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ORIGINAL INVESTIGATIONS

Feasibility Study of the Transcatheter Valve Repair System for Severe Tricuspid Regurgitation

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ABSTRACT

BACKGROUND Tricuspid regurgitation (TR) is a prevalent disease with limited treatment options.

OBJECTIVES This is the first 30-day report of the U.S. single-arm, multicenter, prospective CLASP TR early feasibility study of the PASCAL transcatheter valve repair system in the treatment of TR.

METHODS Patients with symptomatic TR despite optimal medical therapy, reviewed by the local heart team and central screening committee, were eligible for the study. Data were collected at baseline, discharge, and the 30-day follow-up and were reviewed by an independent clinical events committee and echocardiographic core laboratory. Feasibility endpoints included safety (composite major adverse event [MAE] rate), echocardiographic, clinical, and functional endpoints.

RESULTS Of the 34 patients enrolled in the study, the mean age was 76 years, 53% were women, the mean Society of Thoracic Surgeons score was 7.3%, 88% had atrial fibrillation/flutter, 97% had severe or greater TR, and 79% had New York Heart Association (NYHA) functional class III/IV symptoms. Twenty-nine patients (85%) received implants; at 30 days, 85% of them achieved a TR severity reduction of at least 1 grade, with 52% with moderate or less TR ($p < 0.001$). The MAE rate was 5.9%, and none of the patients experienced cardiovascular mortality, stroke, myocardial infarction, renal complication, or reintervention. Eighty-nine percent of the patients improved to NYHA functional class I/II ($p < 0.001$), the mean 6-min walk distance improved by 71 m ($p < 0.001$), and the mean Kansas City Cardiomyopathy Questionnaire score improved by 15 points ($p < 0.001$).

CONCLUSIONS In this early experience, the repair system performed as intended, with substantial TR reduction, favorable safety results with a low MAE rate, no mortality or reintervention, and significant improvements in functional status, exercise capacity, and quality of life. (Edwards CLASP TR EFS [CLASP TR EFS]; NCT03745313)
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ABBREVIATIONS AND ACRONYMS

6MWD = 6-min walk distance

AT = as-treated

EFS = early feasibility study

EROA = effective regurgitant orifice area

ITT = intention-to-treat

KCCQ = Kansas City Cardiomyopathy Questionnaire

LVEF = left ventricular ejection fraction

MAE = major adverse event

NYHA = New York Heart Association

PISA = proximal isovelocity surface area

SLDA = single-leaflet device attachment

TEE = transesophageal echocardiography

TR = tricuspid regurgitation

TTE = transthoracic echocardiography

TV = tricuspid valve

Tricuspid regurgitation (TR) is an increasingly prevalent valve disorder seen with aging populations (1). The etiology of TR in most is functional or secondary, due to concomitant disorders such as mitral regurgitation, pulmonary hypertension, left ventricular dysfunction, or atrial fibrillation/flutter (2,3). Contemporary natural history and outcomes studies have consistently shown that greater TR severity is associated with increased mortality when most patients do not undergo surgical repair (4–9). Currently, there are no Class I indications for surgical repair of isolated TR, and medical therapy is limited to diuretic agents and symptom management (2). Given its high prevalence, adverse prognosis, symptom burden, and direct association with progressive right heart failure, TR represents an important unmet treatment need (10).

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Recent retrospective studies suggest a high in-hospital mortality of ~9% with isolated tricuspid valve (TV) surgery (11,12), resulting in growing interest in transcatheter solutions for TR (13,14). However, there are limited Conformité Européene (CE mark)-approved transcatheter devices to treat TR (15–17). In a compassionate use experience, the PASCAL transcatheter valve repair system (Edwards Lifesciences, Irvine, California) demonstrated high procedural success, acceptable safety, and significant clinical improvement in patients with challenging tricuspid anatomy and severe TR (17).

The PASCAL repair system recently received CE-mark approval as a leaflet repair system to treat TR. The implant consists of a central spacer that acts as a filler in the regurgitant orifice of the TV. The spacer is, in turn, connected to 2 broad paddles with clasps that can be simultaneously or independently maneuvered for optimal leaflet capture. This is the first report of the 30-day outcomes from the ongoing U.S. prospective, multicenter, single-arm CLASP TR early feasibility study (EFS) (Edwards PASCAL TrAnScatheter Valve RePair System in Tricuspid Regurgitation [CLASP TR] Early Feasibility Study) of this repair system in the treatment of symptomatic severe TR.

