TAVR: A New Treatment Option for Aortic Stenosis
Alexis Auger, MSN, NP-BC
DISCLOSURES

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SESSION OBJECTIVES

• Describe the TAVR procedure.
• Understand the current FDA indications for TAVR.
Transcatheter Aortic Valve Replacement: A New Treatment Option for Aortic Stenosis

Alexis Auger, MSN, NP-BC
Nurse Practitioner, Heart Valve Program
The Changing Face of Valve Disease

- Shift from rheumatic to “degenerative” etiologies
- Moderate to severe valve disease occurs in*:
  - 1.9% people 55 to 64 years-old
  - 8.5% people 65 to 74 years-old
  - 13.2% people 75 years and older
- Prevalence of valve disease increase as the elderly population continues to grow
- Elderly have an inherent increase in risks associated with surgery and complexity of medical management

Prevalence of Valve Disease by Age

Distribution of Native Heart Valve Disease

Iung et al. Nat. Rev. Cardiol. 2011;8: 162-172
Diagnosis of Severe Aortic Stenosis

- Severe aortic stenosis is defined by ACC/AHA guidelines as:
  - Aortic valve area less than 1.0 cm\(^2\)
  - Mean gradient greater than 40 mm Hg \textit{or} jet velocity greater than 4.0 m per second
Aortic Valve Stenosis: Etiology

- Calcific aortic stenosis
  - With any underlying aortic valve morphology
- Congenital aortic stenosis
  - Typically bicuspid or unicuspid aortic valve
- Rheumatic heart disease
- Rare causes (e.g., radiation-induced)
Calcific Aortic Stenosis: Risk Factors

- Male gender
- Hypertension
- Elevated LDL cholesterol
- Cigarette smoking
- Underlying bicuspid or unicuspid aortic valve
- End-stage renal disease
- Paget’s disease
Calcific Aortic Stenosis: Mechanisms

- Calcific aortic stenosis is a biologically active process
- Lipid accumulation
  - LDL accumulation and oxidation
- Inflammation
  - T-cells, monocytes, inflammatory mediators, cytokines
- Calcification
  - Osteoblast expression, bone formation
Do Statins Slow the Progression of Aortic Stenosis?

- Six retrospective studies had found statin therapy was associated with a reduced rate of AS progression.
- However, three prospective randomized trials have failed to show a decrease in hemodynamic progression of AS or a delay in AVR…

Helske S, Otto CM. Circulation 2009;119:2653-2655
Retrospective Cleveland Clinic Analysis: Progression of Aortic Atenosis in Nonstatin and Statin-Treated Patients.

Novaro G M et al. Circulation 2001;104:2205-2209
SALTIRE Trial: Progression of Aortic Stenosis by Aortic Jet Velocity

Trials of Statin Therapy to Slow AS Progression: SEAS (Simvastatin and Ezetimibe in Aortic Stenosis)

Trials of Statin Therapy to Slow AS Progression: ASTRONOMER (AS Progression Observation, Measuring Effects of Rosuvastatin)

![Graph showing changes in aortic valve area over months with patient data for Rosuvastatin and Placebo groups.](image)

Timing of Therapy May Affect Efficacy

- Retrospective echo database analysis of 1046 patients
  - Statin therapy slowed progression of aortic stenosis among those with aortic sclerosis and mild aortic stenosis
  - Statin therapy did not slow progression in moderate AS

<table>
<thead>
<tr>
<th>Group</th>
<th>Change in Aortic Valve Disease Severity</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonstatin</td>
<td>Statin</td>
<td></td>
</tr>
<tr>
<td>Aortic sclerosis</td>
<td>78 (48%)</td>
<td>35 (33%)</td>
</tr>
<tr>
<td>Mild AS</td>
<td>197 (55%)</td>
<td>52 (37%)</td>
</tr>
<tr>
<td>Moderate AS</td>
<td>152 (71%)</td>
<td>38 (61%)</td>
</tr>
</tbody>
</table>

What is the Future for Statin Therapy in Aortic Stenosis?

