Red Fish On A Fly

Severe Aortic Stenosis

- Disease State and Overview of Etiology
- Symptoms and Prognosis

Aortic Stenosis

Images courtesy of Renu Virmani MD at the CVPath Institute

Independent clinical factors associated with degenerative aortic valve disease include the following:

- Increasing age
- Male gender
- Hypertension
- Smoking
- Elevated lipoprotein A
- Elevated LDL cholesterol

Major Risk Factors

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

Multiple Modalities May Be Used to Diagnose Severe Aortic Stenosis
According to the 2008 ACC/AHA guidelines, severe aortic stenosis is defined as:

- Aortic valve area (AVA) less than 1.0 cm$^2$
- Mean gradient greater than 40 mmHg or jet velocity greater than 4.0 m/s

Echocardiographic Guidelines are the Gold Standard in Assessing Severe Aortic Stenosis

- 5 year survival of breast cancer, lung cancer, colorectal cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

Sobering Perspective

Addressing a Serious Unmet Need

- Studies show at least 40% of SAS patients are not treated with an AVR

Options for Aortic Valve Replacement

- Transcatheter Aortic Valve Replacement (TAVR)
- Surgical Aortic Valve Replacement (SAVR)
- Minimal Incision Valve Surgery (MIVS)
- Transfemoral Approach
- Transapical Approach
- Transcatheter Aortic Valve Replacement (TAVR)
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, at high or intermediate risk for surgical aortic valve replacement.

What is TAVR?

- For patients who are either at intermediate, 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

Transfemoral Procedural Animation

Balloon Aortic Valvuloplasty

- Graded pericardial tissue
- Leaflets matched for thickness and elasticity
Some patients may not have adequate vascular access to accommodate the sheath used during transfemoral procedures.

For these patients, the transapical, supra-aortic, or subclavian or caval access 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.
Definitive Results Through Rigorous Design

- The Partner Trial Cohort B Inclusion Criteria

Edwards SAPIEN THV Improved Survival

- All-Cause Mortality
  - NYHA Class 6 Over Time

Edwards SAPIEN THV Reduced Symptoms

- NYHA Class 6 Over Time

Complications

- Table showing complications and their rates.

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.

Edwards SAPIEN THV Improved Cardiac Function

- Mean Gradient Over Time

Complications

- Table showing complications and their rates.

Stroke was defined as follows: Neurological deficit lasting ≥ 24 hours or lasting less than 24 hours with a brain imaging study showing an infarction.

Major vascular complications were defined as any thoracic aortic dissection, access site or access-related vascular injury (disssection, stenosis, perforation, rupture, arteriovenous 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.

Bleeding event is defined as ≥ 2 units within the index procedure.
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, arteriovenous 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 irreversible end-organ damage.

Edwards SAPIEN THV Had Higher Incidence of Bleeding Events

Bleeding event is defined as ≥ 2 units within the index procedure.

Critical Insights

Study Design & Inclusion Criteria

NYHA Class

ITT Population
Retrospective Analysis: PPMI Resulted in Increased Long-term Mortality & Readmission


| Mortality | Retrospective analysis of 1,263 TAVR patients, PPMI resulted in:
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<tbody>
<tr>
<td>PPMI</td>
<td>Increased mortality (HR: 1.40; P=.04)</td>
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<tr>
<td></td>
<td>Greater readmission (HR: 1.28, P&lt;.001)</td>
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<td></td>
<td>Longer hospital stay (P=.001)</td>
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</tbody>
</table>

TVT Registry Analysis: PPMI is an Independent Predictor of 1-year Mortality

TVT registry analysis of 9,785 TAVR patients:

- PPMI independent predictor of 1-year mortality (HR: 1.31)
- Use of self-expandable valves independent predictor of PPMI

Key Takeaways - Cohort B

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; 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 post-procedural events after TAVR. There was no late (>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

Key Takeaways – Cohort A

- Characteristics of a TAVR Patient:
  - Severe, symptomatic native aortic valve stenosis
  - History of stroke/CVA
  - Reduced EF
  - Prior CABG
  - History of AFib
  - Prior open chest surgery
  - Fatigue, slow gait
  - Peripheral vascular disease
  - Old age
  - Heavily calcified aorta
  - Prior chest radiation
  - History of COPD
  - Frailty
  - History of renal insufficiency

Key Strategic Considerations

- There are options on how a valve clinic can be organized

Following Patient Referral, the TAVR Team will Perform Further Evaluation

- Note: The above is a suggested process. The sequence and timing may vary depending on individual patient factors, and should be at the discretion of the Heart Team.

