EDITORIALS

Informed Shared Decisions for Patients with Aortic Stenosis

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Valve replacement is the only effective treatment for adults with severe, symptomatic aortic stenosis. The ideal prosthetic valve would be associated with minimal risk and discomfort at implantation, would have hemodynamics similar to those of a normal valve, would not require anticoagulation, and would be durable for the patient's lifetime. We are moving closer to this goal, as evidenced by sequential randomized clinical trials of transcatheter aortic-valve replacement (TAVR), initially in patients at prohibitive or high estimated risk for death with surgical aortic-valve replacement, then in patients at intermediate risk, and now — in the trials by Mack et al.[1] and Popma et al.,[2] the results of which are reported in this issue of the *Journal* — in patients at low risk, defined as a risk of less than 3 to 4%.

In the trial by Mack et al., among patients with severe aortic stenosis, death, stroke, or rehospitalization at 1 year (the primary composite end point) occurred in 8.5% of the patients who were randomly assigned to undergo TAVR with a balloon-expandable prosthesis, as compared with 15.1% of those who were randomly assigned to undergo surgical aortic-valve replacement.[1] In the trial by Popma et al., death or disabling stroke at 2 years (the primary composite end point in that trial) occurred in 5.3% of the patients who were randomly assigned to undergo TAVR with a self-expanding prosthesis, as compared with 6.7% of those who were randomly assigned to undergo surgery.[2] The two trials provide strong evidence that TAVR is noninferior, and even superior, to surgery over 1-year and 2-year time frames. In addition, TAVR resulted in fewer strokes, less bleeding, and less atrial fibrillation than surgery, as well as a shorter hospital stay and faster recovery.

Thus, it is time for a paradigm shift in how we approach decisions about valve type in patients with aortic stenosis. Estimated surgical risk no longer dictates the choice between surgery and TAVR; instead, the primary considerations are life expectancy and valve durability, both of which are related to the patient's age.[3] For example, in the United States, women who are 70 years of age have an average life expectancy of 16 years, whereas women who are 50 years of age have a life expectancy of 33 years. Conversely, the durability of surgical aortic-valve replacement is inversely related to the patient's age at the time of valve replacement; the 15-year risk of reoperation is approximately 5% among patients who are 70 years of age at the time of surgery, as compared with 25% among patients who are 50 years of age.[4,5]

Because of these considerations, current guidelines recommend the use of a mechanical valve in adults younger than 50 years of age, unless long-term anticoagulation is contraindicated or declined by the patient.[6] Among adults 50 to 70 years of age, long-term outcomes are similar with mechanical and biologic valves; the risk of bleeding and thrombosis associated with mechanical valves is balanced against the risk of valve deterioration and reintervention associated with bioprosthetic valves. In most patients older than 70 years of age, the use of a bioprosthetic valve is appropriate; in this group of patients, TAVR is likely to become the preferred option over surgery. Even so, caution is needed, because robust data regarding the durability of the transcatheter bioprosthetic valve beyond 5 years are not yet available.[7]

We also need to consider how many patients with severe aortic stenosis are similar to the pa-

tients enrolled in these two trials. Nearly all the patients in these trials had high-gradient severe aortic stenosis with normal ventricular function, and none had a bicuspid valve, even though this condition accounts for nearly half of all aortic-valve replacements. In addition, aortic-valve, coronary, and peripheral vascular anatomy was suitable for the transcatheter approach. In terms of demographics, the mean age of the patients was approximately 74 years, and 65 to 70% were men.

Why were so few women included in these trials? Possible explanations include incorrect diagnosis of aortic stenosis in older women, who frequently have low-flow, low-gradient severe aortic stenosis; inappropriate biases in referral; and anatomical factors (e.g., annular size, coronary ostial height, and vascular access) that render current TAVR valves poorly suited to women. Regardless of the possible reasons, the inadequate inclusion of women should be remedied in future studies.

Valve disease is a lifelong condition that is not cured by valve replacement; a dysfunctional native valve is simply replaced with an imperfect prosthetic valve. Nearly everyone would choose a transcatheter procedure over open-heart surgery if they are thinking only about short-term pain, risk, and disability. But many patients, particularly younger ones, might accept greater up-front risk and pain to ensure a better outcome over their lifetimes. In younger patients, concerns include the risk of permanent pacemaker implantation, deterioration of the valve, and associated conditions, such as aortic dilatation, that might be better treated with a surgical approach.

How can we actively involve patients in this decision-making process? My approach is to start with an evaluation of the patient's symptoms, the severity of the aortic stenosis, associated cardiac and noncardiac conditions, and overall health status. The next step is to consider whether a mechanical or bioprosthetic valve is most appropriate, in alignment with the patient's preferences and values. Then, if a bioprosthetic valve is chosen, the discussion focuses on comparing TAVR with surgery in the context of estimated remaining years of life and valve durability, highlighting uncertainties in the current data. This is challenging, given the paucity of reliable information sources for patients.[8-10] Physicians and patients need tools that provide accurate data in accessible, continuously updated, and understandable formats to allow truly informed shared decisions for patients with aortic stenosis.

Disclosure forms provided by the author are available with the full text of this editorial at NEJM.org.

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Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients

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ABSTRACT

BACKGROUND

Among patients with aortic stenosis who are at intermediate or high risk for death with surgery, major outcomes are similar with transcatheter aortic-valve replacement (TAVR) and surgical aortic-valve replacement. There is insufficient evidence regarding the comparison of the two procedures in patients who are at low risk.

METHODS

We randomly assigned patients with severe aortic stenosis and low surgical risk to undergo either TAVR with transfemoral placement of a balloon-expandable valve or surgery. The primary end point was a composite of death, stroke, or rehospitalization at 1 year. Both noninferiority testing (with a prespecified margin of 6 percentage points) and superiority testing were performed in the as-treated population.

RESULTS

At 71 centers, 1000 patients underwent randomization. The mean age of the patients was 73 years, and the mean Society of Thoracic Surgeons risk score was 1.9% (with scores ranging from 0 to 100% and higher scores indicating a greater risk of death within 30 days after the procedure). The Kaplan–Meier estimate of the rate of the primary composite end point at 1 year was significantly lower in the TAVR group than in the surgery group (8.5% vs. 15.1%; absolute difference, −6.6 percentage points; 95% confidence interval [CI], −10.8 to −2.5; P<0.001 for noninferiority; hazard ratio, 0.54; 95% CI, 0.37 to 0.79; P=0.001 for superiority). At 30 days, TAVR resulted in a lower rate of stroke than surgery (P=0.02) and in lower rates of death or stroke (P=0.01) and new-onset atrial fibrillation (P<0.001). TAVR also resulted in a shorter index hospitalization than surgery (P<0.001) and in a lower risk of a poor treatment outcome (death or a low Kansas City Cardiomyopathy Questionnaire score) at 30 days (P<0.001). There were no significant between-group differences in major vascular complications, new permanent pacemaker insertions, or moderate or severe paravalvular regurgitation.

CONCLUSIONS

Among patients with severe aortic stenosis who were at low surgical risk, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than with surgery. (Funded by Edwards Lifesciences; PARTNER 3 ClinicalTrials.gov number, NCT02675114.)

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The role of transcatheter aortic-valve replacement (TAVR) in the treatment of patients with severe, symptomatic aortic stenosis has evolved on the basis of evidence from clinical trials.[1-11] Previous randomized trials of TAVR with both balloon-expandable valves[1-7] and self-expanding valves[8-11] showed that, in patients who were at intermediate or high risk for death with surgery, TAVR was either superior or noninferior to standard therapies, including surgical aortic-valve replacement; these results led to an expansion of guideline recommendations for TAVR.[12,13] Moreover, technological enhancements and procedural simplification have contributed to increased use of TAVR, such that more patients now undergo TAVR than isolated surgery for aortic-valve replacement in the United States.[14] However, most patients with severe aortic stenosis are at low surgical risk,[15] and there is insufficient evidence regarding the comparison of TAVR with surgery in such patients.[16,17] We report the findings of the Placement of Aortic Transcatheter Valves (PARTNER) 3 trial, in which TAVR was compared with surgery in low-risk patients.

Methods

Trial Design and Oversight

The PARTNER 3 trial was a multicenter, randomized trial in which TAVR with transfemoral placement of a third-generation balloon-expandable valve was compared with standard surgical aortic-valve replacement in patients with severe aortic stenosis and a low risk of death with surgery. A list of participating sites and investigators is provided in the Supplementary Appendix, available with the full text of this article at NEJM.org. The trial protocol, available at NEJM.org, was designed by the trial sponsor (Edwards Lifesciences) and the steering committee, with guidance from the Food and Drug Administration. The protocol was approved by the institutional review board at each site. The sponsor funded all trial-related activities and participated in site selection, data collection and monitoring, and statistical analysis. The principal investigators (the first two authors) and steering committee monitored all aspects of trial conduct. The principal investigators had unrestricted access to the data, prepared all drafts of the manuscript, and vouch for the completeness and accuracy of the data and analyses and the fidelity of the trial to the protocol. Details regarding the trial design and administrative data are provided in Sections A and B and Figure S1 in the Supplementary Appendix.

