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Original Research

One-Year Outcomes of Early, Compassionate Use of the PASCAL Ace Implant System for Transcatheter Mitral Valve Repair

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ABSTRACT

Background: Continued development of transcatheter mitral repair technologies is needed to address the large and diverse population of high-risk patients with symptomatic mitral regurgitation (MR). The new PASCAL Ace implant system, with its narrower profile, complements the original PASCAL transcatheter valve repair system. The aim of this study is to report 1-year outcomes from the early, compassionate-use observational experience with the novel PASCAL Ace implant system.

Methods: After heart team assessment, adults with symptomatic moderate-to-severe (3+) or severe (4+) MR despite optimal medical therapy were treated under compassionate use at 3 hospitals internationally. Data were prospectively collected, and outcomes were assessed over a 12-month follow-up period.

Results: Seventeen patients (mean age 76 years, 65% male, mean Society of Thoracic Surgeons Predicted Risk of Operative Mortality score 9.6) were treated. MR etiology was degenerative in 29%, functional in 65%, and mixed in 6%; 59% were in New York Heart Association (NYHA) class III-IV. Technical success was achieved in 100%, and procedural success in 94%. At 1 year, MR grade $\leq$2+ was achieved in 93% ($p < 0.001$) with 88% survival rate and 94% free from heart failure hospitalization. The composite major adverse event rate was 6% and 100% of patients had $\leq$NYHA class II symptoms ($p < 0.001$).

Conclusions: At 1 year, the PASCAL Ace implant system demonstrated feasibility in this early, compassionate use experience in a small group of symptomatic patients with anatomically complex MR. The unique features of the PASCAL Ace implant may expand the treatable MR population.

ABBREVIATIONS

MAE, major adverse event; MR, mitral regurgitation; NYHA, New York Heart Association; TEER, transcatheter edge-to-edge repair.

Introduction

Mitral regurgitation (MR) is the most prevalent valvular disease,[1,2] with all etiologies associated with increased mortality, heart failure hospitalization, and poor quality of life.[3] However, only a minority of patients with symptomatic MR undergo surgical treatment, due to the higher surgical morbidity of older age, left ventricular systolic impairment, and multimorbidity.[4,5] With the projected number of people with moderate or severe valvular heart disease estimated to at least double by 2046 alongside the aging population,[1] the prevalence of symptomatic MR in patients of high surgical risk will see the demand for transcatheter interventions significantly increase.

There is growing interest in percutaneous technologies, including mitral transcatheter edge-to-edge repair (TEER) and replacement devices, particularly in patients with high surgical risk.[5,6] The PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine,

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California) deploys an implant comprised of 2 clasps and paddles that enable mitral leaflet approximation around an anatomic spacer that fills the regurgitant orifice, thereby reducing MR.[7]

The clasps can be deployed independently for sequential leaflet capture and are enclosed by contoured paddles that reduce leaflet stress. Uniquely, the PASCAL implant can be elongated, enabling safe retrieval from the left ventricle with minimal risk of chordal entanglement. The multicenter Edwards PASCAL Transcatheter Mitral Valve Repair System Study[8] showed that mitral leaflet repair with the original PASCAL repair system is associated with high survival, a low complication rate, and a significant and sustained reduction in MR at 1 year.[9]

Anatomic heterogeneity across a spectrum of mitral valve pathologies coupled with the increasing volume of patients with symptomatic valvular disease necessitates expansion of the transcatheter therapeutic armamentarium for MR.[7,10-12] The PASCAL Ace implant is designed to complement the original PASCAL implant and features narrower paddles (6 mm in PASCAL Ace vs. 10 mm in the original PASCAL) with a central spacer. Despite its smaller profile, the PASCAL Ace implant features an

