ORIGINAL ARTICLE

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

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ABSTRACT

BACKGROUND

Although transcatheter aortic-valve replacement (TAVR) is an accepted alternative to surgery in patients with severe aortic stenosis who are at high surgical risk, less is known about comparative outcomes among patients with aortic stenosis who are at intermediate surgical risk.

METHODS

We evaluated the clinical outcomes in intermediate-risk patients with severe, symptomatic aortic stenosis in a randomized trial comparing TAVR (performed with the use of a self-expanding prosthesis) with surgical aortic-valve replacement. The primary end point was a composite of death from any cause or disabling stroke at 24 months in patients undergoing attempted aortic-valve replacement. We used Bayesian analytical methods (with a margin of 0.07) to evaluate the noninferiority of TAVR as compared with surgical valve replacement.

RESULTS

A total of 1746 patients underwent randomization at 87 centers. Of these patients, 1660 underwent an attempted TAVR or surgical procedure. The mean (±SD) age of the patients was 79.8±6.2 years, and all were at intermediate risk for surgery (Society of Thoracic Surgeons Predicted Risk of Mortality, 4.5±1.6%). At 24 months, the estimated incidence of the primary end point was 12.6% in the TAVR group and 14.0% in the surgery group (95% credible interval [Bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority, >0.999). Surgery was associated with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements, whereas TAVR had higher rates of residual aortic regurgitation and need for pacemaker implantation. TAVR resulted in lower mean gradients and larger aortic-valve areas than surgery. Structural valve deterioration at 24 months did not occur in either group.

CONCLUSIONS

TAVR was a noninferior alternative to surgery in patients with severe aortic stenosis at intermediate surgical risk, with a different pattern of adverse events associated with each procedure. (Funded by Medtronic; SURTAVI ClinicalTrials.gov number, NCT01586910.)

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*A complete list of investigators in the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial is provided in the Supplementary Appendix, available at NEJM.org.

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Transcatheter aortic-valve replacement (TAVR) with the use of a self-expanding prosthesis is superior to medical therapy in patients with severe, symptomatic aortic stenosis in whom surgical aortic-valve replacement has been associated with prohibitive risk.[1] Among patients who are at high risk for standard surgery, TAVR may be the preferred option.[2-4] The adoption of TAVR in patients with aortic stenosis at high risk for surgery has been rapid, as shown by enrollment in the ongoing Society of Thoracic Surgeons–American College of Cardiology Transcatheter Valve Therapy Registry.[5]

The comparative efficacy of TAVR and surgery has been less well studied among patients with aortic stenosis who are at lower surgical risk.[6-8] A randomized trial comparing balloon-expandable TAVR and surgery among intermediate-risk patients showed that TAVR was noninferior to surgery 2 years after randomization.[9] Given the higher rates of residual aortic-valve regurgitation and pacemaker use in TAVR patients,[2] and more frequent stroke, atrial fibrillation, acute kidney injury, and blood transfusions in surgical patients,[2] a randomized comparison of TAVR and surgery among intermediate-risk patients was warranted.

The purpose of the Surgical Replacement and Transcatheter Aortic Valve Implantation (SURTAVI) trial was to compare the safety and efficacy of TAVR performed with the use of a self-expanding bioprosthesis with surgical aortic-valve replacement in patients who were deemed to be at intermediate risk for surgery.

Methods

Trial Design

The SURTAVI trial was a multinational, randomized, noninferiority clinical trial designed to compare the safety and efficacy of TAVR and surgery in patients with symptomatic, severe aortic stenosis at intermediate surgical risk. Eligible patients were recruited at 87 centers and underwent randomization in a 1:1 ratio to undergo TAVR with the use of a self-expanding bioprosthesis or surgery (Table S1 and Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. It was approved by the local institutional review board or medical ethics committee at each center. All the patients provided written informed consent.

Medtronic funded the trial and developed the protocol (available at NEJM.org) in collaboration with the executive committee. Medtronic representatives were responsible for site selection, data monitoring, and trial management. An independent academic clinical-events committee (Cardialysis) adjudicated all end points using standard definitions (Table S2 in the Supplementary Appendix). Paradigm Biostatistics performed the Bayesian analysis for all end-point comparisons; an independent statistical consultant (Berry Consultants) validated the primary Bayesian end-point analysis. The data and safety monitoring board provided study oversight with periodic safety review and recommendations relating to trial design and conduct.

The first and third authors prepared all drafts of the manuscript, and all the authors made the decision to submit the manuscript for publication. No one who is not an author contributed to the writing of the manuscript. The authors attest that the trial was performed according to the protocol and vouch for the accuracy and completeness of the reported data.

