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Health-Related Quality of Life After Transcatheter or Surgical Aortic Valve Replacement in High-Risk Patients With Severe Aortic Stenosis

Results From the PARTNER (Placement of AoRTic TraNscathetER Valve) Trial (Cohort A)

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Objectives This study sought to compare health status and quality-of-life outcomes for patients with severe aortic stenosis (AS) and high surgical risk treated with either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (AVR).

Background For high-risk patients with severe AS, TAVR has been shown to result in similar 12-month survival but differing adverse events compared with AVR.

Methods We evaluated the health status of 628 patients with severe, symptomatic AS at high risk of surgical complications who were randomized to either TAVR or AVR in the PARTNER Trial. Health status was assessed at baseline and 1, 6, and 12 months using the Kansas City Cardiomyopathy Questionnaire, the Short Form-12, and the EuroQol-5D.

Results The primary outcome, the Kansas City Cardiomyopathy Questionnaire summary score, improved more rapidly with TAVR, but was similar for the 2 groups at 6 and 12 months. However, there was a significant interaction between the benefit of TAVR and access site (transapical vs. transfemoral). Patients eligible for transfemoral TAVR demonstrated significant health status benefits with TAVR versus AVR at 1 month (difference, 9.9 points; 95% confidence interval: 4.9 to 14.9; $p < 0.001$), whereas patients treated via the TA approach demonstrated no benefits with TAVR compared with AVR at any time point. Results for Kansas City Cardiomyopathy Questionnaire subscales and generic measures demonstrated similar patterns.

Conclusions In high-risk patients with severe AS, health status improved substantially between baseline and 1 year after either TAVR or AVR. TAVR via the transfemoral, but not the transapical route, was associated with a short-term advantage compared with surgery. (Placement of AoRTic TraNscathetER Valve [PARTNER] trial; NCT00530894) (J Am Coll Cardiol 2012;60:548–58) © 2012 by the American College of Cardiology Foundation

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For decades, surgical aortic valve replacement (AVR) has been the only effective therapy for severe aortic stenosis (AS). AVR improves on the otherwise very poor natural history of severe, untreated AS (1) and also relieves symptoms and improves quality of life (QOL) to age-adjusted population norms, even among elderly patients (2,3). More recently, transcatheter AVR (TAVR), which can be performed using 1 of several access sites including a percutaneous transfemoral (TF) arterial approach (4) or by direct transapical (TA) puncture of the left ventricle via a limited anterior thoracotomy (5), has been developed as a less invasive alternative to AVR. TAVR has been shown to improve QOL in several nonrandomized series (5–7) and to greatly improve both survival (8) and QOL (9) compared with standard therapy in patients who are not candidates for surgery.

Recently, in a population of AS patients at high risk of adverse surgical outcomes, the PARTNER (Placement of AoRTic TraNscathetER Valve) trial Cohort A demonstrated similar 12-month survival among patients randomized to either TAVR or AVR (10). Periprocedural adverse events differed between TAVR and AVR, however, with some (e.g., cerebrovascular and vascular complications) occurring more frequently with TAVR and others (major bleeding, new atrial fibrillation) occurring more frequently with surgery. Other 12-month outcomes were generally similar. In addition, TAVR was associated with a higher incidence of paravalvular regurgitation (10), which may have adverse short- and long-term health consequences (11).

In light of these observations, a more complete understanding of the impact of these alternative approaches to aortic valve replacement on health status (which includes symptoms, functional status, and QOL) (12), as assessed from the patient's perspective, may be relevant for clinical decision making. To address these questions, we conducted a prospective evaluation of health status after either TAVR or AVR as part of the PARTNER trial.

Methods

Study design. The design of the PARTNER trial along with a full list of inclusion and exclusion criteria was reported previously (8,10). The PARTNER program screened 3,105 patients with severe, symptomatic AS at 25 study centers (22 in the United States). Severe AS was defined as an aortic valve area of <0.8 cm^2 with either a mean valve gradient of at least 40 mm Hg or a peak velocity of at least 4.0 m/s. In addition, all patients were required to be at high risk of operative complications with an expected risk of perioperative mortality of $\geq$15% (as determined by 2 surgeons at the study center and the study's executive committee).

Once a patient was deemed appropriate for inclusion in the trial, but before randomization, a detailed assessment of the iliofemoral and aortic anatomy was performed to determine whether the patient was suitable for TAVR via the TF approach. Those patients found to be suitable for the TF approach were then randomized to TF TAVR versus AVR (TF cohort), whereas those patients who were not suitable for a TF approach were randomized to transapical TAVR versus AVR (TA cohort).

Measurement of health status. Health status was evaluated in all patients using validated written questionnaires at baseline and 1, 6, and 12 months after randomization. Baseline questionnaires were completed at the enrolling centers before randomization. Follow-up questionnaires were administered during scheduled follow-up visits at the enrolling centers or by mail. Validated translations of the original questionnaires were provided to non-English speakers.

Abbreviations and Acronyms

- **AS** = aortic stenosis
- **AVR** = aortic valve replacement
- **CI** = confidence interval
- **EQ-5D** = EuroQol
- **KCCQ** = Kansas City Cardiomyopathy Questionnaire
- **QOL** = quality of life
- **SF-12** = Medical Outcomes Study Short-Form 12
- **TA** = transapical
- **TAVR** = transcatheter aortic valve replacement
- **TF** = transfemoral

The Kansas City Cardiomyopathy Questionnaire (KCCQ) was used to assess disease-specific health status, and its overall summary score was defined prospectively as the primary endpoint for this analysis. The KCCQ is a 23-item questionnaire designed and validated to evaluate self-reported health status in patients with heart failure (13). The conceptual domains of the KCCQ include symptoms, physical limitation, social limitation, self-efficacy, and QOL. These scales, as well as an overall summary scale, are scored from 0 to 100, with higher scores indicating fewer symptoms and better QOL. KCCQ summary scores have previously been shown to correspond roughly with New York Heart Association functional class as follows: class I, a score of 75 to 100; class II: 60 to 74; class III: 45 to 59; and class IV: 0 to 44 (14). The KCCQ has been shown to independently predict mortality and health care costs in heart failure populations (15,16). Among outpatients with heart failure, small, moderate, or large clinical improvements as rated by treating physicians corresponded with changes in the KCCQ summary score of approximately 5, 10, and 20 points (14).

