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Transcatheter Aortic-Valve Replacement for Asymptomatic Severe Aortic Stenosis

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ABSTRACT

BACKGROUND

For patients with asymptomatic severe aortic stenosis and preserved left ventricular ejection fraction, current guidelines recommend routine clinical surveillance every 6 to 12 months. Data from randomized trials examining whether early intervention with transcatheter aortic-valve replacement (TAVR) will improve outcomes in these patients are lacking.

METHODS

At 75 centers in the United States and Canada, we randomly assigned, in a 1:1 ratio, patients with asymptomatic severe aortic stenosis to undergo early TAVR with transfemoral placement of a balloon-expandable valve or clinical surveillance. The primary end point was a composite of death, stroke, or unplanned hospitalization for cardiovascular causes. Superiority testing was performed in the intention-to-treat population.

RESULTS

A total of 901 patients underwent randomization; 455 patients were assigned to TAVR and 446 to clinical surveillance. The mean age of the patients was 75.8 years, the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 1.8% (on a scale from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after surgery), and 83.6% of patients were at low surgical risk. A primary end-point event occurred in 122 patients (26.8%) in the TAVR group and in 202 patients (45.3%) in the clinical surveillance group (hazard ratio, 0.50; 95% confidence interval, 0.40 to 0.63; P<0.001). Death occurred in 8.4% of the patients assigned to TAVR and in 9.2% of the patients assigned to clinical surveillance, stroke occurred in 4.2% and 6.7%, respectively, and unplanned hospitalization for cardiovascular causes occurred in 20.9% and 41.7%. During a median follow-up of 3.8 years, 87.0% of patients in the clinical surveillance group underwent aortic-valve replacement. There were no apparent differences in procedure-related adverse events between patients in the TAVR group and those in the clinical surveillance group who underwent aortic-valve replacement.

CONCLUSIONS

Among patients with asymptomatic severe aortic stenosis, a strategy of early TAVR was superior to clinical surveillance in reducing the incidence of death, stroke, or unplanned hospitalization for cardiovascular causes. (Funded by Edwards Lifesciences; EARLY TAVR ClinicalTrials.gov number, NCT03042104.)

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*A complete list of the EARLY TAVR investigators is provided in the Supplementary Appendix, available at NEJM.org.

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Aortic stenosis affects more than 3% of adults 65 years of age or older.[1,2] Current guidelines include aortic-valve replacement as a class I recommendation for patients with symptomatic severe aortic stenosis and for patients with asymptomatic severe aortic stenosis and a left ventricular ejection fraction of less than 50%, a positive stress test, or other indications for open-heart surgery.[3,4] Clinical and echocardiographic follow-up every 6 to 12 months is recommended for patients with no symptoms or other indication for aortic-valve replacement. Previous retrospective studies[5-10] and two randomized trials[11,12] showed the benefits of early surgical aortic-valve replacement in patients with asymptomatic severe aortic stenosis. These trials included small sample sizes with younger patients, many with bicuspid or very severe aortic-valve disease.[11] Because of the lack of strong evidence supporting an early aortic-valve replacement strategy for patients with asymptomatic severe aortic stenosis, especially from studies examining the use of transcatheter aortic-valve replacement (TAVR), a randomized trial to reassess current approaches to guideline management is warranted.

Methods

Trial Design and Oversight

The trial design and rationale have been described previously.[13] The Evaluation of TAVR Compared to Surveillance for Patients with Asymptomatic Severe Aortic Stenosis (EARLY TAVR) trial is a prospective, multicenter, open-label, randomized, controlled trial in which TAVR with transfemoral placement of a balloon-expandable valve (SAPIEN 3 or SAPIEN 3 Ultra, Edwards Lifesciences) was compared with clinical surveillance among patients with asymptomatic severe aortic stenosis and indications for clinical surveillance according to current guidelines.[3] The protocol (available with the full text of this article at NEJM.org) was developed by the first and last authors, steering committee, and trial sponsor (Edwards Lifesciences) in conjunction with the Food and Drug Administration and was approved by the institutional review board at each site. A list of participating sites and investigators is provided in Section A in the Supplementary Appendix (available at NEJM.org). The sponsor funded all trial-related activities, participated in site selection, oversaw data collection and monitoring, and performed analyses according to the statistical analysis plan (available with the protocol). Primary and secondary end-point events and their components, as well as safety and effectiveness outcomes, were adjudicated by an independent clinical events committee whose members were aware of the treatment-group assignments. An independent data and safety monitoring board provided safety oversight for the trial. Echocardiographic assessments were evaluated at an independent core laboratory. The first two authors and the last author oversaw the trial conduct, prepared all drafts of the manuscript, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Patient Selection

Patients were eligible for enrollment if they were 65 years of age or older, had asymptomatic severe aortic stenosis with anatomy suitable for transfemoral TAVR, and provided written informed consent. Eligibility was assessed at each site by an independent, physician-led case review board. Patients with a Society of Thoracic Surgeons Predicted Risk of Mortality score greater than 10% (scores range from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after surgery), a left ventricular ejection fraction of less than 50%, or any other class I indication for aortic-valve replacement were excluded. A list of inclusion and exclusion criteria is available in Section B in the Supplementary Appendix. Asymptomatic status was determined by a negative treadmill stress test. If a patient was unable to perform the stress test (e.g., because of orthopedic limitations), eligibility was confirmed through a detailed physician assessment of the medical history.[13] The representativeness of the patient population is provided in Section C in the Supplementary Appendix.

