Is TAVI ready for prime time in:

- Intermediate risk patients?
- Low risk patients?

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Clinique PASTEUR, Toulouse, France,
Conflicts of interest:

- Consultant for Edwards LifeSciences
- Consultant for Medtronic
- Consultant for Boston Scientific
TAVI procedures worldwide

> 250 000 procedures in > 65 countries
What do we know about

TAVI in intermediate-risk patients
Key Message

We are already treating intermediate risk patients
### 2014 ACC/AHA guidelines

<table>
<thead>
<tr>
<th></th>
<th>Low Risk (Must Meet ALL Criteria in this column)</th>
<th>Intermediate Risk (Any 1 criterion in this column)</th>
<th>High Risk (Any 1 criterion in this column)</th>
<th>Prohibitive Risk (Any 1 criterion in this column)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>STS PROM</strong></td>
<td>&lt;4% AND</td>
<td>4% to 8% OR</td>
<td>&gt;8% OR</td>
<td>Predicted risk with surgery of death or major morbidity (all-cause) &gt;50% at 1 y OR</td>
</tr>
<tr>
<td><strong>Frailty†</strong></td>
<td>None AND</td>
<td>1 Index (mild) OR</td>
<td>≥ 2 Indices (moderate to severe) OR</td>
<td></td>
</tr>
<tr>
<td><strong>Major organ system compromise not to be improved postoperatively</strong></td>
<td>None AND</td>
<td>1 Organ system OR</td>
<td>No more than 2 organ systems OR</td>
<td>≥ 3 Organ systems OR</td>
</tr>
<tr>
<td><strong>Procedure- specific impediment</strong></td>
<td>None</td>
<td>Possible procedure-specific impediment</td>
<td>Possible procedure-specific impediment</td>
<td>Severe procedure-specific impediment</td>
</tr>
</tbody>
</table>

*STS PROM* = Society of Thoracic Surgeons Predicted Risk Model
†Frailty = Presence of frailty and frailty syndromes

Predicted risk with surgery of death or major morbidity (all-cause) >50% at 1 year.
How frequent is a lower risk profile?

<table>
<thead>
<tr>
<th></th>
<th>TAVR Group (N=394)</th>
<th>Surgical Group (N=401)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>83.2±7.1</td>
<td>83.5±6.3</td>
</tr>
<tr>
<td>Female sex — no. (%)</td>
<td>183 (46.4)</td>
<td>189 (47.1)</td>
</tr>
<tr>
<td>NYHA class — no. (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class II</td>
<td>56 (14.2)</td>
<td>53 (13.2)</td>
</tr>
<tr>
<td>Class III</td>
<td>258 (65.5)</td>
<td>277 (69.1)</td>
</tr>
<tr>
<td>Class IV</td>
<td>80 (20.3)</td>
<td>71 (17.7)</td>
</tr>
<tr>
<td>STS PROM estimate†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean estimate — %</td>
<td>7.3±3.0</td>
<td>7.5±3.2</td>
</tr>
<tr>
<td>&lt;4% — no. (%)</td>
<td>33 (8.4)</td>
<td>42 (10.5)</td>
</tr>
<tr>
<td>4–10% — no. (%)</td>
<td>308 (78.2)</td>
<td>288 (71.8)</td>
</tr>
<tr>
<td>&gt;10% — no. (%)</td>
<td>53 (13.5)</td>
<td>71 (17.7)</td>
</tr>
<tr>
<td>Logistic EuroSCORE — %‡</td>
<td>17.6±13.0</td>
<td>18.4±12.8</td>
</tr>
</tbody>
</table>

Adams et al. NEJM 2014
Intermediate-risk patients are already referred to TAVI

Discussion

The prospective PRAGMATIC AS survey represents a snapshot of contemporary management of patients with degenerative AS in selected countries in Europe and highlights the following. 1) Risk estimation was primarily based on Heart Team decision. 2) Overall, nearly half of the patients were considered at low operative risk (these patients were predominantly sent for SAVR), a quarter of patients were at intermediate risk (two thirds of these underwent TAVI), and almost all patients at high risk were sent for TAVI. 3) Overall, 30-day all-cause mortality was low, being highest for patients at higher operative risk, and neurological events were rare. 4) TAVI was associated with more permanent pacemaker implantations and shorter hospital stay compared to SAVR.
Key Message

