All real world DCB studies are not created equal

Deep dive session

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Germany
Disclosure

Speaker name:
Erwin Blessing, MD

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)

X I do not have any potential conflict of interest
Are all DCB created equal?

*Drug is the same, everything else differs!*

<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>Drug</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Medtronic</strong></td>
<td>IN.PACT</td>
<td>Paclitaxel</td>
<td>3.5</td>
<td>Urea</td>
</tr>
<tr>
<td><strong>BARD</strong></td>
<td>Lutonix</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polysorbate/Sorbitol</td>
</tr>
<tr>
<td><strong>Spectranetics</strong></td>
<td>Stellarex</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Polyethylene Glycol</td>
</tr>
<tr>
<td><strong>Boston Scientific</strong></td>
<td>Ranger</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>Citrate Ester</td>
</tr>
<tr>
<td><strong>BIOTRONIK</strong></td>
<td>Passeo-18 Lux</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>BTHC</td>
</tr>
<tr>
<td><strong>B BRAUN</strong></td>
<td>SeQuent Please OTW</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Resveratrol</td>
</tr>
<tr>
<td><strong>iVascular</strong></td>
<td>Luminor</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Ester</td>
</tr>
<tr>
<td><strong>COOK</strong></td>
<td>Advance 18 PTX</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>none</td>
</tr>
<tr>
<td><strong>Aachen Resonance</strong></td>
<td>Elutax SV</td>
<td>Paclitaxel</td>
<td>2.2</td>
<td>none</td>
</tr>
<tr>
<td><strong>BIOSENSORS</strong></td>
<td>BioPath (FREEWAY)</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shellac</td>
</tr>
<tr>
<td><strong>CARDIONOVUM</strong></td>
<td>Legflow</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Shellac</td>
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<td>Paclitaxel</td>
</tr>
<tr>
<td>Spectranetics®</td>
<td>Stellarex</td>
<td>Paclitaxel</td>
</tr>
<tr>
<td>Boston Scientific</td>
<td>Ranger</td>
<td>Paclitaxel</td>
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<td>Passeo-18 Lux</td>
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**What is different?**

- ≠ PTX dose (2.0 - 3.5 µg/mm²)
- ≠ Excipients (or no excipient)
- ≠ Drug formulation (e.g. crystal / amorphous or hybrid)
- ≠ Coating Methods
- ≠ IFU - usage method (e.g. with or w/out protective sheath)
- ≠ Clinical evidence (vs. lack of)
Are all DCB effective?

The answer lies in clinical evidence!

Clinical practice should be evidence-based & clinical decision making should be evidence-driven!
Level 1 evidence from Pivotal RCTs available only for a small hand-full of DCBs in the market

Primary patency rates may be calculated differently, and therefore may not be directly comparable; chart is for illustration purposes only.

Beyond RCTs: Why do we need global registries and single-arm studies?

- A venue to continue to **build upon outcomes from randomized, pivotal trials**
- Broad inclusion criteria and number of included subjects make the **results more generalizable to**
- Potentially **evaluate lesions that may not have been included in the randomized trials**, such as longer, complex lesions (TASC C & D, ISR, CTOs, etc.)

![The pyramid of evidence](image-url)
Real-World is Not Well-Defined

- No definition for study rigor, quality, or clinical relevance
- Level of evidence: Single-arm studies and observational registries are not the same!
- Data collection and analysis
- Monitoring
- Core Lab adjudication
- Clinical Events Committee

Quality of Evidence Matters!
4 global DCB registries with data available

IN.PACT Global (IN.PACT)

ILLUMENATE Global (Stellarex)

Lutonix Global (Bard)