Patient Selection

Eligible patients with symptomatic, severe aortic stenosis were determined by the local multidisciplinary heart team to be at intermediate surgical risk, which was defined as an estimated risk of 30-day surgical death of 3 to 15%, according to the criteria of the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM), as well as such nontraditional factors as coexisting illnesses, frailty, and disability. Severe aortic-valve stenosis was defined as an initial aortic-valve area of 1.0 cm^2 or less or an aortic-valve area index of less than 0.6 cm^2 per square meter of body-surface area and a mean gradient of more than 40 mm Hg or a maximum aortic velocity of more than 4 m per second at rest or with dobutamine provocation in patients with a left ventricular ejection fraction of less than 55% or a Doppler velocity index of less than 0.25 on resting echocardiography. A detailed list of inclusion and exclusion criteria is provided in Table S3 in the Supplementary Appendix. An international screening committee confirmed patient eligibility (Table S2 in the Supplementary Appendix).

TRIAL PROCEDURES

The randomization of patients was stratified according to clinical site and the need for surgical coronary revascularization, as recommended by the multidisciplinary heart team. The choice and size of the surgical bioprosthesis were left to the discretion of the surgeon. Patients in the surgery group underwent coronary revascularization at the time of aortic-valve replacement if needed. After the procedure, a daily regimen of at least 81 mg of aspirin was prescribed indefinitely, including for patients who were receiving warfarin.

Among the patients in the TAVR group, the selection of the bioprosthesis size and access site were based on preprocedural computed tomography. The CoreValve bioprosthesis was used in 724 of 863 patients (84%); the Evolut R bioprosthesis was used in 139 (16%) (Fig. S1 in the Supplementary Appendix). Transfemoral access was preferred; subclavian or direct aortic approaches were used in patients with unsuitable iliofemoral anatomy. The use of embolic protection during the TAVR procedure was not permitted. Percutaneous coronary intervention, when indicated, was performed either as a staged procedure before TAVR or at the time of TAVR as a concomitant procedure. Dual antiplatelet therapy with aspirin (at a dose of 81 to 100 mg) and clopidogrel (75 mg) was recommended for 3 months after the procedure; thereafter, the same dose of either aspirin or clopidogrel was recommended as indefinite monotherapy. Patients requiring warfarin or another anticoagulant were treated with antiplatelet monotherapy after the procedure.

TRIAL END POINTS

The primary end point was a composite of death from any cause or disabling stroke at 24 months. (Trial end-point definitions are provided in Table S4 in the Supplementary Appendix.) Disabling stroke was defined according to the criteria of the Valve Academic Research Consortium-2 (VARC-2).[10] All the patients were seen by a trained neurologist or stroke specialist, and neurologic events were adjudicated by a neurologist on the clinical-events committee.

Prespecified analyses of death from any cause or disabling stroke at 12 months were completed for selected subgroups (Fig. S4 in the Supplementary Appendix). Secondary end points included major adverse cardiovascular and cerebrovascular events, which consisted of death from any cause, myocardial infarction, all types of strokes, and any reintervention. Additional secondary safety and efficacy end points are described in the protocol and in the Methods section in the Supplementary Appendix.

An independent echocardiographic core laboratory at the Mayo Clinic provided serial echocardiographic assessments with the use of VARC-2 criteria,[10] which include aortic-valve hemodynamics and total aortic and paravalvular regurgitation through 24 months. Health-related quality-of-life assessments through 24 months were provided by the clinical sites with the use of the Kansas City cardiomyopathy questionnaire (KCCQ).[11] (KCCQ summary scores range from 0 to 100, with a correlation between scores of >60 and New York Heart Association class I or II and a 10-point increase corresponding to moderate clinical improvement.)

STATISTICAL ANALYSIS

The trial design called for the use of Bayesian statistical methods. We determined that TAVR would be declared noninferior to surgery for the primary outcome if the posterior probability of noninferiority with a margin of 0.07 was more than 0.971, as calculated by means of Bayesian analysis. The prespecified value of 0.971 was selected empirically through simulation to achieve a type I error at an alpha level of less than 0.05. A sample size of 1600 attempted aortic-valve procedures was chosen on the basis of an assumed 17% incidence of death from any cause or disabling stroke at 24 months among the patients undergoing surgery. A Bayesian interim analysis was prespecified when 1400 patients had reached the 12-month follow-up.

We evaluated the primary and secondary end points in a modified intention-to-treat population of patients who had undergone randomization and an attempted procedure. We imputed the outcome of patients without a known outcome at 24 months according to the prespecified statistical model, which was based on the patient's last known status at the latest known time point: at the time of the procedure or at 1 month, 6 months, 12 months, or 18 months. A sensitivity analysis was performed to account for missing data, including the patients who were lost to follow-up or withdrew from the study. Secondary end points were tested with the use of a hierarchical testing procedure. Primary and secondary end

points were also analyzed in the intention-to-treat population. Details with respect to the analysis populations, sensitivity analyses, and hierarchical testing methods are provided in the Methods section in the Supplementary Appendix.

