THE CONSTANTLY CHANGING PATIENT ELIGIBILITY CRITERIA: PAST CURRENT AND FUTURE DIRECTIONS
TAVR: standard treatment for severe AS in high risk or inoperable patients.

Expansion to intermediate and low risk patients.

More than 200,000 TAVRs implanted worldwide

Remarkable increase in the number of centers

Multiple areas were evidence and even expert consensus are lacking
250 centers from 38 countries

2005 to 2015: 68,936 procedures,
Previous year range 10 to 600
TAVR/year
• Heart team: 97% centers
• Risk score:
  • One: 99.2%
  • Two: 54.8%
• Additional test:
Aortic Stenosis
Where to next?

- **Surgery:**
  - "Play of Chance" (~5%)
  - Extreme Risk (~10%)
  - High Risk (~10%)
  - **Intermed. Risk** (~15%)
  - Low Risk (~60%)

- **TAVR:**
  - No
  - Preferred
  - OK
  - SURTAVI
  - Partner II
  - Not indicated

**Pyramid Diagram:**
- Futile
- TAVR
- TAVR or AVR
- Surgery (AVR)
TAVI Implantations
Increase in cases: 2010 - 2018

CAG: EU 14%
US 27%

~90K procedures by 2018

(X 1000)

Multiple Industry Sources - 2013
Evolution in Patient Selection
Lower Risk AS Patients

Inoperable (extreme risk)

<table>
<thead>
<tr>
<th>Procedure</th>
<th>STS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER B TAVR</td>
<td>11.2%</td>
</tr>
<tr>
<td>PARTNER IB SAPIEN</td>
<td>11.0%</td>
</tr>
<tr>
<td>PARTNER IB SAPIEN XT</td>
<td>10.3%</td>
</tr>
<tr>
<td>CoreValve ER</td>
<td>10.3%</td>
</tr>
<tr>
<td>CoreValve ER Continued Access</td>
<td>9.0%</td>
</tr>
<tr>
<td>TVT Registry SAPIEN TF</td>
<td>7.0%</td>
</tr>
</tbody>
</table>

High-Risk

<table>
<thead>
<tr>
<th>Procedure</th>
<th>STS Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>PARTNER A TAVR</td>
<td>11.8%</td>
</tr>
<tr>
<td>PARTNER TF Continued Access</td>
<td>10.9%</td>
</tr>
<tr>
<td>CoreValve HR</td>
<td>7.3%</td>
</tr>
<tr>
<td>TVT Registry SAPIEN TF</td>
<td>5.0%</td>
</tr>
</tbody>
</table>

TCT 2014
PARTNER 1B

Established TAVR as Standard of Care for Inoperable Pts
TAVR Mortality Stratified by Age (ITT)

- ST ≥ 85 (n=89) - 96.0%
- ST < 85 (n=93) - 91.8%
- TAVR ≥ 85 (n=83) - 73.5%
- TAVR < 85 (n=96) - 70.4%
Υψηλού κινδύνου ασθενείς

CoreValve US Pivotal: High Risk

Possible Superiority of TAVR in High-Risk Patients
PARTNER 1A

Survival With Edwards SAPIEN THV Was Equivalent to AVR in High-Risk Patients

PRIMARY ENDPOINT: ALL-CAUSE MORTALITY AT 1 YEAR (ITT)\(^4\)

Mortality at 1 year
Edwards SAPIEN THV 24.2%
AVR 26.8%
\((P = .001 \text{ for non-inferiority})^4\)
TAVI IN INTERMEDIATE RISK PATIENTS
PARTNER II Trial
Study design

Symptomatic Severe Aortic Stenosis

Operable (STS ≤24)

ASSESSMENT: Transfemoral Access

Yes

Transfemoral (TF)
1:1 Randomization
TF TAVR SAPIEN XT vs Surgical AVR

No

Transapical (TA) / TransAortic (TAo)
1:1 Randomization
TAVR: TA / TAo SAPIEN XT vs Surgical AVR

Inoperable

ASSESSMENT: Transfemoral Access

Yes

n = 2000 Randomized Patients

Primary Endpoint: All-Cause Mortality + Disabling Stroke at Two Years (Non-inferiority)

Two Parallel Randomized Trials + 6 Nested Registries

n = 560 Randomized Patients

Primary Endpoint: All-Cause Mortality + Disabling Stroke + Repeat Hospitalization at One Year (Non-inferiority)

