Use of Ultrasound to enhance Paclitaxel delivery in CLI patients with femoro-popliteal disease: PACUS trial

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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
Treatment Of CLI Continues To Be The Biggest Challenge In PAD

Critical Limb Ischemia represents over 20% of the PAD disease today and is expected to reach 30% by 2018 due to growing numbers of diabetes and increase of aging population (MRG 2014)

CLI (SFA/BTK) Current Treatment

- Standard of care at present is PTA

- Use of BMS, DES and DEB have not yet shown to lessen TLR and amputation rate

- The biggest challenge to treat CLI and patients with calcific lesions is inability of therapeutic drugs to penetrate the media-intima calcium to reach the vessel wall

A NEW PARADIGM OF TREATMENT

• Conventional PTA and stenting are compressing the atherosclerotic plaque. The effect of drug eluting devices may be reduced by calcifications located within the vessel wall

• Low frequency Ultrasound-Plasty may remodel calcifications and improve drug penetration to the vessel wall
The Genesis™ System

**Hardware**
- Generator
- Timer
- ON/OFF Switch
- Irrigation Pump
- Transducer
- IV Pole
- Foot switch cable

**Catheter**
- .6 mm tip
- 1.6mm catheter
- RX any 0.014’guidewire
- 200 cm long
- 5F sheath compatible
- Ultrasound active member with adjustable length 10-100mm
**Method of Action**

- **Vessel**
- **Irrigation Outlet**
- **Catheter Tip Marker**
- **Diseased Area After Balloon Angioplasty**
- **Surface Waves**
- **Catheter Body**
- **Media-Intima Calcium After POBA**
- **Tip**
- **Vessel**
- **US Active Member**

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**Images**:

- Top image: Diagram showing a cross-section of a vessel with labeled parts.
- Bottom left image: Image showing a cross-section of a vessel.
- Bottom right image: Image showing a cross-section of a vessel with a diseased area.

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**Notes**:

- **Catheter Tip Marker** indicates the tip of the catheter within the vessel.
- **Irrigation Outlet** likely represents a point where fluid or medication is introduced.
- **Diseased Area After Balloon Angioplasty** highlights the area affected by the procedure.
- **Surface Waves** may indicate areas of stress or activity on the vessel's surface.
- **Media-Intima Calcium** refers to calcium deposits within the vessel walls.
Method of Action

- **Catheter Body**
- **Media-Intima Calcium After POBA**
- **Surface Waves**
- **Catheter Tip Marker**
- **Irrigation Outlet**
- **Diseased Area After Balloon Angioplasty**
- **US Active Member**
- **Vessel**
- **Introducer**
- **Paclitaxel delivery**
- **Media/Intimal Modified Calcium**
- **Distal Balloon**

Chemical formula: $C_{47}H_{51}NO_{14}$
STUDY

• **DESIGN:** Prospective, randomized, double-arm, single-center clinical evaluation of ultrasound utilizing CardioProlific Genesis™ System followed by local administration of liquid mixture of Paclitaxel and Iopromide-370 @ 1.0 µg/mm³ in FEM/pop district

• **OBJECTIVE:** to evaluate the safety and efficacy of ultrasound energy to facilitate Paclitaxel delivery in CLI patients due to FEM/Pop vessel disease

• **CO-INVESTIGATORS:**
  - Roberto Gandini, PhD, MD
    Tor Vergata University, Rome, Italy
  - Costantino Del Giudice, MD
    Université Paris Descartes, Paris, France

325 patients with CLI evaluated between November 2013 and February 2015

56 patients enrolled and randomized in PACUS trial

269 patients excluded:
  - isolated BTK (56)
  - Refused informed consent (48)
  - Subintimal recanalization (152)
  - Needed SFA stenting (13)

Study group
28 patients were treated with ultrasound + local administration Paclitaxel

Clinical follow-up at 12 months in 92.8% (N=26)
2 deaths

Control group
28 patients were treated with the In.Pact Admiral DEB

Clinical follow-up at 12 months in 89.3% (N=25)
3 deaths
Inclusion Criteria:

• Patients with CLI (Rutherford Class 4-6) associated with femoral-popliteal lesions
• Symptomatic long segmental stenosis, CTOs and severe calcifications
• No lesion length limit
• Successful intraluminal recanalization without need of a stent to obtain a satisfactory angiographic result
• At least one patent BTK vessel
• Patients older than 18 years

Exclusion criteria:

• Rutherford category < 4
• Pregnancy
• Known allergies to study medications
• Need of target vessel stenting
Case 1

