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Health Status after Transcatheter Tricuspid-Valve Repair in Patients with Severe Tricuspid Regurgitation: Results from the TRILUMINATE Pivotal Trial

Brief Title: Health Status after T-TEER

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ABSTRACT

Background: In the TRILUMINATE Pivotal trial, tricuspid transcatheter edge-to-edge repair (T-TEER) reduced TR and improved health status compared with medical therapy alone with no benefit on heart failure hospitalizations or survival.

Objective: To better understand the health status benefits of T-TEER within the TRILUMINATE Pivotal trial.

Methods: TRILUMINATE randomized patients with severe TR to T-TEER (n=175) or medical therapy (n=175). Health status was assessed at baseline and at 1, 6, and 12 months with the KCCQ (range 0-100; higher=better), which was compared between treatment groups using mixed effects linear regression. Alive and well was defined as KCCQ-OS >=60 and no decline from baseline of >10 points at 1 year.

Results: Compared with medical therapy, T-TEER significantly improved health status at 1 month (mean between-group difference in KCCQ-OS 9.4 points, 95% CI 5.3-13.4), with a small additional improvement at 1 year (mean between-group difference 10.4 points, 95% CI 6.3-14.6). T-TEER patients were more likely to be alive and well at 1 year (T-TEER vs. medical therapy: 74.8% vs. 45.9%, $p<0.001$), with a number needed-to-treat of 3.5. Interaction analyses demonstrated that the benefit of T-TEER diminished as baseline KCCQ-OS increased ($p_{int}<0.001$). Exploratory analyses suggested that much of the health status benefit of T-TEER could be explained by TR reduction and that improvement in health status after T-TEER was strongly correlated with reduced 1-year mortality and heart failure hospitalization.

Conclusion: T-TEER with the TriClip system resulted in substantial and sustained health status improvement in patients with severe TR compared with medical therapy alone.

CONDENSED ABSTRACT

In this prespecified analysis of the TRILUMINATE Pivotal trial, we examined the health status outcomes of patients with severe, symptomatic tricuspid regurgitation randomized to transcatheter edge-to-edge repair (T-TEER) versus medical therapy alone. Compared with medical therapy alone, T-TEER resulted in substantially better health status at 1 month that was sustained through 1 year. At 1 year, 75% of the T-TEER patients were alive and well versus 46% in the medical therapy arm, with a number needed-to-treat of 3.5 patients to derive the benefit.

KEYWORDS: tricuspid valve regurgitation, transcatheter valve, quality of life

ABBREVIATIONS

CI = confidence interval

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-OS = KCCQ-overall summary score

NNT = number needed to treat

NYHA = New York Heart Association

SF-36 = Medical Outcomes Study Short-Form 36 Health Survey

SF-36 PCS = physical summary score

SF-36 MCS = mental summary score

TRILUMINATE Pivotal = Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal

TR = tricuspid regurgitation

T-TEER = tricuspid-edge-to-edge transcatheter valve repair

TRIAL REGISTRATION: ClinicalTrials.gov number, NCT03904147

Severe tricuspid regurgitation (TR) is associated with increased mortality (1,2), increased risk of heart failure hospitalization, reduced functional capacity (3,4), and impaired patient-reported health status (i.e., symptoms, functional status, quality of life) (5-11). Tricuspid-edge-to-edge transcatheter valve repair (T-TEER) with the TriClip device (hereafter referred to as transcatheter tricuspid valve repair system) (Abbott, Santa Clara, CA) effectively reduces tricuspid regurgitation (TR) with low risk for periprocedural complications (7,12,13). Early, uncontrolled studies suggested that T-TEER also improved functional outcomes (11,14,15) and health status (7,11). The Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal (TRILUMINATE Pivotal) recently compared T-TEER with the transcatheter tricuspid valve repair system versus medical therapy alone and found no difference with respect to death or heart failure hospitalizations at 1 year, but there was a significant improvement in patient-reported health status with T-TEER (12).

Although prolonging survival and reducing heart failure hospitalizations are important goals when treating patients with severe TR, improving patients' health status may be just as important—particularly in patients who are older, symptomatic, and have a high comorbidity burden (16,17). To better understand the impact of T-TEER on patients' health status and thereby quantify the procedure's potential benefit, we performed an in-depth analysis of the health status outcomes in the TRILUMINATE Pivotal trial. Our goals were to more fully describe the timing and magnitude of the health status benefits of T-TEER as well as to explore any heterogeneity in the health status benefit across different patient characteristics. Furthermore, since patient-reported outcomes may be subject to bias in an unblinded trial, we sought to understand the biologic correlates of health status after T-TEER and the clinical relevance of the observed health status benefit in the trial.

METHODS

Study Design. The design and primary results of the TRILUMINATE Pivotal trial (ClinicalTrials.gov: NCT03904147) have been published (12). Briefly, the TRILUMINATE Pivotal trial was a prospective, multicenter, randomized, open-label trial of T-TEER with the transcatheter tricuspid valve repair system versus medical therapy alone in patients with severe symptomatic TR. Patients were eligible for participation in the trial if they had severe, massive, or torrential TR confirmed by an independent echocardiography laboratory, New York Heart Association (NYHA) class II-IVa symptoms, pulmonary artery systolic pressure <70 mmHg, had no other cardiovascular conditions in need of interventional or surgical correction (e.g., severe mitral regurgitation), and were on stable guideline-directed medical therapy for heart failure for at least 30 days. All echocardiograms were assessed by an independent core laboratory, and all deaths and heart failure hospitalizations were adjudicated by an independent clinical events committee. The protocol was approved by the Food and Drug Administration and by the institutional review boards of the participating centers. All patients provided written informed consent.

