Catheter Based Treatment of Valvular Heart Disease In the Adult

Spring 2016

Professor of Medicine & Surgery
Associate Dean for International Medicine
University of Miami Miller School of Medicine
Support for Educational Conferences
- Most Cardiovascular Corporations

Current Sponsored Research Support –
- Medtronic
  - CoreValve Trials, Simplicity trials
  - Direct Flow medical

Other Conflicts:
1. Tendyne Medical Inc. /ABBOTT
   - Medical Director and stock holder
2. Intergene International LLC - Medical Advisory Board
3. Aegis Medical - Medical Advisory Board
4. St. George Medical - consultant
5. de Marchena Wellness - President
6. Argo medical consultant
SOME DEVICES PRESENTED ARE INVESTIGATIONAL
AORTIC STENOSIS
Prevalence and Surgical Incidence of Calcific Aortic Stenosis

- Aortic stenosis is the most common acquired valvular disorder found in developed countries.
- The prevalence of calcific aortic stenosis increases with age.
- Mild to severe AS is present in 12% > 65 years
  - Severe AS in 3.4%
- Around 50,000 AVR are performed annually
Severe Symptomatic Aortic Stenosis

Percent of Cardiology Patients Treated

At Least 30% of Patients with Severe Symptomatic AS are “Untreated”!

2. Iung B et al. A prospective survey of patients with valvular heart disease in Europe: The Euro Heart Survey on Valvular Heart Disease. European Heart Journal 2003;24:1231-1243 (*includes both Aortic Stenosis and Mitral Regurgitation patients)
Transcatheter heart valves aim to address an unmet patient need

Nearly half of untreated patients are deemed too sick for surgery

Edwards sponsored survey
The Edwards SAPIEN Transcatheter Heart Valve

Transfemoral Procedure Using the RetroFlex Delivery System
All Cause Mortality

HR [95% CI] = 0.54 [0.38, 0.78]
P (log rank) < 0.0001

All-Cause Mortality
Transfemoral (N=492)

HR [95% CI] = 0.83 [0.60, 1.15]
P (log rank) = 0.25

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR</td>
<td>244</td>
</tr>
<tr>
<td></td>
<td>215</td>
</tr>
<tr>
<td></td>
<td>188</td>
</tr>
<tr>
<td></td>
<td>119</td>
</tr>
<tr>
<td></td>
<td>59</td>
</tr>
<tr>
<td>AVR</td>
<td>248</td>
</tr>
<tr>
<td></td>
<td>180</td>
</tr>
<tr>
<td></td>
<td>168</td>
</tr>
<tr>
<td></td>
<td>109</td>
</tr>
<tr>
<td></td>
<td>56</td>
</tr>
</tbody>
</table>
All-Cause Mortality
Transapical (N=207)

HR [95% CI] = 1.22 [0.75, 1.98]
P (log rank) = 0.41

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>TAVR</strong></td>
<td>104</td>
</tr>
<tr>
<td><strong>AVR</strong></td>
<td>103</td>
</tr>
</tbody>
</table>
NYHA Functional Class

- **Baseline**: TAVR vs. AVR
  - P = 1.00

- **30 Days**: TAVR vs. AVR
  - P < 0.001

- **6 Months**: TAVR vs. AVR
  - P = 0.05

- **1 Year**: TAVR vs. AVR
  - P = 0.75

Patients Surviving, %

- I
- II
- III
- IV

Legend:
- TAVR: Transcatheter Aortic Valve Replacement
- AVR: Aortic Valve Replacement
Diamond cell configuration

Nitinol: memory shaped/no recoil Multi-level design incorporates three different areas of radial and hoop strength

- Low radial force area orients the system
- Constrained area avoids coronaries and features supra-annular valve leaflets
  - High radial force provides secure anchoring and constant force mitigates paravalvular leak

Radiopaque
CoreValve Delivery Catheter

- Over-the-wire (0.035” compatible)
- Radiopaque tip
- 18Fr Valve capsule
- Radiopaque marker
- 12Fr Flexible shaft
Loading must take place while submersed in cold saline.
CT Images: Annulus Measurements – August 11, 2011

