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Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

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ABSTRACT

BACKGROUND

Previous trials have shown that among high-risk patients with aortic stenosis, survival rates are similar with transcatheter aortic-valve replacement (TAVR) and surgical aortic-valve replacement. We evaluated the two procedures in a randomized trial involving intermediate-risk patients.

METHODS

We randomly assigned 2032 intermediate-risk patients with severe aortic stenosis, at 57 centers, to undergo either TAVR or surgical replacement. The primary end point was death from any cause or disabling stroke at 2 years. The primary hypothesis was that TAVR would not be inferior to surgical replacement. Before randomization, patients were entered into one of two cohorts on the basis of clinical and imaging findings; 76.3% of the patients were included in the transfemoral-access cohort and 23.7% in the transthoracic-access cohort.

RESULTS

The rate of death from any cause or disabling stroke was similar in the TAVR group and the surgery group (P=0.001 for noninferiority). At 2 years, the Kaplan–Meier event rates were 19.3% in the TAVR group and 21.1% in the surgery group (hazard ratio in the TAVR group, 0.89; 95% confidence interval [CI], 0.73 to 1.09; P=0.25). In the transfemoral-access cohort, TAVR resulted in a lower rate of death or disabling stroke than surgery (hazard ratio, 0.79; 95% CI, 0.62 to 1.00; P=0.05), whereas in the transthoracic-access cohort, outcomes were similar in the two groups. TAVR resulted in larger aortic-valve areas than did surgery and also resulted in lower rates of acute kidney injury, severe bleeding, and new-onset atrial fibrillation; surgery resulted in fewer major vascular complications and less paravalvular aortic regurgitation.

CONCLUSIONS

In intermediate-risk patients, TAVR was similar to surgical aortic-valve replacement with respect to the primary end point of death or disabling stroke. (Funded by Edwards Lifesciences; PARTNER 2 ClinicalTrials.gov number, NCT01314313.)

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*A complete list of investigators in the Placement of Aortic Transcatheter Valves (PARTNER) 2 trial is provided in the Supplementary Appendix, available at NEJM.org.

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Transcatheter aortic-valve replacement (TAVR) is a new therapy for patients with severe aortic stenosis who are not candidates for surgery[1,2] or who are at high risk for complications due to surgery.[3,4] The acceptance of the use of TAVR in high-risk patients was based on evidence from clinical trials[5,6] that used early-generation TAVR devices; these procedures were associated with considerable procedure-related complications.[7-9] Recently, increased operator experience and enhanced transcatheter valve systems have led to a worldwide trend to use TAVR in patients who are at low or intermediate risk.[10-12] This trend has been evaluated in small observational studies,[13-17] but since most patients who are currently recommended for surgery are at low or intermediate risk,[5,6,18] the expansion of the use of TAVR mandates rigorous clinical-trial validation. We report the results from the Placement of Aortic Transcatheter Valves (PARTNER) 2 cohort A randomized trial, in which TAVR with a second-generation valve system was compared with conventional surgery in patients with severe aortic stenosis and intermediate-risk clinical profiles.

METHODS

PATIENTS

From December 2011 through November 2013, we enrolled 2032 patients with severe aortic stenosis and cardiac symptoms at 57 centers in the United States and Canada. Patients were considered to be at intermediate risk on the basis of clinical assessments by a multidisciplinary heart team, which used a guideline that was based on a risk model developed by the Society of Thoracic Surgeons (STS) to estimate the risk of death at 30 days after surgery.[19] Scoring on the STS risk model uses an algorithm that is based on the presence of coexisting illnesses to predict mortality at 30 days. The STS score equals the predicted mortality expressed as a percentage. In this trial, the guideline was a risk score of at least 4.0%; the upper limit applied by the case review committee was 8.0%, but this value was not prespecified. Patients with an STS risk score of less than 4.0% could also be enrolled if there were coexisting conditions that were not represented in the risk model.

The complete list of inclusion and exclusion criteria is provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org. Patients with concomitant noncomplex coronary artery disease requiring revascularization could be enrolled and treated according to the judgment of the heart team with percutaneous coronary intervention (PCI) or coronary-artery bypass graft (CABG) surgery.

DEVICE AND PROCEDURE

The balloon-expandable SAPIEN XT heart-valve system (Edwards Lifesciences) and the TAVR procedure have been described previously.[20] The major differences of the SAPIEN XT system, as compared with the first-generation SAPIEN valve system, are a thinner strut cobalt–chromium frame, a partially closed resting geometry of the bovine pericardial leaflets, the addition of a valve size that is 29 mm in diameter, and a reduced-profile delivery catheter (Fig. S1 in the Supplementary Appendix). Patients assigned to TAVR underwent either transfemoral or transthoracic placement of the valve. Transthoracic placement used the same valve placed through either the transapical or transaortic access route. All the patients received aspirin (81 mg) and clopidogrel (≥300 mg) before the procedure and heparin during the procedure; patients continued to take aspirin indefinitely and clopidogrel for a minimum of 1 month.

