Drug eluting balloon for bifurcation lesion: is it useful?

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Potential conflicts of interest

Speaker’s name: Bruno García del Blanco

☐ I have the following potential conflicts of interest to report:

☐ Research contracts
☐ 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
Theoretical advantages of DEB in bifurcations

- Cont. most accepted technique Provisional Stent
- Less metal in a non tubular anatomy.
- Less anatomy distortion
- Shorter period of drug delivery (not related to strut apposition).
- Avoid the polymers.
- Less DAPT time – better re.endothelization.
Previous studies DEB for bifurcation

Treatment of bifurcation lesions with a drug-eluting balloon: the PEPCAD V (Paclitaxel Eluting PTCA Balloon in Coronary Artery Disease) trial

Detlef G. Mathey, MD; Imke Wendig, MD; Michael Boxberger, PhD; Klaus Bonaventura, MD; Franz X. Kleber, MD

- LL in MB – 0.38 MM
- LL in SB – 0.21 MM
- 1st DEB SB (POBA if DEB didn’t cross before)
- 2nd DEB MB
- 3rd BMS MB
- 4th POBA if…
- 3 month DAPT

- N – 28 patient dual centre registry
- 9 month angio F/up

...BUT 1/28 TLR and 2 late Trombosis!
Coronary bifurcation lesions treated with the drug-eluting balloon: a preliminary insight from the DEBIUT study

Anouar Belkacemi, MD; Pierfrancesco Agostoni, MD, PhD; Michiel Voskuil, MD, PhD; Pieter R. Stella*, MD, PhD

University Medical Center Utrecht, department of Interventional Cardiology, Utrecht, The Netherlands

**DIOR 1st generation**
- Paclitaxel balloon surface: 3 μg/mm²
- Crystalin coating method with Paclitaxel (Ph.Eur. 5.0) and DMSO (Dimethylsulfoxid)
- 3-folded to protect the drug from early wash-off

**DIOR 2nd generation**
- Paclitaxel balloon surface: 3 μg/mm²
- Coating method is a 1:1 mixture of Paclitaxel (Ph.Eur. 5.0) and Shellac (Ph.Eur. 4.8)
- Shellac is FDA approved and well established in cosmetics, as food coating and tablet coating

Figure 1. Flow-chart of the consecutive procedures in the three groups.
Previous studies DEB for bifurcation

Coronary bifurcation lesions treated with the drug-eluting balloon: a preliminary insight from the DEBIUT study

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Randomised patients (n=117)
- Sequential MB/SB dilatation with regular balloon

Sequential MB/SB dilatation with DEB
- Provisional T-stenting with BMS
- Kissing balloon with regular balloons

3-month dual antiplatelet therapy

Randomisation
- Group A (n=37)
- Group B (n=40)
- Group C (n=40)

Figure 1. Flow-chart of the consecutive procedures in the three groups.

Europagation 2011; 7: K66-K69

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DIOR 2nd generation
- Shellac gives the balloon a shiny experience.

DIOR 2nd - 1:1 mixture of Paclitaxel and Shellac
Previous studies DEB for bifurcation

**Original Studies**

A Multicenter Randomized Comparison of Drug-Eluting Balloon Plus Bare-Metal Stent Versus Bare-Metal Stent Versus Drug-Eluting Stent in Bifurcation Lesions Treated With a Single-Stenting Technique: Six-Month Angiographic and 12-Month Clinical Results of the Drug-Eluting Balloon In Bifurcations Trial

Pieter R. Stella,1 MD, PhD, Anouar Belkacemi,2 MD, Christophe Dubois,2 MD, PhD, Hendrik Nathoe,1 MD, PhD, Jo Densa,2 MD, PhD, Christoph Naber,2 MD, Tom Adriaenssens,2 MD, Eric van Belle,1 MD, PhD, Pieter Doevendans,1 MD, PhD, and Pierfrancesco Agostini,1 MD, PhD

