The Controversy about Paclitaxel Safety: Where Do We Stand? A Summary of Concerns, Available Data and Open Questions

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Disclosures: Dr. Andrew Holden

- Dr. Holden is a Medical Advisory Board Member for Medtronic, Boston Scientific, and Gore
- Dr. Holden is a Clinical Investigator for Medtronic, Boston Scientific, Gore, Abbott, Cagent, Endologix, Intact Vascular, Shockwave, Bard, Cook, Endospan, Intervene, Spectranetics, TriReme, Merit, Reflow, Terumo, Surmodics
- No other relevant disclosures
BACKGROUND

- JAHA meta-analysis of summary-level published and presented studies raised concerns about paclitaxel devices for the treatment of femoropopliteal disease.¹
- Authors found a significant increase in all-cause mortality between 2 and 5 years for patients treated with femoro-popliteal disease receiving Paclitaxel coated devices compared to controls.

Unprecedented response from professional societies (eg SCAI, CIRSE, MHRA, SVS), industry and individual physicians

Major criticisms of the meta-analysis included:

- Summary level data analysis with inherent limitations
- Trials included were efficacy trials, not designed or powered for mortality
- No clustering of causes of death or mechanism of action
- Lack of Paclitaxel dose effect
- Lack of mortality signal consistency across geographies and studies
- Signal not seen in large population real world observational studies
- Inherent bias in trail design (especially ascertainment bias) and undetected cross-over

Ultimately, FDA convened a General Issues Panel on Paclitaxel Devices for PAD in June 2019
There are a number of paclitaxel-coated balloons or paclitaxel-eluting stents approved or under study for peripheral vascular use in the U.S. Currently, the FDA believes that the benefits continue to outweigh the risks for approved paclitaxel-coated balloons and paclitaxel-eluting stents when used in accordance with their indications for use.

While the analyses are ongoing, our preliminary review of this data has identified a potentially concerning signal of increased long-term mortality among the 975 subjects in these 3 trials, there was an approximately 50% increased risk of mortality in subjects treated with paclitaxel-coated devices versus those treated with control devices (20.1% versus 13.4% crude risk of death at 5 years).

For most patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents should generally be used until additional analysis of the safety signal has been performed.
FDA PANEL UPDATE – AUGUST 7, 2019

**AUGUST 7, 2019 US FDA Letter to HCPs**
- Applies to all paclitaxel coated devices
- **RISK:** Includes Hazard Ratios derived from the FDA and VIVA IPD meta-analysis presented at the FDA Panel.
- **RISK CAUTION STATEMENT:** Data should be interpreted with caution due to limitations:
  - Wide confidence intervals due to a small sample size
  - Pooling of studies of different devices
  - Substantial amounts of missing study data
  - No clear evidence of a paclitaxel dose effect on mortality
  - No identified pathophysiologic mechanism for the late deaths
- **RISK-BENEFIT:** For many patients, alternative treatment options to paclitaxel-coated balloons and paclitaxel-eluting stents provide a more favorable benefit-risk profile based on currently available information. Benefits outweigh risks in patients at high risk for restenosis and repeat femoropopliteal interventions
- **CLINICAL TRIALS:** Studies of these devices may continue and should collect long-term safety (including mortality) and effectiveness data.
SUMMARY-LEVEL VS PATIENT-LEVEL META-ANALYSIS

- Summary level meta-analysis provides an overview of general safety and efficacy of a device class but is only hypothesis generating.
- Patient level meta-analysis allows access to patient narratives, time to events, comorbidities, mortality adjudication and accurate per patient dose calculations.
- Strenuous efforts by industry sponsors of pivotal randomized trials have provided improved trial patient level details, including vital status.
- No patient-level analysis has confirmed a mortality signal with Paclitaxel (Medtronic, Cook, Bard BD, Boston Scientific, Philips, Surmodics).
As RCTs have achieved improved follow-up and vital status assessment, the hazard ratio and risk ratio have declined, approaching the null.
LACK OF A PACLITAXEL DOSE EFFECT

- The JAMA meta-analysis authors claimed a Paclitaxel dose effect and quoted this biological gradient as a key Bradford Hill criterion to claim Paclitaxel caused increased mortality rather than was associated with it.

- No paclitaxel dose effect has been demonstrated in any patient level analysis and the FDA panel noted there was no evidence of a dose effect.

Pooled Medtronic IN.PACT IDE and Japan Trials

LACK OF A PACLITAXEL DOSE EFFECT

- Independent analysis by the FDA of the 3 pivotal IDE trials with 5-year follow-up now confirms the lowest dose device was associated with the highest mortality and the highest dose device is associated with the lowest mortality.

