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Quality of Life After Transcatheter Tricuspid Valve Replacement

1-Year Results From TRISCEND II Pivotal Trial

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ABSTRACT

BACKGROUND Severe tricuspid regurgitation (TR) often causes substantial impairment in patient-reported health status (ie, symptoms, physical and social function, and quality of life), which may improve with transcatheter tricuspid valve replacement (TTVR).

OBJECTIVES We performed an in-depth analysis of health status of patients enrolled in the TRISCEND (Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device) II pivotal trial to help quantify the benefit of intervention to patients.

METHODS The TRISCEND II pivotal trial randomized 400 patients with symptomatic and severe or greater TR 2:1 to TTVR with the EVOQUE tricuspid valve replacement system plus optimal medical therapy (OMT) or OMT alone. Health status was assessed with the Kansas City Cardiomyopathy Questionnaire and the 36-Item Short Form Health Survey. Changes in health status over 1 year were compared between treatment groups using mixed-effects repeated-measures models.

RESULTS The analysis cohort included 392 patients, of whom 259 underwent attempted TTVR and 133 received OMT alone (mean age 79.2 ± 7.6 years, 75.5% women, 56.1% with massive or torrential TR). Patients had substantially impaired health status at baseline (mean Kansas City Cardiomyopathy Questionnaire Overall Summary Score [KCCQ-OS] 52.1 ± 22.8; mean 36-Item Short Form Health Survey physical component summary score 35.2 ± 8.4). TTVR+OMT patients reported significantly greater improvement in both disease-specific and generic health status at each follow-up time point. Mean between-group differences in the KCCQ-OS favored TTVR+OMT at each time point: 11.8 points (95% CI: 7.4-16.3 points) at 30 days, 20.8 points (95% CI: 16.1-25.5 points) at 6 months, and 17.8 points (95% CI: 13.0-22.5 points) at 1 year. In subgroup analyses, TTVR+OMT improved health status to a greater extent among patients with torrential or massive TR vs severe TR (treatment effect 23.3 vs 22.6 vs 11.3; interaction $P = 0.049$). At 1 year, 64.6% of TTVR+OMT patients were alive and well (KCCQ-OS ≥60 points and no decline of ≥10 points from baseline) compared with 31.0% with OMT alone.

CONCLUSIONS Compared with OMT alone, treatment of patients with symptomatic and severe or greater TR with TTVR+OMT resulted in substantial improvement in patients' symptoms, function, and quality of life. These benefits were evident 30 days after TTVR, continued to increase through 6 months, and remained durable through 1 year. (TRISCEND II Pivotal Trial [Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device]; NCT04482062) (JACC. 2024;■:■–■) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

KCCQ = Kansas City Cardiomyopathy Questionnaire

KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score

MCS = mental component summary score

NNT = number needed to treat

PCS = physical component summary score

SF-36 = 36-Item Short Form Health Survey

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

TR = tricuspid regurgitation

TTVR = transcatheter tricuspid valve replacement

Severe tricuspid regurgitation (TR) can result in a substantial burden of symptoms, such as dyspnea, fatigue, and edema, which can negatively impact patients' physical and social function and their quality of life.[1-4] Although it was expected that treatment of severe TR would lead to reductions in both mortality and heart failure hospitalization, to date, the only proven benefit of transcatheter tricuspid valve intervention is improved health status.[5-7] In both the TRILUMINATE Pivotal (Trial to Evaluate Cardiovascular Outcomes in Patients Treated with the Tricuspid Valve Repair System Pivotal)[3] and Tri.Fr (Evaluation of Tricuspid Valve Percutaneous Repair System in the Treatment of Severe Secondary Tricuspid Disorders)[6] trials, tricuspid transcatheter edge-to-edge repair (T-TEER) led to substantial improvement in disease-specific health status compared with optimal medical therapy (OMT) alone—a benefit that increased with greater reductions in TR severity.[3,4]

While T-TEER generally results in meaningful reduction in TR for appropriately selected patients, many patients are left with mild or moderate residual TR.[5,8,9] In contrast, transcatheter tricuspid valve replacement (TTVR) can completely eliminate TR in the vast majority of patients.[10] Whether these procedural results translate into greater clinical benefit remains unknown. The TRISCEND (Edwards EVOQUE Transcatheter Tricuspid Valve Replacement: Pivotal Clinical Investigation of Safety and Clinical Efficacy using a Novel Device; NCT04482062) II pivotal trial is the first randomized trial to compare TTVR+OMT vs OMT alone for symptomatic severe or greater TR. In this trial, TTVR with the EVOQUE valve (Edwards Lifesciences) was superior to OMT alone for the hierarchical composite endpoint.[7] However, similar to T-TEER, the benefit of TTVR was primarily driven by improvements in health status, with no significant reduction in either death or heart failure hospitalization. To more completely characterize the health status benefit of TTVR, we performed a detailed analysis of health status outcomes in the TRISCEND II pivotal trial. In addition to describing the magnitude, timing, and durability of benefit, we sought to understand the impact of specific patient characteristics on the health status benefit of TTVR.

