Non stent based intracoronary drug delivery

Dariusz Dudek
Department of Interventional Cardiology
Jagiellonian University, Krakow, Poland

The European Association of Percutaneous Cardiovascular Interventions (EAPCI ESC)
Chair of the Scientific Programme Committee
Drug Eluting Balloons (DEB) - history

- Drug-coated balloons were first investigated in the 1990s, but difficulties in transferring the drug into the tissue quickly enough.

- The concept: delivering a rapid release of drugs into the arterial tissue is more effective than the gradual release of drugs, as seen with drug-eluting stents.
Why Drug Eluting Balloons (DEB) ?

• 1st: ease of use in coronaries and peripheral, especially below the knees.

• 2nd is cost: balloon catheters have traditionally been less expensive than stents.

• 3rd is improved safety – no chronic polymer effects + reduced drug exposure = optimal biocompatibility

• 4th is to use in situations where DES problematic or less effective; e.g. ISR, bifurcations (ostium sidebranch), diabetics, small vessels, diffuse disease, can’t deliver stent locations (distal, tortuous, etc.)
DEB mechanism of action

Embedded PTx particles as sustained release reservoir

Dissolution & Tissue Absorption

Systemic Loss

Vessel Wall
Requirements for a successful Drug Eluting Balloons (DEB)

• Combination of drug (usually paclitaxel) and solvent
• Coating method
• Drug transfer to the tissue
• Biological efficacy, dose dependency
• Balloon inflation time, safety in overdosing
• Clinical efficacy
<table>
<thead>
<tr>
<th></th>
<th>DES</th>
<th>DEB</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Platform of drug delivery</strong></td>
<td>Stent scaffolding</td>
<td>Balloon</td>
</tr>
<tr>
<td><strong>Retention</strong></td>
<td>Polymer based</td>
<td>Embedded imprinted</td>
</tr>
<tr>
<td><strong>Drug dose</strong></td>
<td>Low: &lt;100 to 200 µg</td>
<td>High: 300 to 600 µg</td>
</tr>
<tr>
<td><strong>Release kinetics</strong></td>
<td>Slow and controlled</td>
<td>Fast release</td>
</tr>
<tr>
<td><strong>Distribution</strong></td>
<td><strong>Strut based vascular penetration</strong></td>
<td><strong>Balloon surface homogenous distribution</strong></td>
</tr>
<tr>
<td><strong>Advantages</strong></td>
<td>Mechanical support</td>
<td>Leave no implant</td>
</tr>
<tr>
<td></td>
<td>Abluminal trapping</td>
<td>Larger surface area</td>
</tr>
<tr>
<td></td>
<td>Less drug spillage into the circulation</td>
<td>Less drug localization in the vessel wall</td>
</tr>
<tr>
<td></td>
<td>Proven efficacy in many indications</td>
<td>Accessible to complex lesions and long segments</td>
</tr>
<tr>
<td></td>
<td>No acute recoil tackled dissection</td>
<td>May no require prolonged dual antiplatelet therapy</td>
</tr>
</tbody>
</table>
Wound healing and drug distribution
Drug Eluting Stent (DES) S vs. DEB

I. hours
- Inflammation phase
- Enzymes
- Triggering signals

II. 10-14 days
- Proliferation
- Endothelialization

Paclitaxel distribution in tissue after chronic dosing using a DES

Paclitaxel distribution in tissue after acute dosing using DIOR

III. weeks to months
- Remodeling
Additives are crucial for drug tissue uptake
Pharmacokinetic Study for New Generation DEB Coronary artery tissue – new DEB vs literature data

Paclitaxel tissue concentration in pig coronary arteries

*Pantera Lux [n=6]*
*SeQuent Please literature data [n=25]*
*DIOR literature data*

