Surgical and Transcatheter Aortic Valve Replacement: An Update on a Disruptive Technology

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Cardiothoracic Surgery
Bryan Heart

Disclosures

• None relevant to the presentation

Overview

• Background of Valvular Heart Disease
• Aortic Valve Stenosis, SAVR and TAVR
  – Clinical Benefits
  – Complications
  – Durability
• Patient Selection and Outcome Monitoring
• Ongoing Research Efforts
• Summary
Background

• Surgical Valve Replacement has been the gold standard for treatment of severe valve stenosis since the 1960's.
• In 2010, the STS database reported over 65,000 patients underwent surgical valve replacement.
• Median mortality rates for surgical AVR in the STS database range from 2-3%.
• Unfortunately, as our population ages, the surgical risk is increasing.

US Population Projection by Age Group: US Census Bureau

Valvular Heart Disease Increases with Age—Pooled Echo Data from ARIC/CARDIA/CHS

References:
Stassianno P, JACC, 2009
Figures for projections from 2010 through 2050 are from: Table 12. Projections of the Population by Age and Sex for the United States: 2010 to 2050 (NP2008-121), Population Division, U.S. Census Bureau; Release Date: August 14, 2008
Nkomo VT et al. Lancet 2006; 368:3005-13
Aortic Stenosis

Normal

Degenerative Calcified

Bicuspid

Rheumatic

Natural History of Aortic Stenosis

Survival (percent)

Age (years)

Average Age Death

Latent Period

Increasing obstruction, myocardial overload

Symptoms

Adapted from Rees and Braunwald, Circulation 1968;38:V-61

Severe AS without AVR

Non-operated Patients with Severe AS

Unoperated

Unoperated symptomatic

Unoperated symptomatic risk/AVR median

Rationale for Decisions to Not Perform AVR in Symptomatic Patients with Severe AS

<table>
<thead>
<tr>
<th></th>
<th>All Sites (n=126)</th>
<th>University (n=53)</th>
<th>VA (n=20)</th>
<th>Private (n=53)</th>
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<tbody>
<tr>
<td>Comorbidities/operative risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Patient declined</td>
<td>24 (19%)</td>
<td>2 (4%)</td>
<td>5 (25%)</td>
<td>17 (32%)</td>
</tr>
<tr>
<td>Symptom not from AS</td>
<td>24 (19%)</td>
<td>11 (21%)</td>
<td>5 (25%)</td>
<td>8 (15%)</td>
</tr>
<tr>
<td>Subvalvular stenosis</td>
<td>3 (2%)</td>
<td>3 (6%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Died before surgery</td>
<td>4 (3%)</td>
<td>4 (8%)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>AS not recognized</td>
<td>10 (8%)</td>
<td>3 (6%)</td>
<td>2 (10%)</td>
<td>5 (9%)</td>
</tr>
</tbody>
</table>


Diagnostic Criteria for Severe Aortic Stenosis in the TAVR Era

- Echo based (transthoracic)
- Mean aortic gradient > 40 mmHg or
- Peak velocity > 4.0 m/sec
- and Valve area of <0.8 cm² (Indexed EOA of <0.5 cm²/m²)
- In setting of low gradient AS, dobutamine up to 20 mcg/kg/min can be given

Surgical AVR Risk Categories

*(risk is a continuum)*

Operable AS patients

- Too Sick
- Inoperable
- Low-Intermediate Risk: 90%
- High Risk: 10%
Factors Associated with Increased Risk for Surgical Aortic Valve Replacement

Clinical
- Prior Sternotomy
- Female gender
- Renal dysfunction
- Diabetes
- Moderate to severe COPD
- Low EF
- NYHA Class IV
- Cerebrovascular disease
- Immunosuppression

Anatomic
- Porcelain aorta
- Prior radiation
- Bypass graft course under sternum
- Prior sternectomy

Non-Traditional
- Frailty
- High operative risk
  - Cirrhosis

Frail Patients Are at Increased Risk for Mortality and Prolonged Institutional Care After Cardiac Surgery

