Clinical and Echocardiographic Outcomes at 30 Days with the SAPIEN 3 TAVR System in Inoperable, High-Risk and Intermediate-Risk AS Patients

Susheel Kodali, MD
on behalf of The PARTNER Trial Investigators
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
- Steering Committee
- SAB (Equity)
- Honoraria

**Company**
- Edwards Lifesciences, Medtronic, Boston Scientific, Claret Medical
- Edwards Lifesciences, Claret Medical, Meril
- Thubrikar Aortic Valve, Inc
- St. Jude Medical, Claret Medical
Background

• Based on randomized trials with first generation devices, transcatheter aortic valve replacement (TAVR) has been incorporated into the treatment strategy for high-risk and inoperable patients with severe AS.

• Procedural complications remain a concern with TAVR, including stroke, vascular complications, paravalvular leak (PVL) and conduction disturbances.

• Addressing these limitations will support TAVR use in lower-risk populations.
Evolution of the Edwards Balloon-Expandable Transcatheter Valves

- SAPIEN (2006)
- SAPIEN XT (2009)
- SAPIEN 3 (2013)

* Sheath compatibility for a 23 mm valve
SAPIEN 3 Transcatheter Heart Valve
Distinguishing Features

- Bovine pericardial tissue
- Low frame height
- Enhanced frame geometry for ultra-low delivery profile
- Outer skirt to reduce PVL
SAPIEN 3 Commander Delivery System

Distinguishing Features

- Improved coaxial alignment

- Accurate positioning

<table>
<thead>
<tr>
<th>SAPIEN 3 Valve Size</th>
<th>20 mm</th>
<th>23 mm</th>
<th>26 mm</th>
<th>29 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Expandable Sheath</td>
<td>14F</td>
<td>14F</td>
<td>14F</td>
<td>16F</td>
</tr>
<tr>
<td>Minimum Access Vessel Diameter</td>
<td>5.5 mm</td>
<td>5.5 mm</td>
<td>5.5 mm</td>
<td>6.0 mm</td>
</tr>
</tbody>
</table>
The PARTNER II S3 Trial

Purpose

To evaluate the safety and efficacy of the SAPIEN 3 transcatheter heart valve system at 30 days in inoperable, high-risk, and intermediate-risk patients.
The PARTNER II S3 Trial
Study Design

Symptomatic Severe Aortic Stenosis

Intermediate Risk Operable (PII S3i)
- ASSESSMENT: Optimal Valve Delivery Access
  - Transfemoral (TF)
    - TF TAVR SAPIEN 3
  - Transapical / Transaortic (TA/TAo)
    - TAA TAVR SAPIEN 3

SAPIEN 3
- 2 Single Arm Non-Randomized Historical-Controlled Studies
- PII A SAVR
- PII A SAPIEN

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
Key Inclusion Criteria

- Risk determined by STS score and heart team:
  - **High Risk / Inoperable (S3HR):** STS score > 8 or heart team determination
  - **Intermediate Risk (S3i):** STS score between 4 and 8 or heart team determination

- Severe aortic stenosis determined by echocardiography:
  - Valve area < 0.8 cm\(^2\) or Valve area index < 0.5 cm\(^2\)/m\(^2\) and mean gradient > 40mmHg or peak velocity > 4 m/s
Key Exclusion Criteria

- MI within one month
- Bicuspid aortic valve
- Severe aortic regurgitation
- Prior prosthetic valve in any position
- Untreated significant CAD (S3HR only)
- LVEF < 20%
- Stroke or TIA within 6 months
- Upper GI bleed within 3 months
- Creatinine > 3.0 or dialysis
- Estimated life expectancy < 24 months
Study Methodology

• All patients presented on a screening call for approval prior to implant.

• 3D imaging of annulus (CT or 3D TEE) recommended for S3HR and required for majority of S3i with core lab analysis prior to implant.

• All patients evaluated by a neurologist at baseline and at follow-up time points.

