Asymptomatic Severe Aortic Stenosis

Torsten Vahl, MD

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Cardiovascular Research Foundation
New York City
Disclosure Statement of Financial Interest

I, Torsten Vahl, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
History

84 yoM with

- HTN
- Hodgkins Lymphoma in remission
- CAD s/p 3-vessel CABG 2003
- Severe Aortic Stenosis
  Referred for TAVR evaluation for increase in PV to 4.2 m/s compared with 3.6 m/s 6 months ago. Patient denies any CP, SOB or syncope but family and cardiologist concerned that patient is less active than before.
<table>
<thead>
<tr>
<th>Echo Variable (TTE/TEE)</th>
<th>Measure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jet Velocity</td>
<td>4.2 m/s</td>
</tr>
<tr>
<td>Mean Gradient</td>
<td>40.7 mmHg</td>
</tr>
<tr>
<td>Calculated AVA</td>
<td>0.7 cm²</td>
</tr>
<tr>
<td>Calculated AVA index</td>
<td>0.4 cm²/m²</td>
</tr>
<tr>
<td>TTE/TEE annulus diameter</td>
<td>25.3 mm</td>
</tr>
<tr>
<td>Ejection Fraction</td>
<td>60%</td>
</tr>
<tr>
<td>Severity of AR</td>
<td>Trace</td>
</tr>
<tr>
<td>Severity of MR</td>
<td>Mild</td>
</tr>
</tbody>
</table>
Stress Echo: 3:53 min Bruce protocol (5.6 METS), expected 6:35 min, stopped due to SOB, no CP
Rest BP 134/80, HR 56  Peak BP 154/64 HR 115
Inferior Hypokinesis, no evidence of ischemia
Coronary Angiogram
Coronary Angiogram
CT Angio
TAVR with 26 mm Sapien 3 valve
Asymptomatic Severe Aortic Valvular Stenosis: Diagnostic Approaches and Therapeutic Strategies

MARTIN B. LEON, MD & TORSTEN VAHL, MD

COLUMBIA UNIVERSITY MEDICAL CENTER & NY PRESBYTERIAN HOSPITAL
Disclosure Statement of Financial Interest
ACC NY CV, New York City; Dec 9 – 11, 2016

Martin B. Leon, MD

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

<table>
<thead>
<tr>
<th>Affiliation / Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant / Research Support</td>
<td>Abbott, Boston Scientific, Edwards Lifescience, Medtronic, St. Jude Medical</td>
</tr>
<tr>
<td>Consulting Fees / Honoraria</td>
<td>Abbott, Boston Scientific</td>
</tr>
<tr>
<td>Shareholder / Equity</td>
<td>Claret, Valve Medical</td>
</tr>
</tbody>
</table>
Asymptomatic Severe AS

Background
Aortic Stenosis

By John Ross, Jr., M.D. and Eugene Braunwald, M.D.

Natural Hx of AS = Medical Dogma!
The most revered and cited image in all of cardiovascular medicine!

Circulation 1968;38:1S5 V-61-V-67
Aortic Stenosis

By John Ross, Jr., M.D. and Eugene Braunwald, M.D.

Based upon a handful of hastily gathered post-mortem clinical case studies in younger patients with usually rheumatic or congenital valvular aortic stenosis.
PARTNER 1B – RCT of Symptomatic Severe AS (inoperable patients)
TAVR vs. Standard Medical Therapy (n = 358 patients; 5-year follow-up)

50% all-cause mortality at 1 year
Prospective validation of the dire prognosis of “untreated” symptomatic severe aortic stenosis

Aortic Stenosis

By John Ross, Jr., M.D. and Eugene Braunwald, M.D.

