ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement in Low-Risk Patients at Five Years

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ABSTRACT

BACKGROUND

A previous analysis in this trial showed that among patients with severe, symptomatic aortic stenosis who were at low surgical risk, the rate of the composite end point of death, stroke, or rehospitalization at 1 year was significantly lower with transcatheter aortic-valve replacement (TAVR) than with surgical aortic-valve replacement. Longer-term outcomes are unknown.

METHODS

We randomly assigned patients with severe, symptomatic aortic stenosis and low surgical risk to undergo either TAVR or surgery. The first primary end point was a composite of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure. The second primary end point was a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days, analyzed with the use of a win ratio analysis. Clinical, echocardiographic, and health-status outcomes were assessed through 5 years.

RESULTS

A total of 1000 patients underwent randomization: 503 patients were assigned to undergo TAVR, and 497 to undergo surgery. A component of the first primary end point occurred in 111 of 496 patients in the TAVR group and in 117 of 454 patients in the surgery group (Kaplan–Meier estimates, 22.8% in the TAVR group and 27.2% in the surgery group; difference, −4.3 percentage points; 95% confidence interval [CI], −9.9 to 1.3; P=0.07). The win ratio for the second primary end point was 1.17 (95% CI, 0.90 to 1.51; P=0.25). The Kaplan–Meier estimates for the components of the first primary end point were as follows: death, 10.0% in the TAVR group and 8.2% in the surgery group; stroke, 5.8% and 6.4%, respectively; and rehospitalization, 13.7% and 17.4%. The hemodynamic performance of the valve, assessed according to the mean (±SD) valve gradient, was 12.8±6.5 mm Hg in the TAVR group and 11.7±5.6 mm Hg in the surgery group. Bioprosthetic-valve failure occurred in 3.3% of the patients in the TAVR group and in 3.8% of those in the surgery group.

CONCLUSIONS

Among low-risk patients with severe, symptomatic aortic stenosis who underwent TAVR or surgery, there was no significant between-group difference in the two primary composite outcomes. (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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Transcatheter aortic-valve replacement (TAVR) has been increasingly used as an alternative to surgery for treating patients with severe, symptomatic aortic stenosis.[1,2] Randomized trials of both balloon-expandable and self-expanding TAVR valves have shown that in patients at intermediate or high risk for death by 30 days after surgery, TAVR was either noninferior or superior to surgical aortic-valve replacement at 5 years of follow-up.[3-11] In two randomized trials involving younger patients who were at low surgical risk, TAVR was either noninferior or superior to surgery at 2 or 3 years.[12-15] The Placement of Aortic Transcatheter Valves (PARTNER) 3 trial showed that the rate of the composite end point of death, stroke, or rehospitalization at 1 and 2 years was significantly lower with TAVR than with surgery.[13-15] Here, we report the 5-year outcomes in this trial.

Methods

Trial Design and Oversight

This multicenter, randomized trial compared the use of the SAPIEN 3 transcatheter heart valve (Edwards Lifesciences) with surgical aortic-valve replacement in patients with severe, symptomatic aortic stenosis who were at low surgical risk. The trial design, details regarding oversight, and results at 1 and 2 years have been published previously.[13,15] The trial protocol (available with the full text of this article at NEJM.org) was designed by the sponsor (Edwards Lifesciences), with input from the trial steering committee and the Food and Drug Administration, and was approved by the institutional review board at each site. The sponsor funded all trial-related activities and participated in site selection, data collection, monitoring, and statistical analysis. The trial leadership had unrestricted access to all the data, prepared all the drafts of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patients

Patients were eligible for inclusion if they had severe, symptomatic aortic stenosis and were considered to be at low surgical risk on the basis 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 on the basis of assessment by the heart team. Patients also had to be eligible for TAVR through transfemoral access. The eligibility of all the patients was reviewed and approved by a case review board. Key anatomical and clinical exclusions have been reported previously and are provided in the Supplementary Appendix, available at NEJM.org.[13] Details about the representativeness of the patients in the trial are also provided in the Supplementary Appendix.

Randomization, Procedures, and Follow-up

Patients were assigned in a 1:1 ratio to undergo either TAVR with a SAPIEN 3 valve or surgical aortic-valve replacement with a commercially available bioprosthetic valve. The SAPIEN 3 system and the procedures for TAVR and surgery have been described previously.[13] Clinical outcomes and transthoracic echocardiography data were assessed at baseline, after the implantation procedure, at hospital discharge, 30 days, 6 months, 1 year, and then annually to 5 years.

End Points

The original primary end point, assessed at 1 year, was a nonhierarchical composite of death from any cause, stroke, or rehospitalization related to the procedure, the valve, or heart failure (see the Supplementary Appendix). A time-to-first-event analysis was used to evaluate this end point. However, some patients had more than one end-point event or more than one rehospitalization over the 5-year period. To better reflect the patient outcomes through 5 years, two primary end points were prespecified in the 5-year extension statistical analysis plan: the original nonhierarchical composite end point and a hierarchical composite end point that included death from any cause, disabling stroke, nondisabling stroke, and the number of rehospitalization days (see the Supplementary Appendix). Secondary end points of interest at 5 years were death or disabling stroke, new-onset atrial fibrillation, aortic-valve reintervention, endocarditis, and clinically significant valve thrombosis; definitions are provided in the Supplementary Appendix. Valve thrombosis was defined according to Valve Academic Re-

search Consortium 3 (VARC-3) criteria as clinically significant bioprosthetic-valve dysfunction as assessed with echocardiography or contrast-enhanced computed tomography with either no (stage 1), moderate (stage 2), or severe (stage 3) hemodynamic valve deterioration.[16] A clinical events committee adjudicated key 5-year clinical outcomes, including all components of the primary end points, valve thrombosis, and valve reintervention. Other secondary end points included functional status and quality of life as assessed with the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS). KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status. The secondary end point of alive with a KCCQ-OS score of 75 or higher indicated the status of being alive and well.

