One-year outcomes associated with a novel stented bovine pericardial aortic bioprosthesis

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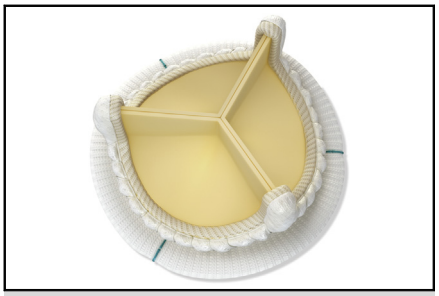
ABSTRACT

Objectives: The study objectives were to evaluate the safety, effectiveness, and hemodynamic performance of a new stented bovine pericardial aortic valve.

Methods: This trial enrolled patients with symptomatic moderate or severe aortic stenosis or chronic, severe aortic regurgitation. We assessed death, valve-related adverse events, functional recovery, and hemodynamic performance at discharge, 3 to 6 months, and 1 year, as required by the US Food and Drug Administration for regulatory approval. The primary analysis compared late linearized rates of valve-related adverse events after implantation with Food and Drug Administration–specified objective performance criteria to determine whether the adverse event rates associated with the valve are within acceptable limits. Adverse events included thromboembolism, thrombosis, all and major hemorrhage, all and major paravalvular leak, and endocarditis.

Results: The primary analysis included 864 patients who received an implant and 904.1 valve-years of follow-up. A total of 577 patients completed the 1-year evaluation. The primary end point was met for death, thromboembolism, thrombosis, all and major paravalvular leak, and endocarditis, but not for all and major hemorrhage. At 1 year, freedom from all death and from valve-related death was 96.4% and 99.7%, respectively. From baseline to 1 year, New York Heart Association class changed as follows: I, 10.8% to 73.7%; II, 48.9% to 22.6%; III, 38.0% to 3.5%; and IV, 2.3% to 0.2%. Effective orifice area increased from 0.9 ± 0.5 to 1.5 ± 0.4 ($P < .0001$), and mean aortic gradient decreased from 42.7 ± 16.5 to 12.5 ± 4.3 ($P < .0001$).

Conclusions: This analysis of a new stented bovine pericardial aortic valve demonstrated low overall mortality and valve-related adverse events, and hemodynamic performance comparable to that of other surgical aortic valves. (J Thorac Cardiovasc Surg 2018;156:1368-77)



The Avalus aortic valve bioprosthesis is a novel trileaflet, stented, bovine pericardial valve. Used with permission. © Medtronic 2018.

Central Message

This analysis of a novel stented bovine aortic valve demonstrated low overall mortality and valve-related AEs, and hemodynamic performance comparable to that of other surgical aortic valves.

Perspective

The Avalus (Medtronic, Minneapolis, Minn) valve has an excellent safety profile and favorable clinical outcomes and hemodynamics through the first year after implantation. For all valve-related AEs except all and major hemorrhage, the valve performed well. The unexpected linearized late hemorrhage rates are likely due to preexisting patient conditions requiring anticoagulation and the length of follow-up.

See Editorial Commentary page 1378.

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Abbreviations and Acronyms

AE = adverse event
AVR = aortic valve replacement
EOA = effective orifice area
EOAI = effective orifice area index
NYHA = New York Heart Association
OPC = objective performance criteria
PERIGON = PERIcardial SurGical AOrtic Valve ReplacemeNt Pivotal Trial for the Avalus valve
PPM = prosthesis–patient mismatch
PVL = paravalvular leak

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During the past several decades, there has been continued improvement in aortic bioprosthetic valve design to improve valve longevity, ease implantation, reduce transvalvular gradients, decrease thrombogenicity, and aid in later valve-in-valve transcatheter replacement. The Avalus aortic valve bioprosthesis (Medtronic, Minneapolis, Minn) was developed to continue this evolution in aortic tissue valve design. It is a trileaflet, stented, low-profile, bovine pericardial valve with a flexible sewing cuff, a polyester-covered, barium sulfate–impregnated base frame, and alpha amino oleic acid–treated, laser-cut leaflets. The safety and clinical and hemodynamic performance of this novel bioprosthesis are being evaluated in the PERIcardial SurGical AOrtic Valve ReplacemeNt (PERIGON) Pivotal Trial for the Avalus valve, a prospective, nonrandomized, international study. Early results from this trial demonstrated a good safety profile and hemodynamic performance, although bleeding rates exceeded objective performance criteria (OPC).[1] This article reports data from a larger cohort of patients with 1 year of follow-up.

MATERIALS AND METHODS

Study Design

The trial enrolled patients with symptomatic moderate or severe aortic stenosis or chronic, severe aortic regurgitation to receive a new bovine stented aortic valve. The trial design was based on recommendations of the US Food and Drug Administration and the International Organization for Standardization for cardiac valve prostheses to fulfill requirements for regulatory approval.[2,3] The trial was conducted at 19 sites in the United States, 13 sites in Europe, and 4 sites in Canada (Table E1).

Device Description

The Avalus bioprosthesis is indicated for the replacement of a diseased, damaged, or malfunctioning native or prosthetic aortic valve. It comprises a polyester-covered base frame and trileaflet support frame that are injection-molded using a polyetheretherketone material. The base frame contains barium sulfate for radiographic visualization. The laser-cut leaflets consist of bovine pericardial tissue cross-linked in buffered glutaraldehyde. The valve is treated with alpha amino oleic acid to mitigate calcification.[4] The base frame cover contains a polyester sewing ring with markers for suturing and for seating the valve in the supra-annular position. The valve is available in sizes of 17, 19, 21, 23, 25, 27, and 29 mm.

Patient Selection

Inclusion criteria. Patients with moderate or greater aortic stenosis or regurgitation with a clinical indication for aortic valve replacement (AVR) were considered for participation in the study. Concomitant procedures were allowed, but were limited to left atrial appendage ligation, coronary artery bypass graft, closure of a patent foramen ovale, ascending aortic aneurysm or dissection repair not requiring circulatory arrest, and resection of a subaortic membrane not requiring myectomy. These limitations were recommended by regulatory agencies and went into effect after the first 120 patients were enrolled.

Exclusion criteria. Patients were excluded for preexisting prosthetic valve or annuloplasty device; need for replacement or repair of the mitral, pulmonary, or tricuspid valve; previous implant and explant of study valve; active endocarditis, myocarditis, or other systemic infection; anatomic abnormality that increased surgical risk of morbidity or mortality (ie, ascending aortic aneurysm or dissection repair requiring circulatory arrest, acute type A aortic dissection, ventricular aneurysm, porcelain aorta, hostile mediastinum, hypertrophic obstructive cardiomyopathy, documented pulmonary hypertension [systolic >60 mm Hg]); noncardiac major/progressive disease with life expectancy of less than 2 years; renal failure (defined as dialysis therapy or glomerular filtration rate <30 mL/min/1.73 m^2); hyperparathyroidism; participation in another investigational trial or observational study; pregnant, lactating, or planning pregnancy during the trial period; documented history of substance abuse; greater than mild mitral valve or tricuspid valve regurgitation on echocardiography; systolic ejection fraction less than 20% on echocardiography; grade IV diastolic dysfunction; documented bleeding diatheses; prior acute preoperative neurologic deficit or myocardial infarction without return to baseline or stabilization 30 days or more before enrollment; or need for emergency surgery.

Procedure

Surgeons were allowed to use their preferred surgical approach for AVR, which included median sternotomy (79.4%), hemisternotomy (13.7%), right thoracotomy (5.4%), and other techniques (1.5%). Cardioplegia and cardiopulmonary bypass strategies were also left to the surgeon's discretion. Supra-annular (84.3%) positioning of the valve was recommended by the manufacturer, but intra-annular (14.9%), subannular (0.6%), and other (0.2%) positions were allowed. The most common suturing techniques were noneverting mattress sutures (49.0%) and simple interrupted sutures (29.9%). Pledgets were used in 54.4% of patients. Postoperative anticoagulation per local institutional practice was recommended.

