, with noninferiority of the PASCAL system compared with the MitraClip system. The absolute difference in the 30-day composite MAE rate (PASCAL − MitraClip) was −1.3%. The 1-sided 95% upper confidence bound was 5.1%, which was within the prespecified noninferiority margin of 15% (Figure 3).

The MAE rate was 3.4% (4 of 116) for the PASCAL group, comprising 1 cardiovascular death (0.9%), 3 patients with severe bleeding (2.6%), 1 nonelective mitral valve reintervention (0.9%), and no stroke, myocardial infarction, or new need for renal replacement therapy (Table 3). The single cardiovascular death (procedure related, possibly device related) occurred in a patient who experienced anesthesia-induced hypotension and pulseless electric activity during the procedure. The patient was stabilized and discharged to a rehabilitation facility followed by hospice and died at home of cardiac failure. One patient had a single-leaflet device attachment and underwent nonelective mitral valve reintervention (device related) with an additional PASCAL device, which resulted in 2+ residual MR.

TABLE 1 Baseline Characteristics

	PASCAL (n = 117)	MitraClip (n = 63)	*P* Value
Demographics			
Age, y	81.1 ± 6.9 (117)	81.2 ± 6.2 (63)	0.926
Male	78/117 (66.7)	43/63 (68.3)	0.869
Body mass index, kg/m^2	25.9 ± 5.4 (117)	26.2 ± 4.8 (63)	0.499
STS score for mitral valve repair, %	4.1 ± 2.8 (117)	3.6 ± 2.2 (63)	0.476
STS score for mitral valve replacement, %	5.7 ± 3.3 (117)	5.1 ± 2.6 (63)	0.437
EuroSCORE II, %	3.9 ± 2.9 (117)	4.1 ± 3.1 (63)	0.736
NYHA functional class III/IV	71/117 (60.7)	39/63 (61.9)	1.000
Medical history/comorbidities			
Atrial fibrillation	67/117 (57.3)	38/63 (60.3)	0.752
Cardiomyopathy	16/117 (13.7)	11/63 (17.5)	0.517
Coronary artery disease (≥50% stenosis)	46/117 (39.3)	25/63 (39.7)	1.000
Renal insufficiency[a] (eGFR < 60 ml/min)	35/117 (29.9)	24/63 (38.1)	0.318
Diabetes	19/117 (16.2)	15/63 (23.8)	0.235
Hypertension	98/117 (83.8)	57/63 (90.5)	0.263
Hyperlipidemia	87/117 (74.4)	39/63 (61.9)	0.090
Myocardial infarction	19/117 (16.2)	7/63 (11.1)	0.385
Peripheral arterial disease	3/117 (2.6)	2/63 (3.2)	1.000
Anemia (chronic, Hb ≤ 9 g/dL)	7/117 (6.0)	5/63 (7.9)	0.755
Stroke	9/117 (7.7)	1/63 (1.6)	0.169
TIA	10/117 (8.5)	3/63 (4.8)	0.547
COPD	20/117 (17.1)	12/63 (19.0)	0.838
Pacemaker/ICD	7/117 (6.0)	9/63 (14.3)	0.096
PCI	27/117 (23.1)	14/63 (22.2)	1.000
Coronary artery bypass graft	15/117 (12.8)	6/63 (9.5)	0.630
Gastrointestinal or esophageal bleeding	10/117 (8.5)	7/63 (11.1)	0.600
Pulmonary hypertension[b]	53/117 (45.3)	30/63 (47.6)	0.876
Home oxygen use	6/117 (5.1)	3/63 (4.8)	1.000
Hospitalizations for heart failure (≥1 in past 12 mo)	40/117 (34.2)	25/63 (39.7)	0.516
Aortic valve surgery/intervention	14/117 (12.0)	2/63 (3.2)	0.056
Tricuspid valve surgery/intervention	0/117 (0.0)	1/63 (1.6)	0.350
Echocardiographic measures			
Degenerative mitral regurgitation etiology	117/117 (100)	63/63 (100)	–
MR 3+[c]	29/115 (25.2)	13/63 (20.6)	0.581
MR 4+[c]	86/115 (74.8)	50/63 (79.4)	0.581
Effective regurgitant orifice area, cm^2	0.50 ± 0.15 (80)	0.50 ± 0.20 (49)	0.857
Left ventricular end-systolic dimension, mm	38.3 ± 7.7 (116)	39.8 ± 7.8 (62)	0.215
Left ventricular end-diastolic dimension, mm	57.1 ± 6.5 (117)	57.4 ± 6.5 (63)	0.889
Left ventricular end-systolic volume, mL	59.5 ± 28.8 (113)	63.7 ± 27.4 (63)	0.195
Left ventricular end-diastolic volume, mL	143.3 ± 48.6 (113)	149.9 ± 44.8 (63)	0.180
Left ventricular ejection fraction, %	59.6 ± 8.7 (117)	58.3 ± 9.0 (63)	0.346
Transmitral mean gradient, mm Hg	2.5 ± 1.1 (113)	2.4 ± 1.1 (59)	0.400
Pulmonary artery systolic pressure, mm Hg	42.3 ± 11.4 (99)	45.6 ± 14.6 (51)	0.225
TAPSE, mm	20.6 ± 5.4 (86)	21.0 ± 5.6 (47)	0.875
Left atrial volume, cm^3	116.3 ± 37.6 (116)	121.3 ± 45.8 (63)	0.859
TR 3+[d]	3/116 (2.6)	3/63 (4.8)	0.426
Mitral valve area, cm^2	6.1 ± 1.4 (90)	6.0 ± 1.6 (50)	0.556

