3-Year Results From the US Pivotal High Risk Randomized Trial Comparing Self-Expanding Transcatheter and Surgical Aortic Valves

G. Michael Deeb, MD
On Behalf of the US Pivotal Trial Investigators
Dr. Deeb serves:
• On an Advisory Board, as a Proctor and Research Investigator for Medtronic
• As a Consultant and Research Investigator for Edwards Lifesciences
• As a Consultant and Proctor for Terumo
• As a Research Investigator for Gore

• He receives no personal remunerations

Medtronic personnel performed all statistical analyses and verified the accuracy of the data, and assisted in the graphical display of the data presented.
Background

• In years 1 and 2 of this randomized high-risk study, TAVR with self-expanding valve showed survival advantage (clinical benefit) over surgical AVR.¹,²

• This analysis presented today was to determine:
  — If the clinical benefit is sustained for TAVR vs. SAVR through 3 years
  AND
  — If signals of hemodynamic deterioration exist

Pivotal Trial Design

US Pivotal Trial

- Extreme Risk
  - Iliofemoral Access > 18 Fr Sheath
    - TAVR Iliofemoral
    - TAVR Non-Iliofemoral

- High Risk
  - Randomization* 1:1
    - TAVR (any route)
    - SAVR (any type)

* Randomization stratified by intended access site
Study Device and Access Routes

4 Valve Sizes (23, 26, 29, 31 mm) (18–29 mm Annular Range)

18F Delivery System

Transfemoral Subclavian Direct Aortic

All Access
Inclusion Criteria

- Severe aortic stenosis: $\text{AVA} \leq 0.8 \text{ cm}^2$ OR $\text{AVA/IA} \leq 0.5 \text{ cm}^2/\text{m}^2$ AND $\text{MVG} > 40 \text{ mm Hg}$ OR peak velocity $> 4 \text{ m/sec}$ at rest or with dobutamine stress echocardiogram if LVEF <50%

- NYHA functional class II or greater for heart failure

- 30-Day mortality risk of $\geq 15\%$ AND combined mortality/morbidity <50% as assessed by 2 local CV surgeons and 1 cardiologist (STS PROM & Incrementals)

- Patient eligibility verified by a National Screening Committee
Exclusion Criteria

- Recent active GI bleed <3 months
- Recent stroke <6 months
- Recent MI ≤30 days
- Any interventional procedure with BMS (<30 days) or DES (<6 months)
- Significant untreated CAD
- Creatinine clearance <20 mL/min
- LVEF <20%
- Life expectancy <1 year due to comorbidities
- Annulus <18 mm or >29 mm
Methodology

• 3-Year follow-up analysis with a median of 35.8 months TAVR and 34.6 months SAVR
• Surgical valve selection based on the surgeons preference
• Site-reported echocardiographic results through 3 years
• Signals of hemodynamic deterioration was defined as an increase in mean AVG of >50% from 1-month to 3-year follow-up
• Event rates are presented as Kaplan-Meier estimates and comparisons are based on two-tailed log-rank test
US Pivotal Trial
High Risk 3-Year Results
As-Treated Population
N=750

Underwent attempted TAVR
N=391

1-Year TAVR
N=324/329 (98.5%)

2-Year TAVR
N=280/297 (94.3%)

3-Year TAVR
N=228/246 (92.7%)

Underwent attempted SAVR
N=359

1-Year SAVR
N=265/282 (94.0%)

2-Year SAVR
N=219/235 (93.2%)

