

Alterra Adaptive Presept and SAPIEN 3 THV for Congenital Pulmonic Valve Dysfunction

An Early Feasibility Study



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ABSTRACT

OBJECTIVES The aim of this study was to demonstrate the safety and functionality of the Alterra Adaptive Presept and SAPIEN 3 transcatheter heart valve (THV) in patients with dysfunctional, dilated right ventricular outflow tract (RVOT) greater or equal to moderate pulmonary regurgitation (PR).

BACKGROUND Significant variations in the size and morphology of the RVOT affect the placement of transcatheter pulmonary valves. The Alterra Presept internally reduces and reconfigures the RVOT, providing a stable landing zone for the 29-mm SAPIEN 3 THV.

METHODS Eligible patients had moderate or greater PR, weighed >20 kg, and had RVOT diameter 27 to 38 mm and length >35 mm. The primary endpoint was device success, a 5-item composite: 1 Alterra Presept deployed in the desired location, 1 SAPIEN 3 THV implanted in the desired location within the Presept, right ventricular-to-pulmonary artery peak-to-peak gradient <35 mm Hg after THV implantation, less than moderate PR at discharge, and no explantation 24 h post-implantation. The secondary composite endpoint was freedom from THV dysfunction (RVOT/pulmonary valve (PV) reintervention, greater or equal to moderate total PR, mean RVOT/PV gradient \geq 35 mm Hg at 30 days and 6 months. Descriptive statistics are reported.

RESULTS Enrolled patients (N = 15) had a median age and weight of 20 years and 61.7 kg, respectively; 93.3% were in New York Heart Association functional class I or II. Device success was 100%. No staged procedures were necessary. No THV dysfunction was reported to 6 months. No serious safety signals were reported.

CONCLUSIONS This early feasibility study demonstrated the safety and functionality of the Alterra Adaptive Presept in patients with congenital RVOT dysfunction and moderate or greater PR. Durability and long-term outcome data are needed. (J Am Coll Cardiol Intv 2020;13:2510–24) © 2020 by the American College of Cardiology Foundation.

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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 JACC: Cardiovascular Interventions [author instructions page](#).

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Currently available transcatheter heart valve (THV) technology is applicable to a subset of patients with right ventricular outflow tract (RVOT) dysfunction, typically those with circumferential conduits or surgically placed bioprosthetic valves (1,2). However, the majority of patients with clinical indications for RVOT intervention do not have conduits or surgical valves; instead they have histories of RVOT reconstruction with a patch or transcatheter intervention with disruption of the pulmonary valve (PV) and consequent pulmonary regurgitation (PR). The combination of chronic PR across a patched and/or native RVOT leads to distortion and dilation of that region and usually precludes treatment with currently available balloon-expandable THVs because of the absence of an appropriate landing zone (3). The post-intervention “native” RVOT is geometrically heterogeneous, in terms of both shape and size, and is dynamically compliant, which adds to the challenge for replacement with existing THVs. Currently, several devices designed to treat native RVOT dysfunction are in clinical trials (4-6).

The Alterra Adaptive Prestent (Edwards Lifesciences, Irvine, California) was designed to provide an internal framework to reduce and reconfigure RVOT morphology, creating a suitable landing zone for a 29-mm SAPIEN 3 THV (Edwards Lifesciences) (7). Herein, we report procedural, 30-day, and 6-month outcomes from the ALTERRA (Multicenter Early Feasibility Study of Congenital Pulmonic Valve

Dysfunction Studying the SAPIEN 3 THV With the Alterra Adaptive Prestent) study. This trial was conducted as an early feasibility study (EFS), a program of the U.S. Food and Drug Administration (FDA) to evaluate the clinical safety and functionality of innovative devices in a limited number of patients.

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METHODS

PATIENTS AND STUDY PROTOCOL. This prospective, single-arm EFS (protocol 2016-04; NCT03130777) was designed to determine the safety and functionality of the Alterra Adaptive Prestent in patients with dysfunctional RVOTs or PVs meeting indications for treatment of moderate or severe PR. The study was conducted from August 22, 2017, through Jun 28, 2018, at 4 U.S. investigational sites (Supplemental Table 1).

The study was conducted under investigational device exemption G170053. The FDA and the Institutional Review Boards of all participating centers approved the protocol before patient enrollment. All eligible patients or their guardians provided written informed consent before study procedures commenced.

The primary outcome was a 5-item, nonhierarchical composite measure of post-procedural device success, including placement of the Alterra Prestent and a 29-mm SAPIEN 3 THV in the intended location (Supplemental Table 2). The secondary outcome was a 3-item composite measure of freedom from THV dysfunction at 30 days and 6 months post-procedure (Supplemental Table 2).

PATIENT COHORT AND SELECTION. In brief, eligible patients weighed at least 20 kg and had moderate or greater PR (per American Society of Echocardiography and European Association of Cardiovascular Imaging guidelines) (Table 1). Patients considered suitable candidates for implantation had proximal and distal landing zone diameters of ≥ 27 and ≤ 38 mm and a minimum of 35 mm from contractile tissue to lowest pulmonary artery (PA) takeoff immediately before Alterra Adaptive Prestent insertion. Patients who met all inclusion criteria and no exclusion criteria were evaluated for treatment.

Baseline assessments to evaluate candidacy for transcatheter PV replacement (TPVR) included physical examination, standard blood tests, transthoracic echocardiography (TTE), and electrocardiography

ABBREVIATIONS AND ACRONYMS

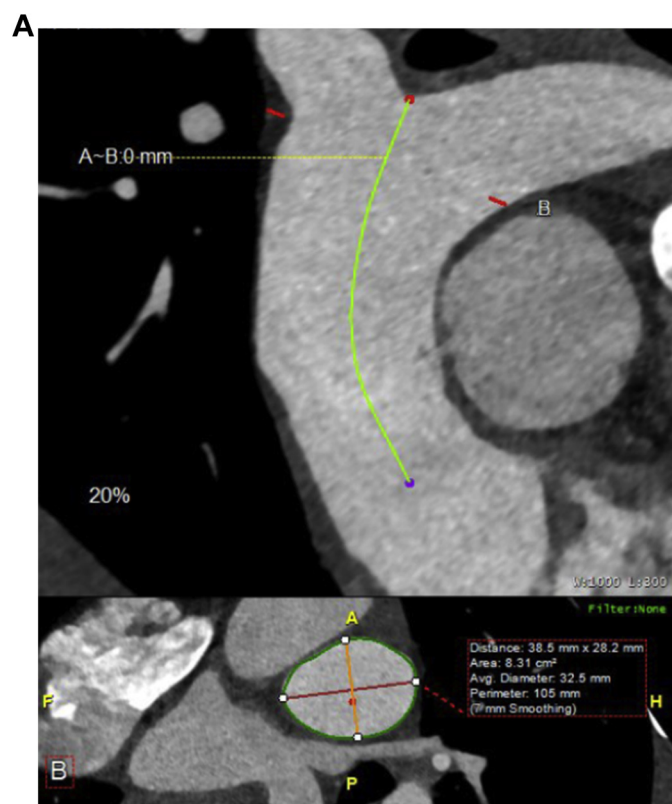
- AE** = adverse event
- CT** = computed tomographic
- EFS** = early feasibility study/studies
- FDA** = U.S. Food and Drug Administration
- IQR** = interquartile range
- PA** = pulmonary artery
- PR** = pulmonary regurgitation
- PV** = pulmonary valve
- RV** = right ventricular
- RVOT** = right ventricular outflow tract
- THV** = transcatheter heart valve
- TPVR** = transcatheter pulmonary valve replacement
- TTE** = transthoracic echocardiography

TABLE 1 Inclusion and Exclusion Criteria and Outcome Measures

Inclusion criteria
<ul style="list-style-type: none"> The patient or patient's legally authorized representative has been informed of the nature of the study, agrees to its provisions, and has provided written informed consent. Pediatric or adult patient whose weight is ≥ 20 kg (44 lb). The patient has a dysfunctional RVOT/PV. RVOT/PV proximal and distal landing zone diameter ≥ 27 mm and ≤ 38 mm and/or minimum of 35 mm from contractile tissue to lowest pulmonary artery takeoff immediately prior to Alterra Adaptive Prestent insertion.
Exclusion criteria
<ul style="list-style-type: none"> Active infection requiring current antibiotic therapy (if temporary illness, patient may be a candidate 2 weeks after discontinuation of antibiotics). History of or active endocarditis (active treatment with antibiotics) within the past 180 days. Leukopenia (WBC count $< 2,000$ cells/μl), anemia (Hgb < 7 g/dl), thrombocytopenia (platelets $< 50,000$ cells/μl) or any known blood clotting disorder. Inappropriate anatomy for introduction and delivery of the Alterra Adaptive Prestent or the SAPIEN 3 THV.

