Not All Paclitaxel-Eluting Balloon Catheters Are Created Equal

Martin Unverdorben
Clinical Research Institute, Center for Cardiovascular Diseases
Rotenburg/Fulda, Germany
R&D B Braun, Allentown, PA, USA
Agenda

- Principles of Balloon-Based Vascular Drug Delivery
- Technologies/Devices for Balloon-Based Vascular Drug Delivery
- Animal Data
  - Genie Dior
- Clinical Data
  - Elutax Sequent Please
  - Amphirion
DES vs. DEB (PACCOCATH)

- Slow (months) drug release from stent struts
- ~100 - 200 µg paclitaxel / sirolimus on device
- Polymers with associated reactions
- Implies stent deployment

- Burst drug release from balloon
- ~ 300-600 µg paclitaxel on device
- No polymers
- Stenting optional

Hwang, Circulation 2001; 104: 600-5
Scheller Heart 2007, 93: 539-41
Paccocath
Paclitaxel Binding to Hydrophobic Sites Within Arterial Tissue

ex vivo perfusion of calf carotid arteries, transmural distribution

Paclitaxel in iopromide (Ultravist®)

- Solubility > 200 µM if 1% ethanol is added = 20 times higher than in saline
- No difference in tolerance during coronary angiography compared to plain contrast media

**Cell culture experiment on short-term application**

<table>
<thead>
<tr>
<th>Concentration [µmol/l]</th>
<th>Saline control</th>
<th>Iopromide Paclitaxel 1.46 µM 60 min</th>
<th>Paclitaxel 14.6 µM 60 min</th>
<th>Iopromide Paclitaxel 14.6 µM 10 min</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>* p&lt;0.05 compared to control</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Porcine coronary model**

- M. Unverdorben, et al., Invest Radiol 2002; 37: 29-34
Agenda

- Principles of Balloon-Based Vascular Drug Delivery
- Technologies for Balloon-Based Vascular Drug Delivery
- Animal Data
- Clinical Data
Local Drug Delivery

Active system: porous balloon (rabbit carotid artery)

Herdeg et al. Cathet Cardiovasc Diagn 1997;41:308-314
Genie™

- Reaches adjacent segments
- Easy use of other drugs
- Additional device/step
- Technology complex
- Handling needs training

Neointimal area
- 2.37±0.23mm²
- 1.04±0.1mm²

P<0.001

Herdeg, C EuroInterv 2007;3:286-8
Dior™

- **Handling** like a typical PTCA catheter
- **Inflation** up to 60 seconds for full drug release
- **1st inflation** of 20s releases $\approx 35-79\%$ of the drug
- **2nd inflation** of 20s releases another $\approx 35-79\%$ of the drug

**Concern:** reproducibility of drug delivery, clinical outcome
DIOR I Surface (SEM)

Dior - “roughened surface”, not nanoporous
DRUG LOADING

- 2 µg paclitaxel per square millimeter balloon surface

- No polymer or solvent use when releasing the drug

- Drug wash-off protection through:
  - encasing the drug in the balloon’s microporous surface
  - “hiding” the drug between the folds
  - paclitaxel is hydrophobic and releases after contact with the arterial wall
SeQuent® (uncoated balloon)

SeQuent® Please* (coated balloon)

*SeQuent® Please (B. Braun Vascular Systems, Berlin, Germany) is manufactured based on the PACCOCATH technology with 3µg paclitaxel/mm²; CE marked in the EU, approved in other countries
The Matrix Coating

PACCOCATH technology creates a unique **matrix coating**

pure paclitaxel  
without

paclitaxel + hydrophilic spacer  
with PACCOCATH technology

- **huge contact surface** between lipophilic drug and the vessel wall
- **high bioavailability** of paclitaxel at the target site for rapid drug absorption by the vessel wall
- **uniform/complete application** of the drug after 1st balloon expansion
Release Kinetics of Paclitaxel-Eluting Devices

Comparison Taxus® vs Coroflex® vs SeQuent Please®

Boston MR SR  Braun Nr. 1-3

eluiertes Taxol (kumuliert) [µg]

Time [h]

≈100,00

≈10,00

8,00

6,00

4,00

2,00

0,00

0 50 100 150 200 250 300

Boston MR
Boston SR
B.Braun Nr.1
B.Braun Nr.2
B.Braun Nr.3

M.Unverdorben  M'sia LIVE 2009  Kuala Lumpur
PACCOCATH
Efficacy versus paclitaxel dose / mm² balloon surface

