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Transcatheter Valve Replacement in Severe Tricuspid Regurgitation

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ABSTRACT

BACKGROUND

Severe tricuspid regurgitation is associated with disabling symptoms and an increased risk of death. Data regarding outcomes after percutaneous transcatheter tricuspid-valve replacement are needed.

METHODS

In this international, multicenter trial, we randomly assigned 400 patients with severe symptomatic tricuspid regurgitation in a 2:1 ratio to undergo either transcatheter tricuspid-valve replacement and medical therapy (valve-replacement group) or medical therapy alone (control group). The hierarchical composite primary outcome was death from any cause, implantation of a right ventricular assist device or heart transplantation, postindex tricuspid-valve intervention, hospitalization for heart failure, an improvement of at least 10 points in the score on the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS), an improvement of at least one New York Heart Association (NYHA) functional class, and an improvement of at least 30 m on the 6-minute walk distance. A win ratio was calculated for the primary outcome by comparing all possible patient pairs, starting with the first event in the hierarchy.

RESULTS

A total of 267 patients were assigned to the valve-replacement group and 133 to the control group. At 1 year, the win ratio favoring valve replacement was 2.02 (95% confidence interval [CI], 1.56 to 2.62; $P<0.001$). In comparisons of patient pairs, those in the valve-replacement group had more wins than the control group with respect to death from any cause (14.8% vs. 12.5%), postindex tricuspid-valve intervention (3.2% vs. 0.6%), and improvement in the KCCQ-OS score (23.1% vs. 6.0%), NYHA class (10.2% vs. 0.8%), and 6-minute walk distance (1.1% vs. 0.9%). The valve-replacement group had fewer wins than the control group with respect to the annualized rate of hospitalization for heart failure (9.7% vs. 10.0%). Severe bleeding occurred in 15.4% of the valve-replacement group and in 5.3% of the control group ($P=0.003$); new permanent pacemakers were implanted in 17.4% and 2.3%, respectively ($P<0.001$).

CONCLUSIONS

For patients with severe tricuspid regurgitation, transcatheter tricuspid-valve replacement was superior to medical therapy alone for the primary composite outcome, driven primarily by improvements in symptoms and quality of life. (Funded by Edwards Lifesciences; TRISCEND II ClinicalTrials.gov number, NCT04482062.)

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*The investigators in the TRISCEND II trial are listed in the Supplementary Appendix, available at NEJM.org.

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Severe tricuspid regurgitation is associated with disabling symptoms and an increased risk of death.[1] Isolated tricuspid-valve surgery is performed infrequently,[2,3] and patients often present late in the disease process, with high rates of operative death and complications.[4] In a randomized trial[5] that compared the safety and effectiveness of tricuspid transcatheter edge-to-edge repair (T-TEER) with medical therapy, investigators found that patients had reduced tricuspid regurgitation and improved quality of life. Quality-of-life improvements in patients with tricuspid regurgitation may be associated with better clinical outcomes.[6,7] However, T-TEER often leaves residual tricuspid regurgitation,[8] and greater residual tricuspid regurgitation is associated with worse outcomes.[9,10] Transcatheter tricuspid-valve replacement reduces tricuspid regurgitation to a level that is deemed to be mild or less in more than 95% of patients[11] and may improve quality of life, functional capacity, and survival, as compared with medical therapy.

A Quick Take is available at NEJM.org

We designed the TRISCEND II pivotal trial (EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy Using a Novel Device) to compare the safety and effectiveness of transcatheter tricuspid-valve replacement using the EVOQUE tricuspid valve-replacement system (Edwards Lifesciences) along with medical therapy to medical therapy alone in the treatment of patients with symptomatic, severe tricuspid regurgitation (Fig. S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org).

METHODS

TRIAL DESIGN AND OVERSIGHT

In this multinational, prospective, randomized, controlled trial, we used a phased primary analysis plan that was designed under the Food and Drug Administration Breakthrough Devices Program.[12] The initial 150 patients who underwent randomization were designated as the breakthrough pathway cohort and were evaluated for safety at 30 days and for tricuspid regurgitation, quality of life, and functional outcomes at 6 months. This cohort's outcomes are described in Figures S2 and S3 and Tables S1 through S4. Here, we report data for the full cohort of 400 patients who were assessed with respect to a primary safety and effectiveness outcome at 1 year.

The protocol (available with the statistical analysis plan at NEJM.org) was designed by the principal investigators and key opinion leaders, the steering committee, and the sponsor (Edwards Lifesciences) in consultation with the Food and Drug Administration. It was approved by the institutional review board at each site. The sponsor financed trial-related activities and participated in site selection, trial management, monitoring, and data management and analysis. Investigators at each trial site gathered data. The principal investigators had unrestricted access to the data, wrote the first draft of the manuscript, made the decision to submit the manuscript for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol.

Trial oversight was conducted by a data and safety monitoring board and central screening committee whose members were unaware of trial-group assignments, along with a clinical events committee and members of an echocardiographic core laboratory who reviewed the data in an unblinded manner.

PATIENTS, RANDOMIZATION, AND TRIAL PROCEDURES

Patients were eligible for enrollment after providing written informed consent and undergoing evaluation by a heart team. Patients were at least 18 years of age with severe tricuspid regurgitation according to the following scale: 0, none or trace; 1, mild; 2, moderate; 3, severe; 4, massive; and 5, torrential.[13] All the patients had signs or symptoms of tricuspid regurgitation or had been hospitalized for associated heart failure despite medical therapy. In addition, all the patients were eligible for valve replacement with the use of the EVOQUE system. Patients were excluded if they had severely depressed right ventricular systolic function, had undergone heart transplantation, had anatomy that precluded proper device delivery, had an estimated glomerular filtration rate of 25 ml per minute per 1.73 m^2 of body-surface area or less or were receiving long-term renal-replacement therapy, or had a life expectancy of less than 12 months (Table S5).

