ORIGINAL ARTICLE

TAVR in Patients with Moderate Aortic Stenosis with At-Risk Features

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ABSTRACT

BACKGROUND

For patients with moderate aortic stenosis, current guidelines recommend clinical surveillance with echocardiographic assessment every 1 or 2 years. Whether transcatheter aortic-valve replacement (TAVR) will improve outcomes in these patients remains unknown.

METHODS

We conducted an international, open-label, randomized trial to evaluate whether TAVR will result in better outcomes than clinical surveillance among patients with moderate aortic stenosis with at least one at-risk feature (i.e., a symptom or structural or functional abnormality that has been shown to be associated with faster disease progression or adverse cardiovascular outcomes). The patients were assigned in a 1:1 ratio to undergo transfemoral TAVR with a balloon-expandable valve or clinical surveillance. The primary effectiveness end point was a composite of death from any cause or a heart-failure event with or without hospitalization at 2 years. Superiority testing was performed in the intention-to-treat population.

RESULTS

A total of 744 patients underwent randomization: 373 patients were assigned to the TAVR group and 371 to the clinical-surveillance group. The mean age of patients was 78 years, 39.1% were women, and 45.6% were at low surgical risk. The mean aortic-valve area was 1.2 cm^2, and the mean aortic-valve peak velocity was 3.3 m per second. At 2 years, the Kaplan–Meier estimate of the percentage of patients with a primary effectiveness end-point event was 16.7% in the TAVR group and 23.9% in the clinical-surveillance group (risk difference, –7.2 percentage points; 95% confidence interval, –13.1 to –1.3; P=0.02 for superiority). The Kaplan–Meier estimate of the percentage of patients who died from any cause was 8.4% in the TAVR group and 7.3% in the clinical-surveillance group; the estimates for a heart-failure event were 10.8% and 19.0%, respectively. The incidence of procedure-related adverse events did not differ meaningfully between the patients in the TAVR group and those in the clinical-surveillance group who underwent aortic-valve replacement.

CONCLUSIONS

Among patients with moderate aortic stenosis and at-risk features, a strategy of TAVR was superior to clinical surveillance in lowering the incidence of death or a heart-failure event at 2 years. (Funded by Edwards Lifesciences; PROGRESS ClinicalTrials.gov number, NCT04889872.)

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*The PROGRESS trial investigators and members of the trial administration are listed in the Supplementary Appendix, available at NEJM.org

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Aortic stenosis is a progressive disease that affects more than 3% of persons 65 years of age or older in developed countries.[1-3] For patients with moderate aortic stenosis, current guidelines recommend clinical surveillance with echocardiographic assessment every 1 or 2 years, with aortic-valve replacement deferred until the stenosis becomes severe or there is another indication for cardiac surgery.[4,5] However, moderate aortic stenosis is a heterogeneous disease with variable and unpredictable progression.[6,7] Some patients with moderate aortic stenosis have a prognosis similar to that seen with severe aortic stenosis,[1,8-11] particularly those with at-risk features (i.e., a symptom or structural or functional abnormality that has been shown to be associated with faster disease progression or adverse cardiovascular outcomes).[1,8-10,12-22] We designed the Prospective, Randomized, Controlled Trial to Assess the Management of Moderate Aortic Stenosis by Clinical Surveillance or Transcatheter Aortic Valve Replacement (PROGRESS) to evaluate whether transcatheter aortic-valve replacement (TAVR) will improve outcomes among patients with moderate aortic stenosis, as compared with clinical surveillance.

Methods

Trial Design and Oversight

The PROGRESS trial was a prospective, international, multicenter, open-label, randomized, controlled trial in which TAVR with transfemoral placement of a balloon-expandable valve (SAPIEN 3, SAPIEN 3 Ultra, or SAPIEN 3 Ultra RESILIA; Edwards Lifesciences) was compared with guideline-recommended clinical surveillance among patients with moderate aortic stenosis and at least one at-risk feature. The design and rationale of the trial have been described previously.[12] The protocol (available with the full text of this article at NEJM.org) was developed by the principal investigators, steering committee, and trial sponsor (Edwards Lifesciences) in conjunction with the Food and Drug Administration and approved by the institutional review boards at each site. All the patients provided written informed consent. The participating sites, investigators, and members of the steering committee are listed in Section A in the Supplementary Appendix (available at NEJM.org); additional details regarding trial oversight, author responsibilities, and the role of the sponsor are provided in Section B. The authors 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 moderate aortic stenosis according to echocardiographic assessment, and had at least one of the following at-risk features: valve-related symptoms (e.g., New York Heart Association [NYHA] class II or higher, chest pain, or syncope), a left ventricular ejection fraction of less than 60%, grade 2 or higher diastolic dysfunction according to American Society of Echocardiography guidelines at the time of enrollment,[23] a stroke volume index of less than 35 ml per square meter, persistent or any episode of paroxysmal atrial fibrillation within 6 months before randomization, an N-terminal pro–B-type natriuretic peptide (NT-proBNP) level greater than three times the upper limit of the normal range, or an elevated aortic-valve calcium score as assessed by the computed tomography (CT) core laboratory. An elevated aortic-valve calcium score was defined as a score greater than 1200 Agatston units (a metric that combines the area and density of observed coronary-artery calcification) for women or greater than 2000 Agatston units for men.[20]

