ORIGINAL ARTICLE

Transcatheter Repair for Patients with Tricuspid Regurgitation

Paul Sorajja, M.D., Brian Whisenant, M.D., Nadira Hamid, M.D., Hursh Naik, M.D., Raj Makkar, M.D., Peter Tadros, M.D., Matthew J. Price, M.D., Gagan Singh, M.D., Neil Fam, M.D., Saibal Kar, M.D., Jonathan G. Schwartz, M.D., Shamir Mehta, M.D., Richard Bae, M.D., Nishant Sekaran, M.D., Travis Warner, M.D., Moody Makar, M.D., George Zorn, M.D., Erin M. Spinner, Ph.D., Phillip M. Trusty, Ph.D., Raymond Benza, M.D., Ulrich Jorde, M.D., Patrick McCarthy, M.D., Vinod Thourani, M.D., Gilbert H.L. Tang, M.D., Rebecca T. Hahn, M.D., and David H. Adams, M.D., for the TRILUMINATE Pivotal Investigators*

ABSTRACT

BACKGROUND

Severe tricuspid regurgitation is a debilitating condition that is associated with substantial morbidity and often with poor quality of life. Decreasing tricuspid regurgitation may reduce symptoms and improve clinical outcomes in patients with this disease.

METHODS

We conducted a prospective randomized trial of percutaneous tricuspid transcatheter edge-to-edge repair (TEER) for severe tricuspid regurgitation. Patients with symptomatic severe tricuspid regurgitation were enrolled at 65 centers in the United States, Canada, and Europe and were randomly assigned in a 1:1 ratio to receive either TEER or medical therapy (control). The primary end point was a hierarchical composite that included death from any cause or tricuspid-valve surgery; hospitalization for heart failure; and an improvement in quality of life as measured with the Kansas City Cardiomyopathy Questionnaire (KCCQ), with an improvement defined as an increase of at least 15 points in the KCCQ score (range, 0 to 100, with higher scores indicating better quality of life) at the 1-year follow-up. The severity of tricuspid regurgitation and safety were also assessed.

RESULTS

A total of 350 patients were enrolled; 175 were assigned to each group. The mean age of the patients was 78 years, and 54.9% were women. The results for the primary end point favored the TEER group (win ratio, 1.48; 95% confidence interval, 1.06 to 2.13; P=0.02). The incidence of death or tricuspid-valve surgery and the rate of hospitalization for heart failure did not appear to differ between the groups. The KCCQ quality-of-life score changed by a mean (±SD) of 12.3±1.8 points in the TEER group, as compared with 0.6±1.8 points in the control group (P<0.001). At 30 days, 87.0% of the patients in the TEER group and 4.8% of those in the control group had tricuspid regurgitation of no greater than moderate severity (P<0.001). TEER was found to be safe; 98.3% of the patients who underwent the procedure were free from major adverse events at 30 days.

CONCLUSIONS

Tricuspid TEER was safe for patients with severe tricuspid regurgitation, reduced the severity of tricuspid regurgitation, and was associated with an improvement in quality of life. (Funded by Abbott; TRILUMINATE Pivotal ClinicalTrials.gov number, NCT03904147.)

From Allina Health Minneapolis Heart Institute at Abbott Northwestern Hospital, Minneapolis (P.S., N.H., R. Bae); Intermountain Medical Center, Murray, UT (B.W., N.S.); St. Joseph's Hospital and Integrated Medical Services, Phoenix, AZ (H.N., T.W.); Cedars–Sinai Medical Center, Los Angeles (R.M., M.M.), Scripps Clinic Green Hospital, La Jolla (M.J.P.), UC Davis Medical Center, Sacramento (G.S.), Los Robles Regional Medical Center, Thousand Oaks (S.K.), and Abbott Structural Heart, Santa Clara (E.M.S., P.M.T.) — all in California; Kansas University Medical Center, Kansas City (P.T., G.Z.); St. Michael's Hospital, Toronto (N.F.), and McMaster University, Hamilton, ON (S.M.) — both in Canada; Carolinas Medical Center, Charlotte, NC (J.G.S.); Ohio State University, Columbus (R. Benza); Montefiore Medical Center, Bronx (U.J.), and Mount Sinai Health System (G.H.L.T., D.H.A.) and New York–Presbyterian Columbia University Medical Center (R.T.H.), New York — all in New York; Northwestern University, Chicago (P.M.); and Marcus Valve Center, Piedmont Heart Institute, Atlanta (V.T.). Dr. Sorajja can be contacted at paul.sorajja@allina.com or at the Valve Science Center, Minneapolis Heart Institute Foundation, 920 E. 28th St., Suite 200, Minneapolis, MN 55417.

*The TRILUMINATE Pivotal Investigators are listed in the Supplementary Appendix, available at NEJM.org.

This article was published on March 4, 2023, at NEJM.org.