Table 3. Risk-Adjusted Impact of Frailty on In-Hospital Mortality

<table>
<thead>
<tr>
<th>Preop Characteristics</th>
<th>OR 95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frail</td>
<td>1.8 1.1-3.0</td>
<td>0.03</td>
</tr>
<tr>
<td>Age</td>
<td>1.0 1.4-1.9</td>
<td>0.0001</td>
</tr>
<tr>
<td>Female sex</td>
<td>1.2 0.8-1.6</td>
<td>0.36</td>
</tr>
<tr>
<td>COPD</td>
<td>1.3 0.9-1.8</td>
<td>0.22</td>
</tr>
<tr>
<td>EF</td>
<td>2.3 1.5-3.3</td>
<td>0.0002</td>
</tr>
<tr>
<td>Cr</td>
<td>2.2 1.5-3.0</td>
<td>0.0001</td>
</tr>
<tr>
<td>LVEF</td>
<td>1.3 1.2-2.2</td>
<td>0.03</td>
</tr>
<tr>
<td>Urgency of surgery</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urgent/emergent</td>
<td>3.1 3.3-4.1</td>
<td>0.0001</td>
</tr>
<tr>
<td>In-Pressor</td>
<td>1.6 1.1-2.4</td>
<td>0.03</td>
</tr>
<tr>
<td>Elective</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Procedure (other vs isolated CABG)</td>
<td>1.8 1.3-2.5</td>
<td>0.0008</td>
</tr>
<tr>
<td>Reoperation (vs first operation)</td>
<td>1.7 1.2-2.7</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Lee DH et al Circulation. 2010; 121: 973-978

Individualized Risk Calculation

http://riskcalc.sts.org/atswebriskcalc/#/calculate
Disruptive Technology: The Tale of TAVR

• “Disruptive Technology” was first described by Clayton M. Christensen in his 1997 Best-Seller, The Innovators Dilemma.
• An innovation that creates a new market (percutaneous valve implantation) and value network that will eventually disrupt an already existing market (open heart surgery) and replace an existing product (traditional surgical heart valves).

A Disruptive Technology

Percutaneous Implanted Heart Valve
1st animal implant 1989
The Andersen Valve

FIM for AS: The Cribier-Edwards Valve

Alain Cribier, MD, Rouen, France 2002

Antegrade transseptal approach

PARTNER Study Design—2007!

Symptomatic Severe Aortic Stenosis

Cohort A

Cohort B

Edwards – SAPIEN THV

Balloon Expandable Percutaneous Valve

Edwards-SAPIEN THV

Two Valve Sizes: -23 mm -26mm

Bovine Tissue

TheraFix Treatment

Paracardial Mapping

Leaflet Deflection

Proprietary Processing

New Skirt Height

Untreated Equine Tissue

Current Skirt Height

Cribier-Edwards THV

Two Sheath Sizes: -22F (inner diameter) -24F

N = 609

N = 598

High Risk

Inoperable

ASSESSMENT: Transfemoral Access

TF TAVR

Primary Endpoint: All-Cause Mortality

Over Length of Trial (Superiority)

Co-Primary Endpoint: Composite of All-Cause Mortality

and Repeat Hospitalization (Superiority)

1:1 Randomization

TA TAVR

VS AVR

N = 248 N = 104 N = 103 N = 244

PARTNER Study Design—2007!

Total Patients Screened

3,105 Total Patients Screened

3,105 Total Patients Screened

Total = 1,057 patients

2 Parallel Trials: Individually Powered

N = 599

N = 598

High Risk

ASSESSMENT: Transfemoral Access

TF TAVR

Primary Endpoint: All-Cause Mortality

At 1 yr (Non-inferiority)

ASSESSMENT: Transfemoral Access

TF TAVR

Primary Endpoint: All-Cause Mortality

At 1 yr (Non-inferiority)

ASSESSMENT: Transfemoral Access

TF TAVR

Primary Endpoint: All-Cause Mortality

At 1 yr (Non-inferiority)

ASSESSMENT: Transfemoral Access

TF TAVR

Primary Endpoint: All-Cause Mortality

At 1 yr (Non-inferiority)
Baseline Characteristics—Cohort B

<table>
<thead>
<tr>
<th></th>
<th>TAVR (N=179)</th>
<th>Control (N=179)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>83 ± 9</td>
<td>83 ± 8</td>
</tr>
<tr>
<td>Female gender</td>
<td>54.2%</td>
<td>54.1%</td>
</tr>
<tr>
<td>STS Risk Score</td>
<td>11.2 ± 5.8</td>
<td>12.2 ± 6.1</td>
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<tr>
<td>STS &gt; 15%</td>
<td>21.2%</td>
<td>24.7%</td>
</tr>
<tr>
<td>Prior MI</td>
<td>18.6%</td>
<td>26.4%</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>37.4%</td>
<td>45.6%</td>
</tr>
<tr>
<td>Cerebrovascular Dz</td>
<td>27.4%</td>
<td>27.5%</td>
</tr>
<tr>
<td>COPD (O2 dependent)</td>
<td>21.2%</td>
<td>25.7%</td>
</tr>
<tr>
<td>Creatinine &gt; 2.0 mg/dl</td>
<td>5.6%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Frailty</td>
<td>18.1%</td>
<td>28.0%</td>
</tr>
</tbody>
</table>