Pre-procedure

Post-procedure

6m follow-up
Case 2

Pre-procedure  Post-procedure  6m follow-up
Case 3

Pre-procedure

Post-procedure

6m follow-up

13
Case 4

Pre-procedure  Post-procedure  6m follow-up

Proximal segment not treated with US+Paclitaxel
Case 5

Pre-procedure  Post-procedure  6m follow-up
Case 6

Pre-procedure

Post-procedure

6m follow-up
## Patients Information

### Demographics Variables

<table>
<thead>
<tr>
<th></th>
<th>Study n = 28</th>
<th>Control n = 28</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>74.2±7</td>
<td>75.5±9.1</td>
<td>0.86</td>
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<tr>
<td>Hypertension</td>
<td>27 (96.4%)</td>
<td>26 (92.9%)</td>
<td>0.55</td>
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<tr>
<td>Diabetes</td>
<td>13 (46.4%)</td>
<td>12 (42.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Smoke</td>
<td>23 (82.1%)</td>
<td>21 (75.0%)</td>
<td>0.58</td>
</tr>
<tr>
<td>History of CAD</td>
<td>12 (42.9%)</td>
<td>14 (50.0%)</td>
<td>0.59</td>
</tr>
<tr>
<td>Previous neurological disease</td>
<td>9 (32.1%)</td>
<td>7 (25.0%)</td>
<td>0.55</td>
</tr>
<tr>
<td>Renal failure</td>
<td>5 (17.9%)</td>
<td>9 (32.1%)</td>
<td>0.22</td>
</tr>
<tr>
<td>Rutherford Scale</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 4</td>
<td>13 (46.4%)</td>
<td>12 (42.9%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Class 5</td>
<td>14 (50.0%)</td>
<td>13 (46.4%)</td>
<td>0.79</td>
</tr>
<tr>
<td>Class 6</td>
<td>1 (3.6%)</td>
<td>3 (10.7%)</td>
<td>0.3</td>
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</table>

### Patients Information

#### Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion Characteristics</th>
<th>Study n = 28</th>
<th>Control n = 28</th>
<th>P Value</th>
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<tbody>
<tr>
<td>Isolated SFA location</td>
<td>19 (67.9%)</td>
<td>20 (71.4%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Proximal Popliteal involvement</td>
<td>9 (32.1%)</td>
<td>8 (28.6%)</td>
<td>0.77</td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>168.8±54.4</td>
<td>164±14.4</td>
<td>0.1</td>
</tr>
<tr>
<td>CTOs</td>
<td>20 (71.4%)</td>
<td>15 (53.6%)</td>
<td>0.17</td>
</tr>
<tr>
<td>Severe calcifications</td>
<td>21 (75.0%)</td>
<td>23 (82.0%)</td>
<td>0.5</td>
</tr>
</tbody>
</table>

# Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Study</th>
<th>Control</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Technical Success</td>
<td>100% (28/28)</td>
<td>100% (28/28)</td>
<td></td>
</tr>
<tr>
<td>Restenosis at 1m FU (DUS-PVR≤2.5)</td>
<td>0% (0/28)</td>
<td>0% (0/28)</td>
<td></td>
</tr>
<tr>
<td>Restenosis at 6m FU (Angiographic)</td>
<td>3.6% (1/28)</td>
<td>36% (6/28)</td>
<td>0.04</td>
</tr>
<tr>
<td>Restenosis at 12m FU (DUS-PVR≤2.5)</td>
<td>3.8% (1/26)</td>
<td>32% (8/25)</td>
<td>0.008</td>
</tr>
<tr>
<td>TLR at 6m FU</td>
<td>0% (0/28)</td>
<td>10.7 (3/28)</td>
<td>0.08</td>
</tr>
<tr>
<td>TLR at 12m FU</td>
<td>3.8 (1/26)</td>
<td>36% (9/25)</td>
<td>0.004</td>
</tr>
<tr>
<td>Clinical improvement at 12m FU</td>
<td>92.3% (24/26)</td>
<td>68.0% (17/25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Procedure related death at 12m FU</td>
<td>0% (0/28)</td>
<td>0% (0/28)</td>
<td></td>
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<tr>
<td>Non-Procedural death at 12m FU</td>
<td>7.1% (2/28)</td>
<td>10.7 (3/28)</td>
<td>0.64</td>
</tr>
<tr>
<td>Amputations at 12m FU</td>
<td>0% (0/26)</td>
<td>16% (4/25)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Freedom from TLR

Patients at risk:
- Study group: 28, 28, 25
- Control Group: 28, 25, 18

89.3% Freedom from TLR at 12m FU
64.3% Freedom from TLR at 12m FU

### 18 Month FU

<table>
<thead>
<tr>
<th>Event</th>
<th>Study</th>
<th>Control</th>
<th>P Value</th>
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</thead>
<tbody>
<tr>
<td>Restenosis at 18m FU (DUS-PVR≤2.5)</td>
<td>7.6% (2/26)</td>
<td>48% (12/25)</td>
<td>0.002</td>
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<tr>
<td>TLR at 18m FU</td>
<td>7.6% (2/26)</td>
<td>44% (11/25)</td>
<td>0.003</td>
</tr>
<tr>
<td>Clinical improvement at 18m FU</td>
<td>92.3% (24/26)</td>
<td>68.0% (17/25)</td>
<td>0.03</td>
</tr>
<tr>
<td>Non-Procedural death at 18m FU</td>
<td>7.1% (2/28)</td>
<td>10.7% (3/28)</td>
<td>0.64</td>
</tr>
<tr>
<td>Amputations at 18m FU</td>
<td>0% (0/26)</td>
<td>20% (5/25)</td>
<td>0.02</td>
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</table>

Del Giudice C, Gandini R, Sapoval M. In press
Conclusions

- Study Limitations:
  - Single center
  - Small number of patients
  - Included treatment of multiple vascular beds: SFA, Popliteal, Infrapopliteal

- Ultrasound energy changes compliance of the media-intima calcium and facilitates Paclitaxel delivery to the SFA-Pop vessel wall

- Safe non-implant solution for drug delivery to the vessel wall

- The Genesis ™ System is easy to use, and capable to treat any lesion length and vessel size at any locations with one device

- Encouraging results in CLI cases demonstrate great potential for this technology in the entire PAD

- A larger clinical study is required to validate this promising new therapy
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