Developing Interventional Strategies for Management of Valvular Heart Disease

TAVR and MitraClip: Expanding Success and Indications

Paul Zellers, DO FACC
Objectives

- **Aortic Stenosis (AS)**
  - Aortic Valve Replacement (AVR): when to refer, when to fix
  - Evolution of Transcatheter Aortic Valve Replacement (TAVR)
  - TAVR Landmark Trials: outcomes, adverse events
  - TAVR vs SAVR: current guidelines

- **Mitral Regurgitation (MR)**
  - MitraClip technology
  - Primary vs Secondary MR
  - MitraClip landmark trials
  - Indications for MitraClip

*Images contributed by Abbott Vascular*
Aortic Stenosis
Pathology/Epidemiology

• Aortic stenosis causes progressive obstruction of the left ventricular outflow tract resulting in pressure hypertrophy of the left ventricle and ultimately heart failure.

• Valvular AS has several causes:
  • **Age related calcification/degeneration** - “wear and tear” manifesting usually in the 6th and 7th decades
  • Rheumatic
  • Congenital (bicuspid) - clinical manifestation earlier, 5th or 6th decade
Aortic Stenosis

Clinical Course

• Symptoms:
  
  • Chest pain - *myocardial ischemia, supply/demand mismatch*
  
  • Dyspnea - *Heart Failure*
  
  • Syncope - *multifactorial*
## Aortic Stenosis

### Surveillance

<table>
<thead>
<tr>
<th>Stage</th>
<th>Aortic Stenosis*</th>
<th>Aortic Regurgitation</th>
<th>Mitral Stenosis</th>
<th>Mitral Regurgitation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Progressive</td>
<td>Every 3–5 y</td>
<td>Every 3–5 y (mild severity)</td>
<td>Every 3–5 y</td>
<td>Every 3–5 y (mild severity)</td>
</tr>
<tr>
<td>(stage B)</td>
<td>(mild severity $V_{\text{max}}$ 2.0–2.9 m/s)</td>
<td>(MVA $&gt;1.5 \text{ cm}^2$)</td>
<td></td>
<td>(MVA $&gt;1.5 \text{ cm}^2$)</td>
</tr>
<tr>
<td></td>
<td>Every 1–2 y</td>
<td>Every 1–2 y (moderate severity)</td>
<td></td>
<td>Every 1–2 y (moderate severity)</td>
</tr>
<tr>
<td></td>
<td>(moderate severity $V_{\text{max}}$ 3.0–3.9 m/s)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>Every 6–12 mo</td>
<td>Every 6–12 mo</td>
<td>Every 1–2 y</td>
<td>Every 6–12 mo</td>
</tr>
<tr>
<td>(stage C)</td>
<td>($V_{\text{max}} \geq 4 \text{ m/s}$)</td>
<td>Dilating LV: more frequently</td>
<td>(MVA 1.0–1.5 cm$^2$)</td>
<td>Dilating LV: more frequently</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Once every year</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(MVA $&lt;1.0 \text{ cm}^2$)</td>
<td></td>
</tr>
</tbody>
</table>

Patients with mixed valve disease may require serial evaluations at intervals earlier than recommended for single valve lesions.

*With normal stroke volume.

LV indicates left ventricle; MVA, mitral valve area; VHD, valvular heart disease; and $V_{\text{max}}$, maximum velocity.
Aortic Stenosis

Surveillance

• Premature AVR carries risk of cardiac surgery

• Delayed AVR due to unrecognized symptoms can lead to poor outcomes

• Observational Study, 3 tertiary centers, 369 patients.

Evaluation of Patients With Severe Symptomatic Aortic Stenosis Who Do Not Undergo Aortic Valve Replacement

The Potential Role of Subjectively Overestimated Operative Risk

David S. Bach, MD; Derrick Siao, MD; Steven E. Girard, MD, PhD; Claire Duvernoy, MD; Benjamin D. McCallister, Jr, MD; Sarah K. Gualano, MD

Conclusions—One third of patients with severe AS are symptomatic but do not undergo AVR,

Circ Cardiovasc Qual Outcomes. 2009
Severe Aortic Stenosis

Outcomes

Evaluation of Patients With Severe Symptomatic Aortic Stenosis Who Do Not Undergo Aortic Valve Replacement

The Potential Role of Subjectively Overestimated Operative Risk

David S. Bach, Derrick Siao, Steven E. Girard, Claire Duvernoy, Benjamin D. McCallisterJr, and Sarah K. Gualano

RECOVERY
#AHA19

**Trial Description:** Patients with asymptomatic very severe aortic stenosis (peak velocity ≥4.5 m/sec) were randomized in a 1:1 fashion to either early surgery or watchful waiting. Patients were followed for 6.2 years.

**RESULTS**
- Primary endpoint, operative mortality or CV mortality at 4 years, for early surgery vs. watchful waiting: 1% vs. 6% (p < 0.05)
- CV mortality at 4 years: 1% vs. 15% (p < 0.05)
- All-cause mortality at 8 years: 10% vs. 32% (p < 0.05)
- Heart failure hospitalization: 0% vs. 11% (p < 0.05)

**CONCLUSIONS**
- Early surgery among patients with asymptomatic but very severe AS (AVA 0.75 cm², mean gradient ≥50 mm Hg, peak velocity ≥4.5 m/sec) results in improved survival out to 8 years compared with watchful waiting
- These are important findings, and will likely change guidelines on this topic

Aortic Stenosis

When to fix

Abnormal Aortic Valve With Reduced Systolic Opening

Severe AS
$V_{max} \geq 4 \text{ m/s}$
$\Delta P_{max} \geq 60 \text{ mm Hg}$

Symptomatic (stage D1)

