Disease State Overview Etiology, Symptoms and Prognosis
Aortic Stenosis

Gross specimen of minimally diseased aortic valve (left) and severely stenotic aortic valve (right)

Images courtesy of Renu Virmani MD at the CVPath Institute
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\(^3\)
What Causes Aortic Stenosis in Adults?

More Common

- **Age-Related Calcific Aortic Stenosis**: Aortic stenosis in patients over the age of 65 is usually caused by calcific (calcium) deposits associated with aging.

- **Infection**: Aortic stenosis can be caused by various infections.

- **Rheumatic Fever**: Adults who have had rheumatic fever may also be at risk for aortic stenosis.

- **Congenital Abnormality**: In some cases adults may develop aortic stenosis resulting from a congenital abnormality.

Less Common
Symptoms of Aortic Stenosis

What are the symptoms of aortic stenosis?

- **Angina** - A sensation of aching, burning, discomfort, fullness, pain, or squeezing in the chest. It may also be felt in the arms, back, jaw, neck, shoulders and throat.

- **Fainting** - A sudden and brief loss of consciousness.

- **Shortness of breath** - Feeling winded and tired when walking or lying down.

- **Dizziness (after periods of inactivity)**.

- **Rapid or irregular heartbeat**.

- **Palpitations** – An uncomfortable awareness of the heart beating rapidly or irregularly.
Preliminary Diagnosis of Aortic Stenosis

- Detection and estimation of disease severity can often be achieved by auscultation
  - Audible systolic heart murmur
    - Longer duration with later peak is consistent with more severe stenosis
    - Loudness of the murmur does not necessarily correlate with the severity of stenosis
  - Soft or absent second heart sound
- Delayed carotid upstroke
Multiple Modalities May Be Used to Diagnose Severe Aortic Stenosis\(^6\)
According to the 2008 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
Survival after onset of symptoms is 50% at 2 years\textsuperscript{1}

Surgical intervention for severe aortic stenosis should be performed promptly once even minor symptoms occur\textsuperscript{1}
- As seen previously, survival after onset of symptoms in patients with aortic stenosis is 50% at 2 years.\(^1\)

- The PARTNER Trial showed that in inoperable patients with severe aortic stenosis who did not receive a valve replacement, 50% died within 1 year.

- Despite the frequent utilization of BAV, standard therapy did not do much to alter the dismal course of disease for inoperable patients with severe aortic stenosis.
Studies show at least 40% of SAS patients are not treated with an AVR$^{9-15}$
Sobering Perspective

5-Year Survival

<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Survival, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast Cancer</td>
<td>23</td>
</tr>
<tr>
<td>Lung Cancer</td>
<td>4</td>
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<tr>
<td>Colorectal Cancer</td>
<td>12</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>30</td>
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<tr>
<td>Ovarian Cancer</td>
<td>28</td>
</tr>
<tr>
<td>Severe Inoperable AS*</td>
<td>3</td>
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</tbody>
</table>

*Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tuczu, MD, Cleveland Clinic

5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis
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.
Options for Aortic Valve Replacement

- **High Risk Patients**
  - Transapical Transcatheter Aortic Valve Replacement (TAVR)
  - Transfemoral Transcatheter Aortic Valve Replacement (TAVR)
  - Surgical Aortic Valve Replacement (SAVR)
- **Inoperable Patients**
  - Transfemoral Transcatheter Aortic Valve Replacement (TAVR)

**Minimal Incision Valve Surgery (MIVS)**

- Transapical Approach
- Transfemoral Approach
Transcatheter Aortic Valve Replacement (TAVR)

TAVR Procedure Overview
The Edwards SAPIEN transcatheter heart valve is indicated for patients with severe symptomatic calcified native aortic valve stenosis who have been examined by a Heart Team including an experienced cardiac surgeon and cardiologist and found to be either inoperable or at high risk for surgical aortic valve replacement.
What is TAVR?