METHODS

STUDY DESIGN. The design and primary results of the TRISCEND II pivotal trial have been published.[7,11] Study sites obtained applicable regulatory approval, and all patients provided written informed consent. The TRISCEND II pivotal trial was a prospective, multicenter, randomized, open-label trial of TTVR with the EVOQUE system with OMT vs OMT alone in patients with symptomatic and severe or greater TR, as confirmed by an independent echocardiography laboratory. Patients were randomized 2:1 to TTVR+OMT vs OMT alone, with randomization stratified by study site. As determined by the local heart team, patients were required to have signs of TR, symptoms from TR, or a prior heart failure hospitalization from TR. Key exclusion criteria were severely depressed right ventricular systolic function; prior heart transplantation; anatomy precluding proper device delivery, deployment, or function; estimated glomerular filtration rate ≤25 mL/min/1.73 m^2 or required chronic renal replacement therapy; or life expectancy <1 year.

The primary clinical endpoint was a hierarchical composite at 1 year of all-cause mortality, right ventricular assist device implantation or heart transplantation, tricuspid valve intervention, heart failure hospitalization, improvement in Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) ≥10 points, improvement in NYHA functional class ≥I, and improvement in 6-minute walk

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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distance ≥30 m. Key study endpoints including all deaths and heart failure hospitalizations were adjudicated by an independent clinical events committee.

HEALTH STATUS OUTCOMES. Health status was evaluated at baseline and at 30 days, 6 months, and 1 year from baseline with the Kansas City Cardiomyopathy Questionnaire (KCCQ)[12] and the Medical Outcomes Study 36-Item Short Form Health Survey (SF-36),[13] which were self-administered. The KCCQ is a heart failure–specific health status instrument 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 TRISCEND II pivotal trial. Scores for individual domains and the KCCQ-OS range from 0 to 100 with higher scores indicating better health status, and changes in KCCQ-OS of 5, 10, and 20 points correspond with small, moderate, or large clinical changes, respectively.[14] The KCCQ has undergone extensive reliability and validity testing in several forms of left-sided heart failure[15-17] including aortic stenosis,[18] and was recently shown to be psychometrically valid in patients with severe TR.[4] The SF-36 assesses 8 dimensions of health status and provides a physical component summary score (PCS) and a mental component summary score (MCS), which are scaled to an overall population mean of 50 ± 10. Higher scores indicate better health status, and the minimum clinically important change is ∼2.5 points.[19]

STATISTICAL ANALYSIS. To align with the primary endpoint analysis, all health status analyses were performed in the modified intention-to-treat safety population comprising all control patients and all TTVR+OMT patients who had an attempted study procedure. Within each treatment group, scores for each health status measure at each follow-up time point were first compared with baseline using paired *t*-tests or Wilcoxon rank sum tests (for non-normal distributions). For the primary quality-of-life analysis, between-group differences in health status scores over 1 year were estimated using mixed-effects linear repeated-measures models that included time, treatment, and interactions between treatment and time. 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. Mean differences in health status scores (and associated 95% CIs) between treatment assignments at each follow-up time point were derived from these models.

We explored potential heterogeneity in the effect of TTVR+OMT on KCCQ-OS at 1 year by introducing interaction terms between treatment and baseline patient factors in the mixed-effects linear repeated-measures model. Prespecified patient factors included age (less than vs greater than or equal to median), sex, baseline TR severity, chronic lung disease, 6-minute walk distance (less than vs greater than or equal to median), left ventricular ejection fraction (<50% vs ≥50%), tricuspid annular plane systolic excursion (<17 mm vs ≥17 mm), right ventricular fractional area change (<35% vs ≥35%), cardiac index (<2.0 L/min/m^2 vs ≥2.0 L/min/m^2), pulmonary hypertension, heart failure hospitalization in prior year (≤1 vs >1), and daily diuretic dose at baseline (furosemide equivalents: ≤40 mg vs >40 mg). We also examined the interaction between treatment and baseline KCCQ-OS, which was modeled as both a continuous variable using a restricted cubic spline and categorized as tertiles for presentation.

To aid in clinical interpretability of between-group differences in the KCCQ-OS, we 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" (KCCQ-OS ≥60 and no decline ≥10 points from baseline).[20] 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 (NNTs) were estimated. We also examined the proportion of patients with different levels of change in KCCQ-OS: ≥20 points (large improvement), ≥10 and <20 points (moderate improvement), ≥5 and <10 points (small improvement), >-5 and <5 points (no change), ≤-5 points (worse), and dead. We compared these outcomes between treatment groups using multinomial logistic regression.

