Prospective US investigational device exemption trial of a sutureless aortic bioprosthesis: One-year outcomes

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ABSTRACT

Objectives: We performed a prospective, single-arm clinical trial approved under a Food and Drug Administration Investigational Device Exemption to assess safety and efficacy of Perceval, a sutureless bovine pericardial aortic valve representing the initial US experience.

Methods: From June 2013 to January 2015, 300 patients (mean age 76.7 ± 7.7 years, 54.3% men, 37.3% ≥ 80 years, median Society of Thoracic Surgeons Predicted Risk of Mortality 2.8%), underwent Perceval valve implantation at 18 centers across the United States. Twenty patients (6.7%) had a bicuspid aortic valve and 5 (1.7%) patients had previous aortic valve replacement. A minimally invasive approach was used in 80 (26.7%) and concomitant procedures were performed in 113 (37.8%) patients.

Results: Two hundred eighty-nine patients (96.3%) were successfully implanted. Operative mortality (≤ 30 days) was 1.3% ($n = 4$) (observed to expected ratio of 0.40). One-year results included all-cause mortality in 5.2% ($n = 15$), stroke in 1% ($n = 3$), and endocarditis in 1.7% ($n = 5$). New permanent periprocedural pacemaker rate was 10.7% ($n = 30/281$); 2.5% ($n = 7/281$) resulted from third-degree atrioventricular block. One-year valve-related reoperation was 2.1% ($n = 6$). At 1-year follow-up, 98% of patients were in New York Heart Association class I/II, left ventricular mass index decreased from 103.5 ± 30.1 g/m² at discharge to 95.8 ± 27.1 g/m² ($P = .001$), and 3 (1.3%) moderate paravalvular leaks were identified. Health-related quality of life score increased from 62.7 ± 21.8 before surgery to 85.5 ± 17.8 at 1 year ($P < .001$).

Conclusions: These results confirm the safety and effectiveness of the Perceval sutureless aortic valve replacement in study patients with lower mortality than

Perceval Sutureless aortic valve.

Central Message

The results of the initial US experience for Perceval in a prospective, single-arm clinical trial confirm safety and efficacy outcomes both in isolated and combined procedures regardless of surgical approach.

Perspective

There is an extensive medical literature for Perceval from centers outside of the United States; this initial US experience further confirms sutureless aortic valve replacement is a safe and effective therapy for patients with aortic valve stenosis. The device may be used in isolated and combined procedures via open or minimally invasive approaches.

See Commentary on page 1783.

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Abbreviations and Acronyms

AVR	= aortic valve replacement
BAV	= bicuspid aortic valve
CAVALIER	= Perceval S valve clinical trial for extended CE mark
EOA	= effective orifice area
HR-QoL	= health-related quality of life
ICU	= intensive care unit
IDE	= Investigational Device Exemption
KCCQ	= Kansas City Cardiomyopathy Questionnaire
LV	= left ventricle
NYHA	= New York Heart Association
PMI	= pacemaker insertion
PVL	= paravalvular leak
STS-PROM	= Society of Thoracic Surgeons Predicted Risk of Mortality

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expected from a risk prediction model. Persistent hemodynamic benefit and improvement in quality of life at 1 year support the importance of this device in the management of aortic valve disease. (*J Thorac Cardiovasc Surg* 2019;157:1773-82)

Aortic valve replacement (AVR) is the procedure of choice for patients with severe symptomatic aortic stenosis.¹ These patients often have multiple age-related comorbidities that may increase the risk of conventional surgical AVR.²⁻⁴ Sutureless AVR has emerged as a promising technique with good hemodynamic properties and is a viable option for patients with high surgical risk.⁵ The concept of sutureless bioprosthetic aortic valves combines the advantage of aortic annular debridement and the possibility of performing concomitant procedures with shorter aortic crossclamp and procedural times compared with standard surgical AVR. The Perceval Sutureless Aortic Valve Prosthesis (LivaNova, London, United Kingdom) was introduced in 2007. Three European trials have demonstrated its safety and efficacy in intermediate- and high-risk patients with severe symptomatic aortic stenosis.⁶⁻¹⁰ Shorter procedure times, favorable hemodynamic performance, and facilitation of

minimally invasive surgical approaches have been documented in this experience.

The first North-American experience occurred in Canada and confirmed excellent short-term hemodynamic performance and clinical outcomes.¹¹ The current report documents the initial US experience, which was a prospective trial performed under a Food and Drug Administration Investigational Device Exemption (IDE).

METHODS**Study Design**

The Perceval IDE trial was designed as a multicenter, prospective, non-randomized, single-arm clinical trial (NCT01810679; www.clinicaltrials.gov) to evaluate the safety and efficacy of the Perceval valve (LivaNova). The institutional review board at each participating institution approved the study, and all patients provided written informed consent. Inclusion and exclusion criteria are listed in [Table E1](#) and the investigational plan is provided as an [Online Data Supplement](#).

An independent Clinical Events Committee adjudicated all reported instances of death, explantation, valve dysfunction, and adverse events as requested by the investigators or the independently appointed Data Safety Monitoring Board during their periodic review. The investigators had full authority to publish the data without restriction from the sponsoring company.

Surgical Technique

The Perceval sutureless valve is a new-generation bioprosthetic aortic valve composed of glutaraldehyde-fixed bovine pericardial leaflets treated with homocysteic acid to mitigate calcification within a stent made of a super-elastic nickel–titanium alloy (Nitinol) covered by Carbofilm (LivaNova) ([Figure 1](#)). The features and implantation regimen have been described previously.¹² To summarize, the valve is collapsed with a dedicated accessory device and is deployed using a delivery system with step-wise release of the valve inflow and outflow, followed by postimplantation dilation performed with a specifically designed low-pressure balloon catheter at 4 atmospheres pressure. The valve is available in 4 sizes: S, M, L, and XL, corresponding to annulus sizes from 19 to 27 mm.