Patients

Patients were eligible for inclusion in the trial if they had severe calcific aortic stenosis and were considered to be at low surgical risk according to the results of clinical and anatomical assessment, including a Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score of less than 4% (with scores ranging from 0 to 100% and higher scores indicating a greater risk of death within 30 days after the procedure) and agreement by the site heart team and the trial case review committee. Patients had to be eligible for TAVR with transfemoral placement of the balloon-expandable SAPIEN 3 system (Edwards Lifesciences). Patients with clinical frailty (as determined by the heart team), bicuspid aortic valves, or other anatomical features that increased the risk of complications associated with either TAVR or surgery were excluded. Details regarding inclusion and exclusion criteria are provided in Section C in the Supplementary Appendix. All the patients provided written informed consent.

Randomization and Procedures

Eligible patients were randomly assigned, in a 1:1 ratio, to undergo either TAVR with the SAPIEN 3 system or surgical aortic-valve replacement with a commercially available bioprosthetic valve. Randomization was conducted with the use of an electronic system, with block sizes of four, and was stratified according to site.

The SAPIEN 3 system and the procedures for TAVR and surgery have been described previously[18]; details are provided in Section D in the Supplementary Appendix. All TAVR procedures used the transfemoral access route. Balloon aortic valvuloplasty before and after TAVR was performed at the operator's discretion. Patients received aspirin (81 mg) and clopidogrel (≥300 mg) before TAVR and were advised to continue taking these medications for at least 1 month after the procedure.

End Points

The primary end point was a composite of death from any cause, stroke, or rehospitalization at 1 year after the procedure. All the patients underwent neurologic examinations at baseline and

at 30 days. Patients who had suspected stroke after the procedure underwent serial neurologic examinations, including assessment with the National Institutes of Health Stroke Scale and the modified Rankin scale at 90 days after the event. Rehospitalization was defined as any hospitalization related to the procedure, the valve, or heart failure.

Key secondary end points were prespecified for hierarchical testing to control type 1 error. These included stroke, a composite of death or stroke, and new-onset atrial fibrillation at 30 days, as well as the length of the index hospitalization and a poor treatment outcome, which was a composite of death or a low Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score (with scores ranging from 0 to 100 and higher scores indicating fewer physical limitations and a greater feeling of well-being) at 30 days. Analyses of change in New York Heart Association (NYHA) functional class, 6-minute walk-test distance, and KCCQ summary score were also performed. A list of all the secondary safety and effectiveness end points and their definitions are provided in Sections E and F in the Supplementary Appendix. All components of the primary end point and key secondary end points were adjudicated by a clinical events committee whose members were aware of the treatment assignments.

STATISTICAL ANALYSIS

We estimated that a sample of 864 patients would provide the trial with 90% power to show the noninferiority of TAVR to surgery with regard to the primary end point at 1 year, assuming a Kaplan–Meier estimate of the rate of 14.6% in the TAVR group and 16.6% in the surgery group. A sample size of 1000 patients was chosen to allow for withdrawals, crossovers, and loss to follow-up. To test for noninferiority, we determined whether the upper boundary of the 95% confidence interval for the difference in the rate of the primary end point between the TAVR group and the surgery group was less than the prespecified noninferiority margin of 6 percentage points.

If the requirement for noninferiority was met, testing for the superiority of TAVR to surgery with regard to the primary end point was to be performed at a two-sided alpha level of 0.05. The primary analysis was performed in the as-treated population, which included patients who underwent randomization and in whom the index procedure was initiated. Sensitivity analyses of the primary end point were performed in the intention-to-treat population, as well as with the use of multiple imputation to account for missing data (Section G in the Supplementary Appendix). An analysis of the hierarchical composite of death, stroke, or rehospitalization was performed with the use of the win ratio method.[19] Prespecified subgroup analyses, with tests for interaction, were also performed.

There were two categories of secondary end points. For key secondary end points, testing for superiority was performed in a prespecified hierarchical order with the use of a gatekeeping method to control for multiple comparisons; P values are presented with claims of significance. For other secondary end points, analyses were performed without correction for multiple comparisons; hazard ratios and 95% confidence intervals are presented without P values or claims of significance, and inferences drawn from these 95% confidence intervals may not be reproducible.

Continuous variables, which are presented as means with standard deviations or medians with interquartile ranges, were compared with the use of Student's t-test or the Wilcoxon rank-sum test. Categorical and ordinal variables, which are presented as proportions, were compared with the use of Fisher's exact test or the Wilcoxon rank-sum test. Continuous variables obtained after baseline were compared with the use of analysis of covariance with adjustment for the baseline measurement. Time-to-event analyses were performed with the use of Kaplan–Meier estimates and were compared with the use of the log-rank test. Echocardiographic analyses were performed in the valve-implant population, which included patients in whom the intended valve was implanted. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From March 2016 through October 2017, a total of 1000 patients were enrolled at 71 sites; 979 of the patients were from the United States, 8 from Canada, 7 from Australia or New Zealand, and 6 from Japan. The patients were randomly assigned to undergo either TAVR (503 patients) or surgery (497 patients). The assigned procedure was performed in 950 patients (496 in the TAVR group and 454 in the surgery group), who com-

posed the as-treated population, and the intended valve was implanted in 948. Among the patients who did not undergo the assigned procedure (7 in the TAVR group and 43 in the surgery group), the most common reason was withdrawal from the trial (in 41 patients), mainly owing to the decision not to undergo surgery or the preference to undergo surgery at a nontrial site. Details regarding enrollment, randomization, and follow-up are provided in Figure S2 in the Supplementary Appendix.

Characteristics of the patients at baseline were balanced in the two groups (Table 1, and Fig. S3 in the Supplementary Appendix), except for a higher percentage of patients with an NYHA class of III or IV in the TAVR group than in the surgery group (31.2% vs. 23.8%). The patients enrolled in this trial were younger (mean age, 73 years), included more men (69.3%), and had lower STS-PROM scores (mean score, 1.9%) and fewer coexisting conditions than patients enrolled in previous randomized trials of TAVR.[1-3] Baseline characteristics were similar in the as-treated population and in patients who underwent randomization and were not included in the as-treated population (Table S1 in the Supplementary Appendix).

PROCEDURAL OUTCOMES

The median time from randomization to the index procedure was 11 days. One TAVR procedure was converted to surgery, and one surgical procedure was aborted. Concomitant procedures were performed in 7.9% of the patients in the TAVR group and in 26.4% of the patients in the surgery group. Concomitant coronary revascularization was performed in 6.5% and 12.8%, respectively. In the TAVR group, conscious sedation was used in 65.1% of the patients. In the surgery group, minimally invasive surgery was performed in 24.3% of the patients, and the surgical valve was 23 mm in diameter or larger in 79.9%. Details regarding the procedures are provided in Tables S2 and S3 and Figure S4 in the Supplementary Appendix.

There were six deaths during the index hospitalization, which occurred in two patients in the TAVR group and in four patients in the surgery group. Other serious intraprocedural complications that occurred in the TAVR group included implantation of a second valve, annulus rupture, coronary-artery obstruction, and ventricular perforation (in one patient each) (Tables S4 and S5 in the Supplementary Appendix).

PRIMARY END POINT

At 1 year, data regarding the primary end point were available for 98.4% of the patients. The composite of death from any cause, stroke, or rehospitalization had occurred in 42 patients (8.5%) in the TAVR group as compared with 68 patients (15.1%) in the surgery group. The requirements for both noninferiority and superiority were met, with an absolute difference between the TAVR group and the surgery group of −6.6 percentage points (95% confidence interval [CI], −10.8 to −2.5; P<0.001 for noninferiority) and a hazard ratio of 0.54 (95% CI, 0.37 to 0.79; P=0.001 for superiority) (Fig. 1A).

Results of an analysis performed with the use of the hierarchical win ratio method (win ratio, 1.88; 95% CI, 1.29 to 2.76) were consistent with those of the primary analysis. Results of sensitivity analyses of the primary end point performed in the intention-to-treat population and with the use of multiple imputation for missing data were also consistent with those of the primary analysis, as were results of analyses involving patients who underwent revascularization or other concomitant procedures and those who did not. Subgroup analyses of the primary end point at 1 year showed no heterogeneity of treatment effect in any of the subgroups that were examined (Fig. 2). Details regarding these analyses are provided in Tables S6, S7, and S8 and Figure S5 in the Supplementary Appendix.

Data regarding the individual components of the primary end point are shown in Figure 1B, 1C, and 1D, and in Table S9 in the Supplementary Appendix. At 1 year, the Kaplan–Meier estimate of the rate was 1.0% in the TAVR group as compared with 2.5% in the surgery group (hazard ratio, 0.41; 95% CI, 0.14 to 1.17) for death from any cause, 1.2% as compared with 3.1% (hazard ratio, 0.38; 95% CI, 0.15 to 1.00) for stroke, and 7.3% as compared with 11.0% (hazard ratio, 0.65; 95% CI, 0.42 to 1.00) for rehospitalization.

