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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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*A complete list of the PARTNER 3 Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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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).

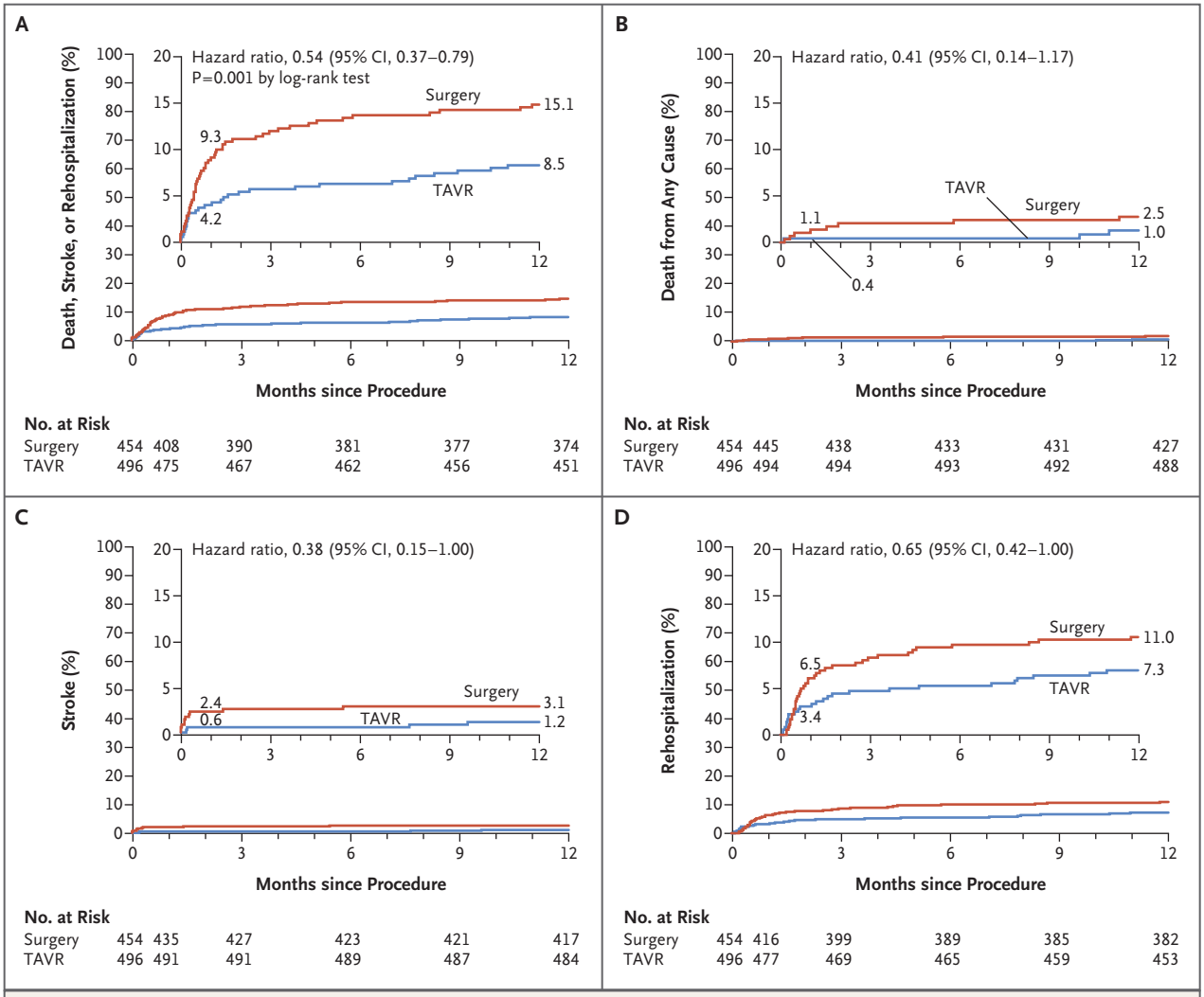

Figure 1. Time-to-Event Curves for the Primary Composite End Point and the Individual Components of the Primary End Point.

