Aortic Stenosis: Options for Treatment is Patients at High-Risk for Conventional AVR

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Within the past 12 months, I have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Physician Name</th>
<th>Company/Relationship</th>
</tr>
</thead>
</table>

Disclaimer: “Caution – Percutaneous Aortic Valves are investigational devices, limited by United States to Investigation use only.”
The Aortic Valvar Complex

- Left coronary artery
- Right coronary artery
- Left bundle branch
- Membranous septum
- Non-coronary sinus
- Mitral valve
- Central fibrous body (right fibrous trigone)
- Tricuspid valve
- Atrioventricular node
Normal Aortic Valve: Aortic View
4D Echocardiography: Cubic Spline Reconstruction
Lipid Build-Up in Non Coronary Cusp
Calcific Degenerative Aortic Stenosis

Deformed
Eccentric
Calcified
Nodular
Rigid

HOSTILE TARGET

• Difficult to displace
• Prone to fragmentation and embolization
3 Mensio CT Angiography 4D Reconstruction
Prevalence of Aortic Valve Disease in the Elderly

Cardiovascular Health Study (N = 5201 patients > 65 years)

Aortic Sclerosis, %

- 65-75: 20%
- 75-85: 35%
- 85: 48%

Frank Aortic Stenosis, %

- 65-75: 1.3%
- 75-85: 2.4%
- > 85: 4.0%

**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.

<table>
<thead>
<tr>
<th>Age</th>
<th>Life expectancy for US population</th>
<th>Years</th>
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<tbody>
<tr>
<td>65</td>
<td></td>
<td>18.2</td>
</tr>
<tr>
<td>70</td>
<td></td>
<td>14.7</td>
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<tr>
<td>75</td>
<td></td>
<td>11.5</td>
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<tr>
<td>80</td>
<td></td>
<td>8.8</td>
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<tr>
<td>85</td>
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<td>6.5</td>
</tr>
<tr>
<td>90</td>
<td></td>
<td>4.8</td>
</tr>
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</table>

Aortic Valve Replacement in the Gold Standard For Aortic Stenosis
3.1.7. Indications for Aortic Valve Replacement

Class I

1. AVR is indicated for symptomatic patients with severe AS* (Level of Evidence: B)
2. AVR is indicated for patients with severe AS* undergoing coronary artery bypass graft surgery (CABG). (Level of Evidence: C)
3. AVR is indicated for patients with severe AS* undergoing surgery on the aorta or other heart valves. (Level of Evidence: C)
4. AVR is recommended for patients with severe AS* and LV systolic dysfunction (ejection fraction less than 0.50). (Level of Evidence: C)

Class IIa

AVR is reasonable for patients with moderate AS* undergoing CABG or surgery on the aorta or other heart valves (see Section 3.7 on combined multiple valve disease and Section 10.4 on AVR in patients undergoing CABG). (Level of Evidence: B)
Don’t Mess With the Guidelines – or Surgeons
Are all patients with symptomatic aortic stenosis now being treated with definitive surgical aortic valve replacement?
But 30-60% of AS Patients Go Untreated...

Severe Symptomatic Aortic Stenosis
Percent of Cardiology Patients Treated

Under-treatment especially prevalent among patients managed by Primary Care physicians

Iung B et al European Heart Journal 2003;24:1231-1243 (*includes both Aortic Stenosis and Mitral Regurgitation patients)
Pellikka, Sarano et al Circulation 2005
Better accounting is needed to estimate 30-day surgical risk . . . Top five conditions

- Severe Pulmonary Disease
- Severe Liver Disease (MELD, Childs)
- RV Function and Right Heart Failure
- Frailty (and Cognitive Dysfunction)
- Ilio-Femoral Vascular Disease
Frailty Assessment

Patient A vs. Patient B

Same age and predicted risk
One passes the “eyeball test” – one does not

Frailty is being studied systematically as part of the PARTNER U.S. IDE study

Photos courtesy of Michael J. Mack, MD
Medical City Dallas
Study Devices

Edwards-SAPIEN THV

23mm and 26mm valve sizes

Retroflex 1

22F and 24F sheath sizes
EDWARDS TAVR
Transfemoral and Transapical
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., E. Murat Tuzcu, M.D., John G. Webb, M.D., Gregory P. Fontana, M.D., Raj R. Makkar, M.D., David L. Brown, M.D., Peter C. Block, M.D., Robert A. 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. Petersen, M.D., Jodi J. Akin, M.S., William N. Anderson, Ph.D., Duolao Wang, Ph.D., and Stuart Pocock, Ph.D., for the PARTNER Trial Investigators*
PARTNER B: All Cause Mortality

