How to Define a Poor Outcome After Transcatheter Aortic Valve Replacement

Conceptual Framework and Empirical Observations From the Placement of Aortic Transcatheter Valve (PARTNER) Trial

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Background—Transcatheter aortic valve replacement (TAVR) has emerged as a less invasive option for valve replacement of patients with severe aortic stenosis. Although it has been recommended that TAVR should not be offered to patients who will not improve functionally or derive meaningful survival benefit from the procedure, no guidance exists on how best to identify such patients. The first step in this process is to define a poor outcome that can then be used as a foundation for subsequent case identification. We sought to evaluate potential definitions of a poor outcome after TAVR that combine both mortality and quality of life components.

Methods and Results—Using data from 463 patients who underwent TAVR as part of the Placement of Aortic Transcatheter Valve (PARTNER) trial, we evaluated 6-month mortality and quality of life outcomes using the Kansas City Cardiomyopathy Questionnaire to explore potential definitions of a poor outcome. We then compared the strengths and weaknesses of each potential definition by examining the relationship between baseline and 6-month Kansas City Cardiomyopathy Questionnaire scores for each patient. Based on these analyses, we argue that the most appropriate definition of a poor outcome after TAVR is (1) death, (2) Kansas City Cardiomyopathy Questionnaire overall summary score <45, or (3) Kansas City Cardiomyopathy Questionnaire decrease of ≥10 points, which best reflects a failure to achieve the therapeutic goals of TAVR.

Conclusions—Using empirical data on a large number of patients enrolled in the PARTNER trial, we propose a definition for poor outcome after TAVR that combines both mortality and quality of life measures into a single composite endpoint. Use of this endpoint (or other similar endpoints) in future studies can facilitate development of predictive models that may be useful to identify patients who are poor candidates for TAVR and to provide such patients and their families with appropriate expectations of functional recovery after TAVR. (Circ Cardiovasc Qual Outcomes. 2013;6:00-00.)

Key Words: aortic valve stenosis □ quality of life □ transcatheter aortic valve □ valve
WHAT IS KNOWN

• It has been recommended that transcatheter aortic valve replacement (TAVR) should not be offered to patients who have limited potential to derive functional improvement or live longer after TAVR; however, there has been no guidance about how to prospectively identify these patients.

• To predict which patients are at high risk for a poor outcome after TAVR, we must first define which outcome (encompassing both a mortality and a quality of life component) constitutes a poor versus acceptable outcome.

• TAVR offers the possibility of both a quality and a quantity of life benefit, and patients may choose to undergo TAVR for one or both of these 2 potential benefits depending on how symptomatic they are from their aortic stenosis before the procedure.

WHAT THE STUDY ADDS

• Using mortality and quality of life data from the Placement of AoRtic TraNs cathetER Valve (PARTNER) trial of patients undergoing TAVR, this article considers 4 potential definitions for a poor outcome after TAVR that combine mortality and quality of life end points and examining the advantages and disadvantages of each definition:

• The authors suggest defining a poor outcome at 6 months after TAVR as (1) death, (2) a poor quality of life, or (3) a substantial worsening of quality of life and provide quantitative definitions for the second and third criteria; this end point can then be used to facilitate development of predictive models that may be useful to identify patients who are poor candidates for TAVR.

replacement may not have a positive effect on their survival and QoL.

Although several studies have begun to explore methods to identify patients at high risk for poor outcomes after TAVR, to date these studies have focused almost exclusively on mortality.11–15 Given the age and underlying burden of comorbidity among patients currently considered for TAVR, improved health status and QoL may be even more important treatment goals than extending life.16,17 Consequently, integrating QoL outcomes into the definition of a poor (and, conversely, an acceptable) outcome is particularly relevant in these challenging and complex patients.10 The first step in examining this issue must be to rigorously define what constitutes a poor outcome of TAVR. Although some might consider these definitions to be self-evident, there is actually a large range of definitions that could be considered, each of which may have different implications for patient selection and shared decision making. In an effort to explore these issues, we used data from the Placement of AoRtic TraNs cathetER Valve (PARTNER) trial to examine the strengths and weaknesses of alternative definitions of a poor outcome after TAVR.