DOI: 10.1056/NEJMoa2300525

Untreated severe tricuspid regurgitation is associated with substantial morbidity and often with a poor quality of life. Patients often have congestive right heart failure and impaired cardiac output, which lead to symptoms of excessive fatigue and peripheral edema. Many patients also have poor long-term survival.[1]

Recent recognition that tricuspid regurgitation has independent prognostic implications for clinical outcomes has refocused attention on treatment options, including medical therapies and surgery. Medical therapy for tricuspid regurgitation is largely limited to diuretic agents, which can lead to abatement of symptoms in some patients. Many patients have progression to the point that they are periodically hospitalized or attend clinic visits to receive intravenous diuretics when their fluid status is not well-managed. Surgical treatment of isolated tricuspid regurgitation is challenging because of associated patient factors that increase the risk of surgery, including right ventricular dysfunction and hepatorenal dysfunction due to chronic venous hypertension, often in patients who have previously undergone cardiac surgery. In American cardiology and surgical guidelines, tricuspid-valve surgery has a class I recommendation only for patients with severe tricuspid regurgitation at the time of left heart cardiac surgery.[2] The 2021 European Society of Cardiology and European Association for Cardio-Thoracic Surgery guidelines also have tricuspid-valve surgery as a class I recommendation for symptomatic patients with severe isolated primary tricuspid regurgitation and without severe right ventricular dysfunction.[3] In national registries, operative mortality from isolated tricuspid-valve surgery has ranged from 8 to 10%, although more favorable outcomes have been reported in specialized valve centers.[4-8]

Treatment of tricuspid regurgitation with transcatheter edge-to-edge repair (TEER) has emerged as a safe and potentially effective therapy for patients with tricuspid regurgitation.[9-11] This percutaneous procedure involves a transvenous approach and approximates the tricuspid-valve leaflets by deploying a clip to hold the leaflets together and reduce tricuspid regurgitation without the need for cardiopulmonary bypass or cardiac surgery. Several studies have shown a successful reduction in tricuspid regurgitation that was associated with improvement in symptoms, although the clinical benefit of tricuspid TEER as compared with medical therapy alone remains uncertain.[10,11] We therefore conducted a randomized clinical trial to evaluate the safety and effectiveness of tricuspid TEER in symptomatic patients with severe tricuspid regurgitation.

Methods

Trial Design

The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal (TRILUMINATE Pivotal) is an international, randomized, controlled trial of tricuspid TEER performed with the TriClip Transcatheter Tricuspid Valve Repair system (Abbott Structural Heart) in symptomatic patients with severe tricuspid regurgitation. Lists of the members of the leadership committees, the participating centers, and the investigators are provided in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org.

The protocol was designed by the principal investigators (two authors who were not employees of the sponsor) in collaboration with the steering committee and sponsor, Abbott Structural Heart. The full trial protocol, including the statistical analysis plan, is available at NEJM.org. The protocol was approved by the Food and Drug Administration and by the institutional review boards of the participating centers. The sponsor participated in site selection, trial management, data collection, and data analyses. All the patients provided written informed consent for participation. The principal investigators had unrestricted access to the data (after data unblinding), wrote the manuscript, made the decision to submit it for publication, and vouch for the accuracy and completeness of the data and for the fidelity of the trial to the protocol. Analyses of the data were performed by the trial sponsor.

Investigational Device

Tricuspid TEER was performed with the TriClip Transcatheter Tricuspid Valve Repair system (Fig. S1). The system consists of a 25-French delivery catheter that is used to place one or more TriClip devices on the tricuspid-valve leaflets with the use of echocardiographic and fluoroscopic guidance. The procedure is performed

through the femoral vein, and patients undergoing the procedure are placed under general anesthesia. The TriClip device permanently apposes the tricuspid-valve leaflets, thereby reducing tricuspid regurgitation.

ENROLLMENT, RANDOMIZATION, AND FOLLOW-UP

Patients were eligible for participation in the trial if they had tricuspid regurgitation that was confirmed by an independent echocardiography laboratory as severe, were symptomatic (New York Heart Association [NYHA] functional class II, III, or IVa), had a pulmonary artery systolic pressure of less than 70 mm Hg, were receiving stable (≥30 days) guideline-directed medical therapy for heart failure, had no other cardiovascular conditions in need of interventional or surgical correction (e.g., severe aortic stenosis or mitral regurgitation), and were at intermediate or greater surgical risk as determined by the local heart team, which consisted of board-certified specialists in cardiac surgery, interventional cardiology, echocardiology, and heart failure. Patients in the TEER group underwent the procedure within 14 days after randomization.

Clinical follow-up was conducted at 1, 6, and 12 months. Follow-up visits for all patients consisted of symptom assessment, a 6-minute walk test, and quality-of-life measurement with the Kansas City Cardiomyopathy Questionnaire (KCCQ). Scores on the KCCQ range from 0 to 100, with higher scores indicating better quality of life. A full description of the trial inclusion and exclusion criteria and further details regarding eligibility, enrollment, randomization, and follow-up are provided in the Supplementary Appendix and Table S2. A trial flow chart is provided in Figure S2. This report includes our findings from the randomized phase of the trial at the 1-year follow-up.