Asymptomatic (stage C)

LVEF <50%
(stage C2)

Other cardiac surgery

$V_{max} \geq 5 \text{ m/s}$
$\Delta P_{max} \geq 60 \text{ mm Hg}$
Low surgical risk

Abnormal ETT

$\Delta V_{max} > 0.3 \text{ m/s/y}$
Low surgical risk

$V_{max} \geq 3 \text{ m/s}$
$\Delta P_{max} 3-3.9 \text{ mm Hg}$

Symptomatic

LVEF <50%

YES

NO

Other cardiac surgery

Symptomatic

DSE with
AVA $\leq 1 \text{ cm}^2$ and
$V_{max} \geq 4 \text{ m/s}$
(stage D2)

AVA $\leq 1 \text{ cm}^2$
and LVEF $\geq 50%$
(stage D3*)

AS likely cause of symptoms

Asymptomatic (stage B)

AVR (I)

AVR (IIa)

AVR (IIb)

AVR (IIa)

AVR (IIb)

Class I

Class IIa

Class IIb

PRACTICE GUIDELINE

2014 AHA/ACC Guideline for the Management of Patients With Valvular Heart Disease
A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines

Developed in Collaboration With the American Association for Thoracic Surgery,
American Society of Echocardiography, Society for Cardiac Angiography and Interventions,
Society of Cardiovascular Anesthesiologists, and Society of Thoracic Surgeons
Transcatheter Aortic Valve Replacement (TAVR)

Concepts

- For the past 50 years Aortic stenosis standard of care has been surgical aortic valve replacement (SAVR)

- 30-40% of patients with severe aortic stenosis are unsuitable for open heart surgery

  - Porcelain Aorta

  - Prior sternotomy, LIMA-LAD
Percutaneous Aortic Valve Intervention

History

• 1980’s - initial optimism for balloon valvuloplasty (BAV)
  • Procedural complications
  • No mortality benefit
  • Early restenosis
  • Palliative bridge
Percutaneous Aortic Valve Intervention

History

• 1992 Anderson et al - first report of porcine percutaneous AV fixed to steel frame via 50 prolene sutures mounted on a balloon. 41F catheter
  • 9 pig models (2 with significant PVL, 3 with coronary flow obstruction)
  • Too large for human use
• 2000 Bonhoeffer et al - bovine jugular vein valve on platinum stent, 12 yo boy in pulmonic position
• 2000 Cribier et al - balloon expandable bovine pericardial valve, 24F catheter (Sheep)
  • 4/6/02 Cribier - 57 yo male with severe AS, h/o Aortobifem bypass. Antegrade. Valve on 30mm balloon, 24F
    • Normalization of AV gradients
    • Clinical Improvement in 2 days
    • Expired 3m later
• 2005 Paniagua - first retrograde TAVR
• 2006 Webb - 15/18 patients with successful implants. Rapid ventricular pacing

Figure 2. PHV delivery within the native calcific valve via antegrade approach. Left, Maximal balloon inflation (23 mm) for valve delivery. Middle, The PHV in position at mid part of the native aortic valve, pushing aside the calcific leaflets. Right, Supraaortic angiogram after PHV implantation showing no aortic regurgitation across the PHV and a mild paravalvular regurgitation (arrow). Both coronary ostia are patent and removed from the valve prosthesis [17]
A long road
25 Years from BAV
18 Years from concept
10 Years from FIM

Thousands of patients enrolled in feasibility and post-market registries

Oct 2011 - FDA Approval: Non Surgical Patients (PARTNER B)
Oct 2012 - FDA Approval: High Risk patients (PARTNER A)

International TF and TA Feasibility Studies
Edwards Lifesciences TF & TA Feasibility Studies (antegrade)
F.I.M. THV implantation
Animal implantations (sheep)

« Percutaneous Valve Technology » (prototypes)
Post-mortem studies of intra-valvular stenting
F.I.M. Balloon Aortic Valvuloplasty
TAVR

A Tale of 2 Valves: Medtronic Corevalve, Edwards Sapien Valve

4 Valve Sizes (23, 26, 29, 31 mm)
(18-29 mm Annular Range)
PARTNER A/B (NEJM 2010)

- TAVR vs SAVR in patients with severe aortic stenosis at high surgical risk, STS >10 (A)
- TAVR vs Medical therapy in patients with severe aortic stenosis whom are inoperable (B)
PARTNER A

Outcomes

All-Cause Mortality (ITT)

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

TCT 2014
Partner A

Adverse Events

Strokes (ITT Population)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AVR (N = 351)</td>
<td>TAVR (N = 348)</td>
</tr>
<tr>
<td>Major Vascular complications</td>
<td>13 (3.8)</td>
<td>39 (11.3)</td>
</tr>
<tr>
<td>Major bleeding – no. (%)</td>
<td>88 (26.7)</td>
<td>52 (15.7)</td>
</tr>
<tr>
<td>New PM – no. (%)</td>
<td>16 (5.0)</td>
<td>21 (6.4)</td>
</tr>
<tr>
<td>Endocarditis – no. (%)</td>
<td>3 (1.0)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>SVD§ requiring AVR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI – no. (%)</td>
<td>2 (0.6)</td>
<td>0</td>
</tr>
<tr>
<td>Acute kidney inj* – no. (%)</td>
<td>20 (6.5)</td>
<td>18 (5.4)</td>
</tr>
</tbody>
</table>