- For patients who are either at high risk or too sick for open-heart surgery, TAVR may be an alternative.
- This less invasive procedure allows the aortic valve to be replaced with a new valve while the heart is still beating.
Edwards SAPIEN Transcatheter Heart Valve

- Bovine pericardial tissue
- Leaflets matched for thickness and elasticity
- Stainless steel frame
- PET skirt
Transfemoral Procedural Animation
Balloon Aortic Valvuloplasty
Sheath Insertion
Tracking the Delivery System Over the Aortic Arch
Edwards SAPIEN Transcatheter Heart Valve Deployment
Some patients may not have adequate vascular access to accommodate the sheath used during transfemoral procedures.

For these patients, the transapical procedure may be an option.

During the transapical approach, the Edwards SAPIEN transcatheter heart valve is delivered through the apex of the heart by making a small incision between the ribs.
Transapical Procedural Animation
The PARTNER Trial
Definitive Results Through Rigorous Design

THE PARTNER TRIAL PROTOCOL

Severe Symptomatic Native Aortic Valve Stenosis

ASSESSMENT: OPERABILITY
(N = 3,105)

Yes

Cohort A
High-Risk
(n = 699)

ASSESSMENT
Transfemoral Access

Yes

TF
(n = 492)

No

TA
(n = 207)

No

2 Cohorts
Individually Powered
(n = 1,057)

Yes

ASSESSMENT
Transfemoral Access

Yes

Not in Study

No

Cohort B
Inoperable
(n = 358)
Definitive Results Through Rigorous Design

**THE PARTNER TRIAL COHORT B INCLUSION CRITERIA**

**Severe Symptomatic Native Aortic Valve Stenosis**

- **ASSESSMENT: OPERABILITY**
  - (N = 3,105)
  - **Yes**
  - **No**

**Cohort A**
- **High-Risk**
  - (n = 699)
  - **Yes**
  - **No**

**2 Cohorts**
- **Individually Powered**
  - (n = 1,057)

**Cohort B**
- **Inoperable**
  - (n = 358)

**COHORT B KEY INCLUSION CRITERIA**

- Predicted operative mortality or irreversible morbidity: > 50%
- NYHA functional class: ≥Ⅱ
- AVA: < 0.8 cm²
- Mean gradient: > 40 mmHg
- Peak jet velocity: > 4.0 m/s

*Patient selection required at least two cardiothoracic surgeons and a cardiologist to agree that patients were not suitable candidates for surgery.

†This mean score reflects enrolled patient group; not required for inclusion.
Definitive Results Through Rigorous Design

THE PARTNER TRIAL COHORT B ENDPOINTS

Severe Symptomatic Native Aortic Valve Stenosis

ASSESSMENT: OPERABILITY
(N = 3,105)

Yes

Cohort A
High-Risk
(n = 699)

2 Cohorts
Individually Powered
(n = 1,057)

Cohort B
Inoperable
(n = 358)

No

ASSESSMENT
Transfemoral Access

Yes

TF
(n = 492)

No

TA
(n = 207)

COHORT B PRIMARY ENDPOINT
All-cause mortality over length of trial
(Superiority)
Edwards SAPIEN THV Improved Survival

**ALL-CAUSE MORTALITY**

\[ P \text{ (log rank)} < 0.0001 \]
\[ \Delta \text{ at 2 yrs} = 24.7\% \]
\[ \text{NNT} = 4.0 \text{ pts} \]

- Standard Therapy: 68.0%
- Edwards SAPIEN THV: 43.3%

30.7% vs 50.7%
Edwards SAPIEN THV Improved Cardiac Function

Mean Gradient Over Time

Error bars = ± 1 Std Dev

THE PARTNER TRIAL COHORT B
Edwards SAPIEN THV Reduced Symptoms

NYHA CLASS OVER TIME

P = .61

P < .0001

P < .0001

P < .0001

Patients, %

THE PARTNER TRIAL COHORT B
Edwards SAPIEN THV Had Higher Incidence of Stroke

Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.
Edwards SAPIEN THV Had Higher Incidence of Major Vascular Complications

Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (dissection, stenosis, perforation, rupture, arterio-venous fistula, pseudoaneurysm, or hematoma) leading to either death, need for significant blood transfusion (> 3 units), or percutaneous or surgical intervention, and/or distal embolization (non-cerebral) from a vascular source requiring surgery or resulting in amputation or irreversible end-organ damage.
Critical Insights