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Bailout stenting of the side branch</th>
<th>Final kissing balloon</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS + DEB</td>
<td>4 (10%)</td>
<td>39 (97.5%)</td>
</tr>
<tr>
<td>BMS + POBA</td>
<td>2 (5.4%)</td>
<td>36 (97.3%)</td>
</tr>
<tr>
<td>DES</td>
<td>2 (5%)</td>
<td>40 (100%)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Late luminal loss, mm</th>
<th>Proximal main branch</th>
<th>Distal main branch</th>
<th>Side branch</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMS + DEB</td>
<td>0.58 ± 0.65</td>
<td>0.41 ± 0.60</td>
<td>0.19 ± 0.66</td>
</tr>
<tr>
<td>BMS + POBA</td>
<td>0.60 ± 0.65</td>
<td>0.49 ± 0.85</td>
<td>0.21 ± 0.57</td>
</tr>
<tr>
<td>DES</td>
<td>0.13 ± 0.45</td>
<td>0.19 ± 0.64</td>
<td>0.11 ± 0.43</td>
</tr>
</tbody>
</table>

p

BMS: bare metal stent; DEB: drug-eluting balloon; DES: drug-eluting stent; MB: main branch; SB: side branch.
Previous studies DEB for bifurcation

Original Studies

A Multicenter Randomized Comparison of Drug-Eluting Balloon Plus Bare-Metal Stent Versus Bare-Metal Stent Versus Drug-Eluting Stent in Bifurcation Lesions Treated With a Single-Stenting Technique: Six-Month Angiographic and 12-Month Clinical Results of the Drug-Eluting Balloon In Bifurcations Trial

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<table>
<thead>
<tr>
<th></th>
<th>DEB with BMS N = 40</th>
<th>BMS N = 37</th>
<th>DES N = 40</th>
<th>P value DEB vs. BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>In-hospital</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peri-procedural myocardial infarction</td>
<td>3 (7.5%)</td>
<td>2 (5.4%)</td>
<td>3 (7.5%)</td>
<td>0.69</td>
</tr>
<tr>
<td><strong>Between discharge and 6 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>–</td>
</tr>
<tr>
<td>Target lesion revascularization</td>
<td>6 (15%)</td>
<td>10 (27%)</td>
<td>6 (15%)</td>
<td>0.30</td>
</tr>
<tr>
<td>Target-vessel revascularization</td>
<td>0</td>
<td>2 (5.4%)</td>
<td>1 (2.5%)</td>
<td>0.14</td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>0</td>
<td>0</td>
<td>1 (2.5%)</td>
<td>–</td>
</tr>
<tr>
<td><strong>Between 6 months and 12 months</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
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<td>Death</td>
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<tr>
<td>Stent thrombosis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Cumulative major adverse cardiac events</td>
<td>8 (20%)</td>
<td>11 (29.7%)</td>
<td>7 (17.5%)</td>
<td>0.32</td>
</tr>
</tbody>
</table>
1. Due to un-anticipated good results in de POBA arm, the primary endpoint was not reached (Late loss prox.MB (0.64 vs 0.42)). And, because of this lack of power also the 50% reduction in SB-late loss was not statistically significant (0.23 vs. 0.11).

2. However there are strong trends which show a favorable outcome combining DEB with a BMS in MB and using a DEB in SB with regards to late loss and especially binary restenosis rates.

3. Also in secondary endpoints there is a strong trend towards favoring DEB + BMS in terms of TVR, TLR and total MACE rates compared to BMS/POBA.

4. No cases of Geographic Miss were observed in DEB arm.

5. The use of BMS + DEB in bifurcations with only 3 months of DAPT seems very safe with 0% occurrence of SAT.

6. The non-powered randomised comparison between all three arms shows a clear unfavorable outcome for the use of BMS/POBA in bifurcations.
Ongoing studies DEB for bifurcation

- Spanish multicentric study
- 110 patients recruited
- F/Up angio 9 months
- Next year 2013 analysis

Group DEB
- 1st POBA MB+SB
- 2nd DEB SB
- 3rd BMS MB
- 4th DEB MB
## BIOTRONIK clinical program

### Global headquarter driven trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Device</th>
<th>Lesion type</th>
<th>Primary endpoint</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>BIOLUX-I¹</td>
<td>Pantera Lux</td>
<td>Bifurcations (main branch DES, side branch DEB)</td>
<td>LLL @ 9 months</td>
<td>35</td>
<td>4 centers enrolling in Australia, 19 patients (as per Nov 2(^{nd}) 2011)</td>
</tr>
</tbody>
</table>