Based upon a handful of hastily gathered post-mortem clinical case studies in younger patients with usually rheumatic or congenital valvular aortic stenosis.
Currently, the most vexing management issues in caring for AS patients are:

1. Asymptomatic severe AS
2. Low flow – low gradient AS
Asymptomatic Severe AS

Guidelines and Practice
Recommendations and Levels of Evidence for Diagnosis, Follow-up, and Timing of Aortic Valve Replacement in Patients With Asymptomatic Severe Aortic Stenosis

<table>
<thead>
<tr>
<th>Indications for aortic valve replacement</th>
<th>ACC/AHA</th>
<th>ESC/EACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left ventricular ejection fraction &lt;50%</td>
<td>I, B</td>
<td>I, C</td>
</tr>
<tr>
<td>Undergoing other cardiac surgery</td>
<td>I, B</td>
<td>I, C</td>
</tr>
<tr>
<td>Symptoms on exercise test clearly related to aortic stenosis</td>
<td>I, B</td>
<td>I, C</td>
</tr>
<tr>
<td>Decreased exercise tolerance</td>
<td>Ila, B</td>
<td>Ila, C</td>
</tr>
<tr>
<td>Exercise fall in systolic blood pressure</td>
<td>Ila, B</td>
<td>Ila, C</td>
</tr>
<tr>
<td>Very severe AS (PV ≥ 5.0 m/s [ACC]; &gt;5.5m/s [ESC] and low surgical risk)</td>
<td>Ila, B</td>
<td>Ila, C</td>
</tr>
</tbody>
</table>

**3 Class I indications...3 Class IIa indications...**

**Level of evidence B or C**

**No Randomized Trials!**

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>ACC/AHA</th>
<th>ESC/EACTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Echocardiography every 6-12 months</td>
<td>1, C</td>
<td>-</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; EACTS = European Association for Cardio-Thoracic Surgery; European ESC = European Society of Cardiology
ACC/AHA and ESC/EACTS Guidelines

Asymptomatic Severe AS
MG≥40mmhg, AVA≤ 1.0 cm² and EF >50%

Exercise Testing (ACC/AHA Class IIa)

PV ≥5m/s (ACC/AHA) or ≥5.5m/s (ESC): Class IIa
PV progression≥0.3m/s/year: ACC/AHA IIb and ESC Class IIa
Severe LVH: ESC Class IIb
Repeatedly markedly elevated BNP: ESC Class IIb

PV ≥5m/s (ACC/AHA) or ≥5.5m/s (ESC): Class IIa
PV progression≥0.3m/s/year: ACC/AHA IIb and ESC Class IIa
Severe LVH: ESC Class IIb
Repeatedly markedly elevated BNP: ESC Class IIb

Limiting Symptoms
Angina
Syncope
Dyspnea

Decrease exercise tolerance
Abnormal SBP response (drop or <20mmhg rise)

ACC/AHA Class I
ESC Class I
ACC/AHA Class IIa
ESC Class IIa
ESC Class IIb

Exercise Imaging (ACC/AHA class IIa)

Increase in MG with exercise by >20 mm Hg

If Stress Test and Stress Echo Normal:
Clinical and Echo follow-up 6-12 months - ACC/AHA Class I

Nishimura et al. J Am Coll Cardiol. 2014; 63(22):e57-185
“In severe AS, an exercise test was performed in only 5.7% of patients with no symptoms...”

“This under-use may be explained by an insufficient implementation of the current guidelines and fear of complications or inexperience in exercise testing...”
Why Early SAVR in Asymptomatic Severe AS is Rarely Performed?

Sudden Death with Asymptomatic AS

\[ \sim 1-2\% \text{ per year} \]

Peri-operative Mortality with Surgery

\[ \sim 1-5\% \]

The dominant strategy is watchful waiting (active surveillance)!
Practical Issues with “Watchful Waiting” Strategy

- Clinicians still fear stress tests with severe AS patients; low penetration and underused
- Stress Imaging requires expertise and specific set-up that most community hospitals don’t have
- Sub-optimal follow-up and lost of follow-up is frequent
- Many sudden deaths occurred in Asx patients with no Class I indication of AVR and no preceding symptoms

- “Wishful Thinking” Strategy...
Why Early SAVR in Asymptomatic Severe AS is Rarely Performed?