In the present study, the valve was implanted via full median sternotomy, partial upper sternotomy, or right anterolateral thoracotomy, according to individual surgeon preference. Postoperative anticoagulation was left to the discretion of individual investigators and was performed according to patients' clinical status and individual center standard practice.

Follow-up

Patients were evaluated at the following time points: preoperatively, at hospital discharge/within 30 days, postoperatively between 3 and 6 months, and at 12 months. All patients underwent clinical evaluation, laboratory testing, and transthoracic echocardiography at each follow-up visit. Intraoperative transesophageal echocardiography was used in all patients.

Echocardiography

Aortic geometry and diameters were determined from 2-dimensional parasternal long-axis views. Subaortic and aortic Doppler flow velocities were recorded from the apical 3-chamber or 5-chamber view using pulse-wave and continuous-wave Doppler, respectively. Peak and mean aortic valve pressure gradients and effective orifice area (EOA) were ascertained; peak and mean aortic valve pressure gradients were calculated from velocity measurements using a modified Bernoulli equation.¹³ All echocardiographic examinations were blinded for patient status and analyzed by an independent echocardiography core laboratory (MedStar Health Research Institute, Washington, DC).

FIGURE 1. Perceval sutureless aortic valve.

Quality of Life

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess disease-specific health status, and its overall summary score to provide health-related quality of life (HR-QoL) measures for each patient. The KCCQ is a 23-item questionnaire designed and validated for self-reported health status in patients with heart failure.¹⁴ The conceptual domains of the KCCQ include symptoms, physical limitation, social limitation, self-efficacy, and quality of life. These scales, as well as an overall summary scale, are scored from 0 to 100, with greater scores indicating fewer symptoms and better HR-QoL.

Study Objectives and End Points

The Perceval US IDE Trial was designed to assess device safety and effectiveness. Safety of the Perceval valve was evaluated based on the following adverse events: valve thrombosis, thromboembolism, perivalvular leak (all and major), hemorrhage (all and major), and endocarditis. The primary composite effectiveness endpoints included implant success (defined as leaving the operating room with the originally implanted Perceval valve in place); absence of moderate-to-severe paravalvular leak (PVL); freedom from structural dysfunction; and absence of migration. Secondary effectiveness endpoint was implant success in all patients with an attempted implant ($n = 300$). [Video 1](#) provides a summary of the main features of the present study.

Data Analysis

Categorical variables are reported as absolute and relative frequencies. For continuous data, means and standard deviations were calculated. Where clinically relevant, statistical comparisons between groups were performed using the Fisher exact test for categorical data and Student t test for continuous data.

Cumulative survival and freedom from events were estimated using the Kaplan–Meier method, with 95% confidence intervals until a cut-off follow-up of 365 days. The degree of uncertainty in each actuarial analysis

VIDEO 1. This narrated video describes the main features of the Investigational Device Exemption trial as well as the main advantages related to the use of the Perceval valve, demonstrating the unique features of this sutureless aortic valve. Video available at: [https://www.jtcvs.org/article/S0022-5223\(18\)32824-1/fulltext](https://www.jtcvs.org/article/S0022-5223(18)32824-1/fulltext).

is expressed with 95% confidence limits. The 95% confidence interval bounds for the cumulative freedom were calculated according to the method proposed by Greenwood.¹⁵

Site-reported adverse events at 30 days (0-30 days), at 3 to 6 months, and at 1-year rates were reported as number of events divided by the total number of patients in which the implant was attempted.¹⁶ Statistical analyses were performed using SAS software (version 9.4; SAS Institute Inc, Cary, NC). For all tests, a P of .05 or less (2-sided) was considered as statistically significant, unless otherwise specified.

RESULTS

Patients Characteristics

From June 2013 to January 2015, a total of 356 patients were enrolled from 18 US centers. Fifty-six (15.7%) patients were excluded according to predetermined criteria ([Figure E1](#)) because of patient anatomic reasons ($n = 14$, 25%), aortic annulus size exceeding the largest available prosthesis size ($n = 14$, 25%), patient/surgeon preference ($n = 16$, 29.1%), other reasons ($n = 9$), and patient death before surgery ($n = 3$, 5.4%). Anatomic reasons for study exclusion included patients with a ratio of the diameters of the sino-tubular junction to the aortic annulus greater than 1.3 ($n = 4$), aortic root aneurysm ($n = 4$), bicuspid valve ($n = 1$), enlarged annulus ($n = 1$), unspecified anatomic reasons ($n = 2$), heavily calcified aorta ($n = 1$), and concentric left ventricular hypertrophy ($n = 1$).

A Perceval valve was successfully implanted in 289 of 300 patients for a success rate of 96.3%. Eleven patients had an unsuccessful implantation attempt: 6 patients had the valve removed due to PVL ($n = 4$), or device dislodgement ($n = 2$), with the subsequent decision to proceed with standard surgical valve replacement; 2 patients could not be

sized appropriately due to bicuspid valve disease ($n = 1$) or an annulus outside the study parameters ($n = 1$); 2 patients suffered annular bleeding probably related to annular debridement and required standard AVR; 1 patient suffered a limited aortic dissection related to aortic calcification and required root replacement.