TRIAL END POINTS

The primary end point was a hierarchical composite that included death from any cause or tricuspid-valve surgery; hospitalization for heart failure; and an improvement in quality of life as measured with the KCCQ, with an improvement defined as an increase of at least 15 points assessed at the 1-year follow-up. The secondary end points evaluated at 1 year were freedom from major adverse events (defined as death from cardiovascular causes, new-onset kidney failure, endocarditis treated with surgery, and nonelective cardiovascular surgery for a TriClip device–related adverse event) within 30 days (TEER group only), the change from baseline in the KCCQ score at the 1-year follow-up, a reduction in the severity of tricuspid regurgitation to moderate or less by the 30-day follow-up, and the change from baseline in the 6-minute walk distance at the 1-year follow-up. The severity of tricuspid regurgitation was assigned a grade of 1 (trace or mild), 2 (moderate), 3 (severe), 4 (massive), or 5 (torrential) (see the Supplementary Methods section). All echocardiography data, including the severity of tricuspid regurgitation, were assessed at an independent echocardiographic core laboratory, and adverse events were adjudicated by an independent clinical events committee (Table S3).

STATISTICAL ANALYSIS

Under the assumption of a 1-year incidence of death or tricuspid-valve surgery of 15% in the TEER group and 20% in the control group, an annualized rate of hospitalization for heart failure of 0.35 events per patient-year and 0.50 events per patient-year, respectively, and an improvement in the KCCQ score of at least 15 points from baseline occurring in 45% of the patients in the TEER group and in 20% of the patients in the control group, we calculated that a sample of 350 patients would provide 84% power to show superiority of TEER to the control, with a two-sided alpha level of 0.05.[1,10-15] A prespecified sample-size reestimation based on the first 150 patients who underwent randomization and who had reached the 1-year follow-up was performed by a contract research organization (Cytel), and the results confirmed that 350 patients would provide adequate power for the primary analysis.

Analysis of the primary end point was performed with the use of the Finkelstein–Schoenfeld method and a win ratio. The win ratio is calculated by forming all possible pairs of one patient from the TEER group and one patient from the control group and then dividing the number of pairs in which the patient in the TEER group has a better outcome than the patient in the control group (i.e., a win in the TEER group) by the number of pairs in which a patient in the control group has a better outcome than the patient in the TEER group (i.e., a win in the

control group). A 95% confidence interval for the win ratio was calculated with the bootstrap method. If the results for the primary end point were significant, analysis of four powered secondary end points would then be performed in a prespecified hierarchical order to control for multiple comparisons.

The analysis of the primary end point was conducted in the intention-to-treat population, which included all patients who underwent randomization, grouped according to their assigned treatment. We also conducted analyses in a per-protocol population (patients who underwent randomization and had no major protocol deviations), an as-treated population (patients who underwent randomization, grouped according to the treatment received), and an attempted-procedure population (patients who had been randomly assigned to the TEER group, with the exception of those who withdrew consent before the index procedure).

Additional details regarding the statistical analysis are provided in the Supplementary Appendix. All statistical analyses were performed with SAS software, version 9.4 (SAS Institute).

RESULTS

TRIAL POPULATION

Between August 21, 2019, and September 29, 2021, a total of 350 patients from 65 centers in the United States, Europe, and Canada were enrolled in the randomized phase of the trial, with 175 patients assigned to the TEER group and 175 to the control group. The mean (±SD) age of the patients was 78±7 years (range, 51 to 96), and 54.9% of the patients were women (Table 1). A total of 315 patients (90.0%) had atrial fibrillation, and 283 (80.9%) had hypertension. Previous mitral or aortic-valve interventions had occurred in 129 patients (36.9%), 88 patients (25.1%) had been hospitalized for heart failure within 1 year before enrollment, and 52 patients (14.9%) had previously received a cardiac implantable electronic rhythm device. Of the 344 patients who could be evaluated, 323 (93.9%) had functional tricuspid regurgitation (Table S4). On echocardiography at baseline, the mean left ventricular ejection fraction was 59.0±9.9% and the mean cardiac output was 4.2±1.2 liters per minute. The mean right ventricular end-diastolic diameter was 5.1±0.8 cm at the base, the mean tricuspid-valve annular diameter was 4.4±0.7 cm, and the mean right atrial volume was 148.1±84.3 ml. The severity of tricuspid regurgitation was categorized as grade 4 or 5 (massive or torrential) in 239 of the 338 patients who could be evaluated (70.7%). Baseline characteristics appeared to be well matched between the groups and were representative of patients with isolated tricuspid regurgitation (Table S5). Information on medication use is provided in Tables S6 and S7, and data on numbers of completed visits through 1 year are provided in Figure S3.

PROCEDURAL OUTCOMES

Three patients who had been randomly assigned to the TEER group withdrew consent before the index procedure. Among the 172 patients in the attempted-procedure population, the device was successfully implanted in 170 (98.8%), with a mean of 2.2±0.7 clips per patient (Table S8). The mean device time for TEER (i.e., the time from device insertion to device removal) was 90±66 minutes. The median length of stay in the hospital was 1.0 day (interquartile range, 1.0 to 2.0), and 168 of 172 patients (97.7%) were discharged home. Four patients were discharged to a nursing home. No deaths occurred during the hospital stay. One patient (0.6%) in the TEER group died within 30 days after the procedure; the death was adjudicated as not related to the device or procedure.

