Aortic Stenosis. TAVR – available devices

Ioannis Iakovou, MD, PhD
Interventional Cardiology
Onassis Cardiac Surgery Center
Athens, Greece
TAVI is a “Breakthrough” Technology –

• Dramatic global growth and universal acceptance with seemingly unlimited future potential!

TAVI growth has been fueled by:

• the multi-disciplinary heart team
• commitment to evidence-based medicine
• striking reduction in complications
• simplification of the procedure
• rapid technology enhancement
TAVI is Available in More Than 65 Countries Around the World

In the next 10 years, TAVI growth will increase X4!

Approx 300000 total implants
TAVR “Underutilization” is Largely Driven by Variation in Health Policy and Reimbursement

2016: 374 cases in Greece, 21.3% OCSC
2017: 405 cases, aprox → 40/mil of inhabitants
Foundational randomized trials did provoke some concern about the safety of TAVR due to the incidence of certain complications, including stroke, conduction disturbances, paravalvular leak, and vascular trauma.
Foundational TAVR Devices

30-Day All Stroke

Weighted average (n=8,987)

4.2%

<table>
<thead>
<tr>
<th>Device</th>
<th>N</th>
<th>30-Day Stroke</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN:</td>
<td>179</td>
<td>6.7%</td>
</tr>
<tr>
<td>SAPIEN XT:</td>
<td>276</td>
<td>4.1%</td>
</tr>
<tr>
<td>SAPIEN XT:</td>
<td>348</td>
<td>4.6%</td>
</tr>
<tr>
<td>Intermediate Risk</td>
<td>284</td>
<td>4.3%</td>
</tr>
<tr>
<td>US Pivotal:</td>
<td>1,011</td>
<td>5.5%</td>
</tr>
<tr>
<td>CoreValve:</td>
<td>489</td>
<td>4.0%</td>
</tr>
<tr>
<td>High Risk US Pivotal</td>
<td>390</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Foundational TAVR Devices
New Permanent Pacemaker Implantation

Weighted average (n=8,987)
11.3%

Foundational TAVR Devices

Vascular Complications

Weighted average (n=8987)
7.7%

*Definitions vary across studies

<table>
<thead>
<tr>
<th>30-Day Major Vascular Complications</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>CoreValve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme Risk P 1B N=179</td>
<td>16.2%</td>
<td>11.0%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Extreme Risk P 2B N=276</td>
<td>15.2%</td>
<td>9.5%</td>
<td>5.9%</td>
</tr>
<tr>
<td>High Risk P 1A N=348</td>
<td></td>
<td>7.9%</td>
<td></td>
</tr>
<tr>
<td>Extreme Risk P 2B N=284</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate Risk P 2A N=1,011</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Extreme Risk US Pivotal N=489</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High Risk US Pivotal N=390</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Minimum Vessel Diameter (mm)

8.0/7.0  7.0  8.0/7.0  7.0  6.0/6.5  6.0

Foundational TAVR Devices

Paravalvular Leak

Weighted average (n=5,127)
Mild 34% / Moderate-Severe 10%

<table>
<thead>
<tr>
<th>Device</th>
<th>30-Day Paravalvular Leak</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>SAPIEN</strong></td>
<td></td>
</tr>
<tr>
<td>Extreme Risk P 1B N=153</td>
<td>12,0%</td>
</tr>
<tr>
<td>Extreme Risk P 2B N=225</td>
<td>43,0%</td>
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<tr>
<td>High Risk P 1A N=287</td>
<td>41,0%</td>
</tr>
<tr>
<td><strong>SAPIEN XT</strong></td>
<td></td>
</tr>
<tr>
<td>Extreme Risk P 2B N=236</td>
<td>24,2%</td>
</tr>
<tr>
<td>Intermediate Risk P 2A N=872</td>
<td>37,9%</td>
</tr>
<tr>
<td><strong>CoreValve</strong></td>
<td></td>
</tr>
<tr>
<td>Extreme Risk US Pivotal N=418</td>
<td>11,4%</td>
</tr>
<tr>
<td>High Risk US Pivotal N=356</td>
<td>35,7%</td>
</tr>
</tbody>
</table>

Iterative devices have been designed to mitigate complications, simplify the procedure, and improve upon current anatomic exclusions to enable the treatment of more patients.

