Paclitaxel safety in patients with CLTI

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Disclosure

Speaker name:
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I have the following potential conflicts of interest to report:

☑ Consulting
☐ Employment in industry
☐ Stockholder of a healthcare company
☐ Owner of a healthcare company
☐ Other(s)

☐ I do not have any potential conflict of interest
Risk of CLTI

• The morbidity and mortality associated with PAD are known to be equal to or higher than those associated with coronary heart disease (CHD).

• Recent review by Baumgartner et al.

  • Risk of all-cause mortality was more than two-fold higher among patients with CLI (183 vs 81 events/1000 person-years; Relative risk [RR], 2.26; 95% confidence interval [CI], 1.77–2.89).

  • Risk of MI was also more than two-fold higher among patients with CLI (42 vs 16 events/1000 person-years; RR, 2.63; 95% CI, 1.49–4.64).

  • Risk of major amputation almost four-fold higher (100 vs 26 events/1000 person-years; RR, 3.85; 95% CI, 2.52–5.87).

  • Risk of CV mortality and MACE were approximately one and a half-fold higher (74 vs 52 events/1000 person-years; RR, 1.42; 95% CI, 1.01–2.01 and 95 vs 55 events/1000 person-years; RR, 1.73; 95% CI, 1.25–2.38).

1 https://doi.org/10.1016/j.atherosclerosis.2019.09.012
Risk of CLTI _ How to overcome?

• Revascularization is key element of improvement of PAD outcomes
  • Limb salvage
    • Associated with reduced mortality
  • Possibility to walk pain free and exercise reduces CV mortality and morbidity

• Revascularization in CLTI/mainly BTK has limited success rates with conventional angioplasty (POBA)
  • High rates of CDTLR

Drug coated devices raised hope for CLTI improvement !
Risk of Paclitaxel

• Meta-analysis 2018\textsuperscript{1} challenged the use of paclitaxel coated devices in general with following statement

\begin{itemize}
  \item Paclitaxel-coated devices for FP lesions increase the overall risk of death at 2 and 5 year FU
\end{itemize}

Faced significant criticism regarding its methodology including pooling study level data—patient level data was not available—not using a survival analysis method, and not accounting for patients who were lost to follow-up

• Several FU evaluations of RCT and real world patient data have revised the meta-analysis findings \textsuperscript{2-4}

\begin{itemize}
  \item Schneider PA et al. J Am Coll Cardiol 2019;73:2550-63.
  \item Gray WA et al. Circulation 2019;140:1145-55.
\end{itemize}
Risk of Paclitaxel_CLTI

• Several RCT’s have been conducted as well as real world data with regard to paclitaxel coated devices and treatment of CLTI patients

• Meta-analysis published 2020 is addressing the issue of Paclitaxel coated devices in CLTI
  – Mortality After Paclitaxel-Coated Device Use in Patients With Chronic Limb-Threatening Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials; Journal of Endovascular Therapy 2020, Vol. 27(2) 175–185
1450 patients were randomized to a paclitaxel-coated device (n=866) or an uncoated control (n=584)

Six studies included below-the-knee lesions, and 5 studies included lesions above-the-knee

There was no association between lesion location and mortality risk

Eight studies used paclitaxel-coated balloons; 1 study used paclitaxel-eluting stents

In 1 study the devices contained a paclitaxel dose of 2 μg/mm, all other devices delivered a paclitaxel dose of 3 or 3.5 μg/mm
Risk of Paclitaxel_CLTI_metanalsis
### Subgroup and Sensitivity Analyses for All-Cause Mortality

<table>
<thead>
<tr>
<th>Paclitaxel dose, µg/mm²</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;2.0</td>
<td>1.01 (0.78 to 1.31)</td>
</tr>
<tr>
<td>2.0–3.0</td>
<td>0.90 (0.54 to 1.49)</td>
</tr>
<tr>
<td>3.5</td>
<td>0.86 (0.64 to 1.14)</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Device type</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug-coated balloon</td>
<td>0.91 (0.70 to 1.17)</td>
</tr>
<tr>
<td>Drug-coated stent</td>
<td>0.82 (0.45 to 1.48)</td>
</tr>
</tbody>
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<table>
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<tr>
<th>Lower limb</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Above the knee</td>
<td>0.61 (0.31 to 1.20)</td>
</tr>
<tr>
<td>Below the knee</td>
<td>0.96 (0.80 to 1.16)</td>
</tr>
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<table>
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<tr>
<th>Lesion length, cm</th>
<th>Risk Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10</td>
<td>0.80 (0.45 to 1.41)</td>
</tr>
<tr>
<td>≥10</td>
<td>0.87 (0.66 to 1.14)</td>
</tr>
</tbody>
</table>

*Data are given as the risk ratio (95% confidence interval).*
Risk of Paclitaxel_CLTI_metanalysis

• Mean follow-up was 25.6 months (range 6–60)
• 10 of 11 studies reported a minimum 12-month follow-up
• There were 18.6% (161) deaths among 866 subjects in the paclitaxel device group and 19.9% (116) deaths among 584 subjects in the non-coated control group (RR 0.93, 95% CI 0.78 to 1.12, p=0.45)

The authors conclude: There was no observed difference in short- to midterm mortality among a pooled patient population of predominately CLTI patients treated with paclitaxel-coated balloons or stents compared with uncoated controls.
Risk of Paclitaxel_CLTI_BTK_RCT data

- The IN.PACT DEEP Clinical Drug-Coated Balloon Trial 5-Year Outcomes; Zeller T et al; J Am Coll Cardiol Intv 2020;13:431–43

- Tibial artery revascularization using drug-coated balloon angioplasty resulted in comparable long-term safety and effectiveness as PTA.
- Paclitaxel exposure was not related to increased risk for amputation or all-cause mortality at 5-year follow-up.

IN.PACT DEEP Trial: Mortality Through 5 Years
Risk of Paclitaxel CLTI BTK RCT data

Lutonix BTK IDE Study: 12-Month Results & Interim Safety Analyses at Three Years

Freedom from all Cause Death at 3 years

Hazard Ratio: 1.04 [0.63, 1.71]

Kaplan-Meier Estimate of Freedom from All-Cause Death comparable between groups at 1095 Days (3 years)
Risk of Paclitaxel_CLTI_Real world data

Survival benefit after paclitaxel

No. at risk
- No paclitaxel: 3634, 2131, 1316, 812, 461, 257
- Paclitaxel: 3634, 2306, 1480, 907, 544, 277

Adjusted HR 0.93
95% CI, 0.85-1.01
Trend toward better survival with paclitaxel

Propensity matched. CLTI patients treated with PTX for Fem-pop disease

Barmer Insurance-Germany

Behrendt et al. Eur J Vasc Endovasc Surg 2020 in press

Secemsky et al. JAMA Cardiology 2019
Risk of Paclitaxel_CLTI

Data so far do not show increased mortality with regard to the usage of paclitaxel coated devices in CLTI patients