PA = pulmonary artery; PV = pulmonary valve; RV = right ventricular; RVOT = right ventricular outflow tract; THV = transcatheter heart valve; TTE = transthoracic echocardiography; WBC = white blood cell.

FIGURE 1 Delineation of Stepwise Process Used for Patient Selection Using Multimodality Imaging



(A) The entire Alterra deployment zone is measured using gated computed tomography. (B) A perimeter plot is created. (C) Following this, a virtual implant is created in systole (red) and diastole (blue). (D) A 3-dimensional printed model is then created. LPA = left pulmonary artery; MPA = main pulmonary artery; RPA = right pulmonary artery.

Continued on the next page

(Supplemental Table 3). Additionally, patients were evaluated for pulmonary regurgitant fraction, right ventricular (RV) function and end-diastolic volume, and biventricular function using cardiac magnetic resonance imaging and 2-dimensional phase contrast magnetic resonance angiography. Patients with moderate or greater PR, who met RV volumetric criteria for valve replacement, or had functional limitations attributed to chronic PR, and RVOTs not amenable for traditional transcatheter therapy, were referred for an electrocardiographically synchronized, contrast-enhanced computed tomographic (CT) angiography.

Anatomic analysis of the RVOT at baseline, including lengths, diameters, and circumference along the length of the potential deployment zone, was performed from the gated CT scan that covered

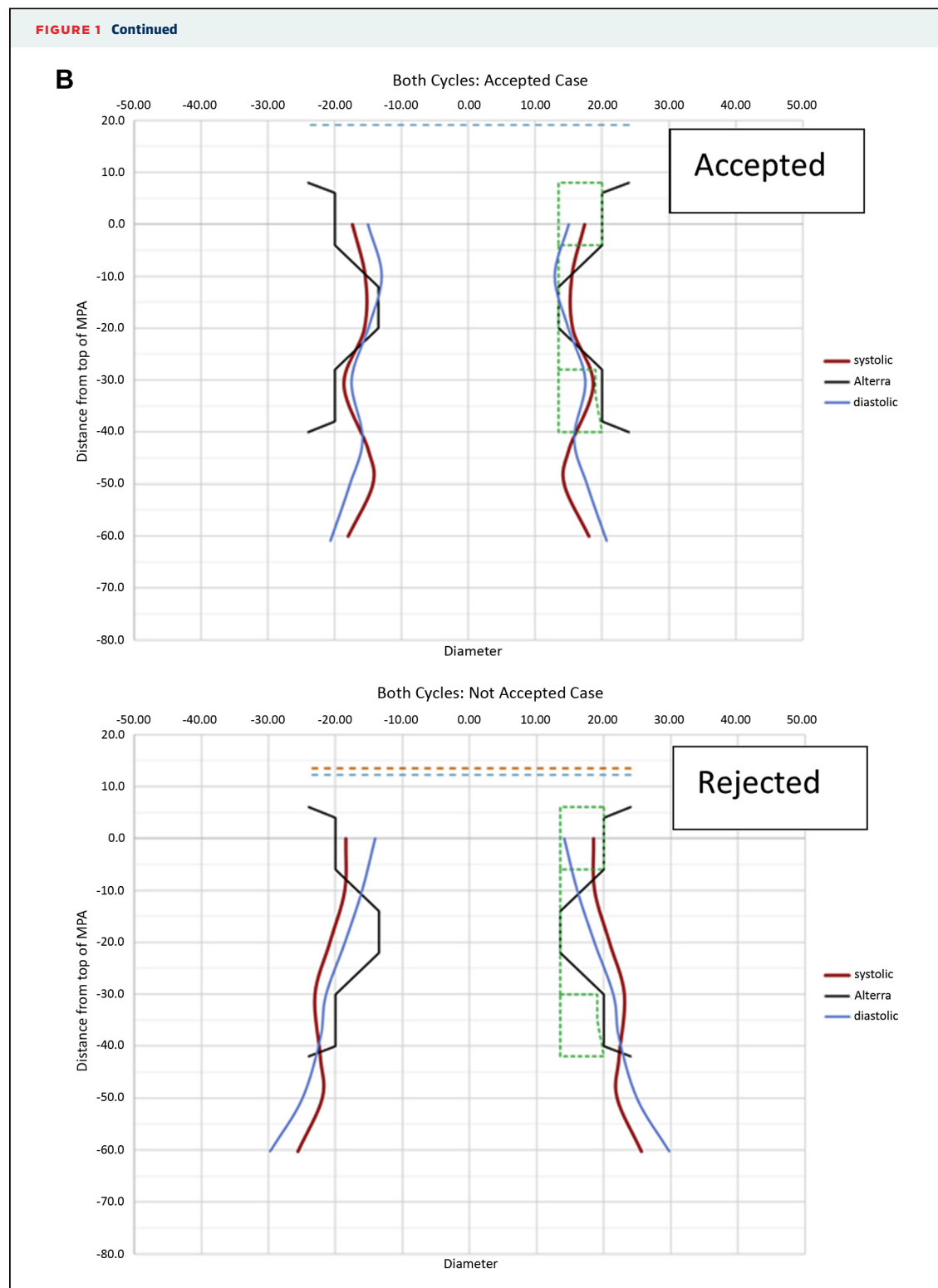
the entire RVOT and main PA throughout the entire cardiac cycle (Figure 1A). Centerline-based measurements of the RVOT circumference were made from the raw data obtained during peak systole at the time of maximal main PA distension and diastole. Perimeter plots of each patient's RVOT, in both systole and diastole, were created from the bifurcation of the branch pulmonary arteries to the contractile RV tissue (Figure 1B), similar to those previously published (8). The diameter and perimeter plots were created in 5-mm increments and analyzed in relation to the diameter and perimeter of the unconstrained device using presets determined by the engineers. Virtual implants of an unconstrained, fully expanded device were evaluated for device contact with vessel walls in both systole and diastole (Figure 1C).

Three-dimensional physical models of the RVOT at peak systole and diastole were created for each patient using PolyJet (Stratasys Direct, Los Angeles, California) printing technology (Figure 1D) to assess device interaction at inflow apices, potential for para-Alterra leak, and diastolic shortening of the RVOT and its impact on device stability. A screening committee reviewed all patient data and judged candidacy on the basis of clinical and anatomic data.

VALVE SYSTEM AND PROCEDURAL DETAILS. The Alterra Adaptive Prestant (Figure 2) was previously described by Zahn et al. (7). Briefly, it is a self-expanding Nitinol device, partially covered with expanded polytetrafluoroethylene. The device comes loaded within a self-sheathed delivery system. When in position, it is delivered using a control wheel by slow, controlled sheath retraction (Supplemental Figure 1) (7).

The SAPIEN 3 THV is a balloon-expandable, tri-leaflet, bovine pericardial tissue valve mounted on a cobalt-chromium frame. In addition to an internal skirt, the valve inflow is covered by an outer polyethylene terephthalate cuff for enhanced para-valvular sealing. The valve was delivered using a commercially available Commander delivery system (Edwards Lifesciences) (9). For delivery in the RVOT, the SAPIEN 3 THV is crimped on the Commander delivery system with the skirt of the valve facing the proximal shaft.