SECONDARY END POINTS

For key secondary end points, results of prespecified hierarchical testing are shown in Table 2. At 30 days, TAVR resulted in a lower rate of stroke than surgery (0.6% vs. 2.4%; hazard ratio, 0.25; 95% CI, 0.07 to 0.88; P=0.02) and in lower rates of death or stroke (1.0% vs. 3.3%; hazard ratio, 0.30; 95% CI, 0.11 to 0.83; P=0.01) and new-onset atrial fibrillation (5.0% vs. 39.5%; hazard

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	TAVR (N=496)	Surgery (N=454)
Age — yr	73.3±5.8	73.6±6.1
Male sex — no. (%)	335 (67.5)	323 (71.1)
Nonwhite race or ethnic group — no. (%)†	38 (7.7)	45 (9.9)
Body-mass index‡	30.7±5.5	30.3±5.1
STS score§	1.9±0.7	1.9±0.6
EuroSCORE II score¶	1.5±1.2	1.5±0.9
NYHA class III or IV — no. (%)	155 (31.2)	108 (23.8)
Coronary artery disease — no./total no. (%)	137/494 (27.7)	127/454 (28.0)
Previous myocardial infarction — no./total no. (%)	28/495 (5.7)	26/452 (5.8)
Previous stroke — no./total no. (%)	17/496 (3.4)	23/453 (5.1)
Carotid disease — no./total no. (%)	61/481 (12.7)	50/442 (11.3)
Peripheral vascular disease — no./total no. (%)	34/494 (6.9)	33/453 (7.3)
COPD — no./total no. (%)	25/495 (5.1)	28/454 (6.2)
Creatinine >2 mg/dl — no. (%)‖	1 (0.2)	1 (0.2)
Diabetes — no./total no. (%)	155/496 (31.2)	137/453 (30.2)
Atrial fibrillation — no./total no. (%)	78/496 (15.7)	85/453 (18.8)
Permanent pacemaker — no. (%)	12 (2.4)	13 (2.9)
Left bundle-branch block — no./total no. (%)	15/495 (3.0)	15/453 (3.3)
Right bundle-branch block — no./total no. (%)	51/495 (10.3)	62/453 (13.7)
Overall frailty — no./total no. (%)**	0/495	0/453
Pulmonary hypertension — no./total no. (%)	23/495 (4.6)	24/454 (5.3)
Aortic-valve area — cm^2	0.8±0.2	0.8±0.2
Aortic-valve gradient — mm Hg	49.4±12.8	48.3±11.8
Left ventricular ejection fraction — %	65.7±9.0	66.2±8.6
Moderate or severe regurgitation — no./total no. (%)		
Aortic	19/484 (3.9)	11/446 (2.5)
Mitral	6/477 (1.3)	14/437 (3.2)
Tricuspid	8/473 (1.7)	10/430 (2.3)
Systolic annular perimeter on CT — mm	78.1±6.9	78.6±7.2
Systolic annular area on CT — mm^2	473.5±83.3	479.6±87.6

* Plus–minus values are means ±SD. There were no significant between-group differences in baseline characteristics, except for New York Heart Association (NYHA) class III or IV ($P<0.05$). Data on aortic-valve area were available for 459 patients in the TAVR group and 424 patients in the surgery group; aortic-valve gradient, 484 and 442, respectively; left ventricular ejection fraction, 472 and 436; and systolic annular perimeter and area on computed tomography (CT), 486 and 441. COPD denotes chronic obstructive pulmonary disease, and TAVR transcatheter aortic-valve replacement.

† Race or ethnic group was reported by the patient.

‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.

§ Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores range from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure. STS-PROM uses an algorithm that is based on the presence of coexisting illnesses in order to predict 30-day operative mortality. The STS-PROM score equals the predicted mortality expressed as a percentage. Less than 5% of patients in the population on which the STS-PROM algorithm is based had a predicted operative mortality (score) of more than 10%.

¶ Scores on the European System for Cardiac Operative Risk Evaluation (EuroSCORE) II range from 0 to 100, with higher scores indicating a greater risk of death within 30 days after the procedure.

‖ To convert the values for creatinine to micromoles per liter, multiply by 88.4.

** Overall frailty was defined as the presence of three or more of the following criteria: grip strength of less than 18 kg, 5-meter walk-test time of more than 6 seconds, serum albumin level of less than 3.5 g per deciliter, and Katz Activities of Daily Living total score of 4 or less (with scores ranging from 0 to 6 and higher scores indicating greater independence in performing activities of daily living).

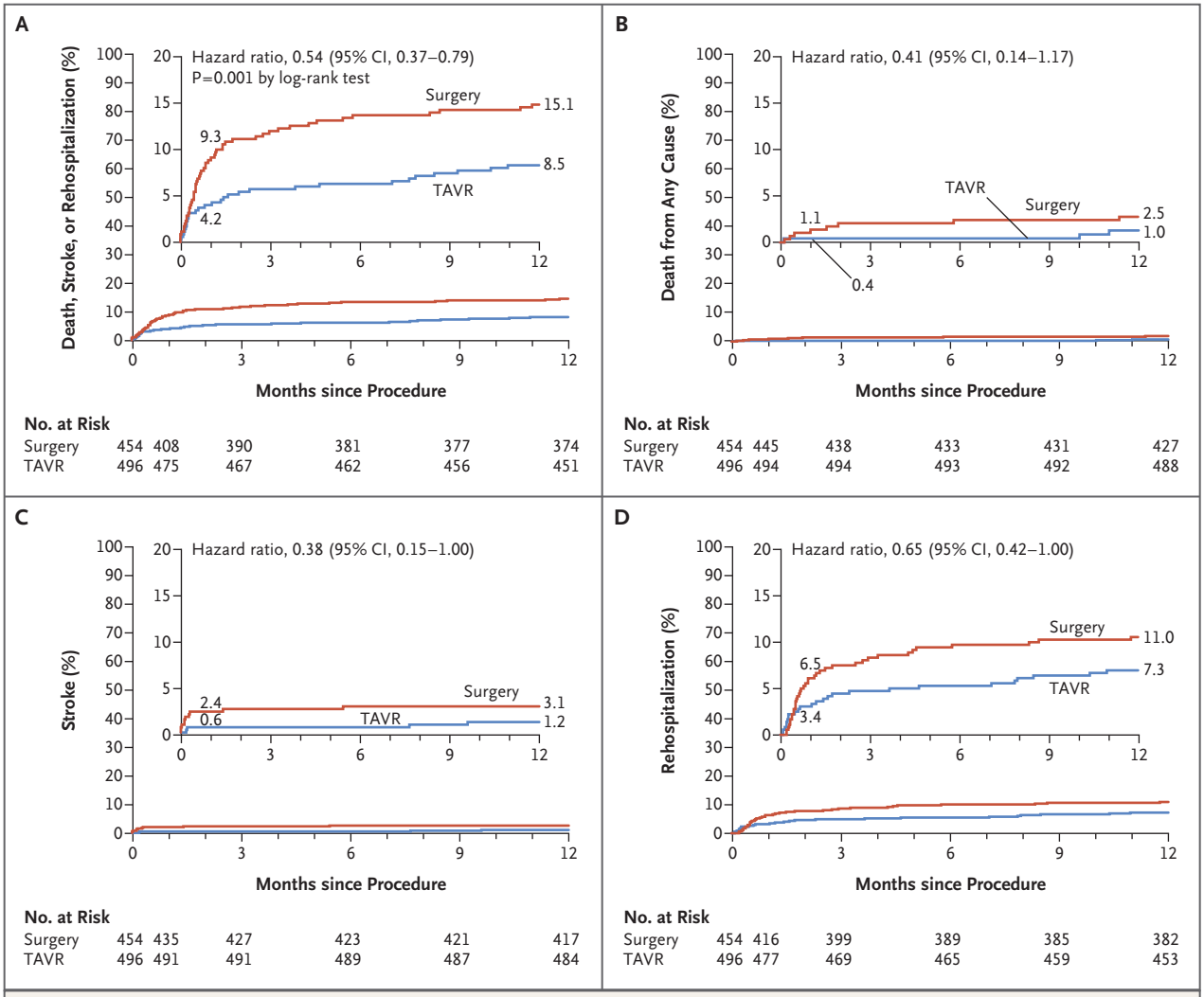

Figure 1. Time-to-Event Curves for the Primary Composite End Point and the Individual Components of the Primary End Point.

Shown are Kaplan–Meier estimates of the rate of the primary composite end point (Panel A) and the individual components of the primary end point, which are death from any cause (Panel B), stroke (Panel C), and rehospitalization (Panel D), in patients who underwent transcatheter aortic-valve replacement (TAVR) and those who underwent surgical aortic-valve replacement. The insets show the same data on an enlarged y axis.

ratio, 0.10; 95% CI, 0.06 to 0.16; P<0.001). TAVR also resulted in a shorter index hospitalization than surgery (3 days vs. 7 days, P<0.001) and in a lower risk of a poor treatment outcome (death or a low KCCQ score) at 30 days (3.9% vs. 30.6%, P<0.001), a result that was confirmed with the use of multiple imputation for missing data (Table S10 in the Supplementary Appendix). At 1 year, the rate of death or disabling stroke was 1.0% in the TAVR group as compared with 2.9% in the surgery group (hazard ratio, 0.34; 95% CI, 0.12 to 0.97).