ECHOCARDIOGRAPHIC ASSESSMENT

At baseline, 169 of 173 patients in the TEER group and 163 of 165 patients in the control group had severe or worse tricuspid regurgitation. At the 1-year follow-up, the severity of tricuspid regurgitation was moderate or less in 126 of 143 patients in the TEER group and in 8 of 141 patients in the control group. The differences in the denominators reflect the numbers of patients with available and interpretable echocardiographic data at each time point. At baseline and at the 1-year follow-up, quantitative measurements of tricuspid regurgitation severity were assessed (Table S9). The severity of tricuspid regurgitation through the 1-year follow-up (paired analysis) is shown in Figure S4.

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	TEER Group (N=175)	Control Group (N=175)
Age — yr	78.0±7.4	77.8±7.2
Female sex — no. (%)	98 (56.0)	94 (53.7)
New York Heart Association class III or IV — no. (%)	104 (59.4)	97 (55.4)
Atrial fibrillation — no. (%)	153 (87.4)	162 (92.6)
Atrial flutter — no./total no. (%)	20/174 (11.4)	22/174 (12.6)
Dyslipidemia — no. (%)	117 (66.9)	92 (52.6)
Hypertension — no. (%)	142 (81.1)	141 (80.6)
Stroke — no. (%)	11 (6.3)	19 (10.9)
Transient ischemic attack — no. (%)	13 (7.4)	17 (9.7)
Diabetes mellitus — no. (%)	28 (16.0)	27 (15.4)
Peripheral vascular disease — no. (%)	16 (9.1)	18 (10.3)
Coronary-artery bypass grafting — no. (%)	31 (17.7)	36 (20.6)
Percutaneous coronary intervention — no. (%)	26 (14.9)	23 (13.1)
Kidney disease — no. (%)	62 (35.4)	62 (35.4)
Liver disease — no. (%)	11 (6.3)	16 (9.1)
Chronic obstructive pulmonary disease — no. (%)	19 (10.9)	24 (13.7)
CRT, CRT-D, ICD, or permanent pacemaker — no. (%)	28 (16.0)	24 (13.7)
Previous cardiac or transcatheter therapy — no. (%)†		
Aortic-valve intervention	27 (15.4)	27 (15.4)
Surgical mitral-valve repair	14 (8.0)	9 (5.1)
Percutaneous mitral-valve repair	18 (10.3)	22 (12.6)
Mitral-valve replacement	10 (5.7)	9 (5.1)
Tricuspid-valve repair	1 (0.6)	0
Hospitalization for heart failure within 1 yr before enrollment — no. (%)	44 (25.1)	44 (25.1)
KCCQ score‡	56.0±23.4	54.1±24.2
B-type natriuretic peptide level — pg/ml§	382.0±347.5	355.4±283.4
Body-mass index¶	27.0±5.8	26.9±5.2
6-min walk distance — m‖	240.5±117.1	253.6±129.1
Glomerular filtration rate — ml/min/1.73 m^2**	54.1±20.4	56.9±20.0
Medications — no. (%)		
β-receptor antagonist	114 (65.1)	115 (65.7)
ACE-I, ARB, or ARNI	68 (38.9)	66 (37.7)
Vasodilator	14 (8.0)	17 (9.7)
Diuretic	152 (86.9)	161 (92.0)

* Plus–minus values are means ±SD. ACE-I denotes angiotensin-converting–enzyme inhibitor, ARB angiotensin-receptor blocker, ARNI angiotensin receptor–neprilysin inhibitor, CRT cardiac resynchronization therapy, CRT-D cardiac resynchronization therapy defibrillator, ICD implantable cardioverter–defibrillator, and TEER transcatheter edge-to-edge repair.
† Patients may have had more than one type of intervention.
‡ Scores on the Kansas City Cardiomyopathy Questionnaire (KCCQ) range from 0 to 100, with higher scores indicating better quality of life. Data were available for 175 patients in the TEER group and 174 patients in the control group.
§ Data were available for 105 patients in the TEER group and 98 patients in the control group.
¶ The body-mass index is the weight in kilograms divided by the square of the height in meters.
‖ Data were available for 164 patients in the TEER group and 169 patients in the control group.
** Data were available for 168 patients in the TEER group and 164 patients in the control group.

