ADULT

Sutureless versus conventional bioprostheses for aortic valve replacement in severe symptomatic aortic valve stenosis

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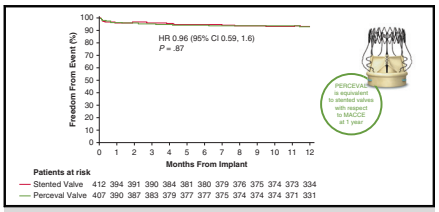
ABSTRACT

Objective: Sutureless aortic valves are a novel option for aortic valve replacement. We sought to demonstrate noninferiority of sutureless versus standard bioprostheses in severe symptomatic aortic stenosis.

Methods: The Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement is a prospective, randomized, adaptive, open-label trial. Patients were randomized (March 2016 to September 2018) to aortic valve replacement with a sutureless or stented valve using conventional or minimally invasive approach. Primary outcome was freedom from major adverse cerebral and cardiovascular events (composite of all-cause death, myocardial infarction, stroke, or valve reintervention) at 1 year.

Results: At 47 centers (12 countries), 910 patients were randomized to sutureless (n = 453) or conventional stented (n = 457) valves; mean ages were 75.4 ± 5.6 and 75.0 ± 6.1 years, and 50.1% and 44.9% were female, respectively. Mean ± standard deviation Society of Thoracic Surgeons scores were 2.4 ± 1.7 and 2.1 ± 1.3, and a ministernotomy approach was used in 50.4% and 47.3%, respectively. Concomitant procedures were performed with similar rates in both groups. Noninferiority was demonstrated for major adverse cerebral and cardiovascular events at 1 year, whereas aortic valve hemodynamics improved equally in both groups. Use of sutureless valves significantly reduced surgical times (mean extracorporeal circulation times: 71.0 ± 34.1 minutes vs 87.8 ± 33.9 minutes; mean crossclamp times: 48.5 ± 24.7 vs 65.2 ± 23.6; both $P < .0001$), but resulted in a higher rate of pacemaker implantation (11.1% vs 3.6% at 1 year). Incidences of perivalvular and central leak were similar.

Conclusions: Sutureless valves were noninferior to stented valves with respect to major adverse cerebral and cardiovascular events at 1 year in patients undergoing aortic valve replacement (alone or with coronary artery bypass grafting). This suggests that sutureless valves should be considered as part of a comprehensive valve program. (J Thorac Cardiovasc Surg 2021;161:920-32)



Freedom from MACCE to 1 year was similar with sutureless or stented valves. *CI*, Confidence interval; *HR*, hazard ratio.

CENTRAL MESSAGE

In patients with severe stenosis undergoing isolated AVR or AVR plus CABG, the sutureless valve reduced operative time and was noninferior to conventional bioprostheses for 1-year major complications.

PERSPECTIVE

According to the results of the prospective, randomized PERSIST-AVR trial, the sutureless valve reduced operative time and was noninferior to stented valves for the freedom from MACCE at 1 year. In patients with severe symptomatic aortic valve stenosis undergoing AVR with or without CABG, the sutureless valve should be considered as part of a comprehensive valve program.

See Commentaries on pages 933, 934, and 935.

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Abbreviations and Acronyms

AVR = aortic valve replacement
CABG = coronary artery bypass grafting
MACCE = major adverse cerebral and cardiovascular events
PERSIST-AVR = Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement

Scanning this QR code will take you to the table of contents to access supplementary information. To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

Aortic valve stenosis is the most frequent cardiac valve disease requiring surgical intervention.[1] Relieving aortic valve dysfunction substantially improves patient quality of life and survival.[2,3] Despite recent developments and promising clinical results in catheter-based valve implantation,[4-6] surgical aortic valve replacement (AVR) remains the procedure of choice for aortic valve stenosis in several clinical settings.[1] Traditionally, surgical options for AVR have been confined to the choice between mechanical and biological prostheses.[1] However, biological prosthetic valves have undergone major advances in valve design and implantation techniques, largely in relation to transcatheter and minimally invasive access.[7] In light of this, sutureless technologies have been introduced as next-generation surgical aortic valves, with the aim of combining the precision of surgical implantation with innovative elements similar to transcatheter technologies that decrease the physiologic impact of surgical procedures.[7-12] Current clinical experience demonstrates promising results for sutureless valve technologies, such as reduced cardiac ischemia and cardiopulmonary bypass times, and facilitated minimally invasive procedures.[13-16] Based on the growing use of rapid-deployment techniques, the need for a randomized trial to assess safety and clinical efficacy in patients undergoing sutureless valve implantation versus sutured bioprostheses was recognized by the cardiovascular community. We therefore conducted the Perceval Sutureless Implant Versus Standard-Aortic Valve Replacement (PERSIST-AVR) trial to evaluate the early and midterm outcomes of sutureless tissue valve implantation to treat aortic valve stenosis, with or without concomitant coronary artery disease, compared with conventional stented tissue valves.

MATERIALS AND METHODS

Study Design

Details about the design of the PERSIST-AVR trial have been published.[17] In brief, the PERSIST-AVR trial is a multicenter, prospective, randomized, open-label, noninferiority trial with an adaptive design. The trial was conceived to demonstrate the noninferiority of the sutureless prosthesis (Perceval, LivaNova plc, London, United Kingdom) compared with standard aortic valves, using a conventional or minimally invasive approach, in patients with severe symptomatic aortic valve stenosis. Details about the organization of the trial and a list of participating centers are provided in Online Data Supplement. The protocol was developed in collaboration with the Steering Committee in accordance with principles delineated in current guidelines and outcome criteria.[18,19] The protocol was approved by the institutional review board or medical ethics committee at each center. All patients provided written informed consent. LivaNova funded all trial-related activities, participated in site selection, and supported data monitoring, trial management, and statistical analysis. The data and safety monitoring board provided study oversight, with periodic safety review and recommendations relating to trial design and conduct. An independent clinical events committee adjudicated all clinical events related to the primary and secondary outcomes. Per protocol, an adaptive design was used to determine the study sample size through interim analysis conducted by an independent statistical unit (Berry Consultants, Austin, Tex).

Patient Selection

Adults with severe symptomatic aortic valve stenosis who were candidates for surgical AVR of the native aortic valve were eligible. Severe aortic valve stenosis was defined as: an initial aortic-valve area of 1.0 cm^2 or less or an indexed aortic-valve area of less than 0.6 cm^2/m^2; and a mean gradient of more than 40 mm Hg or a maximum aortic velocity of more than 4 m per second at rest. Dobutamine provocation was used in patients with left ventricular ejection fraction less than 55% or a Doppler velocity index of less than 0.25 on resting echocardiography.[7,8] A preoperative computed tomography scan was used to measure the annulus to confirm the compatibility with available sutureless valve size. Concomitant procedures such as coronary artery bypass grafting (CABG), treatment of atrial fibrillation, septal myectomy, and aortic root enlargement were allowed.