Values are mean ± SD (N) or n/N (%). For continuous variables, *P* values were based on the Kruskal-Wallis test; for categorical variables, *P* values were based on the Fisher exact test. [a]eGFR ≤ 25 mL/min was an exclusion criterion. [b]PASP ≥ 30 mm Hg (52/53 PASCAL). [c]Transesophageal echocardiography was used for baseline qualification for 2 patients, as MR grade was not evaluable on transthoracic echocardiography. [d]Severe TR (4+) was an exclusion criterion.

COPD = chronic obstructive pulmonary disease; eGFR = estimated glomerular filtration rate; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter-defibrillators; MR = mitral regurgitation; NYHA = New York Heart Association; PASP = pulmonary artery systolic pressure; PCI = percutaneous coronary intervention; STS = Society of Thoracic Surgeons; TAPSE = tricuspid annular plane systolic excursion; TIA = transient ischemic attack; TR = tricuspid regurgitation.

Two patients had procedure related bleeding events (TEE-related sublingual hematoma, hematoma at the contralateral access site), and 1 patient had both device and procedure related bleeding event due to acute postprocedural anemia following mitral valve reintervention described previously.

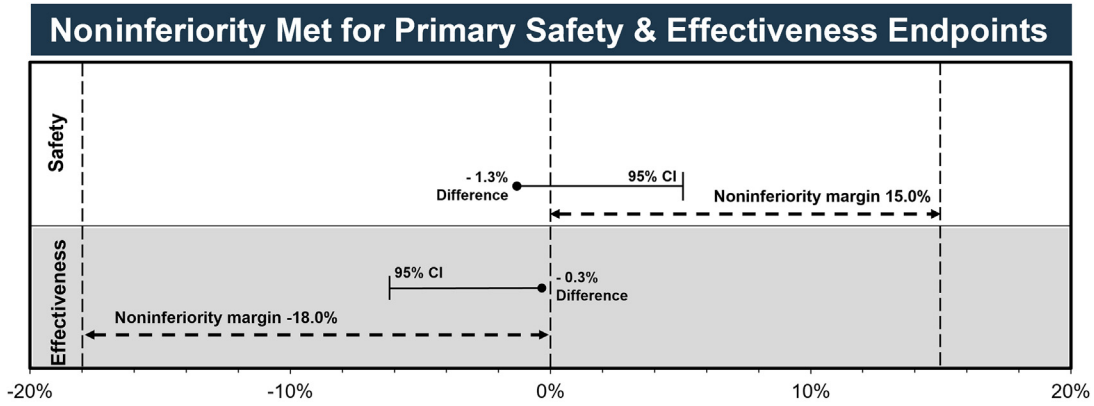
In the MitraClip group, the MAE rate was 4.8% (3 of 63), comprising 1 cardiovascular death (1.6%),