Table 2. Primary and Secondary End Points.*

End Point	TEER Group (N=175)	Control Group (N=175)	Difference (95% CI)	P Value
Primary				
Hierarchical composite of death from any cause or tricuspid-valve surgery; hospitalization for heart failure; and improvement of ≥15 points in KCCQ score at 1 yr — no. of wins†	11,348	7643	1.48 (1.06 to 2.13)	0.02
Secondary, listed in hierarchical order				
Kaplan–Meier estimate of percentage of patients with freedom from major adverse events through 30 days after the procedure (lower 95% confidence limit)‡	98.3 (96.3)	—	—	<0.001
Change in KCCQ score from baseline to 1 yr — points§	12.3±1.8	0.6±1.8	11.7 (6.8 to 16.6)	<0.001
Tricuspid regurgitation of no greater than moderate severity at 30-day follow-up — no. of patients/total no. (%)¶	140/161 (87.0)	7/146 (4.8)	—	<0.001
Change in 6-min walk distance from baseline to 1 yr — m‖	−8.1±10.5	−25.2±10.3	17.1 (−12.0 to 46.1)	0.25

* Plus–minus values are means ±SD. All analyses were performed in the intention-to-treat population (all patients who underwent randomization, grouped according to their assigned treatment) unless otherwise noted. CI denotes confidence interval.

† The between-group difference for this end point is expressed as the win ratio, which is calculated by forming all possible pairs of one patient from the TEER group and one patient from the control group and then dividing the number of pairs in which the patient in the TEER group has a better outcome than the patient in the control group (i.e., a win in the TEER group) by the number of pairs in which a patient in the control group has a better outcome than the patient in the TEER group (i.e., a win in the control group). The P value is from a Finkelstein–Schoenfeld analysis.

‡ This end point was assessed in the attempted-procedure population (patients in the TEER group, excluding those who withdrew consent before the index procedure), which included 172 patients. The P value is from a one-sided Z test for the comparison with a performance goal of 90%.

§ A KCCQ score of 0 was imputed for all patients who had a heart failure–related death from cardiovascular causes or received tricuspid-valve surgery before completing the 1-year follow-up. Data were available for 155 patients in each group. The P value is from an analysis of covariance (ANCOVA) test.

¶ Data were available for 161 patients in the TEER group and 146 patients in the control group. The P value is from a Pearson's chi-square test.

‖ A 6-minute walk distance of 0 was imputed for all patients who had a heart failure–related death from cardiovascular causes or received tricuspid-valve surgery before completing the 1-year follow-up. Patients who, for cardiac reasons, were unable to exercise were also assigned a distance of 0. Data were available for 131 patients in the TEER group and 136 patients in the control group. The P value is from an ANCOVA test.

PRIMARY END POINT

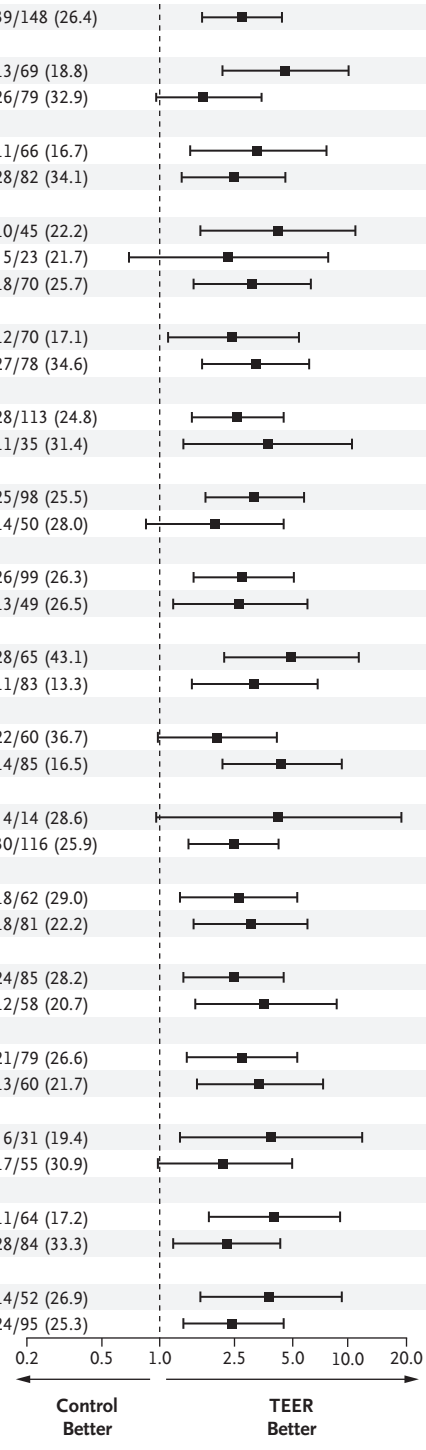
On the basis of 11,348 wins for the TEER group, 7643 wins for the control group, and 11,634 ties between the groups, the win ratio for the primary end point was 1.48 (95% confidence interval, 1.06 to 2.13; P=0.02) (Table 2). Details regarding the win ratio for the primary composite end point, the individual components of the composite end point, and the Finkelstein–Schoenfeld analyses are shown in Table S10. The results of the as-treated and per-protocol analyses and of a sensitivity analysis that included events after diagnosis of coronavirus disease 2019 (Covid-19) rather than censoring them appeared similar to those of the intention-to-treat analysis (Table S11).

