Long-Term Outcomes of Inoperable Patients With Aortic Stenosis Randomly Assigned to Transcatheter Aortic Valve Replacement or Standard Therapy

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**Background**—The long-term outcomes of transcatheter aortic valve replacement (TAVR) in inoperable patients with severe aortic stenosis remain unknown.

**Methods and Results**—In the Placement of Aortic Transcatheter Valves (PARTNER) study, 358 patients were randomly assigned to TAVR or standard therapy. We report the 3-year outcomes on these patients, and the pooled outcomes for all randomly assigned inoperable patients (n=449) in PARTNER, as well, including the randomized portion of the continued access study (n=91). The 3-year mortality rate in the TAVR and standard therapy groups was 54.1% and 80.9%, respectively (P<0.001; hazard ratio, 0.53; 95% confidence interval, 0.41–0.68; P<0.001). In survivors, there was significant improvement in New York Heart Association functional class sustained at 3 years. The cumulative incidence of strokes at 3-year follow-up was 15.7% in TAVR patients versus 5.5% in patients undergoing standard therapy (hazard ratio, 2.81; 95% confidence interval, 1.26–6.26; P=0.012); however, the composite of death or strokes was significantly lower after TAVR versus standard therapy (57.4% versus 80.9%, P<0.001; hazard ratio, 0.60; 95% confidence interval, 0.46–0.77; P<0.001). Echocardiography showed a sustained increase in aortic valve area and decrease in transvalvular gradient after TAVR. Analysis of the 449 pooled randomly assigned patients (TAVR, n=220; standard therapy, n=229) demonstrated significant improvement in all-cause mortality and functional status during early and 3-year follow-up. The results of the pooled cohort were similar to the results obtained from the pivotal PARTNER trial.

**Conclusions**—TAVR resulted in better survival and functional status in inoperable patients with severe aortic stenosis with durable hemodynamic benefit on long-term follow-up. However, high residual mortality, even in successfully treated TAVR patients, highlights the need for more strategic patient selection.

**Clinical Trial Registration**—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00530894.

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**Key Words:** aortic valve • aortic valve stenosis • outcome assessment (health care)

Degenerative aortic stenosis (AS) is one of the most commonly acquired valvular heart diseases in aging adults. In patients with symptomatic AS, surgical aortic valve replacement has been the treatment of choice for >4 decades. However, a significant proportion of patients with severe symptomatic AS do not undergo aortic valve replacement because of a high estimated surgical mortality and morbidity. Recently, transcatheter aortic valve replacement (TAVR) has emerged as an important treatment option for these high-risk patients. The Placement of Aortic Transcatheter Valves (PARTNER) trial demonstrated improved outcomes including decreased mortality, increased functional capacity, and good hemodynamic performance among these so-called inoperable patients.
patients undergoing TAVR in comparison with those managed medically at 1- and 2-year clinical follow-up.\textsuperscript{5,7} There is a paucity of reliable long-term outcomes on patients treated with TAVR. The objective of this article is to report the 3-year (or longer) clinical and echocardiographic outcomes of inoperable patients randomly assigned to TAVR or standard therapy in the PARTNER trial. In addition, we are also reporting the early and long-term outcomes of all randomly assigned inoperable PARTNER patients, including a small cohort of patients randomly assigned in a subsequent continued access study that was enrolled after completion of the pivotal randomized trial.

Methods

The PARTNER trial, Cohort B was a multicenter randomized study involving severe symptomatic AS patients (aortic valve area <0.8 cm\(^2\)), who were not candidates for surgical aortic valve replacement because of clinical and anatomic factors. The Heart Team, comprising experienced cardiac surgeons, interventional cardiologists, and others, was responsible for determining the risk status of patients. The operative definition for inoperable patients was a probability of death or serious irreversible morbidity after surgical aortic valve replacement estimated to exceed 50%. Complete details on inclusion and exclusion criteria have been reported previously.\textsuperscript{5} Patients were randomly assigned (1:1 ratio) to TAVR or standard therapy, which included balloon aortic valvuloplasty at the discretion of the treating physicians. The PARTNER trial also included a high-risk surgical cohort; results from the high-risk, but operable cohort have also been previously reported.\textsuperscript{4,5} The study was approved by the institutional review board at each study site, and all patients provided written informed consent.