Mean age was 76.7 ± 7.7 years, and 37.3% ($n = 112$) of patients were octogenarians. The median Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) was 2.8 (interquartile range of 1.9-4.2). The majority of patients underwent full sternotomy ($n = 220$; 73.3%), and 43.3% received a size L ($n = 130$). Coronary artery bypass grafting was the most common concomitant procedure ($n = 89$; 29.7%). Overall mean aortic crossclamp time was 53.2 ± 22.8 minutes, 44.5 ± 13.8 minutes for isolated AVR and 71 ± 21.5 minutes for AVR with concomitant procedures. Preoperative and operative patient data are shown in Tables 1 and 2, for the overall patient cohort and for patients with bicuspid aortic valve (BAV). Mean intensive care unit (ICU) and hospital length of stay were 3.1 ± 3.0 days and 8.0 ± 4.7 days, respectively. Mean ICU and hospital lengths of stay were longer for the initial 20 patients included in each center compared with patients managed later in the experience (ICU: 3.4 ± 3.4 vs 2.4 ± 1.8 days; length of stay: 8.4 ± 4.9 vs 7.1 ± 4.2).

At discharge, the majority of patients (56.1%; 161/287) were on single antiplatelet therapy (acetylsalicylic acid, clopidogrel, other) or in combination with oral anticoagulants (warfarin) (24.7%; 71/287). Only 1 patient was maintained on warfarin alone. Dual antiplatelet therapy was given to 17.4% (50/287) of patients. At 1 year, 63.3% of patients (155/245) were treated with single antiplatelet therapy, or in combination with oral anticoagulants (14.3%; 35/245); the remaining patients were on dual antiplatelet therapy (10.2%; 25/245) or on warfarin alone (5.7%; 14/245).

Periprocedural Outcomes

Four patients died after Perceval implantation before discharge, for an operative mortality of 1.3%. Three patients (0.7%) died due to cardiovascular causes (bleeding from aortic tear 5 days after procedure, cardiopulmonary arrest 3 days postsurgery, and 1 procedure-related death 3 days postsurgery due to aortic dissection in a patient who experienced a failure to implant of the Perceval valve and underwent a traditional valve implant) and 1 (0.3%) due to noncardiovascular cause (ischemic hepatitis 3 days after surgery) (Table 3). A stroke occurred in 2 patients (0.7%), and a postoperative pacemaker implantation (PMI) was required in 10.7% (30/281); 2.5% (7/281) of these resulted from third-degree atrioventricular block.

Time-Related Outcomes

Mortality. A total of 11 late deaths occurred between the 30-day and 1-year time points including 6 (2.1%) due to

TABLE 1. Baseline characteristics: implant attempted patients (N = 300)

Variables	Number (%) or mean $\pm$ SD	
Demographic	All (N = 300)	BAV (N = 20)
Age, y	76.7 ± 7.7	67.9 ± 7.1
<80	188 (62.7)	19 (95)
≥ 80	112 (37.3)	1 (5)
BSA, m ²	1.9 ± 0.3	1.9 ± 0.2
Sex, male	163 (54.3)	10 (50)
Previous cardiac procedures*		
Cardiac surgery	40 (13.3)	1 (5)
AVR	5 (1.7)	1 (5)
Aortic valve repair	1 (0.3)	–
Aortic aneurysm repair	1 (0.3)	–
CABG	13 (4.3)	–
Others	10 (3.3)	–
Cardiac interventional procedures	125 (41.7)	4 (20)
PCI/PCI + stent	57 (19.0)	1 (5)
Pacemaker/defibrillator	19 (6.3)	–
Other	49 (16.3)	3 (15)
Risk score		
Mean STS score	3.3 ± 2.3	2.0 ± 1.5
Median STS score [Q1; Q3]	2.8 [1.9; 4.2]	1.4 [1.0; 3.0]
NYHA class		
I	22 (7.5)	3 (15)
II	146 (49.5)	13 (65)
III	118 (40.0)	4 (20)
IV	9 (3.1)	0 (0)
Missing	5	–
Preoperative comorbidities		
Dyslipidemia	256 (85.3)	17 (85)
Hypertension	246 (82.0)	13 (65)
Coronary artery disease	179 (59.7)	7 (35)
Angina	65 (21.7)	3 (15)
Tobacco use	166 (55.3)	6 (30)
Diabetes	103 (34.3)	8 (40)
Arrhythmia	95 (31.7)	5 (25)
Chronic lung disease	72 (24.0)	3 (15)
Cerebrovascular disease	39 (13.0)	1 (5)
Peripheral vascular disease	34 (11.3)	3 (15)
Pulmonary hypertension	32 (10.7)	3 (15)
Myocardial infarction (>30 d)	30 (10.0)	0 (0)
Pre-existing conduction abnormality	27 (9.0)	1 (5)
Renal failure	15 (5.0)	0 (0)
Neurologic dysfunction	11 (3.7)	1 (5)
Immunosuppressive treatment	8 (2.7)	1 (5)
Hemodynamic characteristics		
Left ventricular ejection fraction	60.5 ± 9.9	64.7 ± 7.5
Mean aortic gradient, mm Hg	45.4 ± 14.7	50.4 ± 10.9
Effective orifice area, cm ²	0.8 ± 0.2	0.7 ± 0.2

SD, Standard deviation; BAV, bicuspid aortic valve; BSA, body surface area; AVR, aortic valve replacement; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; STS, Society of Thoracic Surgeons; Q1; Q3, interquartile range; NYHA, New York Heart Association. *Subjects may have more than one previous cardiac procedures.