METHODS

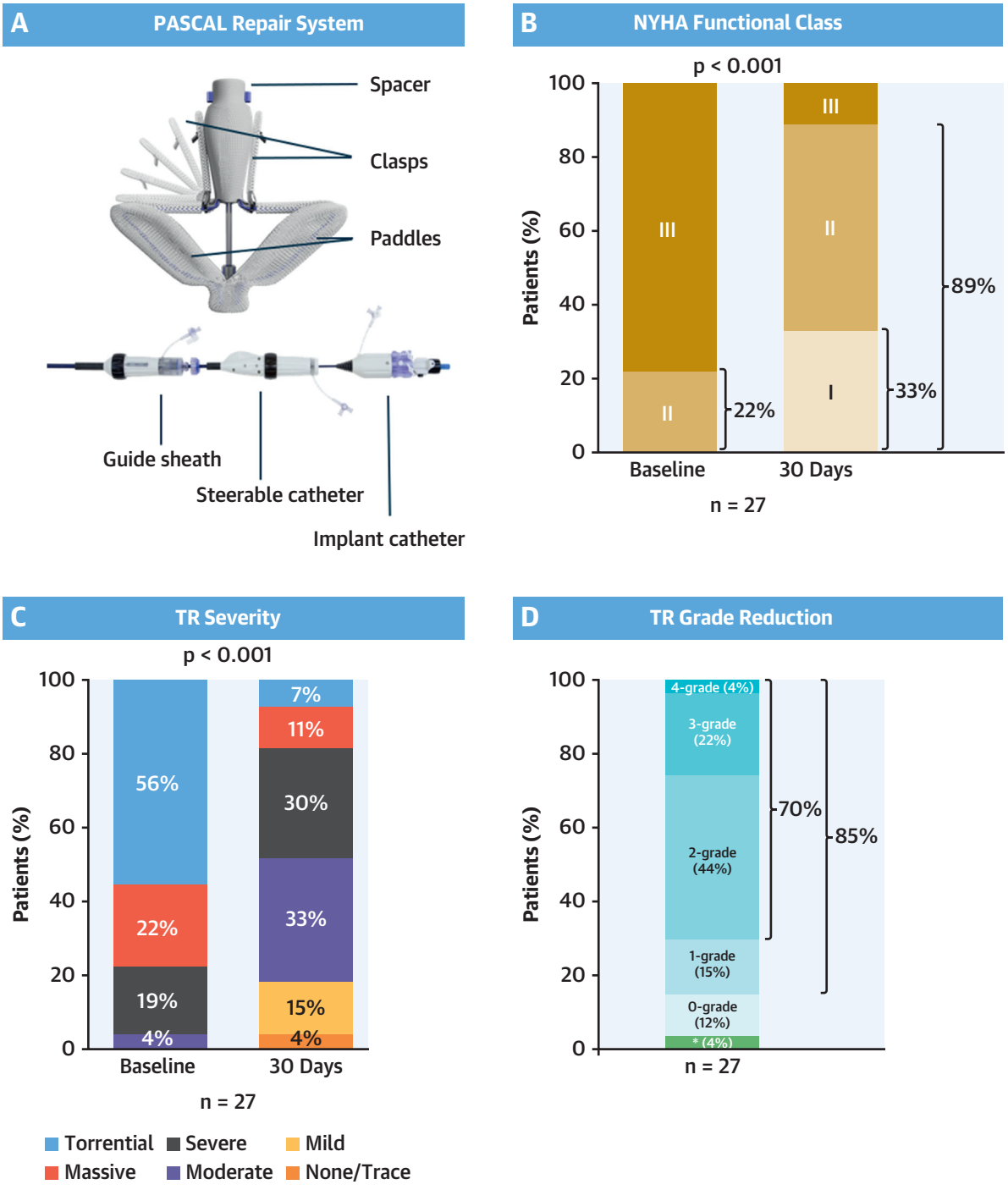
STUDY DESIGN AND PATIENT SELECTION. Eligibility criteria were age ≥18 years with severe symptomatic functional or degenerative TR, as assessed by an independent echocardiography core laboratory (Cardiovascular Research Foundation, New York, New York), despite optimal medical therapy (primarily diuretic agents) per the local heart team. All patients were determined by the local heart team to be appropriate for transcatheter tricuspid repair. Key exclusion criteria included anatomic features precluding proper implant deployment, such as a septolateral coaptation gap >10 mm, leaflet length <8 mm, pacemaker lead-induced TR, previous TV repair that would interfere with implant placement, and primary non-degenerative TV disease (carcinoid, rheumatic, endocarditis, traumatic, tricuspid stenosis, iatrogenic). Other exclusions included left ventricular ejection fraction (LVEF) <30%, severe right ventricular dysfunction, pulmonary systolic pressure >60 mm Hg, severe concomitant valve disease, and significant renal dysfunction (chronic dialysis or estimated glomerular filtration rate ≤30 ml/min/1.73 m^2). A complete list of inclusion and exclusion criteria are listed in the Supplemental Appendix.

STUDY OVERSIGHT. The CLASP TR EFS was conducted in conformity with the Declaration of Helsinki, Good Clinical Practice principles, and in accordance with ISO 14155:2011. The study was approved by local ethics committees and is registered with clinicaltrials.gov (NCT03745313). All participants were screened by a multidisciplinary team consisting of implanters, echocardiographers, and the independent echocardiography core laboratory to verify eligibility, following which the participants provided written informed consent.

Site-measured echocardiograms were analyzed by the independent core laboratory based on previously published guidelines (18,19). All major adverse events (MAEs) throughout the 30-day follow-up period were adjudicated by an independent Clinical Event Committee. Other implant-related adverse events, such as single-leaflet device attachment (SLDA), were assessed by the echocardiography core laboratory as necessary. The study was funded by the sponsor (Edwards Lifesciences), who participated in site selection, data collection and monitoring, and statistical analysis. The principal investigator and steering committee monitored all aspects of study conduct and had open data access.

ECHOCARDIOGRAPHY. TR severity and anatomic feasibility were assessed using transthoracic echocardiography (TTE) or transesophageal echocardiography (TEE). TEE and fluoroscopy were used for intraprocedural implantation of the device with the use of adjunctive imaging modalities such as intracardiac echocardiography left up to the discretion of the investigators. TTE was performed at baseline and

CENTRAL ILLUSTRATION **The PASCAL Transcatheter Valve Repair System**



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(A) The PASCAL repair system. The implant contains 2 broad paddles with clasps that can be simultaneously or independently maneuvered for tricuspid valve leaflet capture. The delivery system consists of a 22-F guide sheath, a steerable guide catheter, and an implant catheter to enable maneuvering the clasp into a coaxial position prior to grasping the tricuspid valve leaflets. **(B)** New York Heart Association (NYHA) functional class at baseline and 30 days post-procedure. **(C)** Tricuspid regurgitation (TR) severity at baseline and 30 days post-procedure in paired analysis. **(D)** Grade reduction of TR severity at 30 days post-procedure. *One patient showed worsening of TR grade due to single-leaflet device attachment at 30 days. The p values for categorical variables were derived from the Wilcoxon signed-rank test. Values are represented as means.