Primary End Points

The primary safety end points were death and valve-related thromboembolism, thrombosis, hemorrhage, paravalvular leak (PVL), endocarditis, hemolysis, structural valve deterioration, nonstructural

dysfunction, reintervention, and explant.[5] Effectiveness was assessed by New York Heart Association (NYHA) functional classification and hemodynamic performance. Hemodynamic performance included effective orifice area (EOA), EOA index (EOAI), peak pressure gradient, mean pressure gradient, valvular regurgitation, cardiac output, and cardiac index. The protocol calls for evaluations to be performed at baseline (ie, preoperative visit), time of implant, and discharge up to 30 days, 3 to 6 months, and 1 year. Baseline evaluations were completed within 45 days of the scheduled implant procedure except transthoracic echocardiography, which was completed within 90 days before the procedure. Follow-up will continue annually through 5 years with telephone contacts at 18 and 30 months. Table E2 details the information collected at each visit. New pacemaker implantation rate was not a defined end point in the study; however, these data were collected as reported treatments on adverse event (AE) forms when applicable. Patients in whom implantation of the study valve was attempted but not completed were followed for 30 days for safety reporting and then exited from the study.

Statistical Analysis

The analysis for this article was performed when the study accumulated 800 valve-years of follow-up. The safety objective was assessed by comparing linearized late valve-related AE rates from patients who received the study valve to acceptable linearized valve-related AE rates (ie, OPC) as defined by the Food and Drug Administration (Table E3).[2,3] The primary hypothesis was that the true linearized AE rate for the study valve would be significantly less than or equal to twice the OPC ($2 \times$ OPC) for commercial bioprosthetic heart valves. The sample size estimation was based on the methods of Grunkemeier and colleagues,[6] who determined that the amount of data required to test the null hypothesis using the smallest acceptable AE rate (1.2% per valve-year, excluding valve thrombosis, major hemorrhage, and major PVL) was 800 valve-years. This estimation assumes a 95% confidence level, a power of 0.80, and an annual attrition rate of 5%.

For categoric variables, the number and percentage of patients are presented. For continuous variables, the means and standard deviations are presented. Survival was analyzed using the Kaplan–Meier method. Paired analyses were also performed for hemodynamic and effectiveness end points, and *t* tests were used to compare hemodynamic endpoints at baseline and 1 year. For NYHA class, the chi-square or Fisher exact test was used as applicable. $P < .05$ was considered statistically significant.

RESULTS

Patients

From May 12, 2014, to June 30, 2016, 962 consecutive patients were enrolled. Seven patients did not complete the baseline evaluation, and 1 died. Ninety-seven patients withdrew before valve implantation. Of these, 64 withdrawals occurred before the procedure (12 patients withdrew consent, 28 were withdrawn by their physician, and 24 withdrew for "other" reasons). Thirty-three withdrawals occurred at the time of the procedure (29 patients did not receive the study valve, 3 patients were withdrawn by their physician, and 1 withdrew for an "other" reason). The most common reason for withdrawal before or during the procedure was the need for an unallowed concomitant procedure. A total of 864 patients received the study valve, and 577 have completed 1 year of follow-up (Figure E1). The number of total valve-years was 904.1 and late valve-years was 834.2.

Mean age was 70.4 ± 8.9 years, and 74.5% of patients were male. Eighty-seven percent of patients had a baseline NYHA classification of II or III. The most common comorbid conditions were hypertension (76.2%), dyslipidemia (59.8%), and coronary artery disease (42.1%) (Table 1). The primary indication for AVR was aortic stenosis for 85.4% of patients (n = 738), aortic regurgitation for 5.3% of patients (n = 46), mixed stenosis and regurgitation

TABLE 1. Baseline characteristics and comorbidities

Characteristic	Patients (N = 864)
Age, y	70.4 ± 8.9
Male (%)	644 (74.5)
Body surface area, m^2	2.0 ± 0.2
NYHA class (%)	
I	98 (11.3)
II	410 (47.5)
III	342 (39.6)
IV	14 (1.6)
STS risk, %	
Mortality	2.0 ± 1.4
Morbidity or mortality	14.8 ± 6.0
Angina (%)	329 (38.1)
Chronic obstructive pulmonary disease (%)	109 (12.6)
Congestive heart failure (%)	183 (21.2)
Coronary artery disease (%)	364 (42.1)
Diabetes mellitus (%)	227 (26.3)
Dyslipidemia (%)	517 (59.8)
Hypertension (%)	658 (76.2)
Left ventricular hypertrophy (%)	341 (39.5)
Myocardial infarction (%)	73 (8.4)
Peripheral vascular disease (%)	67 (7.8)
Renal dysfunction/insufficiency (%)	89 (10.3)
Stoke/cerebrovascular accident (%)	31 (3.6)
Transient ischemic attack (%)	45 (5.2)
Previous percutaneous coronary intervention (%)	125 (14.5)
Previous percutaneous valvuloplasty (%)	1 (0.1)
Implanted pacemaker (%)	24 (2.8)
Implanted defibrillator (%)	2 (0.2)
Previous aortic valve repair (%)	2 (0.2)
Previous aortic valve implant (%)	6 (0.7)
Rhythm on 12-lead electrocardiogram (%)*	
Sinus	693 (80.5)
Pacing	19 (2.2)
Atrial fibrillation	35 (4.1)
Other	114 (13.2)
Atrioventricular block (%)*	110 (12.8)
Left bundle branch block (%)*	27 (3.1)
Right bundle branch block (%)*	88 (10.2)

Values are n (%) or mean ± standard deviation. *NYHA*, New York Heart Association; *STS*, Society of Thoracic Surgeons. *N = 861 for electrocardiogram measures.

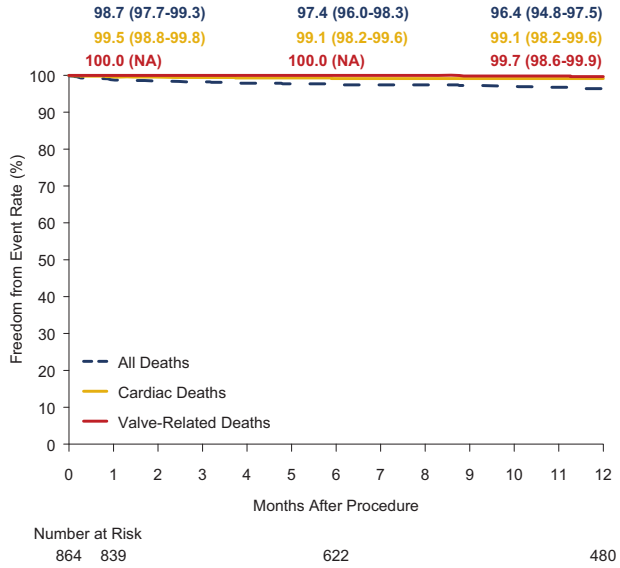


FIGURE 1. Kaplan–Meier estimates of freedom from all, cardiac, and valve-related death from baseline through 1 year. *NA*, Not applicable.

for 8.6% of patients (n = 74), and a failed bioprosthesis for 0.7% of patients (n = 6).

Procedure

The mean cardiopulmonary bypass time was 105.0 ± 42.3 minutes (89.0 ± 30.8 minutes for isolated AVR and 120.5 ± 46.1 minutes for AVR with concomitant procedures). The mean crossclamp time was 79.0 ± 31.9 minutes (65.7 ± 23.2 minutes for isolated AVR and 91.9 ± 33.8 minutes for AVR with concomitant procedures). Coronary artery bypass grafting was the most common concomitant procedure (32.5%) (Table E4).