<table>
<thead>
<tr>
<th>Frame</th>
<th>Nitinol</th>
<th>Nitinol</th>
<th>Cobalt Chromium</th>
<th>Nitinol</th>
<th>Nitinol</th>
</tr>
</thead>
<tbody>
<tr>
<td>PVL Management</td>
<td>Extended Skirt</td>
<td>Adaptive Seal</td>
<td>PET Fabric Skirt</td>
<td>Pericardial cuff</td>
<td>Pericardial skirt</td>
</tr>
<tr>
<td>Annular Range</td>
<td>18-34 mm</td>
<td>20-27 mm</td>
<td>16-28 mm</td>
<td>19-27 mm</td>
<td>21-27 mm</td>
</tr>
<tr>
<td>Positioning</td>
<td>Recapturable</td>
<td>Recapturable</td>
<td>--</td>
<td>Recapturable</td>
<td>--</td>
</tr>
<tr>
<td>Caliber</td>
<td>14 Fr / 16 Fr equiv.</td>
<td>18 Fr</td>
<td>14 Fr / 16 Fr</td>
<td>18 Fr / 19 Fr</td>
<td>18 Fr</td>
</tr>
</tbody>
</table>

- Evolut R
- Lotus
- SAPIEN 3
- Portico
- ACURATE neo
SAPIEN 3
Design Features

- Balloon-expandable cobalt chromium frame
- Bovine pericardial intra-annular valve
- Outer PET fabric skirt to reduce PVL
- Annular range: 16 – 28 mm
  - 4 valve sizes: 20, 23, 26, 29 mm
- Expandable 14Fr (vessels ≥ 5.5 mm) or 16Fr (vessels ≥ 6.0 mm) delivery sheaths for TF delivery
  - 14Fr: 20, 23, 26 mm THVs
  - 16Fr: 29 mm THV
Evolut R
Design Features

- Self-expanding Nitinol frame
- Porcine pericardial supra-annular valve
- Optimized sealing: extended skirt and more conformable frame
- Recapturable
- Annular range: 18 – 30 mm
  - 4 valve sizes: 23, 26, 29, 34 mm
  - 14Fr –equivalent profile, vessels ≥ 5.0 mm
  - 34 mm system: 16Fr-equivalent, vessels ≥ 5.5 mm
Lotus
Design Features

- Mechanically-expanded braided Nitinol frame
- Bovine pericardial valve
- Adaptive seal designed to minimize PVL
- Repositionable and recapturable
- No rapid pacing needed to deploy
- Annular range: 20 – 27 mm
  - 3 valve sizes: 23, 25, 27 mm
- 18Fr sheath, vessels ≥ 6.0 mm
Portico
Design Features

- Self-expanding Nitinol frame
- Intra-annular bovine pericardial valve
- Porcine pericardium sealing cuff
- Resheathable and recapturable
- Rapid pacing is not required for full deployment
- Annular range: 19 – 27 mm
  - 4 valve sizes: 23, 25, 27, 29 mm
- 18Fr sheath for 23 and 25 mm THVs
- 19Fr for 27 and 29 mm THVs
ACURATE Neo
Design Features

- Self-expanding Nitinol frame
- Porcine pericardial supra-annular valve
- Inner and outer pericardial skirts to minimize PVL
- Upper crown for supra-annular anchoring
- Lower crown minimizes protrusion into the LVOT
- Annular range: 21 – 27 mm
  - 3 valve sizes: S, M, L
- 18Fr – sheath compatible, vessels ≥ 6.0mm
All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated)

PARTNER 1 and 2 Trials
(Overall and TF Patients)
Strokes (All) at 30 Days
Edwards SAPIEN Valves

PARTNER 1 and 2 Trials
(Overall and TF Patients)

Neurologist evaluations (pre- and post)

<table>
<thead>
<tr>
<th>Group</th>
<th>Strokes (%)</th>
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</thead>
<tbody>
<tr>
<td>P1B (TF)</td>
<td>6.7%</td>
</tr>
<tr>
<td>P1A (All)</td>
<td>5.6%</td>
</tr>
<tr>
<td>P2B (TF)</td>
<td>4.1%</td>
</tr>
<tr>
<td>P2B XT (TF)</td>
<td>4.3%</td>
</tr>
<tr>
<td>S3HR (All)</td>
<td>1.5%</td>
</tr>
<tr>
<td>S3i (All)</td>
<td>2.6%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>SAPIEN</th>
<th>179</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN XT</td>
<td>344</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>276</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>284</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>583</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>1076</td>
</tr>
</tbody>
</table>
Moderate/Severe PVL at 30 Days
Edwards SAPIEN Valves

