Drug Elution In The SFA: How Does It Work? What Are The Hurdles?

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Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Employment in industry: No


Owner of a healthcare company: No

Stockholder of a healthcare company: No
SFA needs drug

**ISAR-STATH trial**

- **PEB+Stent**: Paclitaxel-eluting balloon + BMS
- **BA+Stent**: Balloon angioplasty + BMS
- **DA**: Directional Atherectomy

**Graph Details**
- **Freedom from TLR**
- **Days after Procedure**
- **No. at risk**
  - BA+Stent: 52, 52, 51, 45, 40, 38, 33, 30, 29, 26, 22, 20, 19
  - DA: 55, 54, 51, 43, 37, 30, 27, 23, 21, 18, 17, 15, 15

**Statistical Significance**
- $P=0.003$
Type of drugs on DES/DCB 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)
Why clinical outcomes are different by location – Above knee

- Self expanding Stents used
  - ≤6 months following implantation
  - >6-12 months following implantation

- Calcium: Hard plaque resists balloon remodeling
- Dissection: hold flap back for healing
- Recoil: Significant loss of luminal area

Stents May Be Required in a Fair Number of Cases But Is It Safe and More Efficacious to Use Zilver Ptx After DCB?

Paclitaxel or Sirolimus (+Analogs)
- Tissue penetration of paclitaxel is greater than Sirolimus and its Analogs.
- Paclitaxel Coated Balloons with excipient are efficacious because of paclitaxel crystallinity, greater penetration and use of excipient which allows for sustained release of drug.

Inter-strut distance increases as stent continues to expand resulting in decreasing drug availability between struts

Efficacy ↓

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

Mean neointima thickness, mm

Maximum inter-strut distance

Nakano et al. Eur Heart J 2013:34:3304-3313
Paclitaxel eluting devices are now the gold standard for SFA

DES vs. standard care
(Paclitaxel) (POBA/provisional BMS)

DCB vs. POBA
(Paclitaxel)

There are no large head to head randomized trials comparing DES to DCB for SFA disease.

<table>
<thead>
<tr>
<th>Device</th>
<th>Company</th>
<th>Coating</th>
<th>Drug dose ($\mu g/mm^2$)</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,</td>
<td>Medtronic Vascular, Santa Clara, CA, USA</td>
<td>Paclitaxel–urea</td>
<td>3.5</td>
<td>Yes</td>
</tr>
<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>
</tr>
<tr>
<td>Ranger</td>
<td>Boston Scientific</td>
<td>Paclitaxel–Acetyl Tributyl Citrate 2</td>
<td>2.0</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>Yes</td>
</tr>
<tr>
<td>Stellarex®</td>
<td>Covidien, Mansfield, MA, USA</td>
<td>Paclitaxel–polyethylene glycol</td>
<td>2.0</td>
<td>Yes</td>
</tr>
<tr>
<td>SurVeil™ DCB</td>
<td>SurModics, MN, USA</td>
<td>Paclitaxel–proprietary photolink®</td>
<td>2.0</td>
<td>Yes</td>
</tr>
</tbody>
</table>
Lutonix® 035 vs. In.Pact™ Admiral
First Comparative Study in Swine

• Blinded study – Side-by-side
• 1x and 3x dose
• Evaluated skeletal muscle and coronary band at 28 and 90 days
  ▪ Distal drug concentration
  ▪ Histology
    • Distal embolization
    • Vascular changes

Comparison of Particulate Embolization after Femoral Artery Treatment with IN.PACT Admiral versus Lutonix 035 Paclitaxel-Coated Balloons in Healthy Swine
Frank D. Kolodgie, PhD, Erica Pacheco, MS, Kazuyuki Yahagi, MD, Hiroyoshi Mori, MD, Elena Ladich, MD, and Renu Virmani, MD

J Vasc Interv Radiol 2016; 27:1676–1685

Different test methods may yield different results. Pre-clinical test data on file. Pre-clinical results may not be indicative of clinical performance.
Evaluation of distal emboli

Femoral Artery

- Straight Femoral Muscle
- Cranial Tibial Muscle

- Semimembranosus Muscle
- Gracilis Muscle
- Semitendinosus Muscle
- Gastrocnemius Muscle
- Coronary Band

Popesko. ATLAS of topographical anatomy of the domestic animals 2nd edition
### Downstream Incidence of Distal Embolization (%)

#### A

**28-Day Survival**
- **Single Balloon (1x)**
  - Lutonix 035: 7.7% (0-11.5), n=5
  - IN.PACT: 15.4% (11.5-30.8), n=5
  - P = 0.04