TCT 2014
PARTNER B

Outcomes

All Cause Mortality (ITT)
Landmark Analysis

- HR [95% CI] = 0.53 [0.41, 0.68]
- p (log rank) < 0.0001

- HR [95% CI] = 2.03 [1.36, 3.04]
- p (log rank) = 0.0005

- HR [95% CI] = 1.90 [1.05, 3.43]
- p (log rank) = 0.03

Mortality or Stroke (ITT)

- HR [95% CI] = 0.60 [0.46, 0.77]
- p (log rank) < 0.0001

- NNT = 5.0 pts
- NNT = 5.8 pts
- NNT = 4.8 pts
- NNT = 4.3 pts

TCT 2014
US CoreValve

High/Extreme Risk

- A randomized comparison of self-expanding Transcatheter versus surgical aortic valve replacement in patients with severe AS deemed high risk for surgery
US CoreValve
High/Extreme Risk

**All-Cause Mortality**

- Transcatheter
- Surgical

\[ \Delta = 6.5 \]

\[ \Delta = 4.8 \]

\[ 18.9\% \]

\[ 28.6\% \]

\[ 14.1\% \]

\[ 22.2\% \]

Log-rank \( P = 0.04 \)

**All Stroke**

- Transcatheter
- Surgical

\[ \Delta = 5.7 \]

\[ \Delta = 3.8 \]

\[ 16.6\% \]

\[ 10.9\% \]

\[ 8.7\% \]

Log-rank \( P = 0.05 \)
### Other Clinical Endpoints

<table>
<thead>
<tr>
<th>Events</th>
<th>1 Month</th>
<th></th>
<th></th>
<th></th>
<th>1 Year</th>
<th></th>
<th></th>
<th></th>
<th>2 Years</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vascular complications (major)</td>
<td>6.2</td>
<td>1.7</td>
<td>0.002</td>
<td>6.4</td>
<td>2.0</td>
<td>0.003</td>
<td>7.1</td>
<td>2.0</td>
<td>0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>20.0</td>
<td>7.1</td>
<td>&lt;0.001</td>
<td>22.5</td>
<td>11.6</td>
<td>&lt;0.001</td>
<td>25.8</td>
<td>12.8</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bleeding (life threatening or disabling)</td>
<td>13.6</td>
<td>35.1</td>
<td>&lt;0.001</td>
<td>16.5</td>
<td>38.4</td>
<td>&lt;0.001</td>
<td>18.1</td>
<td>39.6</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>New onset or worsening atrial fibrillation</td>
<td>11.7</td>
<td>31.0</td>
<td>&lt;0.001</td>
<td>16.4</td>
<td>33.2</td>
<td>&lt;0.001</td>
<td>19.5</td>
<td>34.9</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Paravalvular Regurgitation (Paired)

- **ACC 2015**
- **SAVR**
  - Discharge: N=156
  - 1 Month: N=156
  - 1 Year: N=156
  - 2 Years: N=156
- **TAVR**
  - Discharge: N=233
  - 1 Month: N=233
  - 1 Year: N=233
  - 2 Years: N=233

<table>
<thead>
<tr>
<th>Severity</th>
</tr>
</thead>
<tbody>
<tr>
<td>None/Trace</td>
</tr>
<tr>
<td>0.6%</td>
</tr>
<tr>
<td>1.3%</td>
</tr>
<tr>
<td>96.2%</td>
</tr>
<tr>
<td>62.2%</td>
</tr>
</tbody>
</table>
## ACC AHA Guidelines 2014

### AVR for Aortic Stenosis

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>COR</th>
<th>LOE</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical AVR is recommended in patients who meet an indication for AVR (Section 3.2.3) with low or intermediate surgical risk</td>
<td>I</td>
<td>A</td>
</tr>
<tr>
<td>For patients in whom TAVR or high-risk surgical AVR is being considered, members of a Heart Valve Team should collaborate to provide optimal patient care</td>
<td>I</td>
<td>C</td>
</tr>
<tr>
<td>TAVR is recommended in patients who meet an indication for AVR for AS who have a prohibitive surgical risk and a predicted post-TAVR survival &gt;12 mo</td>
<td>I</td>
<td>B</td>
</tr>
<tr>
<td>TAVR is a reasonable alternative to surgical AVR in patients who meet an indication for AVR (Section 3.2.3) and who have high surgical risk (Section 2.5)</td>
<td>IIa</td>
<td>B</td>
</tr>
<tr>
<td>Percutaneous aortic balloon dilation may be considered as a bridge to surgical or transcatheter AVR in severely symptomatic patients with severe AS</td>
<td>IIb</td>
<td>C</td>
</tr>
<tr>
<td>TAVR is not recommended in patients in whom existing comorbidities would preclude the expected benefit from correction of AS</td>
<td>III: No Benefit</td>
<td>B</td>
</tr>
</tbody>
</table>
## Severe Aortic Stenosis

**Intermediate Risk: STS>4**

<table>
<thead>
<tr>
<th>Valve Technology</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
<th>SAPIEN 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheath Compatibility</td>
<td>22-24F</td>
<td>16-20F</td>
<td>14-16F</td>
</tr>
</tbody>
</table>

**Available Valve Sizes**

- SAPIEN: 23mm, 26mm, 29mm*
- SAPIEN XT: 23mm, 26mm, 29mm*
- SAPIEN 3: 23mm, 26mm, 29mm

*First Implant Oct 30, 2012
To compare safety and effectiveness of TAVR with second generation Sapien XT versus SAVR in intermediate risk patients.