3-Year SAVR
N=179/194 (92.3%)
# Baseline Demographics

<table>
<thead>
<tr>
<th>Characteristic, mean ± SD or %</th>
<th>TAVR N=391</th>
<th>SAVR N=359</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>83.2 ± 7.1</td>
<td>83.3 ± 6.4</td>
</tr>
<tr>
<td>Men</td>
<td>52.9</td>
<td>52.4</td>
</tr>
<tr>
<td>Society of Thoracic Surgeons (STS) Predicted Risk of Mortality (%)</td>
<td>7.3 ± 3.0</td>
<td>7.5 ± 3.3</td>
</tr>
<tr>
<td>New York Heart Association (NYHA) class III/IV</td>
<td>85.4</td>
<td>86.9</td>
</tr>
<tr>
<td>Prior coronary artery bypass surgery</td>
<td>29.4</td>
<td>31.5</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>34.8*</td>
<td>45.1*</td>
</tr>
<tr>
<td>Insulin requiring</td>
<td>11.0</td>
<td>13.1</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>12.5</td>
<td>14.0</td>
</tr>
<tr>
<td>Modified Rankin 0 or 1</td>
<td>74.5</td>
<td>87.2</td>
</tr>
<tr>
<td>Modified Rankin &gt;1</td>
<td>25.5</td>
<td>12.8</td>
</tr>
<tr>
<td>STS severe chronic lung disease</td>
<td>13.6</td>
<td>8.9</td>
</tr>
</tbody>
</table>

*P <0.01

*ACC2016*
# Incremental Risk Factors

<table>
<thead>
<tr>
<th>Assessment, %</th>
<th>TAVR N=391</th>
<th>SAVR N=359</th>
</tr>
</thead>
<tbody>
<tr>
<td>Home oxygen</td>
<td>12.8</td>
<td>11.4</td>
</tr>
<tr>
<td>Liver cirrhosis</td>
<td>2.6</td>
<td>1.9</td>
</tr>
<tr>
<td>Anemia with prior transfusion</td>
<td>18.2</td>
<td>15.9</td>
</tr>
<tr>
<td>Severe (&gt;5) Charlson comorbidity*</td>
<td>54.0</td>
<td>57.8</td>
</tr>
<tr>
<td>Falls in past 6 months</td>
<td>18.5</td>
<td>18.1</td>
</tr>
<tr>
<td>5-Meter gait speed &gt;6 seconds</td>
<td>79.3</td>
<td>80.2</td>
</tr>
<tr>
<td>Assisted living</td>
<td>9.7</td>
<td>10.9</td>
</tr>
<tr>
<td>Katz ≥1 activities of daily living deficits</td>
<td>10.7</td>
<td>12.3</td>
</tr>
</tbody>
</table>

*Charlson Score: = 1 MI, CHF, PVD, CVD, dementia, chronic lung disease, connective tissue disease, ulcer, mild liver disease, DM; = 2 hemiplegia, mod-severe kidney disease, diabetes with end organ damage, leukemia, lymphoma; = 3 moderate or severe liver disease; = 6 metastatic solid tumor, AIDS.
All-Cause Mortality or Stroke

Log-rank P=0.006  Δ9.4

No. at Risk 0 12 24 36
TAVR 391 319 273 165
SAVR 359 257 208 128
All-Cause Mortality or Major Stroke