Generic health status was evaluated with the Medical Outcomes Study Short-Form 12 (SF-12) questionnaire (17) and the EuroQol (EQ-5D) (18). The SF-12 was derived from the larger Short Form-36 questionnaire, one of the most extensively validated and most frequently used generic QOL measures; the physical and mental summary scores obtained from the SF-12 correlate highly with those calculated using the original longer questionnaire (17). These summary scores are scaled to an overall U.S. population norm of 50 $\pm$ 10; higher scores are better. Minimum clinically important differences on the SF-12 summary scales are 2 to 2.5 points (19,20). The EQ-5D is a generic health state classification system comprising 5 domains (mobility, self-care, usual activities, pain/discomfort, and

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anxiety/depression). The health states defined by the EQ-5D have been transformed to preference-based utilities based on responses from a U.S. reference population (21). These utilities take on possible values ranging from 0 to 1, with 1 representing ideal health and 0 representing the worst imaginable health state (usually death).

Statistical analysis. Patients with missing baseline KCCQ scores were excluded from our analysis because both within-group and between-group statistical comparisons were adjusted for baseline values. The remaining patients made up the analytic population for our study. All patients were grouped according to their randomized treatment assignment in accordance with the intention-to-treat principle. A secondary analysis was performed after excluding 21 subjects who did not undergo their assigned treatment (as-treated population).

Summary measures for the KCCQ, SF-12, and EQ-5D were generated using the scoring algorithms published by their developers (13,21,22). Patients' baseline characteristics and baseline KCCQ, SF-12, and EQ-5D scores were compared between groups using 2-sample Student *t* tests for continuous variables and chi-square tests for categorical variables. Mean changes from baseline within each of the treatment groups at 1, 6, and 12 months were estimated for each of the health status measures and tested for significance using paired Student *t* tests. These analyses allowed us to estimate the extent of improvement from baseline after both TAVR and AVR at different points during the first year of follow-up.

For each of the primary and secondary QOL outcomes, longitudinal random-effects growth curve models were used to examine the relative impact of TAVR versus AVR over time (23). These growth curve models used available QOL data from all follow-up time points (1, 6, and 12 months) and adjusted for baseline score as well as age, sex, and oxygen-dependent chronic obstructive pulmonary disease. The models also included the TAVR access site (TF vs. TA cohort) and treatment assignment, as well as the interaction between these factors, as covariates. The analytic plan specified that if a significant ($p < 0.05$) interaction between treatment and procedural approach was observed on the KCCQ summary score at any time point, then all QOL outcomes would be analyzed separately for the TF and TA groups. Linear and quadratic effects of time were considered as well as all 2- and 3-way interactions between treatment, time, and TAVR access site. Starting with the highest order time-by-treatment interaction, variables were retained in the model if $p \leq 0.05$ using a backward elimination procedure. Estimates of differences in mean scores between treatment groups at each follow-up time point along with their associated confidence intervals (CIs), and p values were obtained from the growth curve models. To address the potential impact of missing data on our results, we repeated the growth curve models after imputing worst case values (defined as the 10th percentile response for a given time point) for surviving patients with missing scores.

To provide further clinical perspective on changes in health status over time, we derived categorical variables for the change in the KCCQ summary score from baseline to each follow-up time point. For these analyses, we defined 6 ordinal categories based on previously established thresholds for clinically relevant change (14): dead; worse (decrease from baseline of >5 points); unchanged (change between −5 and 5 points); slightly improved (increase between 5 and 10 points); moderately improved (increase between 10 and 20 points); and substantially improved (increase >20 points). We then compared the relative impact of TAVR versus AVR using ordinal logistic regression, with treatment group, TAVR access site, and the 2-way interaction between these variables as covariates.

All analyses were performed using SAS version 9.2 (SAS Institute, Cary, North Carolina). All p values are 2 tailed, and $p < 0.05$ was used to denote statistical significance in all cases, with no adjustments for multiple comparisons.

Results

Patient population and baseline health status. Of the 699 patients randomized to TAVR or AVR in the PARTNER trial, 628 completed baseline health status questionnaires and were included in our analysis. The baseline characteristics of these patients, stratified by TAVR procedural approach (TF cohort, n = 446; TA cohort, n = 182), are shown in Table 1. As previously reported, the PARTNER trial patients were elderly (mean age, 83 years) with a high burden of both cardiac and noncardiac comorbid conditions. As expected, patients who were ineligible for the TF approach and thus randomized within the TA cohort were more likely to have cerebrovascular disease, peripheral artery disease, and previous coronary artery bypass graft. The baseline characteristics of the patients randomized to TAVR and AVR were well balanced in both the TF and TA subgroups. The 71 patients who did not complete the baseline questionnaires and were therefore excluded were slightly older, but otherwise similar to the patients included in our analysis (Online Table 1).

Baseline KCCQ, SF-12, and EQ-5D scores are also shown in Table 1. The overall population had a mean baseline KCCQ summary score of 41.9, a value that is generally consistent with New York Heart Association class IV heart failure. Mean baseline SF-12 physical scores were 30.2, ~2 SDs below the overall mean for the U.S. population, and baseline mental scores were 47.2. Mean baseline EQ-5D scores were 0.67. In both the TF and TA cohorts, slight imbalances in the baseline scores were seen, with mean KCCQ scores ~3 to 6 points lower among patients randomized to TAVR, depending on the subscale, and mean SF-12 scores 1 to 2 points lower. Baseline scores were similar in the TF and TA cohorts.