% inhibition of neointimal area

μg paclitaxel/mm² balloon surface area

no worries about balloon overlap
In.Pact Amphirion™

Invatec
Agenda

- Principles of Balloon-Based Vascular Drug Delivery
- Technologies for Balloon-Based Vascular Drug Delivery
- Animal Data
- Clinical Data
QCA in Swine (28 Days)

- Control (n=11)
- DIOR (n=9)
- PACCOCATH (n=8)

* : n.s. vs. Control (p>0.05)
+ : p<0.001 vs. Control
# : p<0.001 vs. DIOR

(Cremers B, Clin Res Cardiol 2009 online)
Histology in Swine (28 Days)

- Control (n=11)
- DIOR (n=9)
- PACCOCATH (n=8)

* : n.s. vs. Control (p>0.05)
+ : p<0.05 vs. Control
# : p<0.05 vs. DIOR
§ : p<0.001 vs. Control
≠ : p<0.01 vs. DIOR

(Cremers B, ESC 2008)
Percent stenosis (angiography); negative values indicate persistent over-dilatation.

FreePac and Paccocath versus Control each p = 0.25

FreePac and Paccocath versus Control each p < 0.001; FreePac versus Paccocath p = 0.68
Clinical Data

- Native coronary arteries
- Bifurcations
- In-stent restenosis
**LOCAL TAX study**  
**Study design**

**Inclusion criteria:**
- age: 18 - 80 years
- symptomatic CHD and/or documented myocardial ischemia
- de-novo stenoses (50%-99 %) in native coronary arteries
- Target vessel diameter $\geq 2.5$ mm, lesion length $\leq 20$ mm.

<table>
<thead>
<tr>
<th>Coronary angiography</th>
<th>randomization (n=204)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>I. bare metal stent + paclitaxel locally (n=68)</td>
</tr>
<tr>
<td></td>
<td>II. bare metal stent (n=68)</td>
</tr>
<tr>
<td></td>
<td>III. TAXUS™ stent (n=68)</td>
</tr>
</tbody>
</table>

- safety follow up 4 hours 24 hours 30 days MACE 6 months follow up angiography optional IVUS

- ASS 100 mg  
- Clopidogrel loading 600 mg  
- Clopidogrel 75 mg for 6 months
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Bare metal stent (n=56)</th>
<th>Bare metal stent + local paclitaxel (n=54)</th>
<th>Paclitaxel-eluting stent (n=54)</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent late loss (mm)</td>
<td>0.98 ± 0.72</td>
<td>0.61 ± 0.44</td>
<td>0.44 ± 0.49</td>
</tr>
<tr>
<td>In-segment late loss (mm)</td>
<td>0.95 ± 0.77</td>
<td>0.62 ± 0.45</td>
<td>0.44 ± 0.58</td>
</tr>
<tr>
<td>In-stent MLD (mm)</td>
<td>1.46 ± 0.69</td>
<td>1.84 ± 0.59</td>
<td>2.04 ± 0.59</td>
</tr>
<tr>
<td>In-segment MLD (mm)</td>
<td>1.41 ± 0.66</td>
<td>1.71 ± 0.55</td>
<td>1.77 ± 0.60</td>
</tr>
<tr>
<td>In-stent % DS</td>
<td>42.07 ± 24.88</td>
<td>30.49 ± 16.53</td>
<td>21.85 ± 19.18</td>
</tr>
<tr>
<td>In-segment % DS</td>
<td>43.19 ± 24.89</td>
<td>34.02 ± 15.61</td>
<td>31.23 ± 18.93</td>
</tr>
<tr>
<td>In-stent binary restenosis –no. (%)</td>
<td>21 (37.5)</td>
<td>6 (11.1)</td>
<td>3 (5.6)</td>
</tr>
<tr>
<td>In-segment binary restenosis –no. (%)</td>
<td>22 (39.3)</td>
<td>8 (14.8)</td>
<td>8 (14.8)</td>
</tr>
</tbody>
</table>
### LOCAL TAX study
Results of Clinical Follow-Up

