ORIGINAL ARTICLE

Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients

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ABSTRACT

BACKGROUND

Transcatheter aortic-valve replacement (TAVR) is an alternative to surgery in patients with severe aortic stenosis who are at increased risk for death from surgery; less is known about TAVR in low-risk patients.

METHODS

We performed a randomized noninferiority trial in which TAVR with a self-expanding supraannular bioprosthesis was compared with surgical aortic-valve replacement in patients who had severe aortic stenosis and were at low surgical risk. When 850 patients had reached 12-month follow-up, we analyzed data regarding the primary end point, a composite of death or disabling stroke at 24 months, using Bayesian methods.

RESULTS

Of the 1468 patients who underwent randomization, an attempted TAVR or surgical procedure was performed in 1403. The patients' mean age was 74 years. The 24-month estimated incidence of the primary end point was 5.3% in the TAVR group and 6.7% in the surgery group (difference, −1.4 percentage points; 95% Bayesian credible interval for difference, −4.9 to 2.1; posterior probability of noninferiority >0.999). At 30 days, patients who had undergone TAVR, as compared with surgery, had a lower incidence of disabling stroke (0.5% vs. 1.7%), bleeding complications (2.4% vs. 7.5%), acute kidney injury (0.9% vs. 2.8%), and atrial fibrillation (7.7% vs. 35.4%) and a higher incidence of moderate or severe aortic regurgitation (3.5% vs. 0.5%) and pacemaker implantation (17.4% vs. 6.1%). At 12 months, patients in the TAVR group had lower aortic-valve gradients than those in the surgery group (8.6 mm Hg vs. 11.2 mm Hg) and larger effective orifice areas (2.3 cm^2 vs. 2.0 cm^2).

CONCLUSIONS

In patients with severe aortic stenosis who were at low surgical risk, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the composite end point of death or disabling stroke at 24 months. (Funded by Medtronic; ClinicalTrials.gov number, NCT02701283.)

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*A complete list of investigators, institutions, and research personnel participating in the Evolut Low Risk Trial is provided in the Supplementary Appendix, available at NEJM.org.

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In previous studies, we have shown that transcatheter aortic-valve replacement (TAVR) with the use of a self-expanding supraannular bioprosthesis is superior to medical therapy or surgery in patients with severe, symptomatic aortic stenosis who are at prohibitive or high risk for complications or death from surgery[1-3] and is a noninferior approach in patients deemed to be at intermediate surgical risk.[4,5] Societal guidelines have endorsed the use of TAVR in patients who are at increased risk for complications or death from surgery,[6,7] and the expanded use of TAVR in the United States is closely monitored.[8] The number of TAVR procedures performed in the United States has now surpassed the number of isolated surgical aortic-valve replacements.[9]

Use of TAVR in patients at low surgical risk requires compelling evidence of safety and effectiveness, given the low mortality and stroke incidence with aortic-valve surgery in relatively young, healthy patients.[9] Other outcomes, such as aortic-valve reintervention, coronary-artery obstruction, permanent pacemaker use, and longer-term valve durability, are metrics that also require scrutiny in this population. One small randomized study of TAVR with a self-expanding bioprosthesis as compared with surgery provides support for the safety of TAVR with a self-expanding bioprosthesis in low-risk patients up to 5 years after the procedure.[10,11]

The purpose of the current trial (Evolut Surgical Replacement and Transcatheter Aortic Valve Implantation in Low Risk Patients) was to evaluate the safety and effectiveness of TAVR with a self-expanding bioprosthesis as compared with surgical aortic-valve replacement in patients deemed to have a low risk of death with surgery.

Methods

Trial Design

This study was a multinational, randomized, noninferiority clinical trial comparing the safety and efficacy of TAVR with those of surgery in patients with severe aortic stenosis who were deemed to be at low risk for death at 30 days with surgery. The trial was conducted in compliance with the International Conference on Harmonisation and the Declaration of Helsinki. Patients were enrolled at 86 centers in Australia, Canada, France, Japan, the Netherlands, New Zealand, and the United States (Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org). Local institutional review boards or medical ethics committees approved the protocol, available at NEJM.org.