ECHOCARDIOGRAPHIC ASSESSMENTS

All echocardiograms were assessed by a core laboratory with the use of standard hemodynamic measures. Total aortic regurgitation and paravalvular aortic regurgitation were assessed with the use of a multiparametric integrative approach.[16] Valve durability was assessed with the use of the VARC-3 definition of bioprosthetic-valve failure, which includes the occurrence of valve reintervention, valve-related death, or deterioration in hemodynamic valve function between the day 30 and follow-up echocardiograms. All potential cases of bioprosthetic-valve failure were adjudicated by a group of three experts for confirmation of the presence, stage, and cause of valve failure.[16]

STATISTICAL ANALYSIS

For the first primary end point (a nonhierarchical composite of death from any cause, stroke, or rehospitalization), we used the Wald test[17] to determine the superiority of TAVR to surgery; the percentage of patients with an event in each group at 5 years was estimated with the Kaplan–Meier method, and Greenwood's formula was used to estimate standard errors. The odds ratio and 95% confidence interval from the time-adjusted logistic-regression model were also calculated. The second primary end point (a hierarchal composite that included death from any cause, disabling stroke, nondisabling stroke, and the number of rehospitalization days) was tested with the use of the win ratio method (see the Supplementary Appendix).[18] The type I error was controlled between the two primary end points with the use of the Hochberg method.[19]

Time-to-event analyses from baseline to 1 year, 1 to 5 years (landmark analysis), and baseline to 5 years were performed, and hazard ratios and 95% confidence intervals were calculated for the clinical end points (see the Supplementary Appendix). If there was clear evidence of nonproportionality of hazards, the odds ratio and 95% confidence interval from the time-adjusted logistic-regression model were also reported.[20] For continuous variables, the means and the difference between the means, along with the 95% confidence intervals, were reported. For categorical variables, the percentage of patients in each trial group, the difference in the percentages, and the 95% confidence intervals were reported. The widths of the confidence intervals for continuous and categorical variables have not been adjusted for multiplicity and should not be used to infer definitive treatment effects. Additional methods are described in the Supplementary Appendix.

All clinical end-point analyses were performed in the as-treated population, which included the patients who had undergone randomization and in whom the index procedure was initiated (see the Supplementary Appendix). Echocardiographic end-point analyses were performed in the valve-implant population, which included the 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, PROCEDURES, AND FOLLOW-UP

A total of 1000 patients underwent randomization at 71 clinical sites: 503 patients were assigned to undergo transfemoral TAVR and 497 to undergo surgery. The as-treated population included 496 patients in the TAVR group and 454 in the surgery group. A total of 948 patients (495 in the TAVR group and 453 in the surgery group) received the intended valve. Details regarding the implanted valve sizes and surgical valve types were published previously[21] and are provided in Figure S1 and Table S1 in the Supplementary Appendix. The mean age of the patients was 73 years, 69.3% of

the patients were men, and the mean STS-PROM score was 1.9% (Table S2). Details regarding randomization and follow-up through 5 years are shown in Figure 1. Follow-up data through 5 years were available for 91.6% of the patients, with a disproportional loss to follow-up in the surgery group; follow-up data were available for 469 of 496 patients (94.6%) in the TAVR group and 401