Core laboratory members reviewed echocardiograms before enrollment using screening procedures as described previously.[14] The sponsor analyzed computed tomography scans to ensure anatomic suitability.

RANDOMIZATION AND TRIAL PROCEDURES

Patients underwent randomization in a 2:1 ratio to undergo transcatheter tricuspid-valve replacement plus medical therapy (valve-replacement group) or medical therapy alone (control group). Medical treatment was determined by the heart team and included stable oral diuretic medications, unless the patient had a history of unacceptable side effects. For patients receiving valve replacement, warfarin or another anticoagulant plus aspirin was recommended for at least 6 months after the procedure.

The severity of tricuspid regurgitation was evaluated by transesophageal echocardiography during the procedure and by transthoracic echocardiography at discharge. Patients were followed at 30 days, 6 months, and 1 year and will be followed annually through 5 years.

OUTCOMES

The primary outcome was a hierarchical composite (in rank order) of death from any cause, durable implantation of a right ventricular assist device or heart transplantation, tricuspid-valve surgery or percutaneous tricuspid intervention after any index intervention, annualized rate of hospitalization for heart failure, an improvement of at least 10 points in the score on the Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS), an improvement of at least one New York Heart Association (NYHA) functional class, and an increase in the 6-minute walk distance of at least 30 m.

The KCCQ-OS score is a patient-reported measure of quality of life, with scores ranging from 0 to 100 and higher scores indicating a better quality of life. The minimal clinically important difference is 5 points, and a 10-point improvement indicates a moderate-to-large change in health status.[15] The NYHA functional classification stratifies patients' heart failure according to symptoms. Classes range from I through IV, with class I representing no limitations on physical activity and class IV indicating symptoms of heart failure at rest. A complete list of outcomes is provided in Table S6.

STATISTICAL ANALYSIS

We determined that the enrollment of 400 patients would provide the trial with 80.9% power to show the superiority of transcatheter tricuspid-valve replacement plus medical therapy over medical therapy alone. The hierarchical composite outcome required a two-part analysis to test for superiority. First, the Finkelstein–Schoenfeld method was used to assess statistical significance at a two-sided alpha level of 0.05,[16] then the win-ratio method measured the magnitude of the treatment effect. The win ratio was calculated by systematically comparing all possible patient pairs, starting with the first outcome in the hierarchy, to determine wins for either trial group. For example, a win in the valve-replacement group with respect to death from any cause meant that in a pair of patients from each treatment group, the patient in the valve-replacement group was alive and the patient in the control group died. In case of a tie, pairs moved to the next level in the hierarchy for comparison, with an overall win ratio calculated from the total wins for valve replacement divided by those for the control group.[17] The 95% two-sided confidence interval was calculated by means of the unmatched approach. Confidence intervals are reported without adjustment for multiplicity and are not used for hypothesis testing. SAS Software, version 9.4 (SAS Institute), was used for all statistical calculations.

Analyses of the primary and safety outcomes were conducted in the modified intention-to-treat safety population, which included all the patients in the valve-replacement group who had undergone an attempted trial procedure (skin incision) or medical therapy. The effectiveness outcomes were analyzed in patients in the modified intention-to-treat population, which included those who had undergone guide-sheath insertion or medical therapy. These populations are defined in the Supplementary Appendix.

Missing data were censored for time-dependent outcomes on the date of the last patient participation because of withdrawal or loss to follow-up. Unless otherwise specified, only patients with available data that were required for the outcome analysis were included in the statistical analyses. Paired analyses included only the patients who were alive at follow-up. To address potential attrition bias owing to differential