Death from any cause or tricuspid-valve surgery occurred in 16 patients (9.4%) in the TEER group and 18 patients (10.6%) in the control group. The annualized rate of hospitalization for heart failure was 0.21 events per patient-year in the TEER group and 0.17 events per patient-year in the control group (Fig. S5 and Table S18). A total of 73 of 147 patients (49.7%) in the TEER group and 39 of 148 patients (26.4%) in the control group had a 15-point or greater improvement in their KCCQ score. The magnitude of the change in KCCQ score appeared to favor TEER across subgroups based on demographic characteristics, coexisting conditions, previous interventions, hemodynamic characteristics, and right heart size and function (Fig. 1).

Figure 1 (facing page). Subgroup Analyses of the Improvement in Quality of Life at 1 Year.

Percentages of patients with an improvement of at least 15 points in the Kansas City Cardiomyopathy Questionnaire (KCCQ) score are shown; scores on the KCCQ range from 0 to 100, with higher scores indicating better quality of life. The severity of tricuspid regurgitation was assigned a grade of 1 (trace or mild), 2 (moderate), 3 (severe), 4 (massive), or 5 (torrential). Mean values at baseline were used as reference points to determine cutoff values for all continuous variables. TEER denotes transcatheter edge-to-edge repair.

Subgroup	No. of Patients	TEER Group	Control Group	Odds Ratio (95% Confidence Interval)
		patients with ≥15-point improvement in KCCQ/total no. (%)		
All Patients	295	73/147 (49.7)	39/148 (26.4)	2.76 (1.69–4.49)
Age				
<78 yr	140	37/71 (52.1)	13/69 (18.8)	4.69 (2.19–10.05)
≥78 yr	155	36/76 (47.4)	26/79 (32.9)	1.83 (0.96–3.52)
Sex				
Male	126	24/60 (40.0)	11/66 (16.7)	3.33 (1.46–7.63)
Female	169	49/87 (56.3)	28/82 (34.1)	2.49 (1.33–4.64)
Tricuspid regurgitation severity				
Grade 3	85	22/40 (55.0)	10/45 (22.2)	4.28 (1.67–10.94)
Grade 4	56	13/33 (39.4)	5/23 (21.7)	2.34 (0.70–7.86)
Grade 5	139	36/69 (52.2)	18/70 (25.7)	3.15 (1.54–6.44)
New York Heart Association class				
I or II	138	23/68 (33.8)	12/70 (17.1)	2.47 (1.11–5.49)
III or IV	157	50/79 (63.3)	27/78 (34.6)	3.26 (1.69–6.26)
Hospitalization for heart failure within the past year				
No	230	54/117 (46.2)	28/113 (24.8)	2.60 (1.49–4.56)
Yes	65	19/30 (63.3)	11/35 (31.4)	3.77 (1.35–10.56)
Kidney disease				
No	199	53/101 (52.5)	25/98 (25.5)	3.22 (1.77–5.87)
Yes	96	20/46 (43.5)	14/50 (28.0)	1.98 (0.85–4.62)
Previous mitral or aortic intervention				
No	189	45/90 (50.0)	26/99 (26.3)	2.81 (1.53–5.16)
Yes	106	28/57 (49.1)	13/49 (26.5)	2.67 (1.18–6.07)
KCCQ				
<50	118	42/53 (79.2)	28/65 (43.1)	5.05 (2.21–11.52)
≥50	177	31/94 (33.0)	11/83 (13.3)	3.22 (1.50–6.93)
6-min walk distance				
<240 m	121	33/61 (54.1)	22/60 (36.7)	2.04 (0.98–4.21)
≥240 m	164	37/79 (46.8)	14/85 (16.5)	4.47 (2.17–9.21)
Left ventricular ejection fraction				
<50%	33	12/19 (63.2)	4/14 (28.6)	4.29 (0.97–18.97)
≥50%	234	55/118 (46.6)	30/116 (25.9)	2.50 (1.44–4.34)
Right ventricular end-diastolic dimension				
<5 cm	133	37/71 (52.1)	18/62 (29.0)	2.66 (1.30–5.46)
≥5 cm	156	35/75 (46.7)	18/81 (22.2)	3.06 (1.53–6.12)
Right atrial volume				
<150 ml	186	50/101 (49.5)	24/85 (28.2)	2.49 (1.35–4.60)
≥150 ml	103	22/45 (48.9)	12/58 (20.7)	3.67 (1.55–8.69)
Tricuspid annular plane systolic excursion				
<1.7 cm	151	36/72 (50.0)	21/79 (26.6)	2.76 (1.40–5.45)
≥1.7 cm	134	36/74 (48.6)	13/60 (21.7)	3.43 (1.59–7.36)
Central venous pressure				
<10 mm Hg	66	17/35 (48.6)	6/31 (19.4)	3.94 (1.30–11.95)
≥10 mm Hg	99	22/44 (50.0)	17/55 (30.9)	2.24 (0.98–5.09)
Mean pulmonary artery pressure				
<25 mm Hg	138	34/74 (45.9)	11/64 (17.2)	4.10 (1.85–9.06)
≥25 mm Hg	157	39/73 (53.4)	28/84 (33.3)	2.29 (1.20–4.38)
Cardiac output				
<4 liters/min	96	26/44 (59.1)	14/52 (26.9)	3.92 (1.66–9.25)
≥4 liters/min	198	47/103 (45.6)	24/95 (25.3)	2.48 (1.36–4.54)



