Transcatheter Aortic Valve Replacement (TAVR) & Trends in CV Anesthesia

Dr Sharif Al-Ruzzehh
MD, PhD, FASE, FRCS, FRCSEd
Cardiac Anesthesiologist
NO DISCLOSURES
Prevalence of Aortic Stenosis

- Aortic stenosis is estimated to be prevalent in up to 7% of the population over the age of 65

- It is more likely to affect men than women; 80% of adults with symptomatic aortic stenosis are male
Major Risk Factors

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

- Aortic stenosis  2% US population >65yrs old
- Aortic sclerosis  29% US population >65 yrs old
- Aortic sclerosis  50% greater risk of mortality and myocardial infarction.
- Aortic sclerosis progresses to aortic stenosis in 9% over 5 years
What Causes Aortic Stenosis in Adults?

More Common

- Age-Related Calcific Aortic Stenosis
  - Aortic stenosis in patients over the age of 65 is usually caused by calcific (calcium) deposits associated with aging

Less Common

- Rheumatic Fever
  - Adults who have had rheumatic fever may also be at risk for aortic stenosis

- Congenital Abnormality
  - In some cases adults may develop aortic stenosis resulting from a congenital abnormality
Three Major Etiologies for aortic stenosis
Aortic Stenosis Is Life Threatening and Progresses Rapidly

- Survival after onset of symptoms is 50% at 2 years and 20% at 5 years
- Surgical intervention for severe aortic stenosis should be performed promptly once even minor symptoms occur
5 – Year Survival

5-Year Survival*

<table>
<thead>
<tr>
<th>Condition</th>
<th>Survival, %</th>
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<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 Tuzcu, MD, Cleveland Clinic
Echocardiographic Guidelines are the Gold Standard in Assessing Severe AS

Grading the Severity of Aortic Stenosis per the ACC/AHA Guidelines

<table>
<thead>
<tr>
<th>Indicator</th>
<th>Mild</th>
<th>Moderate</th>
<th>Severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet velocity (m/s)</td>
<td>&lt; 3.0</td>
<td>3.0 - 4.0</td>
<td>&gt; 4.0</td>
</tr>
<tr>
<td>Mean gradient (mmHg)</td>
<td>&lt; 25</td>
<td>25 - 40</td>
<td>&gt; 40</td>
</tr>
<tr>
<td>Valve area (cm²)</td>
<td>&gt; 1.5</td>
<td>1.0 – 1.5</td>
<td>&lt; 1.0</td>
</tr>
<tr>
<td>Valve area index (cm²/m²)</td>
<td>N/A</td>
<td>N/A</td>
<td>&lt; 0.6</td>
</tr>
</tbody>
</table>

According to the 2014 ACC/AHA guidelines, severe aortic stenosis is defined as:

- Aortic valve area (AVA) less than 1.0 cm
- Mean gradient greater than 40 mmHg or jet velocity greater than 4.0 m/s
Multiple Diagnostic Modalities

- Auscultation
- Trans-thoracic Echo (TTE)
- Cardiac Cath.
- Chest X-ray
- Electrocardiogram
3D TEE Planimetry
• Low Flow, Low Gradient Severe AS

* Paradoxical Low Flow, Low Gradient Severe AS
Low Flow, Low Gradient AS

- Low gradient with a small calculated valve area in the setting of poor systolic function. This may result in lack of referral for AVR because of the low gradient.

- Dobutamine Stress Echo:
  - By increasing cardiac output, we can determine if the AS is severe by reassessing the gradient across the aortic valve (increases) AND the aortic valve area (decreases).
  - Assess myocardial contractile reserve
    - Does the cardiac output improve by 20% or more.
  - Critical for decision making regarding aortic valve replacement.
Some patients with severe aortic stenosis based on valve area have a lower than expected gradient (e.g. mean gradient < 30 mmHg) despite preserved LV ejection fraction (e.g. EF > 50%)

- Up to 35% of patients with severe aortic stenosis present with low flow, low gradient
- These low gradients often lead to an underestimation of the severity of the disease, so many of these patients do not undergo surgical aortic valve replacement

Dobutamine stress in low gradient, low ejection fraction AS
Chambers, Heart. 2006 April; 92(4): 554–558
SAVR Greatly Improves Survival
Options for AVR

- Transcatheter Aortic Valve Replacement (TAVR)
- Surgical Aortic Valve Replacement (SAVR)
- Minimal Incision Valve Surgery (MIVS)

Inoperable OR High Risk

Patients Suitable for Open Chest Surgery
What is TAVR-Transcatheter Aortic Valve Replacement?

- An aortic valve replacement as an alternative to traditional thoracotony.
- Less invasive than traditional thoracotomy for patients considered too high risk for traditional surgery.
Two TAVR Options

• Edwards Sapien Valve  
• Stainless Steel Frame  
• More Aortic Regurg, less AV block/PPM  
• Better for severe bulky calcification.