Health Status Outcomes. Disease-specific health status was evaluated at baseline and at 1 month, 6 months, and 1 year from baseline with the Kansas City Cardiomyopathy Questionnaire (KCCQ) (18). The KCCQ is a heart failure-specific health status measure that consists of 23 questions and encompasses 5 domains: physical limitation, symptoms, quality of life, social limitation, and self-efficacy. The first 4 domains are combined into an overall summary score (KCCQ-OS), which was the primary health status outcome of the TRILUMINATE Pivotal trial. Scores for domains and the summary score range from 0 to 100 with higher scores indicating better health status. KCCQ-OS scores correlate roughly with

NYHA class as follows: class I ~KCCQ-OS 75-100; class II ~KCCQ-OS 60-74; class III ~KCCQ-OS 45-59; and class IV ~KCCQ-OS 0-44 (19), and changes in KCCQ-OS of 5, 10, and 20 points correspond with small, moderate, or large clinical changes, respectively (20).

Generic health status was evaluated at baseline and at 1-month and 1-year follow-up using the Medical Outcomes Study Short-Form 36 (SF-36) Health Survey (21). The SF-36 assesses 8 dimensions of health status and provides physical and mental component summary scores (PCS, MCS), which are scaled to an overall population mean of 50 and standard deviation of 10; higher scores indicate better health status, and the minimum clinically important change is ~2.5 points (22).

Statistical Analysis. The primary analytic cohort consisted of all randomized patents with at least one follow-up KCCQ assessment. Unless otherwise specified, all analyses were performed according to the intention-to-treat principle. The primary endpoint was the change in KCCQ-OS from baseline over the 1-year follow-up period. Within each treatment group, mean scores for each health status measure at each follow-up time point were compared with baseline using paired Wilcoxon tests. For the primary analysis, between-group differences of health status scores over time were estimated from mixed effects linear repeated measures models. Models included time (as indicated by the follow-up visit sequence), treatment, and interactions between treatment and time (to account for a possible change in treatment effect over time), with health status differences between treatment assignments (and associated 95% confidence intervals [CI]) derived at each follow-up time point from the final models. These models incorporated all available health status scores, including those for patients who subsequently died, withdrew from the study, or were lost to follow-up, under the assumption of missing at random. Missing data and data for patients who died were not imputed.

We explored potential heterogeneity in health status differences at 1-year follow-up by performing subgroup analyses according to age, sex, previous mitral or aortic intervention, basal right ventricular end-diastolic diameter, tricuspid annular plane systolic excursion, central venous pressure, mean pulmonary artery pressure, cardiac index, baseline TR severity, and 6-minute walk distance. These analyses were performed by introducing interaction terms between treatment and each patient factor in the linear mixed models. We also examined the interaction between change in KCCQ-OS and baseline KCCQ-OS, which was modeled as a nonlinear continuous variable with an orthogonal polynomial of the 3rd degree.

To aid in clinical interpretability, we plotted cumulative response curves for change in KCCQ-OS at 1 month and at 1 year by treatment assignment. These curves display the changes in KCCQ-OS on the x-axis and the percentage of patients by treatment group who achieved at least that amount of change on the y-axis. We then calculated the proportion of patients in each treatment group at each time point who were alive with a moderately large health status improvement (change ≥10 points from baseline), alive with a large health status improvement (change ≥20 points from baseline), and "alive and well" as previously defined (KCCQ-OS ≥60 and no decline ≥10 points from baseline) (23). Proportions were compared between groups at each time point using chi-square tests, and absolute risk differences (with 95% CI) and numbers needed to treat (NNT) were estimated.

Since the KCCQ is a patient-reported outcome and vulnerable to bias in an open-label trial, we performed two exploratory analyses to examine the validity and clinical relevance of the observed changes in KCCQ. For both of these analyses, in order to improve statistical power, we included all available patients who were treated with T-TEER in the TRILUMINATE program (including as-treated randomized T-TEER patients from the Pivotal trial, roll-in patients from the

Pivotal trial [n=130], and patients from the single-arm TRILUMINATE early feasibility study [n=97] (7)). First, we examined whether the observed changes in KCCQ-OS could be explained by objectively measured changes in TR after T-TEER by constructing linear regression models for change in KCCQ-OS at 1-month and 1-year based on concurrent changes in TR grade at follow-up, baseline TR grade, age, sex, chronic lung disease, and baseline KCCQ-OS. Second, to explore the clinical relevance of the observed changes in KCCQ-OS among patients treated with T-TEER, we used Cox proportional hazards regression models to examine the association between change in KCCQ-OS at 1 month and subsequent death, heart failure hospitalization, and death or heart failure hospitalization—adjusted for baseline KCCQ-OS, age, sex, and chronic lung disease. As a secondary analysis, we repeated these Cox proportional hazards models including medical therapy patients and used interaction terms to test whether the relationship between 1-month change in KCCQ-OS and 1-year clinical outcomes differed according to treatment group.