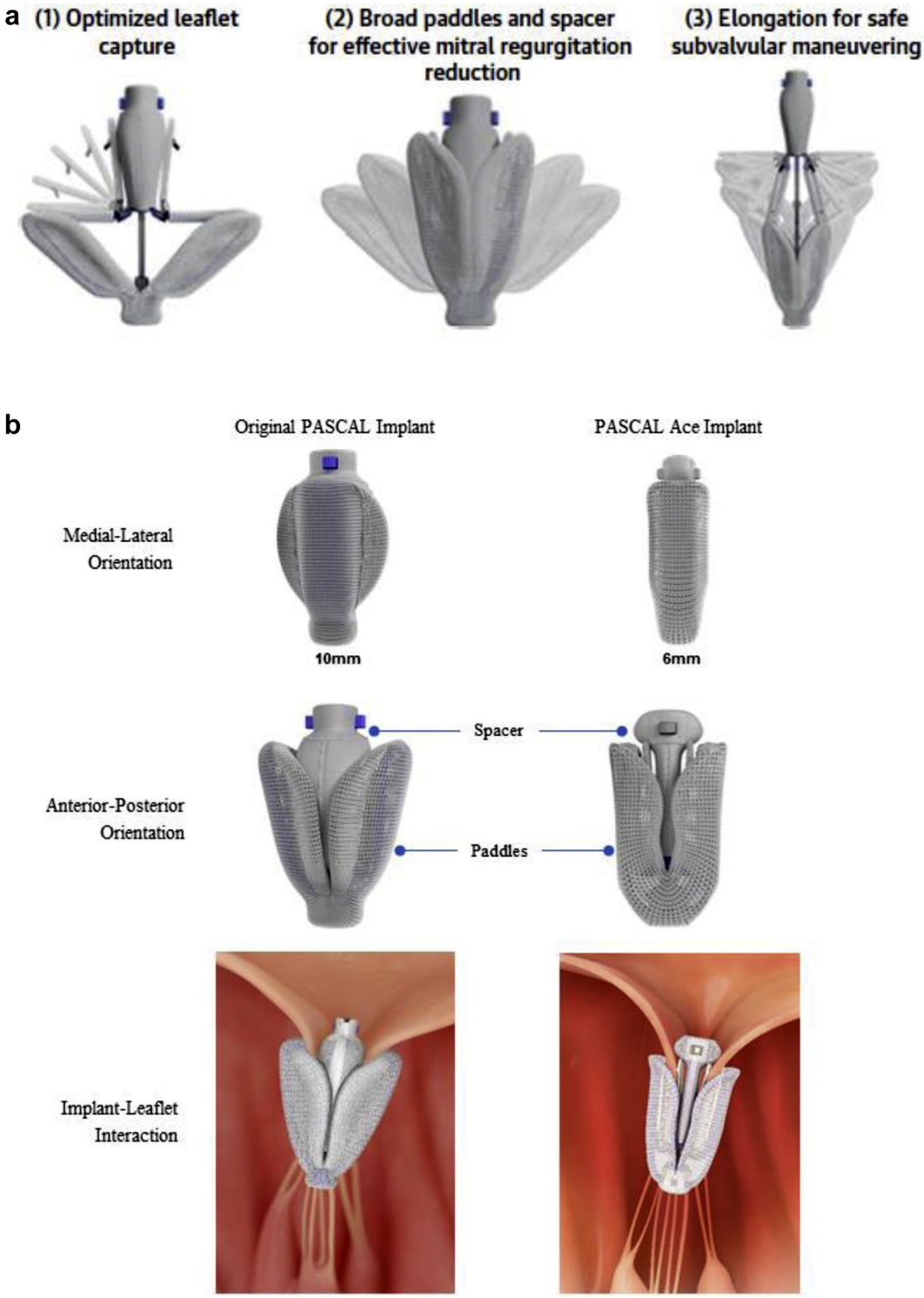

Figure 1. (a) The Edwards PASCAL Ace transcatheter valve repair system; (b) comparison of the original PASCAL and PASCAL Ace implants.

increased curvature of the paddles around the anatomic spacer, which enables greater approximation of valve leaflet relative to implant size, thereby potentially enhancing MR reduction. We herein report the international multicenter, first-in-human, compassionate use observational experience using the PASCAL Ace implant system.

Methods

Patients were treated under compassionate use at 3 hospitals in Australia and Canada. Adult patients presenting with symptomatic moderate-to-severe (3+) or severe (4+) MR in New York Heart Association (NYHA) functional class II-IV despite optimally tolerated medical therapy and assessed by a local multidisciplinary structural heart team for suitability to transcatheter mitral valve repair were considered eligible for treatment with the PASCAL Ace implant system.

Patients were offered treatment under a compassionate use program, including patients unsuitable for surgery or at high surgical risk and those deemed technically difficult and/or anatomically challenging for successful treatment with available therapies.

Patients were not offered treatment if they had a life expectancy of <1 year due to noncardiac pathology, had undergone previous mitral valve replacement, or had an intracardiac thrombus. All suitable patients were informed about the compassionate use of the proposed procedure with the novel PASCAL Ace implant complementing the existing original PASCAL implant and provided written and verbal informed consent prior to screening.

While echocardiographic data were not adjudicated by a core laboratory, the 3 hospitals collaborated to ensure consistency of reporting with echocardiographic assessment of MR severity at baseline, 30 days, and 1 year based on current guidelines,[13,14] using the core laboratory echocardiographic assessment criteria consistent with the CLASP study.[9]

The PASCAL Ace Implant System

The PASCAL Ace implant system complements the design of the original PASCAL repair system. The system retains the features of simultaneous or independent clasp movement for sequential leaflet capture and a central spacer to occupy the regurgitant orifice and paddles that curve around the central spacer to enhance the security of leaflet capture while distributing leaflet tension. The system also has a highly steerable sheath that is designed to enable safe implant positioning during independent leaflet capture and device elongation to escape chordal entanglement (Figure 1a).

Compared with the original PASCAL implant, the PASCAL Ace implant has a smaller central spacer, narrower paddles (6 mm vs. 10 mm) producing a lower profile with increased angle of curvature around the central spacer, creating a larger "neo-coaptation" area relative to device size, and distributing tension across the captured leaflet tissue (Figure 1b). These design features may be particularly useful in patients with smaller mitral valve areas (MVAs), smaller left atrial size relative to leaflet excursion, commissural jets, and potentially those with more redundant leaflet tissue such as degenerative myxomatous or Barlow-type mitral valves.

The delivery system consists of a 22-Fr steerable guide sheath, steerable catheter, and an implant catheter with the implant attached to the tip. As with the original PASCAL implant, the 3-plane movement of the guide sheath and steerable catheter are controlled using knobs on the handle, as is clasp movement and device deployment.

