Insights on paclitaxel safety from the femoral-popliteal RCTs

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Disclosures

Consulted for:
Boston Scientific, Surmodics, Cagent, CSI, Philips, Medtronic, Intervene, Limflow, Silk Road, Cagent, Devoro
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Summary Level Meta-analysis of Paclitaxel in the Femoropopliteal Disease

4/5 Years

Paclitaxel-Femoropopliteal Arteries

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>Weight (fixed)</th>
<th>Weight (random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>THUNDER</td>
<td>12</td>
<td>8</td>
<td>1.69</td>
<td>1.69</td>
<td>[0.76; 3.78]</td>
<td>23.9%</td>
<td>26.9%</td>
</tr>
<tr>
<td>ZILVER-PTX</td>
<td>42</td>
<td>12</td>
<td>2.09</td>
<td>2.09</td>
<td>[1.13; 3.65]</td>
<td>47.7%</td>
<td>46.3%</td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>54</td>
<td>24</td>
<td>1.92</td>
<td>1.92</td>
<td>[0.86; 4.30]</td>
<td>28.5%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

Random effects model

Heterogeneity: $I^2 = 0\%$, $Q^2 = 0$, $p = 0.92$

Based on earnings reports, market research reports, physician & hospital inputs

Katsanos et al. JAHA 2018;7:e011245
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Characteristics of These Trials

- Powered for one-year patency, not long-term mortality.

- Small control groups (some RCTs 2:1) = unstable estimates.

- Was there bias in mortality assessment (ascertainment bias)?

- Were both groups treated the same after randomization (treatment bias?)

- Is there a dose response (biologic gradient)?
- Is there clustering of deaths as to cause (mechanism)?
- Is there a consistent danger signal?
- Is this a causal relationship or an association?

Austin Bradford-Hill. Criteria for causation, 1965
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No Dose Effect On Mortality

Dose administered vs All-cause mortality

Dose tercile vs Freedom from All-cause mortality

FDA Panel June 19-20, 2019 Figures 37-40
Schneider et al. J Am Coll Cardiol 2019;73:2550
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No Dose Effect on Mortality

Pooled IN.PACT IDE and Japan Trials
5-Year Mortality by Dose Tercile (As Treated)

Presented by L. Mauri, MD
FDA Panel, June 19, 2019.

VIVA/Namsa
Individual Patient Data Project

No dose effect: Medium dose lower risk than low or high dose.

K Rocha-Singh, TCT 2019
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Ascertainment Bias: When Missing Patients Were Identified the Risk Decreased

5 Year Point Estimate from FDA: RR 1.72

After Vital Status Ascertainment: 1.57

Decrease 21%

Pooled IN.PACT IDE and Japan: Mortality difference between DCB and PTA through 5 years Before (4%) and after (2.7%) updated vital status data (As Treated)

Hazard Ratio 1.63→1.39
Decrease 38%

FDA panel packet June 19-20, 2019 Whatley E. Presentation at FDA panel: June 19, 2019
Mauri L. Presentation at FDA panel June 20, 2019
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Geographic Factors Play a Role

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Follow-up Visit Attendance by Region

Treatment bias?

DCB and PTA patients treated differently
Difference in treatment is greater in US than other geographies

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Efficacy Has Been Consistent But the Mortality Risk Has Not

Improved vital status follow up
Ascertainment bias

Geographic variation
Inconsistent signal
Treatment bias?
“The Panel concluded that a late mortality signal associated with the use of paclitaxel-coated devices to treat femoropopliteal PAD was present. …the magnitude of the signal should be interpreted with caution because of multiple limitations in the available data including… small sample size, pooling of studies of different paclitaxel-coated devices that were not intended to be combined, substantial amounts of missing study data…

No clear evidence of a paclitaxel dose effect on mortality, and no identified pathophysiologic mechanism for the late deaths.”
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SWEDEPAD RCT

- **SWEDEPAD RCT**
  - **Nordanstig et al.** *N Engl J Med* 2020, Dec 9, DOI: 10.1056
  - 2289 patients up to 4 years F/U
  - Paclitaxel vs plain device
  - CLTI 1480, claudication 809
  - Femoral-popliteal target lesion >80%
  - Lost to follow up 0
  - Overall mortality:
    - drug-10.2% vs non-drug-9.9% (HR 1.06)

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**Overall Population**

- **Hazard ratio, 1.06 (95% CI, 0.92–1.22)**

**Cumulative Incidence of Death (%)**

- **Years since Randomization**
  - **0**
  - **1**
  - **2**
  - **3**
  - **4**

**Drum-coated device**

**Uncoated device**

**No. at Risk**

- **Drug-coated device**
  - 1149
  - 1032
  - 728
  - 386
  - 131

- **Uncoated device**
  - 1140
  - 1027
  - 729
  - 403
  - 151

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Conclusion

• New data with more to follow.

• Working together: problem-solving across specialties, countries, manufacturers, regulatory agencies.

• Paclitaxel consistently efficacious but mortality signal not consistent.
  • No dose response and no mechanism.
  • Signal diminished with vital status ascertainment.
  • Signal primarily observed in the US.
  • Possibility of treatment bias associated with trial design or practice patterns may help explain inconsistency of signal.

• Trial design improvements: size, quality of follow-up, veracity of medical management and vital status ascertainment.