Complete data regarding secondary end points at 30 days and 1 year are provided in Tables S9 and S11 through S16 and Figures S6 through S9 in the Supplementary Appendix. The percentage of patients who were discharged to home or self-care was 95.8% in the TAVR group as compared with 73.1% in the surgery group. There were no significant differences between the two groups with regard to most safety end points at 30 days, including major vascular complications and new permanent pacemaker insertions. The percentage of patients with new left

Subgroup	No. of Patients	TAVR	Surgery	Difference (95% CI)	P Value for Interaction
		no. of events/total no. (%)		*percentage points*	
Overall	950	42/496 (8.5)	68/454 (15.1)	−6.6 (−10.8 to −2.5)	
Age					0.21
≤74 yr	516	29/273 (10.6)	36/243 (14.9)	−4.3 (−10.1 to 1.5)	
>74 yr	434	13/223 (5.8)	32/211 (15.3)	−9.5 (−15.3 to −3.7)	
Sex					0.27
Female	292	13/161 (8.1)	24/131 (18.5)	−10.4 (−18.3 to −2.5)	
Male	658	29/335 (8.7)	44/323 (13.8)	−5.1 (−9.9 to −0.3)	
STS-PROM score					0.98
≤1.8	464	21/232 (9.1)	36/232 (15.7)	−6.7 (−12.6 to −0.7)	
>1.8	486	21/264 (8.0)	32/222 (14.5)	−6.5 (−12.2 to −0.8)	
Left ventricular ejection fraction					0.48
≤65	384	20/208 (9.6)	30/176 (17.2)	−7.6 (−14.5 to −0.7)	
>65	524	21/264 (8.0)	32/260 (12.4)	−4.4 (−9.6 to 0.7)	
NYHA class					0.54
I or II	687	23/341 (6.8)	50/346 (14.5)	−7.8 (−12.4 to −3.2)	
III or IV	263	19/155 (12.3)	18/108 (16.9)	−4.7 (−13.5 to 4.1)	
Atrial fibrillation					0.67
No	786	33/418 (7.9)	51/368 (14.0)	−6.1 (−10.5 to −1.7)	
Yes	163	9/78 (11.6)	17/85 (20.3)	−8.7 (−19.9 to 2.5)	
KCCQ overall summary score					0.27
≤70	407	23/219 (10.5)	37/188 (19.9)	−9.4 (−16.5 to −2.4)	
>70	536	18/275 (6.5)	29/261 (11.2)	−4.6 (−9.2 to 0.2)	

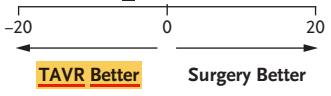

Figure 2. Subgroup Analyses of the Primary Composite End Point of Death from Any Cause, Stroke, or Rehospitalization.

All percentages are Kaplan–Meier estimates. Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) scores range from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after the procedure. Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores range from 0 to 100, with higher scores indicating fewer physical limitations and a greater feeling of well-being. NYHA denotes New York Heart Association.

bundle-branch block at 1 year was 23.7% in the TAVR group as compared with 8.0% in the surgery group (hazard ratio, 3.43; 95% CI, 2.32 to 5.08). The percentage of patients with life-threatening or major bleeding was 3.6% in the TAVR group as compared with 24.5% in the surgery group (hazard ratio, 0.12; 95% CI, 0.07 to 0.21). Changes from baseline in the NYHA class, 6-minute walk-test distance, and KCCQ score at 30 days and 1 year are shown in Figure 3.

ECHOCARDIOGRAPHIC FINDINGS

At 30 days, the mean aortic-valve gradient was 12.8 mm Hg in the TAVR group and 11.2 mm Hg in the surgery group. The mean aortic-valve area was 1.7 cm^2 and 1.8 cm^2, respectively. The percentage of patients with moderate or severe paravalvular regurgitation did not differ significantly between the TAVR group and the surgery group (0.8% and none, respectively, at 30 days; 0.6% and 0.5% at 1 year). The percentage of patients with mild paravalvular regurgitation at 1 year was higher with TAVR than with surgery (29.4% vs. 2.1%). There were no episodes of valve thrombosis associated with clinical events. Six asymptomatic patients (five in the TAVR group and one in the surgery group) had findings suggestive of valve thrombosis, including increased valve gradients and evidence on imaging of restricted leaflet motion. Details regarding echocardiographic findings are provided in Tables S17 and S18 and Figures S10 through S13 in the Supplementary Appendix.

DISCUSSION

There are three main findings of the PARTNER 3 trial. First, TAVR, performed by means of transfemoral placement of the balloon-expandable SAPIEN 3 system, was superior to surgery

Table 2. Key Secondary End Points.*

End Point	TAVR (N=496)	Surgery (N=454)	TAVR vs. Surgery (95% CI)†	P Value‡
New-onset atrial fibrillation at 30 days — no./total no. (%)§¶	21/417 (5.0)	145/369 (39.5)	0.10 (0.06 to 0.16)	<0.001
Length of index hospitalization — median no. of days (interquartile range)	3.0 (2.0 to 3.0)	7.0 (6.0 to 8.0)	−4.0 (−4.0 to −3.0)	<0.001
Death from any cause, stroke, or rehospitalization at 1 year — no. (%)§	42 (8.5)	68 (15.1)	0.54 (0.37 to 0.79)	0.001
Death, KCCQ score of <45, or decrease from baseline in KCCQ score of ≥10 points at 30 days — no./total no. (%)‖	19/492 (3.9)	133/435 (30.6)	−26.7 (−31.4 to −22.1)	<0.001
Death or stroke at 30 days — no. (%)§	5 (1.0)	15 (3.3)	0.30 (0.11 to 0.83)	0.01
Stroke at 30 days — no. (%)§	3 (0.6)	11 (2.4)	0.25 (0.07 to 0.88)	0.02

* Key secondary end points were tested in a prespecified hierarchical order with the use of a gatekeeping method to control for multiple comparisons.
† For the first, third, fifth, and sixth end points, the value is a hazard ratio. For the second end point, the value is a difference in medians estimated with the use of bootstrap techniques. For the fourth end point, the value is a difference in proportions and is presented in percentage points.
‡ For the first, third, fifth, and sixth end points, the P value was based on the log-rank test. For the second end point, the P value was based on the Wilcoxon rank-sum test. For the fourth end point, the P value was based on Fisher's exact test.
§ The percentages are Kaplan–Meier estimates.
¶ Patients who had atrial fibrillation before the procedure were excluded from the analysis.
‖ Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary scores range from 0 to 100, with higher scores indicating fewer physical limitations and a greater feeling of well-being.

with regard to the primary composite end point of death, stroke, or rehospitalization at 1 year. Multiple sensitivity analyses confirmed the robustness of the results of the primary analysis. Results for the three components of the primary end point favored TAVR at both 30 days and 1 year. Second, analyses of key secondary end points, which were adjusted for multiple comparisons, showed that TAVR was associated with a significantly lower rate of new-onset atrial fibrillation at 30 days, a shorter index hospitalization, and a lower risk of a poor treatment outcome (death or a low KCCQ score) at 30 days than surgery. Third, patients who underwent TAVR had more rapid improvements in the NYHA class, 6-minute walk-test distance, and KCCQ score than those who underwent surgery.

During the past decade, recommendations for TAVR in patients with severe, symptomatic aortic stenosis have been expanded to include strata with incrementally lower surgical risk.[12,13,20,21] Current clinical practice has restricted the use of TAVR in patients who are at low risk and in younger patients, for whom surgery is standard therapy. Previous research that supports the use of TAVR in low-risk patients is limited, mostly consisting of retrospective, observational studies.[22-27] One randomized trial of TAVR with an early-generation self-expanding valve in 280 patients at all risk levels (>80% with an STS-PROM score of <4%) showed that TAVR was noninferior to surgery with more than 5 years of follow-up.[16] A recent prospective series of TAVR with balloon-expandable and self-expanding valves in 200 low-risk patients without frailty from 11 U.S. centers showed no deaths or disabling strokes at 30 days.[17]

In the PARTNER 3 trial, surgical outcomes were excellent: in the surgery group, the rate of death at 30 days was 1.1%, and the rate of a composite of death or disabling stroke at 1 year was 2.9%. Nevertheless, in the TAVR group, the rate of death at 30 days was even lower (0.4%), and the rate of death or disabling stroke at 1 year was only 1.0%. Complications that were more frequent with TAVR than with surgery in previous trials[1-3,6,28-32] occurred with similar frequency in the two groups in this trial, including major vascular complications, new permanent pacemaker insertions, moderate or severe paravalvular regurgitation, and coronary-artery obstruction. Life-threatening or major bleeding occurred less frequently with TAVR than with surgery. Results for other secondary end points, including new left bundle-branch block and mild paravalvular regurgitation, favored surgery. Between-group differences in transvalvular aortic-valve gradients

