When Valve Surgery is Not an Option: Tackling the Choice of TAVR Devices

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Disclosures

**Speaker’s Bureau:**
- Amgen

**Medical/Scientific Boards:**
- CardioSolutions
- Toshiba

**Stockholder:**
- CardioSolutions

**Grant/Research Support:**
- Medtronic
- Direct Flow
- Abbott
- CardioKinetix
- Sunshine Heart
- Insert Company Name
Incidence and Prevalence

• Aortic stenosis is the most common acquired valvular disorder found in developed countries
  • Affects approximately 5 out of every 10,000 people in the United States

• Mild to severe AS present in up to 9% of adults over age 65 years

• The prevalence of calcific aortic stenosis increases with age and is expected to double in the next 20 years*

Symptomatic Patients with Severe AS Require Urgent Attention

Valvular Aortic Stenosis In Adults
(Average Course)

Surgical intervention should be performed promptly
even once minor symptoms occur.

Latent Period
Increasing Obstruction Myocardial Overload

Onset Severe Symptoms
- Angina
- Syncope
- CHF

Prevalence of Aortic Stenosis in Patients Age 65 and Over

- **Annual AVR Patients**: 60K
- **Addressable Patients**: 320K

19% of those who would benefit from AVR actually get it.

- **U.S. Population > 65**: 40M
- **Prevalence Rate**: U.S. Census, 2010
- **Prevalence**: 4%
- **Operable AS (%)**: 20%
- **Calculation**: Cardiovascular Health Study

*L.E.K. Consulting Estimate*
Treatment of Severe Aortic Stenosis (AS)

• SAVR is the gold standard for treatment of severe AS\(^1\)
• However, 33% of all patients $\geq 75$ years of age with severe AS are declined for surgery\(^2\)
  – Of these patients who ultimately undergo SAVR, a portion are at high risk for morbidity/mortality from the procedure
  – Of the 100 patients who underwent SAVR during the study period, 5% died during the postoperative period (30 days)

SAVR=surgical aortic valve replacement.
Surgery is Safer than Ever

Unadjusted Aortic Valve Operative Mortality
Yearly Over Last 10 Years

Percentage of Patients

2001 2010

0% 0%
1% 1%
2% 2%
3% 3%
4% 4%

Should early elective surgery be performed in patients with severe but asymptomatic aortic stenosis? Eur Heart J. 2002;23:1417-1421

Characteristics of an Inoperable Patient Cohort B

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
- Heavily calcified aorta
- Prior chest radiation
- History of CAD
- History of COPD
- History of renal insufficiency
- Diabetes and hypertension
Currently approved TAVR Options

- Edwards Sapien Valve
- Stainless Steel Frame
- More Perivalvular leak, less AV block/PPM
- Trans-Apical Option

- Medtronic CoreValve
- Nitinol Frame-self expanding
- Less Perivalvular Leak, More heart block/PPM
- Less Risk of Annular Rupture
Transcatheter Aortic Valve Replacement
Using a Self-Expanding Bioprosthesis in Patients With Severe Aortic Stenosis at Extreme Risk for Surgery

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Theodore Schreiber, MD,¶ Thomas G. Gleason, MD,¶ John Conte, MD,‡ Maurice Buchbinder, MD,¶ G. Michael Deeb, MD,¶ Blue Cross Blue Shield, MD,F Patrick W. Serruys, MD, PhD,§ Sharil Chenoweth, MS,¶‡ Jar K. Oh, MD,¶¶ for the CoreValve United States Clinical Investigators:
Boston, Massachusetts; New York, New York; Houston, Texas; Columbus, Ohio; Indianapolis, Indiana; Durham, North Carolina; Detroit and Ann Arbor, Michigan; Pittsburgh, Pennsylvania; Baltimore, Maryland; Los Angeles, California; Research, the Netherlands; and Mexico City, Mexico.

Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery

Transcatheter Aortic-Valve Replacement with a Self-Expanding Prosthesis

Cohort A
Transcatheter Aortic-Valve Replacement in High-Risk Patients

Cohort B
Transcatheter Aortic-Valve Implantation for Aortic Stenosis in Patients Who Cannot Undergo Surgery
Effective and Lasting Drop in Gradient
Durability

LOW AND STABLE AORTIC VALVE GRADIENT

MEAN GRADIENT, mm Hg

Baseline Year 1 Year 2 Year 3 Year 4 Year 5

Edwards THV 310 219 156 106 79 56

SAVR 299 158 123 88 61 48
Paravalvular Leak

- The Transfer or Trading of Disease states
- Similar pathophysiology to Acute AI
- Left ventricle is not able to adequately compensate for the regurgitant volume, and excessive backward blood flow impairs forward stroke volume
Impact of Total AR on Mortality (AT)

TAVR Patients:

Sapien

<table>
<thead>
<tr>
<th>AR Level</th>
<th>No. at Risk</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
<th>30</th>
<th>36</th>
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<tbody>
<tr>
<td>None-Tr</td>
<td>131</td>
<td>121</td>
<td>114</td>
<td>102</td>
<td>93</td>
<td>80</td>
<td>63</td>
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<tr>
<td>Mild</td>
<td>171</td>
<td>146</td>
<td>125</td>
<td>117</td>
<td>110</td>
<td>94</td>
<td>62</td>
<td></td>
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<tr>
<td>Mod-Sev</td>
<td>34</td>
<td>24</td>
<td>21</td>
<td>18</td>
<td>15</td>
<td>12</td>
<td>9</td>
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</tr>
</tbody>
</table>

Mortality:
- None - Trace: 12.3%
- Mild: 26.0%
- Moderate - Severe: 38.2%

Months post Procedure:
- 0: 12.3%
- 6: 26.0%
- 12: 38.2%
- 18: 53.7%
- 24: 60.8%
- 30: 44.6%
- 36: 35.3%
Impact of PVL on Late Mortality

CoreValve

Extreme Risk Study | Iliofemoral Pivotal

Log rank P Value <0.0001

- None/Trivial N=208: 87.5%
- Mild N=180: 23.9%
- Moderate N=54: 22.2%
- Severe N=8: 17.8%

All-Cause Mortality (%) vs. Months Post Procedure
US Pivotal Extreme Risk – PVL Paired Analysis

Discharge: N=440

1.6% of patients were in the 'Died' category.
9.1% of patients had no echo at 1 year.
40.7% of patients were in the '≤ Mild' category.
48.6% of patients were in the 'Moderate' category.

 Improvement in Moderate PVL Discharge to 1 Year

Patients with echos at both discharge and 1 Year:
- 29 patients in the '≤ Mild' category.
- 24 patients in the 'Moderate' category.

83% of patients improved from discharge to 1 Year.
Paravalvular Leak
Sapien vs. CoreValve

Sapien

CoreValve

> Mild PVL Increase Mortality

> Moderate PVL Increase Mortality
The Aortic Annulus is Dynamic – Patient Example

Four-dimensional multidetector CT image of the aortic annulus in a patient with severe aortic stenosis shows change in measurements during the cardiac cycle.

- **Annulus**
  - Dynamic
  - Elliptical
  - Calcifications
Intaprocedural TEE

Hingepoint to Hingepoint 18.5mm

20.7mm
Significant PVL following 23mm Sapien
Sizing by 2D TEE

Female

- 674.6 ± 132.0
- 1.07 ± 0.1
- 29.2 ± 2.8

- 699.3 ± 131.6
- 29.7 ± 2.7

- 386.9 ± 58.5
- 1.29 ± 0.1
- 22.6 ± 1.7

- 374.0 ± 94.2
- 1.51 ± 0.2
- 22.9 ± 3.0
Retrospective analysis of Baseline CT

Hingepoint-hingepoint
18.5 mm

\[ D_{\text{max}} = 27.0 \text{ mm} \]
\[ D_{\text{min}} = 18.7 \text{ mm} \]
\[ D_{\text{mean}} = 22.9 \text{ mm} \]
\[ D_{\text{circ}} = 24.3 \text{ mm} \]
\[ D_{\text{CSA}} = 23.6 \text{ mm} \]
Distribution of Annulus Ellipticity Index

n=177

p=0.52

Ellipticity Ratio (Dmax/Dmin)

Males

Females
Conduction Disturbances after TAVR

• Cardiac conduction disturbances remain a frequent complication of TAVR
  – New Left Bundle Branch Block (LBBB)
  – Permanent Pacemaker (PPM)

• Conduction disturbances after aortic valve therapies attributable to:
  – High frequency of comorbid conduction disease
  – Close anatomic proximity of aortic valve complex to the cardiac conduction system
Relationship of the Aortic Valve Complex and the Cardiac Conduction System

Ferreira. PACE 2010;33:1364-72
Mechanisms of Conduction Disturbances During TAVR

• Autopsy studies:
  – Direct compression
  – Hemorrhage / hematoma
  – Ischemic Injury
  – Inflammation

• Up to 50% of conduction disturbances occur during wire manipulation and BAV

Saji. Cardiovasc Interv Ther 2013 [Epub].
# New LBBB After TAVR

- The incidence of new-onset LBBB varies with valve system and time after TAVR
- Majority are transient: resolve by discharge in 30-50%

<table>
<thead>
<tr>
<th></th>
<th>N</th>
<th>ESV</th>
<th>MCV</th>
<th>Definition New-LBBB</th>
<th>LBBB ESV</th>
<th>LBBB MCV</th>
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<tr>
<td>Nazif 2014</td>
<td>1151</td>
<td>1151</td>
<td></td>
<td>Persist</td>
<td>10.5%</td>
<td></td>
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<tr>
<td>Testa 2013</td>
<td>818</td>
<td></td>
<td>818</td>
<td>Any/Persist</td>
<td>43%/27%</td>
<td></td>
</tr>
<tr>
<td>Houthuizen 2012</td>
<td>679</td>
<td>387</td>
<td>292</td>
<td>Any</td>
<td>12%</td>
<td>51%</td>
</tr>
<tr>
<td>Urena 2014</td>
<td>668</td>
<td>668</td>
<td></td>
<td>Any/Persist</td>
<td>19%/12%</td>
<td></td>
</tr>
<tr>
<td>Wenaweser 2013</td>
<td>508</td>
<td></td>
<td>508</td>
<td>?</td>
<td>35%</td>
<td></td>
</tr>
</tbody>
</table>