We used a Bayesian analogue of a two-sample t-test to compare continuous variables as means (±SD) and a Bayesian version of a comparison of proportions to compare categorical variables as frequencies and percentages. Event rates are summarized as Bayesian posterior medians with 95% credible intervals, which were calculated from the 2.5th and 97.5th percentiles. We also performed Kaplan–Meier survival analyses.

RESULTS

BASELINE CHARACTERISTICS

A total of 1746 patients underwent randomization at 87 centers in the United States, Europe, and Canada from June 19, 2012, to June 30, 2016 (Fig. S2 in the Supplementary Appendix). The modified intention-to-treat population included 1660 patients (864 in the TAVR group and 796 in the surgery group). In this population, 2 patients in the TAVR group and 1 in the surgery group did not undergo implantation. In addition, TAVR was performed in 2 patients in the surgery group and surgery was performed in 1 patient in the TAVR group, which resulted in 863 patients who underwent the assigned procedure in the TAVR group and 794 who underwent the assigned procedure in the surgery group (Fig. S2 in the Supplementary Appendix). Revascularization was recommended in 332 of 1660 patients (20%) in the two groups.

Baseline demographic and clinical characteristics of the patients are provided in Table 1. The mean age was 79.8±6.2 years. All the patients were at intermediate risk for surgery (STS-PROM value, 4.5±1.6%), and most had coexisting illnesses, including diabetes (in 34.5%), chronic lung disease (in 34.5%), and frailty (5-meter gait speed of >6 seconds, 52.3%; falls within 6 months, 12.2%). A complete list of coexisting illnesses, including frailty and disability, is provided in Table S5 in the Supplementary Appendix.

A total of 71 patients in the intention-to-treat population who were assigned to the surgery group did not undergo the procedure (Fig. S2 in the Supplementary Appendix). A comparison of these patients with the 796 patients who underwent surgery identified no differences in baseline demographic characteristics, surgical frailty, disability, or coexisting illnesses (Tables S6 and S7 in the Supplementary Appendix).

PROCEDURAL OUTCOMES

Early (≤30 day) acute kidney injury stage 2 or 3 and new or worsening atrial fibrillation occurred more often in the surgery group than in the TAVR group, whereas major vascular complications and the need for permanent pacemaker implantation occurred more often in the TAVR group (Table 2). There were no significant differences in 24-month mortality among the patients who required a new pacemaker (Fig. S3 in the Supplementary Appendix). Transfusions were more common in the surgery group than in the TAVR group, including an increase by a factor of 3.5 in the need for four or more red-cell units (Table 2). Other outcomes were similar in the two groups. A detailed description of procedural outcomes is provided in the Supplementary Appendix.

PRIMARY END POINT

The primary Bayesian analysis was performed in 1660 patients in the modified intention-to-treat population when 1400 patients had reached 12 months of follow-up. The incidence of the primary end point at 24 months was 12.6% in the TAVR group and 14.0% in the surgery group (95% credible interval [Bayesian analysis] for difference, −5.2 to 2.3%; posterior probability of noninferiority, >0.999) (Table 3 and Fig. 1). Similar results were found in the intention-to-treat population (13.2% in the TAVR group and 14.1% in the surgery group; 95% credible interval for difference, −4.7 to 2.7%; posterior probability of noninferiority, >0.999) (Table S8 in the Supplementary Appendix). A sensitivity analysis that was performed to account for patients who were lost to follow-up showed no important difference in the primary conclusions (Results section in the Supplementary Appendix). At 24 months, the rate of death from any cause was 11.4% in the TAVR group and 11.6% in the surgery group (95% credible interval for difference, −3.8 to 3.3%); the rate of disabling stroke was also similar in the two groups (Table 3 and Fig. 1). No significant differences with respect to geographic region or trial site were found for the primary outcome. Prespecified subgroup analyses of death from any cause or disabling stroke

