Interventional Cardiology - The Revolution

1. Balloon (PTCA): Andreas Gruntzig performs the first PTCA in Zürich, Switzerland.
2. Bare Metal Stent (BMS): Julio Palmieri and Richard Schatz develop a stainless steel stent for coronary applications.

Is There a Role For Drug Coated Balloon?

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Interventional Cardiology - The 4th Revolution

‘Leaving Nothing Behind’

DCB

- The drug coated balloon (DCB) platform offers several theoretical benefits over stent-based technologies.
- DCB allows the homogenous transfer of an anti-proliferative drug to reduce neo-intimal hyperplasia whilst maintaining normal vessel anatomy, function, and avoiding permanent vascular implants.
**Components of DEB**

Conventional semi-compliant angioplasty balloons covered with an anti-proliferative drug which is released into the vessel wall during inflation of the balloon.

**Drug distribution**

- **Drug-Eluting Stent**
  - Slow release
  - Persistent drug exposure
  - ~ 100 - 200 µg dose
  - Polymer
  - Stent mandatory

- **Drug-Coated Balloon**
  - Immediate release
  - Short-lasting exposure
  - ~ 300 - 600 µg dose
  - No polymers

Active substance on DEB is lipophilic with high absorption rate through vessel wall. Ideal drug: rapid uptake and prolonged retention.
Why Paclitaxel?

- Highly lipophilic – Rapid intracellular uptake and retention in vessel wall for nearly a week
- Acts by irreversible binding to microtubules, inhibiting cell division and migration - structural intracellular changes cause long-lasting effects
- Short incubation time (3 minutes) with paclitaxel almost completely inhibits vascular smooth muscle cell proliferation for up to 12-14 days
- Zotarolimus – Also lipophilic, potential candidate for DCB applications

CE approved - DCBs
Practical points before DCB use

- Proper vessel preparation with predilation balloon 0.5-1.0 mm smaller than intended DEB
- Ensure adequate 1:1 sizing between vessel and DCB
- Shorten transfer time from access sheath to DEB inflation
- Single prolonged inflation for complete drug release till manufacturer’s recommended time (60 or 30 sec) – if not tolerated, fractional release in quick intermittent inflations till recommended time is complete

Randomised controlled trials with DCB
Drug-Coated Balloon

- In-Stent Restenosis
- Small Vessel Disease
- Bifurcation Lesions
- De-Novo Coronary Lesions
Treatment of Coronary In-Stent Restenosis with a Paclitaxel-Coated Balloon Catheter

Bruno Scheller, M.D., Christoph Hehrlein, M.D., Wolfgang Bockisch, M.D., Wolfgang Blum, M.D., Daniel Ilg, M.D., Michael Bühn, M.D., and Ulrich Speck, Ph.D.

ABSTRACT

Treatment of coronary in-stent restenosis is hampered by a high incidence of recurrent in-stent restenosis. We assessed the efficacy and safety of a paclitaxel-coated balloon in this setting.

METHODS

We enrolled 52 patients with in-stent restenosis in a randomized, double-blind, multicenter trial to compare the effects of a balloon catheter coated with paclitaxel (3 µg per square millimeter of balloon surface area) with those of an uncoated balloon catheter in coronary angioplasty. Secondary end points included the cases of restenosis (as a binary variable) and major adverse cardiac events.

PACCOCATH ISR I + II

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

- Efficacy and Safety of Paclitaxel-Coated Balloons in Coronary In-Stent Restenosis
- Two trials
  - separately randomized
  - double-blind, multicenter
  - identical protocol
  - 108 patients in total
- Paccocath ISR I: 52 patients
- Paccocath ISR II: 56 patients
PACCOCATH ISR I + II

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

<table>
<thead>
<tr>
<th>Variable</th>
<th>Uncoated Balloon (N=54)</th>
<th>Paclitaxel-Coated Balloon (N=54)</th>
<th>Absolute Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Follow-up</td>
<td>5.2 ± 1.5 yrs</td>
<td>5.6 ± 0.9 yrs</td>
<td>0.556</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>8 (14.8 %)</td>
<td>5 (9.3 %)</td>
<td>0.556</td>
<td></td>
</tr>
<tr>
<td>MI</td>
<td>8 (14.8 %)</td>
<td>5 (9.3 %)</td>
<td>0.556</td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>21 (38.9 %)</td>
<td>5 (9.3 %)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0</td>
<td>0</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td>5 (9.3 %)</td>
<td>5 (9.3 %)</td>
<td>1.000</td>
<td></td>
</tr>
<tr>
<td>MACE</td>
<td>32 (59.3 %)</td>
<td>15 (27.8 %)</td>
<td>0.002</td>
<td></td>
</tr>
</tbody>
</table>

PEPCAD II
Paclitaxel-Coated Balloon Catheter Versus Paclitaxel-Coated Stent for the Treatment of Coronary In-Stent Restenosis

Effectiveness of DCB in Pts with in-DES restenosis

Follow-up rate: 94% (47/50 Lesions, PEB group: 23, BA group: 24)