Procedure

All patients were assessed prior to intervention with 2D and 3D transthoracic and transesophageal echocardiography to define the etiology of MR, grade of severity, and evaluate anatomic suitability for transcatheter leaflet repair with the PASCAL Ace implant system.

Cases were performed in a hybrid operating room or catheterization laboratory under general anesthesia, with both fluoroscopy and transesophageal echocardiographic guidance.

Transseptal puncture was performed, aiming for a mid-posterior puncture >3.5 cm above the mitral annulus; the implant was then guided into the left atrium, and the steerable catheter used to align toward the target leaflet zone. The mitral valve was crossed with paddles opened, and the device advanced through the mitral valve and oriented using 2D or 3D echocardiographic guidance. Leaflets were grasped either simultaneously or individually, and leaflet insertion was independently adjusted to optimize capture as desired. After echocardiographic confirmation of adequate leaflet insertion, the paddles were closed, and the degree of residual MR and mean transmitral gradient were assessed, prior to device deployment. After deployment, the degree of MR and mitral gradient in the now double-orifice mitral valve were reassessed, and if desired to optimize MR reduction, a second device could be implanted.

On-table extubation after the procedure was routinely performed. After the procedure, patients were monitored in a coronary care unit and underwent transthoracic echocardiography prior to discharge.

Follow-up was conducted at 30 days and 1 year after device implantation and included clinical review, transthoracic echocardiography, 6-minute walk test, and routine pathology sampling.

Outcomes

Clinical outcomes and echocardiographic data were retrospectively assessed at each hospital.

Technical success immediately following implantation and procedural success at 30 days per the Mitral Valve Academic Research Consortium criteria were retrospectively analyzed.[15] *Technical success* was defined as leaving the catheterization laboratory with absence of procedural mortality; successful access, delivery, and retrieval of the device delivery system; successful deployment and correct positioning of the first intended device; and freedom from emergency surgery or reintervention related to the device. *Procedural success* was defined as successful device implantation, MR ≤2+, mean gradient <5 mmHg, proper placement and positioning of the device, continued intended safety and performance of the device, and absence of major serious adverse events (MAEs), including freedom from repeat surgical or percutaneous interventions.

Safety outcomes at 30 days and adverse events at 1 year were retrospectively analyzed using a composite of MAEs including cardiovascular mortality, severe bleeding,[15] stroke, myocardial infarction, and renal impairment (doubling of creatinine). All-cause mortality, heart failure admission, reintervention due to device-related complication, and functional outcomes including change in NYHA class and in 6-minute walk distance were also retrospectively analyzed.

Statistical Analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and compared using 2-sided Student's paired *t*-test or Wilcoxon rank-sum test; and categorical variables are presented as number and percentages and compared using the Wilcoxon signed-rank test. A 2-sided p value of <0.05 was used to indicate statistical significance. All data were analyzed using SPSS Version 27 (IBM, Armonk, New York).

Results

Patient Population and Baseline Characteristics

Between December 13th, 2018, and September 27th, 2019, 17 patients (mean age 76 ± 13 years, 65% male) with symptomatic MR grade 3+/4+ and deemed poorly suited for alternative therapies at the time underwent mitral TEER with the PASCAL Ace implant system in 1 of 3

tertiary hospitals in Australia and Canada with experience in percutaneous mitral valve repair.

Table 1 summarizes the baseline characteristics. Patients were considered to be at high surgical risk, with a mean Society of Thoracic Surgeons predicted risk of mortality score for mitral valve repair of 9.6 ± 6.1%, and 76% of patients had ≥3 comorbidities. Forty-one percent of patients were in NYHA functional class II, and 59% were in NYHA functional class ≥III. Forty-seven percent of patients had a prior hospital admission for heart failure, with 88% being treated with a diuretic. The mean 6-minute walk distance was 291 ± 135 meters.

Baseline echocardiographic parameters are shown in Table 2. Of the 17 patients, 29% had moderate-to-severe (3+) and 71% had severe (4+) MR, with a mean effective regurgitant orifice area of 0.44 ± 0.3 cm^2, mean regurgitant volume of 58 ± 19 mL, and mean jet width of 14 ± 4 mm. Twenty-nine percent were classified as degenerative, and 71% as functional or mixed in etiology. The mean left ventricular ejection fraction was 48 ± 17%, mean pulmonary artery systolic pressure was 46 ± 17 mmHg, and 41% had ≥moderate concomitant aortic or tricuspid valve dysfunction.

Of the 17 patients, 53% (n = 9) had anatomically complex MR and were considered technically difficult or anatomically challenging for successful treatment with available therapies. Specifically, 2 patients had coaptation gap width >15 mm, 2 had MVAs ≤4.0 cm^2, 1 had a flail gap >10 mm due to Barlow syndrome with multiple scallop prolapse and flail, 1 had a cleft in the grasping area, 1 had a posterior leaflet length <10 mm, and 3 patients had commissural jets (Table 3).[12,16]

No patients were unsuitable for TEER as per the Heart Valve Collaboratory TEER Consensus guidelines.[17] However, 3 patients had borderline features, including 2 patients with MVA of 3.5 cm^2 and 1 patient with severe bileaflet prolapse due to Barlow disease.

