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ORIGINAL INVESTIGATIONS

Transcatheter Edge-to-Edge Repair in Patients With Anatomically Complex Degenerative Mitral Regurgitation

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ABSTRACT

BACKGROUND Mitral valve transcatheter edge-to-edge repair is safe and effective in treating degenerative mitral regurgitation (DMR) patients at prohibitive surgical risk, but outcomes in complex mitral valve anatomy patients vary.

OBJECTIVES The PASCAL IID registry assessed safety, echocardiographic, and clinical outcomes with the PASCAL system in prohibitive risk patients with significant symptomatic DMR and complex mitral valve anatomy.

METHODS Patients in the prospective, multicenter, single-arm registry had 3+ or 4+ DMR, were at prohibitive surgical risk, presented with complex anatomic features based on the MitraClip instructions for use, and were deemed suitable for the PASCAL system by a central screening committee. Enrolled patients were treated with the PASCAL system. Safety, effectiveness, and functional and quality-of-life outcomes were assessed. Study oversight also included an echocardiographic core laboratory and clinical events committee.

RESULTS The study enrolled 98 patients (37.2% ≥2 independent significant jets, 15.0% severe bileaflet/multi scallop prolapse, 13.3% mitral valve orifice area <4.0 cm^2, and 10.6% large flail gap and/or large flail width). The implant success rate was 92.9%. The 30-day composite major adverse event rate was 11.2%. At 6 months, 92.4% patients achieved MR ≤2+ and 56.1% achieved MR ≤1+ ($P < 0.001$ vs baseline). The Kaplan-Meier estimates for survival, freedom from major adverse events, and heart failure hospitalization at 6 months were 93.7%, 85.6%, and 92.6%, respectively. Patients experienced significant symptomatic improvement compared with baseline ($P < 0.001$).

CONCLUSIONS The outcomes of the PASCAL IID registry establish the PASCAL system as a useful therapy for prohibitive surgical risk DMR patients with complex mitral valve anatomy. (PASCAL IID Registry within the Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical Trial [CLASP IID] NCT03706833)
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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

DMR = degenerative mitral regurgitation

EQ-5D-5L = EuroQol-5 Dimension-5 Level

KCCQ = Kansas City Cardiomyopathy Questionnaire

MAE = major adverse events

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

NYHA = New York Heart Association

TEE = transesophageal echocardiography

TTE = transthoracic echocardiography

Mitral valve transcatheter edge-to-edge repair (M-TEER) is a safe and effective treatment for degenerative mitral regurgitation (DMR) in patients who are at prohibitive risk for surgery.[1] However, M-TEER outcomes in patients with complex mitral valve anatomy can vary.[2,3] In the EVEREST II (Endovascular Valve Edge-to-Edge Repair Study), several mitral valve anatomic characteristics were proposed as predictors of procedural success with optimal mitral regurgitation (MR) reduction.[3,4] These anatomic characteristics constituted the "on-label" indication for U.S. Food and Drug Administration approval of the MitraClip system (Abbott Vascular) in 2013 for treating prohibitive-risk DMR patients.[5]

In 2020, the American College of Cardiology/American Heart Association valvular heart disease guidelines recommended M-TEER as a Class IIa indication for DMR patients at high or prohibitive risk with favorable mitral valve anatomy.[1] In 2021, the European Society of Cardiology and the European Association for Cardio-Thoracic Surgery guidelines for the management of valvular heart disease broadly recommended M-TEER as a Class IIb indication for inoperable or high-surgical-risk DMR patients without anatomic limitations.[6]

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Patients frequently present with less-favorable complex mitral valve anatomy, yet are considered for M-TEER because of prohibitive surgical risk.[7] Retrospective studies report comparable early M-TEER outcomes in patients with complex and noncomplex mitral valve anatomy[8,9]; however, prospective studies in DMR patients with complex anatomy are scarce.

The prospective PASCAL IID registry was designed to address patients who were not randomizable in the CLASP IID trial (Edwards PASCAL TrAnScatheter Valve RePair System Pivotal Clinical Trial; NCT03706833) because of the presence of complex mitral valve anatomic characteristics based on the special populations section of the MitraClip Instructions for Use (IFU).[5] We report early outcomes to 6 months with the PASCAL transcatheter valve repair system (Edwards Lifesciences) in prohibitive-risk patients with 3+ or 4+ DMR and complex mitral valve anatomy.

METHODS

STUDY DESIGN. The PASCAL IID registry, within the construct of the CLASP IID trial (NCT03706833), is a prospective, multicenter, multinational, single-arm registry for patients who were nonrandomizable in the CLASP IID trial. Patients with significant symptomatic DMR who were at prohibitive risk for surgery and had complex mitral valve anatomy were considered for enrollment in the PASCAL IID registry. Safety, echocardiographic, and clinical outcomes were assessed.

After providing written informed consent and meeting eligibility criteria for the CLASP IID trial as assessed by the local heart team, patients were presented to a central screening committee (CSC) for determination of eligibility for the CLASP IID randomized cohort or PASCAL IID registry cohort. Patients who were ineligible for randomization because of anatomic characteristics based on the special patient populations section of the MitraClip IFU[5] were considered for the PASCAL IID registry. Patients deemed suitable for the PASCAL system by the CSC were enrolled in the registry and treated with the PASCAL system. Study assessments are conducted at baseline, during hospital stay, at discharge, or 7 days postprocedure (whichever was earlier) and follow-up is conducted at 30 days, 6 months, 1 year and annually for 5 years (Supplemental Figure 1). This report does not include the first experience with the PASCAL system comprising up to 3 roll-in patients per site, which was previously published.[10]

PATIENT SELECTION. Eligible patients were ≥18 years of age, had 3+ or 4+ DMR as assessed by