Table 1. Characteristics of the Patients at Baseline.*

Variable	Valve Replacement (N=259)	Control (N=133)
Mean age (95% CI) — yr	79.3 (78.4–80.2)	79.1 (77.8–80.4)
Female sex — no. (%)	194 (74.9)	102 (76.7)
Race or ethnic group — no. (%)†		
American Indian or Alaskan Native	2 (0.8)	0
Asian	14 (5.4)	8 (6.0)
Black	12 (4.6)	5 (3.8)
Native Hawaiian or other Pacific Islander	0	1 (0.8)
White	195 (75.3)	98 (73.7)
Other	13 (5.0)	10 (7.5)
Missing data	23 (8.9)	11 (8.3)
Mean body-mass index — 95% CI‡	26.8 (26.1–27.6)	27.0 (26.1–27.9)
Atrial fibrillation — no. (%)	249 (96.1)	123 (92.5)
Mean STS mortality score (95% CI) — %§		
Patients with mitral-valve repair	6.7 (6.1–7.3)	7.0 (6.2–7.7)
Patients with mitral-valve replacement	9.6 (9.0–10.2)	10.0 (9.1–10.9)
Mean EuroSCORE II (95% CI) — %¶	5.4 (4.9–5.9)	5.6 (4.9–6.4)
NYHA class III or IV — no. (%)	189 (73.0)	92 (69.2)
Mean KCCQ-OS score (95% CI)‖	52.8 (50.1–55.5)	50.6 (46.9–54.3)
Mean 6-min walk distance (95% CI) — m	236.4 (225.0–247.7)	240.8 (225.7–255.8)
Hypertension — no. (%)	235 (90.7)	122 (91.7)
Chronic kidney disease — no. (%)	140 (54.1)	79 (59.4)
COPD — no. (%)	40 (15.4)	26 (19.5)
Previous CABG — no. (%)	36 (13.9)	26 (19.5)
Previous myocardial infarction — no. (%)	29 (11.2)	19 (14.3)
Previous stroke — no. (%)	39 (15.1)	12 (9.0)
Ascites — no. (%)	48 (18.5)	29 (21.8)
Liver disease — no. (%)	29 (11.2)	15 (11.3)
Stage II to V renal insufficiency — no. (%)	140 (54.1)	79 (59.4)
Gastrointestinal bleeding — no. (%)	22 (8.5)	20 (15.0)
Valve surgery or intervention — no. (%)	87 (33.6)	41 (30.8)
Pacemaker or cardiovascular implantable electronic device — no. (%)	99 (38.2)	53 (39.8)
Hospitalization for heart failure in previous 12 mo — no. (%)	88 (34.0)	48 (36.1)
Mean left ventricular ejection fraction (95% CI) — %	54.4 (53.2–55.6)	54.3 (52.4–56.2)
Cause of tricuspid regurgitation — no. (%)		
Primary**	38 (14.7)	19 (14.3)
Secondary	192 (74.1)	95 (71.4)
Mixed	25 (9.7)	12 (9.0)
Indeterminate	4 (1.5)	7 (5.3)

Table 1. (Continued.)

Variable	Valve Replacement (N=259)	Control (N=133)
Tricuspid regurgitation grade ≥ severe — no. (%)	259 (100)	133 (100)
Severe	122 (47.1)	50 (37.6)
Massive	60 (23.2)	34 (25.6)
Torrential	77 (29.7)	49 (36.8)
Mean pulmonary-artery systolic pressure (95% CI) — mm Hg	38.6 (37.2–39.9)	37.6 (35.7–39.6)
Mean tricuspid annular plane systolic excursion (95% CI) — mm	16.3 (15.7–16.8)	15.6 (14.8–16.4)

* CABG denotes coronary-artery bypass grafting, COPD chronic obstructive pulmonary disease, and IQR interquartile range.
† Race or ethnic group was reported by the patients.
‡ The body-mass index is the weight in kilograms divided by the square of the height in meters.
§ The Society of Thoracic Surgeons (STS) mortality score consists of to 30 variables that predict short- and long-term mortality and morbidity after cardiac surgery. Scores range from less than 4% (low risk), 4 to 8% (intermediate risk), to more than 8% (high risk).
¶ The European System for Cardiac Operative Risk Evaluation (EuroSCORE II) predicts risk of in-hospital death after cardiac surgery. Scores range from less than 4% (low risk), 4 to 8% (intermediate risk), to more than 8% (high risk).
‖ The Kansas City Cardiomyopathy Questionnaire overall summary (KCCQ-OS) score is a patient-reported measure of quality of life ranging from 0 to 100, with higher scores indicating better quality of life.
** This category includes tricuspid regurgitation related to a lead from a cardiovascular implantable electronic device.

withdrawal rates, vital-status sweeps were performed for patients who had withdrawn from the trial. Additional details are provided in the Supplementary Appendix.

RESULTS

PATIENTS

From May 2021 through April 2023, a total of 400 patients underwent randomization (267 assigned to the valve-replacement group and 133 to the control group) across 45 centers in the United States and Germany. The procedure was attempted in 259 patients assigned to valve replacement (Fig. S4). The mean age of the patients was 79.2 years, 75.5% were women, and 94.9% had atrial fibrillation; the mean Society of Thoracic Surgeons mortality score for mitral replacement was 9.7% (Table 1). The baseline characteristics of the patients were similar in the two groups; none of the between-group differences were significant. The demographic characteristics of the patients were broadly representative of the population of patients with severe tricuspid regurgitation (Table S7). Valve-replacement procedural outcomes are described in Table S8.

PRIMARY SAFETY AND EFFECTIVENESS OUTCOMES

At 1 year, the win ratio favoring valve replacement was 2.02 (95% confidence interval [CI], 1.56 to 2.62; P<0.001) (Fig. 1). In comparisons of patient pairs, tricuspid-valve replacement had more wins than medical therapy alone with respect to death from any cause (14.8% vs. 12.5%), postindex tricuspid-valve intervention (3.2% vs. 0.6%), an improvement of at least 10 points in the score on the KCCQ-OS (23.1% vs. 6.0%), an improvement of at least one NYHA functional class (10.2% vs. 0.8%), and an improvement of at least 30 m on the 6-minute walk distance (1.1% vs. 0.9%). The valve-replacement group had fewer wins with respect to the annualized rate of hospitalization for heart failure (9.7% vs. 10.0%). No patients in either group underwent implantation of a right ventricular assist device or heart transplantation. The results of subgroup analyses were consistent with those of the primary analysis (Fig. S5).