TRIAL DESIGN

The trial incorporated two parallel prospective, multicenter, randomized trials that used the SAPIEN XT valve system. The results from the PARTNER cohort B trial have been reported previously,[21] and the design of the PARTNER cohort A trial is shown in Figure S2 in the Supplementary Appendix. After fulfilling the enrollment criteria, patients underwent an evaluation of their peripheral arteries before randomization to separate patients who were eligible for transfemoral placement from those requiring transthoracic placement. Patients were stratified in cohorts according to access route (transfemoral or transthoracic) and were then randomly assigned (in a 1:1 ratio) to undergo either transcatheter or surgical aortic-valve replacement. The cohorts defined according to assignment to access route constituted a prespecified subgroup, but the study was not powered for an analysis of this subgroup. The intention-to-treat population was used in the analyses of the primary and secondary end

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points. The as-treated analysis included only patients who at least began to undergo the procedure (i.e., received sedation or anesthesia in the procedure room) even if the procedure was not completed, and the valve-implant subgroup, which included patients who received the intended valve therapy, was used for all echocardiographic analyses.

TRIAL OVERSIGHT

The trial was designed and monitored by the sponsor (Edwards Lifesciences) and the executive committee, which included five cardiac surgeons and five interventional cardiologists. The sponsor funded the trial and participated in the selection of the trial sites, the collection of the data, and data monitoring. The executive committee met in person every 8 to 12 weeks to monitor all aspects of trial conduct. All the patients were reviewed before randomization by means of teleconference calls by the case-review committee. The data were analyzed by an independent biostatistical consultant who is one of the authors.

The principal investigators and other members of the executive committee had unrestricted access to the data after the database was locked, and they prepared all drafts of the manuscript. The first author wrote the first draft of the manuscript. No one who is not an author contributed to the writing of the manuscript. The members of the executive committee attest to the completeness and accuracy of the reported data and analyses and to the adherence of the trial to the protocol (available at NEJM.org). The trial was approved by the institutional review board at each site, and written informed consent was obtained from all the patients.

END POINTS

The primary end point was a nonhierarchical composite of death from any cause or disabling stroke at 2 years in the intention-to-treat population; all the patients were followed for at least 2 years. Disabling stroke was defined as a score of at least 2 on the modified Rankin scale (scores range from 0 [no symptoms] to 6 [death]) at 90 days after the index clinical event.[22] All the patients were seen by trained neurologists, and neurologic events were adjudicated by a stroke neurologist who was on the clinical-events committee and unaware of which procedure the patients were assigned to. Definitions of specific end points are provided in Table S2 in the Supplementary Appendix. All echocardiograms from the valve-implant population were analyzed by the core laboratory. The grading of paravalvular aortic regurgitation was based on an expanded and more granular classification scheme that was then collapsed to the standard classification scheme.[23]

STATISTICAL ANALYSIS

We estimated that a sample of 2000 patients would provide the trial with a power of at least 80% to show the noninferiority of TAVR to surgery with respect to the primary end point at 2 years, assuming an event rate of 30% in each group. Analyses of the primary end point were prespecified and powered for both the intention-to-treat population and the as-treated population.

We used Fisher's exact test to compare categorical variables. Continuous variables, which are presented as means with standard deviations, were compared with the use of Student's t-test or the Wilcoxon rank-sum test. Time-to-event analyses, which were based on all available follow-up data, were performed with the use of Kaplan–Meier estimates and were compared with the use of the log-rank test. The relationship of the baseline covariates to the primary end point was evaluated with the use of a Cox proportional-hazards regression model to calculate hazard ratios in the subgroups and to test for interactions.

Throughout the article, the term "risk ratio" refers to a point-in-time analysis, with the use of the Kaplan–Meier event rates and the Greenwood standard error; the term "hazard ratio" refers to the result from a Cox proportional-hazards analysis. Noninferiority was to be established if the upper boundary of the two-sided 95% confidence interval (one-sided alpha, 0.025) for the risk ratio of the primary end point at 2 years was below the prespecified noninferiority ratio of 1.20.

Multivariate models used automatic variable selection, starting with all variables showing a P value of less than 0.20 in univariate analyses. An additional time-dependent covariate analysis was performed to test the association of complications during TAVR or surgery with mortality. All P values in the article are presented without correction for multiple comparisons and should

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be interpreted accordingly. All the statistical analyses were performed with the use of SAS software, version 9 (SAS Institute).

RESULTS

PATIENTS

Among the 2032 patients who underwent randomization, 1011 were assigned to TAVR and 1021 to surgery. A total of 1550 patients (76.3%) were suitable candidates for transfemoral placement, and 482 patients (23.7%) were in the transthoracic cohort. The 236 patients in the TAVR group who were in the transthoracic cohort underwent either transapical access (174 patients) or transaortic access (62).

The characteristics of the patients at baseline were well balanced in the two trial groups (Table 1). The mean STS score was 5.8% in each group; 6.7% of the patients had an STS score that was less than 4.0%, 81.3% had a score that was between 4.0% and 8.0%, and 12.0% had a score that was greater than 8.0%.

A total of 94 patients (4.6%) were enrolled but did not undergo the assigned procedure, including 17 patients in the TAVR group and 77 in the surgery group. The main reason for nontreatment was withdrawal from the trial, most commonly owing to a decision after randomization not to undergo surgery.

PROCEDURE OUTCOMES

A total of 18 patients (0.9%; 10 patients in the TAVR group and 8 in the surgery group) died during the procedure or within 3 days afterward. In 28 patients (1.4%; 20 patients in the TAVR group and 8 in the surgery group), the assigned procedure was initiated but the patient did not receive a valve implant. The reasons for the valve not being implanted are shown in Figure S3 in the Supplementary Appendix.

