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 (ER - 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

- Focal non-responding Ca
  - SUPERA
- Diffuse non-responding Ca
  - AHERECTOMY + SUPERA

High Risk Restenosis

- Angioplasty responder
  - PAVE & CRACK BYPASS
  - DCB
  - DES
  - BMS with correct COF
“3 questions/answers” - based treatment algorithm

Angioplasty Responder

- **Severe Calcium**
  - **High Risk Restenosis**
    - **Angioplasty responder**
      - **Y**
        - **DCB**
        - **N**
          - **DES**
          - **BMS with correct COF**

- **Focal non-responding Ca**
  - **SUPERA**

- **Diffuse non-responding Ca**
  - **ATHERECTOMY + SUPERA**

- **PAVE & CRACK BYPASS**
High Risk of Restenosis?

<table>
<thead>
<tr>
<th>Patient Specific Factors</th>
<th>Lesion Specific Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Limb Ischemia</td>
<td>Length</td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>Small vessel diameter</td>
</tr>
<tr>
<td>End Stage Renal Disease</td>
<td>Occlusion</td>
</tr>
<tr>
<td>Poor Run-off</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 measuring (100x)</td>
<td>Crystalline, hydrophilic coating</td>
<td>Amorphous, lipophilic coating</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 response</td>
<td>Rigid crystalline coating affected by mechanical stress factors</td>
<td>Elastic, polymeric amorphous coating not affected by mechanical stress</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

<table>
<thead>
<tr>
<th>N = 120</th>
<th>Procedure time (min-max)</th>
</tr>
</thead>
</table>
| Male (%)
65.80% (79/120) | 52.17 (19-165) minutes |
| Age (min – max) | Scopy time (min – max) |
71.06 (35.05 – 93.16) years | 7.32 (1.7 – 39.24) minutes |

*missing information for 2 patients

<table>
<thead>
<tr>
<th>N = 120</th>
<th>Contrast (min – max)</th>
<th>Cross-over (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nicotine abuse (%)</td>
<td>88.09 (9 – 195) mL</td>
<td>83.33% (100/120)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>Procedure time (min-max)</td>
<td>78.33%</td>
</tr>
</tbody>
</table>
77.50% (93/120) | Scopy time (min – max) |
| Diabetes mellitus (%) | *missing information for 2 patients | 83.33% (100/120) |
30.00% (36/120) | Contrast (min – max) |
| Renal insufficiency (%) | 88.09 (9 – 195) mL | 83.33% (100/120) |
15.00% (18/120) | Procedure time (min-max) |
| Hypercholesterolemia (%) | Scopy time (min – max) |
53.30% (64/120) | *missing information for 2 patients |
| Obesity (%) | Contrast (min – max) |
19.20% (23/120) | 88.09 (9 – 195) mL |
Rutherford Classification

Claudicants
77.5% (95/120)

Renal insufficiency
15.00% (18/120)

Hypercholesterolemia
53.30% (64/120)

Obesity
19.20% (23/120)

Nicotine abuse
56.67% (68/120)

Hypertension
77.50% (93/120)

Diabetes mellitus
30.00% (36/120)

Male
65.80% (79/120)

Age
71.06 (35.05 – 93.16) years

Contrast
88.09 (9 – 195) mL

Cross-over
83.33% (100/120)

Inflow Lesion
10.83% (13/120)

Outflow lesion
21.67% (26/120)
## Reflow study: Lesion characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>N = 120</td>
<td></td>
</tr>
<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!

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<thead>
<tr>
<th>Lesion length (min – max)</th>
<th>216.08 (150 – 390) mm</th>
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<tbody>
<tr>
<td>Occlusion (%)</td>
<td>45.00% (54/120)</td>
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<tr>
<td>Calcified lesion (%)</td>
<td>67.50% (81/120)</td>
</tr>
</tbody>
</table>
Reflow study: Freedom TLR @12/24 m

Freedom from Target Lesion Revascularization

79.90% (120 pts)

72.50% (prelim 70 pts)
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)

All included patients could be categorized as "patients at high risk for restenosis"
Reflow study: clinical outcome

![Evolution Rutherford Classification Graph]

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>1MFU</th>
<th>6MFU</th>
<th>12MFU</th>
<th>24MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rutherford 5</td>
<td>14</td>
<td>6</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rutherford 4</td>
<td>2</td>
<td>0</td>
<td>0</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Rutherford 3</td>
<td>49</td>
<td>1</td>
<td>4</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rutherford 2</td>
<td>5</td>
<td>1</td>
<td>5</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>Rutherford 1</td>
<td>0</td>
<td>2</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>Rutherford 0</td>
<td>0</td>
<td>60</td>
<td>40</td>
<td>47</td>
<td>40</td>
</tr>
</tbody>
</table>
Reflow study : safety profile (full cohort)

<table>
<thead>
<tr>
<th>Primary Safety Endpoint (120 pts)</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>

<table>
<thead>
<tr>
<th>MAEs (N=120 pts)</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 (%)  
- BMS: 64.8%
- DES: 74.5%
- bypass: 72.5%
- DCB: 71.1%

12M Freedom from TLR (%)  
- BMS: 68.2%
- DES: 80.4%
- bypass: 76.2%
- DCB: 79.9%

24M Primary Patency (%)  
- Preliminary cohort 70/120
  - BMS: N/A
  - DES: 62.0%
  - bypass: 59.9%
  - DCB: 66.2%

24M Freedom from TLR (%)  
- Preliminary cohort 70/120
  - BMS: N/A
  - DES: 72.9%
  - bypass: 67.9%
  - DCB: 72.5%

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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