<table>
<thead>
<tr>
<th>Variable</th>
<th>Bare metal stent (n=67)</th>
<th>Bare metal stent + local paclitaxel (n=67)</th>
<th>Paclitaxel-eluting stent (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>At 30 days</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>MI</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Subacute closure</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>TLR</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
<tr>
<td>MACE + TLR</td>
<td>0</td>
<td>0</td>
<td>1 (1.5)</td>
</tr>
</tbody>
</table>

---

**Intention-to-Treat-Analyses**
Paclitaxel-Eluting Devices in Small Vessel Disease
Balloon vs Stent

Stenosis [%]
80
70
60
50
40
30
20
10
0

6-mo follow-up

PEB (DIOR) PES (TAXUS)

P = 0.029

(B. Cortese et al. Euro PCR 2009)
The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease

PEPCAD I-SVD

SeQuent® Please
1-Year Event Free Survival

- Total
- DEB only
- DEB + Stent

Months post PCI
### Total Length of Stents Deployed [mm]

<table>
<thead>
<tr>
<th></th>
<th>Recurrence</th>
<th>No Recurrence</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.4 ± 8.4</td>
<td></td>
<td>14.4 ± 10.2</td>
<td>0.035</td>
</tr>
</tbody>
</table>

### Geographic Mismatch (GMM)

<table>
<thead>
<tr>
<th></th>
<th>GMM</th>
<th>No GMM</th>
<th>Total</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrence</td>
<td>10</td>
<td>3</td>
<td>13</td>
<td>0.029</td>
</tr>
<tr>
<td>No Recurrence</td>
<td>3</td>
<td>13</td>
<td>16</td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>13</td>
<td>16</td>
<td>29</td>
<td></td>
</tr>
</tbody>
</table>

### Binary restenosis

- **Binary restenosis in segment**: 4/73 (5.5%) vs. 13/29 (44.8%) (p = 0.029)
- **Binary restenosis in lesion**: 4/73 (5.5%) vs. 12/29 (41.3%)

### Other Events

- **TLR**: 4/82 (4.9%) vs. 9/32 (28.1%)
- **Stent thromboses with PCI**: N/A vs. 2/120 (1.7%)
- **Myocardial infarction**: 1/82 (1.2%) vs. 1/32 (3.3%)
- **Death**: 0/82 (0%) vs. 0/30 (0%)
- **Total MACE**: 5/82 (6.1%) vs. 12/32 (37.5%)
- Native coronary arteries
- Bifurcations
- In-stent restenosis
Safety and Efficacy of Drug-Eluting Balloons in Percutaneous Treatment of Bifurcation Lesions: The DEBIUT (Drug-Eluting Balloon in Bifurcation UTrecht) Registry

James C. Fanggiday, MD, Pieter R. Stella,* MD, Siyrous Hoseyni Guyomi, MD, and Pieter A. Doevedans, MD, PhD

The use of paclitaxel-coated balloon catheters is effective and safe in PCI for coronary artery bifurcation lesions, without clinical signs of restenosis at 4 months follow up. Although all patients stopped Clopidogrel at 3 months after the index procedure so far no late thrombosis was reported.
<table>
<thead>
<tr>
<th>Study Essentials</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
</tr>
<tr>
<td><strong>Patients</strong></td>
</tr>
<tr>
<td><strong>Primary Endpoint</strong></td>
</tr>
<tr>
<td><strong>Angiographic FU</strong></td>
</tr>
<tr>
<td><strong>No of FU patients</strong></td>
</tr>
<tr>
<td><strong>Registry</strong></td>
</tr>
<tr>
<td>20</td>
</tr>
<tr>
<td>MACE by telephone at 4 months</td>
</tr>
<tr>
<td>not performed</td>
</tr>
<tr>
<td>not reported</td>
</tr>
</tbody>
</table>
The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease

PEPCAD V-BIF

PI: F.X.Kleber, D.Mathey
Berlin/Hamburg, Germany

Core Lab/CEC: R.Degenhardt/M.Unverdorben
Rotenburg an der Fulda, Germany, Allentown, PA
### Baseline Angiography (ITT: N=28)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Count (Percentage)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-vessel disease [%]</td>
<td>13/28 (46.4%)</td>
</tr>
<tr>
<td>2-vessel disease [%]</td>
<td>12/28 (42.9%)</td>
</tr>
<tr>
<td>3-vessel disease [%]</td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>Medina 1.0.0</td>
<td>2/28 (7.1%)</td>
</tr>
<tr>
<td>Medina 0.1.1</td>
<td>8/28 (28.6%)</td>
</tr>
<tr>
<td>Medina 1.0.1</td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>Medina 1.1.1</td>
<td>9/28 (32.1%)</td>
</tr>
<tr>
<td>Medina 0.1.0</td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>Medina 0.0.1</td>
<td>1/28 (3.6%)</td>
</tr>
<tr>
<td>Medina 1.1.0</td>
<td>1/28 (3.6%)</td>
</tr>
<tr>
<td>Unknown*</td>
<td>1/28 (3.6%)</td>
</tr>
</tbody>
</table>

*one CD missing due to technical problems
PEPCAD V BIF Conclusions

- In the PEPCAD V pilot trial, the DEB (SeQuent® Please, B.Braun) in combination with a BMS (Coroflex®, B.Braun) shows excellent procedural results in bifurcational lesions, with no MACE up to 30 days.

- The method may help to improve and simplify the treatment of bifurcation lesions.

  D. Mathey, PI PEPCAD V, TCT 2008

The 9-month follow-up data will be presented at the TCT September 2009
Native coronary arteries

Bifurcations

In-stent restenosis
### MACE in ISR DIOR™

#### 6 Months Clinical Follow-Up

<table>
<thead>
<tr>
<th>Patients (n=29)</th>
<th>N</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiac Death</td>
<td>-</td>
<td>0</td>
</tr>
<tr>
<td>CCS grade</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>24</td>
<td>82.7</td>
</tr>
<tr>
<td>2</td>
<td>1</td>
<td>3.4</td>
</tr>
<tr>
<td>3</td>
<td>2</td>
<td>6.9</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>6.9</td>
</tr>
<tr>
<td>Non-Q Wave MI</td>
<td>1</td>
<td>2.9</td>
</tr>
<tr>
<td>TLR</td>
<td></td>
<td>13.7</td>
</tr>
<tr>
<td>TVR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>non-TVR</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MACE_TLR</td>
<td>7</td>
<td>20%</td>
</tr>
<tr>
<td>ALL MACE</td>
<td>9</td>
<td>25%</td>
</tr>
</tbody>
</table>

*1 patient lost to FU. 6 pts not yet reached 6 month FU.

Mauri L. et al., Spring Meeting 2008, Leipzig, Germany"
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>

P = 0.002
TLR, MI, acute/subacute closure, stroke, or death

24 Month Clinical Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Uncoated balloon</th>
<th>Drug-coated balloon</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>TLR</td>
<td>20 (37 %)</td>
<td>3 (6 %)</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>5 (9 %)</td>
<td>1 (2 %)</td>
<td>0.577</td>
</tr>
<tr>
<td>Death</td>
<td>3 (6 %)</td>
<td>2 (4 %)</td>
<td>0.912</td>
</tr>
<tr>
<td>Stroke</td>
<td>3 (6 %)</td>
<td>2 (4 %)</td>
<td>0.840</td>
</tr>
<tr>
<td>MACE</td>
<td>25 (46 %)</td>
<td>6 (11 %)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Intention-to-treat analysis; p-values adjusted according to Fisher's method of combining independent tests

Mantel-Cox log-rank test; p-values adjusted according to Fisher's method of combining independent tests
The Paclitaxel-Eluting PTCA-Balloon Catheter in Coronary Artery Disease

PEPCAD II-ISR

PI: Martin Unverdorben
As-Treated

Randomized
N=131

Sequent Please
n=66

Taxus
n=65

4 protocol violators
Lesion too long (41.1mm)
Multilesion PCI in metal jacket
Significant flap after PCI
Severe renal failure

66 DEB
56 DEB only
6 DEB + BMS
4 DEB (cross-over)

1 randomization error + 3 crossing failure treat/w DEB

60 DES
2 with additional DES

1 crossing failure treat/w convert balloon
12-Month Event Free Survival (ITT/As-Treated)

- **ITT/As-Treated**
  - DES/ITT
  - DEB/ITT
  - DES/AsT
  - DEB/AsT

- **P* = 0.09**
  - ITT

- **P* = 0.02**
  - As-Treated

*Logrank test*

Subjects [%]

- 100
- 95
- 90
- 85
- 80
- 75
- 70

Months post PCI

0 5 10 15

Circulation 2009;119:2986-94

M.Unverdorben

Kuala Lumpur
Summary

- The currently available balloon catheters differ with respect to...
  - the technology
  - the availability of clinical data
  - the clinical outcome

- Some of the currently available balloon catheters seem to be similar in technology, however clinical data are missing.