P=NS for all comparisons

PARTNER Cohort B—Inoperable
Primary Endpoint: All-Cause Mortality

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

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael Mack, M.D., D. Craig Miller, M.D., Jeffrey W. Moses, M.D., Lars G. Svensson, M.D., Ph.D., F. Meera Tekico, M.D., John C. Webb, M.D., Gregory F. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Black, M.D., Robert K. Guyton, M.D., Augusto D. Pichard, M.D., Joseph E. Bavaria, M.D., Howard C. Herrmann, M.D., Pamela C. Douglas, M.D., John L. Pflanzer, M.D., Joel J. Abo, M.S., William N. Anderson, Ph.D., Dooly Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>Control</th>
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<tbody>
<tr>
<td>TAVR</td>
<td>179</td>
<td>139</td>
</tr>
<tr>
<td>Control</td>
<td>179</td>
<td>129</td>
</tr>
</tbody>
</table>
| All Cause Mortality (%) & Months

 Standard Rx  | TAVR  | Control |
-------------|-------|---------|
 0            | 67    | 50      |
 1 yr         | 122   | 102     |
 2 yr         | 115   | 90      |
 3 yr         | 100   | 83      |
 4 yr         | 94    | 76      |
 5 yr         | 89    | 64      |

Standard Rx

TAVR

All Cause Mortality (%)

Standard Rx

TAVR

Repeat Hospitalizations

<table>
<thead>
<tr>
<th></th>
<th>TAVR (N=179)</th>
<th>Control (N=179)</th>
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</thead>
<tbody>
<tr>
<td>Repeats</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Standard Rx</td>
<td>179</td>
<td>86</td>
</tr>
<tr>
<td>TAVR</td>
<td>179</td>
<td>115</td>
</tr>
</tbody>
</table>

p (log rank) < 0.0001

\[
\text{HR [95% CI]} = 0.41 [0.30, 0.58] \\
p (log rank) < 0.0001
\]
Quality of Life Assessment for TAVR:
Kansas City Cardiomyopathy Questionnaire

- 546 patients with HF
- KCCQ assessed at baseline and 5 weeks
- Extent of deterioration or improvement assessed by physician based on sx and exam and correlated with KCCQ-Overall Summary Score

Primary Endpoint:
KCCQ Overall Summary

Primary Endpoint:
KCCQ Overall Summary

- Symptom Score
  - MCID = 5 points
  - Δ = 10.2, P<0.001
  - Δ = 17.5, P<0.001
  - Δ = 18.0, P<0.001

- Physical Limitations
  - MCID = 5 points
  - Δ = 16.2, P<0.001
  - Δ = 24.8, P<0.001
  - Δ = 29.9, P<0.001

- Quality of Life
  - MCID = 5 points
  - Δ = 15.2, P<0.001
  - Δ = 25.3, P<0.001
  - Δ = 27.5, P<0.001

- Social Limitations
  - MCID = 5 points
  - Δ = 14.8, P<0.001
  - Δ = 24.8, P<0.001
  - Δ = 26.9, P<0.001
KCCQ-Summary: Substantial Improvement *

* Improvement ≥ 20 points vs. baseline among patients with available QOL data

NYHA Functional Class: Durable Results Up to 5 Years

Five Year Mortality: Inoperable Arm of PARTNER

Mortality Stratified by STS Risk Score


Transfemoral and Transapical Approach Used in PARTNER

TAVR Procedure
PARTNER Study Design—2007!