PARTNER 2
**Partner 2**

**Outcomes**

**Primary Endpoint (ITT)**
All-Cause Mortality or Disabling Stroke

- **Surgery**
- **TAVR**

HR [95% CI] = 0.89 [0.73, 1.09]  
$p$ (log rank) = 0.253

<table>
<thead>
<tr>
<th>TAVR</th>
<th>SAVR</th>
<th>Relative Risk Ratio</th>
<th>Non- Inferiority p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$n = 1011$</td>
<td>$n = 1021$</td>
<td>0.92</td>
<td>0.001</td>
</tr>
<tr>
<td>19.3%</td>
<td>21.1%</td>
<td>$1.09$</td>
<td>$97.5%$ CI</td>
</tr>
</tbody>
</table>

Pre-specified non-inferiority margin = 1.2

Favors TAVR  
Risk ratio (test/control)  
Favors Surgery

ACC 2016
### Adverse Events

#### Other Clinical Endpoints (ITT)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>30 Days</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAVR</strong> (n = 1011)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>0.99</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>0.22</td>
<td>0.56</td>
</tr>
<tr>
<td>Major Vascular Complications</td>
<td>0.008</td>
<td>0.006</td>
</tr>
<tr>
<td>Life-Threatening / Disabling Bleeding</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI (Stage III)</td>
<td>0.006</td>
<td>0.02</td>
</tr>
<tr>
<td>New Atrial Fibrillation</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>0.17</td>
<td>0.29</td>
</tr>
<tr>
<td>Re-intervention</td>
<td>0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>NA</td>
<td>0.22</td>
</tr>
</tbody>
</table>

#### Paravalvular Regurgitation (VI)

<table>
<thead>
<tr>
<th>3-Class Grading Scheme</th>
<th>TAVR</th>
<th>Surgery</th>
<th>TAVR</th>
<th>Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
<tr>
<td>20%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>40%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>60%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>80%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

ACC 2016
• Safety and efficacy of TAVR with self expanding prosthesis versus SAVR in intermediate risk patients with severe AS
Study Timeline

- **2012**: First patient enrolled June 19, 2012
- **2013**: CoreValve: 23, 26 and 29 mm (US)
- **2014**: CoreValve: 23, 26 and 29 mm (CAN, EU)
- **2015 April**: CoreValve: 31 mm (US, CAN, EU)
- **2016**: Enrollment completed June 30, 2016
  - Evolut R (US)
  - Primary endpoint assessment Dec 2016

CoreValve (n=724) 94% TF 4% DA 2% SCA
Evolut R (n=139)
SURTAVI

Outcomes

All-Cause Mortality or Disabling Stroke

NYHA Functional Class

ACC 2017
## Adverse Events

### 30-Day Safety and Procedure-related Complications

<table>
<thead>
<tr>
<th>Event</th>
<th>TAVR (N=864)</th>
<th>SAVR (N=796)</th>
<th>95% CI for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality or disabling stroke</td>
<td>2.8</td>
<td>3.9</td>
<td>-2.8, 0.7</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>2.2</td>
<td>1.7</td>
<td>-0.9, 1.8</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>1.2</td>
<td>2.5</td>
<td>-2.6, 0.1</td>
</tr>
<tr>
<td>All stroke</td>
<td>3.4</td>
<td>5.6</td>
<td>-4.2, -0.2</td>
</tr>
<tr>
<td>Overt life-threatening or major bleeding</td>
<td>12.2</td>
<td>9.3</td>
<td>-0.1, 5.9</td>
</tr>
<tr>
<td>Transfusion of PRBCs* - n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 units</td>
<td>756 (87.5)</td>
<td>469 (58.9)</td>
<td>24.4, 32.5</td>
</tr>
<tr>
<td>2 – 4 units</td>
<td>48 (5.6)</td>
<td>136 (17.1)</td>
<td>-14.5, -8.5</td>
</tr>
<tr>
<td>≥ 4 units</td>
<td>31 (3.6)</td>
<td>101 (12.7)</td>
<td>-11.7, -6.5</td>
</tr>
<tr>
<td>Acute kidney injury, stage 2-3</td>
<td>1.7</td>
<td>4.4</td>
<td>-4.4, -1.0</td>
</tr>
<tr>
<td>Major vascular complication</td>
<td>6.0</td>
<td>1.1</td>
<td>3.2, 6.7</td>
</tr>
<tr>
<td>Cardiac perforation</td>
<td>1.7</td>
<td>0.9</td>
<td>-0.2, 2.0</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>1.1</td>
<td>3.8</td>
<td>-4.2, -1.1</td>
</tr>
<tr>
<td>Permanent pacemaker implant</td>
<td>25.9</td>
<td>6.6</td>
<td>15.9, 22.7</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>12.9</td>
<td>43.4</td>
<td>-34.7, -26.4</td>
</tr>
</tbody>
</table>
Choice of TAVR Versus Surgical AVR in the Patient with Severe Symptomatic AS

Severe AS
Risk Assessment (STS score)

- STS Score < 4 (Low Risk) → SAVR (Class I)
- STS Score 4-8 (Intermediate Risk) → TAVR (Class IIa)
- STS Score 8-15 (High Risk) → TAVR (Class I)
- STS Score > 15 (Prohibitive Risk) → TAVR (Class I)

Severe AS Symptomatic (stage D)

Low surgical risk → Surgical AVR (Class I)
Intermediate surgical risk → Surgical AVR (Class I)
High surgical risk → TAVR (Class IIa)
Prohibitive surgical risk → TAVR (Class I)

AS = Aortic stenosis; AVR = Aortic Valve Replacement; TAVR = Transcatheter Aortic Valve Replacement
Severe Aortic Stenosis