There is no evidence that all drug-eluting balloon catheters are equal.
Thank you very much!

- Ralf Degenhardt
- Tina Iffland
- Melanie Häussler
Late Lumen Loss (Swine)

Late lumen loss [mm]

not significant

ns vs. Kontrolle

SeQuent® Please

p<0.001

SeQuent®

Please vs. DIOR

uncoated balloon

DIOR®

Eurocor

p<0.001 vs. Kontrolle+DIOR

BRAUN

Kontrolle

DIOR

PACCOCATH
PEPCAD I - PEB + BMS

PEB 17 mm  BMS 25 mm

6 month control angiography

Geographic Mismatch
The Challenge
# Outcome (ITT: N=131)

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>DEB (N=66)</th>
<th>DES (N=65)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: clinical [months]</td>
<td>6.2 ± 0.9</td>
<td>6.2 ± 0.9</td>
<td>1</td>
</tr>
<tr>
<td>Follow-up: clinical [N]</td>
<td>64 (97.0%)</td>
<td>65 (100%)</td>
<td>0.5</td>
</tr>
<tr>
<td>Follow-up: angiographic [N]</td>
<td>57 (86.4%)</td>
<td>59 (90.8%)</td>
<td>0.6</td>
</tr>
<tr>
<td>Late lumen loss [mm]</td>
<td>0.20 ± 0.45</td>
<td>0.45 ± 0.68</td>
<td>0.02</td>
</tr>
<tr>
<td>Binary restenosis in segment</td>
<td>4/57 (7.0%)</td>
<td>12/59 (20.3%)</td>
<td>0.06</td>
</tr>
<tr>
<td>TLR</td>
<td>4/64 (6.3%)</td>
<td>10/65 (15.4%)</td>
<td>0.1</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0/64 (0.0%)</td>
<td>1/65 (1.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>*2/64 (3.1%)</td>
<td>**1/65 (1.5%)</td>
<td>1</td>
</tr>
<tr>
<td>Total MACE (w/o non-cardiac death)</td>
<td>5/64 (7.8%)</td>
<td>11/65 (16.9%)</td>
<td>0.2</td>
</tr>
</tbody>
</table>

*1 each: non-cardiac & cardiac but not lesion related
** non-cardiac death

*1/65 NSTEMI due to side branch occlusion
## Outcome (AsT: N=126)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DEB (N=66)</th>
<th>DES (N=60)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up: clinical [months]</td>
<td>6.2 ± 0.8</td>
<td>6.2 ± 0.8</td>
<td>0.7</td>
</tr>
<tr>
<td>Follow-up: clinical [N]</td>
<td>64 (97.0%)</td>
<td>60 (100%)</td>
<td>0.4</td>
</tr>
<tr>
<td>Follow-up: angiographic [N]</td>
<td>58 (87.9%)</td>
<td>54 (90.0%)</td>
<td>0.8</td>
</tr>
<tr>
<td>Late lumen loss [mm]</td>
<td>0.19 ± 0.38</td>
<td>0.47 ± 0.71</td>
<td>0.03</td>
</tr>
<tr>
<td>Binary restenosis in segment</td>
<td>2/58 (3.4%)</td>
<td>11/54 (20.4%)</td>
<td>0.007</td>
</tr>
<tr>
<td>TLR</td>
<td>2/64 (3.1%)</td>
<td>10/60 (16.7%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0/64 (0.0%)</td>
<td>f1/60 (1.7%)</td>
<td>1</td>
</tr>
<tr>
<td>Death</td>
<td>*2/64 (3.1%)</td>
<td>**1/60 (1.7%)</td>
<td>1</td>
</tr>
<tr>
<td>Total MACE (w/o noncardiac death)</td>
<td>3/64 (4.7%)</td>
<td>11/60 (18.3%)</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*1 cardiac, not lesion related  2 non cardiac  
** non-cardiac death

fNSTEMI due to side branch occlusion

Circulation 2009;119:2986-94
The procedural outcome

The 6-month outcome
Thrombosis and PACCOCATH

The paclitaxel-eluting balloon catheters based on the PACCOCATH technology were not associated with any late thrombosis in >500 patient years according to PACCOCATH I/II (ISR), PEPCAD II ISR, and PEPCAD I SVD despite shorttime (1 month) clopidogrel application.
Study Design
- Prospective, non-randomized, dual-center, one-arm phase-II pilot study