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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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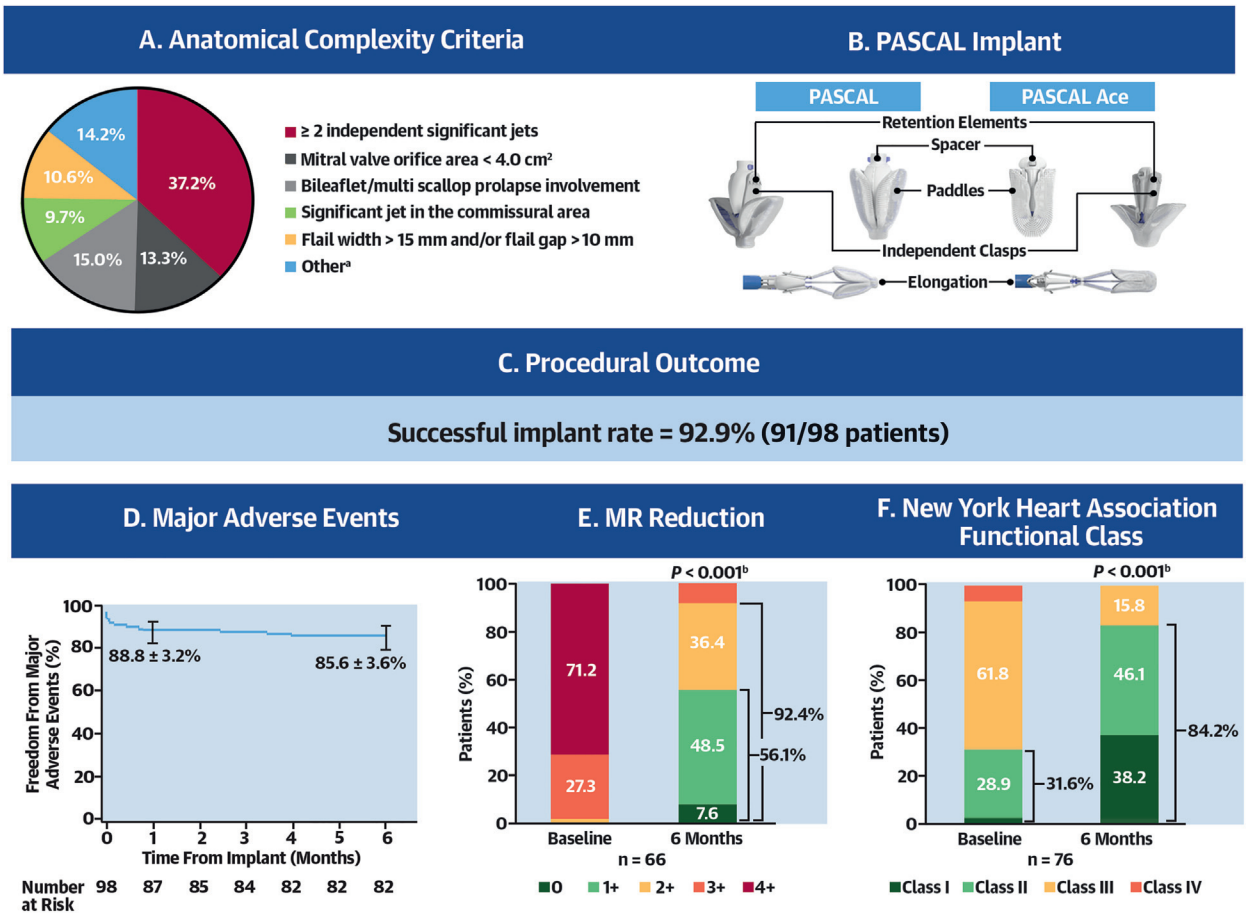
CENTRAL ILLUSTRATION **PASCAL IID Registry Outcomes at 6 Months**



Hausleiter J, et al. J Am Coll Cardiol. 2023;81(5):431–442.

(A) Anatomical complexity criteria. [a]Other includes presence of significant cleft or perforation in grasping area (6.2%), moderate to severe calcification in the grasping area (3.5%), leaflet mobility length <8 mm (3.5%), and history of endocarditis and significant tissue defects in the leaflet (0.9%). **(B)** PASCAL implant. **(C)** Procedural outcomes. Successful implant: patients with study device implanted, deployed as intended and delivery system retrieved successfully. Categorical variables: % (n/N). **(D)** Kaplan-Meier estimates for freedom from major adverse events (MAE) (KM estimate ± SE). Error bars represent 95% CI. Composite MAE includes cardiovascular mortality, stroke, MI, new need for renal replacement therapy, severe bleeding, and nonelective mitral valve reintervention (either percutaneous or surgical). **(E)** Mitral regurgitation (MR) reduction by echocardiographic core laboratory assessed by transthoracic echocardiography (TTE). Baseline qualification for some patients included transesophageal echocardiography (TEE). **(F)** New York Heart Association functional class. The *P* values were calculated by [b]Wilcoxon signed rank test. Graphs **(E,F)** show paired analysis. MAE = major adverse events.

transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE), left ventricular ejection fraction ≥20%, and left ventricular end-diastolic diameter ≤80 mm. The patients were candidates for M-TEER with the PASCAL system and were deemed to be at prohibitive surgical risk by the local heart team. Prohibitive risk assessments were based on the recommendations in the MitraClip IFU. Patients presented with at least 1 of the following complex mitral valve anatomic features: moderate to severe calcification in the grasping area, severe bileaflet/multi scallop prolapse involvement, significant cleft or perforation in the grasping area, leaflet mobility length <8 mm, ≥2 independent significant jets (a significant secondary jet was defined as a jet of ≥2+ severity when adjudicated independently of the predominant jet by quantitative and semiquantitative parameters), 1 significant jet in the commissural area, or mitral valve orifice area <4.0 cm^2.