Eligibility was assessed at each site and by an independent, physician-led case-review board. Patients with a left ventricular ejection fraction of less than 20% or clinically significant, untreated coronary artery disease warranting revascularization were excluded. Full details of the inclusion and exclusion criteria are 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 undergo TAVR or clinical surveillance (the intention-to-treat population). The patients in the TAVR group underwent transfemoral TAVR, and those in the clinical-surveillance group received standard management according to society guidelines. The cases of patients in the clinical-surveillance group in whom an indication for aortic-valve replacement developed during follow-up were presented to a case-review board, and aortic stenosis severity was assessed by the echocardiographic core labo-

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ratory; however, the decision to intervene was ultimately made by the local heart team. Clinical and echocardiographic assessments were planned annually through 10 years after randomization. Additional details are provided in Section D in the Supplementary Appendix.

TRIAL END POINTS

The primary effectiveness end point was a nonhierarchical composite of death from any cause or a heart-failure event with or without hospitalization at 2 years, which was assessed in the intention-to-treat population from the time of randomization. A heart-failure event was documented if it met all three of the following criteria: there was at least one new or worsening symptom, evidence of heart-failure decompensation was obtained from at least two objective assessments, and the event led to at least one heart-failure treatment. The complete definition, adapted from the Heart Failure Collaboratory–Academic Research Consortium, is provided in Section E in the Supplementary Appendix.[24] In the clinical-surveillance group, a delayed aortic-valve replacement could fulfill the heart-failure treatment criterion, but for a heart-failure event to be documented, the other two criteria needed to be met as well; a delayed aortic-valve replacement alone did not constitute a heart-failure event.

The primary safety end point was a nonhierarchical composite of death from any cause, stroke, life-threatening or fatal bleeding, stage 4 acute kidney injury, hospitalization for a device- or procedure-related complication, or valve dysfunction leading to reintervention at 30 days. Safety was assessed from the time of the procedure in the TAVR group among the patients who had undergone the index procedure (the as-treated population).

Five secondary end points were evaluated in the intention-to-treat population according to the following prespecified hierarchy at 2 years: a composite of death from any cause, stroke, or hospitalization for heart failure; being alive with an improvement in the Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score of at least 10 points from baseline that was sustained at both 1 and 2 years (scores range from 0 to 100, with higher scores indicating better health status); hospitalization for heart failure; left ventricular mass index; and diastolic dysfunction of grade 2 or higher.[23] Primary and secondary end-point events and their components, as well as additional clinical events, were adjudicated by an independent clinical-events committee, whose members were aware of the trial-group assignments. An independent data and safety monitoring board provided safety oversight for the trial. Echocardiographic and CT imaging and biomarker levels were evaluated by independent core laboratories.

STATISTICAL ANALYSIS

The statistical methods of the trial have been published previously[12] and are described in the statistical analysis plan, available with the protocol, and in Section F in the Supplementary Appendix. The sample size was determined with respect to the primary safety end point. On the basis of data from previous studies that used the SAPIEN 3 valve and considering the mix of surgical risk among the patients in the enrolled trial population at time of performance-goal development,[25-27] we assumed a 30-day primary safety end-point event rate of 8.2% in the TAVR group with a 5.5 percentage-point margin to derive a performance goal for success of 13.7%. With these assumptions, we calculated that 298 patients in the TAVR group would provide the trial with 85% power, at a one-sided alpha level of 0.025, to demonstrate the safety of TAVR against the performance goal. We anticipated an attrition of 5% and therefore planned for 628 patients to undergo randomization.

With an assumed 2-year incidence of a primary effectiveness end-point event of 15% in the TAVR group and 30% in the clinical-surveillance group, we calculated that the planned sample size would provide more than 99% power to show the superiority of TAVR over clinical surveillance for the primary effectiveness end point. In accordance with the *Journal's* statistical guidelines, the primary effectiveness end point was evaluated at a two-sided significance level of 0.05. The Wald test with Kaplan–Meier estimates of the first event and Greenwood variance was used for between-group comparisons.

The incidence of a primary safety end-point event and the upper limit of the one-sided 97.5% confidence interval were evaluated with the Wilson score method and compared against the prespecified performance goal of 13.7%. Secondary end points were tested sequentially in a prespecified hierarchical order with a gatekeeping proce-

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dure that was initiated only after both primary effectiveness and safety end points had met their success criteria, and the testing was continued until the first nonsignificant result in order to control the overall family-wise type I error rate. In accordance with the *Journal's* statistical guidelines, secondary end points were evaluated with two-sided testing procedures at a significance level of 0.05. Two-sided 95% confidence intervals are reported for primary effectiveness and secondary end points.

