Surgical Heart Valve Therapies

Anita B. Bessler
Corporate Vice President,
Heart Valve & Cardiac Surgery Systems

Surgical Heart Valve Therapy (HVT)

Executive Summary

- Heart valve market remains attractive
  - Significant opportunity for growth in tissue and repair
  - Acceleration of mechanical decline
- HVT growth is a strategic imperative
  - Increase growth rate of core heart valve business
  - Drive heart valve market expansion
- Investments will drive growth
  - Four new product launches in 2007
  - Sales channel expansion
Edwards is the Global Leader in Heart Valve Therapy

2006 Estimated Global HVT Market ($)

~$1.2 billion
4%-5% growth

Source: Company estimates

Overall Market Growth Remains Steady at 4% - 5% for Total HVT

2006 Estimated Global Market (in Revenue)

Source: Company estimates
Global Valve Procedure Growth is Driven by Aging Population & Earlier Referrals

- >65 years is the fastest growing population
- Improved diagnosis
  - Echocardiography technology
- Earlier referrals
  - Better outcomes with earlier intervention

Source: Company estimates
Edwards Tissue Implant Registry, U.S. Census Bureau, 2004

Significant Opportunity Remains for Global Mechanical to Tissue Conversion

Aortic
~$680M

Mitral
~$520M

Source: 2006 Company estimates
Edwards Lifesciences
Overwhelming clinical evidence
- STS database
- Coumadin warning
- ACC / AHA guidelines
- AHA abstract
- “Why Compromise with Anticoagulation?” campaign

**Edwards to Discontinue Mechanical Valves in 2007**

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Heart Valve Therapy
Edwards Performance Drivers
Growth has been Driven by an Unequaled Tissue Portfolio

PERIMOUNT: #1 in the hearts of the world

A MAGNAture of Performance
A Lasting Improvement
Uncompromised

MAGNA Success

Driven by:
- Superior hemodynamics over other tissue valves
- ThermaFix tissue treatment - enhancing durability
- Built on a proven durability foundation of 20 years

“In patients with an annulus 21mm to 23mm, the Magna was significantly superior to the other investigated devices…” Botzenthardt, et al
**ThermaFix Process:**
Mitigating Structural Valve Deterioration

- First and only process to remove both major calcium binding sites
- Reducing the risk of calcification

*CaCl2 Content - Bovine Pericardial Tissue 150 Day Neonatal Wistar Rat Subcutaneous Implants*

| Glut Only XenoLogiX ThermaFix | Residual Glut + Phospholipid
|---|---|
| 44% Reduction with ThermaFix | 81% Reduction with ThermaFix

**The Legacy Continues**

**PERIMOUNT: #1 in the hearts of the world**

<table>
<thead>
<tr>
<th>Aortic</th>
<th>Mitral</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EU Launch</strong>&lt;br&gt;A MAGNAtude of Performance</td>
<td><strong>U.S. Launch</strong>&lt;br&gt;A Lasting Improvement</td>
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<tr>
<td><strong>U.S. Launch</strong>&lt;br&gt;Uncompromised</td>
<td><strong>PERIMOUNT THEON</strong>&lt;br&gt;PERIMOUNT</td>
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<tr>
<td><strong>PERIMOUNT</strong>&lt;br&gt;Porcine</td>
<td><strong>PERIMOUNT</strong>&lt;br&gt;Porcine</td>
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</table>
Edwards Global Partnering and Growth Initiatives

Edwards Continues to Partner with Surgeons

Surgeon Education

MIS Skills Training

Patient Education

Patient Referral Program

Reimbursement Information

Edwards Lifesciences
Edwards is Addressing Under-Treatment

Patient Referral Program: Four Key Drivers

- Grassroots Program
- Patient Awareness
- Clinician Education
- Build U.S. Database

Edwards is Addressing Under-Treatment

Execution of Planned Initiatives Over Next Three Years Could Expand Market by 1% - 2%

- Target ~10% of the ~15K with addressable causes of under-treatment, spurring market growth
- “Falsely” asymptomatic represent another source of growth

Annual Flow of Symptomatic, Severe Aortic Stenosis Patients

- Surgery
- No Surgery
- High operative risk, prohibitive comorbidities
- Patient refusal
- Age
- Not offered

Other*:

* Other includes those with financial concerns, don't want to live longer, etc.
Source: Internal analysis