Within-group comparisons. Follow-up questionnaires were obtained from >80% of surviving subjects at each time point, with slightly more missing data in the AVR than the

Table 1 Baseline Characteristics and Quality-of-Life Scores

	TF Cohort			TA Cohort		
	TAVR (n = 230)	AVR (n = 216)	p Value	TAVR (n = 98)	AVR (n = 84)	p Value
Demographic and clinical characteristics						
Age, yrs	83.8 ± 6.8	84.6 ± 6.5	0.24	82.6 ± 7.0	83.2 ± 5.9	0.56
Male, %	60.4	55.6	0.30	51.0	59.5	0.25
STS risk score	11.8 ± 3.2	11.5 ± 3.3	0.23	11.8 ± 3.7	11.7 ± 3.2	0.76
Previous MI, %	27.4	24.1	0.42	27.6	36.9	0.18
Previous CABG, %	39.1	40.7	0.73	51.0	56.0	0.51
Cerebrovascular disease, %	22.6	22.7	0.99	36.7	29.8	0.32
Peripheral artery disease, %	35.1	35.7	0.90	61.2	62.7	0.84
COPD (oxygen dependent), %	8.3	7.4	0.74	11.2	7.1	0.35
LV ejection fraction, %	52.1 ± 14.2	53.7 ± 13.3	0.25	53.1 ± 12.4	53.4 ± 11.0	0.86
Frailty, %	16.0	16.6	0.89	14.3	18.1	0.49
Quality-of-life scores						
KCCQ overall summary	39.3 ± 21.7	43.8 ± 22.6	0.03	40.3 ± 22.1	46.2 ± 19.8	0.06
KCCQ physical limitation	40.6 ± 26.2	43.4 ± 26.8	0.29	40.9 ± 24.1	48.6 ± 23.2	0.03
KCCQ symptoms	48.9 ± 23.9	52.2 ± 23.8	0.15	49.9 ± 23.7	55.5 ± 22.1	0.10
KCCQ quality of life	34.1 ± 22.2	39.2 ± 24.3	0.02	34.7 ± 26.9	40.4 ± 22.3	0.13
KCCQ social limitation	32.3 ± 29.3	38.3 ± 28.7	0.04	34.6 ± 30.0	40.5 ± 26.9	0.18
SF-12 physical summary	29.7 ± 7.7	30.6 ± 8.1	0.28	29.4 ± 7.4	31.7 ± 8.5	0.06
SF-12 mental summary	47.0 ± 11.5	47.1 ± 11.0	0.96	46.6 ± 11.4	48.7 ± 9.6	0.18
EQ-5D utilities	0.66 ± 0.20	0.66 ± 0.21	0.77	0.67 ± 0.19	0.72 ± 0.17	0.07

Values are mean ± SD or %.

AVR = aortic valve replacement; CABG = coronary artery bypass graft; COPD = chronic obstructive pulmonary disease; EQ-5D = EuroQol; KCCQ = Kansas City Cardiomyopathy Questionnaire; LV = left ventricular; MI = myocardial infarction; SF-12 = Medical Outcomes Study Short-Form 12; STS = Society of Thoracic Surgeons; TA = transapical; TAVR = transcatheter aortic valve replacement; TF = transfemoral.

TAVR patients (Online Table 2). Within-group changes between baseline and 1-, 6-, and 12-month follow-up for each health status measure, stratified by access site, are shown in Tables 2 (TF cohort) and 3 (TA cohort). Both TAVR and AVR subjects, regardless of procedural approach, demonstrated substantial (>20 point) and highly statistically significant improvements in the KCCQ summary score at 6 and 12 months. SF-12 physical scores improved from baseline by at least 4.5 points in each treatment group at 6 and 12 months. EQ-5D utilities increased by 0.08 to 0.10 at 6 and 12 months with both TAVR and AVR in the TF cohort; in the TA cohort, the increase in EQ-5D scores was slightly less but nonetheless significant for both treatment groups (0.04 to 0.06).

KCCQ summary scores were improved at 1 month in all groups; however, the changes were modestly larger for TAVR patients treated via the TF approach (mean increase, 23.7 points, 95% CI, 20.1 to 27.3; $p < 0.001$) than for any of the other groups (mean increases of 12.1 to 12.5 points). KCCQ subscales and generic QOL measures were all significantly improved at 1 month in the TF-TAVR group. For the TF-AVR group and both TA groups, some but not all secondary QOL measures were improved at 1 month.

Between-group comparisons. For the overall population, TAVR resulted in more rapid improvement in the KCCQ summary scale than AVR, with a significant benefit at 1 month (mean adjusted difference, 5.5; 95% CI: 1.2 to 9.8; $p = 0.01$) but no significant difference at either 6 months (mean adjusted difference, −2.6; 95% CI: −6.7 to 1.6; $p = 0.22$) or 12 months (mean adjusted difference, −0.5; 95% CI: −4.8 to 3.8; $p = 0.82$). However, there was a significant interaction between treatment assignment and access site, particularly at the 1-month time point. Therefore, all QOL analyses were performed separately for the TF and TA cohorts.

The results from the growth curve models for the KCCQ summary scale according to time point and access site are summarized in Table 4 and Figure 1. At 1 month, in the TF cohort, patients assigned to TAVR had significantly higher (i.e., better) scores on the KCCQ summary scale compared with patients assigned to surgical AVR (adjusted mean difference between TAVR and AVR, 9.9 points; 95% CI, 4.9 to 14.9; $p < 0.001$). In contrast, in the TA cohort, 1-month scores on the KCCQ summary scale tended to favor AVR (mean difference, −5.8 points; 95% CI: −13.9 to 2.2; $p = 0.15$). The interaction between treatment group and access site was highly significant ($p = 0.001$) at 1 month. At 6 and 12 months, there were no significant differences in the KCCQ summary scores between patients assigned to TAVR versus AVR in the TF cohort. In the TA cohort, TAVR patients had lower mean KCCQ summary scores at 6 months (adjusted difference, −7.9 points; $p = 0.04$), but there was no difference between the 2 treatments at 12 months. The interactions between treatment group and access site were not statistically significant at 6 or 12 months.

