Advancements in the Treatment Options for ISR Laser/DCB/DES

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Disclosures

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Nitinol stents are being used more commonly in the therapy of SFA, popliteal, and infrapopliteal disease as multiple reports have shown improved patency and better symptomatic relief as compared with balloon angioplasty. (Crucial with flow-limiting dissections)

In-stent restenosis over time is common

Interventional therapy of ISR has historically been associated with high restenosis rates and complications.


3 Ms. Sabina A. Murphy. RESILIENT (RESILIENT – Presented at TCT 2007) Cardiosource, American College of Cardiology. 10/23/07.
>200M People Living with PAD Globally
<2% Treated Surgically or Endovascularly

>400,000 FemPop Stents Implanted WW Every Year

250,000 ISR Cases

U.S. ISR Incidence
- >200,000 Stents / Year implanted
- Stent volume growing 6-7% annually
- 30-40% 1st time ISR Incidence within 2 years of implant

115,000 US ISR Cases
• Restenosis is usually secondary to intimal in-growth in a fully expanded stent and reocclusion usually has superimposed thrombus. (Several investigators have noted increased incidence when stent fractures are present.)
• Historically treatment of long diffuse disease and occlusions showed very poor patency (one study < 20%) at 3 months with high embolization rate during intervention.
Histology

- Neointimal hyperplasia
  - 15% cellular
  - 85% extracellular matrix
  - Very high water content
A Novel Mechanism Explaining Early Lumen Loss Following Balloon Angioplasty for the Treatment of In-Stent Restenosis

Mariano Albertal, MD, PhD, Alexandre Abizaid, MD, PhD, Juan S. Muñoz, MD, Gary S. Mintz, MD, Andrea S. Abizaid, MD, PhD, Fausto Feres, MD, PhD, Marinella Centemero, MD, PhD, Rodolfo Staico, MD, Luiz A. Mattos, MD, PhD, Roselei Graebin, MD, Amanda Sousa, MD, PhD, and J. Eduardo Sousa, MD, PhD

We performed serial intravascular ultrasound analysis in patients who underwent balloon dilatation for in-stent restenosis. Early lumen loss was detected by intravascular ultrasound and was associated with minimal changes at the edges and at the external elastic membrane. These results on intravascular ultrasound suggest compression and decompression as the main mechanisms for early lumen loss after dilatation of in-stent restenotic lesions. ©2005 by Excerpta Medica Inc.

(Am J Cardiol 2005;95:751-754)

IVUS 30 min post POBA
Rationale of ISR Therapy

- Suboptimal results with balloon angioplasty are common
  - PTA dilatation of intimal hyperplasia compresses aqueous extra-cellular matrix, however rehydration ensues.
  - Thrombotic material may embolize and is thrombogenic.
  - Elastic recoil (NO POSITIVE REMODELING)
- Suboptimal results with repeat bare metal stenting within ISR
  - Embolization
  - No barrier to intimal ingrowth/won’t seal pseudo aneurysms
  - Lumen compromised by at least the stent strut thickness
- Mechanical stabilization of fractured stents with either covered stents or Nitinol stents is probably crucial.
- There are two FDA approved therapies for ISR that may be utilized alone or in conjunction (Laser/Gore® Viabahn® Device).
**Fem-pop ISR Treatment (PTA)**

**Tosaka Classification**

- **Class I**: Short, focal lesions (≤ 50mm)
- **Class II**: Diffuse lesions (> 50mm)
- **Class III**: Total Occlusions

**2-Year Restenosis Rate**

- 0%
- 20%
- 40%
- 60%
- 80%
- 100%
Treating FemPop In-stent Restenosis

• Factors to consider before attempting FemPop, in-stent restenosis intervention.
  • Length of lesion
  • Location of lesion (in-stent or edge stenosis)
  • Stenosis versus occlusion
  • Acuity of symptoms (old vs. new thrombus)
  • Is the stent fully expanded or compressed
  • Type of stent (covered vs. bare metal)
  • Stent fractures
  • Runoff vessel status
  • Location in the artery
  • Vessel Diameter
GORE® VIABAHN® Endoprosthesis for In-Stent Restenosis — RELINE Clinical Study\(^1\)

Prospective, randomized trial conducted at seven centers in Europe
GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface* versus PTA for treatment of in-stent restenosis of the SFA.