<table>
<thead>
<tr>
<th>Paclitaxel-Eluting Balloon</th>
<th>Conventional Balloon Angioplasty</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late luminal loss (in-lesion)</td>
<td>0.17 ± 0.45 0.72 ± 0.56 0.001</td>
</tr>
<tr>
<td>Late luminal loss (in-segment)</td>
<td>0.18 ± 0.45 0.72 ± 0.55 0.001</td>
</tr>
<tr>
<td>Binary restenosis</td>
<td>2 (8.7) 15 (62.5) 0.0001</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>1 (4.3) 10 (41.7) 0.003</td>
</tr>
</tbody>
</table>

HABARA
Effectiveness of Paclitaxel-Eluting Balloon Catheter in Patients With Sirolimus-Eluting ISR


JACC Cardiovascular Interventions, 2011;4: 149-54
DCB: INDICATIONS and EVIDENCE
In-stent restenosis

ESC guidelines on myocardial revascularization 2014

<table>
<thead>
<tr>
<th>Restenosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Repeat PCI is recommended, if technically feasible.</td>
</tr>
<tr>
<td>DES are recommended for the treatment of in-stent re-stenosis (within BMS or DES).</td>
</tr>
<tr>
<td>Drug-coated balloons are recommended for the treatment of in-stent restenosis (within BMS or DES).</td>
</tr>
<tr>
<td>IVUS and/or OCT should be considered to detect stent-related mechanical problems.</td>
</tr>
</tbody>
</table>
PEPCAD I

Treatment of small coronary arteries with a paclitaxel-coated balloon catheter

- Prospective, single-arm, observational, multi-center
- 118 patients, angiographic follow-up 89%
- Paclitaxel eluting balloon Sequent Please in patients with lesions in coronary arteries of 2.25 – 2.8 mm in diameter.
- Endpoint: late lumen loss at 6 months.

**PEPCAD I**

Treatment of small coronary arteries with a paclitaxel-coated balloon catheter

- DEB only: 6 Months Results

<table>
<thead>
<tr>
<th>Follow-up angiography (82 Patients)</th>
<th>DEB ITT</th>
<th>DEB Only</th>
</tr>
</thead>
<tbody>
<tr>
<td>Late lumen loss In-segment 0.16 ± 0.38 mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binary restenosis rate In-segment 4 (5.5 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Target lesion revascularization 4 (4.9 %)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death 0</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Follow-up angiography (82 Patients)

- DEB ITT: 114
- DEB Only: 82

- Stent thrombosis: 1.7% (DEB ITT), 0% (DEB Only)
- TLR: 11.9% (DEB ITT), 4.9% (DEB Only)
- Death: 2.9% (DEB ITT), 0% (DEB Only)
- MI: 1.7% (DEB ITT), 1.3% (DEB Only)
- MACE: 15.3% (DEB ITT), 6.1% (DEB Only)

**PICOLETO**
Paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomized clinical trial

Paclitaxel-coated balloon DIOR® vs. Taxus DES in small coronary vessels (≤ 2.75 mm), n=28 + 29 patients

<table>
<thead>
<tr>
<th>Intervention Type</th>
<th>Trial Name</th>
<th>Type of comparison</th>
<th>Sample size (n)</th>
<th>Type of DEB</th>
<th>Angiographic and Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Small Vessel</td>
<td>PICOLETO</td>
<td>DEB vs PES</td>
<td>160</td>
<td>Balloon</td>
<td>8 m late loss</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>BMS DEB</td>
<td>group: 35.7%</td>
</tr>
</tbody>
</table>

Cortese B et al. Heart 2010;96:1291-1296

**Drug-Coated Balloon**

- In-Stent Restenosis
- Small Vessel Disease
- Bifurcation Lesions
- De-Novo Coronary Lesions
DCB

*De Novo* lesions: Bifurcation

Two strategies

Sequential DEB treatment of the bifurcation branches followed by BMS implantation in the MB – RCT available

Simple MV stenting followed by kissing DEB – Recent with sparse evidence
Drug-Coated Balloon

- In-Stent Restenosis
- Small Vessel Disease
- Bifurcation Lesions
- De-Novo Coronary Lesions

Two Different Causes for Restenosis

- Recoil & Negative Remodeling
- Stenting (BMS, DES) Drug-Eluting Bioresorbable Vascular Scaffold (BVS) Stent
Two Different Causes for Restenosis

Recoil & Negative Remodeling
Neointimal Hyperplasia

Stenting (BMS, DES) Drug-Eluting Bioresorbable Vascular Scaffold (BVS) Stent

Drug-Coated Balloon
(Drug-Eluting Bioresorbable Vascular Scaffold (BVS) Stent)

