Drug eluting balloons: the technology behind

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Working principle

• PTA dilatation, short time drug-elution, long term effect
  – Restore and maintain patency
  – Balloon-type deliverability
  – Avoid ISR frequency and burden
  – Preserve future options
Drug-eluting technology

- Drugs used
  - 'olimus' – group
  - Paclitaxel
Drug features/selection for DCB

- Chemical structure (lipophylic > hydrophylic)
- Rapid drug transfer (<60s)
- Efficient (low loss rate during delivery)
- Wide therapeutic window (toxicity)
- System stability (chemical stability, packing, storing etc.)
Drug selection

μg Drug in Tissue at 24 Hours

μg Drug Remaining on Balloon

Gray & Granada, Circulation 2010; June 22
Rapamycin (‘olimus’) 

- Natural lipophilic immunosuppressant macrocyclic lactone 
- Anti-inflammatory and antiproliferative cytostatic effect
Paclitaxel

- From the bark of the pacific yew tree (Taxus brevifolia)
- Synthetically manufactured as an antineoplastic drug (Taxol)
- Highly lipophilic (rapid cellular uptake and retention at site of delivery)
- Deep tissue absorption/penetration
- Hydrophobic = limited wash-out
- Sustained neointimal suppression
- Dose for local application 300 times less than the concentration used for systemic chemotherapy (DCB 2 \( \mu \)g/mm\(^2\) or 3 \( \mu \)g/mm\(^2\) of the balloon surface)
Paclitaxel

- Paclitaxel is a potent inhibitor of smooth muscle cell proliferation, SMC migration, and extracellular Excipient formation in vitro, with all three phases of the restenosis process inhibited effectively.

- The effective transfer of drug to the arterial wall is controlled by how the drug is loaded on the balloon (coating engineering) and the relative solubility of the drug between cell wall and coating (excipient).
Effect

- Rapamycin is cytostatic and inhibits cell-cycle progression from the G1 to the S phase
- Paclitaxel is cytotoxic and restrains the cell division, which prevents a progression of intimal hyperplasia
Effect

Paclitaxel Apoptosis
DES vs. DCB

Drug-Eluting Stent
- Slow release
- Persistent drug exposure
- ~ 100 - 200 µg dose
- (Polymer)
- Stent mandatory

Drug-coated Balloon
- Immediate release
- Short-lasting exposure
- ~ 300 - 600 µg dose
- No polymers
- Excipient optional
Drug Coated Balloon: Concept

- Local delivery of drug exactly on site, avoids systemic exposure
  - Effective concentration can be achieved
  - Exact control of dose possible
Advantages DCB

• Homogeneous drug transfer
• Concentration highest at time of injury
  – Prevents initiation of chain of events leading to neointimal proliferation
• Absence of stent struts
  – Limited need for dual antiplatelet therapy
• Respects original anatomy (bifurcation) and diminishes abnormal flow pattern
Advantages DCB

• Anti-proliferative therapy while leaving nothing behind
• Broad anatomical applicability
• Avoid stent fracture and ISR burden
• Preserve future options
• Matches patient’s quality of life expectancy
Neointima Inhibition: Comparison of Effectiveness of Non-Stent-based Local Drug Delivery and a Drug-eluting Stent in Porcine Coronary Arteries¹

**Purpose:** To compare the inhibition of neointimal proliferation by using non-stent-based local drug delivery and a drug-eluting stent in porcine coronary arteries.

**Materials and Methods:** Experiments were conducted with permission of the animal protection committee of the local government. Paclitaxel was either dissolved in a nonionic contrast medium or coated on balloons. Stents were crimped on the coated balloon.