Key exclusion criteria were contraindication for TEE or unsuccessful screening TEE, evidence of severe right ventricular dysfunction or intracardiac

TABLE 1 Baseline Characteristics (N = 98)

Demographics	
Age, y	81.1 ± 6.5 (98)
Male	60/98 (61.2)
Body mass index, kg/m^2	25.5 ± 4.6 (98)
STS score for mitral valve repair, %	4.6 ± 4.0 (98)
STS score for mitral valve replacement, %	6.6 ± 4.9 (98)
EuroSCORE II, %	5.0 ± 4.5 (98)
NYHA functional class III/IV	68/98 (69.4)
Medical history/comorbidities	
Atrial fibrillation	68/98 (69.4)
Cardiomyopathy	20/98 (20.4)
Coronary artery disease (≥50% stenosis)	40/98 (40.8)
Renal insufficiency[a] (eGFR <60 mL/min)	42/98 (42.9)
Diabetes	18/98 (18.4)
Hypertension	79/98 (80.6)
Hyperlipidemia	72/98 (73.5)
Myocardial infarction	15/98 (15.3)
Peripheral arterial disease	7/98 (7.1)
Anemia (chronic, Hgb ≤9 g/dL)	4/98 (4.1)
Stroke	5/98 (5.1)
TIA	6/98 (6.1)
COPD	16/98 (16.3)
Pacemaker/ICD	16/98 (16.3)
PCI	20/98 (20.4)
Coronary artery bypass graft	18/98 (18.4)
Gastrointestinal or esophageal bleeding	10/98 (10.2)
Pulmonary hypertension (PASP ≥30 mm Hg)	56/98 (57.1)
Home oxygen use	11/98 (11.2)
Hospitalizations for heart failure (≥1 in past 12 months)	35/97 (36.1)
Aortic valve surgery/intervention	14/98 (14.3)
Tricuspid valve surgery/intervention	0/98 (0.0)
Echocardiographic measures	
Degenerative mitral regurgitation etiology	98/98 (100)
MR 3+[b]	29/97 (29.9)
MR 4+[b]	67/97 (69.1)
Effective regurgitant orifice area, cm^2	0.47 ± 0.20 (58)
Left ventricular end-systolic dimension, mm	38.5 ± 9.5 (95)
Left ventricular end-diastolic dimension, mm	57.5 ± 7.4 (98)
Left ventricular end-diastolic dimension 60-80 mm	35/98 (35.7)
Left ventricular end-systolic volume, mL	62.3 ± 40.6 (94)
Left ventricular end-diastolic volume, mL	144.7 ± 56.1 (94)
Left ventricular ejection fraction	59.0 ± 10.4 (98)
Left ventricular ejection fraction 20%-50%	18/98 (18.4)
Mean transmitral gradient, mm Hg	2.5 ± 1.1 (90)
Pulmonary artery systolic pressure, mm Hg	42.8 ± 12.7 (88)
TAPSE, mm	19.7 ± 4.9 (71)
Left atrial volume, mm	129.8 ± 51.3 (98)
TR ≥ moderate-severe[c]	1/98 (1.0)
Mitral valve area, cm^2	5.6 ± 1.7 (76)

Values are mean ± SD (n) or n/N (%). [a]eGFR ≤25 mL/min was an exclusion criterion. [b]Baseline qualification for some patients included TEE. [c]Severe TR was an exclusion criterion.

COPD = chronic obstructive pulmonary disease; 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.

mass per echocardiographic core laboratory assessment, refractory heart failure requiring advanced intervention, clinically significant and untreated coronary artery disease requiring revascularization, unstable angina, evidence of acute coronary syndrome or recent myocardial infarction (MI), recent stroke, need for emergent or urgent surgery for any reason, or any planned cardiac surgery within the next 12 months. Inclusion and exclusion criteria are provided in Supplemental Table 1.

THE PASCAL SYSTEM AND IMPLANTATION PROCEDURE. The PASCAL system includes a 22-F guide sheath; a steerable catheter with controls for navigation and positioning of the implant; and an implant catheter with a preattached implant that facilitates implant elongation, independent leaflet grasping, and controlled deployment. The guide sheath, steerable catheter, and implant catheter can be maneuvered in 3 independent planes. The PASCAL Precision system was introduced during the study and is designed for intuitive control, precise implant delivery, and improved user experience. These systems are collectively referred to as the PASCAL system.

The PASCAL platform comprises 2 implant options, PASCAL and PASCAL Ace, collectively referred to as the PASCAL implant with differentiated features to address a wide range of mitral valve anatomies (**Central Illustration B**). Features include a flexible nitinol construction that enables gentle passive closure with acute implant flexing, a central spacer that bridges the coaptation gap and fills the regurgitant orifice, broad contoured paddles designed to distribute load and reduce tension on the leaflets, and clasps with a single row of retention elements designed to minimize leaflet tissue damage. The clasps can be operated simultaneously or independently to facilitate optimal leaflet capture, and the implant can be elongated to a smooth, narrow profile to facilitate navigation within the dense subvalvular chordae or during retrieval if necessary. The implantation procedure is described in the Supplemental Methods: Section 1.[10-15]

STUDY CONDUCT AND OVERSIGHT. The study is sponsored by Edwards Lifesciences and is part of the CLASP IID trial registered on ClinicalTrials.gov (NCT03706833). The study investigation plan was designed in accordance with the Mitral Valve Academic Research Consortium[16,17] and was approved by the Institutional Review Board/Ethics Committee at each participating center. The study conforms to the Declaration of Helsinki, Good Clinical Practice

principles, and ISO 14155:2011. All patients provided written informed consent, and the CSC made the final decision on patient eligibility for participation in the registry. Echocardiograms were evaluated by an independent echocardiographic core laboratory (Cardiovascular Core Lab at Atlantic Health System Morristown Medical Center, Morristown, New Jersey, USA), and prespecified adverse events were adjudicated by a clinical events committee (CEC). A data safety monitoring board reviewed aggregate safety data to assess the overall safety of the study. The sponsor participated in site selection, study management, and data analysis. All sites were required to have prior M-TEER 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 paper. Trial organization, leadership, participating sites, and key personnel are provided in Supplemental Tables 2 and 3.