- **Overlapping Balloons (3x)**
  - Lutonix 035: 7.7% (0-15.4), n=5
  - IN.PACT: 38.5% (15.4-42.3), n=5
  - P = 0.07

**90-Day Survival**
- **Overlapping Balloons (3x)**
  - Lutonix 035: 0% (0-11.5), N=5
  - IN.PACT: 46.2% (19.2-57.7), N=5
  - P = 0.01

#### B

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of micro-vessels with paclitaxel-associated findings</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day (1x, n=5)</td>
<td>1 (0-2)</td>
<td>4 (2-12)</td>
<td>0.03</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>1 (0-12)</td>
<td>26 (11-34)</td>
<td>0.07</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0 (0-3)</td>
<td>11 (5-15)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

#### C

<table>
<thead>
<tr>
<th>Survival Treatment &amp; Arteries</th>
<th>Lutonix 035</th>
<th>IN.PACT</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel concentration in downstream tissues (ng/g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28-day (1x, n=5)</td>
<td>1.3 (0.6-2.3)</td>
<td>1.5 (1.1-65.8)</td>
<td>60.8 (32.6-118.1)</td>
</tr>
<tr>
<td>28-day (3x, n=5)</td>
<td>3.7 (1.3-10.9)</td>
<td>31.5 (5.9-54.1)</td>
<td>170.9 (19.7-221.5)</td>
</tr>
<tr>
<td>90-day (3x, n=4)</td>
<td>0.6 (0.5-6.4)</td>
<td>2.7 (0.0-25.5)</td>
<td>16.1 (12.8-319.2)</td>
</tr>
</tbody>
</table>
High (20x and 40x) power images of vascular changes in skeletal muscle at 28 days.

Vascular changes include pyknotic nuclei embedded in homogenous pink material (yellow arrow), representing fibrinoid necrosis (black arrows), with surrounding inflammatory cells (blue arrows).

High (40x) power images of crystalline material (red arrows) at 28d
Three Case Reports for Downstream Effect of IN.PACT DCB Use: Particulate Embolization Related?

- **Downstream Panniculitis Secondary to Drug–Eluting Balloon Angioplasty.** Ibrahim et al, JACC 2016

- **Vasculitis resulting from a superficial femoral artery angioplasty with a paclitaxel-eluting balloon.** Thomas et al, JVS 2014

- **Acute hypersensitivity reaction to femoral drug-coated balloons.** Lake et al, Vasa 2017
# Calcification Grade

Prevalence of Calcification by CT Angiography in 60 Symptomatic patients

Calcification in 10 asymptomatic legs. (preliminary data)

<table>
<thead>
<tr>
<th>AK</th>
<th>Intimal</th>
<th>65.9%</th>
<th>24.4%</th>
<th>8.9%</th>
<th>0.8%</th>
</tr>
</thead>
<tbody>
<tr>
<td>444 lesions</td>
<td>Medial</td>
<td>90.6%</td>
<td>7.2%</td>
<td>1.9%</td>
<td>0.2%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>BK</th>
<th>Intimal</th>
<th>81.1%</th>
<th>10.0%</th>
<th>6.9%</th>
<th>0.2%</th>
</tr>
</thead>
<tbody>
<tr>
<td>1126 lesions</td>
<td>Medial</td>
<td>98.2%</td>
<td>1.5%</td>
<td>0.3%</td>
<td>0%</td>
</tr>
</tbody>
</table>
Inverse relationship between the primary patency and late lumen loss (LLL) with calcium groups after 12 months of follow up

After revascularization of SFA lesion by In.Pact DCB.
# Provisional stenting is mandatory in some cases

## Table: Stent Rates Across Different Trials

<table>
<thead>
<tr>
<th>DCB trials</th>
<th>In.Pact SFA&lt;sup&gt;1&lt;/sup&gt;</th>
<th>In.Pact Registry&lt;sup&gt;2&lt;/sup&gt;</th>
<th>In.Pact LL Subgroup (15-25cm)&lt;sup&gt;3&lt;/sup&gt;</th>
<th>In.Pact LL Subgroup (&gt;25cm)&lt;sup&gt;3&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provisional stent rates</td>
<td>7.3%</td>
<td>24.7%</td>
<td>33.3%</td>
<td>52.6%</td>
</tr>
<tr>
<td>Patients</td>
<td>16/220</td>
<td>160/648</td>
<td>33/99</td>
<td>30/57</td>
</tr>
</tbody>
</table>

## Table: Modern Stent Trials

<table>
<thead>
<tr>
<th>Modern stent trials</th>
<th>Resilient (PTA arm)&lt;sup&gt;4&lt;/sup&gt;</th>
<th>Zilver PTX RCT (PTA arm)&lt;sup&gt;5&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Provisional stent rates</td>
<td>40%</td>
<td>50%</td>
</tr>
<tr>
<td>Patients</td>
<td>29/72</td>
<td>120/238</td>
</tr>
</tbody>
</table>

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6. Medicare Part B claims indicate an SFA stent is used nearly half of the time. (PSPSF, 2013)
How does DCB effect compare with DES?
Is it safe to use DES after DCB?

