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Temporal Trends in Quality of Life Outcomes after Transapical TAVR: A PARTNER Trial Substudy

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Abstract

Background—In the PARTNER randomized controlled trial (RCT), which represented the first exposure to transapical transcatheter aortic valve replacement (TA-TAVR) for many clinical sites, high risk patients undergoing TA-TAVR derived similar health-related quality-of-life (HRQoL) outcomes when compared with surgical AVR (SAVR). With increasing experience, it is possible that HRQoL outcomes of TA-TAVR may have improved.

Methods and Results—We evaluated HRQoL outcomes at 1-, 6-, and 12-month follow-up among 875 patients undergoing TA-TAVR in the PARTNER non-randomized continued access (NRCA) registry, and compared these outcomes with those of the TA-TAVR and SAVR patients

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DISCLOSURES

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in the PARTNER RCT. HRQoL was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Medical Outcomes Study Short Form-12, and the EuroQoL-5D, with the KCCQ overall summary score serving as the primary endpoint. The NRCA TA-TAVR and RCT TA-TAVR and SAVR groups were generally similar. The primary outcome, the KCCQ summary score, did not differ between the NRCA TA-TAVR and the RCT TA-TAVR group at any follow-up timepoints, although there were small differences in favor of the NRCA cohort on several KCCQ subscales at 1 month. There were no significant differences in follow-up HRQOL between the NRCA-TAVR and the RCT SAVR cohorts on the KCCQ overall summary scale or any of the disease-specific or generic subscales.

Conclusions—Despite greater experience with TA-TAVR in the NRCA registry, HRQoL outcomes remained similar to those of TA-TAVR in the original RCT cohort and no better than those with SAVR. These findings have important implications for patient selection for TAVR when transfemoral access is not an option.

Clinical Trial Registration—Placement of AoRTic TraNscathetER Valve [PARTNER] trial; NCT00530894; http://clinicaltrials.gov/show/NCT00530894

Keywords

transcatheter aortic valve replacement; transapical; quality of life

Transapical (TA) access for transcatheter aortic valve replacement (TAVR) with the Edwards-SAPIEN valve is an accepted approach for high-risk patients with severe aortic stenosis (AS) in whom vascular anatomy precludes safe transfemoral (TF) access. Although the TA approach avoids potential access-site complications of the iliac and femoral vessels, TA access has its own limitations, including pain related to an anterior lateral thoracotomy and an increased risk of respiratory complications due to splinting and left lung atelectasis.[1–3] Given the more invasive nature of the TA compared with the TF approach, whether TA-TAVR maintains the health-related quality-of-life (HRQoL) advantages of TF-TAVR over traditional surgical aortic valve replacement (SAVR) remains uncertain.

One of the main advantages of TAVR versus SAVR is the more rapid recovery from TAVR, which resulted in improved early HRQoL in the randomized Placement of AoRTic TraNscathetER Valve (PARTNER) A trial.[4] However, this benefit of TAVR differed according to access site. In contrast to the TF approach, which was associated with significant early improvements in HRQoL compared with SAVR, patients who required TA access had no HRQoL benefit over SAVR at any time point following the procedure.[4] Moreover, there was a statistically significant difference in Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score in favor of SAVR at 6 months as well as trends in other HRQoL metrics favoring SAVR at the 1-month timepoint. Since the patients enrolled in the high-risk cohort of the PARTNER trial represented some of the first TA-TAVR procedures for many study sites, however, it is possible that TA results have improved with greater experience.[5] We therefore sought to examine HRQoL outcomes after TA-TAVR in the larger and more contemporary non-randomized continued access registry (NRCA) of the PARTNER trial. We compared these outcomes with those of patients who underwent either TA-TAVR or SAVR within the TA cohort of the randomized PARTNER trial.

METHODS

Study design

The design of the PARTNER trial, along with its inclusion and exclusion criteria, is detailed in previous publications.[6, 7] Patients deemed eligible for trial entry had severe AS, as defined by an aortic valve area of <0.8 cm^2 and either a mean valve gradient of ≥40 mmHg or peak velocity of ≥4.0 m/sec. For Cohort A, all patients were required to be operable, but at high surgical risk with an expected risk of perioperative mortality >15% as determined by 2 surgeons. All patients had New York Heart Association class II, III, or IV heart failure symptoms. Prior to randomization, patients underwent assessment of aortic and iliofemoral anatomy to determine suitability for a TF approach with the SAPIEN heart valve system (Edwards Lifesciences, Irvine, CA). Those found suitable for TF access were randomized to TF-TAVR or SAVR. Those whose anatomy was prohibitive for the TF approach were randomized to TA-TAVR or SAVR. After enrollment of the randomized controlled trial (RCT) was completed with 699 patients, a prespecified NRCA registry provided treatment for 2068 additional patients, of whom 977 underwent TA-TAVR, with the remainder receiving TF-TAVR. The study was approved by the Institutional Review Board at each participating site and all patients provided written informed consent.