<table>
<thead>
<tr>
<th>Objective</th>
<th>Evaluate the performance of the GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface and PTA in treating in-stent restenosis in the SFA.</th>
</tr>
</thead>
</table>
| **Primary Endpoints** | Primary Patency at 12 months  
— Patency loss by PSVR > 2.5 assessed by color duplex ultrasound  
Proportion of patients experiencing composite adverse events within 30 days of procedure |
| **Secondary Endpoints** | Primary patency (hemodynamic and angiographic)  
Primary assisted and secondary patency  
Target lesion revascularization  
Clinical success  
Serious adverse events  
Stent fracture at 12 months |

* Note: The GORE® VIABAHN® Endoprosthesis with Heparin Bioactive Surface is known in some markets as the GORE® VIABAHN® Endoprosthesis with PROPATEN Bioactive Surface.

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## RELINE Clinical Study Randomization

<table>
<thead>
<tr>
<th>Group</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>100 patients</td>
<td>Randomly allocated to treatment (1:1 randomization)</td>
</tr>
<tr>
<td>47 patients</td>
<td>Randomized to GORE® VIABAHN® Endoprosthesis (intent-to-treat)</td>
</tr>
<tr>
<td>8 patients</td>
<td>Excluded from analysis by primary investigator due to inclusion / exclusion and procedural violations</td>
</tr>
<tr>
<td>39 patients</td>
<td>Analyzed (per-protocol)</td>
</tr>
<tr>
<td>53 patients</td>
<td>Randomized to PTA (intent-to-treat)</td>
</tr>
<tr>
<td>9 patients</td>
<td>Excluded from analysis by primary investigator due to inclusion / exclusion and procedural violations</td>
</tr>
<tr>
<td>44 patients</td>
<td>Analyzed (per-protocol)</td>
</tr>
</tbody>
</table>

Primary Patency

Superior primary patency with GORE® VIABAHN® Endoprosthesis in the per-protocol analysis (shown below), intent-to-treat analysis, and in comparison to optimal PTA cohort.


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RELINE Clinical Study Conclusions

• Evidence from the RELINE Clinical Study support the safety and effectiveness of the GORE® VIABAHN® Endoprosthesis in relining failed bare metal stents.

• Superior primary patency at one year in the GORE® VIABAHN® Endoprosthesis group.

• Patients in the GORE® VIABAHN® Endoprosthesis arm were approximately three times less likely to require a TLR.

• Freedom from serious device-related adverse events similar in both arms of the study.
10 Technical Considerations

1. Avoid excessive oversizing
2. Treat all of the disease
3. Prescribe appropriate antiplatelet therapy
4. Assure adequate inflow and outflow
5. Place device at the SFA origin if disease is present
6. Overlap devices by at least 1 cm
7. Post-dilate
8. Do not use PTA outside of the device
9. Regular duplex ultrasonography follow-up
10. Treat progressing disease (Do not wait for total occlusion or recurrent symptoms)
EXCITE ISR
(308 nm excimer laser atherectomy to treat ISR)

Principal investigators Eric Dippel/MD/Craig Walker MD
EXCITE Trial Designed to Provide Level 1 Clinical Evidence in ISR Therapy

Design & Oversight
- Prospective, randomized control, multi-center trial
  - Laser + PTA (ELA) vs. PTA alone (PTA)
- Independent DSMB adjudicating all study events
- Angiographic and Ultrasound Core Laboratory
- 2:1 randomization scheme (ELA:PTA)
- Statistical endpoints designed to demonstrate superiority

Primary Safety Endpoint - Major Adverse Events (MAE) during hospitalization through 37-day follow-up to include all death, unplanned major amputation, or target lesion revascularization

Primary Efficacy Endpoint - Freedom from clinically driven TLR through 6 month follow-up (212 days)
EXCITE ISR Trial Overview

EXCITE ISR

**DESIGN:**
Prospective, randomized, multi-center clinical evaluation of excimer laser atherectomy (ELA) for ISR

**PRIMARY SAFETY ENDPOINT:**
Major Adverse Events (MAE) during hospitalization through 37-day follow-up to include all death, unplanned major amputation, or target lesion revascularization

**PRIMARY EFFECTIVENESS ENDPOINT:**
Freedom from clinically driven TLR through 6 month follow-up (212 days)

Principal investigator: C. Walker/E. Dippel

252 patients enrolled between June 2011 and March 2014 in 40 clinical sites in United States

7 lesions uncrossable

252 lesions crossable by guidewire

170 ELA + PTA

Primary Safety endpoint at 37 days (n=158)

Primary Efficacy endpoint at 212 days (n=157)

82 PTA

Primary Safety endpoint at 37 days (n=77)

