Percutaneous Valve Interventions

Stanton J. Rowe
President,
Percutaneous Valve Interventions

Edwards is Best Positioned to Capitalize on Percutaneous Valve Opportunities

- #1 global valve replacement and repair developer, manufacturer and marketer
- Strong intellectual property positions
- Strong interventional cardiology relationships
- A portfolio of pioneering percutaneous valve therapies
- Dedicated resources focused on PVI
Multiple Potential Percutaneous Replacement Indications

- Aortic Stenosis
- Congenital Pulmonic Valve Disease
- Aortic Insufficiency
- Valve-in-a-Valve
- Cribier-Edwards Valve

Operative Risk AVR / MVR

<table>
<thead>
<tr>
<th></th>
<th>AVR Low Risk</th>
<th>AVR High Risk</th>
<th>MVR Low Risk</th>
<th>MVR High Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>High Volume</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low Volume</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

Medicare Database, Goodney et al, Circulation 2003
Many Patients Do Not Receive Surgery Due to Co-Morbidities

Reasons for Absence of Intervention in Symptomatic Patients (NYHA Class III / IV) Extra Cardiac Causes

<table>
<thead>
<tr>
<th>(%)</th>
<th>AS</th>
<th>AR</th>
<th>MS</th>
<th>MR</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>≥ 1 Cause (%)</td>
<td>68</td>
<td>50</td>
<td>45</td>
<td>52</td>
<td>55</td>
</tr>
<tr>
<td>Age</td>
<td>35</td>
<td>22</td>
<td>18</td>
<td>27</td>
<td>27 (1*)</td>
</tr>
<tr>
<td>Renal failure</td>
<td>10</td>
<td>11</td>
<td>0</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>COPD</td>
<td>21</td>
<td>0</td>
<td>6</td>
<td>14</td>
<td>14</td>
</tr>
<tr>
<td>Other EC</td>
<td>26</td>
<td>22</td>
<td>30</td>
<td>31</td>
<td>32</td>
</tr>
<tr>
<td>Short life expectancy</td>
<td>26</td>
<td>22</td>
<td>15</td>
<td>17</td>
<td>19</td>
</tr>
</tbody>
</table>

(* age as the sole reason)

Many Patients Do Not Receive Surgery Due to Co-Morbidities

Older Aortic Stenosis Patients Are Less Likely to Have Surgery

Frequency of AVR as Function of Age in Severe AS Population

Loma Linda, Pai, et al; 740 patients
Untreated Aortic Stenosis Results in Significantly Higher Mortality

<table>
<thead>
<tr>
<th>Univariate Predictors of Survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>No AVR</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>CHF</td>
</tr>
<tr>
<td>Chronic Renal Insufficiency</td>
</tr>
<tr>
<td>PASP&gt;=60mmHg</td>
</tr>
<tr>
<td>3 or 4+ MR</td>
</tr>
</tbody>
</table>

Loma Linda, Pai, et al; 740 patients

Many Patients With Severe Aortic Stenosis Are Not Surgically Treated
The Initial Targets for Percutaneous Aortic Valve Replacement

- Surgical Risk: Aortic Valve Replacement Surgery
- Non-Surgical: High Risk Surgical
- Refusal of Surgery

Global Aortic Valve Procedure Evolution

- Percutaneous
- Tissue
- Mechanical

2005: $300M
2010: $300M
2014: $800M

Source: Company estimates
Severe calcific AS
Gradient 68mmHg, AVA 0.5 cm²
Massive pulmonary edema
NYHA class IV
2 previous BAV
Previous stroke
Previous AMI
5 stents on coronary arteries
Insulin diabetes
Severe peripheral artery disease

Percutaneous Opportunity: Mitral Valve Repair Improves Patient Survival

- Mitral regurgitation of moderate degree or more is frequent, particularly in the aging population
  - 2 to 2.7 million Americans are afflicted
  - Will increase to 3.8 to 4.8 million Americans by 2030

Maurice Enriquez-Sarano, M.D., cardiologist, The Mayo Clinic
"We know from previous studies that patients with symptomatic mitral regurgitation are at increased risk of death, but for those without symptoms the picture has been murkier; in this study we followed a large population of asymptomatic patients prospectively to identify keys to improved long-term outcomes, and to determine when patients should consider surgery."

Patients with a regurgitant orifice larger than 40 mm² who were treated only with medication were more than five times more likely to die than those with the same severity of regurgitation who underwent valve repair surgery
Two Leading Percutaneous Mitral Valve Technologies

- Mitral Regurgitation
  - Ischemic Disease
  - Mixed Disease
  - Leaflet Disease
- Coronary Sinus Repair
- Edge-to-Edge Repair

The Initial Targets for Percutaneous Mitral Valve Repair

- Medical Therapy for MR
- Refusal of Surgery
- Surgical Patients
- Mitral Valve Repair & Replacement Surgery Candidates
- Edge-to-Edge
- Coronary Sinus
10% of CHF Patients Would Benefit From Mitral Repair

