Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis

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Background—Transcatheter aortic valve replacement (TAVR) has been shown to improve survival compared with standard therapy in patients with severe aortic stenosis who cannot have surgery. The effects of TAVR on health-related quality of life have not been reported from a controlled study.

Methods and Results—The Placement of Aortic Transcatheter Valves (PARTNER) trial randomized patients with symptomatic, severe aortic stenosis who were not candidates for surgical valve replacement to TAVR (n=179) or standard therapy (n=179). Health-related quality of life was assessed at baseline and at 1, 6, and 12 months with the Kansas City Cardiomyopathy Questionnaire (KCCQ) and the 12-item Short Form-12 General Health Survey (SF-12). The primary end point was the KCCQ overall summary score (range, 0–100; higher=better). At baseline, mean KCCQ summary scores (35±20) and SF-12 physical summary scores (28±7) were markedly depressed. Although the KCCQ summary score improved from baseline in both groups, the extent of improvement was greater after TAVR compared with control at 1 month (mean between-group difference, 13 points; 95% confidence interval, 8–19; P<0.001) with larger benefits at 6 months (mean difference, 21 points; 95% confidence interval, 15–27; P<0.001) and 12 months (mean difference, 26 points; 95% confidence interval, 19–33; P<0.001). At 12 months, TAVR patients also reported higher SF-12 physical and mental health scores with mean differences compared with standard care of 5.7 and 6.4 points, respectively (P<0.001 for both comparisons).

Conclusions—Among inoperable patients with severe aortic stenosis, compared with standard care, TAVR resulted in significant improvements in health-related quality of life that were maintained for at least 1 year.

Clinical Trials Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00530894. (Circulation. 2011;124:00-00.)

Key Words: aortic valve stenosis □ heart valves □ quality of life

Aortic stenosis is a common condition among the elderly and is associated with poor survival without surgery once symptoms develop. In addition, patients with severe aortic stenosis experience progressive symptoms and reduced functional status and quality of life. Despite the success of surgical valve replacement at alleviating symptoms and extending survival, a substantial minority of patients with severe aortic stenosis go untreated because of comorbid medical conditions and cardiovascular abnormalities that result in prohibitive surgical risk. One-year mortality rates may be as high as 50% to 60% in these patients.

After the first human report in 2002, transcatheter aortic valve replacement (TAVR) has emerged as a less invasive treatment option for patients with aortic stenosis and high or unacceptable surgical risk. Recently, the Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated that for patients who are not suitable candidates for surgery, TAVR led to a 20% absolute reduction in all-cause mortality at 1 year compared with standard therapy but also to an increase in the incidence of major strokes and vascular complications.
For patients with severe heart failure and the elderly in general, improvements in symptoms, functional status, and quality of life may be even more important than improvements in longevity. Thus, a full characterization of the impact of TAVR on patients with severe aortic stenosis requires an understanding of the effects of the intervention on patients’ health status. We therefore performed a prospective quality-of-life substudy among patients enrolled in the PARTNER trial and present here the results for the cohort of patients who were not candidates for surgical valve replacement and were therefore randomized to TAVR or standard therapy.

Methods

Study Design

The design and initial results of the PARTNER trial (cohort B) have been published previously. In brief, the PARTNER program enrolled patients with severe aortic stenosis; New York Heart Association class II, III, or IV heart failure symptoms; and high surgical risk based on the Society for Thoracic Surgeons (STS) risk score and qualified physician assessments. Patients included in the present study were not considered to be suitable candidates for cardiac surgery owing to coexisting medical conditions associated with a predicted probability of death or permanent disability ≥50% as determined by least 2 surgical investigators and reaffirmed by the study’s executive committee. These patients were then randomized to TAVR with the Edwards SAPIEN heart valve system (Edwards Lifesciences, Irvine, CA) or to standard medical care, which often included balloon aortic valvuloplasty at the discretion of the investigators. The study was approved by the institutional review board at each participating site, and all patients provided written informed consent.