Methods

Study Population and Protocol

Patients for our study were drawn from the PARTNER trial of patients with severe symptomatic aortic stenosis who were considered potential candidates for TAVR. Details of the study inclusion and exclusion criteria have been described previously.3,5 Briefly, enrolled patients were required to have severe aortic stenosis (aortic valve area of <0.8 cm² with either a mean aortic valve gradient of ≥40 mm Hg or a peak aortic jet velocity of ≥4.0 m/s), New York Heart Association (NYHA) class II or greater heart failure symptoms, and high surgical risk based on the Society for Thoracic Surgeons risk score and other factors. Eligible patients were classified as either high risk but suitable for surgical aortic valve replacement (cohort A)3 or ineligible for cardiac surgery because of coexisting medical conditions associated with a predicted probability of death or permanent disability ≥50% (cohort B).6 Cohort A patients were randomized to either TAVR or surgical AVR, whereas cohort B patients were randomized to TAVR versus medical therapy. For the purposes of this study, only patients who were randomized to TAVR and actually underwent the procedure were included in the study population.

Patients were assessed for clinical factors and health status at baseline and at 1, 6, and 12 months after randomization. The baseline health status questionnaires were administered before randomization, and follow-up questionnaires were administered during in-person visits to the enrolling centers or by E-mail. An independent clinical events committee adjudicated all serious adverse events. The institutional review boards at each participating site approved the study, and all patients provided written informed consent before participation.

Assessment of Health Status

Although patients with severe aortic stenosis may experience angina or syncope as their major presenting symptom, heart failure symptoms predominate among patients presenting for aortic valve replacement.18,19 As such, use of a heart failure–specific instrument has been suggested as a potentially useful approach for monitoring symptoms and QoL in this population.20 Although overall health status would be expected to improve among highly symptomatic patients undergoing TAVR, generic health status measures are less sensitive to change and do not specifically assess symptoms and functional status along the disease pathway of aortic stenosis. As such, they would not be as sensitive or specific as a disease-specific measure for determining whether a patient has had an acceptable outcome after TAVR.

For this study, disease-specific health status, which includes symptoms, functional status, and QoL, was assessed by means of the Kansas City Cardiomyopathy Questionnaire (KCCQ),21 a 23-item self-administered questionnaire that addresses specific health domains pertaining to heart failure: physical limitation, symptoms, QoL, social limitation, symptom stability, and self-efficacy. The first 4 of these domains are combined into an overall summary scale, which was the primary health status outcome for our study. Values for each domain (including the summary scale) range from 0 to 100, with higher scores indicating lower symptom burden and better QoL. Linguistically and culturally validated translations of the KCCQ were provided to non-English speakers.

Based on previous work, a KCCQ summary score >75 corresponds roughly to NYHA functional class I, and scores of 60 to 75, 45 to 60, and <45 correspond to NYHA functional classes II, III, and IV, respectively.22 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 ≥5, 10, and 20 points, respectively. The KCCQ has undergone extensive reliability and validity testing in various heart failure populations,23,24,25 as well as in patients with severe aortic stenosis,26 and it has been shown to predict mortality, readmission,25,26 and costs.27

Conceptual Framework

A poor outcome of an intervention is, by definition, one in which there is a failure to achieve the expected treatment goals of that intervention. To determine the most appropriate definition for poor
outcome after TAVR, it is important to clarify the treatment goals of TAVR, particularly from patients’ perspectives. In patients with severe symptomatic aortic stenosis, TAVR has 2 important potential benefits: improved survival and reduced symptoms. Although most patients likely choose TAVR for some combination of these potential benefits, the relative importance of these benefits likely varies by patients’ characteristics before treatment. Clinical logic would suggest that most patients who have minimal symptoms choose to undergo TAVR primarily to achieve an expected improvement in survival. Conversely, patients with substantial symptoms and functional limitation from their aortic stenosis most likely choose to undergo TAVR for an expected improvement in symptoms.