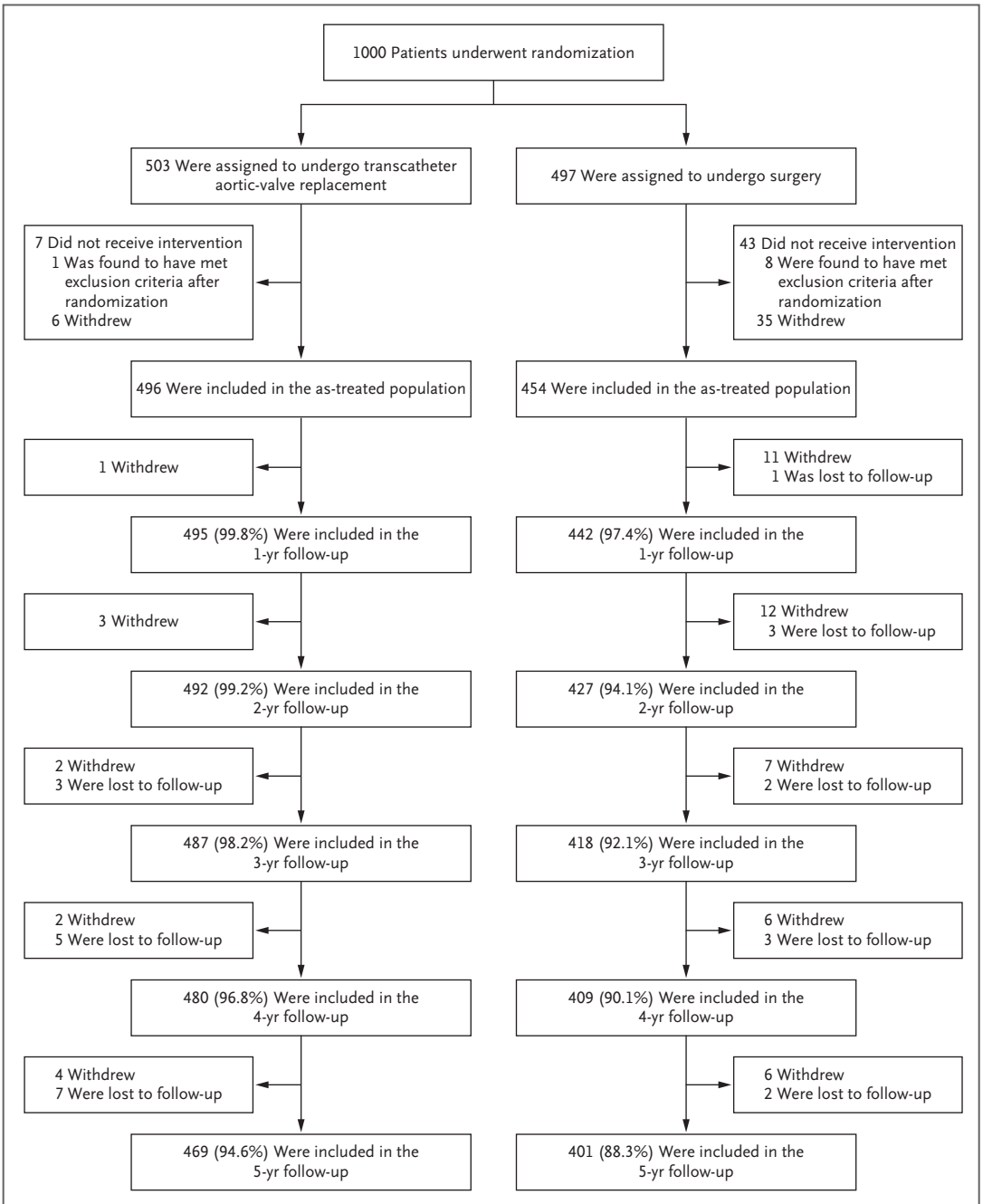


Figure 1. Randomization and Follow-up.

Patients who met the composite primary end point of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure but who withdrew or were lost to follow-up are considered to have completed follow-up because they had already died, had a stroke, or had rehospitalization before trial exit. Data from the vital-status sweep are not shown.

of 454 (88.3%) in the surgery group. A vital-status sweep yielded data for 66 of 95 patients who had been lost to follow-up or had withdrawn from the trial (21 patients assigned to the TAVR group and 45 assigned to the surgery group) (Fig. S2). Therefore, vital status could be determined for 486 of 496 patients (98.0%) in the TAVR group and 441 of 454 patients (97.1%) in the surgery group.

PRIMARY END POINTS

The composite of death, stroke, or rehospitalization related to the valve, the procedure, or heart failure (the first primary end point) occurred in 111 of 496 patients in the TAVR group and in 117 of 454 patients in the surgery group. The Kaplan–Meier estimates were 22.8% in the TAVR group and 27.2% in the surgery group (difference, –4.3 percentage points; 95% confidence interval

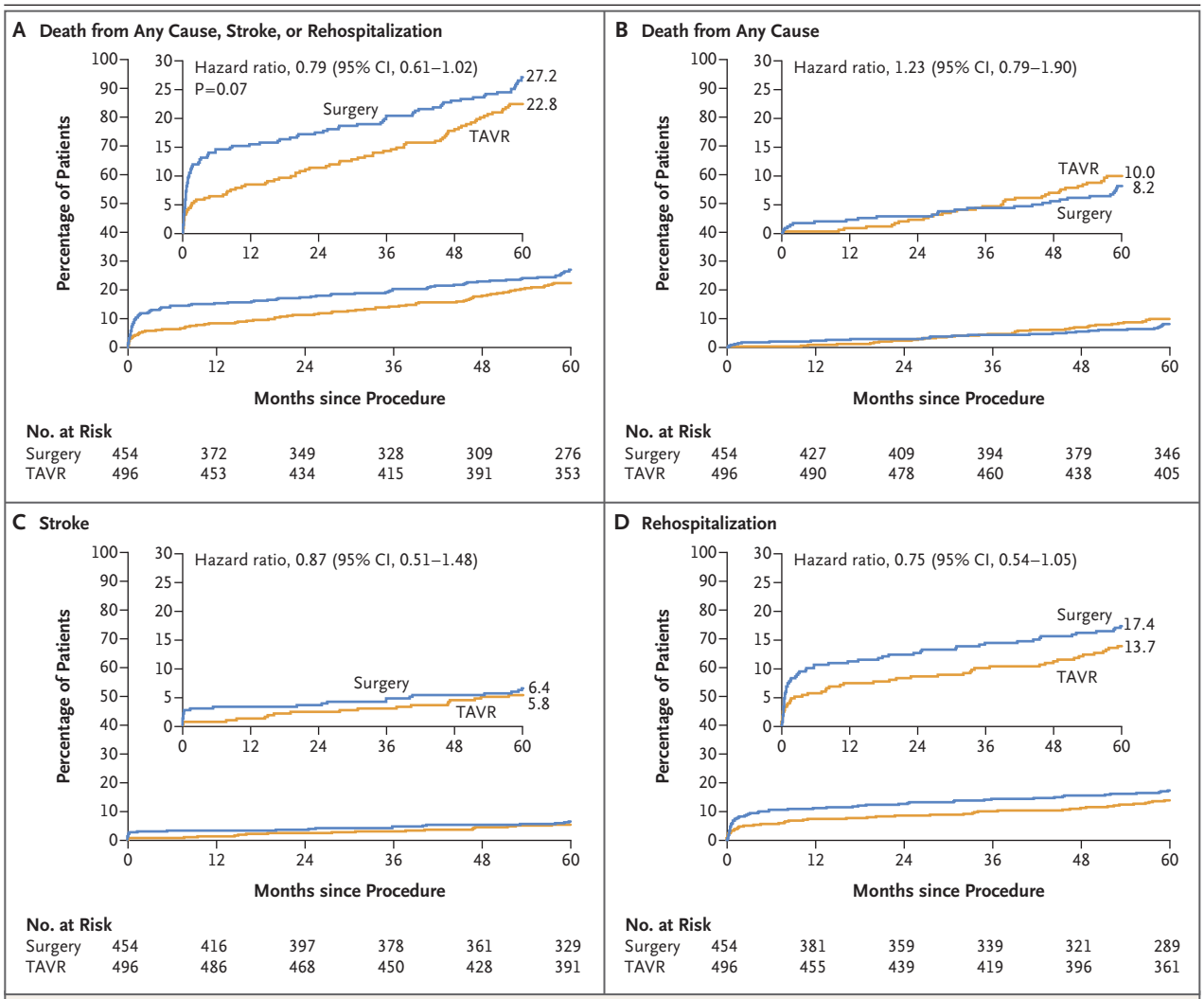


Figure 2. Kaplan–Meier Curves for the First Primary End Point and Its Components.