• **Primary Analysis:** As treated patients

• S3HR and S3i combined for echocardiographic analyses (valve implant patients).
The PARTNER II S3 Trial: S3HR

Participating Sites

583 Patients Enrolled at 29 US Participating Sites
The PARTNER II S3 Trial: S3i Participating Sites

1076 Patients Enrolled at 51 US Participating Sites
### The PARTNER II S3 Trial: S3HR & S3i

#### Top 10 Enrollment Sites

<table>
<thead>
<tr>
<th>S3HR</th>
<th>S3i</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cedars-Sinai Medical Ctr.</strong> Los Angeles, CA</td>
<td><strong>Cedars-Sinai Medical Ctr.</strong> Los Angeles, CA</td>
</tr>
<tr>
<td><strong>Columbia University Medical Ctr.</strong> New York, NY</td>
<td><strong>University of Pennsylvania</strong> Philadelphia, PA</td>
</tr>
<tr>
<td><strong>Emory University</strong> Atlanta, GA</td>
<td><strong>Emory University</strong> Atlanta, GA</td>
</tr>
<tr>
<td><strong>University of Pennsylvania</strong> Philadelphia, PA</td>
<td><strong>University of Texas, Houston</strong> Houston, TX</td>
</tr>
<tr>
<td><strong>Heart Hospital Baylor Plano</strong> Plano, TX</td>
<td><strong>Columbia University Medical Ctr.</strong> New York, NY</td>
</tr>
<tr>
<td><strong>Ochsner Hospital</strong> New Orleans, LA</td>
<td><strong>Heart Hospital Baylor Plano</strong> Plano, TX</td>
</tr>
<tr>
<td><strong>University of Texas, Houston</strong> Houston, TX</td>
<td><strong>Cleveland Clinic Foundation</strong> Cleveland, OH</td>
</tr>
<tr>
<td><strong>Stanford University Medical Ctr.</strong> Stanford, CA</td>
<td><strong>Newark Beth Israel Medical Ctr.</strong> Newark, NJ</td>
</tr>
<tr>
<td><strong>Newark Beth Israel Medical Ctr.</strong> Newark, NJ</td>
<td><strong>The Christ Hospital</strong> Cincinnati, OH</td>
</tr>
<tr>
<td><strong>Washington Hospital Ctr.</strong> Washington, DC</td>
<td><strong>Mayo Clinic</strong> Rochester, MN</td>
</tr>
</tbody>
</table>

- Cedars-Sinai Medical Ctr.: 73
- Columbia University Medical Ctr.: 65
- Emory University: 63
- University of Pennsylvania: 43
- Heart Hospital Baylor Plano: 30
- Ochsner Hospital: 26
- University of Texas, Houston: 25
- Stanford University Medical Ctr.: 24
- Newark Beth Israel Medical Ctr.: 21
- Washington Hospital Ctr.: 19
- Cedars-Sinai Medical Ctr.: 106
- University of Pennsylvania: 66
- Emory University: 62
- University of Texas, Houston: 52
- Columbia University Medical Ctr.: 48
- Heart Hospital Baylor Plano: 46
- Cleveland Clinic Foundation: 41
- Newark Beth Israel Medical Ctr.: 38
- The Christ Hospital: 38
- Mayo Clinic: 35
Co-Principal Investigators

Susheel Kodali  
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Vinod Thourani  
Emory University, GA

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University of Virginia, VA

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Study Flow: S3HR & S3i
30 Day Patient Status

S3HR
n = 583
13 Deaths
n = 570
SAPIEN 3
0 Withdrawal
3 LTFU
567 / 570 or 99.5% follow-up visits performed at 30 Days

S3i
n = 1076
12 Deaths
n = 1064
SAPIEN 3
0 Withdrawal
5 LTFU
1059 / 1064 or 99.5% follow-up visits performed at 30 Days
Baseline Patient Characteristics
S3HR Patients

Average STS = 8.6% (Median 8.4%)

Average Age = 82.6yrs

N = 583
Baseline Patient Characteristics
S3i Patients

Average STS = **5.3%** (Median 5.2%)

Average Age = **81.9yrs**

N = 1076

**Graphs and Pie Charts:**
- Female: 38%
- Male: 62%
- TA, 7%
- TAO, 4%
- TF, 89%

**Bar Charts:**
- 20 mm: 4.1%
- 23 mm: 32.2%
- 26 mm: 43.7%
- 29 mm: 20.0%
## Baseline Patient Characteristics
### Demographics