All analyses were performed with SAS version 9.4 (SAS Institute, Cary, NC) and R (R foundation, Vienna Austria). Statistical significance was defined as a 2-sided p-value <0.05, and there was no correction for multiple comparisons (24).

RESULTS

Patient Population. Between August 21, 2019, and September 29, 2021, 350 patients from 80 centers in the United States, Europe, and Canada were randomized in the TRILUMINATE Pivotal trial (175 in each treatment arm). We excluded 6 patients in the T-TEER arm and 12 patients in the medical therapy alone arm who were missing all follow-up KCCQ scores. Baseline characteristics were well balanced between treatment groups (Table 1). The mean age of the analytic cohort was 78±7 years, 45% were men, and 12% had chronic lung

disease. TR severity at baseline was determined to be moderate in 2%, severe in 28%, massive in 19%, and torrential in 51%.

Baseline Health Status and Within-Group Comparisons. Compliance with KCCQ completion was >93% at each time point and did not differ significantly between treatment groups (Supplemental Table 2). Both disease-specific and generic health status were markedly impaired at baseline (Table 1). Mean KCCQ-OS score at baseline was 55.8±23.6, with the lowest domain score being Quality of Life at 48.2±26.3. Mean SF-36 PCS was 35.0±10.0 (1.5 standard deviations below the US population mean), and mean SF-36 MCS was 46.9±12.4. Among patients randomized to T-TEER, the KCCQ-OS score increased by an average of 14.3 points by 1 month (95% CI 10.9 to 17.2), with similar within-group changes at later time points (Table 2). All KCCQ domains improved significantly by 1 month, with the largest change observed in the Quality of Life domain (mean change 19.8 points, 95% CI 16.7 to 25.0). Scores on the SF-36 PCS and MCS both also increased significantly at 1 month, with changes of 4.9 points (95% CI 3.5 to 6.1) and 2.0 points (95% CI 0.1 to 3.3), respectively, that were sustained at 1 year. Among patients randomized to medical therapy alone, the KCCQ-OS increased, on average, by 4.8 points by 1 month (95% CI 2.0 to 6.8) and was maintained at 1-year (mean within-group difference 4.8 points, 95% CI 1.3 to 7.1) with no significant improvement in the SF-36 PCS or MCS scores over time.

Between-Group Comparisons. Among surviving patients at 1 month, the KCCQ-OS increased to a greater extent in the T-TEER arm compared with medical therapy alone (mean between-group difference 9.4 points, 95% CI 5.3 to 13.4, $p<0.001$; Central Illustration), with small additional improvements at 6 months (mean between-group difference 11.2 points, 95% CI 7.1 to 15.4; $p<0.001$) and 1 year (mean between-group difference 10.4 points, 95% CI 6.3 to

14.6; p<0.001). T-TEER provided greater benefit compared with medical therapy alone for each of the KCCQ domains, with the largest effects on the Quality of Life and Social Limitations domains (mean 1-year between-group differences for Quality of Life domain: 14.1 points, 95% CI 9.1 to 19.2; Social Limitations domain: 14.0 points, 95% CI 7.8 to 20.3; Supplemental Table 2). Compared with medical therapy alone, there was a modest benefit of T-TEER on the SF-36 PCS at 1 year (mean between-group difference: 5.2 points, 95% CI 2.3 to 7.1) with no significant effect on SF-36 MCS (mean between-group difference 1.5 points, 95% CI -0.9 to 3.8; Supplemental Table 2 and Figures 1A and 1B).

At both 1 month and 1 year, more patients who were randomized to T-TEER had improved KCCQ-OS scores and fewer patients had worsened from baseline compared with medical therapy alone (Figure 2). Integrating survival with health status outcomes, 41.5% of patients in the T-TEER arm were alive with a large health status improvement at 1 year compared with 15.5% in the medical therapy alone arm (NNT 3.9, 95% CI 2.8 to 6.7). Patients randomized to T-TEER were also more likely to be alive and well at 1 year (74.8% vs. 45.9%, NNT 3.5, 95% CI 2.5 to 5.5; Table 3).

Subgroup Analyses. Subgroup analyses demonstrated that the impact of T-TEER on 1-year health status was generally consistent across prespecified subgroups (Table 4). However, the health status benefit of T-TEER compared with medical therapy alone was greater in patients who had preserved cardiac index (treatment effect for 1-year KCCQ-OS in patients with cardiac index <2 L/min/m2=1.6 [95% CI -8.1 to 11.4]; vs. ≥2 L/min/m2=13.3 [95% CI 8.0, 18.6]; interaction p=0.041). The strongest treatment interaction was with baseline KCCQ-OS (interaction p<0.001), for which the non-linear continuous model suggested that the benefit of T-TEER diminished as baseline KCCQ-OS increased (Figure 3). The lower bound of the 95% CI

for the benefit of T-TEER compared with medical therapy crossed 0 at a baseline KCCQ-OS score of ~80 points, suggesting that the health status benefit of T-TEER remained significant when baseline KCCQ-OS was <80.