Table 1
Baseline clinical characteristics

Parameter	N = 17
Age (y)	76 ± 13
Male	11 (65)
EuroScore II (%)	5.7 ± 4.7
STS-PROM for mitral valve repair (%)	9.6 ± 6.1
6-min walk distance (meters)	291 ± 135
Comorbidities	
≥2 comorbidities	17 (100)
≥3 comorbidities	13 (76)
Hypertension	9 (53)
Diabetes mellitus	1 (6)
Coronary artery disease	8 (47)
Previous MI	5 (29)
Previous PCI	6 (35)
Previous cardiac surgery	3 (18)
Severe pulmonary hypertension (PASP > 60 mmHg)	6 (35)
Chronic lung disease ≥ moderate	5 (29)
Atrial fibrillation	11 (65)
Chronic renal failure (eGFR < 60 mL/min)	8 (47)
Previous cerebrovascular event	1 (6)
Heart failure	
NYHA functional class III-IV	10 (59)
Previous hospital admission for heart failure	8 (47)
Medical treatment	
Beta-blocker	14 (82)
ACE-I/ARB	9 (53)
ARNI	2 (12)
MRA	8 (47)
Diuretic	15 (88)
Anticoagulation	10 (59)
NT-proBNP (pg/mL)	3518 ± 2633
Device treatment, n (%)	
Pacemaker/defibrillator	5 (29)
Cardiac resynchronization	1 (6)

Notes. Data are n (%), median (IQR), or mean ± SD unless otherwise specified.
ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor blocker neprilysin inhibitor; BNP, brain natriuretic peptide; eGFR, estimated glomerular filtration rate; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonist; NYHA, New York Heart Association; PASP, pulmonary artery systolic pressure; PCI, percutaneous coronary intervention; STS-PROM, Society of Thoracic Surgeons predicted risk of mortality.

Table 2
Baseline echocardiographic characteristics

Parameter	Result
MR severity	
Moderate to severe (3+)	5 (29)
Severe (4+)	12 (71)
MR etiology	
Functional (FMR)	11 (65)
Degenerative (DMR)	5 (29)
Mixed	1 (6)
LVEDD (mm)	55 ± 13
LVEDV indexed (mL/m^2)	75 ± 40
Ejection fraction (%)	48 ± 17
Mean transmitral gradient (mmHg)	2 ± 1
Mitral annular calcification ≥ mild	6 (35)
EROA (cm^2)	0.44 ± 0.3
Regurgitant volume (mL)	58 ± 19
Vena contracta width (mm)	7 ± 1
Jet width (mm)	14 ± 4
PASP (mmHg)	46 ± 17
Aortic disease ≥ moderate	2 (12)
Tricuspid disease ≥ moderate	5 (29)

Notes. Data are n (%), median (IQR), or mean ± SD unless otherwise specified.
DMR, degenerative mitral regurgitation; EROA, estimated regurgitant orifice area; FMR, functional mitral regurgitation; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; MR, mitral regurgitation; PASP, pulmonary artery systolic pressure.

Procedural and In-Hospital Outcomes

Procedural data and in-hospital outcomes are summarized in Table 4. There were no periprocedural adverse events. The mean number of implants per patient was 1.2, where 18% (n = 3) of patients received more than 1 implant.

Technical success was achieved in 100% (n = 17) of patients. The mean procedure time was 135 ± 59 minutes. There were no cases of intraprocedural or postprocedural single leaflet device attachment (SLDA). After successful implantation, 88% of patients were discharged home after a median 2.4 [1, 6] days in admission, while the remaining 12% (n = 2) were discharged to inpatient rehabilitation where they spent an additional 6 and 13 days prior to discharge home.

Table 3
Anatomically challenging features for percutaneous mitral repair[†]

Anatomical feature	N (%)
Any anatomically challenging feature	9 (53)
Coaptation width >15 mm	2 (12)
MVA ≤ 4.0cm^2	2 (12)
Flail gap > 10 mm	1 (6)[*]
Commissural jet	3 (18)
Cleft in grasping area	1 (6)
Posterior leaflet length <10 mm	1 (6)

MVA, mitral valve area.
[*] Patient had Barlow syndrome with multiple scallops.
[†] Unfavorable anatomic characteristics for percutaneous mitral valve repair, (1) valve geometry: coaptation depth ≥11 mm, flail gap >10 mm, coaptation width >15 mm, MVA ≤4.0 cm^2, mean gradient ≥5 mmHg; (2) valve anatomy: perforation or cleft, significant calcification in grasping area, commissural pathology, Barlow syndrome with multiple scallop flail.

Table 4
Procedural data

Parameter	Result
Technical success*	17 (100)
Number of PASCAL Ace implants deployed	20
Patients with 1 implant	14 (82)
Patients with >1 implant	3 (18)
PASCAL Ace implant location	
A1-P1	1 (5)
A2-P2	17 (85)
A3-P3	2 (10)
Implants per patient	1.2
Procedure time (min)	135 ± 59
Fluoroscopy time (min)	41 ± 21
Length of hospital stay (d)	2.4 [1, 6]

Notes. Data are n (%) or mean ± SD or median [IQR].
* Defined as leaving the catheterization laboratory with absence of procedural mortality, successful access, delivery, and retrieval of the device delivery system; successful deployment and correct positioning of the first intended device; and freedom from emergency surgery or reintervention related to the device.