Measurement of Health Status

Health status, which includes symptoms, functional status, and quality of life, was evaluated with standardized written questionnaires at baseline and 1, 6, and 12 months after randomization. The baseline questionnaires were administered before randomization. Follow-up questionnaires were administered during in-person visits to the enrolling centers or by mail. Linguistically and culturally validated translations of the original questionnaires were provided to each participating site, and all patients provided written informed consent.

Disease-specific health status was assessed with the Kansas City Cardiomyopathy Questionnaire (KCCQ). The KCCQ consists of 23 questions addressing 5 health domains pertaining to heart failure: symptoms, physical limitation, social limitation, self-efficacy, and quality of life. These individual scales are combined into an overall summary scale with values ranging from 0 to 100. Table 1 summarizes the results of the KCCQ at baseline and follow-up.

### Table 1. Baseline Patient Characteristics and Quality-of-Life Scores

<table>
<thead>
<tr>
<th></th>
<th>TAVR (n=179)</th>
<th>Control (n=179)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>83±9</td>
<td>83±8</td>
<td>0.95</td>
</tr>
<tr>
<td>Female sex, %</td>
<td>54.2</td>
<td>54.1</td>
<td>0.92</td>
</tr>
<tr>
<td>White race, %</td>
<td>92</td>
<td>91</td>
<td>0.57</td>
</tr>
<tr>
<td>STS risk score</td>
<td>11.2±5.8</td>
<td>12.1±6.1</td>
<td>0.14</td>
</tr>
<tr>
<td>STS score &gt;15, %</td>
<td>21.2</td>
<td>24.6</td>
<td>0.45</td>
</tr>
<tr>
<td>Prior MI, %</td>
<td>18.6</td>
<td>26.4</td>
<td>0.10</td>
</tr>
<tr>
<td>Prior CABG, %</td>
<td>37.4</td>
<td>45.6</td>
<td>0.17</td>
</tr>
<tr>
<td>Cerebrovascular disease, %</td>
<td>27.4</td>
<td>27.5</td>
<td></td>
</tr>
<tr>
<td>COPD (oxygen dependent), %</td>
<td>21.2</td>
<td>25.7</td>
<td></td>
</tr>
<tr>
<td>Creatinine &gt;2.0 mg/dL, %</td>
<td>5.6</td>
<td>9.6</td>
<td></td>
</tr>
</tbody>
</table>

Quality-of-life measures

- KCCQ overall summary: 36.2±20.5 vs 34.4±20.1 (P=0.44)
- 75–100, %: 4.1 vs 3.8 (P=0.70)
- 60–74, %: 10.6 vs 7.0 (P=0.45)
- 45–59, %: 15.9 vs 17.8 (P=0.50)
- 0–45, %: 69.4 vs 71.3 (P=0.50)

KCCQ symptoms: 47.7±22.6 vs 46.0±24.0 (P=0.52), KCCQ physical limitation: 34.6±25.7 vs 30.7±24.9 (P=0.19), KCCQ social limitation: 27.8±26.9 vs 26.6±25.7 (P=0.70), KCCQ quality of life: 33.6±21.7 vs 32.8±22.9 (P=0.74), SF-12 physical: 28.2±7.7 vs 27.7±6.9 (P=0.54), SF-12 mental: 44.5±12.2 vs 45.2±11.0 (P=0.57)

Statistical Analysis

Summary scores for each of the SF-12 and KCCQ scales were generated according to the scoring algorithms published by their developers. The KCCQ overall summary score was prespecified as the primary end point of the quality-of-life study. All other end points were considered secondary. For baseline characteristics and quality-of-life scores, between-group comparisons were performed with the χ² test for categorical variables and 2-sample t tests for continuous 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 for patients with available quality-of-life data and tested for significance with paired t tests. Although these analyses do not provide formal between-group comparisons, they have the advantage of testing each patient against his or her own baseline value (thus correcting for any potential survivor bias introduced by the attrition of sicker patients over time).