Exploratory Analyses. We performed two exploratory analyses among patients treated with T-TEER to better understand the extent to which the health status benefit of T-TEER represents a true biologic effect and to examine the clinical significance of changes in KCCQ. These analyses were restricted to patients who underwent T-TEER, to eliminate any placebo effect related to the open-label nature of the study, and included patients randomized to T-TEER and an additional 227 patients treated with T-TEER in the single-arm trial and roll-in patients in the Pivotal trial; baseline characteristics of these patients were generally similar to those in the randomized cohort (Supplemental Table 1). In the first analysis, multiple linear regression (adjusting for baseline TR grade, baseline KCCQ-OS, and clinical factors) demonstrated a strong correlation between change in TR grade after T-TEER and concurrent change in KCCQ-OS, such that every 1-grade improvement in TR was associated with a 4.1-point increase in KCCQ-OS (95% CI 1.8 to 6.5; Table 5). In the second exploratory analysis, there was a strong relationship between the change in KCCQ-OS at 1 month after T-TEER and subsequent 1-year clinical outcomes (Figure 4). Specifically, a 10-point increase in KCCQ-OS at 1 month after T-TEER was associated with a 24% lower hazard for death (95% CI 0.64-0.90; p=0.001), a 25% lower hazard for heart failure hospitalization (95% CI 0.64-0.89; p=0.001), and a 26% lower hazard for the composite of death or heart failure hospitalization (95% CI 0.65-0.84; p<0.001). When we also included the medical therapy patients in this analysis, there were no significant interactions between treatment group and the relationship between change in the KCCQ-OS score and outcomes, and the overall prognostic associations remained largely unaffected

DISCUSSION

In the TRILUMINATE Pivotal trial, T-TEER was superior to medical therapy alone for the hierarchical composite endpoint of all-cause death or tricuspid-valve surgery, heart failure hospitalization, and increase of ≥15 points on the KCCQ-OS, with a win-ratio of 1.48 (95% CI 1.06-2.13) (12). However, this result was driven primarily by the health status results, with no meaningful between-group differences in mortality or heart failure hospitalization. In this prespecified health status analysis, we found that T-TEER resulted in substantial benefits in patients' symptoms, functional status, and quality of life compared with medical therapy alone. The health status benefits of T-TEER were evident by 1-month after randomization and were sustained through 1-year follow-up. Integrating survival with health status, patients randomized to T-TEER were more likely to be alive with a large health status improvement and also more likely to be alive and well at 1 year, with a number needed to treat of <4 patients for both outcomes. Although previous single-arm studies have demonstrated that reducing TR (either by T-TEER or by valve replacement) is associated with improved health status (5,7,10), this is the first study to demonstrate that these benefits are substantial when compared with a randomized, medical therapy control group.

Targeting Patients for T-TEER. Although subgroup analyses demonstrated results that were generally consistent with those for the overall population, there were several findings that merit further discussion. Patients who had a preserved cardiac index (≥2 L/min/m2) appeared to derive greater health status benefit from T-TEER than those with depressed cardiac index. Since most patients in the TRILUMINATE trial had normal left ventricular systolic function, it is likely that a depressed cardiac index was a reflection of intrinsic right-ventricular dysfunction. By far , the strongest treatment interaction was with the baseline KCCQ-OS score, as patients

with lower KCCQ-OS scores were more likely to improve after T-TEER. Taken together, these findings suggest that the ideal patients to target for T-TEER may be those who are symptomatic from their TR but have reasonable right-heart function. These findings align with prior studies that have demonstrated that patients with a single diseased aortic or mitral valve, minimal competing comorbidities and concomitant cardiac issues, and a high symptom burden derive the greatest health status benefit from intervention on that valve (25-27).

Clinical Validity. One of the major issues surrounding the health status benefit of T-TEER is the susceptibility of patient-reported outcomes to bias given the unblinded trial design (28). These concerns are amplified by the lack of evidence of benefit on the clinical outcomes of death or heart failure hospitalization, which are less susceptible to bias (12). While it is likely that some of the observed benefit of T-TEER on health status represents either a form of response bias (i.e., reporting a change in symptoms or quality of life because of an unconscious desire to please the investigator) or a true a placebo effect (i.e., a beneficial outcome related to the belief that the treatment works), there are several considerations that suggest it is unlikely that all of the observed benefit is attributable to placebo.

First, the magnitude of benefit (compared with medical therapy alone) is larger than would be expected from placebo. Previous studies have demonstrated that, for a patient-reported outcome, the effect size for placebo therapy is typically 0.25-0.3 (change in a measure divided by the baseline standard deviation of that measure [i.e., signal/noise]) (28). Given the baseline standard deviation of the KCCQ-OS in the TRILUMINATE Pivotal trial, the expected magnitude of a placebo effect would be ~5-6 points—lower than the observed treatment benefit of 10.4 points. Although larger effects have been reported for the placebo arm of blinded randomized trials (29), it is important to distinguish the placebo response (i.e., the change from

baseline in the placebo arm of a trial) from the placebo effect (i.e., the difference between a placebo and no treatment) (30). Second, placebo effects are typically short-lived. The fact that the health status benefit of T-TEER was sustained without attenuation through 1 year of follow-up suggests a true biologic effect.