- CHF represents a significant portion of untreated mitral valve disease
- 5+ million CHF patients
  - 24% are Class III and IV
  - Among Class III and IV, moderate to severe MR = 39% or 460,000 patients
- This population is a principal target of the coronary sinus approach

The Edge-to-Edge Opportunity is Large

- Leaflet disease has a prevalence in U.S. of ~300,000
  - Excessive tissue
  - Poor leaflet coaptation
- Edge-to-Edge percutaneous repair is:
  - A less-invasive option for the ~50,000 U.S. patients currently treated by open heart mitral valve surgery
  - A treatment option for the medically managed
Global Mitral Valve Procedure Evolution

<table>
<thead>
<tr>
<th>Procedures</th>
<th>2005</th>
<th>2010</th>
<th>2014</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percutaneous Repair</td>
<td>50k</td>
<td>100k</td>
<td>200k</td>
</tr>
<tr>
<td>Surgical Replacement</td>
<td>150k</td>
<td>200k</td>
<td>250k</td>
</tr>
<tr>
<td>Surgical Repair</td>
<td>200k</td>
<td>150k</td>
<td>100k</td>
</tr>
</tbody>
</table>

Percutaneous Mitral Opportunity

Source: Company estimates

Who Is the Customer?

- Percutaneous Valve Replacement
- Percutaneous Mitral Valve Repair
- Referrals

CT Surgeon

Hybrid

Interventional Cardiologist
Technology Evolution: Angioplasty
Restenosis Rates & Market Size

Percutaneous Heart Valve Therapies
Staged Market Penetration
Edwards is the Clear Leader in Percutaneous Valve Development

- Only company with 3 active clinical programs
- First aortic valve replacement without open heart surgery
- Largest series of percutaneous aortic valve replacements
- First IDE approved in the U.S. for a percutaneous aortic valve
- Longest implant duration for a PHV
- First permanent coronary sinus implant
- First coronary sinus implant demonstrating efficacy at 6 months (4+ to 0)
- First edge-to-edge repair of a mitral valve in < 2 hours
- All 3 percutaneous programs are in second generation products

Edwards Lifesciences

Helping Patients is Our Life’s Work, and
Percutaneous Valve Replacement

Larry Wood
Vice President and General Manager
Percutaneous Valve Interventions – Replacement

Percutaneous Aortic Program Update

- Key Advancements
- Key Learnings
- Clinical Update
- Regulatory Status
Antegrade Transeptal Approach

Retrograde Procedure
Key Advancements

- Simplified procedure using retrograde approach
- Developed custom delivery system to improve access, provide steerability and facilitate crossing the native valve
- 26mm valve allowed optimal sizing and reduced PV leak
- Over 25 cases performed in Vancouver with new delivery system

Steerability to Optimize Access
Articulating Tip Facilitates Tracking Over the Arch

Articulating Tip/Pushability Eases Valve Crossing
Stable Placement/Rapid Pacing

Optimal Sizing Decreases PV Leak
Valve Durability

- Strength of balloon expandable stent maintains optimal geometry
- Excellent clinical durability >2 years
- Transfer of manufacturing to Edwards further improves durability potential

Key Procedural/Training Steps

- Arterial access management is key
  - A longer sheath eases placement
  - Screening ensures proper patient selection
- Coronary artery obstruction
  - Can be screened for during balloon pre-dilatation
- Cardiac output and placement
  - Good visualization and placement in native valve
  - Rapid pacing and procedural coordination important
Clinical Update

- To-date, 75+ cases performed worldwide with Cribier-Edwards PHV
- We continue to learn and evolve the procedure with increasing success
- Vancouver experience (25+ cases) with advanced retrograde system gives us confidence on restart of US trial

Vancouver Experience: First 18 Patients

- AV area 0.6 to 1.6 cm²
- Moderate paravalvular AI 2/18 pts, doing well
- Unsuccessful implant 3/18 pts, doing well
  - 2 implanted in descending aorta
  - 1 removed on short delivery catheter
- Predicted Mortality 22 %
  - (Euroscore logistic)
- Actual Mortality 11 %
  - (30 day)
Regulatory Status

- Expect FDA approval before year end to restart clinical trial in US
  - Feasibility trial expected to be a 30 patient non-randomized study
  - Will include 26mm valve and retrograde system
  - Pivotal trial design will be finalized following completion of the feasibility study
- European trial sites continue to enroll patients and have received revised protocol which includes retrograde system and 26mm valve

Platform Technology Leads to Additional Applications

- Aortic insufficiency
- Valve-in-a-valve applications
  - Replacing a failing tissue valve with a percutaneous valve
  - Mitral or aortic position
- Pulmonic valve replacement
  - Failed Ross procedures
  - Congenital defects
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life is now
Percutaneous Valve Repair

Don Bobo
Vice President and General Manager
Percutaneous Valve Interventions - Repair

Anatomy of Mitral Valve Disease

~2M patients (US) have an existing diagnosis of mitral regurgitation (MR)

Untreated, MR worsens over time in most patients

Surgery reserved for the most severe symptoms

Results in ~50k procedures/year (US)

Causes of MR include ischemic disease (functional) or leaflet disease (degenerative)
Our Target: Patients with Moderate to Severe Mitral Regurgitation (MR)

Annual Diagnosis of Moderate to Severe MR is ~200k

Annual Incidence of Mitral Regurgitation (U.S.)