Panel A shows the Kaplan–Meier estimates of the first composite primary end point of death from any cause, stroke, or rehospitalization, and Panels B, C, and D show the estimates for the components. Rehospitalization was defined as rehospitalization related to the procedure, the valve, or heart failure. According to the statistical analysis plan, the analysis of the composite primary end point involved the difference in the Kaplan–Meier estimates between the transcatheter aortic-valve replacement (TAVR) group and the surgery group, calculated on the basis of the Wald test (difference, –4.3 percentage points; 95% CI, –9.9 to 1.3; P=0.07). The odds ratio and 95% confidence interval for death from any cause were calculated because there was evidence of nonproportionality of hazards from baseline to 5 years (odds ratio, 1.24; 95% CI, 0.79 to 1.97). The inset in each panel shows the same data on an enlarged y axis.

Table 1. Key Clinical End Points.*

End Point	Baseline to 5 Years			1 Year to 5 Years		
	TAVR (N=496)	Surgery (N=454)	Hazard Ratio (95% CI)	TAVR (N=490)	Surgery (N=427)	Hazard Ratio (95% CI)
	no. of patients with event (Kaplan–Meier estimate, %)			*no. of patients with event (Kaplan–Meier estimate, %)*		
Death, stroke, or rehospitalization†	111 (22.8)	117 (27.2)	0.79 (0.61–1.02)‡	69 (15.7)	47 (13.7)	1.17 (0.81–1.70)
Death from any cause	48 (10.0)	34 (8.2)	1.23 (0.79–1.90)§	43 (9.1)	23 (5.9)	1.61 (0.97–2.67)
Death from cardiovascular causes	26 (5.5)	21 (5.1)	1.08 (0.61–1.92)§	22 (4.7)	12 (3.1)	1.58 (0.78–3.19)
Death from noncardiovascular causes	22 (4.8)	13 (3.3)	1.46 (0.74–2.90)§	21 (4.6)	11 (2.8)	1.64 (0.79–3.41)
Stroke	27 (5.8)	27 (6.4)	0.87 (0.51–1.48)	21 (4.6)	12 (3.2)	1.49 (0.73–3.02)
Disabling stroke	13 (2.9)	11 (2.7)	1.03 (0.46–2.30)	12 (2.7)	6 (1.6)	1.73 (0.65–4.61)
Nondisabling stroke	15 (3.2)	16 (3.7)	0.82 (0.40–1.65)	10 (2.2)	6 (1.5)	1.41 (0.51–3.89)
Death or disabling stroke	55 (11.5)	41 (9.8)	1.17 (0.78–1.75)§	50 (10.6)	27 (6.9)	1.60 (1.00–2.55)
Rehospitalization†	65 (13.7)	74 (17.4)	0.75 (0.54–1.05)	29 (6.9)	24 (6.9)	0.98 (0.57–1.69)
Aortic-valve reintervention	12 (2.6)	12 (3.0)	0.86 (0.39–1.92)	9 (2.0)	10 (2.6)	0.77 (0.31–1.90)
Endocarditis	6 (1.3)	8 (2.0)	0.65 (0.23–1.87)	5 (1.1)	6 (1.5)	0.72 (0.22–2.35)
Valve thrombosis¶	12 (2.5)	1 (0.2)	10.52 (1.37–80.93)	10 (2.1)	1 (0.2)	8.72 (1.12–68.12)
New-onset atrial fibrillation‖**	55 (13.7)	155 (42.4)	0.25 (0.19–0.34)	21 (6.0)	5 (2.6)	2.30 (0.87–6.10)
New pacemaker‖**	63 (13.5)	43 (10.4)	1.33 (0.90–1.96)	25 (6.1)	18 (4.9)	1.22 (0.67–2.24)
Serious bleeding‖	49 (10.2)	64 (14.8)	0.65 (0.45–0.95)	25 (5.6)	18 (5.1)	1.15 (0.63–2.11)
Myocardial infarction‖	10 (2.1)	18 (4.4)	0.48 (0.22–1.05)	6 (1.3)	10 (2.6)	0.51 (0.19–1.41)
Revascularization‖	17 (3.7)	25 (6.0)	0.59 (0.32–1.09)	12 (2.7)	12 (3.2)	0.85 (0.38–1.88)
Percutaneous coronary intervention	16 (3.5)	20 (4.9)	0.69 (0.36–1.34)	11 (2.5)	12 (3.2)	0.78 (0.35–1.78)
Coronary-artery bypass grafting	2 (0.5)	5 (1.1)	0.36 (0.07–1.85)	1 (0.2)	0	—

* The total number of patients in each column header represents the number of patients at risk for death at the beginning of the interval. TAVR denotes transcatheter aortic-valve replacement.

† Rehospitalization was defined as rehospitalization related to the valve, the procedure, or heart failure.

