How to Proceed to Generate More Evidence on Patient Safety With Drug-eluting Devices

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Disclosure

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Potential conflicts of interest to report:

Consulting: Silk Road, Surmodics, Profusa, CSI, Cardinal, Terumo

Chief Medical Officer: Intact Vascular, Cagent, Vesper

Scientific Advisory Board: Abbott, Medtronic, Boston Scientific
Summary-level versus Patient-level Meta-Analysis

**Summary-Level**
- Generate hypotheses
  - Allows for overview of general safety and efficacy in a device class

**Patient-Level**
- Aggregation of data from clinical trials to ask questions from a larger population
  - Assumptions based on patient follow-up, data distribution, differences in study set-up

- Identify and observe trends
  - Raw data is more complete and allows for further interrogation of how individual patient data is tied to outcomes
Drug-eluting Devices
Some unique characteristics of these trials.

- Powered for shorter-term patency, not long-term mortality.
- Control groups are small (some RCTs 2:1).
- Not clear if valid to include DCB and DES in same analysis.
- Expected attrition due to age and co-morbid factors.
- Missing data, censored patients.
- Assumptions about drug kinetics.
- Chance results (lowest mortality ever reported in PTA group in an RCT).
<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 57</td>
<td>12</td>
<td>48</td>
<td></td>
<td>1.69</td>
<td>[0.75; 3.78]</td>
<td>23.9%</td>
<td>26.9%</td>
</tr>
<tr>
<td>ZILVER-PTX 9,19</td>
<td>42</td>
<td>297</td>
<td></td>
<td>2.09</td>
<td>[1.13; 3.85]</td>
<td>47.7%</td>
<td>46.3%</td>
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<tr>
<td>IN.PACT SFA 10,56</td>
<td>24</td>
<td>184</td>
<td></td>
<td>1.92</td>
<td>[0.86; 4.30]</td>
<td>28.5%</td>
<td>26.8%</td>
</tr>
</tbody>
</table>

Fixed effect model  
529  334

Random effects model
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $p = 0.92$

Figure 3. Random effects forest plot of all-cause death at 4 to 5 years. Pooled point estimate was expressed as risk ratio (RR).

Conclusions—There is increased risk of death following application of paclitaxel-coated balloons and stents in the femoropopliteal artery of the lower limbs. Further investigations are urgently warranted.

Coincidental, statistical aberration, real danger sign?  
What is the mechanism?

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Drug-eluting Devices

VIVA: Vascular Leaders Forum

Washington, DC March 1-2

Multidisciplinary, multispecialty vascular specialists
Trial Principal Investigators
Regulatory agencies
Paclitaxel device manufacturers
Oncology, pharmacology, basic science, statistics
Drug-eluting Devices

VIVA: Vascular Leaders Forum

Washington, DC March 1-2

Conflict-of-interest management plan
Answer specific questions that will help inform clinicians until more data is developed

Written report

Steering Committee:
Peter Schneider, Gary Ansel, Josh Beckman, Chris White, Michael Jaff, John Laird, Sean Lyden
Drug-eluting Devices

Patient Level Data

No assumptions about trial conduct or pharmacokinetics or data quality.

Case-by-case analysis.

Calculated doses.

Analyze individual cases of mortality.

Propensity matching.

Test hypotheses: Analyze other potential variables.
VIVA will collaborate with all 5 US companies with commercially available DCB/DES products to share de-identified patient-level data. Vivaphysicians.org

The data sharing agreement will be between each company and an external third party statistical consultant to be selected by a five-member Steering Committee via an RFP process with the consent of the VIVA Executive Committee (the RFPs have been distributed).

Krishna Rocha-Singh: Coordinator and Technical Advisor

The SC members are: Chris White, Philip Goodney, Michael Jaff, Juan Granada and Sanjay Misra. This committee will also manage the data presentation/publication process.
A tentative statistical plan to be discussed with a representative from the statistics group at the VLF meeting in March.

The FDA has agreed to comment on the statistic methodologies proposed by the Steering Committee in consultation with the statistical advisor.

All 5 companies (Medtronic, Cook, Boston Scientific, Bard and Philips) are named in a press release about this process.
Unknowns:
• Comparative state of the different databases for these devices and trials.
• Timeline.
• Whether all our concerns will be addressed.
• Whether other trends/issues will be identified.
Drug-Eluting Devices
An Opportunity for the Vascular Community

• Come together and problem-solve.
• Demonstrate best care of our patients.
• To do no harm.
• Dig deeper and understand better the advantages and disadvantages of pharmacologic therapy as part of our lower extremity treatments.
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