Drug Coated Balloons: For all or some?

Prof. Dr. med. Gunnar Tepe
Rosenheim, Germany
• IMPORTANT INFORMATION: These materials are intended to describe common clinical considerations and procedural steps for the on-label use of referenced technologies as well as current standards of care for certain conditions. Of course, patients and their medical circumstances vary, so the clinical considerations and procedural steps described may not be appropriate for every patient or case. As always, decisions surrounding patient care depend on the physician’s professional judgment in light of all available information for the case at hand.

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Disclosure

Speaker name: Gunnar Tepe

I have the following potential conflicts of interest to report:

- Consulting
- Employment in industry
- Stockholder of a healthcare company
- Owner of a healthcare company
- Other(s)

- I do not have any potential conflict of interest
The Growing Burden of PAD

Worldwide Prevalence of PAD Grew by 23.5% in the Decade 2000 - 2010

People Living with PAD (millions)

- Worldwide
- Low-income Countries
- High-income Countries

Year

2000

2010

DCB Trial Outcomes: 12M in Perspective

Results from different trials are not directly comparable. Information provided for educational purposes.

Historical patient population for DCB studies

- DCB trial/registry patients represent population with less-complex lesions
  - Primarily TASC A/B, lesion length <10 cm
  - Less calcification
  - Fewer occlusions

*TransAtlantic Inter-Society Consensus (TASC) II Lesion Classification (Type A, B, C, D) for peripheral arterial disease*
Considerations for DCB vs DES in PAD

Severe calcium
- Consider adjunctive atherectomy

Pre-dilate to assess vessel response
- Uncoated balloon angioplasty

Pre-Dilatation

- Successful Pre-Dilatation
  - DCB/DES
  Lesion complexity to be considered
- Residual Stenosis, Dissection, or Recoil
  - DES
Stents used in DCB studies

- Stents are utilized in DCB studies
- Longer mean lesion length is correlated with higher provisional stenting rate

**Provisional Stenting**

- FEMPAC
- PACIFIER
- THUNDER
- IT Registry
- IN.PACT SFA
- Bad Krozingen
- Leipzig Registry
- Illumenate FIH
- In.PACT Global Reg
- In.PACT Global LL (15-25 mm)
- In.PACT Global LL (>25 mm)
- Ranger Registry

Provisional Stenting in RCTs may not be representative of actual stenting in studies due to study design. Results from different trials are not directly comparable. Information provided for educational purposes.

Stents used in Real World DCB studies

- Real world DCB studies show higher rates of provisional stenting than those observed in Randomized Controlled Trials

Results from different trials are not directly comparable. Information provided for educational purposes.

Severe calcification
DCB and Stent studies

- Severe calcification and TLR rates in DCB and Stent studies

**Results from different trials are not directly comparable. Information provided for educational purposes.**

5. Laird J. Endovascular Today Feb 2015;
6. Ansel G. TCT 2015;
8. www.accessdata.fda.gov;
10. Powell, R. Charing Cross 2015;
Severe calcification

DCB and Stent studies

- Severe calcification was more prevalent in stenting studies
- Severe calcification did not have a negative effect on TLR rate in the MAJESTIC study

Results from different trials are not directly comparable. Information provided for educational purposes.
# Peripheral Drug-Coated Balloons