**Analytic Approach**

For the purposes of this study, we used various combinations of mortality and health status outcomes 6 months after TAVR to define clinical success or failure. Although this time frame is somewhat arbitrary, given the advanced age of the TAVR population, we felt that even relatively brief improvements in health and survival would be important. We did not consider a 1-month time frame to be appropriate for this evaluation, however, because some patients might not have fully recovered from the procedure and would require more time to improve their functioning and symptom control to establish a new steady state.

For each conceptual definition of clinical success or failure, we considered a poor outcome to be either death or failure to achieve a specific level of QoL 6 months after TAVR. We then plotted 6-month versus baseline KCCQ scores among those who were alive at 6 months, and we characterized the cohort of patients who would be considered to have had a poor outcome according to each of the 4 potential definitions. As there is no gold standard for a poor outcome after TAVR, we considered the strengths and weaknesses of each of the definitions qualitatively using the conceptual framework outlined above. All statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute, Inc., Cary, NC).

**Results**

**Patient Population**

A total of 527 patients underwent initial TAVR as part of the PARTNER trial (348 in cohort A; 179 in cohort B) via either the transfemoral (n=423) or transapical (n=104) route. Of these patients, 89 died within 6 months of TAVR. Among the 438 patients who survived for 6 months, KCCQ data were available for 374 (85%) patients. As such, our analytic population included 463 patients who underwent TAVR and were either dead or completed the KCCQ at 6 months after their procedure. Patients who were alive but missing 6-month data (n=64) had similar demographic and clinical characteristics to those with 6-month KCCQ data, except that patients with missing data were more likely to be classified as NYHA functional class II or IV at baseline (100% versus 92%; P=0.013). However, baseline KCCQ scores were similar between the 2 groups (missing versus not missing: 40.6 versus 39.1; P=0.662).

The baseline characteristics of the study population are shown in Table 1. The mean age of the population was 84 years, half were women, and 73% had a history of coronary artery disease. Mean aortic valve gradient was 43 mm Hg, and >90% had NYHA class III or IV symptoms. Eighty percent of patients were treated via the transfemoral route, and the average estimated risk of operative mortality for the patients was 12%.

**Potential Definitions**

We considered 4 potential definitions of a poor outcome after TAVR, each of which includes death as a poor outcome. Table 1. Baseline Demographic and Clinical Characteristics of the Analytic Population

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>n=463</th>
</tr>
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<tbody>
<tr>
<td>Age, y</td>
<td>83.5±7.4</td>
</tr>
<tr>
<td>Female, %</td>
<td>46.6</td>
</tr>
<tr>
<td>White, %</td>
<td>93.2</td>
</tr>
<tr>
<td>Coronary artery disease, %</td>
<td>73.2</td>
</tr>
<tr>
<td>Peripheral vascular disease, %</td>
<td>38.6</td>
</tr>
<tr>
<td>Diabetes mellitus, %</td>
<td>38.2</td>
</tr>
<tr>
<td>Oxygen-dependent lung disease, %</td>
<td>13.8</td>
</tr>
<tr>
<td>Creatinine, mg/dL</td>
<td>1.30±0.47</td>
</tr>
<tr>
<td>Mini-Mental State Examination Score</td>
<td>26.7±3.5</td>
</tr>
<tr>
<td>NYHA class, %</td>
<td></td>
</tr>
<tr>
<td>II</td>
<td>6.3</td>
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<tr>
<td>III</td>
<td>44.5</td>
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<tr>
<td>IV</td>
<td>49.2</td>
</tr>
<tr>
<td>Mean aortic valve gradient, mm Hg</td>
<td>43.3±14.9</td>
</tr>
<tr>
<td>Ejection fraction, %</td>
<td>52.9±13.2</td>
</tr>
<tr>
<td>Cohort A (vs B), %</td>
<td>66.2</td>
</tr>
<tr>
<td>Transfemoral approach, %</td>
<td>80.1</td>
</tr>
<tr>
<td>STS Mortality Risk Score, %</td>
<td>11.7±4.4</td>
</tr>
</tbody>
</table>