Medtronic funded the trial and developed the protocol in collaboration with the executive committee (see Table S2 in the Supplementary Appendix for members of committees). Medtronic was responsible for site selection, data monitoring, and trial management. Paradigm Biostatistics performed the Bayesian end-point comparisons; an independent statistical consultant validated all end-point analyses. An independent data and safety monitoring board provided study oversight.

The principal investigators (the first and last authors) wrote the first draft of the manuscript; all the authors critically reviewed it, made revisions, and supported the decision to submit the manuscript for publication. The authors attest that the trial was performed according to the protocol and vouch for the accuracy and completeness of the data.

Patient Selection

Eligible patients had severe aortic-valve stenosis with suitable anatomy for TAVR or surgery and no more than a predicted 3% risk of death by 30 days with surgery, as assessed by members of the local heart team. Aortic stenosis was defined as an aortic-valve area of 1.0 cm^2 or less (or aortic-valve area index of ≤0.6 cm^2 per square meter) or a mean gradient of 40 mm Hg or more or maximal aortic-valve velocity of 4.0 m or more per second as assessed by transthoracic echocardiography performed with the patient at rest. A detailed list of inclusion and exclusion criteria, including criteria for inclusion of asymptomatic patients, is provided in Table S3 in the Supplementary Appendix. The screening committee confirmed all decisions regarding patient selection (see the Methods section in the Supplementary Appendix). All patients provided written informed consent.

Study Procedures

Randomization was performed in a 1:1 ratio, with variable block sizes, with an electronic randomization system. Randomization was stratified by site and the need for coronary-artery revascularization. Patients assigned to TAVR were treated with one of three self-expanding, supraannular bioprostheses (CoreValve, Evolut R, or Evolut PRO;

Medtronic) (Fig. S1 in the Supplementary Appendix). The size and type of surgical valve were at the discretion of the surgeon, although candidates for mechanical valves were excluded. Patients were evaluated at baseline, at discharge, and at 1, 6, 12, 18, and 24 months after the procedure. All echocardiographic studies were assessed at an independent core laboratory (Mayo Clinic). Health-related quality of life was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). KCCQ summary scores range from 0 to 100, with higher scores indicating better health status; scores higher than 60 correlate with New York Heart Association (NYHA) class I or II, and a 10-point increase corresponds to moderate clinical improvement.[12,13]

STUDY END POINTS

The primary safety and effectiveness end point was a composite of death from any cause or disabling stroke at 24 months. Disabling stroke was defined by a score on the modified Rankin scale of 2 or more (with scores ranging from 0 [no symptoms] to 6 [death]) at 90 days and an increase of at least 1 category from baseline (i.e., before the stroke). There were seven prespecified secondary end points that were tested hierarchically for either noninferiority or superiority (see the Hierarchical Testing section in the Supplementary Appendix). Additional secondary safety end points included a composite of death, disabling stroke, life-threatening bleeding, major vascular complication, or stage 2 or 3 acute kidney injury at 30 days; and prosthetic-valve endocarditis, prosthetic-valve thrombosis, prosthetic-valve dysfunction requiring a repeat procedure, stroke, and life-threatening bleeding at 12 months. The full list of secondary end points is provided in the Methods section in the Supplementary Appendix.

An independent academic clinical-events committee (Baim Institute for Clinical Research, Boston) adjudicated all end points, using standard definitions (Table S4 in the Supplementary Appendix). End-point adjudication was blinded when feasible (for some end points, knowledge of treatment assignment was inherent in the end-point assessment).

STATISTICAL ANALYSIS

This trial used Bayesian adaptive statistical methods with noninformative prior distributions to assess the primary end point. We hypothesized that TAVR would be noninferior to surgery with respect to the primary end point with a noninferiority margin of 6%. The primary end point was to be tested for the superiority of TAVR to surgery if the primary objective (noninferiority with respect to the primary end point) and all seven prespecified hierarchical secondary objectives met their designated success criterion (in the hierarchical testing order). The prespecified success criteria were a posterior probability greater than 0.972 for noninferiority and greater than 0.984 for superiority, criteria that were selected empirically through extensive simulations to achieve a type I error rate of no more than 0.05 for noninferiority testing and no more than 0.025 for superiority testing.