Identifying the Inoperable Patient

- 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

Identifying the High Risk Patient

- 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
Intermediate Risk SURTAVI COR Valve

- STS 4.4%+/−1.6% Any cause death or disabling stroke
- No embolic protection allowed
- 12.6% primary endpoint TAVR/14% in surgical group
- Stroke similar in both groups/better in transfemoral TAVR
- More bleeding in surgical group/less PPM in TAVR group
- More vascular access complications in TAVR group (4%)
- More AFIB in surgical group
- More pacers in TAVR constant despite EvoluteR in 27% of pt.
- Shorter LOS in TAVR (not an endpoint)
- More AR in TAVR but better orifice area in TAVR

PARTNER 2 Intermediate risk

- SAPIEN XT second generation device
- Better Areas with TAVR
- More AR 3.7% severe and 21% mild/moderate
- Transfemoral had lower death/stroke Apical access similar to surgery
- SAPIEN XT already replaced by SAPIEN 3
- Similar Pacer rates 8.5/6.9 TAVR/SURG

LOW RISK TRIALS

- ENROLLMENT BEGAN 2016/COMPLETE 2021Medtronic
- Low Risk defined as surgical mortality at 30 days <3%
- These patients have the longest expected lifespan

LOW RISK

- WAKSMAN et al multicenter investigator initiated trial
- 11 centers
- No mortality first 125 patients at 30 days/no strokes
- 4% major vascular access complications
- 4.8% AFIB
- 4.8% new pacer
- HALT Hypo-attenuating leaflet thickening 12.5%
- 14.4% on antiplatelet RX (n=97) none on warfarin or direct anticoagulant (n=21)
- Subclinical thrombosis may result in diminished durability

LOW RISK TRIALS

- MEDTRONIC 1200 patients with EVOLUTE R
- PARTNER 3 EDWARDS 1300 patients with SAPIEN 3
- NOTION 2 European trial
- STS score <2%

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

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

<table>
<thead>
<tr>
<th>Grading the Severity of Aortic Stenosis per the ACC/AHA Guidelines</th>
<th>Severe</th>
<th>MODERATE</th>
<th>Mild</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)</td>
<td>&gt;5.0</td>
<td>3.0-4.0</td>
<td>&lt;3.0</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&gt;40</td>
<td>25-40</td>
<td>&lt;25</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>&gt;1.0</td>
<td>1.0-1.5</td>
<td>&lt;1.0</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt;8.8</td>
</tr>
</tbody>
</table>

*Source: American College of Cardiology. American Heart Association.
Dobutamine stress echocardiography can be used to differentiate between true and pseudo severe aortic stenosis. It better defines the severity of aortic stenosis, accurately assesses contractile/pump reserve, and some patients with severe aortic stenosis based on valve area may have a lower than expected gradient (e.g., mean gradient < 30 mmHg) despite preserved LV ejection fraction (e.g., EF > 50%). Up to 35% of patients with severe aortic stenosis present with low flow, low gradient. These low gradients often lead to an underestimation of the severity of the disease, so many of these patients do not undergo surgical aortic valve replacement.

Paradoxical Low Flow and/or Low Gradient Severe Aortic Stenosis

Chambers, Heart. 2006 April; 92(4): 554–558

Frailty: An Important Parameter

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

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Multiple Modalities for Assessing Frailty

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:

- Columbia Frailty Index
- Gait speed
- Grip strength
- Exhaustion implied in symptomatic AS
- Serum albumin
- Katz ADLs (Independence in dressing, bathing, toileting, transferring, feeding, continence)

Columbia Frailty Index, adapted from Fried, J Gerontol Med Sci 2001

Multiple Modalities for Assessing Frailty

Columbia 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 1

Apparently healthy — although not healthy, dependence on others for activities of daily living is minimal

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

Katz Activities of Daily Living (ADL) survey

- Measures continence, feeding, dressing, bathing, transferring, toileting

Tape measure

- Ideally 15-foot course in clinic hallway

Stop watch

Dynamometer

Serum albumin

Vessel diameters must be a minimum of 5.5mm

Newer Medtronic devices require 5mm access vessels

Assessing Appropriate Vascular Access
Aortic stenosis is considered severe when:
- Valve area is < 1.0 cm²
- Jet velocity is > 4.0 m/s
- Pressure gradient > 40 mmHg

Due to the complexity of patient screening for TAVR, refer patients with severe aortic stenosis who are inoperable or at high/intermediate risk for surgery to a TAVR Heart Team for further evaluation.