Among 10 of 994 patients in the TAVR group (0.1%) with valve embolization, 4 had a second transcatheter valve implanted, the procedure was aborted in 2, the procedure was converted to surgery in 3, and 1 died. A second transcatheter valve was placed within the first valve in 22 additional patients (2.2%) because of moderate or severe aortic regurgitation. A total of 86 of 944 patients (9.1%) had concomitant planned or unplanned procedures during surgery, including aortic endarterectomy, aortic-root enlargement or replacement, and mitral-valve or tricuspid-valve repair or replacement. Among the patients in whom the randomly assigned procedure was initiated, 137 of 944 patients in the surgery group (14.5%) underwent CABG, and 39 of 994 in the TAVR group (3.9%) underwent PCI.

DEATH AND STROKE

There was no significant difference in the primary end point of death from any cause or disabling stroke at 2 years between the TAVR group and the surgery group in either the intention-to-treat analysis (hazard ratio in the TAVR group, 0.89; 95% confidence interval [CI], 0.73 to 1.09; P=0.25) or the as-treated analysis (hazard ratio, 0.87; 95% CI, 0.71 to 1.07; P=0.18) (Fig. 1). The risk ratio at 2 years for the primary end point in the TAVR group as compared with the surgery group was 0.92 (95% CI, 0.77 to 1.09) in the intention-to-treat analysis and 0.90 (95% CI, 0.75 to 1.08) in the as-treated analysis. The risk ratio met the criterion for noninferiority (P=0.001 in the intention-to-treat analysis and P<0.001 in the as-treated analysis) (Fig. S7 in the Supplementary Appendix).

In the transfemoral-access cohort, TAVR resulted in a lower rate of death from any cause or disabling stroke than did surgery (hazard ratio in the intention-to-treat analysis, 0.79; 95% CI, 0.62 to 1.00; P=0.05; hazard ratio in the as-treated analysis, 0.78; 95% CI, 0.61 to 0.99; P=0.04) (Fig. 1). However, there was no significant between-group difference in the transthoracic-access cohort (hazard ratio in the intention-to-treat analysis, 1.21; 95% CI, 0.84 to 1.74; P=0.31; hazard ratio in the as-treated analysis, 1.14; 95% CI, 0.79 to 1.65; P=0.47) (Fig. S4 in the Supplementary Appendix). Results of subgroup analyses with interaction testing for the primary end point were consistent across all the subgroups shown in Fig. 2.

The results with respect to the individual components of the primary end point, death or stroke, were also similar in the two groups (Table 2). At 2 years, the rate of death from any cause was 16.7% after TAVR and 18.0% after surgery, and the rate of disabling stroke was 6.2% after TAVR and 6.4% after surgery. Earlier outcomes at 30 days and 1 year similarly showed no significant differences between TAVR and surgery with respect to the primary end point and with respect to the individual components of death or stroke

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Table 1. Characteristics of the Patients at Baseline.*

Characteristic	TAVR (N=1011)	Surgery (N=1021)
Age — yr	81.5±6.7	81.7±6.7
Male sex — no. (%)	548 (54.2)	560 (54.8)
Body-mass index†	28.6±6.2	28.3±6.2
STS risk score‡	5.8±2.1	5.8±1.9
NYHA class III or IV — no./total no. (%)	782/1011 (77.3)	776/1020 (76.1)
Coronary artery disease — no. (%)	700 (69.2)	679 (66.5)
Previous myocardial infarction — no. (%)	185 (18.3)	179 (17.5)
Previous CABG — no. (%)	239 (23.6)	261 (25.6)
Previous PCI — no. (%)	274 (27.1)	282 (27.6)
Previous balloon aortic valvuloplasty — no. (%)	51 (5.0)	50 (4.9)
Cerebral vascular disease — no. (%)	325 (32.1)	317 (31.0)
Peripheral vascular disease — no. (%)	282 (27.9)	336 (32.9)
Diabetes mellitus — no. (%)	381 (37.7)	349 (34.2)
COPD — no. (%)		
Any	321 (31.8)	306 (30.0)
Oxygen-dependent	34 (3.4)	32 (3.1)
Creatinine >2 mg/dl — no. (%)§	51 (5.0)	53 (5.2)
Atrial fibrillation — no. (%)	313 (31.0)	359 (35.2)
Permanent pacemaker — no. (%)	118 (11.7)	123 (12.0)
Frail condition — no./total no. (%)		
5-Meter walk-test time >7 sec	416/936 (44.4)	418/901 (46.4)
Serum albumin <3.5 g/dl	150/988 (15.2)	140/951 (14.7)
Liver disease — no. (%)	19 (1.9)	26 (2.5)
Aortic-valve area — cm^2	0.7±0.2	0.7±0.2
Mean gradient — mm Hg	44.9±13.4	44.6±12.5
Left ventricular ejection fraction — %	56.2±10.8	55.3±11.9
Left ventricular mass index — g/m^2	119.8±31.5	120.6±32.6
Moderate or severe mitral regurgitation — no./total no. (%)	151/899 (16.8)	171/894 (19.1)

* Plus–minus values are means ±SD. There were no significant between-group differences in the characteristics at baseline, except for peripheral vascular disease (P=0.02) and atrial fibrillation (P=0.05). Data on left ventricular ejection fraction were missing for 348 patients in the TAVR group and 347 in the surgery group. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, NYHA New York Heart Association, PCI percutaneous coronary intervention, and TAVR transcatheter aortic-valve replacement.