All independent studies including > 500 patients
Persist: New LBBB persistent to hospital discharge
Any: New LBBB occurring any time during hospital
Goes away with time
ADVANCE Trial

% of Patients with Conduction Disturbance

- Post-Procedure: 45.4% (New-onset LBBB) vs. 39.0% (New-onset 1st degree AV block), p<0.01
- Day 7: 37.1% (New-onset LBBB) vs. 24.5% (New-onset 1st degree AV block), p<0.01
- Day 30: 25.8% (New-onset LBBB) vs. 10.2% (New-onset 1st degree AV block), p<0.01
Every millimeter counts
ADVANCE Trial

J Am Coll Cardiol Intv. 2015;8(6):837-846
Impact of Conduction Disturbances on Outcomes: Duration of hospital stay and repeat hospitalization

**LBBB**
- Post-procedure hospital days: LBBB vs no LBBB 6.8 vs 6.1 days, p=0.007

**PPM**
- Post-procedure hospital days: PPM vs no PPM 7.3 vs 6.2 days, p <0.001


Nazif. TCT 2013
Does New-Onset LBBB after TAVR predict mortality?

Houthuizen: N=697
387 MCV, 292 ESV

New LBBB assoc. with 1-yr mortality, independent of device

Impact of Persistent New LBBB on Mortality

De Carlo et al: 275 MCV
Testa et al: 879 MCV
Wenaweser et al: 508 MCV

Urena et al: 202 ESV
Franzoni et al: 87 MCV, 151 ESV
Urena et al: 668 ESV

PARTNER

Death (%)

No. at risk:

Nazif et al: 1151 ESV
Testa et al: 879 MCV
Wenaweser et al: 508 MCV

P = 0.668
HR: 0.90 [95% CI: 0.56, 1.45]

Overall Mort: Discharge LBBB
Overall Mort: No Discharge LBBB

HR: 0.90 [95% CI: 0.56, 1.45]
P = 0.668
Balance of the Evidence

Houthuizen (N=697)
Pereira (N=58)
TOTAL N= 755

No Δ Mortality

Testa (N=879)
DeCarlo (N=275)
Wenaweser (N=508)
Franzoni (N=238)
Urena (N=668)
Nazif (N=1151)
TOTAL N=3719
Clinical Implications of PPM post TAVR
No Impact on Mortality

PARTNER: 1973 ESV

1556 Pts: 698 MCV, 858 ESV

Nazif. TCT 2013

Urena. Circulation 2014;129:1233-43
Challenges addressed

- Edwards Sapien 3 (14 Fr Delivery System)
- Medtronic Evolut R (Recapturable and Retrievable)
- Medtronic Engager TA Valve
- St. Jude Medical Portico Valve
- Boston Scientific Lotus Valve (Recapturable and Retrievable)
- Direct Flow (Recapturable and Retrievable)
- Jena Valve
Minimize Risk of Aortic Regurgitation
• Double-ring design conforms to anatomy for a better seal

Optimize Positioning
• Full hemodynamic assessment before final detachment
• Repositionable
• Fully retrievable

Improve TAVI Procedure
• Fully competent during positioning
• No post dilatation or rapid pacing
• Flexible, low profile delivery system
The Direct Flow valve can be repositioned multiple times to achieve excellent patient outcomes.

After repositioning, AR can be eliminated before permanent fixation.
Lotus Valve System Design Goals

Controlled Mechanical Expansion

- Valve deployed via controlled mechanical expansion
- No rapid pacing during deployment
- Valve functions early enabling controlled deployment
- Ability to assess valve in final configuration before release

- Braided Nitinol Frame
- Central Radiopaque Positioning Marker
- Bovine Pericardium
- Locking Mechanism
- Adaptive Seal
- ~70mm
REPRISE II Case Example
23 mm Lotus valve retrieval and exchange for 27 mm Lotus valve

Lotus valve is repositionable throughout entire deployment process

Images courtesy of Ian Meredith AM, MBBS, PhD
Lotus Valve System Design Goals
Minimize Paravalvular Leak (PVL)

Non–circular Annulus + Irregular Calcification → PVL

Lotus Valve
Adaptive seal to mitigate PVL

Conclusion

• TAVR has been the single most disruptive technology in the cardiovascular arena since the advent of coronary angioplasty
• RCT’s have demonstrated effective, durable therapy in extreme and high risk patients
• New “problems” developed with the first and second generation systems
• Third and forth generation systems are currently in trials to address the problems
• Results will tell if efficacy and durability are comparable
•
Thank You