An All-comers Randomized Clinical Trial Comparing Transcatheter with Surgical Aortic Valve Replacement in Patients with Aortic Valve Stenosis

On behalf of NOTION investigators:  
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Copenhagen University Hospital, Denmark
Funding

• The Danish Heart Foundation
TAVR in Extreme-Risk Patients

**PARTNER TRIAL**

- Hazard ratio, 0.58 (95% CI, 0.43–0.78)
- P<0.001

**US COREVALVE EXTREME RISK STUDY**

- All Cause Mortality or Major Stroke, %
- P < 0.0001
- Performance Goal = 43%
- 26.0% [22.1,29.9]

Leon MB et al, NEJM 2010

Popma JJ et al, JACC 2014
TAVR in High-Risk Patients

**PARTNER TRIAL**

- Hazard ratio, 0.93 (95% CI, 0.71–1.22)
- P=0.62

**US COREVALVE HIGH RISK STUDY**

- P=0.04 for superiority

*Smith CR et al, NEJM 2011*

*Adams DH et al, NEJM 2014*
TAVR in Intermediate-Risk Patients

Propensity-score matched study
Piazza et al, JACC 2014

HR (95% CI): 0.90 (0.57-1.42); p=0.64
Operative Risk and TAVR vs. SAVR Trials

- **Low risk**: STS < 4%
- **Intermediate risk**: 4 – 10%
- **High risk**: 10% < - 15%
- **Extreme risk**: > 15%

- **US COREVALVE PARTNER**
- **NOTION**
- **SURTAVI PARTNER II**
**Nordic Aortic Valve Intervention (NOTION) Trial**

<table>
<thead>
<tr>
<th>Objective:</th>
<th>Compare TAVR vs. SAVR in patients &gt; 70 years eligible for surgery (all-comers population)</th>
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</thead>
<tbody>
<tr>
<td>Primary outcome:</td>
<td>Composite rate of death from any cause, stroke or myocardial infarction at 1 year (VARC II-defined)</td>
</tr>
<tr>
<td>Secondary outcomes:</td>
<td>Safety and efficacy (NYHA), echocardiographic outcomes (VARC II-defined)</td>
</tr>
<tr>
<td>Design:</td>
<td>Prospective, multicenter, non-blinded, randomized trial</td>
</tr>
<tr>
<td>Enrollment period:</td>
<td>December 2009 - April 2013</td>
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</tbody>
</table>
Participating Centers

Rigshospitalet, Copenhagen
University Hospital, Copenhagen, Denmark

Sahlgrenska University Hospital, Gothenburg, Sweden

Odense University Hospital, Odense, Denmark
Trial Investigators and CEC

**Principal Investigators:**
Lars Søndergaard
Daniel Andreas Steinbrüchel

**Co-investigators:**
Hans Gustav Hørsted Thyregod
Peter Skov Olsen
Nikolaj Ihlemann
Olaf Walter Franzen
Thomas Engstrøm

Peter Bo Hansen
Lars Willy Andersen
Henrik Nissen
Bo Juel Kjeldsen
Petur Petursson

**Clinical Events Committee:**
Kristian Thygesen (chair), cardiologist
Bo Norrving, neurologist
Torben Schroeder, vascular surgeon
Enrollment Criteria

Main inclusion criteria:

• 70 years or older
• Severe aortic valve stenosis on echocardiogram
• Expected to live more than 1 year
• Anatomical suitable for both procedures

Main exclusion criteria:

• Severe coronary artery disease
• Severe other heart valve disease
• Prior heart surgery
• Indication for acute treatment
• Recent stroke or myocardial infarction
• Severe pulmonary or renal failure
Device and Access Routes

Self-expanding bio-prosthesis
4 valve sizes
(annulus diameter 18-29 mm)

18 Fr delivery system

Subclavian

Transfemoral
Sample Size Determination

Alternative hypothesis: TAVR is superior to SAVR regarding the composite rate of death from any cause, stroke or myocardial infarction after 1 year

Sample Size Determination:

1:1 treatment allocation
Two-sided alpha = 0.05
Power = 80%

Expected rate_{SAVR} = 15%
Expected rate_{TAVR} = 5%

Trial Size: 280 patients
Primary Analysis Population

• Intention-to-treat

  All randomized patients.

