Transcatheter Aortic Valve Replacement

June 2, 2015
6:00-7:00
UVM Community Medical School Series

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Disclosures

• Research grants from Medtronic (Corevalve Trials and Registries), Abbott Vascular

• Consulting for Medtronic, Edwards, Boston Scientific

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Aortic Stenosis is a Disease of A Heart Valve

About the Heart

How the Heart Works
A healthy heart beats approximately 100,000 times a day and pumps about five quarts of blood each minute, or 75 gallons (284 liters) every hour.

A normal heart has four chambers. The upper two chambers are the right and left atria. The lower two chambers are the right and left ventricles. The heart’s job is to supply the body with oxygen-rich blood. Blood is pumped through the four chambers with the help of four heart valves—the tricuspid, pulmonary, mitral and aortic valves.
Aortic Stenosis is not a New Disease: Leonardo Da Vinci
Aortic Stenosis is a Blockage of A Heart Valve which Limits Blood Flow to Your Body

Symptoms of Severe AS
Signs and symptoms of severe AS can include:
- Chest pain or tightness
- Feeling faint or fainting with activity
- Dizziness
- Fatigue
- Shortness of breath
- Irregular heart beat (palpitations)
- Unusual sound heard during a heartbeat (murmur)
Calcific Aortic Stenosis is a Disease of the Elderly

- Mechanism of stenosis is similar to atherosclerosis\(^1\)
  - Mainly solid calcium deposits within the valve cusps
  - Similar risk factors to Coronary Artery Disease (CAD)
  - High coincidence of CAD and AS in same individual\(^2\)
  - 6th, 7th, and 8th decades of life

What Causes Aortic Stenosis in Adults

Less Common

- Congenital Abnormality

More Common

- Rheumatic Fever
- Age-Related Calcific Aortic Stenosis

Images courtesy of John Webb, MD at St. Paul’s Hospital and Renu Virmani, MD at the CVPath Institute
Aortic Stenosis Prevalence

• Aortic Stenosis (AS) is the most prevalent native valve disease

• Prevalence:
  - 2% of people over 65
  - 3% of people over 75
  - 4% of people over 85

• Over 100,000 people in the U.S. are diagnosed with severe aortic stenosis each year

• Prevalence of AS and co-morbidities that increase the risk of surgical valve replacement, increase with age

Over 40 Million People in the US Over the Age of 65$^1$

- Aortic stenosis is estimated to be prevalent in up to 7% of the population over the age of 65$^2$

- Between 1990 and 2020, the population from 65 – 74 years will increase 74%

- 80% of adults with symptomatic aortic stenosis are male$^3$

Source: US Census Bureau, (US Census, 2010)$^1$
Intervention and Life Expectancy of the Elderly

Life Expectancy for U.S. Population

- Those expecting to live for more than 1 year are likely to derive significant benefit from AVR

Severe Aortic Stenosis Is Life Threatening and Progresses Rapidly

- After the onset of symptoms, patients with severe aortic stenosis have a survival rate as low as 50% at 2 years and 20% at 5 years without aortic valve replacement\(^2\)

- The PARTNER Trial demonstrated that 50% of inoperable patients died within 1 year without a valve replacement
Symptoms of Aortic Stenosis

- Shortness of breath
- Angina
- Fatigue
- Syncope or presyncope
- Other
  - Rapid or irregular heartbeat
  - Palpitations

The symptoms of aortic disease are commonly misunderstood by patients as ‘normal’ signs of aging. Many patients initially appear asymptomatic, but on closer examination up to 37% exhibit symptoms.
Aortic Stenosis:
Symptoms May Be Subtle in the Elderly

- Angina, Shortness of Breath and Syncope
- Onset of dyspnea and other heart failure symptoms foretell the worst outlook for aortic stenosis patients

Aortic Stenosis Diagnosis is Not Difficult: Starts with a Heart Murmur on Exam

1Gorlin R, Gorlin SG. Am Heart J 1951; 41: 1-29.
Intensive Lipid Lowering with Simvastatin and Ezetimibe in Aortic Stenosis

Anne B. Rossebø, M.D., Terje R. Pedersen, M.D., Ph.D.,
Kurt Boman, M.D., Ph.D., Philippe Brudi, M.D., John B. Chambers, M.D.,
Kenneth Egstrup, M.D., Ph.D., Eva Gerdts, M.D., Ph.D.,
Christa Gohlke-Bärwolf, M.D., Ingar Holme, Ph.D.,
Y. Antero Kesäniemi, M.D., Ph.D., William Malbecq, Ph.D.,
Christoph A. Nienaber, M.D., Ph.D., Simon Ray, M.D.,
Terje Skjærpe, M.D., Ph.D., Kristian Wachtell, M.D., Ph.D.,
and Ronnie Willenheimer, M.D., Ph.D., for the SEAS Investigators*

