ORIGINAL ARTICLE

# Two-Year Outcomes after Transcatheter or Surgical Aortic-Valve Replacement

Susheel K. Kodali, M.D., Mathew R. Williams, M.D., Craig R. Smith, M.D., Lars G. Svensson, M.D., Ph.D., John G. Webb, M.D., Raj R. Makkar, M.D., Gregory P. Fontana, M.D., Todd M. Dewey, M.D., Vinod H. Thourani, M.D., Augusto D. Pichard, M.D., Michael Fischbein, M.D., Ph.D., Wilson Y. Szeto, M.D., Scott Lim, M.D., Kevin L. Greason, M.D., Paul S. Teirstein, M.D., J. Chris Malaisrie, M.D., Pamela S. Douglas, M.D., Rebecca T. Hahn, M.D., Brian Whisenant, M.D., Alan Zajarias, M.D., Duolao Wang, Ph.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., and Martin B. Leon, M.D., for the PARTNER Trial Investigators*


## ABSTRACT

### BACKGROUND

The Placement of Aortic Transcatheter Valves (PARTNER) trial showed that among high-risk patients with aortic stenosis, the 1-year survival rates are similar with transcatheter aortic-valve replacement (TAVR) and surgical replacement. However, longer-term follow-up is necessary to determine whether TAVR has prolonged benefits.

### METHODS

At 25 centers, we randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either surgical aortic-valve replacement or TAVR. All patients were followed for at least 2 years, with assessment of clinical outcomes and echocardiographic evaluation.

### RESULTS

The rates of death from any cause were similar in the TAVR and surgery groups (hazard ratio with TAVR, 0.90; 95% confidence interval [CI], 0.71 to 1.15; P=0.41) and at 2 years (Kaplan–Meier analysis) were 33.9% in the TAVR group and 35.0% in the surgery group (P=0.78). The frequency of all strokes during follow-up did not differ significantly between the two groups (hazard ratio, 1.22; 95% CI, 0.67 to 2.23; P=0.52). At 30 days, strokes were more frequent with TAVR than with surgical replacement (4.6% vs. 2.4%, P=0.12); subsequently, there were 8 additional strokes in the TAVR group and 12 in the surgery group. Improvement in valve areas was similar with TAVR and surgical replacement and was maintained for 2 years. Paravalvular regurgitation was more frequent after TAVR (P<0.001), and even mild paravalvular regurgitation was associated with increased late mortality (P<0.001).

### CONCLUSIONS

A 2-year follow-up of patients in the PARTNER trial supports TAVR as an alternative to surgery in high-risk patients. The two treatments were similar with respect to mortality, reduction in symptoms, and improved valve hemodynamics, but paravalvular regurgitation was more frequent after TAVI creased late mortality. (Funded by Edwards Lifescien NCT00530894.)

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*The investigators, institutions, and research organizations participating in the Placement of Aortic Transcatheter Valves (PARTNER) trial are listed in the Supplementary Appendix, available at NEJM.org.

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AORTIC STENOSIS IS ASSOCIATED WITH high mortality after the appearance of cardiac symptoms.[1] Nevertheless, many patients do not undergo surgical aortic-valve replacement owing to real or perceived increased risks associated with surgery.[2-5] Transcatheter aortic-valve replacement (TAVR) has emerged as an alternative therapy in high-risk patients with aortic stenosis.[6-10] Observational registries from various countries have reported 1-month and 1-year outcomes after TAVR,[11-14] but there are limited long-term follow-up data.[15]

The Placement of Aortic Transcatheter Valves (PARTNER) trial was a randomized trial comparing TAVR with standard-of-care therapies in high-risk patients with aortic stenosis. One-year mortality outcomes from PARTNER showed that TAVR was superior to standard therapy in patients who could not undergo surgery[16] and was noninferior to surgical replacement in high-risk patients who could undergo surgery.[17] However, longer-term data are required to assess valve durability and to monitor late clinical complications, before TAVR is used more widely in clinical practice. This report describes the 2-year (and longer) clinical outcomes and echocardiographic findings after TAVR or surgical aortic-valve replacement in the high-risk patients in the PARTNER trial who could undergo surgery.