Site Image of Ao Annulus measurements – not provided

Ao Annulus mean diameter 23.4 mm

- 24.9 x 21.9 Major x Minor aortic annulus diam.
- 72.0 Aortic Annulus perimeter (22.9 x 3.14)
- 32.9 Max Ascending Aorta diameter
- 29.1 – 28.1 Sinus of Valsalva width
- 24.5 – 21.7 Sinus of Valsalva height (all in mm)

Ao Annulus mean diameter 22.6 mm

- 24.2 X 20.9 Major x Minor aortic annulus diameter
- 71.2 Aortic Annulus perimeter (22.7 x 3.14)
- 31.3 Max Ascending Aorta diameter
- 29.3 – 28.3 Sinus of Valsalva width
- 21.2 – 20.5 Sinus of Valsalva height (all in mm)
- 26.2 – 24.6 Sinotubular Junction width (STJ)
CT 3D Reconstructions

AP of Abdominal Aorta and iliacs

Tortuosity: (per site) severe common iliacs & mod ext. iliacs
Calcification: (per site) mod LFA, LCI & RCI

Lateral of Abdominal Aorta and iliacs
SELECTION OF FLUOROSCOPIC PROJECTIONS

LAO 40 Cr 20

LAO 40 Cr 30

LAO 30 Cr 30

Kapadia S - Cleveland Clinic
STUDY DEVICE AND ACCESS ROUTES

Transfemoral
Subclavian
Direct Aortic
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR N=390</th>
<th>SAVR N=357</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>83.1 ± 7.1</td>
<td>83.2 ± 6.4</td>
</tr>
<tr>
<td>Men, %</td>
<td>53.1</td>
<td>52.4</td>
</tr>
<tr>
<td>STS Predicted Risk of Mortality, %</td>
<td>7.3 ± 3.0</td>
<td>7.5 ± 3.4</td>
</tr>
<tr>
<td>Logistic EuroSCORE, %</td>
<td>17.7 ± 13.1</td>
<td>18.6 ± 13.0</td>
</tr>
<tr>
<td>NYHA Class III/IV, %</td>
<td>85.6</td>
<td>86.8</td>
</tr>
<tr>
<td>Prior Coronary-artery Bypass Surgery</td>
<td>29.5</td>
<td>31.1</td>
</tr>
<tr>
<td>Diabetes Mellitus, %</td>
<td>34.9*</td>
<td>45.4*</td>
</tr>
<tr>
<td>Insulin Requiring Diabetes, %</td>
<td>11.0</td>
<td>13.2</td>
</tr>
<tr>
<td>Prior Stroke, %</td>
<td>12.6</td>
<td>14.0</td>
</tr>
<tr>
<td>Modified Rankin 0 or 1, %</td>
<td>74.5</td>
<td>87.2</td>
</tr>
<tr>
<td>Modified Rankin &gt; 1, %</td>
<td>25.5</td>
<td>12.8</td>
</tr>
<tr>
<td>STS Severe Chronic Lung Disease, %</td>
<td>13.3</td>
<td>9.0</td>
</tr>
</tbody>
</table>

*P < 0.01
2-Year All-cause Mortality

<table>
<thead>
<tr>
<th></th>
<th>No. at Risk</th>
<th>Months Post-Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgical</td>
<td>357 341</td>
<td>0 6 12 18 24</td>
</tr>
<tr>
<td>Transcatheter</td>
<td>390 377</td>
<td>0 6 12 18 24</td>
</tr>
</tbody>
</table>

- Surgical: 4.5%, 3.3%, 19.1%
- Transcatheter: 3.3%, 14.2%
ALL-CAUSE MORTALITY OR STROKE

Log-rank P=0.006 \( \Delta 9.4 \)

36-month comparison of TAVR and SAVR:

- TAVR:
  - 0 months: 391
  - 12 months: 319
  - 24 months: 273
  - 36 months: 165