Low Risk Patients: STS <4

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

Michael J. Mack, M.D., Martin B. Leon, M.D., Vinod H. Thourani, M.D., Raj Makkar, M.D., Sushil K. Kodali, M.D., Mark Russo, M.D., Samir R. Kapadia, M.D., S. Chris Malaisrie, M.D., David J. Cohen, M.D., Philippe Pibarot, D.V.M., Ph.D., Jonathon Leipsic, M.D., Rebecca T. Hahn, M.D. (for the PARTNER 3 Investigators)

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


SAPIEN 3 Transcatheter Heart Valve

Distinguishing Features

- Enhanced frame geometry for ultra-low delivery profile
- Bovine pericardial tissue
- Low frame height
- Outer skirt to reduce PVL

CoreValve 31 = 3.6% Evolut R = 74.1% Evolut PRO = 22.3%
Evolution of the Edwards Balloon-Expandable Transcatheter Valves

Patients with severe AS and low surgical risk
TAVR vs surgery
Clinical outcomes

1000 patients (mean age, 73 years), male population (69.3%), with lower STS-PROM scores (mean 1.9%) and fewer comorbidities (low-risk surgical candidates)

TAVR (n=503)
Surgery (n=497)
**Evolut LR**

### Study Timeline and Valves Studied

**2016**
- First Patient Randomized: Mar 28, 2016
- CoreValve 31 mm
- Evolut R: 23, 26, 29
- Added Evolut R 34 mm

**2017**
- Evolut PRO: 23, 26, 29 mm

**2018**
- Last Patient Randomized: Nov 27, 2018
- Primary Endpoint Assessment: Dec 27, 2018

### Vascular access
- 99% transfemoral
- 0.6% subclavian
- 0.4% direct aortic

**Patients with severe AS and low surgical risk**

### TAVR with self-expanding valve vs. surgery

**Clinical outcomes**

- **1,468** patients with severe aortic stenosis with suitable anatomy for TAVR or surgery and no more than 3% risk of death by 30 days with surgery were randomized to:
  - **TAVR with self-expanding valve (n=734)**
  - **Surgery (n=734)**
Evolut Low Risk
#ACC19

**Trial Description:** Patients with severe aortic stenosis with low STS PROM score (<3%) were randomized in a 1:1 fashion to either TAVR with CoreValve Evolut or SAVR. They were followed for 24 months.

**RESULTS**
- Primary endpoint: All-cause mortality/disabling stroke for TAVR vs. SAVR at 24 months: 5.3% vs. 6.7%, p < 0.05 for noninferiority, p > 0.05 for superiority
- Disabling stroke at 2 years: 1.1% vs. 3.5%, p < 0.05; mortality: both 4.5%, p > 0.05
- New permanent pacemaker at 30 days: 17.4% vs. 6.1%, p < 0.05; moderate-severe paravalvular leak (PVL): 3.5% vs. 0.5%, p < 0.05; mean aortic gradient at 1 year: 8.6 vs. 11.2 mm Hg, p < 0.05, mean EOA at 1 year: 2.3 vs. 2.0, p < 0.05

**CONCLUSIONS**
- TAVR with the self-expanding CoreValve Evolut valve was noninferior to SAVR for treatment of severe symptomatic aortic stenosis in low-risk patients
- Strokes, atrial fibrillation, and severe bleeding were higher with SAVR; need for permanent pacemaker and moderate-severe PVL was higher with TAVR
- Landmark trial; longer-term results are awaited

**PARTNER 3**
(STS 1.9, 30-day mortality 1.1%)

**Benefit**
- 15 deaths prevented*
- 19 total strokes prevented
- 37 rehospitalizations prevented
- 182 fewer major bleeding events
- 72 fewer AKI events
- 339 fewer atrial fibrillation cases
- Superior functional capacity
- Shorter hospital stay
- Avoidance of sternotomy/bypass

**Risk**
- 13 excess major vascular AEs†
- 273 excess mild PVR
- 19 excess pacemaker‡
- No excess valve thrombosis

**Evolut LR**
(STS 1.9, 30-day mortality 1.3%)

**Benefit**
- 24 disabling strokes prevented
- 34 HF hospitalizations prevented
- 57 fewer major bleeding events
- 19 fewer AKI events
- 285 fewer atrial fibrillation cases
- Superior functional capacity
- Shorter hospital stay
- Avoidance of sternotomy/bypass

**Risk**
- No excess major vascular AEs
- 314 excess mild PVR
- 126 excess pacemaker
- No excess valve thrombosis
## CENTRAL ILLUSTRATION  Evolution of TAVR Over the Last Decade

<table>
<thead>
<tr>
<th>Year</th>
<th>SAPIEN</th>
<th>CoreValve</th>
</tr>
</thead>
<tbody>
<tr>
<td>2019</td>
<td>(STS 1.9) Low risk N = 950</td>
<td>2019</td>
</tr>
<tr>
<td>2016</td>
<td>(STS 5.8) Intermediate risk N = 2,032</td>
<td>2017</td>
</tr>
<tr>
<td>2011</td>
<td>(STS 11.8) High risk N = 699</td>
<td>CoreValve HR N = 795</td>
</tr>
<tr>
<td>2010</td>
<td>(STS 11.2) Prohibitive/Extreme risk N = 358</td>
<td>CoreValve ER N = 489</td>
</tr>
</tbody>
</table>

### U.S. Food and Drug Administration approval
- **SAPIEN**
  - 8/2019
- **CoreValve**
  - 8/2019

### Center for Medicare and Medicaid Services National Coverage Determination (Coverage with Evidence Development)
- 6/2019
- 5/2012
- 5/2012

### 2017 ACC/AHA guideline recommendations
- No
- Class Ila, Level of Evidence: B
- Class I, Level of Evidence: A
- Class I, Level of Evidence: A

