High risk of restenosis patients’ treatment: Update in the REFLOW trial

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Disclosure slide

Speaker name: Koen Deloose, MD

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

☒ Consulting: Abbott, BD, Biotronik, Boston Scientific, Cook, CTI vascular, iVascular, Medtronic, Philips, Terumo, CyndRX, Profusa

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

☐ I do not have any potential conflict of interest
Recommendations

While further investigation is in progress, the FAMHP takes this safety signal very seriously and makes the following recommendations (FR - NL) to healthcare professionals:

- **Do not use paclitaxel DCBs or DESs as a preferred treatment for intermittent claudication until further notice.** Carefully estimate the risks and benefits for each patient.
- **Discuss the risks and benefits of all available treatment options for PAV with patients.** Inform patients about the uncertainty of increased mortality.
- **Ensure proper follow-up** for patients who have already been treated with a paclitaxel DCB or DES.
- **Report any adverse event** involving a paclitaxel DCB or DES to FAMHP using our online adverse event form.

Patients who are worried or have any questions about these aids should talk to their attending physician.

**Federal Agency for Medicines and Health Product, July 3rd 2019**
How to continue...?
“3 questions/answers” - based treatment algorithm

Severe Calcium

Angioplasty Responder

High Risk Restenosis

Y

Focal non-responding Ca

SUPERA

Y

Y

ATHERECTOMY + SUPERA

Diffuse non-responding Ca

PAVE & CRACK BYPASS

N

Angioplasty responder

BMS with correct COF

DCB

DES

N

N
“3 questions/answers” - based treatment algorithm

Angioplasty Responder

- Y

- N

Severe Calcium

- N

High Risk Restenosis

Angioplasty Responder

- Y

- N

Focal non-responding Ca

SUPERA

Atherectomy + SUPERA

Diffuse non-responding Ca

PAVE & CRACK BYPASS

BMS with correct COF

DCB

DES

Y

N

Y

N

N
# High Risk of Restenosis?

<table>
<thead>
<tr>
<th>Patient Specific Factors</th>
<th>Lesion Specific Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Critical Limb Ischemia</strong></td>
<td><strong>Length</strong></td>
</tr>
<tr>
<td><strong>Diabetes Mellitus</strong></td>
<td><strong>Small vessel diameter</strong></td>
</tr>
<tr>
<td><strong>End Stage Renal Disease</strong></td>
<td><strong>Occlusion</strong></td>
</tr>
<tr>
<td><strong>Poor Run-off</strong></td>
<td></td>
</tr>
</tbody>
</table>

A study investigating the Efficacy of the LEGFLOW Paclitaxel-Eluting for the treatment of long femoropopliteal lesions (TASC C&D)

• **Study Objective:**
To evaluate the performance of LEGFLOW Paclitaxel-Eluting Peripheral balloon catheter for treatment of long femoropopliteal lesions (TASC C&D) in 120 patients.

• **Primary Endpoint:**
Primary Patency @12 months, defined as absence of hemodynamically significant stenosis on DUS (peak systolic velocity ratio ≤2.4) @target lesion & without reintervention.
We need a stable coating matrix...

<table>
<thead>
<tr>
<th></th>
<th>OLDER GENERATION CRYSTALLINE COATINGS</th>
<th>NEWER GENERATION AMORPHOUS COATINGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device</td>
<td>Surface covered with white powder</td>
<td>Smooth, transparent surface</td>
</tr>
<tr>
<td>Optical image</td>
<td>Crystalline, hydrophilic coating</td>
<td>Amorphous, lipophilic coating</td>
</tr>
<tr>
<td>measuring (100x)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Look</td>
<td>Crystalline sugar</td>
<td>Honey</td>
</tr>
<tr>
<td>matrix</td>
<td>Rigid crystal shape of crystalline excipient/PTX</td>
<td>Non crystalline PTX melted with polymeric excipient in an elastic matrix</td>
</tr>
<tr>
<td>Mechanical stress</td>
<td>Rigid crystalline coating affected by mechanical stress factors</td>
<td>Elastic, polymeric amorphous coating not affected by mechanical stress</td>
</tr>
<tr>
<td>response</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Reflow study: participating centers/timeline