High-Risk Operable PARTNER Cohort A
Primary Endpoint: All-Cause Mortality

Five Year Mortality: PARTNER Study High Risk Cohort

Mack MJ et al Lancet 2015; 385: 2477–84
Subgroup Analysis—Cohort A

Functional Status at Five Years

Complications of TAVR vs SAVR

- Stroke
- Paravalvular Leak (Aortic Insufficiency)
- Need for New Permanent Pacemaker
### Neurological Events at 30 Days and 1 Year All Patients (N=699)

<table>
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<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>TAVR (N = 348)</td>
<td>AVR (N = 351)</td>
</tr>
<tr>
<td>All Stroke or TIA – no. (%)</td>
<td>15 (5.5)</td>
<td>8 (2.4)</td>
</tr>
<tr>
<td>TIA – no. (%)</td>
<td>1 (0.3)</td>
<td>2 (0.6)</td>
</tr>
<tr>
<td>All Stroke – no. (%)</td>
<td>16 (4.6)</td>
<td>8 (2.3)</td>
</tr>
<tr>
<td>Major Stroke – no. (%)</td>
<td>12 (3.5)</td>
<td>7 (2.1)</td>
</tr>
<tr>
<td>Minor Stroke – no. (%)</td>
<td>3 (0.9)</td>
<td>3 (0.9)</td>
</tr>
<tr>
<td>Death/maj stroke – no. (%)</td>
<td>24 (6.9)</td>
<td>28 (8.2)</td>
</tr>
</tbody>
</table>

### Five Year Risk of TIA/Stroke: PARTNER Study High Risk Cohort

Mack MJ et al Lancet 2015; 385: 2477–84

![Graph showing risk of TIA/Stroke over time for TAVR and SAVR interventions.]

### Paravalvular Leak—Achille’s Heel of TAVR
**Mortality and Post Procedural PVL TAVR Patients**

- Mild
- Moderate
- Severe

**Key Questions about TAVR after the PARTNER Trial**

- Stroke (?
  higher with TAVR that SAVR)
- Major Bleeding
- Vascular Complications (current device too big)
- Paravalvular Leak
- Need for permanent pacemaker
- ? Valve durability

**New Technology: Medtronic CoreValve**

- Self-Expanding, Nitinol Scaffold, Porcine Pericardium
CoreValve High Risk US Trial
Surgical AVR vs TAVR


Other Clinical Endpoints

<table>
<thead>
<tr>
<th>Events*</th>
<th>1 Month</th>
<th>1 Year</th>
<th>2 Years</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
</tr>
<tr>
<td>Vascular complications (major)</td>
<td>6.2</td>
<td>1.7</td>
<td>0.002</td>
</tr>
<tr>
<td></td>
<td>6.4</td>
<td>2.0</td>
<td>0.003</td>
</tr>
<tr>
<td></td>
<td>7.1</td>
<td>2.0</td>
<td>0.001</td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>20.0</td>
<td>7.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>12.5</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>25.8</td>
<td>12.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding (life-threatening or disabling)</td>
<td>13.6</td>
<td>35.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>16.5</td>
<td>38.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>18.1</td>
<td>39.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset or worsening atrial fibrillation</td>
<td>11.7</td>
<td>31.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>16.4</td>
<td>33.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>19.5</td>
<td>34.9</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td></td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Percentages reported are Kaplan-Meier estimates and logrank P values
Change in Paravalvular Regurgitation Over Time—CoreValve Pivotal Trial

Valve Durability at 5 Years—PARTNER High Risk Group
Aortic Valve Mean Gradient

No structural valve deterioration that required re-intervention.

p < 0.0001

TRANSCATHETER AORTIC VALVE IMPLANTATION
VASCULAR ACCESS SHEATH DIMENSIONS
Pros and Cons of Current Valves

Edwards Sapien 3
- Annular location below coronary arteries
- Cuff below reduces paravalvular leak
- Balloon expandable
- Small Profile
- Can be mounted for delivery via any approach
- Low pacer rate
- Can’t move it

Medtronic Evolut R
- Self-expanding “gentle” valve
- Recapturable, repositionable
- Approved for Valve in Valve
- Smallest
- Low likelihood of coronary obstruction
- Higher pacer rate
- Limited in delivery locations

The PARTNER II Trial:
Study Design

The PARTNER II Trial: Symptomatic Severe Aortic Stenosis

Part I: 3000 Randomized Patients
- Operable
  - Transapical (TA)
  - Transfemoral (TF)
- Inoperable
  - Transapical (TA)
  - Transfemoral (TF)
- 1:1 Randomization

Primary Endpoint: All-Cause Mortality + Major Stroke at One Year (Non-inferiority)

All-Cause Mortality at 30 Days
Edwards SAPIEN Valves (As Treated)