  Patients were analyzed according to randomization, regardless of whether a procedure was actually attempted or which prosthesis was actually implanted.
**Trial Flow**

All randomized $n=280$

**ITT TAVR**
$n=145$
- Died prior to procedure $n=3$
- AT TAVR $n=142$
- Implanted TAVR $n=139$

**ITT SAVR**
$n=135$
- Died prior to procedure $n=1$
- AT SAVR $n=134$
- Implanted SAVR $n=135$

Crossover TAVR to SAVR $n=1$
Crossover SAVR to TAVR $n=1$
Crossover TAVR to SAVR $n=3$
Not implanted $n=2$
Trial Compliance

Baseline

1 Month Follow-Up

3 Months Follow-Up

1 Year Follow-Up

ITT TAVR
N=145

100%
(145/145)

96.4%
(135/140)

96.4%
(135/140)

98.5%
(134/136)

ITT SAVR
N=135

100%
(135/135)

92.1%
(116/126)

93.6%
(117/125)

96.0%
(119/124)
## Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR n=145</th>
<th>SAVR n=135</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yrs)</td>
<td>79.2 ± 4.9</td>
<td>79.0 ± 4.7</td>
<td>0.71</td>
</tr>
<tr>
<td>Male</td>
<td>53.8</td>
<td>52.6</td>
<td>0.84</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons (STS) Score</td>
<td>2.9 ± 1.6</td>
<td>3.1 ± 1.7</td>
<td>0.30</td>
</tr>
<tr>
<td>STS Score &lt; 4%</td>
<td>83.4</td>
<td>80.0</td>
<td>0.46</td>
</tr>
<tr>
<td>Logistic EuroSCORE I</td>
<td>8.4 ± 4.0</td>
<td>8.9 ± 5.5</td>
<td>0.38</td>
</tr>
<tr>
<td>NYHA class III or IV</td>
<td>48.6</td>
<td>45.5</td>
<td>0.61</td>
</tr>
<tr>
<td>Characteristic, % or mean ± SD</td>
<td>TAVR n=145</td>
<td>SAVR n=135</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------------------------------------</td>
<td>------------</td>
<td>------------</td>
<td>---------</td>
</tr>
<tr>
<td>Diabetes</td>
<td>17.9</td>
<td>20.7</td>
<td>0.55</td>
</tr>
<tr>
<td>Peripheral Vascular Disease</td>
<td>4.1</td>
<td>6.7</td>
<td>0.35</td>
</tr>
<tr>
<td>Prior Stroke</td>
<td>6.2</td>
<td>9.6</td>
<td>0.29</td>
</tr>
<tr>
<td>Chronic Obstructive Pulmonary Disease</td>
<td>11.7</td>
<td>11.9</td>
<td>0.97</td>
</tr>
<tr>
<td>Creatinine &gt; 2 mg/dl</td>
<td>1.4</td>
<td>0.7</td>
<td>&gt;0.99</td>
</tr>
<tr>
<td>Prior Myocardial Infarction</td>
<td>5.5</td>
<td>4.4</td>
<td>0.68</td>
</tr>
<tr>
<td>Prior Percutaneous Coronary Intervention</td>
<td>7.6</td>
<td>8.9</td>
<td>0.69</td>
</tr>
</tbody>
</table>
Primary Outcome*

Composite rate of death from any cause, stroke or myocardial infarction 1 year after the procedure

TAVR 13.1% vs. SAVR 16.3%

Absolute difference -3.2%; p=0.43 (for superiority)

*Intention-to-treat population
Death from Any Cause, Stroke or Myocardial Infarction at 1 Year in As-Treated Population

P-value (log-rank) = 0.26

No. at Risk:
- TAVR: 142, 133, 129, 118
- SAVR: 134, 118, 115, 105

All-Cause Mortality, MI, or Stroke (%)
- SAVR: 6.3%, 11.9%, 15.7%
- TAVR: 0%, 0%, 11.3%
Death from Any Cause at 1 Year

P-value (log-rank) = 0.38

No. at Risk:

- TAVR: 142 139 137 126
- SAVR: 134 128 125 115
All Stroke at 1 Year

- SAVR
- TAVR

P-value (log-rank) = 0.44

Months Post-Procedure

0% 2% 4% 6% 8% 10%

All Stroke (%)

No. at Risk:
- TAVR: 142 137 134 123
- SAVR: 134 124 120 110
Myocardial Infarction at 1 Year

P-value (log-rank) = 0.33

No. at Risk:
- TAVR: 142 135 132 121
- SAVR: 134 122 120 110
## Secondary Outcomes at 30 Days