Enrollment in the inoperable cohort of the randomized trial was completed in March 2009. A decision was made to extend the random assignment of inoperable patients in a continued access study to prevent enrollment bias in the ongoing high-risk randomized study, which completed enrollment 6 months later. In addition to the outcomes of patients in the prespecified randomized PARTNER trial, we also report the outcomes of all patients who were randomly assigned to TAVR or standard therapy in PARTNER, including those in the pivotal randomized trial (n=358) and those in the continued access study (n=91). The pooled data from all randomly assigned patients (n=449) have not been included in previous articles of the PARTNER trial.\textsuperscript{5,6}

Procedure

The SAPIEN heart valve system (Edwards Lifesciences, Irvine, CA) was used in this study. It consisted of a balloon-expandable, stainless steel stent frame housing a trileaflet bovine pericardial valve within a deflectable delivery catheter. The procedure was performed under general anesthesia via common femoral artery access. Both transesophageal echocardiography and fluoroscopic guidance were used for deployment of the valve.

Study End Points

The prespecified primary end point of the PARTNER trial was all-cause mortality over the duration of the trial. All clinical end points for the pooled randomized cohort were analyzed at 1-year, 2-year, and 3-year follow-up periods from the completion of randomization in the pivotal trial. End points in the analysis included all-cause mortality, cardiovascular mortality, stroke, vascular complications, major bleeding, and functional status. Serial echocardiographic assessments of aortic valve and left ventricular hemodynamic performance were analyzed in a core echocardiography laboratory.

Statistical Analysis

All analyses of clinical outcomes were performed from the intention-to-treat population, which included all patients who underwent random assignment, regardless of the treatment received. However, echocardiographic analyses were performed according to the treatment received. Categorical variables are presented as proportions, and continuous variables are presented as means with standard deviations (SDs). Categorical variables were compared between the treatment groups by using the Fisher exact test, and continuous variables were compared between the treatment groups by using the Student t test. Kaplan-Meier estimates were used to construct survival curves for time-to-event variables and are presented at exact time points. The Kaplan-Meier estimates between the study groups were compared by using the log-rank test over the length of follow-up. Hazard ratios were calculated by using the Cox regression analysis. All-cause death was additionally analyzed by comparing the rates at the exact 1-, 2-, and 3-year time points after randomization. The last date a patient was alive was derived from the database, with information from office visits, telephone calls, dates on which adverse events were reported, and the actual reported date of death. The close date for this analysis was March 16, 2012, which is 3 years after the last patient was randomly assigned in the pivotal study. Univariate analyses were performed without imputation for missing values. After completion of 1 year of follow-up for all randomly assigned pivotal study patients, standard therapy group patients were permitted to cross over to the TAVR group. Data from a minority of the patients in the standard therapy group, who crossed over to TAVR, were censored at the time of crossover. The randomized continued access study was not powered as an independent study, and therefore separate analyses of that group are not presented. Analysis of the pooled randomly assigned patients was anticipated in the protocol and is presented for completeness. All statistical analyses were performed with the use of SAS software, version 9.3 (SAS Institute). A P value of <0.05 was considered statistically significant.

Results

Patient Characteristics and Enrollment

Patients in the inoperable cohort of the PARTNER trial (cohort B) were enrolled at 21 centers worldwide (17 centers in the United States) between May 11, 2007 and March 16, 2009. A total of 358 inoperable patients with severe AS were randomly assigned to either TAVR or standard medical therapy.

Baseline characteristics of the study groups have been reported previously.\textsuperscript{5,6} There was a higher incidence of atrial fibrillation in the standard therapy group than in the TAVR group (48.4% versus 32.9%; \textit{P}=0.04). Although the proportion of chronic obstructive pulmonary disease was significantly higher in the standard therapy patients (52.5% versus 41.3%; \textit{P}=0.04), the proportion of oxygen-dependent chronic obstructive pulmonary disease was similar in both groups (25.7% versus 21.2%; \textit{P}=0.38). The Society of Thoracic Surgeons (STS) risk estimate for mortality was high in both groups (mean [SD] STS score in TAVR and standard therapy groups: 11.2% [5.8] and 12.1% [6.1], respectively). Several patients had anatomic or clinical comorbidities, other than those included in the STS score, that contributed to the Heart Team’s assessment of inoperable status. These comorbidities included a porcelain aorta (15.1%), chest wall deformity (6.7%), chronic obstructive pulmonary disease requiring supplemental oxygen (23.5%), effects of previous chest wall radiation (8.7%), and frailty (23.1%), as defined according to prespecified criteria.

