Trans Catheter Aortic Valve Replacement

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AnMed Health Heart and Vascular Care
No financial conflict of interest related to this talk

Will discuss some non-FD approved devices
Objectives

- Review the clinical course of severe symptomatic aortic stenosis
- Identify treatment options for severe symptomatic aortic stenosis
- Review clinical trial data regarding TAVR
- Discuss future developments in TAVR
Aortic stenosis is estimated to be prevalent in up to 7% of the population over the age of 65\(^1\).

It is more likely to affect men than women; 80% of adults with symptomatic aortic stenosis are male\(^3\).
Aortic stenosis in patients over the age of 65 is usually caused by calcific (calcium) deposits associated with aging.

Adults who have had rheumatic fever may also be at risk for aortic stenosis.

In some cases adults may develop aortic stenosis resulting from a congenital abnormality.
3 Major Etiologies for aortic stenosis
Symptoms of aortic stenosis

- Shortness of breath
- Syncope/ pre-syncope
- Angina
- Fatigue
- Dyspnea on exertion
- CHF
- A-fib related
Aortic Stenosis Is Life Threatening and Progresses Rapidly

- Survival after onset of symptoms is 50% at 2 years and 20% at 5 years\(^1\)
- Surgical intervention for severe aortic stenosis should be performed promptly once even minor symptoms occur\(^1\)
5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis
Measurement of Aortic Stenosis Severity

LVOT diameter 1.9 cm

LVOT velocity 0.8 m/s

AS Jet 3.6 m/s

$SV_{LVOT} = SV_{AS jet}$

$CSA_{LVOT} \times VT_{LVOT} = AVA \times VT_{AS jet}$

$AVA = \frac{VT_{LVOT} \times CSA_{LVOT}}{VT_{AS jet}}$
SAVR: Mechanical Valve
SAVR: Bio-prosthetic Valve
Study data demonstrate that early and late outcomes were similarly good in both symptomatic and asymptomatic patients.

It is important to note that among asymptomatic patients with SAS, omission of surgical treatment was the most important risk factor for late mortality.
Studies show at least 40% of patients with severe AS are not treated with an AVR.
What is TAVR—Transcatheter Aortic Valve Replacement?

- An aortic valve replacement as an alternative to traditional thoracotomy.
- Less invasive than traditional thoracotomy for patients considered too high risk for traditional surgery.
Two TAVR Options

- Edwards Sapien Valve
- Stainless Steel Frame
- More Aortic Regurg, less AV block/PPM
- Better for severe bulky calcification.

- Medtronic CoreValve
- Nitinol Frame-self expanding
- Less Aortic Regurg, More heart block/PPM
Patients at Extreme Surgical Risk

Foundational trials tested new TAVR therapy in patients without the option for a surgical aortic valve replacement

US CoreValve Pivotal Trial

CoreValve, N=489, STS 10.3%

PARTNER 1B

SAPIEN, N=179, STS 11.2%
PARTNER showed that by 3 years, TAVR had reduced mortality by approximately 30% compared to standard medical management.

Similar survival results were achieved with CoreValve in the US Pivotal Trial.
*In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.*
Median Survival

- Standard Therapy: 11.1 Months
- TAVR: 29.7 Months

p (log rank) < 0.0001
Patients at High Surgical Risk

Trials randomizing high risk patients to either TAVR or SAVR soon followed

**US CoreValve Pivotal Trial**

CoreValve, N=390, STS 7.3% vs. SAVR, N=357, STS 7.5%

**PARTNER 1A**

SAPIEN, N=348, STS 11.8% vs. SAVR, N=351, STS 11.7%
PARTNER showed that ~35% of patients survived to 5 years, regardless of treatment.

This study provided the first confirmation that TAVR is a reasonable alternative to surgery in high risk patients.