Intermediate risk patients have a better outcome
PARTNER 1B

R. Makkar et al. JACC 2014;63:901-911
2-Year All-Cause Mortality  CoreValve ADVANCE Registry

<table>
<thead>
<tr>
<th>Years Post-TAVI</th>
<th>STS≤7</th>
<th>STS&gt;7</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>697</td>
<td>671</td>
</tr>
<tr>
<td>1</td>
<td>591</td>
<td>415</td>
</tr>
<tr>
<td>2</td>
<td>298</td>
<td>279</td>
</tr>
<tr>
<td></td>
<td>214</td>
<td>143</td>
</tr>
</tbody>
</table>

P-value (log rank) <0.01
Key Message

TAVI is comparable to surgery in Intermediate risk patients
BERn-MUnich-rotterDAm

A 3-Center Comparison of 1-Year Mortality Outcomes Between Transcatheter Aortic Valve Implantation and Surgical Aortic Valve Replacement on the Basis of Propensity Score Matching Among Intermediate-Risk Surgical Patients

BERMUDA

510 matched patients (STS scores 3-8%)

255 TAVR patients
255 SAVR patients

Piazza, et al., J Am Coll Cardiol Intv 2013; 6: 443-51
30-day All-cause mortality

1-year All-cause mortality

**BERn-MUich-rotterDAm**

**30-day All-cause mortality**

- HR (95% CI): 1.12 (0.58-2.15); \( p = 0.74 \)

**1-year All-cause mortality**

- HR (95% CI): 0.90 (0.57-1.42); \( p = 0.64 \)
Transcatheter or Surgical Aortic-Valve Replacement in Intermediate-Risk Patients

Martin B. Leon, M.D., Craig R. Smith, M.D., Michael J. Mack, M.D.

Table 1. Characteristics of the Patients at Baseline.*

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>TAVR (N=1011)</th>
<th>Surgery (N=1021)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age — yr</td>
<td>81.5±6.7</td>
<td>81.7±6.7</td>
</tr>
<tr>
<td>Male sex — no. (%)</td>
<td>548 (54.2)</td>
<td>560 (54.8)</td>
</tr>
<tr>
<td>Body mass indexkg</td>
<td>28.6±6.2</td>
<td>28.3±6.2</td>
</tr>
<tr>
<td>STS risk score $^a$</td>
<td>5.4±2.1</td>
<td>5.8±1.9</td>
</tr>
</tbody>
</table>

*The hazard ratio for death from any cause or disabling stroke is 0.89 (95% CI, 0.71–1.09) for TAVR vs. surgery, P=0.25. The hazard ratio for death from any cause or disabling stroke is 0.87 (95% CI, 0.71–1.07) for TAVR vs. surgery, P=0.18.

The New England Journal of Medicine

Original Article
TAVI seems promising in low risk patients
The NOTION trial was the first to randomize TAVI with CoreValve to SAVR in low and intermediate risk patients.
### The NOTION Trial
Randomized Low-Risk Patients

<table>
<thead>
<tr>
<th>Main inclusion criteria</th>
<th>Main exclusion criteria</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Severe AS</td>
<td>• Severe CAD</td>
</tr>
<tr>
<td>• Age ≥70 years</td>
<td>• Severe other valve disease</td>
</tr>
<tr>
<td>• Life expectancy ≥ 1 year</td>
<td>• Prior heart surgery</td>
</tr>
<tr>
<td>• Suitable for TAVR &amp; SAVR</td>
<td>• Need for acute treatment</td>
</tr>
<tr>
<td></td>
<td>• Recent stroke or MI</td>
</tr>
<tr>
<td></td>
<td>• Severe lung disease</td>
</tr>
<tr>
<td></td>
<td>• Severe renal failure</td>
</tr>
</tbody>
</table>

*Thyregod et al., JACC 2015*
# The NOTION Trial
**Randomized Low-Risk Patients**

## NOTION Trial | Select Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic, % or mean ± SD</th>
<th>TAVI 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>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>NYHA class III or IV</td>
<td>48.6</td>
<td>45.5</td>
<td>0.61</td>
</tr>
</tbody>
</table>