The estimated sample size of 1200 patients was selected on the basis of an assumed 15% incidence of death or disabling stroke at 24 months; 1468 patients were ultimately enrolled to permit completion of a randomized substudy of valve leaflet immobility and thrombosis and to meet Japanese regulatory requirements. A prespecified Bayesian interim analysis was to be performed 12 months after the 850th patient underwent the study procedure (see the Methods section in the Supplementary Appendix). For patients who did not complete 24 months of follow-up, we imputed their outcome according to a prespecified statistical model, which was based on the patient's last known clinical status. A sensitivity analysis was performed to account for missing data, including data for the patients who were lost to follow-up or withdrew from the study.

The primary analysis cohort was the as-treated population, which comprised patients who were randomly assigned to a group and who underwent an attempted procedure. Secondary analyses of the primary end point were also performed in the intention-to-treat population, the "implanted" population (patients in whom an aortic valve was implanted), and the per-protocol population. Details regarding the primary objective, analysis populations, sensitivity analyses, and hierarchical testing methods among secondary end points 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 with a noninformative prior distribution. Event rates are summarized as Bayesian posterior medians with 95% credible intervals, which were calculated from the 2.5th and 97.5th percentiles

of the posterior distributions. The Bayesian credible intervals for secondary end points use marginal posterior distributions that are probably narrower than those that are based on a true multidimensional posterior for the collection of outcomes. Caution should therefore be exercised in drawing inferences about absolute treatment effects with the 95% Bayesian credible intervals, owing to the multiplicity of secondary end-point comparisons.

RESULTS

BASELINE CHARACTERISTICS

From March 28, 2016, to November 27, 2018, a total of 1468 patients underwent randomization; 734 were assigned to TAVR and 734 were assigned to surgery. After randomization, the assigned procedure was not attempted in 12 patients assigned to TAVR and 53 patients assigned to surgery; in 3 patients assigned to surgery, TAVR was attempted instead (Fig. S2 and Results section in the Supplementary Appendix). The as-treated cohort included 1403 patients: 725 in the TAVR group and 678 in the surgery group.

Demographic and baseline characteristics and cardiac risk factors are shown in Table 1. The mean age of the patients was 74 years, 34.9% were women, and all the patients were at low surgical risk. There were no significant differences between the two treatment groups. Among patients who were assigned to the surgery group, the baseline characteristics of those who actually underwent surgery were similar to the characteristics of those who did not undergo surgery (Table S5 in the Supplementary Appendix). A detailed description of procedural end points is provided in the Results section in the Supplementary Appendix.

At this prespecified interim analysis, 12-month follow-up was available for 432 patients in the TAVR group and 352 in the surgery group; 24-month follow-up was available for 72 patients in the TAVR group and 65 patients in the surgery group. The median follow-up time in each group was 12.2 months.

PRIMARY SAFETY AND EFFECTIVENESS END POINT

The incidence of death or disabling stroke at 24 months (the primary end point) was 5.3% in the TAVR group (95% Bayesian credible interval, 3.3 to 8.0) and 6.7% in the surgery group (95% Bayesian credible interval, 4.4 to 9.6). The prespecified criterion for noninferiority was met (difference, −1.4 percentage points; 95% Bayesian credible interval for the difference, −4.9 to 2.1; posterior probability of noninferiority, >0.999) (Fig. 1); the prespecified criterion for superiority was not met (posterior probability of superiority, 0.779). A noninferiority analysis using the intention-to-treat cohort yielded similar results. A sensitivity analysis that was performed to account for patients who were lost to follow-up also had similar results (details on these analyses are provided in Tables S6 through S8 and the Methods section in the Supplementary Appendix).

The 24-month estimated incidence of death from any cause was 4.5% in the TAVR group and 4.5% in the surgery group (difference, 0 percentage points; 95% credible interval for the difference, −3.2 to 3.2). The 24-month estimated incidence of disabling stroke was 1.1% in the TAVR group and 3.5% in the surgery group (difference, −2.3 percentage points; 95% credible interval for the difference, −4.8 to −0.4). No significant treatment-by-subgroup interactions were noted for the primary end point (Fig. S3 in the Supplementary Appendix).

