Aortic Stenosis and Transcatheter Aortic Valve Replacement

February 1, 2013
Michael C. Reed, MD
International Heart Institute
St. Patrick Hospital
Missoula, MT
Case

84 year-old man with

• Severe AS (mean gradient 62 mmHg, peak velocity 5.22 m/s, AVA 0.77 cm²)

• NYHA class III CHF/EF 30%

• CKD

• CAD s/p multivessel PCI

• Moderate COPD

• Moderate Pulmonary HTN
Case

84 year-old man with

- STS score = 16.2% mortality and 49.5% mortality or morbidity
- Aortic annulus 22 mm on TTE
- REIA 9mm, LEIA 9 mm

- Still lives independently, fishes, goes for walks
- Turned down for surgical AVR
Aortic Stenosis

- Etiology
- Pathophysiology
- Clinical presentation
- Natural history
- Treatment

TRANSCATHETER AORTIC VALVE REPLACEMENT (TAVR)
Aortic Stenosis

- Etiology
- Pathophysiology
- Testing
- Natural history
- Treatment
Aortic Stenosis: Etiology

- Supravalvular
- Subvalvular
- Valvular
Aortic Stenosis:  Valvular

- Age related etiology
  - <30 yrs: congenital (unicuspid, bicuspid)
  - 40-60 yrs: calcified bicuspid or rheumatic
  - >70 yrs: senile degenerative*

*By far the most common
Prevalence of Aortic Stenosis

16.5 Million People in US Over the Age of 65

Percentage Diagnosed with Aortic Stenosis: 7%
Aortic Stenosis

- Etiology
- **Pathophysiology**
- Clinical presentation
- Natural history
- Treatment
Aortic Stenosis: Pathophysiology

- Obstruction
  - Increased Afterload
  - Hypertrophy
  - Decreased Coronary Flow
- Diastolic dysfunction
- Myocardial O2 supply-demand mismatch
Aortic Stenosis: Pathophysiology

• Early stage = left ventricular hypertrophy with preserved systolic function
  – Attempt to reduce wall stress as pressure increases

• Late stage = left ventricular dilatation and systolic failure
Aortic Stenosis

- Etiology
- Pathophysiology
- Clinical presentation
- Natural history
- Treatment
Aortic Stenosis: Clinical presentation
Aortic Stenosis: Clinical symptoms

- Syncope
- Angina
- Dyspnea
Aortic Stenosis: Physical Exam

- Timing of peak
- Duration
- Absent A2
## Severity of Aortic Stenosis

<table>
<thead>
<tr>
<th></th>
<th>Mean Gradient</th>
<th>Aortic valve area</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild</td>
<td>10-25 mmHg</td>
<td>&gt;1.5 cm squared</td>
</tr>
<tr>
<td>Moderate</td>
<td>25-40 mmHg</td>
<td>1.0-1.5 cm squared</td>
</tr>
<tr>
<td>Severe*</td>
<td>&gt;40 mmHg</td>
<td>&lt;1.0 cm squared</td>
</tr>
</tbody>
</table>

*Peak aortic valve velocity >4 m/s
Aortic Stenosis: Echocardiogram

• Peak velocity and mean pressure gradient
• LV size and function
• Location of the stenosis
• Concomitant LVOT obstruction
• Concomitant mitral valve disease
Potential limitations of Echocardiogram

• Can underestimate mean gradient if jet not parallel to doppler probe

• In low flow (low cardiac output) state, gradient will underestimate severity of AS
Aortic Stenosis: Doppler Echocardiogram
Aortic Stenosis: Indications for heart catheterization/valve study

Clinical exam
- Mild-Mod AS
- Severe AS

Doppler
- Mild-Mod
- Severe

Observe
- Cardiac catheterization

Surgery
Aortic Stenosis

- Etiology
- Pathophysiology
- Clinical presentation
- Natural history
- Treatment
Aortic Stenosis: Natural history

Ross J Jr. and Braunwald E: Circ 38 (Suppl 5)61,1968
Aortic Valve Replacement Greatly Improves Survival

Patient Survival\(^{16}\)

- AVR, No Symptoms
- AVR, Symptoms
- No AVR, No Symptoms
- No AVR, Symptoms

Survival, %

Years
Severe Inoperable AS: Survival

5-Year Survival

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>
</tr>
<tr>
<td>Colorectal Cancer</td>
<td>12</td>
</tr>
<tr>
<td>Prostate Cancer</td>
<td>30</td>
</tr>
<tr>
<td>Ovarian Cancer</td>
<td>28</td>
</tr>
<tr>
<td>Severe Inoperable AS*</td>
<td>3</td>
</tr>
</tbody>
</table>