Mortality

Figure 1A demonstrates the cumulative mortality in the 2 study groups during the 3-year follow-up period. At 3-year
follow-up, mortality rates in the TAVR and standard therapy groups were 54.1% and 80.9%, respectively \((P<0.001)\). The number needed to treat to prevent a death at 1, 2, and 3 years was estimated to be 5.0, 4.0, and 3.7 patients, respectively. Figure 1B demonstrates the differences in the cardiovascular-related mortality between the TAVR and the standard therapy groups. The incidence of cardiovascular-related mortality was 41.4% and 74.5% in the TAVR and standard therapy groups, respectively \((P<0.001)\) after the 3-year follow-up (Table 1).

Landmark analyses demonstrated that the differences in survival remained significant after the first year of follow-up, and after the second year as well (Figure 2). Conditional on survival up to the 1-year follow-up, the 3-year all-cause mortality rate was 33.7% and 61.2% in the TAVR and standard therapy groups, respectively \((P=0.005)\). Conditional on survival up to the 2-year follow-up, the 3-year all-cause mortality rate in the TAVR and the standard therapy groups was 19.3% and 40.3%, respectively \((P=0.03);\) Figure 2).

**Stroke**

In the TAVR cohort, the cumulative incidence of stroke at 3-year follow up was 15.7% (Table 1). The incidence rate of stroke in the TAVR arm was significantly higher than the cumulative incidence rate of 5.5% observed at 3-year follow up in the standard therapy arm (hazard ratio [HR], 2.81; 95% confidence interval [CI], 1.26–6.26; \(P=0.012\)). Despite the higher risk for strokes in the TAVR group, the 3-year incidence of the composite of death or stroke was significantly lower in the TAVR group in comparison with the standard therapy group (57.4% versus 80.9%, \(P<0.001\); HR, 0.60; 95% CI, 0.46–0.77; \(P<0.001\)).

**Major Bleeding and Vascular Complications**

At 3-year follow-up, the cumulative Kaplan-Meier incidence of major bleeding episodes in the TAVR group and the standard

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**Table 1. All Major Clinical Outcomes at 3-Years Follow-Up (Pivotal Study Group, n=358)**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Standard Therapy, %</th>
<th>TAVR, %</th>
<th>(P) Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>80.9</td>
<td>54.0</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>74.5</td>
<td>41.4</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Stroke</td>
<td>5.5</td>
<td>15.7</td>
<td>0.004</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>2.8</td>
<td>17.4</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>32.9</td>
<td>32.0</td>
<td>0.92</td>
</tr>
<tr>
<td>Renal failure</td>
<td>11.1</td>
<td>3.2</td>
<td>0.08</td>
</tr>
<tr>
<td>New pacemaker</td>
<td>8.6</td>
<td>7.6</td>
<td>0.75</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.8</td>
<td>2.3</td>
<td>0.32</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.5</td>
<td>4.1</td>
<td>0.59</td>
</tr>
<tr>
<td>Aortic valvuloplasty</td>
<td>85.3</td>
<td>3.8</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>75.7</td>
<td>43.5</td>
<td>(&lt;0.0001)</td>
</tr>
<tr>
<td>NYHA III (all patients)</td>
<td>4.8</td>
<td>29.7</td>
<td>(&lt;0.0001)</td>
</tr>
</tbody>
</table>

All estimates represent Kaplan–Meier estimates. NYHA indicates New York Heart Association; and TAVR, transcatheter aortic valve replacement.
therapy group was 32.0% and 32.9%, respectively (HR, 1.69; 95% CI, 1.06–2.70; P=0.03). The 3-year cumulative incidence of major vascular complications in the TA VR and the standard therapy groups was 17.4% and 2.8%, respectively (HR, 8.27; 95% CI, 2.92–23.44; P<0.001). There were no vascular complications in the TA VR group after 2 months of follow-up. The risk of developing renal failure during follow-up was less after TA VR than after standard therapy, although it did not reach statistical significance (P=0.08).