Differences between TAVR and control group scores at each follow-up time point were estimated from longitudinal random-effect growth curve models that were fit to the repeated measurements for each health status outcome. These longitudinal analyses used all available quality-of-life data, including data from patients who subsequently died, withdrew, or were lost to follow-up, and accommodate missing data under the missing at random assumption.
KCCQ summary

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>61.6 ± 26.2</td>
<td>24.8</td>
<td>20.2 to 29.3</td>
<td>&lt;0.001</td>
<td>49.2 ± 24.3</td>
<td>10.4</td>
<td>6.0 to 14.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>70.7 ± 23.0</td>
<td>33.5</td>
<td>28.9 to 38.1</td>
<td>&lt;0.001</td>
<td>50.5 ± 26.1</td>
<td>11.7</td>
<td>6.1 to 17.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>69.4 ± 25.3</td>
<td>31.8</td>
<td>26.4 to 37.2</td>
<td>&lt;0.001</td>
<td>47.0 ± 24.6</td>
<td>4.1</td>
<td>-2.2 to 10.5</td>
<td>0.20</td>
</tr>
</tbody>
</table>

KCCQ total symptoms

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>69.4 ± 23.3</td>
<td>20.8</td>
<td>16.3 to 25.4</td>
<td>&lt;0.001</td>
<td>60.0 ± 25.0</td>
<td>10.2</td>
<td>6.0 to 14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>77.2 ± 18.9</td>
<td>29.2</td>
<td>24.4 to 34.1</td>
<td>&lt;0.001</td>
<td>59.3 ± 25.1</td>
<td>9.2</td>
<td>3.5 to 14.9</td>
<td>0.002</td>
</tr>
<tr>
<td>12 mo</td>
<td>75.3 ± 22.8</td>
<td>26.2</td>
<td>21.0 to 31.5</td>
<td>&lt;0.001</td>
<td>58.9 ± 26.0</td>
<td>5.0</td>
<td>-1.6 to 11.5</td>
<td>0.13</td>
</tr>
</tbody>
</table>

KCCQ physical limitations

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>53.3 ± 31.5</td>
<td>15.2</td>
<td>9.0 to 21.2</td>
<td>&lt;0.001</td>
<td>42.1 ± 27.9</td>
<td>6.7</td>
<td>1.7 to 11.7</td>
<td>0.009</td>
</tr>
<tr>
<td>6 mo</td>
<td>57.4 ± 30.8</td>
<td>20.3</td>
<td>13.6 to 267.0</td>
<td>&lt;0.001</td>
<td>42.0 ± 28.6</td>
<td>8.5</td>
<td>2.0 to 14.9</td>
<td>0.01</td>
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<tr>
<td>12 mo</td>
<td>56.4 ± 33.2</td>
<td>16.8</td>
<td>10.4 to 23.3</td>
<td>&lt;0.001</td>
<td>39.9 ± 27.4</td>
<td>-1.9</td>
<td>-9.4 to 5.6</td>
<td>0.62</td>
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</table>

KCCQ social limitation

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
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<tbody>
<tr>
<td>1 mo</td>
<td>55.7 ± 36.7</td>
<td>26.0</td>
<td>18.6 to 33.5</td>
<td>&lt;0.001</td>
<td>40.7 ± 31.2</td>
<td>9.3</td>
<td>3.4 to 15.2</td>
<td>0.02</td>
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<tr>
<td>6 mo</td>
<td>68.5 ± 32.7</td>
<td>36.2</td>
<td>28.4 to 44.1</td>
<td>&lt;0.001</td>
<td>41.1 ± 33.4</td>
<td>10.8</td>
<td>2.2 to 19.4</td>
<td>0.01</td>
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<tr>
<td>12 mo</td>
<td>64.7 ± 33.2</td>
<td>34.2</td>
<td>25.9 to 42.6</td>
<td>&lt;0.001</td>
<td>50.5 ± 26.1</td>
<td>3.1</td>
<td>-5.7 to 12.0</td>
<td>0.48</td>
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</table>