SECONDARY SAFETY MEASURES

The incidence of the secondary composite safety end point at 30 days was 5.3% in the TAVR group and 10.7% in the surgery group (Table 2). The incidence of death from any cause at 30 days was 0.5% in the TAVR group and 1.3% in the surgery group; causes of death are shown in Table S9 in the Supplementary Appendix. The ratio of observed to expected incidence of death from any cause by 30 days (with expected risk calculated on the basis of the Society of Thoracic Surgeons Predicted Risk of Mortality [STS-PROM] model) was 0.26 in the TAVR group and 0.68 in the surgery group. New atrial fibrillation at 30 days occurred in 7.7% of the patients in the TAVR group and in 35.4% in the surgery group (difference, −27.7 percentage points; credible interval for the difference, −31.8 to −23.6), whereas permanent pacemaker implantation occurred in 17.4% of the patients in the TAVR group and in 6.1% in the surgery group (difference, 11.3 percentage points; credible interval for the difference, 8.0 to 14.7) (Table 2). Incidences of stroke, prosthetic-valve thrombosis, endocarditis, and reintervention were similar in the two groups at 12 months.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	As-Treated Analysis		Intention-To-Treat Analysis	
	TAVR (N=725)	Surgery (N=678)	TAVR (N=734)	Surgery (N=734)
Age — yr	74.1±5.8	73.6±5.9	74.0±5.9	73.8±6.0
Female sex — no. (%)	261 (36.0)	229 (33.8)	266 (36.2)	246 (33.5)
NYHA class — no. (%)				
I	76 (10.5)	63 (9.3)	77 (10.5)	73 (9.9)
II	467 (64.4)	422 (62.2)	476 (64.9)	456 (62.1)
III	181 (25.0)	190 (28.0)	180 (24.5)	202 (27.5)
IV	1 (0.1)	3 (0.4)	1 (0.1)	3 (0.4)
STS-PROM — %†	1.9±0.7	1.9±0.7	1.9±0.7	1.9±0.7
Diabetes mellitus — no. (%)	228 (31.4)	207 (30.5)	228 (31.1)	224 (30.5)
Serum creatinine >2 mg/dl — no. (%)	3 (0.4)	1 (0.1)	3 (0.4)	1 (0.1)
Dialysis — no. (%)	0	1 (0.1)	0	1 (0.1)
Hypertension — no./total no. (%)	614/724 (84.8)	559/677 (82.6)	622/733 (84.9)	608/733 (82.9)
Peripheral arterial disease — no./total no. (%)	54/718 (7.5)	56/678 (8.3)	55/727 (7.6)	62/733 (8.5)
Cerebrovascular disease — no. (%)	74 (10.2)	80 (11.8)	74 (10.1)	84 (11.4)
Chronic obstructive pulmonary disease — no./total no. (%)	104/695 (15.0)	117/649 (18.0)	106/703 (15.1)	121/703 (17.2)
Cardiac risk factors				
SYNTAX score‡	1.9±3.7	2.1±3.9	1.9±3.7	2.1±3.8
Previous coronary-artery bypass surgery — no. (%)	18 (2.5)	14 (2.1)	18 (2.5)	17 (2.3)
Previous percutaneous coronary intervention — no. (%)	103 (14.2)	87 (12.8)	102 (13.9)	93 (12.7)
Preexisting pacemaker or defibrillator — no. (%)	23 (3.2)	26 (3.8)	25 (3.4)	28 (3.8)
Previous myocardial infarction — no. (%)	48 (6.6)	33 (4.9)	49 (6.7)	39 (5.3)
Previous atrial fibrillation or atrial flutter — no./total no. (%)	111/722 (15.4)	98/678 (14.5)	113/731 (15.5)	109/734 (14.9)
Aortic-valve gradient — mm Hg§	47.0±12.1	46.6±12.2	47.2±12.3	46.7±12.2
Aortic-valve area — cm^2§	0.8±0.2	0.8±0.2	0.8±0.2	0.8±0.2
Left ventricular ejection fraction — %§	61.7±7.9	61.9±7.7	61.7±7.9	61.9±7.7

* Plus–minus values are means ±SD. There were no significant differences between the treatment groups. Percentages may not total 100 because of rounding. To convert the values for serum creatinine to micromoles per liter, multiply by 88.4. NYHA denotes New York Heart Association, and TAVR transcatheter aortic-valve replacement.
† The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) provides an estimate of the risk of death at 30 days among patients undergoing surgical aortic-valve replacement on the basis of several demographic and procedural variables.
‡ The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score is a measure of the severity and extent of coronary artery disease. Low SYNTAX scores (<18) are associated with a higher success rate with PCI, scores between 18 and 27 with an intermediate success rate, and scores higher than 27 with a low success rate.
§ These data were reported by the individual trial site.