Treatment effects were summarized with appropriate effect measures and with corresponding confidence intervals or limits. Prespecified subgroup analyses were performed for the primary and secondary end points and are described in Section G in the Supplementary Appendix. The widths of the confidence intervals have not been adjusted for multiplicity and should not be used for hypothesis testing, unless otherwise noted. To address missing data, time-to-event analyses were performed under the assumption of noninformative censoring, and other analyses were based on observed data without imputation of missing data. Details regarding a prespecified interim analysis are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From October 2021 through January 2024, a total of 1294 patients were screened, of whom 744 were randomly assigned to a trial group (373 patients to the TAVR group and 371 patients to the clinical-surveillance group). The patients were enrolled at 74 sites across 6 countries (87.1% of the patients were from the United States, and 12.9% were from Japan, Australia, the Netherlands, Canada, and Switzerland) (Table S1 and Fig. S1 in the Supplementary Appendix). Among the 1294 patients screened, the most common reasons for screen failure were the absence of moderate aortic stenosis according to echocardiographic criteria (in 214 patients [16.5%]) and anatomical exclusions for transfemoral TAVR (in 139 patients [10.7%]). Detailed reasons for screen failure are provided in Table S2. The representativeness of the enrolled population is described in Section H in the Supplementary Appendix.

The baseline characteristics of the patients appeared to be balanced between the trial groups (Table 1 and Table S3). The mean age of the patients was 78.4 years, and 39.1% were women. The mean Society of Thoracic Surgeons Predicted Risk of Mortality score was 3.0% (on a scale from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after surgery), and 45.6% of the patients were considered to be at low surgical risk, as evaluated by the local heart team. The severity of aortic stenosis appeared to be similar in the trial groups (mean aortic-valve area, 1.2 cm^2); the distribution of severity is shown in Figure S2. Among 738 evaluable patients, the majority (676 [91.6%]) had concordant moderate aortic stenosis, with both valve area and velocity or gradient measurements in the moderate range. Only 8.5% of the patients had a left ventricular ejection fraction of less than 50%, and 3.0% had an ejection fraction of 40% or less. The median aortic-valve calcium score was 1209 Agatston units. A bicuspid aortic valve was present in 7.4% of patients. The mean KCCQ-OS score was 64.2, and 35.5% of the patients had an NYHA class of III or IV.

The prevalence of at-risk features appeared to be well balanced between the trial groups. The most common feature was the presence of valve-related symptoms (in 96.4%), followed by diastolic dysfunction of grade 2 or higher (in 43.8%). A total of 72% of the patients had two or more at-risk features, and 40% had three or more. Baseline medication use also appeared to be similar in the groups (Table S4).

PRIMARY END POINTS

A total of 356 patients (95.4%) in the TAVR group and 341 (91.9%) in the clinical-surveillance group were included in the analysis of the primary effectiveness end point. At 2 years, a primary effectiveness end-point event (death from any cause or a heart-failure event with or without hospitalization) had occurred in 60 patients (Kaplan–Meier estimate, 16.7%) in the TAVR group and in 85 patients (Kaplan–Meier estimate, 23.9%) in the clinical-surveillance group (difference, –7.2 percentage points [95% confidence interval {CI}, –13.1 to –1.3; P=0.02]; hazard ratio, 0.67 [95% CI, 0.48 to 0.93]) (Fig. 1A and Table 2). At 2 years, death from any cause had occurred in 30 patients (Kaplan–Meier estimate, 8.4%) in the TAVR group and in 26 patients (Kaplan–Meier estimate, 7.3%)

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in the clinical-surveillance group (Fig. 1B and Table 2). The results for death from cardiovascular causes and from noncardiovascular causes are shown in Figure S3, and the causes of death are shown in Table S5. A heart-failure event with or without hospitalization occurred in 38 patients (Kaplan–Meier estimate, 10.8%) in the TAVR group and in 66 patients (Kaplan–Meier estimate, 19.0%) in the clinical-surveillance group (Fig. 1C and Table 2). The results for all the prespecified subgroups appeared to be consistent with those of the primary analysis (Fig. 2 and Fig. S4).

At 30 days, a primary safety end-point event (death from any cause, stroke, life-threatening or fatal bleeding, stage 4 acute kidney injury, hospitalization for a device- or procedure-related complication, or valve dysfunction leading to reintervention at 30 days) had occurred in 21 of 358 patients (5.9%; two-sided 95% CI, 3.9 to 8.8) in the TAVR group who had undergone the index procedure. The upper limit of the one-sided 97.5% confidence interval of 8.8% for the incidence of a primary safety end-point event was below the 13.7% performance goal for success (P<0.001) (Table 2).

SECONDARY END POINTS

At 2 years, death, stroke, or hospitalization for heart failure had occurred in 64 patients (17.7%) in the TAVR group and in 83 patients (23.3%) in the clinical-surveillance group. A total of 134 of 344 patients (39.0%) in the TAVR group and 76 of 327 (23.2%) in the clinical-surveillance group were alive and had an improvement in the KCCQ-OS score of at least 10 points from baseline that was sustained at 1 and 2 years. Hospitalization for heart failure had occurred in 26 patients (Kaplan–Meier estimate, 7.4%) in the TAVR group and in 52 patients (Kaplan–Meier estimate, 14.9%) in the clinical-surveillance group (Fig. S5). The mean (±SD) left ventricular mass index was 97.1±28.3 g per square meter in the TAVR group and 101.1±30.1 g per square meter in the clinical-surveillance group (Table 2). At 2 years, diastolic dysfunction of grade 2 or higher had occurred in 107 of 275 patients (38.9%) in the TAVR group and in 97 of 266 patients (36.5%) in the clinical-surveillance group.