TABLE 1 Baseline Characteristics (N = 34)

Age, yrs	76.3 ± 10.4
Female	18 (52.9)
EuroSCORE II	5.3 ± 5.2 (32)
STS score, %*	7.3 ± 4.7 (34)
NYHA functional class III or IV	27 (79.4)
Comorbidities	
Systemic hypertension	32 (94.1)
Pulmonary hypertension (sPAP ≥30 mm Hg)	23 (67.6)
Diabetes	4 (11.8)
Renal insufficiency or failure	15 (44.1)
Chronic obstructive pulmonary disease	9 (26.5)
Dyslipidemia	28 (82.4)
Atrial fibrillation/flutter	30 (88.2)
Ventricular tachycardia/ fibrillation	1 (2.9)
Coronary artery disease	11 (32.4)
Prior stroke/transient ischemic attack	9 (26.4)
Prior myocardial infarction	3 (8.8)
Percutaneous coronary intervention	7 (20.6)
Prior pacemaker/ICD/CRT	4 (11.8)
Prior carotid surgery	2 (5.9)
Prior aortic valve intervention	5 (14.7)
Prior mitral valve intervention	7 (20.6)
Coronary artery bypass graft	10 (29.4)
Prior heart failure hospitalization in last 12 months	16 (47.1)

Values are mean ± SD, n (%), or mean ± SD (n). *STS score calculated for mitral valve repair.

CRT = cardiac resynchronization therapy; EuroSCORE = European System for Cardiac Operative Risk Evaluation; ICD = implantable cardioverter-defibrillator; NYHA = New York Heart Association; sPAP = systolic pulmonary artery pressure; STS = Society of Thoracic Surgeons.

for all post-procedural clinical follow-up timepoints (discharge and 30 days). Proximal isovelocity surface area (PISA) effective regurgitant orifice area (EROA) was assessed using 2-dimensional color-flow Doppler, whereas the mean vena contracta width was calculated as an average of the measured diameters in 2 orthogonal planes (simultaneous multiplane image) or from the 4-chamber view and the inflow view. Standard 2-dimensional color Doppler methods were used to assess TR, and TR severity was graded according to the 5-grade scheme proposed by Hahn and Zamorano (20).

THE PASCAL TRANSCATHETER VALVE REPAIR SYSTEM. The PASCAL implant consists of a central spacer and adjacent paddles and clasps that attach the implant to the native leaflets to reduce regurgitation. The central spacer helps fill the regurgitant orifice and minimize stress on the leaflets. The clasps can be actuated either simultaneously or independently when clasping the leaflets. The delivery system consists of a 22-F guide sheath, a steerable guide catheter, and an implant catheter, and allows for high degrees of freedom when maneuvering to the valve to achieve coaxial positioning before leaflet clasping (Central Illustration).

THE IMPLANTATION PROCEDURE. The repair system is introduced percutaneously via the common femoral vein under general anesthesia. The guide sheath and introducer are inserted over the guidewire into the right atrium. The steerable catheter is maneuvered for optimal positioning of the implant using TEE guidance. The implant can capture the leaflets either independently or simultaneously, and, if entangled with subvalvular structures such as dense chordae tendineae before implant release, the implant can be elongated and repositioned. Once the leaflets are secured between the clasps and paddles, the implant is closed and ultimately released. Before release, the delivery system and the implant can be retrieved and removed.

RECOMMENDED ANTIPLATELET/ANTICOAGULATION THERAPY. Heparin was administered intraprocedurally to maintain an activated clotting time of at least 250 s. Patients received anticoagulation therapy and/or short-term antiplatelet therapy of oral aspirin 81 mg/day for 30 days post-procedure.

STUDY ENDPOINTS. The safety endpoint was a composite of MAEs at 30 days that included cardiovascular mortality, stroke, myocardial infarction, reintervention (percutaneous or surgical), major access site and vascular complications, renal complications requiring unplanned dialysis or renal replacement therapy, and severe bleeding. Severe bleeding was defined by the Mitral Valve Academic Research Consortium as major, extensive, life-threatening, or fatal bleeding (21). Performance endpoints included procedural success (computed as implant deployed as intended and the delivery system successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory, with evidence of TR grade reduction by ≥1 grade at the end of the procedure, without the need for a surgical or percutaneous intervention before hospital discharge), and clinical success (computed as procedural success and no MAE at 30 days). Echocardiographic endpoints included TTE (TR severity, PISA EROA, and mean vena contracta) at baseline, discharge, and 30 days. Clinical and functional endpoints included all-cause mortality, New York Heart Association (NYHA) functional classification, edema, 6-min walk distance (6MWD), and Kansas City Cardiomyopathy Questionnaire (KCCQ) score.

STATISTICAL ANALYSIS. Unless otherwise noted, intention-to-treat (ITT) analysis was performed on all assessments. The ITT population was defined as

patients who signed informed consent, met eligibility criteria, and in whom the study procedure was attempted (i.e., skin incision to introduce the repair system). The as-treated (AT) population was defined as patients in whom the study implant was deployed and remained in position at the time of the patient's exit from the cardiac catheterization laboratory. AT analysis was performed only for specified parameters (implant, procedural, and clinical success rates). Procedural and clinical successes were not calculated for patients who had any missing parameters for computing performance endpoints. Patients with missing assessments at baseline and/or 30 days were excluded from all respective analyses.

