SAPIEN 3: Evaluation of a Balloon-Expandable Transcatheter Aortic Valve in High-Risk and Inoperable Patients With Aortic Stenosis – One-Year Outcomes

Howard C. Herrmann, MD
on behalf of The PARTNER II Trial Investigators
Disclosure Statement of Financial Interest

Howard C. Herrmann, MD

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Affiliation/Financial Relationship

• Grant/Research Support
• SAB (Equity)
• Honoraria

Company

• Abbott Vascular, Boston Sci, Cardiokinetx, Edwards Lifesciences, Gore, Medtronic, Mitraspan, Siemens, St. Jude Medical
• MicroInterventional Devices
• Edwards Lifesciences
Background

- The initial PARTNER Trial for high-risk (HR) and inoperable (INOP) patients demonstrated the early promise of TAVR with first generation devices.

- At 1 year, mortality was 24% in HR (equivalent to SAVR) and 31% in INOP patients.

- 30-Day outcomes with the SAPIEN 3 (S3) TAVR system were presented at ACC 2015 demonstrating very low rates of adverse events.

- This presentation reports the study results in HR and INOP patients at 1 year.
The PARTNER II S3 Trial
Study Design

ASSESSMENT by Heart Valve Team

Intermediate Risk Operable
(PII S3i)

ASSESSMENT: Optimal Valve Delivery Access

Transfemoral (TF)
TF TAVR SAPIEN 3

Transapical / Transaortic (TA/TAo)
TAA TAVR SAPIEN 3

High-Risk Operable / Inoperable
(PII S3HR)

ASSESSMENT: Optimal Valve Delivery Access

Transfemoral (TF)
TF TAVR SAPIEN 3

Transapical / Transaortic (TA/TAo)
TAA TAVR SAPIEN 3

n = 1076 Patients
n = 583 Patients

2 Single Arm Non-Randomized Historical-Controlled Studies

The PARTNER II S3 Trial Study Design

1 Year
SAPIEN 3 Transcatheter Heart Valve
Distinguishing Features

- Bovine pericardial tissue
- Outer sealing skirt to reduce PVL
- Low frame height
- Enhanced frame geometry for low delivery profile
Key Inclusion Criteria

• Risk determined by STS score and Heart Team:
  – **High-Risk:** STS score > 8 or Heart Team determination
  – **Inoperable:** Risk of death or serious morbidity > 50% (assessed by a cardiologist and 2 cardiac surgeons)

• Severe aortic stenosis determined by echocardiography:
  – Valve area < 0.8 cm² or valve area index < 0.5 cm²/m² and mean gradient > 40mmHg or peak velocity > 4 m/s
The PARTNER II S3 Trial
Participating Sites

583 Patients Enrolled at 29 US Participating Sites

Co-Principal Investigators
Susheel Kodali
Columbia University, NY
Vinod Thourani
Emory University, GA

Univ. of Washington
Seattle, WA
Providence St. Vincent Medical Ctr.
Portland, OR
Cedars-Sinai Medical Ctr.
Los Angeles, CA
Mercy General Hospital
Sacramento, CA
Stanford University Medical Ctr.
Stanford, CA
Intermountain Medical Ctr.
Murray, UT

Northwestern Univ.
Chicago, IL
Prairie Heart Research Institute
Springfield, IL
Barnes-Jewish Hospital
Saint Louis, MO
Oklahoma Heart
Oklahoma City, OK
Medical City Dallas
Dallas, TX
Heart Hospital Baylor Plano
Plano, TX
Austin Heart
Austin, TX

Mayo Clinic
Rochester, MN
Northwestern Univ.
Chicago, IL
Prairie Heart Research Institute
Springfield, IL
Barnes-Jewish Hospital
Saint Louis, MO
Oklahoma Heart
Oklahoma City, OK
Medical City Dallas
Dallas, TX
Heart Hospital Baylor Plano
Plano, TX