STUDY OUTCOMES. Major adverse events (MAE) were CEC-adjudicated and comprised cardiovascular mortality, stroke, MI, new need for renal replacement therapy, severe bleeding events (major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium criteria), and nonelective mitral valve reintervention (either percutaneous or surgical). MR severity, transmitral gradients, and other echocardiographic parameters were assessed by the echocardiographic core laboratory. Other outcomes included CEC-adjudicated all-cause mortality and heart failure hospitalization (HFH), and functional and quality-of-life outcomes such as New York Heart Association (NYHA) functional class,[18] 6-minute walk distance (6MWD),[18] Kansas City Cardiomyopathy Questionnaire (KCCQ),[18,19] and EuroQol-5 Dimension-5 Level (EQ-5D-5L) score.[18,20] Echocardiography and clinical assessments including NYHA functional class were conducted at 30 days and 6 months, with follow-up at 1 year and annually thereafter for 5 years. KCCQ and EQ-5D-5L are assessed up to 2 years (30 days, 6 months, and 1 and 2 years) and 6MWD is assessed up to 1 year (30 days, 6 months, and 1 year).

ECHOCARDIOGRAPHIC ASSESSMENTS. Echocardiograms by TTE and TEE were collected according to standardized protocols for screening and procedural planning. All implant procedures were performed under TEE guidance, and TTE was utilized for postprocedure follow-up. Echocardiograms were assessed by the echocardiographic core laboratory according to pre-established protocols based on the American Society of Echocardiography (ASE) guidelines[21,22] and graded on a scale from 0 to 4+ (Supplemental Table 4).

FIGURE 1 Patient Disposition and Flow for the PASCAL IID Registry

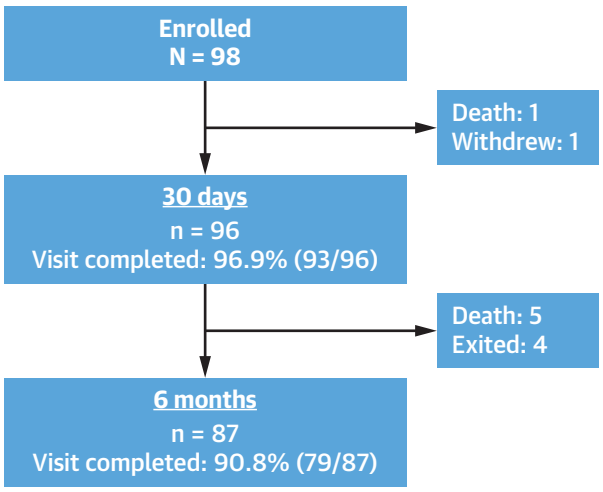


Illustration of patient enrollment and follow-up with visit windows of 30 ± 7 days and 6 months ± 30 days.

STATISTICAL ANALYSIS. Continuous variables were summarized with the number of observations, mean ± SD, median (IQR: Q1, Q3), range (minimum-maximum), and 95% CI based upon t-distribution. Differences between time points for continuous data were summarized with the mean difference and 95% CI, and *P* values for continuous variables including KCCQ, 6MWD, and EQ-5D-5L were calculated using Student's *t*-test. For categorical and qualitative variables, summaries include the count and percentage of patients. For categorical data such as NYHA functional class, differences between time points were compared using Wilcoxon signed rank test. At each assessment, descriptive statistics were presented, including paired change from baseline to subsequent time points for selected outcomes. For variables ascertained at follow-up, the denominator was based on the number of evaluable patients. Unless otherwise noted, patients with missing data were excluded from the denominator. Kaplan-Meier estimates were used to analyze time-to-event variables, and the exponential Greenwood method was used to calculate SE. All statistical analyses were performed on a modified intention-to-treat population (mITT). The mITT safety population comprised patients in whom the study procedure was attempted, defined as skin incision. The mITT effectiveness

TABLE 2 Anatomical Complexity Criteria

Anatomic Criteria[a]	(N = 113)
Presence of ≥2 independent significant jets	42/113 (37.2)
Evidence of severe bileaflet/multi scallop prolapse involvement	17/113 (15.0)
Mitral valve orifice area <4.0 cm^2	15/113 (13.3)
Large flail gap and/or large flail width[b]	12/113 (10.6)
Presence of 1 significant jet in the commissural area	11/113 (9.7)
Presence of significant cleft or perforation in the grasping area	7/113 (6.2)
Leaflet mobility length <8 mm	4/113 (3.5)
Evidence of moderate to severe calcification in the grasping area	4/113 (3.5)
History of endocarditis and significant tissue defects in the leaflet	1/113 (0.9)
Total Number of Anatomic Criteria Met[c]	**(N = 98)**
1	83/98 (84.7)
2	15/98 (15.3)

[a]Categorical variables are expressed as n/N (%), where n = number in each anatomic complexity category and N = total number of complexities. [b]Flail width >15 mm and/or flail gap >10 mm. [c]Categorical variables are expressed as n/N (%), where n = number of patients with anatomic criteria met and N = total number of patients with complexities.

population comprised the mITT safety population with the study device attempted, defined as a guide sheath or steerable guide inserted into the femoral vein. Analysis of MR severity at baseline and subsequent time points was performed using TTE measurements. All statistical analyses were performed using SAS Software version 9.4 or higher (SAS Institute, Inc).