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

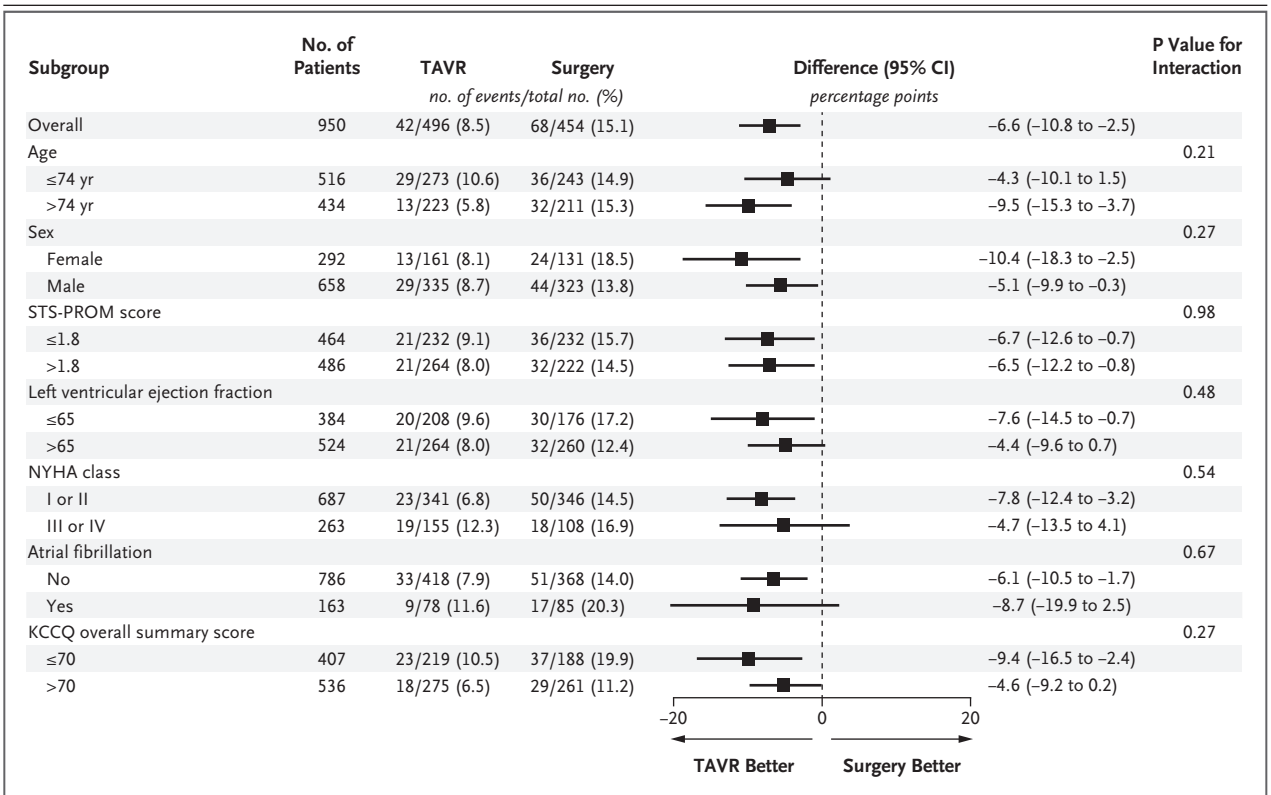

Figure 2. Subgroup Analyses of the Primary Composite End Point of Death from Any Cause, Stroke, or Rehospitalization.