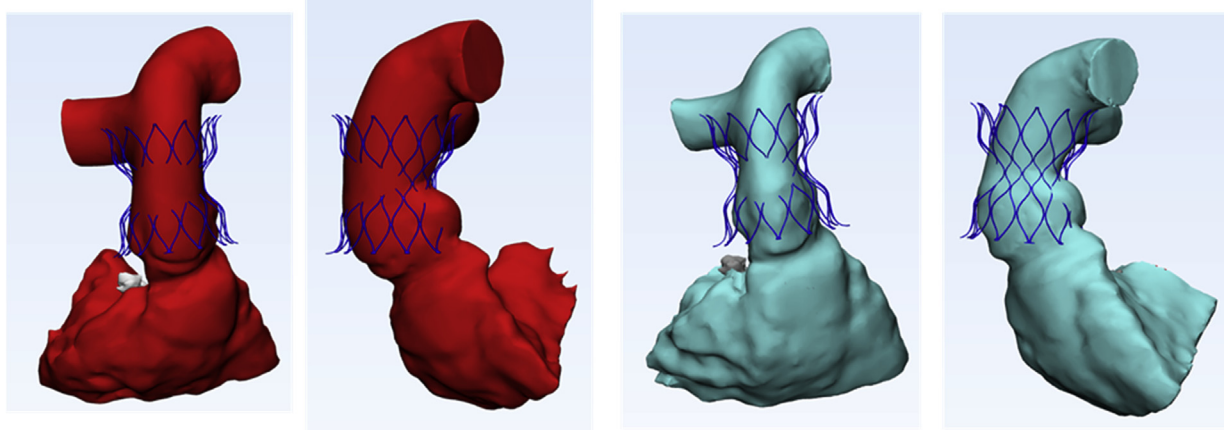
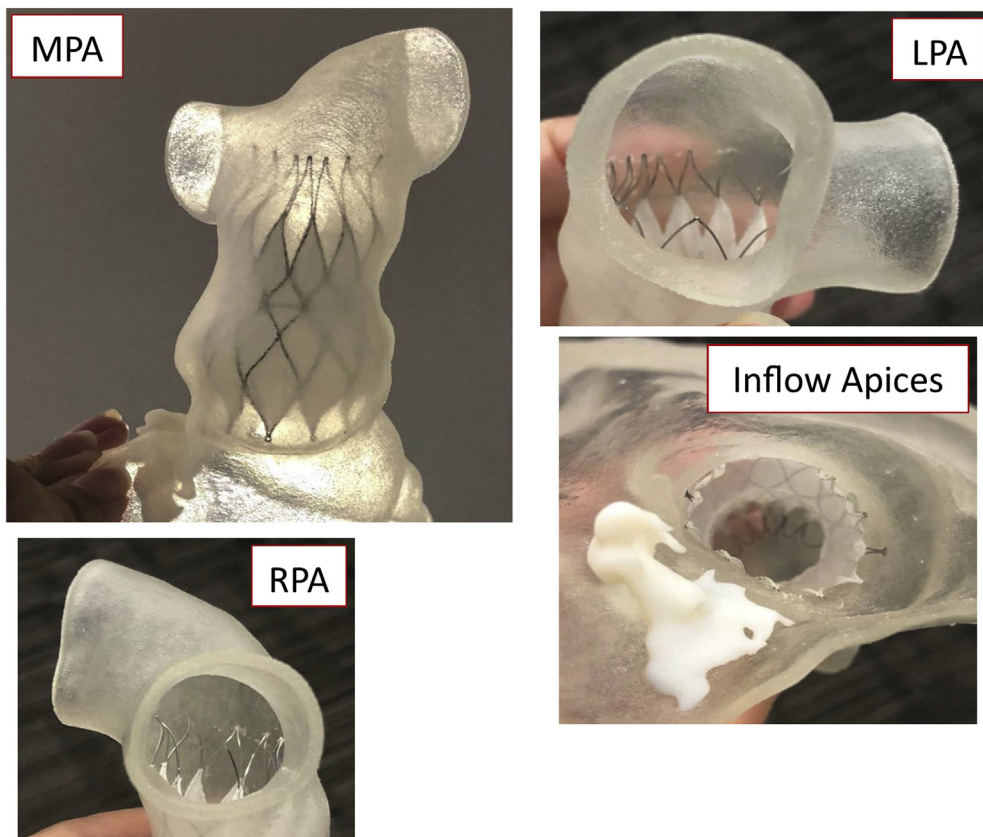
PROCEDURAL DETAILS. All procedures were performed under general anesthesia with endotracheal intubation. Femoral venous access was used for Prestant and valve implantation, with additional access to perform angiography and pacing during valve delivery in some patients. Heparin was



administered at the beginning of the procedure. Baseline right and left heart catheterization and cine angiography in the RVOT and the aorta were performed in all patients. Selective coronary

angiography was not performed systematically in the trial.

The Alterra Adaptive Prestent was advanced over a Lunderquist wire (Cook Medical, Bloomington,

FIGURE 1 Continued**C****D**

Indiana) or Meier wire (Boston Scientific, Marlborough, Massachusetts) through a 16-F eSheath (Edwards Lifesciences). The wire position was left to the discretion of the implanter and was guided by individual patient anatomy and PolyJet modeling.

Deployment of the Alterra Adaptive Presept was initiated in a proximal branch PA and then withdrawn into the intended landing zone. Device deployment was slow and controlled, with adjustments based on fluoroscopic appearance aided by

serial cine angiography, using a second RV/PA catheter. Once the distal part of the pre-stent was engaged in the main PA, the remaining pre-stent was deployed. The delivery catheter was removed under fluoroscopic guidance, ensuring that the nose cone was not ensnared in the device. If there was any fluoroscopic concern for distortion of the Alterra Adaptive PreStent during delivery system retrieval, the stiff guidewire was removed, and a softer wire was advanced via the delivery catheter. When used, the softer wire facilitated nose cone removal through the pre-stent without engaging the distal struts (Figure 3).

After assessing position of the Alterra Adaptive PreStent, a SAPIEN 3 THV was implanted as previously described. The SAPIEN 3 THV was deployed with or without the use of rapid ventricular pacing, per operator preference.

Post-implantation, angiography was performed in the main PA to evaluate device positioning and PR. Aortic root injection or selective coronary artery angiography was performed to document aortic root configuration and the absence of coronary compression. Additional post-implantation evaluations included an invasive measure of RV-PA peak-to-peak gradient, pulmonary arterial pressure, and right atrial pressure. Valve function and valve and paravalvular leak were assessed with intracardiac echocardiography (Figure 4).