SECONDARY EFFECTIVENESS MEASURES

Results of hierarchical analyses of the secondary effectiveness end points are provided in Table 3; all these end points met the prespecified test threshold. Symptoms graded by NYHA class decreased significantly from baseline in both groups, and this reduction in symptoms persisted throughout the 12-month follow-up period (Fig. S4 in the Supplementary Appendix). Hospitalization for heart failure during the 12-month follow-up period occurred in 3.2% of the patients in the TAVR group and in 6.5% in the surgery group (difference, −3.4 percentage points; 95% credible interval for the difference, −5.9 to −1.0). The KCCQ overall summary score (±SD) measuring quality of life was 88.7±14.2 in the TAVR group

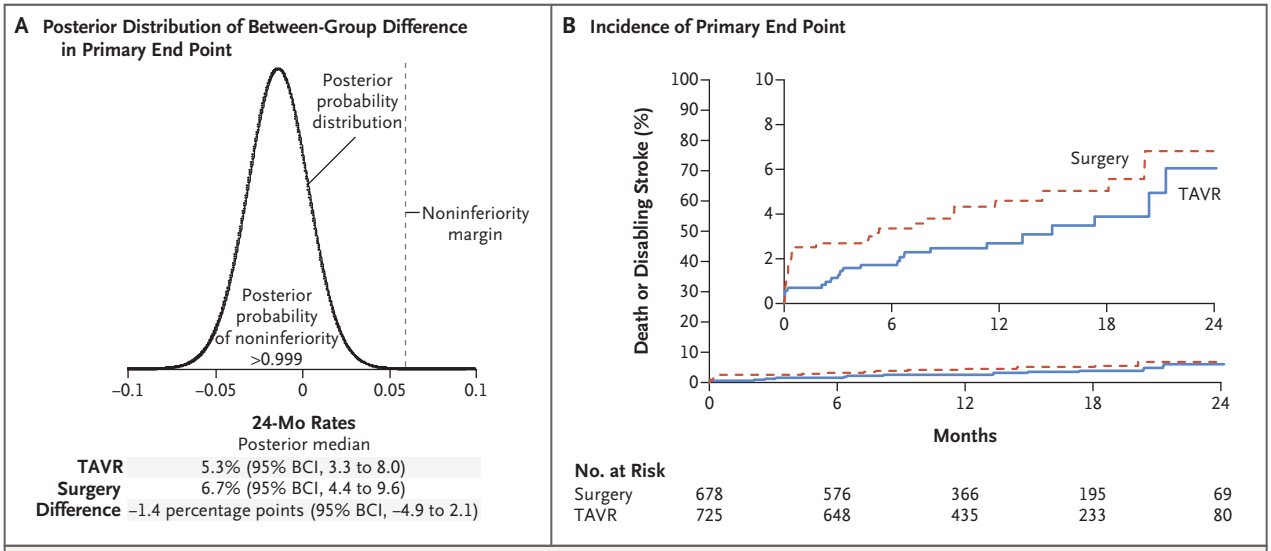


Figure 1. Posterior Distribution and Time-to-Event Curves for the Primary End Point.

The posterior distribution for the difference between the treatment groups in the incidence of death from any cause or disabling stroke at 24 months (the primary end point), shown in Panel A, confirmed that the noninferiority criterion for the primary end point was met. BCI denotes Bayesian credible interval, and TAVR transcatheter aortic-valve replacement. Panel B shows Kaplan–Meier time-to-event curves for the primary end point. The inset shows the same data on an enlarged y axis.

and 78.6±18.9 in the surgery group at 30 days, with no difference between groups observed at 12 months (Table S10 in the Supplementary Appendix). Among patients who were discharged from the hospital after undergoing TAVR, there was no significant difference in the incidence of death by 12 months between those who received a new permanent pacemaker and those who did not (3.4% and 1.2%, respectively).