- SAVR:
  - 0 months: 359
  - 12 months: 257
  - 24 months: 208
  - 36 months: 128

ACC2016
ALL STROKE

ACC 2016

Graph showing the percentage of patients experiencing all stroke over months with TAVR and SAVR treatments. The graph indicates a log-rank P-value of 0.034 and a Δ6.4 difference. At 36 months, TAVR has 12.6% and SAVR has 19.0%.
NYHA CLASS SURVIVORS

- **SAVR N=350**
  - Baseline: 18.3%
  - 1 Month: 34.0%
  - 1 Year: 56.8%

- **TAVR N=390**
  - Baseline: 16.9%
  - 1 Month: 45.2%
  - 1 Year: 57.7%

- **SAVR N=318**
  - Baseline: 15.4%
  - 1 Month: 42.5%
  - 1 Year: 69.7%

- **TAVR N=361**
  - Baseline: 13.3%
  - 1 Month: 41.0%
  - 1 Year: 36.7%

- **SAVR N=236**
  - Baseline: 4.4%
  - 1 Month: 19.2%
  - 1 Year: 0.8%

- **TAVR N=305**
  - Baseline: 0.3%
  - 1 Month: 0.3%
  - 1 Year: 0.0%
VALVE HEMODYNAMICS*

TAVR had significantly better valve performance vs SAVR at all follow-ups (P<0.001)
ALL-CAUSE MORTALITY – STS ≤ 7%

Log-rank P=0.018  Δ11.4

TAVR  SAVR

No. at Risk

0 12 24 36

0% 10% 20% 30% 40% 50% 60%

All-Cause Mortality (%)

Months

TAVR  14.0  14.9  26.2  38.5
SAVR  10.4  14.9  26.2  38.5

202 182 166 101
181 151 121  71
SAV Information

stent posts in relation to coronary artery origins

Edwards Perimount® 2800 Valve

Please provide as much detail as possible about the failed bioprosthetic surgical valve:

Manufacturer and Model:
Edwards Perimount 2800 Valve

Date of aortic valvular surgery:

Gradient after surgical aortic valve:

Failure Mode of surgical aortic bioprosthesis:

☐ Stented
☐ Stentless
☐ Homograft

☐ Stenosis
☐ Regurgitation
☐ Combined
☐ Unknown
UNSHEATHING AND RESHEATHING OF THE VALVE
<table>
<thead>
<tr>
<th>Frame Material</th>
<th>CoreValve</th>
<th>Sapien XT</th>
<th>Direct Flow</th>
<th>Lotus</th>
<th>Portico</th>
<th>Symetis</th>
<th>Sapien 3</th>
<th>Centera</th>
<th>Evolut R</th>
<th>Valve Med</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nitinol</td>
<td>Cobalt chromium</td>
<td>Polyester fabric</td>
<td>Braided Nitinol</td>
<td>Nitinol</td>
<td>Nitinol</td>
<td>Cobalt chromium</td>
<td>Nitinol</td>
<td>Nitinol</td>
<td>Nitinol</td>
<td>Nitinol</td>
</tr>
<tr>
<td>Tissue</td>
<td>Porcine pericardial inner skirt</td>
<td>Bovine pericardial inner skirt</td>
<td>Bovine Pericardial</td>
<td>Bovine Pericardial with PET outer skirt</td>
<td>Bovine Pericardial inner and outer skirt</td>
<td>Porcine Pericardial</td>
<td>Bovine Pericardial inner skirt</td>
<td>Porcine pericardial inner skirt (outer skirt in development)</td>
<td>Bovine Leaflet</td>
<td></td>
</tr>
<tr>
<td>Valve Design</td>
<td>Supra-annular</td>
<td>Intra-annular</td>
<td>Intra-annular</td>
<td>Intra-annular</td>
<td>Intra-annular</td>
<td>Intra-annular</td>
<td>Intra-annular</td>
<td>Supra-annular</td>
<td>Intra-annular</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>AOA®</td>
<td>ThermaFix®</td>
<td>Anti-Ca++ Recapture</td>
<td>Recapture</td>
<td>Linx Recapture</td>
<td>None</td>
<td>Therma-Fix Future GLX</td>
<td>Therma-Fix Future GLX Recapture</td>
<td>AOA® Recapture</td>
<td>Modular approach</td>
</tr>
</tbody>
</table>
1 Month Moderate & Severe PVL
Echo Core Lab Adjudicated Clinical Trials