Rossebo NEJM 2008
Aortic Valve Surgery: Life Saving Therapy


**Aortic Stenosis is a Fatal Disease**

- Despite frequent BAV, **standard therapy did not alter the dismal course of disease for inoperable patients** in The PARTNER Trial
  - 50% died within 1 year
  - 94% died within 5 years

---

THE PARTNER TRIAL

* In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.

- All-Cause Mortality (%)
  - Control Group (Med Rx and BAV) (n = 179)
  - **93.6%**
  - **87.5%**
  - **80.9%**
  - **68.0%**
  - **50.8%**

- **HR [95% CI] = 0.50 [0.39, 0.65]**
  - p (log rank) < 0.0001
Worse Prognosis than Many Metastatic Cancers

5-Year Survival (Distant Metastasis)

- 5 year survival of breast cancer, lung cancer, prostate cancer, ovarian cancer and severe inoperable aortic stenosis

*Using constant hazard ratio. Data on file, Edwards Lifesciences LLC. Analysis courtesy of Murat Tuczu, MD, Cleveland Clinic
Treatment: Surgical

Surgical treatment of AS may have operative mortality of less than 5%
Studies show at least 40% of severe aortic stenosis (SAS) patients are not treated with an AVR.
Are There Any Other Options? Balloon Aortic Valvuloplasty
Aortic Valvuloplasty: Temporary Benefit Only

Event-free Survival*, n=165

* Freedom from death, AVR, or repeat BAV

What if You Could Implant a New Valve Percutaneously?

The Edwards Sapien Valve
Alain Cribier: First Human Transcatheter Valve Replacement (2002)
Absolute Reduction in Mortality in Inoperable Patients

The Edwards SAPIEN valve significantly improves survival

21.8% absolute reduction in mortality

Despite expert care and frequent BAV, standard therapy failed to alter the dismal natural course of disease

* In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.
## TAVR in Extreme Risk Patients: High Death Rate in Both Arms

### Table. Interventional Cardiology Trials at the Extreme of Mortality

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>SHOCK(^5)</th>
<th>PARTNER B(^\ddagger)</th>
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<tbody>
<tr>
<td>Study design</td>
<td>Randomized clinical trial</td>
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<tr>
<td>Randomized sample size, n</td>
<td>302</td>
<td>358</td>
</tr>
<tr>
<td>Primary end point</td>
<td>Death at 30 d</td>
<td>Death at 1 y</td>
</tr>
<tr>
<td>Expected mortality in control group</td>
<td>75% at 30 d</td>
<td>37.5% at 1 y</td>
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<tr>
<td>Expected impact of novel therapy</td>
<td>20% Absolute reduction in death at 30 d</td>
<td>12.5% Absolute reduction in death at 1 y</td>
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<tr>
<td>Achieved mortality in the novel treatment arm</td>
<td>47% at 30 d</td>
<td>31% at 1 y</td>
</tr>
<tr>
<td>Primary end point achieved</td>
<td>No</td>
<td>Yes</td>
</tr>
<tr>
<td>Key secondary end point</td>
<td>Significant mortality reduction with early revascularization at 6-mo follow-up</td>
<td>Significant mortality reduction with TAVR persisting for 3 y</td>
</tr>
<tr>
<td>Exploratory subgroup analyses</td>
<td>No benefit of early revascularization in the elderly</td>
<td>No benefit of TAVR in patients with STS score &gt; 15%</td>
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<tr>
<td>Subsequent or planned confirmatory trials</td>
<td>No</td>
<td>No</td>
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Transcatheter Aortic Valve Replacement: Process
Transcatheter Aortic Valve Replacement: Process
Corevalve: All Cause Mortality or Major Stroke

* Calculated rate for 117 events in 179 patients (65.4%, lower confidence bound of 57.9% by Exact method) (Makkar RR, et al, New Engl J Med, 2012)
Quality of Life Improvement 2 Years after Corevalve Extreme Risk TAVR

92% of Patients Improved at Least 1 NYHA Class by 2 Years
58% of Patients Improved at Least 2 NYHA Classes by 2 Years

93%
Corevalve High Risk Trial

As-Treated Population
N=750

Underwent Attempted TAVR
N=391

1-Year TAVR
N=323/328
(98.5%)

