Update on TAVR

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Disclosure Statement of Financial Interest

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>Grant/Research Support</th>
<th>Consulting Fees/Honoraria</th>
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<tbody>
<tr>
<td>Abbott Vascular</td>
<td>Edwards Lifesciences</td>
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<td>Edwards Lifesciences</td>
<td>Bayer</td>
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<td>St. Jude Medical</td>
<td>Boston Sci</td>
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<td>Medtronic</td>
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<td>Gore</td>
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<td>Siemens</td>
<td>Univ Laval</td>
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- **Equity**
  - Microinterventional Devices

- **Discussion may include unapproved and off-label devices, procedures, and indications**
### Status of TAVI by Surgical Risk Level

<table>
<thead>
<tr>
<th>Trial</th>
<th>Device</th>
<th>Risk</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER 1B</td>
<td>SAPIEN</td>
<td>Inoperable</td>
<td>TAVR &gt; Medical Therapy</td>
</tr>
<tr>
<td>PARTNER 1A</td>
<td>SAPIEN</td>
<td>High Risk</td>
<td>TAVR = SAVR</td>
</tr>
<tr>
<td>PARTNER 2A</td>
<td>SAPIEN XT</td>
<td>Intermediate Risk</td>
<td>TF TAVR &gt; SAVR</td>
</tr>
<tr>
<td>PARTNER S3i</td>
<td>SAPIEN 3</td>
<td>Intermediate Risk</td>
<td>TAVR &gt; SAVR</td>
</tr>
<tr>
<td>PARTNER 3</td>
<td>SAPIEN 3</td>
<td>Low Risk</td>
<td>Enrolling</td>
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**Valve Technology**
- **SAPIEN**
- **SAPIEN XT**
- **SAPIEN 3**

**Sheath Compatibility**
- **22-24F**
- **16-20F**
- **14-16F**
• Randomized comparison of TAVR and SAVR in severe symptomatic AS at intermediate risk for surgery
  • 1660 patients
  • STS PROM 4.5%
  • SAVR: more AKI, AF, Transfusion
  • TAVR: more AR, PPM, lower grads

Take-Home Messages:

1. In intermediate risk patients with severe symptomatic AS, TAVR is non-inferior to SAVR for death/disabling stroke at 2 years
2. Will likely change the guideline to class I from IIa

Reardon et al, NEJM 2017;378:1321-1331
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated)

**PARTNER 1 and 2 Trials**
(Overall and TF Patients)

- **P1B (TF)**: 6.3%
- **P1A (All)**: 5.2%
- **P1A (TF)**: 3.7%
- **P2B (TF)**: 4.5%
- **P2B XT (TF)**: 3.5%
- **S3HR (All)**: 2.2%
- **S3HR (TF)**: 1.6%
- **S3i (All)**: 1.1%
- **S3i (TF)**: 1.1%

### Participant Numbers

- **SAPIEN**: 175 344 240 271 282 583 491 1072 947
- **SAPIEN 3**: SXT 583 491 1072 947
Estimated Global TAVR Procedure Growth

In the next 5 years, TAVR growth will double.
In the next 10 years, TAVR will increase X4!

SOURCE: Credit Suisse TAVI Comment – January 8, 2015. ASP assumption for 2024 and 2025 based on analyst model. Revenue split assumption in 2025 is 45% U.S., 35% EU, 10% Japan, 10% ROW.
Penn TAVR Program: Growth in Procedures

Penn Medicine Transcatheter Total Volume FY08-current

<table>
<thead>
<tr>
<th># TRANSCATHETER CASES</th>
<th>Total FY08</th>
<th>Total FY09</th>
<th>Total FY10</th>
<th>Total FY11</th>
<th>Total FY12</th>
<th>Total FY13</th>
<th>Total FY14</th>
<th>Total FY15</th>
<th>Total FY16</th>
<th>Total FY17</th>
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<tr>
<td>Series1</td>
<td>10</td>
<td>27</td>
<td>39</td>
<td>79</td>
<td>193</td>
<td>212</td>
<td>270</td>
<td>324</td>
<td>391</td>
<td>414</td>
</tr>
</tbody>
</table>

~2000
TAVR at Penn Today ≈ 500 Cases Annually

- Hybrid OR
- Heart team intact (Anesthesia, CV Surgery, Cardiology)
- MAC predominately (vs CS)
- Peripheral access (no PA catheter, no RIJ line)
- Percutaneous access
- Fast track to floor
- D/C home POD # 2-3

“It Takes a Village!”

“Justice’s Tolerance Seen in His Sacramento Roadside Arrest”

“Tales from a NY Times”
What additional evidence is required to make TAVR suitable for everyone?