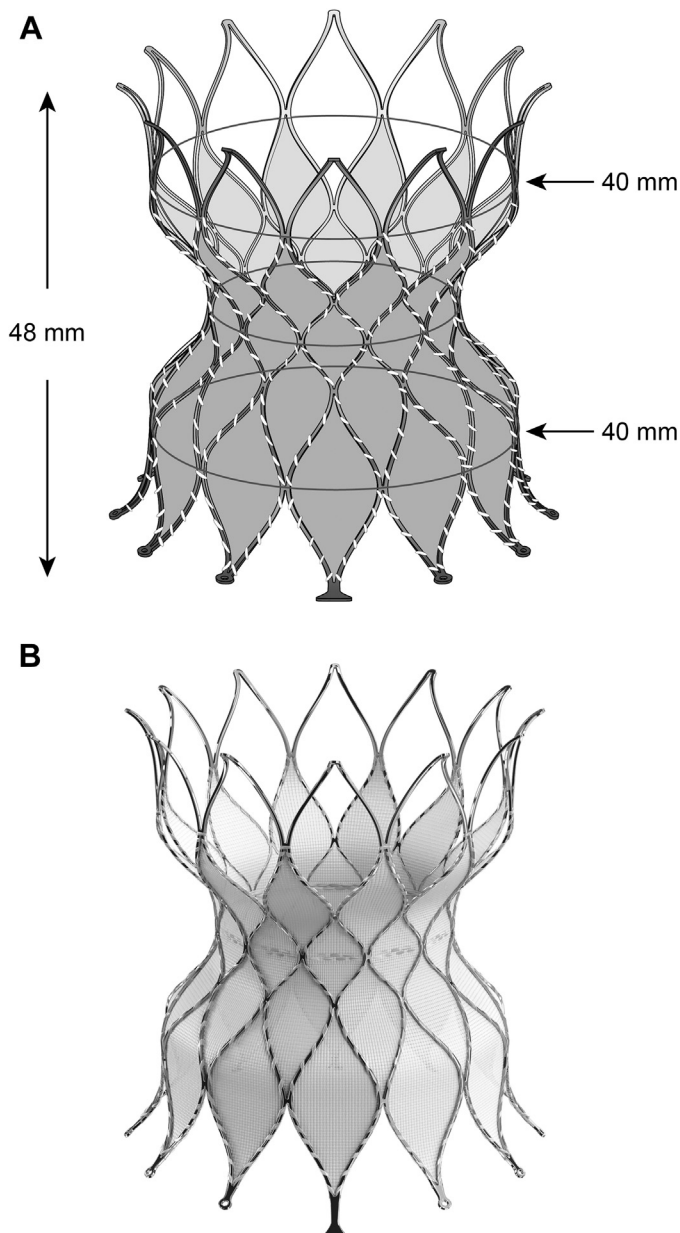
Patients underwent TTE, electrocardiography, and chest radiography before discharge; cardiac medications and adverse events (AEs) were documented. All patients received prophylactic antibiotics during the procedure and were discharged on antiplatelet therapy.

FOLLOW-UP ASSESSMENTS. Post-procedural follow-up assessments were scheduled for 30 days, 6 months, 12 months, and annually for 5 years. Herein, we report the 30-day and 6-month follow-up data.

SAFETY. AEs and serious AEs were monitored throughout the study and follow-up periods. All site-reported and clinical events committee (CEC)-adjudicated events, including major adverse cardiac and cerebrovascular events, a composite of all-cause death, RVOT reintervention, myocardial infarction, stroke, vascular access site- or access-related complication, and pulmonary embolism, were monitored by an independent medical reviewer.

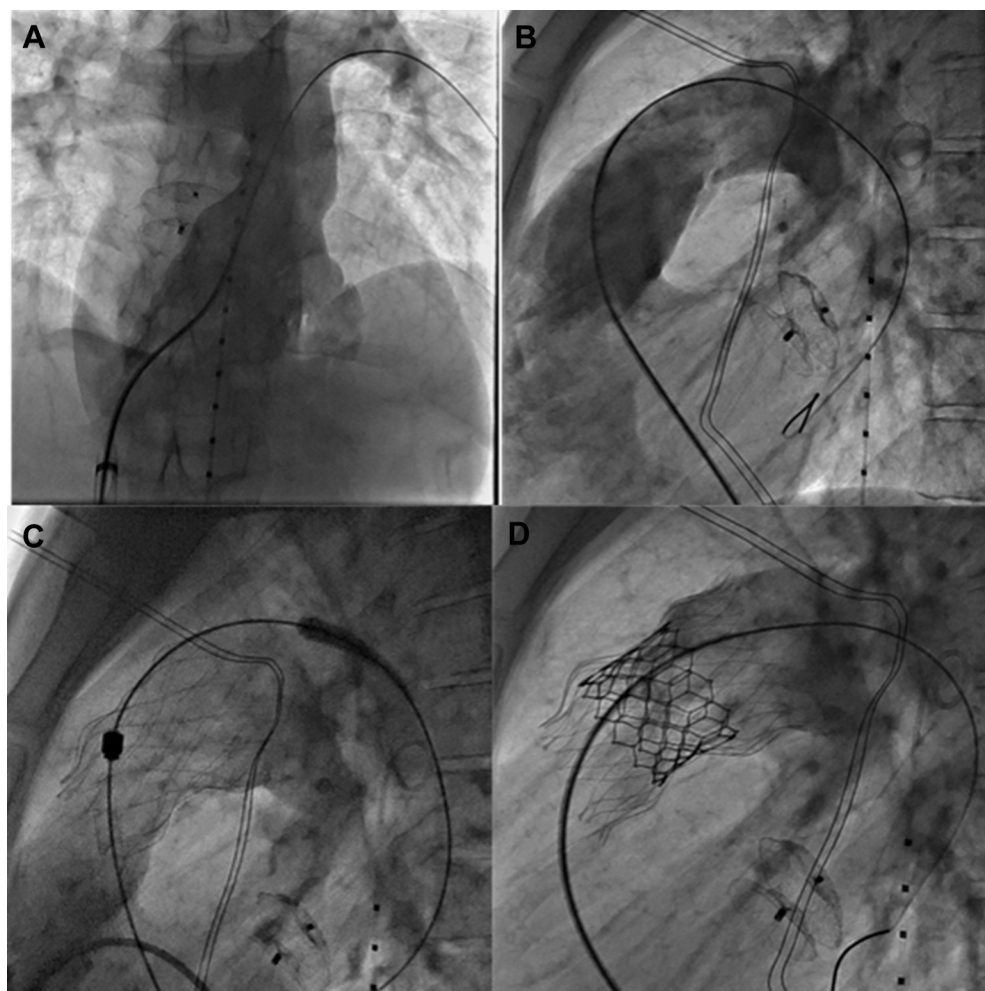
Endpoint events and device- and procedure-related AEs, as determined by the site or the Edwards safety officer, were assessed by a CEC.

FIGURE 2 Alterra Adaptive PreStent



(A) The Alterra Adaptive PreStent frame has inflow and outflow diameters equal to 40 mm. The unconstrained pre-stent is 48 mm long. (B) The proximal inflow section has 2 triangular tabs attached to the catheter of the delivery system. The distal outflow section has open cells to permit blood flow in the event the stent extends across the origin of a branch pulmonary artery.

DATA ANALYSIS. On the basis of the study objectives and FDA guidance on investigational device exemptions for EFS, a sample size of 15 patients was planned. Descriptive statistics were conducted for baseline characteristics, procedural information, the

FIGURE 3 Alterra Prestent Procedure

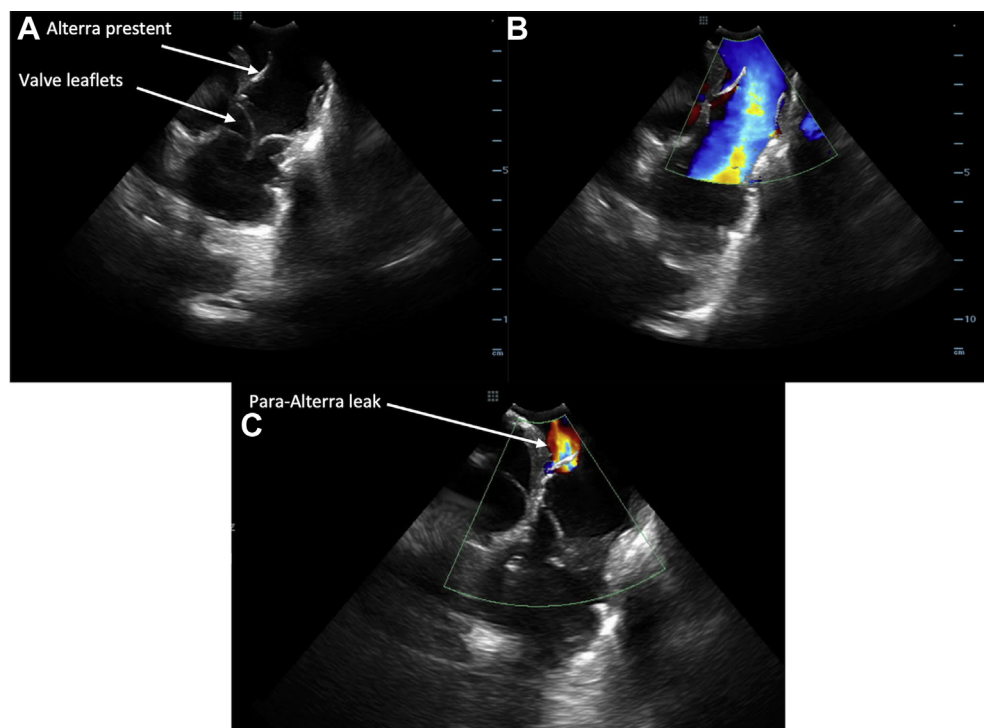
Images **A** and **B** show contrast opacification of the right ventricular outflow tract (RVOT) in anteroposterior and lateral projections, respectively. The RVOT is severely dilated, with dilated proximal branch pulmonary arteries. Minimal valve tissue is visualized. Image **C** shows contrast angiography in the RVOT post-deployment of the Alterra Adaptive Prestent. The Alterra pre-stent has been deployed in a good position, with appropriate proximal and distal engagement. Image **D** shows contrast angiography in the main pulmonary artery post-deployment of a 29-mm SAPIEN 3 transcatheter heart valve. There is minimal pulmonary regurgitation.