Study Design:

Devices Used in Study:
- DCB = In.Pact Admiral
- DES = Zilver PTX
- BMS = Zilver 635 Bare
- POBA = Advance 35LP
What Histological Markers Indicate Efficacy?

- Endothelial cell loss
- Inter-strut SMC density
- Fibrin deposition
- Medial SMC loss (Depth and Circumference)
- Medial proteoglycan/collagen replacement
Histological Analysis in Porcine Superficial Femoral Artery

### Medial SMC Loss (Depth)

- **DCB alone**: 
- **DCB+BMS**: 
- **DCB+DES**: 
- **POBA+DES**:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score</th>
<th>Comparison 1</th>
<th>Comparison 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCB alone</td>
<td>0</td>
<td>p=0.007</td>
<td></td>
</tr>
<tr>
<td>DCB+BMS</td>
<td>1</td>
<td></td>
<td>p=0.008</td>
</tr>
<tr>
<td>DCB+DES</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POBA+DES</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Medial SMC Loss (Circumferential)

- **DCB alone**: 
- **DCB+BMS**: 
- **DCB+DES**: 
- **POBA+DES**:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Score</th>
<th>Comparison 1</th>
<th>Comparison 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCB alone</td>
<td>0</td>
<td>p=0.003</td>
<td></td>
</tr>
<tr>
<td>DCB+BMS</td>
<td>1</td>
<td></td>
<td>p=0.005</td>
</tr>
<tr>
<td>DCB+DES</td>
<td>2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>POBA+DES</td>
<td>3</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Fibrin Deposition

- **DCB alone**: 
- **DCB+BMS**: 
- **DCB+DES**: 
- **POBA+DES**:

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Comparison 1</th>
<th>Comparison 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>DCB alone</td>
<td>p&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>DCB+BMS</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>DCB+DES</td>
<td></td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td>POBA+DES</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

**Table:**

<table>
<thead>
<tr>
<th>Medial SMC loss (Depth) score</th>
<th>Circumferential</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>none</td>
</tr>
<tr>
<td>1</td>
<td>SMC loss &lt;25% of medial thickness</td>
</tr>
<tr>
<td>2</td>
<td>25-50%</td>
</tr>
<tr>
<td>3</td>
<td>51-75%</td>
</tr>
<tr>
<td>4</td>
<td>&gt;75%</td>
</tr>
</tbody>
</table>
Histologic findings of emboli/vascular changes following stent implantation

Percentage of sections with distal emboli

DCB alone  DCB+BMS
DCB+DES  POBA+DES

DCB usage

p=0.02
Porcine PTX: 1-month histological images

DCB+DES

POBA+DES

DCB+BMS

DCB alone
Conclusion

• In SFA lesions, 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±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.

• Irrespective of preceding DCB or POBA, DES showed maximum biologic change in neointima/media suggestive of superior drug effect with DES.

• Distal emboli were exclusively seen in groups with DCBs.

• DES + DCB or POBA showed greater desired biologic effect as compared to BMS + DCB or DCB alone. No untoward effects were observed in the DCB+DES group.

• In severe calcified lesions with evidence of vessel dissection, prolapse, or angiographic unacceptable results following DCB usage, DES should be used rather than BMS.
Acknowledgments

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Jinky Beyer
Lila Adams, HT
Frank D Kolodgie, PhD
Liang Guo, PhD
Renu Virmani, MD

My email: afinn@cvpath.org
Histological Analysis of DCB/BMS, DCB/ZPTX, and POBA/ZPTX in Porcine Superficial Femoral Artery

**% strut with >50% fibrin**

![Graph showing % strut with >50% fibrin](image)

*p=0.01*

**Interstrut SMC Density Score**

![Graph showing interstrut SMC density score](image)

*p=0.005*

**Medial PGs/collagen score**

![Graph showing medial PGs/collagen score](image)

*p=0.006*

**Medial SMC Loss (Circumf) Score**

![Graph showing medial SMC loss (circumf) score](image)

*p=0.01*

**Key Takeaway:** Drug Effects were much less with DCB/BMS versus Zilver Ptx Groups
Porcine PTX: 1-month histological images

Key Takeaway: Zilver Ptx Groups Had More Evidence of Drug Effect
Histologic findings of emboli/vascular changes following stent implantation

Key Takeaway: Distal emboli were exclusively seen in groups with DCBs.