TABLE 2 Procedural Outcomes

	PASCAL (n = 117)	MitraClip (n = 63)	*P* Value
Successful implantation rate[a]	116/117 (99.1)	63/63 (100.0)	1.000
Procedure time, min[b]	88.0 (68.5-122.0) (116)	79.0 (58.0-106.0) (62)	0.023
Device time, min[c]	60.0 (38.0-96.0) (117)	41.0 (26.0-67.0) (61)	<0.001
Fluoroscopy duration, min	23.0 (15.0-34.0) (115)	20.0 (14.0-29.0) (63)	0.146
Mean number of devices implanted in patients who received a device	1.5 ± 0.6 (116)	1.6 ± 0.7 (63)	0.215
Number of implanted devices			0.170
1	63/117 (53.8)	30/63 (47.6)	0.439
2	49/117 (41.9)	26/63 (41.3)	1.000
3	4/117 (3.4)	7/63 (11.1)	0.052
Location of implanted devices			0.251
A1-P1	7/171 (4.1)	3/100 (1.6)	
A2-P2	141/171 (82.5)	79/100 (79.0)	
A3-P3	17/171 (9.9)	17/100 (17.0)	
Other[d]	6/171 (3.5)	1/100 (1.0)	
Device type			
PASCAL	78/116 (67.2)	–	
PASCAL Ace	28/116 (24.1)	–	
PASCAL and PASCAL Ace	10/116 (8.6)		
MitraClip NT, NTR, or XTR	–	24/61 (39.3)	
MitraClip NT, NTW, XT, or XTW (G4)	–	37/61 (60.7)	
Total length of stay for the index procedure, days	1.0 (1.0-2.0) (117)	1.0 (1.0-2.0) (63)	0.505

Values are n/N (%), median (IQR) (N), or mean ± SD (N). For continuous variables, *P* values were based on the Kruskal-Wallis test; for categorical variables, *P* values were based on the Fisher exact test. [a]Successful implantation: patients with study device implanted, deployed as intended, and delivery system retrieved successfully. [b]Procedure time: from procedure start (femoral vein puncture or skin incision) to femoral vein access closure. [c]Device time: from PASCAL implant system or MitraClip delivery system insertion into left atrium to guide sheath or steerable guide removal. [d]Other includes A1-P2, P1-P2, A2-P3 and P1-A2.

FIGURE 3 Primary Safety and Effectiveness Endpoints for the CLASP IID Randomized Trial



Endpoint	PASCAL (n=117)	MitraClip (n=63)	Difference	95% CI
Safety	**3.4%** (4/116)	**4.8%** (3/63)	**- 1.3%**	**+ 5.1%**
Effectiveness	**96.5%** (110/114)	**96.8%** (60/62)	**- 0.3%**	**- 6.2%**

Primary endpoint outcomes. CIs based on unpooled *z* test with continuity correction. Primary safety endpoint (composite major adverse event [MAE] rate at 30 days) analysis includes patients who had an MAE or did not have an MAE but were followed for at least 30 days. The analysis window for the primary effectiveness endpoint was defined as days 23 to 270.

2 patients with severe bleeding (3.2%), and no stroke, myocardial infarction, new need for renal replacement therapy, or nonelective mitral valve reintervention (Table 3). The cardiovascular death (device related) occurred after irrecoverable entrapment of a second MitraClip device in the subvalvular chordal apparatus, resulting in 4+ residual MR and death. There were 2 patients with severe bleeding events: right humerus fracture from a postprocedure fall requiring surgery with subsequent severe bleeding (possibly procedure related) and gastrointestinal bleeding secondary to dual antiplatelet therapy (possibly device related, probably procedure related).

