The NEW ENGLAND JOURNAL of MEDICINE

ESTABLISHED IN 1812 JUNE 9, 2011 VOL. 364 NO. 23

Transcatheter versus Surgical Aortic-Valve Replacement in High-Risk Patients

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ABSTRACT

BACKGROUND

The use of transcatheter aortic-valve replacement has been shown to reduce mortality among high-risk patients with aortic stenosis who are not candidates for surgical replacement. However, the two procedures have not been compared in a randomized trial involving high-risk patients who are still candidates for surgical replacement.

METHODS

At 25 centers, we randomly assigned 699 high-risk patients with severe aortic stenosis to undergo either transcatheter aortic-valve replacement with a balloon-expandable bovine pericardial valve (either a transfemoral or a transapical approach) or surgical replacement. The primary end point was death from any cause at 1 year. The primary hypothesis was that transcatheter replacement is not inferior to surgical replacement.

RESULTS

The rates of death from any cause were 3.4% in the transcatheter group and 6.5% in the surgical group at 30 days ($P=0.07$) and 24.2% and 26.8%, respectively, at 1 year ($P=0.44$), a reduction of 2.6 percentage points in the transcatheter group (upper limit of the 95% confidence interval, 3.0 percentage points; predefined margin, 7.5 percentage points; $P=0.001$ for noninferiority). The rates of major stroke were 3.8% in the transcatheter group and 2.1% in the surgical group at 30 days ($P=0.20$) and 5.1% and 2.4%, respectively, at 1 year ($P=0.07$). At 30 days, major vascular complications were significantly more frequent with transcatheter replacement (11.0% vs. 3.2%, $P<0.001$); adverse events that were more frequent after surgical replacement included major bleeding (9.3% vs. 19.5%, $P<0.001$) and new-onset atrial fibrillation (8.6% vs. 16.0%, $P=0.006$). More patients undergoing transcatheter replacement had an improvement in symptoms at 30 days, but by 1 year, there was not a significant between-group difference.

CONCLUSIONS

In high-risk patients with severe aortic stenosis, transcatheter and surgical procedures for aortic-valve replacement were associated with similar rates of survival at 1 year, although there were important differences in periprocedural risks. (Funded by Edwards Lifesciences; Clinical Trials.gov number, NCT00530894.)

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

N Engl J Med 2011;364:2187-98.

After the appearance of symptoms, aortic stenosis is associated with a high rate of death if left untreated.[1-10] Although surgical aortic-valve replacement improves symptoms and survival,[11-15] observational studies have identified various subgroups of patients (i.e., those with an advanced age and those with poor left ventricular function or other coexisting disorders) who are at increased risk for operative complications or death.[16-21] In such patients, a less invasive treatment may be a desirable alternative.

Transcatheter aortic-valve replacement treats aortic stenosis by displacing and functionally replacing the native valve with a bioprosthetic valve delivered on a catheter through the femoral artery (transfemoral placement) or the left ventricular apex (transapical placement).[22-34] In the randomized Placement of Aortic Transcatheter Valves (PARTNER) trial, a subgroup of patients with aortic stenosis who were not candidates for surgical aortic-valve replacement and who underwent transfemoral placement had an improvement of 20% in the 1-year survival rate and also had reduced symptoms.[35] This report describes results for the high-risk subgroup of patients in the PARTNER trial who were still candidates for surgical valve replacement and who were randomly assigned to undergo either transcatheter or surgical replacement of the aortic valve.

A video showing transcatheter aortic-valve replacement is available at NEJM.org

METHODS

PATIENTS

From May 11, 2007, through August 28, 2009, we enrolled 699 patients with severe aortic stenosis and cardiac symptoms (New York Heart Association [NYHA] class II function or worse) at 22 centers in the United States, 2 centers in Canada, and 1 center in Germany. All the patients were considered to be candidates for conventional surgical aortic-valve repair. Severe aortic stenosis was defined as an aortic-valve area of less than 0.8 cm^2 plus either a mean valve gradient of at least 40 mm Hg or a peak velocity of at least 4.0 m per second. Patients were deemed to be at high risk for operative complications or death on the basis of coexisting conditions that were associated with a risk of death of at least 15% by 30 days after the procedure. The final determination of high operative risk was made by surgeons at each study center, but we used as a guideline a score of at least 10% on the risk model developed by the Society for Thoracic Surgeons, which uses an algorithm that is based on the presence of coexisting illnesses in order to estimate the 30-day operative mortality. Less than 5% of patients in the population from which the algorithm was derived had a predicted operative risk (risk score) of more than 10%.[36]

Exclusion criteria were a bicuspid or noncalcified valve, coronary artery disease requiring revascularization, a left ventricular ejection fraction of less than 20%, an aortic annulus diameter of less than 18 mm or more than 25 mm, severe (4+) mitral or aortic regurgitation, a recent neurologic event, and severe renal insufficiency. Complete inclusion and exclusion criteria are provided in Table 1 in the Supplementary Appendix (available with the full text of this article at NEJM.org).

The executive committee conducted Web-based conference calls to review and approve all potential study participants before randomization. Of the 3105 patients who were screened at all the study centers and by the executive committee, 34% underwent randomization, and 23% were assigned to the high-risk subgroup for which the results are reported here.

