Strokes after TAVR: Perspectives from the PARTNER Trial

Susheel Kodali, MD
Co-Director, Heart Valve Center
Columbia University
New York, NY
Disclosure Statement of Financial Interest

Susheel Kodali, 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.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Edwards Lifesciences</td>
</tr>
<tr>
<td>Steering Committee</td>
<td>Edwards Lifesciences, Claret Medical, Meril</td>
</tr>
<tr>
<td>SAB (Equity)</td>
<td>Thubrikar Aortic Valve, Inc</td>
</tr>
</tbody>
</table>
Perspective #1

*Stroke following TAVR was an immediate concern and led to discussions about its role in surgical candidates*
Transcatheter Aortic-Valve Implantation — At What Price?
Hartzell V. Schaff, M.D.

In 2000, Bonhoeffer et al. described transvenous placement of a pulmonary-valve prosthesis and speculated that similar technology might be used in other cardiac valves, including the aortic position.¹ Two years later, the first transcatheter insertion of an aortic-valve prosthesis was performed by Cribier et al.² Transcatheter aortic-valve patients who are eligible for transfemoral insertion and may decrease vascular injury.

But the increased risk of stroke associated with transcatheter replacement, as compared with surgical replacement, is a special concern. Smith and colleagues report a 5.5% risk of stroke or transient ischemic attack within 30 days after
PARTNER Trial

Standardized Definitions

• All neurologic events were reviewed and adjudicated by an independent CEC

• Definitions
  • **TIA**
    - Focal neurologic event that was fully reversible in < 24 hours in the absence of any new imaging findings of infarction or other primary medical cause (hypoglycemia, hypoxia, etc).
  
  • **Stroke**:
    - Focal neurologic deficit lasting ≥ 24 hours OR
    - Focal neurologic deficit lasting < 24 hours with imaging findings of acute infarction or hemorrhage.
    - Stroke was further classified as ischemic, hemorrhagic (epidural, subdural, subarachnoid), or ischemic with hemorrhagic conversion.
Why not TIA?

• Difficult to ascertain in this elderly population
• Clinical significance remains unclear
• Etiology may not be the same as stroke
Neuro events at 30 days and 1 year

**Inoperable cohort B**

### Major Stroke

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>5.0</td>
<td>1.1</td>
<td>0.06</td>
</tr>
<tr>
<td>Standard Rx</td>
<td>7.8</td>
<td>3.9</td>
<td>0.18</td>
</tr>
</tbody>
</table>

### All Stroke

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>6.7</td>
<td>1.7</td>
<td>0.03</td>
</tr>
<tr>
<td>Standard Rx</td>
<td>10.6</td>
<td>4.5</td>
<td>0.04</td>
</tr>
</tbody>
</table>

*P = 0.06, P = 0.18, P = 0.03, P = 0.04*
All Stroke : PARTNER A (ITT)

<table>
<thead>
<tr>
<th>Group</th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALL</td>
<td>4.6</td>
<td>2.4</td>
</tr>
<tr>
<td>TF</td>
<td>3.7</td>
<td>1.7</td>
</tr>
<tr>
<td>TA</td>
<td>6.8</td>
<td>4.3</td>
</tr>
<tr>
<td>ALL</td>
<td>6</td>
<td>3.2</td>
</tr>
<tr>
<td>TF</td>
<td>4.6</td>
<td>2.3</td>
</tr>
<tr>
<td>TA</td>
<td>9.3</td>
<td>5.4</td>
</tr>
</tbody>
</table>

Smith et al, NEJM, June 2011
PARTNER-A Neurological Events (TF)

As Treated

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day</td>
<td>11(4.6)</td>
<td>1.3 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2.5 (1.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.04</td>
</tr>
<tr>
<td>1 year</td>
<td>14(6.1)</td>
<td>1.8 (0.8)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3.5 (1.9)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>P=0.03</td>
</tr>
</tbody>
</table>