## METHODS

### PATIENTS

Patient selection for this cohort of the PARTNER trial has been described previously.[17] Inclusion criteria were severe symptomatic aortic stenosis (an aortic-valve area ≤0.8 cm² plus a peak velocity ≥4 m per second or a mean valve gradient ≥40 mm Hg) and high-risk status for surgical aortic-valve replacement, as determined by experienced surgeons. Patients were considered to be at high surgical risk if they had coexisting conditions that were associated with a risk of death of at least 15% by 30 days after the operation.

### STUDY DEVICE AND PROCEDURE

The SAPIEN heart-valve system (Edwards Lifesciences) and the TAVR procedure have been described previously.[16,17] Most procedures were performed in a hybrid operating room with a fixed fluoroscopic imaging system, while the patient was under general anesthesia, and with transesophageal echocardiography. Transapical TAVR was performed through a small intercostal incision over the left ventricular apex with the use of a dedicated delivery catheter and the same SAPIEN valve.

Heparin was administered during the procedure, and dual antiplatelet therapy (aspirin and clopidogrel) was recommended for 6 months afterward. The outpatient regimen was frequently modified by the treating physicians because of increased bleeding risks.

### STUDY DESIGN AND OVERSIGHT

The study design and data-management practices have been described previously.[16,17] A total of 699 patients from 25 sites were randomly assigned to TAVR or surgical replacement. Patients assigned to TAVR were treated by either the transfemoral or transapical approach on the basis of whether peripheral arteries could accommodate the large sheaths required (22 French for the 23-mm valve and 24 French for the 26-mm valve). Patients who were randomly assigned to surgical replacement were stratified according to whether a transfemoral or transapical approach would have been used.

The study was designed and monitored by the sponsor, Edwards Lifesciences, and the executive committee, which included four interventional cardiologists and four cardiac surgeons. The sponsor funded the study and participated in the selection and management of the sites, the collection of the data, and data monitoring. The first author and members of the executive committee had unrestricted access to the data after the database had been locked and prepared all drafts of the manuscript; they attest to the completeness and accuracy of the reported data and to the adherence of the study to the protocol (available with the full text of this article at NEJM.org). The trial was approved by the institutional review board at each site. Written informed consent was obtained from all patients.

### STUDY END POINTS

The prespecified primary end point of the PARTNER trial was all-cause mortality at 1 year for the pooled cohort. Prespecified secondary end points included cardiovascular mortality, stroke, repeat hospitalization, acute kidney injury, vascular complications, bleeding events, and New York Heart Association (NYHA) functional class. All patients were followed for at least 2 years and had annual clinical visits and echocardiographic evaluations. Crossovers between the two treatment groups were not permitted. A clinical-events committee was

responsible for adjudicating all end points. Definitions of the end points are identical to those in the original trial and have been reported elsewhere.[16,17]

### STATISTICAL ANALYSIS

For data analyses, the intention-to-treat analysis started at the time of randomization, and the as-treated analysis started at the time of induction of anesthesia in the procedure room. All clinical outcomes were primarily analyzed with the use of an intention-to-treat analysis, but the results of as-treated analyses are also presented for comparison. All echocardiographic analyses were performed with the use of the as-treated data. Categorical variables were compared with the use of Fisher's exact test. Continuous variables, presented as means ±SD, were compared with the use of Student's t-test. Survival curves for time-to-event variables were constructed with the use of Kaplan–Meier estimates based on all available data and were compared with the use of the log-rank test. To study the effect of risk factors on mortality, Cox proportional-hazards regression was performed. For the multivariable analyses, multiple imputations were used to accommodate missing baseline variables. The multivariable models included covariates with 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 surgical replacement with subsequent mortality. All statistical analyses were performed with the use of SAS software, version 9.2.