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The inclusion and exclusion criteria are provided in Online Data Supplement.

Study Procedures

Enrolled patients were randomly assigned, in a 1:1 ratio, to treatment with the sutureless or the stented biological valve. The choice of the surgical bioprosthesis in the stented valve arm was left to the discretion of the surgeon. A blocked randomization list was generated by the sponsor, stratified by country and surgical approach to ensure proportional assignment. To minimize selection bias, randomization was performed after a computed tomography scan confirmed eligibility for the current sutureless valve implantation, suitability for the proposed surgical access (full sternotomy or ministernotomy), and the decision about an isolated or concomitant procedure was decided. Right anterior minithoracotomy was not allowed because of variable experience among the centers or suitability for the comparator standard valve. Details on the sutureless valve and implantation procedure have been published (Video 1).[20,21] Clinical follow-up, which is ongoing, was performed at hospital discharge, between 1 and 3 months, at 1 year, and annually until 5 years. Details about trial assessment at each stage are shown in the Online Data Supplement.

Study Outcomes

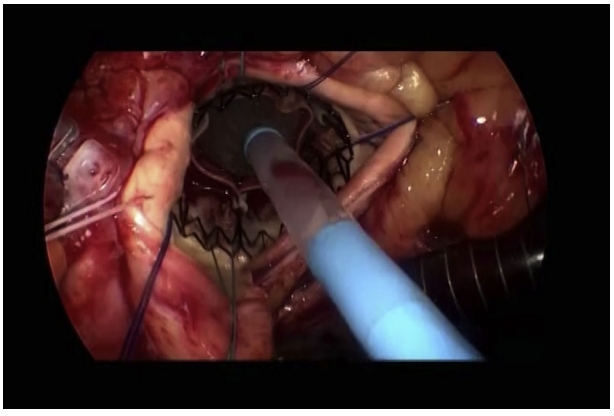
The primary outcome to assess the safety and efficacy of the sutureless valve versus standard sutured stented valves was freedom from major cerebral and cardiovascular events (MACCE), a composite of death from any cause, myocardial infarction, stroke, or valve reintervention at 1 year. Myocardial infarction and stroke were defined according to the Universal Definition of Myocardial Infarction[18] and the Valve Academic Research Consortium-2[22] criteria. Trial definitions are provided in Online Data Supplement. Secondary outcomes included morbidity parameters, components of the primary outcome, comparison of surgical times between the 2 arms, evaluation of clinical status (New York Heart Association class) at 1 to 3 months and at 1 year, and valve hemodynamics.

Statistical Analysis

The trial design was based on the use of a Bayesian adaptive Goldilocks approach,[23] with 2 planned interim analyses (after recruiting 900 and 1050 patients) with the aim of stopping enrollment earlier than the maximum sample size of 1234 subjects. Stopping rules were defined a priori empirically through computer-based simulations conducted to optimize study operating characteristics. If the Bayesian posterior probability of noninferiority, with a margin of 5%, in the per-protocol population exceeded 99.6% at the first interim analysis or 99.3% at the second interim analysis, accrual would end, but patient follow-up would continue as planned, and the primary analysis would take place when all patients completed follow-up for the primary outcome. At the primary analysis, noninferiority would be concluded if the posterior probability exceeded 99.75%. All thresholds were selected to control the type I error rate at no more than 2.5% 1-sided, which was verified by simulations. The modified intention-to-treat population, defined as the randomized population who received any valve, was used to assess the sensitivity of the primary analysis.

As indicated in the statistical analysis plan, if noninferiority was concluded, a test for superiority was carried by assessing if the posterior probability of superiority exceeded 97.75%. No alpha adjustment was performed because the test is hierarchically nested within the noninferiority comparison and is a closed-testing procedure. Additional logistic regression analysis (including as covariates the implanted valve groups and as stratification factors country and surgical approach) to assess the sensitivity of noninferiority results to possible confounding impact of the stratification factors was performed. Finally, a Kaplan–Meier for cumulative freedom from 1-year from MACCE and the Greenwood standard errors for each arm were performed to confirm the robustness of results to the statistical method.

Surgical times were analyzed in a superiority context in the safety population. Mortality and morbidity rates were assessed using descriptive statistics broken down by adverse event type and timing (intraoperative/perioperative or after intervention according to Valve Academic Research Consortium-2 definitions). Details on analysis populations, safety, and sensitivity analyses are provided in Online Data Supplement.



VIDEO 1. The intraoperative implant steps (valve approach and sutureless tissue valve implantation) are shown. Video available at: https://www.jtcvs.org/article/S0022-5223(20)33339-0/fulltext.

RESULTS

Patient Population

A total of 914 patients were enrolled, and 910 underwent randomization at 47 centers in Europe, Canada, United States, Chile, and Israel from March 2016 to September 2018; 453 patients were assigned to the sutureless group, and 457 patients were assigned to the stented group. Rates of implant success were comparable in the sutureless and stented groups. The reasons for nonimplantation are shown in Online Data Supplement. The population in the primary outcome analysis (per protocol) included 819 patients: 407 in the sutureless group and 412 in the stented group. After randomization, 12 patients did not received implants, 2 patients received implants with a nonstudy valve, and 59 patients (28 patients in the sutureless and 31 patients in the stented group) crossed over to the other study arm (Online Data Supplement). Reasons for cross-over are detailed in Online Data Supplement. At 1 year, data on the primary outcome were complete for 831 of 840 (98.9%) of the intention-to-treat population.

At the time of randomization, the baseline characteristics of the 2 trial groups were well balanced (Table 1). A ministernotomy approach was used in 50.4% of the sutureless group and 47.3% of the stented group. The number of concomitant procedures was also well balanced between the 2 groups.

Primary Outcome

The composite MACCE outcome occurred in 8.1% of patients in the sutureless group and in 7.8% of patients in