**Functional Status**

Repeat hospitalization (Table 1), as a measure of functional stability, favored TAVR-treated patients (43.5% after TAVR versus 75.7% after standard therapy, P<0.001). Figure 3 shows the distribution of all randomly assigned patients according to New York Heart Association (NYHA) functional class on follow-up. At 3-year follow-up, 29.7% patients randomly assigned to the TAVR arm were alive with NYHA class I or II symptoms in comparison with only 4.8% patients randomly assigned to the standard therapy arm (P<0.001). Among survivors, at 3 years, 71.0% of TAVR patients had NYHA class I or II symptoms versus 50.0% of patients undergoing standard therapy.

**Durability and Hemodynamics**

Mean (±SD) aortic valve area at 30-day follow-up was 1.55 (±0.43) cm² among patients undergoing TAVR, which was significantly improved, in comparison with 0.64 (±0.18) cm² before the procedure (P<0.001). The valve area remained stable over the course of follow-up with mean (±SD) aortic valve area measurements of 1.62 (±0.47) cm², 1.56 (±0.47) cm², and 1.52 (±0.48) cm² at 1-year, 2-year, and 3-year follow-up, respectively. Similar to the aortic valve area, there was a sustained reduction in the mean transvalvular gradient across the aortic valve over follow-up. Mean (±SD) transvalvular gradient before TAVR was 44.2 (±14.9) mm Hg, which was significantly higher than the post-TAVR gradient, 10.2 (±4.5) mm Hg at 30-day follow-up. Mean (±SD) transvalvular gradients at 1-year, 2-year, and 3-year follow-up were 10.8 (±5.5) mm Hg, 10.8 (±4.5) mm Hg, and 11.3 (±6.1) mm Hg, respectively.

Table 2 indicates the proportion of paravalvular aortic regurgitation on follow-up echocardiography in patients undergoing
TAVR. In 44 patients with 3-year echocardiographic follow-up, presence of none-trace aortic regurgitation was seen in 63.9% patients, mild aortic regurgitation in 31.8% patients, and moderate-severe aortic regurgitation in 4.5% patients. Among the 44 patients who had echocardiographic data available at 30 days post-TA VR and at 3 years, aortic regurgitation grade was unchanged in 52.3%, decreased in 31.8%, and increased in 15.9%. Although the cumulative mortality estimates demonstrated a modest trend toward a higher mortality in patients with mild or moderate-severe aortic regurgitation, the difference failed to reach statistical significance (Figure 4).

Impact of Comorbidities
Stratification of 3-year mortality according to the STS score (<5%, 5%–14.9%, or ≥15%) revealed a trend toward increasing mortality with higher STS score categories among patients undergoing TAVR (Figure 5A; P log-rank, 0.054). However, there was no significant difference in all-cause mortality between the STS score categories undergoing standard medical therapy (Figure 5B; P=0.72). Comparison of the 2 treatment strategies among the 3 STS score strata are demonstrated in Figure 6. At 3 years, the absolute difference in all-cause mortality between the standard therapy and the TAVR groups was 66.8%, 22.3%, and 20.8% for the STS score strata of <5.0, 5.0 to 14.9, and ≥15.0, respectively.