• Medtronic CoreValve  
• Nitinol Frame-self expanding  
• Less Aortic Regurg, More heart block/PPM
TAVI Devices 2013

Human Implants: > 60,000 worldwide

CE Approved:
- Edwards Sapien XT
- Medtronic CoreValve
- CoreValve Evolut 23
- JenaValve TA
- Symetis Acurate
- Direct Flow Medical
- St. Jude Portico 23
- Medtronic Engager

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Edwards Sapien THV (1st generation) 22/24 Fr with RetroFlex 3 delivery system

Edwards Sapien XT (2nd generation) 18/19 Fr with NovoFlex delivery system

Medtronic Engager TA valve (Venter Embracer)

St. Jude Medical Portico valve

Medtronic CoreValve

Boston Scientific Lotus self-exp valve (Sadra Lotus)

JenaValve
SAPIEN 3 Transcatheter Heart Valve

20, 23, 26, and 29 mm sizes

Bovine Thermafix Tissue Leaflets

Balloon-expandable Cobalt Chromium Frame with larger landing zone

External Sealing Cuff

Florida Hospital Memorial Medical Center
Multiple Options for Vascular Access

- Transaortic
- Transeptal
- IVC to Aorta Entry
- Common Iliac
- RPA
- Transapical
- Transfemoral
- Carotid
- Subclavian/axillary

Florida Hospital Memorial Medical Center
## Evolution of balloon-expandable transcatheter heart valves

<table>
<thead>
<tr>
<th>Features</th>
<th>SAPIEN Model 9300TFX 26mm</th>
<th>SAPIEN XT Model 9300TFX 26mm</th>
<th>SAPIEN 3 Model 9600TFX 26mm</th>
</tr>
</thead>
<tbody>
<tr>
<td>Crimped profile</td>
<td>8.3mm</td>
<td>8mm</td>
<td>6.7mm</td>
</tr>
<tr>
<td>Frame height (expanded)</td>
<td>16.1mm</td>
<td>17.2mm</td>
<td>20mm</td>
</tr>
<tr>
<td>Frame height (crimped)</td>
<td>18.1mm</td>
<td>20.1mm</td>
<td>28mm</td>
</tr>
<tr>
<td>Frame shortening (deployment)</td>
<td>2mm</td>
<td>2.9mm</td>
<td>8mm</td>
</tr>
<tr>
<td>Delivery System</td>
<td>Retroflex3</td>
<td>NovaFlex+</td>
<td>Commander</td>
</tr>
<tr>
<td>Sheath profile (internal)</td>
<td>24F</td>
<td>18F</td>
<td>14F</td>
</tr>
<tr>
<td>Indicated vessel size</td>
<td>7mm</td>
<td>6.5mm</td>
<td>6.0mm</td>
</tr>
</tbody>
</table>
Edwards SAPIEN vs SAPIEN XT Transcatheter Heart Valves

NEW FRAME GEOMETRY
• Less metal content
• Lower crimp profile

NEW FRAME MATERIAL
• Cobalt-chromium
• Greater tensile and yield strength

NEW LEAFLET GEOMETRY
• Partially closed

SAPIEN THV
Stainless Steel

SAPIEN XT THV
Cobalt-chromium

RetroFlex 3
NovaFlex
# Sheath Size Comparison

<table>
<thead>
<tr>
<th>Valve</th>
<th>Valve Size</th>
<th>Sheath ID</th>
<th>Sheath OD</th>
<th>Minimum Vessel Diameter</th>
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</thead>
<tbody>
<tr>
<td>SAPIEN THV</td>
<td>23mm</td>
<td>22F</td>
<td>25F (8.4mm)</td>
<td>7.0mm</td>
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<tr>
<td>SAPIEN XT THV</td>
<td>23mm</td>
<td>18F</td>
<td>22F (7.2mm)</td>
<td>6.0mm</td>
</tr>
<tr>
<td>SAPIEN THV</td>
<td>26mm</td>
<td>24F</td>
<td>28F (9.2mm)</td>
<td>8.0mm</td>
</tr>
<tr>
<td>SAPIEN XT THV</td>
<td>26mm</td>
<td>19F</td>
<td>23F (7.5mm)</td>
<td>6.5mm</td>
</tr>
</tbody>
</table>

33% reduction in CSA
Edwards SAPIEN XT Transcatheter Heart Valve

Three Bovine Pericardial Tissue Leaflets

Fabric Skirt

Cobalt-Chromium Frame

With the introduction of a 29 mm size and lower profile delivery system, the SAPIEN XT THV can treat a wider range of patients.
Edwards SAPIEN 3 Valve

Balloon Expandable

- Designed to further reduce PV leaks.
- TF delivery through a 14 Fr eSheath.
- Dramatically reduced TA profile: 18 F.
- Discrete valve anchors in the annulus.
- Edwards’ bovine pericardial tissue leaflets.

Edwards CENTERA

Self Expanding

- Motorized delivery system for stable deployment and single operator use.
- Repositionable & pre-loaded.
- Delivered through a 14 Fr eSheath.
- Discrete valve anchors in the annulus.
- Edwards’ bovine pericardial tissue leaflets.

