TAVI: Present and Future Perspective

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Massachusetts General Hospital
Professor of Medicine
Harvard Medical School
For patients with symptomatic critical aortic stenosis, aortic valve replacement improves survival and quality of life.

However, the risks of open heart surgery in high-risk surgical patients have prompted investigation of alternative therapies, including balloon aortic valvuloplasty and transcatheter aortic valve implantation (TAVI).
Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

- Technological developments have been rapid in the field of percutaneous aortic valve intervention.
- Two devices have been approved for general use in Europe and USA: the Edwards SAPIEN valve (Edwards Lifesciences, Irvine, CA) and the CoreValve ReValving® System (CoreValve ReValving® Technology Medtronic Inc., Minneapolis, MN).
- Both systems can be delivered via the transfemoral, transapical and the axillary/subclavian routes, depending upon patient characteristics, anatomy, and the device available to the operator.
- There are 15 potential new designs for percutaneous aortic valves in development around the world.
Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

• At centers participating in the Society of Thoracic Surgery national database, the 30-day operative mortality in patients undergoing isolated aortic valve replacement is now 4%. This often-quoted risk, which includes young patients and those with bicuspid valves but excludes morbidity, may therefore represent only the floor of risk.

• In an older, but more inclusive, study from the National Medicare Database of patients 65 years of age, the average mortality was 8.8% and was as high as 13.0% in some centers.
Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

• Surgical AVR remains the gold standard for the treatment of severe, symptomatic aortic stenosis. However, percutaneous treatments are challenging this paradigm in high-risk surgical patients.

• In the past, high-risk and inoperable patients were offered balloon aortic valvuloplasty. This procedure remains an important palliative option but does not alter the natural history of aortic stenosis nor provide an improvement in survival.

• The current era of transcatheter aortic valve implantation built on this procedure and began with the first demonstration of feasibility in 2002.
PVT - The Foundation...

Percutaneous Valve Technologies
Aortic Heart Valve

Polyurethane

23mm max diameter

Bovine pericardium / Stainless steel stent

First Human Implant in 2002
Antegradе Approach: Guidewire Position in LV
Collaboration across the seas....

Drs. John Webb and Alain Cribier
Transcatheter aortic-valve implantation is becoming the standard of care for inoperable patients with severe aortic stenosis and a valid alternative for those at high surgical risk.

Since the first percutaneous transcatheter aortic-valve implantation in humans in 2002, over 50,000 transcatheter aortic valves have been implanted in the last decade, with progressive improvement in the available devices.
Percutaneous transcatheter aortic valve implantation: Present and Future Perspective
Overall, there are two main families of transcatheter prosthesis: self-expandable and nonself-expandable.

The self-expandable devices, for which CoreValve® (Medtronic CV Luxembourg S.a.r.l., Luxembourg) represents the prototype, are characterized by a structure composed of shape memory materials, usually nitinol, which acquire its final shape once released.

By contrast, the non-self-expandable prostheses, mainly represented by the Edwards® valve (Edwards Life Sciences, Inc., CA, USA), require balloon dilatation to reach its final shape.
Although several publications have already provided positive data on both technologies, new clinical studies with improved systems are currently being conducted in order to provide more solid data and potentially expand the spectrum of patients who can benefit from this therapy.

Thus, the aim of this presentation is to review the salient features of the two most used systems today (third-generation CoreValve and Edwards SAPIEN XT®) as well as to provide data on other emerging valves and future perspectives.
Careful selection of appropriate patients is essential to ensure a safe procedure.

This necessitates a multidisciplinary approach (the Heart Team), with multiple imaging modalities used to fully delineate the peripheral vasculature, aortic anatomy and the valve itself.

It is important to remember, however, that just because we can treat aortic valve disease percutaneously, it does not mean that we necessarily should do it.
The gold standard treatment for aortic stenosis remains thoracotomy and surgical replacement of the valve.

Thus, it is essential that cardiac surgeons play a central role in the decision-making processes for transcatheter aortic valve implantation and that they embrace this new and exciting technology, which promises to dramatically change the way their high-risk aortic valve patients are managed over the course of the next 10 years.
The risk of aortic valve replacement increases with age and other comorbidities, including emergency and prior cardiac surgery, lung and renal disease, small body surface area, history of stroke, atrial fibrillation, heart failure, and the need for associated coronary revascularization.