‡ According to the statistical analysis plan, the analysis of the two composite primary end points involved the difference in the Kaplan–Meier estimates between the TAVR group and the surgery group, calculated on the basis of the Wald test (difference, –4.3 percentage points; 95% CI, –9.9 to 1.3; P=0.07).

§ The following odds ratios with 95% confidence intervals were calculated for end points that showed evidence of nonproportionality of hazards from baseline to year 5: odds ratio for death from any cause, 1.24 (95% CI, 0.79 to 1.97); odds ratio for death from cardiovascular causes, 1.08 (95% CI, 0.60 to 1.95); odds ratio for death from noncardiovascular causes, 1.48 (95% CI, 0.74 to 2.97); and odds ratio for death or disabling stroke, 1.18 (95% CI, 0.77 to 1.81).

¶ Valve thrombosis was adjudicated according to Valve Academic Research Consortium 3 criteria.

‖ The outcome was reported by the trial site. Serious bleeding included events that led to death or another serious event; resulted in life-threatening illness, injury, or permanent impairment; resulted in medical or surgical intervention; or resulted in hospitalization or prolongation of existing hospitalization.

** These categories exclude atrial fibrillation and pacemakers that were present at baseline.

[CI], −9.9 to 1.3; P=0.07; hazard ratio, 0.79; 95% CI, 0.61 to 1.02) (Fig. 2A and Table 1). These findings appeared to be consistent in all major subgroups (Fig. S3). The win ratio for the second primary end point (a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days) was 1.17 (95% CI, 0.90 to 1.51; P=0.25) (Fig. 3). The results of a sensitivity analysis that used multiple imputation for missing data and was adjusted for nonproportional hazards seemed to be consistent with those of the primary analysis (Table S3). In a landmark analysis of years 1 to 5, a total of 69 of 453 patients in the TAVR group and 47 of 372 patients in the surgery group had died or had had a stroke or rehospitalization. The Kaplan–Meier estimates were 15.7% in the TAVR group and 13.7% in the surgery group (hazard ratio, 1.17; 95% CI, 0.81 to 1.70) (Table 1 and Fig. S4). The restricted mean event-free survival in the

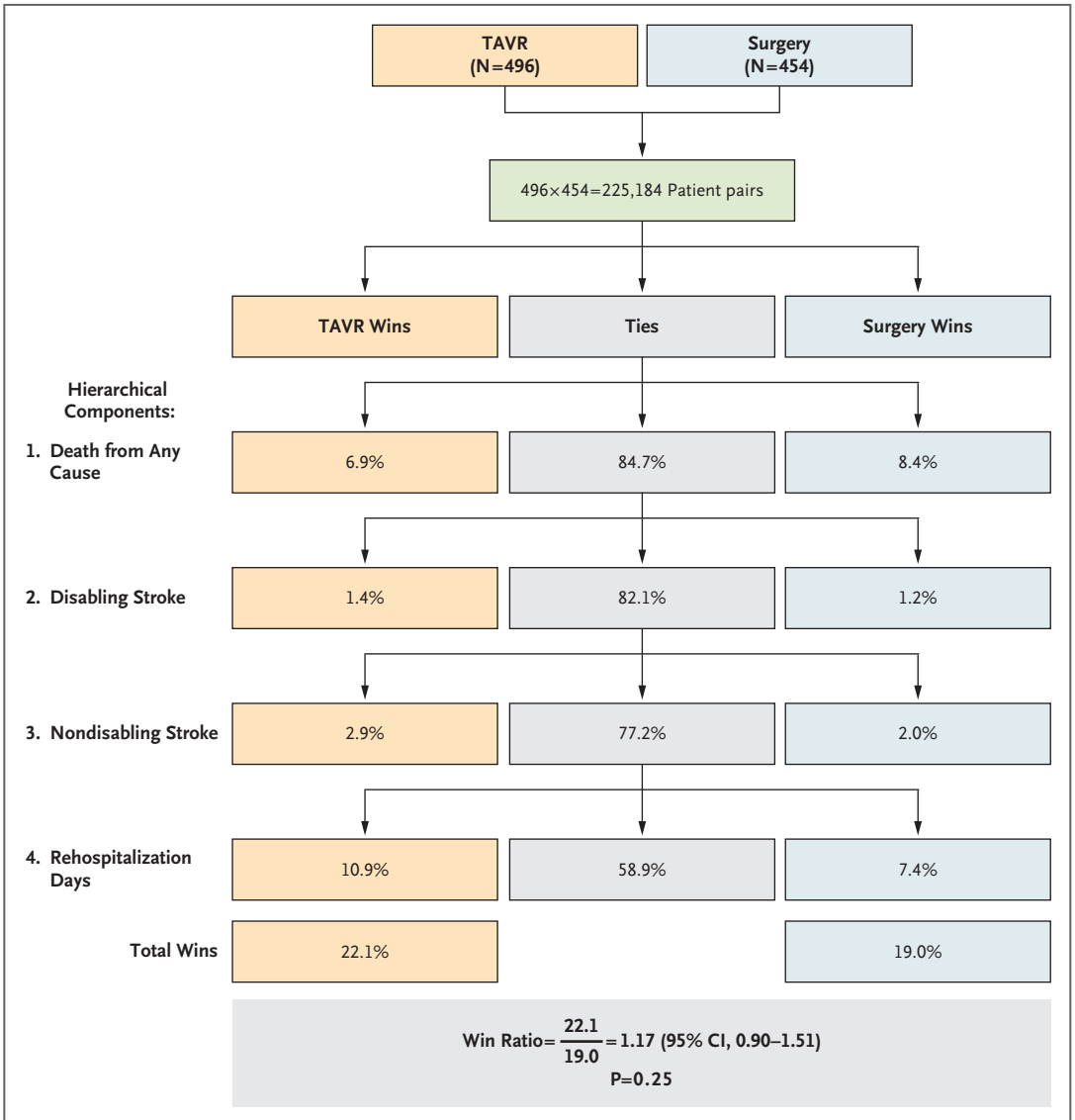


Figure 3. Win Ratio Diagram for the Second Primary End Point.