---


The pivotal trial for each risk category is shown for the balloon-expandable SAPIEN and self-expanding CoreValve and Evolut bioprostheses along with the current status of FDA approval (including date of approval), CMS National Coverage Determination through CED (including the date of approval), and the latest ACC/AHA guideline recommendations issued in 2017 that preceded the publication of the pivotal trials in low-risk patients with severe aortic stenosis. Notably, the CMS National Coverage Determination does not specify which surgical risks are to be covered but refers to “the treatment of symptomatic aortic valve stenosis when furnished according to the United States FDA approved indication” (24), allowing for immediate coverage of low-risk patients following FDA approval in August 2019. Not shown is Boston Scientific LOTUS Edge Valve System that was approved by the FDA for high-risk patients and above in April 2018. A total of 8,386 patients have been evaluated in 8 pivotal trials. CMS = Center for Medicare and Medicaid Services; FDA = U.S. Food and Drug Administration.
2017 ACC Expert Consensus Decision Pathway for Transcatheter Aortic Valve Replacement in the Management of Adults With Aortic Stenosis

A Report of the American College of Cardiology Task Force on Clinical Expert Consensus Documents
Severe Aortic Stenosis
The valve, the patient, the procedure

5.1.4 Overall Procedural Risk

<table>
<thead>
<tr>
<th>Risk categories</th>
<th>Low risk</th>
<th>Intermediate risk</th>
<th>High risk</th>
<th>Prohibitive risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk factors</td>
<td>STS-PROM &lt;4% and no procedure specific impediments</td>
<td>STS-PROM 4%-8% or mild frailty or 1 major organ system compromise not to be improved postoperatively or a possible procedure-specific impediment</td>
<td>STS-PROM &gt;8% or moderate-severe frailty or &gt;2 major organ system compromises not to be improved postoperatively or a possible procedure-specific impediment</td>
<td>STS-PROM &gt;50% at 1 year or &gt;3 major organ system compromises not to be improved postoperatively or severe frailty or severe procedure-specific impediments</td>
</tr>
</tbody>
</table>

5.1.5 Integrated Benefit-Risk of TAVR and Shared Decision-Making

- No current indication for AVR
  - AS not severe or no AS symptoms or other indication for AVR
  - Periodic monitoring of AS severity and symptoms
  - Re-evaluate when AS severe or symptoms occur

- AVR indicated but SAVR preferred over TAVR
  - Lower risk for surgical AVR
  - Mechanical valve preferred
  - Other surgical considerations
  - SAVR recommended in lower-risk patients
  - Valve durability considerations in younger patients
  - Concurrent surgical procedure needed (e.g., aortic root replacement)

- TAVR candidate with expected benefit > risk
  - Symptom relief or improved survival
  - Possible complications and expected recovery
  - Discussion with patient and family
  - Proceed with TAVR imaging evaluation and procedure

- Severe symptomatic AS but benefit < risk (futility)
  - Life expectancy <1 year
  - Chance of survival with benefit at 2 years <25%
  - Palliative care inputs
  - Palliative balloon aortic valvuloplasty in selected patients
STS-ACC TVT Registry of Transcatheter Aortic Valve Replacement

John D. Carroll, MD, a Michael J. Mack, MD, b Sreekanth Vemulapalli, MD, c Howard C. Herrmann, MD, d Thomas G. Gleason, MD, e George Hanzel, MD, f G. Michael Deeb, MD, g Vinod H. Thourani, MD, h David J. Cohen, MD, MSc, i Nimesh Desai, MD, PhD, j Ajay J. Kirtane, MD, SM, k Susan Fitzgerald, MSN, RN, l Joan Michaels, MSN, RN, m Carole Krohn, BSN, RN, n Frederick A. Masoudi, MD, MSPH, o Ralph G. Brindis, MD, MPH, p Joseph E. Bavaria, MD q
AVR Volume

The graph shows the volume of AVR (Aortic Valve Replacement) procedures over the years from 2012 to 2019. The Y-axis represents the number of procedures, ranging from 0 to 80,000. The X-axis represents the years from 2012 to 2019.

- **Isolated SAVRs** (blue line)
- **All SAVRs** (red line)
- **TAVRs** (black line)

Key points:

- **2012**: 4,666
- **2013**: 8,946
- **2014**: 1,6312
- **2015**: 30,159
- **2016**: 30,432
- **2017**: 25,085
- **2018**: 28,925
- **2019**: 20,971

Notable peaks:

- **#1** (2016): 38,035
- **#2** (2018): 59,168

The graph indicates an overall increase in AVR volumes over the years, with some fluctuations.
The median (value in blue box), 25th, and 75th quartile values of the Society of Thoracic Surgeons (STS) 30-day predicted risk of mortality (PROM) score for isolated surgical aortic valve replacement for patients undergoing transcatheter aortic valve replacement through 2019. The decline in STS PROM values coincides with expansion of TAVR indication to intermediate- and low-risk patients.
Median length of stay values in red boxes between 2013 and 2019. The bars represent the 25th and 75th percentiles.
Proportions of patients discharged directly to home (blue), to a rehabilitation facility (red), and to a nursing home (gray) between 2011 and 2019.
Yearly average rate of stroke after TAVR from 2012 through 2019. In-hospital rates are in blue, 30-day in red, and 1-year in gray (1-year values are from CMS-linked data, unavailable after 2017). There has been a small, slow, downward trend in stroke rates. CMS = Centers for Medicare & Medicaid; TAVR = transcatheter aortic valve replacement.
TAVR for AS

Summary

• Severe aortic stenosis is a condition that carries significant morbidity and mortality, especially if symptomatic.

• AS typically affects the elderly population, surgical risk can be high/prohibitive.