ADDITIONAL OUTCOMES

Table S6 shows additional outcomes at 2 years. No apparent between-group difference was found in the incidence of myocardial infarction or in the incidence of stroke. Figure S6 shows the total number of hospitalizations for heart failure through 2 years; the annualized rate of hospitalization for heart failure was 6.2 events per 100 patient-years in the TAVR group and 12.0 events per 100 patient-years in the clinical-surveillance group (hazard ratio from a joint frailty model, 0.52; 95% CI, 0.35 to 0.78). The Kaplan–Meier estimates for heart-failure events without hospitalization were 4.6% in the TAVR group and 4.9% in the clinical-surveillance group.

At 2 years, 3.9% of the patients in the TAVR group, as compared with 10.9% in the clinical-surveillance group, had an NYHA class of III or IV (Fig. S7). The mean KCCQ-OS score was 79.4 in the TAVR group and 73.8 in the clinical-surveillance group; the mean within-patient change in the KCCQ-OS score from baseline to 2 years among those with available data was an increase of 14.3 points in the TAVR group and of 7.7 points in the surveillance group (Fig. S8).

CLINICAL SURVEILLANCE AND PROGRESSION OF AORTIC STENOSIS

Among the 371 patients in the clinical-surveillance group, 99 (27.0%) underwent delayed aortic-valve replacement within 1 year, and 204 (57.4%) underwent the intervention within 2 years after randomization (Fig. 3). The most common reason for undergoing aortic-valve replacement among these patients was progression to severe aortic stenosis with a class 1 indication for aortic-valve replacement, which occurred in 166 of 204 patients (81.4%). Of the 66 patients in the clinical-surveillance group who had a heart-failure event contributing to the primary effectiveness end point, 28 (42.4%) had a delayed aortic-valve replacement with an associated hospitalization for heart failure as a treatment for new or worsening heart failure; of these patients, 21 of 28 (75.0%) had a class 1 indication.

The proportions of patients who underwent delayed aortic-valve replacement at different time intervals and the reasons for the intervention are shown in Figure S9 and Table S7. From baseline to the time of delayed aortic-valve replacement, the mean aortic-valve peak velocity had increased by 0.5 m per second, the mean gradient had increased by 10.5 mm Hg, and the mean valve area had decreased by 0.3 cm^2 (Table S8). The mean

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Table 1. Demographic and Clinical Characteristics of the Patients at Baseline.*

Characteristic	TAVR (N=373)	Clinical Surveillance (N=371)
Age — yr	78.5±6.5	78.3±6.1
Female sex — no. (%)	142 (38.1)	149 (40.2)
Body-mass index†	29.5±5.7	29.7±5.9
STS-PROM score — %‡	3.1±2.6	3.0±2.6
Low surgical risk according to the local heart team — no. (%)	164 (44.0)	175 (47.2)
KCCQ-OS score§	64.5±23.8	63.9±24.1
Hypertension — no. (%)	337 (90.3)	319 (86.0)
Diabetes — no. (%)	135 (36.2)	137 (36.9)
Estimated glomerular filtration rate <45 ml/min/1.73 m^2 — no./total no. (%)	36/372 (9.7)	46/367 (12.5)
Chronic obstructive pulmonary disease — no. (%)	36 (9.7)	43 (11.6)
Peripheral vascular disease — no. (%)	41 (11.0)	42 (11.3)
Previous myocardial infarction — no. (%)	54 (14.5)	53 (14.3)
Previous percutaneous coronary intervention — no. (%)	114 (30.6)	114 (30.7)
Previous coronary-artery bypass graft — no. (%)	63 (16.9)	43 (11.6)
Previous stroke — no. (%)	36 (9.7)	29 (7.8)
Any history of atrial fibrillation — no. (%)	127 (34.0)	119 (32.1)
Right bundle-branch block — no. (%)	62 (16.6)	65 (17.5)
Left bundle-branch block — no. (%)	25 (6.7)	28 (7.5)
Permanent pacemaker or ICD — no. (%)	46 (12.3)	39 (10.5)
Median NT-proBNP level (IQR) — pg/ml¶	349 (160–1006)	364 (143–807)
Echocardiographic and CT core laboratory measure		
Aortic-valve area — cm^2	1.2±0.2	1.2±0.2
Transaortic mean gradient — mm Hg	25.1±5.1	25.4±5.1
Aortic-valve peak velocity — m/sec	3.3±0.3	3.3±0.3
Discordant moderate aortic stenosis — no./total no. (%)‖	36/370 (9.7)	26/368 (7.1)
LV ejection fraction — %**	63.2±9.8	63.6±9.0
Bicuspid aortic valve on CT — no. (%)	30 (8.0)	25 (6.7)
Median aortic-valve calcium score on CT (IQR) — Agatston units††	1235 (836–1780)	1185 (764–1787)
At-risk feature — no. (%)‡‡		
NYHA class ≥II	363 (97.3)	354 (95.4)
LV ejection fraction <60%**	92 (24.7)	94 (25.3)
Diastolic dysfunction ≥grade 2§§	166 (44.5)	160 (43.1)
Stroke volume index <35 ml/m^2	53 (14.2)	31 (8.4)
Atrial fibrillation within 6 mo before randomization¶¶	78 (20.9)	68 (18.3)
NT-proBNP >3 times the upper limit of normal¶	77 (20.6)	82 (22.1)
Elevated aortic-valve calcium score on CT‖‖	105 (28.2)	86 (23.2)

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Table 1. (Continued.)