Results for each of the KCCQ subscales are summarized in Table 4 and Figure 1 as well, and paralleled those seen for

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Table 2 Within-Group Comparisons: Transfemoral Cohort

	TAVR			AVR		
Scale/Time Point	n	Mean Δ vs. Baseline (95% CI)	p Value	n	Mean Δ vs. Baseline (95% CI)	p Value
KCCQ summary						
1 month	197	23.7 (20.1 to 27.3)	<0.001	157	12.1 (7.4 to 16.7)	<0.001
6 months	183	29.8 (25.9 to 33.8)	<0.001	139	26.9 (22.4 to 31.5)	<0.001
12 months	165	28.7 (24.4 to 33.1)	<0.001	136	26.8 (21.8 to 31.7)	<0.001
KCCQ physical limitations						
1 month	175	15.2 (10.4 to 20.0)	<0.001	132	3.2 (−2.7 to 9.0)	0.29
6 months	163	21.9 (17.2 to 26.7)	<0.001	127	20.2 (14.5 to 25.9)	<0.001
12 months	150	18.9 (13.5 to 24.2)	<0.001	117	14.4 (8.9 to 19.9)	<0.001
KCCQ total symptoms						
1 month	196	20.4 (16.7 to 24.2)	<0.001	157	12.8 (7.9 to 17.8)	<0.001
6 months	182	24.8 (20.8 to 28.8)	<0.001	139	24.3 (20.2 to 28.5)	<0.001
12 months	164	24.8 (20.5 to 29.0)	<0.001	133	23.3 (18.3 to 28.4)	<0.001
KCCQ quality of life						
1 month	196	31.5 (27.4 to 35.6)	<0.001	154	18.9 (13.5 to 24.4)	<0.001
6 months	181	38.2 (33.7 to 42.8)	<0.001	137	34.0 (28.7 to 39.3)	<0.001
12 months	165	38.1 (33.6 to 42.7)	<0.001	130	37.3 (31.6 to 42.9)	<0.001
KCCQ social limitation						
1 month	159	24.7 (19.3 to 30.1)	<0.001	115	12.0 (4.9 to 19.1)	0.001
6 months	149	31.8 (25.7 to 37.9)	<0.001	115	28.3 (22.0 to 34.6)	<0.001
12 months	140	33.3 (26.9 to 39.8)	<0.001	103	30.6 (22.8 to 38.4)	<0.001
SF-12 physical						
1 month	184	5.0 (3.5 to 6.4)	<0.001	149	2.6 (0.7 to 4.4)	0.006
6 months	172	6.7 (5.0 to 8.3)	<0.001	134	7.2 (5.1 to 9.2)	<0.001
12 months	155	6.3 (4.5 to 8.2)	<0.001	127	6.1 (4.2 to 8.1)	<0.001
SF-12 mental						
1 month	184	4.3 (2.5 to 6.1)	<0.001	149	−0.3 (−2.6 to 2.1)	0.82
6 months	172	5.1 (3.2 to 7.0)	<0.001	134	4.0 (1.6 to 6.3)	0.001
12 months	155	5.0 (3.1 to 7.0)	<0.001	127	4.7 (2.4 to 6.9)	0.001
EQ-5D utilities						
1 month	192	0.08 (0.04 to 0.11)	<0.001	154	0.02 (−0.02 to 0.06)	0.43
6 months	176	0.10 (0.07 to 0.13)	<0.001	136	0.09 (0.04 to 0.13)	<0.001
12 months	160	0.09 (0.05 to 0.12)	<0.001	129	0.08 (0.04 to 0.12)	<0.001

CI = confidence interval; mo = month/months; other abbreviations as in Table 1.

the KCCQ summary scale. In the TF cohort, there was a significant between-group difference favoring TAVR for all 4 KCCQ subscales at 1 month, but not at 6 or 12 months. In the TA cohort, there were no significant differences between TAVR and AVR on the KCCQ subscales at 1 or 12 months. At 6 months in the TA cohort, patients assigned to TAVR had lower adjusted scores on the KCCQ physical limitation (mean difference, −9.6 points; $p = 0.04$), QOL (mean difference, −8.4 points; $p = 0.06$), and symptom scales (mean difference, −13.2 points; $p < 0.001$) compared with AVR patients.

Results for both the SF-12 and EQ-5D utility scales showed patterns similar to those for the disease-specific scales (Fig. 2). In the TF cohort at 1 month, patients assigned to TAVR demonstrated significantly higher scores for the SF-12 physical (mean difference, 2.0; $p = 0.04$), SF-12 mental (mean difference, 5.4; $p < 0.001$), and EQ-5D utility scales (mean difference, 0.06; $p = 0.01$) scores, differences that were no longer apparent at either 6 or 12 months. In the TA cohort, there were borderline significant differences favoring AVR over TAVR for the SF-12 physical (mean difference, −3.3; $p = 0.05$) and EQ-5D (mean difference, −0.065; $p = 0.05$) scales at 6 months, whereas no significant differences between treatment groups were observed at either 1 or 12 months. Of note, when the growth curve models were repeated for the as-treated population (n = 607), the results were virtually identical (Online Table 3). Likewise, imputing worst case values for patients with missing data altered the results only minimally (data not shown).