Primary effectiveness endpoint. The primary effectiveness endpoint was met, with noninferiority of the PASCAL system compared with the MitraClip system. The proportion of patients with MR ≤2+ at 6 months was 96.5% for the PASCAL group and 96.8% for the MitraClip group, with an absolute difference of −0.3% (PASCAL − MitraClip). The 1-sided 95% lower confidence bound of −6.2% was within the prespecified noninferiority margin of −18% (Figure 3). Median follow-up duration for the primary effectiveness endpoint was 179.5 days (IQR: 162.0-189.0 days) for the PASCAL group and 184.5 days for the MitraClip group (IQR: 155.0-195.0 days).

ECHOCARDIOGRAPHIC OUTCOMES. In both treatment groups, patients experienced significant MR reduction from baseline to 6 months ($P < 0.001$) in paired analysis (Central Illustration D). At discharge, 100% of patients achieved MR ≤2+ in both groups. At 6 months, the proportion of patients with MR ≤2+ was 97.7% in the PASCAL group and 98.1% in the MitraClip group. At discharge, 87.2% of patients in the PASCAL group had MR ≤1+ compared with 88.5% in the MitraClip group. At 6 months, the proportion of patients with MR ≤1+ was sustained in the PASCAL group at 83.7% ($P = 0.317$ vs discharge), while in the MitraClip group, the proportion of patients with MR ≤1+ declined significantly to 71.2% ($P = 0.003$ vs discharge) (Supplemental Figure 2A). Unpaired analysis showed similar trends (Supplemental Figures 2B and 3). Mean transmitral valve gradients remained stable over time in both groups (PASCAL, 3.8 mm Hg at discharge and 3.7 mm Hg at 6 months [$P = 0.896$]; MitraClip, 3.6 mm Hg at discharge and 3.4 mm Hg at 6 months [$P = 0.595$]) (Supplemental Figure 4).

ADDITIONAL OUTCOMES. Adverse events to 6 months are provided in Supplemental Table 6. The Kaplan-Meier estimate for freedom from MAE at 6 months was 93.9% for the PASCAL group and 88.9% for the MitraClip group ($P = 0.231$) (Central Illustration C).

TABLE 3 Clinical Events Committee–Adjudicated Composite Major Adverse Events at 30 Days

	PASCAL (n = 117)[a]	MitraClip (n = 63)
Cardiovascular mortality	1 (0.9)	1 (1.6)
Stroke	0 (0.0)	0 (0.0)
Myocardial infarction	0 (0.0)	0 (0.0)
Need for new renal replacement therapy	0 (0.0)	0 (0.0)
Severe bleeding[b]	3 (2.6)	2 (3.2)
Nonelective mitral valve reintervention (percutaneous or surgical)	1 (0.9)	0 (0.0)
Composite MAE rate	4 (3.4)	3 (4.8)

Values are n (%). The denominator includes patients who had an MAE or did not have an MAE but were followed for at least 30 days. [a]1 patient withdrew prior to 30-day follow-up without an MAE. [b]Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium criteria.

MAE = major adverse event(s).