RESULTS

We report outcomes to 6 months for 98 patients enrolled between April 2019 and December 2021 at 35 sites in the United States, Canada, and Europe. At 30 days and 6 months, follow-up was 96.9% and 90.8% complete, respectively (Figure 1). The median follow-up duration was 1.3 years (IQR: 0.8, 1.8 years).

BASELINE CHARACTERISTICS. Patients were elderly with multiple comorbidities (Table 1). Mean age was 81.1 years, 61.2% were men, and 69.4% were in NYHA functional class III/IV. The mean mitral valve area was 5.6 cm^2 (range: 3.5-10.7 cm^2) and the mean transmitral gradient was 2.5 mm Hg (range: 1.0-6.3 mm Hg). The mean left ventricular ejection fraction was 59.0% (range: 21.0%-83.0%), and mean pulmonary artery systolic pressure was 42.8 mm Hg (range: 22.0-81.0 mm Hg). The most frequently observed comorbidities were hypertension (80.6%), hyperlipidemia (73.5%), atrial fibrillation (69.4%), renal insufficiency (42.9%), and coronary artery disease (40.8%). The STS score for mitral valve repair was 4.6% and mitral valve replacement was 6.6%.

Overall, 82.7% patients were classified as frail, which was the predominant reason for prohibitive risk. Additional reasons included advanced age and other comorbidities (Supplemental Table 5). The most common anatomic complexity was the presence of ≥2 independent significant jets (37.2%), followed by evidence of severe bileaflet/multi scallop prolapse involvement (15.0%), mitral valve orifice area <4.0 cm^2 (13.3%), and large flail gap and/or flail width (10.6%). A total of 84.7% patients met 1 anatomic complexity criterion and 15.3% met 2 criteria (Table 2). In patients who met 2 anatomic criteria, the combination of ≥2 independent significant jets and evidence of severe bileaflet/multi scallop prolapse was the most frequent (60.0%) (Supplemental Table 6).

PROCEDURAL OUTCOMES. Successful implantation of the PASCAL device was achieved in 92.9% (91 of 98) of patients (Central Illustration C). In 1 patient, the device was not deployed as intended. In total, 6 patients did not receive a study device because of inability to grasp leaflets (n = 3), increased transmitral valve gradient (n = 2), or insufficient MR reduction (n = 1). Of these, 1 patient was subsequently treated with the MitraClip system during the index procedure at the discretion of the physician. In patients with 2 anatomic complexities, successful implantation was achieved in 93.3% (14 of 15) of patients, which was comparable to the overall study population. A mean of 1.6 devices were implanted per patient, with a median procedure time of 111.0 minutes and median device time of 79.5 minutes. The median length of hospital stay for the index procedure was 1.0 day (Table 3).

SAFETY OUTCOMES. The 30-day composite MAE rate was 11.2%, comprising 1 (1.0%) cardiovascular mortality, 1 (1.0%) stroke, 1 (1.0%) MI, 1 (1.0%) new need for renal replacement therapy, 7 (7.1%) severe bleeding events, and 1 (1.0%) nonelective mitral valve reintervention (Table 4). The stroke and cardiovascular death occurred in the same patient and were adjudicated as procedure related and possibly device related. This patient experienced a stroke followed by atrial fibrillation and cardiac arrest that resulted in death. The MI and the new need for renal replacement therapy were procedure related and occurred in patients with pre-existing history of right coronary artery lesion and stage IV chronic kidney disease, respectively. Of the 7 severe bleeding events, 2 were adjudicated to be device related and occurred after aborted procedures and were attributed to postoperative anemia following conversion to surgical mitral valve reconstruction and access site bleeding, respectively. There were 4 procedure-related bleeding events attributed to anemia, GI

bleed, esophageal rupture, and oropharyngeal bleed, respectively. The seventh bleeding event (anemia) was adjudicated as unrelated to the device and procedure. The nonelective mitral valve reintervention was caused by a single leaflet device attachment (SLDA) followed by implantation of a MitraClip device, which embolized resulting in patient death on postoperative day 37 (device related).

At 6 months, the composite MAE rate was 14.3% and the HFH rate was 7.1%. The all-cause mortality rate was 6.1%, of which 5.1% were cardiovascular deaths and 1.0% were noncardiovascular deaths. SLDA was reported in 2% of patients (Supplemental Table 7). There were no reports of leaflet perforation or embolization with the PASCAL device. The Kaplan-Meier estimate for freedom from MAE was 85.6% at 6-month follow-up (**Central Illustration D**). The Kaplan-Meier estimates for survival, freedom from cardiovascular mortality, and HFH at 6 months were 93.7%, 94.6%, and 92.6%, respectively (**Figure 2**).

ECHOCARDIOGRAPHIC OUTCOMES. A significant reduction in MR severity from baseline to 6 months ($P < 0.001$) was observed in a paired analysis. At discharge, MR grade was ≤2+ in 95.5% of patients and ≤1+ in 66.7% (overall $P < 0.001$ vs baseline). At 6 months, MR ≤2+ was achieved in 92.4% of patients and MR ≤1+ in 56.1% (overall $P < 0.001$ vs baseline) (**Central Illustration E**, Supplemental Figure 2A). A similar trend in MR reduction was seen in unpaired analysis (Supplemental Figure 2B). The mean transmitral valve gradient for the study population increased after implantation from mean 2.5 ± 1.1 mm Hg at baseline to 4.1 ± 1.7 mm Hg at discharge and remained stable to 6 months at 4.4 ± 2.0 mm Hg ($P = 0.121$ vs discharge) (Supplemental Figure 3).