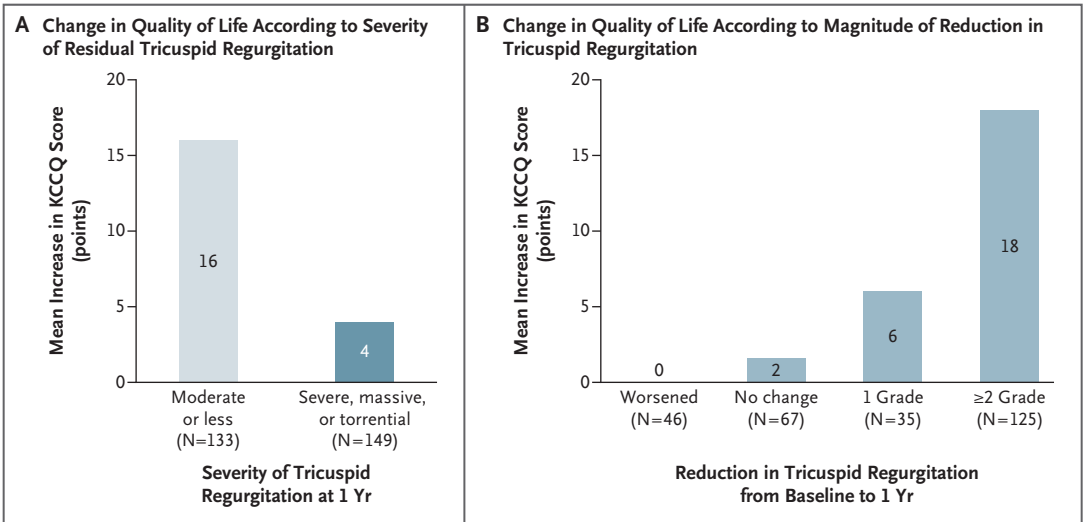


Figure 2. Changes in Quality of Life from Baseline to 1 Year, Stratified According to the Severity of Residual Tricuspid Regurgitation and the Magnitude of the Reduction in Tricuspid Regurgitation.

SECONDARY END POINTS

The results for secondary end points are summarized in Table 2. Freedom from major adverse events at 30 days occurred in 169 of 172 patients (98.3% of the patients in the attempted-procedure population, P<0.001), which exceeded the performance goal of 90%. Three major adverse events occurred within 30 days: new-onset kidney failure in 2 patients and one death from cardiovascular causes. The death occurred after hospital discharge and followed a readmission for a noncardiac procedure. At 1 year, the KCCQ score had increased by a mean of 12.3±1.8 points in the TEER group and 0.6±1.8 points in the control group. Without imputation, the increases in the KCCQ score for these two groups were 15.2±22.3 and 4.8±18.3, respectively (P<0.001). The change in the KCCQ score was associated with the degree of residual tricuspid regurgitation and magnitude of tricuspid regurgitation reduction at the 1-year follow-up (Fig. 2). The mean increase in the KCCQ score at the 1-year follow-up was 15.6±22.0 among patients with moderate or less residual tricuspid regurgitation at 1 year and was 3.8±18.4 among patients with severe or greater residual tricuspid regurgitation. A total of 140 of 161 patients (87.0%) in the TEER group and 7 of 146 patients (4.8%) in the control group had tricuspid regurgitation of no greater than moderate severity at 30 days (P<0.001) (Fig. 3). The difference in the denominator reflects the number of patients with available and interpretable echocardiographic data at each time point. At 1 year, the 6-minute walk distance had changed by a mean of −8.1±10.5 m in the TEER group and −25.2±10.3 m in the control group (P=0.25). Without imputation, the changes in 6-minute walk distance were 11.5±111.4 m in the TEER group and −8.7±109.7 m in the control group (Table S12). The results were similar in sensitivity analyses accounting for the competing risk of death and missing data through multiple imputation (Tables S13 and S14).

ADDITIONAL END POINTS AND SAFETY

The percentage of patients who were in NYHA functional class I or II at the 1-year follow-up was 83.9% (125 of 149 patients) in the TEER group and 59.5% (88 of 148 patients) in the control group (paired analysis is shown in Fig. S6). Adjudicated adverse events are shown in Table S15. Tricuspid-valve surgery during follow-up occurred in 3 of 175 patients (1.8%) in the TEER group and in 6 of 175 patients (3.6%) in the control group. In the TEER group, major bleeding (defined as Bleeding Academic Research Consortium type ≥3a) occurred in 9 of 175 patients (5.2%) within 1 year.[16] A cardiac electronic rhythm device (permanent pacemaker or implantable cardioverter–defibrillator) was placed in 5 patients (2.9%) in the TEER group and 5 pa-

tients (2.9%) in the control group within 1 year. Single-leaflet device attachment occurred in 12 of the 172 patients (7.0%) in the attempted-procedure population within 30 days, with no further events occurring after 30 days; no major adverse events associated with single-leaflet device attachment occurred within 12 months. No device embolization or device thrombosis occurred among patients in the TEER group. A mean tricuspid gradient of 5 mm Hg or greater was found in 8 patients in the TEER group at the 30-day follow-up; these events had no related clinical symptoms and did not lead to any intervention. The percentages of patients with site-reported serious and nonserious adverse events are shown in Tables S16 and S17. The rates of hospitalization for heart failure during the 12 months before and after the index procedure are provided in Table S18.

