What we know about the paclitaxel-related mortality in femoro-popliteal arteries, and how it impacts my practice

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Disclosure

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I have potential conflicts of interest to report:

- [ ] Consulting BD consultant
- [ ] Employment in industry
- [ ] Stockholder of a healthcare company
- [ ] Owner of a healthcare company
- [ ] Other(s)

- [ ] I do not have any potential conflict of interest
Authors conclusion: there is >50% increased risk of all-cause death beyond the first year after the use of paclitaxel-coated balloons and stents in the femoropopliteal artery.

Actual causes remain unknown.

All-cause patient death was evaluated as a primary safety measure in 28 RCTs (4663 patients, 89% with claudication).

**Table S2. Design characteristics of the tested paclitaxel DES and DCB devices.**

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Paclitaxel dose (µg/mm²)</th>
<th>Excipient/spacer</th>
<th>Manufacturer</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT</td>
<td>3.5 µg/mm² (3.7 µg/mm²)</td>
<td>Urea (FreePac)</td>
<td>Medtronic (dose based on FDA submission)</td>
</tr>
<tr>
<td>ZILVER-PTX</td>
<td>3.0 µg/mm² (0.37 µg/mm²)</td>
<td>None (polymer-free stent)</td>
<td>COOK Medical (area adjusted dose in case of stents)</td>
</tr>
<tr>
<td>Cotavance</td>
<td>3.0 µg/mm²</td>
<td>Paccocath (lopudamide iodinated contrast)</td>
<td>Bavaria Medizin Technologie MedRad, later Bayer</td>
</tr>
<tr>
<td>Passeo-18 Lux</td>
<td>3.0 µg/mm²</td>
<td>Butyryl-tri-n-hexyl citrate (BTHC)</td>
<td>Biotronik</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>3.0 µg/mm²</td>
<td>Resveratrol</td>
<td>B.Braun</td>
</tr>
<tr>
<td>FREEWAY</td>
<td>3.0 µg/mm²</td>
<td>Shellac (shellolol and aleuritic acid resin)</td>
<td>Eurocor</td>
</tr>
<tr>
<td>LegFlow</td>
<td>3.0 µg/mm²</td>
<td>Nanocrystalline 0.1-µm paclitaxel in ammonium salt</td>
<td>Cardionovum</td>
</tr>
<tr>
<td>Orchid</td>
<td>3.0 µg/mm²</td>
<td>Magnesium stearate</td>
<td>Acotec Scientific</td>
</tr>
<tr>
<td>Lutonix</td>
<td>2.0 µg/mm²</td>
<td>Polysorbate and sorbitol</td>
<td>C.R. BARD</td>
</tr>
<tr>
<td>Luminor</td>
<td>3.0 µg/mm²</td>
<td>Organic ester</td>
<td>iVascular</td>
</tr>
<tr>
<td>Stellarex</td>
<td>2.0 µg/mm²</td>
<td>Polyethylene glycol</td>
<td>Spectranetics</td>
</tr>
<tr>
<td>Ranger</td>
<td>2.0 µg/mm²</td>
<td>acetyl tributyl citrate – ATBC (Transpax)</td>
<td>Boston Scientific</td>
</tr>
</tbody>
</table>
Drug-coated balloon vs plain balloon angioplasty in de novo femoropopliteal lesions

13 RCTs

Our conclusion: No significant difference in all-cause mortality between the two at:
- 1 year (odds ratio [OR], 0.81; 95% confidence interval [CI], 0.46-1.43),
- 2 years (OR, 1.61; 95% CI, 0.95-2.75),
- or 5 years (OR, 1.92; 95% CI, 0.71-5.19)
• 1-Prior exposure to paclitaxel and crossover rates not accounted for
  • especially for restenotic lesions

• 2-Compliance with pharmaceutical treatments, exercise, and lifestyle care not accounted for

• 3-Studies of device superiority not designed to demonstrate any mortality difference, their primary endpoints were type II statistical error

• 4-Calculated on an intention to treat basis
  • number of originally included patients and not the ones with actual FU available at the relevant time points
  • loss to follow-up? (still assigned as alive patients !!)
• 5-Patient-level data were not available
  • time of event
  • paclitaxel dose, carrier, comorbidities, medications, lesion, and procedural characteristics

• causes of deaths?
  • No death was adjudicated as device or procedure-related by the Clinical Events Committees

• confounding factors unrelated to paclitaxel?
Patient-level mortality analysis
- 4 RCTs

Cause of death:
- cardiac (in 4 vs 6 patients)
- malignant disease (1 lung in each group, 1 liver in the control group, and 2 pancreatic in the DCB group)
- sepsis (pneumonia and peritonitis)
- Others

Authors conclusion: «causes of death were well balanced between the treatment groups with no obvious pattern or trend towards an in-crease in any specific causes of death in the paclitaxel-coated balloon group»
• Analyzed all available RCTs or single-arm registries of at least 200 patients with at least 2-year FU conducted with FDA-approved devices: Zilver PTX DES, Lutonix, IN.PACT and Evercross DCBs

• **Mortality signal identified** for time points beyond 2 years after the index procedure

• **No clear signal** that treatment with paclitaxel-coated devices was associated with an excess rate of a specific CV or non-CV death subtype
  - substantial portion of deaths categorized as other or unknown

• **No evidence** of specific adverse events that may suggest a mechanism for late-term mortality

• **No consistent pattern** of specific baseline characteristics that could identify patients at increased risk of mortality after treatment with a paclitaxel-coated device

• **Patients who died** were older, had more comorbidities, longer lesions, and less frequently used statins...
• Extremely difficult to explain what common toxicological mechanism might play a role in such very different causes of death

• Mortality rates observed in the paclitaxel device RCTs consistent with the ones observed in epidemiologic studies of PAD\textsuperscript{1,2,3}
  • likely reflect the natural progression of the disease
  • in patients suffering from significant concomitant comorbidities
  • and already taking several medications

• **Extremely low doses of paclitaxel on DCBs** (FDA data analysis: day 1 = up to 200 ng/mg, day 60 and beyond = below 1ng/mg) vs chemotherapy (50-100 ng/mg)

Consistently reduced LLL, binary restenosis, and TLR compared with POBA alone.

Consistently reduced Clinically driven TLR up to 2 years.

The panel unanimously agreed that “the short-term benefits of paclitaxel-coated devices continue to outweigh the risks, that patients highly value the improved quality of life and reduced reinterventions, and that these devices should not be removed from the market.”
Take home message

- The power of numbers should not be overestimated
- There are limitations with the currently available clinical data
- A mechanism responsible for late mortality is not evident
- More independent analyses remain warranted
- For now, any conclusion as to the dangers of drug devices seems premature, and risks should be communicated to the patient only to support an informed choice
- Further studies should focus on long-term and patient-level data, with time-to-event analysis for each device in combination with an in-depth query of potential confounders and predictors, including new postapproval studies using a formal noninferiority design to test for mortality with large sample size, postmarket surveillance studies, and even the collection of real-world evidence
VODKA + PAACLITAXEL = DESTROYS THE KIDNEYS
OUZO + PAACLITAXEL = DESTROYS THE LIVER
WHISKEY + PAACLITAXEL = DESTROYS THE HEART
GIN + PAACLITAXEL = DESTROYS THE BRAIN

CAUTION
THIS FLY DESTROYS EVERYTHING
Thank you for your attention
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