• Long term prospective trials are challenging because:
  – The slow natural history of aortic stenosis
  – Many patients with aortic stenosis have independent indications for statin therapy

• Risk stratification:
  – Inflammatory markers (e.g. hs-CRP)
  – Novel imaging modalities

Helske S, Otto CM. Circulation 2009;119:2653-2655
Pathophysiology of Aortic Stenosis
Natural History of Aortic Stenosis

Indications for Aortic Valve Replacement

- **Class I**
  - Symptoms
  - Severe AS, undergoing CABG or other heart surgery
  - Severe AS and LV dysfunction
- **Class IIa**
  - Moderate AS, undergoing CABG or other heart surgery
- **Class IIb**
  - Asymptomatic severe AS and abnormal exercise testing
  - High risk for rapid progression
  - Extremely severe AS (AVA <0.6sqcm, mean gradient >60 mmHg, peak velocity >5 m/sec) and low operative risk
Aortic Valve Replacement Surgery
AVR Operative Mortality

Data from STS Database
High Risk Surgical Patients

- Advanced age (>80)
- Redo cardiac surgery
- LV dysfunction (EF < 30%)
- Atherosclerotic aorta
- Cerebrovascular disease
- Peripheral artery disease
- Chronic kidney disease
- Chronic lung disease
- Diabetes
Surgery in Elderly Patients with Severe AS

Aortic Stenosis >75 years
N=408

No severe AS
N=124

Severe AS
N=284

No symptoms
N=68

Severe symptoms
N=216

No intervention
N=72 (33%)

Intervention
N=144 (67%)

Iung et al. Eur Heart J. 2005; 26: 2714
Alternative Mechanical Therapies for Aortic Stenosis

- Balloon Aortic Valvuloplasty
- Aortic Valve Bypass
- Transcatheter Aortic Valve Replacement
Timeline for Heart Valve Treatments

- 1948 First surgical heart valve replacement performed in United States by Harken
- 1948–2012 Open-heart surgery is exclusive gold standard
- First human use of stent mounted bioprosthesis for pulmonary valve regurgitation, Bonhoeffer et al, 2000
- First-in-man transcatheter aortic valve implantation, Cribier et al, 2002
- 2007 CE Mark approval—that is, conformity with European community standards—of the two TAVR technologies: CoreValve and Sapien
- US Pivotal trial, Medtronic CoreValve, Feb 2011-Sept 2012
Timeline For Heart Valve Treatment

- 2011 November FDA approves Sapien for inoperable patients with valve inserted via the femoral artery
- 2011 December TVT Registry becomes operational
- 2012 October FDA extends Sapien approval to high-risk patients using femoral or other access
- 2013 September FDA extends Sapien to inoperable patients for all vascular access
- 2014 January FDA approves CoreValve for extreme-risk patients
- 2014 June FDA extends CoreValve for high-risk patients
- 2014 December TVT Registry: more than 25,000 patient records entered
PARTNER: Placement of Aortic Transcatheter Valves Trial

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High-Risk AVR Candidate
3,105 Total Patients Screened

Total = 1,057 patients

2 Parallel Trials: Individually Powered

High Risk

Yes
ASSESSMENT: Transfemoral Access

No

Transfemoral (TF)

1:1 Randomization

TF TAVR

AVR

Primary Endpoint: All-Cause Mortality at 1 yr (Non-inferiority)

Transapical (TA)

1:1 Randomization

TA TAVR

VS

AVR

Inoperable

Yes
ASSESSMENT: Transfemoral Access

No

Not In Study

TF TAVR

Standard Therapy

Primary Endpoint: All-Cause Mortality Over Length of Trial (Superiority)
Co-Primary Endpoint: Composite of All-Cause Mortality and Repeat Hospitalization (Superiority)
PARTNER TRIAL

• The primary endpoint of the trial was met:
  – In patients with aortic stenosis at high risk for operation, TAVR was non-inferior to AVR for all-cause mortality at 1 year (24.2% vs. 26.8%, p=0.001 for non-inferiority)
  – Transfemoral TAVR subgroup was also non-inferior to AVR (p=0.002 for non-inferiority)