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>TAVR n=142</th>
<th>SAVR n=134</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause</td>
<td>2.1</td>
<td>3.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Death, cardiovascular</td>
<td>2.1</td>
<td>3.7</td>
<td>0.43</td>
</tr>
<tr>
<td>Bleeding, life-threatening+major</td>
<td>11.3</td>
<td>20.9</td>
<td>0.03</td>
</tr>
<tr>
<td>Cardiogenic shock</td>
<td>4.2</td>
<td>10.4</td>
<td>0.05</td>
</tr>
<tr>
<td>Vascular lesion, major</td>
<td>5.6</td>
<td>1.5</td>
<td>0.10</td>
</tr>
<tr>
<td>Acute kidney injury (stage II+III)</td>
<td>0.7</td>
<td>6.7</td>
<td>0.01</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.4</td>
<td>3.0</td>
<td>0.37</td>
</tr>
<tr>
<td>TIA</td>
<td>1.4</td>
<td>0</td>
<td>0.17</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>2.8</td>
<td>6.0</td>
<td>0.20</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>16.9</td>
<td>57.8</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>34.1</td>
<td>1.6</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
## Secondary Outcomes at 1 Year

<table>
<thead>
<tr>
<th>Outcome, %</th>
<th>TAVR n=142</th>
<th>SAVR n=134</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death, any cause</td>
<td>4.9</td>
<td>7.5</td>
<td>0.38</td>
</tr>
<tr>
<td>Death, cardiovascular</td>
<td>4.3</td>
<td>7.5</td>
<td>0.25</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.9</td>
<td>4.6</td>
<td>0.44</td>
</tr>
<tr>
<td>TIA</td>
<td>2.1</td>
<td>1.6</td>
<td>0.71</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>3.5</td>
<td>6.0</td>
<td>0.33</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>21.2</td>
<td>59.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Pacemaker</td>
<td>38.0</td>
<td>2.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic valve re-intervention</td>
<td>0.0</td>
<td>0.0</td>
<td>na</td>
</tr>
</tbody>
</table>
### NYHA Class in Survivors

<table>
<thead>
<tr>
<th></th>
<th>Baseline (TAVR N=141)</th>
<th>3 Months (TAVR N=135)</th>
<th>1 Year (SAVR N=120)</th>
</tr>
</thead>
<tbody>
<tr>
<td>NYHA I</td>
<td>47.5%</td>
<td>68.9%</td>
<td>67.4%</td>
</tr>
<tr>
<td>NYHA II</td>
<td>5.0%</td>
<td>20.9%</td>
<td>81.7%</td>
</tr>
<tr>
<td>NYHA III</td>
<td>5.2%</td>
<td>29.5%</td>
<td>15.0%</td>
</tr>
<tr>
<td>NYHA IV</td>
<td>3.0%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (%)</strong></td>
<td>100%</td>
<td>100%</td>
<td>100%</td>
</tr>
</tbody>
</table>

- **p=0.99**
- **p=0.23**
- **p=0.01**
Aortic Valve Performance

![Graph showing effective orifice area and mean gradient for TAVR and SAVR at baseline, 3 months, and 12 months.](image)

- **Effective Orifice Area (cm²)**
  - TAVR: 44.9, 1.7, 1.7
  - SAVR: 43.4, 1.4, 1.3
  - Baseline: 0.7, 12.2, 8.3
  - 3 Months: 0.7, 1.7, 8.6
  - 12 Months: 0.7, 1.7, 8.6

- **Mean Gradient (mm Hg)**
  - Baseline: 0.0, 0.0, 0.0
  - 3 Months: 0.0, 0.0, 0.0
  - 12 Months: 0.0, 0.0, 0.0

* *p<0.001*
Aortic Valve Regurgitation

<table>
<thead>
<tr>
<th></th>
<th>3 Months</th>
<th>1 Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>TAVR (n=124)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Trace</td>
<td>23.4%</td>
<td>82.3%</td>
</tr>
<tr>
<td>Mild</td>
<td>61.3%</td>
<td>55.4%</td>
</tr>
<tr>
<td>Moderate</td>
<td>1.8%</td>
<td>28.9%</td>
</tr>
<tr>
<td>Severe</td>
<td>0.8%</td>
<td>14.9%</td>
</tr>
<tr>
<td>SAVR (n=111)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Trace</td>
<td>19.8%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>78.4%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>14.5%</td>
<td></td>
</tr>
<tr>
<td>TAVR (n=121)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Trace</td>
<td>23.4%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>61.3%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0.8%</td>
<td></td>
</tr>
<tr>
<td>SAVR (n=113)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>None/Trace</td>
<td>23.4%</td>
<td></td>
</tr>
<tr>
<td>Mild</td>
<td>61.3%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>1.8%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>0.8%</td>
<td></td>
</tr>
</tbody>
</table>

p<0.001
Conclusions

- The NOTION trial was the first all-comers trial to randomize low-risk patients to TAVR or SAVR.

- TAVR was safe and effective, but not superior to SAVR regarding the composite rate of death from any cause, stroke or myocardial infarction after 1 year.

- Procedural complications were different reflecting very different procedures.

- Larger EOA and lesser gradients with TAVR prosthesis, but more regurgitation.

- Long-term durability and morbidity data are required in lower risk patients.