Safety and efficacy of drug-eluting devices: Where do we stand? What are the concerns?

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LINC AP 2019 – Hong Kong
My disclosures

✗ I do not have any potential conflicts of interest to report

⊙ 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)
DCB in SFA Evidence / proof-of-concept

7 Trials / 6 DEB Technologies; 6-month LLL (Primary Endpoint)

- **PACCOCATH**
  - PTX 3µg/mm² + Ultravist
  - p<0.001
  - 1.70

- **LUTONIX**
  - PTX 2µg/mm² + Polysorbate & Sorbitol
  - p=0.031
  - 1.00

- **IN.PACT**
  - PTX 3µg/mm² + Urea
  - p=0.001
  - 1.09

- **PASSEO 18 LUX**
  - PTX 3µg/mm² + BTHC
  - p=0.033
  - 1.00

- **ADVANCE PTX**
  - PTX 3µg/mm² NO Excipient
  - p=0.12
  - 1.30

- **CVI**
  - PTX / Excipient (?)
  - p=NS
  - 0.44

Lesion length (cm)

- 15
- 13
- 11
- 9
- 7
- 5
- 3
- 1

THUNDER [1]
FEMPAC [2]
LEVANT I [3]
-PACIFIER [4]
BIOLUX P-I [5]
ADVANCE PTX [6]
CVI [7]
Significant and sustained TLR reduction up to 5 years!

**Long-term outcome of DCB in TASC A&B lesions**

**THUNDER**
Freedom from CD-TLR through 5 years

**IN.PACT SFA Trial:**
Freedom from CD-TLR through 5 years

1. Gunnar Tepe et al., 5-year Follow-Up of the THUNDER Trial
2. John R. Laird et al., 5 year results from the IN.Pact SFA randomized trial
Significant and sustained TLR reduction up to 5 years!

**Long-term outcome of DCB & DES**

**IN.PACT SFA Trial:**
Freedom from CD-TLR through 5 years

**ZILVER PTX vs Standard Care:**
Freedom from TLR through 5 years

1. John R. Laird et al., 5 year results from the IN.Pact SFA randomized trial
RCT DCB versus DES in fempop lesions

186 patients enrolled

Randomization & lesion length stratification (n = 150)

Excluded after angiogram:
Lesion too long, n = 6
Lesion too short for required strata, n = 8
In-stent restenosis, n = 3
Thrombotic lesion, n = 7
Infrapopliteal segment involved, n = 6
Failure to cross lesion with a guidewire, n = 6

DCB (n = 75)
short lesion, n = 25
middle lesion, n = 26
long lesion, n = 24

DES (n = 75)
short lesion, n = 25
middle lesion, n = 24
long lesion, n = 26
RCT DCB versus DES in fempop lesions – Patency results

at 3 years seems to be difference in primary patency in favor of DES over DCB

@1YFU: +/- 75% for both groups
@3YFU: +/- 40% for DCB and +/- 50% for DES
RCT DCB versus DES in fempop lesions – f-TLR results

No significant difference in freedom from CD-TLR between DCB and DES treatment!

@1YFU: +/- 85% for both groups
@3YFU: +/- 70% for both groups

Logrank p = 0.74
Difference DCB-DES (95% CI)
1-year: 2.5 (-7.1%, 12.1%)
3-year: 2.4 (-14.8%, 19.6%)

Yvonne Bausback et al., Drug-Eluting Stent versus Drug-Coated Balloon Revascularization in Patients with Femoropopliteal Arterial Disease. JACC Volume 73, Issue6, Feb 2019
Overall, in this pilot study, results for DCB and DES were similar at 12 months. At longer time points, a trend in favor of DES was observed.
Until....

Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

Konstantinos Katsanos, MD, PhD, MSic, EBIR; Stavros Spiliopoulos, MD, PhD, Panagiotis Kitis, MD, PhD, Mitsadis Krokidou, MD, PhD; Dimitrios Karabatis, MD, PhD
All cause death at 2 years

Konstantinos Katsanos et al., Risk of Death Following Application of Paclitaxel-Coated Balloons and Stents in the Femoropopliteal Artery of the Leg: A Systematic Review and Meta-Analysis of Randomized Controlled Trials
All cause death at 4 and 5 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Paclitaxel Events</th>
<th>Paclitaxel Total</th>
<th>Control Events</th>
<th>Control Total</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</td>
<td>12</td>
<td>48</td>
<td>8</td>
<td>54</td>
<td>1.69</td>
<td>1.69</td>
<td>[0.75; 3.78]</td>
<td>23.9%</td>
<td>26.9%</td>
</tr>
<tr>
<td>ZILVER-PTX</td>
<td>42</td>
<td>297</td>
<td>12</td>
<td>177</td>
<td>2.09</td>
<td>2.09</td>
<td>[1.13; 3.85]</td>
<td>47.7%</td>
<td>46.3%</td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>24</td>
<td>184</td>
<td>7</td>
<td>103</td>
<td>1.92</td>
<td>1.92</td>
<td>[0.86; 4.30]</td>
<td>28.5%</td>
<td>26.8%</td>
</tr>
<tr>
<td>Fixed effect model</td>
<td>529</td>
<td></td>
<td>334</td>
<td></td>
<td></td>
<td>1.94</td>
<td>[1.28; 2.96]</td>
<td>100.0%</td>
<td>--</td>
</tr>
<tr>
<td>Random effects model</td>
<td>529</td>
<td></td>
<td>334</td>
<td></td>
<td></td>
<td>1.93</td>
<td>[1.27; 2.93]</td>
<td>--</td>
<td>100.0%</td>
</tr>
</tbody>
</table>

Heterogeneity: $I^2 = 0\%, \tau^2 = 0, p = 0.92$
Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death (0.4±0.1% excess risk of death per paclitaxel mg-year; P<0.001)
Findings of the article...

• In conclusion, there seems to be an increased long-term risk of death beyond the first year following femoropopliteal application of paclitaxel-coated balloons and stents in the lower limbs.

• Meta-regression showed a significant relationship between exposure to paclitaxel (dose-time product) and absolute risk of death.

• Actual causes for this serious late side effect remain unknown.

• Further investigations with longer-term follow-up are urgently warranted.
Criticism of the article... (1)

• Meta-analysis reported long-term mortality data at three discrete timepoints: 1, 2, and 4-5 years, with the caution that its source studies were not designed or powered to evaluate mortality this far out. “These findings are really hypothesis-generating at best”
Meta-analysis can show association, not causation. That’s what RCT’s are for.
ASSOCIATION ≠ CAUSATION

Risk Difference vs. PTX Exposure

\[ \text{Exposure}_i = \text{Dose}_i (\pi \times \text{D}_i \times \text{Length}_i) \times \text{Time}_i \]

Risk Difference vs. # Letters in Study Title

\[ \text{Exposure}_i = \# \text{Letters}_i \times \text{Time}_i \]

<table>
<thead>
<tr>
<th>Study Name</th>
<th># Letters</th>
</tr>
</thead>
<tbody>
<tr>
<td>FAIR</td>
<td>4</td>
</tr>
<tr>
<td>LEVANT II</td>
<td>9</td>
</tr>
<tr>
<td>BATTLE</td>
<td>6</td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>11</td>
</tr>
<tr>
<td>THUNDER</td>
<td>7</td>
</tr>
<tr>
<td>ISAR-PEBIS</td>
<td>10</td>
</tr>
</tbody>
</table>
Criticism of the article... (3)

Mortality Rates from trials of SFA Therapy

![Graph showing mortality rates from trials of SFA Therapy]

- **DCB**
  - IN.PACT SFA-Japan
  - IN.PACT Global
  - LEVANT 1
  - LEVANT 2
  - ILLUMINATE US
  - CONSEQUENT

- **DES**
  - ZILVER PTX
  - MAJESTIC
  - SMART SES and BMS
  - Complete SF SPA
  - DURABILITY II
  - ETAP BMS
  - RESILIENT BMS
  - Dashoff Line