• Death at 30 days was lower than expected in both arms of the trial:
  – TAVR mortality (3.4%) was the lowest reported in any series, despite an early generation device and limited previous operator experience
  – AVR mortality (6.5%) was lower than the expected operative mortality (11.8%)
PARTNER TRIAL

Both TAVR and AVR were associated with important but different peri-procedural hazards:

- Major strokes at 30 days (3.8% vs. 2.1%, p=0.20) and one year (5.1% vs. 2.4%, p=0.07) and major vascular complications were more frequent with TAVR (11.0% vs. 3.2%, p<0.001)

- Major bleeding (9.3% vs. 19.5%, p<0.001) and new onset atrial fibrillation (8.6% vs. 16.0%, p<0.001) were more frequent with AVR

TAVR and AVR are both acceptable therapies in these high-risk patients; differing peri-procedural hazards should influence case-based decision-making.
Sapien Valve
Transcatheter Aortic Valves

Sapien
- Cobalt chromium
- Bovine pericardial
- Balloon expandable
- Annulus diameter 18-27mm
- FDA 2012
- CE Mark 2007

CoreValve
- Nitinol
- Porcine Pericardial
- Self expanding
- Annulus diameter 18-29mm
- FDA 2014
- CE Mark 2007
Access Approach
Calculating Risk

- TAVR in the USA has been approved for patients at high risk, extreme risk or are deemed inoperable
- STS Calculator: <3% - low risk, 3-8% - intermediate risk, >8% - high risk
  - Demographics: age, gender, height, weight
  - Renal Function
  - Arrhythmia
  - Heart Failure, Systolic function and NYHA Class
  - CAD: ischemic symptoms, previous MI, previous cardiac interventions or surgery.
  - Lung disease
  - Peripheral arterial disease
  - DM,
  - HTN
  - Immunocompromise
Calculating Risk

Unrepresented considerations

- Hostile chest
- Liver disease
- Porcelain aorta
- Frailty – 5 Meter walk and Grip strength
- Rehabilitation potential

A TAVR risk scoring tool is in development
TAVR Work Up

• Trans thoracic echocardiogram
• Carotid Ultrasound
• Pulmonary Function Test
• Dental Clearance
• STS Calculation
• Cardiothoracic Surgery Consultation
• Multidisciplinary TAVR meetings
Case Study #1

- 89 yo male with severe symptomatic AS with recurrent syncope and NYHA Class IV heart failure symptoms.
- Past medical history includes prior CABG 1989, coronary PCI 2005, carotid stenosis, atrial fibrillation, moderate COPD, DM2, Hypertension, RBBB, and rheumatoid arthritis.

- TTE 2/2015: severe aortic stenosis; peak trans aortic valve gradient 85 mmHg, the mean gradient is 44 mmHg, and the calculated aortic valve area is 0.8 sqcm. The left ventricular function is normal with an left ventricular ejection fraction of 62%. The estimated RVSP is 30 mmHg. Mild mitral regurgitation.
Aortic annulus diameter is 30 x 22 mm, circumference 87 mm, and area 5.5 cm². Minimal luminal diameter is 7 mm in the right iliac system and 7 mm and the left iliac system.
• Cardiac Catheterization: Diffuse native coronary disease with patent grafts.
• Carotid Ultrasound: 50-70% R carotid stenosis and 0-49% L ICA stenosis
• Pulmonary Function Test: Spirometry consistent with moderate COPD.
• Dental: s/p multiple extractions, now cleared from a dental perspective.
STS Score

- Risk of Mortality: 10.459%
- Morbidity or Mortality: 34.797%
- Long Length of Stay: 22.794%
- Short Length of Stay: 9.636%
- Permanent Stroke: 2.915%
- Prolonged Ventilation: 22.609%
- DSW Infection: 0.575%
- Renal Failure: 18.939%
- Reoperation: 11.099%
31 mm TF CoreValve valve, followed by placement of a second 31mm CoreValve

• Admitted to the ICU post procedure and extubated immediately.

• High grade AV block post procedure day 2. s/p implantation of a permanent dual chamber pacemaker

• TTE: stent mounted bioprosthetic AV. Well seated. peak trans AV gradient 31 mmHg, mean trans AV gradient 14 mmHg, calc AVA 1.5cm². Mild paravalvular leak.