CE Approved
PARTNER I Trial Data

- In the PARTNER I randomized trials:

- “Inoperable” (Cohort B) patients had reduced mortality compared to standard therapy.

- Patients deemed high-risk for surgical AVR (Cohort A) that underwent TAVR had similar mortality compared to their surgical AVR counterparts.
Study Flow
Inoperable Cohort

n = 358
Randomized Inoperable

n = 179
Standard Therapy

85/85 patients
100% followed at 1 Yr

46/46 patients
100% followed at 2 Yr

19/19 patients
100% followed at 3 Yr

124/124 patients
100% followed at 1 Yr

Cross over 11 pts

Cross over 9 pts

101/102 patients*
99.0% followed at 2 Yr

80/82 patients**
97.6% followed at 3 Yr

*One TAVR patient was alive and censored prior to the window
**Two TAVR patients were alive and censored prior to the window (including the one in the same status at 2 years); one TAVR patient withdrew between 2 and 3 years

No patients were lost to follow-up
All Cause Mortality (ITT)
Crossover Patients Censored at Crossover

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

All Cause Mortality (%)

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard Rx</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>179</td>
<td>170</td>
</tr>
<tr>
<td>6</td>
<td>121</td>
<td>138</td>
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<tr>
<td>12</td>
<td>85</td>
<td>124</td>
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<tr>
<td>18</td>
<td>62</td>
<td>110</td>
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<tr>
<td>24</td>
<td>46</td>
<td>101</td>
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<tr>
<td>30</td>
<td>27</td>
<td>88</td>
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<tr>
<td>36</td>
<td>17</td>
<td>70</td>
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</tbody>
</table>

NNT = 3.7 pts
NNT = 4.0 pts

Numbers at Risk
Cardiovascular Mortality (ITT) 
Crossover Patients Censored at Crossover

HR [95% CI] = 0.41 [0.30, 0.56] 
p (log rank) < 0.0001

<table>
<thead>
<tr>
<th>Months</th>
<th>Standard Rx</th>
<th>TAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>179</td>
<td>179</td>
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<tr>
<td>6</td>
<td>121</td>
<td>158</td>
</tr>
<tr>
<td>12</td>
<td>85</td>
<td>124</td>
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<tr>
<td>18</td>
<td>62</td>
<td>110</td>
</tr>
<tr>
<td>24</td>
<td>46</td>
<td>101</td>
</tr>
<tr>
<td>30</td>
<td>27</td>
<td>88</td>
</tr>
<tr>
<td>36</td>
<td>17</td>
<td>70</td>
</tr>
</tbody>
</table>

Numbers at Risk:

NNT = 3.0 pts
NNT = 4.1 pts
Mortality Stratified by STS Score (ITT)

**STS: 0 - 4.9**
- Δ = 66.8%
- NNT = 1.5 pts
- 33.2%

**STS: 5.0 - 14.9**
- Δ = 22.3%
- NNT = 4.5 pts
- 55.2%

**STS ≥ 15**
- Δ = 20.8%
- NNT = 4.8 pts
- 65.8%

**Numbers at Risk**

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
<th></th>
<th></th>
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<th></th>
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<tr>
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<td>8</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>3</td>
<td>0</td>
<td>123</td>
<td>86</td>
<td>61</td>
<td>44</td>
<td>33</td>
<td>19</td>
<td>13</td>
<td>43</td>
<td>27</td>
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<tr>
<td>TAVR</td>
<td>28</td>
<td>26</td>
<td>26</td>
<td>24</td>
<td>21</td>
<td>19</td>
<td>16</td>
<td>113</td>
<td>84</td>
<td>79</td>
<td>70</td>
<td>66</td>
<td>66</td>
<td>44</td>
<td>38</td>
<td>28</td>
</tr>
</tbody>
</table>
TAVI Extreme Risk Study
CoreValve US Pivotal Trial

N=471; 49% Male Gender; STS 10.3 ± 5.6; 92% NYHA III/IV

All Cause Mortality
- 7.9% at 1 month
- 24.0% at 12 months

Cardiovascular Mortality
- 7.9% at 1 month
- 17.9% at 12 months

Major Stroke
- 2.4% at 1 month
- 4.1% at 12 months

Jeffrey J Popma on behalf of the CoreValve US Clinical Investigators
Presented as LBCT at TCT 2013
Study Device and Access Routes

4 valve sizes
(18-29 mm annular range)

18Fr delivery system

Transfemoral
Subclavian
Direct Aortic
Pivotal Trial Design

CoreValve US Pivotal Trial

Extreme Risk
- Iliofemoral Access > 18 Fr Sheath
  - CoreValve Iliofemoral
  - CoreValve Non-Iliofemoral