Safety End Points

Early events (≤30 days). Early mortality occurred in 10 patients (1.2%). The Kaplan–Meier estimates of freedom from all-cause, cardiac, and valve-related mortality at 30 days were 98.7%, 99.5%, and 100%, respectively (Figure 1). Fourteen (1.6%) early hemorrhage events occurred in 13 patients, and of these, 8 (0.9%) were major events occurring in 8 patients. There were 12 (1.4%) early thromboembolic events in 11 patients. Eight (0.9%) of the thromboembolic events resulted in a stroke, and 4 (0.5%) resulted in a transient ischemic attack. At 30 days, PVL was classified as none/trace in 763 patients (94.8%, n = 849), mild in 15 patients (1.8%), moderate in 0 patients (0.0%), and severe in 0 patients (0.0%). Early endocarditis occurred in 2 patients (0.2%), nonstructural valve deterioration occurred in 2 patients (0.2%), and valve-related reintervention occurred in 3 patients (0.3%). Valve explant was required in 3 patients (0.3%) because of endocarditis. There were no occurrences of early valve thrombosis, hemolysis, or structural valve deterioration.

Late events (>30 days). Late mortality occurred in 28 patients (3.4%). The Kaplan–Meier estimates of freedom from all-cause, cardiac, and valve-related mortality at 1 year were 96.4%, 99.1%, and 99.7%, respectively. Thirty late hemorrhagic events occurred in 28 patients; 21 were major events occurring in 19 patients. There were 14 (1.7%) late thromboembolic events. Eight (1.0%) of the thromboembolic events resulted in a stroke, and 6 (0.7%) resulted in a transient ischemic attack. At 1 year, PVL was classified as none/trace in 540 patients (96.1%, n = 562), mild in 14 patients (2.5%), moderate in 3 patients (0.5%), and severe in 0 patients (0.0%). Late endocarditis occurred in 11 patients, nonstructural valve deterioration occurred in 5 patients, and reinterventions occurred in 6 patients. There were 6 valve explants due to endocarditis. There were no occurrences of late valve thrombosis, hemolysis, or structural valve deterioration. A new pacemaker was required by 33 of 864 patients (3.8%).

Eighty-seven patients who received the Avalus bioprosthesis were aged less than 60 years at enrollment. Ten of these patients had 11 valve-related AEs (Table E5).

Late linearized event rates. The 95% upper confidence limits for the late linearized rates for valve-related AEs in the primary analysis were all below the 2 × OPC rates except all and major hemorrhage (Figure 2). The late linearized rate was 3.4% per valve-year for all death, 0.6% per valve-year for cardiac death, 0.5% per valve-year for valve-related death, 1.7% per valve-year for thromboembolism, 0.6% per valve-year for all PVL, 0% per valve-year for major PVL, and 1.3% per valve-year for endocarditis.

For all hemorrhage and major hemorrhage, the late linearized rates were 3.6% and 2.5% per valve-year, respectively, and the 95% upper bound of these rates

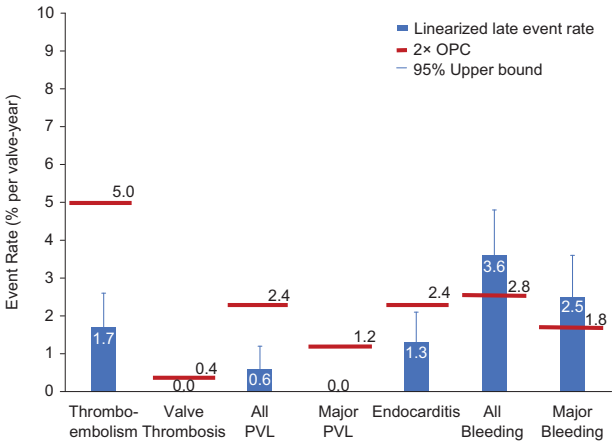


FIGURE 2. Late linearized rates of valve-related AEs (*vertical blue bars*) compared with 2 times the OPC (*red horizontal bars*). The *vertical blue lines* indicate the 95% upper confidence limits of the linearized late event rates. Late events occurred more than 30 days postimplant. *OPC*, Objective performance criteria; *PVL*, paravalvular leak.

were 4.8% and 3.6% per valve-year, respectively. Both the linearized rates and the upper bounds exceeded 2 times the OPC rates of 2.8% and 1.8% per valve-year, respectively. Of the 21 major hemorrhagic events, 17 occurred in patients taking anticoagulants or antiplatelets for preexisting conditions, 2 occurred in patients taking anticoagulants or antiplatelets for new-onset atrial fibrillation, and 2 occurred in patients taking anticoagulants or antiplatelet medications for surgical AVR prophylaxis (Figure E2 shows additional details). Table E6 lists the antiplatelet and anticoagulant use of the study population to 1 year. The linearized late hemorrhage rates were highest in patients taking anticoagulants for preexisting conditions (Table E7).

The linearized late event rates for safety end points not included in the OPC analysis were all very low: hemolysis, 0%; structural valve deterioration, 0%; nonstructural valve dysfunction, 0.6%; reintervention, 0.7%; and explant, 0.7% per valve-year.

Hemodynamic Results

Peak and mean aortic pressure gradients and mean EOA improved substantially after implantation of the study device, and these improvements were maintained at 1 year (Figure 3; $P < .001$ for all, baseline vs 1 year). The peak aortic pressure gradient was 23.9 ± 8.4 mm Hg at discharge/30 days and 23.2 ± 7.8 mm Hg at 1 year (n = 520). The mean aortic pressure gradient was 13.4 ± 4.8 mm Hg at discharge/30 days and 12.5 ± 4.4 mm Hg at 1 year (n = 518). The mean EOA was 1.6 ± 0.4 cm^2 at discharge/30 days and 1.5 ± 0.4 cm^2 at 1 year (n = 394). The mean EOAI was 0.44 ± 0.23 cm^2/m^2 at baseline, 0.81 ± 0.19 cm^2/m^2 at discharge/30 days, and 0.75 ± 0.17 cm^2/m^2 at 1 year (n = 394; $P < .001$, baseline vs 1 year). At discharge/30 days, 163 of 436 patients (37.4%) had no or mild prosthesis–patient mismatch (PPM) (defined as EOAI >0.85 cm^2/m^2), 195 patients (44.7%) had moderate PPM (EOAI >0.65 to 0.85 cm^2/m^2), and 78 patients (17.9%) had severe PPM (EOAI ≤0.65 cm^2/m^2). At 1 year, corresponding values were 107 (24.5%), 197 (45.2%), and 132 (30.3%), respectively. Table 2 presents mean gradient, EOA, EOAI, and degree of PPM by visit and valve size. Table 3 presents mean aortic gradient by degree of PPM, visit, and valve size.

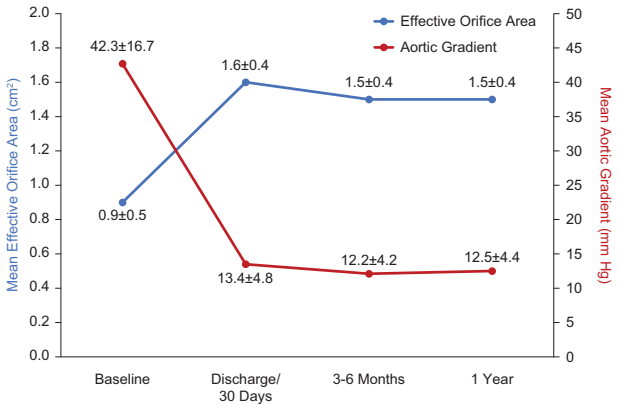


FIGURE 3. Paired analysis of mean aortic pressure gradient and EOA from baseline (ie, preoperative visit) through 1 year. N = 394 for EOA. N = 518 for mean gradient. Echocardiograms were adjudicated by core laboratory.