PARTNER 1 and 2 Trials
(Operable and TF Patients)
Strokes (All) at 30 Days

PARTNER 1 and 2 Trials
(Other than valve-related)

Neurologist evaluations (pre- and post)

Evolut CE Mark: Safety

<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>
<tr>
<td>Major vascular complications</td>
<td>8.3 (5)</td>
<td>8.3 (5)</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeding</td>
<td>5.0 (3)</td>
<td>8.4 (5)</td>
</tr>
<tr>
<td>Embolization or migration</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Coronary obstruction</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Pacemaker*</td>
<td>11.7 (7)</td>
<td>13.4 (8)</td>
</tr>
</tbody>
</table>

*Patients with a prior pacemaker included in the denominator.

Medtronic Evolut R Valve
Current FDA Approval
TAVR is approved for patients with severe aortic stenosis:

- Inoperable or High risk (STS>8% or other high risk clinical features) for surgical AVR
- Symptomatic with ≥NYHA Class II CHF
- Life expectancy >1 year
- Native tricuspid aortic valve
- Degenerated bioprosthetic valve (Medtronic)
- Evaluated by Heart Team (IC and two CT surgeons)

FDA News Release
FDA approves expanded indication for two transcatheter heart valves for patients at intermediate risk for death or complications associated with open-heart surgery

For Immediate Release August 16, 2016

• Expanded indication for Sapien XT and Sapien 3 Valves to intermediate risk patients
• Intermediate risk = STS predicted risk 4-8%

Patient Selection

Clinical Predictors of Increased Risk

- Serum weight < 90 kg
- Very low tricuspid gradient (mean gradient < 2 mmHg)
- Less than two valve disease, mild mitral regurgitation
- Severe aortic regurgitation
- Severe mitral regurgitation
- Severe aortic stenosis
- Moderate tricuspid regurgitation
- Severe mitral stenosis
- Asymptomatic patient with transected coronary artery
- Advanced renal insufficiency
- High STS score (predicted likelihood of mortality > 10%)


Impact of Frailty on 1 Year Mortality

- Serum Albumin < 3.5 g/dL
- Grip strength
  - < 30 kg in men
  - < 20 kg in women
- 5 meter walk time > 6 sec
- Katz ADL's <6/6
  - Bathing
  - Dressing
  - Toileting
  - Transferring
  - Continence
  - Feeding


Current Screening Approach—An Imaging Intensive Technology

- TTE
  - Gradients, annulus
  - DSE for low gradient AS
- TEE
  - Less of a role in screening
- Cardiac catheterization
  - Coronaries, RHC, Ascending and Abdominal aortography and wire straightening
- ETT for severe AS "w/o Sxs"
- Cardiac CT
  - Critical role in screening and procedural planning
- Peripheral CTA
  - Evaluate route
Cardiac CT

- Aortic Valve Area: measured in systole using planimetry was 0.85 cm squared
- Annular Area: 403 mm²
- Aorta at Aortic Valve Annulus: 25 x 19 mm
- Aorta at Sinus: 30.4 mm dia.
- Aorta Sinotubular Junc.: 26 mm dia.
- Aortic valve:
  - Height to RCA: 14 mm
  - Height to LM: 12.7 mm

CT – Lower Extremity Angiography

- REIA: 8.3 mm
- LEIA: 7.3 mm
- RCIA: 8.1 mm
- LCFA: 7.4 mm
- RCI A: 7.4 mm
- LCIA: 7.3 mm
- LCIA: 7.4 mm
- LEIA: 7.1 mm
- LCFA: 7.4 mm
- Aorta: 16 mm

Multi-modality imaging is important for patient selection and treatment guidance
Outcome Monitoring–Mandatory National Registry

- Comprehensive prospective observational database (>400 data elements)—Supported by CMS/FDA
- FU includes 30-days, 1-year (incl. QOL measures)
- TVT compliance linked to reimbursement

Outcome Report Metrics

- In hospital
  - Mortality & Adverse events
  - Procedure success
  - Acute kidney injury

- 30-Day and 1-Year outcomes
  - All cause mortality
  - Stroke
  - MI
  - Bleeding events
  - Valve performance

- Quality of Life (KCCQ)

Real World Experience
One Year Outcomes from TVT Registry

Holmes DR et al. JAMA. 2015;313(10):1019-1028
Multivariable Predictors of Mortality
One Year Outcomes from TVT Registry