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Modified Intention-to-Treat Analysis		Intention-to-Treat Analysis	
	TAVR (N=864)	Surgery (N=796)	TAVR (N=879)	Surgery (N=867)
Age — yr	79.9±6.2	79.7±6.1	79.9±6.2	79.8±6.0
Age group — no. (%)				
<75 yr	156 (18.1)	157 (19.7)	160 (18.2)	167 (19.3)
75 to 85 yr	563 (65.2)	508 (63.8)	571 (65.0)	553 (63.8)
>85 yr	145 (16.8)	131 (16.5)	148 (16.8)	147 (17.0)
Male sex — no. (%)	498 (57.6)	438 (55.0)	508 (57.8)	484 (55.8)
Body-surface area — m^2	1.9±0.2	1.9±0.2	1.9±0.2	1.9±0.2
New York Heart Association class — no. (%)				
II	344 (39.8)	333 (41.8)	350 (39.8)	367 (42.3)
III	472 (54.6)	411 (51.6)	480 (54.6)	448 (51.7)
IV	48 (5.6)	52 (6.5)	49 (5.6)	52 (6.0)
Society of Thoracic Surgeons–Predicted Risk of Mortality score†				
Mean — %	4.4±1.5	4.5±1.6	4.4±1.5	4.5±1.6
Category — no. (%)				
<3%	131 (15.2)	123 (15.5)	136 (15.5)	135 (15.6)
3 to <5%	480 (55.6)	405 (50.9)	484 (55.1)	447 (51.6)
5 to <8%	233 (27.0)	235 (29.5)	238 (27.1)	250 (28.8)
≥8%	20 (2.3)	33 (4.1)	21 (2.4)	35 (4.0)
Logistic EuroSCORE — %‡	11.9±7.6	11.6±8.0	11.9±7.6	11.6±8.0
Medical condition — no. (%)				
Diabetes mellitus	295 (34.1)	277 (34.8)	302 (34.4)	290 (33.4)
Serum creatinine >2 mg/dl	14 (1.6)	17 (2.1)	14 (1.6)	21 (2.4)
Hypertension	801 (92.7)	719 (90.3)	816 (92.8)	787 (90.8)
Previous stroke	57 (6.6)	57 (7.2)	59 (6 .7)	65 (7.5)
Previous TIA	58 (6.7)	46 (5.8)	59 (6.7)	52 (6.0)
Peripheral vascular disease	266 (30.8)	238 (29.9)	269 (30.6)	264 (30.4)
Permanent pacemaker	84 (9.7)	72 (9.0)	86 (9.8)	76 (8.8)
Cardiac risk factors — no. (%)				
Coronary artery disease	541 (62.6)	511 (64.2)	549 (62.5)	556 (64.1)
Previous CABG	138 (16.0)	137 (17.2)	142 (16.2)	145 (16.7)
Previous PCI	184 (21.3)	169 (21.2)	187 (21.3)	182 (21.0)
Previous myocardial infarction	125 (14.5)	111 (13.9)	125 (14.2)	116 (13.4)
Congestive heart failure	824 (95.4)	769 (96.6)	839 (95.4)	834 (96.2)
History of arrhythmia	275 (31.8)	250 (31.4)	279 (31.7)	271 (31.3)
Atrial fibrillation or flutter	243 (28.1)	211 (26.5)	247 (28.1)	230 (26.5)

* Plus–minus values are means ±SD. All the primary and secondary end points were evaluated in a modified intention-to-treat population, which consisted of patients who had undergone randomization and an attempted procedure. There were no significant differences between the groups. To convert the values for creatinine to micromoles per liter, multiply by 88.4. CABG denotes coronary-artery bypass grafting, PCI percutaneous coronary intervention, TAVR transcatheter aortic-valve replacement, and TIA transient ischemic attack.

† The Society of Thoracic Surgeons–Predicted Risk of Mortality score provides an estimate of the rate of death at 30 days among patients undergoing surgical aortic-valve replacement on the basis of a number of demographic and procedure variables.

‡ Scores on the Logistic EuroSCORE range from 0 to 100%, with higher scores indicating greater surgical risk and a score of 20% indicating very high risk.

Table 2. Procedure-Related Complications at 30 Days (Modified Intention-to-Treat Population).*

Complication	TAVR (N=864)	Surgery (N=796)	95% Credible Interval for Difference
Life-threatening or major bleeding — %	12.2	9.3	–0.1 to 5.9
Transfusion of red cells — no. (%)			
0 units	756 (87.5)	469 (58.9)	24.4 to 32.5
1 unit	29 (3.4)	90 (11.3)	–10.5 to –5.5
2 to 4 units	48 (5.6)	136 (17.1)	–14.5 to –8.5
>4 units	31 (3.6)	101 (12.7)	–11.7 to –6.5
Acute kidney injury stage 2 or 3 — %	1.7	4.4	–4.4 to –1.0
Coronary-artery obstruction — %	0.2	0.0	–0.2 to 0.8
Major vascular complication — %	6.0	1.1	3.2 to 6.7
Cardiac perforation — %	1.7	0.9	–0.2 to 2.0
Cardiogenic shock — %	1.1	3.8	–4.2 to –1.1
Permanent pacemaker implantation — %	25.9	6.6	15.9 to 22.7
Atrial fibrillation — %	12.9	43.4	–34.7 to –26.4

* Values are estimated incidence (median of the posterior probability distribution, as calculated by means of Bayesian analysis), except for transfusion values, which are the numbers of patients and percentages. For all the values, 95% credible intervals were calculated for the difference between groups. Percentages may not total 100 because of rounding.

at 12 months identified no significant differences in the treatment effect between TAVR and surgery (Fig. S4 in the Supplementary Appendix).