Sudden Death with Asymptomatic AS

~1-2% per year

Peri-operative Mortality with Surgery

~1-5%

Is TAVR a better option for asymptomatic patients?
Sapien 3 TAVR

Mortality and Stroke: S3i
At 30 Days (As Treated Patients)

Mortality

- All-Cause
- Cardiovascular

Stroke

- All Stroke
- Disabling

O:E = 0.21
(STS 5.3%)

1.1 0.9

2.6 1.0

Kodali S et al. European Heart J 2016
## Asymptomatic Severe AS: **Rationale for Early AVR**

### Pros
- Reduces irreversible myocardial dysfunction
- Decreased operative risk for asymptomatic patients
- Presence of latent symptoms; AS progression highly variable; potential for very rapid deterioration; risk of late (or too late) symptom reporting
- Increasing STS with time... increases surgical risk
- Sudden death without preceding symptoms

### Cons
- Mortality low among the specific subset of low-risk and truly asymptomatic patients with normal stress test and stress echo
- Frequent follow-up could potentially identify patients ready for AVR in a timely fashion
- Inherent procedural mortality and morbidities of AVR
- Long-term complications of AVR (anticoagulation, need for re-op, endocarditis, thrombosis, etc.)
Asymptomatic Severe AS

Prognosis
(natural history)
What is the Epidemiology of Asx Severe AS Patients?

- **~40-50% of all severe AS from major echo databases** \(^1,2,3\)
  - ~10-20% are bicuspid
  - ~20-25% have multiple valve disease, clinically significant CAD, prior AVR

- **Isolated Asymptomatic Severe AS represents ~25-30%** of all severe AS referred to echo lab

- ~500,000 patients > 65 years old in US\(^4\)

\(^1\) Pellikka et al. Circulation. 2005;111:3290-3295
\(^3\) Kitai et al. Heart 2011;97:2029e2032
\(^4\) Source U.S. Census Bureau, 2014
Asymptomatic Severe AS

Natural History, Diagnostic Approaches,

ABSTRACT

Aortic stenosis (AS) is one of the most common valvular diseases encountered in clinical practice. Current guidelines recommend aortic valve replacement (AVR) when the aortic valve is severely stenotic and the patient is symptomatic; however, a substantial proportion of patients with severe AS are asymptomatic at the time of first diagnosis. Although specific morphological valve features, exercise testing, stress imaging, and biomarkers can help to identify patients with asymptomatic severe AS who may benefit from early AVR, the optimal management of these patients remains uncertain and controversial. The current report presents a comprehensive review of the natural history and the diagnostic evaluation of asymptomatic patients with severe AS, and is followed by a meta-analysis from reported studies comparing an early AVR strategy to active surveillance, with an emphasis on the level of evidence substantiating the current guideline recommendations. Finally, perspectives on directions for future investigation are discussed. (J Am Coll Cardiol 2016;67:2263-88) © 2016 by the American College of Cardiology Foundation.
What is the Prognosis of Asx Severe AS Patients?

**Systematic Review and Meta-Analysis**

- MEDLINE, Embase, and Cochrane Central Register of Controlled Trials
- Severe AS asymptomatic patients
- >18 years old and reporting outcomes
- 503 articles
- 27 pertenent observational studies identified
- **4 studies with observational comparison of AVR vs. Medical treatment; N= 2,486 patients**
## Studies Comparing AVR vs. Observation in Asymptomatic Severe AS Patients; N=2,486

<table>
<thead>
<tr>
<th>Authors</th>
<th>AS definition</th>
<th>N</th>
<th>Age</th>
<th>Female</th>
<th>Follow-up (median)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellikka et al. 1990</td>
<td>Severe AS; Doppler PV ≥4m/s</td>
<td>143</td>
<td>72 (mean)</td>
<td>38%</td>
<td>AVR 21 m Medical 20 m</td>
</tr>
<tr>
<td></td>
<td></td>
<td>30 AVR</td>
<td>40 to 94</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>113 Medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pai et al. 2006</td>
<td>Severe AS AVA &lt;0.8cm²</td>
<td>338</td>
<td>71 ± 15</td>
<td>49%</td>
<td>3.5 y</td>
</tr>
<tr>
<td></td>
<td>Very severe AS AVA ≤0.75 cm² AND PV ≥4.5 m/s or a MG ≥50 mmHg</td>
<td>197</td>
<td>63 ± 12</td>
<td>50%</td>
<td>AVR 1265 d Medical 1769 d</td>
</tr>
<tr>
<td></td>
<td></td>
<td>102 AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>239 Medical</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Kang et al. 2010</td>
<td></td>
<td>1808:</td>
<td>71.6±8.7</td>
<td>60%</td>
<td>1361 d</td>
</tr>
<tr>
<td></td>
<td>Severe AS AVA: &lt;1cm²</td>
<td>291</td>
<td>77.8±9.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>MG: &gt;40mmHg</td>
<td>1517</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>PV: &gt;4m/s</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Taniguchi et al. 2015</td>
<td></td>
<td>AVR</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
# Sudden Death in Asx Severe AS

