The Paclitaxel mortality debate – time for regulatory bodies to end this saga?

Except PMDA who has already ended it!

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Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

- **Advisory**
  - Boston
  - Scientific
  - Medtronic
  - Surmodics
  - Reflow Medical

- **Royalties**
  - Surmodics

- **Ownership**
  - Healthcare Insights
There is Real Benefit
PTX Drug Based Vascular Devices

Provisional Zilver PTX vs. BMS

DCB vs PTA

ZILVERPASS: 2-year Freedom from TLR

DCB for AV Fistula
The Sham Controversy
The PAD Drug Based Device Mortality Debate

“The Emperor has New Clothes“
The JAHA Meta-Analysis

Overview

- Noted a Delayed effect
- Aggregate Analysis
- Randomized Trials
  - 28 @ 1-yr = no difference
  - 12 @ 2-yr = difference
  - 3 @ 5-yr = difference

- Only trials with difference at 1-year had late mortality risk so fake trend. No trial except Zilver PTX had delayed mortality and this was only on ITT

- Intention to treat analysis
  - Goes against international panel recs that for safety have to look at who got Tx

- Mixed DES with DCB (wonder why?)
  - No excipient
  - Minimal embolization
  - Complex randomization and cross over
  - High drug density but very low dose

- No Postulated Mechanism and blamed drug even though nonblinded trials and unexpected low control mortality in INPACT trial

JAHA Meta-Analysis
Risk of death at 2 years

12 RCTs with 2,316 cases

Crude risk
7.2% vs 3.8%

Risk Ratio
1.68 (95%CI: 1.15–2.47)

Risk Difference
3.5% (95%CI: 1.7–5.3)

Number-Needed-to-Harm
29 patients (95%CI: 19-59)
History of Paclitaxel Use

Summary points

• Long hx of use
• Toxicity well described
  • Cytopenias that reverse quickly
  • Short term cardiac (transfusion reaction)
  • Neuro (peripheral neuropathy)
  • Pulmonary
• Cardiac use
  • Stent thrombosis increased
  • No increase in mortality (n = 10,000+)
• No increased mortality with prolonged use in curative breast cancer
• Recent data: Considered safe in 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester for mother and fetus
Was the effort a purposeful sham?

- Replicated data controversy from coronary literature that was later debunked but PAD much smaller data set so harder to properly evaluated
  - Mixed devices
  - ITT instead of how treated
  - Incorrect measurement of dosing
  - Published in in low tier journal

- Created urgency

- Different type of drug, emb. Etc
- Stent with 14% of dose of DCB but most of blame?

- Must not have been able to correct manuscript for Circ, Circ intervention etc
- Never seen this urgency published in a manuscript (business decision?)
VIVA: 2018 Vascular Leaders Forum on the Paclitaxel Controversy

Summary points

- Long hx of PTX use
- Toxicity well described
  - Cytopenias that reverse quickly
  - Short term cardiac (transfusion reaction)
  - Neuro (peripheral neuropathy)
  - Pulmonary
- No increase in any specific mortality found in data
- No Mechanism of action proposed or noted
- Similar signal in non drug based devices ie BMS
- Dose miscalculated by original paper, no dose response
- Trial design of ITT
- Hx of Cardiac use
  - Stent thrombosis increased
  - No increase in mortality
- Hx of Long-term Breast cancer use
  - No increased mortality with prolonged use in curative breast cancer
  - Recent data: Considered safe in 2nd and 3rd trimester for mother and fetus

Embarked on evaluating IPD

### Timeline: The Paclitaxel Story

<table>
<thead>
<tr>
<th>Event Date</th>
<th>Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>DEC 6, 2018</td>
<td>Katsanos, et al. meta-analysis published</td>
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<tr>
<td>JAN 17, 2019</td>
<td>US FDA letter to HCPs stating “benefits continue to outweigh the risk for paclitaxel technologies”¹</td>
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<tr>
<td>MAR 15, 2019</td>
<td>US FDA letter to HCPs stating that the treatment of PAD with paclitaxel technologies is potentially associated with increased mortality²</td>
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<tr>
<td>JUN 19-20, 2019</td>
<td>FDA Circulatory Systems Devices Panel on Paclitaxel Devices for PAD</td>
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<tr>
<td>AUG 7, 2019</td>
<td>Updated US FDA letter to HCPs following advisory panel. Recommendation to HCPs include physician-patient discussions and consideration for the benefit-risk profile of each patient³</td>
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⁴ Registry Assessment of Peripheral Intervention Devices (RAPID): a long standing collaborative PPP focused on pre-competitive barriers to PAD technology innovation and patient care from academic, regulatory and industry experts.
RECOMMENDATIONS

Based on the FDA's review of available data and the Advisory Panel conclusions, we recommend that health care providers consider the following recommendations:

- Continue diligent monitoring of patients who have been treated with paclitaxel-coated balloons and paclitaxel-eluting stents.