Some patients may be truly inoperable or denied surgery because of the presence of a porcelain aorta, prior radiation, cirrhosis, generalized frailty, or physician or patient preference. Therefore a nonsurgical alternative for these patients is both welcome and needed.
The past, present and future of TAVI

- Further technological development such as smaller diameter TAVI devices and proof of safety and durability
- Other innovations include use of advanced imaging techniques, such as multi-slice CT scans and 3D echocardiography to determine aortic valve anatomy and calcification. The results help members of the Heart team to determine arterial access site (transfemoral, transapical, Axilary, Ascending Aorta)
Edwards Valve Innovation

- **Starr-Edwards**
  - Mechanical Heart Valve

- **Carpentier-Edwards PERIMOUNT**
  - Magna Ease
    - Bovine Pericardial Heart Valve

- **Cribier-Edwards**
  - Transcatheter Heart Valve

- **Edwards SAPIEN XT**
  - Transcatheter Heart Valve

- **Edwards SAPIEN 3**
  - Transcatheter Heart Valve

**The PARTNER II TRIAL**
The PORTICO St Jude TAVI

Ability to fully resheath and precisely reposition at the implant site prior to valve deployment help minimize procedural risk for the patient.
Is the first TAVI that can completely resheathed into the delivery catheter and repositioned at the implant site or retrieved
Adjunctive Imaging for TAVR

Multi-modality Imaging is the RULE

Screening
Guidance
Follow-up

Angio
CTA
TTE
TEE + 3D

Adapted from: Lutz Buellesfeld
Stroke, major vascular complication and post TAVI AR remain the most concerning risk of TAVI.

New approaches to avoid embolic complications include the introduction of carotid filters and aortic deflectors.

There appear to be two key times for stroke: The first—within 48 hours of the procedure— is likely to involve embolization while the second one occurs 30 days later and is concern for thrombus formation around the valve. This raises important questions whether we should be routinely offering TAVI patients anticoagulation or antiplatelet therapy.
Percutaneous transcatheter aortic valve implantation: Present and Future Perspective

Embolic protection devices currently under investigation in transcatheter aortic valve replacement: Edwards Emboli-X filter (A), Claret CE Pro cerebral protection device (B), and TriGuard™ embolic deflection device (C).
Extending TAVI to intermediate risk patients is currently being explored in two ongoing trials: the SURTAVI trial for the Core Valve device and PARTNERS-2 for the Sapien valve. TAVI procedures to be widely acceptable to younger, lower risk patients.

Looking to the future, it might be possible to use bioresorbable stent in TAVI. Instead of using animal valves, we might be using stem cells seeded on to structural supports.
Edwards SAPIEN XT THV Builds on the Proven Balloon Expandable Platform and Now Allows for a 16F TAVR Procedure*

22F RetroFlex 3 Sheath (Compatible with 23mm SAPIEN valve)

27% Reduction in Profile

16F eSheath (Compatible with 23mm SAPIEN XT valve)

* For the 23mm SAPIEN XT valve
Balloon-Expandable Valves
Designed for Predictable Results

Initial Positioning
- Use Center Marker and fine positioning feature

Deployment
- Slow, controlled initial inflation using nominal volume

Final Placement
- Predictable results
Critical Elements for Durability

Circularity

Bovine Tissue

Leaflet Matching

Carpentier-Edwards ThermaFix™ Process

1. Heat treatment removes unstable glutaraldehyde molecules
2. Patented chemical treatment removes 98% of phospholipids

Edwards Commander Delivery System

- Ultra-low profile 14F eSheath compatible*

<table>
<thead>
<tr>
<th>SAPIEN 3 Valve Size</th>
<th>23 mm</th>
<th>26 mm</th>
<th>29 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards eSheath Introducer Set</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>6.0 mm</td>
</tr>
</tbody>
</table>

*14F eSheath compatible for 23 mm and 26 mm SAPIEN 3 valves. 16F eSheath compatible for 29 mm SAPIEN 3 valve.
Edwards Commander delivery system

- Dual articulation for coaxiality even in challenging anatomies; aids in crossing the native annulus
- Trusted balloon-expandable design with improved control of valve positioning

Partial flex

Distal flex

Fine control of valve positioning
Edwards Certitude delivery system

- Ultra-low profile system – 18F Sheath compatible*
- Integrated pusher
- Articulation feature for ease of coaxial positioning
- Ergonomically designed handle