## RESULTS

### PATIENTS

In the randomized TAVR group, 244 patients had acceptable vascular access and were treated by means of the transfemoral approach, and the remaining 104 patients were treated by means of the transapical approach. Surgical replacement was performed in 351 patients. Figure 1 in the Supplementary Appendix, available at NEJM.org, shows the study-group assignments and follow-up. All patients were followed for at least 2 years (median, 727 days; maximum, 1490 days). The overall study population was elderly (mean age, 84.1±6.6 years), had severe cardiac symptoms (94.1% had NYHA class III or IV status), and had frequent coexisting conditions (75.5% had a history of coronary artery disease, 43.0% had a history of coronary-artery bypass surgery, 42.4% had peripheral vascular disease, 43.3% had pulmonary disease, and 41.3% had diabetes). The TAVR and surgery groups were generally well matched with regard to baseline characteristics (Table 1 in the Supplementary Appendix), except for a slightly higher incidence of renal dysfunction in the TAVR group (creatinine level >2 mg per deciliter [177 μmol per liter]: 10.8%, as compared with 6.4% in the surgery group; P=0.04). The mean Society of Thoracic Surgeons predicted risk of death at 30 days was 11.8±3.4%.

Of the 699 study patients, 42 did not receive the assigned therapy: 4 in the TAVR group and 38 in the surgery group.[17] The main reasons for nontreatment were withdrawal from the study and the patient's decision not to undergo surgery (28 patients).

### MORTALITY AND STROKE

Outcomes at 30 days and 1 year have been described previously.[17] For the duration of the trial, there were no significant differences in survival between the TAVR and surgery groups in either the intention-to-treat analysis (hazard ratio with TAVR, 0.90; 95% confidence interval [CI], 0.71 to 1.15; P=0.41) or the as-treated analysis (hazard ratio, 0.98; 95% CI, 0.76 to 1.25; P=0.85) (Fig. 1). Between 1 and 2 years, there were 32 additional deaths in the TAVR group and 25 in the surgery group. At 2 years, there were no significant differences in mortality from any cause between the TAVR group (33.9%; 95% CI, 28.9 to 39.0) and the surgery group (35.0%; 95% CI, 29.8 to 40.2; P=0.78) (Table 1). Cardiovascular mortality at 2 years was also similar in the TAVR and surgery groups (21.4% [95% CI, 16.8 to 26.0] and 20.5% [95% CI, 15.8 to 25.3], respectively; P=0.80). Similarly, in the as-treated analysis, the TAVR and surgery groups did not differ significantly with respect to all-cause mortality (33.9% and 32.7%, respectively; P=0.75) or cardiovascular mortality (20.8% and 18.5%, respectively; P=0.50) (Table 2 in the Supplementary Appendix).

Between 1 and 2 years, eight strokes occurred (four in the TAVR group and four in the surgery group) and three transient ischemic attacks (two in the TAVR group and one in the surgery group). The frequency of all neurologic events (strokes and transient ischemic attacks) at 2 years was higher with TAVR than with surgical replacement (11.2%