Primary Variable
- Procedural success (main branch: ≤30%, side branch: ≤50%, TIMI Flow 3)

Secondary Variables
- In-segment late lumen loss at 9 months in either branch
- Acute (≤24hrs), subacute (≤30d), & late (≥30d) thrombosis
- At 9 months in either branch...
  - percent in-stent/in-segment stenosis
  - in-stent/in-segment late loss & late loss index
  - binary in-stent/in-segment stenosis rate
- MACE up to 3 years
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>65.8 ± 9.6</td>
</tr>
<tr>
<td>Male</td>
<td>20/28 (71.4%)</td>
</tr>
<tr>
<td>BMI [kg/m²]</td>
<td>27.3 ± 3.8</td>
</tr>
<tr>
<td>Serum cholesterol [mg/dl]</td>
<td>182.1 ± 38.8</td>
</tr>
<tr>
<td>Serum LDL [mg/dl]</td>
<td>115.6 ± 37.2</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>4/28 (14.3%)</td>
</tr>
<tr>
<td>Current/ex-smokers</td>
<td>14/28 (50.0%)</td>
</tr>
<tr>
<td>Hypertension</td>
<td>24/28 (85.7%)</td>
</tr>
<tr>
<td>Family history of CAD</td>
<td>10/28 (35.7%)</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>5/28 (17.9%)</td>
</tr>
<tr>
<td>Peripheral arterial occlusive disease</td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td>Serum creatinine [mg/dL]</td>
<td>0.84 ± 0.18</td>
</tr>
</tbody>
</table>
QCA N=28

Treated vessel

<table>
<thead>
<tr>
<th>Vessel</th>
<th>N/Total (%)</th>
<th>D1</th>
<th>D2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>19/28 (67.9%)</td>
<td>17</td>
<td>2</td>
</tr>
<tr>
<td>LCX</td>
<td>9/28 (32.1%)</td>
<td>OMS 8</td>
<td>PLA 1</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Value</th>
<th>Standard Deviation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Length main/side [mm]</td>
<td>11.55 ± 4.87 / 7.16 ± 4.23</td>
<td></td>
</tr>
<tr>
<td>Reference Ø main/side branch</td>
<td>2.92 ± 0.27 / 2.45 ± 0.25</td>
<td></td>
</tr>
<tr>
<td>MLD pre/post PCI MB [mm]</td>
<td>0.80 ± 0.39 / 2.56 ± 0.44</td>
<td></td>
</tr>
<tr>
<td>MLD pre/post PCI SB [mm]</td>
<td>1.00 ± 0.46 / 1.84 ± 0.35</td>
<td></td>
</tr>
<tr>
<td>Stenosis pre/post PCI MB [%]</td>
<td>64 ± 26 / 14 ± 9</td>
<td></td>
</tr>
<tr>
<td>Stenosis pre/post PCI SB [%]</td>
<td>54 ± 24 / 22 ± 13</td>
<td></td>
</tr>
<tr>
<td>Procedural Data (ITT: N=28)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-----------------------------</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Balloon main branch</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td>Balloon side branch</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td>Stent main branch only</td>
<td>24 (85.7%)</td>
<td></td>
</tr>
<tr>
<td>Stent main and side branch</td>
<td>4 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>Procedural success MB</td>
<td>28 (100%)</td>
<td></td>
</tr>
<tr>
<td>Procedural success SB</td>
<td>28 (100%)</td>
<td></td>
</tr>
</tbody>
</table>
## 30-Day Follow-up

<table>
<thead>
<tr>
<th>Category</th>
<th>Count/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N</strong></td>
<td>28/28 (100%)</td>
</tr>
<tr>
<td><strong>Time [days]</strong></td>
<td>31.25 ± 4.29</td>
</tr>
<tr>
<td><strong>Asymptomatic</strong></td>
<td>25/28 (89.3%)</td>
</tr>
<tr>
<td><strong>Stable angina</strong></td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td><strong>Adverse events</strong></td>
<td>3/28 (10.7%)</td>
</tr>
<tr>
<td></td>
<td>common cold, headache, hematoma</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>0/28 (0%)</td>
</tr>
</tbody>
</table>
Interventional cardiologists are "...medical-technology junkies who thrive on the latest and best products."