High Risk
- Randomization* 1:1
  - CoreValve (any route)
  - SAVR

* Randomization stratified by intended access site
Participating Sites

795 Patients Enrolled at 45 Participating Sites
Study Disposition

Patients Screened
N=995

Randomized
N=795

Intention to Treat TAVR
N=394
- Exited (n=4)
  - 2 Deaths
  - 2 Withdrawals

As Treated TAVR
N=390
- Iliofemoral
  N=323
- Non-iliofemoral
  N=67

Intention to Treat SAVR
N=401
- Exited (n=44)
  - 5 Deaths
  - 36 Withdrawals
  - 3 Others

As Treated SAVR
N=357
US CoreValve High-Risk Study
DH Adams, et al NEJM 2014;370:1790-8

**All-Cause Mortality at 1-Year**

- **Surgical**
  - 3.3% at 1 year
- **Transcatheter**
  - 14.2% at 1 year

SAVR: 19.1%
TAVI: 14.2%
P = 0.04 for superiority

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months Post-Procedure</th>
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<tr>
<td>Surgical</td>
<td>357 341 297 274</td>
</tr>
<tr>
<td>Transcatheter</td>
<td>390 377 353 329</td>
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</tbody>
</table>
# Subgroup Analysis for 1 Year Mortality

DH Adams, et al *NEJM* 2014;370:1790-8

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All-cause Death at 1 Year K-M Rates</th>
<th>Hazard Ratios (95% CI)</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
<td></td>
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<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>15.7</td>
<td>21.4</td>
<td>0.71 (0.43, 1.16)</td>
</tr>
<tr>
<td>≤85</td>
<td>12.9</td>
<td>17.2</td>
<td>0.72 (0.43, 1.20)</td>
</tr>
<tr>
<td><strong>Gender</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>15.5</td>
<td>16.7</td>
<td>0.89 (0.55, 1.47)</td>
</tr>
<tr>
<td>Female</td>
<td>12.7</td>
<td>21.8</td>
<td>0.56 (0.33, 0.95)</td>
</tr>
<tr>
<td><strong>BMI</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>≤30</td>
<td>15.7</td>
<td>20.6</td>
<td>0.73 (0.48, 1.09)</td>
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<tr>
<td>&lt;30</td>
<td>10.3</td>
<td>15.8</td>
<td>0.64 (0.30, 1.38)</td>
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<td><strong>LVEF</strong></td>
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<td>≤60</td>
<td>15.8</td>
<td>19.9</td>
<td>0.76 (0.49, 1.16)</td>
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<tr>
<td>&gt;60</td>
<td>11.6</td>
<td>17.8</td>
<td>0.64 (0.34, 1.22)</td>
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<tr>
<td><strong>Diabetes</strong></td>
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<tr>
<td>No</td>
<td>15.8</td>
<td>22.3</td>
<td>0.67 (0.44, 1.03)</td>
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<tr>
<td>Yes</td>
<td>11.3</td>
<td>15.3</td>
<td>0.72 (0.38, 1.37)</td>
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</tbody>
</table>
Subgroup Analysis for 1 Year Mortality

DH Adams, et al *NEJM* 2014;370:1790-8

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<th>P Value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
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<tr>
<td>Prior CABG</td>
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<tr>
<td>No</td>
<td>16.2</td>
<td>19.6</td>
<td>0.80 (0.53, 1.21)</td>
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<tr>
<td>Yes</td>
<td>9.6</td>
<td>18.1</td>
<td>0.50 (0.24, 1.04)</td>
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<td>PVD</td>
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<td>17.8</td>
<td>0.68 (0.42, 1.11)</td>
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<tr>
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<td>15.3</td>
<td>21.2</td>
<td>0.70 (0.41, 1.19)</td>
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<td>Hypertension</td>
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<td>No</td>
<td>15.8</td>
<td>36.5</td>
<td>0.37 (0.09, 1.54)</td>
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<tr>
<td>Yes</td>
<td>14.1</td>
<td>18.4</td>
<td>0.74 (0.51, 1.07)</td>
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<td>STS Score</td>
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<td></td>
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<tr>
<td>≤7%</td>
<td>10.5</td>
<td>14.2</td>
<td>0.72 (0.40, 1.29)</td>
</tr>
<tr>
<td>&gt;7%</td>
<td>18.2</td>
<td>24.1</td>
<td>0.72 (0.46, 1.13)</td>
</tr>
</tbody>
</table>
Echocardiographic Findings

Post implant, there were significant differences (P < 0.001) between TAVR and SAVR at each time point for both EOA and mean gradient.
Medtronic Evolut R

6-Month Outcomes Following Transcatheter Aortic Valve Implantation With a Novel Repositionable Self-Expanding Bioprosthesis

Ian T. Meredith, AM, MBBS, PhD, MonashHeart & Monash University, Melbourne, Australia
Antony S. Walton, MBBS, Epworth Hospital, Melbourne, Australia
Stephen J. Brecker, MBBS, MD, St. Georges Hospital, London, United Kingdom
Sanjeevan Pasupati, MBChB, Waikato Hospital, Hamilton, New Zealand
Daniel J. Blackman, MD, Leeds General Infirmary, Leeds, United Kingdom
Ganesh Manoharan, MBBCh, MD, Royal Victoria Hospital, Belfast, United Kingdom
# CoreValve Evolut R CE Study

## Overview

### Objective
- To evaluate the safety and clinical performance of the CoreValve Evolut R System (26 mm, 29 mm) in symptomatic extreme- or high-risk patients (Heart Team assessment) with symptomatic aortic stenosis.