• TAVR a proven safe alternative to surgery in these patients.

• Advances in technology and procedure itself has significantly reduced complications.

• TAVR now an alternative to surgery in many patients of all risk categories.
Percutaneous Interventions- Mitral Valve

MitraClip

**Figure 1** Surgical Edge-to-Edge Technique Versus MitraClip

(A) The surgical technique involves a continuous suture of the free edge of the leaflets at the site of the regurgitation. In case the lesion is in the A2-P2 area, a double orifice valve is created. (B) The sutures engage the free edge of the facing leaflets, suture bite depth depends on the amount of redundant tissue (larger in case of degenerative disease, and minimal in case of functional mitral regurgitation). (C) The MitraClip (Abbott Vascular, Menlo Park, California) is implanted in the A2-P2 region, similarly to the surgical technique. The drawing illustrates the clip partially open, to demonstrate tissue penetration into the clip. Once proper leaflet grasping is confirmed, the clip is closed to enhance coaptation. (D) The free edges of the leaflets are engaged between the clip arms and the grippers. The clip is closed with leaflet facing. Compared with surgery where tissue is imbricated into the suture with no evidence of planar surface of coaptation, the MitraClip is designed to induce a linear apposition of leaflets to enhance coaptation. Figure illustration by Craig Shrago.
Mitral Regurgitation (Chronic)

- Primary (degenerative) Mitral Regurgitation: disease of the mitral valve
  - Myxomatous
  - Rheumatic
- Secondary (functional) Mitral Regurgitation:
  - Ischemic
  - dilated cardiomyopathy
- Symptoms:
  - Dyspnea on exertion
  - Orthopnea/PND
  - Fatigue
  - palpitations (atrial fibrillation)
Mitral Regurgitation

Guidelines
EVEREST II (2011)
Randomized Comparison of Percutaneous Mitral Valve Repair and Surgery for Mitral Regurgitation

Key Inclusion/Exclusion Criteria

**Inclusion**
- Candidate for MV Surgery
- Moderate to severe (3+) or severe (4+) MR
  - Symptomatic
    - >25% EF and LVEF ≤55mm
  - Asymptomatic with one or more of the following
    - LVEF 25-60%
    - LVESD ≥40mm
    - Pulmonary hypertension
    - Atrial fibrillation

**Exclusion**
- AMI within 12 weeks
- Need for other cardiac surgery
- Renal insufficiency
  - Creatinine >2.5mg/dl
- Endocarditis
- Rheumatic heart disease
- MV anatomical exclusions
  - Mitral valve area <4.0cm²
  - Leaflet flail width (≥15mm) and gap (≥10mm)
  - Leaflet tethering/coaptation depth (≥11mm) and length (<2mm)

Baseline Demographics & Co-morbidities

**Intention to Treat**

<table>
<thead>
<tr>
<th>Patient Demographics</th>
<th>Percutaneous %</th>
<th>Surgery %</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (mean)</strong></td>
<td>67 years</td>
<td>66 years</td>
<td>0.32</td>
</tr>
<tr>
<td>Male</td>
<td>63</td>
<td>66</td>
<td>0.60</td>
</tr>
<tr>
<td>History of CHF</td>
<td>91</td>
<td>78</td>
<td>0.005</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>47</td>
<td>46</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Prior myocardial infarction</td>
<td>22</td>
<td>21</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Previous cardiovascular surgery</td>
<td>22</td>
<td>19</td>
<td>0.54</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>34</td>
<td>39</td>
<td>0.42</td>
</tr>
<tr>
<td>COPD (with or without home O₂)</td>
<td>15</td>
<td>15</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Moderate to Severe Renal Failure</td>
<td>3</td>
<td>2</td>
<td>0.72</td>
</tr>
<tr>
<td>Diabetes</td>
<td>8</td>
<td>11</td>
<td>0.50</td>
</tr>
</tbody>
</table>

ACC/AHA Guidelines
JACC 52:e1-e142, 2008
Primary Effectiveness Analyses at 1 and 2 Years
Intention to Treat Analysis
Primary Effectiveness:
Freedom from death, MV surgery/re-operation or 3+ or 4+ MR

<table>
<thead>
<tr>
<th>Components of Failure</th>
<th>Percutaneous</th>
<th>Surgery</th>
<th>P-value Percutaneous vs Surgery at 2 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 Year N=181</td>
<td>1 Year N=89</td>
<td>19 (11.0%)</td>
</tr>
<tr>
<td></td>
<td>2 Years N=172</td>
<td>2 Years N=83</td>
<td>19 (11.0%)</td>
</tr>
<tr>
<td>MV Surgery / Re-operation</td>
<td>37 (20.4%)</td>
<td>38 (22.1%)</td>
<td>2 (2.2%)</td>
</tr>
<tr>
<td></td>
<td>38 (21.0%)</td>
<td>34 (19.8%)</td>
<td>18 (20.2%)</td>
</tr>
<tr>
<td>3+ or 4+ MR *</td>
<td>38 (21.0%)</td>
<td>34 (19.8%)</td>
<td>18 (20.2%)</td>
</tr>
<tr>
<td>Freedom from death, MV surgery / re-operation or 3+ or 4+ MR †</td>
<td>100 (55.2%)</td>
<td>89 (51.7%)</td>
<td>65 (73.0%)</td>
</tr>
</tbody>
</table>
EVEREST II
Outcomes (Comparison of Treatment)

Primary Effectiveness Analyses at 1 and 2 Years
Comparison of Treatment Strategy Analysis
Primary Effectiveness:
Freedom from death, MV surgery/re-operation or 3+ or 4+ MR