FUNCTIONAL AND QUALITY-OF-LIFE OUTCOMES. At 6 months, the NYHA functional class improved significantly from baseline ($P < 0.001$) and 84.2% of patients were in NYHA functional class I/II (**Central Illustration F**). The mean overall KCCQ score significantly improved by 14.8 points ($P < 0.001$). The mean EQ-5D-5L score improved by 4.4 points ($P = 0.052$) and the mean 6MWD increased by 16.4 m ($P = 0.184$) (**Figure 3**).

DISCUSSION

The PASCAL IID registry is the first prospective, multinational registry to evaluate M-TEER outcomes using the PASCAL system in high-risk DMR patients with complex mitral valve anatomy with outcomes adjudicated by an echocardiographic core laboratory and a clinical events committee. The PASCAL system demonstrated a high implant success rate in this complex anatomy group and an adverse event rate comparable to prior M-TEER studies.[23,24] Significant MR reduction was achieved at 6 months as assessed by the echocardiographic core laboratory with significant symptomatic improvement.

Complex mitral valve anatomy is frequently observed in patients with symptomatic DMR undergoing M-TEER. The STS/ACC TVT (Society of Thoracic Surgeons/American College of Cardiology Transcatheter Valve Therapy) registry reported prevalence of mitral valve area <4 cm^2, leaflet calcification, and bileaflet prolapse of 20.5%, 18.3%, and 11.8%, respectively, in commercial MitraClip cases.[7] These

TABLE 3 Procedural Outcomes (N = 98)

Successful implant rate[a]	91/98 (92.9)
Procedure time, min[b]	111.0 [84.0, 156.0] (98)
Device time, min[c]	79.5 [49.5, 133.5] (96)
Fluoroscopy duration, min	26.0 [15.0, 39.0] (97)
Number of devices implanted in patients who received a device	1.6 ± 0.56 (92)
Number of implanted devices	
1	41/98 (41.8)
2	48/98 (49.0)
3	3/98 (3.1)
Location of implanted devices	
A1-P1	10/148 (6.8)
A2-P2	107/148 (72.3)
A3-P3	23/148 (15.5)
Other[d]	8/148 (5.4)
Device type	
PASCAL	51/92 (55.4)
PASCAL Ace	31/92 (33.7)
PASCAL and PASCAL Ace	10/92 (10.9)
Total length of stay for the index procedure, d	1.0 [1.0, 3.0] (98)

Values are n/N (%), median [Q1, Q3] (n), or mean ± SD (n). [a]Successful implant: patients with study device implanted, deployed as intended and delivery system retrieved successfully. [b]Procedure time: from procedure start (femoral vein puncture/skin incision) to femoral vein access closure. [c]Device time: from PASCAL implant system insertion into left atrium to guide sheath or steerable guide removal. [d]Other locations include P1-A2, A2-P3, A3, and medial and lateral commissure.

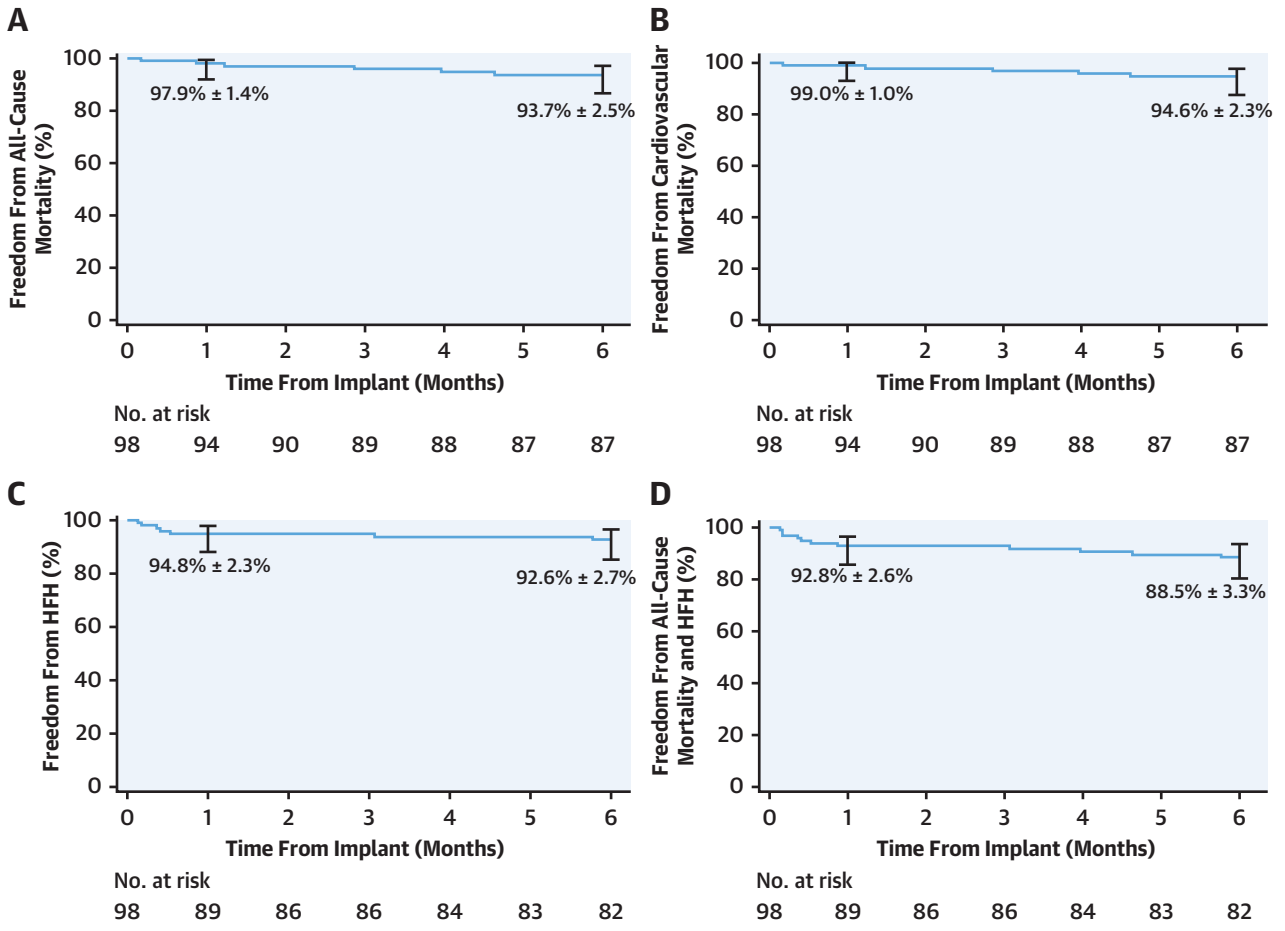
TABLE 4 CEC-Adjudicated Composite Major Adverse Events at 30 Days (N = 98)