Died-28
Exited-3
Pending follow-up-2

2-Year TAVR
N=278/295
(94.2%)

Underwent Attempted SAVR
N=359

1-Year SAVR
N=265/281
(94.3%)

Died-31
Exited-13

2-Year SAVR
N=221/237
(93.2%)
TAVR Superior to Surgical AVR: Corevalve High Risk Trial

Log-rank $P=0.04$

Reardon, ACC 2015
Complications Associated with TAVR

- Stroke (major, minor)
- Paravalvular leak
- Conduction System Abnormalities
- Vascular Access Complications
- Valve Embolization and Malposition

24 Hours SICU Stay
## PARTNER High Risk: Stroke

<table>
<thead>
<tr>
<th>Outcome</th>
<th>30 Days</th>
<th>1 Year</th>
<th>p-value</th>
<th>30 Days</th>
<th>1 Year</th>
<th>p-value</th>
</tr>
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<tr>
<td><strong>TAVR (N = 348)</strong></td>
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<tr>
<td>All Stroke or TIA – no. (%)</td>
<td>19 (5.5)</td>
<td>8 (2.4)</td>
<td>0.04</td>
<td>27 (8.3)</td>
<td>13 (4.3)</td>
<td>0.04</td>
</tr>
<tr>
<td>TIA – no. (%)</td>
<td>3 (0.9)</td>
<td>1 (0.3)</td>
<td>0.33</td>
<td>7 (2.3)</td>
<td>4 (1.5)</td>
<td>0.47</td>
</tr>
<tr>
<td>All Stroke – no. (%)</td>
<td>16 (4.6)</td>
<td>8 (2.4)</td>
<td>0.12</td>
<td>20 (6.0)</td>
<td>10 (3.2)</td>
<td>0.08</td>
</tr>
<tr>
<td>Major Stroke – no. (%)</td>
<td>13 (3.8)</td>
<td>7 (2.1)</td>
<td>0.20</td>
<td>17 (5.1)</td>
<td>8 (2.4)</td>
<td>0.07</td>
</tr>
<tr>
<td>Minor Stroke – no. (%)</td>
<td>3 (0.9)</td>
<td>1 (0.3)</td>
<td>0.34</td>
<td>3 (0.9)</td>
<td>2 (0.7)</td>
<td>0.84</td>
</tr>
<tr>
<td>Death/maj stroke – no. (%)</td>
<td>24 (6.9)</td>
<td>23 (8.2)</td>
<td>0.52</td>
<td>92 (26.5)</td>
<td>93 (28.0)</td>
<td>0.68</td>
</tr>
</tbody>
</table>
Corevalve High Risk Trial: Stroke

- **Surgical**
  - 4.9% at 12 months
- **Transcatheter**
  - 8.8% at 12 months

**No. at Risk**
- Surgical: 357, 322, 274, 249
- Transcatheter: 390, 363, 334, 314

Log-rank $P = 0.10$
CoreValve U.S. Pivotal Trial High Risk Study
Low Rate of Leaky Valve (Paravalvular Leak)

The Product:
Conforming Frame
The CoreValve Nitinol frame conforms and seals to the non-circular annulus

The Proof:
Low Rates of Moderate/Severe PVL
The CoreValve device demonstrates low moderate and severe paravalvular leak rates

UVM Volume Growth of TAVR

Quarterly Volume of TAVR Patients

Research Phase

Clinical Service

Patient Volume Per Quarter

Q1 2012
Q2 2012
Q3 2012
Q4 2012
Q1 2013
Q2 2013
Q3 2013
Q4 2013
Q1 2014
Q2 2014
Q3 2014
Q4 2014*

Q4 2014*
The Edwards SAPIEN XT Transcatheter Heart Valve, model 9300TFX, systems are indicated for relief of aortic stenosis in patients with **symptomatic heart disease due to severe native calcific aortic stenosis** (aortic valve area ≤ 1.0 cm² or aortic valve area index ≤ 0.6 cm²/m², a mean aortic valve gradient of ≥ 40 mmHg, or a peak aortic-jet velocity of ≥ 4.0 m/s), and with native anatomy appropriate for the 23, 26, or 29 mm valve system, who are judged by a heart team, including a cardiac surgeon, to be at **high or greater risk for open surgical therapy** (i.e., Society of Thoracic Surgeons operative risk score ≥ 8% or at a ≥ 15% risk of mortality at 30 days).
Selecting the Right Patients: Aortic Annulus and CT Angio/Echo