*Thyregod et al., JACC 2015*
The NOTION Trial
Randomized Low-Risk Patients

P-Value (log-rank) = 0.43
The NOTION Trial
Randomized Low-Risk Patients
Key Message

FDA approved randomized trial for low risk patients:

- TAVI vs SAVR
- Age ≥ 65
- Medtronic / Evolut R
- Edwards LifeScience/ Sapien 3
- Boston Scientific / Lotus
Remaining issues to solve before expanding TAVI indications
Important limitation for expanding TAVI to low risk patients

1-Unknown Durability

2-Pacemaker

3-Stroke

4-Access to coronary arteries

5-Vascular complications

6-TAVI in bicuspid valves
What do we know about TAVI durability?
Average Survival for an IndividualBorn in the US in 1950

- Males
- Females

- 11.13 yrs
- 13.12 yrs
- 5.98 yrs
- 7.24 yrs

* Adapted from United States Social Security Life Tables (F. Bell and M. Miller)
TAVI durability up to 5 years

CoreValve CE Pivotal Trial

Kovac, Presented at ACC 2014

Mack et al., Lancet 2015
7 years follow-up of our CoreValve and SAPIEN XT patients

90 y.o.
NYHA I
No cardiovascular event
EOA: 1.7 cm² / Mean gradient 9 mmHg
Trace AR / LVEF 50%

86 y.o.
NYHA I
No cardiovascular event
EOA: 1.78 cm² / Mean gradient 8 mmHg
No AR / LVEF 48%
Corevalve Durability Example

2005: CoreValve case in Caracas.
Jose Condado, MD.

CoreValve 25 Fr

2015: 10 y Follow up

PG: 14.6 mm Hg
MG: 8 mm Hg
Trivial PVL

The News
Two Month Follow up of first South American patient shows 58 year old female is fully recovered and has resumed normal activity after non-surgical replacement of defective aortic heart valve using CoreValve's breakthrough ReValving™ procedure
04/04/2005

One of an ongoing series of early cases that demonstrate CoreValve's ReValving™ approach is a successful alternative to open heart surgery

"This patient's life has been transformed—without surgery—from being significantly debilitated to normal function as a direct result of ReValving. The procedure was performed in a hospital outside of a cardiac ICU and evaluated..."
What do we know about

Stroke post TAVI
FRANCE 2 registry (n=3191)

- 3.98% at one year
- major stroke 2.2%
- minor stroke 0.59%
- TIA 1.19%
- Mean delay: 2 (IQR: 0-7) days
- 48.5% within 2 days
- Increased mortality

Tchetch et al, JACC CVI 2014
Embolic protection devices

Conclusions—Embolic debris traveling to the brain was captured in 75% of transcatheter aortic valve replacement procedures where a filter-based embolic protection device was used. The debris consisted of fibrin, or amorphous calcium and connective tissue derived most likely from either the native aortic valve leaflets or aortic wall. (Circulation. 2013;127:2194-2201.)

Van Mieghem et al, Circulation 2013
Leaflets thrombosis

Makkar et al. NEJM 2015
What do we know about TAVI in bicuspid valves?
Procedural Challenges

- Heavily calcified leaflets
- Asymmetric orifice
- Highly angulated annulus
- Dilatation of the ascending aorta
- Sizing issues:
  - Basal virtual ring?
  - Intercommissural distance?

Valve misplacement

Assymetric valve expansion

High residual gradient

Paravalvular regurgitation

Durability

Mylotte et al, JACC 2014
What do we know about

New generation TAVI devices
Evidence Base
New Technologies

- The evidence base with these new devices is growing rapidly. In 2015, data from almost 4,000 patients implanted with new valve systems has been reported.
- Both clinical trial and real-world data are available for some systems.