TABLE 1. Baseline characteristics of the patients and operative characteristics

Characteristic	Per-protocol population		Modified intention-to-treat population	
	Sutureless (N = 407)	Stented (N = 412)	Sutureless (N = 447)	Stented (N = 449)
Age (y)	75.4 ± 5.6	75.0 ± 6.1	75.3 ± 5.8	75.2 ± 6.0
Female sex	204 (50.1)	185 (44.9)	214 (47.9)	209 (46.5)
Body mass index	28.4 ± 4.8	28.3 ± 4.2	28.3 ± 4.8	28.4 ± 4.3
New York Heart Association class				
I	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
II	263 (64.6)	261 (63.3)	290 (64.9)	284 (63.3)
III	138 (33.9)	147 (35.7)	151 (33.8)	161 (35.9)
IV	6 (1.5)	2 (0.5)	6 (1.3)	3 (0.7)
Society of Thoracic Surgeons score	2.4 ± 1.7	2.1 ± 1.3	2.4 ± 1.8	2.2 ± 1.3
euroSCORE II	2.2 ± 1.8	2.0 ± 1.4	2.2 ± 1.8	2.0 ± 1.5
Comorbid conditions				
Coronary artery disease	165 (40.5)	147 (35.7)	183 (40.9)	160 (35.6)
Previous myocardial infarction	18 (4.4)	17 (4.1)	19 (4.3)	17 (3.8)
Previous CABG	1 (0.2)	2 (0.5)	1 (0.2)	2 (0.4)
Previous PCI	37 (9.1)	46 (9.2)	41 (9.2)	49 (10.9)
Heart failure	18 (4.4)	25 (6.1)	21 (4.7)	28 (6.2)
Pre-existing pacemaker implant	9 (2.2)	8 (1.9)	11 (2.5)	8 (1.8)
Diabetes mellitus	110 (27.0)	114 (27.7)	118 (26.4)	130 (29.0)
Hypertension	335 (82.3)	335 (81.3)	364 (81.4)	366 (81.5)
Peripheral vascular disease	31 (7.6)	33 (8.0)	33 (7.4)	35 (7.8)
Chronic lung disease	48 (11.8)	39 (9.5)	56 (12.5)	43 (9.6)
Previous stroke	19 (4.7)	11 (2.7)	23 (5.1)	12 (2.7)
Previous transient ischemic attack*	18 (4.4)	5 (1.2)	20 (4.5)	7 (1.6)
Smoking*	89 (21.9)	118 (28.6)	103 (23.0)	125 (27.8)
Carotid artery disease	41 (10.1)	49 (11.9)	50 (11.2)	55 (12.2)
Malignancy (neoplasia)	33 (8.1)	34 (8.3)	36 (8.1)	39 (8.7)
Dyslipidemia†	225 (55.3)	260 (63.1)	249 (55.7)	285 (63.5)
Operative characteristics				
Surgical approach				
Full sternotomy	202 (49.6)	217 (52.7)	229 (51.2)	229 (51.0)
Ministernotomy	205 (50.4)	195 (47.3)	218 (48.8)	220 (49.0)
Bicuspid aortic valve†	44 (10.8)	45 (10.9)	53 (11.9)	48 (10.7)
Mean annulus diameter (mm)‡	23.9 ± 2.1	23.3 ± 2.0	24.0 ± 2.1	23.2 ± 2.0
Valve size				
S (21 mm)	33 (8.1)	NA	35 (7.8)	NA
M (23 mm)	130 (31.9)	NA	132 (29.5)	NA
L (25 mm)	141 (34.6)	NA	143 (32.0)	NA
XL (27 mm)	103 (25.3)	NA	109 (24.0)	NA
19 mm	NA	22 (5.3)	NA	22 (4.9)
21 mm	NA	122 (29.6)	NA	123 (27.4)
23 mm	NA	170 (41.3)	NA	173 (38.5)
25 mm	NA	89 (21.6)	NA	91 (20.3)
27 mm	NA	9 (2.2)	NA	9 (2.0)
Concomitant procedure	122 (30.0)	119 (28.9)	135 (30.2)	128 (28.5)
Coronary artery bypass	99 (24.3)	92 (22.3)	109 (24.4)	97 (21.6)
Septal myectomy	14 (3.4)	13 (3.2)	14 (3.1)	17 (3.8)
Aortic annulus enlargement	0 (0.0)	4 (1.0)	0 (0.0)	4 (1.0)
Other	15 (3.7)	21 (5.1)	20 (4.5)	22 (4.9)

Values are presented as mean ± standard deviation, median (range), or n (%). *euroSCORE*, European System for Cardiac Operative Risk Evaluation; *CABG*, coronary artery bypass grafting; *PCI*, percutaneous coronary intervention; *NA*, not applicable. *$P < .05$ (per-protocol population). †Sievers type 1 only allowed per protocol. ‡Universal sizer measurement was determined intraoperatively by direct measurement of the aortic annulus with graduated Hegar dilators.

TABLE 2. Clinical outcomes at 30 days and 1 year (per-protocol population)

Outcome	30 d			1 y		
	Sutureless (n = 407)	Stented (n = 412)	95% credible interval*	Sutureless (n = 407)	Stented (n = 412)	95% credible interval
	n (%)			n (%)		
Primary outcome: MACCE	16 (3.9)	16 (3.9)	0.0 (−2.7 to 2.6)	33 (8.1)	32 (7.8)	−0.3 (−4.1 to 3.4)
Components of the primary outcome						
Death from any cause	4 (1.0)	4 (1.0)	0.0 (−1.4 to 1.4)	15 (3.7)	14 (3.4)	−0.3 (−2.9 to 2.3)
Cardiovascular death	3 (0.7)	3 (0.7)	0.0 (−1.3 to 1.2)	7 (1.7)	9 (2.2)	0.5 (−1.5 to 2.4)
Valve-related death	0 (0.0)	0 (0.0)	0.0 (−0.5 to 0.5)	3 (0.7)	2 (0.5)	−0.3 (−1.4 to 0.9)
Myocardial infarction	4 (1.0)	6 (1.5)	0.5 (−1.1 to 2.0)	5 (1.2)	7 (1.7)	0.5 (−1.2 to 2.2)
All stroke	6 (1.5)	8 (1.9)	0.5 (−1.4 to 2.3)	10 (2.5)	13 (3.2)	0.7 (−1.6 to 3.0)
Disabling	4 (1.0)	4 (1.0)	0.0 (−1.4 to 1.4)	8 (2.0)	8 (1.9)	0.0 (−2.0 to 1.9)
Nondisabling	1 (0.3)	1 (0.2)	0.0 (−0.8 to 0.8)	1 (0.2)	3 (0.7)	0.5 (−0.6 to 1.5)
Aortic valve reintervention	4 (1.0)	0 (0.0)	−1.0 (−2.0 to 0.1)	7 (1.7)	4 (1.0)	−0.7 (−2.4 to 0.9)
Secondary outcomes						
Transient ischemic attack	0 (0.0)	2 (0.5)	0.5 (−0.3 to 1.3)	4 (1.0)	4 (1.0)	0.0 (−1.4 to 1.4)
Bleeding event	18 (4.4)	26 (6.3)	1.9 (−1.2 to 5.0)	21 (5.2)	29 (7.0)	1.9 (−1.4 to 5.2)
Life-threatening or disabling	7 (1.7)	13 (3.2)	1.4 (−0.7 to 3.6)	7 (1.7)	13 (3.2)	1.4 (−0.7 to 3.6)
Major	10 (2.5)	10 (2.4)	0.0 (−2.2 to 2.1)	11 (2.7)	13 (3.2)	0.5 (−1.9 to 2.8)
Kidney injury	8 (2.0)	9 (2.2)	0.2 (−1.8 to 2.2)	9 (2.2)	10 (2.4)	0.2 (−1.9 to 2.3)
Endocarditis	0 (0.0)	0 (0.0)	0.0 (−0.5 to 0.5)	6 (1.5)	8 (1.9)	0.5 (−1.4 to 2.3)
New-onset atrial fibrillation	14 (3.4)	32 (7.8)	4.3 (1.2 to 7.5)	16 (3.9)	38 (9.2)	5.3 (1.9 to 8.7)
Pacemaker implant	43 (10.6)	13 (3.2)	−7.4 (−10.8 to −3.9)	45 (11.1)	15 (3.6)	−7.4 (−10.9 to −3.8)
Structural valve dysfunction	0 (0.0)	0 (0.0)	0 (−0.5 to 0.5)	1 (0.2)	0 (0.0)	−0.2 (−0.9 to 0.4)
Valve thrombosis	0 (0.0)	0 (0.0)	0 (−0.5 to 0.5)	1 (0.2)	0 (0.0)	−0.2 (−0.9 to 0.4)