TABLE 2. Operative characteristics: implanted attempted patients (N = 300)

	Number (%) or mean $\pm$ SD	
	All (N = 300)	BAV (N = 20)
Surgical approach		
Full sternotomy	220 (73.3)	13 (65.0)
Minimally invasive	80 (26.7)	7 (35.0)
Mini-sternotomy	67 (22.3)	4 (20.0)
Right anterior thoracotomy	3 (1.0)	3 (15.0)
Minimally invasive unspecified	10 (3.3)	—
Aortic valve diagnosis		
Stenosis	169 (56.3)	12 (60.0)
Stenoregurgitation	126 (42.0)	8 (40.0)
Previous prosthetic structural valve deterioration	5 (1.7)	—
Aortic valve etiology		
Calcification	291 (97.0)	19 (95.0)
Congenital bicuspid valve	20 (6.7)	—
Prosthetic valve in place	5 (1.7)	—
Other etiology*	7 (2.3)	1 (5.0)
Valve size		
S	21 (7.0)	3 (15.0)
M	101 (33.7)	6 (30.0)
L	130 (43.3)	9 (45.0)
XL	48 (16.0)	2 (10.0)
Procedure†		
Isolated AVR	186 (62.2)	15 (78.9)
Concomitant procedures‡	113 (37.8)	4 (21.1)
CABG	89 (29.7)	4 (21.1)
LAA ligation/exclusion	20 (6.7)	—
Septal myectomy	3 (1.0)	—
Maze/ablation	1(0.3)	—
Other procedures§	15 (5.0)	—
Surgical time		
Perceval implant time, min	22.1 $\pm$ 20.8	25.7 $\pm$ 40.1
Crossclamp time, min	53.2 $\pm$ 22.8	52.3 $\pm$ 19.6
Cardiopulmonary bypass time, min	75.0 $\pm$ 30.9	70.2 $\pm$ 27.8

SD, Standard deviation; BAV, bicuspid aortic valve; AVR, aortic valve replacement; CABG, coronary artery bypass graft; LAA, left atrial appendage. *Subject may have more than 1 etiology. Other etiology includes congenital anomaly, rheumatic heart disease, and collagen vascular disease. †Missing information for 1 patient in the bicuspid cohort. ‡Subject may have more than 1 concomitant procedure. §Other procedures include annular repair (2), endarterectomy of ascending aorta, repair of right ventricular laceration, proximal aortic endarterectomy, lung resection (2), intra-aortic balloon pump implant, other noncardiac procedures.

cardiovascular causes: cardiorespiratory failure ($n = 3$), acute myocardial ischemia ($n = 2$), and endocarditis ($n = 1$). Five late deaths were due to noncardiovascular events (Table 3). All-cause mortality at 1 year was 3.8% ($n = 7/182$) for isolated AVR and 7.5% ($n = 8/107$) for AVR with concomitant cardiac procedures. Survival was 96.18% at 3 to 6 months and 94.74% at 12 months (Figure 2, A).

Adverse events. Freedom from valve reoperation was 97.83% at 1 year (Figure 2, B). Six patients had valve explant; 3 patients due to endocarditis at 109, 116, and 225 days after implantation, 2 patients due to aortic insufficiency at 111 and 337 days, and 1 at 16 days due to severe valve stenosis caused by a stent deformation after chest compression. Nonstructural valve dysfunction occurred in 10 patients (3.5%), endocarditis in 5 patients (1.7%), and thromboembolism in 7 patients (2.4%). Freedom from stroke was 98.9% (Figure 2, C). Major bleeding was reported for 38 patients (13.1%), of whom 8 (2.8%) required re-exploration. No occurrence of valve thrombosis was seen as confirmed by echocardiographic examinations (Table 3).

Hemodynamics. The overall mean gradient at discharge was 11.8 mm Hg and decreased to 9.6 mm Hg at 1 year (Table 4). Left ventricle (LV) mass index decreased from 103.5 ± 30.1 g/m² at discharge to 95.8 ± 27.1 g/m² at 1-year follow-up ($P = .001$). Moderate or greater paravalvular insufficiency was observed in 1 patient (0.4%) at discharge and 3 patients (1.3%) at 12-months follow-up. Moderate or greater valvular insufficiency occurred in 0.7% (2/274) patients at discharge and 2.9% (7/236) patients at 1 year (Table E2). Hemodynamic data by valve size are provided in Tables E3 and E4.

Functional health status. Patients' health status improved during follow-up, and 81.2% of patients increased at least 1 New York Heart Association (NYHA) class. At 1-year follow-up, 97.6% of patients were in NYHA class I/II (Figure 3). The KCCQ summary score improved from 62.7 ± 21.8 before surgery to 85.5 ± 17.8 at 1 year ($P < .001$).

BAV patients. Perceval valve implantation was attempted in 20 patients presenting with congenital BAV and successfully implanted in 17 (85%). Preoperative and operative patient data are shown in Tables 1 and 2. The mean age of the BAV patients was 67.9 ± 7.1 , with preoperative STS-PROM of 2.0 ± 1.5 . No deaths, no primary PVL, thromboembolism, or stroke were reported in this group of patients. Two explants occurred due to endocarditis (109 and 225 days after surgery), and 1 new PMI was reported. Hemodynamic findings in the BAV group showed stable improvement in gradients during follow-up. NYHA functional class also improved in 66.7% of the BAV group at 1-year follow-up, with 93.3% of patients in NYHA class I/II.

DISCUSSION

The Perceval valve has been used for AVR since 2007 in multiple European centers participating in consecutive clinical trials.⁶⁻¹⁰ Perceval S valve clinical trial for extended CE mark (CAVALIER) trial initiated in 2010 was the largest, prospective study, involving 658 patients up to a 5-year follow-up.⁸⁻¹⁰ The present IDE trial details the outcomes