Finally, we performed an exploratory analysis to better understand the prognostic importance of the KCCQ-OS. Lower KCCQ-OS scores have been shown to be associated with increased risk of death and heart failure hospitalization in patients with severe TR who were medically managed or who underwent transcatheter tricuspid valve intervention.[4] However, it is unknown whether this association differs between those treated vs not. We used Cox proportional hazards regression models to explore the association of KCCQ-OS at 30 days with the outcomes from 30 days to 1 year (death, heart failure hospitalization, and the composite of death or heart failure hospitalization). Unadjusted models included treatment assignment

and the interaction of treatment by KCCQ-OS, and adjusted models also included age, sex, and chronic lung disease, as prespecified factors.

All analyses were performed using SAS version 9.4 (SAS Institute). Statistical significance was defined as a 2-sided *P* value <0.05, and there was no correction for multiple comparisons.[21]

RESULTS

PATIENT POPULATION. Between May 2021 and April 2023, 400 patients from 45 centers in the United States and Germany were enrolled in the TRISCEND II pivotal trial, with 267 patients randomized to TTVR+OMT and 133 patients randomized to OMT. Of these, 8 patients assigned to TTVR+OMT did not undergo an attempted procedure and were excluded from the modified intention-to-treat population. Baseline characteristics were well balanced between treatment groups (**Table 1**). The mean age was 79.2 ± 7.6 years, 75.5% were women, 56.1% of patients had massive or torrential TR, 95.4% had atrial fibrillation or flutter, and 38.8% had a history of pacemaker or implantable cardioverter-defibrillator.

BASELINE HEALTH STATUS AND WITHIN-GROUP COMPARISONS. Compliance with KCCQ completion was >88% at all time points and did not differ significantly between treatment groups (Supplemental Table 1). Both disease-specific and generic health status were markedly impaired at baseline (**Table 1**). The mean KCCQ-OS score was 52.1 ± 21.8 (median 50.5 [Q1-Q3: 36.7-68.2]), the mean SF-36 PCS was 35.2 ± 8.4, and the mean SF-36 MCS was 49.9 ± 10.9. Within-group differences in health status scores are shown in Supplemental Table 2. Among patients randomized to TTVR+OMT, KCCQ-OS increased by an average of 14.0 points compared with baseline at 30 days (95% CI: 11.0-17.0 points), 20.6 points at 6 months (95% CI: 17.5-23.8 points), and 18.4 points at 1 year (95% CI: 15.4-21.4 points). Individual KCCQ domains, SF-36 PCS, and SF-36 MCS all improved significantly by 30 days, with further improvement through 6 months that was sustained through 1 year. Among patients randomized to OMT alone, health status scores were largely unchanged throughout follow-up, with only the KCCQ quality of life domain showing a significant improvement over time (mean change at 1 year 6.4 points; 95% CI: 0.9-11.9 points).

BETWEEN-GROUP COMPARISONS. Among surviving patients at 30 days, patients randomized to TTVR+OMT reported greater improvement in both disease-specific and generic health status compared with patients randomized to OMT alone (**Table 2**). Mean between-group difference in the KCCQ-OS was 11.8 points (95% CI: 7.4-16.3 points) in favor of TTVR+OMT at 30 days, 20.8 points (95% CI: 16.1-25.5 points) at 6 months, and 17.8 points (95% CI: 13.0-22.5 points) at 1 year (**Central Illustration**). The health status benefit of TTVR+OMT was evident 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 of 23.4 points [95% CI: 18.0-28.8 points] and 21.5 points [95% CI: 14.9-28.0 points], respectively) (**Table 2**). Patients randomized to TTVR+OMT also reported significantly better generic health status compared with OMT at each follow-up time point. At 1-year follow-up, TTVR+OMT led to an improvement in both the SF-36 PCS (mean between-group difference 4.3 points; 95% CI: 2.3-6.2 points) and the SF-36 MCS (mean between-group difference of 6.0 points; 95% CI: 3.7-8.2 points) (**Table 2**).

Integrating survival and health status outcomes, the proportions of patients who were alive with moderately large (≥10 points) and large (≥20 points) improvements in KCCQ-OS at 1 year were greater with TTVR+OMT than OMT alone (**Figure 1A**). For example, at 1 year, 39.5% of patients assigned to TTVR+OMT were alive with a large improvement in health status compared with 19.5% of patients assigned to OMT alone ($P < 0.001$; NNT = 5.0). When we examined the proportion of patients who were alive and well, the benefit of TTVR+OMT was even larger (64.6% vs 31.0%; $P < 0.001$; NNT = 3.0). Finally, the proportion of patients with worse 1-year outcomes (death or a clinically meaningful decline in health status) was larger with OMT alone than with TTVR+OMT (45.1% vs 24.3%) (**Figure 1B**).