Late lumen loss after DCB in De-novo Lesions

<table>
<thead>
<tr>
<th>Trial Number of patients</th>
<th>Intervention</th>
<th>Indication</th>
<th>Late lumen loss</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD I SVD (n=118)</td>
<td>SeQuent™ Please (n=82) vs. SeQuent™ Please + BMS</td>
<td>De novo, small vessels</td>
<td>0.16 mm</td>
<td>6 months</td>
</tr>
<tr>
<td>PEPCAD V (n=28)</td>
<td>SeQuent™ Please</td>
<td>De novo, bifurcation (side branch)</td>
<td>0.21 mm</td>
<td>6 months</td>
</tr>
<tr>
<td>PICCOLETO (n=60)</td>
<td>Dior™ II (n=29) vs. DES</td>
<td>De novo, small vessels</td>
<td>Not published</td>
<td>6 months</td>
</tr>
<tr>
<td>DEBUIT (n=117)</td>
<td>Dior™ (n=40) vs. Dior™ + BMS vs. DES</td>
<td>De novo, bifurcation</td>
<td>0.11 mm</td>
<td>9 months</td>
</tr>
<tr>
<td>Valentines II</td>
<td>Dior™ II</td>
<td>De novo</td>
<td>0.30 (overall)</td>
<td>6-9 months</td>
</tr>
</tbody>
</table>

### Acute and late thrombosis after DCB in De-novo Lesions

<table>
<thead>
<tr>
<th>Trial Number of patients</th>
<th>Intervention</th>
<th>Indication</th>
<th>Duration of DAPT</th>
<th>Acute and late thrombosis at follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEPCAD I SVD* (n=118)</td>
<td>SeQuent™ Please vs. SeQuent™ Please + BMS</td>
<td>De novo, small vessels</td>
<td>1 month</td>
<td>DCB: 0%, DCB + BMS: 6.3%</td>
</tr>
<tr>
<td>PEPCAD V* (n=29)</td>
<td>SeQuent™ Please</td>
<td>De novo, bifurcation (side branch)</td>
<td>3 months</td>
<td>DCB: 0%</td>
</tr>
<tr>
<td>PICCOLETO† (n=60)</td>
<td>Dior™ II (n=29) vs. DES</td>
<td>De novo, small vessels</td>
<td>1 month in cases of stable angina and lone DEB use, 3 months in cases of DEB and provisional stent implantation</td>
<td>DCB: 0%, DES: 0%</td>
</tr>
<tr>
<td>DEBUIT† (n=117)</td>
<td>Dior™ (n=40) vs. Dior™ + BMS vs. DES</td>
<td>De novo, bifurcation</td>
<td>DEB: 3 months, DEB + BMS: 3 months, DES: 12 months</td>
<td>DCB: 0%, DCB + BMS: 0%, DES: 2.5%</td>
</tr>
<tr>
<td>Potsdam Heart Center (n=85)</td>
<td>SeQuent™ Please</td>
<td>De novo</td>
<td>5.4 months</td>
<td>DCB: 0%</td>
</tr>
</tbody>
</table>


### „DEB-only“ Strategy

- **Pre-dilation with conventional balloon, balloon/vessel ratio of 0.8-1.0**
  - (cutting balloon, scoring balloon, high pressure balloon to provide a complete expansion)

- **Acute and late thrombosis at follow-up**
  - DCB: 0%, DCB + BMS: 6.3%

- **Major dissection (Type C-F), residual stenosis ≥ 30%, TIMI flow < III**

- **Acceptable as final result**

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**Note:** The table and diagram provide an overview of clinical trials involving directional coronary brachytherapy (DCB) and its comparison with other interventions in terms of acute and late thrombosis outcomes.
Pre-dilation with conventional balloon, balloon/vessel ratio of 0.8-1.0 (cutting balloon, scoring balloon, high pressure balloon to provide a complete expansion)

- Acceptable as final result
- Major dissection (Type C-F), residual stenosis ≥ 30%, TIMI flow < III
  - DES or BMS spot stenting followed by DCB avoiding geographic mismatch

- DES or BMS spot stenting followed by DCB avoiding geographic mismatch
  - "DEB only" strategy should extend the predilated area by 2-3 mm
  - balloon/vessel ratio 0.8-1.0 - 8-10 atm, 30 sec.
  - DES or BMS spot stenting followed by DCB avoiding geographic mismatch
  - Major dissection (Type C-F), residual stenosis ≥ 30%, TIMI flow < III
DAPT and Triple Therapy as short as possible

4 weeks

- Planned surgery
- Bleeding event
- Increased bleeding risk
- Need for oral anticoagulation / triple therapy
  - Atrial fibrillation
    - Mechanical heart valve
    - Embolism
    - Thrombophilia
  - ...
  - Stent thrombosis
Conclusions

• The use of DCB for the treatment of ISR is well established and appears to yield similar results to DES without the introduction of an additional stent layer.

• DCB may have a role in the context of challenging coronary anatomy and small vessel disease where results with stent insertion are unfavourable.

• The data regarding the use of DCB for the treatment of de-novo coronary disease still favors the new generation of DES.

• The possible reduction in the duration of DAPT to 1 m may represent additional advantages, especially in pts with AF and in patients with increased bleeding risk.

Conclusions

• Further trials are required to clarify the ideal duration of dual anti-platelet treatment following DCB use and to further elucidate the ideal clinical context for their use.