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

‡ Scoring on the risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses in order to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. Less than 5% of patients in the population on which the STS algorithm is based had a predicted operative mortality (risk score) of more than 10%. Data on this score were missing for one patient.

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

(Table 2). There were no significant differences in the primary end point in the post hoc analyses that compared TAVR alone with TAVR plus PCI (19.3% and 20.5%, respectively; P=0.84) and surgery alone with surgery plus CABG (20.9% and 21.5%, respectively; P=0.90).

Multivariate predictors of death from any cause in the overall trial as well as in each of the

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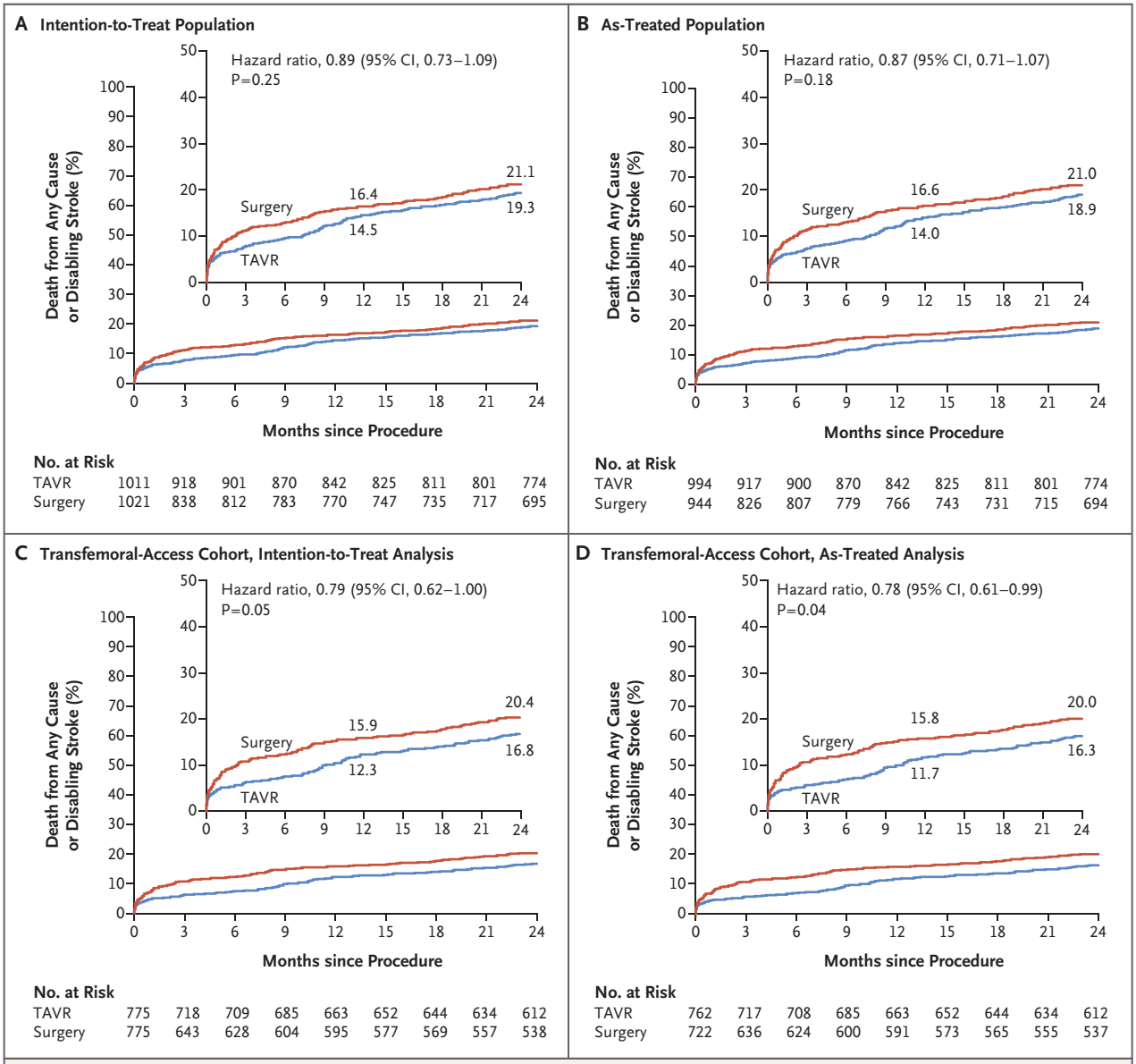

Figure 1. Time-to-Event Curves for the Primary Composite End Point.

The insets show the same data on an enlarged y axis. TAVR denotes transcatheter aortic-valve replacement.

trial groups are presented in Table S7 in the Supplementary Appendix. Treatment assignment to TAVR or surgery was not a significant predictor of mortality. The time-dependent effects of disabling stroke, life-threatening bleeding, acute kidney injury, and major vascular complication were all significantly associated with a higher risk of death over the period of 2 years in both the TAVR group and the surgery group (P<0.001 for all comparisons).