STUDY DEVICE AND PROCEDURE

The SAPIEN heart-valve system (Edwards Lifesciences) and the transcatheter-replacement procedure have been described previously[35] (Fig. 1, and video, available at NEJM.org). Patients who were assigned to the transcatheter group underwent either transfemoral or transapical placement of the aortic valve on the basis of whether peripheral arteries could accommodate the large French sheaths required (22 French for the 23-mm valve and 24 French for the 26-mm valve). Transapical placement was performed through a small intercostal incision over the left ventricular apex with the use of a dedicated delivery catheter and the same Edwards SAPIEN valve. Patients received heparin during the procedure and dual antiplatelet therapy (aspirin and clopidogrel) for 6 months afterward.

STUDY DESIGN

The study design and data-management practices have been described previously[35] (Fig. 1 and Table 2 in the Supplementary Appendix). The study protocol and statistical analysis plan are available at NEJM.org. Patients first underwent evaluation of their peripheral arteries before randomization in order to separate those eligible for transfemoral placement from those who would require transapical placement (Fig. 2 in the Supplementary Ap-

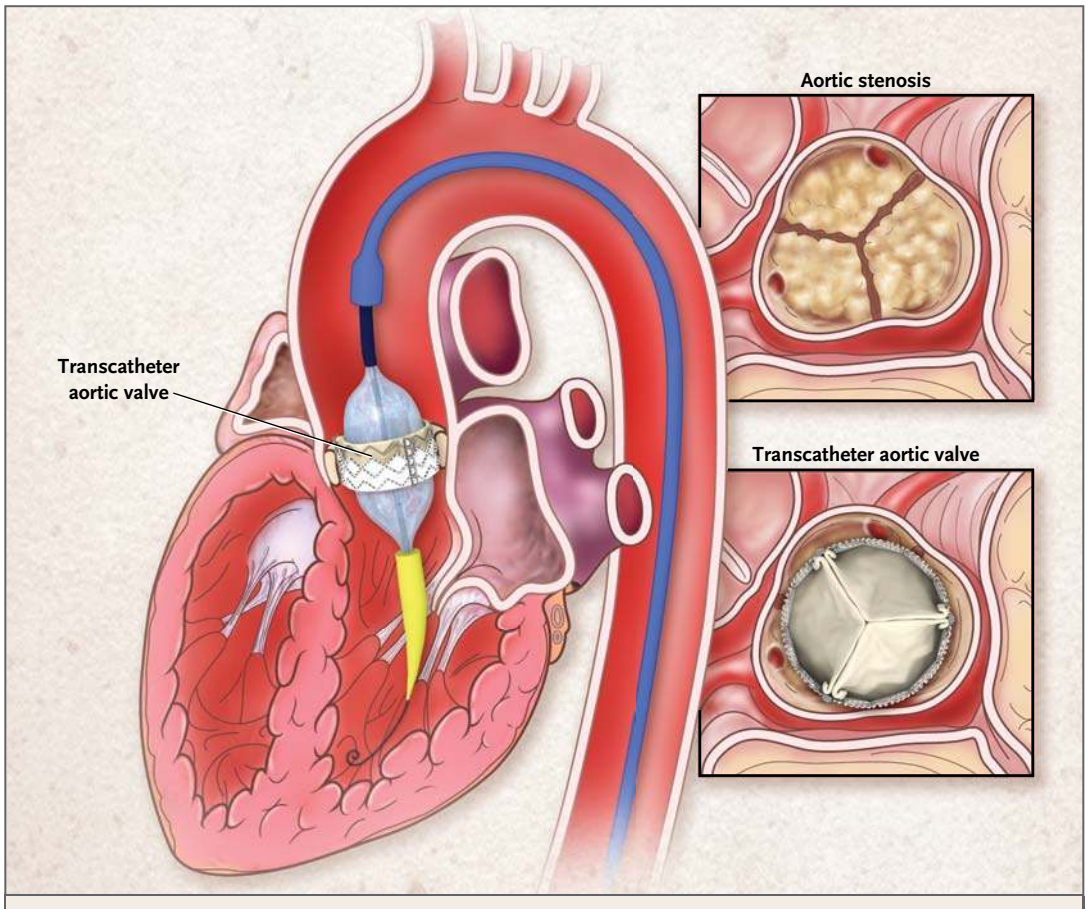

Figure 1. Transcatheter Aortic-Valve Replacement.

The transcatheter valve is positioned at the level of the native aortic valve during the final step of valve replacement, when the balloon is inflated within the native valve during a brief period of rapid ventricular pacing. The delivery system is shown after it has traversed the aorta retrograde over a guidewire from its point of insertion in the femoral artery (transfemoral placement). Before balloon inflation, the valve and balloon are collapsed on the catheter (dark blue) and fit within the sheath (blue). After balloon inflation, the calcified native valve (upper panel) is replaced by the expanded transcatheter valve (lower panel, shown in short-axis view from the aortic side of the valve).

pendix). According to the results of this evaluation, 492 patients were then categorized as being eligible for transfemoral placement (transfemoral-placement cohort), and 207 patients were categorized as being eligible for transapical placement (transapical-placement cohort). With the use of computer-generated randomized blocks at each site and for each subgroup, patients in the two cohorts were then randomly assigned to undergo either transcatheter replacement (348 patients) or surgical replacement (351 patients). 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.