\[ \Delta \text{ at 1 yr} = 20.0\% \]
NNT = 5.0 pts

Numbers at Risk

<table>
<thead>
<tr>
<th></th>
<th>TAVI</th>
<th>Standard Rx</th>
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<tbody>
<tr>
<td>Months</td>
<td>0</td>
<td>179</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>138</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>122</td>
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<td></td>
<td>6</td>
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<td>8</td>
<td>26</td>
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<td></td>
<td>10</td>
<td>179</td>
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<td></td>
<td>12</td>
<td>121</td>
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<td>14</td>
<td>83</td>
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<tr>
<td></td>
<td>16</td>
<td>41</td>
</tr>
<tr>
<td></td>
<td>18</td>
<td>12</td>
</tr>
</tbody>
</table>
How Much Will “Adding ‘Years to Life’ and ‘Life to Years’” Cost?
PARTNER B TAVR Admission Costs

Mean (median) LOS (days)
- ICU: 4.0 (2.0)
- Non-ICU: 6.1 (5.0)
- Total: 10.1 (7.0)
- Post-Procedure: 8.6 (6.0)

(N=175)

Hospital Costs: $73,563

Index Admission Costs:
- Procedure: $78,540
- Non-Procedural: $30,756
- MD Fees: $4,978
- Total: $42,806

Hospital Costs: $73,563
PARTNER B Results: Observed Survival

Difference in In-Trial Life Expectancy = 0.49 years

Based on data available as of 28SEP2010
PARTNER Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT: High-Risk AVR Candidate
3,105 Total Patients Screened

Total = 1,057 patients

High Risk

N = 699

ASSESSMENT: Transfemoral Access

Yes

Transfemoral (TF)

1:1 Randomization

N = 244

TF TAVR

VS

N = 248

AVR

No

Transapical (TA)

1:1 Randomization

N = 248

N = 248

Primary Endpoint: All-Cause Mortality at 1 yr (Non-inferiority)

Inoperable

N = 358

ASSESSMENT: Transfemoral Access

Yes

Not In Study

N = 179

VS

N = 179

TF TAVR

Standard Therapy

No

AVR

Primary Endpoint: All-Cause Mortality Over Length of Trial (Superiority)

Co-Primary Endpoint: Composite of All-Cause Mortality and Repeat Hospitalization (Superiority)
## PARTNER A: Patient Characteristics (1)

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (N = 348)</th>
<th>AVR (N = 351)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr)</td>
<td>83.6 ± 6.8</td>
<td>84.5 ± 6.4</td>
<td>0.07</td>
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<tr>
<td>Male sex - %</td>
<td>57.8</td>
<td>56.7</td>
<td>0.82</td>
</tr>
<tr>
<td>STS Score</td>
<td>11.8 ± 3.3</td>
<td>11.7 ± 3.5</td>
<td>0.61</td>
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<tr>
<td>Logistic EuroSCORE</td>
<td>29.3 ± 16.5</td>
<td>29.2 ± 15.6</td>
<td>0.93</td>
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<tr>
<td>NYHA</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>II - %</td>
<td>5.7</td>
<td>6.0</td>
<td></td>
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<tr>
<td>III or IV - %</td>
<td>94.3</td>
<td>94.0</td>
<td>0.79</td>
</tr>
<tr>
<td>CAD - %</td>
<td>74.9</td>
<td>76.9</td>
<td>0.59</td>
</tr>
<tr>
<td>Previous MI - %</td>
<td>26.8</td>
<td>30.0</td>
<td>0.40</td>
</tr>
<tr>
<td>Prior CV Intervention - %</td>
<td>72.1</td>
<td>71.6</td>
<td>0.93</td>
</tr>
<tr>
<td>Prior CABG - %</td>
<td>42.6</td>
<td>44.2</td>
<td>0.70</td>
</tr>
<tr>
<td>Prior PCI - %</td>
<td>34.0</td>
<td>32.5</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior BAV - %</td>
<td>13.4</td>
<td>10.2</td>
<td>0.24</td>
</tr>
<tr>
<td>Cerebrovascular disease - %</td>
<td>29.3</td>
<td>27.4</td>
<td>0.60</td>
</tr>
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</table>
PARTNER A: All-Cause Mortality
Transfemoral (N=492)