Continuous variables are presented as mean ± SD. Statistical comparisons between baseline and 30 days were performed using paired analyses. Either the Student's *t*-test or the Wilcoxon signed-rank test was performed post hoc. Statistical significance was set at $p < 0.05$ as 2-tailed tests, and the analyses were performed using SAS Software version 9.4 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

BASELINE CHARACTERISTICS. Between February and October 2019, a total of 34 patients from 7 U.S. investigational sites with symptomatic severe TR (by TTE or TEE) had procedures attempted. Reasons for exclusion at screening included suboptimal imaging (32%), septolateral coaptation gap >10 mm (16%), noncardiac clinical exclusions (10%), severe right ventricular dysfunction (6%), non-right-heart-related valve disease (6%), and intracardiac mass (6%). Additional, less frequent exclusions included severe tethering, significant leaflet thickening, and excessive chordae in the grasping area.

The baseline clinical characteristics are shown in Table 1. The mean patient age was 76 ± 10 years, and the mean Society of Thoracic Surgeons score was 7.3%; 53% of patients were women, and 79.4% were in NYHA functional class III/IV. Most patients had atrial fibrillation/flutter (n = 30; 88.2%) and systemic hypertension (n = 32; 94.1%). Other comorbidities included pulmonary hypertension (systolic pulmonary artery pressure ≥30 mm Hg; n = 23; 67.6%), renal insufficiency (n = 15; 44.1%), and diabetes (n = 4; 11.8%). The mean European System for Cardiac Operative Risk Evaluation (EuroSCORE II) was 5.3% (n = 32), and 16 (47.1%) patients had prior heart failure hospitalizations. Baseline liver panel measures were as follows (mean ± SD): albumin: 4.1 ± 0.49 g/dl; bilirubin: 1.0 ± 0.64 mg/dl; alanine transaminase: 20.0 ± 9.52 U/l; aspartate transaminase: 28.6 ± 12.78 U/l; and gamma-glutamyl transferase: 77.1 ± 64.25 U/l. The mean baseline international normalized ratio was 1.9 ± 1.25.

TABLE 2 Baseline Echocardiographic Parameters (N = 34)

TR severity (TTE)	
Moderate*	1/33 (3.0)
Severe	8/33 (24.2)
Massive	6/33 (18.2)
Torrential	18/33 (54.5)
Tricuspid valve morphology	
Degenerative	2/33 (6.1)
Functional	29/33 (87.9)
Mixed	2/33 (6.1)
PISA EROA, cm^2	0.71 ± 0.33 (28)
PISA regurgitant volume, ml	47.4 ± 22.5 (28)
Mean vena contracta, cm	1.48 ± 0.48 (33)
Tricuspid annular diameter (end-diastole, apical 4-chamber), mm	46.10 ± 7.69 (34)
Cardiac output, l/min	4.82 ± 1.70 (31)
LV stroke volume, ml	64.2 ± 18.9 (31)
LV stroke volume index, ml/m^2	34.8 ± 9.7 (30)
LVEF, %	57.4 ± 7.0 (33)
RV end-diastolic diameter (mid), cm	3.99 ± 0.89 (33)
RV FAC, %	38.4 ± 9.0 (32)
Right atrial volume, ml	162.4 ± 104.8 (34)
TAPSE, cm	1.53 ± 0.47 (34)
IVC diameter, cm	2.74 ± 0.88 (34)
TR peak velocity, cm/s	251.5 ± 37.8 (34)
TR jet area, cm^2	16.30 ± 10.36 (29)

Values are n/N (%) or mean ± SD (n). *The core laboratory adjudicated the patient's TR as severe by TEE.

EROA = effective regurgitant orifice area; FAC = fractional area change; IVC = inferior vena cava; LA = left atrium; LV = left ventricular; LVEF = left ventricular ejection fraction; PISA = proximal isovelocity surface area; RV = right ventricle; TAPSE = tricuspid annular plane systolic excursion; TEE = transesophageal echocardiogram; TR = tricuspid regurgitation; TTE = transthoracic echocardiogram.

The mean baseline echocardiographic parameters are listed in Table 2. At baseline by TTE, 97% of patients had severe or greater TR (55% torrential, 18% massive, and 24% severe). The mean PISA EROA was 0.71 ± 0.33 cm^2, with a mean PISA regurgitant volume of 47.4 ± 22.5 ml and a mean right ventricular end-diastolic diameter (mid) of 3.99 ± 0.89 cm. The mean right atrial volume was 162.4 ± 104.8 ml, with a mean inferior vena cava diameter of 2.74 ± 0.88 cm. The mean left ventricular stroke volume index was 34.8 ± 9.73 ml/m^2 and the mean LVEF was 57.4 ± 7.0%.

PROCEDURAL RESULTS. Key procedural characteristics are summarized in Tables 3 and 4. The PASCAL implant was successfully deployed in 29 of 34 (85%) patients by ITT analysis and 29 of 29 (100%) by AT analysis. Procedural and clinical success could not be assessed in 4 patients due to unreadable or missing TEE (Tables 3 and 4). Of note, adjunctive imaging with intracardiac echocardiography was used in addition to TEE. Implants were successfully retrieved in 5 patients (Figure 1) whose leaflets were unable to be

TABLE 3 Procedural Characteristics and Clinical Success (N = 34)

Successful implant rate*	29/34 (85.3)
Procedural success†	24/30 (80.0)
Clinical success‡	22/30 (73.3)
Number of implants	40/34 (1.2)
0	5/34 (15.0)
1	18/34 (53.0)
2	11/34 (32.0)
Time for insertion of first implant to release of final implant, min	167.7 ± 151.8 (29/34)
Fluoroscopy time, min	39.3 ± 20.1 (33/34)
Hospital length of stay, days	2.5 ± 3.6 (32/34)
Median (range)	1.0 (1.0 to 21.0§)
95% confidence interval	1.2-3.8

Values are n/N (%) or mean ± SD (n/N), unless otherwise indicated. *Successful implantation rate: Implant is deployed as intended, and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory. †Procedural success: Successful implantation and at least a 1-grade reduction in TR at the end of procedure, without surgical or percutaneous intervention before hospital discharge. Four patients had unreadable or missing TEE. ‡Clinical success: Procedural success and no MAE at 30 days. §One patient required 21 days of hospitalization due to severe GI bleeding.