Cardiac output was 5.1 ± 1.3 L/min at baseline, 5.1 ± 1.2 L/min at discharge/30 days, and 4.5 ± 1.0 L/min at 1 year ($P < .001$, baseline vs 1 year). The cardiac index was 2.6 ± 0.7 L/min/m^2 at baseline, 2.6 ± 0.6 L/min/m^2 at discharge/30 days, and 2.3 ± 0.5 L/min/m^2 at 1 year ($P < .001$, baseline vs 1 year).

Effectiveness End Points

Approximately three fourths of patients (73.6%) had maintained improvement of 1 to 2 NYHA classes at 1 year; 1.7% had worsened by 1 class, and 23.2% had no change in NYHA class at the same time point. At 1 year of follow-up, 73.7% of patients had NYHA class I functional status, 22.6% had class II, 3.5% had class III, and 0.2% had class IV (Figure 4).

Regurgitation

At discharge/30 days, transvalvular regurgitation was classified as none/trace in 96.9% of patients, mild in 2.9% of patients, moderate in 0.2% of patients, and severe in 0.0% of patients. At 1 year, transvalvular regurgitation was classified as none/trace in 96.9% of patients, mild in 3.1% of patients, moderate in 0.0% of patients, and severe in 0.0% of patients. At discharge/30 days, PVL was classified as none/trace in 97.8% of patients and mild in 2.1% of patients; there were no cases of moderate PVL at this time point. At 1 year, PVL was classified as none/trace in 96.5% of patients, mild in 2.3% of patients, and moderate in 0.6% of patients. There were no cases of severe PVL during 1 year of follow-up.

DISCUSSION

Principle Findings

This prospective, multicenter trial demonstrates the safety and early clinical and hemodynamic performance of the Avalus aortic valve bioprosthesis. There was excellent early and 1-year survival, a low rate of valve-related AEs, sustained improvement in NYHA functional class, and excellent hemodynamic performance of the Avalus valve. These data confirm earlier findings in the PERIGON Pivotal Trial[1] in a larger cohort of patients, providing greater clarity on patient improvement and the early safety and performance of this new bioprosthesis.

In this study, early mortality was 1.2%, and survival at 1 year was 96.4%. These results compare favorably to those reported in the literature for both pericardial

TABLE 2. Mean aortic pressure gradient and valve effective orifice area by visit and valve size

Visit	Valve size							All sizes
	17 mm	19 mm	21 mm	23 mm	25 mm	27 mm	29 mm	
Mean aortic pressure gradient, mm Hg (n)								
Baseline	NA	46.8 ± 23.5 (37)	44.4 ± 15.1 (155)	43.7 ± 14.7 (305)	40.1 ± 17.7 (260)	38.7 ± 18.5 (77)	30.8 ± 14.3 (9)	42.3 ± 16.7 (837)
Discharge up to 30 d	14.0 (1)	18.6 ± 6.2 (37)	15.4 ± 5.1 (153)	13.0 ± 4.5 (302)	12.8 ± 4.0 (257)	10.7 ± 4.0 (73)	9.8 ± 3.9 (9)	13.4 ± 4.8 (789)
1 y	24.0 (1)	17.1 ± 5.0 (27)	14.5 ± 4.3 (106)	12.1 ± 3.8 (205)	11.7 ± 4.0 (170)	10.3 ± 4.2 (43)	9.8 ± 3.1 (5)	12.5 ± 4.4 (557)
Effective orifice area, cm^2 (n)								
Baseline	NA	0.70 ± 0.20 (34)	0.77 ± 0.32 (140)	0.81 ± 0.36 (290)	0.98 ± 0.58 (232)	1.13 ± 0.80 (71)	1.37 ± 1.13 (9)	0.88 ± 0.50 (775)
Discharge up to 30 d	1.40 (1)	1.22 ± 0.24 (30)	1.35 ± 0.28 (137)	1.56 ± 0.32 (257)	1.64 ± 0.34 (228)	1.85 ± 0.44 (65)	2.03 ± 0.40 (9)	1.56 ± 0.37 (727)
1 y	0.62 (1)	1.11 ± 0.25 (25)	1.25 ± 0.25 (99)	1.47 ± 0.32 (201)	1.57 ± 0.31 (167)	1.77 ± 0.41 (41)	2.01 ± 0.23 (5)	1.47 ± 0.35 (539)
Effective orifice area index, cm^2/m^2 (n)								
Baseline	NA	0.40 ± 0.11 (34)	0.42 ± 0.16 (140)	0.41 ± 0.18 (290)	0.48 ± 0.29 (232)	0.53 ± 0.39 (71)	0.66 ± 0.58 (8)	0.45 ± 0.25 (775)
Discharge up to 30 d	0.98 (1)	0.69 ± 0.15 (30)	0.75 ± 0.18 (137)	0.80 ± 0.19 (257)	0.80 ± 0.17 (228)	0.87 ± 0.24 (65)	0.95 ± 0.20 (9)	0.79 ± 0.19 (727)
1 y	0.43 (1)	0.64 ± 0.14 (25)	0.69 ± 0.15 (99)	0.75 ± 0.17 (201)	0.77 ± 0.16 (167)	0.83 ± 0.18 (41)	0.97 ± 0.08 (5)	0.75 ± 0.17 (539)
PPM, % (n/N)								
Discharge up to 30 d								
None	100.0 (1/1)	16.7 (5/30)	24.8 (34/137)	37.4 (96/257)	35.1 (80/228)	41.5 (27/65)	77.8 (7/9)	34.4 (250/727)
Moderate	0.0 (0/1)	40.0 (12/30)	43.1 (59/137)	40.9 (105/257)	47.4 (108/228)	47.7 (31/65)	22.2 (2/9)	43.6 (317/727)
Severe	0.0 (0/1)	43.3 (13/30)	32.1 (44/137)	21.8 (56/257)	17.5 (40/228)	10.8 (7/65)	0.0 (0/9)	22.0 (160/727)
1 y								
None	0.0 (0/1)	8.0 (2/25)	18.2 (18/99)	22.9 (46/201)	26.9 (45/167)	39.0 (16/41)	100.0 (5/5)	24.5 (132/539)
Moderate	0.0 (0/1)	36.0 (9/25)	33.3 (33/99)	50.7 (102/201)	50.3 (84/167)	48.8 (20/41)	0.0 (0/5)	46.0 (248/539)
Severe	100.0 (1/1)	56.0 (14/25)	48.5 (48/99)	26.4 (53/201)	22.8 (38/167)	12.2 (5/41)	0.0 (0/5)	29.5 (159/539)

PPM definitions: none, EOAI >0.85 cm^2/m^2; moderate, 0.65 < EOAI ≤ 0.85 cm^2/m^2; and severe, EOAI ≤0.65 cm^2/m^2. *NA*, Not available; *PPM*, prosthesis–patient mismatch.

and porcine aortic valves. Bavaria and colleagues[7] reported an early mortality of 1.8% and 1-year survival of 95.8% in a multicenter study of the St Jude Trifecta valve (St Jude Medical, St Paul, Minn). Goldman and colleagues[8] recently reported early mortality of 1.5% in their midterm results of the Trifecta valve. Conte and colleagues[9] reported a 1-year survival of 92% in a multicenter assessment of the Mitroflow aortic valve (LivaNova, London, UK). Likewise, Fiegl and colleagues[10] reported a 2.0% 30-day mortality and 90.6% 1-year survival for the Edwards (Irvine, Calif) Magna Ease valve. For the St Jude aortic porcine Epic valve, Jamieson and colleagues[11] reported an early mortality of 3.6% and a linearized late mortality of 5.2% per patient-year.

