Aortic Stenosis:
Current State of Percutaneous Therapies,
Emerging Technologies and Future Directions

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Director of Interventional Cardiology
Massachusetts General Hospital
Professor of Medicine
Harvard Medical School
Tuesday April 23, 2002 at 9:31 am Eastern Time
Press Release

SOURCE: Percutaneous Valve Technologies, Inc. (PVT)
First Heart Valve Replacement Without Open Heart Surgery (April 16, 2002)

Experimental Device Developed By Percutaneous Valve Technologies May Provide Alternative to Open Heart Surgery In the United States

This 57 year old male patient that received the aortic valve procedure, developed by Percutaneous Valve Technologies, had a failing heart and was refused for surgery by three surgical teams because of his deteriorating condition and complicated vascular disease," said Dr. Cribier. "Lacking any other clinical solution for this patient, the PVT valve was a life saving technology. We are pleased to be the world's first clinical site to utilize this device.
Percutaneous Valve Replacement

Fast stimulation and PHV delivery

Courtesy of Alan Cribier, MD
ANTEGRADE TRANSEPTAL APPROACH TO PAVR

Local anesthesia
Procedure duration: 90 min
Fluoroscopy time: 25 min

Gradient (mmHg)
38        0

A V A (cm²)
0.43       1.7
(Echo)
<table>
<thead>
<tr>
<th>Valve Technology</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve Sizes</td>
<td>23 mm</td>
<td>26 mm</td>
<td>20 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>23 mm</td>
<td>26 mm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>29 mm*</td>
<td>29 mm</td>
</tr>
</tbody>
</table>

*First Implant Oct 30, 2012

VH Thourani, ACC 2016
Evolut R
Indicated for transarterial access vessel diameters ≥ 5.0mm.

Core Valve and Evolut R

CoreValve®
with 18Fr Cook Sheath
22 Fr (OD)

Evolut™ R
with 14Fr-Equivalent InLine™ Sheath
True 18Fr (OD)
In the next 10 years, TAVR growth will increase X4!
PARTNER: Placement of AoRTic TranscatheterER Valves Trial

Symptomatic Severe Aortic Stenosis

**ASSESSMENT:** High-Risk AVR Candidate 3,105 Total Patients Screened

- **Total = 1,057 patients**
- **2 Parallel Trials:** Individually Powered

**High Risk**

- **N = 699**
- **ASSESSMENT:** Transfemoral Access
  - **Yes**
    - Transfemoral (TF)
      - **1:1 Randomization**
      - **N = 244**
      - TF TAVR
    - **No**
      - Transapical (TA)
      - **1:1 Randomization**
      - **N = 248**
      - AVR

**Inoperable**

- **N = 358**
- **ASSESSMENT:** Transfemoral Access
  - **Yes**
    - TF TAVR
    - **N = 179**
  - **No**
    - Standard Therapy
    - **N = 179**

**Primary Endpoint:** All-Cause Mortality at 1 yr (Non-inferiority)

**Co-Primary Endpoint:** Composite of All-Cause Mortality and Repeat Hospitalization (Superiority)
Absolute Reduction in Mortality in Inoperable Patients

The SAPIEN valve significantly improves survival

24.7% absolute reduction in mortality

(largest reduction in absolute mortality of any clinical trial in Cardiology)
Reduction in Repeat Hospitalization in Inoperable Patients

The Edwards SAPIEN valve significantly reduces repeat hospitalizations.

37.5% reduction in rehospitalizations at 2 yrs\textsuperscript{18}

In the first year alone, repeat hospitalization costs were $27,000 lower in patients treated with TAVR vs. control group.
At 5 Years

Patients that had TAVR with the Edwards SAPIEN valve showed survival equivalent to SAVR.

ALL CAUSE MORTALITY
At 5 Years

Error Bars Represent 95% Confidence Limits

All-Cause Mortality (%)

Interaction of Smoking Status and TAVR or SAVR

At 5 Years

Patients that had TAVR with the Edwards SAPIEN valve showed survival equivalent to SAVR.