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT Admiral Medtronic</th>
<th>Lutonix™ Bard</th>
<th>Stellarex™ Spectranetics</th>
<th>Ranger™ Boston Scientific</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Product Image</strong></td>
<td><img src="image1.png" alt="IN.PACT Admiral Medtronic" /></td>
<td><img src="image2.png" alt="Lutonix™ Bard" /></td>
<td><img src="image3.png" alt="Stellarex™ Spectranetics" /></td>
<td><img src="image4.png" alt="Ranger™ Boston Scientific" /></td>
</tr>
<tr>
<td><strong>Paclitaxel Dose</strong></td>
<td>3 µg/mm²</td>
<td>2 µg/mm²</td>
<td>2 µg/mm²</td>
<td>2 µg/mm²</td>
</tr>
<tr>
<td><strong>Coating Technology</strong></td>
<td>FreePac™ hydrophilic coating (excipient: urea)</td>
<td>Proprietary hydrophilic nonpolymeric carrier</td>
<td>EnduraCoat™ coating (excipient: Polyethylene Glycol)</td>
<td>TransPax coating (excipient: Citrate ester)</td>
</tr>
<tr>
<td><strong>Guidewire Compatibility</strong></td>
<td>0.035 OTW</td>
<td>0.035 OTW</td>
<td>0.035 OTW</td>
<td>0.14/0.18</td>
</tr>
<tr>
<td><strong>Matrix</strong></td>
<td>SFA: 4-7 mm; 40-120 mm BTK: Recalled</td>
<td>SFA: 4-6 mm; 40-120 mm</td>
<td>SFA: 4-6 mm; 40-120 mm</td>
<td>SFA: 4-8 mm; 30-100 mm BTK: 2-4 mm; up to 150 mm</td>
</tr>
<tr>
<td><strong>CE Mark</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
<tr>
<td><strong>FDA Approval</strong></td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
<td>✓</td>
</tr>
</tbody>
</table>
Next Generation DCB: Boston Scientific Ranger™

Design:

- Sterling balloon platform
- TransPax™ coating technology
  - Paclitaxel
- Ranger™ DCB Loading Tool
  - Designed to protect the drug coating
- Size matrix:
  - SFA: 4-8 mm; 30-100 mm
  - BTK: 2-4 mm; up to 150 mm
**Ranger-SFA Study**

<table>
<thead>
<tr>
<th>Clinical Study Overview: Ranger</th>
<th>Study follow-up complete through 6M</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td>Ranger-SFA</td>
</tr>
<tr>
<td><strong>Primary Investigator</strong></td>
<td>Dierk Scheinert, MD</td>
</tr>
<tr>
<td><strong>Study Sponsor</strong></td>
<td>Hemoteq AG (Würselen, Germany)</td>
</tr>
</tbody>
</table>
| **Study Device**              | Ranger™ Paclitaxel-Coated PTA Balloon Catheter  
Sizes available for the RANGER SFA study: 4-7 mm diameter; 40-100 mm length |
| **Objective**                 | To prove the superior performance of the Ranger™ paclitaxel-coated PTA balloon catheter for angioplasty for femoropopliteal artery lesions when compared to non-coated balloons at six months post-procedure when comparing Late Lumen Loss (LLL). |
| **Study Design**              | Prospective, randomized, multicenter, controlled trial  
(2:1 Ranger DCB vs. uncoated balloon) |
| **Subjects**                  | 105 patients with femoropopliteal artery lesions |
| **Investigational Centers**   | 10 sites (Germany, France, and Austria) |
| **Endpoints**                 | Primary endpoint:  
• In-segment late lumen loss of the treated segment, as observed by angiography at six months post-procedure  
Secondary Endpoints:  
• Restenosis and patency rates  
• Rutherford classification / clinical success  
• Ankle-brachial index / hemodynamic success  
• Quality of life (WIQ, EQ5D, SF12) |
Ranger-SFA Study
Patient Enrollment & Follow-up

105 patients treated at 10 study centers

- Assessed for eligibility (N=131)
  - Excluded: Not meeting inclusion criteria (n=26)

- Enrolled and randomized (N=105)\(^a\)
  - Control (N=34)
    - No 6-month follow-up (n=9)
      - Died n=1
      - Withdrew n=2
      - Missed visit n=6
    - 6-month follow-up visit completed (n=25)

  - Ranger DCB (N=71)
    - No 6-month follow-up (n=8)
      - Withdrew n=2
      - Missed visit n=6
    - 6-month follow-up visit completed (n=63)

\(^a\)Enrollment occurred after successful intraluminal guidewire crossing of the target lesion