% Patients with Mod/Severe PVL

- SAPIEN XT PARTNER II, Inop¹: 24.2%
- SAPIEN PARTNER II Inop¹: 16.9%
- CoreValve ADVANCE²: 14.2%
- CoreValve Extreme Risk³: 11.5%
- CoreValve High Risk⁴: 9.0%
- Portico CE Study⁵: 4.0%
- SAPIEN 3⁶: 3.4%
- Direct Flow DISCOVER⁷: 1.7%
- LOTUS REPRISE II & EXT⁸: 0.6%

N=236, N=225, N=639, N=418, N=390, N=75, N=150, N=100, N=250

## Improving Clinical Outcomes: Competitive Landscape Contd.

<table>
<thead>
<tr>
<th>Study, Sample Size</th>
<th>CoreValve US Pivotal Extreme Risk N=489</th>
<th>Sapien XT PARTNER IIB N=284</th>
<th>DISCOVER CE N=100 (evaluable cohort N=75)</th>
<th>Lotus Reprise II N=120</th>
<th>Portico CE N=83</th>
<th>Acurate CE N=89 TF</th>
<th>CE Pivotal N=150</th>
<th>FIM N=15</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>30 Day Survival</strong></td>
<td>91.6%</td>
<td>96.5%</td>
<td>98.7%</td>
<td>95.8%</td>
<td>96.4%</td>
<td>96.6%</td>
<td>94.7%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>Maj. Vasc Comp</strong></td>
<td>8.2%</td>
<td>9.6%</td>
<td>2.7%</td>
<td>2.5%</td>
<td>6%</td>
<td>3.4%</td>
<td>6%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>PPM Rate</strong></td>
<td>21.6%</td>
<td>6.4%</td>
<td>16%</td>
<td>28.6%</td>
<td>10.8%</td>
<td>9%</td>
<td>13.3%</td>
<td>27%</td>
</tr>
<tr>
<td><strong>PVL</strong></td>
<td>41.5% mild, 11.4% trace/mild, 24.2% mod/severe</td>
<td>75.9% mild, 1.4% mod</td>
<td>28.4% mild, 1.4% mod</td>
<td>20.7% trace/mild, 1.0% moderate</td>
<td>65% mild, 5% mod.</td>
<td>4.9% mod</td>
<td>24.1% mild, 3.4% mod</td>
<td>69% mild, 8% mod</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td>2.3% major</td>
<td>3.2% disabling</td>
<td>2.7% major</td>
<td>1.7% disab.</td>
<td>2.4% major</td>
<td>2.2% major</td>
<td>2.7%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Coronary Occlusions</strong></td>
<td>0%</td>
<td>NR</td>
<td>NR</td>
<td>0.8%</td>
<td>NR</td>
<td>NR</td>
<td>0%</td>
<td>NR</td>
</tr>
<tr>
<td><strong>Annulus Rupture</strong></td>
<td>0.2%</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td>1.2%</td>
<td>1.8%</td>
<td>1.3%</td>
<td>3.3%</td>
<td>1.2%</td>
<td>0%</td>
<td>1.3%</td>
<td>NR</td>
</tr>
</tbody>
</table>
PATHOLOGIC MECHANISMS OF MITRAL REGURGITATION

- LA cavity
  - Posterior wall distension
  - Lack of contraction

- Chordae Tendineae
  - Abnormal insertion
  - Elongation
  - Shortening
  - Rupture
  - Fusion
  - Thickening

- Mitral Annulus
  - Dilatation
  - Calcification

- Leaflets
  - Perforation
  - Cleft
  - Redundancy
  - Prolapse
  - Thickening
  - Commissural fusion