primary endpoint, and AEs. Continuous variables are summarized as median (interquartile range [IQR]), categorical data are summarized as counts and percentages, and AEs are summarized using Kaplan-Meier estimates. All 15 patients enrolled in the study were included in the analyses. Enrolled patients were those who provided written informed consent, passed the initial screenings, and began the Alterra implantation procedure (defined as underwent vascular access).

RESULTS

PATIENT DISPOSITION. Twenty-nine patients were screened for the study and 15 patients were enrolled (52% screening acceptance rate) (Figure 5). The primary reason for exclusion was anatomic unsuitability of the RVOT for the device. Two ineligible patients received primary SAPIEN 3 implantation without the Alterra Adaptive Prestent because of the presence of a landing zone <27 mm in diameter considered

FIGURE 4 Intracardiac Echocardiography Performed Post-Deployment of an Alterra Adaptive Prestent and a 29-mm SAPIEN 3 Transcatheter Heart Valve



Intracardiac echocardiogram (ICE) performed after Alterra and SAPIEN S3 placement. **(A)** ICE evaluation from the right ventricle shows inflow struts of the Alterra Prestent in the right ventricular outflow tract (RVOT). The SAPIEN valve leaflets are visualized with good coaptation. **(B)** Color Doppler evaluation shows no acceleration of color flow within the Alterra Prestent and SAPIEN valve. **(C)** Evaluation of the device in the inflow portion shows a small para-Alterra leak. No valvular obstruction is seen, with mild para-Alterra leak.

suitable for primary SAPIEN implantation (**Central Illustration**). One patient did not receive the device because of pregnancy.

BASELINE AND DEMOGRAPHIC CHARACTERISTICS.

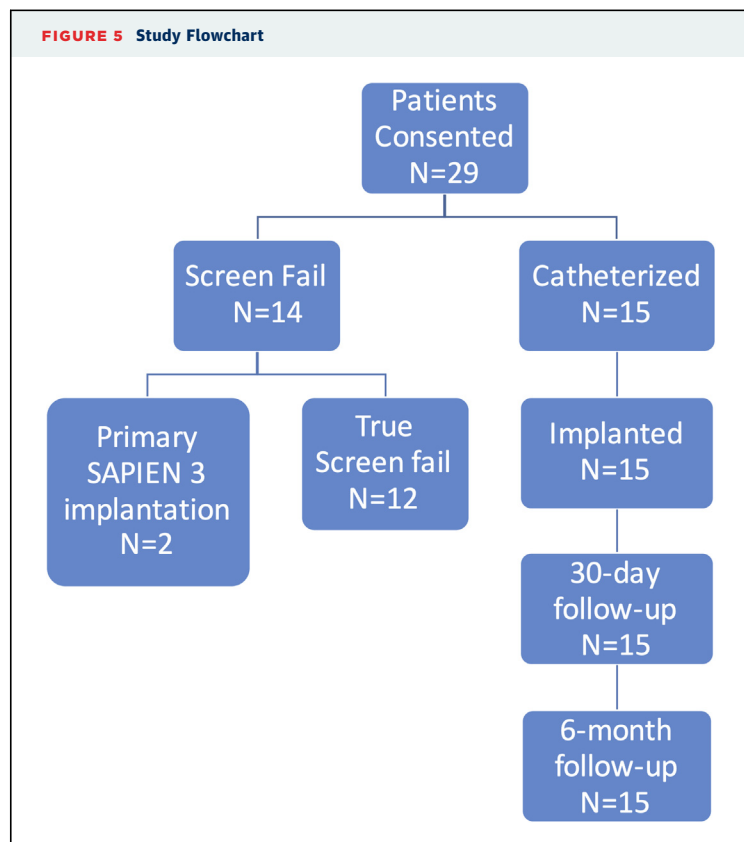
At baseline, the median patient age was 20 years and 66.7% were male; tetralogy of Fallot was the most common cardiovascular condition (53.3%), and 60% were in New York Heart Association functional class I (**Table 2**). The primary indication for the study was PR. No patient had significant RVOT stenosis. The median baseline RV end-diastolic volume index was 166.5 ml/m² (IQR: 135.5 to 182.1 ml/m²). No patient had a history of endocarditis.

PROCEDURAL CHARACTERISTICS. All patients received the Alterra Adaptive Prestent and SAPIEN 3 in a single implantation procedure. The SAPIEN 3 was implanted using the Commander delivery system in all cases. No concomitant procedures were performed. In 1 patient, post-dilation of the proximal portion of the Alterra Adaptive Prestent, before

SAPIEN 3 THV implantation, was performed with a 30 BIB balloon (NuMed, Hopkinton, New York) because of incomplete expansion (**Videos 1A, 1B, and 1C**). Post-dilation fluoroscopy revealed appropriate expansion, and the SAPIEN 3 THV was delivered without incident. There were no episodes of device dislodgement with removal of the Alterra Prestent or during SAPIEN 3 THV implantation. The median fluoroscopy and procedural sheath times were 35.0 min (IQR: 27.0 to 56.0 min) and 69.0 min (IQR: 59.0 to 86.0 min), respectively. Patients were discharged 1 day post-procedure.

PROCEDURAL OUTCOMES. Device success was achieved across all composite endpoints: 1) one Alterra Adaptive Prestent was deployed in the desired location; 2) one SAPIEN 3 THV was implanted within the pre-stent; 3) RV-PA peak-to-peak gradient was <35 mm Hg after THV implantation; 4) less than moderate total PR was detected on TTE; and 5) there were no Alterra explantations at 24 h. No concerns of

FIGURE 5 Study Flowchart

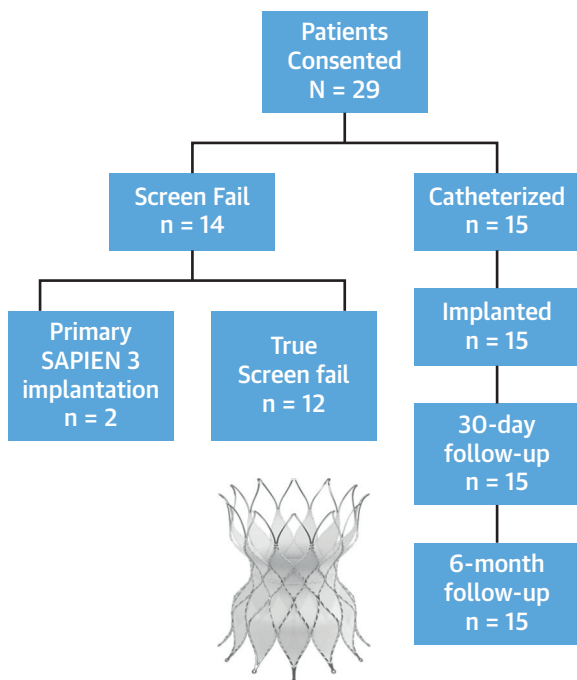


clinically relevant para-Alterra, paravalvular, or valvular regurgitation were observed. The median post-procedural RV-PA peak-to-peak gradient was 6 mm Hg (IQR: 3 to 9 mm Hg).