SECONDARY END POINTS

Results of hierarchical analyses of the secondary end points are provided in Table S9 in the Supplementary Appendix. New York Heart Association symptoms improved significantly in the two groups from baseline, an improvement that persisted throughout the 24-month follow-up period (Fig. S5 in the Supplementary Appendix). Quality of life, as measured by the KCCQ summary score, improved significantly in the two groups through 24 months of follow-up; the TAVR group had a higher proportion of patients with improvement at 1 month than did the surgery group (Fig. S6 in the Supplementary Appendix).

ECHOCARDIOGRAPHIC FINDINGS

Aortic-valve hemodynamics improved in both the TAVR group and the surgery group (Fig. 2). The TAVR group had lower mean aortic-valve gradients and larger aortic-valve areas than did the surgery group. Moderate or severe residual paravalvular regurgitation was more common in the TAVR group at 1 year (5.3% in the TAVR group vs. 0.6% in the surgery group; 95% credible interval for difference, 2.8 to 6.8%) (Table S10 in the Supplementary Appendix).

DISCUSSION

In this trial, we found that TAVR was statistically noninferior to surgery in patients who were deemed to be at intermediate surgical risk by a multidisciplinary heart team. We found that the risk of death or disabling stroke at 24 months ranged from 12.6 to 14.0% among the patients in our trial. Surgery was associated with higher rates of acute kidney injury, atrial fibrillation, and transfusion requirements, whereas TAVR had higher rates of residual aortic regurgitation and need for pacemaker implantation. TAVR resulted in better aortic-valve hemodynamics than surgery, and neither TAVR nor surgery showed evidence of structural valve deterioration at 24 months.

A portfolio of randomized clinical trials compared TAVR with surgery in patients at varying surgical risk.[1,2,9,12,13] This expanding evidence base suggests that the highest mortality benefit for TAVR over surgery (or medical therapy) is seen in patients at high surgical risk.[1,2,12-14] Among the patients at high risk, those in the TAVR group had a lower rate of death than did

Table 3. Clinical Outcomes at 30 Days, 12 Months, and 24 Months (Modified Intention-to-Treat Population).*

Outcome	30 Days			12 Months			24 Months		
	TAVR	Surgery	95% Credible Interval	TAVR	Surgery	95% Credible Interval	TAVR	Surgery	95% Credible Interval
					percent				
Death from any cause or disabling stroke	2.8	3.9	−2.8 to 0.7	8.1	8.8	−3.5 to 2.1	12.6	14.0	−5.2 to 2.3
Death from any cause	2.2	1.7	−0.9 to 1.8	6.7	6.8	−2.7 to 2.4	11.4	11.6	−3.8 to 3.3
Cardiovascular	2.0	1.7	−1.0 to 1.6	4.8	5.5	−2.9 to 1.5	7.7	8.0	−3.3 to 2.6
Valve-related	0.1	0.1	−0.3 to 0.3	0.1	0.3	−0.7 to 0.3	0.2	0.4	−0.9 to 0.5
Aortic-valve reintervention	0.9	0.2	−0.1 to 1.4	2.1	0.5	0.4 to 2.7	2.8	0.7	0.7 to 3.5
All stroke and TIA	4.5	6.5	−4.2 to 0.3	8.2	8.6	−3.1 to 2.4	10.0	11.0	−4.2 to 2.2
All stroke	3.4	5.6	−4.2 to −0.2	5.4	6 .9	−3.9 to 0.9	6.2	8.4	−5.0 to 0.4
Disabling	1.2	2.5	−2.6 to 0.1	2.2	3.6	−3.1 to 0.4	2.6	4.5	−4.0 to 0.1
Nondisabling	2.2	3.1	−2.5 to 0.6	3.7	3.9	−2.2 to 1.7	4.4	4.7	−2.6 to 1.9
TIA	1.5	1.1	−0.7 to 1.5	3.2	2.0	−0.4 to 2.8	4.3	3.1	−0.9 to 3.2
Myocardial infarction	0.9	1.0	−1.0 to 0.9	2.0	1.6	−0.9 to 1.8	2.8	2.2	−1.1 to 2.4
Hospitalization for aortic-valve–related disease	2.9	4.2	−3.1 to 0.5	8.5	7.6	−1.8 to 3.6	13.2	9.7	0.1 to 7.0
MACCE	5.7	7.4	−4.0 to 0.7	13.2	12.8	−2.9 to 3.7	18.6	18.6	−4.2 to 4.2

* Values are estimated incidence (median of the posterior probability distribution, as calculated by means of Bayesian analysis) with the 95% credible interval for the difference between groups. MACCE denotes major adverse cerebrovascular and cardiovascular events and includes death from any cause, myocardial infarction, all stroke, and reintervention.