PARTNER-A Neurological Events (TA)

As Treated

<table>
<thead>
<tr>
<th></th>
<th>TAVR 30 day</th>
<th>AVR 30 day</th>
<th>TAVR 1 year</th>
<th>AVR 1 year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIA</td>
<td>7</td>
<td>4.4</td>
<td>3.7</td>
<td>5.9</td>
</tr>
<tr>
<td>Minor</td>
<td>1.0</td>
<td>1.1</td>
<td>1.0</td>
<td>1.1</td>
</tr>
<tr>
<td>Major</td>
<td>1.1</td>
<td>4.4</td>
<td>9.4</td>
<td>5.9</td>
</tr>
</tbody>
</table>

P=0.5, P=0.37

Neurologic Events in PARTNER-A

TAVR
- Major: 58%
- TIA: 26%
- Minor: 16%
- Total events: 31/344

AVR
- Major: 69%
- TIA: 25%
- Minor: 6%
- Total events: 16/315

47 patients, 49 events
- Ischemic: 72%, hemorrhagic: 0%, (ischemic → hemorrhagic: 4%), unknown: 24%

Perspective #2

TAVR has increased risk of stroke compared to surgical AVR in initial experience
## Risk Factors for Neurologic Events

### Early high peaking hazard phase

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient ± SD</th>
<th>P</th>
<th>R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Early hazard phase</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVR</td>
<td>2.21±0.68</td>
<td>.001</td>
<td>59</td>
</tr>
<tr>
<td>Smaller AVA index in TAVR group</td>
<td>-11.8±5.1</td>
<td>.02</td>
<td>57</td>
</tr>
</tbody>
</table>

*Atrial fibrillation not significant in multivariable analysis*

\[ R(\%) = \text{bagging reliability} \]
## Risk Factors for Neurologic Events

### Late constant hazard phase

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>Coefficient ± SD</th>
<th>P</th>
<th>R (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Constant hazard phase</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TAVR</td>
<td>0.40 ± 0.43</td>
<td>0.4</td>
<td>22</td>
</tr>
<tr>
<td>(Higher) NYHA</td>
<td>0.95 ± 0.40</td>
<td>.02</td>
<td>75</td>
</tr>
<tr>
<td>Stroke or TIA within 6-12 mo</td>
<td>1.93 ± 0.64</td>
<td>.002</td>
<td>60</td>
</tr>
<tr>
<td>Non-TF TAVR candidate</td>
<td>2.3 ± 0.45</td>
<td>&lt;.0001</td>
<td>96</td>
</tr>
<tr>
<td>History of PCI (less risk)</td>
<td>-1.60 ± 0.63</td>
<td>.01</td>
<td>77</td>
</tr>
<tr>
<td>COPD (less risk)</td>
<td>-1.06 ± 0.47</td>
<td>.03</td>
<td>79</td>
</tr>
</tbody>
</table>

\[ R(\%) = \text{bagging reliability} \]
Neurologic event

Considering competing risks

TAVR-TA

AVR-TA

TAVR-TF

AVR-TF

TAVR-TF

TAVR-TA

AVR-TA

AVR-TF

TAVR-TF

67

59

240

104

221

92

114

32

202

77

170

67

179

64

160

62

18

2.2

5.5

12

6.5

2.6

9.1

67

121

92
Perspective #3

Neurologic complications lead to increased mortality in this elderly comorbid population
Mortality vs. Major Stroke (Cohort B) TAVR Patients

Mortality (%)

- Major Stroke (n=15): 66.7%
- No Major Stroke (n=164): 27.7%

P (log rank) <0.0001
“Mortality Cost” of neuro event

- AVR

Observed/Expected

Hazard Ratio

Months after Neurologic Event

Transcatheter Valve Therapies (TVT)
A Multidisciplinary Approach
“Mortality Cost” of neuro event