• Discharged home post procedure day 5.
Case Study #2

- 71 year-old woman with progressively worsening dyspnea on exertion over the past several months. She reports atypical sounding chest discomfort, which she describes as an intermittent, substernal, pinpoint, pain in her chest that is reproducible with palpation.

- Echo 12/2014: severe aortic stenosis; peak trans aortic valve gradient 105 mmHg, the mean gradient is 57 mmHg, and the calculated aortic valve area is 0.8 sqcm. The left ventricular function is normal with an left ventricular ejection fraction of 73%. The estimated RVSP is 34 mmHg.
• Aortic annulus diameter is 24 x 20 circumference 68 mm², and area 3.6 cm².

• Minimal luminal diameter is 7 mm in the right iliac system and 9 mm and the left iliac system.
Cardiac Catheterization: Left dominant coronary system with patent coronary vessels.

Carotid Ultrasound: No hemodynamically significant bilateral internal carotid artery stenosis.

Pulmonary Function Test: deferred given no history of tobacco dependence and normal CXR.

Dental: no evidence of acute or chronic oral infections.
STS SCORE

- Risk of Mortality: 1.575%
- Morbidity or Mortality: 11.634%
- Long Length of Stay: 4.328%
- Short Length of Stay: 44.45%
- Permanent Stroke: 1.178%
- Prolonged Ventilation: 7.474%
- DSW Infection: 0.241%
- Renal Failure: 2.265%
- Reoperation: 5.292%
• Of significant importance is that she is a Jehovah's Witness and refuses blood or blood factor transfusion. She also has recently diagnosed thrombocytopenia.

• She was seen by cardiac surgery and hematology. Given her refusal of blood products, cardiac surgery was felt to be high risk.
• s/p 23mm Sapien transfemoral TAVR
• Admitted to the CCU post procedure and to the floor post procedure day 1.
• Extubated immediately post procedure and remained hemodynamically stable.
• Temp wire in place (which she has not required.
• TTE: stent mounted bioprosthetic AV. Well seated. peak trans AV gradient 31 mmHg, mean trans AV gradient 14 mmHg, calc AVA 1.5cm².
• Discharged home post procedure day 3
Procedural Risks / Outcomes

1. Stroke
2. All cause mortality
3. Transient Ischemic Attacks
4. Pacemaker Implantation
5. Major vascular events
6. Acute kidney injury
7. Repeat aortic valve procedures
8. Quality of Life (QoL)
**Five-Year Outcomes after Randomization to Transcatheter or Surgical Aortic Valve Replacement: Final Results of the PARTNER 1 Trial**

**Purpose:** Five-year outcomes of the PARTNER 1 trial for the Edwards SAPIEN transcatheter valve (either transfemoral and transapical) in high surgical risk, severe aortic stenosis (AS) patients.

**Trial Design:** Randomized, open label, parallel, randomized, safety and efficacy trial comparing the Edwards SAPIEN transcatheter valve vs. either another surgical valve or medical therapy (and/or balloon angioplasty). N=699 high surgical risk patients with severe AS randomized to either transcatheter aortic valve replacement (TAVR) or surgical aortic valve replacement (SAVR). Approach was either transfemoral or transapical.

**Primary Endpoint:** 5-year results comparing TAVR to SAVR.

<table>
<thead>
<tr>
<th>Trial Results @ 5 years</th>
<th>TAVR</th>
<th>SAVR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk of Death @ 5 years</td>
<td>67.8%</td>
<td>62.4%</td>
<td>0.76</td>
</tr>
<tr>
<td>Moderate or severe aortic regurgitation (AR)</td>
<td>14%</td>
<td>1%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Increased 5 year mortality because of AR seen in TAVR</td>
<td>72.4% (mod-severe AR)</td>
<td>56.6% (mild AR or less)</td>
<td>0.003</td>
</tr>
</tbody>
</table>

**Conclusions:** This 5-year f/u found similar results in this patient population for either SAVR or TAVR. The TAVR approach had more aortic regurgitation. There was no deterioration of the valves for either approach that required surgical replacement.