<table>
<thead>
<tr>
<th>Computed Tomography</th>
<th>Echocardiogram</th>
<th>Aortogram</th>
</tr>
</thead>
<tbody>
<tr>
<td>[CT Image]</td>
<td>[Echo Image]</td>
<td>[Aortogram Image]</td>
</tr>
</tbody>
</table>

Photographs courtesy of Nicolo Piazza, MD
Patient Evaluation at Heart Valve Clinic

Example of Testing Conducted at a Heart Valve Clinic

- CT Scan
- Echo
- Labs
- EKG
- Physical Exam
- STS Score
- Independent Living
- Gait Test/Grip Strength
- MMSE2
- NY Heart Failure Class
- Catheterization
Prevalence of frailty increases with aging; old does not necessarily equal frail

Elderly patients achieve measurable benefit from cardiac surgery, particularly in terms of:
- Quality of life
- Increased survival
- Prevention of adverse cardiovascular events

The “Eyeball Test”: Nursing Home, Wheel Chair, Frequent Falls?

Same age (90) and predicted risk (12%)
One passes the “eyeball test,” one does not
Multidisciplinary approach ensures:

- Patient centric care
- Thorough assessment by a team of specialists
- Collaborative treatment decision

UVM TAVR Coordinator: Faye Straight, RN
Faye.straight@uvmhealth.org
Anatomic Features Important for TAVR Sizing

**Primary Features:**
- The aortic annulus
- The sinuses of Valsalva
- The ascending aorta

**Secondary Features:**
- Coronary artery ostia
- Left ventricular outflow tract (LVOT)
Choosing Appropriate Patients:
Vascular Access via CT angiography

Dimensional Analysis

• Measure both left and right iliac and femoral artery axial views to identify minimum diameters

• Measure and record both minimum (minor) and orthogonal (perpendicular) diameters
Direct Aortic Approach Delivery Trajectory

Identify desired access location and pathway
TAVR Has Real Risks
### Reduction in Vascular Complications:

**Next Generation TAVR Devices**

<table>
<thead>
<tr>
<th>Events</th>
<th>SAPIEN</th>
<th>SAPIEN XT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n=271)</td>
<td>(n=282)</td>
</tr>
<tr>
<td>Vascular:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>43</td>
<td>32</td>
</tr>
<tr>
<td></td>
<td>15.9</td>
<td>11.3</td>
</tr>
<tr>
<td>Bleeding:</td>
<td></td>
<td></td>
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<tr>
<td>Disabling</td>
<td>34</td>
<td>22</td>
</tr>
<tr>
<td></td>
<td>12.6</td>
<td>7.8</td>
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</table>

**Major vascular complications reduced by 25% with next generation device**

*PARTNER II Trial Cohort B - Incidence data for this figure only contains data from 23 mm and 26 mm valve sizes and does not include 29 mm.*
# Corevalve Randomized Trial Complications

<table>
<thead>
<tr>
<th>Events*</th>
<th>1 Month</th>
<th>1 Year</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
</tr>
<tr>
<td>Vascular complications (major), %</td>
<td>5.9</td>
<td>1.7</td>
</tr>
<tr>
<td>Pacemaker implant, %</td>
<td>19.8</td>
<td>7.1</td>
</tr>
<tr>
<td>Bleeding (life threatening or disabling), %</td>
<td>13.6</td>
<td>35.0</td>
</tr>
<tr>
<td>New onset or worsening atrial fibrillation, %</td>
<td>11.7</td>
<td>30.5</td>
</tr>
<tr>
<td>Acute kidney injury, %</td>
<td>6.0</td>
<td>15.1</td>
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*Percentages reported are Kaplan-Meier estimates and log-rank P values

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High Risk Study | US Pivotal Trial
Real World SAPIEN Valve Outcomes

30 day STS/ACC TVT Registry Data (Nov 2011 - May 2013):
- 7,710 patients treated at 224 centers
- Median Age of 84
- Patient Risk Profile
  - 20% Inoperable / 80% High-Risk

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<thead>
<tr>
<th>Outcomes (In Hospital)</th>
<th>Overall (n=7,710)</th>
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<tr>
<td>Death (Any Cause)</td>
<td>5.5%</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.0%</td>
</tr>
<tr>
<td>Moderate or Severe Aortic Insufficiency</td>
<td>8.5%</td>
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<tr>
<td>Major Bleeding (VARC)</td>
<td>3.5%</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>6.6%</td>
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<tr>
<td>Hospital Duration, Median Days</td>
<td>6</td>
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## Executive Summary