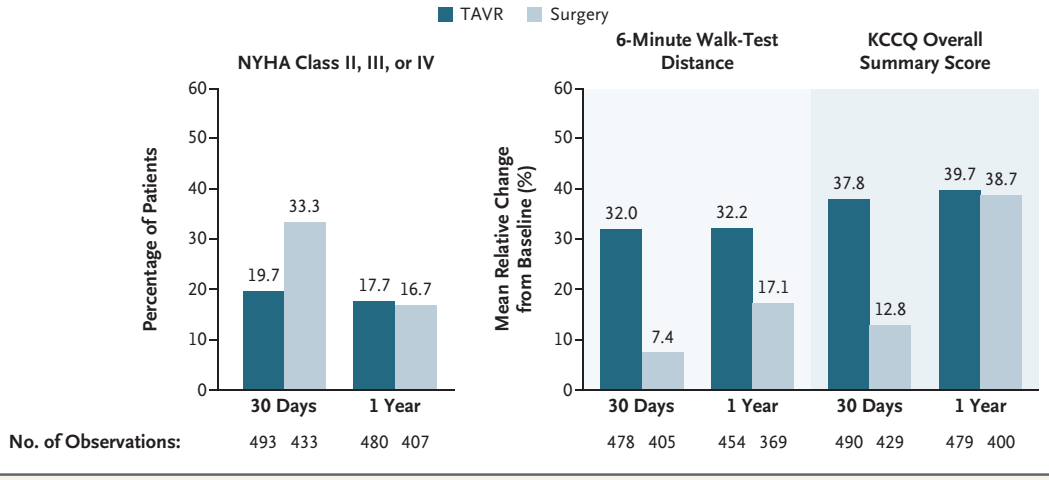

Figure 3. Functional Status and Quality of Life at 30 Days and 1 Year.

NYHA class and 6-minute walk-test distance are measures of functional status, and the KCCQ overall summary score is a measure of quality of life.

also favored surgery, although this was not the case in previous randomized trials of TAVR[2,3,5]; this result was probably due to the greater use of larger surgical valves in this trial.

The most important limitation of this trial is that our current results reflect only 1-year outcomes and do not address the problem of long-term structural valve deterioration.[33,34] Definitive conclusions regarding the advantages and disadvantages of TAVR as compared with surgery (with either bioprosthetic or mechanical valves) depend on long-term follow-up. In this trial involving younger, low-risk patients, the protocol requires clinical and echocardiographic follow-up to continue for at least 10 years.

This trial has several other limitations. First, in this trial, as in previous TAVR trials, adjudication of end points was not blinded, which could have resulted in bias in outcome assessment. Second, the results apply only to the defined trial population, which excluded patients with poor transfemoral access, bicuspid aortic valves, or other anatomical or clinical factors that increased the risk of complications associated with either TAVR or surgery. Third, the findings cannot be extrapolated to TAVR performed with other systems or by less experienced operators.[35,36] Fourth, more patients in the surgery group than in the TAVR group withdrew from the trial (both early and late). Fifth, missing data regarding NYHA class, 6-minute walk-test distance, KCCQ score, and follow-up echocardiograms were not fully accounted for with multiple imputation. Sixth, this analysis did not examine the rate and relevance of asymptomatic valve thrombosis.[37,38] This issue is being examined in a randomized subtrial, in which 435 patients are undergoing serial computed tomographic angiography for the detection of abnormalities in valve-leaflet function, with investigators unaware of imaging findings.

The proof-of-concept first case of TAVR performed by Cribier and colleagues in 2002[39] was intended to open a treatment pathway for the highest-risk patients with limited therapeutic options. Our findings in low-risk patients suggest that the value of TAVR as compared with surgery may be independent of risk profiles.

In conclusion, among patients with severe aortic stenosis who were at low risk for death with surgery, the rate of the composite of death, stroke, or rehospitalization at 1 year was significantly lower with TAVR than with surgical aortic-valve replacement.

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APPENDIX

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ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

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ABSTRACT

BACKGROUND

Transcatheter aortic-valve replacement (TAVR) is an alternative to surgery in patients with severe aortic stenosis who are at increased risk for death from surgery; less is known about TAVR in low-risk patients.

METHODS

We performed a randomized noninferiority trial in which TAVR with a self-expanding supraannular bioprosthesis was compared with surgical aortic-valve replacement in patients who had severe aortic stenosis and were at low surgical risk. When 850 patients had reached 12-month follow-up, we analyzed data regarding the primary end point, a composite of death or disabling stroke at 24 months, using Bayesian methods.

RESULTS

Of the 1468 patients who underwent randomization, an attempted TAVR or surgical procedure was performed in 1403. The patients' mean age was 74 years. The 24-month estimated incidence of the primary end point was 5.3% in the TAVR group and 6.7% in the surgery group (difference, −1.4 percentage points; 95% Bayesian credible interval for difference, −4.9 to 2.1; posterior probability of noninferiority >0.999). At 30 days, patients who had undergone TAVR, as compared with surgery, had a lower incidence of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) and a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%). At 12 months, patients in the TAVR group had lower aortic-valve gradients than those in the surgery group (8.6 mm Hg vs. 11.2 mm Hg) and larger effective orifice areas (2.3 cm^2 vs. 2.0 cm^2).

CONCLUSIONS

In patients with severe aortic stenosis who were at low surgical risk, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the composite end point of death or disabling stroke at 24 months. (Funded by Medtronic; ClinicalTrials.gov number, NCT02701283.)

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*A complete list of investigators, institutions, and research personnel participating in the Evolut Low Risk Trial is provided in the Supplementary Appendix, available at NEJM.org.

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In previous studies, we have shown that transcatheter aortic-valve replacement (TAVR) with the use of a self-expanding supraannular bioprosthesis is superior to medical therapy or surgery in patients with severe, symptomatic aortic stenosis who are at prohibitive or high risk for complications or death from surgery[1-3] and is a noninferior approach in patients deemed to be at intermediate surgical risk.[4,5] Societal guidelines have endorsed the use of TAVR in patients who are at increased risk for complications or death from surgery,[6,7] and the expanded use of TAVR in the United States is closely monitored.[8] The number of TAVR procedures performed in the United States has now surpassed the number of isolated surgical aortic-valve replacements.[9]

Use of TAVR in patients at low surgical risk requires compelling evidence of safety and effectiveness, given the low mortality and stroke incidence with aortic-valve surgery in relatively young, healthy patients.[9] Other outcomes, such as aortic-valve reintervention, coronary-artery obstruction, permanent pacemaker use, and longer-term valve durability, are metrics that also require scrutiny in this population. One small randomized study of TAVR with a self-expanding bioprosthesis as compared with surgery provides support for the safety of TAVR with a self-expanding bioprosthesis in low-risk patients up to 5 years after the procedure.[10,11]

The purpose of the current trial (Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients) was to evaluate the safety and effectiveness of TAVR with a self-expanding bioprosthesis as compared with surgical aortic-valve replacement in patients deemed to have a low risk of death with surgery.

Methods

Trial Design

This study was a multinational, randomized, noninferiority clinical trial comparing the safety and efficacy of TAVR with those of surgery in patients with severe aortic stenosis who were deemed to be at low risk for death at 30 days with surgery. The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. Patients were enrolled at 86 centers in Australia, Canada, France, Japan, the Netherlands, New Zealand, and the United States (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Local institutional review boards or medical ethics committees approved the protocol, available at NEJM.org.

Medtronic funded the trial and developed the protocol in collaboration with the executive committee (see Table S2 in the Supplementary Appendix for members of committees). Medtronic was responsible for site selection, data monitoring, and trial management. Paradigm Biostatistics performed the Bayesian end-point comparisons; an independent statistical consultant validated all end-point analyses. An independent data and safety monitoring board provided study oversight.

The principal investigators (the first and last authors) wrote the first draft of the manuscript; all the authors critically reviewed it, made revisions, and supported the decision to submit the manuscript for publication. The authors attest that the trial was performed according to the protocol and vouch for the accuracy and completeness of the data.

Patient Selection

Eligible patients had severe aortic-valve stenosis with suitable anatomy for TAVR or surgery and no more than a predicted 3% risk of death by 30 days with surgery, as assessed by members of the local heart team. Aortic stenosis was defined as an aortic-valve area of 1.0 cm^2 or less (or aortic-valve area index of ≤0.6 cm^2 per square meter) or a mean gradient of 40 mm Hg or more or maximal aortic-valve velocity of 4.0 m or more per second as assessed by transthoracic echocardiography performed with the patient at rest. A detailed list of inclusion and exclusion criteria, including criteria for inclusion of asymptomatic patients, is provided in Table S3 in the Supplementary Appendix. The screening committee confirmed all decisions regarding patient selection (see the Methods section in the Supplementary Appendix). All patients provided written informed consent.