**CoreValve Pivotal Trial: High-Risk Two-year outcomes**

The clinical outcomes to 2 years included: (A) all-cause mortality; (B) all strokes; (C) major adverse cardiovascular and cerebrovascular event (MACCE) and (D) aortic valve (AV) effective orifice area and mean gradient. TAVR = transcatheter aortic valve replacement.
Randomized trials of TAVR vs. SAVR in patients at intermediate risk

**SURTAVI**
CoreValve and Evolut R

**PARTNER 2A**
SAPIEN XT

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Surgical or Transcatheter Aortic-Valve Replacement in Intermediate-Risk Patients


Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients


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<table>
<thead>
<tr>
<th></th>
<th>SURTAVI</th>
<th>PARTNER 2A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device</strong></td>
<td>CoreValve / Evolut R</td>
<td>SAPIEN XT</td>
</tr>
<tr>
<td><strong>N</strong></td>
<td>864</td>
<td>1011</td>
</tr>
<tr>
<td><strong>Age</strong></td>
<td>79.9 ± 7.2</td>
<td>81.5 ± 6.7</td>
</tr>
<tr>
<td><strong>Male</strong></td>
<td>57.6%</td>
<td>54.2%</td>
</tr>
<tr>
<td><strong>STS</strong></td>
<td>4.4 ± 1.5</td>
<td>5.8 ± 2.1</td>
</tr>
</tbody>
</table>

**Average ages:**
- SURTAVI: 79.9 ± 7.2
- PARTNER 2A: 81.5 ± 6.7

**Gender distribution:**
- Male: 57.6% for SURTAVI, 54.2% for PARTNER 2A
Surtavi Trial
All-Cause Mortality or Disabling Stroke

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>No. at Risk SAVR</th>
<th>No. at Risk TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>796</td>
<td>864</td>
</tr>
<tr>
<td>18</td>
<td>674</td>
<td>755</td>
</tr>
<tr>
<td>12</td>
<td>555</td>
<td>612</td>
</tr>
<tr>
<td>6</td>
<td>407</td>
<td>456</td>
</tr>
<tr>
<td>0</td>
<td>241</td>
<td>272</td>
</tr>
</tbody>
</table>

24 Months

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality or Disabling Stroke</td>
<td>12.6%</td>
<td>14.0%</td>
</tr>
</tbody>
</table>
Surtavi Trial
All-Cause Mortality

- **30 Day**
  - SAVR 1.7%  O:E 0.38
  - TAVR 2.2%  O:E 0.50

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>SAVR</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0-6 months</td>
<td>796</td>
<td>864</td>
</tr>
<tr>
<td>6-12 months</td>
<td>690</td>
<td>762</td>
</tr>
<tr>
<td>12-18 months</td>
<td>569</td>
<td>621</td>
</tr>
<tr>
<td>18-24 months</td>
<td>414</td>
<td>465</td>
</tr>
<tr>
<td>24 months</td>
<td>249</td>
<td>280</td>
</tr>
</tbody>
</table>
Surtavi Trial
All-Cause Mortality

No. at Risk
SAVR 796 690 569 414 249
TAVR 864 762 621 465 280

30 Day
SAVR 1.7% O:E 0.38
TAVR 2.2% O:E 0.50

24 Months

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.4%</td>
<td>11.6%</td>
<td>-3.8, 3.3</td>
<td></td>
</tr>
</tbody>
</table>

24 Months All-Cause Mortality
Surtavi Trial
Disabling Stroke

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>No. at Risk</th>
<th>24 Months</th>
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<td>241</td>
</tr>
<tr>
<td>24</td>
<td>241</td>
<td>272</td>
</tr>
</tbody>
</table>

Disabling Stroke

- TAVR
- SAVR

24 Months

95% CI for Difference:
-2.6%, 4.5%, -4.0, 0.1
### 30 Day Safety Outcomes

#### Significantly better for TAVR
- **Stroke**: 3.4% TAVR, 5.6% SAVR
- **Transfusion use**: 12.5% TAVR, 41.1% SAVR
- **AKI**: 1.7% TAVR, 4.4% SAVR
- **Atrial fibrillation**: 12.9% TAVR, 43.4% SAVR
- **Cardiogenic shock**: 1.1% TAVR, 3.8% SAVR

#### Significantly better for SAVR
- **Major Vasc Comp**: 6.0% TAVR, 1.1% SAVR
- **Pacemaker use**: 25.9% TAVR, 6.6% SAVR

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**Legend:**
- Orange bar: TAVR
- Blue bar: SAVR
• SURTAVI met its primary endpoint: TAVR with a self-expanding CoreValve or Evolut R bioprosthesis is noninferior to SAVR for all-cause mortality or disabling stroke at 24 months.