<table>
<thead>
<tr>
<th>Characteristic (%)</th>
<th>S3HR (n=583)</th>
<th>S3i (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA Class III or IV</td>
<td>90.1</td>
<td>72.6</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>33.1</td>
<td>28.0</td>
</tr>
<tr>
<td>Previous CVA</td>
<td>11.0</td>
<td>8.9</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>35.2</td>
<td>28.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>34.5</td>
<td>34.1</td>
</tr>
<tr>
<td>COPD - O₂ Dependent</td>
<td>11.7</td>
<td>5.0</td>
</tr>
<tr>
<td>CKD - Creat. ≥ 2mg/dL</td>
<td>12.0</td>
<td>7.5</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>43.7</td>
<td>36.0</td>
</tr>
<tr>
<td>Permanent Pacemaker</td>
<td>16.3</td>
<td>13.2</td>
</tr>
<tr>
<td>Frailty</td>
<td>30.9</td>
<td>8.6</td>
</tr>
</tbody>
</table>
## Baseline Echocardiography

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>S3HR (n=583)</th>
<th>S3i (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>AV Area - cm² (mean ± SD)</td>
<td>0.67 ± 0.18</td>
<td>0.70 ± 0.17</td>
</tr>
<tr>
<td>Annulus Diam. - cm (mean ± SD)</td>
<td>2.2 ± 0.2</td>
<td>2.2 ± 0.2</td>
</tr>
<tr>
<td>AV Gradient - mmHg (mean ± SD)</td>
<td>45.5 ± 14.3</td>
<td>46.3 ± 12.7</td>
</tr>
<tr>
<td>LV Ejection Fraction (%)</td>
<td>56.4 ± 14.8</td>
<td>58.6 ± 13.3</td>
</tr>
<tr>
<td>Mod-Severe MR (%)</td>
<td>3.0</td>
<td>2.3</td>
</tr>
</tbody>
</table>
## Procedural Factors

<table>
<thead>
<tr>
<th>Factor</th>
<th>S3HR (n=583)</th>
<th>S3i (n=1076)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Post-Dilatation (%)</td>
<td>14.8</td>
<td>11.3</td>
</tr>
<tr>
<td>&gt;1 Valve Implanted (%)</td>
<td>0.9</td>
<td>0.4</td>
</tr>
<tr>
<td>Valve Embolization (%)</td>
<td>0.2</td>
<td>0.1</td>
</tr>
<tr>
<td>IABP During Procedure (%)</td>
<td>0.5</td>
<td>0.4</td>
</tr>
<tr>
<td>Cardiopulmonary Bypass (%)</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Conscious Sedation (%)</td>
<td>13</td>
<td>17</td>
</tr>
<tr>
<td>Median LOS – Days (Min, Max)</td>
<td>5 (1, 33)</td>
<td>4 (1, 64)</td>
</tr>
</tbody>
</table>
Mortality and Stroke: S3HR
At 30 Days (As Treated Patients)

**Mortality**
- All-Cause: 2.2
- Cardiovascular: 1.4

**Stroke**
- All Stroke: 1.5
- Disabling: 0.9

O:E = 0.26
(STS 8.6%)
Mortality and Stroke: S3i
At 30 Days (As Treated Patients)

O:E = 0.21
(STS 5.3%)
Mortality: S3HR & S3i
At 30 Days (As Treated Patients)

Transfemoral

- All-Cause (S3HR): 1.6%
- Cardiovascular (S3HR): 1.0%
- All-Cause (S3i): 1.1%
- Cardiovascular (S3i): 0.9%

Transapical / Transaortic

- All-Cause (S3HR): 5.4%
- Cardiovascular (S3HR): 3.3%
- All-Cause (S3i): 1.6%
- Cardiovascular (S3i): 0.8%
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated Patients)

PARTNER I and II Trials
Overall and TF Patients

<table>
<thead>
<tr>
<th>SAPIEN</th>
<th>SXT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF) 175</td>
<td>6.3%</td>
<td>S3HR (All) 583</td>
</tr>
<tr>
<td>P1A (All) 344</td>
<td>5.2%</td>
<td>S3HR (TF) 491</td>
</tr>
<tr>
<td>P1A (TF) 240</td>
<td>3.7%</td>
<td>S3i (All) 1072</td>
</tr>
<tr>
<td>P2B (TF) 271</td>
<td>4.5%</td>
<td>S3i (TF) 947</td>
</tr>
<tr>
<td>P2B XT (TF) 282</td>
<td>3.5%</td>
<td></td>
</tr>
</tbody>
</table>