Pooled Randomly Assigned Patients
Table 1 in the online-only Data Supplement demonstrates the baseline characteristics of the 449 pooled randomly assigned patients (TAVR, 220; standard therapy, 229). There was a higher incidence of coronary artery bypass graft surgery and previous balloon aortic valvuloplasty in the standard therapy group than in the TAVR group. Figure 7 demonstrates the cumulative mortality in the 2 study groups of the pooled randomized cohort during the 3-year follow-up period after completion of the pivotal randomized trial. At 30 days, mortality in the standard therapy group was 2.6% in comparison with 5.9% in the TAVR group (P=0.09). At 1-year follow-up, mortality in the TAVR and standard therapy groups was 31.4% and 45.5%, respectively, and at 2-year and 3-year follow-ups, mortality was 44.8% and 54.9% after TAVR and 64.3% and 78.0% after standard therapy (all P<0.001). Table 3 demonstrates all major clinical outcomes in the TAVR and standard therapy groups in the pooled randomized cohorts. Figure 1 in the online-only Data Supplement demonstrates the distribution of NYHA functional class among all patients randomly assigned to TAVR or standard therapy during the course of follow-up. All-cause mortality and the distribution of the NYHA functional class categories were similar across the PARTNER trial and the pooled randomized cohorts.

Univariate analyses with interaction testing were performed to determine if the reduction in mortality after TAVR was consistent across important subgroups (Figure 8). TA VR reduced mortality at 3 years across all subgroups with only significant interaction of body mass index with the hazard of all-cause mortality (P=0.045). Although the difference in all-cause mortality was not statistically significant in patients with body mass index ≤25 (HR, 0.82; 95% CI, 0.67–1.01), there was a significant reduction in mortality in the group of patients with body mass index >25 (HR, 0.60; 95% CI, 0.48–0.76).

Crossover Patients
Of 220 patients initially randomly assigned to standard therapy, 28 crossed over to TAVR between the first and second year of follow-up, and 9 crossed over between the second and third year of follow-up. Of the 28 patients who crossed over between the first and second year, 13 patients died after a mean duration of 259 (±208) days after crossover. Of the 9 patients who crossed over between the second and third year, 2 patients died after a mean duration of 111 (±11) days after crossover. Mean follow-up duration for patients who were alive at the 3-year time point and crossed over to TAVR between 1 to 2 years and 2 to 3 years was 497 (±163) days and 469 (±178)
days, respectively. The Kaplan-Meier estimates of mortality in crossover patients were 8.1% at 30 days postcrossover and 24.9% at 1 year, event rates that were similar to those reported for patients treated in the pivotal trial.

Discussion
In this article, 3-year follow-up of data of all randomly assigned, inoperable patients with severe symptomatic AS, including those randomly assigned in the pivotal and continued access segments of the PARTNER trial are reported. The results indicate significant mortality benefit with TAVR in comparison with standard therapy, accompanied by improved NYHA functional status and fewer hospitalizations over the 3-year follow-up. Moreover, valve function improvement was durable with minimal signs of deterioration over the follow-up. However, the mortality in the TAVR-treated patients remains high at 3 years (≈50%), suggesting the need for improved selection of patients.

The mortality difference between TAVR and standard therapy continued to increase in 2-year survivors, although the number of surviving patients in the standard therapy arm at this follow-up time is very small, suggesting continuous incremental benefit over the 3-year follow-up interval. It is sobering that the residual mortality in patients undergoing TAVR, conditional on survival to 2 years, was 18% in the third year, with 63% of these deaths being cardiac. In several previous studies, investigators have attempted to identify predictors of poor outcome after TAVR. Noncardiac comorbidities that have been associated with poor outcome include chronic obstructive pulmonary disease, chronic kidney disease, diabetes mellitus, previous stroke, liver disease, and frailty.8–13 Cardiac comorbidities associated with poor outcome include low ejection fraction, pulmonary hypertension, severe mitral regurgitation, and coronary artery disease.9,10,14,15 Postprocedural complications such as aortic regurgitation, stroke, acute kidney injury, and vascular complications have also been associated with worsening long-term outcomes.4,16–18 Attempts to investigate whether surgical risk scores, including Euroscore or STS score, could predict poor long-term outcomes have yielded conflicting results.9,19,20 In our analysis, mortality was higher in patients with multiple comorbidities, as evidenced by higher STS scores. Interestingly, even in patients with high STS scores (between 8 and 15), there was a very significant benefit of TAVR, although there were fewer survivors. With extremely high STS scores (>15%), the benefit was difficult to ascertain because of small numbers, but the high mortality in treated patients questions the utility of TAVR in this population. Interestingly, the mortality curves seem to diverge later with increasing STS score, suggesting that removal of AS from multiple comorbidities might not impact early survival, if the comorbidities are lethal within 1 to 2