Cardiovascular mortality	1 (1.0)
Stroke	1 (1.0)
Myocardial infarction	1 (1.0)
New need for renal replacement therapy	1 (1.0)
Severe bleeding[a]	7 (7.1)
Nonelective mitral valve reintervention (percutaneous or surgical)	1 (1.0)
Composite MAE rate	**11 (11.2)**

Values are n (%). Denominator includes patients who had an MAE or did not have an MAE but were followed for at least 30 days. [a]Major, extensive, life-threatening, or fatal bleeding defined by the Mitral Valve Academic Research Consortium criteria. **Bold** represents the composite rate (of all listed endpoints above).

CEC = clinical events committee; MAE = major adverse events.

FIGURE 2 **Freedom From Clinical Events Committee-Adjudicated Mortality and Heart Failure Hospitalization**

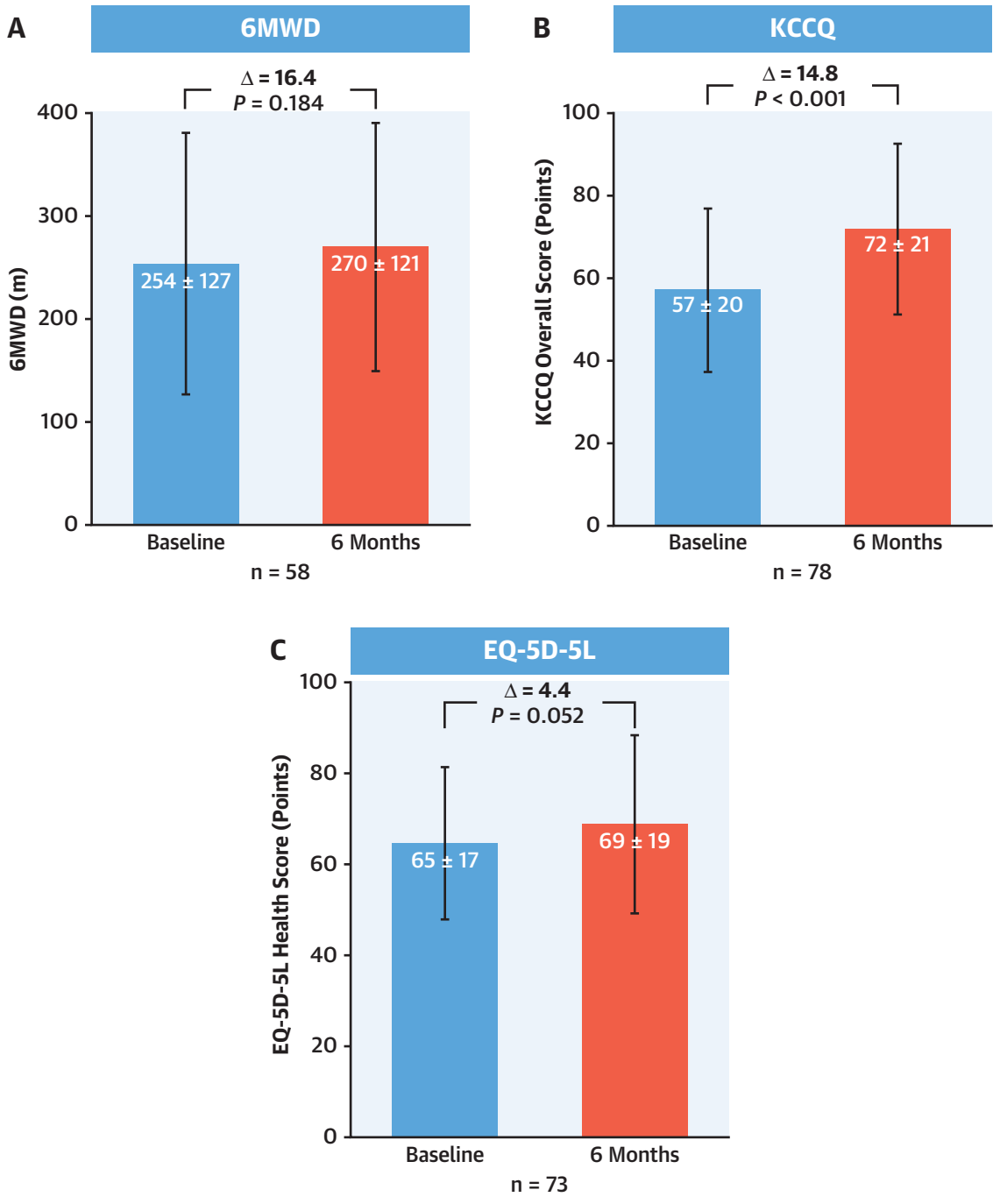


Kaplan-Meier estimates for freedom from **(A)** all-cause mortality, **(B)** cardiovascular mortality, **(C)** heart failure hospitalization (HFH), and **(D)** all-cause mortality and HFH. Graphs show Kaplan-Meier estimate ± SE and error bars represent 95% CI.