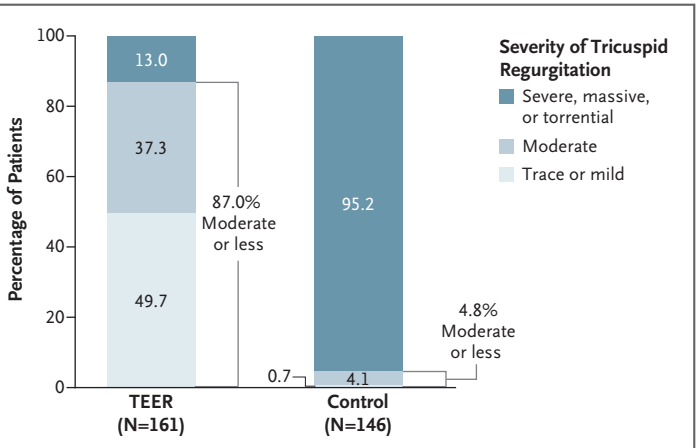


Figure 3. Severity of Tricuspid Regurgitation at 30 Days.

DISCUSSION

In this prospective, randomized, controlled trial involving patients with symptomatic severe tricuspid regurgitation, we found tricuspid TEER to be safe, and the severity of tricuspid regurgitation was reduced to moderate or less at 1 year in the majority of patients who underwent the procedure. Our results with respect to attaining moderate or less tricuspid regurgitation appeared to be better than those previously described in nonrandomized registry studies; this difference is likely to be related to operator experience, the growing experience with procedural imaging, and device design.[9-11] The decrease in tricuspid regurgitation after TEER appeared to be stable at 1 year of follow-up.

The reduction in tricuspid regurgitation was correlated with improvements in quality-of-life scores in the TEER group, with a mean increase in the KCCQ score of approximately 12 points at 1 year, as compared with a mean increase of approximately 1 point in the control group. Almost twice as many patients in the TEER group as in the control group had an improvement of 15 points or greater in their KCCQ score at 1 year. The patients enrolled in our trial had higher baseline KCCQ scores than those in tricuspid registry studies, and the improvement in scores in the TEER group exceeded our initial prediction.[9-11,17]

We did not see apparent between-group differences in mortality or in the rate of hospitalization for heart failure at 1 year, and both death and hospitalization for heart failure occurred less frequently than we had predicted when the trial was designed. The enrolled patients had a broad spectrum of coexisting conditions, since the principal entry requirement was severe symptomatic tricuspid regurgitation amenable to TEER. Our focus was to ensure that tricuspid regurgitation was the likely source of symptoms, and we mandated right heart catheterization to aid in confirming that the patient had received appropriate medical management. The favorable early survivorship we observed may have been related to our rigorous selection process and enrollment of patients with fewer overall coexisting conditions than in previous studies.[1,4,5,9,17-19] The lower-than-expected rate of hospitalization for heart failure may have been attributable to our selection process. Certainly, tricuspid regurgitation can be caused by a number of different underlying conditions, and its reduction with TEER may not address the root causes of the valvular disease. The Hawthorne effect may have also contributed to improved management of the condition in these patients. Given the importance of symptoms and the degree of valve regurgitation for long-term event-free survival and the differences between the two groups at 1 year, longitudinal follow-up for survival and hospitalizations for heart failure will be important.[2,3] The patients enrolled in this trial will be followed for 5 years.

One limitation of our trial is that it was open label, which potentially introduces bias into the

interpretation of the clinical outcomes. However, follow-up assessments were conducted by personnel who were unaware of the group assignments and were performed with the use of standardized scripts to minimize bias. The personnel in the echocardiography core laboratory were aware of the group assignments. Patients in both groups may have been affected by the increased scrutiny associated with participation in a randomized trial. Our trial was also conducted during the Covid-19 pandemic, which may have affected clinical outcomes. We did perform a Covid-19 sensitivity analysis of the primary end point that yielded results similar to those of the main analysis. Finally, patients were selected for the trial on the basis of both clinical and tricuspid-valve anatomical criteria, and a central committee examined the echocardiographic findings for each patient to determine eligibility. Our results may not be applicable to patients with anatomical or hemodynamic findings that differ from those deemed suitable for entry in the present trial.

We found that tricuspid TEER reduced severe tricuspid regurgitation and was associated with improvements in quality of life at 1 year.

Supported by Abbott.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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

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