SAFETY. From 0 to 30 days and from 0 to 180 days, no major adverse cardiac and cerebrovascular events were reported for any patient. CEC-adjudicated events (Table 3) to 6 months included no deaths, RVOT reintervention, stroke, myocardial infarction, endocarditis, device embolism, or coronary artery compression. One patient had a small, localized pericardial effusion on post-procedural TTE suspected to be a hemopericardium; the effusion was not drained. Patient-level details are provided later. One arrhythmia event of atrial fibrillation was reported during the procedure. The patient underwent synchronized cardioversion during the procedure with return of normal sinus rhythm. There were 2 reports of major bleeding, a case of hemopericardium and an epistaxis event. The epistaxis was later readjudicated by the CEC as minor bleeding. In addition, there were 3 other reports of minor bleeding, which included epistaxis in 1 patients and localized groin hematomas in 2 patients. None of these events warranted any additional therapeutic interventions.

Site-reported AEs of interest were reported. One patient developed tricuspid regurgitation during the procedure, considered secondary to tricuspid valve chordal rupture from manipulation of the Commander delivery system. Presently, this patient is asymptomatic and being followed clinically without intervention. Three patients experienced chest pain following the procedure. Two were treated with analgesic agents, and 1 patient received opioids. None had evidence of pericardial effusion by echocardiography or CT imaging, and the pain resolved spontaneously. Self-limited transient ventricular tachycardia occurred in 2 patients post-procedure and was successfully treated with beta-blockers. The CEC adjudicated these events as secondary to device interaction with native tissue within the RVOT. Neither patient had a pre-procedural Holter monitor. The patient with the small, localized pericardial effusion seen on TTE on post-operative day 1 had a pre-procedural upper respiratory tract infection. The effusion was adjudicated by the CEC as a hemopericardium but was clinically treated as reactive pericarditis. The electrocardiogram showed diffuse, nonspecific ST-segment elevation, along with PR prolongation and a C-reactive protein level of 46 mg/ml. A CT scan showed no evidence of vascular perforation, and the patient was discharged on post-operative day 2. The effusion resolved with colchicine and naproxen treatment. On follow-up TTE on post-operative day 3, this patient had an incidental clot attached to the inflow of the Alterra Adaptive Presept with no thrombosis on the SAPIEN 3 THV. The patient was treated with enoxaparin sodium twice daily and warfarin. On follow-up TEE 3 days later, the clot had resolved, and the valve had normal function. The Doppler-derived mean RVOT gradient had mildly worsened compared with post-procedure (to 17.8 mm Hg from 12 mm Hg) at 30 days. At 6 months, the gradient was 20.6 mm Hg, and follow-up echocardiography showed that this patient had prominent native valve leaflet tissue that was not entirely captured by the Alterra Presept. Post-procedural echocardiography showed in-folding of the native leaflet proximal to the Alterra Presept, which caused subvalvular obstruction (Figure 6). Presently, this patient is asymptomatic. This event led to changes in the pre-procedural evaluation, emphasizing the need to evaluate and identify existing structures within the RVOT and proposed landing zone (i.e., leaflet remnants, muscle bundles, and presence of calcification) that could affect device function. In the presence of prominent or redundant native leaflet tissue within the RVOT, all efforts are

CENTRAL ILLUSTRATION Flowchart of Recruitment and Outcomes



Variable	6 Months N = 15
Mean right ventricular outflow tract gradient (mm Hg) Median (quartile 1, quartile 3)	9.0 (6.8, 14.3)
Total pulmonic regurgitation, n (%)	
None	8 (53.3)
Trace	7 (46.7)
Tricuspid regurgitation, n (%)	
None	0
Trace	2 (13.3)
Mild	11 (73.3)
Moderate	2 (13.3)
Severe	0

Shahanavaz, S. et al. J Am Coll Cardiol Interv. 2020;13(21):2510-24.

TABLE 2 Demographics and Baseline Characteristics (n = 15)

Age (yrs)	20.0 (16.0-41.0)
Age	
<12 yrs (child)	0
12-21 yrs (adolescent)	9 (60.0)
>21 yrs (adult)	6 (40.0)
Sex	
Female	5 (33.3)
Male	10 (66.7)
Height (cm)	166.4 (163.5-177.8)
Weight (kg)	61.7 (56.5-89.4)
Body surface area (m ²)	1.7 (1.6-2.0)
Original CHD diagnosis	
PAIV	1.0 (6.7)
Pulmonary valve stenosis	6 (40.0)
Tetralogy of Fallot	8 (53.3)
NYHA functional class	
I	9 (60.0)
II	5 (33.3)
III	1 (6.7)
IV	0
CT/MRI key results	
MPA regurgitation fraction (%) [*] (n = 10)	42.6 (40.5-45.6)
RVEDI (ml/m ²) [†]	166.5 (135.5-182.1)

Values are median (interquartile range) or n (%). ^{*}Data obtained from MRI. [†]Combination of data obtained from gated CT scan and MRI.

CHD = congenital heart defect; CT = computed tomographic; MPA = main pulmonary artery; MRI = magnetic resonance imaging; NYHA = New York Heart Association; PAIV = pulmonary atresia with intact ventricular septum; RVEDI = right ventricular end-diastolic volume index.

made to cover these with the Alterra Presept prior to valve implantation.

Another patient also had an elevated Doppler-derived mean RVOT gradient at 30 days compared with post-procedure (24 mm Hg vs. 15 mm Hg). The 6-month peak RVOT gradient was 31.2 mm Hg. Echocardiography and CT imaging showed no evidence of clot. The inferomedial aspect of the Alterra Adaptive Presept was noted to be projecting into the RVOT because of acute angulation of the RVOT, which explained the elevated gradients (Video 2). At the 6-month follow-up visit, this patient was asymptomatic.

FOLLOW-UP EVALUATION. No THV dysfunction was reported to 6 months: no patient required RVOT/PV reintervention (Table 4), all patients had mild or trivial PR (Figure 7), and the median RVOT Doppler gradient was 9.0 mm Hg (IQR: 6.8 to 14.3 mm Hg) (Table 4), as evaluated by TTE.

No Presept explantation was reported. No significant para-Alterra leak was seen on echocardiography post-implantation or at 6 months. One instance of a single wire type 1 fracture of the inflow of the Alterra frame was noted as an incidental finding on fluoroscopy performed at 6 months. The patient had no change in outflow tract gradient or

TABLE 3 Adverse Events, Clinical Events Committee Adjudicated

	30 Days (n = 15)	6 Months (n = 15)
All-cause mortality	0	0
RVOT reintervention	0	0
Stroke or TIA	0	0
Bleeding*	4 (26.7)	5 (33.3)
Life-threatening/disabling	0	0
Major	1 (6.7)	2 (13.3)
Minor	3 (20.0)	3 (20.0)
Vascular access site- or access-related complication	0	0
Arrhythmia or conduction system injury	1 (6.7)	1 (6.7)
Myocardial infarction	0	0
Endocarditis	0	0
Device embolization	0	0
Pulmonary embolism	0	0
Coronary artery compression	0	0

Values are n (Kaplan-Meier estimate %). *Defined by Valve Academic Research Consortium-2.
 RVOT = right ventricular outflow tract; TIA = transient ischemic attack.

regurgitation associated with this finding. At 6 months, 86.7% of patients were in New York Heart Association functional class I, and 13.3% were in functional class II (Figure 8). No bacterial endocarditis was reported.