The Kaplan–Meier estimates for death from any cause at 1 year were a mean (±SE) of 12.6±2.1% in the valve-replacement group and 15.2±3.3% in the control group; estimates of 20.9±2.6% and 26.1±4.1%, respectively, for hospitalization for heart failure; estimates of 28.4±2.8% and

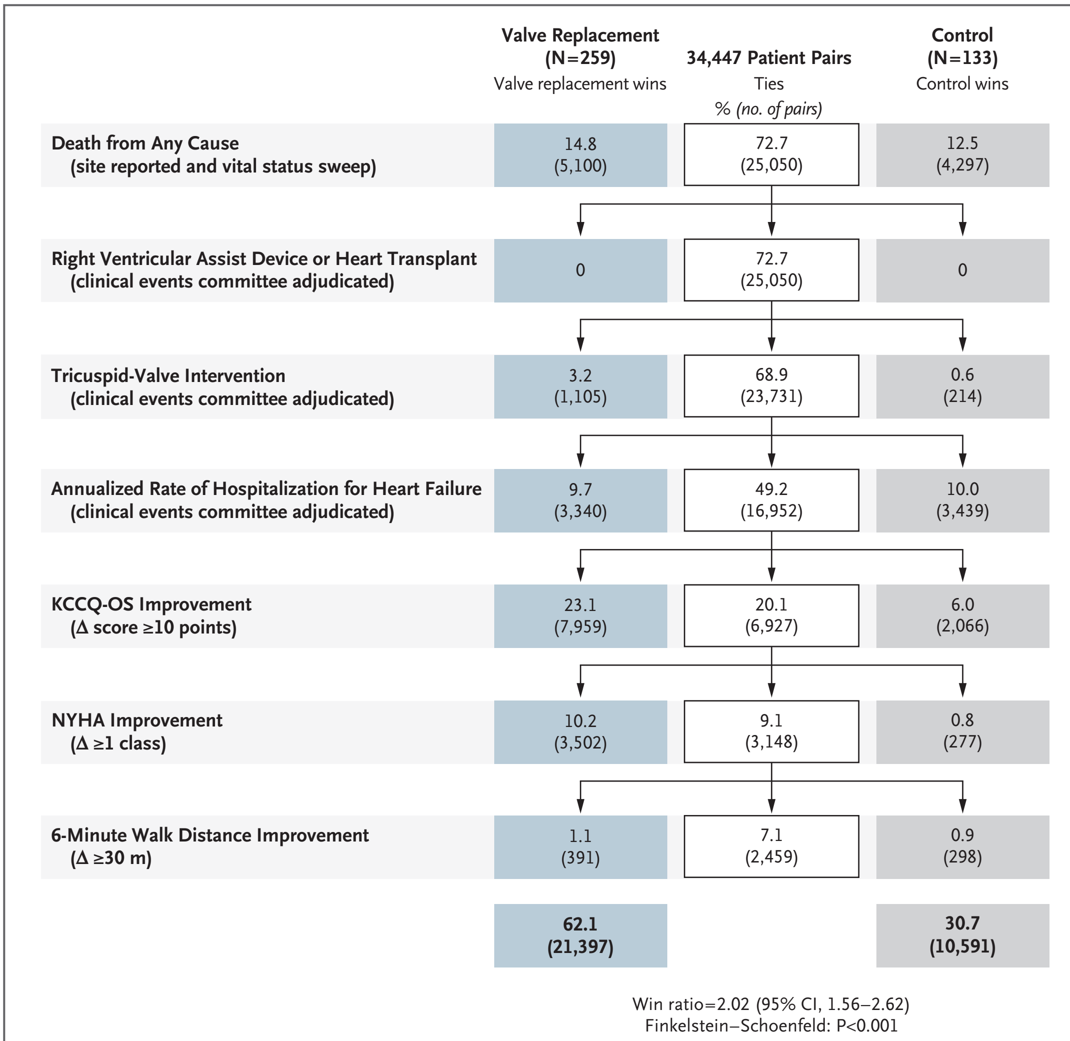

Figure 1. Primary Safety and Effectiveness at 1 Year.

Shown are the components of the win-ratio calculation in the valve-replacement group as compared with the control group. The win ratio was determined from the analysis of the hierarchical composite primary outcome by systematically comparing all possible patient pairs, starting with the first event in the hierarchy. The win ratio was calculated by dividing the number of wins in the valve-replacement group by the number of wins in the control group. This analysis was performed in the modified intention-to-treat safety population, which included all the patients in whom a procedure had been attempted or who had received medical therapy. Values are reported as percentages and numbers of pairs. The results for the composite primary outcome were calculated after the last patient had reached the 12-month follow-up. Included in the control group are 22 patients who crossed over to receive valve replacement within the 1-year visit window (320 to 410 days) after completing their 1-year visit. KCCQ-OS denotes Kansas City Cardiomyopathy Questionnaire overall summary, and NYHA New York Heart Association.

33.3±4.3%, respectively, for a composite of death from any cause or first hospitalization for heart failure; and estimates of 13.7±2.2% and 20.8±3.7%, respectively, for a composite of death from any cause or postindex tricuspid-valve intervention (Fig. 2). The results of sensitivity analyses of death from any cause are provided in Figures S6A through S6D. Among these results, in a landmark analysis starting at 30 days, the Kaplan–Meier estimate of death from any cause at 1 year was 9.4±1.9% in the valve-replacement group and 15.2±3.3% in the control group.