ECHOCARDIOGRAPHIC FINDINGS

Aortic-valve hemodynamics improved from baseline in both groups (Fig. 2). Mean aortic-valve gradients were lower at 12 months in the TAVR group than in the surgery group; the mean effective orifice area was larger in the TAVR group than in the surgery group (Table 3). Moderate or severe total aortic regurgitation was present at 30 days in 3.5% of the patients in the TAVR group and in 0.5% in the surgery group. Severe patient–prosthesis mismatch occurred at 12 months in 1.8% of the patients in the TAVR group and in 8.2% in the surgery group (Table S11 in the Supplementary Appendix).

DISCUSSION

Our study, which used an adaptive Bayesian design, showed that among patients deemed to be at a low risk for death from surgery, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgery with respect to the risk of death or disabling stroke at 24 months. TAVR with a self-expanding supraannular bioprosthesis was associated with a lower incidence of disabling stroke, acute kidney injury, bleeding events, and atrial fibrillation than surgery but with a higher incidence of aortic regurgitation and permanent pacemaker use. Both TAVR and surgery provided functional improvement at 12 months, but the TAVR group had better recovery at 30 days, as indicated by the KCCQ score.

Our study group has conducted a series of clinical studies that have compared TAVR with a self-expanding supraannular bioprosthesis with surgery in patients at various degrees of surgical risk.[2,5,14] The current interim analysis includes patients at the lowest reported risk from surgery among these trials (mean STS-PROM, 1.9%). The 30-day incidence of death in both groups was very low (0.5% in the TAVR group and 1.3% in the surgery group) with a low ratio of observed-to-expected incidence of death in both groups (0.26 in the TAVR group and 0.68 in the surgery group), a finding that is probably attributable to the use of best practices by our heart teams. We selected the primary end point of death from any cause or disabling stroke at 24 months owing to

Table 2. Clinical End Points at 30 Days and at 12 Months.*

End Point	30 Days			12 Months		
	TAVR	Surgery	Difference, TAVR–Surgery (95% BCI)	TAVR	Surgery	Difference, TAVR–Surgery (95% BCI)
	% of patients		*percentage points*	*% of patients*		*percentage points*
Death from any cause or disabling stroke	0.8	2.6	–1.8 (–3.2 to –0.5)	2.9	4.6	–1.8 (–4.0 to 0.4)
Death from any cause	0.5	1.3	–0.8 (–1.9 to 0.2)	2.4	3.0	–0.6 (–2.6 to 1.3)
Death from cardiovascular cause	0.5	1.3	–0.8 (–1.9 to 0.2)	1.7	2.6	–0.9 (–2.7 to 0.7)
All stroke	3.4	3.4	0.0 (–1.9 to 1.9)	4.1	4.3	–0.2 (–2.4 to 1.9)
Disabling	0.5	1.7	–1.2 (–2.4 to –0.2)	0.8	2.4	–1.6 (–3.1 to –0.3)
Nondisabling	3.0	1.7	1.2 (–0.3 to 2.9)	3.4	2.2	1.1 (–0.6 to 2.9)
Transient ischemic attack	0.6	0.8	–0.2 (–1.2 to 0.7)	1.7	1.8	–0.2 (–1.6 to 1.3)
30-Day composite safety end point†	5.3	10.7	–5.4 (–8.3 to –2.6)	NA	NA	NA
Life-threatening or disabling bleeding	2.4	7.5	–5.1 (–7.5 to –2.9)	3.2	8.9	–5.7 (–8.4 to –3.1)
Major vascular complication	3.8	3.2	0.6 (–1.4 to 2.5)	3.8	3.5	0.3 (–1.7 to 2.3)
Acute kidney injury stage 2 or 3	0.9	2.8	–1.8 (–3.4 to –0.5)	0.9	2.8	–1.8 (–3.4 to –0.5)
Atrial fibrillation	7.7	35.4	–27.7 (–31.8 to –23.6)	9.8	38.3	–28.5 (–32.8 to –24.1)
Permanent pacemaker implantation	17.4	6.1	11.3 (8.0 to 14.7)	19.4	6.7	12.6 (9.2 to 16.2)
Myocardial infarction	0.9	1.3	–0.4 (–1.5 to 0.7)	1.7	1.6	0.1 (–1.3 to 1.5)
Coronary-artery obstruction	0.9	0.4	0.5 (–0.3 to 1.4)	0.9	0.4	0.5 (–0.3 to 1.4)
Endocarditis	0.1	0.2	–0.1 (–0.7 to 0.3)	0.2	0.4	–0.2 (–0.9 to 0.5)
Valve thrombosis	0.1	0.1	0.0 (–0.4 to 0.4)	0.2	0.3	–0.1 (–0.9 to 0.5)
Aortic reintervention	0.4	0.4	0.0 (–0.8 to 0.7)	0.7	0.6	0.0 (–1.0 to 0.9)
Hospitalization for heart failure	1.2	2.5	–1.3 (–2.8 to 0.1)	3.2	6.5	–3.4 (–5.9 to –1.0)