OTHER CLINICAL END POINTS

At 30 days, major vascular complications were more frequent in the TAVR group than in the surgery group (7.9% vs. 5.0%, P=0.008) (Table 2). However, several other complications were less frequent in the TAVR group than in the surgery group, including life-threatening bleeding (10.4% vs. 43.4%, P<0.001), acute kidney injury (1.3% vs. 3.1%, P=0.006), and new-onset atrial fibrillation (9.1% vs. 26.4%, P<0.001). The percentage of pa-

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Subgroup	No. of Patients	TAVR	Surgery	Hazard Ratio (95% CI)	P Value
		no. of patients with event/total no. of patients (%)			
Overall	2032	192/1011 (19.3)	202/1021 (21.1)	0.89 (0.73–1.09)	0.25
Age					0.96
<85 yr	1245	111/626 (18.0)	114/619 (19.5)	0.90 (0.69–1.17)	
≥85 yr	787	81/385 (21.5)	88/402 (23.6)	0.89 (0.65–1.20)	
Sex					0.37
Female	924	77/463 (16.9)	88/461 (20.3)	0.81 (0.59–1.10)	
Male	1108	115/548 (21.4)	114/560 (21.7)	0.96 (0.74–1.25)	
Body-mass index					0.37
≤25	611	66/303 (22.1)	75/308 (26.8)	0.78 (0.56–1.09)	
>25	1421	126/708 (18.1)	127/713 (18.8)	0.95 (0.74–1.22)	
STS score					0.60
≤5	897	73/469 (15.8)	75/428 (18.4)	0.84 (0.61–1.16)	
>5	1134	119/542 (22.4)	127/592 (23.1)	0.94 (0.73–1.21)	
Left ventricular ejection fraction					0.27
≤55	496	44/237 (19.1)	53/259 (21.5)	0.84 (0.56–1.25)	
>55	841	85/426 (20.1)	71/415 (18.0)	1.11 (0.81–1.53)	
Moderate or severe mitral regurgitation					0.53
No	1471	132/748 (17.8)	141/723 (20.3)	0.85 (0.67–1.08)	
Yes	322	38/151 (25.9)	39/171 (24.4)	1.00 (0.64–1.57)	
Previous CABG					0.69
No	1532	156/772 (20.6)	158/760 (22.2)	0.91 (0.73–1.13)	
Yes	500	36/239 (15.3)	44/261 (18.0)	0.82 (0.53–1.27)	
Peripheral vascular disease					0.47
No	1414	130/729 (18.2)	134/685 (20.7)	0.85 (0.67–1.09)	
Yes	618	62/282 (22.3)	68/336 (22.0)	0.99 (0.71–1.40)	
5-Meter walk test					0.43
≤7 sec	1003	91/520 (17.7)	97/483 (20.9)	0.82 (0.62–1.09)	
>7 sec	834	85/416 (20.7)	82/418 (20.8)	0.97 (0.71–1.31)	
Access route					0.06
Transfemoral	1550	128/775 (16.8)	149/775 (20.4)	0.79 (0.62–1.00)	
Transthoracic	482	64/236 (27.7)	53/246 (23.4)	1.21 (0.84–1.74)	

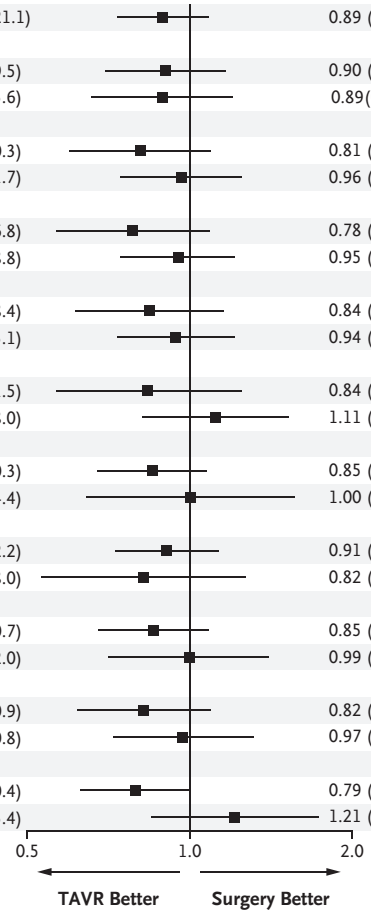

Figure 2. Subgroup Analyses of Death from Any Cause or Disabling Stroke.

All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number of patients in the treatment group. The P value is from the test statistic for testing the interaction between the treatment and any subgroup variable. The body-mass index is the weight in kilograms divided by the square of the height in meters. Scoring on the risk model of the Society of Thoracic Surgeons (STS) uses an algorithm that is based on the presence of coexisting illnesses in order to predict 30-day operative mortality. The STS score equals the predicted mortality expressed as a percentage. Less than 5% of patients in the population on which the STS algorithm is based had a predicted operative mortality (risk score) of more than 10%. Data were missing as follows: on the STS score, for 1 patient in the surgery group; on left ventricular ejection fraction, for 348 patients in the TAVR group and 347 in the surgery group; on moderate or severe mitral regurgitation, for 112 and 127, respectively; and on the 5-meter walk test, for 75 and 120, respectively. CABG denotes coronary-artery bypass grafting.

tients requiring repeat hospitalization was similar at 2 years in the TAVR group and the surgery group (19.6% and 17.3%, respectively; P=0.22). The need for new permanent pacemakers within 30 days after the procedure was similar in the TAVR group and the surgery group (8.5% and 6.9%, respectively; P=0.17). Endocarditis and repeat aortic-valve interventions were uncommon in both the TAVR group and the surgery group (rate of endocarditis at 2 years, 1.2% and 0.7%, respectively; P=0.22; rate of reintervention, 1.4% and 0.6%, respectively; P=0.09).