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

Multiple treatment pathways are now available to treat severe aortic stenosis:
- TAVR
  - For inoperable, high or intermediate risk patients
- Surgical or MS AVR
  - For patients who are suitable for open heart surgery
- Medical Management and Beta Blockers
  - For patients not suitable for crossover procedures
  - Currently only TAVR would be a consideration

Conduction disturbances & PPM have a negative impact on patient outcomes & cost:
- Increased length of stay
- Impaired LV function and rehospitalization for heart failure

Increased long-term mortality among TAVR and surgical AVR patients

Evolut PRO Transcatheter Valve
Building on Proven Design for Advanced Sealing

- Conformable Frame: Self-expanding radial frame conforms to non-circular regurgitation annular geometry
- Consistent Radial Force: Frames exerting and cell geometry optimizes expansion uniformity
- External Wrap: External wrap increases radial force while preserving annular geometry

Evolut PRO Overview | Medtronic

Supra-annular valve design maximizes leaflet coaptation and promotes single digit gradients and large ECAs:
- 7.5 mm Hg single digit gradients
- 2.0 cm² Large EOA

MEDTRONIC
THE MEDTRONIC TAVR ADVANTAGE | January 25, 2017

3/27/2019
**Clinical Trials have Demonstrated**  
**SIGNIFICANT BENEFITS OF A SELF-EXPANDING PLATFORM**

- The only platform to show Superiority in a RCT and show a sustained result to 3 years
- Unsurpassed Hemodynamics

**Evolut PRO system Clinical Trial**  
**PATIENT CHARACTERISTICS**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>mean ± SD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>83.3 ± 7.2</td>
</tr>
<tr>
<td>Female</td>
<td>65.0</td>
</tr>
<tr>
<td>BSA, m²</td>
<td>1.8 ± 0.2</td>
</tr>
<tr>
<td>STS – PROM, %</td>
<td>6.4 ± 3.9</td>
</tr>
<tr>
<td>NYHA Class III or IV</td>
<td>70.0</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>43.3</td>
</tr>
<tr>
<td>Atrial fibrillation / atrial flutter</td>
<td>18.8</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>43.3</td>
</tr>
<tr>
<td>Severe aortic calcification</td>
<td>20.5</td>
</tr>
<tr>
<td>LV ejection fraction, %</td>
<td>56.9 ± 12.4</td>
</tr>
<tr>
<td>Pre-existing pacemaker</td>
<td>15.0</td>
</tr>
</tbody>
</table>

**Evolut PRO Clinical Trial**  
**SYMPTOMATIC IMPROVEMENT**

87.9% of survivors improved NYHA class at 30 days
Low rates of PVL while maintaining low rates of mortality, stroke, and need for pacemaker

Percent of Evaluable Echocardiograms

Forrest, et al., ACC, 2017

Argentina Brown Trout

LONG TERM DURABILITY OF TAVR PROSTHESIS

- BLACKMANN et al JACC 2/2/2019 UK REGISTRY
- 241 patients mean FU 5.8 yrs (5-10)
- 64% SE valve 35.7BE valves
- Lower gradients at 5yrs vs implantation 17 vs 19 mm
- None/trivial AR 47.5/33% SE vs BE
- Mild AR 42.5/57% SE vs BE
- 8.7% severe prosthetic dysfunction 57% AR 43% restenosis
- 91% of patients were free of SVD 5-10 years post TAVR

Durability of Transcatheter and Surgical Bioprosthetic Aortic valves in low risk patients

- Sondergaard et al JACC 2/2/2019
- NOTION (Nordic Aortic Valve intervention trial) SAVR/TAVR
- Moderate/severe SVD defined as >20 mm Hg mean gradient or >10 mm increase > 3 mos post procedure.
- Nonstructural valve deterioration defined as moderate/severe PPM, or moderate/severe paravalvular leak
- Bioprosthetic valve failure defined as valve related death/valve reintervention or severe hemodynamic SVD
- SVD in SAVR 24% SVD in TAVR 4.8%
- NSVD SAVR– TAVR BPV Savr 6.7 vs Tavr 7.5%
- Structural valve failure: Bioprosthetic valve failure
- Nonstructural valve deterioration

Durability TAVR vs SAVR Sondergaard

- Conclusion that thru 6 years SVD (structural valve deterioration) was significantly greater in SAVR vs TAVR.
- BVF (bioprosthetic valve failure) was low in both groups