SUBGROUP ANALYSES. The beneficial effect of TTVR+OMT on 1-year disease-specific health status was consistent across most prespecified subgroups (**Table 3**). However, there were several noteworthy interactions. On average, TTVR+OMT improved health status to a greater extent among patients with worse baseline TR (treatment interaction with baseline TR, $P = 0.049$). While patients with severe TR had a moderately large health status improvement with TTVR+OMT compared with OMT (mean effect 11.3 points; 95% CI: 4.3-18.3), this benefit was estimated to be substantially larger in those with massive or torrential TR (mean treatment effect 22.6 points [95% CI: 13.0-32.3 points] and 23.3 points

TABLE 1 Baseline Characteristics

	TTVR+OMT (n = 259)	OMT (n = 133)	*P* Value
Age, y	79.3 ± 7.4	79.1 ± 7.8	0.786
Female	194 (74.9)	102 (76.7)	0.697
Atrial fibrillation/flutter	250 (96.5)	124 (93.2)	0.140
Hypertension	235 (90.7)	122 (91.7)	0.743
Prior stroke	39 (15.1)	12 (9.0)	0.093
Diabetes mellitus	57 (22.0)	33 (24.8)	0.532
Peripheral vascular disease	18 (6.9)	11 (8.3)	0.636
Prior coronary artery bypass grafting	36 (13.9)	26 (19.5)	0.147
Prior percutaneous coronary intervention	43 (16.6)	23 (17.3)	0.863
Chronic obstructive pulmonary disease	40 (15.4)	26 (19.5)	0.304
History of pacemaker or implantable cardioverter-defibrillator	99 (38.2)	53 (39.8)	0.754
Prior valve surgery or procedure	131 (50.6)	73 (54.9)	0.419
Hospitalization for heart failure in prior year	88 (34.0)	48 (36.1)	0.677
Body mass index, kg/m^2	26.8 ± 5.9	27.0 ± 5.5	0.504
6-min walk distance, m	236.4 ± 92.8	240.8 ± 87.7	0.531
Glomerular filtration rate, mL/min/1.73 m^2	54.7 ± 16.1	51.3 ± 16.0	0.067
Left ventricular ejection fraction, %	54.4 ± 9.9	54.3 ± 11.1	0.921
Severity of tricuspid regurgitation			0.182
Severe	122 (47.1)	50 (37.6)	
Massive	60 (23.2)	34 (25.6)	
Torrential	77 (29.7)	49 (36.8)	
Kansas City Cardiomyopathy Questionnaire			
Overall Summary Score	52.8 ± 22.0	50.6 ± 21.4	0.347
Physical limitations domain	56.6 ± 23.4	54.3 ± 22.0	0.351
Total symptoms domain	55.3 ± 25.2	53.1 ± 24.7	0.406
Quality-of-life domain	46.3 ± 23.8	43.5 ± 23.9	0.255
Social limitation domain	52.4 ± 29.5	51.0 ± 29.4	0.659
Self-efficacy domain	83.0 ± 19.6	81.0 ± 21.1	0.484
Medical Outcomes Study 36-Item Short Form Health Survey			
Physical component summary score	35.5 ± 8.3	34.5 ± 8.5	0.255
Mental component summary score	50.2 ± 10.7	49.4 ± 11.3	0.498
Physical functioning	32.8 ± 8.3	31.3 ± 8.0	0.078
Role physical	35.9 ± 9.5	34.5 ± 9.1	0.221
Bodily pain	47.3 ± 10.7	45.7 ± 11.2	0.205
General health	40.8 ± 9.0	40.7 ± 8.9	0.929
Vitality	42.9 ± 9.8	42.2 ± 10.0	0.508
Social functioning	43.1 ± 11.6	43.8 ± 11.3	0.620
Role emotional	44.8 ± 12.2	43.0 ± 12.5	0.175
Mental health	49.7 ± 10.2	48.2 ± 10.0	0.120

Values are mean ± SD or n (%).
OMT = optimal medical therapy; TTVR = transcatheter tricuspid valve replacement.

[95% CI: 15.1-31.5 points], respectively). In addition, TTVR+OMT improved health status to a greater extent in those with better baseline functional status (treatment interaction with 6-minute walk distance $P = 0.016$) and preserved right ventricular function (treatment interaction with right ventricular fractional area change $P = 0.013$). There were no treatment interactions with age, sex, or left ventricular ejection fraction. The interaction of treatment by baseline KCCQ-OS was also not significant (Supplemental Figure 1), indicating that the extent of health status benefit of TTVR+OMT was relatively consistent across the range of baseline KCCQ-OS scores represented in the study population.

EXPLORATORY ANALYSES. In exploratory analyses, lower KCCQ-OS scores at 30 days were associated with higher subsequent risk of death or heart failure hospitalization (adjusted HR per 10-point increase in KCCQ-OS: 0.81; 95% CI: 0.73-0.90) (Supplemental Table 3). When we analyzed heart failure hospitalization and mortality separately, the association was

TABLE 2 Adjusted Effect of TTVR+OMT vs OMT According to Mixed Linear Regression Models