* Values represent the estimated incidence (median of the posterior probability distribution as calculated by Bayesian analysis). Caution should be exercised regarding drawing inferences about absolute treatment effects with the 95% Bayesian credible interval (BCI), owing to multiple secondary end-point comparisons.
† The 30-day composite safety end point was a composite of death, disabling stroke, life-threatening bleeding, major vascular complication, or stage 2 or 3 acute kidney injury.

the implications of these results for patients and providers considering options for aortic-valve replacement. The estimated 24-month incidence of death from any cause was low (4.5%) in both groups, a finding that reinforced the fact that our study included healthier patients with severe aortic-valve disease.

Neurologic complications associated with aortic-valve replacement are increasingly recognized as critical outcome measures in studies comparing transcatheter and surgical procedures.[15,16] We performed functional neurologic assessments before and after both procedures; a very small number of patients (<2%) in the TAVR group received an embolic protection device (see the Supplementary Appendix). Although the incidence of stroke was similar in the two groups, disabling stroke by 30 days occurred less often in the TAVR group, and the incidence remained lower at 24 months; these findings are similar to those in previous randomized trials of TAVR involving patients at increased surgical risk.[2,4]

Although aortic-valve hemodynamics were substantially improved from baseline in both groups, we found lower aortic-valve gradients and larger aortic-valve areas in the TAVR group, findings that are probably related to the supraannular design of the self-expanding bioprostheses.[2,4,14,17-19] Although 22.1% of the patients in the surgery group received small (19-mm or 21-mm) prostheses, the mean aortic-valve areas were large (2.0 cm^2), and the incidence of 12-month severe prosthesis–patient mismatch (8.2%) was less than in previous reports.[20,21] Nonetheless, valve areas were larger, and the frequency of prosthesis–patient mismatch was lower, with TAVR. In contrast, rates of aortic

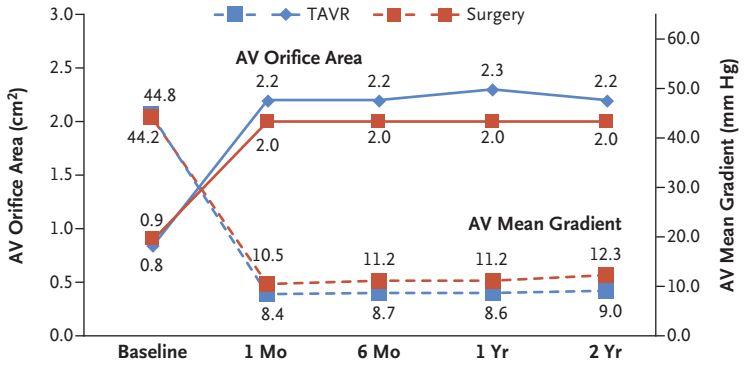
Table 3. Hierarchical Secondary Noninferiority and Superiority Objectives.*