<table>
<thead>
<tr>
<th>Studies</th>
<th>Sudden death (n)</th>
<th>Preceded by symptoms (n)</th>
<th>Not preceded by symptoms (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Pellikka et al. 1990 n=143</em></td>
<td>3</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Rosenheck et al. 2000; n=128</td>
<td>1</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Amato et al. 2001; n=66</td>
<td>4</td>
<td>-</td>
<td>4</td>
</tr>
<tr>
<td>Lancellotti et al 2005; n=69</td>
<td>2</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td><em>Pellikka et al. 2005; n=622</em></td>
<td>11</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Avakian et al. 2008; n=133</td>
<td>7</td>
<td>3</td>
<td>4</td>
</tr>
</tbody>
</table>

~0.8% pts w Sudden death per year; Among all the Sudden Deaths, 73% (32/44) pts had no classical preceding AS symptoms

Levy et al. 2014; n=43 0

*6 cardiac deaths occurred: 1 sudden without symptoms and 5 cardiac but with patients asymptomatic at the last follow-up
Abnormal Stress Tests in Asx Severe AS

<table>
<thead>
<tr>
<th>Study</th>
<th>Moderate-Severe AS</th>
<th>Severe AS only</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>% Abnormal Stress Test</td>
<td>n</td>
</tr>
<tr>
<td>Takeda et al. 2001</td>
<td>27%</td>
<td>13</td>
</tr>
<tr>
<td>Amato et al. 2001</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Alborino et al. 2002</td>
<td>60%</td>
<td>18</td>
</tr>
<tr>
<td>Das et al. 2003</td>
<td>29%</td>
<td>19</td>
</tr>
<tr>
<td>Das et al. 2005</td>
<td>37%</td>
<td>46</td>
</tr>
</tbody>
</table>

Abnormal Stress Test in Asx Severe AS:

Range: 26-67%

~50% pts have Abnormal Stress Test

<table>
<thead>
<tr>
<th>Study</th>
<th>Moderate-Severe AS</th>
<th>Severe AS only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rajani et al. 2010</td>
<td>15%</td>
<td>3</td>
</tr>
<tr>
<td>Donal et al. 2011</td>
<td>33%</td>
<td>69</td>
</tr>
<tr>
<td>Levy et al. 2014</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total

<table>
<thead>
<tr>
<th>% Abnormal Stress test</th>
<th>Range: 15-66%</th>
<th>Pooled: 36.5%</th>
<th>Range: 28-67%</th>
<th>Pooled: 48.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>286</td>
<td>784</td>
<td>212</td>
<td>434</td>
</tr>
</tbody>
</table>
Abnormal stress test associated with 
~6 fold increase in Cardiac Death

Meta-Analysis of Prognostic Value of Stress Testing in Patients With Asymptomatic Severe Aortic Stenosis

Asim M. Rafique, MD, Simon Biner, MD, Indraneil Ray, MD, James S. Forrester, MD, Kirsten Tolstrup, MD, and Robert J. Siegel, MD

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Normal Stress Test</th>
<th>Abnormal Stress Test</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peidro 2007</td>
<td>0/35</td>
<td>2/67</td>
<td>32.2%</td>
<td>0.37 [0.02, 7.90]</td>
</tr>
<tr>
<td>Lancellotti 2005</td>
<td>0/43</td>
<td>3/26</td>
<td>33.5%</td>
<td>0.08 [0.00, 1.56]</td>
</tr>
<tr>
<td>Das 2005</td>
<td>0/79</td>
<td>0/46</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amato 2001</td>
<td>0/22</td>
<td>4/44</td>
<td>34.3%</td>
<td>0.20 [0.01, 3.89]</td>
</tr>
<tr>
<td>Total</td>
<td>0/179</td>
<td>9/183</td>
<td>100.0%</td>
<td>0.18 [0.03, 1.01]</td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 0.52, df = 2 (P = 0.77); I² = 0%
Test for overall effect: Z = 1.95 (P = 0.05)
Abnormal stress test associated with 
~8 fold increase in CV Events
All-Cause Mortality
AVR vs. Medical Therapy in Asymptomatic Severe AS; \( N=2486 \)