<table>
<thead>
<tr>
<th>SAPIEN 3 Valve Size</th>
<th>23 mm</th>
<th>26 mm</th>
<th>29 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Certitude Introducer Sheath</td>
<td>18F</td>
<td>18F</td>
<td>21F</td>
</tr>
</tbody>
</table>
F.I.M. Balloon Aortic Valvuloplasty

1985 - 1994

Post-mortem studies of intra-valvular stenting

« Percutaneous Valve Technology » (prototypes)

1999

Animal implantations (sheep)

2000

F.I.M. THV implantation

2002

Feasibility Studies (antegrade)

2002-03

2004

2005-07

2007

Since 2007

PARTNER US Pivotal

Post market registries

CE mark commercialization

2008-09

International TF and TA Feasibility Studies

2004

Edwards Lifesciences

2005-07

Since 2007

Feasibility Studies (antegrade)

2004

F.I.M. Balloon Aortic Valvuloplasty

1993-1994

2000

1999

1985

FDA Approval (non-surgical and high risk surgical)

Nov 2011

Oct 2012
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)
The PARTNER II Trial
Study Design

Symptomatic Severe Aortic Stenosis

Operable (STS ≥4)

ASSESSMENT by Heart Valve Team

Yes

ASSESSMENT: Transfemoral Access

Transfemoral (TF)

1:1 Randomization

TF TAVR SAPIEN XT vs Surgical AVR

Primary Endpoint: All-Cause Mortality + Disabling Stroke at Two Years (Non-inferiority)

No

Transapical (TA) / TransAortic (TAo)

1:1 Randomization

TAVR: TA / TAo SAPIEN XT vs Surgical AVR

Inoperable

ASSESSMENT: Transfemoral Access

Yes

TF TAVR SAPIEN XT vs TF TAVR SAPIEN

Primary Endpoint: All-Cause Mortality + Disabling Stroke + Repeat Hospitalization at One Year (Non-inferiority)

Two Parallel Randomized Trials + 6 Nested Registries

n = 2000 Randomized Patients

n = 560 Randomized Patients

Operable

6 Nested Registries

Sample Size

NR1 (Sm Vessel) 100
NR2 (Transapical) 100
NR3 (ViV) 100
NR4 (TAo) 100
NR5 (29 mm TF) 50
NR6 (29 mm TA) 50
# Primary Endpoint Events: At 30 Days (ITT)

<table>
<thead>
<tr>
<th>Events</th>
<th>SAPIEN (n=276)</th>
<th>SAPIEN XT (n=284)</th>
<th>p-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All-Cause</td>
<td>14</td>
<td>5.1</td>
<td>10</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>9</td>
<td>3.3</td>
<td>5</td>
</tr>
<tr>
<td><strong>Stroke:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Disabling</td>
<td>8</td>
<td>3.0</td>
<td>9</td>
</tr>
<tr>
<td>All</td>
<td>11</td>
<td>4.1</td>
<td>12</td>
</tr>
<tr>
<td>All + TIA</td>
<td>13</td>
<td>4.8</td>
<td>12</td>
</tr>
<tr>
<td>Death (all-cause) and Stroke (disabling)</td>
<td>19</td>
<td>6.9</td>
<td>18</td>
</tr>
<tr>
<td><strong>Re-hospitalizations</strong></td>
<td>27</td>
<td>10.2</td>
<td>32</td>
</tr>
<tr>
<td>Death (all-cause), Stroke (disabling), and Re-hosp</td>
<td>42</td>
<td>15.3</td>
<td>48</td>
</tr>
</tbody>
</table>

*p-values are KM - Log Rank
# Vascular Complication Categories: At 30 Days (AT)

<table>
<thead>
<tr>
<th>Events</th>
<th>SAPIEN (n=271)</th>
<th></th>
<th>SAPIEN XT (n=282)</th>
<th></th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n</td>
<td>%</td>
<td>n</td>
<td>%</td>
<td></td>
</tr>
<tr>
<td>Perforation</td>
<td>13</td>
<td>4.8</td>
<td>2</td>
<td>0.4</td>
<td>0.003</td>
</tr>
<tr>
<td>Dissection</td>
<td>25</td>
<td>9.2</td>
<td>12</td>
<td>4.3</td>
<td>0.03</td>
</tr>
<tr>
<td>Hematoma</td>
<td>16</td>
<td>5.9</td>
<td>10</td>
<td>3.6</td>
<td>0.23</td>
</tr>
</tbody>
</table>
All-Cause Mortality (ITT)