Figure 5. Cumulative mortality in the TAVR arm (A) and the standard therapy arm (B) stratified by the STS score. STS indicates Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.
years. Similar survival curves for standard therapy across all STS groups confirms the overarching role of aortic stenosis in mortality even in the presence of multiple comorbidities. Considering all these, it is clear that every attempt should be made to identify those patients who are unlikely to survive, despite successful TAVR. It is noteworthy that patients undergoing standard therapy who crossed over to TAVR after ≥1 year had a survival advantage comparable to the main randomized cohort, suggesting that the

Figure 6. Comparison of cumulative mortality on long-term follow-up between TAVR and standard therapy groups stratified by STS score. NNT, number needed to treat; pts, patients; Rx, therapy; STS, Society of Thoracic Surgeons; and TAVR, transcatheter aortic valve replacement.

Figure 7. Cumulative hazard curves comparing all-cause (A) and cardiovascular-related (B) mortality between all patients randomly assigned to TAVR or standard therapy (pooled randomized cohort). CI indicates confidence interval; HR, hazard ratio; NNT, number needed to treat; pts, patients; Rx, therapy; and TAVR, transcatheter aortic valve replacement.
benefits of TAVR persist, even in the advanced stages of heart failure with AS.

Besides mortality, the functional improvement in TAVR patients was remarkably different than in patients undergoing standard therapy and was sustained over the course of 3-year follow-up. Importantly, patients spent considerably more days outside the hospital when treated with TAVR with fewer repeat hospitalization events.

When assessing the potential long-term hazards of TAVR, stroke is certainly an important concern. Between 2 and 3 years, there were 2 patients (ages 90 and 91) with stroke, one with atrial fibrillation and another with known cerebrovascular disease and prior stroke. This observation highlights the fact that the inoperable PARTNER population, unlike most other studies, involved elderly patients with multiple comorbidities, many of which are stroke risk factors. Therefore, the cause-and-effect relationship of TAVR and late strokes was difficult to determine in a stroke-prone population with small numbers of patients at risk and few late events.

The durability of the transcatheter valve has been a special concern and requires systematic echocardiography follow-up at late time points. There was no echocardiographic or clinical evidence of structural valve deterioration with maintained valve areas and gradients at 3-year follow-up. Similarly, although the frequency and severity of paravalvular regurgitation remains a concern for TAVR, there were no late changes, suggesting no concern and requires systematic echocardiography follow-up.

The present report includes the small cohort of 91 patients who were randomly assigned after the completion of enrollment of the pivotal trial and during the continued access phase of the study. The Executive Committee of the study decided to continue randomization after reaching the agreed sample size in deference to the ongoing parallel randomized trial in high-risk patients being conducted with the same device at the same investigator sites. Unless randomization was continued (until completion of the high-risk study), there were concerns that open access to TAVR in an unrestricted registry would distort risk profile designations. All study processes, including inclusion and exclusion criteria, study end points, and follow-up, were identical in the small continued access randomization population. Although it would be inappropriate to analyze this small group of randomly assigned patients as a study cohort, there was a prespecified pooled analysis, incorporating these patients into the larger pivotal randomized study cohorts. Results of the pooled cohort were comparable to the results of the randomly assigned patients, including all major clinical end points.

The present report from the PARTNER group is unique in several respects. At the end of 3 years of follow-up, only 17 patients were alive in the standard therapy group, and this potentially will be the last report on comparison of high-risk inoperable patients randomly assigned to TAVR or standard medical therapy. It is probably one of the most robust randomized trials that has attempted to establish the efficacy of TAVR over medical therapy. Currently, it is the only randomized trial that has included an arm with medical management. Furthermore, it is the first time that we have reported the outcomes on all randomly assigned patients, including those who were randomly assigned after the completion of the pivotal trial.

Despite these strengths, we do acknowledge that there were relatively fewer patients remaining in the standard therapy group beyond 2 years of follow-up, which makes the analysis of secondary end points like stroke and bleeding a little challenging. Furthermore, a large proportion of patients in the standard therapy arm (85.3%) underwent balloon aortic valvuloplasty, which is currently considered as an acceptable palliative modality for the management of symptomatic severe AS. Different regions across the world might differ in terms of the availability of balloon aortic valvuloplasty for these patients, and, hence, the outcomes in the standard therapy arm might be different across different centers.