TABLE 3. Postoperative complications

Complications	Early (discharge or ≤ 30 d)		Total at 6 mo (0-180 d)		Total at 1 y (0-365 d)	
	All (N = 300) n (%)	BAV (N = 20) n (%)	All (N = 289) n (%)	BAV (N = 17) n (%)	All (N = 289) n (%)	BAV (N = 17) n (%)
All deaths	4 (1.3)	0 (0)	11 (3.8)	0 (0)	15 (5.2)	0 (0)
Cardiovascular	3 (1.0)	0 (0)	7 (2.4)	0 (0)	9 (3.1)	0 (0)
Noncardiovascular	1 (0.3)	0 (0)	4 (1.4)	0 (0)	6 (2.1)	0 (0)
Device explant	1 (0.3)	0 (0)	2 (0.7)	0 (0)	6 (2.1)	2 (11.8)
Thromboembolism	5 (1.7)	0 (0)	6 (2.1)	0 (0)	7 (2.4)	0 (0)
Stroke	2 (0.7)	0 (0)	3 (1.0)	0 (0)	3 (1.0)	0 (0)
NSVD	7 (2.3)	0 (0)	9 (3.1)	0 (0)	10 (3.5)	0 (0)
Endocarditis	0 (0)	0 (0)	4 (1.4)	1 (5.9)	5 (1.7)	2 (11.8)
Hemolysis (minor)	5 (1.7)	0 (0)	12 (4.1)	1 (5.9)	13 (4.5)	1 (5.9)
Valve thrombosis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
New PMI*	30 (10.7)	1 (5.0)	35 (12.9)	1 (5.9)	37 (13.7)	1 (5.9)
Atrioventricular block III leading to new PMI*	7 (2.5)	0 (0)	8 (3.0)	0 (0)	8 (3.0)	0 (0)
Renal failure	9 (3.0)	1 (5.0)	12 (4.1)	1 (5.9)	15 (5.2)	2 (11.8)
Myocardial infarction	1 (0.3)	0 (0)	5 (1.7)	0 (0)	6 (2.1)	1 (5.9)
Major bleeding	32 (10.7)	1 (5.0)	35 (12.1)	1 (5.9)	38 (13.1)	1 (5.9)

BAV, Bicuspid aortic valve; NSVD, nonstructural valve dysfunction; PMI, pacemaker insertion. *Patients without preoperative pacemaker, N = 281 at discharge or ≥ 30 days, N = 271 at 6 months and 1 year.

of the Perceval valve in a multicenter prospective study and represents the initial US experience with the valve. This study was performed with data adjudicated by a Clinical Events Committee, oversight by an independent Data Safety Monitoring Board, and review of echocardiographic studies by a core imaging laboratory.

Perceval was successfully implanted in more than 96% of patients. The main anatomic reasons for implant exclusion was the presence of aneurysm or enlargement of the ascending aorta with a sino-tubular junction/aortic annulus ratio greater than 1.3. Eleven patients had an unsuccessful implant due to intraoperative PVL, annular size outside the available valve sizes, and aortic root bleeding in 3 patients. The 30-day and 12-month all-cause mortality rates were 1.3% and 5.2%, respectively, whereas event rates including stroke, endocarditis, device explant, and

structural valve dysfunction were low. The Perceval valve generally demonstrated good hemodynamic performance as measured with low transvalvular mean and peak gradients, and regression of LV mass index. Clinical status of patients improved, with 97.6% of patients enjoying NYHA function class I/II status at 1 year. Furthermore, HR-QoL scores significantly increased from 62.7 ± 21.8 before surgery to 85.5 ± 17.8 at 1 year ($P < .001$).

The short crossclamp time and cardiopulmonary bypass time in isolated AVR reported in this series may have potentially contributed to improved outcomes as demonstrated by the low operative mortality compared with the STS-PROM of 2.8%. Similar reductions in operative times corroborate results in the existing literature; the CAVALIER investigators reported crossclamp and cardiopulmonary bypass times of 41 and 65 minutes, respectively.⁹

FIGURE 2. Survival at 12 months (A), freedom from explants (B), and freedom from stroke (C).

TABLE 4. Time-related hemodynamic changes

	Discharge/30 d				3-6 mo				12 mo			
	All,		BAV,		All,		BAV,		All,		BAV,	
	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)	N	mean (SD)
Aortic mean gradient, mm Hg	245	11.8 (5.4)	15	12.2 (4.4)	233	10.0 (4.9)	15	10.9 (6.2)	216	9.6 (4.5)	13	10.3 (3.7)
Cardiac output, L/min	229	4.8 (1.2)	14	5.0 (1.1)	233	4.8 (1.1)	15	5.6 (1.2)	212	4.8 (1.1)	13	4.9 (0.8)
EOA (TVI), cm	229	1.4 (0.4)	14	1.4 (0.3)	230	1.5 (0.4)	15	1.6 (0.5)	213	1.5 (0.4)	13	1.6 (0.3)
EOAi, cm ² /m ²	229	0.7 (0.2)	14	0.7 (0.2)	230	0.8 (0.2)	15	0.8 (0.3)	213	0.8 (0.2)	13	0.8 (0.2)
Stroke volume, mL	230	64.4 (15.7)	14	66.6 (10.7)	233	73.7 (15.9)	15	83.3 (15.8)	213	75.4 (18.1)	13	78.3 (15.5)
LV mass, g	245	200.9 (64.5)	14	192.3 (37.7)	233	195.7 (63.4)	14	182.6 (40.8)	220	187.5 (60.6)	13	183.2 (35.7)
LV mass index, g/m ²	245	103.5 (30.1)	14	99.1 (21.1)	233	99.8 (28.5)	14	93.1 (19.2)	220	95.8 (27.1)	13	92.5 (20.1)

SD, Standard deviation; BAV, bicuspid aortic valve; EOA, effective orifice area; TVI, time velocity integral; EOAI, effective orifice area index; LV, left ventricle.