In addition to these external comparisons, exploratory analyses of trial-specific data also suggest that the observed health status improvement is, at least partially, biologically-mediated. For example, our explanatory linear regression model demonstrated a strong, independent association between the change in TR grade at 1-year after T-TEER and the concurrent change in the KCCQ-OS score. Since all patients in this model underwent T-TEER, it is unlikely that this "dose-response" relationship can be explained by a traditional placebo effect. Finally, the strongest evidence that the health status benefit associated with T-TEER is a true clinical benefit is the association between the 1-month improvement in KCCQ-OS score and a lower hazard of both death and heart failure hospitalization between 1 month and 1 year of follow-up. This last finding strongly suggests that, not only is the health status benefit associated with T-TEER a true effect, but that the magnitude of benefit achieved is clinically meaningful.

Limitations. Our study should be considered alongside several important limitations. First, health status can only be measured in surviving patients. While the mortality rate of ~10% in the randomized cohort could have impacted the KCCQ estimates for the patients, it is unlikely that a healthy survivor effect would have substantially biased the between-group treatment comparisons, since mortality was nearly identical for the 2 treatment groups. Second, although the health status benefit of T-TEER was durable over the first year of follow-up, the durability of benefit beyond 1 year is not yet known. Third, while we identified several potential treatment interactions, there may be other factors that could modify the health status benefit of T-TEER

(e.g., other measures of right-ventricular function, right ventricular-pulmonary artery coupling) that were not assessed. Fourth, patients may have been aware of their site-assessed TR grade during follow-up, which could have influenced their responses on the KCCQ. Fifth, although the KCCQ has been extensively validated in different heart failure populations, it has not yet been formally assessed in patients with TR. However, the KCCQ captures many of the symptoms of TR, including shortness of breath, orthopnea, fatigue, and lower extremity edema, and early transcatheter tricuspid valve intervention studies have demonstrated both substantial baseline impairment in KCCQ in patients with severe TR and significant improvement in the KCCQ after tricuspid valve intervention (5-7,10,31). Finally, the health status benefits of T-TEER observed in the TRILUMINATE Pivotal trial may not extend to patients outside of the inclusion and exclusion criteria of the trial (e.g., patients with concomitant left-sided valve disease, severe pulmonary hypertension, or lower surgical risk) or treatment with other devices.

CONCLUSION

In the TRILUMINATE Pivotal trial, T-TEER with the transcatheter tricuspid valve repair system resulted in substantial health status improvement compared with medical therapy alone in patients with severe symptomatic TR. The improvement in health status was evident by 1 month, sustained through 1 year, and clinically meaningful with a number needed to treat of 3.5 for 1 additional patient to be alive and well at 1 year. While we cannot fully exclude a placebo effect given the unblinded nature of the study, exploratory analyses showed 1) that the health status benefit correlated strongly with the observed changes in TR grade and 2) that patients who reported improvement in health status at 1 month were less likely to subsequently die or be hospitalized for heart failure—both suggesting a true biologic treatment effect. In total, these findings support the use of T-TEER with the transcatheter tricuspid valve repair system for

improvement in the symptoms, functional limitations, and quality of life in patients with severe TR.

PERSPECTIVES

Competency in Medical Knowledge: In patients with severe, symptomatic tricuspid regurgitation, tricuspid-transcatheter edge-to-edge repair (T-TEER) using the TriClip™ device results in rapid and sustained improvement in patients' symptoms, functional status, and quality of life.

Competency in Patient Care: Patients with lower baseline KCCQ-OS scores were more likely to improve symptomatically after T-TEER, and these patients may be ideal targets for intervention.

Translational Outlook 1: Although exploratory analyses suggest that the health status benefit of T-TEER is a true biologic effect (and not just placebo), further work to clarify the placebo effect of intervention and the long-term clinical implications of health status improvement after intervention would be informative.

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FIGURE LEGEND

Figure 1. Generic Health Status Over 1 Year. Predicted mean health status scores and between group differences as derived from mixed linear regression models, considering all available health status scores. Error bars and value in parentheses represent 95% confidence intervals. A. SF-36 Physical Components Summary Score. B. SF-36 Mental Components Summary Score.

Figure 2. Cumulative Distribution of Change in KCCQ-OS by Treatment Group. A. At 1 Month. B. At 1 Year. Lines represent the percentage of patients in each group with at least an x-point change in KCCQ-OS from baseline.

Figure 3. Predicted Benefit of T-TEER vs. Medical Therapy by Baseline KCCQ-OS. Solid line represents estimated treatment effect at 1 year as a function of baseline KCCQ-OS, and the gray shaded area represents the 95% confidence interval around that estimate.

Figure 4. Change in KCCQ-OS at 1 Month after T-TEER and Subsequent Outcomes. Cox proportional hazards regression models for death or heart failure hospitalization through 1 year; also adjusted for baseline KCCQ-OS, age, sex, and chronic lung disease.

Central Illustration. Disease-Specific Health Status Over 1 Year. Predicted mean health status scores and between group differences as derived from mixed linear regression models, considering all available health status scores. Error bars and value in parentheses represent 95% confidence intervals.