<table>
<thead>
<tr>
<th>Study</th>
<th>Early AVR</th>
<th>Observation</th>
<th>Risk Ratio M-H Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pellikka et al. (17)</td>
<td>2</td>
<td>14</td>
<td>0.54 [0.13, 2.24]</td>
</tr>
<tr>
<td>Pai et al. (19)</td>
<td>10</td>
<td>147</td>
<td>0.16 [0.09, 0.30]</td>
</tr>
<tr>
<td>Kang et al. (25)</td>
<td>3</td>
<td>10</td>
<td>0.28 [0.08, 0.98]</td>
</tr>
<tr>
<td>Taniguchi et al. (26)</td>
<td>40</td>
<td>542</td>
<td>0.38 [0.29, 0.52]</td>
</tr>
</tbody>
</table>

Total (95% CI) 522 1964 100% 0.29 [0.17, 0.51]
Total events 55 713

Heterogeneity: \( \tau^2 = 0.16; \chi^2 = 6.91, \text{df} = 3 \) (\( P = 0.07 \)); \( I^2 = 57\%

Test for overall effect: \( Z = 4.35 \) (\( P < 0.0001 \))

Unadjusted: ~3.5 fold increase in All-Cause Mortality
All-Cause Mortality

AVR vs. Medical Therapy in Asymptomatic Severe AS; N=2,486

Adjusted: ~3.7 fold increase in All-Cause Mortality
Evaluation of Initial Surgical Versus Conservative Strategies in Patients With Asymptomatic Severe Aortic Stenosis:
-Results from the CURRENT AS registry-

Tomohiko Taniguchi, MD
Kyoto University Graduate School of Medicine

Main Analysis Set:
Propensity-score Matched Cohort

3815 consecutive patients with severe AS
(Jan 2003 - Dec 2011, 27 centers in Japan)
- Peak aortic jet velocity >4.0m/s
- Mean aortic pressure gradient >40mmHg
- Aortic valve area <1.0cm²

Symptomatic
2005 patients
- Initial AVR group
  905 patients
- Conservative group
  1100 patients

Asymptomatic
1808 patients
- Initial AVR group
  291 patients
- Conservative group
  1517 patients

Unknown symptomatic status: 2 patients

Primary outcome measure
All-cause death

Conservative group

Initial AVR group

Crude HR 0.60 (0.40-0.88), P=0.009
Adjusted HR 0.64 (0.42-0.94), P=0.02
Log-rank P=0.009

<table>
<thead>
<tr>
<th>Interval</th>
<th>0d</th>
<th>30d</th>
<th>1y</th>
<th>3y</th>
<th>5y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of patients with at least 1 event</td>
<td>3</td>
<td>20</td>
<td>48</td>
<td>60</td>
<td></td>
</tr>
<tr>
<td>N of patients at risk</td>
<td>291</td>
<td>279</td>
<td>252</td>
<td>178</td>
<td>72</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>1.1%</td>
<td>7.2%</td>
<td>17.9%</td>
<td>26.4%</td>
<td></td>
</tr>
<tr>
<td><strong>Initial AVR group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of patients with at least 1 event</td>
<td>1</td>
<td>14</td>
<td>25</td>
<td>33</td>
<td></td>
</tr>
<tr>
<td>N of patients at risk</td>
<td>291</td>
<td>286</td>
<td>266</td>
<td>188</td>
<td>75</td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>0.3%</td>
<td>4.9%</td>
<td>9.0%</td>
<td>15.4%</td>
<td></td>
</tr>
</tbody>
</table>
Primary outcome measure
Heart failure hospitalization