Thirty-Day and 1-Year Outcomes

Clinical follow-up data were retrospectively collected for 100% of surviving patients at 30 days and 1 year and are presented in Tables 5 and 6.

Procedural success was achieved in 94% (n = 16) of patients at 30 days.

The composite MAE rate at 1 year was 6% (n = 1); comprised of 1 patient with a severe gastrointestinal bleeding event secondary to aspirin that occurred 2 months after the procedure.

There were no deaths at 30 days and 2 noncardiovascular deaths at 1 year due to multiorgan failure precipitated by sepsis, giving a 1-year survival rate of 88% (Figure 2). One patient required reintervention due to worsened MR severity after treatment with a single PASCAL Ace implant. This patient underwent coronary bypass grafting and mitral valve replacement surgery 10 months after PASCAL Ace implantation, after being previously excluded from surgery due to age and severe left ventricular (LV) dysfunction. There were no cases of SLDA. A reduction in severity of MR by ≥1 grade was achieved in 93% (14 of 15) of patients at 1 year for whom data were available (Figure 3a), excluding 1 patient who died and 1 who underwent mitral valve surgery. MR grade ≤1 was achieved in 50% of patients at 30 days and in 53% at 1 year, and grade ≤2 was achieved in 94% at 30 days and 93% at 1 year ($p < 0.001$). In the anatomically complex MR subgroup (n = 9), MR grade ≤1 was achieved in 33% of patients at 30 days and 37% at 1 year, and MR grade ≤2 was achieved in 89% at 30 days and 100% at 1 year ($p < 0.001$) (Figure 3b).

The mean transmitral gradient increased from 2 ± 1 mmHg at baseline to 3 ± 2 mmHg at 30 days ($p = 0.001$) and to 4 ± 2 mmHg at 1 year ($p < 0.001$), with no difference between 30 days and 1 year or between 1 and 2 PASCAL Ace implants. In the 3 patients treated for commissural MR compared with noncommissural MR, there was no significant difference in mean transmitral gradient after procedure or change in mean transmitral gradients from baseline to 30 days or baseline to 1 year.

While the effect size and sample size in this cohort were too small to detect a significant change in LV geometry to indicate reverse remodeling, there were nonsignificant reductions in LV dimensions between baseline and 1 year (left ventricular end-diastolic diameter 55 ± 13 mm to 54 ± 13 mm; $p = 0.281$; indexed left ventricular end-diastolic volume 75 ± 42 mL/m^2 to 73 ± 22 mL/m^2; $p = 0.439$); with no change in left ventricular ejection fraction between baseline and 1 year (48 ± 17% to 48 ± 14%). There was a nonsignificant reduction in pulmonary artery systolic pressure between baseline and 1 year (46 ± 17 mmHg to 42 ± 13 mmHg; $p = 0.616$).

At 1 year, 94% of patients were free from heart failure hospitalization, and 100% had an improvement of ≥1 NYHA functional class, with 50% in NYHA class I and 100% in NYHA class I-II (Figure 4a). This was similar in the anatomically complex MR subgroup, in which 89% had an improvement of ≥1 NYHA functional class, and 100% were in NYHA functional class I-II at 1 year (Figure 4b).

Among the 15 patients with paired NT-proBNP-level data at 30 days, there was a nonsignificant reduction between baseline and 30-day NT-proBNP level of 529 pg/mL ($p = 0.341$).

Among the 12 patients with paired 6-minute walk distance data (Figure 5), there was a significant increase in distance of 47 m from baseline to 30 days (284 ± 136 m to 331 ± 133 m; $p = 0.064$) and of 66 m at 1 year (270 ± 81 m to 338 ± 62 m; $p = 0.011$).

Table 5
Echocardiographic variables at baseline, 30 days, and 1 year

Parameter	Baseline	30 d	1 y
LVEDD (mm)	55 ± 13	54 ± 12	54 ± 13
LVEDVi (mL/m^2)	75 ± 40	63 ± 31	73 ± 22
Ejection fraction (%)	48 ± 17	51 ± 17	48 ± 14
Mean transmitral gradient (mmHg)	2 ± 1	3 ± 2	4 ± 2
PASP (mmHg)	46 ± 17	46 ± 14	42 ± 12

Notes. Mean transmitral gradient, $p = 0.001$ (baseline vs. 30 days) and $p < 0.001$ (baseline vs. 1 year). Nonsignificant p values for pairwise comparisons for all other parameters for baseline vs. 30 days and baseline vs. 1 year.
LVEDD, left ventricular end-diastolic diameter; LVEDVi, indexed left ventricular end-diastolic volume; PASP, pulmonary artery systolic pressure.

