Zilver PTX Drug-Eluting Stent Mortality Analysis

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  - Boston Sci
  - Cook
  - Cardinal Health
  - Gore
  - Medtronic
Recent Correction to 5-year Zilver PTX Publication

• Katsanos K, et al. meta-analysis published December 6, 2018 in JAHA

• Data reviewed and errors identified in 5-year Zilver PTX publication
  • Incorrect patient flow diagram submitted during final publication process
  • Mortality numbers transposed in overall primary randomization comparison

• Corrections submitted to Circulation on December 18, 2018 and published on February 19, 2019

<table>
<thead>
<tr>
<th>Risk Ratio (95% CI) for All-cause death at 4 to 5 years</th>
</tr>
</thead>
<tbody>
<tr>
<td>Based on original figure</td>
</tr>
<tr>
<td>Based on corrected figure</td>
</tr>
</tbody>
</table>

* Katsanos K, et al. 2018. JAHA
RCT Patient Flowchart

Primary Randomization

PTA
n = 237

Secondary Randomization

Suboptimal PTA

Optimal PTA

Bare Zilver

Zilver PTX

Zilver PTX
n = 242

Zilver PTX
Randomized Trial

n = 242
Zilver PTX RCT – Intent to Treat
5-year Mortality Analysis

PTA*
- n = 237
  - Died = 24
  - KM = 15.3%

Zilver PTX
- n = 242
  - Died = 41
  - KM = 22.1%

p=0.04

*40% of PTA group = Zilver PTX
Zilver PTX Key Points

• ITT data available to Katsanos K, et al. did not identify all patients who were treated with a Zilver PTX stent
  • Patient-level data were not used in the analysis
  • 40% of patients in the PTA group were treated with a Zilver PTX stent within the first year due to protocol-specified cross-over

• As-treated patient level analysis demonstrates no difference in mortality rate for Zilver PTX compared to PTA/BMS
  • Causes of death for Zilver PTX are similar to PTA/BMS
The RCT study design allowed optimal PTA patients requiring reintervention within the first year post-procedure to cross over to treatment with the Zilver PTX stent.
RCT Patient Flowchart

Primary Randomization

Suboptimal PTA
- Bare Zilver
  - n = 56

Optimal PTA
- n = 118

Secondary Randomization

Zilver PTX
- n = 242 (41)
- PTA
  - n = 237
- Zilver
  - n = 63 (7)

Long-term

Zilver PTX → BMS
- n = 30 (0)
(all within 1st year)

PTA → Zilver PTX
- n = 1 (0)

PTA → BMS
- n = 1 (1)

BMS
- n = 55 (7)

Numbers in parentheses indicate patient deaths.
PTA Group
Composed of Zilver PTX Patients

40% of PTA group = Zilver PTX
70% of patients in study = Zilver PTX
Zilver PTX RCT
5-year Mortality Analysis

PTA / BMS
n = 143
Died = 17
KM = 17.6%

Zilver PTX
n = 242
Died = 41
KM = 22.1%

Zilver PTX
n = 94
Died = 7
KM = 9.4%
Zilver PTX RCT – As-Treated
Final 5-year Mortality Analysis

No significant difference between Zilver PTX and PTA / BMS

p = 0.53
Covariate Analysis – RCT

• Cox proportional hazards model

• Included comorbidities that may be related to mortality as well as other factors of interest

• No significant difference between Zilver PTX and PTA / BMS (p=0.51)

<table>
<thead>
<tr>
<th>Covariate</th>
<th>Multivariate p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>0.0002</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.09</td>
</tr>
<tr>
<td>Diabetes</td>
<td>0.11</td>
</tr>
<tr>
<td>Lesion length</td>
<td>0.12</td>
</tr>
<tr>
<td>Carotid disease</td>
<td>0.13</td>
</tr>
<tr>
<td>Claudication/CLI</td>
<td>0.14</td>
</tr>
<tr>
<td>Smoking</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac arrhythmia</td>
<td>0.21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>0.46</td>
</tr>
<tr>
<td>Gender</td>
<td>0.50</td>
</tr>
<tr>
<td>PTX vs. PTA/BMS</td>
<td>0.51</td>
</tr>
<tr>
<td>Country (US, JP, Germany)</td>
<td>0.59</td>
</tr>
<tr>
<td>Pulmonary disease</td>
<td>0.61</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>0.63</td>
</tr>
<tr>
<td>Previous MI</td>
<td>0.99</td>
</tr>
</tbody>
</table>
Dose Analysis

• Meta-analysis from Katsanos incorrectly identified Zilver PTX as a high dose device, led to incorrect dose calculation
  • Total amount of paclitaxel on a Zilver PTX stent is approximately 10% to 20% of the amount on a DCB

• Zilver PTX has similar total amount of paclitaxel compared to Eluvia with no polymer and a shorter paclitaxel exposure
## Dose Analysis

<table>
<thead>
<tr>
<th>Device</th>
<th>Paclitaxel Density</th>
<th>Total Paclitaxel Load (7 x 80 mm)</th>
<th>Paclitaxel Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Boston Scientific Eluvia</strong></td>
<td>0.167 µg/mm² total area</td>
<td>0.3 mg</td>
<td>≥ 1 year permanent polymer</td>
</tr>
<tr>
<td><strong>Cook Zilver PTX</strong></td>
<td>3 µg/mm² abluminal area</td>
<td>0.7 mg</td>
<td>2 months polymer free</td>
</tr>
<tr>
<td><strong>Bard Lutonix DCB</strong></td>
<td>2 µg/mm² abluminal area</td>
<td>3.5 mg</td>
<td>&lt; 2 months</td>
</tr>
<tr>
<td><strong>Medtronic In.Pact DCB</strong></td>
<td>3.5 µg/mm² abluminal area</td>
<td>6.9 mg</td>
<td>&lt; 2 months</td>
</tr>
</tbody>
</table>