<table>
<thead>
<tr>
<th>Months</th>
<th>No. at Risk</th>
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<tbody>
<tr>
<td>0</td>
<td>TAVR: 244</td>
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<tr>
<td></td>
<td>AVR: 248</td>
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<tr>
<td>6</td>
<td>TAVR: 215</td>
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<td></td>
<td>AVR: 180</td>
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<td>12</td>
<td>TAVR: 188</td>
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<td>AVR: 168</td>
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<td>18</td>
<td>TAVR: 119</td>
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<tr>
<td></td>
<td>AVR: 109</td>
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<tr>
<td>24</td>
<td>TAVR: 59</td>
</tr>
<tr>
<td></td>
<td>AVR: 56</td>
</tr>
</tbody>
</table>

HR [95% CI] = 0.83 [0.60, 1.15]
P (log rank) = 0.25
Aortic Stenosis: The Substrate
Identifying High-Risk Patients
Sapien (PARTNER Trial)
- Inoperable Cohort B
- High Risk: Cohort A

CoreValve Clinical Program
- National Registries
- US Pivotal Trial
- SURTAVI

Complications
Newer TAVR Designs/Indications
CoreValve Bioprosthesis Frame

Outflow Portion

Constrained Portion
(with leaflets)

Inflow Portion
(with skirt)

1. Sits in ascending aorta
2. Orientation

1. Supra-annular leaflet function
2. Designed to avoid coronaries

1. Intra-annular anchoring
2. Mitigates paravalvular aortic regurgitation

Photograph provided by Piazza, Serruys, and DeJaegere
CoreValve US Trial: Extreme Risk

Medtronic CoreValve U.S. Pivotal Trial

"Extreme Risk" Patient Group

Iliofemoral access?

No

CoreValve Observational Up to 100

CoreValve Single Arm N=487

Yes

Inclusion Criteria

- Degenerative AS
  - Mean gradient > 40 mmHg
  - Jet velocity greater than 4.0 m/s
  - Initial AVA ≤ 0.8 cm²
  - Aortic Valve Area Index ≤ 0.5 cm²/m²
- Co-morbidities such as the probability of procedural death or serious, irreversible morbidity should equal or exceed 50% at 30 days.

Endpoints:

- Primary: All-Cause Mortality + Major Stroke at 12 months (compared to Performance Goal)
- Secondary: MACCE, QoL
- Long-Term Safety and Durability
CoreValve US Pivotal Trial: High Risk

**Inclusion Criteria**
- Degenerative AS
  - Mean gradient > 40 mmHg
  - Jet velocity greater than 4.0 m/s
  - Initial AVA ≤ 0.8 cm²
  - Aortic Valve Area Index ≤ 0.5 cm²/m²
- Estimated surgical mortality > 15% at 30 days

**Endpoints:**
- Primary: All-Cause Mortality at 12 months (non-inferiority)
- Secondary: Pre-specified Hierarchical Testing
- Long-Term Safety and Durability
Overview of Cardiac Complications from PAVI

- Conduction abnormalities
- Arrhythmias
- Aortic regurgitation
- Aortic root rupture with balloon valvuloplasty
- Cardiac tamponade
- Mitral valve impingement
- Coronary artery occlusion
- Prosthetic valve embolization

Cardiac complications
Unanticipated Iliac Rupture
Early and Persistent Intraventricular Conduction Abnormalities and Requirements for Pacemaking After Percutaneous Replacement of the Aortic Valve

Nicolo Piazza, MD,* Yoshinobu Onuma, MD,* Emile Jesserun, MD,* Peter Paul Kint, RN,† Anne-Marie Maugesten, RN,* Robert H. Anderson, MD, FRCPATH;‡ Peter P. Th de Jaegere, MD, PhD,* Patrick W. Serruys, MD, PhD*  

Rotterdam, the Netherlands; and London, United Kingdom

Piazza N JACC: CV Intervention 2008;1;310-316
1. Conduction Abnormalities

Timing during procedure . . .

- Wire crossing
- Pre-implant PABV
- Valve implantation

. . . trauma to conduction tissue


Erasmus MC, Thoraxcenter

TCT 2008
Example of an 82-year-old patient two days after successful TAVI
3. Aortic Regurgitation

Severe calcification limited full circular expansion of the prosthesis

87 year old male - PAVI complicated by severe aortic regurgitation and cardiogenic shock - > surgery

Contemporary registries suggest that TAVI is superior to medical therapy and equivalent (or better) than sAVR in high-risk patients, but selection bias is present → RCTs are needed, particularly in “intermediate-risk” patients

All cause mortality may be problematic due to co-morbidities in elderly patients → cardiovascular death may be better

We need better risk scores to identify patient for TAVI

Ongoing RCTs will likely report higher complication rates (e.g., MI, stroke) due to changing definitions and higher surveillance

Demonstration of device durability and appropriate PPM use will be essential for expanding into younger patients

Broader device availability, reducing profile, and enhancement of delivery system will allow improve patient outcomes