Safety of Paclitaxel balloon coatings
Insights from a pathologist

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Potential conflicts of interest

Speaker's name: Renu Virmani, MD

☑️ I have the following potential conflicts of interest to report:

Consultant: 480 Biomedical, Abbott Vascular, Medtronic, and W.L. Gore.

Employment in industry: No


Owner of a healthcare company: No

Stockholder of a healthcare company: No
Drug Coated Balloon (DCB), why is it safe?

- DCBs have no metal struts or polymer that may cause continuous stimulation to the vessel as is observed in DES, which are associated with sustained inflammation.

- DCBs have the potential ability to evenly deliver the drug on the vessel wall. However, the best pharmacokinetics and the best formulation of DCB remain unknown.

- Acute/subacute recoil, and plaque prolapse may occur and dampen its efficacy and poor flow especially in highly calcified arteries, but can be avoided by good preparation of artery prior to use of DCB.
Requirements For DCB

- Must deliver large quantities of the drug within seconds
- Must distribute within the media in the first few days
- Therapeutic drug levels must be maintained for at least several weeks
- Must allow rapid healing as compared to DES
- No need for long-term anticoagulation
- Light microscopy must show biologic effects at 28-days at least
## Drug coated balloon devices (Peripheral artery)

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose (µg/mm²)</th>
<th>CE mark*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Advance 18 PTX™</td>
<td>Cook Medical, Bloomington, IN, USA</td>
<td>Paclitaxel</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Cotavance®</td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Freeway™</td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>IN.PACT™ Admiral, Amphirion, Pacific</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Lutonix DCB® (Moxy)</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Legflow®</td>
<td>Cardionovum, Warsaw, Poland</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
</tr>
<tr>
<td>Passeo-18 Lux®</td>
<td>Biotronik, Bülach, Switzerland</td>
<td>Paclitaxel–butyryl-tri-hexyl citrate</td>
<td>3.0</td>
<td>No → Yes</td>
</tr>
<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>No → Yes</td>
</tr>
</tbody>
</table>

* Lutonix DCB® and IN.PACT™ are currently approved by the FDA for clinical use in USA.

How is DCB different from DES

<table>
<thead>
<tr>
<th>Parameters that distinguish DCB from DES</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low 5-10 μg/mm</td>
<td>Very High 2-3 μg/mm² (=20-30 μg/mm)</td>
</tr>
<tr>
<td>Drug transfer at the time of deployment</td>
<td>Slow</td>
<td>Rapid, all at once</td>
</tr>
<tr>
<td>Reservoir of drug</td>
<td>Polymer</td>
<td>No (excipient important)</td>
</tr>
<tr>
<td>Drug retention in tissues</td>
<td>Short term</td>
<td>Need a drug which binds to cell membranes and is easily transferable to adjacent cells</td>
</tr>
<tr>
<td>Diffusion</td>
<td>Good</td>
<td>Excellent</td>
</tr>
<tr>
<td>Lipophilic</td>
<td>yes</td>
<td>Even better</td>
</tr>
<tr>
<td>Active ingredient</td>
<td>Not necessary</td>
<td>Should be active immediately</td>
</tr>
</tbody>
</table>

**Diagram:**

- **Primary Patency**
  - Zilver PTX: 67.6%
  - Optimal PTA + BMS: 45.5%

- **Images:**
  - DES
  - PTX Coated
  - Uncoated
  - DCB
  - Paccocath

**Graphs:**

- Hwang, Circulation 2001; 104: 600-5
Femoro-Popliteal Artery Biomechanics

- External Iliac
- Femoral
- Popliteal
- Anterior tibial
- Posterior tibial
- Peroneal
- Doralis Pedis

X-ray femoro-popliteal artery

1. Extension / Contraction
2. Torsion
3. Compression
4. Flexion

1. Extension / Contraction
2. Torsion
3. Compression
4. Flexion
Clinical Evidence of DCB Efficacy

6 DEB Technologies / 7 DEB Trials (Primary Endpoint: 6m LLL)

[Graph showing clinical evidence of DCB efficacy with data from various trials and technologies.]

[Reference notes for data sources included at the bottom of the image.]

Coating Integrity is Variable

Braun (Sequent) vs. MDT/Invatec (Admiral)

Lutonix Catheter

PTX in coating after aqueous exposure
Paclitaxel uptake in the Arterial Wall

Paclitaxel uptake in arterial wall 15-25 minutes (n= 6 arteries each)

Vascular changes following Lutonix DCB treatment in Porcine Iliac arteries

1x dose

<table>
<thead>
<tr>
<th>28-days</th>
<th>90-days</th>
<th>180-days</th>
</tr>
</thead>
<tbody>
<tr>
<td>H&amp;E</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td>Actin</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td>Movat</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
<tr>
<td>Masson</td>
<td>[Image]</td>
<td>[Image]</td>
</tr>
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Evaluation of DCB Safety
Effects on Downstream Muscles which may result in necrosis

Marked chronic perivasculitis (x3 dose)

Skeletal Muscle Necrosis

Fibrinoid necrosis and SMC loss (x3 dose)

Small vessels with organizing thrombi (x3 dose)
Embolization incidence(%) to distal skeletal muscle

<table>
<thead>
<tr>
<th></th>
<th>28 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>28 Days</th>
<th>90 Days</th>
<th>180 Days</th>
<th>28 Days</th>
<th>90 Days</th>
<th>180 Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>POBA</td>
<td></td>
<td></td>
<td></td>
<td>DCB1</td>
<td></td>
<td></td>
<td>DCB2</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- Normal
- Embolization
Downstream vascular change following other DCB Technologies

At 7-days
Vascular Changes in the Coronary Band of the Hoof

REPEAT TREATMENT

Fibrinoid Necrosis

Platelet emboli

Fibrin Thrombus with Crystalline material
Safety Profile

All about Balancing Safety, Efficacy and Biologic Response

*Not all balloons are created equal*

- **Efficacy**
  - More
  - Less neointima
  - Absence of restenosis
  - No, early or late thrombosis

- **Safety**
  - Less
  - Rapid Vascular Healing
  - Good Re-Endothelialization
  - No distal Emboli

- **Drug Load**
  - Use of Carrier/Excipient
  - Drug Retention
  - Repeat Inflations

Path
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Stent fracture and Restenosis in SFA and popliteal arteries

Scheinert, D et al, JACC 2005

Iida, O et al, AJC 2006

Fracture (+)
N=22
Patency at 12 months
41.1% vs. 84.3%

Fracture (-)
N=71

Exercise habit (+)
(walk >5000 steps / day)

Exercise habit (-)

Mean; 13.6 months

Nitinol stent
91% (10/11)
P=0.001

Patency at 12 months
41.1% vs. 84.3%
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