Study Procedures

Randomization was performed in a 1:1 ratio, with variable block sizes, with an electronic randomization system. Randomization was stratified by site and the need for coronary-artery revascularization. Patients assigned to TAVR were treated with one of three self-expanding, supraannular bioprostheses (CoreValve, Evolut R, or Evolut PRO; Medtronic) (Fig. S1 in the Supplementary Appendix). The size and type of surgical valve were

at the discretion of the surgeon, although candidates for mechanical valves were excluded. Patients were evaluated at baseline, at discharge, and at 1, 6, 12, 18, and 24 months after the procedure. All echocardiographic studies were assessed at an independent core laboratory (Mayo Clinic). Health-related quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). KCCQ summary scores range from 0 to 100, with higher scores indicating better health status; scores higher than 60 correlate with New York Heart Association (NYHA) class I or II, and a 10-point increase corresponds to moderate clinical improvement.[12,13]

STUDY END POINTS

The primary safety and effectiveness end point was a composite of death from any cause or disabling stroke at 24 months. Disabling stroke was defined by a score on the modified Rankin scale of 2 or more (with scores ranging from 0 [no symptoms] to 6 [death]) at 90 days and an increase of at least 1 category from baseline (i.e., before the stroke). There were seven prespecified secondary end points that were tested hierarchically for either noninferiority or superiority (see the Hierarchical Testing section in the Supplementary Appendix). Additional secondary safety end points included a composite of death, disabling stroke, life-threatening bleeding, major vascular complication, or stage 2 or 3 acute kidney injury at 30 days; and prosthetic-valve endocarditis, prosthetic-valve thrombosis, prosthetic-valve dysfunction requiring a repeat procedure, stroke, and life-threatening bleeding at 12 months. The full list of secondary end points is provided in the Methods section in the Supplementary Appendix.

An independent academic clinical-events committee (Baim Institute for Clinical Research, Boston) adjudicated all end points, using standard definitions (Table S4 in the Supplementary Appendix). End-point adjudication was blinded when feasible (for some end points, knowledge of treatment assignment was inherent in the end-point assessment).

STATISTICAL ANALYSIS

This trial used Bayesian adaptive statistical methods with noninformative prior distributions to assess the primary end point. We hypothesized that TAVR would be noninferior to surgery with respect to the primary end point with a noninferiority margin of 6%. The primary end point was to be tested for the superiority of TAVR to surgery if the primary objective (noninferiority with respect to the primary end point) and all seven prespecified hierarchical secondary objectives met their designated success criterion (in the hierarchical testing order). The prespecified success criteria were a posterior probability greater than 0.972 for noninferiority and greater than 0.984 for superiority, criteria that were selected empirically through extensive simulations to achieve a type I error rate of no more than 0.05 for noninferiority testing and no more than 0.025 for superiority testing.

The estimated sample size of 1200 patients was selected on the basis of an assumed 15% incidence of death or disabling stroke at 24 months; 1468 patients were ultimately enrolled to permit completion of a randomized substudy of valve leaflet immobility and thrombosis and to meet Japanese regulatory requirements. A prespecified Bayesian interim analysis was to be performed 12 months after the 850th patient underwent the study procedure (see the Methods section in the Supplementary Appendix). For patients who did not complete 24 months of follow-up, we imputed their outcome according to a prespecified statistical model, which was based on the patient's last known clinical status. A sensitivity analysis was performed to account for missing data, including data for the patients who were lost to follow-up or withdrew from the study.

The primary analysis cohort was the as-treated population, which comprised patients who were randomly assigned to a group and who underwent an attempted procedure. Secondary analyses of the primary end point were also performed in the intention-to-treat population, the "implanted" population (patients in whom an aortic valve was implanted), and the per-protocol population. Details regarding the primary objective, analysis populations, sensitivity analyses, and hierarchical testing methods among secondary end points are provided in the Methods section in the Supplementary Appendix. We used a Bayesian analogue of a two-sample t-test to compare continuous variables with a noninformative prior distribution. Event rates are summarized as Bayesian posterior medians with 95% credible intervals, which were calculated from the 2.5th and 97.5th percentiles

of the posterior distributions. The Bayesian credible intervals for secondary end points use marginal posterior distributions that are probably narrower than those that are based on a true multidimensional posterior for the collection of outcomes. Caution should therefore be exercised in drawing inferences about absolute treatment effects with the 95% Bayesian credible intervals, owing to the multiplicity of secondary end-point comparisons.

RESULTS

BASELINE CHARACTERISTICS

From March 28, 2016, to November 27, 2018, a total of 1468 patients underwent randomization; 734 were assigned to TAVR and 734 were assigned to surgery. After randomization, the assigned procedure was not attempted in 12 patients assigned to TAVR and 53 patients assigned to surgery; in 3 patients assigned to surgery, TAVR was attempted instead (Fig. S2 and Results section in the Supplementary Appendix). The as-treated cohort included 1403 patients: 725 in the TAVR group and 678 in the surgery group.

Demographic and baseline characteristics and cardiac risk factors are shown in Table 1. The mean age of the patients was 74 years, 34.9% were women, and all the patients were at low surgical risk. There were no significant differences between the two treatment groups. Among patients who were assigned to the surgery group, the baseline characteristics of those who actually underwent surgery were similar to the characteristics of those who did not undergo surgery (Table S5 in the Supplementary Appendix). A detailed description of procedural end points is provided in the Results section in the Supplementary Appendix.

At this prespecified interim analysis, 12-month follow-up was available for 432 patients in the TAVR group and 352 in the surgery group; 24-month follow-up was available for 72 patients in the TAVR group and 65 patients in the surgery group. The median follow-up time in each group was 12.2 months.

PRIMARY SAFETY AND EFFECTIVENESS END POINT

The incidence of death or disabling stroke at 24 months (the primary end point) was 5.3% in the TAVR group (95% Bayesian credible interval, 3.3 to 8.0) and 6.7% in the surgery group (95% Bayesian credible interval, 4.4 to 9.6). The prespecified criterion for noninferiority was met (difference, −1.4 percentage points; 95% Bayesian credible interval for the difference, −4.9 to 2.1; posterior probability of noninferiority, >0.999) (Fig. 1); the prespecified criterion for superiority was not met (posterior probability of superiority, 0.779). A noninferiority analysis using the intention-to-treat cohort yielded similar results. A sensitivity analysis that was performed to account for patients who were lost to follow-up also had similar results (details on these analyses are provided in Tables S6 through S8 and the Methods section in the Supplementary Appendix).

The 24-month estimated incidence of death from any cause was 4.5% in the TAVR group and 4.5% in the surgery group (difference, 0 percentage points; 95% credible interval for the difference, −3.2 to 3.2). The 24-month estimated incidence of disabling stroke was 1.1% in the TAVR group and 3.5% in the surgery group (difference, −2.3 percentage points; 95% credible interval for the difference, −4.8 to −0.4). No significant treatment-by-subgroup interactions were noted for the primary end point (Fig. S3 in the Supplementary Appendix).

SECONDARY SAFETY MEASURES

The incidence of the secondary composite safety end point at 30 days was 5.3% in the TAVR group and 10.7% in the surgery group (Table 2). The incidence of death from any cause at 30 days was 0.5% in the TAVR group and 1.3% in the surgery group; causes of death are shown in Table S9 in the Supplementary Appendix. The ratio of observed to expected incidence of death from any cause by 30 days (with expected risk calculated on the basis of the Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] model) was 0.26 in the TAVR group and 0.68 in the surgery group. New atrial fibrillation at 30 days occurred in 7.7% of the patients in the TAVR group and in 35.4% in the surgery group (difference, −27.7 percentage points; credible interval for the difference, −31.8 to −23.6), whereas permanent pacemaker implantation occurred in 17.4% of the patients in the TAVR group and in 6.1% in the surgery group (difference, 11.3 percentage points; credible interval for the difference, 8.0 to 14.7) (Table 2). Incidences of stroke, prosthetic-valve thrombosis, endocarditis, and reinterven-