TAVR-TF

Observed/Expected

Months after Neurologic Event

Hazard Ratio
"Mortality Cost" of neuro event

Hazard Ratio

TAVR-TA

Observed/Expected

Months after Neurologic Event

TVT Transcatheter Valve Therapies (TVT)
A Multidisciplinary Approach
## PARTNER-1A: Impact of Complications on Mortality

<table>
<thead>
<tr>
<th>Complication</th>
<th># Events (1 year)</th>
<th># Deaths (1 year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Stroke</td>
<td>18</td>
<td>9</td>
</tr>
<tr>
<td>Major Vascular</td>
<td>38</td>
<td>14</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>88</td>
<td>37</td>
</tr>
</tbody>
</table>
Perspective #4

With device iteration and increased operator experience, stroke rates decreased in PARTNER
Stroke Rates Lower in Cohort A

- **Potential Reasons**
  - Patients were healthier than the cohort B patients
  - Cohort A enrolled later and therefore sites were further along on the learning curve
  - Device iteration (Retroflex III catheter introduced during course of enrollment)
Lower Stroke Rate in TF Arm Only

<table>
<thead>
<tr>
<th></th>
<th>TAVR Cohort B TF (n=179)</th>
<th>TAVR Cohort A TF (n=244)</th>
<th>TAVR Cohort A TA (n=104)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke Rate (%)</td>
<td>6.7</td>
<td>3.7</td>
<td>6.8</td>
</tr>
</tbody>
</table>

30 Days

**Potential Reasons**

- TA population represented a sicker patient population with higher stroke risk
- Learning curve since this was the first TA experience for many sites
- Small sample size may have led to exaggerated differences

**Miller et al, JTCVS 2012**
PARTNER Trial Timelines

Allows comparison of stroke rates over time since patients populations are the same and the performing centers are the same.
TAVR Volumes at Sites Increased with NRCA Registry

**RCT-TF (27 sites)**
Mean Enrollment: 15.4

**NRCA-TF (27 sites)**
Mean Enrollment: 37.7

**RCT-TA (14 sites)**
Mean Enrollment: 7.4

**NRCA-TF (22 sites)**
Mean Enrollment: 44.9
Lower Rates with Experience

**Transfemoral**
- TAVR Cohort B TF (n=179)
- TAVR Cohort A TF (n=244)
- TAVR NRCA TF (n=1017)

30 Days
- 6.7
- 3.7
- 3.7

**Transapical**
- PMA TA (n=104)
- NRCA TA (n=988)

30 Days
- 6.8
- 2.1

P = 0.02
Why would stroke rate decrease?

• Increased experience especially in TA arm

• Device improvement
  – Easier to cross \rightarrow less trauma to aortic valve
  – Fewer BAVs prior to valve

• Improved Procedural Technique
  – Better annular sizing
  – Less Post-Dilatation
    • PMA TF (36.7%) vs NRCA TF (9.4%)

• Better Patient Selection
  – Lower Risk
  – Aggressive Anti-Coagulation in high risk patients

Cerebrovascular events (%)

\[ p = 0.006 \]

Nombela-Franco et al. JACC Intv 2012
Timing of strokes suggest multiple etiologies for increased embolic risk
PARTNER-1A: Timing of Neurological Events

ICU stay (d) | AVR | TAVR |
---|---|---|
0-2 | | |
3-5 | | |
6-10 | | |
11-30 | | |
31-364 | | |
365-730 | | |
>730 | | |

- TIA
- Minor Stroke
- Major Stroke

* Adapted from DC Miler and S Kapadia
Etiology of “Delayed” Events

- Late embolization of debris liberated during procedure
- Atrial arrhythmias
- Bleeding events related to pharmacology
Distribution of Stroke within 30 days

% of Total Stroke in 1 month

- Cohort B
- Cohort A
- NRCA (TF)

0-2 days: Cohort B is highest, followed by Cohort A and then NRCA (TF).
2-7 days: Cohort A is slightly higher than Cohort B and NRCA (TF).
7-30 days: NRCA (TF) is the highest, followed by Cohort A and then Cohort B.