MACCE, Major adverse cerebral and cardiovascular events. *Credible interval estimated using Jeffreys method with prior noninformative beta distribution parameters (½, ½).

the stented group (Table 2). Freedom from the primary outcome was 91.6% (95% Bayesian credible interval, 88.7% to 94.1%) in the sutureless group and 92.0% (89.1%, 94.4%) in the stented group (posterior probability of noninferiority 99.09%) (Table 3 and Figure 1). Components of the primary outcome are shown in Figure 2, *B* and *C* and Table 2. Because the posterior predictive probability of noninferiority at the primary analysis was equal to 99.09%, exceeding the threshold of 97.75% with a sample size of 914 patients, noninferiority was concluded. The additional prespecified criterion for superiority was not concluded (posterior probability of superiority 42.22%).

TABLE 3. Secondary noninferiority and superiority objectives

Criterion	Hypothesis	Analysis cohort	Sutureless	Stented	Posterior probability	Threshold	Test result
Noninferiority							
Freedom from MACCE at 1 y	$Pr(MACCE_{CONTROL} - MACCE_{PERCEVAL} < 0.05 \mid Data)$	Per protocol	0.916	0.920	0.9909	0.9775	Passed
Superiority							
Freedom from MACCE at 1 y	$Pr(MACCE_{CONTROL} < MACCE_{PERCEVAL} \mid Data) > 0.9775$	Per protocol	0.916	0.920	0.4222	0.9775	Not passed
Mean extracorporeal circulation time (min)	ECC time sutureless < stented	Safety	71.0 ± 34.1*	87.8 ± 33.9*	NA	NA	Passed† ($P < .0001$)
Mean crossclamp time (min)	Crossclamp time sutureless < stented	Safety	48.5 ± 24.7*	65.2 ± 23.6*	NA	NA	Passed† ($P < .0001$)

MACCE, Major adverse cerebral and cardiovascular events; *Pr*, probability; *ECC*, extracorporeal circulation; *NA*, not available. *Plus–minus values are mean ± standard deviation. All noninferiority objectives were tested with a type I error rate at 2.5% 1-sided, and superiority tests were tested with a type I error rate at 2.5%. If all the tests met their success criterion, the primary outcome of death or disabling stroke at 24 months was tested for superiority with type I error rate at 2.5%. †Based on analysis of covariance after controlling for prognostic perioperative patient characteristics (country, surgical approach, concomitant procedure, sex, age).

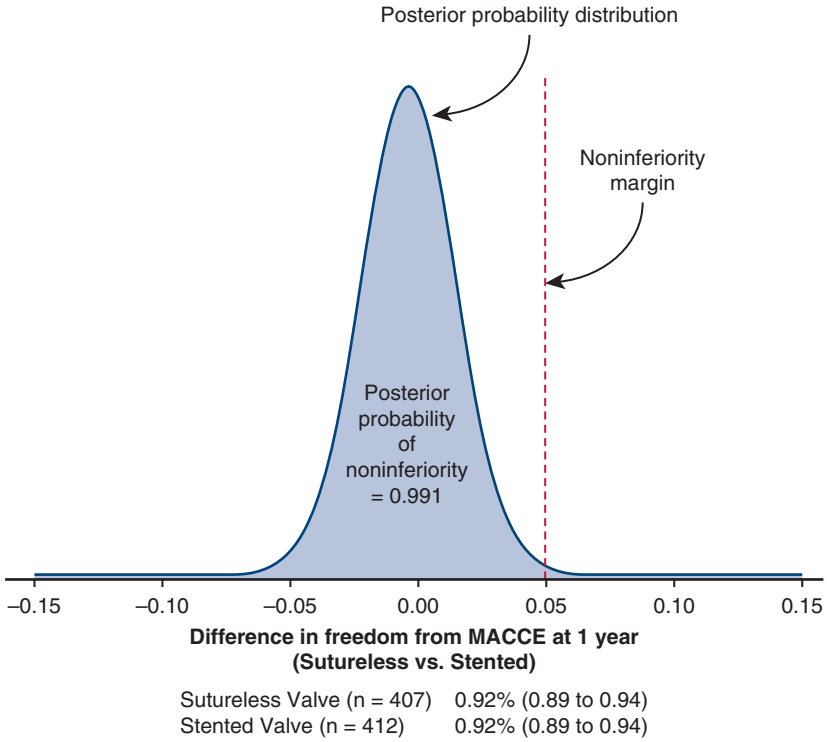


FIGURE 1. Noninferiority analysis. In this Bayesian analysis, the posterior probability distribution for the difference in the primary outcome (freedom from MACCE) in patients with a sutureless valve implant is shown, along with the probability that this difference is less than the noninferiority margin for the sutureless valve. *MACCE*, Major adverse cerebral and cardiovascular events.

The prespecified sensitivity analyses on the modified intention-to-treat population confirmed the noninferiority results (Online Data Supplement).

Interim Analysis

The first interim analysis was conducted on July 6, 2018, by the independent statisticians. The posterior probability of noninferiority in the per-protocol population was 99.82%. Because this posterior probability was greater than the protocol-defined 99.6% threshold, further study enrollment was discontinued. Patient follow-up continued as planned, and the primary analysis took place when all patients completed follow-up for the primary outcome.

Secondary Outcomes

The results of hierarchical analyses of the secondary outcomes are provided in Table 2 and Online Data Supplement. Durations of cardiopulmonary bypass and aortic crossclamping times were significantly ($P < .0001$) shorter for patients undergoing isolated or combined AVR procedures with sutureless valves (Figure 3, *A*, and Table 3).

The rate of permanent pacemaker implantation was higher in the sutureless group, whereas other adverse events occurred similarly (Table 2). New York Heart Association symptoms improved significantly in both groups from baseline and persisted throughout 1-year follow-up (Figure 3, *B*). Aortic valve hemodynamics also improved equivalently in both groups (Figure 4, *A*). Mean aortic valve gradients and aortic valve areas were comparable in the 2 groups at 1-year follow-up. In terms of prosthetic valve function, the incidences of central and paravalvular regurgitation were similar (Figure 4, *B*). One case of valve thrombosis was reported (in the sutureless group).

