Drug eluting devices: Why paclitaxel works above the knee and sirolimus below the knee, is the stent or the drug?

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Conflict of Interest Declaration

• Institution grant/research support

• Speaking Honoraria
  – Abbott, Cook Medical
Restenosis processes and inhibitors

Normal artery + stent

Endothelial injury

Platelet + fibrin + coagulation factors

Cytokines, VEGF, NO, thrombin, low shear stress

Growth factors + cytokines

Endothelial injury

Leucocyte recruitment + chemotactic factors

IL-8, MCP-1

Inflammation

Growth factors (PDGF), thrombin

Contractile → Synthetic smooth muscle cells (SMC)

*Sirolimus
Everolimus
Zotorolimus
Biolimus A9
Tacrolimus

Cytokines (IL-1, IL-6, TNF-α, IFNγ), NO, growth factors (PDGF, TGFβ, IGF, FGF, VEGF, thrombin, ATIII)

Radiation actinomycin-D

Proteoglycans

SMC migration

Collagen type III

Remodelling (collagen type I)

Taxol
Taxane

Anti-mitotic, blocks Microtubular mechanics

Sirolimus and Paclitaxel

Sirolimus

Solid line: FKBP12 binding site
Dotted line: mTOR binding site

Sirolimus inhibits mTOR and is part of the phosphatidylinositol kinase-related family of serine/threonine kinases.

Paclitaxel

Paclitaxel binds to beta-tubulin and impairs microtubular disassembly and halts the cell cycle between G2 and M.

Gupta ML et al. PNAS 2003;100:6394-6397
Sirolimus v. Ptx

• **Sirolimus**
  - Cytostatic
  - Wider therapeutic index with higher doses better tolerated in terms of tissue damage
  - Not as high tissue binding affinity (not as good for balloon delivery)
  - Tissue permanence less than Ptx
  - Less effective in ATK applications where vessels sizes are larger-drug concentrations likely less

• **Paclitaxel**
  - Cytotoxic
  - Low therapeutic index
  - Higher doses cause tissue necrosis, wall damage, etc.
  - Hydrophobic--binds highly to tissue elements and preference for subintimal space
  - Good for balloon delivery
  - Produces more fibrin and tissue damage--higher rates of TVF, stent thrombosis in clinical trials in coronary vessels
Effect of drugs used in DES in animal models

Healthy animal models

- **New Zealand White Rabbit**
  - 15-25 cm
  - 5-10 Kg

- **Yucatan Minipig**
  - 40-60 cm
  - 50-60 Kg

- **Suffolk Cross-bred sheep**
  - 80-100 cm
  - 80-100 Kg

Sirolimus + analogs
Paclitaxel

Coronary: Biologic effects ✓
Peripheral: Biologic effects ✓

Porcine coronary artery
3 months

Rabbit iliac artery
28 days

Sirolimus
Paclitaxel


Nakazawa et al. Am J Cardiol 2007;100[suppl]:36M–44M
Type of drugs on DES/DCB in human

In human coronary
Balloon Expandable Stents
Sirolimus + analogs
Paclitaxel

Successful ✔

Everolimus
13 months

Paclitaxel
9 months
<table>
<thead>
<tr>
<th>Parameters</th>
<th>DES</th>
<th>DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug concentration on the device</td>
<td>Low</td>
<td>Very High (given surface area) 2-3 μg/mm² (≒20-30 μg/mm)</td>
</tr>
<tr>
<td></td>
<td>5-10 μg/mm</td>
<td></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>Longer than DCB</td>
<td>Need the drug in crystalline form and should be easily transferable to adjacent cells. Binds to cell membranes</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>

**BMS**

DES 28 days (Rabbit iliac artery)

DCB 14 days (Porcine iliac artery)
Type of drugs on DES/DCB in human
In human peripheral
(Above the knee)

Sirolimus + analogs  **failed**
Paclitaxel (stent and balloon)  **Successful ✔**

Self-Expandable Stents

Everolimus coated nitinol stent for SFA (STRIDES trial)

Paclitaxel coated nitinol stent for SFA (Zilver PTX trial)

Primary patency/1year
- ZPTX 90%
- BMS 73%

Freedom from TLR/1year
- ZPTX 91%
- BMS 83%

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Circulation: Cardiovascular Interventions October 2011 vol. 4 no. 5 495-504

Type of drugs on DES/DCB in human

In human peripheral (Below the knee)