Fibrinoid necrosis in DCB/BMS (left) and DCB/ZPTX (right).

% Downstream Vascular Changes

* *

*p<0.05 versus POBA/ZPTX
Devices Used in Study:
- **DCB** = In.Pact Admiral
- **DES** = Zilver PTX
- **BMS** = Zilver Bare

Yucatan Minipig

40-60 cm
50-60 Kg
Morphometry and histological Analysis of Zilver PTX with POBA or DCB in Porcine Superficial Femoral Artery

Key Takeaway: Vessel Dimensions were within normal limits in all groups indicating DCB/Zilver Ptx was safe. Drug Effects were similar between POBA/Zilver Ptx versus DCB/Zilver Ptx.
Key Takeaway: DCB + Zilver Ptx was as safe as POBA + Zilver PTX in long term follow-up
Histologic findings of emboli/vascular changes following stent implantation

% Downstream Vascular Changes

<table>
<thead>
<tr>
<th>1-Month n=6</th>
<th>3-Month n=6</th>
<th>6-Month n=8</th>
</tr>
</thead>
<tbody>
<tr>
<td>p=0.058</td>
<td>p=0.02</td>
<td></td>
</tr>
</tbody>
</table>

Fibrinoid necrosis in DCB/ZPTX at 1-month (left) and 3-month (right).

Key Takeaway: Distal emboli were exclusively seen in groups with DCBs
Porcine PTX Long-Term Safety Study

Conclusion: ZPTX + DCB safe

Zilver PTX + DCB is as safe as Zilver PTX + POBA in long-term swine model.
Restenosis processes and inhibitors

Normal artery + stent

Endothelial injury

Platelet + fibrin + coagulation factors

Cytokines, VEGF, NO, thrombin, Low shear stress

Growth factors + cytokines

Inflammation

Leucocyte recruitment + chemotactic factors

IL-8, MCP-1

Growth factors (PDGF), thrombin

P-selectin, and integrins Glycoproteins - Iba and Hb/IIa

Contractile → Synthetic smooth muscle cells (SMC)

*C* Sirolimus

Everolimus

Zotorolimus

Biolimus A9

Tacrolimus

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

Radiation actinomycin-D

Taxol Taxane

Anti-mitotic, blocks Microtubular mechanics

Proteoglycans

SMC migration

Collagen type III

Remodelling (collagen type I)

uPA, tPA, PAI

MMPs (TIMPs)
Sirolimus and Paclitaxel

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

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
Type of drugs on DES in animal

Healthy animal models

New Zealand White Rabbit

Sirolimus + analogs
Paclitaxel

Yucatan Minipig

Coronary: Biologic effects ✓
Peripheral: Biologic effects ✓

Suffolk Cross-bred sheep

Porcine coronary artery
3 months

Sirolimus

Paclitaxel


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

Sirolimus + analogs
Paclitaxel

Balloon Expandable Stents

Successful ✔

Sirolimus + analogs
Paclitaxel

Everolimus
13 months

Paclitaxel
9 months

Balloon Expandable Stents
## DIFFERENCE OF DES AND DCB

<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 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 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></td>
</tr>
</tbody>
</table>

**Notes:**
- **BMS**: 28 days (Rabbit iliac artery)
- **DES**: 14 days (Porcine iliac artery)
Type of drugs on DES/DCB in human peripheral (Above the knee)

**Sirolimus + analogs** failed

**Paclitaxel (stent and balloon)** Successful ✔

Everolimus coated nitinol stent for SFA (STRIDES trial)

Paclitaxel coated nitinol stent for SFA (Zilver PTX trial)

- Primary patency/1year: 68%
- Freedom from TLR/1year: 80%

- ZPTX 90% BMS 73%
- ZPTX 91% BMS 83%
Type of drugs on DES/DCB in human

In human peripheral (Below the knee)

Sirolimus ± analogs/paclitaxel on stent

Successful ✔

Paclitaxel in DCB

failed

Sirolimus + analogs for CLI Pts

Bayesian Network meta analysis

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

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