Categorical results. Figure 3 displays the distribution of patients reporting pre-defined levels of improvement (or worsening) on the KCCQ summary scale from baseline to each follow-up time point. In the TF cohort, at 1-month follow-up, the proportion of patients with at least a small improvement from baseline was greater for the TAVR group than for the AVR group (68.3% vs. 51.0%). By ordinal logistic regression, the distributions of these categorical change scores for the 2 treatment groups were significantly different at 1 month ($p < 0.001$) and 6

Table 3 Within-Group Comparisons: Transapical Cohort

	TAVR			AVR		
Scale/Time Point	n	Mean Δ vs. Baseline (95% CI)	p Value	n	Mean Δ vs. Baseline (95% CI)	p Value
KCCQ summary						
1 month	77	12.5 (6.1 to 19.0)	<0.001	61	12.5 (5.5 to 19.5)	0.0007
6 months	71	23.8 (16.4 to 31.2)	<0.001	56	27.3 (21.0 to 33.7)	<0.001
12 months	66	29.6 (23.2 to 36.1)	<0.001	59	21.6 (13.8 to 29.4)	<0.001
KCCQ physical limitations						
1 month	63	2.4 (−4.9 to 9.7)	0.52	51	1.7 (−7.7 to 11.1)	0.72
6 months	61	12.4 (4.3 to 20.5)	0.003	52	17.3 (9.6 to 25.0)	<0.001
12 months	55	15.5 (7.4 to 23.6)	<0.001	54	11.7 (3.2 to 20.3)	0.008
KCCQ total symptoms						
1 month	77	12.9 (6.2 to 19.6)	<0.001	60	12.1 (5.6 to 18.5)	<0.001
6 months	70	16.6 (9.3 to 23.9)	<0.001	55	25.6 (19.2 to 32.0)	<0.001
12 months	64	23.1 (16.2 to 30.0)	<0.001	59	18.7 (11.2 to 26.3)	<0.001
KCCQ quality of life						
1 month	77	22.1 (13.7 to 30.5)	<0.001	61	20.9 (13.1 to 28.7)	<0.001
6 months	71	32.1 (23.6 to 40.6)	<0.001	56	34.8 (27.4 to 42.2)	<0.001
12 months	65	41.7 (33.1 to 50.2)	<0.001	58	29.5 (20.7 to 38.2)	<0.001
KCCQ social limitation						
1 month	61	6.9 (−3.2 to 17.0)	0.18	46	2.8 (−7.9 to 13.4)	0.60
6 months	58	27.4 (16.4 to 38.4)	<0.001	48	28.6 (19.1 to 38.1)	<0.001
12 months	50	34.2 (24.0 to 44.5)	<0.001	47	22.8 (11.0 to 34.7)	<0.001
SF-12 physical						
1 month	76	2.8 (0.6 to 5.0)	0.01	61	0.5 (−2.1 to 3.0)	0.71
6 months	70	5.2 (2.5 to 7.8)	<0.001	57	7.0 (4.4 to 9.6)	<0.001
12 months	66	7.1 (4.5 to 9.8)	<0.001	58	4.5 (1.2 to 7.8)	0.008
SF-12 mental						
1 month	76	−0.8 (−3.7 to 2.2)	0.60	61	1.7 (−1.4 to 4.8)	0.27
6 months	70	3.3 (0.2 to 6.5)	0.04	57	3.7 (1.0 to 6.3)	0.008
12 months	66	3.6 (0.1 to 7.0)	0.04	58	3.9 (0.6 to 7.2)	0.02
EQ-5D utilities						
1 month	74	−0.02 (−0.08 to 0.03)	0.44	58	0.01 (−0.04 to 0.06)	0.74
6 months	66	0.04 (−0.02 to 0.11)	0.20	52	0.06 (0.01 to 0.12)	0.03
12 months	61	0.06 (0.01 to 0.12)	0.03	54	0.05 (−0.02 to 0.12)	0.14

Abbreviations as in Tables 1 and 2.

months ($p = 0.007$), whereas no significant difference was observed at 12 months. In contrast, among the TA cohort, there were no differences in the distribution of change categories between the TAVR and AVR groups at any time point.

Discussion

In the PARTNER trial, the first randomized, controlled trial comparing TAVR with AVR, we found that both methods of valve replacement led to substantial improvement in both disease-specific and general health status in high-risk surgical candidates. In particular, outcomes at 12 months were similar when comparing TAVR and AVR regardless of the TAVR access site. In addition, among patients who were eligible for a TF approach, there were both statistically significant and clinically relevant differences in health status and QOL at 1-month follow-up in favor of TAVR. On the other hand, among patients who were unsuitable for a TF procedure (and were therefore treated via the TA approach to TAVR), health status was not better at any time point after TAVR than after AVR. Moreover, there were trends and, in some cases, borderline statistically significant differences in favor of AVR both at 1 and 6 months.

The improvements in health status observed 6 and 12 months after both TAVR and AVR were great, highly statistically significant, and clinically meaningful. By 6 months, KCCQ summary scores had generally increased 25 to 30 points, indicating very substantial benefit because changes of as little as 5 points on this scale were previously shown to correlate with changes in survival and medical care costs in heart failure patients (15,16). Improvements in generic measures, in particular, the SF-12 physical summary score (5 to 7 points at 6 and 12 months) were also 2 to 3 times greater than the 2.5-point threshold generally considered to indicate a clinically relevant change (19,20). These results are all the more remarkable when one considers that the PARTNER trial population represents patients with the highest 5% of surgical risk, based on baseline Society of Thoracic Surgeon scores (10).