Randomization, Treatment, and Follow-up

Eligible patients were enrolled and randomly assigned, in a 1:1 ratio, to clinical surveillance or early TAVR. All patients who underwent randomization were considered to be part of the intention-to-treat population. Patients who were assigned to the clinical surveillance group received standard care in accordance with American College of Cardiology and American Heart Association guidelines.[3] The cases of patients in the clini-

cal surveillance group in whom symptoms or other indications for aortic-valve replacement developed during follow-up were presented to a case review board, but the final decision to intervene was made by the treating physician and the patient. Patients in the early TAVR group underwent transfemoral TAVR. Patients in the clinical surveillance group who converted to aortic-valve replacement underwent transfemoral TAVR or another aortic-valve replacement strategy, as indicated. Clinical and echocardiographic assessments were planned through 5 years. Patients were assessed for a minimum of 2 years during the period of data collection for this analysis. Additional details are provided in Section D in the Supplementary Appendix.

TRIAL END POINTS

The primary end point was a composite of death from any cause, stroke, or unplanned hospitalization for cardiovascular causes. Any aortic-valve intervention in the clinical surveillance group (including conversion to aortic-valve replacement) within 6 months after randomization or aortic-valve reintervention in the TAVR group within 6 months after the trial procedure was considered for the purposes of the primary end-point analysis to be an unplanned hospitalization for cardiovascular causes. The 6-month time interval was chosen to reflect the earliest recommended time point for routine follow-up according to current guidelines. Additional details are provided in Section E in the Supplementary Appendix.

There were five prespecified secondary end points. The first was a favorable outcome at 2 years, defined as being alive with a Kansas City Cardiomyopathy Questionnaire (KCCQ) score of at least 75 (scores range from 0 to 100, with higher scores indicating fewer physical limitations and a greater feeling of wellness) that had not decreased more than 10 points from baseline. If a patient in the clinical surveillance group had an aortic-valve intervention within 6 months after randomization, the preprocedure KCCQ score was used; similarly, if a patient in the TAVR group had an aortic-valve reintervention within 6 months after the procedure, the 30-day KCCQ score was used. The second prespecified secondary end point was a composite of integrated measures of left ventricular and left atrial health at 2 years, defined as an absolute left ventricular global longitudinal strain of at least 15%, a left ventricular mass index of less than 115 g per square meter of body-surface area for men or less than 95 g per square meter for women, and a left atrial volume index of 34 ml per square meter or less. The last three prespecified secondary end points were a change in left ventricular ejection fraction from baseline to 2 years, new-onset atrial fibrillation, and a composite of death or disabling stroke. Additional details are provided in Section F in the Supplementary Appendix. Prespecified subgroup analyses, details regarding signs and symptoms at the time of conversion to aortic-valve replacement in the clinical surveillance group, and additional analyses, including an exploratory analysis of the primary end point that focused on advanced signs and symptoms of heart failure (e.g., New York Heart Association class III or IV symptoms), are described in Sections G, H, and I in the Supplementary Appendix. Functional status was assessed with the use of the 6-minute walk test, and the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was analyzed by a biomarker core laboratory.

STATISTICAL ANALYSIS

We estimated that a sample size of 900 patients with at least 271 events would provide the trial with at least 85% power to show the superiority of early TAVR over clinical surveillance with respect to the primary end point, at a two-sided alpha level of 0.05, assuming 10% attrition and assuming that the difference between the groups in the incidence of events at 2 years would be at least 7 percentage points.[13] The primary end point was evaluated in the intention-to-treat population with the use of all data available during follow-up and was compared between the TAVR group and the clinical surveillance group with the use of a log-rank test. We specified that if the two-sided P value for the primary end point would be less than 0.05, secondary end points would then be tested in the intention-to-treat population in a hierarchical order with the use of a gatekeeping approach (for the first through third secondary end points) and the Hochberg method (for the fourth and fifth secondary end points) to account for multiple comparisons. Additional details regarding the analysis populations, end points, and sensitivity analyses are provided in the statistical analysis plan.