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	As-Treated Analysis		Intention-To-Treat Analysis	
	TAVR (N=725)	Surgery (N=678)	TAVR (N=734)	Surgery (N=734)
Age — yr	74.1±5.8	73.6±5.9	74.0±5.9	73.8±6.0
Female sex — no. (%)	261 (36.0)	229 (33.8)	266 (36.2)	246 (33.5)
NYHA class — no. (%)				
I	76 (10.5)	63 (9.3)	77 (10.5)	73 (9.9)
II	467 (64.4)	422 (62.2)	476 (64.9)	456 (62.1)
III	181 (25.0)	190 (28.0)	180 (24.5)	202 (27.5)
IV	1 (0.1)	3 (0.4)	1 (0.1)	3 (0.4)
STS-PROM — %†	1.9±0.7	1.9±0.7	1.9±0.7	1.9±0.7
Diabetes mellitus — no. (%)	228 (31.4)	207 (30.5)	228 (31.1)	224 (30.5)
Serum creatinine >2 mg/dl — no. (%)	3 (0.4)	1 (0.1)	3 (0.4)	1 (0.1)
Dialysis — no. (%)	0	1 (0.1)	0	1 (0.1)
Hypertension — no./total no. (%)	614/724 (84.8)	559/677 (82.6)	622/733 (84.9)	608/733 (82.9)
Peripheral arterial disease — no./total no. (%)	54/718 (7.5)	56/678 (8.3)	55/727 (7.6)	62/733 (8.5)
Cerebrovascular disease — no. (%)	74 (10.2)	80 (11.8)	74 (10.1)	84 (11.4)
Chronic obstructive pulmonary disease — no./total no. (%)	104/695 (15.0)	117/649 (18.0)	106/703 (15.1)	121/703 (17.2)
Cardiac risk factors				
SYNTAX score‡	1.9±3.7	2.1±3.9	1.9±3.7	2.1±3.8
Previous coronary-artery bypass surgery — no. (%)	18 (2.5)	14 (2.1)	18 (2.5)	17 (2.3)
Previous percutaneous coronary intervention — no. (%)	103 (14.2)	87 (12.8)	102 (13.9)	93 (12.7)
Preexisting pacemaker or defibrillator — no. (%)	23 (3.2)	26 (3.8)	25 (3.4)	28 (3.8)
Previous myocardial infarction — no. (%)	48 (6.6)	33 (4.9)	49 (6.7)	39 (5.3)
Previous atrial fibrillation or atrial flutter — no./total no. (%)	111/722 (15.4)	98/678 (14.5)	113/731 (15.5)	109/734 (14.9)
Aortic-valve gradient — mm Hg§	47.0±12.1	46.6±12.2	47.2±12.3	46.7±12.2
Aortic-valve area — cm^2§	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Left ventricular ejection fraction — %§	61.7±7.9	61.9±7.7	61.7±7.9	61.9±7.7

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups. Percentages may not total 100 because of rounding. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. NYHA denotes New York Heart Association, and TAVR transcatheter aortic-valve replacement.

† The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) provides an estimate of the risk of death at 30 days among patients undergoing surgical aortic-valve replacement on the basis of several demographic and procedural variables.

‡ The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is a measure of the severity and extent of coronary artery disease. Low SYNTAX scores (<18) are associated with a higher success rate with PCI, scores between 18 and 27 with an intermediate success rate, and scores higher than 27 with a low success rate.

§ These data were reported by the individual trial site.

tion were similar in the two groups at 12 months.

SECONDARY EFFECTIVENESS MEASURES

Results of hierarchical analyses of the secondary effectiveness end points are provided in Table 3; all these end points met the prespecified test threshold. Symptoms graded by NYHA class decreased significantly from baseline in both groups, and this reduction in symptoms persisted throughout the 12-month follow-up period (Fig. S4 in the Supplementary Appendix). Hospitalization for heart failure during the 12-month follow-up period occurred in 3.2% of the patients in the TAVR group and in 6.5% in the surgery group (difference, −3.4 percentage points; 95% credible

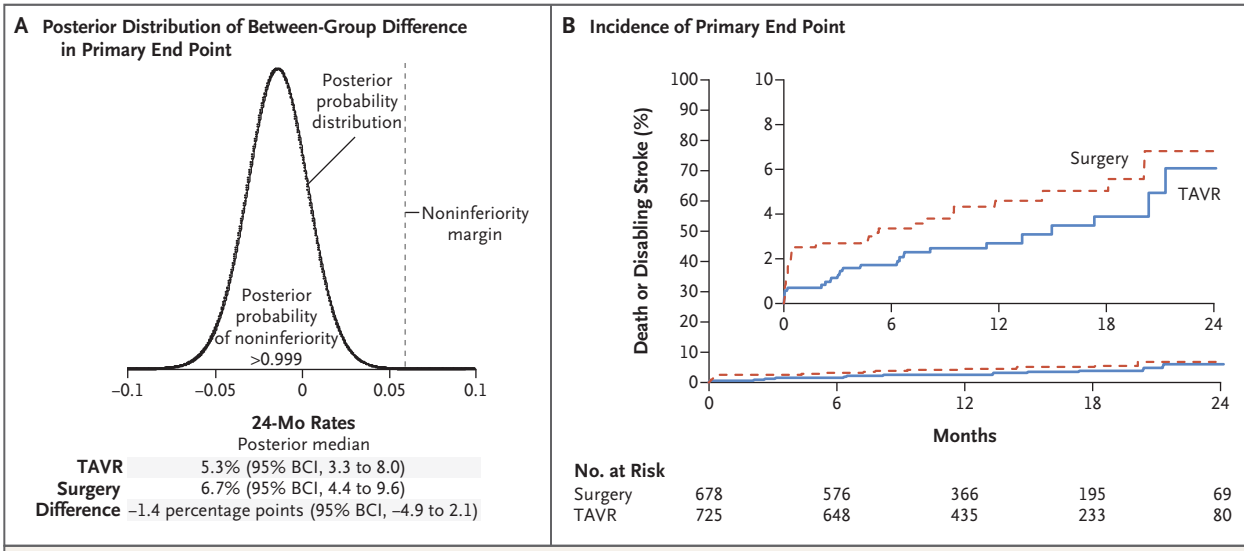

Figure 1. Posterior Distribution and Time-to-Event Curves for the Primary End Point.

The posterior distribution for the difference between the treatment groups in the incidence of death from any cause or disabling stroke at 24 months (the primary end point), shown in Panel A, confirmed that the noninferiority criterion for the primary end point was met. BCI denotes Bayesian credible interval, and TAVR transcatheter aortic-valve replacement. Panel B shows Kaplan–Meier time-to-event curves for the primary end point. The inset shows the same data on an enlarged y axis.

interval for the difference, −5.9 to −1.0). The KCCQ overall summary score (±SD) measuring quality of life was 88.7±14.2 in the TAVR group and 78.6±18.9 in the surgery group at 30 days, with no difference between groups observed at 12 months (Table S10 in the Supplementary Appendix). Among patients who were discharged from the hospital after undergoing TAVR, there was no significant difference in the incidence of death by 12 months between those who received a new permanent pacemaker and those who did not (3.4% and 1.2%, respectively).

ECHOCARDIOGRAPHIC FINDINGS

Aortic-valve hemodynamics improved from baseline in both groups (Fig. 2). Mean aortic-valve gradients were lower at 12 months in the TAVR group than in the surgery group; the mean effective orifice area was larger in the TAVR group than in the surgery group (Table 3). Moderate or severe total aortic regurgitation was present at 30 days in 3.5% of the patients in the TAVR group and in 0.5% in the surgery group. Severe patient–prosthesis mismatch occurred at 12 months in 1.8% of the patients in the TAVR group and in 8.2% in the surgery group (Table S11 in the Supplementary Appendix).

DISCUSSION

Our study, which used an adaptive Bayesian design, showed that among patients deemed to be at a low risk for death from surgery, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the risk of death or disabling stroke at 24 months. TAVR with a self-expanding supraannular bioprosthesis was associated with a lower incidence of disabling stroke, acute kidney injury, bleeding events, and atrial fibrillation than surgery but with a higher incidence of aortic regurgitation and permanent pacemaker use. Both TAVR and surgery provided functional improvement at 12 months, but the TAVR group had better recovery at 30 days, as indicated by the KCCQ score.

Our study group has conducted a series of clinical studies that have compared TAVR with a self-expanding supraannular bioprosthesis with surgery in patients at various degrees of surgical risk.[2,5,14] The current interim analysis includes patients at the lowest reported risk from surgery among these trials (mean STS-PROM, 1.9%). The 30-day incidence of death in both groups was very low (0.5% in the TAVR group and 1.3% in the surgery group) with a low ratio of observed-