KCCQ quality of life

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>65.0 ± 27.9</td>
<td>31.4</td>
<td>26.5 to 36.4</td>
<td>&lt;0.001</td>
<td>50.5 ± 27.6</td>
<td>14.8</td>
<td>9.6 to 19.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>6 mo</td>
<td>76.6 ± 24.7</td>
<td>41.9</td>
<td>36.8 to 47.0</td>
<td>&lt;0.001</td>
<td>51.8 ± 27.6</td>
<td>16.2</td>
<td>9.5 to 22.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 mo</td>
<td>75.9 ± 27.6</td>
<td>41.2</td>
<td>34.7 to 47.6</td>
<td>&lt;0.001</td>
<td>47.6 ± 27.9</td>
<td>6.8</td>
<td>-1.1 to 14.6</td>
<td>0.09</td>
</tr>
</tbody>
</table>

SF-12 physical

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>34.6 ± 10.3</td>
<td>6.3</td>
<td>4.4 to 8.2</td>
<td>&lt;0.001</td>
<td>30.2 ± 7.3</td>
<td>2.0</td>
<td>0.6 to 3.4</td>
<td>0.006</td>
</tr>
<tr>
<td>6 mo</td>
<td>36.0 ± 10.6</td>
<td>7.7</td>
<td>5.4 to 9.9</td>
<td>&lt;0.001</td>
<td>30.5 ± 8.2</td>
<td>2.9</td>
<td>0.7 to 5.0</td>
<td>0.01</td>
</tr>
<tr>
<td>12 mo</td>
<td>34.9 ± 11.1</td>
<td>6.6</td>
<td>4.3 to 8.9</td>
<td>&lt;0.001</td>
<td>29.7 ± 8.5</td>
<td>2.0</td>
<td>-0.5 to 4.6</td>
<td>0.11</td>
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</tbody>
</table>

SF-12 mental

<table>
<thead>
<tr>
<th>Scale/Time Point</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
<th>Mean (± SD) Value</th>
<th>Mean Δ vs Baseline</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 mo</td>
<td>47.9 ± 11.0</td>
<td>2.8</td>
<td>0.2 to 5.4</td>
<td>0.03</td>
<td>48.5 ± 10.9</td>
<td>2.0</td>
<td>-0.1 to 4.1</td>
<td>0.06</td>
</tr>
<tr>
<td>6 mo</td>
<td>36.0 ± 10.6</td>
<td>5.9</td>
<td>3.5 to 8.3</td>
<td>&lt;0.001</td>
<td>46.7 ± 11.8</td>
<td>2.1</td>
<td>-0.6 to 4.8</td>
<td>0.13</td>
</tr>
<tr>
<td>12 mo</td>
<td>53.3 ± 10.0</td>
<td>7.0</td>
<td>4.2 to 9.7</td>
<td>&lt;0.001</td>
<td>46.6 ± 11.7</td>
<td>1.0</td>
<td>-2.2 to 4.1</td>
<td>0.53</td>
</tr>
</tbody>
</table>

CI indicates confidence interval; KCCQ, Kansas City Cardiomyopathy Questionnaire; and SF-12, Short Form-12 General Health Survey.

*P value derived from paired t tests comparing follow-up score and baseline within the specific treatment group.

test.
included age >85 versus ≤85 years; male versus female sex; STS-predicted 30-day mortality rates (categorized as <10%, 10%–15%, or >15%); aortic valve gradient >40 versus ≤40 mm Hg; oxygen-dependent chronic obstructive pulmonary disease versus no oxygen-dependent chronic obstructive pulmonary disease; left ventricular ejection fraction >55% versus ≤55%; and aortic valve area index >0.35 versus ≤0.35 cm²/m². With the exception of the STS risk score, each of the cut points for continuous variables was based on the approximate median value in the study population.

All analyses were performed on an intention-to-treat basis. A 2-tailed P value <0.05 was considered statistically significant for all analyses of between-group differences. No statistical adjustments were made for multiple secondary comparisons. All analyses were performed with SAS for Windows version 9.2 (SAS Institute, Inc, Cary, NC).

Role of the Funding Source
The PARTNER trial was funded by Edwards Lifesciences and designed collaboratively by the Steering Committee and the sponsor. The present analysis was carried out by academic investigators at the Harvard Clinical Research Institute (Boston, MA) and the Health Economics and Technology Assessment Group at Saint Luke’s Mid America Heart and Vascular Institute (Kansas City, MO). The authors had unrestricted access to the study data, drafted the manuscript, made the decision to submit for publication, and vouch for the veracity and completeness of its content.