Criterion	Hypothesis	Analysis Cohort	TAVR	Surgery	Difference, TAVR–Surgery	Posterior Probability	Threshold	Test Result
Noninferiority					(90% BCI)			
Mean gradient at 12 mo (mm Hg)	TAVR < [surgery+5 mm Hg]†	Implanted	8.6±3.7 (409)	11.2±4.9 (339)	−2.6 (−3.1 to −2.1)	>0.999	0.95	Passed
Mean effective orifice area at 12 mo (cm^2)	TAVR > [surgery−0.1 cm^2]†	Implanted	2.3±0.7 (341)	2.0±0.6 (293)	0.3 (0.2 to 0.4)	>0.999	0.95	Passed
Mean NYHA class change from baseline to 12 mo	TAVR > [surgery−0.375]†	As-treated	0.9±0.7 (428)	1.0±0.7 (342)	−0.1 (−0.2 to 0.0)	>0.999	0.95	Passed
Mean KCCQ change from baseline to 12 mo	TAVR > [surgery− 5 points]‡	As-treated	22.2±20.3 (428)	20.9±21.0 (347)	1.3 (−1.2 to 3.8)	>0.999	0.95	Passed
Superiority					(95% BCI)			
Mean gradient at 12 mo (mm Hg)	TAVR < surgery	Implanted	8.6±3.7 (409)	11.2±4.9 (339)	−2.6 (−3.2 to −2.0)	>0.999	0.975	Passed
Mean effective orifice area at 12 mo (cm^2)	TAVR > surgery	Implanted	2.3±0.7 (341)	2.0±0.6 (293)	0.3 (0.2 to 0.4)	>0.999	0.975	Passed
Mean KCCQ change from baseline to 30 days	TAVR > surgery	As-treated	20.0±21.1 (713)	9.1±22.3 (636)	10.9 (8.6 to 13.2)	>0.999	0.975	Passed

* Plus–minus values are means ±SD. The numbers of patients with data are in parentheses. All noninferiority objectives were tested with a type I error standard of 0.05, and superiority tests were tested with a type I error of 0.025. If all the tests met their success criterion, the primary end point of death or disabling stroke at 24 months was tested for superiority with type I error rate of 0.025.

† Clinically meaningful differences of 5 mm Hg for mean gradient, 0.1 cm^2 for effective orifice area, and 0.375 for the NYHA class were determined by the Low Risk Trial Executive Committee.

‡ Kansas City Cardiomyopathy Questionnaire (KCCQ) summary scores range from 0 to 100, with higher scores indicating better health status; scores higher than 60 correlate with NYHA class I or II, and a 10-point increase corresponds to moderate clinical improvement. An increase of 5 points was deemed to be clinically meaningful.[13]



No. of Patients with Echocardiographic Data

AV mean gradient					
TAVR	712	699	619	409	71
Surgery	673	634	542	339	62
AV orifice area					
TAVR	632	610	544	341	59
Surgery	590	541	467	293	53

Figure 2. Aortic-Valve Orifice Area and Mean Gradient to 24 Months.

Shown are the aortic-valve (AV) mean gradient (dashed lines) and the effective AV orifice area (solid lines) for the TAVR group and the surgery group at all time points after the procedure.

regurgitation were higher in the TAVR group. Longer-term follow-up will be necessary to understand the implications of these various valve characteristics on structural valve deterioration and long-term outcomes. We found a low incidence (<1%) of bioprosthetic-valve thrombosis, endocarditis, or need for aortic-valve reintervention with both self-expanding and surgical bioprostheses.

Our study has several limitations. The most important limitation is that this prespecified interim analysis occurred when 850 patients had reached 12 months of follow-up, and complete 24-month follow-up of the entire cohort has not been reached. Definitive conclusions regarding the advantages and disadvantages of TAVR as compared with surgery await long-term clinical and echocardiographic follow-up, which is planned to continue through 10 years for all patients. Second, although the amount of missing data in the trial was small, some patients did not have complete follow-up data on NYHA functional class, KCCQ scores, and echocardiography. Third, end-point adjudication could not be performed in a blinded manner for all end points, which may have resulted in bias in end-point assessment. Fourth, we excluded patients with bicuspid aortic valves and those who were candidates for mechanical valves. Finally, the latest-generation Evolut PRO bioprosthesis was used in only 22.3% of the patients who received TAVR.

In conclusion, in a randomized trial involving patients with severe aortic stenosis who were at low risk for death from surgery, TAVR with a self-expanding supraannular bioprosthesis was noninferior to surgical aortic-valve replacement with respect to death from any cause or disabling stroke at 24 months.

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APPENDIX

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