DISCUSSION

This prospective, randomized, open-label, noninferiority trial demonstrated that in patients with severe symptomatic aortic valve stenosis undergoing open AVR with or without CABG, a sutureless valve was noninferior to stented valves with respect to MACCE at 1 year (Figure 5). The sutureless valve was associated with significantly lower cardiopulmonary bypass and ischemic times in both isolated and combined procedures, with full sternotomy or minimally invasive approaches. The implant success rate was comparable in the 2 groups, demonstrating that a reproducible procedure is achievable with the sutureless valve. The sutureless arm was associated with a higher incidence of perioperative permanent pacemaker implantation. The rate of other adverse events was similarly low in both groups. No differences were found between the groups in terms of aortic valve hemodynamics or other clinical outcomes.

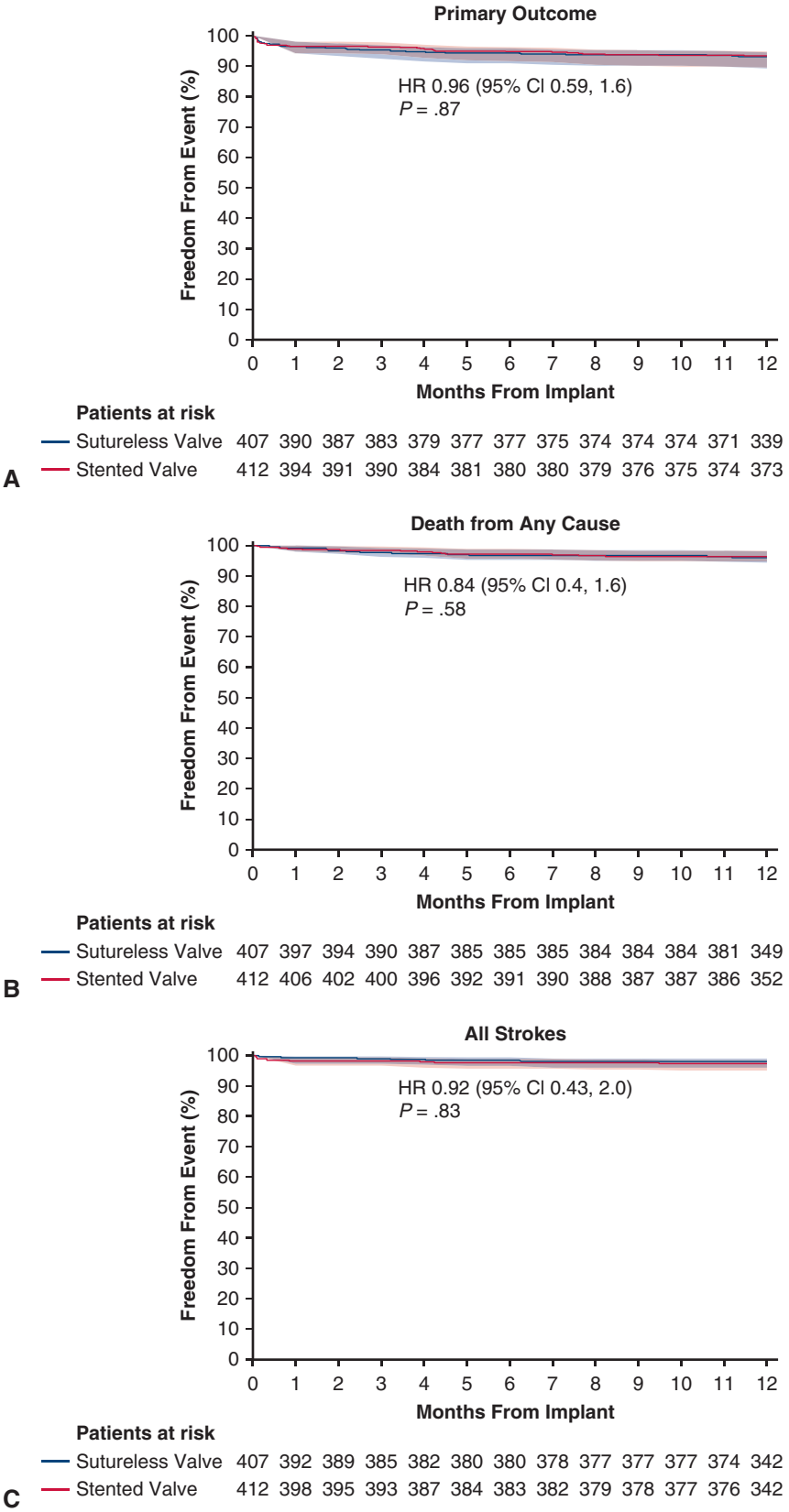
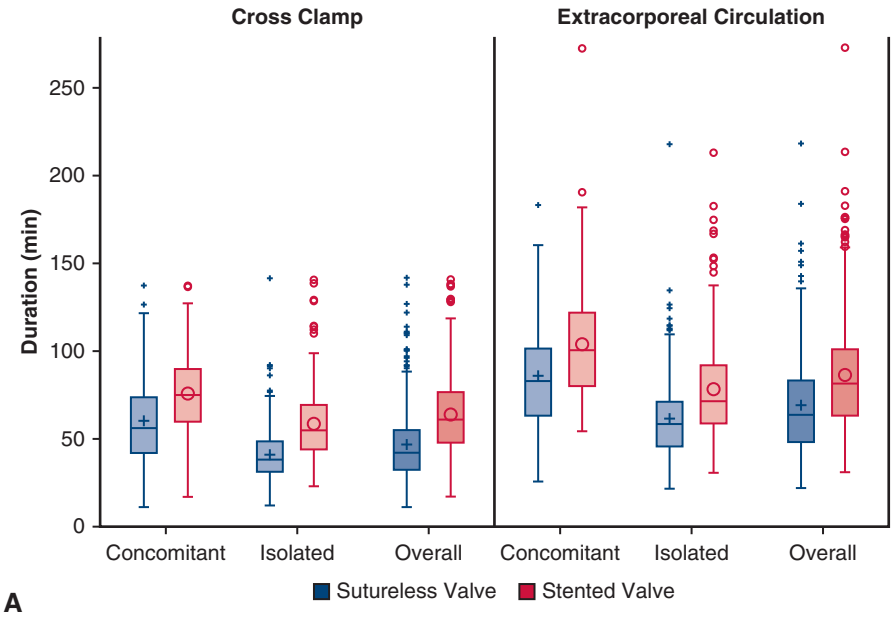


FIGURE 2. Time-to-event curves for (A) the primary outcome (MACCE); (B) death from any cause; and (C) all strokes. All findings were equivalent in the 2 groups. The shaded regions show 95% CIs. *HR*, Hazard ratio; *CI*, confidence interval.