Sirolimus ± analogs/paclitaxel on stent

Paclitaxel in DCB

Sirolimus + analogs for CLI Pts

Successful ✔

Paclitaxel in DCB failed

Bayesian Network meta analysis

Sirolimus ± analogs/paclitaxel on stent

Fusaro et al. JACC intv, 2013:6:1284–1293

Katsanos et al Journal of Endovascular Therapy 23, 851-863

PCB : paclitaxel coated balloon
Coating Integrity is Variable

Lutonix® 035 DCB (dry-expanded)

In.Pact™ (dry expanded)

SurVeil™ DCB (dry-expanded)
Zilver PTX

Self-expanding nitinol stent
No polymer or binder
3 μg/mm² dose density
6 x 20 mm: 220 μg, 10 x 80 mm: 880 μg of paclitaxel

Zilver PTX
83.1%

Optimal PTA + BMS

67.6%


Why clinical outcomes are different by location – Above knee

- Self expanding Stents used
- ≤6 months following implantation
  - Paclitaxel or Sirolimus (+Analogs)
  - Tissue penetration of paclitaxel is greater than Sirolimus and its Analogs.

- >6-12 months following implantation
  - Inter-strut distance increases as stent continues to expand resulting in decreasing drug availability between struts
  - Efficacy ↓

Paclitaxel Coated Balloons with excipient are efficacious because of paclitaxel crystallinity, greater penetration and use of excipient which allows for sustained release of drug.

Overall: $r=0.446$, $p<0.001$

Nakano et al. Eur Heart J 2013;34:3304-3313

Mean neointima thickness, mm

Maximum inter-strut distance
Why clinical outcomes are different by location – Below the knee

• Balloon Expandable Polymer coated Stents

Just after implantation

- Sirolimus ± analog

6-12 months following implantation

- No change in interstrut distance and continued release of drug from polymer

• Paclitaxel Coated Balloon

- Smaller arteries
- High dose, cytotoxic drug with uneven distribution and ↑fibrin deposition
- Distal embolization

Efficacy
Maintained

Ineffective
Conclusions

- Two different types of antiproliferative drugs used for above and below the knee: Paclitaxel (cytotoxic), and Sirolimus+analogs (cytostatic).

- **Above the Knee:**
  - Self expanding stents with sirolimus ±analogs were ineffective above the knee, because of continuous expansion of the stent, with time and decreased efficacy from poor drug penetration of sirolimus or analogs. Improvement of stent technology and use of paclitaxel which is a cytotoxic drug with greater inhibition of proliferation and drug penetration when applied on stent or balloon (with excipient) is efficacious.
  - Balloon coating with excipient and paclitaxel (crystallinity) are essential for the success of drug coated balloons.

- **Below the knee:**
  - Balloon expandable stents with sirolimus or analogs are efficacious in small vessel without anatomic demands because of size and continuous drug release form polymer over a long period. However, drug coated balloons carry high dose of cytotoxic paclitaxel applied on a small vessel with uneven distribution and greater fibrin deposition are ineffective in this setting.
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Preclinical Evaluation in Animals

Healthy animal models

New Zealand White Rabbit
- 15-25 cm
- 5-10 Kg

Yucatan Minipig
- 40-60 cm
- 50-60 Kg

Suffolk Cross-bred sheep
- 80-100 cm
- 80-100 Kg

Peripheral
- 3.8 mm
- 5.5 cm
- 4.9 mm

Coronary
- 5.5 mm
- 24 cm
- 60 cm
<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>
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<tr>
<td>Cotavance®</td>
<td>Bayer Schering Pharma AG, Berlin, Germany</td>
<td>Paclitaxel–iopromide</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td>Freeway™</td>
<td>Eurocor, Bonn, Germany</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
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<tr>
<td>In.Pact™ Admiral,</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
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<tr>
<td>Lutonix® 035 DCB</td>
<td>BARD, Murray Hill, NJ, USA</td>
<td>Paclitaxel–polysorbate/sorbitol</td>
<td>2.0</td>
<td>Yes</td>
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<tr>
<td>Legflow®</td>
<td>Cardionovum, Warsaw, Poland</td>
<td>Paclitaxel–shellac</td>
<td>3.0</td>
<td>Yes</td>
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<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>
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<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel</td>
<td>2.0</td>
<td>No → Yes</td>
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<td>SurVeil™DCB</td>
<td>SurModics, MN, USA</td>
<td>Paclitaxel–proprietary photolink®</td>
<td>2.0</td>
<td>No → No</td>
</tr>
</tbody>
</table>

FDA approval
Clinical trial under FDA
First in man in USA

*CE mark* indicates CE mark approval.

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