Main Inclusion Criteria

- Occlusion or stenosis ≥ 2 cm, mean severity ≥ 70%
- Superficial femoral (SFA) and popliteal artery
- History > 6 weeks (no thrombolysis)
- Rutherford 1 - 5
- Age: 18 - 95 years

Main Exclusion Criteria

- Distal run-off less than one artery
- Creatinine > 2.0 mg%
- PTA at the origin of the SFA
## Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Uncoated Balloon (n = 54)</th>
<th>Uncoated BA + Paclitaxel i.a. (n = 52)</th>
<th>Paccocath (n = 48)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age [years]</td>
<td>68 ± 9*</td>
<td>68 ± 8*</td>
<td>69 ± 8*</td>
</tr>
<tr>
<td>Gender ratio [m/f]</td>
<td>1.8</td>
<td>2.3</td>
<td>1.8</td>
</tr>
<tr>
<td>Smoker [%]</td>
<td>22</td>
<td>27</td>
<td>23</td>
</tr>
<tr>
<td>Diabetes mellitus [%]</td>
<td>46</td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td>Hypertension [%]</td>
<td>83</td>
<td>87</td>
<td>79</td>
</tr>
<tr>
<td>Serum cholesterol ↑ [%]</td>
<td>63</td>
<td>65</td>
<td>69</td>
</tr>
</tbody>
</table>

* mean ± SD
### Lesion Characteristics

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Uncoated BA</th>
<th>Uncoated BA + Paclitaxel i.a.</th>
<th>Paccocath</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>n = 54</td>
<td>n = 52</td>
<td>n = 48</td>
</tr>
<tr>
<td>Lesion length [cm] pre-procedure</td>
<td>7.4 ± 6.7*</td>
<td>7.4 ± 6.5*</td>
<td>7.5 ± 6.2*</td>
</tr>
<tr>
<td>Mean stenosis [%]</td>
<td>91</td>
<td>88</td>
<td>89</td>
</tr>
<tr>
<td>Occlusion [%]</td>
<td>26</td>
<td>27</td>
<td>27</td>
</tr>
<tr>
<td>Mean number of lesions treated</td>
<td>1.6</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>De-novo lesions [%]</td>
<td>70</td>
<td>58</td>
<td>62</td>
</tr>
</tbody>
</table>

* mean ± SD
Cumulative MLD at Month 6

**Paccocath**

- **MLD pre**
- **MLD post**
- **MLD 6M**

**Uncoated BA**

- **MLD pre**
- **MLD post**
- **MLD 6M**

\[ P < 0.01 \]

Tepe, TCT 2007, Washington DC, 23 Oct 07
<table>
<thead>
<tr>
<th>Title</th>
<th>Design</th>
<th>Status</th>
<th>PI/Lab</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD I SVD</td>
<td>Sequent in ≤2.8mm, 120px, multi-center, GER</td>
<td>6mo-FU ✓</td>
<td>MU, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12mo-FU ✓</td>
<td></td>
</tr>
<tr>
<td>PEPCAD II ISR</td>
<td>Sequent vs Taxus in ISR, 131px, multi-center, GER</td>
<td>6mo-FU ✓</td>
<td>MU, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>12mo-FU ✓</td>
<td></td>
</tr>
<tr>
<td>PEPCAD III</td>
<td>Sequent + pre-loaded Coroflex Blue vs Cypher, 600 px, Europe</td>
<td>Q2/07 recruiting ✓</td>
<td>B.SchellerC. Hamm</td>
</tr>
<tr>
<td>PEPCAD IV DM</td>
<td>Sequent vs Taxus in DM, 160px, multi-center, Thailand, Malaysia</td>
<td>Q2/07 recruiting ✓</td>
<td>D.Rosli, CRI</td>
</tr>
<tr>
<td>PEPCAD V BIF</td>
<td>Sequent, 25px, dual-center, GER</td>
<td>Q3/07 recruiting ✓</td>
<td>D.Mathey, F.Kleber CRI</td>
</tr>
<tr>
<td>INDICOR</td>
<td>Coroflex Blue + Sequent, Real World, 125px</td>
<td>IRB, recruiting</td>
<td>U.Kaul, CRI</td>
</tr>
<tr>
<td>PEPCAD CTO</td>
<td>Sequent, 25px, single-center, GER</td>
<td>Q3/07 recruiting ✓</td>
<td>J. Wöhrle</td>
</tr>
</tbody>
</table>
Aussehen von ruhendem und aktiviertem Blutplättchen
Was können wir tun?