Log-rank P = 0.046

Δ6.6

41.6

35.0

TAVR SAVR

16.1 22.2

24.0 32.8

391 359

327 272

284 225

173 143

No. at Risk

TAVR

SAVR

Months

0 12 24 36

All-Cause Mortality or Major Stroke (%)
All Stroke

Log-rank P=0.034  Δ6.4

TAVR  SAVR

0%  5%  10%  15%  20%  25%  30%  35%  40%

No. at Risk  0  12  24  36
TAVR  391  319  273  165
SAVR  359  257  208  128

Months

All Stroke (%)
All-Cause Mortality

- Log-rank P=0.068
- Δ6.2

Number at Risk:
- TAVR: 391, 335, 292, 235, 180
- SAVR: 359, 283, 235, 148

Percentage:
- TAVR: 18.9, 14.1, 21.9, 29.0
- SAVR: 39.1, 32.9

Months: 0, 12, 24, 36
## Sub-Group Analysis for 3-Year Mortality

### CoreValve US Clinical Trials

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All-cause Death at 3 Years KM Rates</th>
<th>Hazard Ratios (95% CI)</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
<td>Hazard Ratios (95% CI)</td>
</tr>
<tr>
<td>Age, years</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;85</td>
<td>38.8</td>
<td>41.9</td>
<td>0.89 (0.63, 1.24)</td>
</tr>
<tr>
<td>≤85</td>
<td>27.5</td>
<td>36.8</td>
<td>0.70 (0.49, 1.00)</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>34.8</td>
<td>40.7</td>
<td>0.84 (0.60, 1.16)</td>
</tr>
<tr>
<td>Female</td>
<td>30.7</td>
<td>37.1</td>
<td>0.75 (0.52, 1.08)</td>
</tr>
<tr>
<td>BMI, kg/m²</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤30</td>
<td>35.4</td>
<td>41.3</td>
<td>0.80 (0.60, 1.06)</td>
</tr>
<tr>
<td>&gt;30</td>
<td>26.5</td>
<td>34.2</td>
<td>0.75 (0.46, 1.23)</td>
</tr>
<tr>
<td>LVEF, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤60</td>
<td>35.7</td>
<td>38.7</td>
<td>0.89 (0.66, 1.21)</td>
</tr>
<tr>
<td>&gt;60</td>
<td>28.3</td>
<td>38.8</td>
<td>0.65 (0.43, 1.00)</td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34.7</td>
<td>43.0</td>
<td>0.74 (0.55, 1.01)</td>
</tr>
<tr>
<td>Yes</td>
<td>29.6</td>
<td>34.5</td>
<td>0.82 (0.55, 1.25)</td>
</tr>
</tbody>
</table>
# Sub-Group Analysis for 3-Year Mortality

## CoreValve US Clinical Trials

### ACC2016

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>All-cause Death at 3 Years KM Rates</th>
<th>Hazard Ratios (95% CI)</th>
<th>Interaction P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
<td></td>
</tr>
<tr>
<td>Prior CABG</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34.8</td>
<td>42.2</td>
<td>0.78 (0.59, 1.04)</td>
</tr>
<tr>
<td>Yes</td>
<td>28.3</td>
<td>32.5</td>
<td>0.81 (0.50, 1.32)</td>
</tr>
<tr>
<td>PVD</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>34.4</td>
<td>38.6</td>
<td>0.84 (0.61, 1.16)</td>
</tr>
<tr>
<td>Yes</td>
<td>30.0</td>
<td>38.8</td>
<td>0.73 (0.49, 1.07)</td>
</tr>
<tr>
<td>Hypertension</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>50.4</td>
<td>59.8</td>
<td>0.56 (0.21, 1.44)</td>
</tr>
<tr>
<td>Yes</td>
<td>32.1</td>
<td>38.2</td>
<td>0.80 (0.62, 1.03)</td>
</tr>
<tr>
<td>STS Score</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤7%</td>
<td>27.1</td>
<td>38.5</td>
<td>0.66 (0.46, 0.95)</td>
</tr>
<tr>
<td>&gt;7%</td>
<td>39.3</td>
<td>39.8</td>
<td>0.95 (0.68, 1.32)</td>
</tr>
</tbody>
</table>
All-Cause Mortality – STS ≤ 7%

Log-rank P=0.018  Δ11.4

No. at Risk

0 12 24 36

TAVR 202 182 166 101
SAVR 181 151 121 71

TAVR  SAVR

14.0 26.2 14.9 27.1
10.4  

Graph showing the comparison of All-Cause Mortality between TAVR and SAVR with STS ≤ 7%.
MACCE

Log-rank P=0.025  Δ7.7

No. at Risk 0 12 24 36
TAVR 391 310 263 158
SAVR 359 255 205 127

MACCE (%) 0% 10% 20% 30% 40% 50% 60%
## Other Endpoints at 3 Years

<table>
<thead>
<tr>
<th>Events</th>
<th>TAVR</th>
<th>SAVR</th>
<th>Log-Rank P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life threatening or disabling bleeding</td>
<td>19.1</td>
<td>41.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>19.8</td>
<td>36.3</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Reintervention</td>
<td>2.5</td>
<td>0.4</td>
<td>0.020</td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>28.0</td>
<td>14.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Aortic valve hospitalization</td>
<td>27.6</td>
<td>21.9</td>
<td>0.087</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.9</td>
<td>1.7</td>
<td>0.346</td>
</tr>
</tbody>
</table>
Over 90% of Patients Had Class I or II Symptoms at 3 Years