Holmes DR et al. JAMA. 2015;313(10):1019-1028

Cumulative TVT Sites
2012 to September 2015

Commercial TAVR Patient Records
Submitted to the TVT Registry

Source: STS/ACC TVT Registry Database as of Sept 1, 2015
TAVR: Age of the Patients

Take-Home Message
There is no age creep in TAVR in the US

Median LOS (Days)

Median STS Risk Score for all TAVR Procedures

Source: STS/ACC TVT Registry Database as of Sept 1, 2015

Source: DCRI Query April 6, 2015
TAVR Access Site Selection

Cardiac Outcomes After TAVR (in-hospital)

Patient Discharge Status

Source: STS/ACC TVT Registry Database as of Sept 1, 2015
TAVR Categories

Operable AS patients

Low-Intermediate Risk

High Risk

90% 10%

Too Sick

Inoperable

Ongoing Research Studies

- Extension into Intermediate Risk Patients
- Approval of New Heart Valve Systems
- New Technologies to Reduce Stroke

CoreValve® SURTAVI Trial

- Randomized 1:1, non-inferiority study
- Multicenter up to 75 centers in
  - Europe
  - Canada
  - United States
- Sample size: Approx. 2,500
- 5-year FU
A Plethora of New Valves!

- Sadra Lotus (TF)
- St. Jude Portico (TF and TA)
- Engager (TA)
- Symetis Acurate (TA and TF)
- Jena Valve (TA and TF)

Reduction of Peri-procedural Stroke

<table>
<thead>
<tr>
<th>Claret Sentinal® Central Protection System</th>
<th>Edwards Emboclose™ Embolic Deflector</th>
<th>TritonX™ Central Protection Device</th>
</tr>
</thead>
<tbody>
<tr>
<td>Filter capture</td>
<td>Deflector</td>
<td>Deflector</td>
</tr>
<tr>
<td>6F (adult)</td>
<td>6F (adult)</td>
<td>9F (fenestrated)</td>
</tr>
<tr>
<td>140 microns pore size</td>
<td>100 microns pore size</td>
<td>130 x 250 microns pore size</td>
</tr>
<tr>
<td>Brachiocephalic and OCC</td>
<td>Aortic arch position</td>
<td>Aortic arch position</td>
</tr>
<tr>
<td>CE marked and commercialized</td>
<td>CE marked</td>
<td>CE marked</td>
</tr>
</tbody>
</table>

SENTINEL Study Design

Pivotal study confirming the therapeutic importance of embolic debris capture and removal during TAVR

Objectives:
- Assess the safety and efficacy of the Claret Medical Sentinal Central Protection System in reducing the volume and number of new ischaemic lesions in the brain and their potential impact on neurocognitive function

Primary Investigators:
- Sanjiv Kapoor, MD
- Claret Medical

Secondary Endpoints:
- Safety follow-up
- Neurological and Neurocognitive Tests

Primary Efficacy Endpoint: Reduction in median total new lesion volume as assessed by DW-MRI

Primary Safety Endpoint: Occurrence of MACE at 30 days
Conclusions

• SAVR remains the Gold Standard treatment for Aortic Stenosis.
• Aortic valve disease is increasing as our patients are living longer and patients are becoming higher risk for sAVR.
• TAVR is currently FDA approved for treatment of high risk or inoperable patients with symptomatic aortic stenosis.
• The PARTNER trial in inoperable patients demonstrated:
  – Marked decreased in mortality at 1 and 5 years
  – Reduced rehospitalization for CHF
  – Improved symptom status and quality of life compared
• Trials of High Risk patients (PARTNER Cohort A and CoreValve Pivotal US Study):
  – Similar or improved survival with TAVR vs SAVR
  – Similar or reduced risk of stroke
  – Similar rates of rehospitalization and similar symptoms at follow up

Conclusions (cont)

• The current generation of balloon expandable and self expanding valves demonstrate further reductions in adverse events.
• Patient selection remains critically important and requires a team approach to optimize outcomes and avoid futile care.
  – Opportunity for new tools to predict adverse events after TAVR.
• The development of the TVT registry has been an important aspect in the regulatory and research agenda for the roll out of TAVR and allows for benchmarking of outcomes nationally.
• Clinical trials are ongoing to extend TAVR to intermediate risk patients, as well as to introduce new valve technologies and techniques to avoid complications.

Discussion/Questions