The trial was approved by the institutional review board at each site. All patients provided written informed consent.

STUDY OVERSIGHT

The study was designed by the sponsor, Edwards Lifesciences, and by the executive committee, which included the first two authors, three interventional cardiologists (who were the coprincipal investigators), along with six other academic authors (three cardiac surgeons). The sponsor funded the studies and participated in the selection and management of the sites, the collection of data, and data monitoring. The executive committee met in person every 6 to 8 weeks to monitor all aspects of the conduct of the trial. Members of the executive committee had unrestricted access to the data after the database was locked and prepared all drafts of the manuscript. The sponsor's statistician performed the data analysis, which was duplicated and verified by the independent statisticians at the

London School of Hygiene and Tropical Medicine. The first author made the decision to submit the manuscript for publication, with the consent of all the other authors. The executive committee attests to the integrity of the trial and the completeness and accuracy of the reported data.

STUDY END POINTS

The primary end point was the rate of death from any cause at 1 year in the intention-to-treat population. All patients were followed for at least 1 year. Crossover between the two study groups was not permitted, except when findings or events during the assigned procedure prevented the planned treatment. Prespecified secondary end points included death from cardiovascular causes, NYHA functional class, repeat hospitalization because of valve- or procedure-related clinical deterioration, myocardial infarction, stroke, acute kidney injury, vascular complications, bleeding, 6-minute walk distance, and valve performance (as assessed on echocardiography). In a retrospective analysis of neurologic events adjudicated by the clinical events committee, major stroke was defined by a score of at least 2 on the modified Rankin scale (which ranges from 0 to 6, with higher scores indicating greater disability).[37] Specific definitions of end points are provided in Table 3 in the Supplementary Appendix. Patients were followed during the index hospitalization and at 30 days, 6 months, 1 year, and yearly thereafter.

STATISTICAL ANALYSIS

We determined that a sample of 650 patients would provide a power of at least 85% to show the noninferiority of transcatheter replacement, as compared with surgical replacement, with respect to the primary end point, assuming a 1-year rate of death of 29% in the transcatheter group and 32% in the surgical group. Noninferiority would be established if the upper limit of the one-sided 95% confidence interval for the between-group difference in mortality was less than 7.5 percentage points, at an alpha level of 0.05. We also determined that enrollment of 450 patients undergoing transfemoral placement would provide a power of at least 85% to show the noninferiority of transcatheter replacement, as compared with surgical replacement, on the assumption of a 1-year rate of death of 25% in the transcatheter group and 30% in the surgical group, with the same 7.5 percentage points noninferiority margin. Additional assumptions in sample-size computations were that 65% of all procedures would be transfemoral placement, that follow-up would continue for at least 12 months after enrollment of the last patient, and that 10% of patients would be lost to follow-up.

We used Fisher's exact test to compare categorical variables. Continuous variables, presented as means (±SD), were compared with the use of Student's t-test. Primary data analysis was performed in the intention-to-treat population, regardless of the treatment that was actually received. The results of as-treated analyses for primary and secondary end points are also provided. Time-to-event analyses, based on all available follow-up data, were performed with the use of Kaplan–Meier estimates and were compared between groups with the use of the log-rank test. A generalized linear model was used to calculate risk ratios in the subgroup analyses and to test for interactions. All statistical analyses were performed with the use of SAS software, version 9.2.

RESULTS

PATIENTS

In the transcatheter group, 244 patients were assigned to undergo transfemoral placement, and 104 were assigned to undergo transapical placement. A total of 351 patients were assigned to undergo surgical replacement, separately randomized to control groups in the transfemoral-placement cohort (248 patients) and the transapical-placement cohort (103 patients). Patients were followed for at least 1 year (median, 1.4 years; maximum, 3.3 years). The baseline characteristics of the patients in the two study groups were well balanced (Table 1). The high overall mean score (11.8%) on the risk model of the Society of Thoracic Surgeons indicated a high operative risk. As compared with patients in the transfemoral-placement cohort, patients in the transapical-placement cohort had significantly increased rates of previous coronary-artery bypass grafting (CABG), cerebrovascular disease, and peripheral vascular disease, despite the similar overall Society of Thoracic Surgeons scores in the two groups (Table 4 in the Supplementary Appendix).

Among the 699 patients who were randomly assigned to a study group, 42 did not undergo the assigned procedure (4 in the transcatheter group and 38 in the surgical group). The main reasons