• TAVR had significantly less 30 day stroke, AKI, atrial fibrillation and transfusion use.

• TAVR resulted in significantly less time in the ICU and the hospital.

• TAVR patients more quickly regained function and quality of life.
The PARTNER 2A Trial
Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT by Heart Valve Team Operable (STS ≥ 4%)

Randomized Patients
n = 2032

Asymptomatic Severe Aortic Stenosis

ASSESSMENT: Operable (STS ≥ 4%)

Randomized Patients
n = 2032

Yes → Transfemoral (TF)

1:1 Randomization (n = 1550)

TF TAVR (n = 775) vs. Surgical AVR (n = 775)

No → Transapical (TA) / TransAortic (TAo)

1:1 Randomization (n = 482)

TA/TAo TAVR (n = 236) vs. Surgical AVR (n = 246)

Primary Endpoint: All-Cause Mortality or Disabling Stroke at Two Years
Primary Endpoint (ITT)
All-Cause Mortality or Disabling Stroke

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>1011</td>
<td>1021</td>
</tr>
<tr>
<td>3</td>
<td>918</td>
<td>838</td>
</tr>
<tr>
<td>6</td>
<td>901</td>
<td>812</td>
</tr>
<tr>
<td>9</td>
<td>870</td>
<td>783</td>
</tr>
<tr>
<td>12</td>
<td>842</td>
<td>770</td>
</tr>
<tr>
<td>15</td>
<td>825</td>
<td>747</td>
</tr>
<tr>
<td>18</td>
<td>811</td>
<td>735</td>
</tr>
<tr>
<td>21</td>
<td>801</td>
<td>717</td>
</tr>
<tr>
<td>24</td>
<td>774</td>
<td>695</td>
</tr>
</tbody>
</table>

HR [95% CI] = 0.89 [0.73, 1.09]
p (log rank) = 0.253
Impact of Transfemoral Access

All-cause Mortality or Disabling Stroke

HR: 0.79 [95% CI: 0.62, 1.00]
p (log rank) = 0.05

All-Cause Mortality or Disabling Stroke (%)

Number at risk:

<table>
<thead>
<tr>
<th></th>
<th>TF Surgery</th>
<th>TF TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF Surgery</td>
<td>775</td>
<td>643</td>
</tr>
<tr>
<td>TF TAVR</td>
<td>775</td>
<td>718</td>
</tr>
</tbody>
</table>

Months from Procedure

- 0 months: 4.9%
- 3 months: 7.7%
- 6 months: 12.3%
- 9 months: 15.9%
- 12 months: 20.4%
- 15 months: 16.8%
- 18 months: 12.3%
- 21 months: 7.7%
- 24 months: 4.9%
The PARTNER 2A Trial
Clinical Implications

• The results from PARTNER 2A support the use of TAVR as an alternative to surgery in intermediate risk patients, similar to those included in this trial.

• In patients who are candidates for transfemoral access, TAVR may result in additional clinical advantages.

• Long-term durability assessments of transcatheter bioprosthetic valves are still lacking and extrapolation of these findings to low-risk patients requires further clinical trial validation.
Randomized Trials for Intermediate Risk Patients

- SURTAVI and PARTNER 2A demonstrated that TAVR may provide clinical advantages compared to SAVR in patients at intermediate surgical risk
- Economic analyses are eagerly awaited to know whether this is a cost-effective treatment option

<table>
<thead>
<tr>
<th></th>
<th>SURTAVI</th>
<th>PARTNER 2A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-inferiority to surgery for all-cause mortality or disabling stroke at 2 years</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Lower rates of high-impact complications (stroke, atrial fibrillation, bleeding, acute kidney injury)</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Favorable forward-flow hemodynamics</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Faster recovery</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Shorter hospital stay</td>
<td>X</td>
<td>Not Reported</td>
</tr>
</tbody>
</table>
TAVR is now a Class I indication for high risk patients, and a reasonable alternative to surgical AVR in patients at intermediate surgical risk.
Currently there is significant clinical investment in applying TAVR to younger patients at low surgical risk, both in North America and in Europe

