Outcomes in the Randomized CoreValve US Pivotal High Risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of 7% or Less

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**IMPORTANCE** Transcatheter aortic valve replacement (TAVR) is now a well-accepted alternative to surgical AVR (SAVR) for patients with symptomatic aortic stenosis at increased operative risk. There is interest in whether TAVR would benefit patients at lower risk.

**OBJECTIVE** The Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) has trended downward in US TAVR trials and the STS/American College of Cardiology Transcatheter Valve Therapy Registry. We hypothesized that if the Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM) alone is sufficient to define decreased risk, the contribution to survival based on the degree of invasiveness of the TAVR procedure will decrease, making it more difficult to show improved survival and benefit over SAVR.

**DESIGN, SETTING, AND PARTICIPANTS** The CoreValve US Pivotal High Risk Trial was a multicenter, randomized, noninferiority trial. This retrospective analysis evaluated patients who underwent an attempted implant and had an STS PROM of 7% or less. The trial was performed at 45 US sites. Patients had severe aortic stenosis and were at increased surgical risk based on their STS PROM score and other risk factors.

**INTERVENTIONS** Eligible patients were randomly assigned (1:1) to self-expanding TAVR or to SAVR.

**MAIN OUTCOMES AND MEASURES** We retrospectively stratified patients by the overall median STS PROM score (7%) and analyzed clinical outcomes and quality of life using the Kansas City Cardiomyopathy Questionnaire in patients with an STS PROM score of 7% or less.

**RESULTS** The mean (SD) ages were 81.5 (7.6) years for the TAVR group and 81.2 years (6.6) for the SAVR group. A little more than half were men (57.9% in the TAVR group and 55.8% in the SAVR group). Of 750 patients who underwent attempted implantation, 383 (202 TAVR and 181 SAVR) had an STS PROM of 7% or less (median [interquartile range]: TAVR, 5.3% [4.3%-6.1%]; SAVR, 5.3% [4.1%-5.9%]). Two-year all-cause mortality for TAVR vs SAVR was 15.0% (95% CI, 8.9-10.0) vs 26.3% (95% CI, 19.7-33.0) (log rank \( P = .01 \)). The 2-year rate of stroke for TAVR vs SAVR was 11.3% vs 15.1% (log rank \( P = .50 \)). Quality of life by the Kansas City Cardiomyopathy Questionnaire summary score showed significant and equivalent increases in both groups at 2 years (mean [SD] TAVR, 20.0 [25.0]; SAVR, 18.6 [23.6]; \( P = .71 \); both \( P < .001 \) compared with baseline). Medical benefit, defined as alive with a Kansas City Cardiomyopathy Questionnaire summary score of at least 60 and a less than 10-point decrease from baseline, was similar between groups at 2 years (TAVR, 51.0%; SAVR, 44.4%; \( P = .28 \)).

**CONCLUSIONS AND RELEVANCE** Self-expanding TAVR compares favorably with SAVR in high-risk patients with STS PROM scores traditionally considered intermediate risk.

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Transcatheter aortic valve replacement (TAVR) with balloon-expandable and self-expanding valves is now an accepted alternative to surgical aortic valve replacement (SAVR) in the treatment of symptomatic severe aortic stenosis in patients at increased risk for surgery.1,2 The Society of Thoracic Surgeons Predicted Risk of Mortality (STS PROM), used alone or in part to select patients for TAVR, has decreased over time since the first randomized trial of balloon-expandable TAVR with a study mean of 11.6%,3 to the 2016 study in intermediate-risk patients with a mean of 5.8%.4 Transcatheter aortic valve replacement using a self-expanding valve (CoreValve bioprosthesis; Medtronic) has shown superior survival compared with SAVR at 1 year5 and 2 years5 in patients with a mean STS PROM score of 7.4%.

The STS/American College of Cardiology Transcatheter Valve Therapy Registry provides medical device surveillance of commercial TAVs in the United States. The initial report of 1-year outcomes described patients with a median STS PROM score of 7.1%,7 indicating a reduction in STS PROM from randomized trials to US commercial use. Concerns around a creep to lower risk based primarily on the STS PROM score have been raised. We hypothesized that as patient risk decreases, the contribution to survival conferred by the less invasive nature of the TAVR procedure would also decrease because patients at lower risk generally tolerate invasive procedures better than those at higher risk. To test this hypothesis, we evaluated patients in the randomized CoreValve US Pivotal High Risk Trial with an STS PROM score of 7% or less.

Methods

Study Design
The CoreValve US Pivotal High Risk Trial was a multicenter, randomized (1:1), noninferiority trial performed at 45 sites in the United States. The trial design and outcomes through 3 years have been previously reported.2,5,6 Each institutional review board approved the study protocol, and all patients provided written informed consent. The formal trial protocols can be found in Supplement 1.

Patient Selection
Patient selection and detailed inclusion and exclusion criteria have been described.5 A patient’s surgical risk was based on the STS PROM score and other factors (eTable 1 in Supplement 2). Increased risk was defined as an expected 30-day risk of mortality of at least 15% but less than 50%. Each site calculated the STS PROM using the STS calculator and submitted the form to the screening committee. The sponsor ensured the accuracy of the documentation.