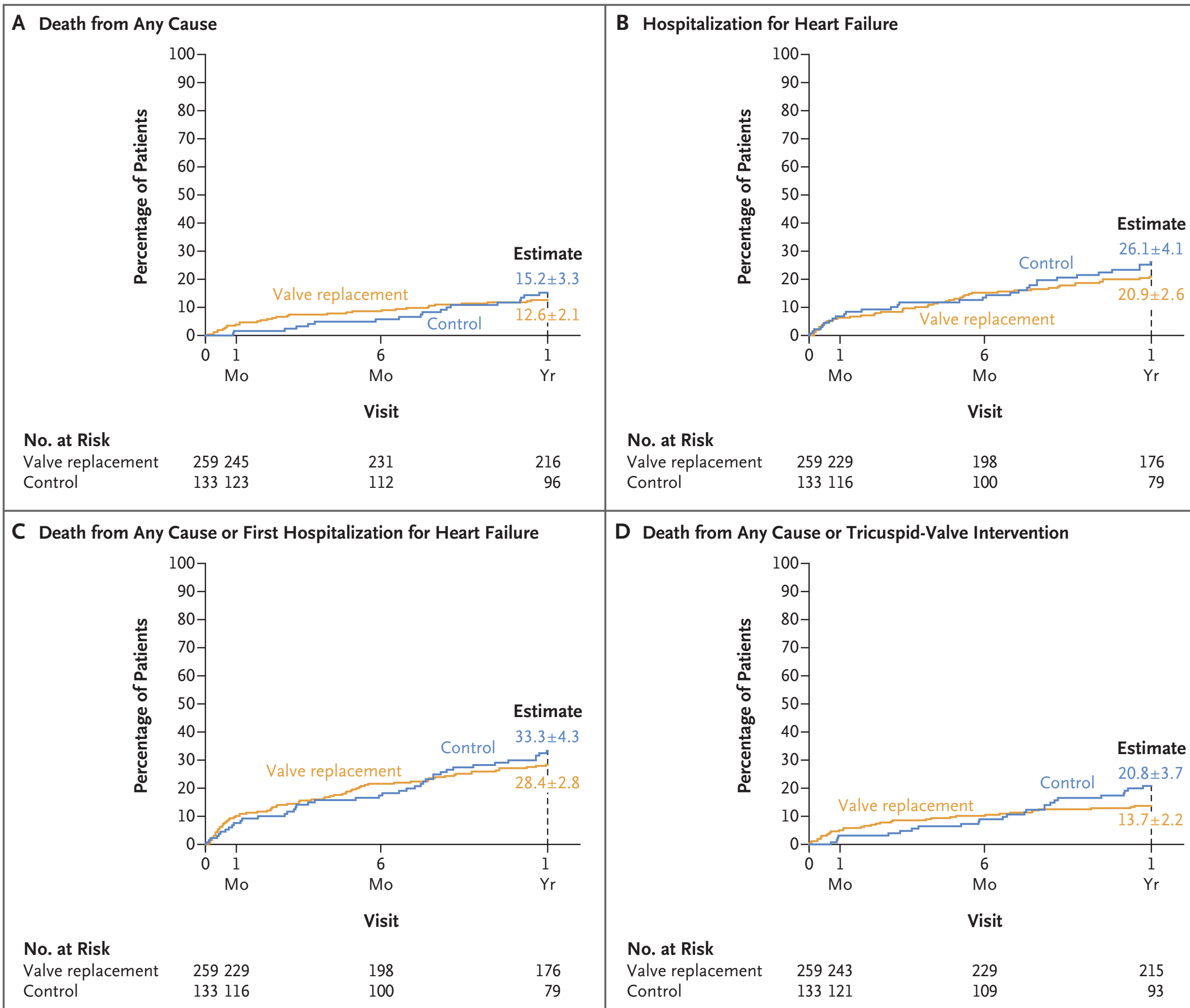

Figure 2. Kaplan–Meier Estimates of CEC-Adjudicated Clinical Events at 1 Year.

Shown are Kaplan–Meier estimates for prespecified events adjudicated by the clinical events committee (CEC) at 1 year. Results are reported as the mean (±SE). These analyses were performed in the modified intention-to-treat safety population.

CLINICAL, FUNCTIONAL, AND QUALITY-OF-LIFE OUTCOMES

The median equivalent daily dose of a diuretic medication from baseline to 1 year in the two trial groups is shown in Table S9, medication changes are provided in Table S10, and paired laboratory data in Table S11. Among the patients in the valve-replacement group, 66.4% had an increase of at least 10 points in the KCCQ-OS score (mean increase, 18.4 points; 95% CI, 15.4 to 21.4), 78.9% had a decrease of at least one NYHA class, and 47.6% increased their 6-minute walk distance by at least 30 m (mean increase, 23.2 m; 95% CI, 9.4 to 37.1). In the control group, these improvements occurred in 36.5%, 24.0%, and 31.8% of the patients, respectively (Fig. 3A).

ECHOCARDIOGRAPHIC OUTCOMES

At 1 year, 72.6% of the patients in the valve-replacement group had no residual tricuspid regurgitation, 22.6% had mild regurgitation, 3.8% had moderate regurgitation, and 0.9% had severe regurgitation. Among the patients in the control group, residual regurgitation was mild in 2.3%,