NYHA indicates New York Heart Association; and STS, Society of Thoracic Surgeons.

Figure illustrates the paired baseline and 6-month KCCQ scores within the study population classified as having a poor or acceptable outcome at 6 months after TAVR according to each of the potential definitions, and Table 2 summarizes the percentage of patients who fall into each outcome category by each definition.

**Definition 1 of Poor Outcome: Death or KCCQ Improvement of <10 Points**

Under this definition, patients who either die or fail to achieve at least a moderate improvement in health status at 6 months would be considered to have had a poor outcome after TAVR. In the PARTNER population, this definition would have identified 39% of patients as having had a poor outcome of TAVR (19% death, 20% limited QoL benefit; Table 2). Because this definition requires patients to realize both a survival and a QoL benefit from TAVR, it has face validity among a group of highly symptomatic patients with aortic stenosis. However, it is evident from Figure A that patients who started with lower KCCQ scores were more likely to achieve a 10-point improvement after TAVR. In addition, any patient with a baseline KCCQ score of >90 would be categorized as having a poor outcome regardless of the KCCQ score at 6 months. Thus, by using this definition for poor outcome, we would preferentially identify patients who started at the higher end of the range of baseline KCCQ values as not deriving a QoL benefit from the procedure. It is not clear that this represents treatment failure, however, because this subgroup was not particularly symptomatic before TAVR and thus was most likely to be undergoing the procedure for its survival benefit. Therefore, it does not seem appropriate to classify this outcome as poor for all TAVR candidates.
**Definition 2 of Poor Outcome: Death or KCCQ <45**

Because a KCCQ overall summary score <45 generally corresponds to NYHA class IV, this definition would classify patients as having a poor outcome if at 6 months after TAVR they were either dead or had poor self-reported health status. One third of PARTNER TAVR patients would be classified as having had a poor outcome after TAVR according to this definition (19% death, 14% poor QoL; Table 2). This definition has face validity in that a patient who continues to have NYHA class IV heart failure symptoms (and thus a poor functional capacity after TAVR) would not be considered to have had an acceptable outcome from the procedure. As shown in Figure B, this definition preferentially identifies patients with lower baseline KCCQ scores as more likely to have a poor outcome. This performance characteristic is intuitively appealing because patients with poor QoL pre-TAVR are more likely to have chosen the intervention for its expected benefits on symptoms and QoL as opposed to its survival benefit. However, this definition ignores patients with relatively high pre-TAVR KCCQ scores whose health status declines after treatment (eg, a patient whose KCCQ overall summary score declines from 80 pre-TAVR to 50 at 6 months after TAVR would still be considered an acceptable outcome).

**Definition 3 of Poor Outcome: Death or KCCQ <45 or KCCQ Decrease of ≥10 Points**

This definition seeks to overcome the limitations of definition 2 by requiring that the patient achieve a minimum QoL level (ie, KCCQ ≥45 = NYHA class III symptoms or better) and not experience a clinically meaningful decline in QoL after procedure (KCCQ decrease of ≥10 points). Approximately 35% of the PARTNER population would be categorized as having had a poor outcome of TAVR according to this definition (19% death, 16% poor QoL; Table 2 and Figure C). A potential criticism of this definition is that patients who begin with low KCCQ scores and improve after TAVR but not to the threshold of 45 would still be considered to have experienced a poor outcome (eg, a patient whose KCCQ overall summary score increases from 10 to 25).