### All-Cause Mortality (ITT)

#### All Patients

- **TAVR**: 348 at Risk, 262 at 12 months, 228 at 24 months, 191 at 36 months, 154 at 48 months, 61 at 60 months
- **SAVR**: 351 at Risk, 236 at 12 months, 210 at 24 months, 174 at 36 months, 131 at 48 months, 64 at 60 months

HR [95% CI] = 1.04 [0.86, 1.24], p (log rank) = 0.76
The CoreValve Pivotal Trial was the first to show a survival advantage with TAVR compared to SAVR, with separation of the all-cause mortality curves maintained to 3 years.
Patients at Intermediate Surgical Risk

Randomized trial data comparing TAVR to SAVR in lower-risk patients recently became available

SAPIEN XT and SAPIEN 3

CoreValve

Transcatheter aortic valve replacement versus surgical valve replacement in intermediate-risk patients: a propensity score analysis


JAMA Cardiology | Brief Report
Outcomes in the Randomized CoreValve US Pivotal High-risk Trial in Patients With a Society of Thoracic Surgeons Risk Score of 7% or Less

Michael J. Reardon, MD; Neal S. Kleinman, MD; David H. Adams, MD; Steven J. Valiquette, MD; Joseph S. Coselli, MD; G. Michael Deeb, MD; Daniel C. Haight, MD; Thomas G. Gleason, MD; Joon Sup Lee, MD; James B. Hermiller Jr, MD; Stony Checoti, MD; John Heiber, MD; William Merhi, DO; George L. Zorn III, MD; Peter Tadros, MD; Newell Robinson, MD; George Petrosian, MD; G. Chad Hughes, MD; J. Kevin Harrison, MD; Brijeshwar Mansi, MD; Mukhtiar Mamaz, MD; John V. Conte, MD; Jon R. Rosas, MD; Vicken Alikhanian, MD; Thomas Pfeffer, MD; Joe K. Oh, MD; Jian Heang, MD; Jeffrey J. Popma, MD

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


The New England Journal of Medicine

Structural Heart Disease

Two-Year Outcomes in Patients With Severe Aortic Valve Stenosis Randomized to Transcatheter Versus Surgical Aortic Valve Replacement
The All-Comers Nordic Aortic Valve Intervention Randomized Clinical Trial

Lars Søndergaard, MD, DMSc; Daniel Andreas Steinbrüchel, MD, DMSc; Nikolaj Ihlemann, MD, PhD; Henrik Nissen, MD, PhD; Bo Juel Kjeldsen, MD, PhD; Peter Petersson, MD, PhD; Anh Thue Ngo, MD, PhD; Niels Thue Olsen, MD, PhD; Yanping Chang, MS; Olaf Walter Franson, MD; Thomas Engstrom, MD, DMSc; Peter Clemmensen, MD, DMSc; Peter Skov Olsen, MD, DMSc; Hans Gustav Horsted Thyregod, MD
The PARTNER 2A Trial showed that TAVR with SAPIEN XT was non-inferior to surgery for the primary endpoint of all-cause mortality or disabling stroke at 2 years.
This study also generated convincing evidence that transfemoral TAVR provides an outcome advantage to intermediate risk patients.

In the as-treated population, TF TAVR significantly reduced all-cause mortality or disabling stroke vs. surgery (p = 0.04).

Smith, et al., presented at ACC 2016
PARTNER S3 HR

Mortality and Stroke: S3HR
At 30 Days (As Treated Patients)

Mortality
- All-Cause
- Cardiovascular

Stroke
- All Stroke
- Disabling

O:E = 0.26
(STS 8.6%)
PARTNER S3

Symptomatic Severe Aortic Stenosis

ASSESSMENT by Heart Valve Team

 Intermediate Risk Operable (PII S3i)

- ASSESSMENT: Optimal Valve Delivery Access
  - Transfemoral (TF)
    - TF TAVR SAPIEN 3
  - Transapical / Transaortic (TA/TAo)
    - TAA TAVR SAPIEN 3
  - PI A SAVR
  - PI A SAPIEN

 SAPIEN 3

- 2 Single Arm Non-Randomized Historical-Controlled Studies

 High Risk Operable / Inoperable (PII S3HR)