In summary, TAVR in comparison with standard therapy results in better survival and functional status for patients with severe AS who were inoperable, and the survival benefits increased during continued follow-up through 3 years. However, high residual mortality, even in the successfully
treated TAVR patients, highlights the need for better case selection, especially in those patients with multiple comorbidities.

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References


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CLINICAL PERSPECTIVE

This article reports 3-year clinical and echocardiographic outcomes of inoperable patients with severe symptomatic aortic stenosis from the only randomized trial of transcatheter aortic valve replacement (TAVR) versus standard therapy (the Placement of Aortic Transcatheter Valves [PARTNER] trial). The results clearly demonstrate significant mortality reduction, reduced hospitalizations, and symptom benefit of TAVR over long-term follow-up. Further, the balloon-expandable bioprosthetic valve was durable over this follow-up period without any indication of structural valve deterioration. However, there was substantial progressive mortality in these elderly patients with aortic stenosis who were undergoing TAVR, mostly owing to comorbidities. Subgroup analyses demonstrate that the benefit of TAVR was highest in patients with anatomic reasons for inoperability with low Society of Thoracic Surgeons scores (eg, radiation heart disease) and that the mortality benefit was muted in the subgroup of patients with many comorbidities characterized by the highest Society of Thoracic Surgeons scores. The results of this study can inform symptomatic patients with severe aortic stenosis who are deemed inoperable (or an extreme surgical risk) that treatment with this first-generation TAVR procedure will prolong life, improve functional status, and prevent hospitalizations from heart failure and that the valve is durable over at least 3 years follow-up. One of the current clinical challenges is to better identify patients with severe comorbidities in whom TAVR may be considered futile (ie, with no or limited clinical utility).
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**Supplementary Table 1: Baseline Characteristics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Standard Therapy n = 229</th>
<th>TAVR n = 220</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – yr (SD)</td>
<td>83.2 (8.5)</td>
<td>83.0 (8.5)</td>
<td>0.8</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>111 (48.5)</td>
<td>105 (47.7)</td>
<td>0.9</td>
</tr>
<tr>
<td>STS Score (SD)</td>
<td>12.2 (5.4)</td>
<td>11.4 (6.0)</td>
<td>0.1</td>
</tr>
<tr>
<td>NYHA III or IV (%)</td>
<td>216 (94.3)</td>
<td>204 (92.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>CAD (%)</td>
<td>169 (73.8)</td>
<td>145 (65.9)</td>
<td>0.08</td>
</tr>
<tr>
<td>Prior MI (%)</td>
<td>65 (28.4)</td>
<td>49 (22.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>Prior CABG (%)</td>
<td>98 (42.8)</td>
<td>70 (31.8)</td>
<td>0.02</td>
</tr>
<tr>
<td>Prior PCI (%)</td>
<td>52 (22.7)</td>
<td>57 (25.9)</td>
<td>0.4</td>
</tr>
<tr>
<td>Prior BAV (%)</td>
<td>49 (21.4)</td>
<td>30 (13.6)</td>
<td>0.04</td>
</tr>
<tr>
<td>CVD (%)</td>
<td>59 (25.8)</td>
<td>59 (26.8)</td>
<td>0.6</td>
</tr>
<tr>
<td>PVD (%)</td>
<td>57 (24.9)</td>
<td>66 (30.0)</td>
<td>0.2</td>
</tr>
<tr>
<td>COPD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any (%)</td>
<td>167 (72.9)</td>
<td>141 (64.3)</td>
<td>0.1</td>
</tr>
<tr>
<td>O₂ dependent (%)</td>
<td>55 (24.0)</td>
<td>50 (22.7)</td>
<td>0.8</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/dL (%)</td>
<td>20 (8.8)</td>
<td>12 (5.5)</td>
<td>0.2</td>
</tr>
<tr>
<td>Atrial fibrillation (%)</td>
<td>60 (26.2)</td>
<td>46 (20.8)</td>
<td>0.2</td>
</tr>
<tr>
<td>Permanent pacemaker (%)</td>
<td>45 (19.7)</td>
<td>45 (20.5)</td>
<td>0.9</td>
</tr>
<tr>
<td>Pulmonary HTN (%)</td>
<td>116 (50.7)</td>
<td>105 (47.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Frailty (%)</td>
<td>59 (25.6)</td>
<td>39 (17.8)</td>
<td>0.1</td>
</tr>
<tr>
<td>Porcelain aorta (%)</td>
<td>27 (11.8)</td>
<td>41 (18.6)</td>
<td>0.049</td>
</tr>
<tr>
<td>Chest wall radiation (%)</td>
<td>18 (7.9)</td>
<td>17 (7.7)</td>
<td>1.0</td>
</tr>
<tr>
<td>Chest wall deformity (%)</td>
<td>14 (6.1)</td>
<td>17 (7.7)</td>
<td>0.6</td>
</tr>
<tr>
<td>Liver disease (%)</td>
<td>8 (3.5)</td>
<td>11 (5.0)</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Supplementary figure 1: Comparison of NYHA functional class between the TAVR group and standard therapy in the pooled randomized cohort.
경피적 대동맥판 치환술은 수술이 불가능한 심한 대동맥판 협착증 환자의 장기 생존을 개선한다
강덕현 교수 서울아산병원 심장내과