Edwards Lifesciences
Edwards Global Prospects Remain Bright

- Driven by an aging population more focused on quality of life
- Accelerating mechanical to tissue conversions
- Innovative, premium-priced products
- Growing recognition of under-treatment
- High competitive barriers to entry

Helping Patients is Our Life’s Work, and
Surgical Heart Valve Therapies
North American Sales & Marketing Initiatives

J. Alex Martin
Corporate Vice President, North America

U.S. Heart Valve Executive Summary

- 2007 growth driven by:
  - Three new product introductions
  - Mechanical shift to tissue
  - Sales channel expansion
  - Surgeon education and referral programs
- Edwards growth impacted by timing of product launches
- Slow but steady success in penetrating the under-treated patient populations
Continued Focus on Accelerating Decline of Mechanical Use

- Overwhelming clinical evidence
  - STS database
  - Coumadin warning
  - ACC / AHA guidelines
  - AHA abstract
- “Why Compromise with Anticoagulation?” campaign

Global Summary: Surgical Heart Valve Therapy

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- Investments will drive growth
  - Four new product launches in 2007
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Aortic Stenosis: Undertreated but Ready for Prime Time

David H. Adams, MD
Marie-Josée and Henry R. Kravis Professor and Chairman
Department of Cardiothoracic Surgery
Mount Sinai Medical Center
New York, NY
Disclosures

David H. Adams, MD
Inventor: Edwards Lifesciences
Consultant: Edwards Lifesciences, 3f

Aortic Valve Stenosis

Rajamanna Circulation 2006; 114; 2007-9
Undertreatment of Aortic Stenosis (AS) remains a challenge: Why?

- Patients are believed to be too old
- Patients thought to be asymptomatic and are actually symptomatic
- Incomplete understanding of morbidity and mortality risk

ACC/AHA Guideline Update 2006
Aortic Stenosis

- Aortic valve replacement (AVR) in virtually all symptomatic patients
- Exercise echocardiography in asymptomatic patients
- Age is not a contraindication to surgery
- Tissue valves indicated for broader use

Bonow et al; JACC 48 (3) 2006
**Aortic Stenosis: Symptoms, Symptoms, Symptoms**

![Graph showing survival rate over age with onset severe symptoms indicated by arrows for Angina, Syncope, and Failure.](Ross J Jr, Braunwald E. Circulation 1968;38 (Suppl 1)

**ACC/AHA Guideline Update 2006 Aortic Stenosis**

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[Bonow et al; JACC 48 (3) 2006]
Exercise Echocardiography in asymptomatic patients

<table>
<thead>
<tr>
<th></th>
<th>Genuinely Asymptomatic</th>
<th>Tested Symptomatic</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>67%</td>
<td>33%</td>
</tr>
<tr>
<td></td>
<td>56%</td>
<td>44%</td>
</tr>
</tbody>
</table>

Das 2005

Peidro 2007

Das et al.; Eur Heart Jnl (26) 2005; Peidro; Cardiology 2007; 108 (4): 258-64

Presence of Symptoms Often Missed without Objective Testing in AS

Presence of Symptoms Often Missed without Objective Testing in AS

In this study, symptoms during exercise testing were superior to clinical history and echocardiography in predicting the imminent onset of spontaneous symptoms. Objective

Das et al. E Heart J 2005; 26: 1309-13
Malignant Natural History of Asymptomatic Severe Aortic Stenosis: Benefit of Aortic Valve Replacement

Ramdas G. Pai, MD, Nikhil Kapoor, MD, Ramesh C. Bansal, MD, and Padmim Varadarajan, MD
Division of Cardiology, Loma Linda University Medical Center, Loma Linda, California

- Aortic valve replacement (AVR) in virtually all symptomatic patients
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Table 3. Independent Predictors of Mortality in all the 338 Patients Using Cox Proportional Hazards Model

<table>
<thead>
<tr>
<th>Variable</th>
<th>RR</th>
<th>95% CI</th>
<th>p Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (per 1 year)</td>
<td>1.03</td>
<td>1.01-1.05</td>
<td>0.0002</td>
</tr>
<tr>
<td>Mitral regurgitation grade 3 or 4</td>
<td>1.8</td>
<td>1.4-2.2</td>
<td>0.004</td>
</tr>
<tr>
<td>Chronic renal insufficiency</td>
<td>2.5</td>
<td>1.9-3.1</td>
<td>0.004</td>
</tr>
<tr>
<td>Accessory use</td>
<td>0.53</td>
<td>0.25-1.10</td>
<td>0.01</td>
</tr>
</tbody>
</table>

Cl = confidence interval; IR = risk ratio.