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

• Etiology
• Pathophysiology
• Clinical presentation
• Testing
• Natural history
• Treatment
Treatment = aortic valve replacement

• When AS is severe and symptomatic (I/LOE B)

• Only effective treatment = aortic valve replacement
Severe *asymptomatic* aortic stenosis

• Send for AVR if:
  – EF < 50% (I/LOE C)
  – Fail treadmill (IIb/LOE C)
    • hypotension or marked symptoms

• Consider AVR if (IIb/LOE C):
  – Heavily calcified valve with rapid progression
  – Mean gradient > 60 mmHg (jet velocity > 5 m/s)
    when expected operative mortality is < 1%
## Low output, low gradient aortic stenosis

<table>
<thead>
<tr>
<th>Level</th>
<th>Mean Gradient</th>
<th>Aortic valve area</th>
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<tbody>
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<tr>
<td>Severe*</td>
<td>&gt;40 mmHg</td>
<td>&lt;1.0 cm squared</td>
</tr>
</tbody>
</table>

*Peak aortic valve velocity >4 m/s
Low output, low gradient aortic stenosis

• *Key question:* Is this severe end stage critical aortic stenosis with low cardiac output *OR* mild aortic stenosis with unrelated LV dysfunction (i.e. aortic pseudostenosis)?

• Dobutamine stress echocardiogram or dobutamine cath will distinguish
Low output, low gradient AS

Baseline

Dobutamine
Treatment: Balloon aortic valvotomy

- Indicated as bridge to AVR, palliation in high risk patients
- Risk of stroke, aortic insufficiency, bleeding
- Results transient (6-12 months)
Aortic Stenosis: Natural history

Ross J Jr. and Braunwald E: Circ 38 (Suppl 5)61,1968
Severe AS patients often left untreated

Sources:
Outcomes of unoperated patients:

University of Michigan study – JACC 2007

155 patients with severe AS

75 No-AVR

53 Symptoms

80 AVR

22 No symptoms

Operative Risk

< 5%
25

5 < 10%
9

> 10%
19

11.5% Average

Exercise testing 1 of 22

17 died from complications related to AS – mean time - 4 months post-echo

Why are some patients with severe symptomatic aortic stenosis not sent for AVR?

- Not recognized
- Patient too high risk for surgery
- Patient or clinicians decide not to pursue AVR
Treatment: Traditional landscape

Risk is a spectrum

Low Risk  High Risk  Non-operable  Futile

Surgical AVR  Medical treatment
Treatment: New landscape

Risk is a spectrum

Low Risk  High Risk  Non-operable  Futile

Surgical AVR  TAVR
Transcatheter Aortic Valve Replacement
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- CKD
- CAD s/p multivessel PCI
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Transcatheter Aortic Valve Replacement (TAVR)

FDA APPROVED for NON-OPERABLE and now HIGH-RISK patients

Edwards SAPIEN valve
Edwards SAPIEN Transcatheter Heart Valve

Bovine pericardial tissue
Leaflets matched for thickness and elasticity

PET skirt
Stainless steel frame

The Carpentier-Edwards ThermaFix process* is intended to minimize the risk of calcification, helping preserve valve performance.

*No clinical data are available which evaluate the long-term impact of the Edwards Lifesciences tissue process in patients.
How effective is TAVR?

**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)

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)

No

Not in Study

ASSESSMENT
Transfemoral Access

Yes

TF TAVR
(n = 179)

Standard Therapy
(Control)
(n = 179)

No

Cohort B
Inoperable
(n = 358)

2 Cohorts Individually Powered
(n = 1,057)
Key Exclusions

- Bicuspid or non-calcified aortic valve
- Aortic annulus <18 or >25 mm
- Aortic or iliac dimensions prohibiting sheath insertion
- LVEF < 20%
- Untreated CAD
- Severe AR/MR
- Prosthetic valve
- Creatinine > 3.0
- Inotropes
- Upper GI bleed < 3 months
- Acute MI < 1 month
- CVA/TIA < 6 months
Medical Therapy vs. TAVR (PARTNER B): MORTALITY