	Predicted Mean (95% CI)			
	TTVR+OMT	OMT	Between-Group Difference (TTVR+OMT-OMT)	*P* Value
KCCQ Overall Summary Score				
30 d	67.3 (64.8-69.8)	55.5 (51.8-59.1)	11.8 (7.4-16.3)	<0.001
6 mo	73.8 (71.1-76.4)	53.0 (49.1-56.8)	20.8 (16.1-25.5)	<0.001
1 y	72.4 (69.8-75.1)	54.7 (50.8-58.6)	17.8 (13.0-22.5)	<0.001
KCCQ physical limitations				
30 d	66.9 (64.2-69.7)	58.9 (54.9-62.8)	8.1 (3.3-12.8)	0.001
6 mo	70.0 (67.1-73.0)	55.0 (50.8-59.2)	15.0 (9.9-20.1)	<0.001
1 y	66.9 (63.9-69.8)	56.1 (51.8-60.5)	10.7 (5.5-16.0)	<0.001
KCCQ total symptoms				
30 d	71.3 (68.6-74.1)	58.8 (54.9-62.8)	12.5 (7.7-17.3)	<0.001
6 mo	76.0 (73.2-78.8)	56.6 (52.6-60.7)	19.4 (14.4-24.3)	<0.001
1 y	75.5 (72.6-78.3)	58.7 (54.5-62.9)	16.8 (11.7-21.8)	<0.001
KCCQ quality of life				
30 d	64.9 (61.8-68.0)	48.3 (43.8-52.8)	16.6 (11.1-22.1)	<0.001
6 mo	73.5 (70.4-76.7)	50.0 (45.5-54.5)	23.6 (18.0-29.1)	<0.001
1 y	74.9 (71.8-77.9)	51.5 (47.0-56.0)	23.4 (18.0-28.8)	<0.001
KCCQ social limitations				
30 d	65.7 (62.0-69.4)	54.0 (48.8-59.2)	11.7 (5.3-18.1)	<0.001
6 mo	75.3 (71.8-78.8)	49.0 (43.9-54.1)	26.3 (20.1-32.5)	<0.001
1 y	71.5 (67.8-75.2)	50.0 (44.6-55.4)	21.5 (14.9-28.0)	<0.001
MOS SF-36 physical component				
30 d	39.3 (38.3-40.3)	36.2 (34.8-37.6)	3.1 (1.3-4.8)	<0.001
6 mo	41.3 (40.2-42.4)	35.9 (34.4-37.5)	5.4 (3.5-7.3)	<0.001
1 y	40.4 (39.3-41.5)	36.2 (34.6-37.8)	4.3 (2.3-6.2)	<0.001
MOS SF-36 mental component				
30 d	52.0 (50.7-53.2)	49.1 (47.4-50.9)	2.8 (0.7-5.0)	0.010
6 mo	54.8 (53.5-56.0)	47.8 (46.1-49.6)	6.9 (4.8-9.1)	<0.001
1 y	54.1 (52.8-55.3)	48.1 (46.3-50.0)	5.9 (3.7-8.2)	<0.001

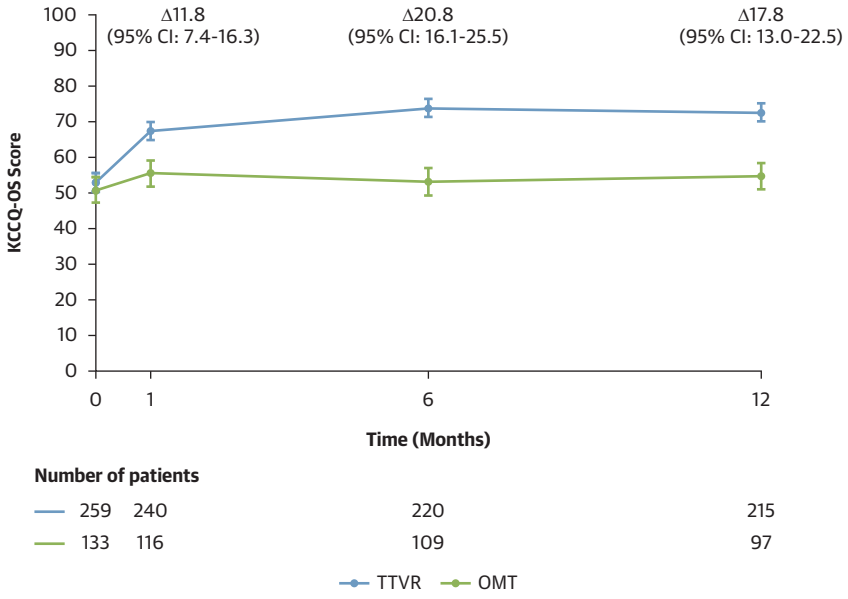
KCCQ = Kansas City Cardiomyopathy Questionnaire; MOS = Medical Outcomes Study; SF-36 = 36-Item Short Form Health Survey; other abbreviations as in Table 1.

only significant for heart failure hospitalization (adjusted HR: 0.80; 95% CI: 0.71-0.90), although the mortality association was directionally consistent (adjusted HR: 0.87; 95% CI: 0.74-1.03). There were no significant interactions between treatment group and the association between 30-day KCCQ-OS and clinical outcomes, suggesting that the relationship between 30-day health status clinical outcomes was independent of how that health status was achieved.