Measurement of HRQoL

Health-related quality of life was assessed at baseline and at 1, 6, and 12 month follow-up using 3 validated instruments: the Kansas City Cardiomyopathy Questionnaire (KCCQ), the Medical Outcomes Study 12-item Short Form (SF-12), and the EuroQOL-5D (EQ-5D). The KCCQ is a 23-item questionnaire addressing specific health domains pertaining to heart failure, including physical limitation, symptom frequency and burden, self-efficacy, and social limitation[8] and has been shown to be reliable and valid in the assessment of HRQoL in patients with severe, symptomatic aortic stenosis.[9] The KCCQ also provides an overall summary score, which ranges from 0 to 100 (with higher scores indicating improved HRQoL). The KCCQ overall summary score has been shown to correspond with New York Heart Association functional classification, with score ranges of 76–100, 61–75, 45–60, and 0–44 corresponding to New York Heart Association classes I, II, III, and IV, respectively.[9] Small, moderate, and large clinical improvements in health status correspond to increases in KCCQ scores of approximately 5, 10, and 20 points, respectively.[10]

The SF-12 is a generic health status instrument that was derived from the original SF-36 health survey, one of the most extensively validated generic health status measures.[11] The SF-12 physical and mental summary scores have been shown to correlate closely with the physical and mental component scores of the SF-36 and are scaled to overall population norms of 50 ± 10, with higher scores representing better health status. Minimum clinically important differences on the physical and mental summary scores are roughly 2 to 2.5 points.[12] The EQ-5D is a health state classification system that is defined by self-ratings in 5 dimensions (self-care, mobility usual activities, pain/discomfort, anxiety/depression).[13] For the purposes of this study, the EQ-5D domains were converted to utilities according to an algorithm developed for the US population.[14] Utilities represent measures of an individual's

strength of preference for his or her current state of health on a scale ranging from 0 to 1, where 0 represents death and 1 represents perfect health.

Statistical analysis

Given the importance of adjusting follow-up HRQoL assessments for baseline values, patients with missing baseline scores were excluded from the analysis. Summary scores for the KCCQ, EQ-5D, and SF-12 were generated according to the scoring algorithms published by their developers.[8, 11, 14] The pre-specified primary endpoint was the KCCQ overall summary score. All other subscales of the KCCQ along with the SF-12 and EQ-5D were considered secondary endpoints.

Separate 2-way comparisons were performed between the NRCA TA-TAVR group and the RCT TA-TAVR and RCT SAVR groups. Baseline differences in clinical characteristics and HRQoL scores were compared between groups using 2-sample Student t tests for continuous variables and chi-square tests for categorical variables. Within group changes from baseline were assessed using paired t tests. Longitudinal mixed effect models were used to examine the between group differences over time. Variables included in the models were time (1, 6, and 12 months), treatment group, baseline HRQoL, age, gender, chronic obstructive pulmonary disease, and the interaction between time and treatment group. The mixed models used all available HRQoL data from all follow-up time points, and accommodate missing data under the missing at random assumption.

All analyses were performed on an as-treated basis, and a 2-tailed p value of <0.05 was considered statistically significant for all comparisons. All analyses were performed using SAS for Windows version 9.2 (SAS Institute, Inc, Cary, NC) by an independent statistician in the Health Economics and Technology Assessment Group at Saint Luke's Mid America Heart Institute.

RESULTS

Patient population and comparison to randomized PARTNER patients

In the NRCA TA-TAVR group, 89.6% (875/977) had baseline HRQoL data. Of the patients randomized to TA-TAVR or SAVR in PARTNER Cohort A, 95.1% (99/104) of the TA-TAVR and 87.0% (80/92) of the SAVR patients had baseline HRQoL data (Figure 1). Among the NRCA TA-TAVR group, patients with baseline HRQoL data were generally similar to those without such data (Supplementary Appendix Table 1).

The baseline characteristics and HRQoL scores of the NRCA TA-TAVR, RCT TA-TAVR, and RCT SAVR patients are summarized in Table 1. Patients in the NRCA TA-TAVR group were slightly older than either the RCT TA-TAVR or RCT SAVR groups. In addition, patients in the NRCA TA-TAVR group were more likely to have undergone percutaneous coronary intervention and balloon aortic valvuloplasty prior to their aortic valve treatment. Patients in the RCT TA-TAVR group were more likely to have a history of cerebrovascular disease than those in the NRCA TA-TAVR group. Otherwise, the baseline characteristics of the 3 groups were similar.

