Drug Eluting Balloons
Background and Rationale

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Disclosure Statement of Financial Interest

Member Advisory Board Eurocor GmbH
Why do we want a DEB in a DES-era?

A: we unfortunately still have DES-restenosis
**And** . . we have economic & health issues:

stent cost and (life ?)-long dual antiplatelet therapy ??

**Still** . . persisting safety issue due to absence of neointimal coverage and late malapposition: patient compliance ?

late & very late stent thrombosis !
Why do we want a DEB?

**DES: still not perfect in:**

1. Small Vessels
2. Bifurcations
3. Diabetics
4. Acute Myocardial infarction

“Late malapposition”
Potential Advantages DEB

Local drug delivery over very short period of time: not weeks / months

Avoid chronic inflammation due to absence polymers

Better re-endothelialization: reduced dual antiplatelet therapy

No distortion of original vessel anatomy (BIF)

No double / triple metal layers in case of ISR or BIF

Easy lesion crossing / deliverability by balloon only
Methods & Techniques

Several techniques and methods however common properties:

- lipophylic drug (rapid absorption) for short inflation times
- sustained retention into tissue (microtubuli / cytoskeleton)
- prevention of drug release before landing at ‘target’ (“wash-off”)
- increased profile compared to non-coated balloon

• 3 μg paclitaxel / mm² balloon surface
Why Paclitaxel?*

1. The ideal drug needs to inhibit cell proliferation without killing the cells.

2. Paclitaxel has a dose dependant effect associated with a large therapeutic window.

How does it work?

Restenosis is a complex mechanism involving many actors

Restenotic Cascade*

* Table adapted from Ferns et al: International Journal of Experimental Pathology, 2000; 81:63-88
Methods & Techniques

*paclitaxel + ‘additives’*

**Paccocath Technology €**: matrix coating with ‘hydrophylic spacer’ which leads to high contact surface, more uniform and complete release between the lipophilic drug molecules and the vessel wall. **High tissue concentration > 450 µM/L**

**Invatec FreePac Technology €**: separates Paclitaxel molecules and balances hydrophilic and lipophilic properties. Facilitates Paclitaxel elution into the vessel wall. Total drug elution time to 30 – 60 seconds. **Tissue concentration ?**

**Lutonix Coating Technology**: active agent and additives which prevents premature release from the balloon surface and facilitates rapid release of drug from the balloon. **Tissue concentration ?**

€: commercially available
Methods & Techniques

Paccocath Technology

pure paclitaxel

matrix coating: paclitaxel + hydrophilic spacer (iopromide)

FreePac Technology

Paclitaxel

Paclitaxel + separator molecule
Methods & Techniques

*paclitaxel without ‘additives’*

**Eurocor Dior Technology €**: shellac® coating and balloon folds to prevent wash-off. Drug delivery by simple diffusion. *Medium tissue concentration 50>x< 200 µM/L*

**Aachen Resonance Elutax Technology €**: drug encased in the surface, 20 % release by diffusion after each inflation. *Tissue concentration ??*

**Acrostak Genie Technology €**: liquid drug delivery by operators discretion. *Dosage ? Tissue concentration ??*

€ Comercially available
DIOR™ Technology:

- Paclitaxel balloon surface: 3 μg/mm²
- Coating method is a 1:1 mixture of Paclitaxel (Ph Eur.) and Shellac (Ph Eur.)
- Additional protection of wash off effect: drug hidden within the balloon folds
- Delivery by simple diffusion (Paclitaxel = lipofylic)
- The Coating is CE marked
- Shellac is well established in Cosmetics, as food coating and Tablet coating.

- Balloon inflation time recommended: 20-30 sec. @ nominal balloon pressure
  - No additional drug release after 45 sec.
Inflation time-dependent tissue concentrations of paclitaxel from the Dior balloon N=29*

Arterial tissue paclitaxel concentration

*Gyöngyösi et al
Clinical Data I

Original Article

Treatment of Coronary In-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter

Bruno Scheller, M.D., Christoph Hehrlein, M.D., Wolfgang Bocksch, M.D., Wolfgang Rutsch, M.D., Dariush Haghi, M.D., Ulrich Dietz, M.D., Michael Böhm, M.D., and Ulrich Speck, Ph.D.