HR [95% CI] = 0.93 [0.66, 1.33]
p (log rank) = 0.706
Disabling Stroke (ITT)

HR [95% CI] = 0.96 [0.43, 2.14]

p (log rank) = 0.926

No. at Risk

SAPIEN 276
SAPIEN XT 284

SAPIEN 241
SAPIEN XT 250

SAPIEN 223
SAPIEN XT 238

SAPIEN 209
SAPIEN XT 227

SAPIEN 134
SAPIEN XT 145
Echocardiographic Findings:
Mean & Peak Gradients (AT, Valve Implant)

<table>
<thead>
<tr>
<th>No. of Echos</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>237</td>
<td>263</td>
</tr>
<tr>
<td>30 Days</td>
<td>224</td>
<td>237</td>
</tr>
<tr>
<td>1 Year</td>
<td>113</td>
<td>118</td>
</tr>
</tbody>
</table>

Graph showing the comparison of peak and mean gradients over time for SAPIEN and SAPIEN XT.
Paravalvular Aortic Regurgitation (Valve Implant)

No. of Echos

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN</td>
<td>225</td>
<td>110</td>
</tr>
<tr>
<td>SAPIEN XT</td>
<td>236</td>
<td>120</td>
</tr>
</tbody>
</table>

- **p = 0.12**
  - SAPIEN: 38.6%
  - SAPIEN XT: 24.2%

- **p = 0.20**
  - SAPIEN: 38.2%
  - SAPIEN XT: 37.7%
PARTNERS II - Results

- SAPIENT XT treatment was associated with reductions in anesthesia time \( (p = 0.02) \), multiple valve implants \( (p = 0.05) \), aborted procedures \( (p = 0.06) \), and the need for IABP hemodynamic support \( (p = 0.06) \).

- At 30 days,
  - All-cause mortality and disabling strokes were similar (Mortality: SAPIEN 5.1% vs. SAPIEN XT 3.5%; Strokes: SAPIEN 3.0% vs. SAPIEN XT 3.2%).
  - Major vascular complications were reduced after SAPIENT XT (from 15.5% to 9.6%, \( p = 0.04 \)), including perforations, dissections, and hematomas.
  - All other clinical endpoints were similar.
PARTNERS II - Results

• At 1 year,
  – All-cause mortality, disabling strokes, and re-hospitalizations were similar, including the non-hierarchical composite primary endpoint (SAPIEN XT 33.9% vs. SAPIEN 34.7%, non-inferiority p-value = 0.0034)
  – Improvement in NYHA class was similar
  – Echo valve performance (EOA and gradients) was similar
Implications

In the inoperable cohort of The PARTNER II Trial, the new lower profile SAPIEN XT THV system was associated with...

• Improved procedural outcomes
• Similar low 30-day mortality and strokes
• Reduced vascular complications
• Similar 1-year major clinical events and valve performance

Therefore, SAPIEN XT represents a worthwhile advance with incremental clinical value and is the preferred balloon-expandable THV system.
Edwards THV Evolution

- **2004**
  - Cribier-Edwards™ THV 23mm

- **2007**
  - Edwards SAPIEN™ THV 23 mm and 26 mm

- **2010**
  - Edwards SAPIEN XT™ THV 23 mm, 26 mm, and 29mm

- **Features**
  - Stainless Steel Frame
  - Bovine Pericardial Tissue

- **2007**
  - Stainless Steel Frame
  - Bovine Pericardial Tissue

- **2010**
  - Cobalt-Chromium Frame
  - Bovine Pericardial Tissue
  - Semi-closed leaflets
  - Reduced crimped profile
Edwards SAPIEN 3 THV

Frame design
- Enhanced frame geometry for ultra-low delivery profile
- High radial strength for circularity and optimal hemodynamics

Bovine pericardial tissue
- Optimized leaflet shape
- Carpentier-Edwards ThermaFix* process for anti-calcification

Low frame height
- Respects the cardiac anatomy

Outer skirt
- Designed to minimize paravalvular leak
The PARTNER II Trial: SAPIEN 3i
Study Design – Intermediate Risk

[Diagram showing study design]

Symmetrical Severe Aortic Stenosis

ASSESSMENT by Heart Valve Team

Intermediate Risk Operable (Pill 33i)

n=1000 Patients

ASSESSMENT: Optimal Valve Delivery Access No stratification

Transfemoral (TF)