Results of time-to-first-event analyses are reported as event counts (the percentage of patients

with an event) from the time of randomization and are presented with the use of Kaplan–Meier curves. Hazard ratios and 95% confidence intervals were calculated with the use of a Cox proportional-hazards model to examine the treatment effect size. The proportional-hazards assumption was tested with the use of a Cox proportional-hazards model that included an interaction term between treatment and time. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing. To address missing data, time-to-event analyses assumed noninformative censoring, and other analyses were based on observed data without imputation of missing data. All statistical analyses were performed with the use of SAS software, version 9.4 (SAS Institute).

RESULTS

PATIENTS

From March 2017 through December 2021, a total of 1578 patients consented to undergo screening, and 901 patients underwent randomization at 75 sites in the United States and Canada (Fig. S1 in the Supplementary Appendix). The most common reasons for not undergoing randomization were symptomatic severe aortic stenosis and exclusion for anatomical reasons. Asymptomatic status was confirmed with a treadmill stress test in 816 patients (90.6%), whereas 85 patients (9.4%) were categorized as asymptomatic on the basis of medical history only. Details regarding treadmill stress tests are provided in Table S1. A total of 455 patients were randomly assigned to undergo TAVR and 446 were assigned to clinical surveillance. Among the patients assigned to TAVR, the median time to the procedure was 14 days (interquartile range, 9 to 24).

Baseline characteristics appeared to be balanced between the two groups (Table 1 and Tables S2 and S3). The mean age of the patients was 75.8 years, 30.9% were women, the mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 1.8%, and 83.6% of patients were considered to be at low surgical risk as evaluated by the local heart team. The severity of aortic stenosis was similar in the two groups (mean peak velocity of 4.3 m per second), and the mean left ventricular ejection fraction was 67.4%. A bicuspid aortic valve was present in 8.4% of patients, and the mean KCCQ score was 92.7 in both groups.

PRIMARY END POINT

The median follow-up time was 3.8 years (interquartile range, 2.8 to 5.0), and 442 patients (97.1%) in the TAVR group and 435 (97.5%) in the clinical surveillance group had available data for the primary end-point analysis. Death from any cause, stroke, or unplanned hospitalization for cardiovascular causes (the composite primary end point) occurred in 122 patients (26.8%) in the TAVR group as compared with 202 patients (45.3%) in the clinical surveillance group (hazard ratio, 0.50; 95% confidence interval [CI], 0.40 to 0.63; P<0.001). The Kaplan–Meier estimates of the primary end point are shown in Figure 1A.

Results for the individual components of the primary end point are shown in Figure 1B, 1C, and 1D (as Kaplan–Meier estimates) and in Table 2. Death from any cause occurred in 38 patients (8.4%) in the TAVR group and in 41 (9.2%) in the clinical surveillance group; among these deaths, 47.4% and 56.1%, respectively, were from cardiovascular causes. Kaplan–Meier estimates of death from cardiovascular and noncardiovascular causes are shown in Figure S2, and details regarding the causes of death are presented in Table S4. There were 11 deaths (6 from cardiovascular causes, including 3 sudden deaths) in the clinical surveillance group that occurred before conversion to aortic-valve replacement, 2 of which occurred within 6 months after randomization. Stroke occurred in 19 patients (4.2%) in the TAVR group and in 30 patients (6.7%) in the clinical surveillance group, and unplanned hospitalization for cardiovascular causes occurred in 95 patients (20.9%) and 186 patients (41.7%), respectively. In the clinical surveillance group, 105 conversions to aortic-valve replacement within 6 months after randomization were included as unplanned hospitalizations for cardiovascular causes. Primary end-point results appeared to be consistent across all prespecified subgroups (Fig. S3).

SECONDARY END POINTS

The results of prespecified, hierarchical testing for secondary end points are shown in Table 2. A favorable outcome at 2 years (defined as being alive and having a KCCQ score of at least 75 that

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	TAVR (N=455)	Clinical Surveillance (N=446)
Age — yr	76.0±6.0	75.6±6.0
Female sex — no. (%)	131 (28.8)	147 (33.0)
Race — no. (%)†		
White	436 (95.8)	422 (94.6)
Black	9 (2.0)	11 (2.5)
Asian	7 (1.5)	9 (2.0)
Multiple or unknown	3 (0.7)	4 (0.9)
Hispanic or Latino ethnic group†	11 (2.4)	9 (2.0)
Body-mass index‡	28.4±4.6	28.6±4.8
STS-PROM score — %§	1.8±1.0	1.7±1.0
Able to perform treadmill stress test — no. (%)¶	411 (90.3)	405 (90.8)
KCCQ score‖	92.7±8.7	92.7±9.4
Hyperlipidemia — no. (%)	375 (82.4)	347 (77.8)
Hypertension — no. (%)	369 (81.1)	365 (81.8)
Diabetes — no. (%)	119 (26.2)	114 (25.6)
Previous myocardial infarction — no. (%)	23 (5.1)	18 (4.0)
Previous stroke — no. (%)	19 (4.2)	20 (4.5)
Peripheral vascular disease — no. (%)	33 (7.3)	21(4.7)
Coronary artery disease — no. (%)	133 (29.2)	113 (25.3)
History of atrial fibrillation — no. (%)	71 (15.6)	59 (13.2)
Permanent pacemaker or ICD — no. (%)	21 (4.6)	9 (2.0)
Chronic obstructive pulmonary disease — no. (%)	13 (2.9)	15 (3.4)
eGFR <45 ml/min/1.73 m^2 — no./total no. (%)	31/455 (6.8)	20/445 (4.5)
Median NT-proBNP level (IQR) — pg/ml**	275.6 (138.8–598.9)	296.8 (147.6–607.7)
Bicuspid aortic valve on computed tomography — no./total no. (%)	37/455 (8.1)	39/444 (8.8)
Echocardiographic core laboratory variables		
Aortic-valve peak velocity — m/sec††	4.3±0.5	4.4±0.4
Mean transaortic gradient — mm Hg‡‡	46.5±10.1	47.3±10.6
Aortic-valve area — cm^2§§	0.9±0.2	0.8±0.2
Left ventricular ejection fraction — %¶¶	67.4±6.5	67.4±6.7