Primary endpoint (late lumen loss in-segment)

<table>
<thead>
<tr>
<th>Uncoated balloon</th>
<th>PACCOCATH</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.74 ± 0.86 mm</td>
<td>0.03 ± 0.48 mm</td>
</tr>
</tbody>
</table>

Figure 1. Cumulative Frequency Distribution of In-Segment Minimal Luminal Diameter on Quantitative Coronary Angiography (Intention-to-Treat Analysis). Data are shown for the uncoated-balloon group and the coated-balloon group before the procedure, after the procedure, and at 6 months.

Clinical Data II

Two year follow-up after treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter

By: Scheller et al.

Clin Res Cardiol 2008; 97: 779-81
### Clinical Data III

**PEPCAD II ISR**

**DEB vs. DES in the treatment of coronary ISR**

<table>
<thead>
<tr>
<th></th>
<th>SeQuent Please</th>
<th>Taxus</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>66</td>
<td>65</td>
<td></td>
</tr>
<tr>
<td>Angiographic follow-up</td>
<td>57 (86.4%)</td>
<td>59 (90.8%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Late lumen loss</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>0.19 ± 0.39 mm</td>
<td>0.45 ± 0.68 mm</td>
<td>0.01</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.17 ± 0.42 mm</td>
<td>0.38 ± 0.61 mm</td>
<td>0.03</td>
</tr>
<tr>
<td>Late lumen loss index</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>0.12 ± 0.26 mm</td>
<td>0.28 ± 0.48 mm</td>
<td>0.03</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.11 ± 0.29 mm</td>
<td>0.30 ± 0.53 mm</td>
<td>0.02</td>
</tr>
<tr>
<td>Binary restenosis rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>In-stent</td>
<td>4 (7%)</td>
<td>10 (16.9%)</td>
<td>0.10</td>
</tr>
<tr>
<td>In-segment</td>
<td>4 (7%)</td>
<td>12 (20.3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Presented by Bruno Scheller @ JIM 09
**Local Delivery of Paclitaxel to Inhibit Restenosis during Angioplasty of the Leg**

Gunnar Tepe, M.D., Thomas Zeller, M.D., Thomas Albrecht, M.D., Stephan Heller, M.D., Uwe Schwarzwälder, M.D., Jean-Paul Beregi, M.D., Claus D. Claussen, M.D., Anja Oldenburg, M.D., Bruno Scheller, M.D., and Ulrich Speck, Ph.D.

**Primary endpoint (late lumen loss in-segment)**

<table>
<thead>
<tr>
<th></th>
<th>PTA uncoated (control)</th>
<th>PACCOCATH</th>
<th>PTA + paclitaxel in contrast medium</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen loss</td>
<td>1.7 ± 1.8 mm</td>
<td>0.4 ± 1.2 mm</td>
<td>2.2 ± 1.6 mm</td>
</tr>
</tbody>
</table>

# Clinical Data V

**Drug Eluting Balloon in bifurcation Trial**

"DEBIUT - registry" 6 mo clinical FU

<table>
<thead>
<tr>
<th>Medina classification type: (proximal main branch, distal main branch, and side branch involvement)</th>
<th>Number of patients ($n = 20$) ($n /%$)</th>
<th>QCA</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.1.1</td>
<td>12 (60)</td>
<td>Main branch</td>
</tr>
<tr>
<td>1.1.0</td>
<td>2 (10)</td>
<td></td>
</tr>
<tr>
<td>1.0.1</td>
<td>4 (20)</td>
<td></td>
</tr>
<tr>
<td>0.1.1</td>
<td>2 (10)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Side branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (mm)</td>
<td>15.5 +/- 5.0</td>
</tr>
<tr>
<td>Stent length (mm)</td>
<td>19.0 +/- 6.0</td>
</tr>
<tr>
<td>Reference vessel diameter (mm)</td>
<td>3.0 +/- 0.6</td>
</tr>
</tbody>
</table>