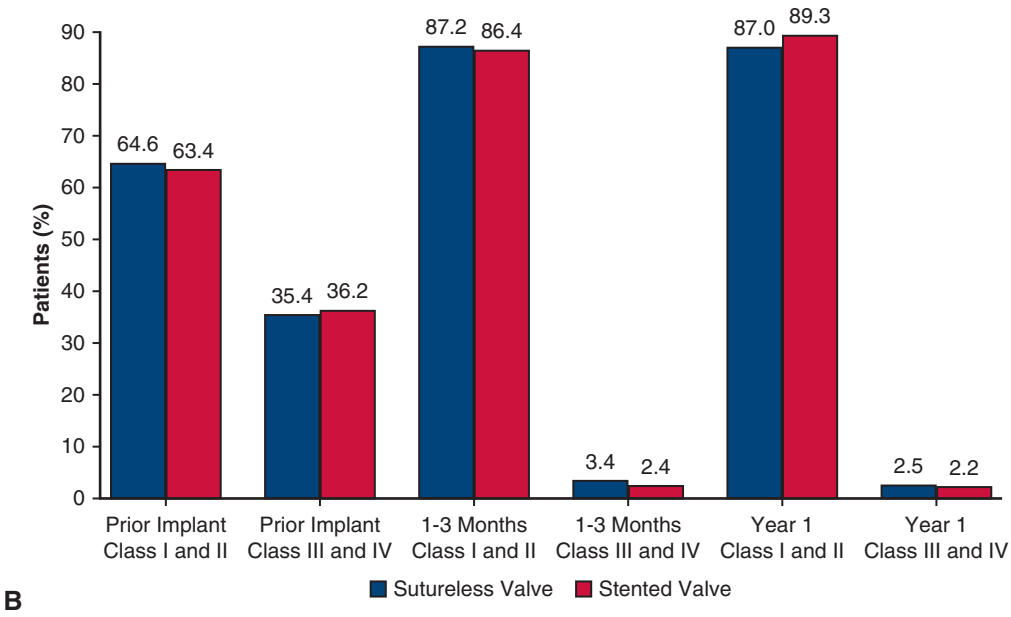


FIGURE 3. Secondary outcomes: (A) crossclamp and extracorporeal circulation times* and (B) NYHA classes. Crossclamp and extracorporeal circulation times were shorter with the sutureless valve; NYHA classes were similar in both groups. **Horizontal lines* indicate median values; *circles* and *crosses* within boxes indicate mean values; *boxes* indicate the 25th and 75th percentiles (interquartile range); the 2 vertical bars (*whiskers*) reach respectively the minimum and the maximum in the data; and circles or crosses above or below the whiskers indicate outliers.

The Perceval valve was designed to enhance surgical valve implantability by using a completely sutureless implantation technique for AVR. Preliminary experiences with the valve have shown favorable early and midterm results.[8-16] Furthermore, the sutureless valve has been demonstrated to facilitate minimally invasive procedures.[12,24] Several propensity-matched studies and meta-analyses, which compared rapid-deployment sutured and sutureless valves with conventional bioprostheses for AVR, have shown superiority of the sutureless valve in terms of surgical times, perioperative atrial fibrillation, transfusion rates, and intensive care unit and hospital stays.[12-16]

Outcomes in this study demonstrate low rates of 30-day and 1-year MACCE and other adverse events in both the sutureless and stented groups, despite the need for

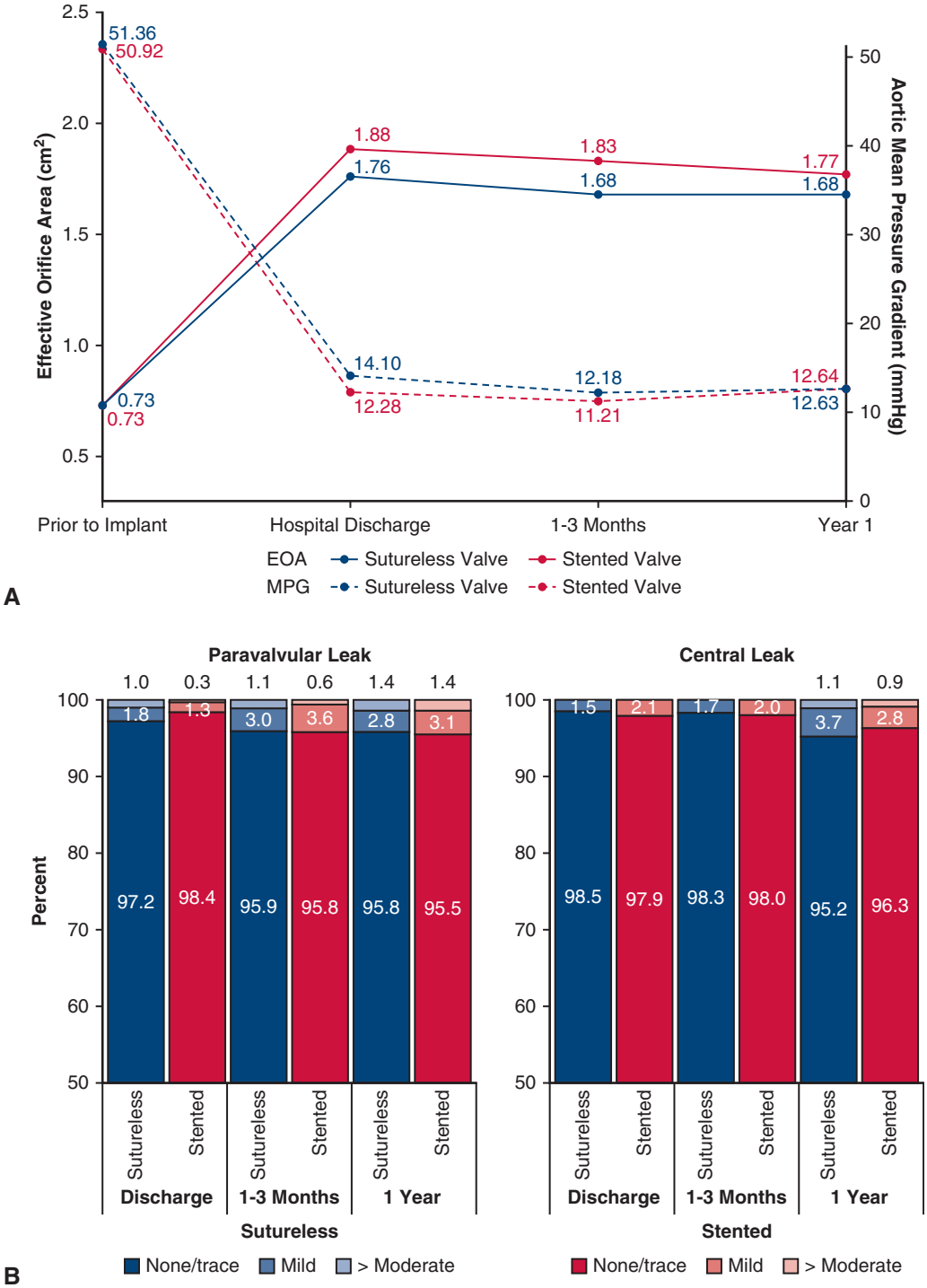


FIGURE 4. Secondary outcomes: (A) effective orifice areas (*solid lines*) and aortic mean pressure gradients (*dashed lines*) and (B) paravalvular and central leaks (per-protocol population). All outcomes were equivalent in the 2 groups. *EOA*, Effective orifice area; *MPG*, mean pressure gradient.