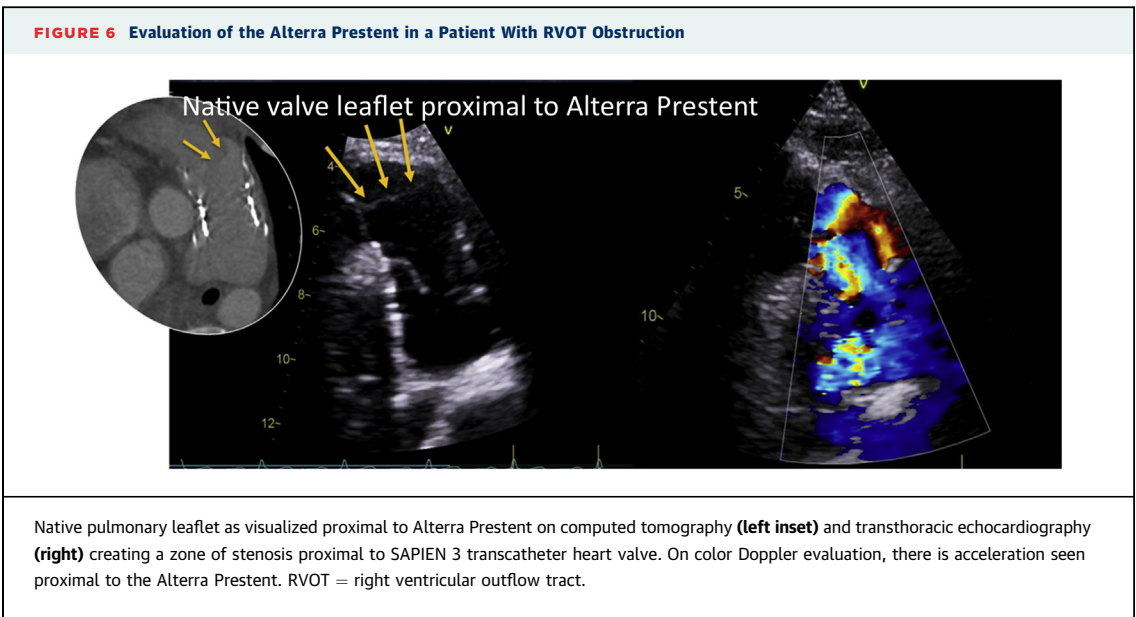
DISCUSSION

Currently approved therapies to manage circumferential RVOTs include surgically placed conduits and

TPVR with bioprosthetic valves. The Melody valve (Medtronic, Minneapolis, Minnesota) was the first FDA-approved transcatheter PV indicated to treat dysfunctional conduits and bioprosthetic valves (10–12). In 2016, the FDA approved the SAPIEN XT valve for TPVR in dysfunctional conduits. COMPASSION S3 is an ongoing trial for approval of the SAPIEN 3 THV in the pulmonary position. A recent meta-analysis demonstrated >95% implantation success for Melody, SAPIEN, and SAPIEN XT valves in the pulmonary position (13).

Unfortunately, most patients with dysfunctional RVOTs have large, compliant, noncircumferential outflow tracts previously modified by either surgical placement of a transannular patch or catheter-based balloon valvuloplasty. Before our study, the SAPIEN XT and SAPIEN 3 valves were successfully implanted in carefully selected patients with large, dilated, native RVOTs (14–16). However, although the 29-mm SAPIEN 3 THV has increased the number of patients who can successfully undergo TPVR, many patients have RVOTs that are too large, distensible, and irregularly shaped to be candidates for simple balloon-expandable TPVR.

In recent years, several self-expanding, percutaneous valve devices have been designed and are in various stages of clinical testing for patients with these types of RVOT. The Venus P-valve (Medtech, Shenzhen, China) is a self-expanding percutaneous valve with a trileaflet porcine pericardial tissue valve sewn inside a Nitinol frame, in diameters up to 32 mm, with flared ends that conform to a dilated native RVOT. The initial 5-patient study



demonstrated excellent short-term PV function after TPVR with the Venus P-valve (4). The Pulsta valve (Taewoong Medical, Seoul, South Korea) comprises a knitted, double-strand, Nitinol wire stent covered by a treated porcine pericardium, with a trileaflet valve of the same material hand sewn to a self-expanding stent frame. It ranges in diameter from 18 to 28 mm, with ends that are 4 mm wider than the center. Kim et al. (6) reported 6-month follow-up outcomes in 10 patients who received the Pulsta valve in an EFS. Trivial PR and no significant pulmonary stenosis were reported. The Harmony TPV (Medtronic) is a porcine pericardial tissue valve mounted in a self-expanding Nitinol frame designed specifically for regurgitant native or patched RVOT anatomy. Early clinical outcomes demonstrated promising device performance and preservation of stent integrity in the majority of cases. Implanted patients had significant improvements in PR compared with baseline, and at 6 months, valve function was preserved.

Unlike other valves designed for the native RVOT, the Alterra Adaptive Prestent is a unique docking adaptor designed to facilitate internal RVOT remodeling by providing a predictable rigid “landing zone” for the 29-mm SAPIEN 3 THV. The docking adaptor concept was first described by Boudjemline et al. (17), who successfully investigated a staged procedure of a balloon-expandable stent deployed within a centrally constricted, covered, self-expanding pre-stent in the RVOT in ewes.

The current EFS demonstrates the technical feasibility, safety, and effectiveness of the Alterra

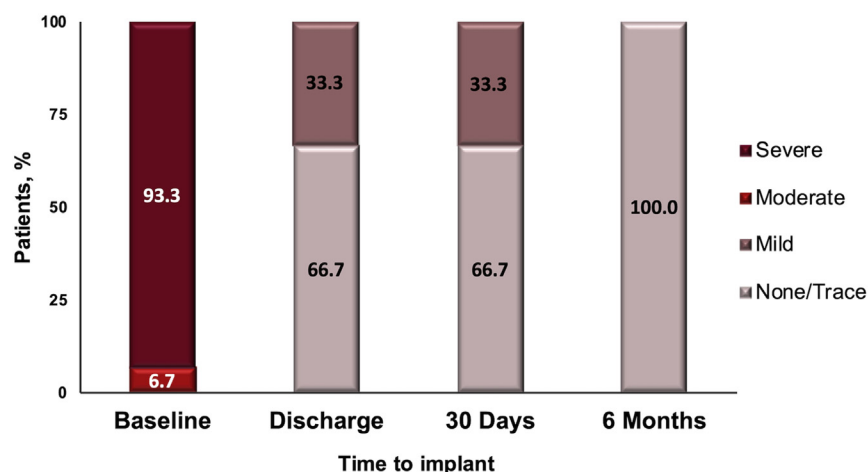
TABLE 4 Valve Performance

	Baseline (n = 15)	Discharge (n = 15)	30 Days (n = 15)	6 Months (n = 15)
Mean RVOT gradient, mm Hg	5.7 (4.1-10.4)	10.5 (5.4-11.8)	8.0 (5.0-11.6)	9.0 (6.8-14.3)
Paravalvular leak				
None	—	11 (73.3)	12 (80.0)	14 (93.3)
Trace	—	3 (20.0)	3 (20.0)	1 (6.7)
Mild	—	1 (6.7)	0	0
Moderate	—	0	0	0
Severe	—	0	0	0
Transvalvular leak				
None	0	13 (86.7)	10 (66.7)	10 (66.7)
Trace	0	1 (6.7)	4 (26.7)	5 (33.3)
Mild	0	1 (6.7)	1 (6.7)	0
Moderate	1 (6.7)	0	0	0
Severe	14 (93.3)	0	0	0
Total pulmonic regurgitation				
None	0	4 (26.7)	4 (26.7)	8 (53.3)
Trace	0	6 (40.0)	6 (40.0)	7 (46.7)
Mild	0	5 (33.3)	5 (33.3)	0
Moderate	1 (6.7)	0	0	0
Severe	14 (93.3)	0	0	0
Tricuspid regurgitation				
None	0	0	0	0
Trace	1 (6.7)	3 (20.0)	2 (13.3)	2 (13.3)
Mild	13 (86.7)	11 (73.3)	12 (80.0)	11 (73.3)
Moderate	1 (6.7)	1 (6.7)	1 (6.7)	2 (13.3)
Severe	0	0	0	0