<table>
<thead>
<tr>
<th>Study</th>
<th>Sponsorship</th>
<th>Countries</th>
<th>Valve Type</th>
<th>Routes</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Medtronic Low Risk&lt;sup&gt;1&lt;/sup&gt;</td>
<td>Industry-sponsored</td>
<td>~1200</td>
<td>up to 80 centers</td>
<td>Evolut R, all routes</td>
<td>10-year follow-up</td>
</tr>
<tr>
<td>PARTNER 3&lt;sup&gt;2&lt;/sup&gt;</td>
<td>Industry-sponsored</td>
<td>1228</td>
<td>up to 64 centers</td>
<td>SAPIEN 3, transfemoral</td>
<td>10-year follow-up</td>
</tr>
<tr>
<td>UK TAVI&lt;sup&gt;3&lt;/sup&gt;</td>
<td>Publically funded</td>
<td>808</td>
<td>All UK TAVI centers</td>
<td>All valves, all routes</td>
<td>5-year follow-up</td>
</tr>
<tr>
<td>NOTION-2&lt;sup&gt;4&lt;/sup&gt;</td>
<td>Physician and industry-sponsored</td>
<td>992</td>
<td>All Nordic countries</td>
<td>All valves, transfemoral</td>
<td>5-year follow-up</td>
</tr>
</tbody>
</table>

## Low Surgical Risk Trials Overview

<table>
<thead>
<tr>
<th></th>
<th>Medtronic Low Risk</th>
<th>PARTNER 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td>Death or major stroke at 2 years</td>
<td>Death, all stroke, or re-hospitalization (valve-related or procedure-related and including heart failure) at 1 year</td>
</tr>
<tr>
<td><strong>Patients</strong></td>
<td>Symptomatic, severe AS and a Heart Team predicted risk of 30-day mortality &lt; 3%</td>
<td>Symptomatic, severe AS and Heart Team assessment of low operative risk and STS &lt; 4%</td>
</tr>
<tr>
<td><strong>Study Design</strong></td>
<td>• Multi-center, prospective, randomized</td>
<td>• Multi-center, prospective, randomized</td>
</tr>
<tr>
<td></td>
<td>• 1:1 randomization to either TAVR or SAVR</td>
<td>• 1:1 randomization to either TAVR or SAVR</td>
</tr>
<tr>
<td><strong>Devices</strong></td>
<td>Investigational TAVR Arm</td>
<td>Investigational TAVR Arm</td>
</tr>
<tr>
<td></td>
<td>• Evolut R</td>
<td>• SAPIEN 3, transfemoral only</td>
</tr>
<tr>
<td></td>
<td>Control Arm</td>
<td>Control Arm</td>
</tr>
<tr>
<td></td>
<td>• Any commercially available bioprosthesis</td>
<td>• Any commercially available bioprosthesis</td>
</tr>
</tbody>
</table>
Medtronic TAVR in Low Risk Patients

Patient Selection

Heart Team Evaluation
One Cardiac Surgeons and One Interventional Cardiologist
Low Surgical Risk (predicted mortality risk <3%)

National Screening Committee
One Cardiac Surgeons and One Interventional Cardiologist
Confirm Low Risk for TAVR and SAVR

1:1 Randomization

TAVR
Leaflet sub-study N=200

SAVR
Leaflet sub-study N=200

4D CT scan to evaluate leaflet mobility
The PARTNER 3 Trial

Study Design

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team
(STS < 4%, TF only)

1:1 Randomization
(n=1228)

TF - TAVR
(SAPIEN 3)

Surgery
(Bioprosthetic Valve)

PARTNER 3 Registries

CT Imaging Sub-Study (n=200)

Actigraphy/QoL Sub-Study (n=200)

CT Imaging Sub-Study (n=200)

Actigraphy/QoL Sub-Study (n=200)

Bicuspid Valves
(n=100)

ViV (AV and MV)
(n=100)

Alternative Access
(n=100)
(TA/TAo/Subclavian)

Primary Endpoint:
Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year post-procedure

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years
• Transcatheter aortic valve insertion has demonstrated to be a valid alternative to surgery in patients with prohibitive, high and intermediate risk for surgery due to advanced aged and/or multiple co-morbidities

• TAVI has evolved to a safe procedure with very low mortality and risk for stroke and quick recovery

• Ongoing trials will hopefully demonstrate the role of TAVI in younger and low risk population
Thank you...