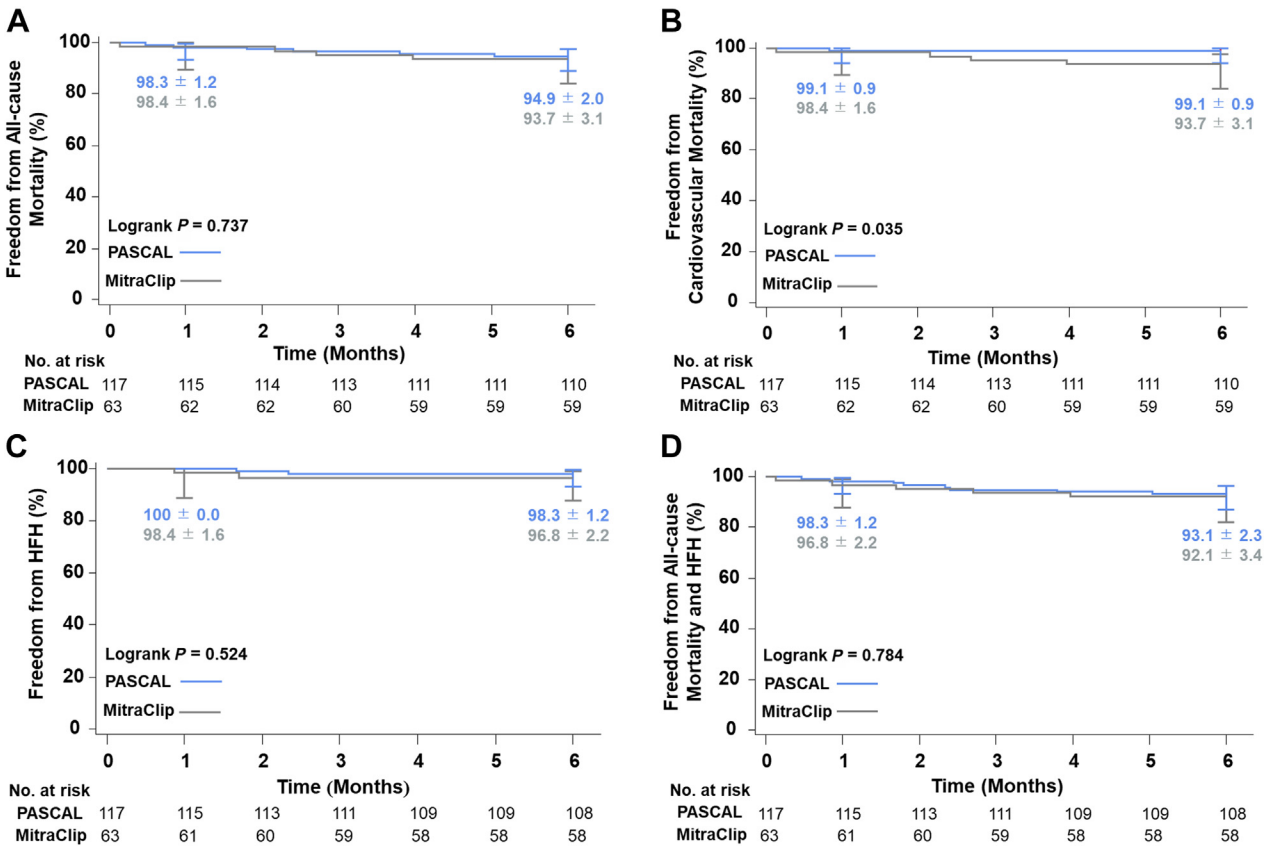
The Kaplan-Meier estimate for survival was 94.9% for the PASCAL group and 93.7% for the MitraClip group ($P = 0.737$), and freedom from cardiovascular mortality was 99.1% and 93.7%, respectively ($P = 0.035$). Of the 3 additional cardiovascular deaths in the MitraClip group between 30 days and 6 months, 1 was device related, due to mitral stenosis requiring cardiac surgery that led to mesenteric ischemia (Figure 4, Supplemental Table 6). The Kaplan-Meier estimate for freedom from HFH was 98.3% for the PASCAL group and 96.8% for the MitraClip group ($P = 0.524$), and freedom from HFH and all-cause mortality was 93.1% and 92.1% ($P = 0.784$), respectively (Figure 4).

At 6 months, there were significant improvements in functional capacity ($P < 0.001$) and quality-of-life outcomes ($P < 0.05$ for all) compared with baseline in both groups (Figures 5 and 6). An analysis of covariance demonstrated no significant differences between groups at 6 months for 6-minute walk distance, Kansas City Cardiomyopathy Questionnaire, and EuroQol 5 Dimension 5 Level outcomes (Figure 6).