5 Nested Registries

- NR1 (Small Vessel): 100
- NR2 (Transapical): 100
- NR3 (VIV): 100
- NR4 (TAo): 100
- NR5 (29 mm TF): 50
- NR6 (29 mm TA): 60
PARTNER IIA
Mean STS Score per month

Mean STS Score ~ 6
## PARTNER 2A
### Patient characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (n = 1011)</th>
<th>Surgery (n = 1021)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age - yrs</td>
<td>81.5 ± 6.7</td>
<td>81.7 ± 6.7</td>
<td>0.63</td>
</tr>
<tr>
<td>Male - %</td>
<td>54.2</td>
<td>54.8</td>
<td>0.79</td>
</tr>
<tr>
<td>STS Score - %</td>
<td>5.8 ± 2.1</td>
<td>5.8 ± 1.9</td>
<td>0.29</td>
</tr>
<tr>
<td>NYHA Class III or IV - %</td>
<td>77.3</td>
<td>76.1</td>
<td>0.53</td>
</tr>
<tr>
<td>CAD - %</td>
<td>69.2</td>
<td>66.5</td>
<td>0.20</td>
</tr>
<tr>
<td>Prior CABG - %</td>
<td>23.6</td>
<td>25.6</td>
<td>0.33</td>
</tr>
<tr>
<td>Cerebrovascular Disease - %</td>
<td>32.1</td>
<td>31.0</td>
<td>0.60</td>
</tr>
<tr>
<td>PVD - %</td>
<td>27.9</td>
<td>32.9</td>
<td>0.02</td>
</tr>
</tbody>
</table>

Leon, Smith et al, NEJM, 2016
PARTNER 2A: 2 Yrs
All cause mortality or disabling stroke

Leon, Smith et al, NEJM, 2016
PARTNER 2A: 2 Yrs
TF TAVI better than Surgery

Leon, Smith et al, NEJM, 2016
## PARTNER 2A: 2 Yrs

### Event rates

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>30 Days</th>
<th></th>
<th></th>
<th>2 Years</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>Surgery</td>
<td>p-value</td>
<td>TAVR</td>
<td>Surgery</td>
<td>p-value</td>
</tr>
<tr>
<td>Rehospitalization</td>
<td>8.5</td>
<td>6.5</td>
<td>0.99</td>
<td>19.8</td>
<td>17.3</td>
<td>0.22</td>
</tr>
<tr>
<td>MI</td>
<td>1.2</td>
<td>1.9</td>
<td>0.22</td>
<td>3.6</td>
<td>4.1</td>
<td>0.56</td>
</tr>
<tr>
<td>Major Vascular Complications</td>
<td>7.9</td>
<td>5.0</td>
<td>0.008</td>
<td>8.6</td>
<td>5.5</td>
<td>0.006</td>
</tr>
<tr>
<td>Life-Threatening / Disabling Bleeding</td>
<td>10.4</td>
<td>43.4</td>
<td>&lt;0.001</td>
<td>17.3</td>
<td>47.0</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>AKI (Stage III)</td>
<td>1.3</td>
<td>3.1</td>
<td>0.008</td>
<td>3.8</td>
<td>8.2</td>
<td>0.02</td>
</tr>
<tr>
<td>New Atrial Fibrillation</td>
<td>9.1</td>
<td>26.4</td>
<td>&lt;0.001</td>
<td>11.3</td>
<td>27.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>8.5</td>
<td>6.9</td>
<td>0.17</td>
<td>11.8</td>
<td>10.3</td>
<td>0.29</td>
</tr>
<tr>
<td>Re-intervention</td>
<td>0.4</td>
<td>0.0</td>
<td>0.05</td>
<td>1.4</td>
<td>0.6</td>
<td>0.09</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.0</td>
<td>0.0</td>
<td>NA</td>
<td>1.2</td>
<td>0.7</td>
<td>0.22</td>
</tr>
</tbody>
</table>

Leon, Smith et al, NEJM, 2016
PARTNER 2A: 2 Yrs

PVL rates

Leon, Smith et al, NEJM, 2016
Structural Interventions

**SURTAVI**

**A** Noninferiority Margin of TAVR

- **Primary Outcomes**
  - **Death from Any Cause**:
    - TAVR: 11.4%
    - Surgery: 11.5%
    - Difference: 0.1%
  - **Disabling Stroke**:
    - TAVR: 3.9%
    - Surgery: 4.0%
    - Difference: 0.1%