The diagram above illustrates the all-cause mortality rates at 30 days for different trials involving Edwards SAPIEN valves. The SAPIEN, SXT, and SAPIEN 3 categories are compared, showing the mortality rates for overall and transfemoral (TF) patients. The data is derived from PARTNER I and II trials.
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated Patients)

PARTNER I and II Trials
TA/TAo Patients

Nested Registries

<table>
<thead>
<tr>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1A (TA) 104</td>
<td>P2B (TA) 125</td>
<td>P2B (TAo) 94</td>
</tr>
<tr>
<td>8.7%</td>
<td>8.1%</td>
<td>6.5%</td>
</tr>
<tr>
<td>P3HR (TA/TAo) 92</td>
<td>S3l (TA/TAo) 125</td>
<td>1.6%</td>
</tr>
</tbody>
</table>
# Strokes

## At 30 Days (As Treated Patients)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>S3HR Overall (n=583)</th>
<th>S3HR TF (n=491)</th>
<th>S3HR TA/TAo (n=92)</th>
<th>S3i Overall (n=1076)</th>
<th>S3i TF (n=951)</th>
<th>S3i TA/TAo (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.54</td>
<td>1.63</td>
<td>1.09</td>
<td>2.60</td>
<td>2.42</td>
<td>4.00</td>
</tr>
<tr>
<td>Disabling*</td>
<td>0.86</td>
<td>0.81</td>
<td>1.09</td>
<td>1.02</td>
<td>0.95</td>
<td>1.60</td>
</tr>
<tr>
<td>Non-Disabling</td>
<td>0.69</td>
<td>0.81</td>
<td>0</td>
<td>1.58</td>
<td>1.47</td>
<td>2.40</td>
</tr>
<tr>
<td>TIA</td>
<td>0.69</td>
<td>0.61</td>
<td>1.09</td>
<td>0.37</td>
<td>0.42</td>
<td>0</td>
</tr>
</tbody>
</table>

*CEC adjudicated or Modified Rankin Score ≥ 2 at 30 days*
All Strokes at 30 Days
Edwards SAPIEN Valves

PARTNER I and II Trials

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Valve</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>6.7%</td>
<td>4.1%</td>
<td>1.5%</td>
</tr>
<tr>
<td>P1A (Overall)</td>
<td>5.6%</td>
<td>4.3%</td>
<td>2.6%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3HR (Overall)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>S3i (Overall)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Participants   | 179    | 276      | 583      | 1076
### Other Clinical Events

#### At 30 Days (As Treated Patients)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>S3HR Overall (n=583)</th>
<th>S3HR TF (n=491)</th>
<th>S3HR TA/TAo (n=92)</th>
<th>S3i Overall (n=1076)</th>
<th>S3i TF (n=951)</th>
<th>S3i TA/TAo (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Vascular Comps.</td>
<td>5.0</td>
<td>5.3</td>
<td>3.3</td>
<td>5.6</td>
<td>5.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Bleeding - Life Threatening</td>
<td>6.3</td>
<td>5.5</td>
<td>10.9</td>
<td>5.4</td>
<td>4.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Annular Rupture</td>
<td>0.3</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarctions</td>
<td>0.5</td>
<td>0.4</td>
<td>1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Obstruction</td>
<td>0.2</td>
<td>0</td>
<td>1.1</td>
<td>0.4</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>0.5</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>13.0</td>
<td>13.2</td>
<td>12.0</td>
<td>10.1</td>
<td>10.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Aortic Valve Re-intervention</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>0.7</td>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td></td>
</tr>
</tbody>
</table>
NYHA Functional Class
At 30 Days (As Treated Patients)

Baseline

- S3HR 583: 90%
- S3i 1075: 73%

30 Days

- S3HR 550: 13%
- S3i 1049: 6%
### Echo Findings: S3HR & S3i

**Aortic Valve Area (Valve Implant Patients)**

<table>
<thead>
<tr>
<th>No. of Echos</th>
<th>Baseline</th>
<th>30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1546</td>
<td>1461</td>
</tr>
</tbody>
</table>

- Valve Area (cm²)
  - Baseline: 0.69
  - 30 Days: 1.67
Echo Findings: S3HR & S3i
Aortic Valve Area (Valve Implant Patients)

![Graph showing valve area over time for different valve sizes.]