concomitant procedures in approximately one-quarter of the patients. These results are comparable to those of other recent trials comparing surgical AVR with transcatheter valve implantation in low-risk patients.[23,25]

Measures of clinical efficacy were comparable in both treatment arms. Although patient selection may have favorably affected our results, this investigation showed that in this population, surgical AVR has a low complication rate. The low rate of atrial fibrillation compared with accepted rates in 30% to 50% of patients in other studies was strongly influenced by the definition in the present study, in which only atrial fibrillation resulted in a serious

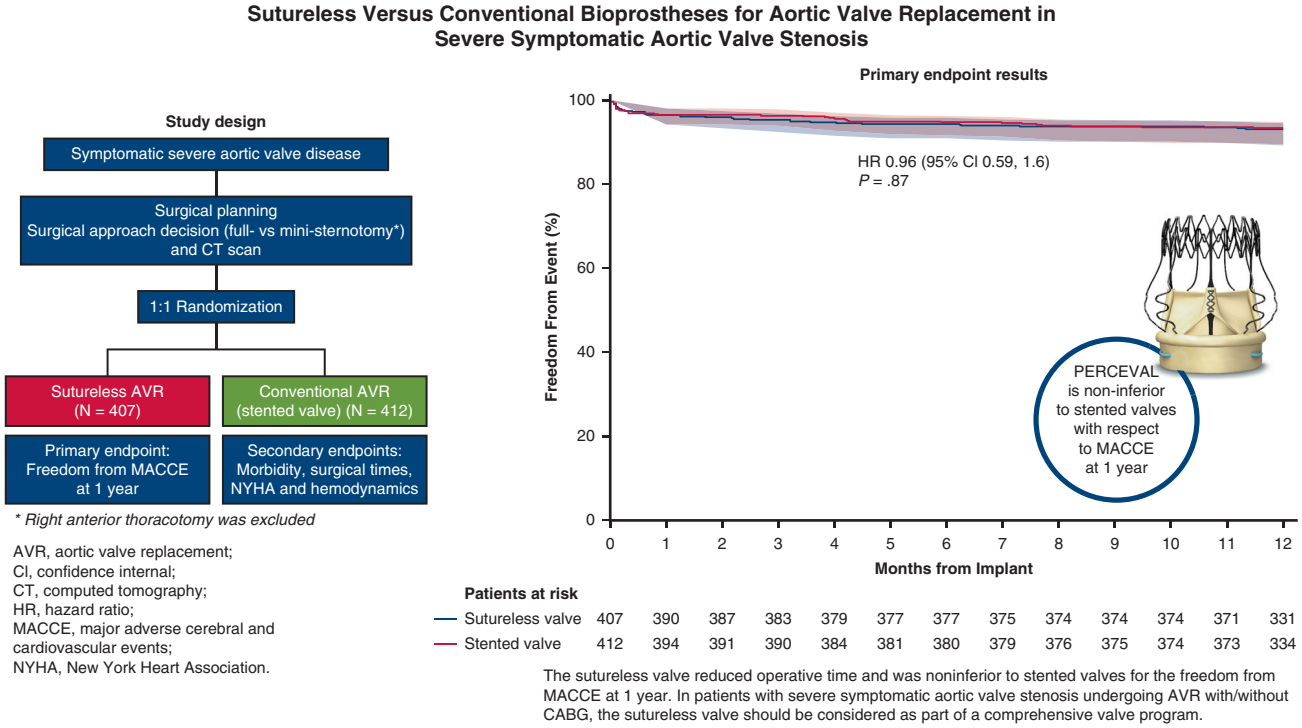


FIGURE 5. Patients randomized to sutureless or conventional (stented) AVRs had similar rates of freedom from the primary outcome (MACCE). The shaded regions show 95% CIs.

adverse event, such as requiring cardioversion was considered to meet the definition for inclusion.[23,25]

This randomized controlled trial demonstrates the superiority of the sutureless valve over stented valves for procedural times, either in isolated or combined procedures. These results did not translate into clearly measurable clinical benefit at 30-day or 1-year follow-up in the overall study findings; however, the ability to discern possible benefits due to reduced procedure times may have been limited in this low-risk study population. Length of cardiopulmonary bypass and cardiac ischemia are well-known determinants of complicated postoperative outcomes.[13,26-28] The relationship between cardiopulmonary bypass time and complications is nonlinear[29]; therefore, the potential benefit of a shorter bypass time with sutureless valves could be relevant mainly in patient requiring long procedural times for complex, multiple procedures. Additional analyses are under way to investigate the potential impact of operative time reduction and clinical benefits among various subgroups.

The need for pacemaker implantation is a well-known complication in patients undergoing AVR. Transcatheter and rapid-deployment procedures have shown higher rates of periprocedural need for permanent pacemaker compared with conventional surgical valve placement.[30-33] New insights into implantation techniques seem to indicate that the rate of permanent pacemaker implantation may be substantially reduced with modified intraoperative approaches.[34-37]

In addition, some design-related factors such as the protrusion of the prosthesis beneath the aortic annulus may contribute to the need for pacemaker implantation after Perceval AVR. This is supported by the finding that the highest pacemaker rates were in patients receiving size XL, with the greatest subannular protrusion compared with smaller sizes (S, M, L). Therefore, specific changes in surgical implantation techniques and valve design may represent critical factors and could reduce PPI rate significantly, warranting further investigations.

The incidence of endocarditis or other valve-related complications was low in both groups. The limited duration of follow-up warrants caution when interpreting these findings, and a longer period of observation is necessary to disclose any potential difference between the 2 groups. The PERSIST-AVR trial includes a planned period of observation of a minimum of 5 years, and longer-term data will become available in the future.

The present study showed comparable bioprosthetic hemodynamic performance at discharge that persisted to 1 year in the sutureless and the stented-valve groups. These findings are in contrast to a recent publication from a national registry that demonstrated higher postoperative

gradients in rapid deployment compared with standard surgical AVR.[15] In contrast to this study and unlike comparisons with transcatheter AVR,[15] no difference was found between study groups with regard to central or paravalvular regurgitation, demonstrating that the sutureless valve ensures correct sealing at the aortic annulus. Equivalent significant and durable improvement in clinical status was observed in the majority of treated patients in the 2 groups throughout the period of follow-up.