HR [95% CI] = 0.56 [0.43, 0.73]

p (log rank) < 0.0001

Δ at 1 yr = 20.0%
NNT = 5.0 pts

Δ at 2 yr = 24.7%
NNT = 4.0 pts

<table>
<thead>
<tr>
<th>Months</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
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</thead>
<tbody>
<tr>
<td>43.3%</td>
<td>50.7%</td>
<td>30.7%</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>68.0%</td>
<td>50.7%</td>
<td>30.7%</td>
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</table>

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Standard Rx</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>179</td>
<td>179</td>
</tr>
<tr>
<td>0</td>
<td>138</td>
<td>138</td>
</tr>
<tr>
<td>6</td>
<td>124</td>
<td>85</td>
</tr>
<tr>
<td>12</td>
<td>110</td>
<td>62</td>
</tr>
<tr>
<td>18</td>
<td>83</td>
<td>42</td>
</tr>
<tr>
<td>24</td>
<td>83</td>
<td>42</td>
</tr>
</tbody>
</table>
Medical Therapy vs. TAVR (PARTNER B): HOSPITALIZATION

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Standard Tx</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat Hospitalizations (No.)</td>
<td>78</td>
<td>151</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Repeat Hospitalizations (%)</td>
<td>35.0%</td>
<td>72.5%</td>
<td>&lt;.0001</td>
</tr>
</tbody>
</table>
Medical Therapy vs. TAVR (PARTNER B): SUMMARY

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>MEDICAL THERAPY</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 year mortality</td>
<td>30.7%</td>
<td>50.7%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>NYHA III/IV</td>
<td>25.2%</td>
<td>58.0%</td>
<td>P&lt;0.001</td>
</tr>
<tr>
<td>30 day major stroke</td>
<td>5.0%</td>
<td>1.1%</td>
<td>P=0.06</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>16.2%</td>
<td>1.1%</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

- **25% absolute reduction in death (NNT to save 1 life = 4)**
- Reduced symptoms, improved quality of life
  - 4/5 patients with no or minimal symptoms at 2 years
- Higher risk of stroke, vascular complications, bleeding
High risk AVR vs. TAVR (PARTNER A):
MORTALITY

HR [95% CI] = 0.88 [0.70, 1.12]
p (log rank) = 0.310

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>6M</th>
<th>12M</th>
<th>18M</th>
<th>24M</th>
<th>30M</th>
<th>36M</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>348</td>
<td>298</td>
<td>260</td>
<td>234</td>
<td>172</td>
<td>70</td>
<td>31</td>
</tr>
<tr>
<td>AVR</td>
<td>351</td>
<td>252</td>
<td>236</td>
<td>217</td>
<td>165</td>
<td>65</td>
<td>32</td>
</tr>
</tbody>
</table>
High risk AVR vs. TAVR (PARTNER A): MAJOR STROKE

- **30 Days**
  - TAVR (n=16): 4.6% (p=0.12)
  - AVR (n=8): 2.4%

- **1 Year**
  - TAVR (n=20): 6.0% (p=0.08)
  - AVR (n=10): 3.2%
<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>30 day mortality</td>
<td>3.4%</td>
<td>6.5%</td>
<td>0.15</td>
</tr>
<tr>
<td>1 year mortality</td>
<td>24.2%</td>
<td>26.8%</td>
<td>0.44</td>
</tr>
<tr>
<td>30 day TIA/stroke</td>
<td>5.5%</td>
<td>2.4%</td>
<td>0.04</td>
</tr>
<tr>
<td>1 year TIA/stroke</td>
<td>8.3%</td>
<td>4.3%</td>
<td>0.04</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>11.0%</td>
<td>3.2%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>9.3%</td>
<td>19.5%</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>&gt;/=Moderate AI</td>
<td>6.9%</td>
<td>0.9%</td>
<td>&lt;0.05</td>
</tr>
</tbody>
</table>
High risk AVR vs. TAVR (PARTNER A): SUMMARY

• Mortality TAVR = surgical AVR

• Stroke/TIA higher in TAVR vs surgical AVR

• Vascular complications and aortic regurgitation remain concerns with TAVR
Meta-analysis of TAVR complications

- Stroke: 4.0% at 30 days
- Major vascular event: 12%. Major bleed: 15.6%
- $\geq$ Moderate paravalvular leak: 7.4%
- Pacemaker: 4.8% Edwards valve, 25% CoreValve
- Major catastrophic event: <2%