DISCUSSION

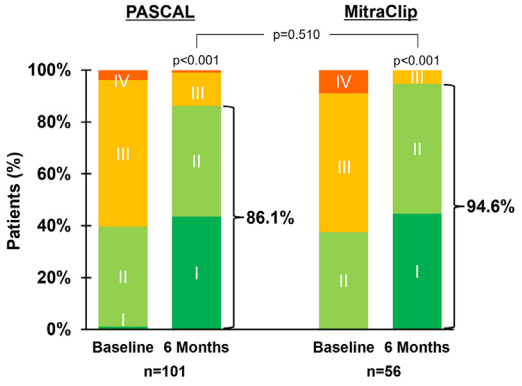
The CLASP IID trial is the first randomized study to directly compare M-TEER outcomes between the PASCAL system and the MitraClip system and demonstrated several key findings. First, the trial met primary safety (30-day composite MAE rate) and effectiveness (6-month MR ≤2+) endpoints, establishing noninferiority of the PASCAL system compared with the MitraClip system. In patients

FIGURE 4 Freedom From Clinical Events Committee-Adjudicated Mortality and Heart Failure Hospitalization



Kaplan-Meier estimates for freedom from **(A)** all-cause mortality, **(B)** cardiovascular mortality, **(C)** heart failure hospitalization (HFH), and **(D)** all-cause mortality and heart failure hospitalization. Graph shows Kaplan-Meier estimate ± SE, and **error bars** represent 95% CIs.

FIGURE 5 New York Heart Association Functional Class at 6 Months



Graph shows paired analysis for New York Heart Association functional class. *P* values for intragroup comparison were calculated using the Wilcoxon signed rank test and for intergroup comparison were calculated using the Wilcoxon rank sum test.

randomized to receive the PASCAL device, there was a high degree of acute reduction to MR ≤1+, which was sustained to 6 months. Although a similar reduction to MR ≤1+ was observed with the MitraClip device at discharge, some loss of efficacy was observed over the same course of follow-up. Finally, though the PASCAL device is relatively larger, the mitral inflow gradients were low and remained stable during follow-up.

Patients in the PASCAL group demonstrated a low 30-day MAE rate that was comparable with that seen in the MitraClip group and consistent with the CLASP study,[20] further establishing the safety of the PASCAL system and M-TEER therapy. Although there were no significant differences in the all-cause mortality and HFH rates between the 2 treatment groups, the cardiovascular mortality rate was significantly higher in the MitraClip group at 6 months. The single-leaflet device attachment rates were low and comparable