GI = gastrointestinal; MAE = major adverse events; other abbreviations as in Table 2.

captured due to complex anatomy (a combination of severe tethering and complex chordal structures, n = 4) and poor-quality echocardiographic imaging (n = 1), with no adverse clinical sequelae. The mean number of implants per patient was 1.2 (0 implants in 15%, 1 implant in 53%, and 2 implants in 32% of patients). The mean time from insertion of the first implant to release of the final implant was 168 ± 152 min, and the mean fluoroscopy duration was 39.3 ± 20.1 min. The mean length of hospital stay was 2.5 ± 3.6 days, and 97% of patients were discharged home.

ECHOCARDIOGRAPHIC RESULTS. At 30 days post-procedure, there was a significant reduction in the percentage of patients with severe or greater TR compared with baseline in paired analyses (48% vs. 96%, respectively; p < 0.001) (Figure 2). In addition, 85% of patients achieved at least 1 TR grade reduction and 70% achieved at least a 2-grade reduction at 30 days. The mean PISA EROA was significantly reduced by 38%, from 0.77 ± 0.32 to 0.48 ± 0.24 cm^2 (p = 0.007), as was the mean vena contracta width, which decreased by approximately one-half, from 1.50 ± 0.48 cm to 0.78 ± 0.36 cm (p < 0.001) (Figure 3 and Table 5).

Evidence of improvement in right-heart parameters was noted from baseline to 30 days post-procedure (Table 5), with reductions in mean right ventricular end-diastolic diameter (mid: 3.9 ± 0.9 cm vs. 3.6 ± 0.8 cm; p = 0.041), right atrial volume (160.5 ± 104.9 ml vs. 144.3 ± 74.3 ml; p = 0.071), and inferior vena cava diameter (2.8 ± 0.9 cm vs. 2.4 ± 0.7 cm; p = 0.03). There was no significant change in right ventricular function; however, there was a significant increase in the mean left ventricular stroke volume index (33.9 ± 8.6 ml/m^2 vs. 38.7 ± 7.5 ml/m^2; p < 0.001) and a trend toward an increased mean LVEF (57.1 ± 7.0% vs. 59.2 ± 7.0; p = 0.061).

CLINICAL AND FUNCTIONAL RESULTS. Functional status, as measured by NYHA functional class, improved significantly, with the number of patients in class I or II increasing from 6 of 27 (22%) at baseline to 24 of 27 (89%) at 30 days (p < 0.001) (Central Illustration, panel B). The mean 6MWD improved by 71 m, from 180 ± 101 m to 251 ± 100 m between baseline and 30 days, respectively (p < 0.001) (Figure 4A). The mean KCCQ overall score improved by 15 points from baseline (52 ± 23 points) to 30 days (67 ± 21 points; p < 0.001) (Figure 4B).

CLINICAL OUTCOMES. Clinical success with the PASCAL repair system was achieved in 22 of 30 (73.3%) patients by ITT analysis (Table 3) and 22 of 25 (88.0%) patients by AT analysis (Table 4). The primary safety endpoint, defined as a composite MAE rate at 30 days, was 5.9% with no mortality, myocardial infarctions, strokes, renal complications, new need for renal replacement therapy, reinterventions, or major access site and vascular complications (Table 6). The rate of severe bleeding was 5.9%, with 2 patients experiencing 3 events. One patient with multiple comorbidities, including atrial fibrillation, chronic iron-deficiency anemia, and a prior gastrointestinal (GI) bleed, experienced post-procedure GI bleeding on day 0 that required lavage and transfusion. The second patient with multiple comorbidities, including paroxysmal atrial fibrillation and a prior GI bleed, experienced acute-on-chronic anemia secondary to GI bleeding, requiring transfusions on post-procedure days 12 and 24. An SLDA was observed on TTE in 1 patient during their 30-day follow-up and confirmed by the core laboratory. The patient had worsened TR but improved NYHA functional status and did not require reintervention (Central Illustration, panel D).

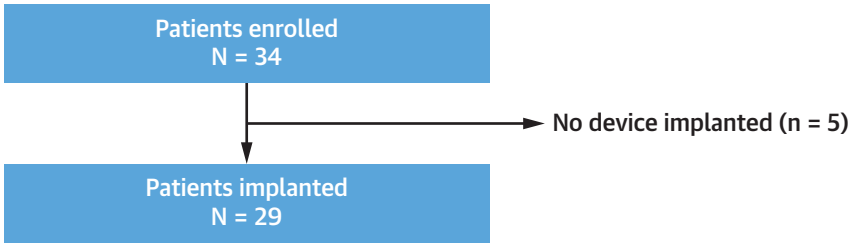
TABLE 4 Procedural Characteristics and Clinical Success (As-Treated Analysis) (N = 29)

Successful implantation rate*	29/29 (100)
Procedural success†	24/25 (96.0)
Clinical success‡	22/25 (88.0)

Values are n/N (%). *Successful implantation rate: Implant is deployed as intended, and the delivery system is successfully retrieved as intended at the time of the patient's exit from the cardiac catheterization laboratory. †Procedural success: Successful implantation and at least a 1-grade reduction in TR at the end of procedure without surgical or percutaneous intervention before hospital discharge. Four patients had unreadable or missing TEE. ‡Clinical success: Procedural success and no MAE at 30 days.

Abbreviations as in Tables 2 and 3.