Characteristic	TAVR (N=373)	Clinical Surveillance (N=371)
No. of at-risk features		
1	106 (28.4)	102 (27.5)
2	114 (30.6)	125 (33.7)
≥3	153 (41.0)	144 (38.8)

* Plus–minus values are means ±SD. There were no significant between-group differences in baseline characteristics except for previous coronary-artery bypass graft and stroke volume index lower than 35 ml per square meter (P<0.05). ICD denotes implantable cardioverter–defibrillator, NYHA New York Heart Association, and TAVR transcatheter aortic-valve replacement.
† The body-mass index is the weight in kilograms divided by the square of the height in meters.
‡ Scores on the Society of Thoracic Surgeons Predicted Risk of Mortality (STS-PROM) range from 0 to 100%, with higher scores indicating a greater risk of death within 30 days after surgery. The STS-PROM uses an algorithm that is based on the presence of coexisting illnesses to predict 30-day operative mortality.
§ Data on Kansas City Cardiomyopathy Questionnaire–Overall Summary (KCCQ-OS) score were available for 367 patients in the TAVR group and 362 patients in the clinical-surveillance group. Scores range from 0 to 100, with higher scores indicating better health status.
¶ Data on the N-terminal pro–B-type natriuretic peptide (NT-proBNP) level were available for 267 patients in the TAVR group and 252 patients in the clinical-surveillance group. These data were assessed by the biomarker core laboratory; the core laboratory did not assess data from outside the United States.
‖ Concordant and discordant moderate aortic stenosis are described in Section C3 in the Supplementary Appendix. Briefly, concordant moderate aortic stenosis is defined as an aortic-valve area and a peak velocity or mean gradient in the moderate range, whereas discordant moderate aortic stenosis is defined as having either an aortic-valve area or a peak velocity or mean gradient in the moderate range.
** Left ventricular (LV) ejection fraction was derived from Simpson's method first; if the Simpson's method reading was missing, then the value was imputed as the midpoint of the visual estimation.
†† Data on the aortic-valve calcium score were available for 369 patients in the TAVR group and 366 patients in the clinical-surveillance group. These data were assessed by the CT core laboratory.
‡‡ Data on at-risk features were reported by the trial sites.
§§ Diastolic dysfunction of grade 2 or higher was defined according to American Society of Echocardiography guidelines[23] at the time of enrollment.
¶¶ Recent atrial fibrillation was defined as any persistent or paroxysmal atrial fibrillation within 6 months before randomization.
‖‖ An elevated aortic-valve calcium score was defined as a score greater than 1200 Agatston units for women and greater than 2000 Agatston units for men.

KCCQ-OS score had decreased from baseline by 9.3 points, and the left ventricular ejection fraction remained unchanged.

PROCEDURAL DETAILS AND PERIPROCEDURAL SAFETY OUTCOMES

Procedural details for the patients in the TAVR group and for those in the clinical-surveillance group who underwent aortic-valve replacement within 2 years after randomization are provided in Table S9. Thirty-day mortality after the procedure was 0% among the patients in the TAVR group and 0.5% among the patients in the clinical-surveillance group who had undergone delayed aortic-valve replacement; the incidence of stroke was 0.8% and 2.5%, respectively (Table S10). New permanent pacemaker implantation was performed in 13.0% of the patients in the TAVR group and in 10.4% of those in the clinical-surveillance group with delayed aortic-valve replacement; the majority of these patients had preexisting right or left bundle-branch block (24 of 41 patients [58.5%] in the TAVR group and 10 of 19 patients [52.6%] in the clinical-surveillance group). The presence of moderate or greater paravalvular regurgitation 30 days after TAVR was 0% after the index TAVR and 0.5% after delayed aortic-valve replacement in the clinical-surveillance group (Table S11).

DISCUSSION

In our trial involving patients with moderate aortic stenosis and at least one at-risk feature,