BIOLUX P-III (Passeo-18 Lux)
## Study Differences

<table>
<thead>
<tr>
<th>Study</th>
<th>Sites</th>
<th>Patients</th>
<th>Authors/References</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT Global ¹</td>
<td>65 sites Europe, Canada, Middle East, Latin America, Asia, Australia</td>
<td>1535 patients</td>
<td>Jaff, M. Insights from the IN.PACT Global Full Clinical Cohort. VIVA 2016.</td>
</tr>
<tr>
<td>ILLUMENATE Global ²</td>
<td>37 sites Europe, Australia, New Zealand</td>
<td>Still enrolling; estimated 501</td>
<td>Krishnan, P. 12-month Interim Results of ILLUMENATE Global Study with the Stellarex DCB. NCVH 2016.</td>
</tr>
<tr>
<td>Lutonix Global ³</td>
<td>10 sites Europe</td>
<td>691 patients</td>
<td>Benenati, JF. A Prospective, Global Multicenter, Single Arm Real-World Registry Investigating the Clinical Use and Safety of the LUTONIX® Drug Coated PTA Dilatation Catheter. BARD Symposium. VIVA 2016</td>
</tr>
<tr>
<td>BIOLUX P-III ⁴</td>
<td>45 sites Europe, Asia, Australia</td>
<td>860 patients</td>
<td>Brodmann, M. BIOLUX P-III All-comers registry 12m data using Passeo-18 Lux DCB. BIOTRONIK Symposium. CIRSE 2016.</td>
</tr>
</tbody>
</table>

2. Krishnan, P. 12-month Interim Results of ILLUMENATE Global Study with the Stellarex DCB. NCVH 2016.
Robust trial design LEADS TO robust outcomes

IN.PACT Global and ILLUMENATE Global combine the rigor of a clinical trial with a clinically diverse, “real-world” subject population

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT GLOBAL ¹</th>
<th>ILLUMENATE Global ⁵</th>
<th>LUTONIX GLOBAL ⁶</th>
<th>BIOLUX P-III ⁷</th>
</tr>
</thead>
<tbody>
<tr>
<td>Consecutive Enrolment</td>
<td>✔️</td>
<td>✔️</td>
<td>❌</td>
<td>?</td>
</tr>
<tr>
<td>Prospective, pre-specified enrolment cohorts</td>
<td>✔️</td>
<td>✔️</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>Independent Angiographic Core Lab</td>
<td>✔️</td>
<td>✔️</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>Independent Duplex Core Lab</td>
<td>✔️</td>
<td>✔️</td>
<td>❌</td>
<td>❌</td>
</tr>
<tr>
<td>Independent CEC</td>
<td>✔️</td>
<td>✔️</td>
<td>?</td>
<td>✔️</td>
</tr>
<tr>
<td>100% Data Monitoring &amp; Data Management Review</td>
<td>✔️</td>
<td>✔️</td>
<td>?</td>
<td>?</td>
</tr>
<tr>
<td>Long-Term Follow-up</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td></td>
<td>5 years</td>
<td>2 years</td>
<td>2 years</td>
<td>2 years</td>
</tr>
</tbody>
</table>

For Qualitative Comparison Purposes Only

Patency & TLR in context

IN.PACT Global (N=1535) [1]
IN.PACT Global Long Lesions (N=157) [2]
IN.PACT Global CTO (N=) [3]
IN.PACT Global ISR (N=) [4]
ILLUMENATE Global (N=) [5]
Lutonix Global (N=691) [6]
BIOLUX P-III (N=860) [7]

12m PP (KM) 12m CD-TLR Lesion length (cm) 12m CD-TLR Lesion length (cm)

7.5% 26.40 91.1% 6.0% 85.3% 11.3% 88.7% 17.20 86.5% 7.20 85.4% 10.12 5.9% 8.40 6.0% 12.09 26.40 22.80 17.20 10.12 8.40

100%
80%
60%
40%
20%
0%

IN.PACT Global
IN.PACT Global Long Lesions
IN.PACT Global CTO
IN.PACT Global ISR
ILLUMENATE Global
Lutonix Global
BIOLUX P-III

High Quality Real-World Assessment
SAVER: Stellarex Vascular e-Registry
ClinicalTrials.gov Identifier: NCT02769273

- Multi-center, international, real-world
- N= 5000 / up to 200 Sites
- Full PAD spectrum: clinical (IC / CLI) and anatomic (ATK/BTK)
- Patient treated as per center’s standard practice
- Independent Clinical Events Committee
- Duplex Core lab evaluation for Imaging cohort*
- Patient Follow up to 3 years
- Largest dataset ever studied within uniform definitions / endpoints

* specific subsets such as CTO, ISR, long lesions, Ca++
DCBs are not created equal

“…not all DCB are created equal and that a ‘class effect’ cannot be anticipated as the results obtained with different DCB are not uniform.”

Conclusion

• All DCB are not created equal
  • Proven technology? Large RCTs (level 1 evidence available for 3 out of >10 DCBs on the market.

• Real-world studies important to add to clinical knowledge of treatment effectiveness

• However: quality of evidence and rigor of study conduct matters and determines the level of evidence provided by a “real-world” study.
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