Table 1. Baseline Characteristics of the Patients.*

Characteristic	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
Age — yr	83.6±6.8	84.5±6.4	0.07
Male sex — no./total no. (%)	201/348 (57.8)	198/349 (56.7)	0.82
Society of Thoracic Surgeons score†	11.8±3.3	11.7±3.5	0.61
Logistic EuroSCORE†	29.3±16.5	29.2±15.6	0.93
New York Heart Association class — no./total no. (%)			0.79
II	20/348 (5.7)	21/349 (6.0)	
III or IV	328/348 (94.3)	328/349 (94.0)	
Coronary artery disease — no./total no. (%)	260/347 (74.9)	266/346 (76.9)	0.59
Previous myocardial infarction — no./total no. (%)	92/343 (26.8)	103/343 (30.0)	0.40
Previous CABG — no./total no. (%)	147/345 (42.6)	152/344 (44.2)	0.70
Previous PCI — no./total no. (%)	116/341 (34.0)	110/338 (32.5)	0.68
Previous balloon aortic valvuloplasty — no./total no. (%)	46/344 (13.4)	35/344 (10.2)	0.24
Cerebral vascular disease — no./total no. (%)	95/324 (29.3)	87/317 (27.4)	0.60
Peripheral vascular disease — no./total no. (%)	148/344 (43.0)	142/341 (41.6)	0.76
COPD — no./total no. (%)			
Any	151/348 (43.4)	151/351 (43.0)	0.94
Oxygen-dependent	32/348 (9.2)	25/351 (7.1)	0.34
Creatinine level >2 mg/dl (177 μmol/liter) — no./total no. (%)	38/343 (11.1)	24/344 (7.0)	0.06
Atrial fibrillation — no./total no. (%)	80/196 (40.8)	73/171 (42.7)	0.75
Permanent pacemaker — no./total no. (%)	69/345 (20.0)	76/347 (21.9)	0.58
Pulmonary hypertension — no./total no. (%)	125/295 (42.4)	110/302 (36.4)	0.15
Frail condition — no./total no. (%)	46/295 (15.6)	53/301 (17.6)	0.58
Extensively calcified aorta — no./total no. (%)	2/348 (0.6)	4/351 (1.1)	0.69
Deleterious effects of chest-wall irradiation — no./total no. (%)	3/348 (0.9)	3/351 (0.9)	1.00
Chest-wall deformity — no./total no. (%)	0	1/351 (0.3)	1.00
Liver disease — no./total no. (%)	7/344 (2.0)	9/346 (2.6)	0.80
Aortic-valve area — cm^2	0.7±0.2	0.6±0.2	0.13
Aortic-valve gradient — mm Hg	42.7±14.6	43.5±14.3	0.45
Left ventricular ejection fraction — %	52.5±13.5	53.3±12.8	0.45
Moderate or severe mitral regurgitation — no./total no. (%)	66/334 (19.8)	71/333 (21.3)	0.63

* Plus–minus values are means ±SD. CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, and PCI percutaneous coronary intervention.

† Scores on the risk model of the Society of Thoracic Surgeons (STS) and scores on the logistic EuroSCORE scale are algorithms that are based on the presence of coexisting illnesses in order to predict the 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%. The EuroSCORE algorithm generates a score that is typically two to three times the STS score for the same patient.

for nontreatment were withdrawal from the study or a decision not to undergo surgical therapy (28 patients) (Table 5 in the Supplementary Appendix). The baseline risk profile of patients who did not undergo the assigned treatment was similar to that of treated patients. The mean (±SE) interval between randomization and treatment was significantly longer in the surgical group than in the transcatheter group (15.6±1.1 days vs. 10.6±0.7 days, P<0.001).

PROCEDURE OUTCOMES

A total of 4 patients died during the procedure (3 in the transcatheter group and 1 in the surgical group) (Table 6 in the Supplementary Appendix). The transcatheter procedure was either aborted or converted to open surgery in 16 of 348 patients (4.6%) as a result of new intraprocedural findings (e.g., an aortic annulus diameter >25 mm), failure to obtain femoral access, or procedural complications. Among these 16 patients, 9 immediately underwent open surgery (including 1 who died), 2 underwent open surgery more than 30 days later, and 5 did not undergo valve replacement (including 3 who died). One patient in the surgical group underwent transapical replacement as a result of an extremely calcified aorta, which was discovered during the surgical procedure. Multiple transcatheter valves (≥2) were implanted in 7 patients because of valve embolization (in 2 patients) or residual aortic regurgitation (in 5 patients in whom a second valve was placed within the first valve); 3 of these 7 patients died. Among 7 other patients with valve embolization, transcatheter placement was aborted in 2 patients and was converted to open surgery in 5 patients. Late interventions (>30 days) after transcatheter placement included balloon aortic valvuloplasty for paravalvular regurgitation in 2 patients and conversion to transapical placement in 1 patient.

MORTALITY AND STROKE

Since there were greater delays in treatment and more withdrawals or decisions to forgo treatment in the surgical group, both intention-to-treat and as-treated analyses are presented for the key study end points. In the intention-to-treat analysis, the rates of death from any cause at 30 days were 3.4% in the transcatheter group and 6.5% in the surgical group (P=0.07) (Table 2). In the as-treated analysis, the rates of death were 5.2% in the transcatheter group and 8.0% in the surgical group (P=0.15) (Table 7 in the Supplementary Appendix). Among patients in the transfemoral-placement cohort, the rates of death from any cause at 30 days were 3.3% in the transcatheter group and 6.2% in the surgical group in the intention-to-treat analysis (P=0.13) (Table 8 in the Supplementary Appendix) and 3.7% and 8.2%, respectively, in the as-treated analysis (P=0.046) (Table 9 in the Supplementary Appendix). Among patients in the transapical-placement cohort, the rates of death at 30 days were 3.8% in the transcatheter group and 7.0% in the surgical group in the intention-to-treat analysis (P=0.32) (Table 10 in the Supplementary Appendix) and 8.7% and 7.6%, respectively, in the as-treated analysis (P=0.79) (Table 11 in the Supplementary Appendix).