• Lower the rate of complications to those of SAVR:
  • Vascular complications <3%
  • New PPM rates <8%
  • Major stroke <1%
  • PVL rate for mod/severe <2%, mild < ?%
  • Hemodynamics and durability similar to surgical valves

• Current limitations of TAVR will be amplified in younger and other lower risk populations
**Medtronic TAVR EnVeoe R**

- **External Skirt Added for PVL Performance**
  - Porcine pericardial tissue skirt sewn to first two inflow cells
  - Extends to partial scallop at inflow
Edwards SAPIEN 3 Ultra System

- SAPIEN 3 Valve
- SAPIEN 3 Ultra Delivery System
- Axela Sheath

On-balloon design removes the need for valve alignment

14F Axela Sheath for all valve sizes with 5.5 mm vessel indication

Seamless sheath design allows for transient expansion and active contraction
New valves will likely provide trade-offs between vascular complications (size), sealing (PVL), and need for PPM.

Assuming all of these are undesirable, which do you consider to be the worst?

1. Vascular complications
2. Mild AR/PVL
3. PPM
Incidence of CVA after TAVI remains clinically significant, particularly in high risk patients

New cerebral lesions are found in the vast majority of patients following TAVI

- 68-100% of TAVI patients affected
- Most patients have multiple infarcts
- “Silent” infarcts associated with
  - 2-4-fold risk of future stroke
  - >3-fold risk of mortality
  - >2-fold risk of dementia
  - Cognitive decline
  - Dementia

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5. Astarci, et al., EJCTS 2011; 40:475-4
6. Lansky, et al., EHJ 2015; May 19
8. Linke, et al., TCT 2014
9. Vahanian, TCT 2014
12. Sacco et al., Stroke 2013
13. Vermeer et al., Stroke 2003
The Claret Montage™ dual-filter Cerebral Protection System was developed to protect the brain from injury caused by embolic debris.

Randomized controlled trial data showing the efficacy of any embolic protection device in TAVR are missing.
SENTINAL TRIAL:
Primary Efficacy Endpoint

42.2% reduction [95% CI: -3.2, 67.6]  

$p = 0.33$

New Lesion Volumes in Protected Territories (mm³)

<table>
<thead>
<tr>
<th></th>
<th>Median ± 95% Confidence Limit</th>
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<tbody>
<tr>
<td>Treatment (N=91)</td>
<td>102.8</td>
</tr>
<tr>
<td>Control (N=98)</td>
<td>178</td>
</tr>
</tbody>
</table>

ANY DEBRIS, Arterial Wall, Valve Tissue, Calcification, Foreign Material, Myocardium, Necrotic Core, Organizing Thrombus, Acute Thrombus (Overall), Acute Thrombus + Tissue / Foreign Material, Acute Thrombus Alone
Are small emboli that do not cause disabling or clinical strokes bad?

1. Very bad

2. Only a little bad and a reasonable trade-off for avoiding surgical recovery

3. Only a little bad, but would persuade me to have surgery if I was intermediate or low risk

4. Not bad at all
When an embolic protection device is avail in my hospital (cost ~1.5-3K), I will use it in...:

1. All patients
2. No patients
3. Selected patients based on device
4. Selected patients based on my assessment of stroke risk
Valve Leaflet Abnormalities

Makkar, et al. 2015
New TAVR Pharmacology Trial

Prospective, randomized, open-label with blinded endpoint evaluation (PROBE), parallel-group, active-controlled, multicenter international study

**Study population:**
Patients with successful TAVR*

**Key excl. criteria:**
- Ongoing indication for DAPT or anticoagulation, previous ischemic stroke, active peptic ulcer or upper GI bleeding, previous ICH, or severe renal insufficiency

**Trial design**

- **N=1520**
- **1:1**
- **2-7 post-TAVR (or upon hospital discharge if earlier than day 2 post-TAVR)**

- **Rivaroxaban 10 mg OD + ASA 75–100 mg**
- **DAPT: Clopidogrel 75 mg OD + ASA 75–100 mg**
- **ASA 75–100 mg**
- **Follow-up period: 30 days**

- 3 months: drop one antiplatelet

- 18 months (12-24 months)

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*~110 sites in Europe & North America (15 countries)

# Majority of patients will be on DAPT after TAVR
Gastric protection recommended throughout study

PIs: Dangas, G. Windecker, S.
US PI: Herrmann, H.
In 5 years all patients receiving bio AVR (TAVR and SAVR) will be treated for 3-6 months with:

1. Dual anti-platelet therapy (current standard of care)
2. Warfarin anticoagulation to INR 2-3
3. DOAC
4. Reduced dose warfarin (INR goal 1.5-2.5)
5. Reduced dose DOAC (rivaraxaban [10 mg] or apixaban [2.5 bid])
6. Echo (TEE) or CT guided therapy
Asymptomatic Severe, Calcific AS

Screening
Not eligible if <65, has Class 1 indication for AVR, bicuspid valve, not suitable for TF access or STS > 10

Asymptomatic N=1,109 pts
Negative stress test OR confirmation via med history*

Randomization 1:1
Stratified by ability to perform stress test

TF- TAVR
Clinical Surveillance

Clinical and Echo Follow-up:
30 days (TAVR only), 1, 2, 3 and 5 years

Symptomatic N=1,000 pts
Positive stress test

Registry

Commercial AVR (TAVR or SAVR), Clinical Trial (P3), etc.