- **BMS**
  - Resolute BMS

- **PTA**
  - LEVANT 1
  - LEVANT 2
  - ILLUMINATE US
  - CONSEQUENT
  - ZILVER PTX
  - ETAP PTX

References:
- IN.PACT Japan: Presented by Iida, O. LINC 2018, Leipzig Germany
- LEVANT 2: Lotniczki HU
- ILLUMINATE US: Presented by Mathews, S. NCVH 2018, New Orleans, USA
- ILLUMINATE EU: Presented by Schoocke, H. CIRSE 2017, Copenhagen, Denmark
- CONSEQUENT: Presented by Gooi W, LINC 2017, Leipzig, Germany
- SMART SES and BMS: Duda et al. J Endovasc Ther 2006; 14; 701-710
- Complete SF SPA: Data on file, Medtronic, Inc.
- Resolute BMS: Lifesmart IFU. Revised 2/04/16
Criticism of the article... (4)

Summary-level versus Patient-level Meta-Analysis

- **Summary-Level**
  - Generate hypotheses
  - Allows for overview of general safety and efficacy in a device class
  - Assumptions based on patient follow-up, data distribution, differences in study set-up

- **Patient-Level**
  - Meta-Analyses
  - Aggregation of data from clinical trials to ask questions from a larger population
  - Identify and observe trends
  - Raw data is more complete and allows for further interrogation of how individual patient data is tied to outcomes
Criticism of the article... (5)

Some unique characteristics of the Drug-Eluting 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.
Comparable research? *Secemsky et al.*

- A multicenter retrospective cohort study included 16,560 patients in 1883 hospitals who were admitted for femoropopliteal artery revascularization in 2016.

- Drug-coated devices (DES/DCB) compared with non-drug-coated devices (BMS/PTA).

- Primary outcome: all-cause mortality
Results -- Drug vs Nondrug

Eric A. Secemsky et al., Association of Survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol. Doi.10.1001
Results -- DCB vs PTA

![Graph showing comparison between DCB and PTA in terms of probability of death over days from procedure.](image)

Log-rank $P = .06$

<table>
<thead>
<tr>
<th>Days From Procedure</th>
<th>DCB</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2709</td>
<td>5796</td>
</tr>
<tr>
<td>60</td>
<td>2477</td>
<td>5203</td>
</tr>
<tr>
<td>120</td>
<td>2344</td>
<td>4803</td>
</tr>
<tr>
<td>180</td>
<td>2252</td>
<td>4693</td>
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<tr>
<td>240</td>
<td>2165</td>
<td>4496</td>
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<tr>
<td>300</td>
<td>1895</td>
<td>3993</td>
</tr>
<tr>
<td>360</td>
<td>1470</td>
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<td>420</td>
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<td>788</td>
<td>1858</td>
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<tr>
<td>540</td>
<td>458</td>
<td>1111</td>
</tr>
<tr>
<td>600</td>
<td>132</td>
<td>375</td>
</tr>
</tbody>
</table>

Eric A. Secemsky et al., Association of Survival with femoropopliteal artery revascularization with drug-coated devices. JAMA Cardiol. Doi.10.1001
Results -- DES vs BMS

There was no evidence of increased all-cause mortality following femoropopliteal artery revascularization with drug-coated devices compared with non–drug-coated devices.
Comparable research? Schneider et al.

• Independently-adjudicated study data of DCB (n=1837) and PTA (n=143).

• Extensive analyses of baseline, procedure, and follow-up data of individual patients.

• Time to survival by paclitaxel dose tercile was analyzed with adjustment of inverse probability weighting to correct baseline imbalances and study as random effect.
Results -- DCB vs PTA

• No significant difference in all-cause mortality between DCB & PTA through 5 years (9.3% vs 11.2% ; p=0.399).

• No deaths were adjudicated by an independent clinical events committee as device-related.

• A survival analysis stratified nominal paclitaxel dose by low (5.019µg), mid (10.007,5µg) and upper (19.978,2µg) terciles. There was no statistically significant difference in all-cause mortality between the three groups through 5 years (p=0.700).
Conclusion? FDA decision

“The agency concluded that it 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”
Safety and efficacy of drug-eluting devices: Where do we stand? What are the concerns?

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