### Design
- Prospective, non-randomized, multicentre, observational study.
- Follow-up at early post-procedure (24h–7 days), 30 days, 6 months, 1 and 2 years post TAVI.
- Multislice CT of the peripheral vascular and aortic annulus.
- 100% source data monitored.

### Endpoints
- **Safety**: All-cause mortality and the rate of any stroke at 30 days.
- **Clinical Performance**: Device success per Valve Academic Research Consortium (VARC-2) and the % of patients with > mild aortic regurgitation at early post procedure (24h–7d).

### Core Labs
- Echocardiography (Mayo Clinic, Rochester, MN).

### Adjudication
- Clinical endpoints reported per VARC-2*.

### Compliance
- 98.3% for 30-day follow-up and 100% for 6-month follow-up.
## CoreValve Evolut R CE Study
### Primary Endpoint Clinical Performance

<table>
<thead>
<tr>
<th>Components of VARC-2 Device Success, % (no./total no.)</th>
<th>N = 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absence of procedural mortality</td>
<td>100 (60/60)</td>
</tr>
<tr>
<td>Correct positioning of 1 valve in proper location</td>
<td>98.3 (59/60)</td>
</tr>
<tr>
<td>Mean gradient &lt; 20 mm Hg or peak velocity &lt; 3 m/sec</td>
<td>98.3 (59/60)</td>
</tr>
<tr>
<td>Absence of moderate or severe regurgitation</td>
<td>93.3 (56/60)</td>
</tr>
<tr>
<td>Absence of patient prosthesis mismatch*</td>
<td>83.6 (46/55)</td>
</tr>
<tr>
<td>VARC-2 device success composite</td>
<td>78.6 (44/56)</td>
</tr>
</tbody>
</table>

*Effective orifice area could not be determined in 5 patients to calculate patient prosthesis mismatch.*
CoreValve Evolut R CE Study
6-Month Valve Haemodynamics

- Effective orifice area
- Mean gradient

### Effective Orifice Area, cm²
- Baseline: 49.1 ± 13.0
- 24 Hrs to 7 Days: 1.9 ± 0.5
- 30 Days: 1.9 ± 0.5
- 6 Months: 1.9 ± 0.4

### Mean Gradient, mm Hg
- Baseline: 0.6 ± 0.2
- 24 Hrs to 7 Days: 9.2 ± 3.9
- 30 Days: 8.1 ± 3.3
- 6 Months: 7.6 ± 3.1

### Patient Count
- Gradient: 60, 60, 57, 52
- EOA: 56, 55, 54, 50

---

Florida Hospital Memorial Medical Center
CoreValve Evolut R CE Study
Repositioning

Successfully used 22 times in 15 patients (25%):

- 10 Partial resheaths among 7 patients
- 12 Full resheaths among 10 patients
- No full recaptures to retrieve
- Resulted in a final implant depth of LCS=6.3±4.1 mm, NCS=5.9±3.4 mm
# CoreValve Evolut R CE Study
## Safety Endpoints to 6 Months

<table>
<thead>
<tr>
<th>Event, K-M rates (no. of patients)</th>
<th>30 Days N=60</th>
<th>6 Months N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.0 (0)</td>
<td>5.0 (3)*</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.0 (0)</td>
<td>3.3 (2)</td>
</tr>
<tr>
<td>All stroke</td>
<td>0.0 (0)</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.0 (0)</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
</tbody>
</table>

*1 non-cardiovascular death due to pneumonia; 2 cardiovascular deaths due to (1) ischaemic heart disease and (1) late disabling stroke
Lotus Valve Reposition Recapture

At this point valve can be fully recaptured and returned to position 1.

1. Crossing native valve
2. Deploy percutaneous valve
3. Expand percutaneous valve
4. Final Release
REPRISE I at 2 years
Mean Aortic Valve Gradient by Patient

Mean: 53.9±20.9
Mean: 13.7±3.7
Mean: 11.7±3.0
Mean: 13.9±3.8
Mean: 15.4±4.6
Mean: 15.5±4.4

Measurement | P value |
---|---|
Baseline to Discharge | <0.001 |
Baseline to 2 Years | <0.001 |
Discharge to 30 Days | 0.06 |
30 Days to 1 Year | 0.008 |
1 Year to 2 Years | 0.94 |

Ian Meredith, TCT 2014. P values: Repeated measures and random effects ANOVA model. Information not intended for use in France. Lotus is an investigational device and not for sale in the US. CE mark received 2013. Information for the Lotus Valve System is for use in countries with applicable product registrations. Indications, contraindications, warnings and instructions for use can be found in the product labeling supplied with each device.
REPRISE I at 2 Years
Effective Orifice by Patient