FIGURE 1 Patient Flowchart

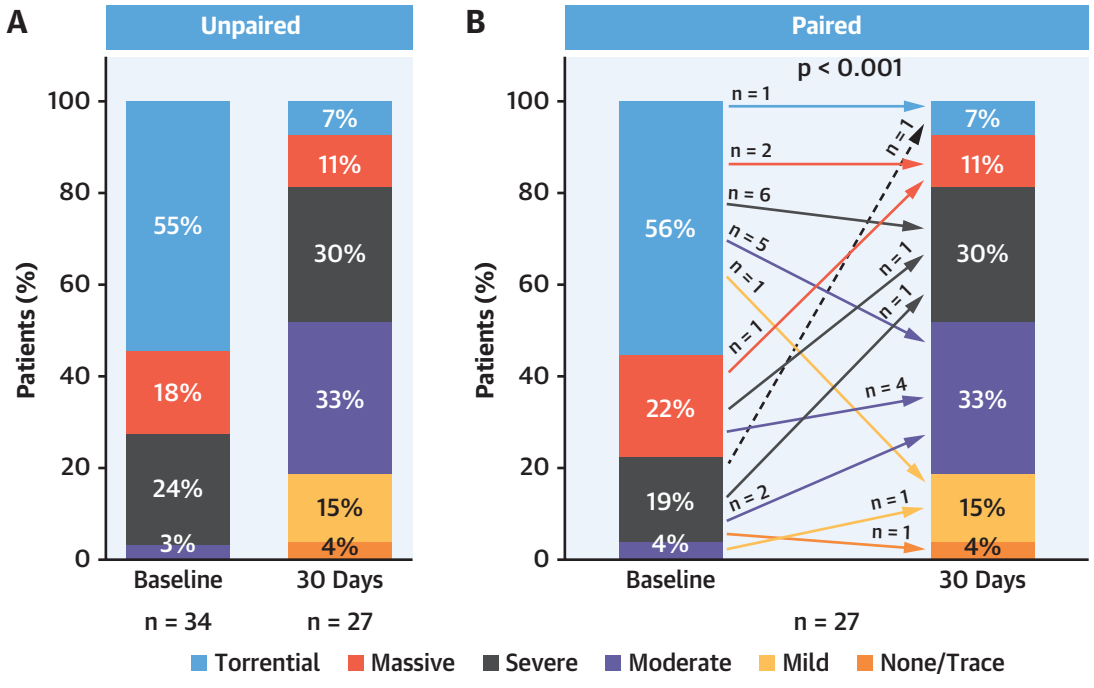


Of the 34 enrolled patients, 5 did not have a device implanted, resulting in 29 patients who received implants.

DISCUSSION

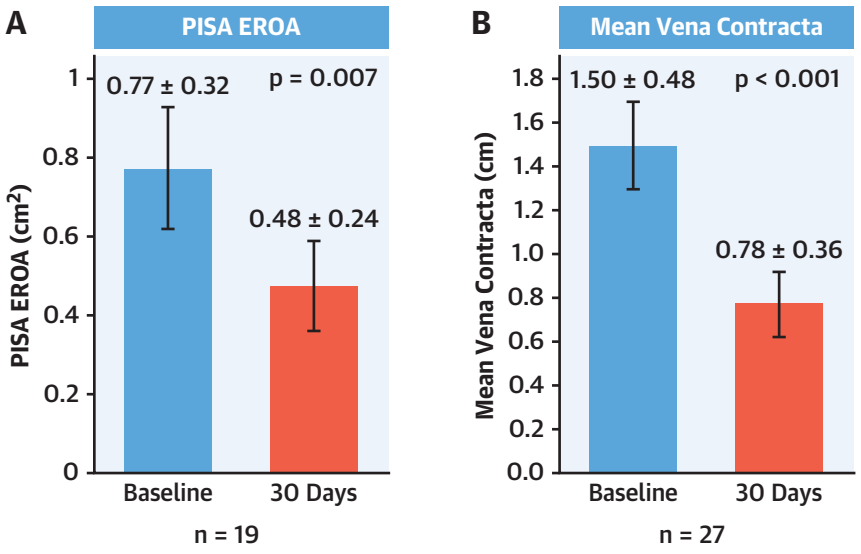
In this first report of the 30-day outcomes from the ongoing U.S. single-arm, multicenter, prospective, CLASP TR EFS of the PASCAL repair system: 1) implantation and procedural success rates were 85% and 80%, respectively; 2) 85% of patients had at least a 1-grade reduction in TR, whereas 70% had a

FIGURE 2 Reduction in TR Severity From Baseline to 30 Days With the Transcatheter Valve Repair System



(A) At 30 days, TR severity was improved, with 52% of patients having moderate or less TR. Five patients did not have a device implanted; for 2 patients, TTE was missing at 30 days, resulting in 27 patients. **(B)** Paired analysis overlaid with a spaghetti plot (**arrow colors** indicate TR severity at 30 days in individual patients) at baseline and at 30 days. The p values for categorical variables were derived from the Wilcoxon signed-rank test. At baseline, 1 patient had moderate-grade TR by TTE and severe-grade or worse TR by TEE. TEE = transesophageal echocardiography; TR = tricuspid regurgitation; TTE = transthoracic echocardiography.

FIGURE 3 Reduction in TR From Baseline to 30 Days With the Transcatheter Valve Repair System



(A) The mean PISA EROA decreased from 0.77 ± 0.32 cm^2 at baseline to 0.48 ± 0.24 cm^2 at 30 days. **(B)** The mean vena contracta width decreased from 1.50 ± 0.48 cm at baseline to 0.78 ± 0.36 cm at 30 days. The p values for continuous variables were derived from paired Student's *t*-tests. Values are mean ± SD. **Error bars** represent 95% confidence intervals. EROA = effective regurgitant orifice area; PISA = proximal isovelocity surface area; TR = tricuspid regurgitation.