Mortality and Morbidity

The overall 1-year mortality results in the present study (94.7%) are similar to those for the recently published CAVALIER trial (95%).^{9,10} Compared with the CAVALIER trial, 30-day mortality was lower in the Perceval US IDE trial (US IDE 1.3% vs CAVALIER 3.7%), as was the mean length of hospital stay (US IDE 8 vs CAVALIER 12 days). This may in part be related to the lower risk profile of patients in the present study (median STS-PROM US IDE 2.8 vs CAVALIER 4.1). Likewise, 12 months after implantation, all-cause mortality (5.2% vs 8.1%), thromboembolism (2.4% vs 6.2%), and stroke rate (1% vs 3%) were lower for in the US IDE trial versus CAVALIER respectively. Recent results from the German Aortic Valve Registry reported greater stroke rates for sutureless and rapid deployment valves as a class compared with standard surgical AVR; however, the rates reported for sutureless/rapid deployment valves were

substantially greater than the stroke rate observed in the current study.¹⁷

Nonstructural valve dysfunction was reported in 10 patients, 7 of whom presented in the early postoperative period and were most likely due to initial malpositioning or oversizing of the valve. The rates of other valve-related adverse events were similarly infrequent and the clinical status of patients significantly improved in both the US IDE and the CAVALIER trials.^{9,10}

Although a significant majority of patients were successfully implanted, early experience with a novel technology likely contributed in some cases. There is no clear explanation for a somewhat-elevated occurrence of major bleeding compared with what might be expected for standard AVR; however, this complication has not previously been reported as a significant issue in the literature for the Perceval valve. In 3 cases, implantation was unsuccessful due to significant root complications (annular bleeding in 2 cases; limited aortic dissection requiring root replacement in one case). Aortic root bleeding observed in this study was likely the result of annular debridement resulting in a full-thickness injury to the aortic annulus. Suture placement during standard surgical AVR might normally be expected to repair this type of injury during implant. It is important to note that due to the absence of annular sutures, full-thickness disruptions of the aortic wall should be identified and securely repaired before Perceval implantation.

In the present study, the need for new PMI appears to be greater compared with conventional valves, with the reported need for PMI ranging from 3.0% to 11.8% after conventional AVR.¹⁸ The Perceval IDE trial represents the initial US experience for the Perceval valve, and there has been a subsequent emphasis on approaches to avoid damage to the conduction system during implantation with particular attention to the depth of implantation. Current practice has evolved with demonstration that optimal positioning of the valve is achieved by placement of the guiding sutures, approximately 2 to 3 mm below the leaflet hinge point as

FIGURE 3. NYHA class changes from preoperative to 12 months. NYHA, New York Heart Association.

stated in the current US Instructions for Use to avoid damage to the conduction system, while maintaining secure placement of the valve.

The importance of implantation depth for pacemaker implantation is highlighted by the recent report from Yanagawa and colleagues,¹⁹ who identified an association between deeper positioning of the prosthesis in the LV outflow tract and postoperative conduction disorders. After modifying their implantation technique by placing the guiding sutures closer to the point of leaflet insertion in the annulus, the authors reduced their pacemaker implantation rate for Perceval from 28% to 0%. Fischlein and colleagues²⁰ also reported improvement for pacemaker rates from an initial value of 10% to a current rate of 3%, as they achieved greater experience with this new technology. Recently published large registry experiences^{17,21} have also reported greater PMI rates compared with standard surgical AVR; however, results from Sutureless and Rapid-Deployment Aortic Valve Replacement International Registry, an international registry of more than 3300 patients undergoing sutureless or rapid deployment AVR, reported a significant decrease in PMI rates over time that the authors attributed to the learning curve for these new valve technologies (from 17.2% in 2007 to 5.4% in 2016).

Hemodynamics

Our study corroborates previous European trials that have demonstrated good hemodynamic performance of Perceval. Significant reduction of transvalvular peak and mean pressure gradient in addition to increased EOA index of the valve resulted in significant regression of LV mass, accompanied by improved NYHA classification status and HR-QoL scores. Overall discharge transprostheses mean gradients were minimally greater than the CAVALIER trial (11.8 mm Hg vs 10.2 mm Hg), whereas EOA values were comparable with CAVALIER results.¹⁰ Mean gradients continued to decrease after discharge and were 9.6 mm Hg for the overall cohort at 1 year of follow-up.

Small sizes showed a greater rate of PPM along with greater transvalvular gradients that decreased at 1-year follow-up. Recent literature has demonstrated that PPM after standard AVR in small-sized bioprostheses is a common finding, particularly when rigorous core laboratory assessments are performed.²² PPM is also greatly affected by patient selection, and the implanting surgeon must consider the appropriate valve and implant techniques required to minimize high gradients and resultant PPM. Rates of moderate or greater isolated PVL were around 1% in the present study, and the presence of moderate or greater central aortic regurgitation was less than 3% at 1-year follow-up. PERSIST-AVR (Perceval Sutureless Implant Versus Standard Aortic Valve Replacement trial, NCT02673697) is an ongoing randomized control trial comparing Perceval to

standard surgical AVR and will be instructive to further establish hemodynamic outcomes.

Functional Status and Quality of Life

Consistent with the reported postoperative hemodynamics, significant and stable improvement of NYHA functional class was observed in the majority of patients. More than 80% of patients in the current trial demonstrated functional status improvement, and 97% of patients were in NYHA class I or II at 1 year. HR-QoL, as measured by the KCCQ summary score, also improved significantly at 12 months, demonstrating a substantial clinical improvement in this patient group. Isolated AVR patients from the Perceval IDE study had a mean increase of more than 20 points in the HR-QOL score at follow-up (22 from baseline to 3-6 months; 22.3 from baseline to 12 months).

BAV Patients

Although a minority of patients in this trial had BAV morphology (N = 20), the present study represents a unique experience compared with previous European trials, which excluded this population. Several recent publications have addressed BAV patients and their potential suitability for Perceval valve implantation. An International Expert Consensus Panel publication advised that congenital BAV patients without raphe (Sievers Type 0) should be avoided for sutureless/rapid deployment AVR, whereas those with 1 or 2 raphe (Sievers Type 1 and 2, respectively) might be considered contingent upon appropriate dimensions of the aortic annulus and ascending aorta.²³ Clinical series recently reported the outcomes of BAV patients successfully managed with Perceval and have provided guidance regarding patient selection and surgical technique.^{24,25} The results of the current report confirm that appropriately selected BAV patients can be successfully treated with Perceval valve.