Likewise, the late linearized rates of AEs observed in this study compare favorably with other contemporary multicenter studies of pericardial aortic valves. Similar late linearized rates with the Avalus valve were observed with the Trifecta valve and the Mitroflow valve for thromboembolism (1.7% vs 1.9% and 1.34% per patient-year, respectively), PVL (0.6% vs 0.0% and 0.6%), major PVL (0.0% vs 0.0% and not available), endocarditis (1.3% vs 1.07% and 1.4%), major hemorrhage (2.5% vs 2.6% and not available), and explant (0.7% vs 0.59% and not available).[7,9] Similar to the Trifecta valve, in this study there were no cases of valve thrombosis or hemolysis. There were also no cases of structural valve deterioration, compared with

TABLE 3. Mean aortic gradient by prosthesis–patient mismatch and valve size

Degree of PPM	Mean aortic gradient, mm Hg (n)							
	17 mm (N = 1)	19 mm (N = 39)	21 mm (N = 157)	23 mm (N = 314)	25 mm (N = 264)	27 mm (N = 80)	29 mm (N = 9)	All sizes (N = 864)
Discharge/30 d								
None	14.00 (1)	14.20 ± 2.86 (5)	13.68 ± 4.76 (34)	11.59 ± 3.70 (96)	11.75 ± 3.47 (80)	9.15 ± 2.66 (27)	10.14 ± 4.41 (7)	11.68 ± 3.85 (250)
Moderate	NA	19.58 ± 5.35 (12)	15.42 ± 4.36 (59)	13.43 ± 4.16 (105)	12.54 ± 3.45 (108)	11.42 ± 4.30 (31)	8.50 ± 0.71 (2)	13.50 ± 4.36 (317)
Severe	NA	19.85 ± 6.66 (13)	17.09 ± 5.98 (44)	14.71 ± 5.06 (56)	15.55 ± 3.97 (40)	14.29 ± 4.75 (7)	NA	15.98 ± 5.37 (160)
1 y								
None	NA	14.00 ± 2.83 (2)	11.72 ± 2.70 (18)	9.35 ± 2.92 (46)	10.40 ± 3.78 (45)	8.00 ± 2.13 (16)	9.80 ± 3.11 (5)	9.95 ± 3.30 (132)
Moderate	NA	16.67 ± 6.32 (9)	13.03 ± 3.66 (33)	12.02 ± 3.28 (102)	11.36 ± 3.25 (84)	10.95 ± 4.56 (20)	NA	12.01 ± 3.71 (248)
Severe	24.00 (1)	18.36 ± 4.38 (14)	16.19 ± 4.25 (48)	14.47 ± 3.93 (53)	14.00 ± 4.73 (38)	14.20 ± 4.87 (5)	NA	15.27 ± 4.48 (159)

PPM definitions: none, EOAI >0.85 cm^2/m^2; moderate, 0.65 < EOAI ≤0.85 cm^2/m^2; and severe, EOAI ≤0.65 cm^2/m^2. *PPM*, Prosthesis–patient mismatch; *NA*, not applicable.

very low rates reported for the Trifecta valve (0.12% per patient-year) and the Mitroflow valve (0.21% per patient-year).

The trial did not meet the expectation for bleeding, because the upper bound of the 95% confidence interval for both all hemorrhage and major hemorrhage was greater than twice the OPC. Of note, the observed rate for major hemorrhage in this trial of 2.5% per patient-year was similar to that observed in the multicenter trial of the St Jude Trifecta valve of 2.6% per patient-year. There are several possibilities as to why the bleeding rate exceeded expectations. As shown in Table E6, a large proportion of patients were taking anticoagulants or antiplatelet medications for preexisting conditions unrelated to valve prophylaxis, whereas only 2 of the major bleeding events were in patients taking anticoagulants for valve prophylaxis (Table E7). Therefore, the majority of bleeding events were likely related to the anticoagulation management of preexisting conditions. In addition, this study analyzed the 1-year results of 577 of the 864 patients enrolled. Therefore, the linearized rates are biased toward the early results of the study. Because bleeding is more likely to occur early than late, the linearized rates of hemorrhage may be artificially high. With longer patient follow-up, we expect the bleeding rates to decrease.

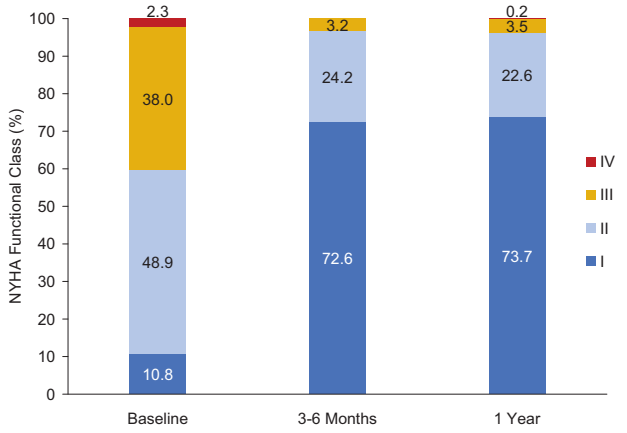


FIGURE 4. Paired analysis of NYHA from baseline (ie, preoperative visit) through 1 year. N = 566. *NYHA*, New York Heart Association.

At 1 year, EOAI was 0.65 cm^2/m^2 or less in 30.3% of patients, more than 0.65 to 0.85 cm^2/m^2 or less in 45.2% of patients, and more than 0.85 cm^2/m^2 in 24.5% of patients. In general, the concern with PPM is high residual postoperative gradients leading to reduced survival. Although there was an increase in PPM as determined by EOAI, there was no corresponding increase in clinically significant mean aortic gradient. In the total trial population, mean gradients are stable to slightly lower at 1 year in the severe PPM group compared with baseline, and all but 1, in a patient who received a 17-mm valve, remain below a threshold of clinical significance (20 mm) (Table 3). A subsequent analysis presented at the 2017 European Association for Cardio-Thoracic Surgery conference demonstrated that there has been no statistically significant difference in outcomes between patients with EOAI less than 0.75 cm^2/m^2 and those with EOAI 0.75 cm^2/m^2 or greater.[12] An article on PPM is currently in development.

In the PERIGON Pivotal Trial, the aortic stenosis was relieved with minimal regurgitation observed at 1 year. Moreover, the majority of subjects had improved NYHA classification at follow-up; 75.0% of the patients improved by at least 1 class at their 1-year visits. These data suggest the clinical effectiveness after 30 days has been maintained. Mean aortic gradient levels at 1-year follow-up were below 20 mm Hg for all groups (no PPM, moderate PPM, and severe PPM) and lower than the mean aortic gradient criteria defining moderate (20-39 mm Hg) or severe (≥40 mm Hg) aortic stenosis in American College of Cardiology/American Heart Association valvular heart disease guidelines.[13] The rates of valve-related death, structural valve deterioration, nonstructural valve dysfunction, reintervention, and explant were comparable to the rates in the literature for other bovine surgical valves.

The majority of patients had sustained improvement in NYHA functional class at 1 year. The observation that 97% of patients were in NYHA functional class I or II compares favorably with that reported for the Trifecta and the Mitroflow valves. This improvement in NYHA functional class is due to the sustained decrease in aortic

gradient and increase in EOA associated with the Avalus valve. As expected, the mean aortic pressure gradients decreased and EOAs increased as valve sized increased, and compared favorably to other aortic valves.[7-11]

Study Limitations

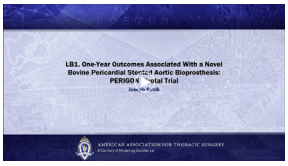
Because of the study design, a portion of the 864 patients who received an implant had not completed their 1-year visit at the time that 800 valve-years of follow-up had been reached. It is possible that some of those patients were still in the early postoperative period and receiving anticoagulation, posing a higher risk of bleeding events. Given the long-term nature of studies of implantable valve bioprostheses, the Food and Drug Administration guidelines use a linearized assumption for analysis of key valve-related events, but also define the threshold of minimum length of follow-up required as 300 subjects at 1-year follow-up. We believe the 577 subjects who had achieved at least 1 year of follow-up at the time of the analysis provide sufficient evidence as to the early performance and safety of the valve. Early bleeding events also may have been influenced by the reduction in allowable concomitant procedures after the first 120 patients were enrolled.