At 1 year, the rate of death from any cause in the intention-to-treat population (the primary study end point) was 24.2% in the transcatheter group as compared with 26.8% in the surgical group (P=0.44). The difference of –2.6 percentage points (two-sided 95% confidence interval [CI], –9.3 to 4.1; upper limit of the one-sided 95% CI, 3.0 percentage points) was within the prespecified noninferiority margin of 7.5 percentage points (P=0.001 for noninferiority) (Table 2 and Fig. 2). Similarly, there were no significant differences in the rates of death between the transfemoral-placement cohort and the surgical group (powered comparison) (rate difference, –4.2 percentage points; upper limit of the 95% CI, 2.3 percentage points; P=0.002 for noninferiority) (Fig. 2B, and Table 8 in the Supplementary Appendix) or between the transapical-placement cohort and the surgical group (unpowered comparison) (Fig. 2C, and Table 10 in the Supplementary Appendix).

According to the risk model of the Society of Thoracic Surgeons,[36] the expected 30-day rate of death in the surgical group was 11.8%. The actual rate of death among patients who underwent surgery (as-treated population) was 8.0%, indicating a better-than-anticipated surgical outcome. There were no important differences in surgical outcomes among centers or individual surgeons.

Rates of all neurologic events (i.e., all strokes and transient ischemic attacks) were higher in the transcatheter group than in the surgical group at 30 days (5.5% vs. 2.4%, P=0.04) and at 1 year (8.3% vs. 4.3%, P=0.04). Rates of major stroke were 3.8% in the transcatheter group and 2.1% in the surgical group at 30 days (P=0.20) and 5.1% and 2.4%, respectively, at 1 year (P=0.07). The rates of a composite of death from any cause or major stroke were similar in the transcatheter group and the surgical group at 30 days (6.9% and 8.2%, respectively; P=0.52) and at 1 year (26.5% and 28.0%, respectively; P=0.68) (Table 2 and Fig. 2).

Subgroup analyses with interaction testing were performed to determine whether the between-group mortality comparisons were consistent across 10 subgroups of patients (Fig. 3). There were significant interactions for the rate of death at 1 year according to sex and status

Table 2. Clinical Outcomes at 30 Days and 1 Year in the Intention-to-Treat Population.*

Outcome	30 Days			1 Year		
	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value	Transcatheter Replacement (N=348)	Surgical Replacement (N=351)	P Value
	no. of patients (%)			*no. of patients (%)*		
Death						
From any cause	12 (3.4)	22 (6.5)	0.07	84 (24.2)	89 (26.8)	0.44
From cardiac causes	11 (3.2)	10 (3.0)	0.90	47 (14.3)	40 (13.0)	0.63
Repeat hospitalization	15 (4.4)	12 (3.7)	0.64	58 (18.2)	45 (15.5)	0.38
Death or repeat hospitalization	25 (7.2)	33 (9.7)	0.24	120 (34.6)	119 (35.9)	0.73
Stroke or transient ischemic attack						
Either	19 (5.5)	8 (2.4)	0.04	27 (8.3)	13 (4.3)	0.04
Transient ischemic attack	3 (0.9)	1 (0.3)	0.33	7 (2.3)	4 (1.5)	0.47
Stroke						
Minor	3 (0.9)	1 (0.3)	0.34	3 (0.9)	2 (0.7)	0.84
Major	13 (3.8)	7 (2.1)	0.20	17 (5.1)	8 (2.4)	0.07
Death from any cause or major stroke	24 (6.9)	28 (8.2)	0.52	92 (26.5)	93 (28.0)	0.68
Myocardial infarction	0	2 (0.6)	0.16	1 (0.4)	2 (0.6)	0.69
Vascular complication						
Any	59 (17.0)	13 (3.8)	<0.001	62 (18.0)	16 (4.8)	<0.001
Major	38 (11.0)	11 (3.2)	<0.001	39 (11.3)	12 (3.5)	<0.001
Acute kidney injury						
Creatinine >3 mg/dl (265 μmol/liter)	4 (1.2)	4 (1.2)	0.95	12 (3.9)	8 (2.7)	0.41
Renal-replacement therapy	10 (2.9)	10 (3.0)	0.95	18 (5.4)	20 (6.5)	0.56
Major bleeding	32 (9.3)	67 (19.5)	<0.001	49 (14.7)	85 (25.7)	<0.001
Endocarditis	0	1 (0.3)	0.32	2 (0.6)	3 (1.0)	0.63
New-onset atrial fibrillation†	30 (8.6)	56 (16.0)	0.006	42 (12.1)	60 (17.1)	0.07
New pacemaker	13 (3.8)	12 (3.6)	0.89	19 (5.7)	16 (5.0)	0.68

* 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 in the study group.
† The presence of new-onset atrial fibrillation was determined in an electrocardiography core laboratory.

with respect to previous CABG, favoring transcatheter replacement in women and in patients without a history of CABG.