$R^2 = 0.9685$

$R^2 = 0.9105$
# Drug-eluting or Delivery Balloon Systems

<table>
<thead>
<tr>
<th>Name</th>
<th>Manufacturer</th>
<th>Principle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paccocath</td>
<td>Bayer (Bavaria Medizin Technologie, Oberpfaffenhofen, Germany)</td>
<td>Paccoath Technology (paclitaxel embedded in hydrophilic iopromide coating)</td>
</tr>
<tr>
<td>SeQuent Please</td>
<td>B. Braun Melsungen AG (Melsungen, Germany)</td>
<td>Improved Paccoath Technology</td>
</tr>
<tr>
<td>Coroflex Blue</td>
<td>B.Braun Melsungen AG</td>
<td>Drug eluting balloon with a thin strut CoCr stent</td>
</tr>
<tr>
<td>DIOR</td>
<td>Eurocor (Bonn, Germany)</td>
<td>Paclitaxel coated onto microporous balloon surface and folded</td>
</tr>
<tr>
<td>MAGICAL</td>
<td>Eurocor</td>
<td>Folded balloon in combination with stent</td>
</tr>
<tr>
<td>Elitex</td>
<td>Aachen Resonance (Aachen, Germany)</td>
<td>Folded balloon</td>
</tr>
<tr>
<td>GENIE</td>
<td>Acrostatk Corporation (Winterthur, Switzerland)</td>
<td>Liquid drug delivery catheter</td>
</tr>
<tr>
<td>IN.PACT Amphirion</td>
<td>Invatec (Italy)</td>
<td>FreePac, a proprietary coating that balances hydrophilic and lipophilic properties</td>
</tr>
<tr>
<td>In.PACT Falcon</td>
<td>Invatec</td>
<td>FreePac</td>
</tr>
<tr>
<td>Advance PTX</td>
<td>Cook Medical (Bloomington, Ind)</td>
<td>DEB</td>
</tr>
<tr>
<td>N/A</td>
<td>Lutonix Inc (Maplegrove, Minn)</td>
<td>DEB</td>
</tr>
</tbody>
</table>
# The PEPCAD Program

Paclitaxel-Eluting PTCA-Catheter in Coronary Artery Disease

<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, 120pts, multi-center, Germany</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, 131pts, multi-center, Germany</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, 637 pts, Europe</td>
<td>Q2 / 07</td>
<td>B.Scheller</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9mo-FU √</td>
<td>C.Hamm</td>
</tr>
<tr>
<td>PEPCAD IV DM</td>
<td>Sequent vs Taxus in DM, 160pts, multi-center, Thailand, Malaysia</td>
<td>Q2 / 07 slow recruiting √</td>
<td>D.Rosli, CRI</td>
</tr>
<tr>
<td></td>
<td></td>
<td>after 85Px</td>
<td></td>
</tr>
<tr>
<td>PEPCAD V BIF</td>
<td>Sequent, 28pts, dual-center, Germany</td>
<td>Q3 / 07 recruiting √</td>
<td>D.Mathey</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>F.Kleber CRI</td>
</tr>
<tr>
<td>PEPCAD CTO</td>
<td>Sequent, 50pts, single-center, Germany</td>
<td>Q3 / 07 recruiting √</td>
<td>J. Wöhrle</td>
</tr>
<tr>
<td>INDICOR</td>
<td>Coroflex Blue + Sequent, Real World, 125pts, India</td>
<td>recruiting √</td>
<td>U.Kaul, CRI</td>
</tr>
</tbody>
</table>

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[Image 0x0 to 720x540]
Drug-Eluting Balloon: an alternative to DES?

DEB+BMS in coronary de-novo lesions
PEPCAD III - Comparison of Paclitaxel-Coated Balloon + Bare Metal Stent with the sirolimus Eluting Cypher stent in the treatment of de-novo lesions

Patients randomized
N = 637

N = 312
DEB+BMS: Paclitaxel-coated balloon + Bare-Metal Stent
Coroflex DEBlue®

N = 296 (95.5%)
Follow-up
9 months

N = 269 (86.8%)
Angiography

N = 325
DES: Sirolimus-eluting stent
Cypher®

N = 313 (96.6%)
Follow-up
9 months

N = 273 (84.3%)
Angiography

Presented by C.W. Hamm @ AHA09
The first drug eluting balloon/stent system did not meet the non-inferiority criteria vs. Cypher.

Safety aspects need to be investigated (Stent Thrombosis)
Dilatation Trial – ongoing trial
(Dior DEB + Genius Magic BMS) vs. Taxus DES

120 patients

GROUP A
Predilation followed by
Dior™ balloon dilatation +
BMS (Genius Magic™)

GROUP B
Taxus Libertè

8-month angiographic follow-up
clinical follow-up at 1, 6 and 12 months
Drug-Eluting Balloon:

an alternative to DES?

in-Stent Restenosis
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>

Table 2. Procedural Data and Angiographic Findings during Intervention and at 6 Months (Intention-to-Treat Analysis).*
Paclitaxel-Coated Balloon Catheter Versus Paclitaxel-Coated Stent for the Treatment of Coronary In-Stent Restenosis