Study Limitations

The study is subject to several limitations, including a selected, nonconsecutive study population. Also, the cross-over rate was reasonably high, with the reasons provided in Online Data Supplement, but the results did not differ between the per-protocol and modified intention-to-treat populations. The decision about valve size was left to the attending surgeon's discretion. However, the rather high rate of size 19 and 21 mm (34.9%) for the stented valve group is in accordance with various other clinical studies[38-42] that present results in bioprostheses at the aortic valve position (Online Data Supplement). Intraoperative, intensive care, and anticoagulation management were at the discretion of the treating physician and center. The study involved centers experienced in the techniques, but recruitment rates were heterogeneous across sites.

CONCLUSIONS

In this prospective, randomized, open-label noninferiority trial, the sutureless valve was noninferior to stented valves for the primary outcome of freedom from MACCE up to 1 year in patients with severe symptomatic aortic valve stenosis undergoing AVR with or without associated CABG. Increased risk of need of pacemaker implantation remains a challenge for sutureless valves especially in patients with large annulus requiring XL size valves, although recent refinements of the sutureless valve design and of the implantation technique have shown reduction of such complications.[24] These findings suggest that sutureless valves could be considered in any case of aortic valve disease as part of a comprehensive valve program.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://aats.blob.core.windows.net/media/20AM/Presentations/Sutureless%20versus%20Conventional%20Biopr.mp4.

Conflict of Interest Statement

T. Fischlein: consultant LivaNova and BioStable. T. Folliguet: consultant LivaNova (Steering Committee). B.M.: consultant LivaNova (Steering Committee and Proctor). M.L.S.: consultant LivaNova (Steering Committee and Proctor). E.E.R.: consultant LivaNova (Steering Committee and Proctor), speaker for Abbott, consultant, speaker and investigator for Edwards and Medtronic. S.P.: consultant LivaNova (Proctor). R.L.: consultant for LivaNova, Medtronic, Advisory Board member for Eurosets and PulseCath (Advisory Board Member). All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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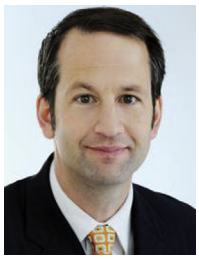
Key Words: aortic valve replacement, randomized controlled trial, sutureless

Discussion

Presenter: Dr Theodor J. M. Fischlein



Dr Michael A. Borger *(New York, NY)*. Cardiac surgery is unfortunately in the area of heart valve therapy relatively sparse in our randomized trial evidence thus far, but there's no doubt about it: As we've learned from our interventional cardiology colleagues, this is the way of the future to more accurately determine if the therapy that we are applying for our patients is the appropriate one. Again, I would just like to congratulate you on bringing a very important trial here to publication. Just as a fine point, it is a noninferiority trial and the conclusions state that the 2 treatment options are equivalent, just statistically proving equivalence is basically impossible. But what you can say is that the one therapy is noninferior to the other, just as a fine critique.

First of all, the implant success rate: there were 5 Perceval patients who were not successful with the implant, and interestingly, 10 conventional bioprosthetic valve

patients who did not receive a successful implant. Can you give us a few more details on those patients, please?

Dr Theodor J. M. Fischlein *(Nürnberg, Germany)*. Well, it was interesting that in the standard valve group, we had some cases with problems in sizing and positioning. We had 2 cases due to valve overlapping the coronary ostia. We also had 2 cases with strong calcification of the annulus area and of the root. There was also 1 case that required replacing the ascending aorta and an instance of congenital abnormality in the standard group. In the Perceval group, it was a problem with the deployment or, let's say, dislodgment of the stent of the Perceval valve.

Dr Borger. Some 35% of the conventional bioprosthetic group patient received a 19 or 21 valve size. Especially in this age group, we tend to try to avoid this, because they may need a TAVI valve-in-valve in the future. Do you think that may have affected the hemodynamic performance in the conventional group? Also, do you have experience with TAVI in a Perceval valve?

Dr Fischlein. To the first part of your question, yes, you are absolutely right. I am not a friend of the size 19. We don't actually use size 19 in our institution; we always do a root enlargement in those cases. And of course, if I look to the gradients, then they have been quite high as you can assume, especially the size 19. If you have to do a valve-in-valve procedure to implant a TAVI prosthesis—yes, we have done this already for the Perceval valve, so it's possible to do that. But of course, if you have to use a 19 standard valve, that could be a problem in the future, absolutely.

But what I always say is, open reoperation for AVR or, let's say, replacement of the prosthesis, I actually view this as not being very high-risk to perform. So also surgery would be a possible situation to do.

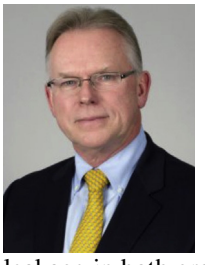
Dr Borger. My last question is: The shorter cardiopulmonary bypass and crossclamp times that you demonstrated and that have been shown and in several other studies as well on sutureless and rapid-deployment valves: Usually we expect that to be associated with less bleeding, maybe shorter ventilation times, maybe shorter intensive care unit, hospital length-of-stay. Did you find that in your study?

Dr Fischlein. We plan do a lot of sub-studies. This is what we are looking forward to as well. Up to now, I couldn't really find any big differences in both groups in regard to bleeding. We had somewhat better results in the Perceval group, and intubation time was also a little bit shorter in the Perceval group. But as you know, in some multicenter studies, and from our center, we could already show a reduction of bleeding postoperatively. Eventually this is also much influenced by the surgical access. If you do just minimal, let's say a ministernotomy or a right anterior minithoracotomy, you have less bleeding. But we will have to look to our cohorts closer as well, and up to now, we had not found any statistical significance between both groups.

Dr Vinod H. Thourani *(Atlanta, Ga)*. I was a little surprised that one of the benefits that people have talked about sutureless valves is being able to do more minimally invasive surgery, and I saw no difference between the stented versus the sutureless. In fact, it was about 50% for both. Could you explain that a little bit? I know the company has advocated that we are able to do more of those with this technique. Did you not find that was not the case?

Dr Fischlein. Well, there was a difference. I hope I understood your question fully, but there was a difference in clamping time and cardiopulmonary bypass time. For the ministernotomy, you're right, it's not like a wow effect. But with Perceval, you could achieve a shorter clamping time as well.

Experienced centers using sutureless devices—especially in isolated AVR cases, always do a ministernotomy. In some cases, we also do a right anterior minithoracotomy. What I want to say is that even with conventional valves experienced surgeons are quite fast using a minimal invasive access. But if I do a right anterior minithoracotomy, I'm happy to have a sutureless valve as well. Much better to have it, and it's much easier to do than with a conventional valve.



Dr Vaughn A. Starnes *(Los Angeles, Calif)*. Given the short follow-up: Did you do echo follow-ups, and did you have any degree of differences of aortic insufficiency in the 2 groups?

Dr Fischlein. Yes, as I've shown, it's interesting: There is no difference in paravalvular leakage and central leakage in both groups.