- die Engstelle (Stenose) aufdehnen (=PTCA)
- eine unbeschichtete Gefäßstütze (bare metal stent = BMS) in der Engstelle plazieren
- ein Zellwachstum hemmendes Medikament in die Gefäßwand bringen
Woher kommen die Nachteile?

- die Engstelle (Stenose) aufdehnen (=PTCA)

- eine unbeschichtete Gefäßstütze (BMS) in der Engstelle plazieren

- ein Zellwachstum hemmendes Medikament mittels Stent in die Gefäßwand bringen

Gefäßlumen
Endothel
Überschießendes Zellwachstum
Stentstrebe

Hwang, Circulation 2001; 104: 600-5

Membrana elastica interna
Lumen vor der Stentimplantation
Lumen nach der Stentimplantation
aufgelagerte Thromben
einsprossende Gefäße
Stent-Streben
Fremdkörperriesenzellen
Macht es Sinn, ...

- die Engstelle (Stenose) aufzudehnen (\(\text{=}\)PTCA)?
  - immer

- eine unbeschichtete Gefäßstütze (BMS) in der Engstelle plazieren?
  - Immer? Fast immer?

- ein Zellwachstum hemmendes Medikament mittels Stent in die Gefäßwand bringen?
  - Immer? Immer öfter? Anders?

SeQuent\textsuperscript{®} Please
Paclitaxel-Eluting Balloon vs Paclitaxel-Eluting Stent in Small Vessel Disease

(B. Cortese et al. Euro PCR 2009)
Recurrence of In-Stent Restenosis (ISR)

- In sirolimus (SES) and paclitaxel-eluting (PES) stent-PCI target lesion revascularization is required in 5.1% and 7.8%, respectively.¹

- In ISR treated with SES or PES the recurrence is 14%-22%.²-⁴

¹Kastrati JAMA 2005;294:819-25  
²Kastrati JAMA 2005;293:165-171  
³Holmes JAMA 2006;295:1264-73  
⁴Stone JAMA 2006;295:1254-63
Recurrence in Small Vessel Disease

- In SVD the restenosis rate following sirolimus or paclitaxel-eluting stent deployment is on the order of 2.3%-31.2%.  

References:

1. Togni JACC 2007;50:1123-31
3. Li Chin Med J 2007;120:569-73
4. Elezi JACC 2006;48:1304-9
7. Stone JAMA 2005;294:1215-23
Recurrence in Bifurcations (BIFs)

- BIFs occur in 15–18% of PCIs\(^1\)

- The recurrence rates for main (MB) and side branch (SB) are: \(^2-4\)
  - DES MB: 4.6–9.5%   SB: 8–14.5%
  - BMS MB: 28.7%   SB: 37.0%

- MB and SB stenting does not exhibit a superior outcome compared to MB stenting only\(^5\)

---

\(^1\) Lefevre J Interv Cardiol 2001;14:573-85
\(^2\) Kang Chin Med J (Engl) 2006;119:1157-64
\(^3\) Pan Am Heart J 2007;153:15 e1-7
\(^4\) Tanabe Am J Cardiol 2004;94:115-8
\(^5\) Steigen Circulation 2006;114:1955-61
Approaches in the Majority of PCI

- **Expand/dilate** ⇒ balloon catheters
  - Recoil
  - Dissection

- **Scaffold** ⇒ stents
  - Permanent vascular irritation (mechanical, polymer)
  - Manoeuverability ↓
  - Cost ↑

- **Antiproliferative** ⇒ drugs
  - Delayed/incomplete endothelialization
  - Late thrombosis ↑?
Facts

- We always need lesion expansion,
- We need the antiproliferative drug (always?),
  however,
- We do not always need the metal

What can we do ???