**Definition 4 of Poor Outcome: Death or KCCQ Decrease of ≥10 Points or KCCQ <45 (Unless KCCQ Increases by ≥10 points)**

This definition addresses the potential criticism of definition 3 by categorizing as acceptable any patient who is alive with at least a modest improvement in health status at 6 months after TAVR regardless of his or her final level of QoL. Relative

<table>
<thead>
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<th>Table 2. Frequency of Poor Outcome After TAVR by Each Definition</th>
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<tr>
<td>Definition 1</td>
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<td>Definition 2</td>
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<td>Definition 3</td>
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<td>Definition 4</td>
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</table>

Sample sizes among definitions may differ slightly because of the amount of QoL data needed to establish the definition of poor outcome. KCCQ indicates Kansas City Cardiomyopathy Questionnaire; QoL, quality of life; and TAVR, transcatheter aortic valve replacement.
to definition 3, definition 4 recategorizes an additional 4% of PARTNER TAVR patients as having had an acceptable outcome, such that 31% of the population would be considered to have had a poor outcome (19% death, 11% poor QoL; Table 2, Figure D). However, the patient who is reclassified as having an acceptable outcome by this definition still has a poor QoL with marked symptom burden and function limitation; thus, although modestly improved, this may still not be an acceptable outcome of TAVR. Of note, this approach adds a level of complexity above definition 3 that results in only minimal reclassification.

**Discussion**

Aortic valve replacement, with either surgery or TAVR, is effective in relieving the hemodynamic obstruction of aortic stenosis and can lead to excellent outcomes in good operative candidates. However, many patients with severe aortic stenosis are less than ideal candidates for surgical valve replacement. Advanced age, multiple comorbidities, deconditioning, and frailty can all contribute to an inability to recover from surgery. Although some patients may clearly be poor candidates for surgical valve replacement, with the emergence of TAVR as a less invasive treatment modality, many of these patients can now be considered for definitive treatment of their aortic stenosis. Nonetheless, some of these potential TAVR candidates do not seem to derive a survival or QoL benefit from the procedure, despite successful relief of the hemodynamic obstruction. Avoiding an unnecessary, expensive, and somewhat risky procedure for such patients would, therefore, seem to be a worthwhile goal. To identify patients in whom valve replacement is unlikely to provide benefit, the first step is to establish a definition for a poor outcome after TAVR. For a procedure such as TAVR that is used to treat a condition that results in both reduced life expectancy and impaired QoL, this definition must include both a mortality and a QoL component. However, combining these 2 endpoints into a single definition of a poor outcome can be challenging. To address this issue, we have explored several alternative definitions of a poor outcome after TAVR and the relative strengths and weaknesses of each approach. We think that this is the first attempt to rigorously and objectively define a poor outcome for TAVR and, as such, an important step along the path to define patients for whom the procedure might be considered inappropriate or, at a minimum, ill-advised because of the likelihood of poor outcome after the treatment.

Because TAVR provides both quality and quantity of life benefits, patients may choose TAVR for a combination of these 2 benefits, but the priority of the benefits is likely to differ across individuals. For patients with a good QoL before TAVR, the most important benefit is likely to be a reduction in the risk of mortality because they already have minimal symptoms or QoL impairment from their aortic stenosis. In these cases, even if there was no QoL improvement after TAVR, the patient would likely consider this to be an acceptable outcome because their preprocedure QoL was reasonable, and they would expect to receive a substantial survival benefit from the procedure. For such patients, the result would be considered acceptable as long as their QoL is not worsened by TAVR.