Results

Patient Population and Baseline Health Status
As previously reported, a total of 358 patients with severe, symptomatic aortic stenosis who were not candidates for surgery were randomized at 21 centers to TAVR (n=179) or standard therapy (n=179). Nine patients assigned to TAVR did not have a valve implanted. A total of 140 of the control group patients (78%) underwent balloon aortic valvuloplasty during follow-up (114 within 1 month of randomization). The 12-month mortality rates were 30.7% in the TAVR arm and 50.7% in the standard therapy arm.

The baseline characteristics of the 2 study groups were similar, and there were no clinically relevant differences between groups in baseline quality-of-life scores (Table 1). The patient population was elderly with a high burden of chronic medical conditions. The mean physical summary scores for the SF-12 at baseline were >2 SDs below the population norm for the United States, and the mean baseline...
KCCQ overall summary scores were in a range previously shown to correspond with New York Heart Association class III and IV functional status.

Within-Group Comparisons
Among surviving patients, quality-of-life questionnaires were completed for >80% of subjects at each time point (baseline, 91%; 1 month, 82%; 6 months, 81%; 12 months, 84%), with a slightly higher completion rate among TAVR patients (88% across follow-up time points versus 76% for the control group). Given the high mortality rate in the trial, 12-month quality-of-life outcome measures were available for only 61% of the originally randomized TAVR patients and 39% of the originally randomized control group patients.

Mean follow-up scores and the mean change from baseline at each follow-up time point are summarized separately for each treatment group in Table 2. Although mean quality-of-life scores improved over time for both treatment groups, comparison of the mean within-patient changes from baseline revealed different patterns of improvement for the TAVR and control patients. For the TAVR group, the mean change from baseline in the KCCQ overall summary score was 25 points at 1 month and increased over time to 34 and 32 points at 6 and 12 months, respectively (P<0.001 for all comparisons).

In contrast, for the control group, scores were significantly improved compared with baseline at both 1 and 6 months (mean changes of 10 and 12 points, respectively; P<0.001 for both comparisons), but the change was no longer significantly different from baseline at 12 months (mean change of 4 points; P=0.20). Similar patterns of within-group changes over time were noted for each of the KCCQ subscales and the SF-12 summary scales (Table 2).

The difference between the temporal patterns for the overall group means and the within-group paired comparisons is explained at least partly by differences in missing data (mainly related to death) between the 2 groups. For the control group, the mean baseline KCCQ overall summary score among the subsets of patients who completed questionnaires at each follow-up time point were progressively higher (37, 39, and 43 points for 1-, 6-, and 12-month respondents, respectively) than for all baseline respondents combined (34 points). There was no such trend for the TAVR group, however, with mean baseline scores of 37, 37, and 38 points for 1-, 6-, and 12-month respondents compared with 36 points for all baseline respondents. Thus, the appearance of sustained improvement in health status at 12 months in the control group relates predominantly to attrition of the sickest patients over time.

Between-Group Comparisons
Predicted mean scores from the longitudinal growth curve models grouped by treatment assignment for each of the quality-of-life scales over the 12-month follow-up period are displayed in Figure 1, and the resulting between-group comparisons are summarized in Table 3. At 1 month, the KCCQ summary score had increased to a greater extent in the TAVR group than in the standard therapy group (mean difference, 13.3 points; 95% CI, 7.6–19.0; P<0.001). The difference between treatment groups in KCCQ summary scores became even larger at 6 months (mean difference, 20.8 points; 95% CI, 14.7–27.0; P<0.001) and 12 months (mean difference, 26.0 points; 95% CI, 18.7–33.3; P<0.001). Results were similar for each of the individual KCCQ scales.

Changes in the SF-12 physical summary score followed a pattern similar to those of the KCCQ summary score, with statistically significant between-group differences in mean scores of 4.5 to 5.7 points at 1, 6, and 12 months (Figure 1 and Table 3). There was no difference in SF-12 mental component summary scores at 1 month, but between-group differences in mean scores of 3.2 and 6.4 points in favor of TAVR were seen at 6 and 12 months.

