Learning Objectives

1. Understand the pathophysiology and natural history of aortic stenosis
2. Learn the various treatment options for aortic stenosis
3. Review of latest trial data related to TAVR

Leonardo Da Vinci gave us the first description of the heart 500 years ago

Aortic Stenosis

Age-related calcific aortic stenosis is the most common cause of AS in adults and its prevalence steadily increases with age. Critical AS affects approximately 3% of patients > 75 years.

Progressive calcification, initially along the flexion lines at their bases, leads to immobilization of one or more aortic cusps leading to left ventricular outflow obstruction \( \rightarrow \) symptoms.

How is Aortic Stenosis Diagnosed?

The murmur of aortic stenosis is often not subtle. Loud, harsh systolic crescendo-decrescendo murmur best heard in the right upper sternal border radiating to the carotids. As aortic stenosis becomes critical, the murmur becomes late peaking and A2 diminishes and can become absent.

It is usually the primary physicians who hear the murmur and order an echo.
Severe aortic stenosis is life threatening and treatment is critical

Adult average course with valvular aortic stenosis

Onset severe symptoms

Average survival, y

Survival, %

Latent period
(Increasing obstruction, myocardial overload)

Angina
Syncope
Failure

Age, years

0 40 50 60 70


Symptoms of aortic stenosis (AS)
- Shortness of breath
- Syncope or presyncope
- Angina
- Fatigue
- Difficulty when exercising
- Swollen ankles and feet
- Rapid or irregular heartbeat
- Palpitations (an uncomfortable awareness of heart beating rapidly or irregularly)

The symptoms of aortic disease are commonly misunderstood by patients as ‘normal’ signs of aging.

Many patients initially appear asymptomatic, but on closer examination up to 37% exhibit symptoms.

Aortic Valve Replacement Greatly Improves Survival

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.

In symptomatic patients with severe aortic stenosis, aortic valve replacement has been shown to improve both symptoms and survival.

* No randomized trial comparing AVR to medical therapy has ever been done.

According to the AHA/ACC guidelines for valvular heart disease, AVR is indicated in virtually all symptomatic patients with severe AS (Class I recommendation, Level of Evidence: B).

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**Echocardiographic Guidelines are the Gold Standard in Assessing Severe Aortic Stenosis**

<table>
<thead>
<tr>
<th>Grading the Severity of Aortic Stenosis per the ACC/AHA Guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)</td>
</tr>
<tr>
<td>Jet velocity (m/s)</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
</tr>
</tbody>
</table>

- According to the ACC/AHA guidelines, severe aortic stenosis is defined as:
  - Aortic valve area (AVA) less than 1.0 cm²
  - Mean gradient greater than 40 mmHg or jet velocity greater than 4.0 m/s

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**Composite of aortic valve-related death or heart failure hospitalization**

A) Symptomatic AS

Group 1 (Ht/Vmax<4.5)

Group 2 (Ht/Vmax<6.0)

Group 3 (Ht/Vmax>6.0)

B) Asymptomatic AS

Group 1 (Ht/Vmax<4.5)

Group 2 (Ht/Vmax<6.0)

Group 3 (Ht/Vmax>6.0)
The first trans-catheter aortic valve implantation was performed antegrade via trans-septal puncture in France in April 2002 by Dr. Alain Cribier.
April 16th 2002: FIM-TAVR, trans-septal

15 min post-TAVR

Leon, Martin B. TAVR in Perspective: Evolution, Impact, and Future Expectations. Oral presentation at the Transcatheter Valve Therapies (TVT) Conference; June 2017; Chicago, IL.
The two current FDA-approved TAVR valves

TAVR Rollout
- TAVR as it relates to device and as a therapy was rolled out in a controlled fashion backed by randomized controlled trials supporting its benefit in each patient risk category
- TAVR should be the role model of how future devices should be approved and implemented in clinical practice