DISCUSSION

The TRISCEND II pivotal trial is the first randomized trial to compare TTVR+OMT vs OMT alone for patients with symptomatic and severe or greater TR. As published elsewhere, in the primary clinical analysis, TTVR with the EVOQUE valve met its primary endpoint, demonstrating superiority over OMT for the hierarchical composite endpoint.[7] This result was driven primarily by improvements in KCCQ-OS and NYHA functional class, however, with no meaningful between-group differences in mortality or heart failure hospitalization. In this prespecified health status analysis of the TRISCEND II pivotal trial, we found that TTVR+OMT resulted in significant improvement in health status compared with OMT alone over the entire 1-year follow-up period. Interestingly, the extent of benefit provided by TTVR+OMT varied over time; at 30-day follow-up, there was a moderately large improvement (~12 points) in the KCCQ-OS compared with OMT alone, which increased to nearly 21 points by 6-month follow-up, with only slight attenuation of the effect at 1 year. At 1 year, 40% of patients randomized to TTVR+OMT were alive with at least a 20-point improvement in KCCQ-OS (a large change) compared with 20% of those

CENTRAL ILLUSTRATION **Disease-Specific Health Status Over 1 Year**



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Predicted mean health status scores and between group differences as derived from mixed-effects linear repeated-measures models. Error bars and values in parentheses represent 95% CI. KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; OMT = optimal medical therapy; TTVR = transcatheter tricuspid valve replacement.

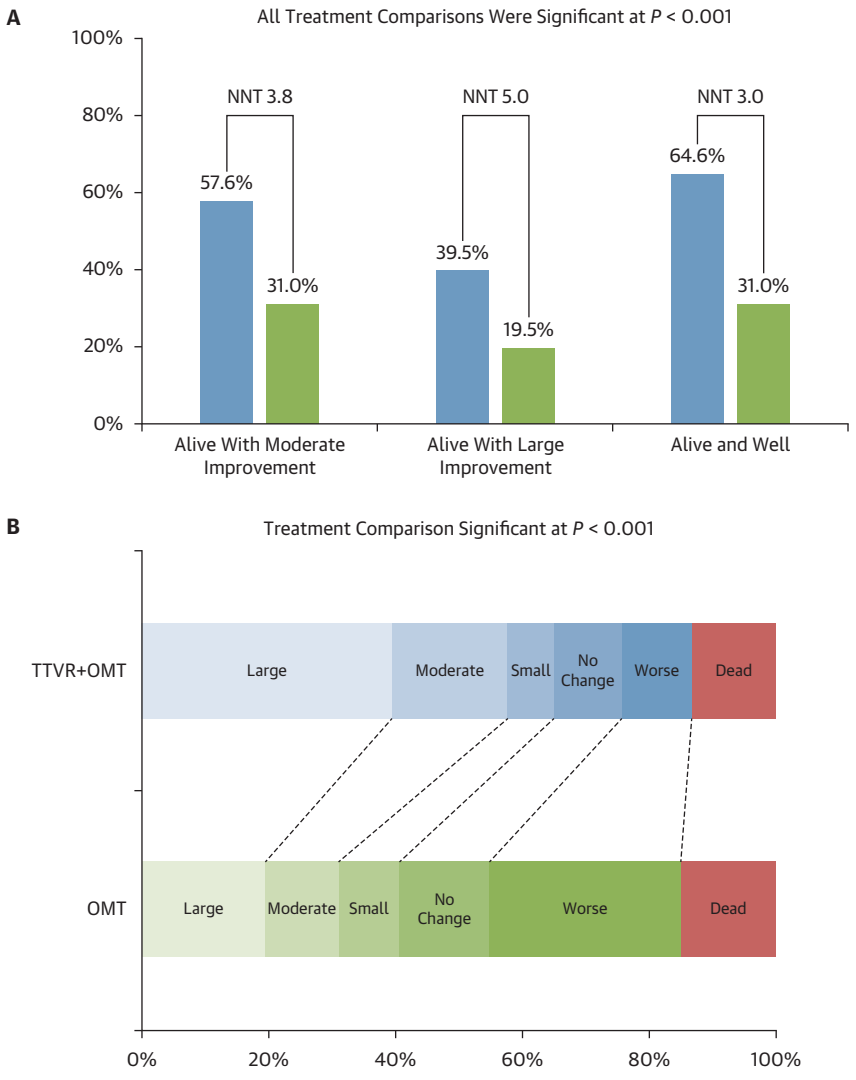
randomized to OMT alone, and 65% of TTVR+OMT patients were alive and well compared with 31% with OMT, with NNTs of 5 and 3 patients, respectively.