Table 1. Baseline Characteristics of the Primary Analytic Cohort*

	T-TEER (n=169)	Medical therapy alone (n=163)	P-Value
Age, years	78.0 ± 7.4	77.6 ± 7.4	0.626
Men	73 (43.2)	77 (47.2)	0.529
Body mass index, kg/m^2	27.0 ± 5.8	26.9 ± 5.4	0.960
Atrial fibrillation	148 (87.6)	151 (92.6)	0.174
Hypertension	138 (81.7)	131 (80.4)	0.873
Prior stroke	11 (6.5)	16 (9.8)	0.367
Diabetes mellitus	27 (16.0)	26 (16.0)	1.000
Peripheral vascular disease	16 (9.5)	15 (9.2)	1.000
Prior coronary artery bypass grafting	31 (18.3)	32 (19.6)	0.873
Prior mitral or aortic intervention	66 (39.1)	55 (33.7)	0.373
Chronic lung disease	17 (10.1)	23 (14.1)	0.335
Permanent pacemaker or defibrillator	27 (16.0)	20 (12.3)	0.417
Severity of tricuspid regurgitation*			0.516
Moderate	4 (2.4)	2 (1.3)	
Severe	44 (26.2)	47 (30.3)	
Massive	36 (21.6)	25 (16.2)	
Torrential	83 (49.4)	80 (51.6)	
LV ejection fraction, %	59.6 ± 9.2	58.5 ± 10.2	0.317
RV end-diastolic diameter, cm	5.0 ± 0.8	5.2 ± 0.8	0.079

TAPSE, cm	1.7 ± 0.4	1.6 ± 0.4	0.750
Central venous pressure, mmHg	11.8 ± 5.2	11.9 ± 5.7	0.860
Mean PA pressure, mmHg	25.3 ± 5.7	25.6 ± 6.3	0.736
Cardiac index, L/min/m^2	2.5 ± 0.7	2.5 ± 0.7	0.985
6-minute walk distance, meters	242 ± 118	263 ± 127	0.123
KCCQ scores			
Overall Summary	56.4 ± 23.5	55.2 ± 23.8	0.653
Physical Limitations	59.1 ± 24.4	60.4 ± 25.6	0.635
Total Symptom	63.0 ± 24.8	59.6 ± 25.8	0.219
Self-Efficacy	79.5 ± 22.0	80.5 ± 22.1	0.690
Quality of Life	50.0 ± 26.4	46.4 ± 26.1	0.204
Social Limitation	52.4± 31.5	54.6 ± 30.8	0.545
SF-36 scores			
Physical Functioning	39.0 ± 25.7	39.9 ± 25.2	0.732
Role Physical	44.6 ± 29.1	43.6 ± 29.8	0.755
Bodily Pain	60.0 ± 27.5	61.1 ± 28.3	0.721
General Health	50.8 ± 20.1	48.8 ± 21.4	0.389
Vitality	36.2 ± 18.7	36.4 ± 18.4	0.934
Social Functioning	66.9 ± 30.5	65.7 ± 30.3	0.720
Role Emotional	70.3 ± 29.4	65.2 ± 33.0	0.134
Mental Health	72.1 ± 19.3	69.4 ± 19.8	0.211
Physical Component Summary	34.6 ± 10.0	35.3 ± 10.1	0.532

Mental Component Summary	47.8 ± 12.3	45.9 ± 12.5	0.164

T-TEER, tricuspid-transcatheter edge-to-edge valve repair; LV, left ventricular; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; PA, pulmonary artery; KCCQ, Kansas City Cardiomyopathy Questionnaire

Data are shown as n (%) or mean ± standard deviation

Echocardiographic parameters including the severity of tricuspid regurgitation severity were assessed by central core laboratory

*6 patients randomized to T-TEER and 12 patients randomized to medical therapy alone were missing all follow-up KCCQ data and were excluded from the primary analytic cohort

Table 2. Mean Scores and Within-Group Changes Compared with Baseline

	T-TEER				Medical Therapy Alone			
	n	Mean ± SD	Paired Difference* (95% CI)	P-Value	n	Mean ± SD	Paired Difference* (95% CI)	P-Value
KCCQ Overall Summary								
Baseline	175	56.0 ± 23.4			174	54.1 ± 24.2		
1 month	167	70.7 ± 22.0	14.3 (10.9 to 17.2)	<0.001	156	59.7 ± 23.0	4.8 (2.0 to 6.8)	<0.001
6 months	151	76.1 ± 20.4	16.9 (13.4 to 20.6)	<0.001	151	61.5 ± 23.3	6.2 (2.1 to 9.2)	0.002
1 year	147	74.1 ± 20.4	15.2 (11.9 to 19.1)	<0.001	149	60.6 ± 21.9	4.8 (1.3 to 7.1)	0.005
KCCQ Physical Limitations								
Baseline	172	58.9 ± 24.1			174	59.2 ± 25.8		
1 month	160	69.6 ± 22.5	10.0 (6.7 to 14.2)	<0.001	155	61.7 ± 25.2	2.5 (0.0 to 6.3)	0.032
6 months	147	73.6 ± 23.1	13.1 (9.6 to 16.7)	<0.001	149	64.8 ± 25.3	4.2 (0.0 to 8.3)	0.066
1 year	144	70.4 ± 24.3	9.2 (6.3 to 14.2)	<0.001	147	63.0 ± 24.0	2.2 (-2.1 to 6.3)	0.377