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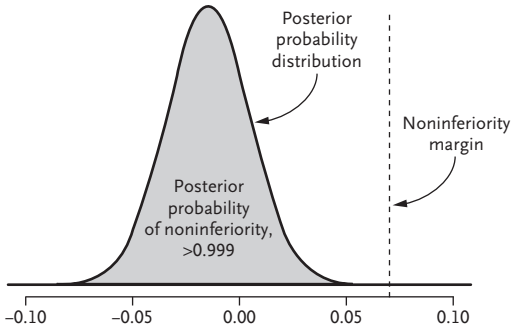
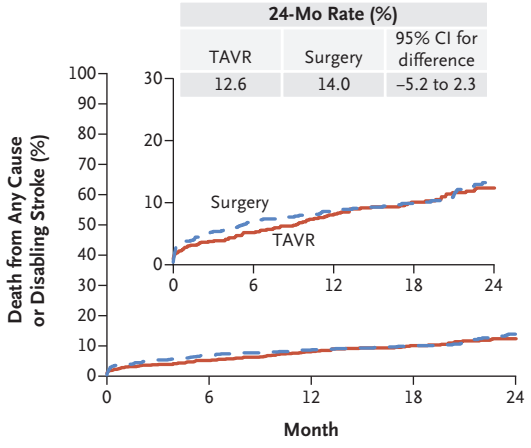
A Noninferiority Margin of TAVR



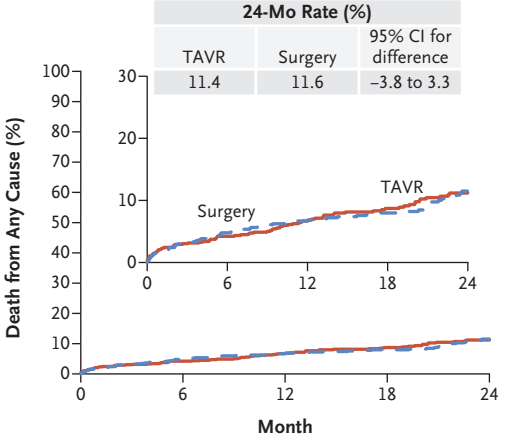
TAVR Posterior Median	Surgery Posterior Median	Difference Posterior Median
	% (95% CI)	
12.6 (10.2 to 15.3)	14.0 (11.4 to 17.0)	−1.4 (−5.2 to 2.3)

B Primary Outcome



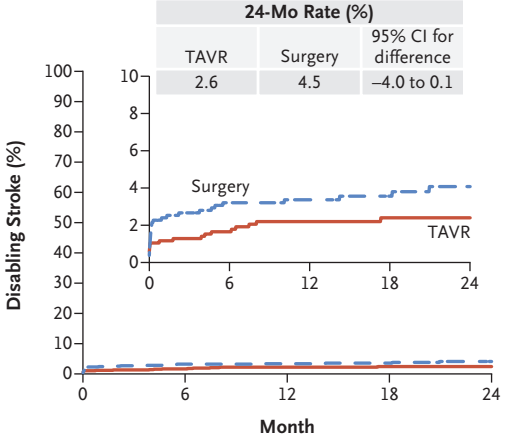
No. at Risk					
TAVR	864	755	612	456	272
Surgery	796	674	555	407	241

C Death from Any Cause



No. at Risk					
TAVR	864	762	621	465	280
Surgery	796	690	569	414	249

D Disabling Stroke



No. at Risk					
TAVR	864	755	612	456	272
Surgery	796	674	555	407	241

Figure 1. Noninferiority Analysis and Time-to-Event Curves for the Primary End Point.

In this Bayesian analysis, the posterior probability distribution for the difference in the primary end point (death from any cause or disabling stroke at 24 months) between patients who underwent transcatheter aortic-valve replacement (TAVR) and those who underwent surgical replacement confirmed that the noninferiority margin for TAVR was met (Panel A). Also shown are time-to-event curves for the primary end point (Panel B), death from any cause (Panel C), and disabling stroke (Panel D), findings that were similar in the two groups. In Panels B, C, and D, the insets show the same data on an enlarged y axis.

those in the surgery group,[2-4] owing to the delayed recovery from surgery-related complications.[15] It is less certain that a mortality benefit of TAVR over surgery will be identified among patients at lower surgical risk. Although a comparison between randomized trials carries inherent risks, both our trial and the previously reported Placement of Aortic Transcatheter Valves (PARTNER) IIA trial achieved their noninferiority end points of death from any cause or disabling

stroke in intermediate-risk populations. The mean STS-PROM value was higher in PARTNER IIA than in our trial (5.8% vs. 4.5%), as was the observed-to-expected 30-day surgical mortality ratio (0.71 vs. 0.38).[14] The observed-to-expected ratio in our trial was one of the lowest such ratios for surgical mortality that have been reported in randomized studies to date.[2,9,13] We attribute this result to the best practices of our cardiac surgical teams, which underscores the importance of the similar 30-day rates of death in the TAVR group and the surgery group (2.2% and 1.7%, respectively). The rates of death from any cause at 24 months were similar in the TAVR group and the surgery group (11.4% and 11.6%, respectively), which supports the similarity of the two techniques at the time of this midterm follow-up. This finding also suggests that the patients in our trial were at lower risk than those in the PARTNER IIA trial, which showed 24-month mortality of 16.7% with TAVR and 18.0% with surgery.[9]