The health status benefit of TTVR+OMT was evident across a range of patient characteristics, although there were some patient factors that were associated with greater or less benefit. In particular, patients with worse baseline functional capacity and impaired right ventricular function each appeared to derive less health status benefit from TTVR+OMT compared with OMT alone. In addition, the treatment benefit of TTVR+OMT vs OMT alone was modified by the extent of TR at baseline, with patients having massive or torrential TR reporting KCCQ-OS improvements that were twice as large as those having severe TR. This finding likely reflects the fact that ~95% of patients treated with TTVR+OMT achieve mild or less TR, such that the extent of TR reduction is directly related to the severity at baseline (ie, worse baseline severity of TR → greater reduction in TR with TTVR → more health status improvement). From a clinical standpoint, these interactions suggest that TTVR may achieve the greatest quality-of-life improvement in patients who have massive or torrential TR and in whom right ventricular function and functional capacity are less impaired.

COMPARISON WITH PRIOR STUDIES. While single-arm clinical trials have consistently shown improved health status after transcatheter tricuspid intervention, the TRISCEND II pivotal trial is only the third randomized trial to compare transcatheter tricuspid valve intervention with OMT alone and the first to test TTVR. Because TR severity and volume status can vary substantially over time in patients with severe or greater TR, inclusion of a control group in these trials is important in order to account for the possibility of spontaneous improvement with medical therapy alone as well as regression to the mean.

In both the TRILUMINATE Pivotal[3] and TRISCEND II pivotal trials, there was a relationship between the extent of TR reduction with device therapy and the health status benefit compared with OMT alone. However, the relationship between the improvement in health status and baseline TR severity differed between the 2 trials. In the TRILUMINATE Pivotal

FIGURE 1 Categorical Outcomes Integrating Health Status and Survival



(A) Proportions of patients with categorial outcomes at 1 year: alive with a moderately large Kansas City Cardiomyopathy Questionnaire Overall Summary Score (KCCQ-OS) improvement (change ≥10 points from baseline), alive with a large KCCQ-OS improvement (change ≥20 points from baseline), and "alive and well" (KCCQ-OS ≥60 and no decline ≥10 points from baseline). (B) Proportions of patients with different levels of change in KCCQ-OS at 1 year: ≥20 points (large improvement), ≥10 and <20 points (moderate improvement), ≥5 and <10 points (small improvement), >−5 and <5 points (no change), ≤−5 points (worse), and dead. NNT = number needed to treat; OMT = optimal medical therapy; TTVR = transcatheter tricuspid valve replacement.

trial, the between-group improvement in KCCQ-OS was similar regardless of whether the patient had severe, massive, or torrential TR at baseline. In contrast, in TRISCEND II pivotal trial, the magnitude of health status benefit was directly related to the baseline severity of TR. These contrasting relationships most likely reflect the differences in the mechanism and degree of TR reduction between the 2 devices. With T-TEER, the extent of TR reduction tends to vary with anatomic complexity, such that patients generally achieve a 2- to 3-grade reduction in TR,[5] regardless of baseline TR grade. In contrast, the extent of TR reduction with TTVR is relatively independent of anatomic complexity, which appears to

TABLE 3 Estimated Effect of TTVR+OMT vs OMT on 1-Year KCCQ-OS Among Key Patient Subgroups