Standard therapy is failing patients with inoperable aortic stenosis

68% Utilization

Based on the 2-year results of Cohort B, patients treated with the Edwards SAPIEN THV:

Only need to treat 4 patients to save a life

4 out of 5 patients were asymptomatic or mildly symptomatic at 2 years

First-generation Edwards SAPIEN THV was associated with important peri-procedural events at 2 years:

- Stroke
- Major vascular complications
- Bleeding Event
**Study Design & Inclusion Criteria**

**Severe Symptomatic Native Aortic Valve Stenosis**
- **Assessment: Operability** (n=3,105)
  - **Yes**
    - **Cohort A High-Risk** (n=699)
      - **Assessment: Transfemoral Access**
        - **Yes**
          - **TF** (n=492)
            - **1:1 Randomization**
              - **TF TAVR** (n=244) vs. **AVR (Control)** (n=248)
        - **No**
          - **TA** (n=207)
            - **1:1 Randomization**
              - **TA TAVR** (n=104) vs. **AVR (Control)** (n=103)

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

**COHORT A: KEY INCLUSION CRITERIA**
- Predicted operative mortality or irreversible morbidity ≥ 15%*
- Guideline: STS score ≥10, amended to ≥ 8
- NYHA functional class ≥ II
- AVA < 0.8 cm²
- Mean gradient > 40 mm Hg
- Peak jet velocity > 4.0 m/s

---

TA, transapical; TF, transfemoral.
* As determined by site surgeon and cardiologist.

**THE PARTNER TRIAL COHORT A**
**All-Cause Mortality**

**ALL-CAUSE MORTALITY AT 1 YEAR AND 2 YEARS**

**ITT Population**

- **HR [95% CI] = 0.88 [0.70, 1.12]**
- **P (log rank) = 0.31**

**Graph**

- **Edwards SAPIEN THV**
- **AVR**

<table>
<thead>
<tr>
<th>Months</th>
<th>Edwards SAPIEN THV</th>
<th>AVR</th>
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<tr>
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<td>348</td>
<td>351</td>
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<td>3</td>
<td>312</td>
<td>274</td>
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<tr>
<td>6</td>
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<td>12</td>
<td>260</td>
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<td>18</td>
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<td>208</td>
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<tr>
<td>24</td>
<td>172</td>
<td>165</td>
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</tbody>
</table>

**Number at Risk**
All Strokes

**STROKE AT 1 YEAR AND 2 YEARS**

**HR [95% CI] = 1.23 [0.66, 2.31]**

\[ P \text{ (log rank)} = 0.51 \]

**AT Population**

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>3</th>
<th>6</th>
<th>9</th>
<th>12</th>
<th>15</th>
<th>18</th>
<th>21</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Event, %</td>
<td>5.8%</td>
<td>3.0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>7.5%</td>
<td>4.4%</td>
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</table>

**Number at Risk**

<table>
<thead>
<tr>
<th>Edwards SAPIEN THV</th>
<th>344</th>
<th>296</th>
<th>281</th>
<th>257</th>
<th>249</th>
<th>233</th>
<th>223</th>
<th>211</th>
<th>146</th>
</tr>
</thead>
<tbody>
<tr>
<td>AVR</td>
<td>313</td>
<td>251</td>
<td>237</td>
<td>231</td>
<td>223</td>
<td>214</td>
<td>206</td>
<td>198</td>
<td>139</td>
</tr>
</tbody>
</table>

**THE PARTNER TRIAL COHORT A**
Major Vascular Complications

**AT Population**

**MAJOR VASCULAR COMPLICATIONS AT 30 DAYS, 1 YEAR, AND 2 YEARS**

- **30 Days**
  - Edwards SAPIEN THV: 11.1%
  - AVR: 3.8%
  - *p < 0.001*

- **1 Year**
  - Edwards SAPIEN THV: 11.1%
  - AVR: 3.8%
  - *p < 0.001*

- **2 Years**
  - Edwards SAPIEN THV: 11.4%
  - AVR: 3.8%
  - *p < 0.001*

Kaplan-Meier estimates.