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

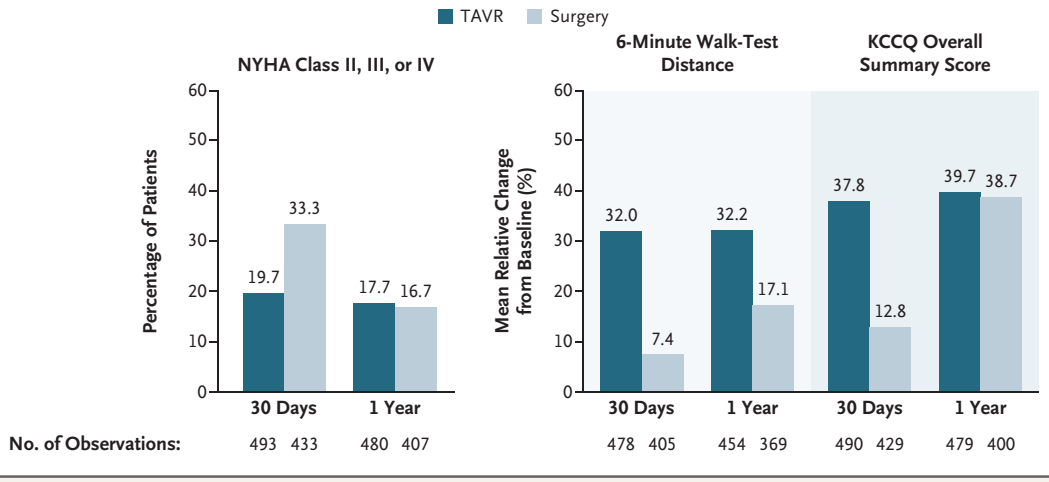

Figure 3. Functional Status and Quality of Life at 30 Days and 1 Year.

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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REFERENCES

1. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
2. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
3. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20.
4. Kapadia SR, Leon MB, Makkar RR, et al. 5-Year outcomes of transcatheter aortic valve replacement compared with standard treatment for patients with inoperable aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2485-91.
5. Mack MJ, Leon MB, Smith CR, et al. 5-Year outcomes of transcatheter aortic valve replacement or surgical aortic valve replacement for high surgical risk patients with aortic stenosis (PARTNER 1): a randomised controlled trial. Lancet 2015;385:2477-84.
6. Webb JG, Doshi D, Mack MJ, et al. A randomized evaluation of the SAPIEN XT transcatheter heart valve system in patients with aortic stenosis who are not candidates for surgery. JACC Cardiovasc Interv 2015;8:1797-806.
7. Thourani VH, Kodali S, Makkar RR, et al. Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis. Lancet 2016;387:2218-25.
8. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
9. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
10. Reardon MJ, Van Mieghem NM, Popma JJ, et al. Surgical or transcatheter aortic-valve replacement in intermediate-risk patients. N Engl J Med 2017;376:1321-31.
11. Gleason TG, Reardon MJ, Popma JJ, et al. 5-Year outcomes of self-expanding transcatheter versus surgical aortic valve replacement in high-risk patients. J Am Coll Cardiol 2018;72:2687-96.
12. Nishimura RA, Otto CM, Bonow RO, et al. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. J Am Coll Cardiol 2017;70:252-89.