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%
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%
- Numbers at Risk:
  - CoreValve, 130, 124, 110, 60
  - SAVR, 143, 131, 85, 42

**PARTNER 1A**
- SAPIEN, N=348, STS 11.8% vs. SAVR, N=351, STS 11.7%
- Numbers at Risk:
  - SAPIEN, 179, 130, 124, 110, 60
  - Standard Therapy, 179, 131, 85, 42

**CoreValve US Clinical Trials**

**All-Cause Mortality (ITT)**

- Transcatheter: 0.93 [0.8, 1.15]
- Surgical: 0.75 [0.6, 1.01]
- **Log-rank P=0.04**
- Numbers at Risk:
  - Transcatheter: 391, 378, 354, 334, 259
  - Surgical: 359, 343, 304, 282, 191

**All-Cause Mortality**

- Transcatheter: 6.5
- Surgical: 28.6
- **Log-rank P=0.04**
Randomized trial data comparing TAVR to SAVR in lower-risk patients recently became available.

**SAPIEN XT and SAPIEN 3**


**CoreValve**

Outcomes in the Randomized CoreValve US Pivotal-High Risk Trial in Patients with Society of Thoracic Surgeons Risk Score of 7% or Less.

**Intermediate Risk**

**PARTNER 2A | SAPIEN XT**

- This study also generated convincing evidence that transfemoral TAVR provides an outcome advantage in intermediate-risk patients.
- In the as-treated population, TF TAVR significantly reduced all-cause mortality or disabling stroke vs. surgery (p = 0.04).

**Low Surgical Risk**

Active Trials Randomizing TAVR to SAVR

Currently there is significant clinical investment in applying TAVR to younger patients at low surgical risk, both in North America and in Europe.

**Medtronic Low Risk**

- **PARTNER 3**
  - N = 1228
  - Up to 64 centers
  - SAPIEN 3, transfemoral
  - 10-year follow-up

- **UK TAVI**
  - N = 808
  - All UK TAVI centers
  - All valves, all routes
  - 5-year follow-up

- **NOTION-2**
  - N = 992
  - All Nordic countries
  - All valves, transfemoral, physician and industry-sponsored
  - 5-year follow-up

**Transcatheter Aortic-Valve Replacement with a Self-Expanding Valve in Low-Risk Patients**


May 2, 2019
10.1056/NEJMc1913261
D01: 10.1056/NEJMc1913261
Clinical Outcomes at 1 Year

Bayesian rates as %

<table>
<thead>
<tr>
<th>Event</th>
<th>TAVR (N=725)</th>
<th>SAVR (N=678)</th>
<th>(95% BCI for Difference)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or disabling stroke</td>
<td>2.7</td>
<td>4.6</td>
<td>(-4.3, 0.4)</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.4</td>
<td>3.0</td>
<td>(-2.6, 1.3)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.7</td>
<td>2.6</td>
<td>(-2.7, 0.7)</td>
</tr>
<tr>
<td>All stroke</td>
<td>4.1</td>
<td>4.3</td>
<td>(-2.4, 1.9)</td>
</tr>
<tr>
<td>Disabling stroke*</td>
<td>0.8</td>
<td>2.4</td>
<td>(-3.8, -0.3)</td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td>1.7</td>
<td>1.8</td>
<td>(-1.6, 1.3)</td>
</tr>
<tr>
<td>Myocardial infection</td>
<td>1.7</td>
<td>1.6</td>
<td>(-1.3, 1.5)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.2</td>
<td>0.4</td>
<td>(-0.9, 0.5)</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>0.2</td>
<td>0.3</td>
<td>(-0.9, 0.5)</td>
</tr>
<tr>
<td>Aortic valve reintervention</td>
<td>0.7</td>
<td>0.6</td>
<td>(-1.6, 0.9)</td>
</tr>
<tr>
<td>Heart failure hospitalization*</td>
<td>3.3</td>
<td>6.5</td>
<td>(-6.5, -1.6)</td>
</tr>
</tbody>
</table>

*Significantly favors TAVR

K-M All-Cause Mortality or Disabling Stroke at 1 Year

Log-rank P = 0.065

K-M Rates of All-Cause Mortality at 1 Year

Log-rank P = 0.412

Transcatheter Aortic-Valve Replacement with a Balloon-Expandable Valve in Low-Risk Patients


May 2, 2013

The New England Journal of Medicine

DOI: 10.1056/NEJMoa1204532
There is interest in using TAVR to intervene earlier in the AS disease process to prevent inevitable myocardial damage and functional decline.