- Papillary Muscle
  - Elongation
  - Ischemia
  - Fibrosis
  - Rupture
  - Replacement

- LV Free Wall
  - Lateral distension
  - Ischemia
PERCUTANEOUS MITRAL VALVE REPAIR

A Monumental Task !!
- 1990 Otavio Alfieri, Milan-Italy
- Suturing in the center, creates a double orifice valve
- Leaves leaflets in close apposition in the beginning of systole
- > 600 procedures reported
- May be done in conjunction with annuloplasty
Alfieri Stitch
ALFIERI STITCH WITH AND WITHOUT ANNULOPLASTY
(FREEDOM FROM REOPERATION)

Annuloplasty
No annuloplasty

$p=0.02$

Alfieri et al; 465 pts; 1991-2005
Percutaneous Mitral Valve Repair

Caution: Investigational Device. Limited by Federal (US) Law to Investigational Use
EVEREST II Randomized Clinical Trial

Study Design

279 Patients enrolled at 37 sites

- Significant MR (3+-4+)
- Specific Anatomical Criteria

Randomized 2:1

Device Group
MitraClip System
N=184

Control Group
Surgical Repair or Replacement
N=95

Echocardiography Core Lab and Clinical Follow-Up:
Baseline, 30 days, 6 months, 1 year, 18 months, and annually through 5 years
EVEREST II RCT: Patient Flow
Per Protocol Cohort: Analysis of Device Performance

Randomized Cohort
n=279

Device Group
n=184

Treated
n=178

Acute Procedural Success
Not Achieved
n=41 23%

Acute Procedural Success (APS) = MR ≤2+ at discharge

Acute Procedural Success Achieved
n=137

30 days
n=136
99% Clinical Follow-up

12 months
n=134
98.5% Clinical Follow-up
98% Echo Follow-up

Control Group
n=95

Treated
n=80
(86% MV repair)

30 days
n=79
99% Clinical Follow-up

12 months
n=74
94% Clinical Follow-up
92% Echo Follow-up

Randomized, not treated
Device, n=6
Control, n=15

Treated
n=178

Randomized Cohort
n=279

Investigational Device only in the US; Not available for sale in the US
EVEREST II RCT: Primary Endpoints
Per Protocol Cohort

Safety
Major Adverse Events
30 days

- Device Group, n=136
  - 9.6%
  - \( p_{\text{SUP}} < 0.0001 \)
- Control Group, n=79
  - 57.0%

Effectiveness
Clinical Success Rate*
12 months

- Device Group, n=134
  - 72.4%
  - \( p_{\text{NI}} = 0.0012 \)
- Control Group, n=74
  - 87.8%

Met superiority hypothesis
- Pre-specified margin = 6%
- Observed difference = 47.4%
- 97.5% LCB = 34.4%

Met non-inferiority hypothesis
- Pre-specified margin = 31%
- Observed difference = 15.4%
- 95% UCB = 25.4%

* Freedom from the combined outcome of death, MV surgery or re-operation for MV dysfunction, MR >2+ at 12 months

LCB = lower confidence bound
UCB = upper confidence bound
**EVEREST II RCT: Primary Safety Endpoint**

**Per Protocol Cohort**

<table>
<thead>
<tr>
<th>30 Day MAE, non-hierarchical</th>
<th># Patients experiencing event</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Device Group (n=136)</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
</tr>
<tr>
<td>Major Stroke</td>
<td>0</td>
</tr>
<tr>
<td>Re-operation of Mitral Valve</td>
<td>0</td>
</tr>
<tr>
<td>Urgent / Emergent CV Surgery</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>0</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>0</td>
</tr>
<tr>
<td>Deep Wound Infection</td>
<td>0</td>
</tr>
<tr>
<td>Ventilation &gt;48 hrs</td>
<td>0</td>
</tr>
<tr>
<td>New Onset Permanent Atrial Fib</td>
<td>0</td>
</tr>
<tr>
<td>Septicemia</td>
<td>0</td>
</tr>
<tr>
<td>GI Complication Requiring Surgery</td>
<td>1 (0.7%)</td>
</tr>
<tr>
<td>All Transfusions &gt;2 units*</td>
<td>12 (8.8%)</td>
</tr>
<tr>
<td><strong>TOTAL % of Patients with MAE</strong></td>
<td><strong>9.6%</strong></td>
</tr>
</tbody>
</table>