At baseline, there were no differences in HRQoL among the 3 groups with respect to the KCCQ summary score, the SF-12 mental score, and EQ-5D utility. There were small but statistically significant differences between the NRCA TA-TAVR group and the RCT TA-TAVR group with respect to the KCCQ total symptoms and quality of life scales as well as the SF-12 physical scale, each of which tended to be higher in the NRCA cohort. In addition, the score on the KCCQ physical limitations scale was higher in the RCT SAVR group as compared with the NRCA TA-TAVR group.

Within-group changes

Within-group changes in each HRQoL scale from baseline to 1-, 6-, and 12-month follow-up are shown in Table 2. For the NRCA TA-TAVR cohort, there were statistically significant and clinically meaningful improvements from baseline across all of the disease-specific and generic health status measures (with the exception of the SF-12 mental scale) beginning at the 1-month timepoint. These changes tended to increase further between 1 and 6 months, beyond which point there were no further consistent improvements. Based on published standards,[10] the extent of improvement on the KCCQ summary scale was “moderately large” at 1 month (12.7 points) and “large” at 6 and 12 months (25.9 and 25.2 points, respectively). Qualitatively similar changes were seen for the RCT TA-TAVR and SAVR groups although the 1-month improvement was not significant for the KCCQ social limitations scale for the RCT TA-TAVR group and for both the physical limitations scale and social limitations scales in the RCT SAVR group.

Longitudinal assessment and between-group comparisons

Adjusted mean scores by treatment group for each of the HRQoL domains and follow-up timepoints are shown in Figure 2, and adjusted between-group differences according to the longitudinal mixed effects model are summarized in Table 3. There was no difference in the KCCQ summary score between the NRCA TA-TAVR and RCT TA-TAVR groups at any follow-up timepoint. However, there were small but statistically significant differences in health status favoring the NRCA TA-TAVR group at either 1 or 6 month follow-up for several of the KCCQ subscales including physical limitations, quality of life, and social limitation as well as the SF-12 mental component and the EQ-5D utilities. There were no significant differences in 12-month health status between the NRCA and RCT TA-TAVR groups on any of the subscales.

When the NRCA TA-TAVR group was compared with the RCT SAVR group, there were no differences in the KCCQ summary score at any follow-up timepoint (Table 3). Moreover, there were no significant between group differences in any of the KCCQ subscales or the generic health status measures at any timepoint.

DISCUSSION

In this study, we have systematically examined health-related quality of life both early and late after TA-TAVR and SAVR using a battery of well-validated instruments. The principal findings of this analysis are: 1) Among patients undergoing TA-TAVR in the PARTNER continued access registry, there were substantial improvements in both disease specific and

generic health status that were comparable to those observed in the randomized PARTNER trial; and 2) Although there was a suggestion of modest early in HRQoL benefit for patients treated with TA-TAVR in the NRCA registry compared with the RCT, the magnitude of these differences was small, and there remained no evidence of either early or late HRQoL improvement with TA-TAVR compared with SAVR.

In a previous study of the PARTNER RCT, Reynolds and colleagues found that HRQoL was better with TF-TAVR when compared with SAVR.[4] However, in patients deemed unsuitable for a TF approach (who were therefore treated with TA-TAVR), there were no HRQoL benefits of TAVR compared with SAVR, and there were trends favoring SAVR at the 1 and 6 month timepoints. Since the PARTNER RCT represented the earliest experience with TA-TAVR for the vast majority of sites, however, it is possible that the lack of QOL benefit with TA-TAVR related mainly to the inexperience of the treating sites rather than any inherent limitations of the TA-TAVR technique. Indeed in the PARTNER RCT, the median number of TA-TAVR procedures was 4 (range, 1–20; Supplementary Appendix Figure 1). Recent studies have reported that the number of cases required to overcome the learning curve ranges from 18–100,[15–17] a level that far exceeded the experience of virtually all of the PARTNER centers at the time of the RCT. The current analysis was therefore performed to determine whether the HRQoL outcomes of TA-TAVR have improved with increasing operator and center experience. Although we did find some evidence that early HRQoL outcomes have improved with greater experience, these differences were modest at best, and there remained no evidence of improved HRQoL compared with SAVR in either the short or the long-term.

Numerous previous studies have demonstrated that TAVR results in substantial HRQoL improvement compared with baseline.[4, 18–20] Most recently, meta-analysis of 62 TAVR studies demonstrated that, TAVR generally results in improved functional status and quality of life[21]—findings that are similar to those with TA-TAVR in the PARTNER trial and NRCA. However, few studies to date have compared patient-reported outcomes of TAVR by access site[22] or compared with a surgical control group.[4]

The lack of early HRQoL benefit with TA-TAVR compared with SAVR, even with greater experience in the NRCA registry, is likely related to both clinical factors and technical aspects of the procedure. The PARTNER trial adopted a “TF-first” mentality, thus relegating TA-TAVR to patients who did not qualify for the TF approach due to anatomical considerations. This strategy may have resulted in higher risk patients undergoing TA-TAVR than would be expected in a real-world clinical setting and could have contributed to worse HRQoL outcomes in this subgroup. Nonetheless, it is important to recognize that randomization in PARTNER was stratified by access site; as a result, those patients who were randomized to SAVR in the TA stratum were similarly high risk.