<table>
<thead>
<tr>
<th>Study</th>
<th>Mean Dose (mg)¹</th>
<th>Mortality Difference (As Treated; Paclitaxel Device vs. PTA)²</th>
</tr>
</thead>
<tbody>
<tr>
<td>ZILVER PTX</td>
<td>1.1</td>
<td>+11.5%</td>
</tr>
<tr>
<td>LEVANT II</td>
<td>3.5</td>
<td>+7.2%</td>
</tr>
<tr>
<td>IN.PACT IDE</td>
<td>7.5</td>
<td>+4.7%</td>
</tr>
</tbody>
</table>

1. FDA Panel Packet “Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent Late Mortality Panel”; Executive Summary. Section 5.3.
2. FDA Panel Packet “Paclitaxel-Coated Drug Coated Balloon and Drug-Eluting Stent Late Mortality Panel”; Appendix P. Figure 14.
Paclitaxel and Mortality: The Dose Argument Is Critical

Andrew Holden, MBChB, FRANZCR, EBIR¹, Ramon L. Varcoe, MBBS, MS (Vasc), FRACS (Vasc), PhD², Michael R. Jaff, DO³, Peter A. Schneider, MD⁴, Gunnar Tepe, MD⁵, and Thomas Zeller, MD⁶

Keywords
Dose effect, drug-coated balloon, drug-eluting stent, drug-eluting technology, femoropopliteal segment, mortality, paclitaxel

LACK OF A PACLITAXEL DOSE EFFECT – WHY IS THIS IMPORTANT?

- Pharmaceutical side effects are almost always **non-stochastic (dose related)**
- If there is no dose effect between Paclitaxel and mortality, then the relationship is likely to be an association rather than causation
Another important Bradford Hill criterion is **consistency** of signal.

However, the Paclitaxel–mortality signal has been inconsistent across studies, devices, and patient geographies.

**LACK OF A CONSISTENT MORTALITY SIGNAL**

### POOLED IN.PACT IDE AND JAPAN TRIALS: HAZARD RATIO FOR MORTALITY BY REGION

<table>
<thead>
<tr>
<th>Subgroup (N&lt;sub&gt;DCB&lt;/sub&gt;/N&lt;sub&gt;PTA&lt;/sub&gt;)</th>
<th>IN.PACT DCB (Mortality)</th>
<th>PTA (Mortality)</th>
<th>Hazard Ratio (95% CI)</th>
<th>p-value for interaction*</th>
</tr>
</thead>
<tbody>
<tr>
<td>US (121/59)</td>
<td>16.7% (20)</td>
<td>10.3% (6)</td>
<td>1.77 (0.71, 4.42)</td>
<td></td>
</tr>
<tr>
<td>EU (99/51)</td>
<td>14.3% (14)</td>
<td>12.2% (6)</td>
<td>1.18 (0.45, 3.07)</td>
<td>0.74</td>
</tr>
<tr>
<td>Japan (68/32)</td>
<td>6.0% (4)</td>
<td>6.6% (2)</td>
<td>0.97 (0.18, 5.27)</td>
<td></td>
</tr>
</tbody>
</table>
# The Viva/NamSA Individual Patient Data (IPD) Project

![Hazard Ratio Forest Plot](image)

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel (Deaths/Subjects)</th>
<th>Control (Deaths/Subjects)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ILLUMINATE Pivotal</td>
<td>22/200</td>
<td>14/100</td>
<td>0.82 (0.42, 1.60)</td>
</tr>
<tr>
<td>ILLUMENATE EU-RCT</td>
<td>31/222</td>
<td>8/72</td>
<td>1.20 (0.55, 2.62)</td>
</tr>
<tr>
<td>IN.PACT SFA I/II</td>
<td>29/220</td>
<td>10/111</td>
<td>1.59 (0.78, 3.27)</td>
</tr>
<tr>
<td>IN.PACT SFA Japan</td>
<td>4/68</td>
<td>2/32</td>
<td>0.97 (0.18, 5.27)</td>
</tr>
<tr>
<td>Levant I</td>
<td>4/49</td>
<td>5/52</td>
<td>0.87 (0.23, 3.27)</td>
</tr>
<tr>
<td>Levant II</td>
<td>55/316</td>
<td>17/160</td>
<td>1.71 (0.99, 2.95)</td>
</tr>
<tr>
<td>Lutonix Japan</td>
<td>2/71</td>
<td>3/38</td>
<td>0.32 (0.05, 1.89)</td>
</tr>
<tr>
<td>Zilver PTX</td>
<td>41/236</td>
<td>24/238</td>
<td>1.80 (1.09, 2.99)</td>
</tr>
<tr>
<td>All Studies</td>
<td>188/1382</td>
<td>83/803</td>
<td>1.38 (1.06, 1.80)</td>
</tr>
</tbody>
</table>

*Favors Paclitaxel  Favor of Control*
These studies are not designed to assess a treatment efficacy effect.