Shown are the results of the win ratio analysis of the second primary end point (a hierarchical composite that included death, disabling stroke, nondisabling stroke, and the number of rehospitalization days related to the valve, the procedure, or heart failure).

analysis of the first primary end point at 5 years was longer by 103 days (95% CI, 26 to 180) with TAVR than with surgery (Table S4).

With respect to the individual components of the first primary end point at 5 years, the Kaplan–Meier estimates were as follows: death from any cause, 10.0% in the TAVR group and 8.2% in the surgery group (odds ratio, 1.24; 95% CI, 0.79 to 1.97); stroke, 5.8% and 6.4%, respectively (hazard ratio, 0.87; 95% CI, 0.51 to 1.48); and rehospitalization, 13.7% and 17.4% (hazard ratio, 0.75; 95% CI, 0.54 to 1.05) (Fig. 2B, 2C, and 2D and Table 1). The Kaplan–Meier estimates at 1 year are provided in Table S5. There were 82 deaths through 5 years of follow-up: 48 in the TAVR group (26 from cardiovascular causes and 22 from noncardiovascular causes) and 34 in the surgery group (21 from cardiovascular causes and 13 from noncardiovascular causes) (Fig. S5 and Tables S6 and S7). Three patients in the TAVR group and 1 patient in the surgery group died from coronavirus disease 2019 (Covid-19). The 5-year mortality was 10.2% in the TAVR group and 9.0% in the surgery group when additional patient information obtained from the vital-status sweep was included. Figure S6 shows the Kaplan–Meier curves for the landmark analysis at 1 year for death from any cause, death from any cause with the inclusion of data from the vital-status sweep, death from cardiovascular causes, and death from noncardiovascular causes. Additional 5-year data — including data for stroke, disabling stroke, death, and rehospitalization — are provided in Table 1, Tables S5 through S8, and Figures S6, S7, and S8.

SECONDARY END POINTS

Data regarding aortic-valve reintervention and endocarditis are provided in Table 1 and Table S10. New-onset atrial fibrillation occurred in 55 patients in the TAVR group and in 155 patients in the surgery group (Kaplan–Meier estimates, 13.7% and 42.4%, respectively). Serious bleeding occurred in 49 patients in the TAVR group and in 64 patients in the surgery group. A new permanent pacemaker was implanted in 13.5% of the patients in the TAVR group and in 10.4% of those in the surgery group (Table 1). Clinically significant valve thrombosis, according to VARC-3 criteria, occurred in 12 patients (2.5%) in the TAVR group and in 1 patient (0.2%) in the surgery group (Table 1). None of the patients with valve thrombosis died. Of the 12 patients in the TAVR group with thrombosis, hemodynamic valve deterioration was absent (stage 1) in 4 patients, was moderate (stage 2) in 5 patients, and was severe (stage 3) in 3 patients (Table S11). Of the 13 patients with thrombosis, 7 had shortness of breath or dyspnea on exertion, 3 had a stroke (1 disabling and 2 nondisabling), and 3 had no symptoms. The patient with thrombosis in the surgery group had no hemodynamic valve deterioration (stage 1) and had dyspnea on exertion. The percentages of patients who received anticoagulation therapy are provided in Table S12.

ECHOCARDIOGRAPHIC FINDINGS

At 5 years, the mean (±SD) aortic-valve gradient according to echocardiography was 12.8±6.5 mm Hg in the TAVR group and 11.7±5.6 mm Hg in the surgery group; the mean aortic-valve area was 1.9±0.5 cm^2 and 1.8±0.5 cm^2 in the two groups, respectively (Fig. 4A and 4B). At 5 years, aortic regurgitation of mild or greater severity was present in 81 of 331 patients (24.5%) in the TAVR group and in 18 of 284 patients (6.3%) in the surgery group; paravalvular aortic regurgitation of mild or greater severity was present in 69 of 331 patients (20.8%) in the TAVR group and in 9 of 283 patients (3.2%) in the surgery group (Fig. S9). In the TAVR group, 5-year mortality was 9.1% among patients with no or trace paravalvular aortic regurgitation at 30 days after the procedure and 11.1% among those who had mild paravalvular aortic regurgitation at 30 days after the procedure (hazard ratio, 0.78; 95% CI, 0.42 to 1.45) (Fig. S10). The Kaplan–Meier estimates of bioprosthetic-valve failure of any cause were 3.3% in the TAVR group and 3.8% in the surgery group. The estimates of irreversible stage 3 (severe) structural or hemodynamic valve deterioration were 1.1% in the TAVR group and 1.0% in the surgery group. The estimates of aortic-valve reintervention were 2.2% and 2.6%, respectively. The estimates of valve-related death were 0.0% in the TAVR group and 0.2% in the surgery group (Fig. 4C and 4D). The incidence of bioprosthetic-valve failure related to structural valve deterioration was 1.4% in the TAVR group and 2.0% in the surgery group (Table S13). At 5 years, 392 of 454 patients (86.3%) in the TAVR group and 334 of 382 patients (87.4%) in the surgery group were alive and had a normally functioning valve.

FUNCTIONAL AND HEALTH STATUS

Functional outcomes appeared to be similar in the two groups. A total of 84.4% of the patients in the TAVR group and 86.0% of those in the surgery group were alive and had New York Heart Association (NYHA) class I or II heart failure at 5 years (Fig. S11). Disease-specific health status appeared to be similar in the two groups, with a mean KCCQ-OS score of 86.2 in the TAVR group and 85.9 in the surgery group (Fig. 4E). At 5 years, 284 of 400 patients (71.0%) in the TAVR group and 238 of 331 patients (71.9%) in the surgery group were alive with a KCCQ-OS score of 75 or higher (Fig. 4F).