Presented by: Michael Mack, ACC.15, San Diego, CA

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CoreValve U.S. Pivotal High Risk Trial

**Purpose:** Safety and efficacy trial of the self-expanding transcatheter aortic valve (the Medtronic CoreValve® System); TAVR- in the Treatment of Symptomatic Severe Aortic Stenosis (AS) in High Risk and Very High Risk Subjects Who Need Aortic Valve Replacement

**Trial Design:** 2-year safety/efficacy outcomes; interventional, randomized, open label trial comparing self-expanding transcatheter and surgical aortic valve replacement in patients with severe aortic stenosis who are high surgical risks. N= 747. Parallel assignment of TAVR or surgical aortic valve replacement (SAVR) in patients with severe AS.

**Primary Endpoint:** All-cause mortality for those at high and extreme risk at 2 years.

<table>
<thead>
<tr>
<th>Trial Results</th>
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</thead>
<tbody>
<tr>
<td>1 year survival TAVR vs. SAVR 4.8%</td>
</tr>
<tr>
<td>Perivalvular leakage</td>
</tr>
<tr>
<td>1 year survival TAVR vs. SAVR 6.4%</td>
</tr>
<tr>
<td>2 year survival TAVR vs. SAVR 6.4%</td>
</tr>
<tr>
<td>Perivalvular leakage 1 year = 6%</td>
</tr>
<tr>
<td>Perivalvular leakage 2 year = 6.1%</td>
</tr>
</tbody>
</table>

**Conclusions:** Survival for patients treated with the self-expanding transcatheter aortic valve demonstrated better survival in this trial at 2 years compared to surgical aortic valve replacement. TAVR results were better for other endpoints, as well.

Presented by: Michael J. Reardon, ACC.15, San Diego, CA
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Early Clinical and Echocardiographic Outcomes with the SAPIEN 3 Transcatheter Aortic Valve Replacement System in Inoperable, High-Risk, and Intermediate-Risk Aortic Stenosis Patients (PARTNER II S3)

**Purpose**: For severe aortic stenosis (AS) patients who qualify for aortic valve replacement, a safety and effectiveness study of the transcatheter heart valve (SAPIEN 3 THV).

**Trial Design**: Interventional, open label safety and efficacy study comparing the SAPIEN 3 THV to .
N= 1661 (583 high-risk, inoperable; 1078 intermediate risk)

**Primary Endpoint**: Rate of all-cause mortality 30 days after the procedure; Paravalvular regurgitation (PVR).

<table>
<thead>
<tr>
<th>Trial Results for Sapien 3 TVAR</th>
<th>High-risk patients</th>
<th>Intermediate-risk patients</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (all-cause)</td>
<td>2.2%</td>
<td>1.1%</td>
<td></td>
</tr>
<tr>
<td>Cardiac-related death</td>
<td>1.4%</td>
<td>0.9%</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>1.5% (0.9% disabling)</td>
<td>2.1% (1% disabling)</td>
<td></td>
</tr>
<tr>
<td>Paravalvular regurgitation</td>
<td>3.7% (0.1% severe) – both groups of patients</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Conclusions**: The rates of death and stroke were low with SAPIEN 3 for both hi-risk and intermediate-risk patients. The rate of Paravalvular regurgitation was also very low. These results compare favorably with surgical outcomes.
Future Growth

- Growth in Numbers
- Minimalist Approach
- Evolution of Technology
- Expanded Indications

<table>
<thead>
<tr>
<th>Year</th>
<th>Number of TAVR Cases per year</th>
</tr>
</thead>
<tbody>
<tr>
<td>2008</td>
<td>5</td>
</tr>
<tr>
<td>2009</td>
<td>12</td>
</tr>
<tr>
<td>2010</td>
<td>42</td>
</tr>
<tr>
<td>2011</td>
<td>48</td>
</tr>
<tr>
<td>2012</td>
<td>43</td>
</tr>
<tr>
<td>2013</td>
<td>81</td>
</tr>
<tr>
<td>2014</td>
<td>94</td>
</tr>
</tbody>
</table>

Total - 325