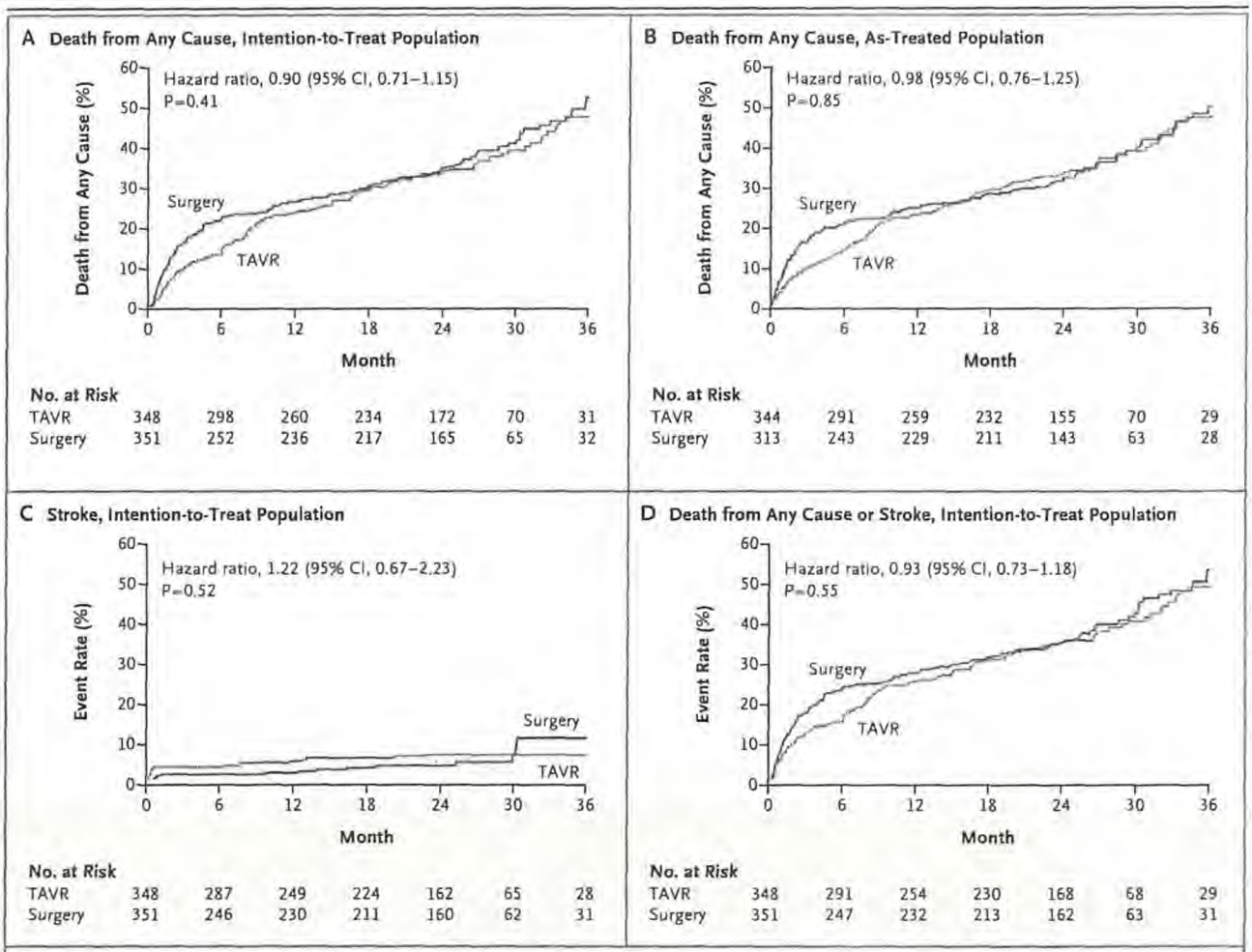


Figure 1. **Time-to-Event Curves for the Primary and Other Selected End Points.**

Events were calculated with the use of Kaplan–Meier methods and compared with the use of a log-rank test. TAVR denotes transcatheter aortic-valve replacement.

vs. 6.5%, P=0.05). However, there was no significant difference in the number of overall strokes between the TAVR and surgery groups (hazard ratio, 1.22; 95% CI, 0.67 to 2.23; P=0.52) (Fig. 1). After the early increased hazard of stroke in the first 30 days associated with TAVR (4.6% with TAVR vs. 2.4% with surgical replacement, P=0.12), there were 8 additional strokes in the TAVR group and 12 in the surgery group, such that the total number of strokes over the follow-up period (36 months) was 24 in the TAVR group and 20 in the surgery group. The composite of the rate of death from any cause or stroke did not differ significantly between the two treatment groups (hazard ratio, 0.93; 95% CI, 0.73 to 1.18; P=0.55) (Fig. 1); at 2 years, the rate was 37.1% in the TAVR group and 36.4% in the surgery group (P=0.85).

### OTHER CLINICAL OUTCOMES

Other clinical events are summarized in Table 1. Major vascular complications and major bleeding events were frequent procedure-related complications in the TAVR and surgery groups, respectively, but after 1 year, these events were uncommon and did not differ significantly between the groups. No patients were treated with balloon aortic valvuloplasty or repeat TAVR between 1 and 2 years. Endocarditis was rare and occurred at a similar rate in the two groups (1.5% in the TAVR group and 1.0% in the surgery group, P=0.61). No patients in either group had structural valve deterioration requiring surgical replacement during follow-up.

At 2 years, there was no significant difference in the rate of repeat hospitalization between the

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