Aortic Valve Area (cm²)

Mean: 1.5±0.2  Mean: 1.6±0.2  Mean: 1.5±0.2  Mean: 1.5±0.2
Mean: 0.7±0.2

Measurement | P value
---|---
Baseline to Discharge | <0.001
Baseline to 2 Years | <0.001
Discharge to 30 Days | 0.04
30 Days to 1 Year | 0.12
1 Year to 2 Years | 0.97

Ian Meredith, TCT 2014. All valve sizes were 23 mm.  
P values: Repeated measures and random effects ANOVA model

Independent Core Lab Adjudication

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REPRISE I at 2 Years
Aortic Regurgitation

- Severe
- Moderate
- Mild
- Trivial
- None

% of Patients

<table>
<thead>
<tr>
<th></th>
<th>Discharge</th>
<th>2 Years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paravalvular</td>
<td>n=8</td>
<td>n=9</td>
</tr>
<tr>
<td>Central</td>
<td>n=10</td>
<td>n=8</td>
</tr>
<tr>
<td>Paravalvular</td>
<td>n=1</td>
<td>n=3</td>
</tr>
</tbody>
</table>

No Moderate / Severe AR by Independent Adjudication

Ian Meredith, TCT 2014.
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REPRISE II (N=120) & Extended Cohort (N=250)

Primary Endpoints

Mean Aortic Valve Gradient at 30 Days (N=120)

- Performance Goal = 18.0mmHg

- Mean = 11.5mmHg

All-cause Mortality at 30 Days (N=250)

- Performance Goal = 16%

- Mean = 4.4%

11.5mmHg ± UCB (12.6mmHg) is significantly below the performance goal (P<0.001)

4.4% ± UCB (6.97%) is significantly below the performance goal (P<0.001)

† Based on an expected mean of ≤15mmHg (literature review) plus a test margin of 3mmHg

* Based on an expected rate of 9.8% (literature review) plus a test margin of 6.2%


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**REPRISE II Extension 30d Pacemaker Analysis (N=250)**

**Significant Multivariate Predictors of PPM**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline RBBB</td>
<td>12.70</td>
<td>4.45, 36.22</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LVOT area overstretch ≥10%</td>
<td>3.42</td>
<td>1.74, 6.74</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>1st degree AV block</td>
<td>2.49</td>
<td>1.13, 5.47</td>
<td>0.02</td>
</tr>
<tr>
<td>LVOT total calcium volume, per 100 mm³ increase</td>
<td>1.80</td>
<td>1.03, 3.14</td>
<td>0.04</td>
</tr>
</tbody>
</table>

**The need for a new pacemaker does not influence 30d or 1yr mortality**

- One study has shown 30-day PPM as a protective factor for the occurrence of unexpected death but this largely remains unknown without further studies.

---

*Based on a 93 study non-overlapping meta-analysis including 37,836 patients reporting 30d PPM implantation rates post TAVR.


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### RESPOND Safety Endpoints at 30 Days
#### 250-Patient Interim Analysis

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>2.0% (5/246)</td>
</tr>
<tr>
<td>Cardiovascular mortality</td>
<td>1.6% (4/246)</td>
</tr>
<tr>
<td>Disabling stroke</td>
<td>3.3% (8/246)</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeding</td>
<td>0.8% (2/246)</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>2.4% (6/246)</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0.8% (2/246)</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>1.6% (4/246)</td>
</tr>
<tr>
<td>Repeat procedure for valve-related dysfunction</td>
<td>0% (0/246)</td>
</tr>
<tr>
<td>Valve- or CHF-related repeat hospitalisation</td>
<td>0.4% (1/246)</td>
</tr>
<tr>
<td>Newly implanted permanent pacemaker</td>
<td>33.7% (83/246)</td>
</tr>
<tr>
<td>Pacemaker dependent at 30 days (site-reported)</td>
<td>34.9% (29/83)</td>
</tr>
</tbody>
</table>

---

Presented by Van Meighem, EuroPCR 2015.

Information not intended for use in France.

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RESPOND 250-Patient Interim Analysis

Mean Aortic Gradient & EOA

Core-lab Adjudicated Data

Mean Aortic Gradient (mmHg)

- Baseline: 38.0 ± 16.5 (n=236)
- Discharge: 0.7 ± 0.2 (n=227)

Mean Effective Orifice Area (cm²)

- Baseline: 1.9 ± 0.4 (n=229), P<0.001 vs baseline
- Discharge: 10.1 ± 3.7 (n=242), P<0.001 vs baseline
Future Developments
Additional Valve Sizes and Low Profile Sheath

Novel, Low Profile Sheath
- Expandable
- 14F Introduction and removal
- Smaller vessel access
US TVT Registry. Mack et al. JAMA 2013;310:2069-77

- Trans-femoral: 64%
- Trans Apical 29%
- Trans Aortic 4%
- Percutaneous Access: 36%
**US TVT Registry.**
Mack et al. JAMA 2013;310: 2069-77