**B** Primary Outcomes

- **24-Mo Rate (%)**
  - TAVR: 11.5%
  - Surgery: 11.6%
  - Difference: -0.1 to 0.2

**C** Death from Any Cause

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk TAVR</th>
<th>No. at Risk Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>864</td>
<td>796</td>
</tr>
<tr>
<td>6</td>
<td>722</td>
<td>821</td>
</tr>
<tr>
<td>12</td>
<td>629</td>
<td>485</td>
</tr>
<tr>
<td>24</td>
<td>349</td>
<td>280</td>
</tr>
</tbody>
</table>

**D** Disabling Stroke

<table>
<thead>
<tr>
<th>Month</th>
<th>No. at Risk TAVR</th>
<th>No. at Risk Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
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<td>280</td>
</tr>
</tbody>
</table>

Reardon MJ et al, NEJM 2017
### SURTAVI

#### Table 2. Procedure-Related Complications at 30 Days (Modified Intention-to-Treat Population). *

<table>
<thead>
<tr>
<th>Complication</th>
<th>TAVR (N = 864)</th>
<th>Surgery (N = 796)</th>
<th>95% Credible Interval for Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life-threatening or major bleeding — %</td>
<td>12.2</td>
<td>9.3</td>
<td>-0.1 to 5.9</td>
</tr>
<tr>
<td>Transfusion of red cells — no. (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0 units</td>
<td>756 (87.5)</td>
<td>469 (58.9)</td>
<td>24.4 to 32.5</td>
</tr>
<tr>
<td>1 unit</td>
<td>29 (3.4)</td>
<td>90 (11.1)</td>
<td>-10.5 to -5.5</td>
</tr>
<tr>
<td>2 to 4 units</td>
<td>48 (5.6)</td>
<td>136 (17.1)</td>
<td>-14.5 to -8.5</td>
</tr>
<tr>
<td>&gt;4 units</td>
<td>31 (3.6)</td>
<td>101 (12.7)</td>
<td>-11.7 to -6.5</td>
</tr>
<tr>
<td>Acute kidney injury stage 2 or 3 — %</td>
<td>1.7</td>
<td>4.4</td>
<td>-4.4 to -1.0</td>
</tr>
<tr>
<td>Coronary-artery obstruction — %</td>
<td>0.2</td>
<td>0.0</td>
<td>-0.2 to 0.8</td>
</tr>
<tr>
<td>Major vascular complication — %</td>
<td>6.0</td>
<td>1.1</td>
<td>3.2 to 6.7</td>
</tr>
<tr>
<td>Cardiac perforation — %</td>
<td>1.7</td>
<td>0.9</td>
<td>-0.2 to 2.0</td>
</tr>
<tr>
<td>Cardiogenic shock — %</td>
<td>1.1</td>
<td>3.8</td>
<td>-4.2 to -1.1</td>
</tr>
<tr>
<td>Permanent pacemaker implantation — %</td>
<td>25.9</td>
<td>6.6</td>
<td>15.9 to 22.7</td>
</tr>
<tr>
<td>Atrial fibrillation — %</td>
<td>12.9</td>
<td>43.4</td>
<td>34.7 to 26.4</td>
</tr>
</tbody>
</table>

* Values are estimated incidence (median of the posterior probability distribution, as calculated by means of Bayesian analysis), except for transfusion values, which are the numbers of patients and percentages. For all the values, 95% credible intervals were calculated for the difference between groups. Percentages may not total 100 because of rounding.

Reardon MJ et al, NEJM 2017
### SURTAVI

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>STS Range</th>
<th>Number of Patients</th>
<th>Event Rate</th>
<th>Hazard Ratio (95% CI)</th>
<th>p Value for Interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>High risk</td>
<td>STS &gt; 8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intermediate</td>
<td>STS 4-8%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low risk</td>
<td>STS &lt; 4%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Reardon MJ et al, NEJM 2017*
SURTAVI
More AR with TAVI

Reardon et al, NEJM, 2017
SURTAVI: 2 Yrs

Intermediate Surgical Risk
Predicted risk of operative mortality ≥3% and <15%

Heart Team Evaluation
Assess inclusion/exclusion
Risk classification

Randomization
Stratified by need for revascularization

Screening Committee
Confirmed eligibility

Baseline neurological assessments

TAVR
TAVR only
TAVR + PCI

SAVR
SAVR only
SAVR + CABG

Reardon et al, NEJM, 2017
SURTAVI: 2 Yrs
All cause mortality or disabling stroke

Reardon et al, NEJM, 2017
SURTAVI: 2 Yrs
TAVI showed better valve hemodynamics

Reardon et al, NEJM, 2017
BERMUDA (BERn MUnich rotterDAm) Triangle Study

3,666 patients enrolled
- TAVI - 782
- SAVR - 2,884

784 matched patients
- TAVI - 392
- SAVR - 392

2,882 patients excluded based on propensity scores

274 patients excluded based on STS score <3% and >8%

510 matched patients (STS scores 3-8%)