TF TAVR SAPIEN 3

Transapical (TA)

TA TAVR SAPIEN 3

Transaortic (TAo)

TAo TAVR SAPIEN 3

SAPIEN 3

2 Single Arm Non-Randomized Historical-Controlled Studies

High Risk Operable / Inoperable (Pill 3HR)

n=500 Patients

ASSESSMENT: Optimal Valve Delivery Access No stratification

Transfemoral (TF)

TF TAVR SAPIEN 3

Transapical (TA)

TA TAVR SAPIEN 3

Transaortic (TAo)

TAo TAVR SAPIEN 3

ENROLLMENT COMPLETED
## Baseline Characteristics (1)

### Operability Risk Assessment

<table>
<thead>
<tr>
<th>Risk Factor</th>
<th>AT* Patients (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (Years)</td>
<td>83.6 ± 5.0</td>
</tr>
<tr>
<td>Female</td>
<td>81 (54.0%)</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>130 (86.7%)</td>
</tr>
<tr>
<td>Severe Pulmonary Hypertension</td>
<td>10 (6.7%)</td>
</tr>
<tr>
<td>Severely Impaired Pulmonary Function Contradicting Surgery</td>
<td>8 (5.3%)</td>
</tr>
<tr>
<td>Hostile Chest</td>
<td>3 (2.0%)</td>
</tr>
<tr>
<td>Severe Liver Disease / Cirrhosis</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Frailty Index VARC-2 (continuous)</td>
<td>1.3 ± 0.9</td>
</tr>
<tr>
<td>Patients with 1 or More Risk Factors</td>
<td>147 (98.0%)</td>
</tr>
</tbody>
</table>

### Non-Cardiac Conditions

<table>
<thead>
<tr>
<th>Condition</th>
<th>AT* Patients (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Renal Insufficiency</td>
<td>60 (40.0%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>48 (32.0%)</td>
</tr>
<tr>
<td>Anemia</td>
<td>46 (30.7%)</td>
</tr>
<tr>
<td>Pulmonary Disease – COPD</td>
<td>40 (26.7%)</td>
</tr>
<tr>
<td>Cancer</td>
<td>32 (21.3%)</td>
</tr>
</tbody>
</table>

### Echo Parameters

<table>
<thead>
<tr>
<th>Parameter</th>
<th>AT* Patients (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Effective Orifice Area (cm²)</td>
<td>0.6 ± 0.2</td>
</tr>
<tr>
<td>Mean Gradient (mm Hg)</td>
<td>45.3 ± 14.3</td>
</tr>
<tr>
<td>LV Ejection Fraction (LVEF) (%)</td>
<td>56.3 ± 9.2</td>
</tr>
<tr>
<td>Mitral Regurgitation (Moderate to Severe)</td>
<td>26 (22.4%)</td>
</tr>
<tr>
<td>Annular Diameter (TEE - mean) (mm)</td>
<td>23.2 ± 2.3</td>
</tr>
</tbody>
</table>

* AT, as-treated.
<table>
<thead>
<tr>
<th>Baseline Characteristics (%)</th>
<th>TF PATIENTS (N = 96)</th>
<th>TAA PATIENTS (N = 54)</th>
<th>P-VALUE</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS PROM Score</td>
<td>7.5 ± 4.26</td>
<td>7.3 ± 4.94</td>
<td>0.813</td>
</tr>
<tr>
<td>Logistic EuroSCORE (%)</td>
<td>19.8 ± 10.9</td>
<td>24.9 ± 14.0</td>
<td>0.022</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>16.7</td>
<td>38.9</td>
<td>0.003</td>
</tr>
<tr>
<td>Previous Myocardial Infarction</td>
<td>11.5</td>
<td>27.8</td>
<td>0.014</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>14.6</td>
<td>27.8</td>
<td>0.056</td>
</tr>
<tr>
<td>Atrial Fibrillation</td>
<td>22.9</td>
<td>35.8</td>
<td>0.125</td>
</tr>
<tr>
<td>Previous Aortic Valvuloplasty</td>
<td>10.4</td>
<td>3.7</td>
<td>0.213</td>
</tr>
<tr>
<td>Previous Pacemaker Implantation</td>
<td>13.5</td>
<td>16.7</td>
<td>0.635</td>
</tr>
<tr>
<td>Carotid Disease</td>
<td>25.0</td>
<td>25.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Porcelain Aorta</td>
<td>1.0</td>
<td>1.9</td>
<td>1.000</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>7.3</td>
<td>7.4</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Procedural Characteristics (1)