- Hybrid OR: 57%
- Hybrid Cath Lab: 28%
- Cath Lab 14%
- Cardio pulmonary bypass: 4%
- Conscious Sedation: 2%
- Percutaneous Access: 36%
- Cross Over to Open Heart surgery: 1%

**Procedural Factors.**
23 TAVR Centers in 8 European Countries

- Hybrid room: 12%
- TAVR in the Cath Lab: 96%
- Cardiac surgeon participate in the procedure: 83%
- CPB machine in Cath lab: 48%
- Conscious Sedation: 2%
- TEE used routinely: 70%
- General anesthesia: 61%
- Percutaneous Access: 70%
Worldwide TAVR Distribution

- United States: 28%
- Western Europe: 61%
- Rest of the World: 11%

Courtesy of BIBA Medtech
### Success rate: 94.1%

<table>
<thead>
<tr>
<th>Condition</th>
<th>Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>6.6</td>
</tr>
<tr>
<td>Annulus Rupture</td>
<td>0.4</td>
</tr>
<tr>
<td>Valve migration</td>
<td>1.3</td>
</tr>
<tr>
<td>Coronary obstruction</td>
<td>0.4</td>
</tr>
<tr>
<td>Tamponade</td>
<td>1.2</td>
</tr>
<tr>
<td>Surgery</td>
<td>0.6</td>
</tr>
<tr>
<td>Stroke with sequelae</td>
<td>2</td>
</tr>
<tr>
<td>Vascular complication</td>
<td>6.6</td>
</tr>
<tr>
<td>Pacemaker</td>
<td></td>
</tr>
<tr>
<td>Edw: 8.1/ MCV: 21</td>
<td></td>
</tr>
</tbody>
</table>

France TAVR 2013. 30 day Results. 41 centres 64% of 3707 TAVR
Germany: TAVR – a Game Changer in AVR

DGTHG Survey on isolated aortic valve implants 2000-2012
(Deutsche Gesellschaft für Thorax-, Herz und Gefäßchirurgie)

(Source: DGTHG Statistik 2010)
Cumulative TVT Sites Enrolled
May 2012-Oct 2013

- May: 29
- June: 59
- July: 76
- August: 89
- September: 117
- October: 134
- November: 149
- December: 160
- January: 164
- February: 191
- March: 201
- April: 213
- May: 223
- June: 236
- July: 244
- August: 245
- September: 250
- October: 250

Florida Hospital Memorial Medical Center
Cumulative TVT Records
May 2012-Oct 2013

- May: 13
- June: 20
- July: 100
- Aug: 333
- Sept: 683
- Oct: 1283
- Nov: 1825
- Dec: 2461
- Jan: 3116
- Feb: 3583
- March: 4551
- April: 5417
- May: 6437
- June: 7210
- July: 7862
- Aug: 8108
- Sept: 9584
- Oct: 10133

Total: 10,133
Shift to lower risk:
Logistic EuroSCORE mean ± SD

28% → 14%

Belgium Registry
Catania SOURCE TF Registry
PARTNER EU TF
Webb et al 2009
France Registry
Siegburg Siegburg-Bern
Corevalve Safety/Efficacy
Grube et al 2007
Germany Registry
Bern-Rotterdam
Australia/New Zealand
Bochum Rotterdam
Amsterdam

Courtesy of Patrick Serruys
Volume per Site (2012q3-2013q2)

# of sites in each volume group:
- <25: 114
- 25-49: 85
- 50-74: 18
- 75-99: 9
- 100+: 6
New Trials / Registries

- UK Satire (TAVR vs SAVR).
- NORDIC Trial (Corevalve vs AVR).
- Activation Trial (PCI or not in TAVI with CAD).
- Simplify TAVI (BAV pre vs no BAV).
- CHOICE (CoreValve vs Edwards)
- Clean TAVI, Sentinel is US (Claret device).
- TAO EmbolX (EmbolX cerebral protection).
- Cooling and Brain Oxygenation (Rhino-chill device).
- BRAVO 2/3 (Bivalirudine).
- AUREA (DAPT vs Oral Anticoagulation)
TRENDS
Prohemostatic Drugs in Cardiac Surgery

- Not much new info: rVIIa, DDAVP, antifibrinolytics
- New but unimpressive: F XIII concentrate

**New and promising: Fibrinogen concentrates:**
- Increasing use in Europe, available in US
  - FDA-approved for congenital fibrinogen deficiency
  - Off-label use hasn’t discouraged us in the past: IV nitroglycerin, DDAVP, FVIIa, aminocaproic acid
FIBROGEN

- Critical importance to plasma->”cell-based” clotting process
- Several studies show [fib] is first to diminish in consumptive processes (others say Va)
- FFP: 300-400 mg/U @ 2 mg/mL
- Cryo: 2.5-4 gm/10 bags (2-300 mL)
- Fibrinogen concentrate (Riastap, Behring, Marburg, Ger): About 1 gm/50 mL vial
**FIBRENOGEN**

**Cryoprecipitate vs Fibrinogen Concentrate**

**Cryoprecipitate**
- Adds VIII, XIII, fibronectin
- Higher risk of immunomodulation and viral transmission
- Slow: Blood typing and thawing required

**Fibrinogen Concentrate**
- Pure fibrinogen
- Pooled human product
- No antibodies, pasteurized: Viral transmission risk very low, not zero
- Fast: Mix and give
FIBRENOGEN

Is “normal” fibrinogen too low?