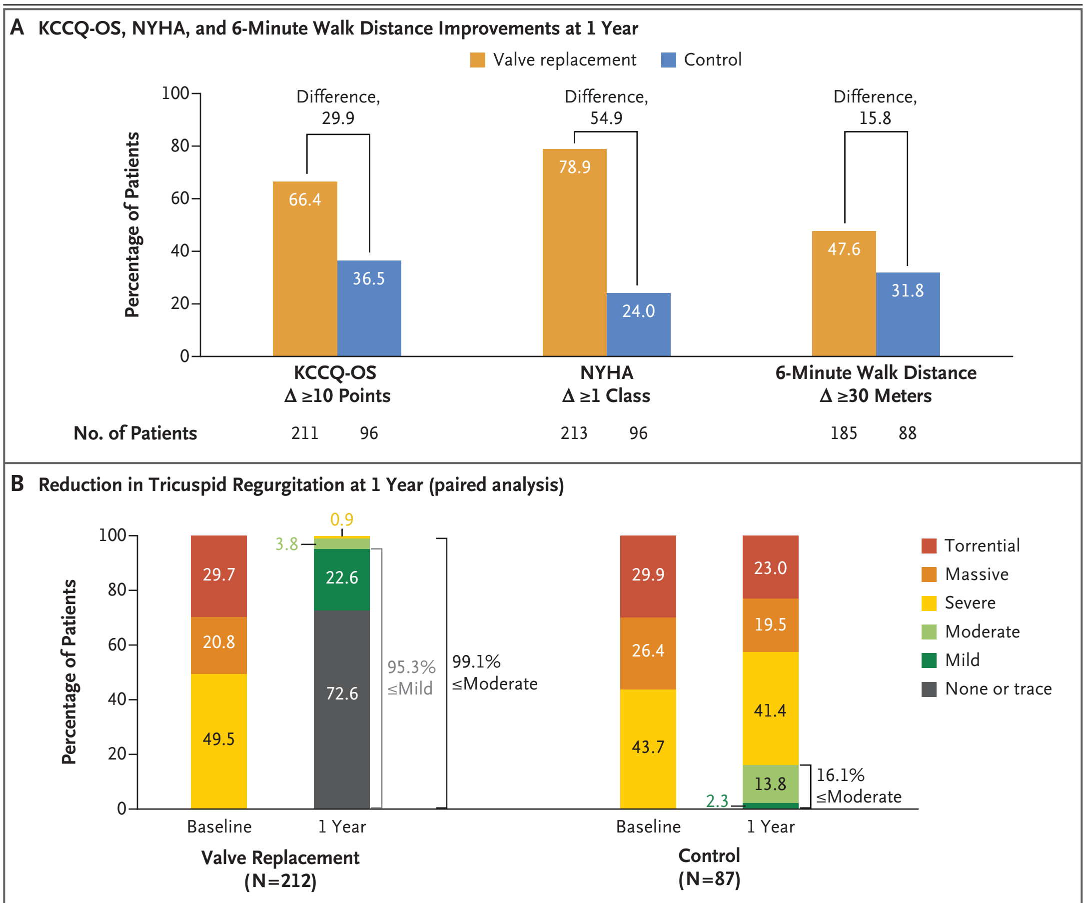

Figure 3. Clinical, Functional, Quality-of-Life, and Tricuspid-Regurgitation Changes at 1 Year.

Panel A shows an improvement of at least 10 points in the score on the KCCQ-OS, an improvement of at least one NYHA functional class, and an improvement of at least 30 m on the 6-minute walk distance at 1 year. Analyses were performed in the modified intention-to-treat safety population. Panel B shows the reduction in tricuspid regurgitation at 1 year in paired analysis. Analyses were performed in the patients in the modified intention-to-treat effectiveness population who had paired data available at baseline and 1 year.

moderate in 13.8%, severe in 41.4%, massive in 19.5%, and torrential in 23.0% (Fig. 3B). Key echocardiographic data are shown in Table S12.

At 1 year, the change from baseline in the right ventricular end-diastolic dimensions was −5.8 mm (95% CI, −7.3 to −4.3) among patients in the valve-replacement group as compared with no change among patients in the control group (0.0 mm; 95% CI, −1.8 to 1.8). The change in the expiration diameter of the inferior vena cava was −4.8 mm (95% CI, −5.8 to −3.9) in the valve-replacement group and −0.3 mm (95% CI, −1.5 to 1.0) in the control group; the change in the tricuspid annular plane systolic excursion was −4.2 mm (95% CI, −5.0 to −3.4) and −0.2 (95% CI, −1.39 to 1.0), respectively, and the change in the right ventricular fractional area was −9.3% (95% CI, −11.0 to −7.5) and −3.9% (95% CI, −6.2 to −1.6), respectively.

SAFETY OUTCOMES

At 30 days, death from any cause had occurred in 3.5% of the patients in the valve-replacement group and in no patients in the control group; death from cardiovascular causes had occurred in 3.1% and no patients, respectively; and severe bleeding had occurred in 10.4% and 1.5%, respectively (Table 2). At 1 year, severe bleeding had occurred in 15.4% of patients in the valve-replacement group and in 5.3% of those in the control group (P=0.003). Sources of severe bleeding are shown in Table S13.