Table 6
Clinical outcomes at 30 days and 1 year

Outcome	30 d	1 y
Procedural success*	16 (94)	-
Major adverse events		
Cardiovascular mortality	0 (0)	0 (0)
Major bleeding†	1 (6)	1 (6)
Stroke	0 (0)	0 (0)
Myocardial infarction	0 (0)	0 (0)
Renal impairment (doubling of creatinine)	1 (6)	1 (6)
Composite MAE‡	1 (6)	1 (6)
Other events		
All-cause mortality	0 (0)	2 (12)
Single leaflet detachment	0 (0)	0 (0)
Heart failure hospitalisation	0 (0)	1 (6)
Reintervention due to device-related complication	0 (0)	1 (6)

Notes. Data are n (%) or mean ± SD unless otherwise specified.
MAE, major adverse event; MI, myocardial infarction; MR, mitral regurgitation.
* Defined as successful device implantation, MR ≤2+, mean gradient <5 mmHg, proper placement and positioning of the device, continued intended safety and performance of the device, absence of MAEs, including freedom from repeat surgical or percutaneous interventions.
† Includes BARC 3a, 3b and 3c types.
‡ Composite MAE defined as MI, bleeding, stroke, new renal replacement therapy, cardiovascular mortality.

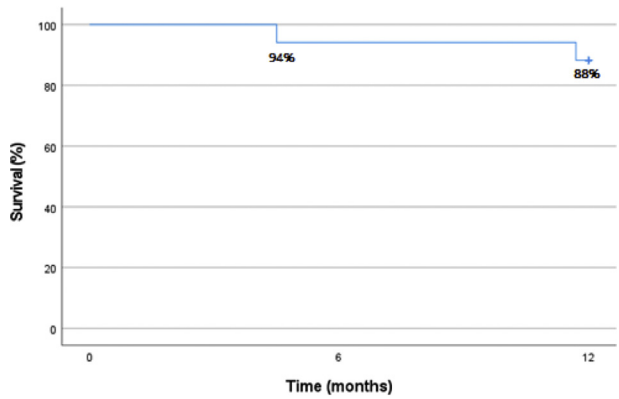

Figure 2. Kaplan-Meier survival estimates to 1 year.

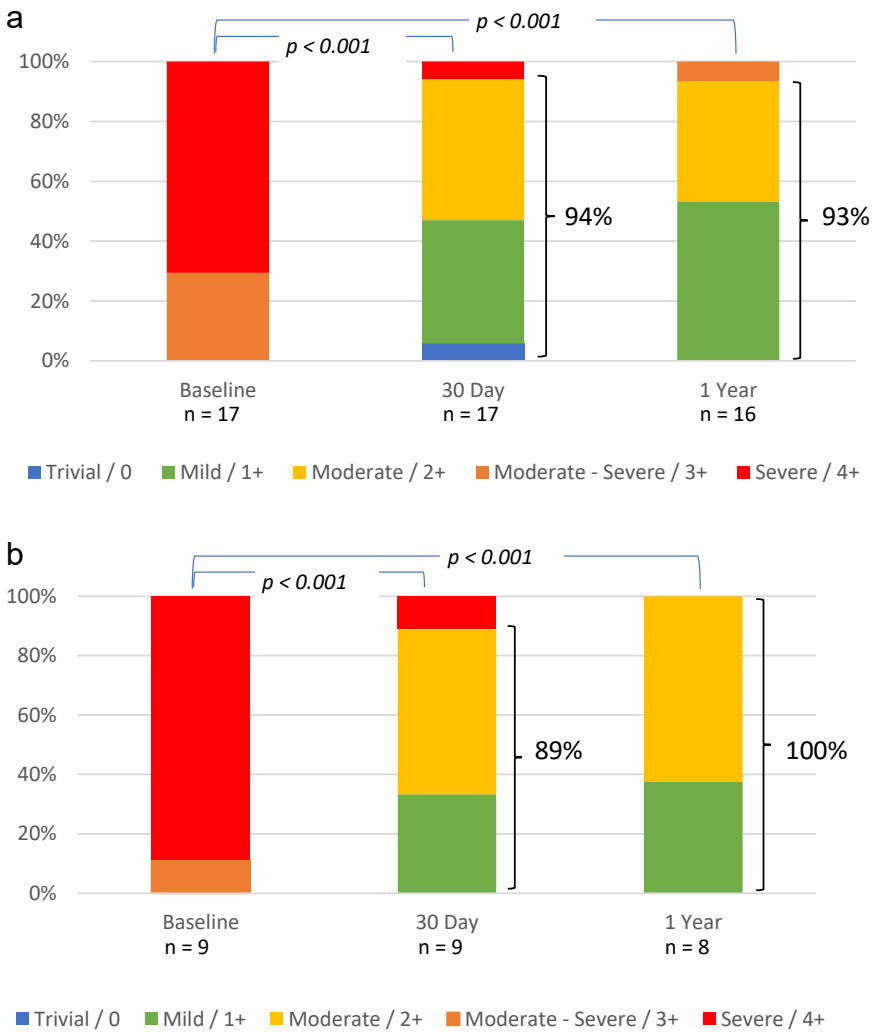

Figure 3. (a) Severity of mitral regurgitation at baseline, 30 days, and 1 year; (b) Severity of mitral regurgitation at baseline, 30 days, and 1 year for subgroup with anatomically complex MR.

Discussion

We report the early, first-in-human, compassionate use experience with the PASCAL Ace implant system in 17 patients comprising a heterogenous cohort of degenerative mitral regurgitation and functional mitral regurgitation patients. This was a high-surgical-risk patient cohort (mean Society of Thoracic Surgeons predicted risk of mortality score for mitral valve repair of 9.6%) with the majority of patients (53%) deemed technically difficult and/or anatomically complex for successful treatment with available therapies. Despite this, the PASCAL Ace implant system demonstrated favorable performance, with 100% technical success, 94% procedural success at 30 days, and sustained MR reduction with 93% of patients having MR $\leq$2+ at 1 year. Functional status, including NYHA class and 6-minute walk distance, was significantly improved (Figure 6).