Blome M, Thromb Haemost 2005;93:1101

- Low normal fibrinogen was a strong post-CPB (T2) predictor of highest blood loss group (Group 3)

- Plt count and aPTT also were quite good
FIBRENOGEN

Fibrinogen: Sufficient by itself in hemodilution?

- Conventional recommendations suggest 75-100 mg/dL as intervention threshold
- In vitro study on hemodiluted WB: Bollinger D, BJA 2009;102:793
- 80% dilution:

<table>
<thead>
<tr>
<th></th>
<th>384 (75)</th>
<th>70 (11)*</th>
<th>81 (4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fibrinogen (mg dl⁻¹)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antithrombin III (%)</td>
<td>106 (14)</td>
<td>18 (2)*</td>
<td>82 (3)</td>
</tr>
<tr>
<td>Factor II (%)</td>
<td>115 (17)</td>
<td>25 (1)*</td>
<td>78 (4)</td>
</tr>
<tr>
<td>Factor VII (%)</td>
<td>107 (25)</td>
<td>16 (4)*</td>
<td>85 (3)</td>
</tr>
<tr>
<td>Factor IX (%)</td>
<td>90 (18)</td>
<td>23 (5)*</td>
<td>74 (5)</td>
</tr>
<tr>
<td>Factor X (%)</td>
<td>113 (16)</td>
<td>19 (4)*</td>
<td>83 (3)</td>
</tr>
</tbody>
</table>
FIBREN OGEN

- Hemodilution effect

Thrombin generation: about 50%

- TEG Before
  - undiluted WB

- TEG After
  - diluted WB

[Graph showing thrombin generation over time with undiluted and diluted samples]
FIBRENOGEN

- Authors suggest 200 mg/dL as target (2 g/L)
- Note that ONLY fibrinogen was replenished
  - Surprising and instructive that this would work

**YET:** Seems likely that 100-150 mg/dL would suffice if FFP/Plts also replenished
FIBRENOGEN

- Prophylactic fibrinogen 2 gms p-CPB in CABG decreases 12-hr blood loss 20% despite ND in (normal) coag tests
FIBRENOGEN

- In post-CPB coagulopathy (clinical Dx, AVRs & Type I aneurysms), fibrinogen (mean 5.7 gm, N=10) as a first intervention reduced the need for RBCs, Plts, & FFP and decreased blood loss
- Induced high-normal fibrinogen concentrations (360±6 mg/dL) in Pts who had low-normal post-CPB fibrinogen (210±3 mg/dL)
- FFP: minimal effect
- 1-day post-op: All Pts had high-normal fibrinogen (>400 mg/dL) regardless of fib/FFP administration
- Similar findings with Thoraco-abdominal aneurysms
  — Rahe-Meyer N, JTCVS 2009;138:694
FIBRENOGEN

Fibrinogen Recommendations

• For higher risk Pts (e.g., long CPB time, pre-op clopidogrel, circ arrest, redo), include [fibrinogen] in late CPB or post-protamine screening tests
  — Can substitute ROTEM FIBTEM or maybe TEG α-angle
• If [fib] < 200 mg/dL (roughly FIBTEM<15) and bleeding after heparin neutralization, strongly consider fibrinogen concentrate 4(+) gms or cryoprecipitate 10 bags as first intervention
Lariat Procedure
Lariat Procedure

www.mymethodist.net

Transvenous, transforaminal, Echo-guided

Percutaneous, subxiphoid

Left atrial appendage

Magnet

Second magnet

Sheath

Loop is tightened

Tightened loop left in place
Lariat Procedure

Lariat Indications: Atrial fibrillation

With contraindication to/ intolerance of anticoagulants

Other factors supporting procedure
• Low tolerance to or success with antiarrhythmics
• Failed atrial fib ablation and/or cardioversions

Touted as 95% successful: Randomized studies?
• Rapidly spreading
Lariat Procedure

Lariat: Anesthetic Considerations

• TEE typically done real-time with live 3D
• General anesthesia is the norm
• Atrial fibrillation – assess pre-procedure rate control
• Potential for rupture/tamponade
  – Solid IV access
  – Arterial catheter seems wise
  – We are using perfusion/CT surgeon back-up at present, but typically not a hybrid OR
Lariat Procedure

Other Nonsurgical LAA closure approaches: WATCHMAN Device
Lariat Procedure

Other LAA Space Occupiers

Amplatzer

PLAATO

- ePTFE membrane
- Left atrial side
- Three rows of anchors
- LAA side
- Diameters from 20 to 32 mm
- Self-expanding nitinol cage
QUESTIONS ?