NYHA Class

<table>
<thead>
<tr>
<th>Year</th>
<th>TAVR (N=391)</th>
<th>SAVR (N=352)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>69.8%</td>
<td>66.5%</td>
</tr>
<tr>
<td>1 Year</td>
<td>57.8%</td>
<td>57.3%</td>
</tr>
<tr>
<td>2 Years</td>
<td>63.1%</td>
<td>57.7%</td>
</tr>
<tr>
<td>3 Years</td>
<td>52.3%</td>
<td>55.5%</td>
</tr>
</tbody>
</table>
Valve Hemodynamics*

TAVR had significantly better valve performance vs SAVR at all follow-ups (P<0.001)

*Site-reported
Hemodynamic Signals*

Mean AV Gradients for Patients With >50% Increase From 1 Month to 3 Years

- **TAVR=18/189 (9.5%)**
- **SAVR=17/135 (12.6%)**

*Site-reported*
Total Aortic Regurgitation*

Significantly less AR with SAVR vs. TAVR at Each Time Point (P<0.001)

<table>
<thead>
<tr>
<th></th>
<th>TAVR</th>
<th>SAVR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Discharge</td>
<td>64.4</td>
<td>78.4</td>
</tr>
<tr>
<td></td>
<td>28.3</td>
<td>34.9</td>
</tr>
<tr>
<td></td>
<td>38.6</td>
<td>42.2</td>
</tr>
<tr>
<td></td>
<td>56.6</td>
<td>51.0</td>
</tr>
<tr>
<td></td>
<td>6.8</td>
<td>28.1</td>
</tr>
</tbody>
</table>

TAVR: N=371, SAVR: N=319

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Conclusions 1

At 3 years in this randomized, prospective, multicenter trial:

- Incidence of all-cause mortality or stroke significantly favors TAVR
- Incidence of all-cause mortality or major stroke significantly favors TAVR
- Incidence of any stroke significantly favors TAVR
- The difference in all-cause mortality between groups maintains separation favoring TAVR
- Incidence of MACCE significantly favors TAVR
Conclusions II

At 3 years in this randomized, prospective, multicenter trial:

- TAVR showed significantly lower, single-digit mean gradients, and larger effective orifice areas than SAVR at all time points.
- Incidence of moderate or greater AR significantly favored SAVR.
- Signals of hemodynamic deterioration defined as an increase in mean gradient of >50% was low and similar between groups.

ACC2016
At 3 years in this randomized, prospective, multicenter trial:

- TAVR showed significantly lower, single-digit mean gradients, and larger effective orifice areas than SAVR at all time points.
- Incidence of moderate or greater AR significantly favored SAVR.
- Signals of hemodynamic deterioration defined as an increase in mean gradient of >50% was low and similar between groups.
- Through 3 years TAVR with a self expanding device maintains clinical benefit over SAVR.
Accepted Manuscript

Three-Year Outcomes in High-Risk Patients Who Underwent Surgical or Transcatheter Aortic Valve Replacement

G. Michael Deeb, MD, Michael J. Reardon, MD, Stan Chetcuti, MD, Himanshu J. Patel, MD, P. Michael Grossman, MD, Steven J. Yakubov, MD, Neal S. Kleiman, MD, Joseph S. Coselli, MD, Thomas G. Gleason, MD, Joon Sup Lee, MD, James B. Hermiller, Jr., MD, John Heiser, MD, William Merhi, MD, George L. Zorn, III, MD, Peter Tadros, MD, Newell Robinson, MD, George Petrossian, MD, G. Chad Hughes, MD, J. Kevin Harrison, MD, Brijeshwar Maini, MD, Mubashir Mumtaz, MD, John Conte, MD, Jon Resar, MD, Vicken Aharonian, MD, Thomas Pfeffer, MD, Jae K. Oh, MD, Hongyan Qiao, PhD, David H. Adams, MD, Jeffrey J. Popma, MD, for the CoreValve US Clinical Investigators
On Behalf of the US Pivotal Clinical Trial Investigators, I Would like to Thank the ACC for the Opportunity and Privilege of Presenting the Data from this Trial