2. Comparison of Treatment Strategies
- Mitral valve surgery following unsuccessful in-hospital percutaneous repair not considered an “endpoint” event
MitraClip
Degenerative Mitral Regurgitation

- FDA approval October 2013: “The MitraClip Clip Delivery System is indicated for the percutaneous reduction of significant **symptomatic** mitral regurgitation (MR ≥3+) due to **primary abnormality** of the mitral apparatus [degenerative MR] in patients who have been determined to be at **prohibitive risk** for mitral valve surgery by a heart team, which includes a cardiac surgeon experienced in mitral valve surgery and a cardiologist experienced in mitral valve disease, and in whom existing comorbidities would not preclude the expected benefit from reduction of the mitral regurgitation.”
**MitraClip Data**

- **EVEREST II**
  - Not as effective as surgery in reducing MR
  - Safer than surgery
  - Despite residual MR, reductions in LV chamber volumes and clinical outcomes assessed by QOL questionnaires similar. Similar findings in 4-5 yr f/u.

The COAPT Trial
Cardiovascular Outcomes Assessment of the MitraClip Percutaneous Therapy for Heart Failure Patients with Functional Mitral Regurgitation

A parallel-controlled, open-label, multicenter trial in 614 patients with heart failure and moderate-to-severe (3+) or severe (4+) secondary MR who remained symptomatic despite maximally-tolerated GDMT

Randomize 1:1*

MitraClip + GDMT
N=312

GDMT alone
N=302

Follow-up at 30d, 6mo, 1y, 18mo, 2y, 3y, 4y, 5y

*Stratified by cardiomyopathy etiology (ischemic vs. non-ischemic) and site
Primary Effectiveness Endpoint
All Hospitalizations for HF within 36 months
All patients, ITT, including crossovers

Cumulative HF Hospitalizations (n)
0 100 200 300 400

Time after randomization (months)
0 6 12 18 24 30 36

# at Risk:
MitraClip + GDMT 302 269 238 219 189 128 93
GDMT alone 312 272 223 185 144 89 68

NNT = 3.2 [95% CI 2.5, 4.5]
NNT = 3.0 [95% CI 2.4, 4.0]

HR [95% CI]# = 0.49 [0.37, 0.63]
P=0.00000006

#Joint frailty model
All-Cause Mortality
All patients, ITT, including crossovers

- MitraClip + GDMT
- GDMT alone

HR [95% CI] = 0.67 [0.52, 0.85]
P = 0.001
NNT = 6.8 [95% CI 4.5, 14.0]
NNT = 7.9 [95% CI 4.6, 26.1]

# at Risk:
- MitraClip + GDMT: 302
- GDMT alone: 312

Time after randomization (months):
- 0: 269, 272
- 6: 238, 223
- 12: 219, 186
- 18: 189, 145
- 24: 128, 91
- 30: 93, 70

Event rates are Kaplan-Meier time-to-first event estimates
Primary Safety Endpoint (MitraClip arm)

Freedom from Device-related Complications

n=293 pts with MitraClip procedure attempted

<table>
<thead>
<tr>
<th></th>
<th>0-30 Days</th>
<th>0-12 Months</th>
<th>0-24 Months</th>
<th>0-36 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>1.4% (4)</td>
<td>3.3% (9)</td>
<td>5.2% (13)</td>
<td>8.7% (18)</td>
</tr>
<tr>
<td>- Device-related complications</td>
<td>1.4% (4)</td>
<td>1.4% (4)</td>
<td>1.4% (4)</td>
<td>1.4% (4)</td>
</tr>
<tr>
<td>• Single leaflet device attachment</td>
<td>0.7% (2)</td>
<td>0.7% (2)</td>
<td>0.7% (2)</td>
<td>0.7% (2)</td>
</tr>
<tr>
<td>• Device embolization</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>• Endocarditis requiring surgery</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>• Mitral stenosis requiring surgery</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
<td>0.0% (0)</td>
</tr>
<tr>
<td>• Any device-related complication requiring non-elective CV surgery</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
<td>0.3% (1)</td>
</tr>
<tr>
<td>- Progressive heart failure</td>
<td>0.0% (0)</td>
<td>2.0% (5)</td>
<td>3.8% (9)</td>
<td>7.4% (14)</td>
</tr>
<tr>
<td>• Left ventricular assist device implant</td>
<td>0.0% (0)</td>
<td>1.2% (3)</td>
<td>2.6% (6)</td>
<td>5.4% (10)</td>
</tr>
<tr>
<td>• Heart transplant</td>
<td>0.0% (0)</td>
<td>0.8% (2)</td>
<td>1.3% (3)</td>
<td>2.6% (5)</td>
</tr>
</tbody>
</table>

Event rates are Kaplan-Meier time-to-first event estimates; includes only first occurrence of each event.
MitraClip
HF and Secondary MR

• FDA March 14, 2019: Expanded approval for treatment of patients with structurally normal mitral valves who develop heart failure and moderate to severe MR despite receiving optimal treatment including HF medications or, for certain patients, cardiac resynchronization therapy.
MitraClip

Summary

• A percutaneous therapy not strongly reflected in our Valve Guidelines as of yet

• As of 2013 FDA approved, and a reasonable option for patients with symptomatic severe (3+/4+) MR in high surgical risk patients versus surgery with comparable outcomes (death, freedom from re-operation, freedom from 3-4 MR, HF/QOL scores, LV volume improvement)

• Must be anatomically feasible: central MR preferred, flail gap <15mm, little calcium

• As of 2019 FDA approved for patients with Heart Failure and moderate to severe MR who are still symptomatic on GDMT with reduced mortality and HF hospitalizations
Thank You!