J Am Coll Cardiol 2012;59:2297-306
TAVR Heart Team

• Multidisciplinary

• Multimodality imaging

• Labor intensive

• Complex patients
Estimating risk of surgery

TAVR patients may present with some of the following:

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


• STS score does not take everything into account (frailty, chest radiation, porcelain aorta, dementia, liver disease, etc.)
TAVR Heart Team Strategy

1. Confirm the patient is diagnosed with severe symptomatic native aortic stenosis

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

3. Evaluate the aortic valvular complex using echocardiography

4. Evaluate the peripheral vasculature and aortic valvular complex using MDCT

5. 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
Evaluating the Aortic Valvular Complex for TAVR Using Echocardiography
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.
Advanced imaging modalities

CTA

- Philips 3D Navigator
- Siemens Dyna CT
- GE Innova Vision
TAVR Paravalvular leak increases mortality
Vessel diameters must be a minimum of:

- ≥ 7 mm non-calcified for a 23 mm valve (requires a 22F RetroFlex 3 sheath)
- ≥ 8 mm non-calcified for a 26 mm valve (requires a 24F RetroFlex 3 sheath)
TAVR in Europe

Source: BIBA Medical, UK-based market analysis
Future devices

- Direct Flow
- Sadra
- St. Jude
- AorTx
- HLT
- EndoTech
- ABPS PercValve
Less paravalvular leak with next generation devices

Sources of paravalvular leak

Skirts help seal sources of leak
Embolic protection devices

SMT  Embrella  Claret
Expandable eSheath

16 French

Unexpanded

18 French

Expanded
Future clinical directions

• Minimizing complications
  – Smaller sheaths
  – Skirted valves with simple peri-procedural retrieval
  – Embolic protection

• High risk, or even intermediate risk patients

• Valve in valve

• Aortic insufficiency

• Mitral stenosis
Thanks!
## Cost-effectiveness of TAVR

<table>
<thead>
<tr>
<th>PROCEDURE</th>
<th>QALY</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR (PARTNER B)</td>
<td>$61,889</td>
</tr>
<tr>
<td>AVR (AGE&gt;80)</td>
<td>$27,182</td>
</tr>
<tr>
<td>CABG (BARI data)</td>
<td>$14,294</td>
</tr>
<tr>
<td>STENTING (BARI data)</td>
<td>$15,179</td>
</tr>
<tr>
<td>Heart transplant</td>
<td>$38,000</td>
</tr>
<tr>
<td>Lung transplant</td>
<td>$77,000</td>
</tr>
<tr>
<td>Liver transplant</td>
<td>$26,000</td>
</tr>
<tr>
<td>LVAD</td>
<td>$78,000</td>
</tr>
<tr>
<td>Driver side air bag</td>
<td>$24,000</td>
</tr>
</tbody>
</table>

Source: Reardon MJ Methodist Debakey CV Journal
Cumulative TAVR in Europe

Source: BIBA Medical, UK-based market analysis
Projection of TAVR in next 3 years

Source: JP Morgan 2011
Bicuspid aortic valve is associated with aorta disease
ACC/AHA Indicators for AVR

TAVR COMPLICATIONS
16 study meta-analysis 3,519 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pooled Estimate (%)</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>STS score</td>
<td>8.7</td>
<td>[7.0, 10.3]</td>
</tr>
<tr>
<td>Log Euroscore</td>
<td>22.8</td>
<td>[20.3, 25.3]</td>
</tr>
<tr>
<td>Age (years)</td>
<td>81.5</td>
<td>[80.8, 82.2]</td>
</tr>
<tr>
<td>Female</td>
<td>52.0</td>
<td>[46.3, 57.6]</td>
</tr>
<tr>
<td>NYHA 3 or 4</td>
<td>82.0</td>
<td>[77.5, 86.5]</td>
</tr>
<tr>
<td>AVA (cm²)</td>
<td>0.61</td>
<td>[0.53, 0.68]</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>47.6</td>
<td>[45.7, 49.5]</td>
</tr>
</tbody>
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J Am Coll Cardiol 2012;59:2297-306
**TAVR COMPLICATIONS**  
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<th>Endpoint</th>
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<tr>
<td><strong>Mortality</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All @ 30 days</td>
<td>7.8</td>
<td>[5.5, 11.1]</td>
</tr>
<tr>
<td>CV @ 30 days</td>
<td>5.6</td>
<td>[3.7, 8.3]</td>
</tr>
<tr>
<td>All @ 1 year</td>
<td>22.1</td>
<td>[17.9, 26.9]</td>
</tr>
<tr>
<td>CV @ 1 year</td>
<td>14.4</td>
<td>10.6, 19.5</td>
</tr>
<tr>
<td><strong>Strokes @ 30 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>3.2</td>
<td>[2.1, 4.8]</td>
</tr>
<tr>
<td>Major + minor</td>
<td>4.0</td>
<td>[2.4, 6.3]</td>
</tr>
<tr>
<td>TIA</td>
<td>1.2</td>
<td>[0.0, 2.3]</td>
</tr>
<tr>
<td>All</td>
<td>5.7</td>
<td>[3.7, 8.9]</td>
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*J Am Coll Cardiol 2012;59:2297-306*
TAVR COMPLICATIONS