CONCLUSIONS

The findings of this study demonstrate that the Avalus valve has an excellent safety profile and favorable clinical outcomes and hemodynamics through the first year after implantation. For all AEs except all and major hemorrhage, the Avalus valve performed well, coming in below the prespecified event rates. The unexpected linearized late hemorrhage rates are likely due to preexisting patient conditions requiring anticoagulation and the length of follow-up in this study.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/17AM/2017-05-01/BallroomABC/05-01-17_BallroomABC_1630_Sabik.mp4.



Conflict of Interest Statement

J.F.S.: Research support – Edwards Lifesciences (Local PI for Intuity Trial), Abbott (North American PI for EXCEL Trial); Advisory board – Medtronic, LivaNova; Educational courses – Medtronic. V.R.: Member, Surgical Advisory Board, Medtronic; Consultant, Abbott Labs. R.L.: Lecture fees, royalties, and serving on an advisory board for Medtronic; lecture fees and serving on an advisory board for LivaNova; and lecture fees, shares, and serving on an advisory board for Highlife. A.P.K.: No conflicts of interest during the course of this work, but is currently an employee of Medtronic. F.D.: None to declare. L.L.: None to declare. V.B.: Consultant for Medtronic and Boston Scientific and speaker fees from Medtronic, Edwards Lifesciences, Boston Scientific, and LivaNova. M.M.: Consultant for Medtronic, Edwards Lifesciences, LSI, and Terumo. N.J.W.: Research grant/contract support from Abbott Vascular, Boston Scientific, Edwards LifeSciences, Medtronic, LivaNova, St Jude. H.J.P.: None to declare. M.J.R.: Fees from Medtronic for educational services. F.M.A.: Directs the academic Echocardiography Core Lab (MedStar Health) for the PERIGON Pivotal trial under a contract between Medtronic and MedStar. C.Z.: Employee of Medtronic. R.J.M.K.: unrestricted research grants from Edwards, Medtronic, and Admedus for his institutional department, and travel expenses and presenter reimbursements from several industries.

Julie Linick, ELS, an employee of Medtronic, created the figures and tables, drafted the "Materials and Methods" and "Results" sections under the direction of the authors, and ensured the technical accuracy of the information.

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Key Words: aortic regurgitation, aortic stenosis, bovine pericardial bioprosthesis, surgical aortic valve replacement

Discussion

Dr W. R. Chitwood *(Greenville, NC).* Thank you, Dr Sabik, for a well-organized and clear presentation of the results of the PERIGON Pivotal Trial, which was designed to evaluate the Medtronic Avalus bovine pericardial valve.

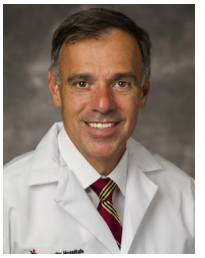
Bioprosthetic valves are now implanted in more than 80% of aortic valve cases; moreover, the age limit continues to decrease. However, no one has developed a Holy Grail valve that compares favorably to the normal aortic valve. Issues of gradient, PVL, and endocarditis have generally been solved, but long-term durability remains the Gordian knot that is left to be untied scientifically.

Dr Sabik, you have shown us 1-year data from this pivotal trial that evaluated this pericardial valve. The comparative pericardial aortic surgical valves to date are the Edwards Magna Ease, with the predicate being the Perimount valve; the St Jude, now Abbott, Trifecta valve; and the Sorin, now LivaNova, Mitroflow valve. Each of these is designed for supra-annular implantation that has been shown to have advantages over porcine stented valves as far as gradient and, in most cases, durability. The Mitroflow and Trifecta valves are structurally different than the Avalus or the Magna Ease valve as far as the attachment location of the leaflets. The Magna Ease and Avalus valves have similar leaflet structure, but the frames and manner of fixation are a bit different.

You and your colleagues wrote an article in *The Annals of Thoracic Surgery* in 2015 that perhaps showed the longest follow-up and the largest series, and that is 12,569 implants between 1982 and 2011 for the Perimount Edwards pericardial valve. The mean age was 70 years, and the explants for structural valve deterioration were 1.9% and 15% at 10 and 20 years. In patients aged less than 60 years, the comparative explant data were 5.6% and 46% for structural valve deterioration, respectively, in other words, much higher for patients who are aged less than 60 years. To this end, we would expect that the Magna Ease valve should have similar results or better.

The new version of the Magna Ease valve, the Resilia, seems to be the best comparator, as 1-year data were presented last year for the COMMENCE trial. So we are comparing valves with 1 year versus 1 year.

The PERIGON pivotal trial was a nonrandomized prospective multi-institutional and international clinical trial that enrolled 864 patients, but the basis for the study was 577 patients with 1-year data. You presented these data nicely, but also Dr Klautz had presented some of the data earlier in Barcelona at the 2016 European Meeting. What is the difference in this part of the trial and what Dr Klautz presented last year?



Dr Joseph F. Sabik *(Cleveland, Ohio).* Obviously we have more patients and longer follow-up and therefore more data. In looking at why it was divided into 2, obviously the requirements for the Conformité Européene mark are less than the Food and Drug Administration mark. So we thought we would look at the data at the time of submitting for Conformité Européene mark as well as submitting for Food and Drug Administration approval. So, again, this study has more patients enrolled and longer follow-up.

Dr Chitwood. As I mentioned, the most recent comparative trial was the Edwards COMMENCE trial. It was presented last year at the American Association for Thoracic Surgery annual meeting. The 1-year results were virtually the same with the exception that the PERIGON trial showed a slightly higher transvalvular gradient at 2 torr and a 0.2 cm^2 lower EOA but substantially higher hemorrhage rates. These 2 issues were concerning. I think you have tried to explain why the hemorrhage rates are higher, but it is still concerning. Did you find the hemorrhage rate was related to the valve or was it related to preexisting conditions and a number of patients were in atrial fibrillation and on anticoagulation medication?

Dr Sabik. We can't be sure, but that was our impression. As you pointed out, not all 800 patients have reached the 1-year mark. The outcomes of the study are still biased toward the early outcomes, and we know that most bleeding tends to occur within the first 6 months. Second, when we looked at the actual patients who bled, most of them bled who were on anticoagulants or antiplatelet agents for other reasons not related to the valve.

It is hard to be sure, but again, our impression was that patients who were on anticoagulants for valve prophylaxis, the bleeding rate was very low, but the bleeding tended to occur in patients on anticoagulants for preexisting conditions.

Dr Chitwood. So bleeding did not seem to be related to the valve?

Dr Sabik. We don't think it's related to the valve, correct.

Dr Chitwood. Compared with this new Edwards Resilia valve, you had slightly higher gradients. This was not a tremendous difference at 2 torr, but everybody is concerned about gradients especially with the low gradient TAVR valves. Does this amount of increased gradient matter?

Why do you think there would be a difference between these 2 valves? They seem to be constructed similarly.

Dr Sabik. There probably are many similar things, but there are some things that are specific to this valve. Is there a difference between 13 and 15 or 14 and 16, you know, probably not, at least not clinically.

But there were specific design features to this valve. Obviously the leaflets are attached inside the stent. The leaflets are made in a certain way; there are precision needle holes to where they are sewn to reduce stress. These were done to increase valve durability. As you said, you are always kind of focused on getting the best hemodynamic results with the same long-term durability, and our hope was with this design that we would have better long-term durability. But again, we are only going to know that over time. Maybe that might result in a 1- or 2-mm increase in gradient, but whether that matters or not, I don't believe it will be clinically significant.

Dr Chitwood. As in other pericardial valves, your data clearly show that with time, the gradient does decrease. Did you have any patient–prosthetic mismatches, because 23% of your patients had a size 19 or 21 valve implanted?