**TVT Registry™**
The University of Vermont Medical Center (186373) compared to Rolling Four Quarters (R4Q) for US Hospitals ending 2014Q4

### Section I: Transcatheter Aortic Valve Replacement (TAVR) Quality Metrics

<table>
<thead>
<tr>
<th>TAVR Outcome Metrics (In-hospital) - Mortality</th>
<th>Distribution of Hospital Performance</th>
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<tbody>
<tr>
<td><strong>Mortality Rate – In Hospital Observed (UNADJUSTED)</strong></td>
<td>10th percentile</td>
</tr>
<tr>
<td>My Hospital</td>
<td>US Hospitals 50th Pctl</td>
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<tr>
<td>1.9%</td>
<td>3.6%</td>
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<tr>
<td>Your hospital’s in-hospital observed, (unadjusted), all-cause mortality rate for all patients. [Detail Line:1500]</td>
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In the absence of serious comorbid conditions, aortic valve replacement (AVR) is indicated in the majority of symptomatic patients with severe aortic stenosis.

Because of the risk of sudden death, AVR should be performed promptly after the onset of symptoms.

Consultation with or referral to a Heart Valve Center of Excellence is reasonable when discussing treatment options for:
- Asymptomatic patients with severe valvular heart disease
- Patients with multiple comorbidities for whom valve intervention is considered.

Age is not a contraindication to surgery.

If surgery is contraindicated, TAVR recommended (extreme risk patients).

If patient is high risk for surgery, TAVR is a reasonable option.

Valve in Valve TAVR: A Growing Indication
CoreValve is Indicated for Symptomatic Patients with a Failed Surgical Bioprosthetic Aortic Valve

The Medtronic CoreValve™ system is indicated for use in patients with symptomatic heart disease due to either severe native calcific aortic stenosis or failure (stenosed, insufficient, or combined) of a surgical bioprosthetic aortic valve who are judged by a heart team, including a cardiac surgeon, to be at high or greater risk for open surgical therapy (i.e., Society of Thoracic Surgeons operative risk score ≥8% or at a ≥15% risk of mortality at 30 days).
Mortality in Lower Risk Patients: STS ≤7%: Corevalve High Risk Trial

![Graph depicting mortality rates for Transcatheter and Surgical procedures over time.]

- Transcatheter:
  - Months Post-Procedure:
    - 0: 14.0%
    - 6: 10.4%
    - 12: 26.3%
    - 18: 15.0%
    - 24: 26.3%
  - Log-rank P = 0.01
- Surgical:
  - Months Post-Procedure:
    - 0: 10.4%
    - 6: 7.1%
    - 12: 14.0%
    - 18: 10.4%
    - 24: 15.0%

No. at Risk:
- Transcatheter: 202, 197, 191, 182, 128
- Surgical: 181, 174, 161, 151, 93
Ongoing UVM Research: CoreValve® SURTAVI Trial
Revised Enrollment: 3% or higher risk per CT surgeon.

- Evaluate the safety and efficacy of TAVI in Subjects with severe, symptomatic AS at intermediate surgical risk by randomizing Subjects to either SAVR or TAVI with the Medtronic CoreValve® System.

- Enrolling approximately 2,500 Subjects randomized 1:1 to TAVI and SAVR in up to 75 European, Canadian, and US centers.
TAVR: A 10 Year Story of Technology and Treatment

- **First successful TAVR procedure in US**
- **Landmark PARTNER clinical trials begin**
- **Edwards SAPIEN heart valve approved for inoperable patients**
- **Edwards SAPIEN heart valve approved for high-risk patients**
- **Corevalve FDA Approval Extreme and High Risk Patients**

**Timeline:**
- **2005:** Edwards SAPIEN Heart Valve
- **2007:** Medtronic Corevalve

**Key Events:**
- **2005:** First successful TAVR procedure in US
- **2007:** Landmark PARTNER clinical trials begin
- **2011:** Edwards SAPIEN heart valve approved for inoperable patients
- **2012:** Edwards SAPIEN heart valve approved for high-risk patients
- **2014:** Corevalve FDA Approval Extreme and High Risk Patients
TAVR Conclusions:
Evolution of a Minimally Invasive Option

- Aortic Stenosis is a fatal disease of the elderly
- TAVR saves lives in patients with no surgical option or at high risk for open heart surgery.
- TAVR technology is evolving to address small but real risk of complications including stroke and bleeding.
- Next steps: TAVR in lower risk patients, TAVR in two days.