OTHER CLINICAL OUTCOMES

At 30 days, the transcatheter group had a significantly higher rate of major vascular complications than did the surgical group (11.0% vs. 3.2%, P<0.001) but had lower rates of major bleeding events (9.3% vs. 19.5%, P<0.001) and new-onset atrial fibrillation (8.6% vs. 16.0%), P=0.006) (Table 2).

At 30 days, more patients in the transcatheter group than in the surgical group had a reduction in symptoms to NYHA class II or lower (P<0.001) (Fig. 4). Among patients who could perform 6-minute walk tests, patients in the transcatheter group walked farther than those in the surgical group (P=0.002) (Fig. 3 in the Supplementary Appendix). At 1 year, patients in the two study groups had an improvement in cardiac symptoms and the 6-minute walk distance, with no evidence of significant between-group differences. Patients in the transcatheter group had a significantly shorter length of stay in the intensive care unit (3 days, vs. 5 days in the surgical group) and a shorter index hospitalization (8 vs. 12 days) (P<0.001 for both comparisons).

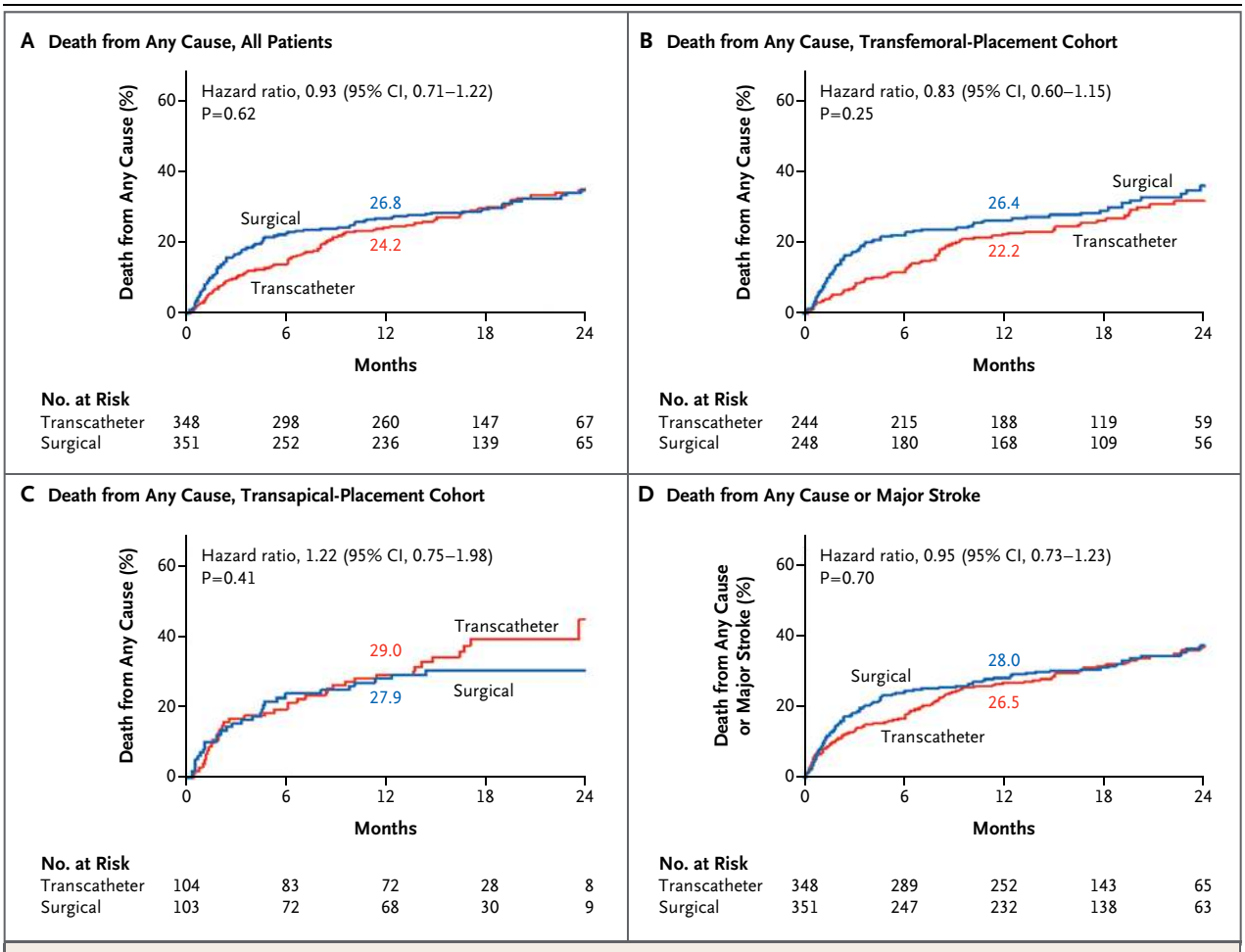

Figure 2. Time-to-Event Curves for the Primary End Point and Other Selected End Points.

Time-to-event curves are shown for death from any cause in all patients (Panel A), in the transfemoral-placement cohort (Panel B), and in the transapical-placement cohort (Panel C) and for a composite of death or major stroke (Panel D) among patients who were randomly assigned to undergo either transcatheter aortic-valve replacement (TAVR) or surgical aortic-valve replacement (AVR). The event rates were calculated with the use of Kaplan–Meier methods and compared with the use of the log-rank test.