<table>
<thead>
<tr>
<th>Interval</th>
<th>0d</th>
<th>30d</th>
<th>1y</th>
<th>3y</th>
<th>5y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Conservative group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N of patients with at least 1 event</td>
<td>291</td>
<td>279</td>
<td>246</td>
<td>161</td>
<td>63</td>
</tr>
<tr>
<td>N of patients at risk</td>
<td>0%</td>
<td>3.0%</td>
<td>13.0%</td>
<td>19.9%</td>
<td></td>
</tr>
<tr>
<td>Cumulative incidence</td>
<td>0%</td>
<td>31</td>
<td>19.9%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

| Initial AVR group |    |     |    |    |    |
| N of patients with at least 1 event | 291 | 286 | 264 | 185 | 75 |
| N of patients at risk | 0% | 1.1% | 2.4% | 3.8% |
| Cumulative incidence | 0% | 0% | 0% | 0% |

Crude HR 0.18 (0.09-0.35), P<0.001
Adjusted HR 0.19 (0.09-0.36), P<0.001
Log-rank P<0.001

The results from the adjusted analysis conducted as a sensitivity analysis were fully consistent with those from the unadjusted analysis.

Asymptomatic Severe AS

“Truly” Asx Severe AS
“Truly” Asymptomatic Severe AS

N=150 with AVA <1cm² (no gradient criteria)

Exclusion: 1) LVEF <55%, 2) other moderate-severe valve disease, 3) Atrial Fibrillation, 4) COPD, 5) positive stress test, 6) incapacity to perform stress test

Endpoint: CV death or need for AVR motivated by the development of symptoms or LVEF<50%
Clinical Outcome in Asymptomatic Severe Aortic Stenosis

Insights From the New Proposed Aortic Stenosis Grading Classification

• **51% (76/150) events** at a mean follow-up **27 months**
• **6% (9/150) deaths;** 5.3% (8/150) cardiac deaths

**CV events at FU:** 29% at 1 year, 49% at 2 years, 60% at 3 years

– Positive stress test during follow-up: 8 (11%)
– LVEF <50%: 2 (3%)
Asymptomatic Severe AS

Early Intervention
“Low hospital mortality tends to justify a policy of accepting patients for operation earlier in the natural progression of their disability, because it is recognized that there is a definite risk of rapid deterioration or sudden death in the earlier policy of deferring operation patients until their disability had become definite and progressive and until their cardiac reserve was nearly depleted.”
Asymptomatic Severe AS

Ineligible if patient < age 65, has Class 1 AVR indication (e.g. EF<50%), bicuspid valve, or STS ≥ 10

Clinical and Echo Screening

Treadmill Stress-Test

Stress-Test Normal

CT Scan and Angiography eligibility

Randomization 1:1
Stratified by STS (<5 vs. ≥5)

N=1,109 pts

TF- TAVR
Clinical Surveillance

Clinical and Echo Follow-up:
30 days (TAVR only), 1, 2, 3 and 5 years

Primary Endpoint (superiority):
2-year composite of all-cause death, all stroke, and repeat cardiovascular hospitalization

Stress-Test Abnormal

Commercial AVR (TAVR or SAVR), or Low Risk Clinical Trial (P3)

Unable to Perform Stress-Test

Registry

Telephone Follow-up:
1 year, 2 years, and 5 years

Principal Investigators:
Philippe Généreux, MD, Patrick T. O’Gara, MD
Asymptomatic Severe AS

Final Thoughts
Asymptomatic severe AS is frequent, representing ~40-50% of the severe AS referred to the echo lab.

- **Stress tests** are abnormal in ~50% of the patients, and are associated with high rates of adverse cardiac events at follow-up.

- Rate of sudden death are ~1% per year, with a high proportion of sudden death occurring without preceding symptoms.

- Echocardiographic predictors (e.g. PV, PV progression, valve calcification, Zva, LV stroke volume, LVH) and biomarkers can better stratify patients.
Asx Severe AS - Final Thoughts

• In “truly” asymptomatic severe AS patients (negative stress tests), the *CV event rate is ~50% at two years* with conservative management

• The strategy of “watching waiting” is problematic resulting in many lost opportunities for optimal outcomes (preservation of LV mechanics, clinical benefits)

• *In the “modern era” of TAVR (1% mortality, 1% strokes) earlier intervention is now seriously possible, but more robust clinical evidence is clearly needed to support a strong recommendation (randomized trials)!*
Aortic Stenosis Redefined: *Functional Classification*

<table>
<thead>
<tr>
<th>Mild AS</th>
<th>Moderate AS Symptoms -</th>
<th>Moderate AS Symptoms +</th>
<th>Severe AS Symptoms -</th>
<th>Severe AS Symptoms +</th>
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<tbody>
<tr>
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<td>TAVR-UNLOAD</td>
<td>EARLY-TAVR</td>
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</tbody>
</table>