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Table 4 Between-Group Comparisons From Longitudinal Growth Curve Models

	TF Cohort		TA Cohort	
Scale/Time Point	Adjusted Mean Difference, TAVR-AVR (95% CI)	p Value	Adjusted Mean Difference, TAVR-AVR (95% CI)	p Value
KCCQ summary				
1 month	9.9 (4.9 to 14.9)	<0.001	−5.8 (−13.9 to 2.2)	0.15
6 months	−0.5 (−5.3 to 4.4)	0.85	−7.9 (−15.7 to −0.2)	0.04
12 months	−1.2 (−6.3 to 3.9)	0.64	0.8 (−7.2 to 8.8)	0.85
KCCQ physical limitations				
1 month	10.9 (4.5 to 17.4)	0.001	−5.8 (−16.3 to 4.8)	0.28
6 months	−0.5 (−6.3 to 5.4)	0.41	−9.6 (−18.9 to -0.2)	0.04
12 months	2.3 (−3.9 to 8.5)	0.47	−4.1 (−13.8 to 5.6)	0.41
KCCQ total symptoms				
1 month	6.6 (1.9 to 11.4)	0.006	−5.1 (−12.8 to 2.5)	0.19
6 months	−2.1 (−6.7 to 2.5)	0.37	−13.2 (−20.5 to −5.9)	<0.001
12 months	−1.1 (−5.8 to 3.7)	0.66	−2.3 (−9.7 to 5.2)	0.55
KCCQ quality of life				
1 month	9.8 (4.0 to 15.6)	0.001	−4.7 (−13.9 to 4.5)	0.32
6 months	0.3 (−5.2 to 5.7)	0.93	−8.4 (−17.0 to 0.2)	0.06
12 months	−1.9 (−7.6 to 3.8)	0.50	4.8 (−4.0 to 13.7)	0.28
KCCQ social limitation				
1 month	10.6 (3.0 to 18.2)	0.007	−5.8 (−17.9 to 6.4)	0.35
6 months	−2.9 (−10.1 to 4.3)	0.43	−3.8 (−15.1 to 7.5)	0.51
12 months	−2.9 (−10.5 to 4.8)	0.46	6.1 (−5.9 to 18.1)	0.32
SF-12 physical				
1 month	2.0 (0.1 to 3.9)	0.04	0.3 (−2.7 to 3.3)	0.85
6 months	−0.9 (−3.0 to 1.2)	0.41	−3.3 (−6.7 to 0.0)	0.05
12 months	−0.4 (−2.8 to 2.0)	0.77	0.2 (−3.5 to 3.8)	0.92
SF-12 mental				
1 month	5.4 (3.1 to 7.7)	<0.001	−4.3 (−7.9 to −0.8)	0.02
6 months	1.2 (−1.0 to 3.5)	0.28	−2.5 (−6.0 to 1.0)	0.16
12 months	0.4 (−1.8 to 2.7)	0.69	−2.5 (−5.9 to 0.9)	0.15
EQ-5D utilities				
1 month	0.06 (0.02 to 0.10)	0.008	−0.06 (−0.13 to 0.02)	0.13
6 months	0.01 (−0.03 to 0.05)	0.57	−0.07 (−0.13 to 0.0)	0.05
12 months	0.03 (−0.02 to 0.07)	0.23	−0.05 (−0.12 to 0.02)	0.17

Abbreviations as in Tables 1 and 2.

Several previous studies have shown that both AVR (2,3) and, more recently, TAVR (5–7,24–28) improve health status and QOL compared with baseline for patients with severe AS. Most of these studies compared scores on the SF-12, SF-36, or the Minnesota Living With Heart Failure Questionnaire from baseline to 1 or 2 follow-up time points and included patients treated predominantly via transarterial TAVR approaches. Our results add to this literature by examining the time course of health status improvement over the first year after intervention in greater detail, and, more importantly, by comparing the benefits of TAVR with those of standard surgical AVR as a function of both time and TAVR access site.

The findings observed in the TF cohort of the PARTNER trial are consistent with the more rapid recovery that would be expected when comparing a percutaneous procedure with traditional valve replacement surgery and are consistent with previously reported benefits of TAVR on New York Heart Association functional class and 6-min walk distance at 30 days (10). Although most of the health status measures had already begun to improve by 1 month in the AVR group, substantial additional improvement was observed at both 6 and 12 months. In contrast, improvement was more rapid for TAVR patients treated via the TF approach, such that the extent of improvement by 1 month was nearly as great as that seen at later time points. As a result, direct between-group comparisons strongly favored TAVR at 1 month in the TF subgroup.

On the other hand, among TA patients (who were, by definition, anatomically unsuitable for a TF approach), there was no short-term advantage for TAVR over AVR in either disease-specific or generic health status. This result was somewhat unexpected, given that TAVR via the TA approach involves a smaller incision than median sternotomy and avoids the need for cardiopulmonary bypass. The explanation for this result is currently unknown. Previous research comparing cardiothoracic surgery performed using thoracotomy incisions and that performed using median