Summary

배경
수술이 불가능한 심한 대동맥판 협착증(aortic stenosis, AS) 환자에서 경피적 대동맥판 치환술(transcatheter aortic valve replacement, TAVR)의 장기 성적은 알려져 있지 않다.

방법 및 결과
PARTNER(Placement of Aortic Transcatheter Valves) 연구에서 수술이 불가능한 심한 AS 환자 358명이 TAVR 또는 표준 치료에 무작위 배정되었다. TAVR군과 표준 치료군에서 3년 사망률은 각각 54.1%와 80.9%이었다(\(P\lt 0.001\); HR, 0.53; 95% CI, 0.41-0.68; \(P\lt 0.001\)). 생존자들에서 New York Heart Association functional class의 유의한 호전은 3년째에도 지속되었다. 3년 추적 시 뇌졸중의 누적 발생률은 TAVR군에서 15.7%였고, 표준 치료군에서는 5.5%였다(HR, 2.81; 95% CI, 1.26-6.26; \(P=0.012\)). 그러나 사망과 뇌졸중의 총합 반도는 TAVR군에서 표준 치료군에 비해 유의하게 낮았다(57.4% vs. 80.9%, \(P\lt 0.001\); HR, 0.60; 95% CI, 0.46-0.77; \(P\lt 0.001\)). 심초음파 검사에서 TAVR 후 대동맥판 면적의 증가와 판막 전후 압력 차의 감소는 지속되었다. PARTNER 연구는 수술이 불가능한 환자들에서 TAVR과 표준 치료를 비교하는 연구(PARTNER B) 및 수술 고위험 환자들에서 TAVR과 수술적 AVR을 비교하는 연구(PARTNER A)로 구성되어 있는데, 수술이 불가능한 환자 358명의 등록이 2009년 3월에 종료되었지만 수술 고위험 환자들의 등록이 종료되는 2009년 8월까지 수술이 불가능한 91명의 환자가 추가적으로 TAVR 또는 표준 치료군에 무작위 배정되었다. 무작위 배정된 449명의 환자(TAVR, 220명; 표준 치료, 229명)를 모두 합하여 분석한 결과, TAVR를 시행 받은 환자들에서 조기 및 3년 추적시 전체 사망률과 기능적 상태가 유의하게 호전되었다. 전체 449명의 코호트 결과들도 주축인 PARTNER 연구에서 얻어진 결과들과 유사하였다.

결론
장기간 추적 관찰 결과, 수술이 불가능한 심한 AS 환자들에서 TAVR은 오래 지속되는 혈류역학적 이상과 함께 보다 양호한 생존과 기능적 상태의 결과를 보였다. 하지만 성공적으로 치료된 TAVR 환자들에서 조기 관찰되는 높은 전기 사망률은 보다 전략적 환자 선정의 필요성을 강조한다.