- When making treatment recommendations, and as part of the informed consent process, consider that there may be an increased rate of long-term mortality in patients treated with paclitaxel-coated balloons and paclitaxel-eluting stents.

- Discuss the risks and benefits of all available PAD treatment options with your patients. 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.

- For individual patients judged to be at particularly high risk for restenosis and repeat femoropopliteal interventions, clinicians may determine that the benefits of using a paclitaxel-coated device outweigh the risk of late mortality.
VIVA Individual Patient Data (IPD) Project: Main Source of New Patient Level Data

Steering Committee
Philip Goodney, MD; Juan Granada, MD; Michael Jaff, DO; Sanjay Misra, MD; Chris White, MD

Statistics Consultants
Sue Duval, PhD (University of Minnesota) John Ioannidis, MD (Stanford University)

Biostatistics Group
NAMSA

Beckman J et. al. *Circulation*. June 2019
Observations Throughout the Independent Analyses

• Higher relative risk of mortality is not demonstrated in all studies and no delayed mortality as treated
• For studies with 5-year data, modified as-treated analysis of additional vital status data shows no mortality signal
• No clustering of adverse events or causes of mortality
• No paclitaxel dose-mortality relationship
• No plausible biologic association of paclitaxel to mortality

• Predictors of mortality are those expected from a PAD patient population
  • Age, renal failure, diabetes, cardiovascular disorders, smoking
  • Paclitaxel is NOT a predictor of mortality
## IPD: Sensitivity analyses

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Hazard Ratio Paclitaxel vs. Control (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary model</td>
<td>1.38 (1.06, 1.80)</td>
</tr>
<tr>
<td>As Treated, unadjusted</td>
<td>1.36 (1.04, 1.78)</td>
</tr>
<tr>
<td>As Treated, adjusted</td>
<td>1.37 (1.04, 1.80)</td>
</tr>
<tr>
<td>With additional long-term follow-up</td>
<td>1.30 (1.03, 1.63)</td>
</tr>
<tr>
<td>Censoring at control crossover to paclitaxel</td>
<td>1.31 (1.00, 1.72)</td>
</tr>
<tr>
<td>Missing data sensitivity / weighted analysis</td>
<td>1.36 (1.05, 1.77)</td>
</tr>
<tr>
<td>Fixed effects two-stage meta-analysis</td>
<td>1.36 (1.05, 1.77)</td>
</tr>
<tr>
<td>Random effects two-stage meta-analysis</td>
<td>1.34 (1.01, 1.78)</td>
</tr>
<tr>
<td>DCB devices only</td>
<td>1.25 (0.92, 1.69)</td>
</tr>
<tr>
<td>Using Zilver 2nd randomization instead of primary</td>
<td>1.19 (0.89, 1.60)</td>
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</table>

The more data obtained the lower the RR and absolute risk is only 4.6%
Drug Eluting Stents Evaluated by Actual Treatment in first Year analyzed to 5 years Purest Data Set

ZILVER PTX RCT

FDA Analysis of Actual Treatment
FDA Panel Pack (Appendix E)

- All patients analyzed by actual treatment
- No mortality signal
Original Authors Response!

• “Lack of conformation in real world data due to use of low dose device?”
• “Risk only evident in claudicants?”
MEDICARE BENEFICIARY DATA ANALYSIS: PAD SEVERITY - WEIGHTED RESULTS*
NO DIFFERENCE IN MORTALITY DESPITE DIFFERENCE IN SEVERITY

Non-CLI: 61.3% (N=93,432)

Log-rank P<0.001
Adjusted HR 0.94; 95%CI 0.92, 0.96

CLI: 38.7% (N=59,041)

Log-rank P<0.001
Adjusted HR 0.94; 95%CI 0.92, 0.97
Randomized Pt. Level Data Set: 5-yr Results Pending

William Gray Personal Communication
Summary

- Non of the trials examined were designed as mortality trials
- As significant loss to follow-up resolved, risk diminished (ascertainment bias)
- As treated analysis demonstrates NO risk!!!!!!!!!!!!!!!!!
- Finding was a delayed effect after drug is out of body and no individual trial really demonstrated this delayed mortality
- No dose response (this isn’t radiation)
- No change in pattern of death from typical PAD
- Death rate similar to previous trials of nonPTX devices
- Mixed devices with varying characteristics to obtain significance (cmon man)
- No evidence of increased risk in very large data sets
The Emperor Has No Clothes on!

FDA etc Should Agree with PMDA
Stop Subjecting Pts. To Unnecessary Repeat Procedures
Put the Bulldog in the Doghouse