Note: Limited 14F eSheath availability during initial patient enrollment period. The 29 mm valve was introduced later in the trial. Due to a low rate of paravalvular leak a strategy of minimal oversizing evolved.
# Procedural Characteristics (2)

<table>
<thead>
<tr>
<th>Variable</th>
<th>TF PATIENTS (N = 96)</th>
<th>ALL PATIENTS (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Femoral Access/Anesthesia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General</td>
<td>63.5%</td>
<td></td>
</tr>
<tr>
<td>Conscious Sedation</td>
<td>36.5%</td>
<td></td>
</tr>
<tr>
<td><strong>Femoral Access/Closure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Percutaneous/Closure Device</td>
<td>95.8%</td>
<td></td>
</tr>
<tr>
<td>Surgical</td>
<td>4.2%</td>
<td></td>
</tr>
<tr>
<td><strong>Procedural Outcomes</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Correct Placement at Intended Site</td>
<td>149 (99.3%)</td>
<td></td>
</tr>
<tr>
<td>Post-dilatation</td>
<td>5 (3.3%)</td>
<td></td>
</tr>
<tr>
<td>Technical Success*</td>
<td>94.0%</td>
<td></td>
</tr>
<tr>
<td><strong>Procedural Events</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conversion to Conventional Surgery</td>
<td>1 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Patient Required ECMO</td>
<td>1 (0.7%)</td>
<td></td>
</tr>
<tr>
<td>Coronary Obstruction</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
<tr>
<td>Valve-in-Valve</td>
<td>0 (0.0%)</td>
<td></td>
</tr>
</tbody>
</table>

*No procedural mortality, correct positioning, and only one valve implanted.*
# Clinical Outcomes at 30 Days (1)

## EVENT RATE IN THE AT POPULATION

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>TF (N = 96)</th>
<th>TAA (N = 54)</th>
<th>Overall (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>2 (2.1%)</td>
<td>6 (11.1%)</td>
<td>8 (5.3%)</td>
</tr>
<tr>
<td>Cardiac Mortality</td>
<td>2 (2.1%)</td>
<td>5 (9.3%)</td>
<td>7 (4.7%)</td>
</tr>
<tr>
<td>All-Stroke*</td>
<td>1 (1.0%)</td>
<td>3 (5.6%)</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>Disabling Stroke</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Major Vascular Complication</td>
<td>5 (5.2%)</td>
<td>4 (7.4%)</td>
<td>9 (6.0%)</td>
</tr>
<tr>
<td>Major Bleeding</td>
<td>19 (19.8%)</td>
<td>11 (20.4%)</td>
<td>30 (20.0%)</td>
</tr>
<tr>
<td>Life-Threatening Bleeding</td>
<td>2 (2.1%)</td>
<td>3 (5.6%)</td>
<td>5 (3.3%)</td>
</tr>
<tr>
<td>Rehospitalization†</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

## EVENT RATE IN THE VI POPULATION

<table>
<thead>
<tr>
<th>Primary Endpoint</th>
<th>TF (N = 95)</th>
<th>TAA (N = 54)</th>
<th>Overall (N = 149)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause Mortality</td>
<td>1 (1.1%)</td>
<td>6 (11.1%)</td>
<td>7 (4.7%)</td>
</tr>
</tbody>
</table>

**Notes:**
- VI, valve implant = all enrolled patients who received a SAPIEN 3 implant, and retain the valve upon leaving the cath lab
- * Severity of the one TF stroke unknown.
- † Rehospitalization for for valve-related symptom or worsening of congestive heart failure.
# Clinical Outcomes at 30 Days (2)

<table>
<thead>
<tr>
<th>Clinical Outcome</th>
<th>TF (N = 96)</th>
<th>TAA (N = 54)</th>
<th>Overall (N = 150)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute Kidney Injury (Stage II/III)</td>
<td>1 (1.0%)</td>
<td>3 (5.6%)</td>
<td>4 (2.7%)</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>2 (2.1%)</td>
<td>0 (0.0%)</td>
<td>2 (1.3%)</td>
</tr>
<tr>
<td>Reintervention*</td>
<td>1 (1.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Valve Thrombosis</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>New-Onset Atrial Fibrillation</td>
<td>7 (7.3%)</td>
<td>11 (20.4%)</td>
<td>18 (12.0%)</td>
</tr>
<tr>
<td>New Permanent Pacemaker Implanted</td>
<td>12 (12.5%)</td>
<td>8 (14.8%)</td>
<td>20 (13.3%)</td>
</tr>
</tbody>
</table>