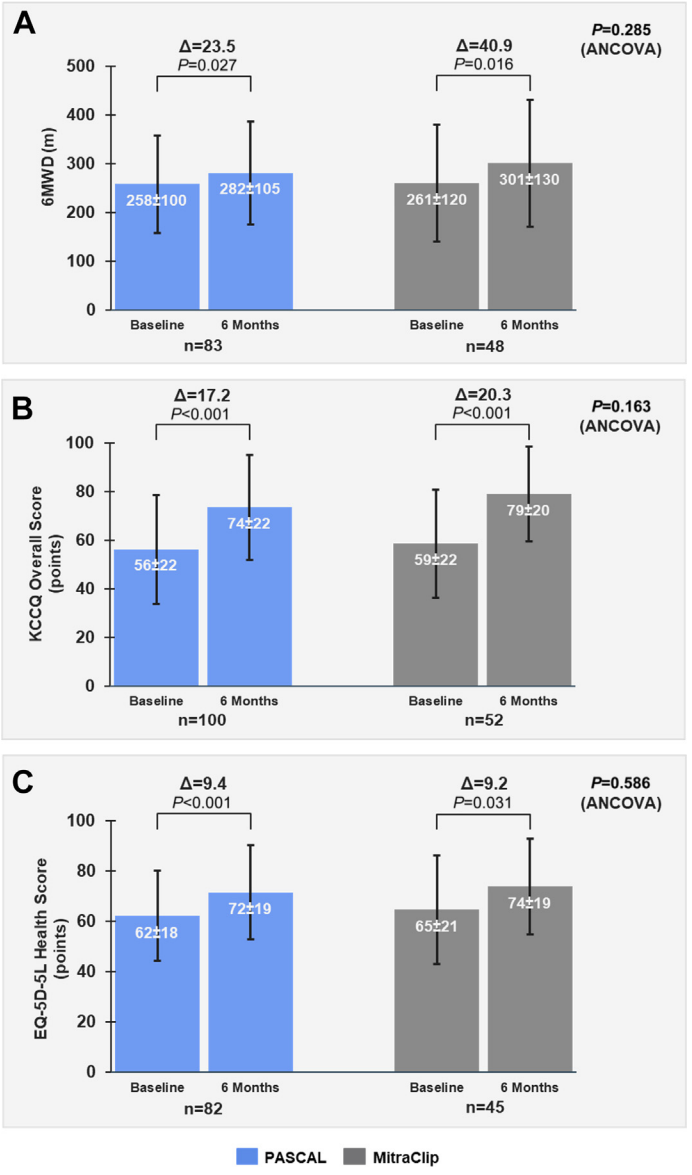
with those reported in the CLASP study[19,20] and the Society of Thoracic Surgeons/American College of Cardiology TVT (Transcatheter Valve Therapy) registry.[29] Leaflet perforation was rare, 1 with the MitraClip implant and none with the PASCAL implant, which uses a single horizontal row of leaflet retention elements designed to facilitate device repositioning and optimization of leaflet grasping while minimizing the risk for leaflet injury. There were no reports of chordal entrapment with the PASCAL implant, which may be attributed to its ability to elongate to a smooth, low profile for maneuvering in dense chordae.

In both treatment groups, patients experienced significant reductions to MR ≤2+ at discharge, which were stable to 6 months. In this interim analysis, for MR ≤1+, the proportion of patients in the PASCAL group was sustained from discharge to 6 months, whereas in the MitraClip group, there was some deterioration over time from discharge to 30 days and 6 months. Although this observation is consistent with other studies reporting a similar trend in MR ≤1+ outcomes,[20,30,31] it should be viewed as hypothesis generating at this time in the trial. Residual MR ≤1+ has been associated with better clinical outcomes compared with MR ≤2+, underscoring the importance of this finding.[32,33] Some characteristics of the PASCAL implant may have contributed to the significant and sustained MR reduction, including the spacer that fills the regurgitant orifice and broad contoured paddles that maximize leaflet coaptation. It is also worth noting that despite the implant size, patients in the PASCAL group demonstrated low transmitral gradients at discharge, which remained stable over time, and this may also be attributed to its flexible nitinol design. The high degree of MR reduction to ≤1+ in combination with a low risk for iatrogenic mitral stenosis is encouraging.

In both groups, there were significant reductions in symptoms and improvements in functional class and quality-of-life measures that were sustained at 6 months. Although the trial was not powered to show differences in functional and quality-of-life outcomes between patients with MR ≤1+ and those with MR ≤2+, if the magnitude of MR reduction to ≤1+ is maintained in the PASCAL group at later time points, differences in symptomatic alleviation and quality-of-life improvement between the groups may become apparent.

Procedure time in the PASCAL group was longer in early cases despite comparable mean number of implantations in both groups. The PASCAL system allows the optimization of leaflet grasping and insertion to maximize MR reduction, which could have resulted in a learning curve for operators, contributing to the longer procedure time. With greater operator experience, a reduction in procedural time was observed. A similar learning curve

FIGURE 6 Functional and Quality-of-Life Outcomes at 6 Months



Graphs show paired analysis (mean ± SD) for 6-minute walk distance (6MWD), Kansas City Cardiomyopathy Questionnaire (KCCQ) overall score, and EuroQol 5 Dimension 5 Level (EQ-5D-5L) health score. *P* values for intragroup comparisons were calculated using Student's *t*-test, and *P* values for intergroup comparisons were calculated using the analysis of covariance (ANCOVA) model adjusted for baseline values and planned treatment as covariates.

was reported in the TVT registry, which demonstrated an association between case experience and improvements in procedural time with the real-world use of MitraClip.[34] The majority of the sites did not have prior experience with the PASCAL system; hence, we anticipate that as operators gain greater experience with the PASCAL system, procedural time will further improve.