Telephone Follow-up:
1, 2, 3 and 5 years

Primary Endpoint (superiority):
2-year composite of all-cause death, all stroke, and unplanned cardiovascular hospitalization

NCT03042104; 1st patient consented March 16th

Principal Investigator:
Philippe Généreux, MD,
Chair: Martin B. Leon, MD
TAVR-UNLOAD Trial Design

**TAVR UNLOAD Trial**
- **Heart Failure**
  - LVEF < 50%
  - NYHA ≥ 2
  - Optimal HF therapy (OHFT)
  - Moderate AS

**Primary Endpoint**
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease, or non-disabling stroke
- Change in KCCQ

**Follow-up:**
- 1 month
- 6 months
- 1 year

**Clinical Endpoints**
- Symptoms
- Echo QoL
- Change in KCCQ

**Reduced AFTERLOAD**
- Improved LV systolic and diastolic function
New indications for TAVR. I recommend TAVR for which of these patients:

1. Asymptomatic AS only if very severe (mean gradient >50 mmHg)
2. Asymptomatic AS if severe (mean gradient >40 mmHg)
3. Moderate AS (AVA >1.0 cm²) if symptomatic with LV dysfunction
4. 1 and 3
5. 2 and 3
Some of the problems associated with this type of analysis...

- 2 center experience, ultra-sick patients, earliest versions of the Sapien THV
- Incorrect statistical methods - THV degeneration is a time-dependent “process”, not a clinical “event”
- Competing risks of frequent deaths in these patients with multiple co-morbidities creates censoring problems
- Echo data are incomplete - ascertainment and interpretation, and definitions used were spurious - creates significant biases
- No. at risk after 5 years drops precipitously - tail shape unreliable
- “Clinical” SVD - freedom from re-intervention - never discussed
Longitudinal Hemodynamics in Partner 1

- All patients with evaluable echoes over time at core lab
  N= 2482 TAVR patients

- Median F/U 3.1 years (Max 5 years)

- Main findings:
  - Stable hemodynamics
  - Only 5 patients had re-intervention for SVD (0.8%)
  - Mod/severe AR 3.7% (slight increase over time)

*Douglas et al, JAMA Cardiology 2017 (in press)
Regarding durability, pick the statement you most agree with:

1. TAVR valves will not be as durable as surgical prostheses, but the difference will be small and won’t influence procedure selection.

2. TAVR valves will be less durable and will make surgery preferable in patients <75 years of age.

3. The difference in durability will only influence me towards surgery in patients <70 years of age.
# Low Risk TAVR Trials

<table>
<thead>
<tr>
<th>Sponsor</th>
<th>Edwards (NCT02675114)*</th>
<th>Medtronic (NCT02701283)*</th>
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<tbody>
<tr>
<td>Device</td>
<td>Sapien 3</td>
<td>Evolut R / EnVeo R</td>
</tr>
<tr>
<td>Design</td>
<td>Prospective, randomized</td>
<td>Prospective, randomized</td>
</tr>
<tr>
<td>Comparator</td>
<td>1:1 to SAVR</td>
<td>1:1 to SAVR</td>
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<tr>
<td>Analysis</td>
<td>Non-inferiority</td>
<td>Non-inferiority</td>
</tr>
<tr>
<td>N</td>
<td>1228</td>
<td>1250</td>
</tr>
<tr>
<td>Inclusion</td>
<td>Heart team risk &lt;4%</td>
<td>Heart team risk &lt;3%</td>
</tr>
<tr>
<td>Substudy</td>
<td>Leaflet mobility (n=400)</td>
<td>Leaflet mobility (n=400)</td>
</tr>
<tr>
<td>PI</td>
<td>Leon / Mack</td>
<td>Popma / Reardon</td>
</tr>
<tr>
<td>1&lt;sup&gt;o&lt;/sup&gt; endpoint</td>
<td>All-cause mort / all stroke / rehosp. (1 year)</td>
<td>All-cause mort / disabling stroke (2 year adaptive)</td>
</tr>
<tr>
<td>Key differences</td>
<td>Excludes EF &lt;45%, age&lt;65 Includes Asx with +ETT</td>
<td>Can include Asx AS with &gt;5.0 m/s, +ETT</td>
</tr>
</tbody>
</table>

* Source: Clinicaltrials.gov
Regarding low risk patients, pick the statement you most agree with:

1. TAVR will eventually replace surgery in most patients, including those at low risk due to the procedural advantages and patient preference to avoid surgery.

2. Despite likely non-inferiority in the low risk trials, surgery should still be preferred due to lack of even mild PVL and known durability.

3. Risk is less important to me than age. Eg., a low risk 78 yo should get TAVR and an intermediate risk 70 yo should get SAVR.