≥2-grade reduction; 3) there were significant improvements in NYHA functional status, 6MWD, and KCCQ score; and 4) there were low rates of adverse events, with a composite MAE rate at 30 days of 5.9% with no cardiovascular mortality or reinterventions.

Over the past decade, transcatheter leaflet repair therapies have been increasingly used for mitral regurgitation and have demonstrated significant improvements in echocardiographic and functional outcomes, as well as survival (22-24). This information has served as the basis for studies evaluating the application of transcatheter leaflet repair technology for TR. However, early experiences quickly demonstrated that translating the successes from the mitral valve to the TV would not be simple for several reasons, including technical, imaging, and anatomic challenges. First, the delivery system for the mitral valve required modification to allow steering into a coaxial position for tricuspid leaflet capture. Second, optimal TEE imaging of TV leaflet capture has proved challenging due to the anatomic relation of the esophagus and the tricuspid annular plane, the highly mobile and markedly thinner leaflets, as well as the frequent shadowing of the TV from both anatomic structures (e.g., a native calcified aortic valve, lipomatous interarterial septum) and prosthetic valves. Finally, variability in TV leaflet number and morphology (complex or noncentral regurgitant orifice) may prevent adequate leaflet coaptation despite proper device implantation (25,26). Although initial benchtop modeling as well as early clinical experiences have demonstrated that septal leaflet grasping is important to achieve TR reduction, persistent regurgitation between the anterior and posterior leaflets is difficult to address in some patients (3,15,27).

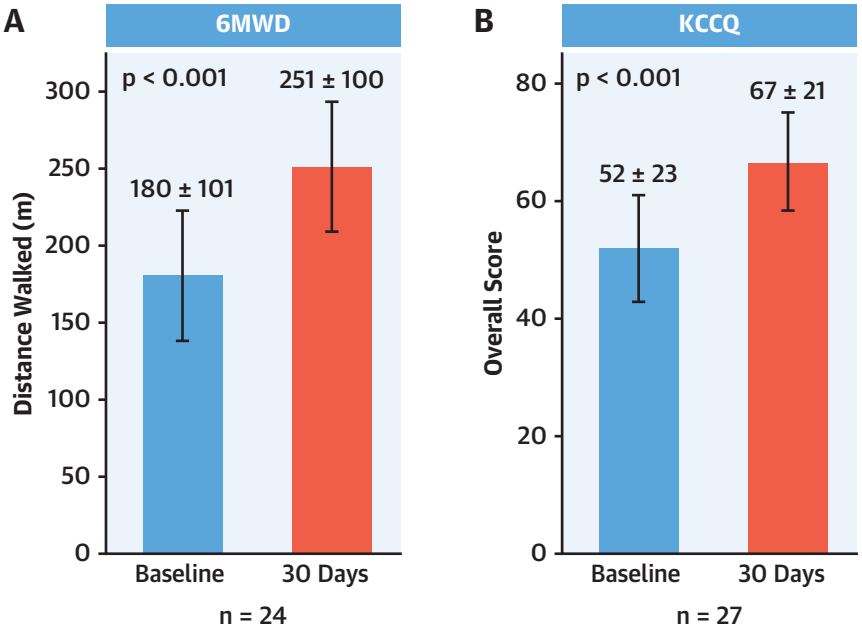
The PASCAL repair system addresses some of the technical challenges by incorporating independent clasping to facilitate treatment of large coaptation gaps and a central spacer to occupy the regurgitant orifice. The elongation ability of this repair system increases procedural safety and confidence, especially while navigating the complex and intricate TV apparatus. In addition, the PASCAL nitinol implant has been engineered to minimize stress on fragile TV leaflets. These versatile characteristics may facilitate achieving significant TR reduction. The implant retrievability feature of the repair system is well

TABLE 5 Paired Analyses of Echocardiographic Variables at Baseline and 30 Days

	Baseline	30 Days	p Value*
PISA EROA, cm^2	0.77 ± 0.32 (19)	0.48 ± 0.24 (19)	**0.007**
PISA regurgitant volume, ml	51.52 ± 22.90 (19)	38.80 ± 17.63 (19)	0.060
Mean vena contracta, cm	1.50 ± 0.48 (27)	0.78 ± 0.36 (27)	**<0.001**
Tricuspid septolateral annular diameter (end-diastole, apical 4-chamber), mm	45.13 ± 6.88 (28)	42.73 ± 5.91 (28)	**0.015**
Cardiac output, l/min	4.77 ± 1.23 (24)	5.10 ± 1.04 (24)	0.225
LV stroke volume, ml	63.89 ± 15.79 (24)	70.00 ± 14.46 (24)	**0.013**
LV stroke volume index, ml/m^2	33.9 ± 8.57 (19)	38.7 ± 7.51 (19)	**<0.001**
LV ejection fraction, %	57.07 ± 6.96 (26)	59.16 ± 7.00 (26)	0.061
RV end-diastolic diameter (mid), cm	3.86 ± 0.89 (26)	3.60 ± 0.78 (26)	**0.041**
RV FAC, %	38.14 ± 9.70 (25)	36.46 ± 7.04 (25)	0.331
Right atrial volume, ml	160.48 ± 104.88 (28)	144.28 ± 74.26 (28)	0.071
TAPSE, cm	1.45 ± 0.42 (28)	1.70 ± 1.49 (28)	0.393
IVC diameter, cm	2.77 ± 0.92 (28)	2.44 ± 0.69 (28)	**0.030**
TR peak velocity, cm/s	245.5 ± 37.6 (28)	266.7 ± 35.7 (28)	**0.003**
TR jet area, cm^2	16.92 ± 10.94 (24)	9.71 ± 5.57 (24)	**<0.001**

Values are mean ± SD (n). **Bold** values are statistically significant. *p values calculated by Student's *t*-test for paired analyses.
Abbreviations as in Table 2.