- ASSESSMENT: Optimal Valve Delivery Access
  - Transfemoral (TF)
    - TF TAVR SAPIEN 3
  - Transapical / Transaortic (TA/TAo)
    - TAA TAVR SAPIEN 3
  - PI A SAVR
  - PI A SAPIEN

n = 1076 Patients

n = 583 Patients
PARTNER S3 IR

- All cause mortality
  - 1.1% vs 4% at 30 days
  - 7.4% vs 13.5% at 1 year

- Disabling Stroke
  - 1% vs 4.4% at 30 days
  - 2.3% vs 5.9% at 1 year

75% reduction in Death and in disabling stroke
Currently there is significant clinical investment in applying TAVR to younger patients at low surgical risk, both in North America and in Europe.
Valve in Valve Implantation
Expanding the Limits

Transapical Transcatheter Aortic Valve for Severe Aortic Regurgitation

Daniel Wendt, MD, PhD,* Philipp Kahlert, MD, PhD,† Susanne Pasa, MD,* Karim El-Chilali, MD,† Fadi Al-Rashid, MD,† Konstantinos Tsagakis, MD,* Daniel Sebastian Dohle, MD,* Raimund Erbel, MD, PhD,† Heinz Jakob, MD, PhD,* Matthias Thielmann, MD, PhD*
Future Trials

- **EARLY TAVR**
  - TAVR in asymptomatic severe AS

- **TAVR UNLOAD**
  - TAVR in moderate AS with CHF/ LV dysfunction
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.
Complications

- Death
- Stroke
- Vascular Complications
- Pacemaker implantation
- Paravalvular regurgitation
- Late valve dysfunction
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>Transfemoral TAVR Devices</th>
<th>Iterative Device Design</th>
</tr>
</thead>
</table>

- **SAPIEN 3**
  - Frame: Nitinol
  - PVL Management: Extended Skirt
  - Annular Range: 18-30 mm
  - Positioning: Recapturable
  - Caliber: 14 Fr / 16 Fr equiv.
  - Nitinol: 18 Fr
  - Cobalt Chromium: PET Fabric Skirt
  - Pericardial cuff: 16-28 mm
  - Recapturable: 14 Fr / 16 Fr

- **Lotus**
  - Frame: Nitinol
  - PVL Management: Adaptive Seal
  - Annular Range: 20-27 mm
  - Positioning: Recapturable
  - Caliber: 18 Fr
  - Cobalt Chromium: PET Fabric Skirt
  - Pericardial cuff: 19-27 mm
  - Recapturable: 14 Fr / 19 Fr

- **Evolut R**
  - Frame: Nitinol
  - PVL Management: Extended Skirt
  - Annular Range: 18-30 mm
  - Positioning: Recapturable
  - Caliber: 18 Fr
  - Cobalt Chromium: PET Fabric Skirt
  - Pericardial cuff: 19-27 mm
  - Recapturable: 14 Fr / 19 Fr

- **Portico**
  - Frame: Nitinol
  - PVL Management: Adaptive Seal
  - Annular Range: 16-28 mm
  - Positioning: Recapturable
  - Caliber: 18 Fr
  - Cobalt Chromium: PET Fabric Skirt
  - Pericardial cuff: 19-27 mm
  - Recapturable: 14 Fr / 19 Fr

- **ACURATE neo**
  - Frame: Nitinol
  - PVL Management: Pericardial skirt
  - Annular Range: 21-27 mm
  - Positioning: Recapturable
  - Caliber: 18 Fr
  - Cobalt Chromium: PET Fabric Skirt
  - Pericardial cuff: 19-27 mm
  - Recapturable: --
TAVR valves - more to come

(A) Lotus (Boston Scientific Inc., Natick, Massachusetts), (B) Direct Flow (Direct Flow Medical Inc., Santa Rosa, California), (C) HLT (Bracco Inc., Princeton, New Jersey), (D) Portico (St. Jude Medical Inc., St. Paul, Minnesota), (E) Engager (Medtronic Inc., Minneapolis Minnesota), (F) JenaClip (JenaValve Inc., Munich, Germany), (G) Acurate valve (Symetis Inc., Ecublens, Switzerland), and (H) Inovare (Braile Biomedica Inc., São José do Rio Preto, Brazil) valves.
Protection of cerebral events during TAVR

Embrella Embolic Deflector
(Edwards Lifesciences)

Triguard
(Keystone Heart, Herzliya Pituach, Israel)
Protection of cerebral events during TAVR