Previous studies have demonstrated that thoracotomy results in greater postoperative pain than median sternotomy, due to rib spreading and respiratory motion.[23] This discomfort could have contributed to short-term HRQoL trends favoring SAVR as well. Procedural modification and localized administration of analgesia may provide some HRQoL benefit in patients undergoing TA-TAVR.[24] However, these maneuvers do not eliminate the apical

puncture and repair inherent to the TA approach, which could adversely impact left ventricular function and cause subsequent functional limitation.[25]

Whether other non-femoral approaches to TAVR, such as the transaortic approach, can overcome these issues and result in HRQoL benefits compared with either TA-TAVR or SAVR is currently unknown. In non-randomized studies, the transaortic approach has been shown to result in similar clinical outcomes when compared with the TA approach.[26, 27] Potential advantages of the transaortic approach are avoidance of a thoracotomy and injury to the myocardium and apex, as well as potential for direct visualization of the aorta. In patients with specific high-risk comorbidities such as chronic obstructive pulmonary disease and left ventricular systolic dysfunction, these advantages of the transaortic approach may result in superior HRQoL outcomes. To date, however, no rigorous studies have compared HRQoL outcomes between the TA and transaortic approaches to TAVR. Studies comparing HRQoL outcomes of TA and alternative accesses would aid in prioritizing TAVR access options.

In addition to providing a sobering reminder that “less invasive” treatments do not always result in improved patient-centered outcomes, the lack of HRQoL benefit with TA-TAVR compared with SAVR has important economic ramifications. In order for TAVR to be economically attractive from a societal perspective, it must either have lower costs or improved health outcomes compared with the available alternatives.[28] In the PARTNER A cost-effectiveness study, initial and 1-year costs were substantially higher with TA-TAVR compared with SAVR.[29] In the case of TAVR for high risk surgical candidates, improved health outcomes can be interpreted as either improved long-term survival or better HRQoL. In the randomized PARTNER trial, however, there was no difference in survival between patients treated with TA-TAVR vs. SAVR.[7] Although 1-year survival was improved with TA-TAVR in the continued access registry,[5] whether this finding reflects improved technique or better patient selection (or both) is unknown. In the absence of definitive evidence of better long-term survival, evidence of improved HRQoL (in either the short or long-term) is therefore critical in order to justify the higher up-front cost of TAVR.

Study limitations

Our findings should be considered in light of a number of important limitations. Most importantly, although the original comparison of TA-TAVR and SAVR in the PARTNER A trial was randomized, the comparison of these 2 cohorts with patients from the NRCA was non-randomized and therefore subject to both measured and unmeasured confounding. The 3 cohorts were all enrolled using the same inclusion and exclusion criteria, however, and there were relatively few differences in observed baseline characteristics between the NRCA and RCT populations. Of note, patients in the RCT TA-TAVR group had a higher prevalence of cerebrovascular disease compared with the NRCA TA-TAVR group. If this difference translated into greater disability in the RCT group, it would have been expected to bias our results toward improved follow-up health status in the NRCA group. Since we did not find such a benefit, however, this baseline imbalance would appear to be an unlikely explanation for our findings. Follow-up health status data were missing on a modest proportion of patients, upwards of 30% in the NRCA cohort at 12-month follow-up, which

could have biased our results. Although it is not possible to prove that follow-up data were truly missing at random, comparison of baseline characteristics between the patients with vs. without missing HRQoL data demonstrated no major differences (Supplementary Appendix Table 1). We also analyzed NRCA TA-TAVR patients with and without HRQoL data at 30-day follow-up in order to further investigate the reasonableness of the missing at random assumption. These groups also exhibited no major differences with regards to demographics and characteristics (Supplementary Appendix Table 2). In addition, the clinical outcomes of these patients are not significantly different with regards to mortality, stroke, and rehospitalization rates. However, the rates of vascular complications and bleeding events were higher in the group of patients without HRQoL data (Supplementary Appendix Table 3). Our primary analytic approach (longitudinal mixed effects models) was chosen in order to minimize the impact of missing data at any specific timepoint. Full details regarding completeness of HRQOL data are summarized in Supplementary Appendix Table 4. Finally, there were many fewer patients enrolled and randomized within the TA cohort of PARTNER A than the TF cohort. Thus, it is possible that the lack of a significant benefit of TA-TAVR compared with SAVR in the RCT was driven, in part, by reduced statistical power. Reduced power is less relevant to the NRCA cohort, however, since it was ~10 times larger than the RCT cohort.