Study End Points
The primary end points for this report were all-cause mortality and quality of life based on the Kansas City Cardiomyopathy Questionnaire overall summary score through 2 years. A good medical benefit was defined as having a Kansas City Cardiomyopathy Questionnaire summary score of at least 60 and with less than a 10-point decrease from baseline, and an acceptable outcome was alive without meeting these criteria.8

Statistical Analysis
Categorical variables were compared using the Fisher exact test or the χ² test. Continuous variables are presented as mean (SD) and compared with the use of the t test. Kaplan-Meier estimates were used to construct survival curves based on all available follow-up data for the time-to-event analysis. Differences in event rates between groups were evaluated using the log-rank test. Death rates for the quality of life analysis were calculated as straight rates for patients with available Kansas City Cardiomyopathy Questionnaire data. All testing used a 2-sided α level of .05. Statistical analyses were performed with the use of SAS software, version 9.2 (SAS Institute).

Results
Of the 750 patients (391 TAVR; 359 SAVR) in the trial, 383 (202 TAVR; 181 SAVR) had an STS PROM score of 7% or less (eFigure 1 in Supplement 2). The median STS PROM score for each group was 5.3%. The only significant baseline differences between groups were that more patients with SAVR had diabetes mellitus and more patients with SAVR had New York Heart Association class III or IV symptoms. Although more patients with TAVR had a hostile mediastinum at baseline, there were no differences in the other indicators of risk not included in the STS PROM (eTable 2 in Supplement 2). Patients were followed up at least 2 years.

All-Cause Mortality, Cardiovascular Mortality, and Quality of Life
Figure 1 shows all-cause mortality and cardiovascular mortality at 2 years. The Kansas City Cardiomyopathy Questionnaire summary score increased significantly from baseline in both the TAVR and SAVR groups but did not differ between the groups at 2 years (mean [SD] TAVR, 70.3 [23.4] vs SAVR, 69.7 [23.1]; P = .85) (eFigure 2 in Supplement 2).

Good medical benefit was similar for both groups (TAVR 51.0% vs SAVR 44.4%, P = .28), as shown in Figure 2.
Echocardiographic Findings

Forward flow hemodynamics were superior for TAVR vs SAVR at each follow-up postimplant. At 2 years, the mean (SD) effective orifice areas were 1.83 (0.47) vs 1.52 (0.46), \( P < .001 \), and the mean (SD) aortic valve gradients were 8.55 (3.52) vs 12.54 (6.82), \( P < .001 \), with similar results at each follow-up (eFigure 3 in Supplement 2). The rates of severe patient-prosthesis mismatch at 2 years also favored TAVR (8.1% vs 25.6%; \( P < .001 \)), with similar results at each follow-up (eTable 3 in Supplement 2).

Complications at 2 Years

Major vascular complications and a new pacemaker were more common in patients with TAVR. Life-threatening or disabling bleeding, new atrial fibrillation, and acute kidney injury were all more common in patients with SAVR (Table).

Discussion

Concern has been raised that risk creep is occurring owing to lower STS PROM scores seen over time in the US trials and the Transcatheter Valve Therapy Registry and that this may change the potential benefit of TAVR in this population. In this subanalysis of the randomized CoreValve US Pivotal High Risk Trial, we observed superior survival, equivalent stroke rates, equivalent improvement in quality of life and similar medical benefit for TAVR vs SAVR at 2 years in high-risk patients with STS PROM scores of 7% or less.

Survival is also affected by procedural complications. Transcatheter aortic valve replacement was associated with more major vascular complications and paravalvular leak.
Table. Additional Clinical Outcomes at 2 Years for High-Risk Patients Treated With TAVR or SAVR Who Had an STS PROM Score of 7% or Less*

<table>
<thead>
<tr>
<th>Event</th>
<th>TAVR (n = 202)</th>
<th>SAVR (n = 181)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major stroke</td>
<td>12 (6.1)</td>
<td>15 (10.1)</td>
<td>.31</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>16 (8.2)</td>
<td>4 (2.2)</td>
<td>.01</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeding</td>
<td>44 (20.2)</td>
<td>67 (34.9)</td>
<td>.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>10 (5.0)</td>
<td>28 (15.6)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>New atrial fibrillation/flutter</td>
<td>47 (23.3)</td>
<td>63 (34.8)</td>
<td>.01</td>
</tr>
<tr>
<td>New permanent pacemaker implant</td>
<td>56 (27.7)</td>
<td>18 (10.5)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

* All data except new atrial fibrillation/flutter are Kaplan-Meier estimates presented as incidents (number of events), and P values are calculated based on the log-rank test.

Conclusions

This analysis of high-risk patients with an STS PROM of 7% or less from a randomized trial of a self-expanding TAV shows superior survival, superior echocardiographic flow parameters, significantly less severe patient-prosthesis mismatch, and similar medical benefit for TAVR compared with SAVR at 2 years.
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**Role of the Funder/Sponsor:** The study sponsor was responsible for study design, selection of the clinical sites, monitoring of the data, management of the case report forms, and statistical analyses but had no role in the preparation, review, or approval of the manuscript and decision to submit the manuscript for publication.

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**Additional Contributions:** Jane Moore, MS, ELS, drafted the study methods, created all tables and figures, and provided technical review of the manuscript. Julie A. Linick, ELS, provided copy editing assistance. We also thank Joleen Perkins, BS, and Eric Vang, PhD, for overall trial management. All are employees of Medtronic. All persons listed in this section are employees of the study sponsor and made the contributions acknowledged here as part of their usual responsibilities of employment.

**REFERENCES**