PARTNERs

Low | Inter | High Ext

Active Surveillance

TAVR

≈2020

2016
Moderate AS + Heart Failure: Introduction to the UNLOAD Trial

Torsten Vahl, MD and Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City
Disclosure Statement of Financial Interest

I, Torsten Vahl, DO NOT have a financial interest/arrangement or affiliation with one or more organizations that could be perceived as a real or apparent conflict of interest in the context of the subject of this presentation.
Transcatheter Aortic Valve Replacement to UNLOad the left ventricle in patients with ADVanced heart failure (TAVR UNLOAD)

Nicolas M. Van Mieghem, MD, PhD
Thoraxcenter, Erasmus MC, Rotterdam

and

Martin B. Leon, MD
Columbia University, CRF, New York City
TAVR UNLOAD Trial

Pathophysiology
Low-Flow, Low-Gradient AS

- **NORMAL-LVEF NORMAL-FLOW HIGH-GRADIENT**
  - 50-70%

- **NORMAL-LVEF «PARADOXICAL» LOW-FLOW LOW-GRADIENT**
  - 10-15%

- **LOW-LVEF «CLASSICAL» LOW-FLOW LOW-GRADIENT**
  - 5-10%

*Pibarot & Dumesnil*  
*JACC, 2012*
Effect of Moderate AS based on LV function

What may be moderate AS for a normal ventricle
May feel like severe AS to an impaired ventricle

Normal LVEF

Reduced LVEF
Hemodynamic Fundamentals

Elderly with decreased arterial compliance
- fixed SBP
- no response to vasodilators

No medical options to reduce the arterial load!

Global Load $\cong Z_{VA} = \text{Transaortic Mean } \Delta P + \text{SBP SVi}$

Valvular Load
Arterial Load

Fixed
Hemodynamic Fundamentals

TAVR will reduce the valvular load and should improve HF symptoms!

Global Load \cong Z_{VA} = \text{Transaortic Mean } \Delta P + \text{SBP } SVi

afterload

Target

Valvular Load

Arterial Load

Fixed

\[ Transaortic \text{ Mean } \Delta P + \text{SBP } SVi \]
Aortic Stenosis and Heart Failure

Heart Failure (Leading cause of hospitalizations)

- Increased AFTERLOAD (sympathetic activity)
  - Impaired LV systolic function
  - Diastolic dysfunction

  - Beta-blockers
  - ACEi/ ARBs
  - MRAs, Diuretics

Aortic Stenosis (Most frequent valvulopathy)

- Increased AFTERLOAD (trans-valvular gradient)
  - Impaired LV systolic function
  - Diastolic dysfunction

Coexistence of Heart Failure and Moderate AS

- High risk population

Early AVR may be beneficial

TAVR

Moderate AS
- watchful waiting

Severe AS
- AVR

Early AVR may be beneficial for high-risk population.
TAVR UNLOAD Trial

Clinical Studies
Duke echo database identified 1634 pts with LV systolic dysfunction (EF ≤ 50%) and AS; 1090 (67%) with moderate AS (mean AV gradient ≥ 25-39 mmHg, mean AVA 1.08 cm²) and 544 (33%) with severe AS (mean AVA 0.72 cm²).

Mean age 75yo and major co-morbidities included CAD 61%, DM 33%, and cerebrovascular disease 20%.

Pts followed at least 5 years after the index echo.
Aortic valve surgery and survival in patients with moderate or severe aortic stenosis and left ventricular dysfunction

Zainab Samad\textsuperscript{1,8}, Amit N. Vora\textsuperscript{1,2}, Allison Dunning\textsuperscript{2}, Phillip J. Schulte\textsuperscript{2}, Linda K. Shaw\textsuperscript{2}, Fawaz Al-Enezi\textsuperscript{1}, Mads Ersbøll\textsuperscript{3}, Robert W. McGarrah III\textsuperscript{1}, John P. Vavalle\textsuperscript{1}, Svatih. Shah\textsuperscript{1,2,4}, Joseph Kisslo\textsuperscript{1}, Donald Glower\textsuperscript{1,5}, J. Kevin Harrison\textsuperscript{1}, and Eric J. Velazquez\textsuperscript{1,2}