Scheinert, D. CIRSE 2016.
Ranger-SFA Study
Lesion Characteristics - Angiographic Core Lab

Similar lesion characteristics between Ranger and control groups

<table>
<thead>
<tr>
<th>Lesion length (mm)</th>
<th>Control (N=34)</th>
<th>Ranger DCB (N=71)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>60 ± 48</td>
<td>68 ± 46</td>
<td>0.7314</td>
<td></td>
</tr>
</tbody>
</table>

| Total occlusion             | 34%            | 34%               | 1.0000 |

<table>
<thead>
<tr>
<th>Calcification</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>None</td>
<td>16%</td>
<td>10%</td>
<td>0.2359</td>
</tr>
<tr>
<td>Mild</td>
<td>28%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td>34%</td>
<td>24%</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>22%</td>
<td>36%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Location</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Proximal SFA</td>
<td>6%</td>
<td>17%</td>
<td>0.2885</td>
</tr>
<tr>
<td>Middle SFA</td>
<td>38%</td>
<td>44%</td>
<td></td>
</tr>
<tr>
<td>Distal SFA</td>
<td>53%</td>
<td>36%</td>
<td></td>
</tr>
<tr>
<td>Proximal popliteal</td>
<td>3%</td>
<td>3%</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>TASC II</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>69%</td>
<td>66%</td>
<td>0.6196</td>
</tr>
<tr>
<td>B</td>
<td>22%</td>
<td>27%</td>
<td></td>
</tr>
<tr>
<td>C</td>
<td>6%</td>
<td>7%</td>
<td></td>
</tr>
<tr>
<td>D</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
</tbody>
</table>

| % Diameter stenosis         | 82 ± 18        | 85 ± 15           | 0.5740 |
| Reference vessel diameter   | 4.5 ± 0.83     | 5 ± 0.89          | 0.0389 |

Scheinert, D. CIRSE 2016.
Ranger-SFA Study
Efficacy and Safety – 6 Months

- LLL was significantly less for Ranger DCB than for control (P=.0017)
  - Primary endpoint was met
- Cumulative TLR rate through 6 months: 12% control vs 5.6% Ranger (P=.47)
- Similar AE and SAE rates between groups
  - No target limb amputations
  - 1 death within 6 months (control group)
- No USADE reported

Study follow-up complete through 6M

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Ranger-SFA Study
Clinical Outcomes

81% of subjects in Ranger DCB group presented with no or mild symptoms (category 0-1) at 6-month follow-up

Distributions for both Control and Ranger DCB groups show a shift to lower Rutherford Categories (improvement)
  - Not significantly different between groups

ABI/Hemodynamic Success
Significant improvement in both groups at 6 months (P<.05)

Walking Function and QoL
No significant differences between groups for WIQ, EQ5D, or SF12

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# Ranger SFA Registry

## Ranger All-Comer Registry
Treatment of femoro-popliteal atherosclerotic lesions using the Drug eluting Balloon Ranger: An All Comers Registry

<table>
<thead>
<tr>
<th><strong>PI</strong></th>
<th>Michael Lichtenberg</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Design</strong></td>
<td>Multicentre, all comer registry</td>
</tr>
<tr>
<td><strong>Centres</strong></td>
<td>Germany (Dr. von Bilderling (Munich), Dr. Ranft, Dr. Niemöller (Bottrop), Dr. Grell (Trier) and Switzerland (Dr. Saucy, Lausanne)</td>
</tr>
<tr>
<td><strong>Population</strong></td>
<td>Planned 180 patients</td>
</tr>
<tr>
<td><strong>Key Inclusion Criteria</strong></td>
<td>PAOD SFA – PIII, Rutherford II - V</td>
</tr>
<tr>
<td><strong>Primary Safety Endpoint</strong></td>
<td>Major Adverse Events (MAE): composite of device or procedure related mortality and major target limb amputation at 6 months</td>
</tr>
<tr>
<td><strong>Primary Efficacy Endpoint</strong></td>
<td>Primary patency at 12 and 24 months, defined as freedom from ≥ 50% restenosis as indicated by duplex ultrasound peak systolic velocity ratio (PSVR) ≥2.4 in the target lesion with no re-intervention</td>
</tr>
</tbody>
</table>