* Plus–minus values are means ±SD. The abbreviation eGFR denotes estimated glomerular filtration rate, ICD implantable cardioverter–defibrillator, IQR interquartile range, and TAVR transcatheter aortic-valve replacement.
† Race and ethnic group were reported by the patient.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) score ranges from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after surgery. STS-PROM uses an algorithm that is based on the presence of coexisting illnesses to predict the number of deaths within 30 days after surgery.
¶ Additional details regarding the treadmill stress test can be found in Table S1 in the Supplementary Appendix.
‖ The Kansas City Cardiomyopathy Questionnaire (KCCQ) score ranges from 0 to 100, with higher scores indicating fewer physical limitations and a greater feeling of wellness. KCCQ score was available for 451 patients in the TAVR group and 440 in the clinical surveillance group.
** N-terminal pro–B-type natriuretic peptide (NT-proBNP) level was available for 414 patients in the TAVR group and 384 in the clinical surveillance group.
†† Aortic-valve peak velocity was available for 451 patients in the TAVR group and 441 in the clinical surveillance group.
‡‡ Mean transaortic gradient was available for 451 patients in the TAVR group and 442 in the clinical surveillance group.
§§ Aortic-valve area was available for 436 patients in the TAVR group and 425 in the clinical surveillance group.
¶¶ Left ventricular ejection fraction is derived with the use of Simpson's method first; if the Simpson's method reading is missing, then the value is imputed with the use of the midpoint of the visual estimation. Left ventricular ejection fraction was available for 451 patients in the TAVR group and 444 in the clinical surveillance group.