13. Baumgartner H, Falk V, Bax JJ, et al. 2017 ESC/EACTS guidelines for the management of valvular heart disease. Eur Heart J 2017;38:2739-91.
14. SAVR TAVR volumes. Presented at a meeting of the Society of Thoracic Surgeons–American College of Cardiology TVT Registry Stakeholder Advisory Group, Washington, DC, March 4, 2019.
15. Thourani VH, Suri RM, Gunter RL, et al. Contemporary real-world outcomes of surgical aortic valve replacement in 141,905 low-risk, intermediate-risk, and high-risk patients. Ann Thorac Surg 2015;99:55-61.
16. Søndergaard L, Ihlemann N, Capodanno D, et al. Durability of transcatheter and surgical bioprosthetic aortic valves in patients at lower surgical risk. J Am Coll Cardiol 2019;73:546-53.
17. Waksman R, Rogers T, Torguson R, et al. Transcatheter aortic valve replacement in low-risk patients with symptomatic severe aortic stenosis. J Am Coll Cardiol 2018;72:2095-105.
18. Kodali S, Thourani VH, White J, et al. Early clinical and echocardiographic outcomes after SAPIEN 3 transcatheter aortic valve replacement in inoperable, high-risk and intermediate-risk patients with aortic stenosis. Eur Heart J 2016;37:2252-62.
19. Pocock SJ, Ariti CA, Collier TJ, Wang D. The win ratio: a new approach to the analysis of composite endpoints in clinical trials based on clinical priorities. Eur Heart J 2012;33:176-82.
20. Vandvik PO, Otto CM, Siemieniuk RA, et al. Transcatheter or surgical aortic valve replacement for patients with severe, symptomatic, aortic stenosis at low to intermediate surgical risk: a clinical practice guideline. BMJ 2016;354:i5085.
21. Otto CM, Kumbhani DJ, Alexander KP, et al. 2017 ACC expert consensus decision pathway for transcatheter aortic valve replacement in the management of adults with aortic stenosis: a report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents. J Am Coll Cardiol 2017;69:1313-46.
22. Schymik G, Heimeshoff M, Bramlage P, et al. A comparison of transcatheter aortic valve implantation and surgical aortic valve replacement in 1,141 patients with severe symptomatic aortic stenosis and less than high risk. Catheter Cardiovasc Interv 2015;86:738-44.
23. Rosato S, Santini F, Barbanti M, et al. Transcatheter aortic valve implantation compared with surgical aortic valve replacement in low-risk patients. Circ Cardiovasc Interv 2016;9(5):e003326.
24. Bekeredjian R, Szabo G, Balaban Ü, et al. Patients at low surgical risk as defined by the Society of Thoracic Surgeons Score undergoing isolated interventional or surgical aortic valve implantation: in-hospital data and 1-year results from the German Aortic Valve Registry (GARY). Eur Heart J 2018 November 16 (Epub ahead of print).
25. Bagur R. Transcatheter aortic valve looking for low-risk patients: a post hoc analysis of SURTAVI keeps opening the door. EuroIntervention 2018;14:846-8.
26. Frank D, Abdel-Wahab M, Gilard M, et al. Characteristics and outcomes of patients ≤75 years who underwent transcatheter aortic valve implantation: insights from the SOURCE 3 Registry. Clin Res Cardiol 2018 December 14 (Epub ahead of print).
27. Finkelstein A, Rozenbaum Z, Halkin A, et al. Outcomes of transcatheter aortic valve implantation in patients with low versus intermediate to high surgical risk. Am J Cardiol 2019;123:644-9.
28. Kodali S, Pibarot P, Douglas PS, et al. Paravalvular regurgitation after transcatheter aortic valve replacement with the Edwards sapien valve in the PARTNER trial: characterizing patients and impact on outcomes. Eur Heart J 2015;36:449-56.
29. Nazif TM, Dizon JM, Hahn RT, et al. Predictors and clinical outcomes of permanent pacemaker implantation after transcatheter aortic valve replacement: the PARTNER (Placement of AoRtic TraNscathetER Valves) trial and registry. JACC Cardiovasc Interv 2015;8:60-9.
30. Fadahunsi OO, Olowoyeye A, Ukaigwe A, et al. Incidence, predictors, and outcomes of permanent pacemaker implantation following transcatheter aortic valve replacement: analysis from the U.S. Society of Thoracic Surgeons/American College of Cardiology TVT Registry. JACC Cardiovasc Interv 2016;9:2189-99.
31. Généreux P, Webb JG, Svensson LG, et al. Vascular complications after transcatheter aortic valve replacement: insights from the PARTNER (Placement of AoRTic TraNscathetER Valve) trial. J Am Coll Cardiol 2012;60:1043-52.
32. Kapadia SR, Huded CP, Kodali SK, et al. Stroke after surgical versus transfemoral transcatheter aortic valve replacement in the PARTNER Trial. J Am Coll Cardiol 2018;72:2415-26.
33. Dvir D, Bourguignon T, Otto CM, et al. Standardized definition of structural valve degeneration for surgical and transcatheter bioprosthetic aortic valves. Circulation 2018;137:388-99.
34. Capodanno D, Petronio AS, Prendergast B, et al. Standardized definitions of structural deterioration and valve failure in assessing long-term durability of transcatheter and surgical aortic bioprosthetic valves: a consensus statement from the European Association of Percutaneous Cardiovascular Interventions (EAPCI) endorsed by the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J 2017;38:3382-90.
35. Carroll JD, Vemulapalli S, Dai D, et al. Procedural experience for transcatheter aortic valve replacement and relation to outcomes: the STS/ACC TVT Registry. J Am Coll Cardiol 2017;70:29-41.
36. Wassef AWA, Rodes-Cabau J, Liu Y, et al. The learning curve and annual procedure volume standards for optimum outcomes of transcatheter aortic valve replacement: findings from an international registry. JACC Cardiovasc Interv 2018;11:1669-79.
37. Makkar RR, Fontana G, Jilaihawi H, et al. Possible subclinical leaflet thrombosis in bioprosthetic aortic valves. N Engl J Med 2015;373:2015-24.
38. Chakravarty T, Søndergaard L, Friedman J, et al. Subclinical leaflet thrombosis in surgical and transcatheter bioprosthetic aortic valves: an observational study. Lancet 2017;389:2383-92.
39. Cribier A, Eltchaninoff H, Bash A, et al. Percutaneous transcatheter implantation of an aortic valve prosthesis for calcific aortic stenosis: first human case description. Circulation 2002;106:3006-8.