16 study meta-analysis 3,519 patients

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<th>Endpoint</th>
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<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascular events @ 30 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>11.9</td>
<td>[8.6, 16.4]</td>
</tr>
<tr>
<td>Minor</td>
<td>9.7</td>
<td>[6.7, 14.0]</td>
</tr>
<tr>
<td>All</td>
<td>18.8</td>
<td>[14.5, 24.3]</td>
</tr>
<tr>
<td><strong>Bleeding @ 30 days</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Life threatening</td>
<td>15.6</td>
<td>[11.7, 20.7]</td>
</tr>
<tr>
<td>Major</td>
<td>22.3</td>
<td>[17.8, 28.3]</td>
</tr>
<tr>
<td>Minor</td>
<td>9.9</td>
<td>[6.9, 14.3]</td>
</tr>
<tr>
<td>All</td>
<td>41.4</td>
<td>[35.5, 47.6]</td>
</tr>
<tr>
<td>Transfusion ≥ 1 unit</td>
<td>42.6</td>
<td>[19.8, 62.4]</td>
</tr>
</tbody>
</table>

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### TAVR COMPLICATIONS

16 study meta-analysis 3,519 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pooled Estimate (%)</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI (peri-procedural)</td>
<td>1.1</td>
<td>[0.2, 2.0]</td>
</tr>
<tr>
<td>Valve performance @ 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AVA ≤ 1.2 cm²</td>
<td>4.8</td>
<td>[3.0, 6.6]</td>
</tr>
<tr>
<td>Mean gradient ≥ 20 mmHg</td>
<td>1.0</td>
<td>[0.0, 2.1]</td>
</tr>
<tr>
<td>AR ≥ moderate (PVL)</td>
<td>7.4</td>
<td>[4.6, 10.2]</td>
</tr>
<tr>
<td>Valve-in-valve</td>
<td>2.3</td>
<td>[1.3, 4.5]</td>
</tr>
<tr>
<td>Valve embolization</td>
<td>1.7</td>
<td>[0.2, 3.3]</td>
</tr>
<tr>
<td>Perm Pacemaker @ 30 days</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards</td>
<td>4.9</td>
<td>[3.9, 6.2]</td>
</tr>
<tr>
<td>MDT-Corevalve</td>
<td>28.9</td>
<td>[23.0, 36.0]</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2012;59:2297-306
## TAVR COMPLICATIONS

16 study meta-analysis 3,519 patients

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Pooled Estimate (%)</th>
<th>[95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endocarditis</td>
<td>0.6</td>
<td>[0.2, 1.4]</td>
</tr>
<tr>
<td>Coronary obstruction</td>
<td>0.7</td>
<td>[0.4, 1.1]</td>
</tr>
<tr>
<td>Tamponade</td>
<td>2.7</td>
<td>[1.7, 4.2]</td>
</tr>
<tr>
<td>LV perforation</td>
<td>0.4</td>
<td>[0.1, 1.5]</td>
</tr>
<tr>
<td>Conversion to surgery</td>
<td>1.3</td>
<td>[0.0, 2.6]</td>
</tr>
<tr>
<td>Unplanned CPB</td>
<td>1.3</td>
<td>[0.3, 2.2]</td>
</tr>
<tr>
<td>Annulus rupture</td>
<td>0.5</td>
<td>[0.2, 1.7]</td>
</tr>
<tr>
<td>Aortic rupture</td>
<td>0.9</td>
<td>[0.4, 2.2]</td>
</tr>
<tr>
<td>Aortic dissection</td>
<td>1.1</td>
<td>[0.4, 2.5]</td>
</tr>
</tbody>
</table>