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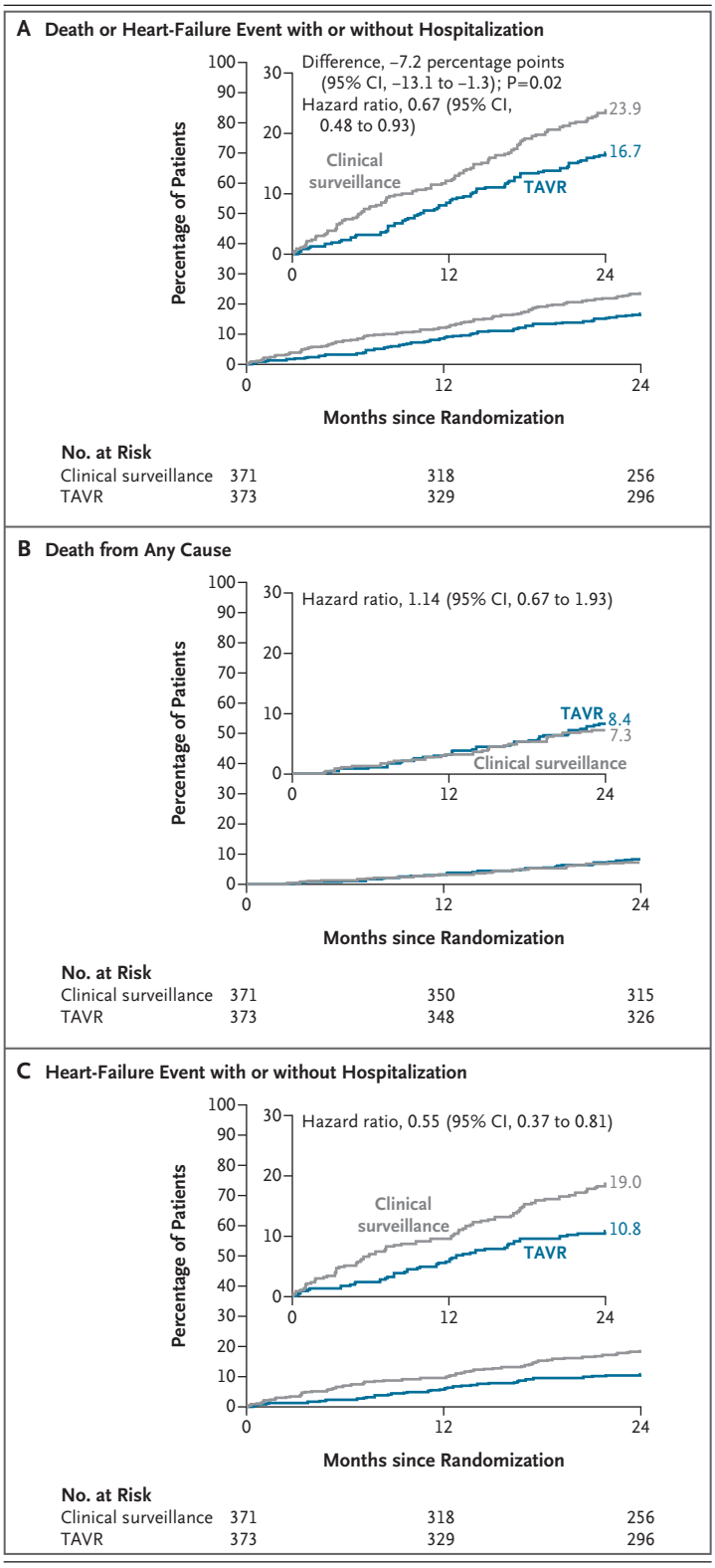


Figure 1. Time-to-Event Curves for the Primary Effectiveness End Point and Its Components.

Panel A shows the Kaplan–Meier estimates of the primary effectiveness end point (a composite of death from any cause or a heart-failure event with or without hospitalization). The Kaplan–Meier estimates for components of the primary effectiveness end point are shown in Panel B (death from any cause) and Panel C (a heart-failure event, with or without hospitalization). The end points were assessed at 2 years in the intention-to-treat population. The analysis of the primary effectiveness end point involved the difference in the Kaplan–Meier estimates between the transcatheter aortic-valve replacement (TAVR) group and the clinical-surveillance group, as calculated with the Wald test (difference, −7.2 percentage points; 95% confidence interval, −13.1 to −1.3; P=0.02 for superiority). Hazard ratios with 95% confidence intervals are also shown for each end point. The proportional-hazards assumption was assessed with a Cox proportional-hazards model that included a treatment-by-time interaction term and was not violated (P=0.69). The widths of the confidence intervals for the components of the primary effectiveness end point have not been adjusted for multiple comparisons and should not be used in place of a hypothesis test. The insets show the same data on an enlarged y axis.

TAVR was shown to be superior to clinical surveillance in lowering the incidence of death or a heart-failure event. The trial also showed that TAVR met its performance goal for success with respect to the primary safety end point, a composite of death from any cause, stroke, life-threatening or fatal bleeding, stage 4 acute kidney injury, hospitalization for a device- or procedure-related complication, or valve dysfunction leading to reintervention at 30 days.

The patients in our trial population had at-risk features that have been linked to rapid disease progression, hospitalization for heart failure, and death.[9,10,13-20] The majority of the patients had cardiac symptoms, frequent coexisting medical conditions, and impaired health status, despite the presence of a preserved left ventricular ejection fraction in most of the patients. TAVR was associated with approximately 50% fewer hospitalizations for heart failure than clinical surveillance. Our results differed from those of the TAVR UNLOAD (Transcatheter Aortic Valve Replacement to Unload the Left Ventricle in Pa-

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Table 2. Primary and Secondary End Points.*