DISCUSSION

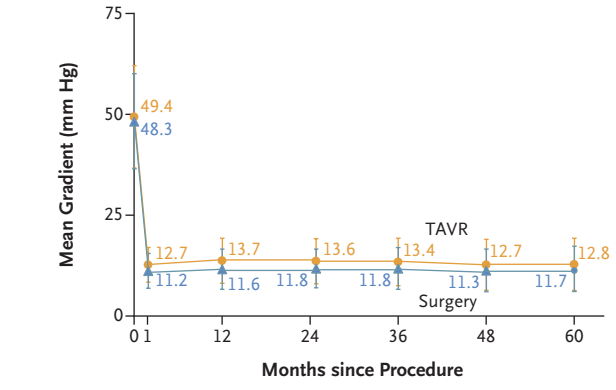
In this 5-year follow-up of the PARTNER 3 trial, the incidence of the composite end point of death, stroke, or rehospitalization was similar in the TAVR group and the surgery group; the incidence of the individual components of the primary end points (including death from any cause, disabling stroke, nondisabling stroke, and rehospitalization) was also similar in the two groups. The restricted mean event-free survival time over 5 years was longer in the TAVR group than in the surgery group, a result driven mainly by the between-group difference in rehospitalization. Aortic-valve durability according to VARC-3 definitions of bioprosthetic-valve failure appeared to be similar in the two groups at 5 years. Among the secondary end points, atrial fibrillation and bleeding appeared to be less frequent in the TAVR group than in the surgery group, whereas paravalvular aortic regurgitation, valve thrombosis, and pacemaker implantation appeared to be less frequent in the surgery group. Functional and health-status outcomes assessed according to NYHA class, KCCQ-OS score, and the percentage of patients who were alive and well at 5 years appeared to be similar in the two groups.

TAVR has been widely adopted over the past decade largely owing to an abundance of clinical evidence from randomized trials, resulting in twice as many patients with severe aortic stenosis being treated as compared with a decade ago.[1,2,22,23] Comparative outcomes between TAVR and surgery among patients who were followed for 5 years and beyond have shown similar findings in high-risk and intermediate-risk patients.[3-11] With respect to low-risk patients, outcomes from the PARTNER 3 trial were reported at 1 year and 2 years, and outcomes from a trial of TAVR with a self-expanding valve as compared with surgery were reported at 1 and 3 years.[12-15] Those reports showed that TAVR resulted in similar or better early outcomes as compared with surgery. Because low-risk patients are typically younger than high-risk patients, longer-term results are critical to inform clinical decision making. We report the longer-term follow-up of low-risk patients undergoing TAVR or surgery, with adjudicated clinical and echocardiographic outcomes.

After the first year, there was an attenuation of the differences between the TAVR group and the surgery group with respect to the nonhierarchical composite primary end point, which had previously favored TAVR. There was a greater number of deaths among patients assigned to TAVR than among those assigned to surgery from year 1 to year 5; these deaths were due to both cardiovascular and noncardiovascular causes (Tables S6 and S7). Whether follow-up during the Covid-19 pandemic disproportionately affected adverse outcomes could not be definitively determined. The incidence of stroke at 5 years appeared to be similar in the two groups, as was the incidence of disabling and nondisabling strokes, with most strokes being ischemic in origin. Although the incidence of stroke at 5 years was low, stroke remains one of the most serious complications of aortic-valve replacement.[24,25]

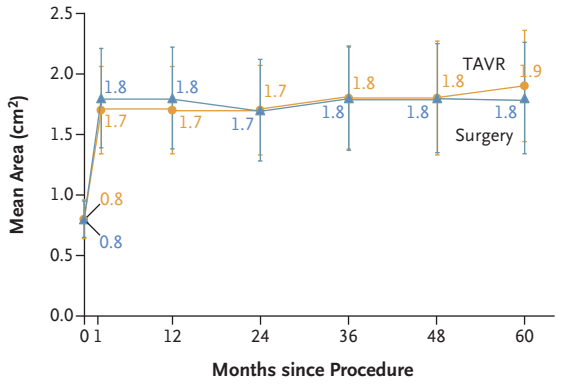
Valve durability is of critical importance, especially in younger patients. Hemodynamic valve performance of both TAVR and surgical valves seemed to be similar to that reported previously at 2 years.[26] The incidence of bioprosthetic-valve failure and of the need for reintervention was similar in the two groups at 5 years; these results are consistent with reported findings in intermediate-risk patients.[27,28] A higher percentage of patients in the TAVR group than in the surgery group had paravalvular aortic regurgitation of mild or greater severity; however, mild aortic regurgitation was not associated with higher mortality at 5 years in the TAVR group.[29,30]

Observed improvements in functional status and quality of life in the first year were greater in the TAVR group than in the surgery group, a finding most likely attributable to the more invasive nature of surgery and the longer recovery time. By 1 year, both groups had similar im-