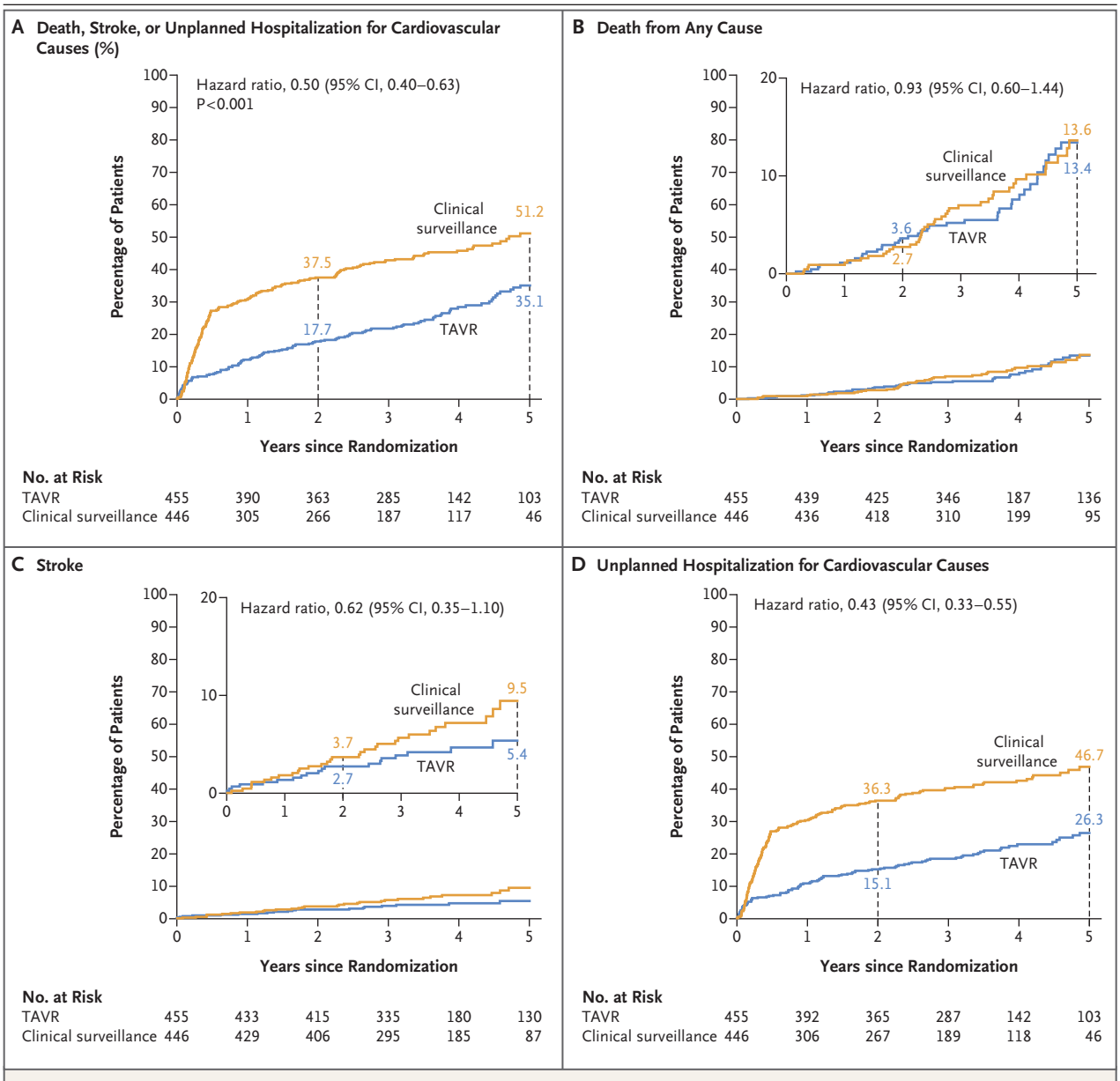

Figure 1. Time-to-Event Curves for the Composite Primary End Point and the Components of the Primary End Point.

Panel A shows Kaplan–Meier estimates of the incidence of death from any cause, stroke, or unplanned hospitalization for cardiovascular causes (the composite primary end point) in patients who underwent transcatheter aortic-valve replacement (TAVR) and in those who underwent clinical surveillance. Panels B through D show estimates of the incidence of the individual components of the primary end point. The insets show the same data on an expanded y axis. The median follow-up was 3.8 years; patients had a minimum follow-up of 2 years. The proportional-hazards assumption was tested with the use of a Cox proportional-hazards model that included an interaction term between treatment and time. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of a hypothesis test.

had not decreased more than 10 points from baseline) occurred in 86.6% of patients in the TAVR group and in 68.0% of patients in the clinical surveillance group (P<0.001). Integrated measures of left ventricular and left atrial health (another secondary composite end point) at 2 years occurred in 48.1% and 35.9% of patients, respectively (P=0.001). At 2-year follow-up, the observed mean KCCQ scores were 94.0 in the TAVR group and 93.0 in the clinical surveillance group. There

Table 2. Primary and Secondary End Points.*

End Point	TAVR (N=455)	Clinical Surveillance (N=446)	Treatment Effect (95% CI)†	P Value‡
Primary end point				
Composite of death, stroke, or unplanned hospitalization for CV causes — no. (%)§	122 (26.8)	202 (45.3)	0.50 (0.40 to 0.63)	<0.001
Death	38 (8.4)	41 (9.2)	0.93 (0.60 to 1.44)	—
Stroke	19 (4.2)	30 (6.7)	0.62 (0.35 to 1.10)	—
Unplanned hospitalization for CV causes§	95 (20.9)	186 (41.7)	0.43 (0.33 to 0.55)	—
Secondary end points				
Favorable outcome at 2 yr — no./total no. (%)¶	354/409 (86.6)	266/391 (68.0)	18.5 (12.6 to 24.3)	<0.001
Alive	425/441 (96.4)	418/430 (97.2)	—	—
KCCQ score ≥75	373/395 (94.4)	313/390 (80.3)	—	—
KCCQ score decrease of ≤10 from baseline	356/392 (90.8)	281/387 (72.6)	—	—
Integrated measures of LV and LA health at 2 yr — no./total no. (%)‖	180/374 (48.1)	121/337 (35.9)	12.2 (4.4 to 19.4)	0.001
LV global longitudinal strain ≥15%**	367/382 (96.1)	320/345 (92.8)	—	—
LV mass index <115 g/m^2 for men or <95 g/m^2 for women	319/386 (82.6)	253/351 (72.1)	—	—
LA volume index ≤34 ml/m^2	214/389 (55.0)	161/353 (45.6)	—	—
Change in LV ejection fraction from baseline to 2 years — %††	−1.2±0.4	−1.3±0.4	0.1 (−0.8 to 1.3)	0.66
New-onset atrial fibrillation — no. (%)‡‡	50 (13.0)	48 (12.4)	1.08 (0.73 to 1.60)	—
Death or disabling stroke — no. (%)	44 (9.7)	50 (11.2)	0.87 (0.58 to 1.31)	—
Death	38 (8.4)	41 (9.2)	—	—
Disabling stroke	8 (1.8)	13 (2.9)	—	—

* Plus–minus values are means ±SE. The values in this table represent all available follow-up data (median follow-up of 3.8 years) unless otherwise specified. Primary and secondary end points were tested in a prespecified hierarchical order with the use of a gatekeeping approach (the primary end point and the first through third secondary end points) and the Hochberg method (the fourth and fifth secondary end points) to control for multiple comparisons. Secondary end points were tested only if testing of the primary end point resulted in a P value of less than 0.05. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of a hypothesis test.