Martin Unverdorben, MD; Christian Vallbracht, MD; Bodo Cremers, MD; Hubertus Heuer, MD; Christian Hengstenberg, MD; Christian Maikowski, MD; Gerald S. Werner, MD; Diethmar Antoni, MD; Franz X. Kleber, MD; Wolfgang Bocksch, MD; Matthias Leschke, MD; Hanns Ackermann, PhD; Michael Boxbberger, PhD; Ulrich Speck, PhD; Ralf Degenhardt, PhD; Bruno Scheller, MD

![Graph comparing restenosis rates for Taxus and SeQuent Please stents.](image-url)
PEPCAD II ISR: Conclusion

DEB for the treatment of coronary in-stent restenosis:

- Safe, high procedural success rate
- Confirms the findings of PACCOCATH ISR I and II trials
- DEB superior to Taxus® in the treatment of ISR
- DEB reduces anti-platelet therapy compared to DES
Drug-Eluting Balloon:

an alternative to DES?

small coronary vessels
PEPCAD I promising but…

PICCOLETO Study

Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial. The PICCOLETO Study

Bernardo Cortese,^1^ Andrea Micheli,^1^ Andrea Picchi,^1^ Amelia Coppolaro,^1^ Loria Bandinelli,^1^ Silva Severi,^2^ Ugo Limbruno^1^

**Table 3** Six months angiographic outcome

<table>
<thead>
<tr>
<th></th>
<th>PCB (n=28)</th>
<th>Taxus stent (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter±SD (mm)</td>
<td>2.54±0.47</td>
<td>2.58±0.24</td>
<td>0.73</td>
</tr>
<tr>
<td>MLD±SD (mm)</td>
<td>1.11±0.65</td>
<td>1.94±0.72</td>
<td>0.0002</td>
</tr>
<tr>
<td>Per cent diameter stenosis±SD</td>
<td>43.6±27.4</td>
<td>24.3±25.1</td>
<td>0.029</td>
</tr>
<tr>
<td>Angiographic binary restenosis</td>
<td>9 (32.1%)</td>
<td>3 (10.3%)</td>
<td>0.043</td>
</tr>
</tbody>
</table>

MLD, minimal lumen diameter; PCB, paclitaxel-coated balloon.

**Table 4** Nine months clinical outcome

<table>
<thead>
<tr>
<th></th>
<th>PCB (n=28)</th>
<th>Taxus stent (n=29)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1 (3.6%)</td>
<td>1 (3.5%)</td>
<td>0.98</td>
</tr>
<tr>
<td>Cardiac death</td>
<td>0</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1 (3.6%)</td>
<td>0</td>
<td>0.30</td>
</tr>
<tr>
<td>Target lesion revascularisation</td>
<td>9 (32.1%)</td>
<td>3 (10.3%)</td>
<td>0.15</td>
</tr>
<tr>
<td>Target vessel revascularisation</td>
<td>9 (32.1%)</td>
<td>4 (13.6%)</td>
<td>0.10</td>
</tr>
<tr>
<td>Stent thrombosis*/abrupt vessel closure</td>
<td>0</td>
<td>0</td>
<td>0.97</td>
</tr>
<tr>
<td>MACE</td>
<td>10 (35.7%)</td>
<td>4 (13.6%)</td>
<td>0.054</td>
</tr>
</tbody>
</table>

MACE, major adverse cardiovascular events; PCB, paclitaxel-coated balloon.

Conclusion: the technology tested in this study during PCI of small vessel disease was inferior to the gold standard treatment with DES. However, the opportunity for treating coronary lesions without placing a (drug-eluting) stent is too attractive to be left out of further experiments.
Drug-Eluting Balloon: an alternative to DES?

Bifurcations
DES like result in MB, superior result in SB

However, in the MB where DEB was used in combination with BMS two patients experienced a late stent thrombosis (incomplete wall apposition and geographic miss)
## DEBIUT Trial

### Results: Clinical outcomes at 6 months (100%)

<table>
<thead>
<tr>
<th></th>
<th>BMS</th>
<th>DEB</th>
<th>DES</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>MI (periprocedural)</strong>&lt;br&gt;(3x ‘N’)</td>
<td>5.4%</td>
<td>7.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td><strong>MI (postprocedural)</strong>&lt;br&gt;(3x ‘N’)</td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>SAT</strong></td>
<td>0%</td>
<td>0%</td>
<td>2.5%</td>
</tr>
<tr>
<td><strong>TVR (non TLR)</strong></td>
<td>5.4%</td>
<td>4.5%</td>
<td>7.5%</td>
</tr>
<tr>
<td><strong>TLR</strong></td>
<td>27.0%</td>
<td>12.5%</td>
<td>10.0%</td>
</tr>
<tr>
<td><strong>Death</strong></td>
<td>0%</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td><strong>MACE</strong></td>
<td>27.0%</td>
<td>15.0%</td>
<td>17.5%</td>
</tr>
</tbody>
</table>

*P* = 0.09

Presented by PR Stella at EuroPCR 2010
Drug-Eluting Balloon: an alternative to DES?