Study is sponsored by Klinikum Arnsberg Lichtenberg, M. DGA 2016.
## Ranger SFA Registry - Interim
### Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion location</th>
<th>Ranger DCB (N=210)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Lesion length (mm)</td>
<td>135 mm (50 – 400 mm)</td>
</tr>
<tr>
<td>SFA Prox</td>
<td>68</td>
</tr>
<tr>
<td>SFA Mid</td>
<td>103</td>
</tr>
<tr>
<td>SFA Distal</td>
<td>99</td>
</tr>
<tr>
<td>POP Prox</td>
<td>61</td>
</tr>
<tr>
<td>POP Mid</td>
<td>43</td>
</tr>
<tr>
<td>POP Distal</td>
<td>12</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
</tr>
<tr>
<td>low</td>
<td>74%</td>
</tr>
<tr>
<td>moderate</td>
<td>23%</td>
</tr>
<tr>
<td>severe</td>
<td>3%</td>
</tr>
<tr>
<td><strong>TASCII</strong></td>
<td></td>
</tr>
<tr>
<td>Average Percent diameter stenosis</td>
<td>91 % ± 10 %</td>
</tr>
<tr>
<td>A</td>
<td>20%</td>
</tr>
<tr>
<td>B</td>
<td>21%</td>
</tr>
<tr>
<td>C</td>
<td>21%</td>
</tr>
<tr>
<td>D</td>
<td>38%</td>
</tr>
</tbody>
</table>

Study is sponsored by Klinikum Arnsberg Lichtenberg, M. DGA 2016.
Ranger SFA Registry - Interim
Patient Outcomes

- 91% of patients improved by at least 1 Rutherford category at 6M
- 80% of patients improved ≥2 Rutherford categories at 6M

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Lichtenberg, M. DGA 2016.
Ranger SFA Registry - Interim
Efficacy and Safety at 6M

- Primary Patency of **91.1%** at 6M by Kaplan Meier Estimate
- Freedom from TLR of **91.9%** at 6M by Kaplan Meier Estimate

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VonBilderling, P. CIRSE 2016.
In the last 6 months, in what percent of your Peripheral Vascular SFA procedures, did you use the following technologies as a primary treatment option? In what percent do you expect to use them one year from now?
DE Technology Adoption Trend
By Country

In the last 6 months, in what percent of your Peripheral Vascular SFA procedures, did you use the following technologies as a primary treatment option? In what percent do you expect to use them one year from now?
DCB adoption in Europe

- Clinical studies consistently show positive data for DCB over POBA
- Significant improvement in outcomes with other Drug Eluting technologies is also consistently shown
- Why is the adoption rate of DET so slow?
  - Reimbursement?
  - More data needed?
  - Hesitant to change practice?

Conclusions

• Significant efficacy of DCB vs uncoated balloon angioplasty in the SFA has been consistently demonstrated

• DCBs have provided higher patency and lower reintervention rates in both RCTs and real-world registries in comparison to uncoated balloons

• Lesion characteristics drive DCB selection, and may influence outcomes
  — In long lesions and severe calcification, additional treatment (vessel prep) or alternative treatment (DES) should be considered

• The Ranger-SFA RCT Study showed:
  — Significantly less late lumen loss for patients treated with Ranger DCB vs control at 6 months
  — TLR rate for Ranger was half of the rate for the Control at 6 months
  — Patients treated with Ranger DCB showed significant improvement in symptoms and hemodynamics from baseline to 6 Months

• The Ranger DCB shows promising results in the real world setting with interim data from the Ranger All Comer Registry showing 91.1% PP at 6M and 91.9% fTLR at 6M

• Despite the overwhelming evidence of efficacy of Drug Eluting technologies over BMS and PTA, adoption of DE technologies in Europe is still low
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