End Point	TAVR (N=373)	Clinical Surveillance (N=371)	Difference (95% CI)	P Value
			percentage points	
Primary effectiveness end point				
Death from any cause or a heart-failure event with or without hospitalization at 2 years — no. (Kaplan–Meier estimate, %)	60 (16.7)	85 (23.9)	–7.2 (–13.1 to –1.3)	0.02
Death from any cause	30 (8.4)	26 (7.3)	1.0 (–2.9 to 5.0)	—
Heart-failure event with or without hospitalization	38 (10.8)	66 (19.0)	–8.2 (–13.4 to –2.9)	—
Primary safety end point				
Death from any cause, stroke, life-threatening or fatal bleeding, stage 4 acute kidney injury, hospitalization for a device- or procedure-related complication, or valve dysfunction leading to reintervention at 30 days				
Incidence (95% CI) — %	5.9 (3.9–8.8)†	—	—	<0.001†
Secondary end points at 2 years, listed in hierarchical order				
Death, stroke, or hospitalization for heart failure — no. (Kaplan–Meier estimate, %)	64 (17.7)	83 (23.3)	–5.6 (–11.5 to 0.3)	0.07
Alive with improvement in KCCQ-OS score of ≥10 points from baseline that was sustained at 1 and 2 years — no./total no. (%)‡	134/344 (39.0)	76/327 (23.2)	15.7 (8.8 to 22.6)	—
Hospitalization for heart failure — no. (Kaplan–Meier estimate, %)	26 (7.4)	52 (14.9)	–7.5 (–12.2 to –2.9)	—
LV mass index — g/m^2§	97.1±28.3	101.1±30.1	–3.7 (–7.8 to 0.5)	—
Diastolic dysfunction ≥grade 2 — no./total no. (%)¶	107/275 (38.9)	97/266 (36.5)	2.4 (–5.7 to 10.6)	—

* Plus–minus values are means ±SD. All analyses were performed in the intention-to-treat population, except for the primary safety end-point analysis, which was performed in the TAVR as-treated population (358 patients). In accordance with the *Journal's* statistical guidelines, two-sided 95% confidence intervals and P values are reported.

† The incidence of a primary safety end-point event was 5.9% (two-sided 95% CI, 3.9 to 8.8). The criterion for significance in the analysis of the primary safety end point was met, with an upper limit of the one-sided 97.5% confidence interval of the incidence that was less than the prespecified performance goal of 13.7%. The P value is for comparison with the performance goal. Of 358 patients who underwent the index TAVR procedure, 21 had a primary safety end-point event.

‡ Scores on the KCCQ-OS range from 0 to 100, with higher scores indicating better health status.

§ Data on LV mass index were available for 312 patients in the TAVR group and 297 patients in the clinical-surveillance group. The between-group difference and confidence interval were estimated with the Hodges–Lehmann estimator associated with the Wilcoxon rank-sum test.

¶ Diastolic dysfunction of grade 2 or higher was defined according to American Society of Echocardiography guidelines at the time of enrollment.[23]

tients with Advanced Heart Failure) trial, which involved 178 patients with a reduced left ventricular ejection fraction (20 to 50%) and was not powered to assess between-group differences in the results for the primary end point.[22] Although current guidelines recommend clinical surveillance with echocardiographic evaluation every 1 or 2 years for moderate aortic stenosis,[4,5] the PROGRESS trial showed that TAVR may represent an appropriate therapeutic strategy for this at-risk subgroup of patients with moderate aortic stenosis.

A high percentage of patients with moderate aortic stenosis in the clinical-surveillance group underwent aortic-valve replacement during the 2-year follow-up, owing mainly to progression to severe aortic stenosis, which is a guideline-recommended class 1 indication for valve replacement. Because we enrolled patients with at-risk features, we observed faster progression than that seen in

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Subgroup	TAVR	Clinical Surveillance	Hazard Ratio (95% CI)
	no. of patients with event/total no. (%)		
All patients, intention-to-treat population	60/373 (16.7)	85/371 (23.9)	0.67 (0.48–0.93)
Age			
<75 yr	8/100 (8.1)	14/96 (15.0)	0.52 (0.22–1.24)
≥75 yr	52/273 (19.9)	71/275 (27.0)	0.70 (0.49–1.00)
Sex			
Female	25/142 (18.5)	33/149 (22.9)	0.75 (0.45–1.26)
Male	35/231 (15.6)	52/222 (24.5)	0.62 (0.40–0.95)
Surgical risk			
Low	12/164 (7.6)	30/175 (17.7)	0.41 (0.21–0.81)
Intermediate	26/126 (21.1)	30/135 (23.3)	0.86 (0.51–1.45)
High or extreme	22/83 (28.0)	25/61 (43.3)	0.58 (0.33–1.03)
NYHA class			
I or II	35/244 (15.0)	47/236 (20.9)	0.70 (0.45–1.08)
III or IV	25/129 (19.8)	38/135 (29.0)	0.63 (0.38–1.05)
History of atrial fibrillation			
No	31/246 (13.0)	54/252 (22.2)	0.56 (0.36–0.87)
Yes	29/127 (23.8)	31/119 (27.5)	0.83 (0.50–1.38)
Aortic-valve area			
≤1.2 cm^2	37/215 (17.7)	53/221 (24.9)	0.66 (0.43–1.01)
>1.2 cm^2	23/158 (15.2)	32/150 (22.4)	0.67 (0.39–1.15)
Aortic-valve peak velocity			
<3 m/sec	14/60 (23.9)	16/52 (32.2)	0.73 (0.36–1.50)
≥3 m/sec	46/313 (15.3)	69/319 (22.5)	0.64 (0.44–0.93)
LV ejection fraction			
<50%	10/34 (29.4)	12/29 (42.7)	0.71 (0.31–1.63)
≥50%	50/339 (15.4)	73/342 (22.2)	0.65 (0.46–0.93)
Cardiac damage			
Stage 0–1	3/76 (4.2)	13/78 (17.3)	0.22 (0.06–0.79)
Stage 2–4	52/242 (22.0)	61/228 (28.0)	0.75 (0.52–1.08)
NT-proBNP			
<3× ULN	34/296 (11.8)	47/289 (16.9)	0.68 (0.44–1.05)
≥3× ULN	26/77 (35.9)	38/82 (48.6)	0.66 (0.40–1.10)
Aortic-valve calcium score			
Not elevated	43/264 (16.8)	66/280 (24.6)	0.66 (0.45–0.96)
Elevated	16/105 (15.9)	18/86 (21.6)	0.70 (0.36–1.36)