While direct comparisons are not practicable, these outcomes align favorably with MR reduction outcomes in other studies of mitral TEER in high-risk heterogenous MR patient cohorts. For example, at 1 year, the reduction to MR <2+ was seen in 79% and 84%, respectively, in the ACCESS-Europe A Two-Phase Observational Study of the MitraClip System in Europe and Endovascular Valve Edge-to-Edge Repair Study II High-Risk studies of early use of the MitraClip system (Abbott Vascular, Inc., Santa Clara, California).[11,18]

The PASCAL Ace implant system demonstrated an acceptable safety profile in this early, compassionate use, high-risk patient cohort. At 1 year, MAE rates were low at 6%. There was no 30-day mortality, and 1-year mortality in this high-risk cohort was 12% with no cardiovascular deaths. The rate of heart failure hospitalization at 1 year was 6%. At 1 year, 1 patient (6%) underwent reintervention with surgical mitral valve replacement, and there were no cases of SLDA. These safety data compare favorably with studies of the MitraClip system in similar patient populations. For example, the ACCESS-EU study reported 30-day and 1-year mortality rates of 3.4% and 17%, respectively, with a 4.8% rate of SLDA and a 6.3% rate of mitral valve surgery at 1 year.[18] A U.S. postmarket study of MitraClip therapy reported 30-day and 1-year mortality rates of 5.2% and 25.8%, respectively, with a 20.2% rate of heart failure hospitalization at 1 year.[19]

The narrower profile PASCAL Ace implant system complements the original PASCAL repair system with its paddles having more conforming curvature around the smaller central spacer—a feature that facilitates greater valve leaflet approximation relative to implant size. The PASCAL delivery system enables steering of catheters in 3 independent planes, facilitating spatially accurate implant placement. These features, coupled with a smaller implant size, potentially make the PASCAL Ace implant system suitable for treatment of anatomically complex MR pathologies, including commissural MR and large flail gaps. Indeed, in our early, compassionate use experience, the PASCAL Ace implant successfully treated a range of mitral pathologies considered anatomically complex and technically challenging for TEER, including flail gap >10 mm due to

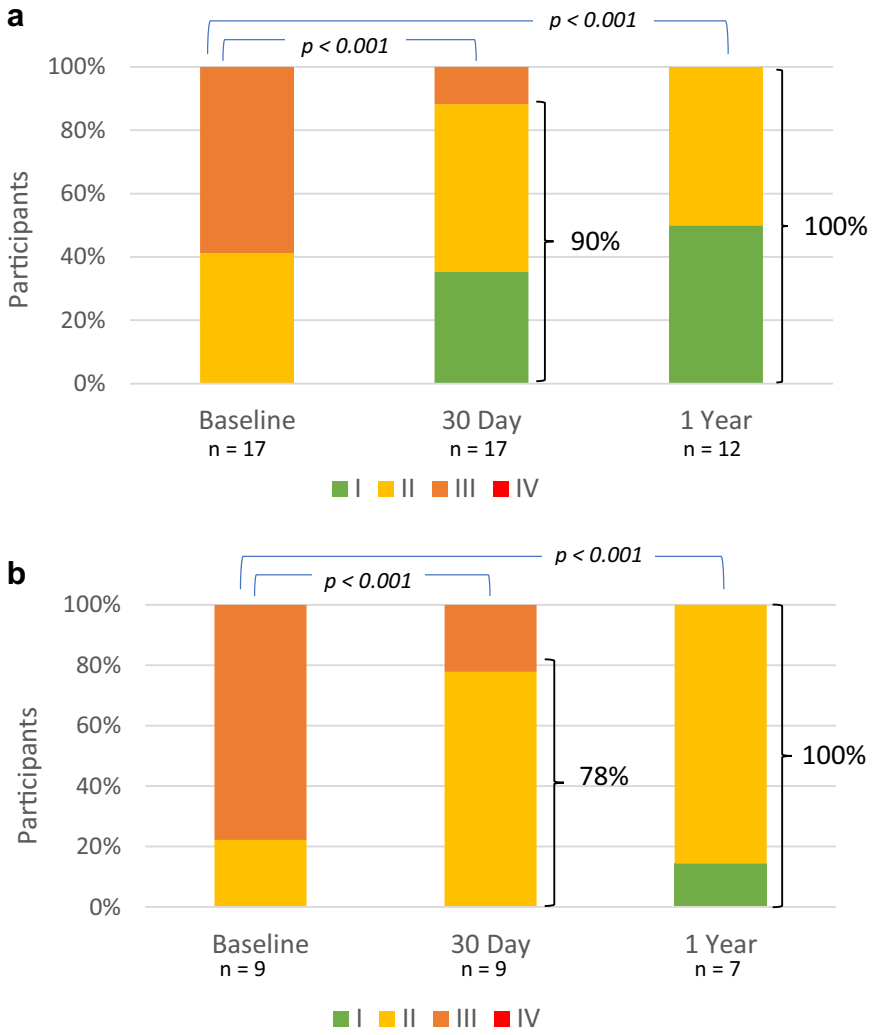

Figure 4. (a) NYHA class at baseline, 30 days, and 1 year; (b) NYHA class at baseline, 30 days, and 1 year for subgroup with anatomically complex MR.