### Local investigator driven trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Market</th>
<th>Study type</th>
<th>Lesion type</th>
<th>Primary endpoint</th>
<th>N</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>PEARL²</td>
<td>Canada</td>
<td>Randomized, multicenter</td>
<td>Bifurcations (main branch DES, side branch DEB vs POBA)</td>
<td>LLL @ 6 months</td>
<td>76</td>
<td>15 patients enrolled (as per Sept 13 2011)</td>
</tr>
<tr>
<td>SARPEDO N³</td>
<td>Hong Kong</td>
<td>Multicenter</td>
<td>Bifurcations (main branch DES, side branch DEB)</td>
<td>Angio FUP @ 6 months</td>
<td>40</td>
<td>2 centers enrolled 16 patients (as per March 2011)</td>
</tr>
</tbody>
</table>
How to deal with ostial bifurcated lesions in which the lesion is just in the ostium of the SB (001 Medina Classification)

- The best strategy remains debatable

ClinicalTrials.gov Identifier: NCT01375465

Ostial Bifurcated lesion

Clinical and Angiographic eligible patients (SB diameter $\geq 2.0$ mm)

TL SB Pre-dilatation (Recommended: cutting balloon)

Dior dilatation: longer than regular balloon, above nominal pressure + at least during 45sec

TL SB Post-dilatation (if needed, shorter than Dior)

Angiographic success: a residual lesion stenosis < 50% in the TL and absence of > type B coronary dissection

No angio success: BMS
Recruitment DIOR 0 0 1

1-2 patients each 2 month

02/2011  02  03  04  05  02/2012  09/2012

3 centers (7-9), 5 centers (1-3 patients)
Restenosis at SB ostium (16% to more than 20%) could be the consequence of:

- poor scaffolding on the origin of the side branch (recoil of the artery)
- endothelial destruction at the origin of the side branch not covered by the DES.
- overstretch of the stent in its proximal segment (lower ratio between struts and arterial wall and lower drug delivery).
- Polymeric coating destruction that could limit the effectiveness of the DES
- Hemodynamical disturbances due to the bifurcation anatomy

Courtesy of P. Guérin, L'Institut du Thorax, University Hospital. Nantes. France
1. Poor scaffolding on the origin of the side branch (recoil of the artery)

Micro focus X ray computer tomography (MFCT)

Micro focus X ray computer tomography (MFCT): NilPax
3. Overstretch of the stent in its proximal segment (lower ratio between struts and arterial wall and lower drug delivery)

- Sixteen 3.5 mm DES deployed in water
- Proximally aggressive postdilatation (NC 5.0 mm balloons)
- 18 atm
- MFCT showed increased cell areas in the transitional region

Basalas et al, EuroIntervention 2010; 6 : 141-148
5. Hemodynamical disturbances due to the bifurcation anatomy: Respect of the blood flow in the bifurcation

Stent-Induced Flow Disturbances Within a Compliant Bifurcation Model In Vitro

- Thrombi at the flow divider sites
- Site of uncovered struts
- Higher risk of stent thrombosis

- Flow disturbances
- Higher risk of stent restenosis

- Stent design:
  - Strut thickness
  - No struts in front of the carena?

RESTENOSIS LOCATION in BIPAX (Nile Pax)

MAIN BRANCH

- Proximal edge: 3.5% (3)
- Ostium 5 mm: 12.8% (11)
- In-stent: 11.6% (10)
- Distal edge: 1.2% (1)

SIDE BRANCH

Costa et al. EuroIntervention 2012; 7: 1301-130 (BIPAX Clinical Trial 9 months, n=87)
DEBSIDE Trial: Assessment of the safety and efficacy of the Danubio Paclitaxel-Eluting Balloon for the treatment of side branches of de novo bifurcation lesions in native coronary arteries

60 Patients non randomized

Primary end point:
Angiographic LLL at the ostium of the SB @ 6 months post-procedure by QCA

Secondary end points:
In-stent LLL in the MB, ABR* rate @ 6 months by QCA
MACE rate, clinically-driven TLR, TVF and TVR in-hospital @ 1, 6 and 12 months, angiographic success

*Angiographic Binary Restenosis

PRINCIPAL INVESTIGATOR
Dr. Jacques BERLAND
ROUEN, Clinique St Hilaire
Center of European Cardiovascular Research (C.E.R.C)

CORE LABORATORY
Dr. Marie-Claude MORICE
• My conclusions:

• Drug coated ballons should be useful for bifurcated lesions but...

  • There aren’t enough data from studies up to now.
    • (still expert recommendations)
  • is a different scenario than ISR.
  • be aware! Not all DEB are equal.

• Main practical questions still open:

  • Which order if we stent. (BMS or DES?)
  • Duration of DAPT?
we should have some answers soon…

Thank you!