		Mean (95% CI)			
	n	TTVR+OMT	OMT	Mean Difference	Interaction *P* Value
Age					0.659
<80 y	175	72.8 (68.9-76.6)	56.2 (50.4-62.0)	16.6 (9.6-23.6)	
≥80 y	217	72.1 (68.5-75.8)	53.4 (48.3-58.6)	18.7 (12.3-25.0)	
Sex					0.993
Female	296	73.5 (70.4-76.5)	55.7 (51.3-60.0)	17.8 (12.5-23.2)	
Male	96	69.2 (63.8-74.5)	51.4 (43.0-59.7)	17.8 (7.9-27.7)	
Baseline TR severity					0.049
Severe	172	69.7 (65.9-73.4)	58.4 (52.5-64.3)	11.3 (4.3-18.3)	
Massive	94	72.5 (66.7-78.2)	49.8 (42.0-57.6)	22.6 (13.0-32.3)	
Torrential	126	77.0 (72.2-81.8)	53.7 (47.0-60.4)	23.3 (15.1-31.5)	
6-min walk distance					0.016
<238.5 m	196	68.6 (64.8-72.4)	56.7 (51.1-62.4)	11.8 (5.1-18.6)	
≥238.5 m	196	76.1 (72.4-79.8)	52.8 (47.5-58.0)	23.3 (16.9-29.7)	
Chronic lung disease					0.981
No	326	72.6 (69.7-75.5)	55.0 (50.6-59.3)	17.7 (12.5-22.9)	
Yes	66	71.1 (64.1-78.1)	53.3 (44.4-62.2)	17.8 (6.5-29.1)	
Left ventricular ejection fraction					0.871
<50%	107	74.1 (68.9-79.4)	55.8 (48.1-63.5)	18.3 (9.1-27.6)	
≥50%	285	71.8 (68.7-74.9)	54.4 (49.9-58.8)	17.5 (12.0-22.9)	
TAPSE					0.286
<17 mm	197	71.8 (68.0-75.7)	52.0 (46.2-57.8)	19.8 (12.8-26.8)	
≥17 mm	151	72.7 (68.3-77.1)	58.5 (52.2-64.9)	14.2 (6.4-21.9)	
Right ventricular FAC					0.013
<35%	99	67.6 (62.4-72.8)	60.5 (52.1-68.9)	7.1 (−2.8 to 17.0)	
≥35%	257	75.0 (71.8-78.2)	53.6 (49.1-58.0)	21.4 (16.0-26.9)	
Cardiac index					0.440
<2 L/min/m^2	243	74.0 (70.5-77.4)	57.5 (52.6-62.4)	16.4 (10.5-22.4)	
≥2 L/min/m^2	120	72.5 (67.8-77.3)	52.0 (44.9-59.1)	20.5 (12.0-29.0)	
Pulmonary hypertension					0.262
No	111	74.0 (69.2-78.8)	52.0 (44.5-59.4)	22.0 (13.2-30.9)	
Yes	281	71.7 (68.6-74.9)	55.7 (51.1-60.2)	16.1 (10.5-21.6)	
Heart failure hospitalization in prior year					0.447
≤1	256	73.2 (70.0-76.5)	54.1 (49.5-58.7)	19.1 (13.5-24.8)	
>1	136	70.9 (66.2-75.5)	55.7 (48.5-62.9)	15.2 (6.6-23.7)	
Daily diuretic dose[a]					0.108
<40 mg	97	76.5 (71.0-82.0)	53.6 (47.1-60.2)	22.9 (14.4-31.4)	
≥40 mg	269	71.0 (67.9-74.1)	56.5 (51.7-61.3)	14.5 (8.7-20.2)	
Baseline KCCQ-OS					0.172
Tertile 1 (0-42.5)	136	70.6 (63.9-77.3)	58.6 (50.2-66.9)	12.1 (4.0-20.2)	
Tertile 2 (43-64)	131	70.7 (66.0-75.4)	52.6 (46.0-59.1)	18.1 (10.1-26.2)	
Tertile 3 (65-100)	124	75.5 (69.0-82.0)	52.5 (44.3-60.7)	23.0 (14.9-31.2)	

[a]Furosemide equivalent (torsemide 20 mg, bumetanide 1 mg).

FAC = fractional area change; KCCQ-OS = Kansas City Cardiomyopathy Questionnaire Overall Summary Score; TAPSE = tricuspid annular plane systolic excursion; TR = tricuspid regurgitation.

translate into a greater reduction in TR (and greater health status benefit) for patients with more severe baseline TR.

In addition to these differences in effectiveness based on TR severity, there were differences in the time course of health status improvement between T-TEER and TTVR. With T-TEER in the TRILUMINATE Pivotal trial, the vast majority of health status improvement was evident within 30 days of treatment. In contrast, with TTVR+OMT there was a

moderately large health status benefit compared with OMT at 30 days that continued to increase through 6 months. Whether this difference in the time course of health status benefit is due to transient right ventricular dysfunction in response to TTVR or to progressive right ventricular remodeling (or some combination of both) is unknown.

STUDY LIMITATIONS. First, although TTVR+OMT was compared against OMT, patient-reported outcomes are susceptible to bias given the unblinded trial design.[22] While a sham-controlled trial would be required to provide unequivocal proof that TTVR provides health status benefits beyond a placebo effect, TRISCEND II pivotal trial provides several lines of evidence that suggest a true biologic effect of TTVR. Importantly, the magnitude and durability of health status benefit with TTVR+OMT are reassuring. In addition, the gradual emergence of health status benefit over the first 6 months of follow-up contrasts with typical placebo effects, which tend to be fully apparent almost immediately after treatment. Finally, the relationship between baseline TR severity and the magnitude of health status benefit of TTVR+OMT also suggests a biologic component.

Second, the durability of the health status benefit of TTVR+OMT beyond 1 year is unknown and may not be informed by longer-term follow-up in the TRISCEND II pivotal trial as OMT patients were allowed to cross over to TTVR after 1-year follow-up.

Third, the number of patients in the OMT arm was relatively small owing to 2:1 randomization and disproportionate withdrawals. As such, our subgroup analyses may have been underpowered to identify important factors that would result in a differential health status benefit with TTVR+OMT. Finally, the health status benefits of TTVR+OMT may not extend to patients outside of the inclusion and exclusion criteria of the trial or to other valve platforms.

CONCLUSIONS

In the TRISCEND II pivotal trial, treatment of patients with symptomatic and severe or greater TR with TTVR+OMT vs OMT resulted in substantial improvement in patients' symptoms, function, and quality of life. These benefits were evident 30 days after TTVR, continued to increase through 6 months, and remained durable through 1 year. Further study is warranted to understand the long-term durability of these benefits as well as to identify the optimal patient population for this novel therapy.

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KEY WORDS quality of life, transcatheter valve, tricuspid valve regurgitation

APPENDIX For an expanded Methods section and supplemental tables and figures, please see the online version of this paper.