Dr Sabik. Yes, there were some, and I apologize, it is in the article, but I don't know the number right offhand.

Dr Chitwood. What about the pacemaker implantation rate for this valve?

Dr Sabik. I'm sorry, I don't know that information either. I will find that out.

Dr Chitwood. Your data were well presented. You always do a great job.

Dr J. M. DiMaio *(Dallas, Tex).* Dr Sabik, can you talk about the treatment of the leaflets, anything different about that? You mentioned various characteristics of the frame.

Dr Sabik. They are laser-cut leaflets and treated with alpha amino oleic acid to prevent calcification. One of the things that is remarkable is that there were no early structural valve failures, because the other valves have shown a bit of structural valve failure even early. One of the things that was done was looking at the stresses across the leaflet, and the holes for where the valve is sutured in place were figured out mathematically ahead of time to reduce stress on the leaflets. So it is one of the things that is a bit different. The stent design is probably a little more rigid, again, so we don't get the posts creeping in resulting in early aortic insufficiency. So things are done, again, to improve durability.

Dr R. Shemin *(Los Angeles, Calif).* Beautiful study, well presented, but I am still struggling to understand where you see the advantage of this valve over the other valves that we currently have, such as the Magna Ease as Ranny Chitwood spoke about.

Dr Sabik. These are early data, and they show the safety and clinical effectiveness of the valve, at least to 1 year. As I mentioned, there were design things that we did to ease implantation but also will help with the long-term durability of the valve, obviously which you are only going to know with time.

Dr Shemin. I think all of us are putting tissue valves in younger patients. We are concerned about valve-in-valve options when these valves ultimately fail. Has this valve been designed in any way to facilitate a valve-in-valve option? Is the valve's annulus expandable to allow a larger transcatheter AVR in the future?

Dr Sabik. The answer to that is yes, the stent design is impregnated with barium to ease in radiographic visualization of the valve if you were to do a valve-in-valve.

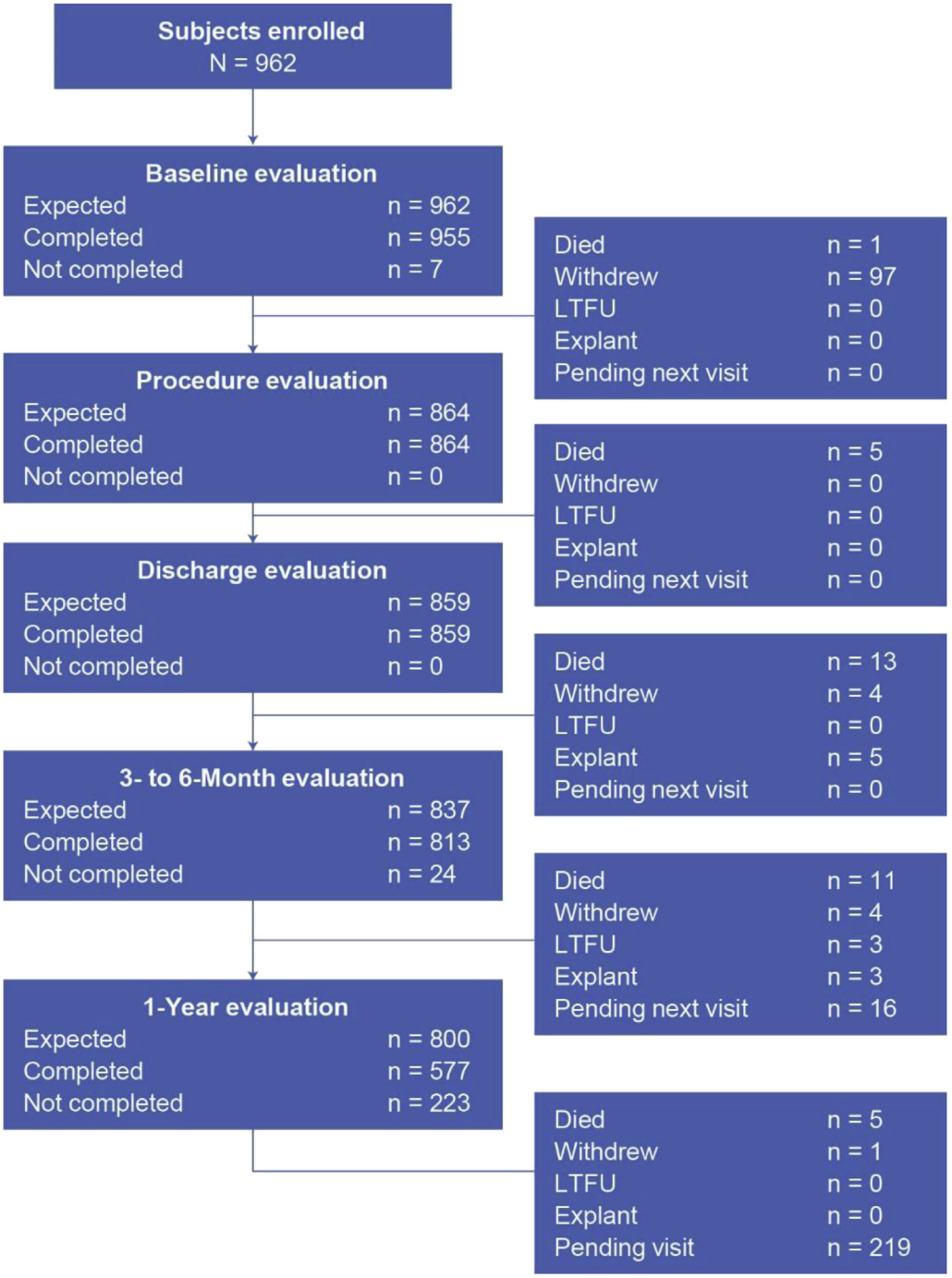


FIGURE E1. CONSORT flow diagram detailing patient disposition from enrollment through 1 year of follow-up. *LTFU*, Lost to follow-up.

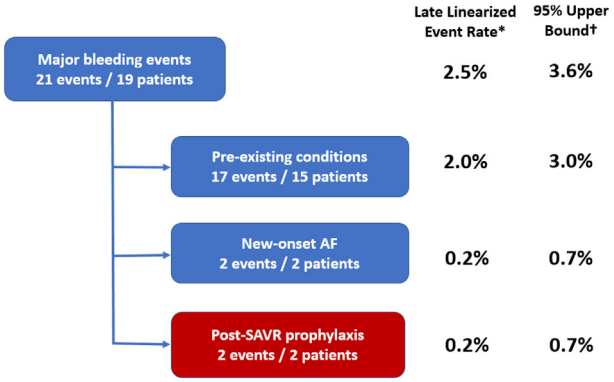


FIGURE E2. Major bleeding events.