William Beaumont Hospital
Royal Oak, MI
Cleveland Clinic
Cleveland, OH
Univ. of Virginia
Charlottesville, VA
Washington Hospital Center
Washington, DC
Emory University
Atlanta, GA

Univ. of Pennsylvania
Philadelphia, PA
Morton Plant Hospital
Clearwater, FL
Winthrop-University Hospital
Mineola, NY
Columbia University & Cornell Medical Ctr.
New York, NY
Newark Beth Israel Medical Ctr.
Newark, NJ
Brigham and Women's
Boston, MA
### The PARTNER II S3 HR / INOP

**Top 10 Enrollment Sites**

<table>
<thead>
<tr>
<th>Medical Center</th>
<th>Location</th>
<th>Enrollment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cedars-Sinai Medical Ctr.  (Los Angeles, CA)</td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Columbia University Medical Ctr.  (New York, NY)</td>
<td></td>
<td>65</td>
</tr>
<tr>
<td>Emory University  (Atlanta, GA)</td>
<td></td>
<td>63</td>
</tr>
<tr>
<td>University of Pennsylvania  (Philadelphia, PA)</td>
<td></td>
<td>43</td>
</tr>
<tr>
<td>Heart Hospital Baylor Plano  (Plano, TX)</td>
<td></td>
<td>30</td>
</tr>
<tr>
<td>Ochsner Hospital  (New Orleans, LA)</td>
<td></td>
<td>26</td>
</tr>
<tr>
<td>University of Texas, Houston  (Houston, TX)</td>
<td></td>
<td>25</td>
</tr>
<tr>
<td>Stanford University Medical Ctr.  (Palo Alto, CA)</td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Newark Beth Israel Medical Ctr.  (Newark, NJ)</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Washington Hospital Ctr.  (Washington, DC)</td>
<td></td>
<td>19</td>
</tr>
</tbody>
</table>
Study Flow
30 Day and 1 Year Patient Status

PII S3 HR / INOP

\[ n = 583 \]

15 Deaths

\[ n = 568 \]

At 30 Days

71 Additional Deaths
5 Withdrew Consent

\[ 485 / 492 \text{ or } 98.6\% \]

Follow-up at 1 year
Baseline & Procedural Characteristics

Median STS = 8.4%

Average Age = 82yrs

N = 583

TF, 84%

TA, 10%

TAo, 6%

Male 58%

Female 42%

20 mm 1.9%

23 mm 34.3%

26 mm 38.9%

29 mm 24.9%
# Baseline Patient Characteristics

## Demographics

<table>
<thead>
<tr>
<th>Characteristic (%)</th>
<th>Overall (n=583)</th>
<th>HR (n=384, 66%)</th>
<th>INOP (n=199, 34%)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>82</td>
<td>83</td>
<td>80</td>
<td>0.001</td>
</tr>
<tr>
<td>Female gender</td>
<td>42</td>
<td>40</td>
<td>46</td>
<td>0.14</td>
</tr>
<tr>
<td>STS Score (median)</td>
<td>8.4</td>
<td>8.6</td>
<td>7.4</td>
<td>0.002</td>
</tr>
<tr>
<td>NYHA Class 3/4</td>
<td>90</td>
<td>90</td>
<td>91</td>
<td>0.82</td>
</tr>
<tr>
<td>DM</td>
<td>35</td>
<td>33</td>
<td>37</td>
<td>0.42</td>
</tr>
<tr>
<td>COPD - O₂ Dependent</td>
<td>27</td>
<td>17</td>
<td>42</td>
<td>0.0001</td>
</tr>
<tr>
<td>CKD - Creat. ≥ 2mg/dL</td>
<td>12</td>
<td>12</td>
<td>12</td>
<td>0.81</td>
</tr>
<tr>
<td>Hostile Chest</td>
<td>10</td>
<td>3</td>
<td>24</td>
<td>0.0001</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>44</td>
<td>42</td>
<td>48</td>
<td>0.16</td>
</tr>
<tr>
<td>Permanent Pacemaker</td>
<td>16</td>
<td>17</td>
<td>15</td>
<td>0.42</td>
</tr>
<tr>
<td>Frailty</td>
<td>31</td>
<td>26</td>
<td>41</td>
<td>0.0002</td>
</tr>
</tbody>
</table>
Survival (All-Cause)
S3 HR / INOP by Cohort at 1 Year