Surgical risk assessment in intermediate-risk patients is often problematic, even for an experienced multidisciplinary heart team. Conventional risk scores, such as the STS-PROM,[16] may be supplemented with other nontraditional surgical risk factors, such as coexisting conditions, frailty, and disability.[17,18] We defined our lower threshold for the heart-team assessment of 30-day surgical risk at 3%, and our results provide reassurance that TAVR is an alternative to surgery in patients at the lower boundaries of intermediate risk.

Neurologic complications associated with aortic-valve replacement are increasingly recognized as critical outcome measures in comparative trials. At 24 months, we found a numerically lower rate of disabling stroke in the TAVR group than in the surgery group, although the difference was not significant; these findings were similar to those in a previous randomized trial involving patients at increased risk for surgery.[3,4] We performed neurologic assessments before and after the procedures in the two groups, although detailed cognitive testing was not performed and embolic protection devices were not allowed during the procedure. Similar to the findings of the pivotal study involving patients at high surgical risk,[2] we found that the rates of acute kidney injury and atrial fibrillation were higher in the surgery group, whereas the rates of residual aortic regurgitation and permanent pacemaker implantation were higher in the TAVR group. Although we might have expected a lower rate of permanent pacemaker implantation with the introduction of the Evolut R valve on the basis of rates of 11.7% and 16.4% in previous studies,[19,20] the rates among patients who received the CoreValve (25.5%) and the Evolut R valve (26.7%) were similar. Whether this finding is related to the small number of Evolut R valves that were implanted late in the trial is unknown and will require further study.[1,2,19,20] The 24-month mortality among patients who required a new pacemaker was similar to that in the overall population.

Aortic-valve hemodynamics were substantially improved in both the TAVR group and the surgery group and probably contributed to the reduction in symptoms and improvement in health-related outcomes that we observed. We identified lower aortic-valve gradients and larger aortic-valve areas in patients treated with TAVR, findings that probably stemmed from the supraannular design of the self-expanding bioprosthesis. Long-term follow-up will be needed to determine the clinical effect of the improved hemodynamics in the TAVR group. Although we did not find evidence of structural valve deterioration at this midterm follow-up, more extended follow-up is needed.

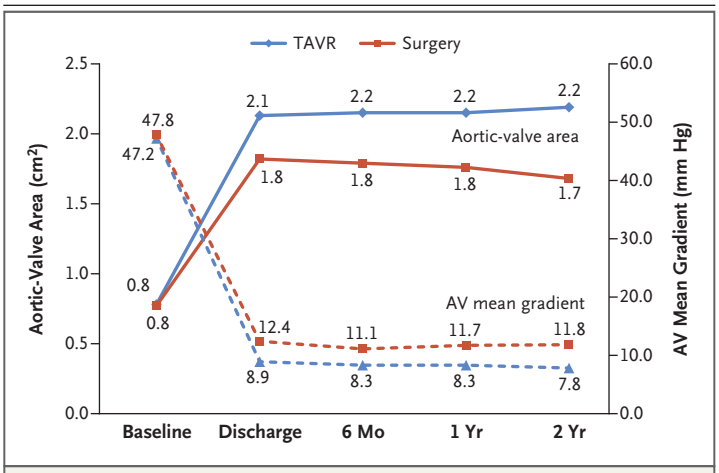


Figure 2. Echocardiographic Findings.

The mean aortic-valve (AV) gradient was significantly lower (dashed lines) and the effective AV orifice area was significantly larger (solid lines) in the TAVR group than in the surgery group at all time points after the procedure.

Our study has several limitations. A relatively high frequency of unplanned withdrawals occurred in the surgery group, primarily because of the withdrawal of patient consent after randomization. We could not identify differences in baseline demographic characteristics among the patients who underwent the assigned surgery and those who did not. The next-generation Evolut R bioprosthesis was used in less than 20% of the patients. We also recognized that long-term follow-up is needed, since a 24-month end-point analysis provides incomplete information about the life cycle of TAVR as compared with surgical bioprostheses.

In conclusion, in a comparison between TAVR and surgical replacement in patients with symptomatic, severe aortic stenosis at intermediate risk for surgery, TAVR was a statistically noninferior alternative to surgery with respect to death from any cause or disabling stroke at 24 months. However, each procedure had a different pattern of adverse events.