100 % successful

No MACE, no SAT

By: Fanggiday et al, CCI vol 71- 529-5352008
Bifurcation intervention with DIOR balloon: DEBIUT study

1. Predilatation with DEB, followed by one BMS (prov. T –technique)
2. Only 3 months of DAPT

Baseline

6 month FU
Bifurcation intervention with DIOR balloon: DEBIUT study
1. The ideal drug needs to inhibit cell proliferation without killing the cells.

2. Paclitaxel has a dose dependant effect associated with a large therapeutic window.

Safe and effective local drug delivery

Long-term efficacy with short-term release

After a “single shot” application of Paclitaxel there is a sustained antiproliferative action on SMC over 14 days in absence of cytotoxic effects. Following such a “single shot” drug delivery the Paclitaxel concentration reaches bottom levels in vascular cells after 24 hours.

*Sequent Please – Paccocath technique
Restenosis Inhibition - Therapeutic Window

Coronary Aneurisms After Paclitaxel - Coated Balloon in Pigs
4 wks.

Coronary Aneurisms After Paclitaxel - Coated Balloon in Pigs Aneurisms in High Dose PEB Group

By Dr. Echevarri –Solaci 2008 Cancun
to Summarize: Where would we want a DEB?

- **In stent restenosis**: avoid double/triple metal layer

- **Small vessels**: DES not perfect, better ‘crossability’

- **Bifurcations**: avoid uncontrolled drug release by (mini-) crushing polymers, SB is small vessel, ease of procedure, no distortion of original BIF-anatomy

- **Acute coronary syndromes**: local plaque stabilization, avoid late malapposition DES

- **Below the Knee**: no stent fractures
Conclusions

1. Early results very promising – especially for ISR and BTK

2. Limited Results on Long term clinical effects de novo lesions

3. Reduction of dual antiplatelet therapy icw. BMS (3ms) seems safe

4. Clinical trials ongoing in bifurcations (DEBIUT), AMI (DEB-AMI), small vessels and de novo lesions (DILATATION) and . . . . soon much more

5. **We need to establish the tissue concentration as a meaningful value and understand which dosage is effective and safe!**
Heart Lung Centre Utrecht - UMCU

2009
1800 PCI
20 ASD / PFO
25 Percut. Valve

Thank You!
Clinical Data VI
Quantitative histological results in overstretch porcine arteries – FU @ 14 days (N=12) **

**Gyöngyösi et al**
**Eurocor Dior™ Technology:**

**Medium Dose Release**

Study design **(Randomized N=12)**

Porcine coronary arteries were dilated (1.3:1 balloon/artery ratio) with either Dior balloon (3 µg/mm² paclitaxel balloon surface) or noncoated balloon.

Follow-up angiography and obdution: 14 days post-balloon dilatation.

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**Non-coated balloon**

**Dior II balloon**

**Gyöngyösi et al**
Bifurcation intervention with DIOR I balloon

Arterial tissue paclitaxel concentration

2h post-dilatation

- Baseline: 1.84 ± 1.963 µg/g
- DIOR in MB: 0.81 ± 0.389 µg/g
- DIOR in SB: 2.642 ± 2.157 µg/g
- Kissing: 4.342 ± 0.734 µg/g
- Final: 5.862 ± 2.094 µg/g

12h post-dilatation

- Baseline: 0 ± 0 µg/g
- DIOR in MB: 0.49 ± 0.195 µg/g
- DIOR in SB: 0.647 ± 0.322 µg/g
- Kissing: 1.227 ± 0.367 µg/g
- Final: 1.219 ± 0.4 µg/g

Gyöngyösi et al., Coron Artery Dis. 2008 Jun;19(4):243-7