© 2006 by The Society of Thoracic Surgeons

ACC/AHA Guideline Update 2006
Aortic Stenosis

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Bonow et al; JACC 48 (3) 2006
Misconceptions About Age Prevent Appropriate Patients from AVR

- Those expecting to live for more than 5 years are likely to derive significant benefit from AVR
- For those who survive 6 months after their operation, life expectancy matches that of age-matched controls


Multiple Studies Quantify the Extent of Undertreatment

Severe, Symptomatic AS: Percent of patients treated

<table>
<thead>
<tr>
<th></th>
<th>US</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Untreated</td>
<td>60%</td>
<td>40%</td>
</tr>
<tr>
<td>Surgically treated</td>
<td>30%</td>
<td>70%</td>
</tr>
<tr>
<td>Surgically treated</td>
<td>32%</td>
<td>68%</td>
</tr>
<tr>
<td>Surgery</td>
<td>41%</td>
<td>59%</td>
</tr>
</tbody>
</table>

**Decision-making in elderly patients with severe aortic stenosis: why are so many denied surgery?**

Bernard Jung, Agnès Cochat, Gabriel Barot, David Meuli-Janssen, François Delahaye, Pillar Teruel, Christa Goldie-Biéville, Eric Boerma, Philippe Ravaud, and Nec Yiharia

1 Cardiology Department, Bichat Hospital, AP-HP, 46 rue Henri-Huchard, 75870 Paris, France; and Epidemiology, Biostatistics, and Clinical Research Department, Agnès Cochat, MD, AP-HP, 46 rue Henri-Huchard, 75870 Paris, France.

**Clinical research**

![Diagram](image1)

**Figure:**

- Aortic stenosis ≥45 years
  - No severe AS (n = 124)
  - Severe AS (n = 794)
- No intervention (n = 72, 33%)
- Intervention (n = 144, 67%)
- Decision not to operate (%)
- Decision to operate (%)

**Table:**

<table>
<thead>
<tr>
<th>Charlson comorbidity index</th>
<th>Decision not to operate</th>
<th>Decision to operate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>20%</td>
<td>80%</td>
</tr>
<tr>
<td>1</td>
<td>75%</td>
<td>25%</td>
</tr>
<tr>
<td>2</td>
<td>90%</td>
<td>10%</td>
</tr>
<tr>
<td>3</td>
<td>95%</td>
<td>5%</td>
</tr>
<tr>
<td>&gt;3</td>
<td>99%</td>
<td>1%</td>
</tr>
</tbody>
</table>

**Conclusion:** The results of the present study showed that AVR surgery improves the survival of elderly patients with severe AS, and patients aged >80 years experience benefits similar to younger patients. Nevertheless, these findings suggest that surgery may not always be offered to elderly patients who might benefit from it.

Charlson et al. JHVD 2006; 15: 312-21
ACC/AHA Guideline Update 2006  
Aortic Stenosis

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Bonow et al; JACC 48 (3) 2006
Adverse Events Are Common with Mechanical Valves

INR-Specific Incidence Of All Adverse Events


Mechanical AVR is not Risk Free

Hemorrhage 1-3% / year
Thromboembolic 1-3% / year
Total 2-6% / year

Pericardial Valves are Quite Durable

Impact of Age at Implant

Risk of Explant at 15 years

18%
8%


SVD-Free Curves (AVR) Show
Why Pericardial Valves lead the Market

Mortality Association with Valve Disease is being Redefined

Nkomo et al; Lancet 2006; 368: 1005-11

Otto CM. JACC 2006; 47 (11):2141-51

Lower Threshold for AVR
Editorial

The Evolving Treatment of Aortic Stenosis
Do New Procedures Provide New Treatment Options for the Highest-Risk Patients?

John D. Carroll, MD

Will percutaneous and apical prosthetic aortic valve insertion join hip replacement, cataract surgery, and hearing aids in the armamentarium of techniques and technologies directed at prolonging the life and maintaining the functional status of mature adults? These new techniques in the treatment of severe aortic stenosis represent a significant breakthrough in the treatment options that clinicians may be able to offer to a large number of patients currently sent home to die.

Carroll; Circulation 2006; 114 (6): 533-5

Aortic Stenosis: Ready for Prime Time

As our ability to diagnose and treat AS improves, the market will grow exponentially

STS 2006