FIGURE 4 The Transcatheter Valve Repair System Improved 6MWD and KCCQ Scores From Baseline to 30 Days



(A) The mean 6MWD increased from 180 ± 101 m at baseline to 251 ± 100 m at 30 days. **(B)** Mean KCCQ score results improved from 52 ± 23 at baseline to 67 ± 21 at 30 days. The p values for continuous variables were derived from paired Student's *t*-tests. Values are mean ± SD. **Error bars** represent 95% confidence intervals. 6MWD = 6-min walk distance; KCCQ = Kansas City Cardiomyopathy Questionnaire.

TABLE 6 CEC-Adjudicated MAEs (N = 34)

Cardiovascular mortality	0
Myocardial infarction	0
Stroke	0
Renal complications requiring dialysis or renal replacement therapy	0
New need for renal replacement therapy	0
Severe bleeding*	2 (5.9)
GI bleed	2 (5.9)
Access site bleed	0
Reintervention related to implant	0
Major access site and vascular complications requiring intervention	0
Composite MAE rate	**2 (5.9)**
Other clinical safety events	
All-cause mortality	0
Heart failure rehospitalization	0
SLDA rate	1 (2.9)

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

CEC = clinical events committee; SLDA = single-leaflet device attachment; other abbreviations as in Table 3.

demonstrated in the CLASP TR EFS, where even though implantation was not feasible in a few patients, the implants were successfully retrieved without chordal entanglement or other adverse events.

To date, there are limited data regarding outcomes with transcatheter treatment of TR. The TRILUMINATE EFS (Trial to Evaluate Treatment With Abbott Transcatheter Clip Repair System in Patients With Moderate or Greater Tricuspid Regurgitation) evaluated the safety and effectiveness of the transcatheter TriClip device (Abbott Vascular, Santa Clara, California) in the treatment of 85 patients with TR (16). The study reported using an average of 2.2 devices (with a 100% successful implantation rate) to achieve ≥1 grade TR reduction in 86% of patients and NYHA functional class I/II in 80% of patients with an SLDA rate of 7%, which was managed conservatively. In the current small EFS, the PASCAL repair system device efficacy seems comparable to that of the TriClip device. Whether there are any real differences in the number of devices required or the SLDA rate, remains speculative at this time. Another transcatheter therapy for TR is being studied. The early feasibility study of the Cardioband Tricuspid System (CE Mark, Edwards Lifesciences) for functional TR evaluated 30 patients treated with this annular reduction device. Thirty-day results demonstrated acceptable safety and performance, significant annular reduction, and significantly improved TR severity, functional status, and quality of life (28).

One clinical characteristic that has been observed across multiple early feasibility studies in transcatheter tricuspid therapy is the large number of patients presenting late in the course of the disease with large regurgitant volumes and right ventricular dysfunction (15,16). As this will likely temper transcatheter therapy results, the use of a more granular grading scheme may be necessary. Although the use of a 5-grade classification with the addition of massive and torrential TR grades (20) is not currently recommended by guidelines (29,30), recent studies demonstrating incremental increases in mortality with the massive and torrential grades, as compared with the severe grade, justify its use in these studies (31,32). Furthermore, prior studies have shown that a single-grade reduction on the 5-grade system is associated with improved outcomes (15). In the current study, although only 52% of patients had moderate or less TR at 30 days, 85% demonstrated at least a 1-grade reduction in TR; in addition, significant improvements were observed in NYHA functional status, 6MWD, and KCCQ score.

Procedural success, defined as successful implantation with at least a 1-grade reduction, has been associated with improved survival (33). Recent studies have shown that predictors of failure for leaflet coaptation devices are insufficient echocardiographic imaging and echocardiographic parameters such as TR jet location(s), coaptation depth, EROA, annular diameter, tenting area, and systolic pulmonary pressure. Other predictors include anatomic features, such as a prominent eustachian ridge, excessive rete chiari, and chordal entrapment (23,26). Advancements in imaging technology, such as 3-dimensional intracardiac echocardiography, combined with increased experience and evidence-based patient selection criteria may further improve procedural success. With increasing procedural experience and advanced imaging upgrades, it is expected that procedural success and the duration of transcatheter tricuspid repair will progressively improve.

STUDY LIMITATIONS. The relatively small number of patients in this single-arm EFS limits conclusions about feasibility; however, the consistent reduction in TR, with right ventricular remodeling and increased forward stroke volume and annular dimensions, was associated with a consistent improvement in quality-of-life measures. Another limitation was missing PISA EROA imaging in many patients, despite site training. This highlights the need for further standardization in TR assessment, as well as the issues of

assessing TR at a single timepoint. Although only 2 patients experienced significant GI bleeding, this remains a concern for patients in this population who frequently have a coagulopathy from liver dysfunction or are taking anticoagulant agents in the setting of atrial fibrillation. Although both significant liver dysfunction and thrombocytopenia were exclusion criteria for this early feasibility trial, the study protocol did not capture the presence of other possible risk factors such as portal hypertension and esophageal varices. In addition, medication data (including diuretic agents) were not systematically collected in this EFS, and the benefit of the repair system on clinical management could not be fully assessed.

CONCLUSIONS

In this early experience, the PASCAL transcatheter valve repair system performed as intended, with substantial TR reductions and favorable safety results with a low MAE rate and no mortality or reintervention. At 30 days, this repair system resulted in significant functional status, exercise capacity, and quality-of-life improvements.

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PERSPECTIVES

COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS: In early experience, the PASCAL transcatheter valve repair system reduced the severity of TR and improved functional status, exercise capacity, and quality of life.

TRANSLATIONAL OUTLOOK: The ongoing multicenter, randomized CLASP-II TR study will extend these findings and help define patients who may benefit from this treatment option.

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APPENDIX For additional details regarding the study protocol, please see the online version of this paper.