Table 2. Clinical End Points at 30 Days and at 12 Months.*

End Point	30 Days			12 Months		
	TAVR	Surgery	Difference, TAVR–Surgery (95% BCI)	TAVR	Surgery	Difference, TAVR–Surgery (95% BCI)
	% of patients		percentage points	% of patients		percentage points
Death from any cause or disabling stroke	0.8	2.6	–1.8 (–3.2 to –0.5)	2.9	4.6	–1.8 (–4.0 to 0.4)
Death from any cause	0.5	1.3	–0.8 (–1.9 to 0.2)	2.4	3.0	–0.6 (–2.6 to 1.3)
Death from cardiovascular cause	0.5	1.3	–0.8 (–1.9 to 0.2)	1.7	2.6	–0.9 (–2.7 to 0.7)
All stroke	3.4	3.4	0.0 (–1.9 to 1.9)	4.1	4.3	–0.2 (–2.4 to 1.9)
Disabling	0.5	1.7	–1.2 (–2.4 to –0.2)	0.8	2.4	–1.6 (–3.1 to –0.3)
Nondisabling	3.0	1.7	1.2 (–0.3 to 2.9)	3.4	2.2	1.1 (–0.6 to 2.9)
Transient ischemic attack	0.6	0.8	–0.2 (–1.2 to 0.7)	1.7	1.8	–0.2 (–1.6 to 1.3)
30-Day composite safety end point†	5.3	10.7	–5.4 (–8.3 to –2.6)	NA	NA	NA
Life-threatening or disabling bleeding	2.4	7.5	–5.1 (–7.5 to –2.9)	3.2	8.9	–5.7 (–8.4 to –3.1)
Major vascular complication	3.8	3.2	0.6 (–1.4 to 2.5)	3.8	3.5	0.3 (–1.7 to 2.3)
Acute kidney injury stage 2 or 3	0.9	2.8	–1.8 (–3.4 to –0.5)	0.9	2.8	–1.8 (–3.4 to –0.5)
Atrial fibrillation	7.7	35.4	–27.7 (–31.8 to –23.6)	9.8	38.3	–28.5 (–32.8 to –24.1)
Permanent pacemaker implantation	17.4	6.1	11.3 (8.0 to 14.7)	19.4	6.7	12.6 (9.2 to 16.2)
Myocardial infarction	0.9	1.3	–0.4 (–1.5 to 0.7)	1.7	1.6	0.1 (–1.3 to 1.5)
Coronary-artery obstruction	0.9	0.4	0.5 (–0.3 to 1.4)	0.9	0.4	0.5 (–0.3 to 1.4)
Endocarditis	0.1	0.2	–0.1 (–0.7 to 0.3)	0.2	0.4	–0.2 (–0.9 to 0.5)
Valve thrombosis	0.1	0.1	0.0 (–0.4 to 0.4)	0.2	0.3	–0.1 (–0.9 to 0.5)
Aortic reintervention	0.4	0.4	0.0 (–0.8 to 0.7)	0.7	0.6	0.0 (–1.0 to 0.9)
Hospitalization for heart failure	1.2	2.5	–1.3 (–2.8 to 0.1)	3.2	6.5	–3.4 (–5.9 to –1.0)

* Values represent the estimated incidence (median of the posterior probability distribution as calculated by Bayesian analysis). Caution should be exercised regarding drawing inferences about absolute treatment effects with the 95% Bayesian credible interval (BCI), owing to multiple secondary end-point comparisons.

† The 30-day composite safety end point was a composite of death, disabling stroke, life-threatening bleeding, major vascular complication, or stage 2 or 3 acute kidney injury.

to-expected incidence of death in both groups (0.26 in the TAVR group and 0.68 in the surgery group), a finding that is probably attributable to the use of best practices by our heart teams. We selected the primary end point of death from any cause or disabling stroke at 24 months owing to the implications of these results for patients and providers considering options for aortic-valve replacement. The estimated 24-month incidence of death from any cause was low (4.5%) in both groups, a finding that reinforced the fact that our study included healthier patients with severe aortic-valve disease.

Neurologic complications associated with aortic-valve replacement are increasingly recognized as critical outcome measures in studies comparing transcatheter and surgical procedures.[15,16] We performed functional neurologic assessments before and after both procedures; a very small number of patients (<2%) in the TAVR group received an embolic protection device (see the Supplementary Appendix). Although the incidence of stroke was similar in the two groups, disabling stroke by 30 days occurred less often in the TAVR group, and the incidence remained lower at 24 months; these findings are similar to those in previous randomized trials of TAVR involving patients at increased surgical risk.[2,4]

Although aortic-valve hemodynamics were substantially improved from baseline in both groups, we found lower aortic-valve gradients and larger aortic-valve areas in the TAVR group, findings that are probably related to the supraannular design of the self-expanding bioprostheses.[2,4,14,17-19] Although

Table 3. Hierarchical Secondary Noninferiority and Superiority Objectives.*

Criterion	Hypothesis	Analysis Cohort	TAVR	Surgery	Difference, TAVR–Surgery	Posterior Probability	Threshold	Test Result
Noninferiority					(90% BCI)			
Mean gradient at 12 mo (mm Hg)	TAVR < [surgery+5 mm Hg]†	Implanted	8.6±3.7 (409)	11.2±4.9 (339)	−2.6 (−3.1 to −2.1)	>0.999	0.95	Passed
Mean effective orifice area at 12 mo (cm^2)	TAVR > [surgery−0.1 cm^2]†	Implanted	2.3±0.7 (341)	2.0±0.6 (293)	0.3 (0.2 to 0.4)	>0.999	0.95	Passed
Mean NYHA class change from baseline to 12 mo	TAVR > [surgery−0.375]†	As-treated	0.9±0.7 (428)	1.0±0.7 (342)	−0.1 (−0.2 to 0.0)	>0.999	0.95	Passed
Mean KCCQ change from baseline to 12 mo	TAVR > [surgery−5 points]‡	As-treated	22.2±20.3 (428)	20.9±21.0 (347)	1.3 (−1.2 to 3.8)	>0.999	0.95	Passed
Superiority					(95% BCI)			
Mean gradient at 12 mo (mm Hg)	TAVR < surgery	Implanted	8.6±3.7 (409)	11.2±4.9 (339)	−2.6 (−3.2 to −2.0)	>0.999	0.975	Passed
Mean effective orifice area at 12 mo (cm^2)	TAVR > surgery	Implanted	2.3±0.7 (341)	2.0±0.6 (293)	0.3 (0.2 to 0.4)	>0.999	0.975	Passed
Mean KCCQ change from baseline to 30 days	TAVR > surgery	As-treated	20.0±21.1 (713)	9.1±22.3 (636)	10.9 (8.6 to 13.2)	>0.999	0.975	Passed

* Plus–minus values are means ±SD. The numbers of patients with data are in parentheses. All noninferiority objectives were tested with a type I error standard of 0.05, and superiority tests were tested with a type I error of 0.025. If all the tests met their success criterion, the primary end point of death or disabling stroke at 24 months was tested for superiority with type I error rate of 0.025.

† Clinically meaningful differences of 5 mm Hg for mean gradient, 0.1 cm^2 for effective orifice area, and 0.375 for the NYHA class were determined by the Low Risk Trial Executive Committee.

‡ Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores range from 0 to 100, with higher scores indicating better health status; scores higher than 60 correlate with NYHA class I or II, and a 10-point increase corresponds to moderate clinical improvement. An increase of 5 points was deemed to be clinically meaningful.[13]

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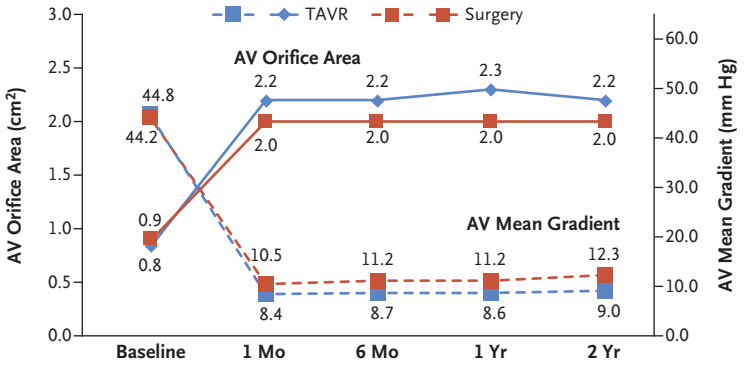

No. of Patients with Echocardiographic Data					
AV mean gradient					
TAVR	712	699	619	409	71
Surgery	673	634	542	339	62
AV orifice area					
TAVR	632	610	544	341	59
Surgery	590	541	467	293	53

Figure 2. Aortic-Valve Orifice Area and Mean Gradient to 24 Months.

Shown are the aortic-valve (AV) mean gradient (dashed lines) and the effective AV orifice area (solid lines) for the TAVR group and the surgery group at all time points after the procedure.

22.1% of the patients in the surgery group received small (19-mm or 21-mm) prostheses, the mean aortic-valve areas were large (2.0 cm^2), and the incidence of 12-month severe prosthesis–patient mismatch (8.2%) was less than in previous reports.[20,21] Nonetheless, valve areas were larger, and the frequency of prosthesis–patient mismatch was lower, with TAVR. In contrast, rates of aortic regurgitation were higher in the TAVR group. Longer-term follow-up will be necessary to understand the implications of these various valve characteristics on structural valve deterioration and long-term outcomes. We found a low incidence (<1%) of bioprosthetic-valve thrombosis, endocarditis, or need for aortic-valve reintervention with both self-expanding and surgical bioprostheses.

Our study has several limitations. The most important limitation is that this prespecified interim analysis occurred when 850 patients had reached 12 months of follow-up, and complete 24-month follow-up of the entire cohort has not been reached. Definitive conclusions regarding the advantages and disadvantages of TAVR as compared with surgery await long-term clinical and echocardiographic follow-up, which is planned to continue through 10 years for all patients. Second, although the amount of missing data in the trial was small, some patients did not have complete follow-up data on NYHA functional class, KCCQ scores, and echocardiography. Third, end-point adjudication could not be performed in a blinded manner for all end points, which may have resulted in bias in end-point assessment. Fourth, we excluded patients with bicuspid aortic valves and those who were candidates for mechanical valves. Finally, the latest-generation Evolut PRO bioprosthesis was used in only 22.3% of the patients who received TAVR.

In conclusion, in a randomized trial involving patients with severe aortic stenosis who were at low risk for death from surgery, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgical aortic-valve replacement with respect to death from any cause or disabling stroke at 24 months.

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Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

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APPENDIX

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