The diagram shows the number of patients with data reported in the US and OUS for different valve systems. The data is as follows:

- **US**:
  - ACURATE neo: 1659
  - JenaValve: 339
  - Portico: 180
  - Direct Flow: 220
  - SAPIEN 3: 475
  - Lotus: 750
  - Evolut R: 251
  - others: 60

- **OUS**:
  - ACURATE neo: 339
  - JenaValve: 180
  - Portico: 220
  - Direct Flow: 475
  - SAPIEN 3: 750
  - Lotus: 251
  - Evolut R: 60
  - others: 60

The patients with data reported are shown on the x-axis, ranging from 0 to 2500.
Paravalvular Leak
Moderate / Severe at 30 Days

Valves designed to mitigate PVL have brought mod / severe rates to 5% or less

<table>
<thead>
<tr>
<th>Valve Type</th>
<th>N</th>
<th>% Patients with Moderate / Severe PVL at 30 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN XT</td>
<td>236</td>
<td>24.2%</td>
</tr>
<tr>
<td>PARTNER IIB</td>
<td>225</td>
<td>16.9%</td>
</tr>
<tr>
<td>CoreValve Extreme Risk</td>
<td>418</td>
<td>11.4%</td>
</tr>
<tr>
<td>CoreValve High Risk</td>
<td>356</td>
<td>9.0%</td>
</tr>
<tr>
<td>Portico CE Study</td>
<td>169</td>
<td>5.3%</td>
</tr>
<tr>
<td>ACURATE CE Trial</td>
<td>89</td>
<td>4.9%</td>
</tr>
<tr>
<td>SAPIEN 3 PARTNER II S3</td>
<td>1504</td>
<td>3.8%</td>
</tr>
<tr>
<td>Evolut R CE</td>
<td>58</td>
<td>3.4%</td>
</tr>
<tr>
<td>Direct Flow DISCOVER CE</td>
<td>74</td>
<td>1.4%</td>
</tr>
<tr>
<td>Lotus REPRISE II + Ext</td>
<td>177</td>
<td>0.6%</td>
</tr>
</tbody>
</table>

Major Vascular Complications
Rates According to VARC 2

Contemporary delivery systems have allowed treatment of a broader range of patients through transfemoral access while simultaneously bringing MVC rates down.
Permanent Pacemakers
Rate at 30 Days

PPM rates with the new valves are largely similar, with the exception of Lotus

% Patients with PPM at 30 Days

<table>
<thead>
<tr>
<th>Valve</th>
<th>Rate at 30 Days</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAPIEN XT PARTNER IIB</td>
<td>6.4%</td>
<td>284</td>
</tr>
<tr>
<td>SAPIEN PARTNER IIB</td>
<td>5.9%</td>
<td>276</td>
</tr>
<tr>
<td>CoreValve Extreme Risk</td>
<td>21.6%</td>
<td>489</td>
</tr>
<tr>
<td>CoreValve High Risk</td>
<td>19.8%</td>
<td>390</td>
</tr>
<tr>
<td>Portico</td>
<td>13.1%</td>
<td>220</td>
</tr>
<tr>
<td>ACURATE CE Trial</td>
<td>9.0%</td>
<td>89</td>
</tr>
<tr>
<td>SAPIEN 3 P II S3 HR</td>
<td>14.6%</td>
<td>583</td>
</tr>
<tr>
<td>Evolut R CE</td>
<td>11.7%</td>
<td>60</td>
</tr>
<tr>
<td>Direct Flow DISCOVER</td>
<td>17.0%</td>
<td>100</td>
</tr>
<tr>
<td>Lotus REPRISE II + Ext</td>
<td>28.9%</td>
<td>250</td>
</tr>
</tbody>
</table>

Predictors of AV block after TAVI

- Pre existing RBBB
- Non coronary cusp calcification
- Depth of biosprothesis implantation
- QRS duration after TAVI (QRSd).

*Piazza et al EuroIntervention (2008) ;4:242-249*
*Bleiziffer et al Jacc cardiac intervention 2010; 3:524-530*
*Latsios et al Catheterization and Cardiovascular Interventions 76:431-439 (2010)*
*Tchetche et al EuroIntervention 2012;8:556-562*
*Mouillet et al Catheterization and Cardiovascular Interventions 81:882–887 (2013)*
*Baan et al*
Pacemaker after TAVI: no impact on mortality

Three large studies demonstrate no association between pacemaker implantation and mortality


No mortality differences between those patients receiving a new pacemaker and those without a new pacemaker out to 6 months.
CONCLUSION
• TAVI is equal to surgery in intermediate risk patients.

• TAVI seems is safe in low-risk patients

• TAVI prostheses are durable up to five years and probably beyond.

• Examples of patients with functioning prosthesis up to 12 years

• TAVI is ready for prime time in intermediate risk patients

• Remaining issues to solve before expanding indications to low risk patients
THANK YOU