**BELGIUM**
- M. Bosiers, K. Deloose, J. Callaert
  - *AZ Sint-Blasius, Dendermonde*
- P. Peeters, J. Verbist, W. Van den Eynde
  - *Imelda Hospital, Bonheiden*
- L. Maene, R. Beelen - *OLV, Aalst*
- K. Keirse - *RZ Heilig Hart, Tienen*
- J. Hendriks, P. Lauwers
  - *University Hospital Antwerp, Edegem*

**GERMANY**
- G. Torsello – *St. Franziskus-Hospital Münster*
- D. Scheinert – *Universitätsklinikum Leipzig*
## Reflow study: patient demographics and procedural characteristics

### N = 120

<table>
<thead>
<tr>
<th>Category</th>
<th>Percentage</th>
<th>Count (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male (%), Male (%)</td>
<td>65.80%</td>
<td>79/120</td>
</tr>
<tr>
<td>Age (min – max), Age</td>
<td>71.06</td>
<td>35.05 – 93.16 years</td>
</tr>
<tr>
<td>Nicotine abuse (%), Nicotine abuse (%)</td>
<td>56.67%</td>
<td>68/120</td>
</tr>
<tr>
<td>Hypertension (%), Hypertension (%)</td>
<td>77.50%</td>
<td>93/120</td>
</tr>
<tr>
<td>Diabetes mellitus (%), Diabetes mellitus (%)</td>
<td>30.00%</td>
<td>36/120</td>
</tr>
<tr>
<td>Renal insufficiency (%), Renal insufficiency (%)</td>
<td>15.00%</td>
<td>18/120</td>
</tr>
<tr>
<td>Hypercholesterolemia (%), Hypercholesterolemia (%)</td>
<td>53.30%</td>
<td>64/120</td>
</tr>
<tr>
<td>Obesity (%), Obesity (%)</td>
<td>19.20%</td>
<td>23/120</td>
</tr>
<tr>
<td>Claudicants, Claudicants</td>
<td>77.5%</td>
<td>95/120</td>
</tr>
<tr>
<td>CLI, CLI</td>
<td>22.5%</td>
<td>27/120</td>
</tr>
</tbody>
</table>

### N = 120

<table>
<thead>
<tr>
<th>Category</th>
<th>Time (min-max)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Procedure time (min-max)</td>
<td>52.17 (19-165) minutes</td>
</tr>
<tr>
<td>Scopy time (min – max)</td>
<td>7.32 (1.7 – 39.24) minutes</td>
</tr>
<tr>
<td>*missing information for 2 patients</td>
<td></td>
</tr>
<tr>
<td>Contrast (min – max)</td>
<td>88.09 (9 – 195) mL</td>
</tr>
<tr>
<td>Cross-over (%)</td>
<td>83.33% (100/120)</td>
</tr>
<tr>
<td>Inflow Lesion (%)</td>
<td>10.83% (13/120)</td>
</tr>
<tr>
<td>Outflow lesion (%)</td>
<td>21.67% (26/120)</td>
</tr>
</tbody>
</table>

### Rutherford Classification

- RF 2: 3 (0.25%)
- RF 3: 13 (1.08%)
- RF 4: 24 (2.0%)
- RF 5: 80 (6.67%)
## Reflow study: Lesion characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N = 120</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion length (min – max)</td>
<td>216.08 (150 – 390) mm</td>
</tr>
<tr>
<td>Ref Vessel Diameter (min – max)</td>
<td>5.40 (4.05 – 6.00) mm</td>
</tr>
<tr>
<td>Pre-dilatation (%)</td>
<td>64.20% (77/120)</td>
</tr>
<tr>
<td>1 DCB (%)</td>
<td>25.83% (31/120)</td>
</tr>
<tr>
<td>2 DCB’s (%)</td>
<td>57.50% (69/120)</td>
</tr>
<tr>
<td>3 DCB’s (%)</td>
<td>16.67% (20/120)</td>
</tr>
<tr>
<td>Post-dilatation (%)</td>
<td>22.50% (27/120)</td>
</tr>
<tr>
<td>Bail-out stenting (%)</td>
<td>35.00% (42/120)</td>
</tr>
<tr>
<td>Occlusion (%)</td>
<td>45.00% (54/120)</td>
</tr>
<tr>
<td>Calcified lesion (%)</td>
<td>67.50% (81/120)</td>
</tr>
</tbody>
</table>
Reflow study: Primary Patency @12/24 m