Survival (%)

$p$ (log rank) = 0.14

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>Overall</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>583</td>
<td>556</td>
</tr>
<tr>
<td></td>
<td>526</td>
<td>504</td>
</tr>
<tr>
<td></td>
<td>352</td>
<td></td>
</tr>
<tr>
<td>HR</td>
<td>384</td>
<td>367</td>
</tr>
<tr>
<td></td>
<td>353</td>
<td>335</td>
</tr>
<tr>
<td></td>
<td>232</td>
<td></td>
</tr>
<tr>
<td>INOP</td>
<td>199</td>
<td>189</td>
</tr>
<tr>
<td></td>
<td>173</td>
<td>169</td>
</tr>
<tr>
<td></td>
<td>120</td>
<td></td>
</tr>
</tbody>
</table>

87.3% HR
85.6% Overall
82.3% INOP
Survival (All-Cause)
S3 HR / INOP by Access at 1 Year

p (log rank) = 0.0006

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>583</td>
</tr>
<tr>
<td>TF</td>
<td>491</td>
</tr>
<tr>
<td>TA / TAo</td>
<td>92</td>
</tr>
</tbody>
</table>

Survival (%)

- 87.7% TF
- 85.6% Overall
- 74.7% TA / TAo
Survival (All-Cause)
S3 HR / INOP Transfemoral Access at 1 Year

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TF HR</td>
<td>324</td>
<td>312</td>
</tr>
<tr>
<td></td>
<td>300</td>
<td>287</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td></td>
</tr>
<tr>
<td>TF INOP</td>
<td>167</td>
<td>163</td>
</tr>
<tr>
<td></td>
<td>149</td>
<td>146</td>
</tr>
<tr>
<td></td>
<td>101</td>
<td></td>
</tr>
</tbody>
</table>
Disabling Strokes
Modified Rankin Score ≥ 2, CEC Adjudicated

There was no difference between TF and TA / TAo.
There was no difference between HR and INOP.

Numbers at Risk

<table>
<thead>
<tr>
<th>Months</th>
<th>Overall</th>
<th>583</th>
<th>551</th>
<th>519</th>
<th>500</th>
<th>346</th>
</tr>
</thead>
</table>

There was no difference between TF and TA / TAo.
There was no difference between HR and INOP.
# Other Clinical Outcomes

**S3 HR / INOP – 30 Days and 1 Year**

<table>
<thead>
<tr>
<th>Clinical Outcomes (%)</th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>2.2</td>
<td>14.4</td>
</tr>
<tr>
<td>Cardiac Mortality</td>
<td>1.4</td>
<td>8.1</td>
</tr>
<tr>
<td>All Stroke</td>
<td>1.4</td>
<td>4.3</td>
</tr>
<tr>
<td>Disabling Stroke</td>
<td>0.9</td>
<td>2.4</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>8.0</td>
<td>17.1</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>13.3</td>
<td>16.9</td>
</tr>
<tr>
<td>Surgical AVR</td>
<td>0.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Structural Valve Deterioration</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Valve Thrombosis</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
NYHA Class
Survivor Analysis

- Baseline: 583 patients
  - Class 4: 30.2%
  - Class 3: 59.9%
  - Class 2: 10.0%

- 30 Days: 550 patients
  - Class 4: 42.0%
  - Class 3: 44.7%
  - Class 2: 11.3%

- 1 Year: 440 patients
  - Class 4: 34.1%
  - Class 3: 58.2%
  - Class 2: 0.9%

- Survival Analysis:
  - p < 0.0001
  - p = NS

- # of Patients
  - Baseline: 583
  - 30 Days: 550
  - 1 Year: 440

Note: p < 0.0001 indicates a statistically significant difference, while p = NS suggests no statistically significant difference.
Mean Gradient & Aortic Valve Area