THE PARTNER TRIAL COHORT A
Major Bleeding

Kaplan-Meier estimates. *Major bleeding is defined as any episode of major internal or external bleeding that caused death, hospitalization or permanent injury (e.g., vision loss) or necessitated transfusion of greater than 3 units PRBCs within a 24-hour period, pericardiocentesis, open and/or endovascular procedure for repair or hemostasis.
At 2 years, in patients with severe symptomatic native aortic valve stenosis who were not suitable candidates for surgery:

- Treatment with the Edwards SAPIEN THV remained superior to standard therapy with incremental benefit from 1 to 2 years, reducing the rates of mortality and repeat hospitalization.

- Treatment with the Edwards SAPIEN THV improved NYHA functional status and decreased class III/IV symptoms compared to standard therapy.

- There were significantly more strokes in patients treated with the Edwards SAPIEN THV than in patients who received standard therapy.

- Patients treated with the Edwards SAPIEN THV also had a higher incidence of major vascular complications and major bleeding than standard therapy patients.
At 2 years, in patients with symptomatic severe aortic stenosis who were high-risk candidates for surgical AVR:

- Edwards SAPIEN THV was non-inferior to surgical AVR with similar rates of all-cause and cardiovascular mortality
- Resulted in symptom improvement that was similar in both groups and maintained through two years
- Hemodynamic performance of the Edwards SAPIEN THV was maintained with similar valve gradients and effective orifice areas compared with surgical AVR
- Both TAVR and AVR had adverse procedural events which impacted subsequent mortality, such as stroke and major bleeding for both procedures, and major vascular complications for TAVR
  - There was no statistically significant difference in stroke rate between Edwards SAPIEN THV and AVR patients despite increased peri-procedural events after TAVR; there was no late (after 30 days) stroke hazard in TAVR patients
- Two-year results from the high-risk operable PARTNER cohort support the use of Edwards SAPIEN THV as an alternative to surgery with similar mortality and clinical benefits
Identifying Potential Candidates for TAVR
Characteristics of a TAVR Patient

TAVR patients may present with some of the following:

- Severe, symptomatic native aortic valve stenosis
- Old age
- History of stroke/CVA
- Reduced EF
- Prior CABG
- History of AFib
- History of syncope
- Heavily calcified aorta
- Prior chest radiation
- History of CAD
- Prior open chest surgery
- History of COPD
- Fatigue, slow gait
- History of renal insufficiency
- Peripheral vascular disease
- Diabetes and hypertension
TAVR Case Study Example

- **John Doe**
  - 85 year old male
  - Weight: 115 kg
  - Height: 175 cm

- **History**
  - History of hypertension
  - Diabetes

- **Characteristics**
  - Delayed carotid upstroke
  - Audible systolic heart murmur
  - Soft or absent second heart sound
  - Reports marked limitation in physical activity due to symptoms such as shortness of breath present even during less than normal activity

**Echocardiographic observations:**
- Jet Velocity: 5.7 m/s
- Mean gradient: 80 mmHg
- AVA: 0.5 cm²
- Annulus measures 20 mm

**DIAGNOSIS:** Patient has severe aortic stenosis and may be a candidate for TAVR
Following Patient Referral, the TAVR Team will Perform Further Evaluation

1. Confirm the patient is diagnosed with severe symptomatic native aortic stenosis
2. Confirm the patient has been evaluated by two cardiac surgeons and meets the indication for TAVR
3. Evaluate the aortic valvular complex using echocardiography
4. Evaluate the aortic valvular complex and peripheral vasculature using CT
5. Evaluate the aortic valvular complex and peripheral vasculature using catheterization
6. Determine access route for transcatheter aortic valve replacement

Note: The above is a suggested flow for the patient screening process, however, the order in which screening tests are conducted varies depending on the patient’s profile and should be at the discretion of the Heart Team.
While some patients may have low STS scores, certain co-existing conditions may preclude them from being suitable candidates for surgery, for example:

- Extensively calcified (porcelain) aorta
- Chest wall deformity
- Oxygen-dependent respiratory insufficiency
- Frailty