PARTNER I and II Trials
Overall and TF Patients

<table>
<thead>
<tr>
<th>Group</th>
<th>P1B (TF)</th>
<th>P1A (Overall)</th>
<th>P2B (TF)</th>
<th>P2B XT (TF)</th>
<th>S3HR (Overall)</th>
<th>S3i (Overall)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Count</td>
<td>179</td>
<td>344</td>
<td>276</td>
<td>284</td>
<td>583</td>
<td>1076</td>
</tr>
<tr>
<td>Rate</td>
<td>12.0%</td>
<td>11.5%</td>
<td>16.9%</td>
<td>24.2%</td>
<td>2.9%</td>
<td>4.2%</td>
</tr>
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Major outcomes of the current new-generation TAVR devices

TODARO et al CARDIAC INTERVENTIONS 2017
New Designs
Continued Improvements

Iterative device modifications continue to roll out

Evolut PRO
Pericardial tissue wrap to enhance sealing

SAPIEN 3 Ultra Delivery System
On-balloon design removes valve alignment step
Pusher is eliminated, reducing steps required during deployment

Lotus Edge
Depth guard to limit implant depth
Better flexibility
SAPIEN Platform Has Now Demonstrated Durability to 9 Years

Vancouver 9 year durability experience

- 9 year experience
- >1,000 implants
- 5 failed valves
Lifetime Management

Key Concerns

As TAVR is applied to younger patients, new strategies will be needed to manage inevitable clinical realities later in their lives.

Failed TAVs

Redo TAVR or surgical revision will be required for a subset of patients.

Coronary Artery Disease

Strategies to manage CAD post TAVR will be needed.

SAPIEN XT at explant (1 year)^2
Rebooting and/or Increasing Momentum

JENA Valve  CENTERA  VENUS A Valve
TAVR Global Landscape (#25)

- J – Valve Ausper
- VitaFlow (Microport)
- Taurus One
- Trinity
- Colibri
- Inovare
- Thubrikar
- Valve Medical
- Triskele
- BioValve (Biotronik)
- MyVal (Meril Lifescience)
- HLT Meridian
- NVT (Nautilus)
- Xeltis
- Zurich TEHV

All of the rest!
International device parade

- China
- China
- China
- UK
- U.S.
- Brazil
- U.S.
- Israel
- UK
- Germany
- India
- U.S.
- Germany
- Switzerland
- Switzerland

TAVR Global Landscape (#25)
Zurich Tissue Engineered Heart Valve

A “Living” Aortic Valve

Courtesy of Simon P. Hoerstrup, MD, PhD
Xeltis- Endogenous Tissue Restoration (ETR)

- Synthetic matrix made of novel bioborbablesupramolecular polymers using electrospinning techniques
- Polymer leaflets mounted on nitinol self-expanding frame
- Regrowth of endogenous tissue coincident with bioabsorption of polymer implant
- Natural self-healing anti-inflammatory leaflets
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TAVR current technology and Newcomers

Caveats to Consider...

• There is no single “perfect” TAVR system - design optimization involves tradeoffs and compromises (e.g. external cuff to reduce PVR adds profile)

• Strong subjective opinions regarding features – which is more important... PVR prevention, ultra-low profile, low PPM rate, retrievable and repositionable, BE vs. SE, etc.

• Significant operator experience necessary to formulate thoughtful impressions – difficult to be an expert with more than ~3 TAVR systems
TAVR in Perspective

The Future

• These next-generation TAVR devices are proving to be considerably safer and more efficient than their ancestors, constituting a large spectrum of valves with different features that allows for almost every different clinical and anatomical scenario and the treatment of an increasing number of patients
• Improved disease awareness and access to TAVR (esp. underserved populations)
• Further innovation of TAVR platforms (e.g. tissue engineered heart valves)
These data have enabled the recent approval of TAVR for patients at intermediate surgical risk in both Europe and the US.