Conclusions

In this systematic evaluation of HRQoL outcomes among patients from both the PARTNER RCT and NRCA registry, we found that TA-TAVR resulted in substantial HRQoL benefits compared with baseline that were evident within 1 month and sustained or enhanced at 1 year follow-up. Although there was a suggestion of modest early improvement in HRQoL in patients treated with TA-TAVR in the NRCA registry compared with the RCT, the magnitude of these differences was small and there remained no evidence of either early or late HRQoL improvement with TA-TAVR compared with SAVR. These findings have important implications for access site selection for patients undergoing TAVR, and further study is warranted to determine whether results are similar with other forms of non-femoral access.

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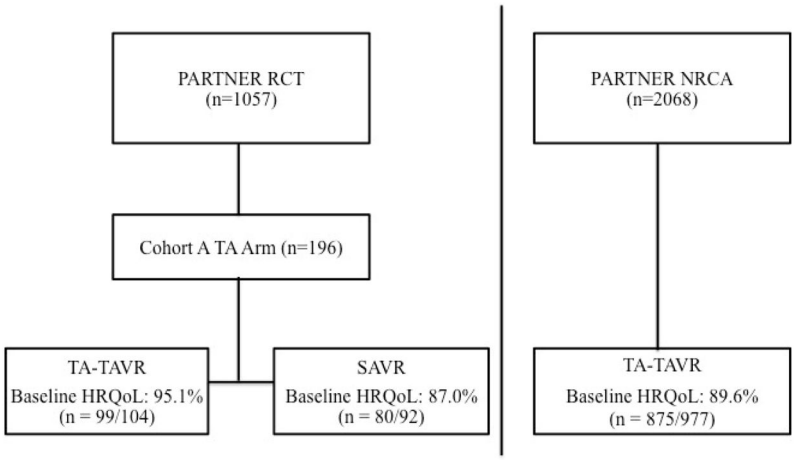

Figure 1.

PARTNER - Cohort A randomized control trial (RCT) transapical (TA) arm (transcatheter aortic valve replacement (TAVR) and surgical aortic valve replacement (SAVR)) and non-randomized continued access (NRCA) registry TA arm designs, including percentages with baseline health-related quality-of-life (HRQoL) data.