Table 2. Safety Outcomes.*

Safety Event	Early Events (≤30 Days)†		Late Events (31 to 365 Days)‡		Cumulative Events (0 to 365 Days)†		P Value§
	Valve Replacement (N=259)	Control (N=133)	Valve Replacement (N=247)	Control (N=128)	Valve Replacement (N=259)	Control (N=133)	
	number of patients (percent)						
Death from any cause¶	9 (3.5)	0	21 (8.5)	14 (10.9)	30 (11.6)	14 (10.5)	0.87
Death from cardiovascular cause	8 (3.1)	0	14 (5.7)	10 (7.8)	22 (8.5)	10 (7.5)	0.85
Myocardial infarction	2 (0.8)	0	3 (1.2)	1 (0.8)	5 (1.9)	1 (0.8)	0.67
Stroke	1 (0.4)	0	3 (1.2)	0	4 (1.5)	0	0.30
New renal-replacement therapy‖	4 (1.5)	NA	4 (1.6)	NA	8 (3.1)	NA	NA
Severe bleeding**	27 (10.4)	2 (1.5)	13 (5.3)	6 (4.7)	40 (15.4)	7 (5.3)	0.003
Nonelective tricuspid-valve reintervention††	2 (0.8)	1 (0.8)	0	3 (2.3)	2 (0.8)	4 (3.0)	0.19
Major access-site and vascular complication‖	8 (3.1)	NA	0	NA	8 (3.1)	NA	NA
Major cardiac structural complication‖	3 (1.2)	NA	0	NA	3 (1.2)	NA	NA
Device-related pulmonary embolism‖	2 (0.8)	NA	1 (0.4)	NA	2 (0.8)	NA	NA
Arrhythmia and conduction disorder resulting in permanent pacing	41 (15.8)	0	5 (2.0)	3 (2.3)	46 (17.8)	3 (2.3)	<0.001
New pacemaker or cardiac implantable electronic device‡‡							
In all patients	40 (15.4)	0	5 (2.0)	3 (2.3)	45 (17.4)	3 (2.3)	<0.001
In patients without preexisting pacemaker§§	40/162 (24.7)	0/80	5/118 (4.2)¶¶	3/76 (3.9)¶¶	45/162 (27.8)	3/80 (3.8)	<0.001

* Safety analyses were performed in the modified intention-to-treat population, which included all the patients in the valve-replacement group who had undergone an attempted trial procedure or received medical therapy, and events were adjudicated by the clinical events committee. NA denotes not applicable.

† Included in this category were patients from day 0 (day of procedure in the valve-replacement group and randomization in the control group).

‡ Patients must have been enrolled for at least 31 days in this category.

§ P values were calculated with the use of Fisher's exact test for the analyses of cumulative events.

¶ Of the 30 events in the valve-replacement group, death was caused by heart failure in 10 patients (6 with biventricular dysfunction and 4 with right ventricular dysfunction), infection and sepsis in 4 patients, noncardiovascular infection and sepsis in 3 patients, stroke in 2 patients, thromboembolism in 2 patients, unknown cause in 2 patients, major bleeding in 1 patient, cancer in 1 patient, sudden unexpected death in 1 patient, trauma in 1 patient, and other noncardiovascular cause in 3 patients (aspiration pneumonia, encephalopathy, and progressive dementia). Of the 14 events in the control group, death was caused by heart failure in 5 patients (4 biventricular dysfunction and 1 right ventricular dysfunction), unknown cause in 4 patients, noncardiovascular infection and sepsis in 3 patients, arrhythmia and conduction-system disturbance in 1 patient, and other noncardiovascular cause (myxedema coma and hypothyroidism) in 1 patient.

‖ This outcome was adjudicated only in the valve-replacement group.

** Severe bleeding was defined as major, extensive, life-threatening, or fatal as defined by the Mitral Valve Academic Research Consortium.

†† In the valve-replacement group, surgical tricuspid-valve replacement was performed in 2 patients. In the control group, surgical tricuspid-valve replacement was performed in 2 patients, transcatheter edge-to-edge repair in 1 patient, and implantation of a transcatheter bicaval valve system in 1 patient.

‡‡ Implantation may have occurred at a later time than the arrhythmia or conduction-disorder event.

§§ In this category, the denominator is the number of patients without a preexisting pacemaker at baseline. In the valve-replacement group, of the 45 patients without a pacemaker, 1 received a dual-chamber leadless pacemaker, 8 received a dual-chamber pacemaker (6 with right atrial and coronary sinus leads, 1 with epicardial leads, and 1 with right atrial and right ventricular leads after surgical tricuspid-valve replacement), 18 received a single-chamber leadless pacemaker, 11 received a single-chamber pacemaker (5 with coronary sinus leads, 3 with left ventricular leads, 1 with a right atrial lead, 1 with an epicardial lead, and 1 with a right ventricular lead), and 6 received a triple-chamber (biventricular) pacemaker (4 with a single coronary sinus lead, 1 with two coronary sinus leads, and 1 with two left ventricular leads).

¶¶ Patients who had a pacemaker implanted in the first 30 days were excluded from this category.

Arrhythmia and conduction disorders leading to the permanent placement of a pacemaker occurred in 17.8% of patients in the valve-replacement group and in 2.3% of those in the control group (P<0.001). Among the patients without pacemakers at baseline, a new pacemaker or cardiac implantable electronic device was placed in 27.8% of the patients in the valve-replacement group and in 3.8% of those in the control group (P<0.001) (Table 2). A complete list of adverse events is provided in Tables S14 and S15.

Discussion

In our trial, patients with severe symptomatic tricuspid regurgitation who underwent transcatheter tricuspid-valve replacement had a significant improvement in clinical events and quality of life (the hierarchical composite primary outcome) as compared with those who received medical therapy alone at 1 year. Tricuspid regurgitation was decreased to a mild degree or less in 95.2% of the patients in the valve-replacement group as compared with 2.3% of those in the control group. Adverse clinical events were mainly periprocedural, including death from cardiovascular causes, severe bleeding, and conduction disorders leading to new pacemaker implantation.