- **Mean Gradient**
  - Baseline: 45.5 mmHg
  - 30 Days: 0.67 mmHg
  - 1 Year: 1.67 mmHg

- **Aortic Valve Area**
  - Baseline: 11.1 cm²
  - 30 Days: 11.3 cm²
  - 1 Year: 11.3 cm²

# of Patients
- Baseline: 568
- 30 Days: 532
- 1 Year: 379
Paravalvular Regurgitation

Paired Analysis

30 Days

- Severe: 2.5%
- Moderate: 33.2%
- Mild: 64.3%
- None / Trace: 100%

1 Year

- Severe: 2.7%
- Moderate: 29.1%
- Mild: 68.1%
- None / Trace: 100%

# of Patients

- 30 Days: 364
- 1 Year: 364

p = 0.99
1 Year KM Survival by 30-Day PVL

No statistical difference between None/Trace and Mild.

Overall: Log-Rank p-value = 0.0058
M / S vs N / T: Log-Rank p-value = 0.0015
M / S vs Mild: Log-Rank p-value = 0.0058

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>None / Trace</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>191</td>
</tr>
<tr>
<td>Mod / Severe</td>
<td>16</td>
</tr>
</tbody>
</table>
All-Cause Mortality at 1 Year
Edwards SAPIEN Valves (As Treated Patients)

**PARTNER I and II Trials**

**TF Patients**

<table>
<thead>
<tr>
<th>Valve</th>
<th>High-Risk</th>
<th>Inoperable</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>30.7%</td>
<td>30.7%</td>
</tr>
<tr>
<td>P1A (TF)</td>
<td>21.4%</td>
<td>21.4%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>23.7%</td>
<td>23.7%</td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>22.5%</td>
<td>22.5%</td>
</tr>
<tr>
<td>S3 Inop (TF)</td>
<td>15.7%</td>
<td>15.7%</td>
</tr>
<tr>
<td>S3HR (TF)</td>
<td>10.7%</td>
<td>10.7%</td>
</tr>
<tr>
<td>S3 CE HR (TF)</td>
<td>8.4%</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

**PARTNER I and II Trials**

<table>
<thead>
<tr>
<th>Valve</th>
<th>Count</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN</td>
<td>175</td>
</tr>
<tr>
<td>SAPIEN SXT</td>
<td>240</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>271</td>
</tr>
<tr>
<td>SAPIEN X</td>
<td>282</td>
</tr>
<tr>
<td>S3 Inop</td>
<td>101</td>
</tr>
<tr>
<td>S3HR</td>
<td>324</td>
</tr>
<tr>
<td>S3 CE HR</td>
<td>96</td>
</tr>
</tbody>
</table>
Conclusions

- In high-risk and inoperable patients, the low rate of 30-day complications with the SAPIEN 3 TAVR system resulted in improved 1-year survival.
  - **Overall Survival:** 85.6%
  - **High-Risk Survival:** 87.3%
  - **High-Risk TF Survival:** 89.3%

- Between 30 days and 1 year, the rates of both disabling stroke and significant paravalvular AR remained low and stable, with no significant differences between TF and alternative access.

- There was no association observed between the occurrence of Mild PVL and mortality at 1 year.

- Hemodynamic valve performance and early symptomatic improvement were sustained at 1 year.
Implications

- The combination of new *design features* of SAPIEN 3, *procedural improvements, operator experience and improved patient selection* have all contributed to a low rate of important adverse events (including stroke) and a high rate of 1-year survival in high-risk and inoperable patients with severe AS.

- These excellent 1 year follow-up data with SAPIEN 3 support the use of *TAVR as the preferred therapy* in high-risk and inoperable patients with aortic stenosis.

- The 1 year outcomes of the Intermediate Risk cohort will be available at ACC 2016.