Very Challenging Lesions!

- Lesion length (min–max): 216.08 (150–390) mm
- Occlusion (%): 45.00% (54/120)
- Calcified lesion (%): 67.50% (81/120)
Reflow study: Freedom TLR @12/24 m

Freedom from Target Lesion Revascularization

79.90% (120 pts)
72.50% (prelim 70 pts)

Number at risk:
70 70 68 68 66 63 60 58 58 56 52 50 49 48 46 45 44 43 43 41 40 38 12
Reflow study: Survival @12/24 m

Reasons of death:
- Hypoglycemic coma (Day 146)
- Atrial fibrillation, acute renal insufficiency, critical stenosis aortic valve (Day 163)
- Pneumonia leading to respiratory arrest (Day 301)
- Hypernatriemia, acute renal insufficiency (Day 318)
- Urethral Cancer (Day 318)
- Reason unknown (Day 335)
- Cerebral hypoxemia (Day 417)
- Reason unknown (Day 464)
- Brain stem infarction (Day 484)
- Admission for hip fracture after fall, died 2 days later (Day 615)

With mean lesion lengths of 216 mm, 45% CTO’s, 67.50% calcified lesions

All included patients could be categorized as “patients at high risk for restenosis”

94.70% (120 pts)
85.60% (prelim 70 pts)
Reflow study: clinical outcome
## Reflow study: safety profile (full cohort)

### Primary Safety Endpoint (120 pts)

<table>
<thead>
<tr>
<th>Event</th>
<th>30 days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Device or procedure related death (N)</td>
<td>0</td>
</tr>
<tr>
<td>CD-TLR (N)</td>
<td>1</td>
</tr>
<tr>
<td>Target Limb Amputation (N)</td>
<td>0</td>
</tr>
</tbody>
</table>

### MAEs (N=120 pts)

<table>
<thead>
<tr>
<th>Event</th>
<th>180d</th>
<th>210d</th>
<th>365d</th>
<th>395d</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death (N)</td>
<td>2</td>
<td>2</td>
<td>6</td>
<td>6</td>
</tr>
<tr>
<td>CD-TLR (N)</td>
<td>11</td>
<td>12</td>
<td>22</td>
<td>26</td>
</tr>
<tr>
<td>Target Limb Major Amputation (N)</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>
Reflow study in perspective...lesions >20cm

12M Primary Patency (%)

12M Freedom from TLR (%)

24M Primary Patency (%)

24M Freedom from TLR (%)

Preliminary cohort 70/120

BMS: Durability 200 study

DES: ZILVERPASS Zilver PTX results

Bypass ZILVERPASS results

DCB: REFLOW results
Reflow study in summary

• Safety issues with some DCB’s created official authority statements, saying that all PTX-based technology needs to be reserved for patients at high risk for restenosis & reintervention

• Newer generation DCB’s, like the Legflow, with stable amorphous SAFEPAX coating, are developed to optimize drug uptake in “hostile environments”

• The Reflow study demonstrates in a complex lesion population (mean lesion length 22cm) good outcomes: full cohort 1 year patency of 71% and freedom from TLR of 80%.

• In a preliminary cohort of 70 patients 24 month data are available: patency of 66% and freedom from TLR of 72%

• If we benchmark with other treatment strategies like BMS, DES and (prosthetic) bypass surgery in these complex lesions @high risk, we can conclude these data are remarkable
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