Limitations

One of the limitations of this study is the relatively short period of follow-up (1 year). These short-term results will need to be supported by studies of greater duration to gain a complete understanding of long-term outcomes for Perceval.

The relatively small proportion of BAV patients included in the present study might be due to the frequent association of this condition with aortic root enlargement or aneurysm, which were exclusion criteria in this trial, therefore potentially reducing the number of eligible BAV patients. Another limitation is incomplete clinical data arising from 11 unsuccessfully implanted patients. These patients were withdrawn from the study and as per study protocol, their clinical data after the perioperative period were not collected. This is a prospective single-arm study that was not intended as a comparative study against other valves,

and so is unable to demonstrate superiority or noninferiority in terms of safety and effectiveness versus any other technology. Larger randomized trials are required to provide Level I evidence in this regard. As mentioned, a large prospective, randomized controlled trial comparing the Perceval valve with standard surgical AVR is currently ongoing to provide greater understanding of the role of Perceval in the surgical management of aortic valve disease. Finally, since the Perceval IDE study is an investigational study of selected patients meeting specific inclusion/exclusion criteria, more data from real-world experience will be needed to fully understand the performance in the general patient population further confirm the findings from this study.

CONCLUSIONS

These US IDE trial results confirm the safety and efficacy of the Perceval sutureless bioprosthesis for replacement of the diseased aortic valve in selected study patients. Despite implantation failure in 3 patients (3/300) due to aortic annular bleeding, we observed low 1-year mortality, stroke, explantation, and valve-related event rates along with stable hemodynamic performance that accompanied significant reduction of transvalvular pressure gradients and LV mass index. Patient quality of life improved significantly, and greater than 90% of the cohort were in NYHA class of I/II after 1 year of follow-up. PMI and aortic regurgitation are inherent potential risks with the Perceval valve, and randomized trials comparing the Perceval to standard sutured prostheses will be instructive to further define outcomes.

Conflict of Interest Statement

Dr Heimansohn: Proctor LivaNova; Patient Selection Committee, Abbott Vascular. Dr Weissmann: research support recipient from Boston Scientific, Medtronic, Edwards Lifesciences, St. Jude Medical, Abbott Vascular, LivaNova. Dr Ailawadi: speaker for Atricure, Convatec; consultant for Abbott Vascular, Edwards Lifesciences, Medtronic, St Jude Medical. Dr Ad: consultant for Cryolife, Atricure, Medtronic, LivaNova; shareholder of Nido Surgical; co-owner LAA occlusion LLC. Dr Thourani: consultant for Edwards Lifesciences, Abbott Vascular; research recipient from Edwards Lifesciences, Abbott Vascular, Boston Scientific, Medtronic. Dr Szeto: speaker for Abbott Vascular, St Jude Medical; consultant for Microinterventional Device; research support recipient from LivaNova, Edwards Lifesciences, Medtronic. Dr Michler: NIH U01 Principal Investigator; Dr Michelena: advisor of Cryolife On-X valve. Dr Dabir: proctor for LivaNova. Dr Moront: Medtronic Heart Valves, consultant and proctor; Edwards LifeSciences, consultant; LSI, consultant; Terumo, consult and trainer. Dr Subramanian: consultant and proctor for LivaNova. Dr Roselli: Speaker for Edwards Lifesciences, St Jude Medical, Vascutek; consultant for Medtronic, LivaNova. All

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Key Words: aortic valve replacement, sutureless valve, aortic stenosis, minimally invasive surgery, hemodynamics, quality of life, concomitant procedures

FIGURE E1. Patient flow chart of the Perceval Investigational Device Exemption trial. *IDE*, Investigational Device Exemption.

TABLE E1. Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
1. Subjects of age >18 years.	1. The subject has pre-existing valve prosthesis or annuloplasty ring in the mitral, pulmonic, or tricuspid position.
2. Subjects with aortic valve stenosis or stenoin insufficiency.	2. The subject requires a double or multiple valve replacement or repair of the mitral, tricuspid, or pulmonic valve.
3. The subject is willing to sign the informed consent.	3. The subject has a previously implanted Perceval valve that requires replacement.
4. The subject in which preoperative evaluation indicated the need for native or prosthetic aortic valve replacement.	4. Subjects requiring simultaneous cardiac procedures, apart from septal myectomy and/or coronary bypass.
5. The subject is located in a geographic location that will enable the subject to return to the study site for all follow-up examinations (ie, geographically stable).	5. The subject has active endocarditis.
6. Subject will be available to the investigator(s) for postoperative follow-up beyond 1 year.	6. Subjects with active myocarditis.
	7. The subject is or will be participating in a concomitant research study of an investigational product.
	8. Subjects with aneurysmal dilation or dissection of the ascending aortic wall.
	9. The subject is a minor, drug abuser, alcohol abuser, prison inmate, institutionalized, or is unable to give informed consent.
	10. The subject has a major or progressive noncardiac disease that, in the investigator's experience, results in a life expectancy of less than 1 year, or the implant of the device produces an unacceptable increased risk to the patient.
	11. Subjects with known hypersensitivity to nickel alloys.
	12. The subject is undergoing renal dialysis for chronic renal failure or has hyperparathyroidism.
	13. The subject has had an acute preoperative neurologic deficit, myocardial infarction, or cardiac event that has not returned to baseline or stabilized for ≥ 30 days before the planned valve implant surgery.
	14. Subject is known to be noncompliant or is unlikely to complete the study.
	15. Subjects with an aortic root enlargement, where the ratio between the diameter of the sino-tubular junction and the annulus diameter, assessed by TTE, is > 1.3 .

TTE, Transthoracic echocardiography.