KCCQ Total Symptoms								
Baseline	175	62.5 ± 24.9			174	58.7 ± 26.4		
1 month	167	73.8 ± 22.0	10.7 (8.3 to 15.1)	<0.001	156	64.3 ± 23.5	4.8 (1.6 to 7.8)	0.003
6 months	151	79.2 ± 19.0	13.1 (9.4 to 17.2)	<0.001	151	66.6 ± 24.1	7.1 (3.1 to 10.4)	0.001
1 year	147	77.7 ± 19.4	11.9 (8.9 to 17.2)	<0.001	149	65.4 ± 23.4	5.1 (1.0 to 8.3)	0.011
KCCQ Quality of Life								
Baseline	175	49.4 ± 26.4			174	45.4 ± 26.4		
1 month	167	69.8 ± 25.4	19.8 (16.7 to 25.0)	<0.001	156	53.8 ± 26.5	7.5 (8.3 to 16.7)	<0.001
6 months	151	75.9 ± 23.4	22.9 (20.8 to 29.2)	<0.001	151	55.4 ± 25.8	8.5 (4.2 to 16.7)	<0.001
1 year	147	73.6 ± 22.8	21.3 (20.8 to 29.2)	<0.001	149	54.0 ± 25.0	7.2 (4.2 to 12.5)	<0.001
KCCQ Social Limitation								
Baseline	163	52.1 ± 31.4			168	52.9 ± 31.4		
1 month	156	70.0 ± 29.5	16.5 (13.5 to 25.0)	<0.001	147	58.1 ± 30.4	5.0 (1.0 to 10.4)	0.016
6 months	137	73.9 ± 27.1	19.8 (16.7 to 29.2)	<0.001	143	60.1 ± 29.4	4.8 (0.0 to 12.5)	0.045

1 year	135	74.0 ± 27.2	19.1 (16.7 to 28.1)	<0.001	144	59.9 ± 28.9	4.8 (-2.1 to 9.4)	0.176
SF-36 Physical Component Summary								
Baseline	173	34.4 ± 9.96			174	35.1 ± 10.1		
1 month	165	39.7 ± 10.3	4.9 (3.5 to 6.1)	<0.001	156	36.3 ± 10.1	1.2 (-0.1 to 2.2)	0.072
1 year	147	39.6 ± 10.5	4.1 (2.4 to 5.6)	<0.001	149	34.5 ± 9.87	-1.2 (-2.6 to -0.1)	0.039
SF-36 Mental Component Summary								
Baseline	174	47.7 ± 12.2			174	45.6 ± 12.6		
1 month	162	49.8 ± 11.5	2.0 (0.1 to 3.3)	0.034	156	46.9 ± 12.5	0.9 (-0.6 to 2.6)	0.204
1 year	146	51.2 ± 10.3	3.3 (1.2 to 4.6)	<0.001	149	47.5 ± 11.6	1.4 (-0.6 to 2.6)	0.250

T-TEER, tricuspid-transcatheter edge-to-edge valve repair; KCCQ, Kansas City Cardiomyopathy Questionnaire

*Paired differences are compared with baseline

Table 3. Categorical Outcomes

	T-TEER	Medical Therapy Alone	Absolute Risk Difference (95% CI)	P-Value	NNT (95% CI)
Alive with moderate improvement (KCCQ-OS change ≥10 points)					
1 month	93/167 (55.7%)	47/155 (30.3%)	25.4% (14.9% to 35.8%)	<0.001	3.9 (2.8 to 6.7)
6 months	90/151 (59.6%)	54/149 (36.2%)	23.4% (12.4% to 34.4%)	<0.001	4.3 (2.9 to 8.1)
1 year	83/147 (56.5%)	55/148 (37.2%)	19.3% (8.1% to 30.5%)	0.001	5.2 (3.3 to 12.3)
Alive with large improvement (KCCQ-OS change ≥20 points)					
1 month	57/167 (34.1%)	24/155 (15.5%)	18.6% (9.5% to 27.8%)	<0.001	5.4 (3.6 to 10.5)
6 months	67/151 (44.4%)	42/149 (28.2%)	16.2% (5.5% to 26.9%)	0.003	6.2 (3.7 to 18.2)
1 year	61/147 (41.5%)	23/148 (15.5%)	26.0% (16.1% to 35.8%)	<0.001	3.8 (2.8 to 6.2)
Alive and well (KCCQ-OS ≥60 points and decline from baseline <10)					
1 month	113/167 (67.7%)	75/155 (48.4%)	19.3% (8.7% to 29.9)	<0.001	5.2 (3.3 to 11.5)
6 months	117/151 (77.5%)	76/149 (51.0%)	26.5% (16.0% to 36.9%)	<0.001	3.8 (2.7 to 6.3)
1 year	110/147 (74.8%)	68/148 (45.9%)	28.9% (18.2% to 39.5)	<0.001	3.5 (2.5 to 5.5)

T-TEER, tricuspid-transcatheter edge-to-edge valve repair; NNT, number needed to treat; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary score