† Treatment-effect values are hazard ratios for the primary end point, new-onset atrial fibrillation, and death or disabling stroke; absolute risk differences, expressed as percentage points, for favorable outcome and integrated measures of left ventricular (LV) and left atrial (LA) health at 2 years; and difference in mean values for change in LV ejection fraction from baseline to 2 years.

‡ P values (two-sided) were calculated with the use of the log-rank test for the primary end point, Fisher's exact test for all other categorical variables, and the Wilcoxon rank-sum test for continuous variables. Tests used all available data at the time the last patient reached 2-year follow-up unless otherwise specified. By study design, the longest follow-up in the TAVR group was 5 years, whereas patients in the clinical surveillance group could undergo follow-up beyond 5 years. Therefore, data do not exceed 1825 days to ensure comparability between the groups. Superiority was determined by comparing the P value against a significance level of 0.05.

§ Unplanned hospitalization for cardiovascular (CV) causes includes aortic-valve interventions (e.g., conversion to aortic-valve replacement) within 6 months after randomization in the clinical surveillance group or aortic-valve reintervention within 6 months after the trial procedure in the TAVR group.

¶ All three criteria had to be present to meet the composite end point of favorable outcome. Favorable outcome was evaluated at 2 years unless a patient in the clinical surveillance group had an aortic-valve intervention within 6 months after randomization, in which case the preprocedure KCCQ score was used; similarly, if a patient in the TAVR group had an aortic-valve reintervention within 6 months after the procedure, the 30-day KCCQ score was used.

‖ All three criteria had to be present to meet the composite end point of integrated measures of LV and LA health.

** LV global longitudinal strain was assessed with the use of four-chamber, three-chamber, and two-chamber imaging; the average of the measurements in the three views was reported as an absolute value. If one view was missing, the four-chamber view was used.

†† LV ejection fraction was derived with the use of Simpson's method first; if the Simpson's method reading was missing, then the value was imputed with the use of the midpoint of the visual estimation. LV ejection fraction was available for 393 patients in the TAVR group and 355 in the clinical surveillance group.

‡‡ New-onset atrial fibrillation was evaluated among the 384 patients in the TAVR group and the 387 patients in the clinical surveillance group who did not have atrial fibrillation at baseline.

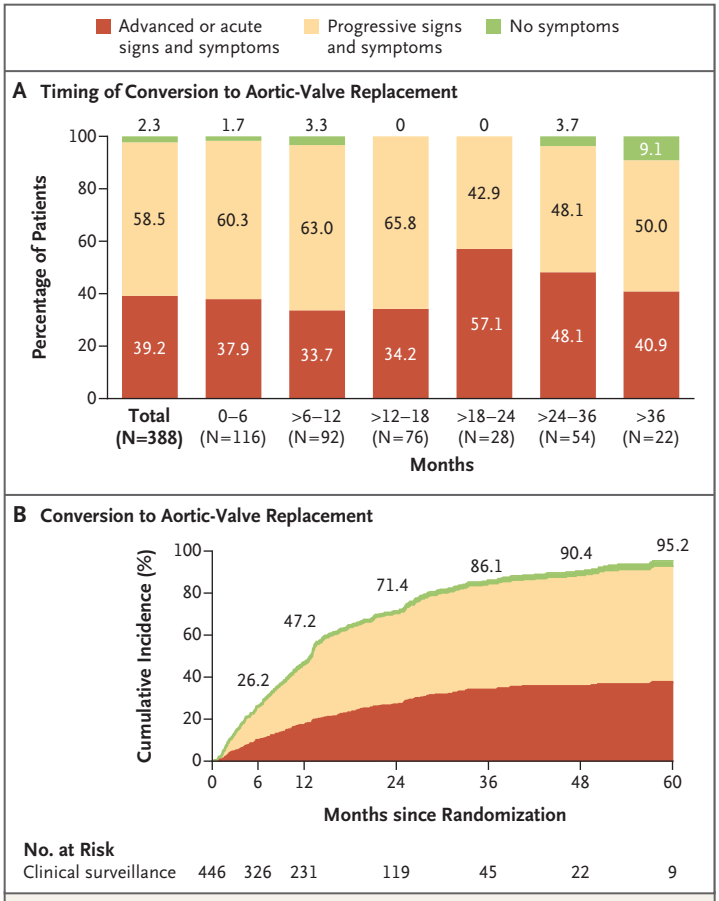

Figure 2. Conversion to Aortic-Valve Replacement.