Claret Montage
(Claret Medical, CA)
Multiple Modalities May Be Used to Diagnose Severe Aortic Stenosis

- Auscultation
- Trans-thoracic Echo (TTE)
- Cardiac Cath.
- Chest X-ray
- Electrocardiogram
Confirm the patient is diagnosed with severe symptomatic native aortic stenosis

Confirm the patient has been independently evaluated by two cardiac surgeons and meets the indication for TAVR

Evaluate the aortic valvular complex using echocardiography

Evaluate the peripheral vasculature and aortic valvular complex using MDCT

Evaluate the peripheral vasculature and aortic valvular complex using catheterization

Note: Evaluation using CT is typically not done unless the Heart Team confirms that patient is a candidate for TAVR
CTA: Critical for determining Access
AnMed Experience

- 20 cases in the last 6 months
- Ages 59 to 85
- High STS scores/ high risk for SAVR
- No Death/CVA/PPM implantation
- No major vascular complications (one pseudoaneurysm)
- One expected ICD to remove life-vest
TAVR video
Conclusions

- TAVR is the only option for extreme risk patients
- TAVR is an equal or better for high risk patients
- TAVR is an equal or better option for intermediate risk patients
- TAVR for low risk patients being studied
Edwards evolution of valve design

SAPIEN    SAPIEN XT    SAPIEN 3
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

Stroke

Weighted average (n=8,987) 4.2%

30-Day All Stroke

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Event Rate</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Extreme Risk P 1B</td>
<td>6.7%</td>
<td>179</td>
</tr>
<tr>
<td>Extreme Risk P 2B</td>
<td>4.1%</td>
<td>276</td>
</tr>
<tr>
<td>High Risk P 1A</td>
<td>4.6%</td>
<td>348</td>
</tr>
<tr>
<td>Extreme Risk P 2B</td>
<td>4.3%</td>
<td>284</td>
</tr>
<tr>
<td>Intermediate Risk P 2A</td>
<td>5.5%</td>
<td>1,011</td>
</tr>
<tr>
<td>Extreme Risk US Pivotal</td>
<td>4.0%</td>
<td>489</td>
</tr>
<tr>
<td>High Risk US Pivotal</td>
<td>4.9%</td>
<td>390</td>
</tr>
</tbody>
</table>

Foundational TAVR Devices
New Permanent Pacemaker Implantation

Weighted average (n=8,987) 11.3%

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Sample Size</th>
<th>30-Day Permanent Pacemaker</th>
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</thead>
<tbody>
<tr>
<td>Extreme Risk P 1B</td>
<td>N=179</td>
<td>3.4%</td>
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References:
### Foundational TAVR Devices

#### Vascular Complications

<table>
<thead>
<tr>
<th>Risk Level</th>
<th>Study</th>
<th>N</th>
<th>30-Day Major Vascular Complications</th>
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<tbody>
<tr>
<td>Extreme Risk</td>
<td>P 1B</td>
<td>179</td>
<td>16.2%</td>
</tr>
<tr>
<td></td>
<td>P 2B</td>
<td>276</td>
<td>15.2%</td>
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<tr>
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<td>348</td>
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#### Minimum Vessel Diameter (mm)

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

*Definitions vary across studies

Foundational TAVR Devices
Paravalvular Leak

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

<table>
<thead>
<tr>
<th>Device</th>
<th>Extreme Risk</th>
<th>High Risk</th>
<th>Intermediate Risk</th>
<th>Extreme Risk</th>
<th>High Risk</th>
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<tbody>
<tr>
<td>SAPIEN</td>
<td>P 1B N=153</td>
<td>P 1A N=287</td>
<td>P 2A N=872</td>
<td>P 1B N=225</td>
<td>P 2A N=356</td>
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<tr>
<td>SAPIEN XT</td>
<td>P 2B N=236</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>CoreValve</td>
<td></td>
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</table>

12.0%  68.0%
17.1%  43.0%
12.0%  41.0%
24.2%  37.9%
3.7%   22.5%
11.4%  41.5%
9.0%   35.7%