- Mild: 65
- Moderate: 140
- Severe: 200

Source: Company estimates

Edwards’ PVI Products Target Both Primary Causes of MR

PVI – Mitral Target Market (Moderate/Severe MR)

<table>
<thead>
<tr>
<th>Primary MR Causes</th>
<th>EW Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primarily Functional MR (Annular Dilatation)</td>
<td>Coronary Sinus</td>
</tr>
<tr>
<td>Mixed</td>
<td>Coronary Sinus + Edge-to-Edge</td>
</tr>
<tr>
<td>Primarily Degenerative MR (Abnormal Leaflets)</td>
<td>Edge-to-Edge</td>
</tr>
</tbody>
</table>

% of Patients

Source: Company estimates
Edge-to-Edge Repair Targets Patients with Degenerative MR

- Focused on repair of diseased, prolapsed leaflets
- Alfieri procedure addresses the inability of the leaflets to properly close and form seal
- Developed in Milan, Italy by Professor Alfieri
  - Used in ~1,200 open heart surgical repair cases
- Five year freedom from re-operation is 70% to 95%

Edge-to-Edge (E2E) Repair Procedure
**Edwards’ E2E Transeptal Guide**

Guide catheter – 16F deflectable

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**Edwards’ E2E Therapy Catheter**

- Therapy catheter – 10F
- “Housing” includes vacuum port, needles, suture
Edwards E2E Fastener Catheter

- Fastener catheter – 6F
  - Low profile
  - Flexible
  - Built-in nitinol clip

E2E System Profile

<table>
<thead>
<tr>
<th>Attribute</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Guide catheter size</td>
<td>16F</td>
</tr>
<tr>
<td>Individual leaflet capture and release</td>
<td>Yes</td>
</tr>
<tr>
<td>Leaflet capture</td>
<td>Vacuum</td>
</tr>
<tr>
<td>Required leaflet coaptation</td>
<td>None</td>
</tr>
<tr>
<td>Estimated procedure time</td>
<td>&lt; 2 hours</td>
</tr>
<tr>
<td>Leaflet attachment</td>
<td>Suture (2mm x 2F)</td>
</tr>
<tr>
<td>Commissural and segmental repairs</td>
<td>Yes</td>
</tr>
</tbody>
</table>
### Edge-to-Edge Status and Timing

- Pre-clinical studies completed in 2004, demonstrating repeatable repair performance
- Ongoing feasibility studies in EU and Canada
- Early cases demonstrated procedural feasibility and identified enhancement opportunities
  - Accommodate a broader range of leaflet thickness
  - Enable multiple stitch repairs
- Anticipate completing feasibility study with enhancements in 1H 2006
  - Pivotal trial strategy and timing to be determined
Functional Mitral Valve Disease

- MR caused by ischemic disease or cardiomyopathy
- Enlargement of the heart leads to dilation of the mitral annulus and MR
- Majority of patients are not treated with surgery

Coronary Sinus and Mitral Valve Annulus
Coronary Sinus Repair Procedure

Coronary Sinus Repair System

Location of Implant (Internal)

Sliding Knob

Handle

Bridge

Proximal Anchor

Distal Anchor

Edwards Lifesciences
Coronary Sinus Repair Procedure

Edwards Coronary Sinus System Profile

<table>
<thead>
<tr>
<th>Attribute</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>System size</td>
<td>9F</td>
</tr>
<tr>
<td>Coronary sinus implant</td>
<td>Self-expanding, Nitinol</td>
</tr>
<tr>
<td>Coronary sinus fixation</td>
<td>Self-expanding anchors</td>
</tr>
<tr>
<td>Coronary sinus access</td>
<td>Internal jugular vein or femoral artery</td>
</tr>
<tr>
<td>Visualization and guidance</td>
<td>Standard flouroscopy</td>
</tr>
<tr>
<td>Repair mechanism</td>
<td>Mitral annulus remodeling over 3-4 weeks</td>
</tr>
<tr>
<td>Repair effectiveness</td>
<td>Designed to reduce coronary sinus diameter ~30%</td>
</tr>
</tbody>
</table>
Coronary Sinus Status and Timing

- Pre-clinical feasibility studies completed in 2004, demonstrating consistent MR reduction
- Ongoing OUS feasibility studies
- Early safety and efficacy data were positive
  - Early patient series exposed an implant durability issue
  - Studies resumed with enhanced devices in 4Q 2005
- Early human experience demonstrated safety and sustained MR reduction at 3 and 6 months
- Anticipate completing feasibility study in 1H 2006
  - Pivotal trial strategy and timing to be determined

Percutaneous Mitral Repair Summary

- Large, untreated population degenerating over time
- Two complementary programs
- Promising early results
- 2006 will be an exciting year as we complete feasibility trials and prepare for pivotal studies
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