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Significant survival benefit in pts with mod AS treated by AVR within 90 days!
Impact of Moderate AS in Patients with Reduced LV Systolic Function

- Retrospective analysis of Doppler-echo and clinical data from 4 large academic medical centers in the Netherlands, Canada, and the U.S.
- 305 patients identified with moderate AS (AVA 1.0 – 1.5 cm²) and reduced LV systolic function (EF ≤ 50%)
- Avg age 73yo, most symptomatic (FC II 42%, FC III/IV 32%), 72% CAD
- Primary endpoint: composite of all-cause mortality, AVR, or HF hospitalization
- Median FU 638 days [IQR 280-1137 days]

Courtesy of Lennart van Gils et al; Erasmus, Rotterdam
Impact of Moderate AS in Patients with Reduced LV Systolic Function

• Composite endpoint in 61% of patients at 4 yrs FU!
• All-cause mortality 40%, SAVR/TAVR 29%, HF hosp 34%

Courtesy of Lennart van Gils et al; Erasmus, Rotterdam
TAVR UNLOAD Trial
Heart Failure
LVEF < 50%
NYHA ≥ 2
Optimal HF therapy
(OHFT)
Moderate AS

TAVR UNLOAD Trial
International Multicenter Randomized

Heart Failure
TAVR + OHFT
Follow-up:
1 month
6 months
1 year
Clinical endpoints
Symptoms
Echo
QoL

Primary Endpoint
Hierarchical occurrence of:
- All-cause death
- Disabling stroke
- Hospitalizations for HF, aortic valve disease
- Change in KCCQ

Reduced AFTERLOAD
Improved LV systolic and diastolic function
TAVR UNLOAD Trial

Heart Team

- Heart Failure Specialist
- Referring Cardiologist
- Imaging Specialist
- Interventional Cardiologist
- Cardiac Surgeon

Multi-disciplinary Heart Team

TAVR UNLOAD

Columbia University Medical Center
NewYork-Presbyterian
TAVR UNLOAD Trial

Key Inclusion Criteria

• New York Heart Association Class ≥ 2
• NT-proBNP > 1500 pg/mL or hospitalization for HF within the last year
• Appropriate guideline-directed HF medical therapy (as tolerated) for ≥ 3 months
• LVEF < 50%, but > 20%
• Anatomically suitable for SAPIEN 3 transfemoral TAVR
TAVR UNLOAD Trial

Key Inclusion Criteria

• Moderate AS confirmed by the echo core lab and defined as:
  
  ➢ Mean transaortic gradient (MG) ≥ 20 mmHg and < 40 mmHg & aortic valve area (AVA) > 1.0 cm² and ≤1.5 cm² at rest

  OR

  ➢ MG ≥ 20 mmHg and < 40 mmHg and AVA ≤ 1.0 cm² at rest AND MG < 40 mmHg and AVA >1.0 cm² with low dose dobutamine stress echo (DSE)
TAVR UNLOAD Trial

Primary Endpoint

• The hierarchical occurrence at 1-year of:
  ➢ all-cause death
  ➢ disabling stroke
  ➢ CV hospitalizations related to heart failure, aortic valve disease (e.g. endocarditis), or non-disabling stroke
  ➢ change in KCCQ from baseline

• Methodology: nonparametric pairwise hierarchical analysis as described by Finklestein-Schoenfeld

• Sample size: 600 patients; randomized 1:1; intention-to-treat analysis population
TAVR UNLOAD Trial

Ready to Go!

Site selection completed
IDE approved by FDA
Reimbursement approved by CMS (U.S.)
Enrolled first patient
TAVR UNLOAD Trial

Final Thoughts
TAVR UNLOAD Trial

Final thoughts…

• Reduced EF heart failure and moderate AS are both difficult to treat (limited medical alternatives) and associated with frequent clinical events.

• Recent clinical results with TAVR in lower risk patient populations indicate improved safety and efficacy (esp. using transfemoral access).

• The TAVR UNLOAD trial tests the hypothesis that early TAVR in patients with moderate AS, symptoms of HF, and reduced EF will be superior to current strategies of watchful waiting and medical therapy.