*p<0.0001* if include Major Bleeding only

(95% CI 34.4%, 60.4%)
EVEREST II RCT: MR Reduction
Per Protocol Cohort

Device Group

Baseline
n=137

12 Months
n=119

Control Group

Baseline
n=80

12 Months
n=67

3+/4+
2+
1+ 2+ 3+/4+
2+
0
36.1%
11.8%
33.6%
18.5%
17.9%
58.2%
7.5%
3.0%
18.4% (7/38) Replacement

7.7% (1/13) Replacement
EVEREST II RCT: NYHA Functional Class

Per Protocol Cohort

Device Group

Control Group

p<0.0001

p<0.0001

97.6% NYHA Class I/II

87.9% NYHA Class I/II

Baseline n=124, Matched data

12 months

Baseline n=66, Matched data

12 months

Percent Patients

I

II

III

IV

I

II

III

IV
Mitral Valve Replacement

A Long Road
Euro Heart Survey on valvular heart disease revealed 49% of patients with severe MR denied surgery.

- Impaired LVEF
- Older age
- Comorbidities

Mirabel M et al. What are the characteristics of patients with severe, symptomatic, mitral regurgitation who are denied surgery?. Eur Heart J 2007
MV Repair vs Replacement During CABG

387 pts with LVEF ≤45% and 3-4+ MR without MS underwent CABG with MV repair in 302 (78%) and MV replacement in 85 (22%).

Death at 1-, 5-, and 10 years were 17.3%, 44.8%, and 75.7%.

5-year survival in propensity matched groups

Survival (%)

Follow-up time (years)

MV repair
MV replacement

P=0.72

54.2%
44.0%

MV repair 76 54 48 43 34 27
MV replacement 76 50 47 43 33 28

Maltais S et al. JTCVS 2011;142:995-1001
ANATOMIC CHALLENGES
VARIABILITY IN NORMAL MITRAL ANNULAR GEOMETRY

Pouch, A et al. Circulation
TMVR CANDIDATES

Micro Interventional - EndoValve  
CardiAQ  
Medtronic  
Edwards Mitral  
Neovasc - Tiara  
Tendyne
**TENDYNE® VALVE DESIGN PROGRESSION**

**Other design considerations / optimization**
- Cuff size and shape
- Leaflet configuration
- Tether attachment
- Valve body shape/height
- Nitinol cell density
- Valve cover materials, in-growth
- Inner attachment
- Ability to retrieve valve
- Animal & human difference

![Acute Human Valve](image)

D-shape laser cut Nitinol

![Oval laser cut Nitinol](image)

Round laser cut Nitinol

![Round braided Nitinol](image)

Round braided Nitinol
57 y.o. man from Myxomatous mitral valvular disease

Echocardiographic findings
- MR grade 4+
- Vena Contracta 8.0 mm
- LA size 6.46 cm
- Regurgitation fraction 35.4%
- LV diastolic 51 mm; Systolic 35 mm
- NYHA Class III
- LVEF 59%
- Carpentier class II with posterior leaflet prolapse

Prolapse of posterior leaflet with restriction

Lutter G… de Marchena E. JACC Intev. 2014;(9):1077-1078
TRANSAPICAL INCISION WITH RETRACTOR
LV PUNCTURE
TENDYNE DELIVERY CATHETER IN APEX
VALVE AT ANNULUS
TRANSCARDIAC ECHO OF LV OUTFLOW POST IMPLANTATION PATIENT 1
3D SHORT AXIS OF VALVE
PRE AND POST VENTRICULOGRAM
PATIENT 1
95 AND 90 Y/O COUPLE; BOTH TREATED WITH TRANS-CATHETER AORTIC VALVE REPLACEMENT
Thank you