**Earlier Intervention**

**Active Trials**

TAVR will be compared to medical therapy in patients with moderate AS, symptoms of heart failure, and reduced EF.

**EARLY TAVR**

TAVR will be applied to asymptomatic patients with severe AS.

**Estimated global TAVR growth**

Between 2018 – 2025, the TAVR market will increase more than 2X.
Transfemoral TAVR Devices
Iterative Device Design

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>Membrane</th>
<th>Annular Range</th>
<th>Positioning</th>
<th>Caliber</th>
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<tbody>
<tr>
<td>Lotus</td>
<td>Nitinol</td>
<td>16-20 mm</td>
<td>16-20 mm</td>
<td>Recapturable</td>
<td>18 Fr</td>
</tr>
<tr>
<td>SAPIEN 3</td>
<td>Nitinol</td>
<td>16-20 mm</td>
<td>16-20 mm</td>
<td>Recapturable</td>
<td>18 Fr</td>
</tr>
<tr>
<td>Portico</td>
<td>Nitinol</td>
<td>15-27 mm</td>
<td>15-27 mm</td>
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<tr>
<td>ACURATE neo</td>
<td>Nitinol</td>
<td>15-27 mm</td>
<td>15-27 mm</td>
<td>Recapturable</td>
<td>18 Fr</td>
</tr>
</tbody>
</table>

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.

Summary - Patient GH
82 yo F who presented in July 2012 with acute CHF. She was known to have severe AS but was previously asymptomatic. Echo in 7/2012 showed an EF of 20%. She was referred by her primary cardiologist for TAVR.

Clinical History
- 82 yo F with:
  - History of atrial fibrillation
  - Severe aortic stenosis
  - Hypertension
  - Hyperlipidemia
  - TB age 15-22
  - Colonic polyps
  - DJD spine with scoliosis
  - Fall in 9/2010 c/b pelvic fx
  - Left wrist fracture 2007

LV function after anesthesia induction
LV End Diastolic Volume – 251 ml

Functional Mitral Regurgitation

Aortic Stenosis & Regurgitation

Trace central AI after deployment
LV function post TAVR

LV End Diastolic Volume – 168 ml

MR post TAVR – where did it go?
What is valve in valve TAVR?

- We typically estimate that a surgical bioprosthesis will last 10-15 years. Valves degenerate by calcification causing stenosis or leaflet tear causing regurgitation.

- Valve in valve TAVR refers to implanting a THV inside of a degenerated surgical valve.

- Valve in valve TAVR was FDA approved in 2015 with both SAPIEN XT and CoreValve THV.

- Many patients undergoing open SAVR are choosing tissue valves, banking on having a valve in valve option in future.
Conscious sedation
Skin to skin 27 minutes
Next day discharge
Mick Jagger gives TAVR a boost!

Mick Jagger is "Between a Rock & A Hard Place" with severe Aortic stenosis which is a "Beast of Burden". With #TAVR, he can strut to "Start Me Up" in no time! Story here: #BarnesAndNoble's own rock 'n' roller Dr. Babaria! #TAVR

#MovesLikeJagger
#MovesLikeTAVR
"Each of us must make the effort to contribute to the best of our ability according to our individual talents. And then we put all the individual talents together for the highest good of the group. ... Understanding that the good of the group comes first is fundamental to being a highly productive member of a team." — John Wooden