AMI
DEB-AMI

- Randomised prospective multi-centre trial, 6M angiographic FU; 5Y clinical FU
- Thrombus aspiration in all
- OCT and Acetylocholine at follow-up in 60 pts.
- Primary endpoint: angiographic late loss
- Secondary endpoint: binary restenosis, MACCE, (late- _ malaposition,
  Endothelial (dys-)function, clinical fu – 5 years

presented by V. Lim at Sing Live 2009
Future: New coating and drug alternatives

Objectives to be Achieved:
- Reduced total dose on the balloon surface.
- Increased coating solubility and stability.
- Drug concentration stable along the balloon length.
Nanoparticle polymer free sirolimus coated balloon delivery catheter
Catheter-Based Delivery of Fluid Paclitaxel
LOCAL TAX Study

- A prospective, RCT comparing the local delivery of fluid paclitaxel after BMS implantation (n=67) with the implantation of a BMS (n=68) and the implantation of a PES (n=67)
- The primary end point was in-stent late lumen loss 6 months after PCI
- IC infusion of fluid paclitaxel by Genie catheter

Late luminal loss (in segment, mm)

Delivery of Fluid Paclitaxel:

significantly lowered the incidence of clinical events and restenosis compared with BMSs and showed similar effectivity as paclitaxel-eluting stents

Circ Cardiovasc Interv 2009;2;294-301
Drug-Eluting Balloon:
an alternative to DES?

Peripheral Artery Vascular Disease
Inhibition of Restenosis in Femoropopliteal Arteries
Paclitaxel-Coated Versus Uncoated Balloon: Femoral Paclitaxel Randomized Pilot Trial

Michael Werk, MD; Soenke Langner, MD; Bianka Reinkensmeier, MS; Hans-Frank Boettcher, MD; Gunnar Tepe, MD; Ulrich Dietz, MD; Norbert Hosten, MD; Bernd Hamm, MD; Ulrich Speck, PhD; Jens Ricke, MD

Werk et al., Circulation 2008; 118: 1358-65
Guidelines for Drug Eluting Balloons (DEB)

ESC, ACC/AHA (cardiology)
There are no such guidelines…

TASC II (endovascular)
There are no such guidelines…
Drug Eluting Balloon (DEB) - common opinion and conclusions

• Catheter-based local drug delivery has been unsuccessful in humans because the drug delivered by this method is not retained at the site of injury but is quickly washed away into the coronary circulation

• BUT ……..
Drug-Eluting Balloon (DEB)

Alternative to DES
- Treatment of coronary ISR (avoids a second stent)
  - DEB + BMS: clopidogrel 1-3 months;
    versus DES: clopidogrel 12 months
- De-novo and restenotic lesions in Peripheral Artery Vascular Disease

Possible alternative
- Small coronary vessels
  Bifurcations lesions
  Long lesions (avoids full-metal jacket)
  AMI (Large thrombus burden lesions and risk of DES thrombosis)
- Contraindication to prolonged double antiplatelet therapy
Drug-Eluting Balloon (DEB)

DEB are not a replacement for DES, .... but ..... 
new generation DEBs with new design for paclitaxel uptake and new drugs are tested in ongoing trials

More scientific trials and more consistent data are needed to find the final indications for DEB in cardiology
“Non-stent-based local drug delivery and, particularly, a drug-eluting balloon could dramatically fulfill the goal of DES without duplicating the issues encountered with this technology. It could be of special interest for high-risk restenotic lesions such as small vessel-, bifurcation-, or in-stent restenotic lesions.”

- Homogenous drug transfer to the vessel wall
- Drug concentrations highest at the time of injury (neointimal process most vigorous)
- Absence of drug could help to better re-endothelialize the stent (if used)
- Absence of polymer (decreased stimulus of chronic inflammation)
- Absence of stent (original anatomy / physiology of the arteries)
- Overdependence on antiplatelet therapy could be limited
- Local drug delivery possible in situations in which stents are not used or undesirable