Panel A shows the clinical presentation (signs and symptoms) of the patients in the clinical surveillance group who converted to aortic-valve replacement after randomization, stratified according to timing of conversion. Panel B shows the cumulative incidence curve of conversions to aortic-valve replacement through 5 years after randomization, stratified according to clinical presentation at the time of conversion. Progressive signs and symptoms were defined as at least one of the following: New York Heart Association class II symptoms, an increase in heart-failure medication dose from baseline, or an increase in N-terminal pro–B-type natriuretic peptide (NT-proBNP) level by a factor of 1.5 to less than 3 from baseline coupled with a preprocedure NT-proBNP level of more than 187.5 pg per milliliter if the patient was 75 years of age or younger at the time of conversion to aortic-valve replacement or of more than 675 pg per milliliter if the patient was older than 75 years at the time of conversion to aortic-valve replacement. Advanced signs and symptoms and acute decompensation were defined as at least one of the following: New York Heart Association class III or IV symptoms, hospital admission for acute heart failure or pulmonary edema, syncope, ventricular arrhythmia, resuscitation after cardiac arrest, atrial fibrillation, left ventricular ejection fraction of less than 50%, or an increase in NT-proBNP level by a factor of at least 3 from baseline coupled with a preprocedure NT-proBNP level of more than 375 pg per milliliter if the patient was 75 years of age or younger at the time of conversion to aortic-valve replacement or of more than 1350 pg per milliliter if the patient was older than 75 years at the time of conversion to aortic-valve replacement.

were no apparent differences between the groups in the change in left ventricular ejection fraction at 2 years. During the entire follow-up, new-onset atrial fibrillation occurred in 50 patients (13.0%) in the TAVR group and in 48 patients (12.4%) in the clinical surveillance group; death or disabling stroke occurred in 44 patients (9.7%) in the TAVR group and in 50 patients (11.2%) in the clinical surveillance group.

With regard to exploratory end points, the hazard ratio for a composite of death from cardiovascular causes or stroke was 0.74 (95% CI, 0.48 to 1.14), and the hazard ratio for a composite of death, stroke, or hospitalization for heart failure was 0.60 (95% CI, 0.44 to 0.83). Kaplan–Meier estimates of hospitalizations for heart failure appeared to be higher among patients assigned to clinical surveillance than among those assigned to TAVR (hazard ratio with TAVR, 0.32; 95% CI, 0.18 to 0.58) (Fig. S4).

CLINICAL SURVEILLANCE

Among the 446 patients randomly assigned to clinical surveillance, 388 (87.0%) underwent aortic-valve replacement during follow-up; the median time from randomization to conversion to aortic-valve replacement was 11.1 months (interquartile range, 5.0 to 19.7). Kaplan–Meier estimates of the percentage of patients who converted to aortic-valve replacement were 26.2% (116 patients) at 6 months, 47.2% (208 patients) at 1 year, and 71.4% (312 patients) at 2 years (Fig. S5). Among the patients in the clinical surveillance group who underwent aortic-valve replacement, the median time to the procedure from symptom onset or from the decision to intervene was 32 days (interquartile range, 18 to 58); 87.9% of these patients underwent the procedure within 3 months. Data on clinical presentation at the time of aortic-valve replacement in the clinical surveillance group are shown in Figure 2 and Table S5. Advanced signs and symptoms of symptomatic aortic-valve disease occurred in 152 of the 388 patients (39.2%), including 44 of the 116 patients (37.9%) who converted within the first 6 months. When only interventions resulting from advanced signs and symptoms, regardless of timing of intervention, were included in an exploratory analysis of the primary end point, the results remained consistent with those of the primary analysis (Fig. 3).

The percentage of patients with a left ventricular ejection fraction of 60% or lower increased from 12.7% at screening to 20.7% at the time of conversion to aortic-valve replacement, and the median NT-proBNP level increased from 298.6 to 462.2 pg per milliliter (Table S6). The mean 6-minute walk test distance decreased by 46.4 m, and the mean KCCQ score decreased by 14.8 points (Fig. S6).

SAFETY END POINTS

Details regarding characteristics of the procedure in patients in the TAVR group and in patients in the clinical surveillance group who converted to aortic-valve replacement are provided in Table S7. No patients in either group died from cardiovascular causes within 30 days after the procedure, whereas 0.9% of the patients in the early TAVR group and 1.8% of the patients in the clinical surveillance group who converted to aortic-valve replacement had a stroke within 30 days (Table S8). There were no apparent differences between the groups in other periprocedural complications.