Example: Porcelain aorta in TAVR candidate

The baseline characteristics of the patients in the two groups were generally well balanced (Table 1). The overall patient population was at high risk (STS score, 11.6±6.0%). However, there were many patients with low STS scores but with co-existing conditions that contributed to the surgeons’ determination that the patient was not a suitable candidate for surgery, including an extensively calcified (porcelain) aorta (15.1%), chest-wall deformity or deleterious effects of chest-wall irradiation (13.1%), oxygen-dependent respiratory insufficiency (23.5%), and frailty, as determined by the surgeons according to prespecified criteria (23.1%).
Patients may be considered at high risk for surgical valve replacement if they have an STS operative risk score of ≥ 8% or are judged by the Heart Team to be at a ≥15% risk of mortality for surgical aortic valve replacement.
Ensuring the Appropriate Annular Size Range

- The Edwards SAPIEN transcatheter heart valve is offered in two sizes, 23 mm and 26 mm, and accommodates an annular size range of 18 mm to 25 mm.
Frailty is an important parameter in assessing operative risk.

Transcatheter aortic valve replacement is a new therapy for high risk inoperable patients with severe aortic stenosis.

Prevalence of frailty increases with aging; old does not necessarily equal frail.

Elderly patients achieve measurable benefit from cardiac surgery, particularly in terms of:
- Quality of life
- Increased survival
- Prevention of adverse cardiovascular events
Various tests may be used as objective measures of frailty, and markers of frailty may include a decline in lean body mass, strength, endurance, weight loss, grip strength, etc.

Examples of frailty measures may be found in published literature, including the 7-point Clinical Frailty Scale developed by the Canadian Study of Health and Aging.

**CSHA Frailty Scale**

**Very fit** — robust, active, energetic, well motivated and fit; these people commonly exercise regularly and are in the most fit group for their age.

**Well** — without active disease, but less fit than people in category 1.

**Well, with treated comorbid disease** — disease symptoms are well controlled compared with those in category 4.

**Apparently vulnerable** — although not frankly dependent, these people commonly complain of being “slowed up” or have disease symptoms.

**Mildly frail** — with limited dependence on others for instrumental activities of daily living.

**Moderately frail** — help is needed with both instrumental and non-instrumental activities of daily living.

**Severely frail** — completely dependent on others for the activities of daily living, or terminally ill.
Vessel diameters must be a minimum of:

- ≥ 7 mm for a 23 mm valve (requires a 22F RetroFlex 3 sheath)
- ≥ 8 mm for a 26 mm valve (requires a 24F RetroFlex 3 sheath)
Some patients may not have adequate vascular access to accommodate the sheath used during transfemoral procedures.

For these patients, the transapical procedure may be an option.

During the transapical approach, the Edwards SAPIEN transcatheter heart valve is delivered through the apex of the heart by making a small incision between the ribs.
Aortic stenosis is considered severe when:

- Valve area is < 1.0 cm²
- Pressure gradient > 40 mmHg
- Jet velocity is > 4.0 m/s

Patients with Severe Aortic Stenosis who are Inoperable or at High Risk for Surgery Should be Referred to a TAVR Heart Team

Due to the complexity of patient screening for TAVR, refer patients with severe aortic stenosis who are inoperable or at high risk for surgery to a TAVR Heart Team for further evaluation.
Multiple treatment pathways are now available to treat severe aortic stenosis

- **TAVR**
  - For inoperable and high risk patients

- **Surgical or MIS AVR**
  - For patients who are suitable for open-chest aortic valve replacement

- **Medical Management and BAV**
  - For patients not suitable for invasive procedures

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**Devising a Treatment Plan – A Collaborative Process**

- **Patient with severe aortic stenosis identified by referring physician**
- **Patient referred to TAVR valve clinic**
- **Additional testing completed**
- **Multidisciplinary review & treatment decision by TAVR Heart Team**
- **Treatment decision discussed with referring physician**
- **Ultimate treatment choice is a collaborative decision between the physicians, patient, and patient’s family**
Find a TAVR Center Near You

To find a TAVR center near you, visit: http://www.edwards.com/tavrsitefinder
Novant-Presbyterian Medical Center TAVR Program

- January 12, 2012-First in the Carolinas
- 37 patients treated to date
- Average age 86
- 2 peri procedure mortalities
- All valves successfully deployed
- Enhanced quality of life