The CLASP IID randomized trial further establishes the PASCAL system as a safe and effective treatment option for prohibitive risk patients with significant symptomatic DMR. Its addition to the M-TEER armamentarium will expand transcatheter treatment options for patients. The outcomes between the 2 treatment groups were largely comparable at 6 months, but certain factors may be considered for device selection. First, there was some deterioration in the MR ≤1+ outcomes with the MitraClip system as well as a higher rate of cardiovascular mortality at 6 months, but outcomes in the full cohort of patients and longer term data are needed to further elucidate these findings. Second, the distinct design characteristics of the 2 devices must be considered in relation to patient anatomy. For instance, patients with smaller mitral valve areas may benefit from the PASCAL device, which has a flexible nitinol design. In addition, the smooth narrow profile and elongation capability may allow operators to use the device with confidence in chordal dense areas. The MitraClip device with its multiple grippers may be better suited for patients with calcium in the grasping area. We expect operator preferences around device selection to evolve with continued device innovation.

STUDY LIMITATIONS. One inherent limitation of this study is that treatment allocation was unblinded, potentially biasing the assessment of outcomes. However, rigorous study oversight and independent adjudication of outcomes by the clinical events committee and the echocardiography core laboratory help mitigate the bias. Although the early results are promising and consistent with prior reports, outcomes for the full cohort and further follow-up are needed to validate these findings. In addition, the ability to perform meaningful analysis corelating device iterations to outcomes is limited by sample size. It is also important to note the limitations resulting from the concurrent COVID-19 pandemic, which affected patient follow-up. The follow-up window for the primary effectiveness endpoint was extended to accommodate delays in assessments. A sensitivity analysis was performed and confirmed no difference in results.

CONCLUSIONS

The CLASP IID trial is the first head-to-head trial comparing M-TEER outcomes with the PASCAL system and the MitraClip system in patients with significant symptomatic DMR (3+ or 4+) at prohibitive risk for mitral valve surgery. The prespecified primary safety and effectiveness endpoints of the trial were met, and the results demonstrated that the PASCAL system was safe, effective, and noninferior to the MitraClip system in this patient population, establishing it as a beneficial therapy for patients with DMR. The excellent safety and effectiveness outcomes in both treatment groups are indicative of the tremendous improvements in contemporary M-TEER technology as well as operator skill and experience and will expand treatment options for patients.

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PERSPECTIVES

WHAT IS KNOWN? Severe symptomatic DMR has a poor prognosis in the absence of treatment, and new transcatheter options are emerging.

WHAT IS NEW? The CLASP IID trial is the first randomized controlled trial to directly compare 2 contemporary transcatheter edge-to-edge repair therapies. In this trial, the PASCAL system was noninferior to the MitraClip system with respect to safety and effectiveness in patients at prohibitive surgical risk with 3+ or 4+ DMR. Patients treated with the PASCAL system had low event rates, significant and sustained MR reduction to ≤2+, and significant improvements in functional and quality-of-life outcomes. Additionally, in the PASCAL group, patients demonstrated sustained MR ≤1+ durability.

WHAT IS NEXT? Continued patient follow-up to 5 years will confirm long-term outcomes with the PASCAL system in comparison with the MitraClip system.

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KEY WORDS CLASP IID, MitraClip system, mitral valve transcatheter edge-to-edge repair, M-TEER, PASCAL system, TMVr, transcatheter mitral valve repair

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