Barlow's syndrome, commissural MR, and a short posterior leaflet length <10 mm. There was substantial MR reduction observed in this cohort with the PASCAL Ace implant system, with MR grade ≤2 achieved in 89% of patients at 30 days and 100% at 1 year.

Notably, our cohort did not include patients considered unsuitable for mitral TEER, as defined by the Heart Valve Collaboratory TEER Consensus Guideline[17] that recommends percutaneous valve replacement instead of repair for management of MR in such patients.

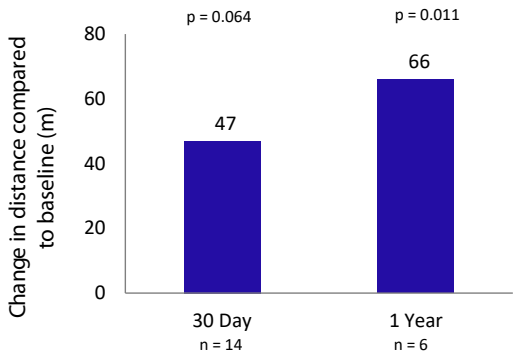

Figure 5. Change in 6-minute walk distance at 30 days and 1 year, compared with baseline.

The procedure time for the PASCAL Ace implant (mean 135 ± 59 minutes) was similar to both original PASCAL implant (128 ± 60 minutes) and MitraClip (145 ± 69 minutes).[1,19] Moreover, the mean

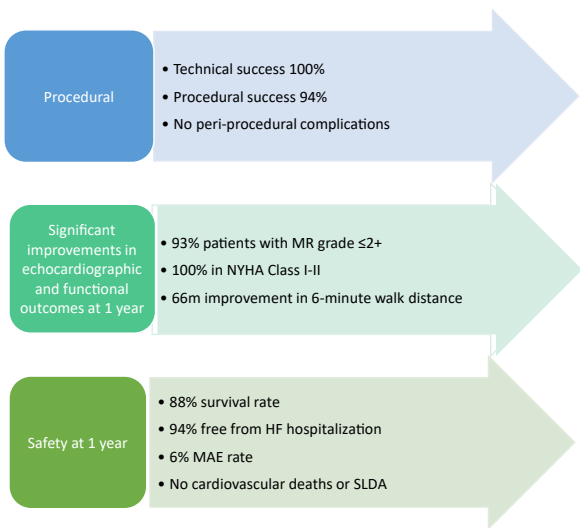

Figure 6. Summary of procedural, echocardiographic, functional, and safety outcomes at 1 year.

number of PASCAL Ace implants deployed in this compassionate use experience was 1.2 implants per patient (with 18% of cases requiring 2 devices) compared with mean 1.7 (with 62% requiring 2 or more devices) in Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation,[20] suggesting favorable MR reduction with a single PASCAL Ace implant in the majority, which has positive implications for patients with smaller MVAs and higher transmitral gradients at baseline.

Limitations

In the context of compassionate use, patient selection was essentially "all-comer," and therefore, the patients were a heterogeneous mix of pathologies and anatomical variants; the generalizability to a specific functional mitral regurgitation or degenerative mitral regurgitation cohort is consequently limited by these broad acceptance criteria. A major limitation of this early use feasibility experience was the small sample size of only 17 patients. Further clinical use of the PASCAL Ace implant system is required to define the patient population most effectively managed with this system. All procedures were carried out by transcatheter proceduralists with experience in percutaneous mitral leaflet repair with both original PASCAL repair and MitraClip systems; thus, the generalizability of these early results may be limited to similarly experienced proceduralists, particularly in the case of technically challenging anatomy. Echocardiographic interpretation was performed by local echocardiologists at each hospital and not by a single core laboratory. Standard guidelines for grading of MR severity were utilized; however, there remains potential for interobserver reporting bias.

Conclusion

The PASCAL Ace implant system demonstrated feasibility in this first-in-human, compassionate use experience in a small group of symptomatic patients with a high proportion of anatomically complex mitral valve pathology. Results from this initial experience representing device learning curve demonstrated an acceptable safety profile, 100% technical success and 94% procedural success at 30 days with sustained MR reduction, and functional status improvement at 1 year. Utilizing the unique features of the PASCAL Ace implant system may expand the treatable MR population. Since these early, compassionate use cases, the PASCAL Ace implant system is now approved for use in Europe and Australia, with ongoing real-world experience expected to further establish suitable anatomies for PASCAL Ace vs. the original PASCAL.

Impact on Daily Practice

Continued development of transcatheter mitral repair technologies is important to address the large and diverse population of high-risk, symptomatic MR patients. The new PASCAL Ace implant system complements the original PASCAL system and is designed to further optimize the treatment of patients. In early, compassionate use experience, the PASCAL Ace implant system demonstrated positive outcomes at 1-year follow-up in a small group of patients with symptomatic and anatomically complex MR with limited treatment options. With growing approval for use worldwide, the PASCAL Ace implant system may expand the treatable MR population, with real-world experience ongoing.

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Ethics Statement

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.

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