* courtesy Samir Kapadia
Stroke Timing within 1 year

% of Total Stroke in 1 year

- Cohort B
- Cohort A
- NRCA (TF)

0-2 days:
- Cohort B: 30%
- Cohort A: 50%
- NRCA (TF): 60%

2-7 days:
- Cohort B: 20%
- Cohort A: 10%
- NRCA (TF): 15%

7-30 days:
- Cohort B: 15%
- Cohort A: 25%
- NRCA (TF): 20%

30-365 days:
- Cohort B: 40%
- Cohort A: 35%
- NRCA (TF): 30%

References:
- Leon et al., NEJM
- Smith et al., NEJM
- Kodali et al., ACC 2013

* courtesy Samir Kapadia
Perspective #6

There does not appear to late hazard for embolic events after TAVR
PARTNER 1 A - Stroke (ITT)

<table>
<thead>
<tr>
<th>Months Post Randomization</th>
<th>No. at Risk TAVR</th>
<th>No. at Risk AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>348</td>
<td>351</td>
</tr>
<tr>
<td>6</td>
<td>287</td>
<td>246</td>
</tr>
<tr>
<td>12</td>
<td>250</td>
<td>230</td>
</tr>
<tr>
<td>18</td>
<td>228</td>
<td>217</td>
</tr>
<tr>
<td>24</td>
<td>211</td>
<td>197</td>
</tr>
<tr>
<td>30</td>
<td>176</td>
<td>169</td>
</tr>
<tr>
<td>36</td>
<td>139</td>
<td>139</td>
</tr>
</tbody>
</table>

HR [95% CI] = 1.09 [0.62, 1.91]

p (log rank) = 0.763
PARTNER 1A Strokes (AT)

<table>
<thead>
<tr>
<th>Time Period</th>
<th>TAVR</th>
<th>AVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤ 30 Days</td>
<td>15</td>
<td>8</td>
</tr>
<tr>
<td>30 Days - 1 Year</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>1 - 2 Years</td>
<td>4</td>
<td>4</td>
</tr>
<tr>
<td>2 - 3 Years</td>
<td>1</td>
<td>9</td>
</tr>
<tr>
<td>&gt; 3 Years</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>
Perspective #7

Next Generation devices have not significantly reduced the risk of stroke following TAVR
The PARTNER II Inoperable Cohort Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT by Heart Valve Team

Inoperable

ASSESSMENT: Transfemoral Access

1:1 Randomization

n = 560 Randomized Patients

TF TAVR SAPIEN XT vs TF TAVR SAPIEN

Primary Endpoint: All-Cause Mortality + Disabling Stroke + Repeat Hospitalization at One Year (Non-inferiority)
PARTNER II Trial with Sapien XT valve demonstrated stable stroke rates

PARTNER II Trial
• Randomized trial of Sapien vs Sapien XT
• Inoperable patients only
• Patients assessed at baseline and follow-up by neurologists

Transfemoral

- TAVR Cohort B TF (n=179)
- TAVR Cohort A TF (n=244)
- TAVR NRCA TF (n=1017)
- TAVR PII B Sapien (n=276)
- TAVR PII B Sapien XT (n=284)

30 Days

- 6.7
- 3.7
- 3.7
- 4.1
- 4.3
Final Thoughts

- Device iteration and improvements in procedural technique have helped decrease 30 day stroke rates after TAVR.
- Comparisons between trials difficult despite standardization of definitions due to differences in patient characteristics as well as rigor of neurologic assessment.
- Embolic phenomenon will always be an issue with TAVR.
- Goal should be to reduce the clinical impact to an acceptable level.
- Continued iteration in devices as well as accessory devices such as filters and deflectors will potential help achieve this goal.

Stroke Risk After Isolated AVR in STS Database

Brown et al, JTCVS 2009