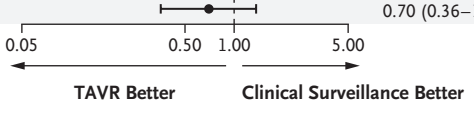


Figure 2. Subgroup Analyses of the Primary Effectiveness End Point.

Shown are the results of subgroup analyses of the primary effectiveness end point (a composite of death from any cause or a heart-failure event with or without hospitalization). Percentages shown are Kaplan–Meier estimates. Additional information regarding the subgroup assessments according to baseline characteristics is provided in Section G in the Supplementary Appendix. Surgical risk was assessed by the local heart team at the trial site. The staging classification for cardiac damage was developed by Généreux et al.[28] An elevated aortic-valve calcium score was defined as a score greater than 1200 Agatston units for women and greater than 2000 Agatston units for men. LV denotes left-ventricular, NT-proBNP N-terminal pro–B-type natriuretic peptide, NYHA New York Heart Association, and ULN upper limit of the normal range.

previous studies.[29] These patients also had a clinically meaningful decline in health status before treatment that may have been prevented with an earlier intervention or more frequent surveillance.

Approximately 16% of the patients who had provided written informed consent and had been initially thought to have moderate aortic stenosis by referral physicians were ultimately found to have lesser or greater disease severity. This discrepancy underscores the clinical challenge of

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accurately determining the severity of aortic stenosis in clinical practice and may explain the heterogeneity in mortality and morbidity observed in large observational registries.[1,8] This finding also supports a strategy of prompt referral to a dedicated valve clinic to better characterize aortic stenosis severity and to determine appropriate management.[30,31]

A strategy of TAVR was superior to clinical surveillance in lowering the incidence of death or a heart-failure event despite the fact that 57.4% of the patients in the clinical-surveillance group underwent aortic-valve replacement within 2 years after randomization. This factor may have mitigated the occurrence of hospitalization for heart failure or death in the clinical-surveillance group owing to the prompt detection of progression to severe aortic stenosis and thereby potentially leading to an underestimation of the benefit of earlier intervention as compared with clinical surveillance and medical therapy.[32,33]

Our trial has several limitations. First, the trial was open-label, and the clinical-events committee was aware of trial-group assignments, which may have introduced observer or reporting bias. Second, the findings may not be generalizable beyond the specific population studied, which was restricted to patients who were 65 years of age or older and suitable for transfemoral TAVR with the trial valve. Whether these results apply to patients without at-risk features remains to be determined. Third, further refinement of medical therapy might have lessened the incidence or degree of heart-failure decompensation; however, guideline-directed therapy for heart failure is established primarily for patients with a reduced left ventricular ejection fraction (≤40%), who represented only 3.0% of the PROGRESS trial population. Furthermore, supporting evidence from trials of sodium–glucose cotransporter 2 inhibitors in patients with heart failure with preserved ejection fraction excluded patients with clinically significant valvular disease, and recommendations for their use were published after enrollment in the PROGRESS trial had begun.[34-36]

Among patients with moderate aortic stenosis and at-risk features, a strategy of TAVR was superior to guideline-recommended clinical surveillance in lowering the incidence of death from any cause or a heart-failure event with or without hospitalization at 2 years.

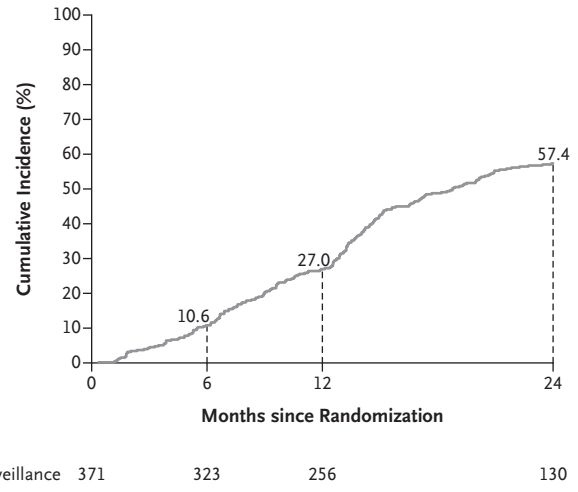


Figure 3. Timing of Delayed Aortic-Valve Replacement in the Clinical-Surveillance Group.

Shown is the cumulative incidence curve for patients in the clinical-surveillance group who underwent delayed aortic-valve replacement within 2 years after randomization (204 patients, of whom 199 [97.5%] underwent TAVR and 5 [2.5%] underwent surgery).

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