255 patients analyzed (TAVI)
255 patients analyzed (SAVR)
BERMUDA (BERn MUnich rotterDAm) Triangle Study

One Year Outcome In Intermediate Risk Patients

HR 1.00 (0.63-1.59)  
\( p=0.24 \)

TAVI 18.8%  
SAVR 17.0%

Months after index PCI
Cumulative incidence (%)
No. at risk
TAVI 261 203 214 262 168 164 178 163 153 148 144 140 133
SAVR 255 220 224 210 211 209 201 200 190 192 188 180 152
Surgical AVR (Class I)

Severe AS
Symptomatic
(stage D)

Low surgical risk

Surgical AVR (Class I)

Intermediate surgical risk

Surgical AVR (Class I)  TAVR (Class IIa)

High surgical risk

Surgical AVR or TAVR (Class I)

Prohibitive surgical risk

TAVR (Class I)

2017 ACC/AHA Guidelines for the management of valvular heart disease
Χαμηλού κινδύνου ασθενείς
Most of the patients are low risk patients

**Surgery (AVR)**

- **Low Risk**
  - OR risk: < 4%
  - % patients: 70%
- **Intermed Risk**
  - OR risk: 4-8%
  - % patients: 20%
- **High Risk**
  - OR risk: >8%
  - % patients: 10%
The PARTNER 3 Trial
Study Design

Symptomatic Severe Calcific Aortic Stenosis

Low Risk ASSESSMENT by Heart Team
(STS < 4%, TF only)

1:1 Randomization
(n=1228)

TF - TAVR
(SAPIEN 3)
CT Imaging Sub-Study (n=200)
Actigraphy/QoL Sub-Study (n=200)

Surgery
(Bioprosthetic Valve)
CT Imaging Sub-Study (n=200)
Actigraphy/QoL Sub-Study (n=200)

PARTNER 3 Registries

Alternative Access
(n=100)
(TA/TAo/Subclavian)

Bicuspid Valves
(n=100)

ViV (AV and MV)
(n=100)

PRIMARY ENDPOINT:
Composite of all-cause mortality, all strokes, or re-hospitalization at 1 year post-procedure

Follow-up: 30 days, 6 mos, 1 year and annually through 10 years
STS AND MORTALITY

**STS < 5**
- Standard Rx (n = 12)
- TAVR (n = 28)
- Mortality %:
  - Standard Rx: 100%
  - TAVR: 41.1%

**STS 5-15**
- Standard Rx (n = 123)
- TAVR (n = 113)
- Mortality %:
  - Standard Rx: 61.6%
  - TAVR: 82.4%
  - p (log rank) < 0.0001

**STS > 15**
- Standard Rx (n = 43)
- TAVR (n = 38)
- Mortality %:
  - Standard Rx: 57.8%
  - TAVR: 91.8%
  - p (log rank) = 0.0098
In-hospital and 30-day Mortality after TAVI

New Risk Score

Development Cohort:
C-statistic (new Score) = 0.67
C-statistic (logistic Euroscore) = 0.59

Relationship between the score value and predicted early mortality after transcatheter aortic valve implantation

*Iung et al, Heart 2014*
• **Criteria:**
  - Slowness - Gait speed < 7 sec
  - Weakness - Grip strength < 18 Kg
  - BMI < 20 or weight loss 5 kg/year
  - Low physical activity
  - Self-reported exhaustion

• **Katz Index** (bathing, dressing, feeding, continence, toileting, transferring) (<4/6)

• Karnogsky score (>40%).

*Qian-Li Xue, Clin Geriatr Med 2011*
Background – PARTNER 1 Frailty

- Frailty Score ≥ 6
- Frailty Score < 6

Time in Months

P = 0.004
7 year Post TAVI follow-up
Conclusions

• TAVI is feasible and safe and more effective in intermediate risk pts
• TAVI is equal or even better than surgery in lower risk pts
• Several questions need to be resolved in this population