TABLE E1. Study sites and principal investigators

Center name	Site principal investigator
Deutsches Herzzentrum München Klinik an der TU München, München, Germany	Rüdiger Lange
Hôpital Haut-Lévêque – CHU de Bordeaux, Pessac Cedex, Bordeaux, France	Louis Labrousse
Leids Universitair Medisch Centrum, Leiden, The Netherlands	Robert Klautz
NHS Foundation Trust - St Thomas' Hospital, London, United Kingdom	Vinayak Bapat
Herzzentrum Leipzig GmbH, Leipzig, Germany	Michael Borger
Erasmus Medisch Centrum, Rotterdam, The Netherlands	A. Pieter Kappetein
Klinikum und Fachbereich Medizin Johann Wolfgang Goethe, Frankfurt am Main, Germany	Anton Moritz
Universitätsklinikum Köln - Anstalt des öffentlichen Rech, Cologne, Germany	Thorsten Wahlers
Medizinische Hochschule Hannover, Hannover, Germany	Malakh Lal Shrestha
Hôpital Bichat - Claude Bernard, Paris, France	Patrick Nataf
Inselspital - Universitätsspital Bern, Bern, Switzerland	Thierry Carrel
Ospedale San Raffaele – Milano, Milan, Italy	Ottavio Alfieri
UniversitätsSpital Zürich, Zurich, Switzerland	Volkmar Falk
Institut universitaire de cardiologie et pneumologie Quebec, Québec, Canada	François Dagenais
Toronto General Hospital, Toronto, Canada	Vivek Rao
Ottawa Heart Institute, Ottawa, Canada	Marc Ruel
Montreal Heart Institute, Montreal, Canada	Raymond Cartier
The Toledo Hospital, Toledo, Ohio	Michael Moront
Piedmont Atlanta Hospital, Atlanta, Ga	Morris Brown
Mount Sinai Medical Center, New York, NY	David Adams
University of Michigan Health System - University Hospital, Ann Arbor, Mich	Himanshu Patel
Houston Methodist Hospital, Houston, Tex	Michael Reardon
Heart Hospital of Austin, Austin, Tex	John Oswalt
Aurora Saint Luke's Medical Center, Milwaukee, Wis	David Kress
University of Washington Medical Center, Seattle, Wash	Gabriel Aldea
Abbott Northwestern Hospital, Minneapolis, Minn	Vibhu Kshettry
Cleveland Clinic Foundation, Cleveland, Ohio	Gosta Pettersson
OhioHealth Riverside Methodist Hospital, Columbus, Ohio	Steve Duff
New York-Presbyterian Hospital/Columbia University Medical, New York, NY	Michael Borger
University of Florida Health Shands Hospital, Gainesville, Fla	Thomas Beaver
Massachusetts General Hospital, Boston, Mass	Thoralf Sundt
Oklahoma Heart Hospital, Oklahoma City, Okla	Goya Raikar
Maimonides Medical Center, Brooklyn, NY	Greg Ribakove
University of Maryland Medical Center, Baltimore, Md	James Gammie
University of Southern California University Hospital, Los Angeles, Calif	Craig Baker
University of Colorado Hospital, Aurora, Colo	David Fullerton

TABLE E2. Data collected at follow-up evaluations

Evaluation	Data collected
Baseline*	• Demographic information • Medical history • Pregnancy test for women of childbearing potential • Physical examination • NYHA functional classification • Society of Thoracic Surgeons risk scores • 12-lead electrocardiogram • Hematology/chemistry data (including serum creatinine) • Transthoracic echocardiogram • Relevant medications • AEs
Implant	• Procedure details, including condition of explanted valve and any additional procedures or interventions • Valve data (ie, size, serial number, disposition of implanted valve, or opened packages) • Device failure or malfunction • Perioperative transesophageal echocardiography • Relevant medications • AEs or device deficiency
Discharge/30 d, 3-6 mo, 1 y, and annual visits through 5 y	• NYHA classification • 12-lead electrocardiogram • Hematology/chemistry data • Transthoracic echocardiogram • Relevant medications • AEs or device deficiency
18 and 30 mo (via telephone)	• Vital status • Relevant medications • AEs or device deficiency

AE, Adverse event; *NYHA*, New York Heart Association. *All baseline evaluations were completed within 45 days of the scheduled implant procedure except transthoracic echocardiogram, which was required to be completed within 90 days of the procedure.

TABLE E3. Objective performance criteria for heart valve substitutes

	Rigid	Flexible	2 × OPC	Late linearized event rate	95% upper bound of late linearized event rate
Thromboembolism	3.0	2.5	5.0	1.7	2.55
Valve thrombosis	0.8	0.2	0.4	0.0	0.00
All hemorrhage	3.5	1.4	2.8	3.6	4.81
Major hemorrhage	1.5	0.9	1.8	2.5	3.55
All PVL	1.2	1.2	2.4	0.6	1.18
Major PVL	0.6	0.6	1.2	0.0	0.00
Endocarditis	1.2	1.2	2.4	1.3	2.11

OPC and late linearized event rates are in % per patient-year. Late events include events that occurred more than 30 days postprocedure. Late linearized rates were calculated by dividing the number of late events by the sum of the late patient-years of experience and expressed as a percentage. The OPC rates for valve-related events are defined by the International Organization for Standardization 5840:2009 standards and the Food and Drug Administration heart valve guidance.[E1,E2] *OPC*, Objective performance criteria; *PVL*, paravalvular leak.

E-References

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E2. Cardiovascular implants. Cardiac valve prostheses. Standard EN ISO 5840: 2009 Geneva, Switzerland: International Organization for Standardization; October 31, 2009; withdrawn October 31, 2015. Available at: http://shop.bsigroup.com/ProductDetail/?pid=000000000030205036. Accessed December 12, 2016.

TABLE E4. Additional procedural details

Characteristic	Patients (N = 864), (%)
Concomitant procedures	
Coronary artery bypass grafting	281 (32.5)
Implantable cardiac device	1 (0.1)
LAA closure	66 (7.6)
PFO closure	10 (1.2)
Resection of subaortic membrane not requiring myectomy	18 (2.1)
Ascending aortic aneurysm not requiring circulatory arrest	64 (7.4)
Dissection repair not requiring circulatory arrest	1 (0.1)
Other	132 (15.3)
Annular enlargement	11/341 (3.2)
Aortic root/STJ enlargement	56/344 (16.3)
Patch closure	29/344 (8.4)
Aortic root replacement	1/344 (0.3)
Other technique	26/344 (7.6)
Implanted valve size	
17 mm	1 (0.1)
19 mm	39 (4.5)
21 mm	157 (18.2)
23 mm	314 (36.3)
25 mm	264 (30.6)
27 mm	80 (9.3)
29 mm	9 (1.0)

LAA, Left atrial appendage; *PFO*, patent foramen ovale; *STJ*, sinotubular junction.

TABLE E5. Valve-related adverse events in patients aged less than 60 years at enrollment

Event	No. of events	No. of patients
Thromboembolism	4	3
Valve thrombosis	0	0
Major hemorrhage	1	1
Structural valve deterioration	0	0
Major PVL	1	1
Endocarditis	1	1
Reintervention	2	2
Explant	2	2
Death	0	0

PVL, Paravalvular leak.

TABLE E6. Medication use from baseline through 1 year

Medication	Baseline (N = 864)	Discharge (N = 859)	3-6 mo (N = 811)	1 y (N = 576)
Aspirin or antiplatelet	500 (57.9%)	480 (55.9%)	552 (68.1%)	427 (74.1%)
Anticoagulant	49 (5.7%)	86 (10.0%)	73 (9.0%)	45 (7.8%)
Aspirin or antiplatelet + anticoagulant	35 (4.1%)	282 (32.8%)	119 (14.7%)	48 (8.3%)

TABLE E7. Late linearized rates with 95% upper bounds of all and major hemorrhage for patients taking anticoagulants versus patients not taking anticoagulants

Hemorrhage event by medication indication	Late linearized event rate, %*	95% upper bound of the late linearized rate, %	2 × OPC, %†
All hemorrhage, all patients	3.6	4.81	2.8
Patients taking postimplant prophylaxis	0.6	1.18	
Coumadin and aspirin	0.5	1.01	
Aspirin only	0.1	0.47	
Patients medicated for postimplant new-onset AF	0.5	1.01	
Patients medicated for preexisting conditions	2.5	3.55	
Major hemorrhage	2.5	3.55	1.8
Patients taking postimplant prophylaxis	0.2	0.66	
Coumadin and aspirin	0.1	0.47	
Aspirin only	0.1	0.47	
Patients medicated for postimplant new-onset AF	0.2	0.66	
Patients medicated for preexisting conditions	2.0	2.98	

AF, Atrial fibrillation; *OPC*, objective performance criteria. *Late events include events that occurred >30 days postprocedure. Late linearized rates (% per patient-year) were calculated by dividing the number of late events by the sum of the late patient-years of experience and expressed as a percentage. †OPC rates are provided as % per patient-year.