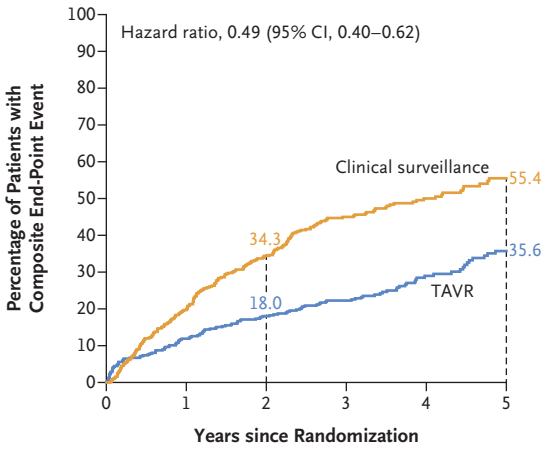

Figure 3. Exploratory Analysis of the Primary End Point.

Shown are the results of an exploratory analysis of the primary end point that examined a composite of death from any cause, stroke, unplanned hospitalization for cardiovascular causes, or valve-related interventions among patients in either group with advanced signs or symptoms, regardless of the timing of the intervention. The widths of the confidence intervals have not been adjusted for multiple comparisons and should not be used in place of a hypothesis test.

DISCUSSION

The EARLY TAVR trial compared an interventional strategy with a clinical surveillance strategy among patients with asymptomatic severe aortic stenosis and evaluated the role of TAVR in this patient population. The trial showed that early TAVR was superior to clinical surveillance with respect to the primary composite end point of death, stroke, or unplanned hospitalization for cardiovascular causes and with respect to a favorable outcome at 2 years, which was defined as being alive and having a KCCQ score of at least 75 with a decrease of no more than 10 points from baseline; the trial also showed that integrated measures of left ventricular and left atrial health at 2-year follow-up were better with early TAVR than with clinical surveillance.

Within the first 6 months, approximately one in four patients assigned to clinical surveillance underwent aortic-valve replacement, and more than one third of these patients presented with advanced signs and symptoms of aortic-valve disease. Patients in the clinical surveillance group had a decline in quality of life, as assessed with the KCCQ, before conversion to aortic-valve replacement, with recovery occurring within 30 days after the procedure. By 2 years, more than 70% of the patients assigned to clinical surveillance had undergone aortic-valve replacement. In our study, more than 30% of the patients in the clinical surveillance group presented with advanced symptoms before aortic-valve replacement regardless of the timing of conversion, a finding that is similar to findings in observational studies.[14] In addition, clinical surveillance was associated with worsening left ventricular and left atrial function, which highlights the unpredictable nature of the progression of aortic stenosis[15-17] and the development and accumulation of cardiac damage while patients have asymptomatic disease.[18,19] Longer follow-up is ongoing and may help determine whether changes in clinical outcomes related to cardiac damage will emerge.

The percentage of patients who died appeared to be similar in the two groups and was lower than that shown in previous trials.[11,12] The lower mortality in our trial may be explained, in part, by the less invasive nature of TAVR as compared with surgery and the high quality of clinical surveillance in our trial, in which all aspects of

the future TAVR procedure and care were planned before enrollment. This led to prompt conversion to aortic-valve replacement, with 87.9% of patients undergoing the procedure within 3 months after symptoms developed or aortic-valve replacement became indicated.[20] This level of vigilance may not be replicated in the real world, especially in care contexts in which aortic stenosis is undertreated.[2,20-22] In addition, the availability of TAVR may have resulted in a lower threshold for conversion to aortic-valve replacement once symptoms developed.

An unexpected finding was that strokes occurred more frequently in the clinical surveillance group than in the TAVR group. Further studies are needed to confirm and explain this finding. Because more than 70% of patients assigned to clinical surveillance had undergone aortic-valve replacement by 2 years, concerns about differences in valve durability between the groups may not be relevant. Earlier aortic-valve replacement resulting in the need for additional interventions because of bioprosthetic-valve failure also seems unlikely in a population of older adults with a life expectancy that may be shorter than the durability of the valve.

This trial has limitations. First, the members of the independent clinical events committee that adjudicated end points were aware of the treatment assignments. Second, the results apply only to the trial population, which included predominantly patients at low surgical risk who were at least 65 years of age with anatomical and clinical characteristics suitable for transfemoral TAVR. Third, the findings cannot be extrapolated to TAVR performed with valves other than the balloon-expandable valve used in this trial. Fourth, less-intensive clinical surveillance than was performed in our trial and the absence of preemptive procedural planning may result in different outcomes. Fifth, the majority of the participants were White, and results may not be generalizable to other races or ethnic groups. Finally, part of this trial was conducted during the coronavirus disease 2019 pandemic, which may have affected outcomes.

Among patients with asymptomatic severe aortic stenosis, a strategy of early TAVR was superior to guideline-recommended clinical surveillance in reducing the composite end point of death, stroke, or unplanned hospitalization for cardiovascular causes.

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APPENDIX

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