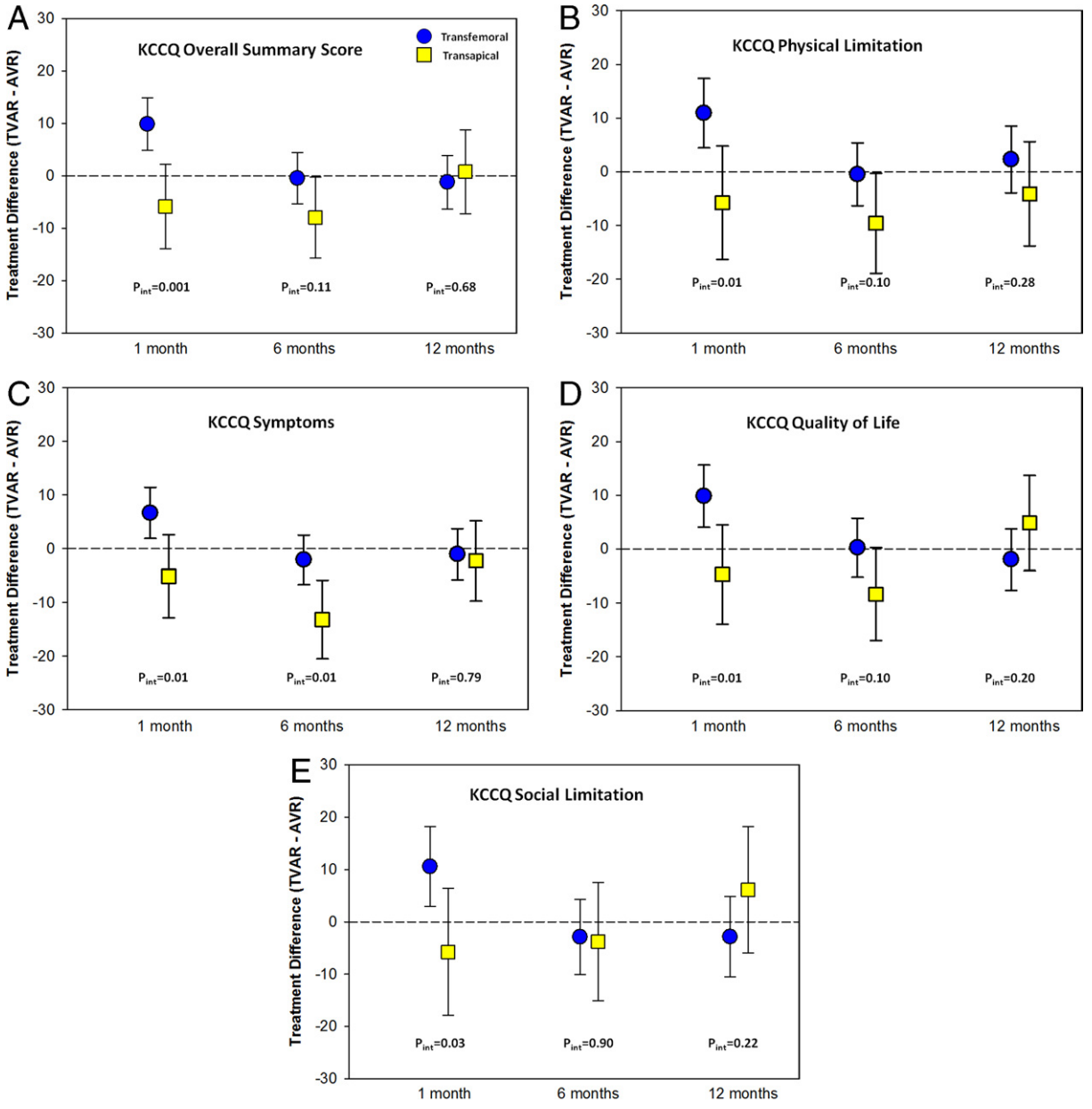

Figure 1 **Between-Group Differences: KCCQ**

The difference between transcatheter aortic valve replacement (TAVR) and aortic valve replacement (AVR) on the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary **(A)** and subscale **(B to E)** scores, based on longitudinal growth curve models, at 1-, 6-, and 12-month follow-up. Results are reported separately for the transfemoral (TF) cohort **(blue circles)** and the transapical (TA) cohort **(yellow squares)**. p Values for the interaction (int) between treatment (TAVR vs. AVR) and access site (TF or TA) are shown. Error bars denote 95% confidence intervals.

sternotomy incisions has not conclusively shown that recovery from thoracotomy incisions is faster or easier. In fact, in some studies, ratings of pain during the early postoperative period have actually been worse with thoracotomy than median sternotomy, results that have been hypothesized to relate to delayed effects of rib spreading and/or respiratory motion (29–31). Careful attention to pain control, such as with epidural anesthesia, could potentially mitigate these issues in the future.

Another potential explanation for the lack of benefit with TA-TAVR versus AVR could relate to differences in either the number or nature of major complications for the 2 procedures. Of note, the rate of major strokes in the TA cohort was somewhat higher for TAVR than AVR at both 30 days and 1 year (10), but the absolute magnitude of these differences was small. Other adverse events were similar between groups except for major bleeding, which was more common after AVR (8.7% vs. 17.9%, p = 0.05). Based on

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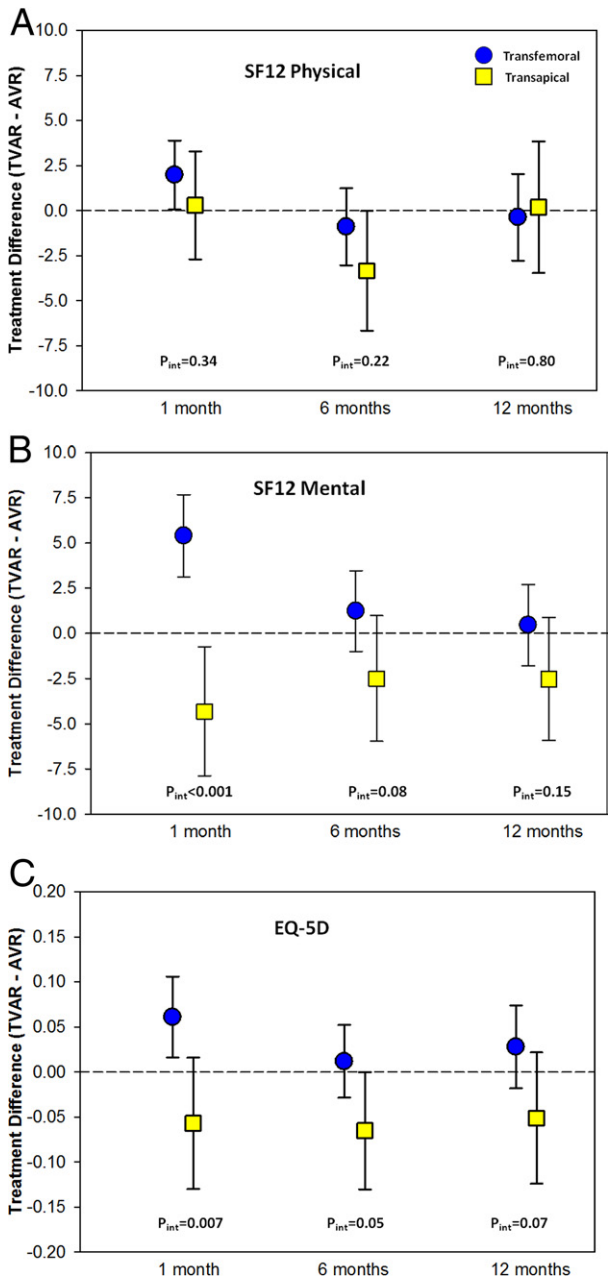