There was a significant reduction in symptoms to New York Heart Association (NYHA) class II or I at 30 days in both the TAVR group and the surgery group, and the NYHA class was

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Table 2. Clinical End Points at 30 Days, 1 Year, and 2 Years.*

End Point	At 30 Days			At 1 Year			At 2 Years		
	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value	TAVR (N=1011)	Surgery (N=1021)	P Value
	no. of patients (%)			*no. of patients (%)*			*no. of patients (%)*		
Death from any cause or disabling stroke	62 (6.1)	80 (8.0)	0.11	145 (14.5)	160 (16.4)	0.24	192 (19.3)	202 (21.1)	0.33
Death									
From any cause	39 (3.9)	41 (4.1)	0.78	123 (12.3)	124 (12.9)	0.69	166 (16.7)	170 (18.0)	0.45
From cardiac causes	33 (3.3)	32 (3.2)	0.92	70 (7.1)	77 (8.1)	0.40	97 (10.1)	104 (11.3)	0.38
Not from cardiac causes	6 (0.6)	9 (0.9)	0.41	53 (5.6)	47 (5.2)	0.71	69 (7.4)	65 (7.4)	0.98
Neurologic event									
Any event	64 (6.4)	65 (6.5)	0.94	99 (10.1)	93 (9.7)	0.76	121 (12.7)	103 (11.0)	0.25
Transient ischemic attack	9 (0.9)	4 (0.4)	0.17	23 (2.4)	16 (1.8)	0.38	34 (3.7)	20 (2.3)	0.09
Any stroke	55 (5.5)	61 (6.1)	0.57	78 (8.0)	79 (8.1)	0.88	91 (9.5)	85 (8.9)	0.67
Disabling stroke	32 (3.2)	43 (4.3)	0.20	49 (5.0)	56 (5.8)	0.46	59 (6.2)	61 (6.4)	0.83
Nondisabling stroke	23 (2.3)	18 (1.8)	0.43	30 (3.0)	24 (2.5)	0.44	33 (3.4)	27 (2.9)	0.51
Rehospitalization	64 (6.5)	62 (6.5)	0.99	142 (14.8)	135 (14.7)	0.92	183 (19.6)	156 (17.3)	0.22
Death from any cause or rehospitalization	99 (9.8)	101 (10.2)	0.78	234 (23.4)	225 (23.3)	0.97	303 (30.5)	281 (29.6)	0.67
Death from any cause, any stroke, or rehospitalization	140 (13.9)	153 (15.3)	0.37	274 (27.4)	276 (28.3)	0.64	344 (34.6)	326 (33.9)	0.75
Myocardial infarction	12 (1.2)	19 (1.9)	0.22	24 (2.5)	29 (3.0)	0.47	33 (3.6)	37 (4.1)	0.56
Major vascular complication	80 (7.9)	51 (5.0)	0.008	84 (8.4)	54 (5.3)	0.007	86 (8.6)	55 (5.5)	0.006
Life-threatening or disabling bleeding	105 (10.4)	442 (43.4)	<0.001	151 (15.2)	460 (45.5)	<0.001	169 (17.3)	471 (47.0)	<0.001
Acute kidney injury	13 (1.3)	31 (3.1)	0.006	32 (3.4)	48 (5.0)	0.07	36 (3.8)	57 (6.2)	0.02
New atrial fibrillation	91 (9.1)	265 (26.4)	<0.001	100 (10.1)	272 (27.2)	<0.001	110 (11.3)	273 (27.3)	<0.001
New permanent pacemaker	85 (8.5)	68 (6.9)	0.17	98 (9.9)	85 (8.9)	0.43	114 (11.8)	96 (10.3)	0.29
Endocarditis	0	0	—	7 (0.8)	6 (0.7)	0.84	11 (1.2)	6 (0.7)	0.22
Aortic-valve reintervention	4 (0.4)	0	0.05	11 (1.2)	4 (0.5)	0.10	13 (1.4)	5 (0.6)	0.09
Coronary obstruction	4 (0.4)	6 (0.6)	0.53	4 (0.4)	6 (0.6)	0.53	4 (0.4)	6 (0.6)	0.53

* All percentages are Kaplan–Meier estimates at the specific time point and thus do not equal the number of patients divided by the total number of patients in the treatment group. P values are for point-in-time comparisons.

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maintained for 2 years (P<0.001 for all comparisons) (Fig. S8 in the Supplementary Appendix). Patients in the TAVR group had fewer cardiac symptoms at 30 days than did those in the surgery group (P=0.001), but the frequency of cardiac symptoms did not differ significantly at later time points. Patients in the TAVR group had a significantly shorter duration of stay in the intensive care unit (ICU) than did those in the surgery group (median, 2 vs. 4 days; P<0.001), as well as a shorter index hospitalization (median, 6 vs. 9 days; P<0.001).