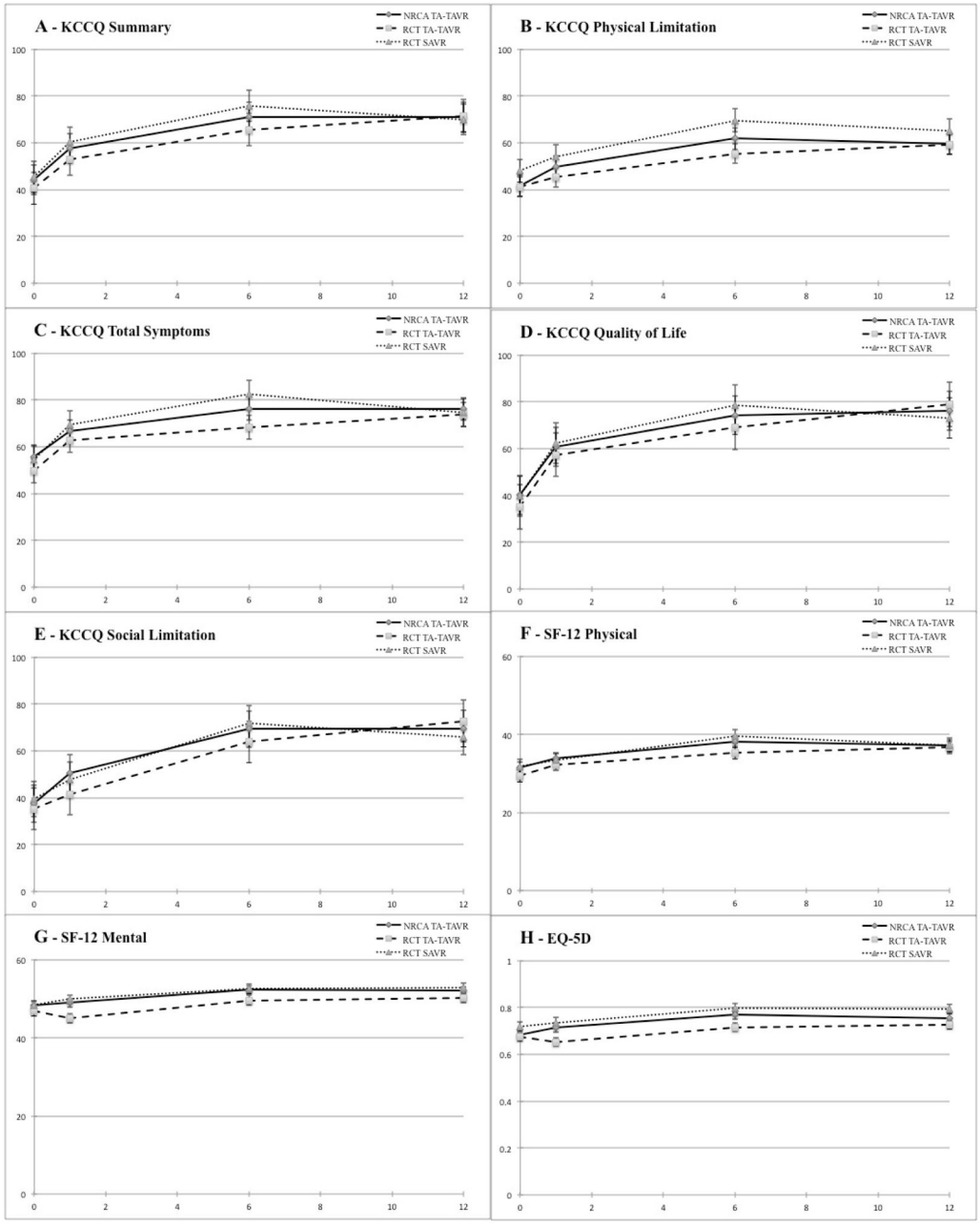

Figure 2.

Adjusted mean scores derived from longitudinal growth curve models for Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score (A), KCCQ subscales (B–E), the Short-Form 12 (SF-12) physical (F) and mental (G) scores, and EuroQol-5D (EQ-5D) utilities (H).

Table 1

Baseline characteristics and health-related quality-of-life scores

	NRCA TA-TAVR (n=875)	RCT TA-TAVR (n=99)	p-value*	RCT SAVR (n=80)	p-value*
Demographic and clinical characteristics					
Age (years)	84.6 ± 6.3	82.6 ± 6.9	<0.01	83.4 ± 5.5	0.02
Male (%)	47.1	51.5	0.40	58.8	0.05
STS Score	12.0 ± 4.2	11.8 ± 3.7	0.64	11.8 ± 3.1	0.70
Previous MI (%)	29.4	28.3	0.82	36.3	0.20
Prior CABG (%)	51.1	50.5	0.91	57.5	0.27
Prior PCI (%)	46.6	32.3	<0.01	43.0	0.55
Prior BAV (%)	28.6	12.1	<0.01	12.5	<0.01
LV ejection fraction (%)	52.2 ± 12.6	53.1 ± 12.3	0.50	53.3 ± 10.8	0.44
Cerebrovascular Disease (%)	29.9	41.8	0.02	33.3	0.54
Peripheral Vascular Disease (%)	61.7	62.2	0.91	63.3	0.78
Diabetes Mellitus (%)	35.0	40.4	0.28	48.8	0.01
Renal Disease (Cr ≥ 2 mg/dL)(%)	16.7	13.1	0.36	22.5	0.19
Liver Disease (%)	2.7	2.0	0.67	0.0	0.13
COPD (Oxygen dependent) (%)	8.7	12.1	0.26	8.8	0.98
Major arrhythmia (%)	48.5	53.5	0.34	47.5	0.86
Permanent pacemaker (%)	21.3	20.2	0.80	21.3	0.99
Pulmonary hypertension (%)	36.8	46.5	0.06	29.1	0.17
Quality-of-life scores					
KCCQ Summary	44.2 ± 21.5	40.6 ± 22.1	0.11	45.4 ± 19.7	0.64
KCCQ Physical Limitation	41.6 ± 24.5	41.2 ± 24.3	0.89	48.1 ± 23.4	0.03
KCCQ Total Symptoms	55.7 ± 22.8	49.6 ± 23.3	0.01	54.3 ± 21.6	0.61
KCCQ Quality of Life	40.2 ± 23.6	35.0 ± 26.6	0.04	39.7 ± 22.2	0.85
KCCQ Social Limitation	37.4 ± 28.2	35.3 ± 30.1	0.51	39.4 ± 26.9	0.54
SF-12 Physical	31.4 ± 8.1	29.4 ± 7.4	0.02	31.8 ± 8.6	0.69
SF-12 Mental	48.2 ± 11.2	46.8 ± 11.4	0.24	48.4 ± 9.6	0.86

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	NRCA TA-TAVR (n=875)	RCT TA-TAVR (n=99)	p-value*	RCT SAVR (n=80)	p-value*
EQ-5D Utilities	0.68 ± 0.19	0.67 ± 0.19	0.61	0.72 ± 0.17	0.12

*p-values relate to the comparison with NRCA TA-TAVR

Values are mean ± SD or %.