In sensitivity analyses in which missing KCCQ summary scores for surviving patients were imputed as the lowest observed values for each respective time point, the between-group differences became larger than in our primary analysis,
with mean differences of 17.9 points (95% CI, 11.6–24.2), 25.8 points (95% CI, 18.2–33.3), and 28.9 points (95% CI, 20.7–37.0) at 1, 6, and 12 months, respectively \( (P<0.001 for all comparisons)\).

**Categorical Analyses**

Table 4 presents the frequency with which patients achieved \( \geq 10 \)-point or \( \geq 20 \)-point improvements over baseline in the KCCQ summary score. These are expressed as both the proportion of respondents at each time point (top half of table), termed large and very large improvements, and as the proportion of all randomized patients (bottom half of table), termed favorable and excellent outcomes, respectively. At each time point, TAVR patients were more likely to have experienced clinically meaningful improvements in health status, with increasing benefit over time. At the 12-month follow-up, the number needed to treat to achieve a favorable outcome was 3.0 (95% CI, 2.3–4.0) and to achieve an excellent outcome was 3.5 (95% CI, 2.7–4.9).

**Subgroup Analyses**

The results of prespecified subgroup analyses for the primary quality-of-life end point are summarized in Figure 2. At the 6-month follow-up (Figure 2A), there were consistent health status benefits among patients stratified by age, sex, STS risk level, baseline aortic valve gradient, ejection fraction, and aortic valve area index. The extent of benefit with TAVR was less for patients with oxygen-dependent chronic obstructive pulmonary disease at this time point (5.6 versus 23.7 points; \( P=0.02 \) for interaction). By the 1-year follow-up, there were no significant differences in the effect of TAVR on the primary quality-of-life end point across each of the subgroups, including the presence or absence of oxygen-dependent chronic obstructive pulmonary disease (24.5 versus 25.8; \( P=0.74 \) for interaction).

**Discussion**

The PARTNER trial, the first randomized clinical trial of TAVR, demonstrated a large survival benefit with TAVR compared with standard therapy in patients with severe aortic stenosis who were not suitable candidates for surgical aortic valve replacement. In this preplanned substudy, we found that TAVR also provides substantial benefits over standard therapy in terms of symptoms and health-related quality of life. These differences were seen as early as 1 month and continued to increase over the 12-month follow-up of the study.

Measures of both disease-specific and generic quality of life improved to a greater extent with TAVR than with standard therapy, with effect sizes that were both large and clinically meaningful. In previous studies, changes of as little as 5 points on the KCCQ summary scale have been shown to correlate with important differences in survival and healthcare costs in heart failure patients. In our study, the mean between-group differences in the KCCQ summary score 6 and 12 months after enrollment met or exceeded the 20-point threshold considered to signify a very large improvement in...
heart failure status, and >75% of surviving patients had at least moderately large (10-point) improvements over baseline. Moreover, the proportion of patients who achieved an excellent outcome at 12 months (defined as surviving with at least a 20-point improvement in the KCCQ summary score) was far greater with TAVR than with standard care (absolute treatment difference, 28%; number needed to treat, 3.5).

The minimally important difference in SF-12 summary scales is 2 to 2.5 points. For both the physical and mental summary scales of the SF-12, the difference between groups at 6 and 12 months was roughly twice this threshold. The mental component summary scores did not differ between groups at 1 month, but these scores were higher at baseline in both groups than the physical summary scores. The magnitude of improvement in SF-12 physical scores with TAVR is roughly equivalent to reversing by 10 years the normal decline in physical health observed with aging in the general population.

We observed improvement from baseline in the control group in both pairwise comparisons and categorical analyses—at least at 1 and 6 months. This improvement may have been due to a transient effect of balloon aortic valvuloplasty, which was performed in the majority of control group patients. Additional factors contributing to this increase may have included enhanced medical attention related to clinical trial participation, regression to the mean, or placebo effects (related to the valvuloplasty procedures).