Figure 2 **Between-Group Differences: Generic Scales**

The difference between TAVR and AVR on the Medical Outcomes Study Short-Form 12 (SF-12) **(A and B)** and Euro-Qol (EQ-5D) **(C)** scores are shown based on longitudinal growth curve models at 1, 6, and 12 months. Results are reported separately for the TF cohort **(blue circles)** and the TA cohort **(yellow squares)**. Abbreviations as in Figure 1.

these data, it seems unlikely that differences in specific complication rates are solely responsible for the lack of benefit in health status outcomes with the TA approach. Finally, it is possible that the apical puncture and repair performed for TA-TAVR could conceivably result in greater impairment of left ventricular function than AVR leading to more functional limitations.

Study limitations. In interpreting these results, it is also important to recognize that the PARTNER trial represents a very early experience with TAVR procedures in the United States, particularly for the TA approach. Among the 14 sites at which TA-TAVR procedures were performed in the PARTNER trial, the median number of procedures per center was 4 (range, 1 to 20), with more than 10 procedures performed at only 5 sites. Like most complex cardiac procedures, TAVR has a well-documented learning curve, and the site-level volume of TA procedures done in the PARTNER trial was clearly below the level at which learning curve effects begin to dissipate (32). Thus, many aspects of the care of TAVR patients are likely to improve with time and experience. In addition, far fewer total patients were randomized within the TA subgroup compared with the TF subgroup, such that the TA subgroup had less statistical power for all trial endpoints.

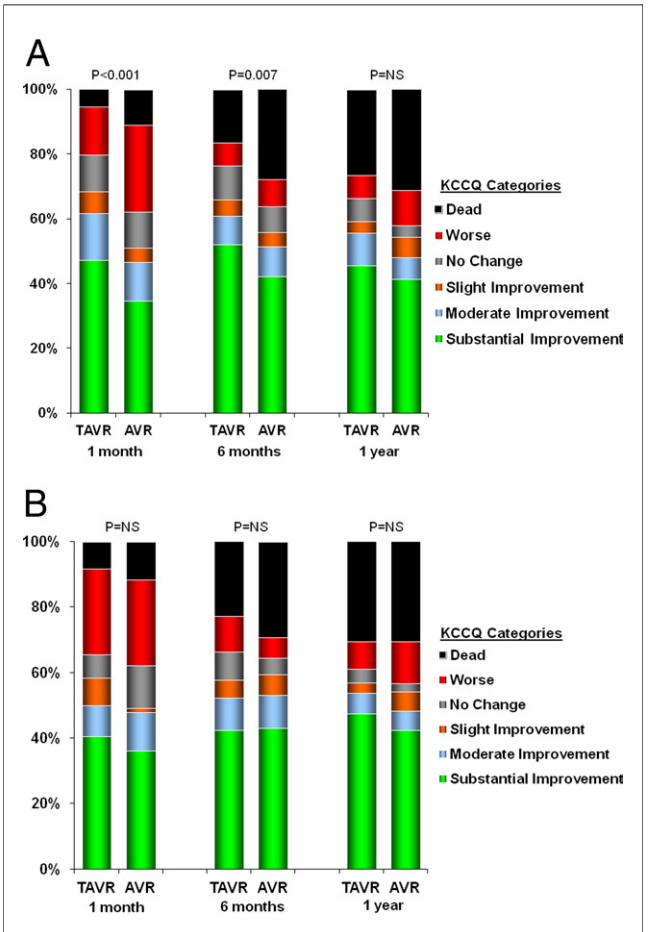

Figure 3 **Categorial Results**

The proportions of TAVR and AVR patients achieving pre-specified categorical levels of change from baseline to 1-, 6-, and 12-month follow-up according to the KCCQ overall summary score. Results are shown separately for the TF cohort **(A)** and the TA cohort **(B)**. p Values are based on ordinal logistic regression. Abbreviations as in Figure 1.

Our results could have been affected by missing data if, for example, patients with the poorest health status were the ones most likely not to complete questionnaires. Because we observed slightly more missing data in the AVR group than the TAVR group, and the rates of death and most major complications were similar between groups, this seems like an unlikely explanation for our findings. Moreover, a sensitivity analysis in which we imputed worst case values for those patients with missing follow-up data did not alter any of our main results.

The PARTNER trial was unblinded, and patients randomized to TAVR could have experienced subjective improvements in some aspects of their health status based on expectations that the new procedure was less invasive than surgical AVR. It would not have been feasible to conduct the PARTNER trial in a blinded fashion, however, and consequently there is no definitive way to address this theoretical concern. Finally, our analysis was also limited to 12 months of follow-up. Although the frequent sampling of patients during the first year provided rich information about the time course of improvement during this critical period, our analysis does not provide information about any potential long-term differences in health status that could arise as a consequence of differences in long-term device performance or other factors.

Conclusions

The PARTNER trial has confirmed that correction of severe AS either by TAVR or AVR leads to very great improvement in patient-reported symptoms, functional status, and QOL over the first year of follow-up, even in a population selected for high surgical risk. The more rapid recovery from TAVR via the TF approach is associated with short-term benefits in health status, which may be important from the patient's perspective. On the other hand, for patients who were ineligible for a TF approach (and thus underwent TAVR via the TA approach), in this early experience with TAVR procedures, there was no evidence of health status benefits either in the short or medium term. Future studies are necessary to determine whether ongoing improvements in procedural techniques or ancillary care lead to differences in recovery for TAVR patients treated via the TA approach.

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Key Words: aortic stenosis ■ AVR ■ quality of life ■ TAVR.

APPENDIX

For supplemental tables, please see the online version of this article.