However, for patients who have a poor QoL before TAVR, we suspect, based on both our clinical experience and previous studies of patients with severe heart failure,16,17 that the primary motivation for undergoing TAVR is for its QoL benefit. Thus, if a patient’s QoL failed to improve to a minimum acceptable level after TAVR, this would not be considered an acceptable result. As a result of these differing priorities of survival and QoL for patients with differing clinical manifestations of aortic stenosis, we favor definition 3 or 4 as providing a reasonably balanced and nuanced summary of the overall success (or failure) of TAVR. In our experience, these definitions seem to most commonly encompass the values and goals of the patients who are considering TAVR. Ultimately, we favor definition 3 because definition 4 adds substantial complexity to the definition with minimal net reclassification. Furthermore, in our experience, patients who continue to have poor QoL after TAVR are unlikely to view the procedure as having been successful, even if their QoL is improved from baseline. Future prospective evaluations of patients’ perspectives of the benefits of TAVR are needed to confirm our assessment.

**Insights From Other Patient Populations**

A unique consideration in evaluating TAVR is that a range of patients who are candidates for TAVR may prioritize the QoL and survival benefits differently. It is reasonable to assume that highly symptomatic patients choose the procedure for symptom relief, whereas those without significant functional impairment choose the procedure to prolong their lives (while maintaining their current health status). Few other procedures in cardiovascular medicine have such a balance of survival and QoL motivations and, therefore, need to consider both factors in any definition of a poor outcome.

One example of a procedure that provides both survival and QoL benefits is the use of left ventricular assist devices (LVADs) as destination therapy for advanced heart failure. Similar to TAVR candidates, patients who are considered for LVADs are highly symptomatic and would be expected to have a markedly reduced life expectancy without intervention. In the Randomized Evaluation of Mechanical Assistance for the Treatment of Congestive Heart Failure (REMATCH) trial of patients with end-stage heart failure ineligible for cardiac transplantation, there was a 27% absolute reduction in 1-year mortality with LVAD implantation versus medical therapy.28 Patients who received LVADs also had markedly improved QoL. However, approximately half of the patients treated with LVADs died within the first year, and only 1 in 4 survived for 2 years, results similar (albeit even more extreme) to those observed in the inoperable cohort of the PARTNER trial (cohort B).3 Although some of the deaths observed in REMATCH were because of device-related complications from the LVAD, other patients were simply too ill to survive the operation and recovery period. Even with improvements in device technology and surgical experience, more recent results among patients undergoing LVADs for destination therapy demonstrated that one quarter of patients died in the hospital after device implantation, and half were dead at 1 year.29 In that study, the authors constructed a risk score for poor 1-year outcome and identified poor nutrition,
implications

patients with severe aortic stenosis considering TA VR would define a poor (or acceptable) outcome. Ultimately, the ability to tailor risk predictions to an individual’s own unique concept of a successful and poor outcome would be ideal. Second, our definition of a poor outcome was derived from 2 clinical trials of sick and highly symptomatic patients. As TAVR outcomes improve with device modifications and greater experience and the procedure expands into the population of patients who are less sick, this definition may need to be refined. Nonetheless, even as it expands into lower-risk patients, TAVR is likely to continue to be offered to challenging patients at high surgical risk for whom our proposed categorization of a poor outcome would still be relevant. Furthermore, our systematic approach could be used to reevaluate what constitutes an acceptable outcome after TAVR as the patient population changes.

Conclusions

Although clinical trials have demonstrated that TAVR is associated with significant QoL and survival benefits for patients at high surgical risk, not all patients derive these benefits, and many never fully recover from the procedure. We propose a specific definition for poor outcome after TAVR, which combines these 2 domains of health into a single composite end point. According to this definition, a patient would be considered as having a poor outcome after TAVR if he or she is either dead, has a poor QoL, or has a substantial decline in QoL from baseline to 6 months. Establishing this definition is a first step in a research agenda aimed at determining which patient characteristics are associated with a high risk of a poor outcome so that patients can be provided with appropriate expectations of functional recovery after TAVR and clinicians can target therapy to those most likely to derive meaningful long-term benefit.

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Disclosures

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