high prevalence rates are surprising given current U.S. regulatory indications and highlight a considerable unmet clinical need for efficacious M-TEER therapies to address such anatomic features. In the PASCAL IID registry, mitral valve anatomy was highly heterogenous, which may have contributed to the longer procedure time, and the most prevalent complexity criteria were ≥2 independent jets, severe bileaflet or multi scallop prolapse involvement, and mitral valve area <4 cm^2. In addition, 15.3% of patients presented with 2 or more anatomic complexity criteria. In this patient population with heterogeneous valvular complexity, a high implant success rate was achieved, accompanied by significant MR reduction and improvements in functional and quality-of-life outcomes.

In the PASCAL IID registry, significant MR reduction to ≤2+ was achieved at discharge and sustained at 6 months. These results are consistent with the PASCAL group of the CLASP IID randomized trial in patients with noncomplex anatomy.[25] Importantly, the proportion of patients with MR ≤2+ surpassed 90% in both the randomized and registry cohorts at 6 months, although the proportion of patients with MR ≤1+ was higher in the randomized cohort (noncomplex anatomy) compared with the registry cohort (complex anatomy). The 30-day composite MAE rate was higher in the registry cohort compared with the randomized cohort, with severe bleeding as the main contributor. The higher rate of severe bleeding in the registry could be attributed to a higher prevalence of comorbidities, including renal

FIGURE 3 Functional and Quality-of-Life Outcomes at 6 Months



Graphs show paired analysis (mean ± SD) for **(A)** 6-minute walk distance (6MWD), **(B)** Kansas City Cardiomyopathy Questionnaire (KCCQ), and **(C)** EuroQol-5 Dimensions (EQ-5D-5L), and *P* values were calculated using Student's *t*-test.

insufficiency, pulmonary hypertension, and atrial fibrillation. In addition, patients with severe bleeding had a history of medical conditions treated with anticoagulation or antiplatelet therapy. Notably, for a complex anatomy population, the rates of cardiovascular mortality, stroke, MI, new need for renal replacement therapy, and mitral valve reintervention were all low at 1%.

Comparisons between the registry and the randomized cohorts are for illustrative purposes because the patient populations differ. Patients in the registry had higher EuroSCORE II and more comorbidities, including higher rates of atrial fibrillation, pulmonary hypertension, peripheral arterial disease, renal insufficiency, prior pacemaker/ICD, coronary artery bypass graft, and home oxygen use. Overall, the registry patients not only had complex mitral valve anatomy, but also represented a sicker patient population. Nevertheless, key outcomes including MR reduction to ≤2+, rates of cardiovascular mortality and heart failure hospitalization, and functional and quality-of-life assessments were favorable.

Significant improvement from baseline was observed in NYHA functional class and KCCQ score. Although improvement from baseline was also observed with 6MWD and EQ-5D-5L, statistical significance was not achieved at 6 months. This could be explained by the fact that 6MWD and EQ-5D-5L outcomes can be influenced by multiple factors unrelated to mitral regurgitation, such as overall health status, age, underlying comorbidities, mobility challenges that are common in elderly frail patients, as well as limited sample size.

In this population of patients considered difficult to treat with M-TEER, the low SLDA rate and the absence of device embolization or leaflet perforation with the PASCAL system are encouraging. The mean transmitral valve gradient was below 5 mm Hg, which was important considering that 13.3% of patients had a mitral valve area <4 cm^2. This supports the possibility that patients with smaller mitral valve area can be treated successfully with the PASCAL system.

Several design features of the PASCAL system may have contributed to these positive outcomes, including independent leaflet capture and leaflet optimization capability, single row of retention elements, and flexible nitinol material which distributes the stress on the leaflets unlike a rigid device. The ability to treat commissural jets may be facilitated by the unique implant elongation feature to navigate in tight commissural spaces and avoid chordal entanglement.

There was no prespecified guidance for device selection in the registry, and decisions regarding device selection were based on patient anatomy, physician preference, and device availability. Future prospective evaluations in larger cohorts will help identify the anatomic characteristics that will benefit the most from M-TEER therapy with the PASCAL system as well as help refine device selection strategies. Additionally, the subset of mitral valve anatomic complexities that may be better treated with valve replacement remains to be defined.

STUDY LIMITATIONS. The PASCAL IID registry has some limitations. First, the registry is a single-arm study without blinding to treatment, which may have introduced bias in the outcome assessments. Second, the study was not powered to assess outcomes against prespecified performance goals. The limited sample size precluded meaningful analysis correlating specific anatomic characteristics to treatment outcomes. Finally, the concurrent COVID-19 pandemic affected patient follow-up and assessments.

CONCLUSIONS

In the prospective PASCAL IID registry, the PASCAL system demonstrated significant MR reduction and symptomatic improvement in patients with complex anatomic features historically considered less suitable for M-TEER. These results add to the growing body of evidence affirming the PASCAL system as a useful therapy to treat degenerative mitral regurgitation in prohibitive-surgical-risk patients with complex mitral valve anatomy.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:

In patients with DMR and complex mitral valve anatomy at prohibitive surgical risk, transcatheter edge-to-edge repair with the PASCAL system reduces MR and improves function and quality of life, with favorable survival outcomes.

TRANSLATIONAL OUTLOOK:

Prospective evaluation of larger patient populations with complex mitral valve anatomies is needed to characterize patients who are most likely to benefit from this procedure.

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