ECHOCARDIOGRAPHIC FINDINGS

In the case of both therapies, from baseline to 30 days, the aortic-valve areas and the left ventricular ejection fraction increased significantly and the mean aortic-valve gradients decreased significantly; these changes were sustained through 2 years (Fig. 3, and Table S8 in the Supplementary Appendix). The improvements in aortic-valve areas and gradients at all time points were significantly greater after TAVR than after surgery.

The frequency and severity of paravalvular aortic regurgitation were greater after TAVR than after surgery (Fig. 3). In the TAVR group at 30 days, mild paravalvular aortic regurgitation was observed according to the standard classification scheme in 22.5% of patients, and moderate or severe paravalvular aortic regurgitation in 3.7%. Patients in the TAVR group who had moderate or severe, but not mild, paravalvular aortic regurgitation (according to either the standard or expanded classification scheme) at 30 days had higher mortality during 2 years of follow-up than did patients who had no or trace regurgitation (P<0.001) (Fig. 3).

DISCUSSION

The main results from the PARTNER 2 cohort A randomized trial involving intermediate-risk patients can be summarized as follows. First, TAVR, performed in experienced centers, with the use of a lower-profile, next-generation device, was noninferior to surgery with respect to outcomes at 2 years (death from any cause or disabling stroke). Second, bioprosthetic-valve gradients were lower and the areas were greater with the SAPIEN XT valve, as compared with surgical valves, whereas the incidence of paravalvular aortic regurgitation was higher after TAVR than after surgery. Third, several benefits with regard to secondary end points were associated with TAVR, including lower risks of bleeding events, acute kidney injury, and new-onset atrial fibrillation, as well as more rapid early recovery that resulted in shorter durations of stay in the ICU and hospital.

Although the trial cohort represents a lower-risk category than cohorts in previous trials,[3,4] these patients are still among the highest-risk quintile of patients with aortic stenosis who are candidates for surgery in the United States[18,24] and elsewhere.[25,26] Our findings of the noninferiority of TAVR to surgery were robust, with similar between-group outcomes for the end points of death and stroke and with consistency across all the subgroups tested. The possible superiority of TAVR over surgery in the transfemoral-access cohort is a new finding for balloon-expandable transcatheter valves. It requires prospective evaluation in a suitably powered superiority study. If this finding is confirmed, it probably reflects increased operator experience and the effect of a low-profile enhanced TAVR system combining to reduce procedure-related complications.[27] Conversely, the outcomes after transthoracic TAVR were similar to or worse than those with surgery and appeared to be inferior to those with transfemoral TAVR. A previous study involving high-risk patients treated with TAVR also showed higher rates of adverse periprocedural events and death among propensity-matched patients who underwent transapical access than among those who underwent transfemoral access.[28] Further studies would be needed to explore the hypothesis that in intermediate-risk patients who are not candidates for TAVR with transfemoral access, TAVR with transthoracic access may have similar or worse outcomes than surgery.

As has been shown previously,[3,4] there was a greater increase in valve areas with TAVR than with surgery in this trial, most likely owing to valve-sizing differences and the ability of transcatheter valves to expand to the anatomical annulus size, which is not possible with a fixed-size surgical sewing ring. Larger valve areas with TAVR would be expected to decrease the incidence of patient–prosthesis mismatch, which might result in better late clinical outcomes.[29] The frequency and severity of paravalvular aortic