TABLE E2. Aortic regurgitation—echocardiographic core laboratory assessment

	Discharge/30 d				3-6 mo				12 mo			
	All (N = 274)	%	BAV (N = 17)	%	All (N = 249)	%	BAV (N = 15)	%	All (N = 236)	%	BAV (N = 13)	%
PVL												
None/trace	250	91.2	12	70.6	221	88.8	15	100	217	91.9	13	100
Mild	8	2.9	2	11.8	13	5.2	0	0	9	3.8	0	0
Moderate or greater	1	0.4	0	0	3	1.2	0	0	3	1.3	0	0
Not evaluable	15	5.5	3	17.6	12	4.8	0	0	7	3.0	0	0
Central regurgitation												
None/trace	201	73.4	9	52.9	163	65.5	10	66.7	137	58.1	7	53.8
Mild	56	20.4	5	29.4	65	26.1	3	20.0	83	35.2	4	30.8
Moderate or greater	2	0.7	0	0	11	4.4	2	13.3	7	2.9	2	15.4
Not evaluable	15	5.5	3	17.6	10	4.0	0	0	9	3.8	0	0
Total aortic regurgitation												
None/trace	197	71.9	9	52.9	155	62.2	10	66.7	132	55.9	7	53.8
Mild	65	23.7	5	29.4	71	28.5	3	20.0	91	38.6	4	30.8
Moderate or greater	5	1.8	1	5.9	20	8.0	2	13.3	13	5.5	2	15.4
Not evaluable	7	2.6	2	11.8	3	1.2	0	0	0	0	0	0

BAV, Bicuspid aortic valve; PVL, paravalvular leak.

TABLE E3. Hemodynamic performance evaluated by transthoracic echocardiography

	Discharge/30 d		3-6 mo		12 mo	
	N	Mean (SD) [min-max]	N	Mean (SD) [min-max]	N	Mean (SD) [min-max]
Aortic mean gradient, mm Hg						
Size S	17	16.0 (6.9)	15	13.5 (8.9)	13	12.6 (5.6)
Size M	79	13.6 (5.9)	72	11.5 (4.4)	66	10.9 (4.9)
Size L	107	11.0 (4.7)	103	9.4 (4.4)	98	9.0 (3.8)
Size XL	42	8.8 (3.4)	43	7.6 (2.9)	39	7.7 (4.1)
EOA (TVI), cm ²						
Size S	16	1.1 (0.2)	15	1.1 (0.2)	13	1.1 (0.2)
Size M	73	1.3 (0.3)	70	1.4 (0.4)	66	1.4 (0.4)
Size L	101	1.5 (0.4)	102	1.6 (0.4)	95	1.6 (0.3)
Size XL	39	1.7 (0.4)	43	1.7 (0.4)	39	1.7 (0.4)
EOAi, cm ² /m ²						
Size S	16	0.6 (0.2)	15	0.6 (0.2)	13	0.7 (0.2)
Size M	73	0.7 (0.2)	70	0.8 (0.2)	66	0.8 (0.2)
Size L	101	0.7 (0.2)	102	0.8 (0.2)	95	0.8 (0.2)
Size XL	39	0.8 (0.2)	43	0.8 (0.2)	39	0.8 (0.2)
LVOT diameter, cm						
Size S	17	1.8 (0.1) [1.7; 2.0]	18	1.8 (0.1) [1.7; 1.9]	16	1.8 (0.1) [1.7; 1.9]
Size M	82	1.9 (0.1) [1.7; 2.2]	75	1.9 (0.1) [1.7; 2.2]	73	1.9 (0.1) [1.6; 2.2]
Size L	115	2.0 (0.1) [1.8; 2.4]	110	2.0 (0.1) [1.8; 2.4]	101	2.0 (0.1) [1.7; 2.4]
Size XL	45	2.1 (0.1) [1.9; 2.3]	44	2.1 (0.1) [1.8; 2.4]	42	2.1 (0.1) [1.8; 2.4]
LV mass, g						
Size S	18	164.6 (75.9)	18	163.7 (63.3)	16	166.5 (57.7)
Size M	80	182.3 (56.1)	75	178.3 (59.5)	71	171.0 (54.4)
Size L	106	200.9 (52.9)	101	199.4 (56.5)	93	186.6 (56.2)
Size XL	41	253.2 (72.6)	39	234.1 (69.8)	40	227.3 (65.2)
LV mass index, g/m ²						
Size S	18	91.8 (35.8)	18	91.8 (30.1)	16	94.0 (28.5)
Size M	80	99.4 (25.9)	75	96.4 (27.4)	71	93.1 (26.1)
Size L	106	100.8 (27.5)	101	98.5 (26.0)	93	91.7 (24.8)
Size XL	41	123.6 (34.0)	39	113.8 (32.5)	40	110.5 (29.3)

SD, Standard deviation; EOA, effective orifice area; TVI, time velocity integral; EOAI, effective orifice area index; LVOT, left ventricle outflow tract; LV, left ventricle.

TABLE E4. Patient prosthesis mismatch (EOAi < 0.65)

Follow-up	Overall		Valve size							
			S		M		L		XL	
Discharge	N	% (N = 283)	N	% (N = 19)	N	% (N = 93)	N	% (N = 123)	N	% (N = 48)
	91	32.2%	8	42.1%	30	32.3%	41	33.3%	12	25.0%
3-6 mo	N	% (N = 256)	N	% (N = 18)	N	% (N = 80)	N	% (N = 114)	N	% (N = 44)
	79	30.9%	11	61.1%	28	35.0%	34	29.8%	6	13.6%
12 mo	N	% (N = 243)	N	% (N = 16)	N	% (N = 77)	N	% (N = 106)	N	% (N = 44)
	68	28.0%	6	37.5%	25	32.5%	27	25.5%	10	22.7%

EOAi, Effective orifice area index.