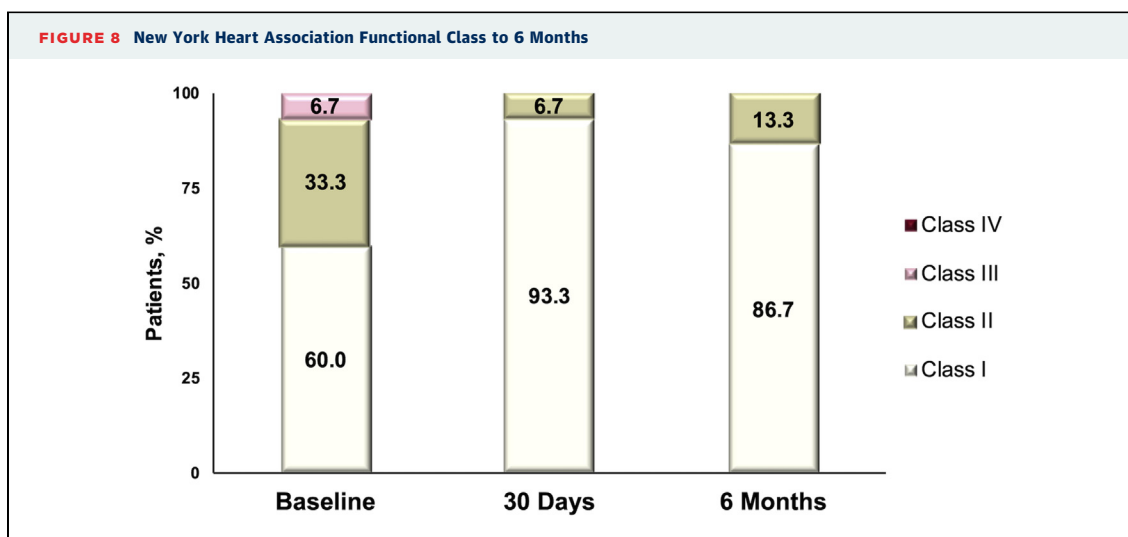
Values are median (interquartile range) or n (%).
RVOT = right ventricular outflow tract.

Adaptive Prestent and 29-mm SAPIEN 3 THV implanted during a single procedure in patients with large, dysfunctional RVOTs. Device implantation success was 100% in our carefully screened subset of patients. This compares favorably with the Harmony

FIGURE 7 Total Pulmonic Regurgitation



Core lab data



and Venus P-valve early trial reports of 95% and 92% implantation success rates, respectively (5,18). Although pre-stent and valve placement is a 2-step procedure, this trial demonstrated that it can be safely performed in the same setting, avoiding a second invasive procedure. Procedural times were acceptable, and fluoroscopy times were comparable with those for single-step, native RVOT devices (18). No immediate or early surgical device removal was required, unlike other self-expanding native RVOT devices (4,5,16).

We attribute the success of this study, in part, to our in-depth pre-procedural evaluations involving cross-sectional imaging, virtual implantation, PolyJet modeling, and implantation within the models. This comprehensive, patient-specific preparation provided us with valuable insights about “device fit” within different anatomic variations. With a combination of engineering analysis and clinical judgment, the pre-procedural evaluation also took into consideration “device engagement,” device interaction in the inflow and outflow apices in heterogeneous landing zones. Both of these aspects were critical in preventing device embolization, especially when advancing the SAPIEN 3 THV mounted on the Commander delivery system. The flared inflow portion of the device, which is covered, helped seal the RVOT within the implanted cohort and prevented para-Alterra leaks. There was no evidence of significant para-Alterra leaks in the implanted patients.

Also significant from our study was the high screening acceptance rate for this single-size device: 52% of patients were suitable for Alterra and SAPIEN 3 placement, 59% when considering the 2 patients who

received the SAPIEN 3 alone. This compares favorably with the 32% screening acceptance rate for the initial Harmony valve (5). We attribute our high acceptance rate to the larger circumferential device dimensions of the Alterra pre-stent compared with several of the other native RVOT devices. The mean PV annulus of the implanted cohort was 36.3 mm in systole compared with the mean PV annulus of 25 mm (range: 18 to 32 mm) in the Harmony valve cohort and a median PV annulus of 22.7 mm (range: 18 to 27 mm) in the Venus P-valve cohort (4,5,7,18).

At 30 days and 6 months, we found no evidence of THV dysfunction, all-cause mortality, major adverse cardiac and cerebrovascular events, or other important safety signals. The absence of significant frame fractures or device infolding affecting device stability and function was also notable in the Alterra cohort. The Venus P-valve trials demonstrated frame fracture in 27% of cases, along with device infolding that caused obstruction (18,19). Unlike comparable device trials (5), our trial had no surgical explantations. These extensive pre-procedural evaluations continue in the ongoing pivotal trial of the Alterra Adaptive PreStent and SAPIEN 3 THV (NCT03130777).

The safety and durability of the SAPIEN 3 THV has been evaluated in larger cohorts in the aortic position and shorter term studies within the pulmonary position with good outcomes (13,20). Case reports of tricuspid valve injury with possible entrapment of the chordae in the delivery system have led to modifications of the delivery technique. A new delivery system has been specifically designed to navigate the complexity of the right heart and is currently being evaluated.

The preliminary findings of this EFS suggest that the Alterra Adaptive PreStent may significantly increase the number of patients eligible for TPVR by creating a stable landing zone for the SAPIEN 3 THV in patients whose anatomy is unsuitable for currently approved balloon-expandable valves.

STUDY LIMITATIONS. This EFS was limited to a small cohort of patients, who underwent rigorous evaluation before device implantation. The applicability of this device to all patients with RVOT dysfunction cannot be currently extrapolated, because of the extreme variation in RVOT morphology. A select group of experienced physicians implanted the device, which might have skewed results of the study.

CONCLUSIONS

This EFS of the Alterra Adaptive PreStent showed excellent clinical outcomes of less than mild PV and paravalvular regurgitation in all patients. The Alterra Adaptive PreStent has the potential to expand the number of patients with dysfunctional RVOTs who are candidates for TPVR.

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AUTHOR RELATIONSHIP WITH INDUSTRY

Edwards Lifesciences sponsored this study. Dr. Shahanavaz is a consultant for Medtronic; and is a proctor for Edwards Lifesciences. Dr. Balzer is a consultant and proctor for Medtronic and Edwards Lifesciences. Dr.

Babaliaros is a consultant for Edwards Lifesciences; and has equity in TransMural Systems. Dr. Dimas is a consultant for Medtronic and Abbott Laboratories/St. Jude Medical. Dr. Reddy is a consultant for B. Braun Interventional Systems. Dr. Leipsic is a core laboratory consultant for Edwards Lifesciences, Medtronic, and Abbott Laboratories; and is a consultant for Circle CVI. Dr. Blanke is a consultant for Edwards Lifesciences. Dr. Gorelick is an employee of Edwards Lifesciences. Dr. Zahn is a proctor and consultant for Medtronic and Edwards Lifesciences. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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PERSPECTIVES

WHAT IS KNOWN? Congenital defects of the RVOT and PV are common and often require many invasive surgical repairs to improve patient quality of life and life span.

WHAT IS NEW? The Alterra Adaptive PreStent is a docking station that reduces RVOT diameter, creating a stable landing zone for the SAPIEN 3 29-mm THV. These devices can be deployed in 1 procedure, obviating the need for a second invasive procedure.

WHAT IS NEXT? Longitudinal studies in larger cohorts are needed to determine the durability of the Alterra Adaptive PreStent and SAPIEN 3 THV in the RVOT/PV position.

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KEY WORDS Alterra Adaptive Presept, pulmonary regurgitation, right ventricle outflow tract/pulmonary valve dysfunction, transcatheter pulmonary valve replacement, SAPIEN 3 THV

 **APPENDIX** For supplemental Methods, tables, a figure, and videos, please see the online version of this paper.