Table 4. Estimated Effect of T-TEER on KCCQ-OS at 1-year Among Key Subgroups

	n	T-TEER Mean (95% CI)	Medical Therapy Alone Mean (95% CI)	Mean Difference (95% CI)	Interaction P-Value
Age					0.088
<78 years	140	17.3 (12.6 to 22.0)	2.7 (-2.2 to 7.5)	14.6 (7.9 to 21.4)	
≥78 years	155	13.2 (8.7 to 17.8)	6.7 (2.2 to 11.2)	6.5 (0.1 to 12.9)	
Sex					0.835
Female	169	17.4 (13.1 to 21.7)	7.7 (3.3 to 12.1)	9.7 (3.6 to 15.8)	
Male	126	12.0 (6.9 to 17.1)	1.3 (-3.6 to 6.2)	10.7 (3.6 to 17.8)	
Previous aortic or mitral intervention					0.536
No	189	16.5 (12.3 to 20.7)	4.9 (0.9 to 8.9)	11.6 (5.7 to 17.4)	
Yes	106	13.2 (7.9 to 18.5)	4.7 (-1.1 to 10.4)	8.5 (0.7 to 16.3)	
Right ventricular end-diastolic diameter at base					0.762
<5 cm	133	17.1 (12.4 to 21.8)	5.8 (0.8 to 10.9)	11.3 (4.4 to 18.2)	
≥5 cm	156	13.4 (8.8 to 18.0)	3.5 (-0.9 to 8.0)	9.8 (3.5 to 16.2)	

Tricuspid annular plane systolic excursion					0.174
<1.7 cm	151	16.9 (12.2 to 21.6)	3.2 (-1.3 to 7.7)	13.8 (7.3 to 20.2)	
≥1.7 cm	134	13.5 (8.9 to 18.2)	6.4 (1.2 to 11.5)	7.2 (0.2 to 14.1)	
Central venous pressure					0.565
<10 mmHg	66	17.7 (11.0 to 24.4)	3.4 (-3.7 to 10.5)	14.3 (4.5 to 24.1)	
≥10 mmHg	99	15.3 (9.3 to 21.3)	4.8 (-0.6 to 10.1)	10.6 (2.5 to 18.6)	
Mean pulmonary artery pressure					0.915
<25 mmHg	138	13.9 (9.2 to 18.5)	3.6 (-1.4 to 8.6)	10.3 (3.4 to 17.1)	
≥25 mmHg	157	16.5 (11.9 to 21.2)	5.8 (1.4 to 10.1)	10.8 (4.4 to 17.2)	
Cardiac index					0.041
<2 L/min/m^2	67	10.0 (2.9 to 17.1)	8.4 (1.6 to 15.1)	1.6 (-8.1 to 11.4)	
≥2 L/min/m^2	225	16.8 (13.0 to 20.5)	3.5 (-0.3 to 7.3)	13.3 (8.0 to 18.6)	
Severity of tricuspid regurgitation (baseline)					0.617

Moderate	6	3.2 (-16.7 to 23.1)	0.8 (-27.4 to 28.9)	2.4 (-32.1 to 36.9)	
Severe	85	15.3 (9.0 to 21.6)	2.6 (-3.3 to 8.5)	12.7 (4.1 to 21.4)	
Massive	57	13.2 (6.3 to 20.2)	3.3 (-4.8 to 11.5)	9.9 (-0.8 to 20.6)	
Torrential	139	16.8 (12.0 to 21.6)	5.5 (0.8 to 10.3)	11.2 (4.5 to 18.0)	
6-minute walk distance					0.086
<236 m	118	14.4 (9.3 to 19.5)	8.8 (3.6 to 14.0)	5.6 (-1.7 to 12.9)	
≥236 m	167	15.3 (10.9 to 19.8)	1.4 (-2.9 to 5.6)	14.0 (7.9 to 20.1)	

T-TEER, tricuspid-transcatheter edge-to-edge valve repair; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary score

Table 5. Association of Change in KCCQ-OS with Change in TR Grade

	1 Month		1-Year	
	Estimate for Change in KCCQ-OS (95% CI)	**p-value**	**Estimate for Change in KCCQ-OS (95% CI)**	**p-value**
Change in TR from baseline (per 1-grade decrease)	2.2 (0.2 to 4.1)	0.031	4.1 (1.8 to 6.5)	0.001
Adjusted for the following:				
Baseline KCCQ-OS Score (per 10 points)	-4.5 (-5.4 to -3.7)	<0.001	-5.1 (-6.0 to -4.1)	<0.001
Age (per 10 years)	-1.9 (-4.4 to 0.5)	0.120	-3.1 (-5.8 to -0.4)	0.025
Male	-2.3 (-6.2 to 1.7)	0.254	-2.3 (-6.6 to 2.1)	0.306
Chronic lung disease	1.4 (-3.9 to 6.7)	0.594	4.8 (-1.0 to 10.5)	0.103
Baseline TR grade (REF: moderate)				
Severe	7.1 (-7.8 to 22.0)	0.348	11.4 (-4.8 to 27.5)	0.168

Massive	0.9 (-14.4 to 16.3)	0.909	4.6 (-12.2 to 21.5)	0.589
Torrential	3.3 (-12.3 to 18.8)	0.681	2.8 (-14.5 to 20.1)	0.752

TR, tricuspid regurgitation; KCCQ-OS, Kansas City Cardiomyopathy Questionnaire-Overall Summary score