SAPIEN
SAPIEN XT
CoreValve

30-Day Paravalvular Leak

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>Device</th>
<th>Frame</th>
<th>Nitinol</th>
<th>Nitinol</th>
<th>Cobalt Chromium</th>
<th>Nitinol</th>
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<th>Caliber</th>
</tr>
</thead>
<tbody>
<tr>
<td>Evolut R</td>
<td>PVL Management</td>
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<tr>
<td>Lotus</td>
<td>Annular Range</td>
<td>Adaptive Seal</td>
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<td>--</td>
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</tr>
<tr>
<td>SAPIEN 3</td>
<td>Positioning</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Portico</td>
<td>Caliber</td>
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<td></td>
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<tr>
<td>ACURATE neo</td>
<td>Nitinol</td>
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</tbody>
</table>
A literature search was conducted to identify studies reporting procedural and 30-day outcomes for groups of patients treated with new valves in real-world practice.

- The rates of paravalvular leak, new pacemaker implantation, stroke, and major vascular complications were tabulated and the weighted average was calculated for each valve type.
Real-World Evidence Base
New Transfemoral Valves

45 unique cohorts were identified through the literature search, representing over 15,000 patients treated with new valves in real-world practice.
In contemporary practice, the overall stroke rate remains around 3.5%.
New Permanent Pacemakers
Real-World Evidence

- The rate of new permanent pacemaker implantation is sensitive to device type.
- The rates are typically around 15% with Evolut R and SAPIEN 3, and approximately 2x higher with the Lotus valve.

<table>
<thead>
<tr>
<th>Device</th>
<th>Rate</th>
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<tr>
<td>Lotus</td>
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<tr>
<td>Evolut R</td>
<td>18.2%</td>
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<tr>
<td>SAPIEN 3</td>
<td>13.4%</td>
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<tr>
<td>ACURATE Neo</td>
<td>8.0%</td>
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<td>Portico</td>
<td>6.4%</td>
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</table>
### Moderate / Severe Paravalvular Leak

#### Real-World Evidence

- The Lotus valve virtually eliminates moderate or severe PVL
- Other valves have brought the rates to ~5% or less

<table>
<thead>
<tr>
<th>Valve</th>
<th>Weighted Averages</th>
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<td>2.3%</td>
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<td>Lotus</td>
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</table>
Major vascular complications have come down under 5% across all valve types.
The preferred access site has been dynamic in the US as the regulatory landscape has changed.

With the introduction of Evolut R and SAPIEN 3, more than 90% of TAVRs are performed through the TF approach.

1 Carrol, et al., presented at TCT 2016
Increased use of the transfemoral approach has facilitated a simpler procedure, shown by the decreased use of general anesthesia in favor of conscious sedation.

Wide variation in anesthesia mode likely reflects geographical differences and individual physician preferences.
Foundational TAVR Devices

Stroke

Weighted average (n=8,987)
4.2%

<table>
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<th>Category</th>
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Foundational TAVR Devices
New Permanent Pacemaker Implantation

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# Foundational TAVR Devices

## Vascular Complications

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<th>Study</th>
<th>N</th>
<th>30-Day Major Vascular Complications</th>
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<tr>
<td>Extreme Risk P2B</td>
<td>Webb, et al., J Am Coll Cardiol Intv 2015;8:1797-806</td>
<td>276</td>
<td>15.2%</td>
</tr>
<tr>
<td>High Risk P1A</td>
<td>Smith, et al., N Engl J Med 2011;364:2187-98</td>
<td>348</td>
<td>11.0%</td>
</tr>
<tr>
<td>Intermediate Risk P2A</td>
<td>Popma, et al., J Am Coll Cardiol 2014;63:1972-81</td>
<td>1011</td>
<td>7.9%</td>
</tr>
<tr>
<td>High Risk US Pivotal</td>
<td></td>
<td>390</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

**Minimum Vessel Diameter (mm):**

- Extreme Risk P1B: 8.0/7.0
- Extreme Risk P2B: 7.0
- High Risk P1A: 8.0/7.0
- Extreme Risk P2B: 7.0
- Intermediate Risk P2A: 6.0/6.5
- Extreme Risk US Pivotal: 6.0
- High Risk US Pivotal: 6.0

*Definitions vary across studies*
Foundational TAVR Devices
Paravalvular Leak

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