- **Valve Area (cm²)**
- **Baseline 30 Days**
  - Overall: 0.62, 1.22
  - 29 mm: 0.70, 1.67
  - 26 mm: 0.69, 1.74
  - 23 mm: 0.63, 1.90
  - 20 mm: 0.75, 1.90

- **Overall No. of Echos**: 1546
- **30 Days**
  - Overall: 1461
Echo Findings: S3HR & S3i
Mean Gradients (Valve Implant Patients)

No. of Echos

Overall: 1602
Baseline: 1531

46.0
11.3

Gradient (mmHg)

0.0
10.0
20.0
30.0
40.0
50.0
60.0

No. of Echos
Overall

Baseline
1602

30 Days
1531
Echo Findings: S3HR & S3i
Mean Gradients (Valve Implant Patients)

Baseline 30 Days

Overall 1602 1531

No. of Echos Overall

Mean Gradients (Valve Implant Patients)

- 20 mm
- 23 mm
- 26 mm
- 29 mm

Gradient (mmHg)
Paravalvular Leak: S3HR & S3i (Valve Implant Patients)

- None/Trace: 55.0%
- Mild: 41.3%
- Moderate: 3.7%
- Severe: 0.1%

No. of Echos: 1,504

30 Days
**PARTNER I and II Trials**

- **P1B (TF):** 12.0% (179)
- **P1A (Overall):** 11.5% (344)
- **P2B (TF):** 16.9% (276)
- **P2B XT (TF):** 24.2% (284)
- **S3HR (Overall):** 2.9% (583)
- **S3i (Overall):** 4.2% (1076)
Conclusions (1)

• In high-risk and inoperable patients (S3HR), the SAPIEN 3 TAVR system demonstrated low mortality and stroke and excellent clinical outcomes at 30 days:
  - **Mortality**: 2.2% (TF 1.6%, TA/TAo 5.4%)
  - **Disabling Stroke**: 0.9%

• In intermediate-risk patients (S3i), SAPIEN 3 was associated with strikingly low mortality and strokes at 30 days:
  - **Mortality**: 1.1% (TF 1.1%, TA/TAo 1.6%)
  - **Disabling Stroke**: 1.0%
Conclusions (2)

• Other important clinical findings with SAPIEN 3 (both S3HR & S3i) include:
  – Major vascular complications: ~5%
  – Annular rupture: ~0.2%
  – Coronary obstruction: ~0.3%
  – New pacemakers: ~10%

• Significant paravalvular regurgitation with SAPIEN 3 (both S3HR & S3i) was rare:
  – Severe: 0.1%
  – Moderate: 3.7%
Implications

• The rapid evolution of balloon-expandable TAVR, both procedural developments and technical enhancements, represented in the SAPIEN 3 clinical and echo results, indicates at least parity with the best surgical outcomes in comparable patients.

• **SAPIEN 3 TAVR should now be considered as an alternative to surgery, even in lower risk patients with aortic stenosis.**
Primary Endpoint: S3HR

- **Primary Endpoint:** Non-Hierarchical composite of Death + All Stroke + Total AR ≥ Moderate

- Patients in S3HR cohort are confirmed to be comparable to patients in P1A SAPIEN group via propensity modeling on baseline characteristics.

- Overall treatment effect is adjusted for propensity quintiles defined by propensity scores.

- Patients that received SAPIEN 3 have 9% lower event rate than patients that received SAPIEN.
Primary Endpoint: S3HR

Primary Endpoint: Non-Hierarchical Composite of Death + All Stroke + Total AR ≥ Moderate

Proportion Difference between SAPIEN 3 and SAPIEN: -9.0%*
Two-sided 95% Stratified Newcombe CI: [-13.9%, -4.5%]

Primary Non-Inferiority Endpoint Met: \( p < 0.001 \)
Sequential Superiority Endpoint Met: \( p < 0.01 \)