BAV = balloon aortic valvuloplasty; CABG = coronary artery bypass grafting; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQol 5D; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MI = myocardial infarction; NRCA = non-randomized continued access registry; PCI = percutaneous coronary intervention; SAVR = surgical aortic valve replacement; SF-12 = Medical Outcomes Study Short-Form 12; STS = Society of Thoracic Surgeons; TA = transapical; TAVR = transcatheter aortic valve replacement.

Table 2

Within-group comparisons of HRQoL compared with baseline

	NRCA TA-TAVR			RCT TA-TAVR			RCT SAVR		
Scale/Timepoint	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**
KCCQ Summary									
1 month	711	12.7 (10.7, 14.7)	<0.01	78	12.4 (6.0, 18.8)	<0.01	61	12.5 (5.5, 19.5)	<0.01
6 months	611	25.9 (23.9, 28.0)	<0.01	72	24.0 (16.7, 31.2)	<0.01	55	27.7 (21.3, 34.1)	<0.01
12 months	506	25.2 (23.0, 27.4)	<0.01	67	29.5 (23.1, 35.9)	<0.01	58	22.2 (14.3, 30.0)	<0.01
KCCQ Physical Limitation									
1 month	637	7.3 (4.7, 9.8)	<0.01	64	1.3 (−6.1, 8.8)	0.72	51	1.7 (−7.7, 11.1)	0.72
6 months	540	18.8 (16.3, 21.4)	<0.01	62	11.5 (3.3, 19.7)	<0.01	51	17.6 (9.8, 25.4)	<0.01
12 months	455	16.2 (13.5, 18.9)	<0.01	56	14.7 (6.7, 22.8)	<0.01	53	12.7 (4.2, 21.2)	<0.01
KCCQ Total Symptoms									
1 month	703	10.2 (8.2, 12.2)	<0.01	78	13.2 (6.5, 19.8)	<0.01	60	12.1 (5.6, 18.5)	<0.01
6 months	601	19.3 (17.2, 21.3)	<0.01	71	17.5 (10.3, 24.6)	<0.01	54	25.9 (19.4, 32.4)	<0.01
12 months	498	18.6 (16.4, 20.8)	<0.01	65	23.3 (16.5, 30.1)	<0.01	58	19.4 (11.9, 27.0)	<0.01
KCCQ Quality of Life									
1 month	699	20.0 (17.6, 22.4)	<0.01	78	22.3 (14.0, 30.6)	<0.01	61	20.9 (13.1, 28.7)	<0.01
6 months	600	33.5 (31.2, 35.9)	<0.01	72	33.2 (24.8, 41.5)	<0.01	55	35.5 (28.0, 42.9)	<0.01
12 months	499	35.1 (32.6, 37.6)	<0.01	66	41.9 (33.5, 50.3)	<0.01	57	29.7 (20.8, 38.6)	<0.01
KCCQ Social Limitation									
1 month	584	11.5 (8.5, 14.6)	<0.01	61	6.9 (−3.2, 17.0)	0.18	46	2.8 (−7.9, 13.4)	0.60
6 months	511	30.8 (27.8, 33.8)	<0.01	59	27.2 (16.2, 38.2)	<0.01	47	29.0 (19.4, 38.7)	<0.01
12 months	438	28.5 (25.3, 31.8)	<0.01	50	34.2 (24.0, 44.5)	<0.01	47	22.8 (11.0, 34.7)	<0.01
SF-12 Physical									
1 month	602	2.4 (1.7, 3.2)	<0.01	77	2.7 (0.5, 4.9)	0.02	61	0.5 (−2.1, 3.0)	0.71
6 months	528	6.6 (5.7, 7.6)	<0.01	71	5.1 (2.5, 7.7)	<0.01	56	6.9 (4.2, 9.5)	<0.01
12 months	423	5.4 (4.4, 6.5)	<0.01	67	7.0 (4.3, 9.6)	<0.01	57	4.7 (1.3, 8.0)	<0.01
SF-12 Mental									
1 month	602	0.2 (−0.8, 1.2)	0.69	77	−0.7 (−3.6, 2.2)	0.64	61	1.7 (−1.4, 4.8)	0.27