However, they do know 3 things very accurately – patients who had a peripheral arterial intervention, whether they were exposed to Paclitaxel devices or not and their vital status (mortality).

As such, they are very relevant in this discussion.
LARGE POPULATION OBSERVATIONAL STUDIES

Mortality after use of paclitaxel-based devices in peripheral arteries: a real-world safety analysis

Eva Freisinger, Jeanette Koepe, Joachim Gerss, Dennis Goerlich, Nasser M. Malyar, Ursula Marschall, Andreas Faldum, and Holger Reinecke

- Data from 9.2 million insurants of the German BARMER health insurance scheme
- 64,771 patients who received POBA, BMS, DCB and DES from 2007 to 2015 were followed for at least 2 years
- Multivariable Cox regression analysis showed paclitaxel-based DES not to be associated with increased long-term mortality for over 11 years past-application (all P > 0.057)
- DCB was associated with decreased mortality for the 1st year (HR 0.92, P<0.001) with an indifferent correlation in years thereafter (all P > 0.202)

Treatment with **drug-coated device** was associated with a **lower incidence of all-cause mortality** compared to **non-drug coated devices** through 600 days (p=0.007)

Authors conclude no evidence of increased all-cause mortality following femoropopliteal artery revascularization with drug-coated devices compared with non–drug-coated devices.
### PACLITAXEL SAFETY: EVENT TIMELINE POST FDA PANEL

<table>
<thead>
<tr>
<th>JUNE 19-20, 2019</th>
<th>FDA General Issues Panel on Paclitaxel Devices for PAD</th>
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<tbody>
<tr>
<td>AUGUST 7, 2019</td>
<td>Updated US FDA letter to HCPs following advisory panel.</td>
</tr>
<tr>
<td>Cardiovascular &amp; Interventional Radiological Society</td>
<td>SEPT 7-10th</td>
</tr>
<tr>
<td>Transcatheter Cardiovascular Therapies</td>
<td>SEPT 25-28th</td>
</tr>
<tr>
<td>Vascular Interventional Advances</td>
<td>NOV 4-6th</td>
</tr>
<tr>
<td>VEITH Symposium</td>
<td>NOV 18-23rd</td>
</tr>
</tbody>
</table>

**Summary-level meta-analysis**
- DCB significantly increased the risk of freedom from TLR – 24 month RR 1.24
- DCB increased the risk of all-cause mortality at 24 months – RR 1.53 (random effects model)
- Considerable heterogeneity

**Klumb et al, E Clin Med (Lancet) 2019;16:42-50**
### EVIDENCE-BASED REVIEW

**Risk of Death and Amputation with Use of Paclitaxel-Coated Balloons in the Infrapopliteal Arteries for Treatment of Critical Limb Ischemia: A Systematic Review and Meta-Analysis of Randomized Controlled Trials**

Konstantinos Katsanos, MD, MSc, PhD, Stavros Spiliopoulos, MD, PhD, Panagiota Kitrou, MD, PhD, Miltiadis Krokidis, MD, PhD, Ioannis Paraskevopoulos, MD, PhD, and Dimitrios Karnabatidis, MD, PhD

- Study-level meta-analysis
- 8 RCTs comparing BTK DCBs to POBA
- 1,420 patients analyzed up to 1 year follow-up
- Amputation free survival (AFS) – freedom from all-cause death and major amputation
- 12-month AFS significantly worse with paclitaxel devices HR 1.52

Katsanos et al, JVIR 2019; doi.org/10.1016/j.jvir.2019.11.015
The clinical benefits of Paclitaxel-eluting devices in PAOD are proven including significantly improved patency and freedom from CD-TLR.

Summary level meta-analyses show an elevated late mortality with Paclitaxel devices compared to controls.

However, patient-level analyses do not confirm this and the mortality signal is weakening with improved follow-up.

There are a number of findings that make it unlikely that Paclitaxel is causing increased late mortality – lack of dose effect, mode of action or supportive findings in large population-based observational studies.

SO WHERE ARE WE AT AND WHERE TO NOW?
However, many physicians remain reluctant to use Paclitaxel devices, particularly given the lack of clear guidelines from regulatory bodies and international societies.

It is important that future studies avoid some of the unforeseen pitfalls of previous trials – avoid ascertainment bias, record all previous and future revascularizations, maintain optimum medical therapy etc.

Industry and societies are collaborating to obtain more data from RCTs, registries and observational studies and a further FDA update is expected in 2020.

Drive consensus towards accepted definitions of patients deemed high-risk for re-stenosis.

Avoid losing a highly effective therapy for patients who may really benefit from it.
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