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**Figure 3:** Examples of transverse histologic slices through arteries treated with stents. (Hematoxylin-eosin stain.) $CM_{Pac}$ = paclitaxel in contrast medium. Only a thin layer of neointimal tissue between the vessel lumen and the black stent struts is found in the vessel treated with the DEB, whereas neointimal proliferation resulted in substantial lumen narrowing in the control vessel.
Animal studies

![Graph showing area stenosis for different treatments: control, CM Pac, Paccocath, Cypher. The graph indicates a significant difference with p=0.001.](image)

- **Control**: High area stenosis.
- **CM Pac**: Moderate area stenosis.
- **Paccocath**: Lower area stenosis.
- **Cypher**: Lowest area stenosis.

The graph demonstrates a statistically significant difference in area stenosis among the different treatments.
Excipient

- Optimize drug transfer
  - Separate Paclitaxel molecules
  - Amplify drug surface exposure
  - Increase drug bioavailability

Virmani R – CIRSE 2012
Excipients

- Iopromide
- Urea
- Shellac (natural resin)
- Butyryl-tri-hexyl citrate (BTHC)
- Sorbitol
- Polyethylene Glycol
- Etc. etc.
Fig. 3 Representative examples of histological findings 4 weeks after stent implantation. Bare metal stent implanted with uncoated balloon catheter (control, left). Bare metal stent implanted with roughened-surface DEB (middle). Bare metal stent implanted with matrix-coated DEB (right)
Importance of excipient

Fig. 2 Results of quantitative coronary angiography (QCA) of stented porcine coronary arteries after 28 days. Implantation of bare metal stents using conventional PCI catheters and paclitaxel-coated PCI catheters. Values are mean ± SD.

Cremers B et al, Clin Res Cardiol 2009
Coating technology/formulation

- Loss during transit
- Duration of effect
Loss during transit

- High coating stability
- Limited drug loss

PTX particulate loss after transit

Number of particulates ≥10 μm/r:mm of DCB length lost during transit.
Duration of effect

- Crystalline vs. amorphous: Benefits and trade-offs
  - Crystalline: high drug retention and biological effectiveness
  - Amorphous: uniform coating and low embolic burden/vascular toxicity
Formulation

Paclitaxel Formulation Types
Impact on Biological Performance

<table>
<thead>
<tr>
<th></th>
<th>Crystalline</th>
<th>Amorphous</th>
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<tbody>
<tr>
<td>Particles Released</td>
<td>+++</td>
<td>++</td>
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<tr>
<td>Uniform Coating</td>
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<tr>
<td>Drug Transfer to Vessel</td>
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<td>Drug Retention vs. Time</td>
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<tr>
<td>Biological Effectiveness</td>
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<tr>
<td>Vascular Toxicity</td>
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</table>
Duration of effect

• Solid paclitaxel (crystalline)
  – Long-term biologic activity
  – Solid phase paclitaxel dissolves slowly

• Soluble paclitaxel (amorphous)
  – Short-term biologic activity
  – Soluble paclitaxel is metabolized

• Same concentration of paclitaxel on balloon does not always lead to same effect
Duration of effect

Drug Dissolution In Vitro

- Solid phase drug has a dissolution half life on the order of days in a highly convective aqueous system with solubilizing proteins.
- Sequestered drug in a non-convective system is likely to have a much longer half life.
<table>
<thead>
<tr>
<th>Manufacturer</th>
<th>DCB</th>
<th>Drug</th>
<th>Dose (µg/mm²)</th>
<th>Excipient</th>
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<tbody>
<tr>
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<td>PTX</td>
<td>3.5</td>
<td>Urea</td>
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<tr>
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<td>PASSEO 18 LUX</td>
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<td>Butyryl-tri-hexyl Citrate</td>
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<tr>
<td>Cook</td>
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<td>Shellac</td>
</tr>
</tbody>
</table>

12 DCBs (= Drug, ≠ Doses, ≠ Excipients, ≠ Technologies)
Conclusions

• All DCB’s use the same drug (paclitaxel)
• Differences in coating technology, excipient choice, dose and formulation have an influence on the final clinical outcome
• Not all DCB’s are equal
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