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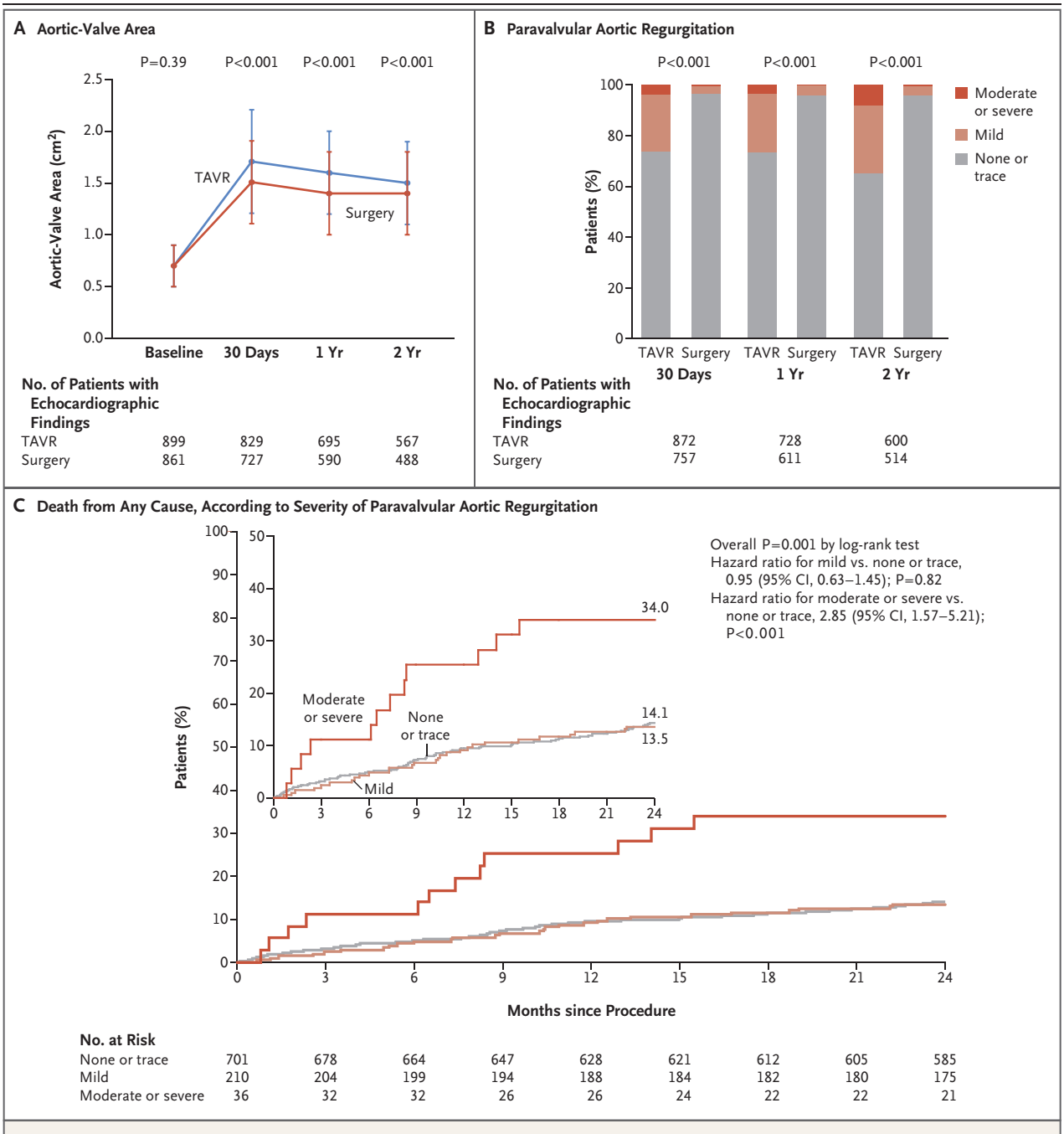

Figure 3. Echocardiographic Findings.

Panel A shows the change in aortic-valve area from baseline to 2 years, and Panel B the percentage of patients with paravalvular aortic regurgitation at 30 days, 1 year, and 2 years after the procedure. Panel C shows time-to-event curves for death from any cause according to the severity of paravalvular aortic regurgitation (post hoc analysis). The inset shows the same data on an enlarged y axis.

regurgitation was greater after TAVR than after surgery. In this trial, the incidence of moderate or severe paravalvular aortic regurgitation at 30 days was less than 4%, and unlike findings in previous PARTNER trials,[30] only moderate or severe, but not mild, paravalvular aortic regurgitation was associated with higher subsequent mortality.

Even with careful neurologic evaluations in all patients, the frequency of stroke was the same

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as or less than that in previous studies, and there were no significant differences between the TAVR group and the surgery group. The reasons for the lower incidence of neurologic events in this trial are probably multifactorial, including improved intraprocedural treatment of patients, the effect of a low-profile TAVR system, and more diligent treatment of new atrial fibrillation. The risks of all major complications with TAVR affecting late mortality were lower in this trial than in earlier randomized trials; such complications include strokes, major vascular or bleeding events, acute kidney injury, moderate or severe paravalvular aortic regurgitation, and other rare but potentially catastrophic adverse events (e.g., annulus rupture, valve embolization, and coronary obstruction).[1-4,21,27,31]

Coronary revascularization was more commonly performed in the surgery group than in the TAVR group (14.5% vs. 3.9%), and the addition of either CABG or PCI to valve-replacement therapies had no deleterious effect on mortality or the rate of stroke. Although this trial was not powered or designed to address the issue of concomitant valve replacement and coronary revascularization, these results are counter to previous findings that the addition of CABG to surgical aortic-valve replacement resulted in higher mortality.[32-34]

Our trial has several limitations. First, the high frequency of unexpected withdrawals in patients who were scheduled to undergo surgery mandated a careful examination of both the intention-to-treat population and the as-treated population. Nevertheless, the prespecified analysis of the primary and secondary end points in the as-treated population revealed no important differences from the results of the intention-to-treat analysis. Second, further technological advances may favorably influence the outcomes with TAVR in the future, and the SAPIEN XT valve that was used in this trial has already been replaced by the SAPIEN 3 valve system.[35,36] Third, in this trial, multislice computed tomography was not used consistently to assess aortic annulus dimensions for appropriate valve sizing.[37] Also, the recent finding of subclinical valve-leaflet thrombosis with the use of high-resolution imaging techniques was not systematically evaluated in the current trial.[38] Finally, long-term assessments of the durability of bioprosthetic transcatheter valves (i.e., through 10 years) remain a limitation, although 5-year echocardiographic evaluations from the earlier PARTNER trials indicate no evidence of important premature or accelerated structural valve deterioration.[39,40]

In conclusion, we found that in intermediate-risk patients with severe symptomatic aortic stenosis, surgical and transcatheter valve replacement were similar with respect to the primary end point of death or disabling stroke for up to 2 years and resulted in a similar degree of lessening of cardiac symptoms.

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

APPENDIX

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