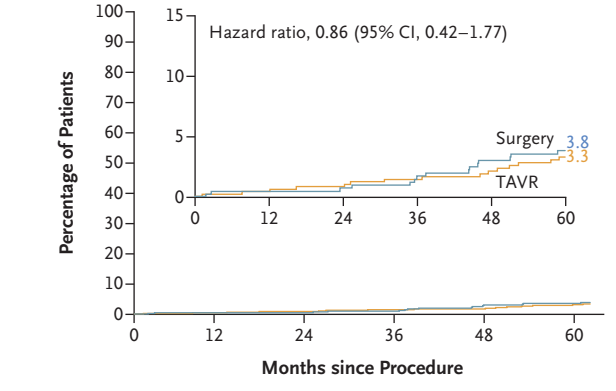
No. at Risk

TAVR	483 492	474	437	372	348	329
Surgery	442 432	391	360	304	305	282



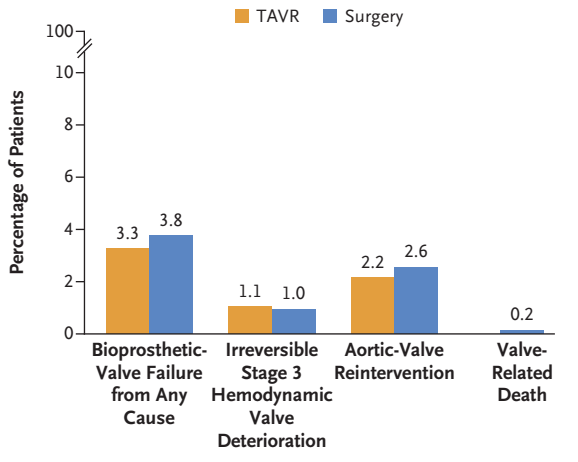
No. at Risk

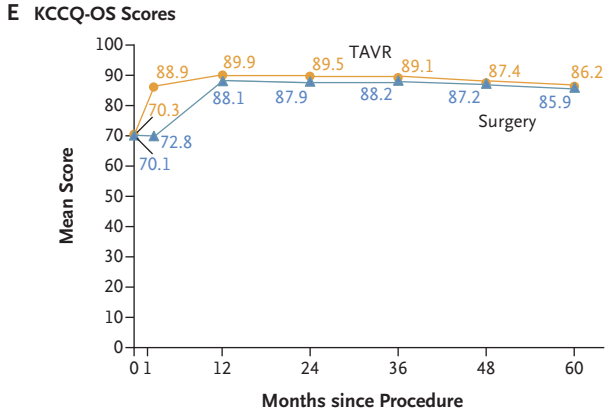
TAVR	458 482	450	416	347	334	320
Surgery	424 415	371	342	289	295	275



No. at Risk

TAVR	496	489	475	454	430	392
Surgery	454	426	407	390	369	334





No. at Risk

TAVR	493 491	481	444	406	381	354
Surgery	448 433	403	367	340	321	301

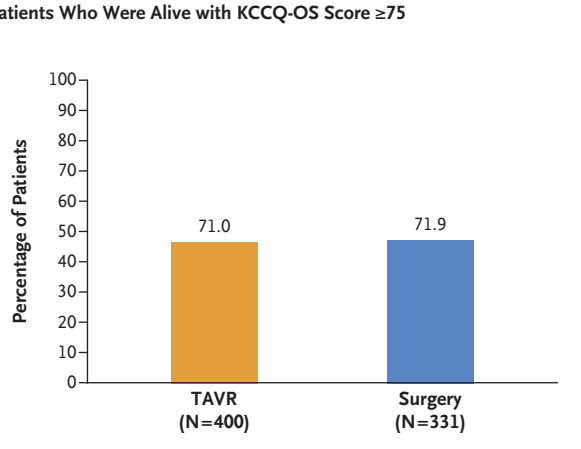


Figure 4 (facing page). Echocardiographic Outcomes, Bioprosthetic-Valve Failure, and Quality-of-Life Outcomes.

The mean aortic-valve gradients, shown in Panel A, and the mean aortic-valve areas, shown in Panel B, were assessed by an echocardiography core laboratory. I bars indicate standard deviations. Kaplan–Meier estimates for bioprosthetic-valve failure, adjudicated according to Valve Academic Research Consortium 3 criteria, are shown in Panel C. The inset in Panel C shows the same data on an enlarged y axis. The components of bioprosthetic-valve failure at 5 years are shown in Panel D. The mean Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) scores are shown in Panel E, and the percentage of patients who were alive with a KCCQ-OS score of 75 or higher are shown in Panel F. KCCQ-OS scores range from 0 to 100, with higher scores indicating better health status.

provements in NYHA functional class and mean KCCQ-OS scores that were sustained to 5 years. Furthermore, the percentage of patients who were alive with a KCCQ-OS score of 75 or higher (indicative of being well) appeared to be similar in the two groups.

Clinically significant valve thrombosis was rare but occurred in more patients in the TAVR group than in the surgery group over the course of 5 years. The reasons for the greater incidence of valve thrombosis among TAVR patients remain speculative, but this event did not appear to affect valve durability at 5 years. It is possible that the differences between the groups in the use of anticoagulation therapies during the first years after the procedure may have contributed to the higher incidence of thrombosis in the TAVR group, but this is also unknown. Patients in this trial will continue to be followed for 10 years to shed further light on the durability of both the transcatheter and surgical bioprosthetic valves.

The main limitations of this trial have been discussed previously.[13,15] This report addresses some of those limitations by focusing on longer-term clinical outcomes and valve durability. However, other limitations remain, including the constraints of a carefully 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. It is important to note, as reported previously, that more patients who underwent surgery than who underwent TAVR withdrew from the trial, which potentially biased the findings. To help address missing vital-status data, a vital-status sweep was conducted to obtain information about the patients who withdrew or were lost to follow-up; the data from this sweep reduced the mortality difference between the two groups. However, these data cannot correct for possible bias in underreporting of nonfatal events. Last, missing data regarding NYHA class, KCCQ-OS score, and follow-up echocardiography could not be fully accounted for with multiple imputation.

Among patients with severe, symptomatic aortic stenosis at low surgical risk who underwent TAVR or surgery, the incidence of the two primary composite end points appeared to be similar in the two groups at 5 years of follow-up.

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

APPENDIX

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