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APPENDIX

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REFERENCES

1. Popma JJ, Adams DH, Reardon MJ, et al. Transcatheter aortic valve replacement using a self-expanding bioprosthesis in patients with severe aortic stenosis at extreme risk for surgery. J Am Coll Cardiol 2014;63:1972-81.
2. Adams DH, Popma JJ, Reardon MJ, et al. Transcatheter aortic-valve replacement with a self-expanding prosthesis. N Engl J Med 2014;370:1790-8.
3. Reardon MJ, Adams DH, Kleiman NS, et al. 2-Year outcomes in patients under-

going surgical or self-expanding transcatheter aortic valve replacement. J Am Coll Cardiol 2015;66:113-21.
4. Deeb GM, Reardon MJ, Chetcuti S, et al. 3-Year outcomes in high-risk patients who underwent surgical or transcatheter aortic valve replacement. J Am Coll Cardiol 2016;67:2565-74.
5. Holmes DR Jr, Nishimura RA, Grover FL, et al. Annual outcomes with transcatheter valve therapy: from the STS/ACC TVT Registry. Ann Thorac Surg 2016;101:789-800.
6. Piazza N, Kalesan B, van Mieghem N, et al. A 3-center comparison of 1-year mortality outcomes between transcatheter aortic valve implantation and surgical aortic valve replacement on the basis of propensity score matching among intermediate-risk surgical patients. JACC Cardiovasc Interv 2013;6:443-51.
7. Iturra SA, Suri RM, Greason KL, et al. Outcomes of surgical aortic valve replacement in moderate risk patients: implications for determination of equipoise in the transcatheter era. J Thorac Cardiovasc Surg 2014;147:127-32.
8. Tamburino C, Barbanti M, D'Errigo P, et al. 1-Year outcomes after transfemoral transcatheter or surgical aortic valve replacement: results from the Italian OBSERVANT study. J Am Coll Cardiol 2015;66:804-12.
9. Leon MB, Smith CR, Mack MJ, et al. Transcatheter or surgical aortic-valve replacement in intermediate-risk patients. N Engl J Med 2016;374:1609-20.
10. Kappetein AP, Head SJ, Généreux P, et al. Updated standardized endpoint definitions for transcatheter aortic valve implantation: the Valve Academic Research Consortium-2 consensus document. J Thorac Cardiovasc Surg 2013;145:6-23.
11. Arnold SV, Reynolds MR, Wang K, et al. Health status after transcatheter or surgical aortic valve replacement in patients with severe aortic stenosis at increased surgical risk: results from the CoreValve US Pivotal Trial. JACC Cardiovasc Interv 2015;8:1207-17.
12. Leon MB, Smith CR, Mack M, et al. Transcatheter aortic-valve implantation for aortic stenosis in patients who cannot undergo surgery. N Engl J Med 2010;363:1597-607.
13. Smith CR, Leon MB, Mack MJ, et al. Transcatheter versus surgical aortic-valve replacement in high-risk patients. N Engl J Med 2011;364:2187-98.
14. Siontis GC, Praz F, Pilgrim T, et al. Transcatheter aortic valve implantation vs. surgical aortic valve replacement for treatment of severe aortic stenosis: a meta-analysis of randomized trials. Eur Heart J 2016;37:3503-12.
15. Guadiani V, Deeb GM, Popma JJ, et al. Causes of death in the randomized CoreValve US Pivotal High-Risk Trial. J Thorac Cardiovasc Surg 2017 February 4 (Epub ahead of print).
16. O'Brien SM, Shahian DM, Filardo G, et al. The Society of Thoracic Surgeons 2008 cardiac surgery risk models: part 2 — isolated valve surgery. Ann Thorac Surg 2009;88:Suppl:S23-S42.
17. Green P, Woglom AE, Genereux P, et al. The impact of frailty status on survival after transcatheter aortic valve replacement in older adults with severe aortic stenosis: a single-center experience. JACC Cardiovasc Interv 2012;5:974-81.
18. Hermiller JB Jr, Yakubov SJ, Reardon MJ, et al. Predicting early and late mortality after transcatheter aortic valve replacement. J Am Coll Cardiol 2016;68:343-52.
19. Popma JJ, Reardon MJ, Khabbaz K, et al. Early clinical outcomes after transcatheter aortic valve replacement using a novel self-expanding bioprosthesis in patients with severe aortic stenosis who are suboptimal for surgery: results of the Evolut R U.S. Study. JACC Cardiovasc Interv 2017;10:268-75.
20. Manoharan G, Walton AS, Brecker SJ, et al. Treatment of symptomatic severe aortic stenosis with a novel resheathable supra-annular self-expanding transcatheter aortic valve system. JACC Cardiovasc Interv 2015;8:1359-67.