ECHOCARDIOGRAPHIC FINDINGS

Aortic-valve gradients and areas improved significantly after the two procedures at both 30 days and 1 year (Table 12 in the Supplementary Appendix). At 1 year, transcatheter replacement was slightly superior to surgical replacement with respect to the mean aortic-valve gradient (10.2±4.3 mm Hg vs. 11.5±5.4 mm Hg, P=0.008) and mean valve area (1.59±0.48 cm² vs. 1.44±0.47 cm², P=0.002). Moderate or severe paravalvular regurgitation was more frequent in the transcatheter group than in the surgical group at 30 days (12.2% vs. 0.9%) and at 1 year (6.8% vs. 1.9%) (P<0.001 for both comparisons).

DISCUSSION

In this study, we affirmed the primary noninferiority hypothesis that was tested in the original PARTNER trial: transcatheter aortic-valve replacement was similar to surgical replacement with respect to rates of death from any cause at 1 year among patients with aortic stenosis who were at high risk for increased operative complications and death. The end point of the rate of death at 1 year among patients in the transfemoral-placement cohort (powered comparison) was also noninferior in the transcatheter group, as compared with the surgical group.

Subgroup	Death from Any Cause		Risk Ratio (95% CI)	P Value for Interaction
	Transcatheter Replacement	Surgical Replacement		
	no./total no. (%)			
Overall	84/348 (24.1)	89/351 (25.4)	0.95 (0.73–1.23)	
Age				0.52
≤85 yr	40/185 (21.6)	43/173 (24.9)	0.87 (0.60–1.27)	
>85 yr	44/163 (27.0)	46/176 (26.1)	1.03 (0.72–1.47)	
Sex				0.05
Male	57/201 (28.4)	48/198 (24.2)	1.17 (0.84–1.63)	
Female	27/147 (18.4)	41/151 (27.2)	0.68 (0.44–1.04)	
Body-mass index				0.66
≤26	45/165 (27.3)	51/186 (27.4)	0.99 (0.71–1.40)	
>26	38/181 (21.0)	38/160 (23.8)	0.88 (0.59–1.31)	
STS score				0.87
≤11	35/176 (19.9)	38/175 (21.7)	0.92 (0.61–1.38)	
>11	48/171 (28.1)	51/174 (29.3)	0.96 (0.69–1.34)	
Left ventricular ejection fraction				0.80
≤55%	44/168 (26.2)	46/166 (27.7)	0.95 (0.66–1.35)	
>55%	38/170 (22.4)	38/172 (22.1)	1.01 (0.68–1.50)	
Pulmonary hypertension				0.80
No	32/150 (21.3)	35/161 (21.7)	0.98 (0.64–1.50)	
Yes	48/175 (27.4)	50/167 (29.9)	0.92 (0.66–1.28)	
Moderate or severe mitral regurgitation				0.12
No	66/268 (24.6)	58/262 (22.1)	1.11 (0.82–1.52)	
Yes	16/66 (24.2)	25/71 (35.2)	0.69 (0.41–1.17)	
Previous CABG				0.02
No	44/198 (22.2)	59/192 (30.7)	0.72 (0.52–1.01)	
Yes	38/147 (25.9)	29/152 (19.1)	1.35 (0.88–2.08)	
Peripheral vascular disease				0.57
No	44/196 (22.4)	50/199 (25.1)	0.89 (0.63–1.27)	
Yes	39/148 (26.4)	36/142 (25.4)	1.04 (0.70–1.54)	
Cohort				0.43
Transapical	30/104 (28.8)	27/103 (26.2)	1.10 (0.71–1.71)	
Transfemoral	54/244 (22.1)	62/248 (25.0)	0.89 (0.64–1.22)	

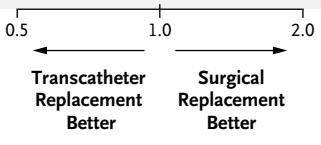

Figure 3. Subgroup Analyses for Death from Any Cause at 1 Year.

Subgroup analyses are shown for the primary end point of death from any cause at 1 year among patients in the intention-to-treat population who were randomly assigned to undergo either transcatheter aortic-valve replacement or surgical aortic-valve replacement. The P value for interaction represents the likelihood of interaction between the variable and the relative treatment effect. The body-mass index is the weight in kilograms divided by the square of the height in meters. CABG denotes coronary-artery bypass grafting, and STS Society of Thoracic Surgeons.