J Am Coll Cardiol 2012;59:2297-306
Definitive Results Through Rigorous Design

THE PARTNER TRIAL PROTOCOL

Severe Symptomatic Native Aortic Valve Stenosis

ASSESSMENT: OPERABILITY (N = 3,105)

Cohort A High-Risk (n = 699)

ASSESSMENT: Transfemoral Access

Yes

TF (n = 492)

TA (n = 207)

1:1 Randomization

TF TAVR (n = 244) vs AVR (Control) (n = 248)

TA TAVR (n = 104) vs AVR (Control) (n = 103)

2 Cohorts Individually Powered (n = 1,057)

Cohort B Inoperable (n = 358)

ASSESSMENT: Transfemoral Access

Yes

TF (n = 179)

1:1 Randomization

TF TAVR (n = 179) vs Standard Therapy (Control) (n = 179)

No

Not in Study
Definitive Results Through Rigorous Design

THE PARTNER TRIAL COHORT B 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)

Cohort B
Inoperable
(n = 358)

No

2 Cohorts
Individually Powered
(n = 1,057)

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)

No

2 Cohorts Individually Powered
(n = 1,057)

Cohort B Inoperable
(n = 358)

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)

COHORT B PRIMARY ENDPOINT
All-cause mortality over length of trial
(Superiority)

COHORT B CO-PRIMARY ENDPOINT
Composite of all-cause mortality or repeat hospitalization (Superiority)
Edwards SAPIEN THV Improved Survival

ALL-CAUSE MORTALITY

P (log rank) < .0001
Δ at 2 yrs = 24.7%
NNT = 4.0 pts

0 20 40 60 80 100
All-Cause Mortality, %

0 6 12 18 24
Months

Standard Therapy
Edwards SAPIEN THV

68.0%
43.3%

Numbers at Risk

Edwards SAPIEN THV 179
Standard Therapy 179

Edwards SAPIEN THV 138 124 110 83
Standard Therapy 121 85 62 42

THE PARTNER TRIAL COHORT B
Edwards SAPIEN THV Improved Cardiac Function

Mean Gradient Over Time

Numbers Observed

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Edwards SAPIEN THV</td>
<td>162</td>
<td>143</td>
<td>89</td>
<td>65</td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>172</td>
<td>124</td>
<td>54</td>
<td>22</td>
</tr>
</tbody>
</table>

Error bars = ± 1 Std Dev
Edwards SAPIEN THV Reduced Symptoms

THE PARTNER TRIAL COHORT B
Edwards SAPIEN THV Improved Quality of Life

MCID, minimum clinically important difference.

THE PARTNER TRIAL COHORT B
Complications

**Complications**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>5.00%</td>
<td>2.80%</td>
<td>30.70%</td>
</tr>
<tr>
<td>Death or repeat hospitalization</td>
<td>11.70%</td>
<td>12.30%</td>
<td>44.10%</td>
</tr>
<tr>
<td>Stroke</td>
<td>7.30%</td>
<td>1.70%</td>
<td>11.20%</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>16.80%</td>
<td>1.10%</td>
<td>17.40%</td>
</tr>
<tr>
<td>Bleeding events</td>
<td>16.20%</td>
<td>2.20%</td>
<td>17.30%</td>
</tr>
<tr>
<td>New pacemaker implantation</td>
<td>3.40%</td>
<td>5.10%</td>
<td>4.70%</td>
</tr>
</tbody>
</table>

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 (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.

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, 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.
Edwards SAPIEN THV Had Higher Incidence of Bleeding Events

<table>
<thead>
<tr>
<th></th>
<th>30 Days</th>
<th>1 Year</th>
<th>2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Outcome</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Edwards SAPIEN THV</td>
<td>16.20%</td>
<td>17.30%</td>
<td>17.30%</td>
</tr>
<tr>
<td>Standard Therapy</td>
<td>2.20%</td>
<td>2.20%</td>
<td>2.20%</td>
</tr>
</tbody>
</table>

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

Standard therapy is failing patients with inoperable aortic stenosis

68% mortality at 2 years

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

THE PARTNER TRIAL COHORT B
Key Takeaways

TAVR with the first-generation Edwards SAPIEN THV:

• Demonstrated 20% absolute reduction in all-cause mortality at 1 year and 25% at 2 years
• Resulted in improved hemodynamics, NYHA functional class, and quality of life vs. standard therapy
• Was associated with important peri-procedural events
  – Stroke
  – Major vascular complications
  – Bleeding events