The improvement in functional and quality-of-life metrics that was observed after valve replacement is clinically relevant[15,18] and exceeds the magnitude of improvement reported previously after T-TEER.[5] In the control group in our trial, regression of tricuspid regurgitation to less than severe at 1 year was reported in 16.1% of the patients, as might be expected from the results of natural history studies.[19] However, the reduction in tricuspid regurgitation to a mild degree or less in 95% of the patients in the valve-replacement group occurred even though more than 50% of the patients had either massive or torrential tricuspid regurgitation at baseline. The forest plot in Figure S5 further shows that the largest increases in the win ratio in the valve-replacement group occurred among patients with the greatest severity of regurgitation at baseline. Arnold et al. found that after T-TEER, every improvement of one grade in tricuspid regurgitation was associated with a 4.1-point increase in the KCCQ-OS score (95% CI, 1.8 to 6.5).[6]

Reduction in regurgitation by transcatheter tricuspid-valve replacement also affected right ventricular reverse remodeling (Table S12), which may influence long-term outcomes, similar to what is reported after tricuspid-valve surgery.[20] As expected, measures of right ventricular function, such as tricuspid annular plane systolic excursion and fractional area change, decreased after reduction in regurgitation[21]; however, the remaining right ventricular contractile function was associated with increases in forward stroke volume after valve replacement. In addition, valve replacement was associated with a reduction in markers of liver congestion (Table S11).

The adverse event rate was driven primarily by severe bleeding and the need for new pacemaker implantation. Patients in this trial had a high prevalence of renal insufficiency and history of bleeding, both risk factors for severe bleeding. Gastrointestinal bleeding rates exceed 15 per 100 patient-years in medically treated patients with tricuspid regurgitation, of whom more than 80% receive long-term anticoagulation and more than 20% have cirrhosis.[22] The severe bleeding that occurred in 10.4% of the patients in the valve-replacement group within 30 days after the procedure may be related to the protocol recommendation of anticoagulation plus an antiplatelet agent, given the marked increase in the use of combination therapy at 30 days after the procedure (Table S10). Rates of severe bleeding that occurred between 31 and 365 days appeared to be similar in the two groups (5.3% vs. 4.7%) (Table 2), despite the observed higher use of combination therapy in the valve-replacement group, which suggests that management of thrombosis risk may not increase bleeding risk beyond 30 days. A single-site report showed that after a periprocedural change in anticoagulation management, 30-day bleeding complications after valve replacement decreased with no increase in valve thrombosis.[23] This finding suggests that bleeding episodes may not be inherent to device therapy but rather that careful management of periprocedural anticoagulation and antithrombotic therapy is needed. The risks of bleeding associated with antithrombotic therapies should be part of the discussion among members of the multidisciplinary heart team regarding the appropriateness of transcatheter tricuspid-valve replacement.

Both preexisting and new cardiac implantable electronic devices are challenges in valve replacement. New pacemaker implantation at 30 days was performed in 15.4% of the patients in the valve-replacement group and in 24.7% of those without a preexisting pacemaker in the valve-replacement group, percentages that were similar to those reported for both surgical tricuspid-valve repair (6 to 14%) and replacement (15 to 34%)[4,24-26]; studies show that patients who received a permanent pacemaker after surgical valve replacement did not have worse long-term survival.[24,27] In patients with preexisting transvalvular leads, lead entrapment by the valve may result in malfunction of the cardiac implantable electronic device.[24] Follow-up, including periodic interrogation of preexisting leads,[24,27] is encouraged.

Our trial was not powered to detect differences in individual components of the composite primary outcome, including death from any cause and hospitalization for heart failure. The observed benefit of transcatheter tricuspid-valve replacement was driven primarily by improvements in symptoms, quality of life, and functional capacity. In a quantitative patient-preference study, Iyer et al. developed a discrete-choice experiment to explore the risk–benefit tradeoffs of treatment for tricuspid regurgitation.[28] Shortness of breath was identified as the most important attribute that determined a patient's choice of a procedure over medical management. Shared decision-making discussions with patients and family members must balance the procedural risks of death, bleeding, and need for cardiac pacing against expected symptomatic benefits and the patient's goals for therapy.

Our trial has several limitations. The 2:1 randomization ratio resulted in a small control group, which was further reduced by disproportionate withdrawals from the control group, missing follow-up data, and crossovers to valve replacement. Crossovers, which were allowed after the 1-year visit, may have introduced an inherent survival bias, confounding the analysis of longer-term follow-up. The relatively small observed between-group differences in mortality or hospitalization for heart failure at 1 year may have been confounded by the cause of tricuspid regurgitation. The high prevalence of hypertension, atrial fibrillation, and a left ventricular ejection fraction of more than 50% suggests that many patients had atrial secondary tricuspid regurgitation,[29] which is associated with lower mortality than ventricular secondary tricuspid regurgitation.[30-32] The protocol-defined modified intention-to-treat analysis excluded eight patients who had undergone randomization but had no attempted procedure; this exclusion was intended to enhance the precision of the primary efficacy and safety comparisons in the patient population of interest.[33] Procedural complications may have been exaggerated by early operator inexperience, reinforcing the importance of expertise in imaging the tricuspid valve. Finally, our results may not be generalizable to patients with more varied anatomies and coexisting conditions.

In patients with severe tricuspid regurgitation, transcatheter tricuspid-valve replacement plus medical therapy was superior to medical therapy alone. Tricuspid regurgitation was reduced to a mild degree or less in nearly all the patients who underwent valve replacement, with associated improvements in symptomatic, functional, and quality-of-life outcomes, as well as favorable numerical trends in mortality and hospitalization for heart failure at 1 year. Periprocedural risks must be considered in the context of these benefits.

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A data sharing statement provided by the authors is available with the full text of this article at NEJM.org.

APPENDIX

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