Procedure-specific outcomes are best revealed in early (30-day) results. The surgical outcomes in this trial were excellent, as compared with those in studies involving high-risk patients with aortic stenosis.[16-21] In the as-treated population, the ratio of observed operative mortality to predicted mortality (according to the risk model of the Society of Thoracic Surgeons) was 0.68. Rates of death in the transcatheter group at 30 days (3.4% in the intention-to-treat analysis and 5.2% in the as-treated analysis) were also excellent, as compared with earlier results in the PARTNER trial in patients who were not candidates for surgical valve replacement[35] and with data from other registries of transcatheter replacement.[24-26,29-34] As in previous observational studies of transcatheter

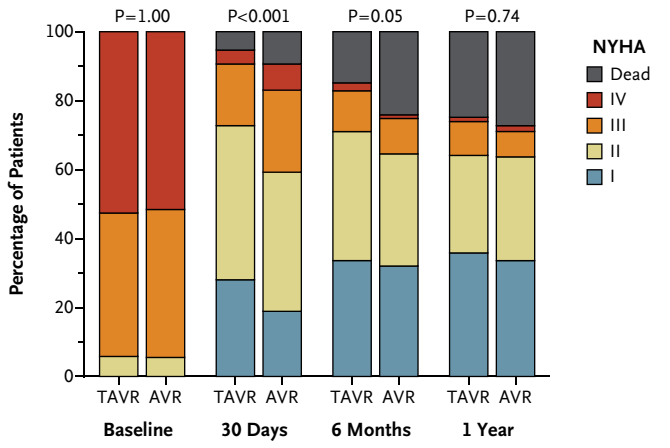

Figure 4. Symptom Status.

Shown is the New York Heart Association (NYHA) functional status (according to time point) for 697 of 699 patients who were randomly assigned to undergo either transcatheter aortic-valve replacement (TAVR) or surgical aortic-valve replacement (AVR).

replacement,[27,28,30,31,34] the rates of death at 30 days were higher among patients who had undergone transapical placement than among those who had undergone transfemoral placement. Possible reasons for these increased rates in the transapical cohort include an increased rate of coexisting disorders, a more protracted learning curve for surgeons, a smaller number of patients who were evaluated, and important procedural differences. Procedure-specific complications in the transcatheter group included conversion to an open surgical procedure, valve embolization, and reintervention for regurgitation of bioprosthetic valves. The results of the subgroup analyses, which must always be interpreted with caution, suggest that transcatheter replacement was associated with lower mortality than surgical replacement among women and patients without a history of CABG.

Clinical benefits of transcatheter replacement included significantly shorter stays in the intensive care unit and in the hospital. In addition, the NYHA functional class and 6-minute walk distance were strikingly improved at 1 year in the two study groups, although at 30 days, the benefits were greater with transcatheter replacement than with surgical replacement.

The approximate doubling in the rate of all new neurologic events (including major strokes) after transcatheter replacement, as compared with surgical replacement, remains a concern and is consistent with previous findings in the PARTNER trial[35] and with recent studies indicating an increased rate of new cerebral perfusion abnormalities associated with transcatheter replacement.[38-40] Most strokes appeared to be procedure-related and embolic. Rates of stroke were similar whether the access was transfemoral or transapical. Despite a higher frequency of stroke with transcatheter replacement, the composite end point of death from any cause or major stroke was similar in the two study groups at both 30 days and 1 year. Future studies will determine whether delivery systems with smaller diameters, procedural changes, or embolic-protection devices can reduce the incidence of stroke after transcatheter replacement.

Other periprocedural hazards reflected the inherent differences between an open operation and a transcatheter procedure. As expected, open surgery was associated with more frequent episodes of major bleeding and new-onset atrial fibrillation. There were more major vascular complications associated with transcatheter replacement. It is possible that the smaller-catheter systems already in use, combined with increased surgical experience and improved case selection, will reduce vascular complications.

Bioprosthetic-valve gradients and orifice areas were slightly better after transcatheter replacement than after surgical replacement, probably because of the less bulky support frame with transcatheter replacement. However, transcatheter replacement resulted in much more frequent paravalvular aortic regurgitation. Although this condition was stable at 1 year, repeat intervention was required in some cases, and the long-term clinical consequences are unknown.

Our study has several limitations. First, withdrawals and decisions to forgo the procedure among patients who were assigned to undergo surgical replacement were unexpectedly frequent, and approximately 5% of patients who were assigned to the transcatheter group did not undergo the procedure. Consequently, a balanced perspective on early procedure-related outcomes requires an analysis of both the intention-to-treat and as-treated study populations. Nevertheless, for the main comparisons of rates of death, neurologic events, and procedural hazards, the two study groups did not differ significantly in the as-treated population. Second, a definitive assessment of the durability of the prosthetic valves used in trans-

catheter replacement awaits longer follow-up. Third, we used an early version of the transcatheter device, predominantly in centers with no previous experience with the procedure. Finally, the study had insufficient statistical power to reach robust conclusions with respect to specific subgroups of patients, including any possible differences in outcome between the transapical and transfemoral procedures.

In conclusion, we have shown that in patients with aortic stenosis who are at high risk for operative complications and death, surgical aortic-valve replacement and balloon-expandable transcatheter replacement were associated with similar mortality at 30 days and 1 year and produced similar improvements in cardiac symptoms. Our findings indicate that transcatheter replacement is an alternative to surgical replacement in a well-chosen, high-risk subgroup of patients with aortic stenosis. In the absence of long-term follow-up data, recommendations to individual patients must balance the appeal of avoiding the known risks of open-heart surgery against the less invasive transcatheter approach, which has different and less well understood risks, particularly with respect to stroke. Additional randomized trials will be required to determine whether transcatheter replacement is equivalent to surgical replacement with respect to the clinical benefit for lower-risk patients with aortic stenosis.

Supported by Edwards Lifesciences.

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

APPENDIX

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