* Valve Malposition requiring a second valve on Day 0
Clinical Improvement at 30 Days

**NYHA Class**
- Baseline: N = 150
  - NYHA Class I: 13.3%
  - NYHA Class II: 78.0%
  - NYHA Class III: 45.2%
  - NYHA Class IV: 8.7%
- 30 Days: N = 135
  - NYHA Class I: 48.2%
  - NYHA Class II: 4.7%

**Angina CCS Class**
- Baseline: N = 150
  - CCS Class I: 0.8%
  - CCS Class II: 11.9%
  - CCS Class III: 13.4%
  - CCS Class IV: 66.0%
- 30 Days: N = 134
  - CCS Class I: 9.3%
  - CCS Class II: 10.0%
  - CCS Class III: 1.3%
  - CCS Class IV: 85.1%

\[ p < 0.0001 \]
\[ p = 0.0027 \]
Improvement in Quality of Life at 30 Days

**VAS EQ-5D**

- Baseline: 56.9
- 30 Days: 64.7
- p < 0.0001

**6-Minute Walk Test**

- Baseline: 210.9
- 30 Days: 241.6
- p = 0.0031

N = 146
N = 127
N = 76
N = 76

VAS, Visual Analogue Scale.

* p-values from paired t-test baseline vs follow-up.
**Echocardiographic Data**

**Mean Gradient & Effective Orifice Area (EOA)**

* mVI population (Overall, N = 149; TF, N=95). The modified valve implant (mVI) population consists of all VI patients who retained the study valve at the time of assessment.

![Diagram showing mean gradient and effective orifice area for baseline, discharge, and 30 days.](chart)

### **EOA**

<table>
<thead>
<tr>
<th>No. of Patients</th>
<th>Baseline</th>
<th>Discharge</th>
<th>30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>EOA</td>
<td>110</td>
<td>99</td>
<td>100</td>
</tr>
<tr>
<td>Mean Gradient</td>
<td>125</td>
<td>116</td>
<td>122</td>
</tr>
</tbody>
</table>

*p < 0.0001*
Echocardiographic Data at 30 Days

**TOTAL AR**
(N = 149)

<table>
<thead>
<tr>
<th>None/Trace</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF</td>
<td>69.2%</td>
<td>28.2%</td>
<td>2.6%</td>
</tr>
<tr>
<td>TAA</td>
<td>79.5%</td>
<td>15.4%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>72.6%</td>
<td>23.9%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>

**PARAVALVULAR AR**
(N = 149)

<table>
<thead>
<tr>
<th>None/Trace</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>TF</td>
<td>68.8%</td>
<td>28.6%</td>
<td>2.6%</td>
</tr>
<tr>
<td>TAA</td>
<td>79.5%</td>
<td>15.4%</td>
<td>5.1%</td>
</tr>
<tr>
<td>Overall</td>
<td>72.4%</td>
<td>24.1%</td>
<td>3.4%</td>
</tr>
</tbody>
</table>
Conclusions – The SAPIEN 3 Trial

- Outcomes at 30 days were excellent
- TF SAPIEN 3 implantation was associated with a very low mortality of 2.1%, stroke of 1.0%, and very few access-site complications
- TF implantation was associated with a very low mortality of 1.1% in the valve implant population
- 99.3% of valves were implanted at the intended location - due to precise SAPIEN 3 positioning
- 96.6% of patients had ≤ mild PVL. There was no severe PVL
- Post-implant maneuvers were rarely needed despite reduced oversizing – procedural post-dilatation (3.3%), valve-in-valve implants (0%)
- The SAPIEN 3 THV may enable treatment of intermediate-risk patients with aortic stenosis
New TAVI Systems - *Transfemoral*

- Direct Flow
- Sadra
- St. Jude
- AorTx
- HLT
- EndoTech
- ABPS PercValve
New TAVI Systems - *Transapical*

- Jena Valve

- MDT (Engager)

- Symetis

  (73 pts, + CE approval)

  (40 pts)

  (90 pts, + CE approval)
New Edwards Sapien 3 Valve Platform