	NRCA TA-TAVR			RCT TA-TAVR			RCT SAVR		
Scale/Timepoint	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**	**n**	**Mean Δ vs. Baseline (95% CI)**	**p-value**
6 months	528	4.0 (2.9, 5.0)	<0.01	71	3.4 (0.3, 6.5)	0.03	56	3.9 (1.2, 6.6)	<0.01
12 months	423	3.1 (1.9, 4.4)	<0.01	67	3.3 (−0.1, 6.7)	0.06	57	4.3 (1.1, 7.6)	0.01
EQ-5D Utilities									
1 month	665	0.02 (0.00, 0.04)	0.02	75	−0.03 (−0.08, 0.03)	0.35	58	0.01 (−0.04, 0.06)	0.74
6 months	578	0.08 (0.06, 0.10)	<0.01	67	0.04 (−0.03, 0.10)	0.25	51	0.07 (0.01, 0.12)	0.03
12 months	474	0.06 (0.04, 0.08)	<0.01	62	0.06 (0.01, 0.12)	0.03	53	0.05 (−0.01, 0.12)	0.11

HRQoL = health-related quality of life; EQ-5D = EuroQol 5D; KCCQ = Kansas City Cardiomyopathy Questionnaire; NRCA = non-randomized continued access registry; SAVR = surgical aortic valve replacement; SF-12 = Medical Outcomes Study Short-Form 12; TA = transapical; TAVR = transcatheter aortic valve replacement.

Table 3

Adjusted between group differences according to longitudinal mixed effects models

	NRCA TA-TAVR vs RCT TA-TAVR		NRCA TA-TAVR vs RCT SAVR	
Scale/Timepoint	**Predicted Mean Difference**: NRCA - RCT (95% CI)**	**p-value**	**Predicted Mean Difference**: NRCA - RCT (95% CI)**	**p-value**
KCCQ Summary				
1 month	4.2 (−0.9, 9.3)	0.11	−3.8 (−9.6,2.0)	0.20
6 months	2.2 (−2.1,6.4)	0.32	−2.3 (−7.0,2.5)	0.35
12 months	−0.3 (−5.5,4.9)	0.91	−0.4 (−6.2,5.3)	0.88
KCCQ Physical Limitations				
1 month	6.2 (−0.4,12.8)	0.07	−2.1 (−9.6,5.4)	0.58
6 months	4.8 (−0.6,10.3)	0.08	−2.2 (−8.3,3.8)	0.47
12 months	3.1 (−3.6,9.9)	0.36	−2.4 (−9.6,4.8)	0.52
KCCQ Total Symptoms				
1 month	1.7 (−3.5,6.9)	0.51	−3.2 (−9.0,2.5)	0.27
6 months	5.5 (−0.5,10.5)	0.03	−7.4 (−12.8, −1.9)	0.01
12 months	0.9 (−4.2,6.0)	0.73	−0.3 (−5.8,5.2)	0.91
KCCQ Quality of Life				
1 month	3.4 (−2.4,9.3)	0.25	−3.9 (−10.3,2.6)	0.24
6 months	0.9 (−3.7,5.6)	0.70	−1.5 (−6.6,3.6)	0.56
12 months	−2.1 (−8.2,4.0)	0.50	1.3 (−5.3,7.9)	0.70
KCCQ Social Limitation				
1 month	8.5 (−1.0,16.1)	0.03	0.8 (−7.7,9.3)	0.86
6 months	2.4 (−3.5,8.3)	0.42	0.4 (−6.2,7.0)	0.90
12 months	−5.0 (−13.0,3.0)	0.22	0.0 (−8.5,8.4)	1.00
SF-12 Physical				
1 month	1.4 (−0.3,3.2)	0.11	1.1 (−1.0,3.3)	0.30
6 months	1.3 (−0.4,2.9)	0.15	−1.4 (−3.9,1.1)	0.26
12 months	1.0 (−1.5,3.5)	0.42	0.4 (−2.4,3.2)	0.79
SF-12 Mental				
1 month	2.7 (0.4,5.0)	0.02	−0.9 (−3.5,1.7)	0.48
6 months	2.1 (0.3,3.9)	0.02	−0.9 (−2.8,1.1)	0.39
12 months	1.5 (−1.1,4.0)	0.26	−0.8 (−3.5,1.9)	0.56
EQ-5D Utilities				
1 month	0.06 (0.01,0.11)	0.02	0.00 (−0.06, 0.05)	0.88
6 months	0.04 (0.00,0.08)	0.04	−0.02 (−0.06, 0.03)	0.46
12 months	0.02 (−0.03,0.07)	0.41	−0.03 (−0.09, 0.03)	0.28

* Longitudinal mixed effects models adjusted for age, gender, COPD, and baseline HRQoL

** Positive values indicate better HRQoL with NRCA TA-TAVR, whereas negative values indicate worse HRQOL with NRCA TA—TAVR.

COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQol 5D; HRQoL = health-related quality-of-life; KCCQ = Kansas City Cardiomyopathy Questionnaire; NRCA = non-randomized continued access registry; SAVR = surgical aortic valve replacement; SF-12 = Medical Outcomes Study Short-Form 12; TA = transapical; TAVR = transcatheter aortic valve replacement.