Previous observational studies have shown that surgical aortic valve replacement, even among octogenarians, can greatly improve functional status and return quality-of-life scores to age-adjusted norms. However, by design, such studies included only patients who were considered to be acceptable candidates for cardiac surgery. Recently, several small studies have also demonstrated significant improvement in health status after TAVR, but none of these studies included a parallel control group.

Given the advanced age and poor general health of the patients enrolled in the PARTNER trial, it is important to establish how TAVR, a relatively new procedure with distinct

![Figure 2. Estimated effect of transcatheter aortic valve replacement (TAVR) vs standard therapy on the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 6 months (A) and 12 months (B) according to prespecified patient subgroups. Treatment effects, associated 95% confidence intervals, and interaction P values were derived from longitudinal growth curve models. STS indicates Society of Thoracic Surgeons; AV, atrioventricular; and COPD, chronic obstructive pulmonary disease.](http://circ.ahajournals.org/)

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Figure 2. Estimated effect of transcatheter aortic valve replacement (TAVR) vs standard therapy on the Kansas City Cardiomyopathy Questionnaire (KCCQ) overall summary score at 6 months (A) and 12 months (B) according to prespecified patient subgroups. Treatment effects, associated 95% confidence intervals, and interaction P values were derived from longitudinal growth curve models. STS indicates Society of Thoracic Surgeons; AV, atrioventricular; and COPD, chronic obstructive pulmonary disease.
risks and limitations, affects health status compared with the best alternative therapy. Health-related quality-of-life end points are particularly relevant in this setting, given the increased risks of both stroke and major vascular complications that were observed with TAVR in the PARTNER trial. Our results suggest that despite multiple comorbid conditions and advanced age, patients similar to those enrolled in this trial can expect very meaningful improvements in symptoms, functional status, and quality of life after TAVR.

Our study has several limitations. Most important, the proportion of patients with available data diminished over time as a result of deaths and nonresponses of surviving patients, both of which were more common in the control group. To supplement our primary analysis based on longitudinal growth curve models, we used several analytic approaches to address the potential bias introduced by missing data, including the imputation of “worst case” values to surviving patients with missing data, the creation of categorical variables (“favorable” and “excellent”) outcomes that treated missing data for any reason (including death) as “treatment failures,” and comparisons of within-patient changes from baseline at individual follow-up time points based on patients with available quality-of-life measurements. Each of these supplemental analyses demonstrated benefits of TAVR that were comparable to or in some cases larger than those seen in our primary analysis. We therefore believe it is unlikely that the magnitude of differences between groups seen in our primary analyses was overestimated as a result of biases caused by missing data.

The PARTNER trial was unblinded; therefore, we cannot exclude the possibility that some of the observed benefit of TAVR was related to a placebo-like effect. However, it is noteworthy that we also observed trends toward improved quality of life in the standard therapy group, particularly in the first 6 months, but these trends diminished by 12 months, whereas health status measures in the TAVR group continued to improve.

These results encompass only 1 year of follow-up. Thus, the longer-term durability of the observed improvements in quality of life after TAVR remains unknown. Finally, the current data are uninformative regarding how changes in quality of life after TAVR may compare with those after surgical aortic valve replacement in lower-risk patients. This is the subject of ongoing investigation.

Conclusions
For patients with severe aortic stenosis who were not surgical candidates, TAVR resulted in marked improvements in health status and quality of life compared with standard therapy over 1 year of follow-up. Taken together with previously reported benefits on both survival and rehospitalization, these findings further support the notion that TAVR should be considered a valuable therapeutic option for patients with severe aortic stenosis who are not candidates for valve replacement surgery.

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References

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Many patients with severe aortic stenosis do not undergo surgical valve replacement because of prohibitive operative risk. In a cohort of such patients, the Placement of Aortic Transcatheter Valves (PARTNER) trial recently showed that transcatheter aortic valve implantation (TAVI) increased 12-month survival by an absolute margin of 20% but was associated with increased risks of vascular complications and stroke compared with standard therapy, which included balloon aortic valvuloplasty for aortic stenosis: improved quality of life for elderly patients. Can J Cardiol. 1998;4:223–227.


Health-Related Quality of Life After Transcatheter Aortic Valve Replacement in Inoperable Patients With Severe Aortic Stenosis

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