### 5-year Mortality Rate

<table>
<thead>
<tr>
<th>Dose Group 1</th>
<th>Dose Group 2</th>
<th>Dose Group 3</th>
<th>Dose Group 4</th>
<th>Dose Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>11.5%</td>
<td>13.6%</td>
<td>13.4%</td>
<td>20.0%</td>
<td>13.2%</td>
</tr>
</tbody>
</table>

p=0.72

~0.3 mg  
~30 mm  

Increasing Total Paclitaxel Dose
Increasing Lesion Length  

~3 mg  
~300 mm  

No impact of Zilver PTX paclitaxel dose on mortality rate
## Causes of Death Through 5 Years – RCT and BMS

<table>
<thead>
<tr>
<th>Cause</th>
<th>RCT – PTX (n=336)</th>
<th>RCT – PTA / BMS (n=143)</th>
<th>p-value</th>
<th>Zilver BMS Study* (n=110)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>4.8%</td>
<td>5.6%</td>
<td>0.66</td>
<td>4.5%</td>
</tr>
<tr>
<td>Cancer</td>
<td>4.8%</td>
<td>1.4%</td>
<td>0.11</td>
<td>6.4%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.8%</td>
<td>1.4%</td>
<td>&gt; 0.99</td>
<td>1.8%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6%</td>
<td>0.7%</td>
<td>&gt; 0.99</td>
<td>0.0%</td>
</tr>
<tr>
<td>Trauma</td>
<td>0.0%</td>
<td>1.4%</td>
<td>0.09</td>
<td>0.0%</td>
</tr>
<tr>
<td>GI</td>
<td>0.3%</td>
<td>0.0%</td>
<td>&gt; 0.99</td>
<td>0.9%</td>
</tr>
<tr>
<td>Multiple/Unknown</td>
<td>2.1%</td>
<td>1.4%</td>
<td>&gt; 0.99</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

No increased rate of cardiovascular, cancer, or other cause of death for Zilver PTX compared to PTA or BMS

* The Zilver BMS study enrolled 110 patients with femoropopliteal artery disease for 5-year follow-up, ClinicalTrials.gov Identifier: NCT00827619
Japan Post-Market Studies – Zilver PTX and BMS Single Arm Studies

- No exclusion criteria
  - Challenging patient population, including CLI patients
- 904 Zilver PTX patients
  - 5-year follow-up
- 190 BMS patients
  - 3-year follow-up
  - Separate study, not randomized
- No significant difference in mortality (p=0.92)
- Same mortality rate of 5.1% per year for PTX & BMS
  - Linear from 0-3 and 3-5 years

### Mortality

<table>
<thead>
<tr>
<th></th>
<th>PTX</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 years</td>
<td>15.6%</td>
<td>15.3%</td>
</tr>
<tr>
<td>5 years</td>
<td>25.7%</td>
<td>-</td>
</tr>
</tbody>
</table>
Dose Exposure Analysis – Japan

<table>
<thead>
<tr>
<th></th>
<th>Dose Group 1</th>
<th>Dose Group 2</th>
<th>Dose Group 3</th>
<th>Dose Group 4</th>
<th>Dose Group 5</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year Mortality Rate</td>
<td>17.4%</td>
<td>23.9%</td>
<td>16.1%</td>
<td>21.3%</td>
<td>21.5%</td>
</tr>
<tr>
<td>p</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

No impact of Zilver PTX paclitaxel dose on mortality rate
## Causes of Death Through 5 Years – RCT & Japan

<table>
<thead>
<tr>
<th>Cause</th>
<th>RCT – PTX (n=336)</th>
<th>RCT – PTA / BMS (n=143)</th>
<th>Japan – PTX (n=904)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>4.8%</td>
<td>5.6%</td>
<td>6.1%</td>
</tr>
<tr>
<td>Cancer</td>
<td>4.8%</td>
<td>1.4%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Pulmonary</td>
<td>1.8%</td>
<td>1.4%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Stroke</td>
<td>0.6%</td>
<td>0.7%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Trauma/Accident</td>
<td>0.0%</td>
<td>1.4%</td>
<td>0.2%</td>
</tr>
<tr>
<td>GI</td>
<td>0.3%</td>
<td>0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Infection</td>
<td>0%</td>
<td>0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Renal</td>
<td>0%</td>
<td>0%</td>
<td>0.8%</td>
</tr>
<tr>
<td>Multiple/Unknown</td>
<td>2.1%</td>
<td>1.4%</td>
<td>5.9%</td>
</tr>
</tbody>
</table>

*Preliminary analysis

Similar causes of death as RCT
No Increased Long-term Mortality with DES

- Medicare CMS population
- 51,456 patients
  - 47,351 BMS
  - 4,105 DES (Zilver PTX)
- Similar mortality for BMS and DES through 4.1 years
  - Overall adjusted p=0.53
  - Without CLI adjusted p=0.95
  - With CLI adjusted p=0.32

Conclusions

• Conclusion of Katsanos K, et al. was not based on patient-level data and miscalculated the dose exposure

• As-treated patient-level analysis of RCT data shows no increased long-term mortality risk with Zilver PTX compared to PTA and BMS
  • Covariate analysis supports no significant difference
  • No impact of Zilver PTX paclitaxel dose on mortality rate
  • No significant differences in causes of death

• Mortality rates for the Zilver PTX stent are consistent with rates reported in literature for PAD patients

• Japan data confirm RCT findings showing no increased long-term mortality risk with Zilver PTX compared to BMS

• Cook will continue to work with global regulatory authorities and independent physician led groups to evaluate safety using patient-level data