Primary Efficacy endpoint at 212 days (n=73)
### Baseline Lesion Characteristics

#### Angiographic Core Lab Assessment

<table>
<thead>
<tr>
<th></th>
<th>ELA + PTA (N=169)</th>
<th>PTA Alone (N=81)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Lesion Length (cm)</td>
<td>19.3</td>
<td>18.9</td>
<td>0.78</td>
</tr>
<tr>
<td>Diameter Stenosis</td>
<td>82.0 %</td>
<td>83.5 %</td>
<td>0.49</td>
</tr>
<tr>
<td>Popliteal Lesion</td>
<td>21.6 %</td>
<td>22.5 %</td>
<td>0.97</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>31.7 %</td>
<td>35.0 %</td>
<td>0.37</td>
</tr>
<tr>
<td>TASC C/D</td>
<td>58.9 %</td>
<td>54.7 %</td>
<td>0.57</td>
</tr>
<tr>
<td>Calcium (Mod/Sev)</td>
<td>27.6 %</td>
<td>10.0 %</td>
<td>0.005</td>
</tr>
<tr>
<td>≤1 runoff vessel</td>
<td>38.2 %</td>
<td>24.4 %</td>
<td>0.03</td>
</tr>
<tr>
<td>Stent Fracture</td>
<td></td>
<td></td>
<td>0.01</td>
</tr>
<tr>
<td>None</td>
<td>86.0 %</td>
<td>97.5 %</td>
<td></td>
</tr>
<tr>
<td>Type 1 or 2</td>
<td>11.0 %</td>
<td>2.5 %</td>
<td></td>
</tr>
<tr>
<td>Type 3, 4 or 5</td>
<td>3.0 %</td>
<td>0 %</td>
<td></td>
</tr>
</tbody>
</table>

- Longest lesions in any IDE peripheral study
- 20% of lesions > 30 cm
Laser atherectomy is superior to PTA alone for treatment of femoropopliteal ISR

<table>
<thead>
<tr>
<th></th>
<th>Laser + PTA n=170</th>
<th>PTA n=82</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean lesion length</td>
<td>19.6 cm</td>
<td>19.3 cm</td>
</tr>
<tr>
<td>Calcium (mod/sev)</td>
<td>27.6 %**</td>
<td>10.0 %</td>
</tr>
<tr>
<td>Stent Fracture</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Type 1 or 2</td>
<td>11.0 %**</td>
<td>2.5 %</td>
</tr>
<tr>
<td>Type 3, 4 or 5</td>
<td>3.0 %</td>
<td>0 %</td>
</tr>
<tr>
<td>Residual Stenosis &gt;30%</td>
<td>4.2%*</td>
<td>13.4%</td>
</tr>
<tr>
<td>Procedural Success#</td>
<td>93.5%**</td>
<td>82.7%</td>
</tr>
<tr>
<td>Bailout stenting after treatment</td>
<td>4.1%</td>
<td>11.1%</td>
</tr>
<tr>
<td>Major dissection</td>
<td>2.4%</td>
<td>7.4%</td>
</tr>
</tbody>
</table>

20% of lesions > 30 cm

*<30% residual stenosis by visual assessment without bailout procedure  
*P<0.05  
**P<0.01

![Primary Endpoints](image)

- P<0.01
- P<0.01
# 12 Month Follow Up

<table>
<thead>
<tr>
<th></th>
<th>Laser + PTA</th>
<th>PTA Alone</th>
<th>P- Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients with 12 Month Visit</strong></td>
<td>100 (59%)</td>
<td>42 (51%)</td>
<td></td>
</tr>
<tr>
<td><strong>Average Lesion Length (cm)</strong></td>
<td>19.2</td>
<td>16.3</td>
<td>0.19</td>
</tr>
<tr>
<td><strong>TASC C/D Lesion (%)</strong></td>
<td>58.9</td>
<td>20.5</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Withdrawn/ LTF</strong></td>
<td>24 (14%)</td>
<td>12 (15%)</td>
<td></td>
</tr>
<tr>
<td><strong>Survival (%)</strong></td>
<td>98.3</td>
<td>94.8</td>
<td>0.15*</td>
</tr>
<tr>
<td><strong>Freedom from TLR (%)</strong></td>
<td>53.8</td>
<td>41.7</td>
<td>0.02*</td>
</tr>
<tr>
<td><strong>Freedom from Amputation (%)</strong></td>
<td>100</td>
<td>98.5</td>
<td>0.14*</td>
</tr>
<tr>
<td><strong>WIQ Average</strong></td>
<td>60.5</td>
<td>61.5</td>
<td>0.91</td>
</tr>
<tr>
<td><strong>ABI Average</strong></td>
<td>0.8</td>
<td>0.8</td>
<td>0.58</td>
</tr>
<tr>
<td><strong>Rutherford Class Average</strong></td>
<td>1.22</td>
<td>0.93</td>
<td>0.20</td>
</tr>
<tr>
<td><strong>New Stent Fracture (%)</strong></td>
<td>2.9† (5/170)</td>
<td>3.7 (3/82)</td>
<td>na</td>
</tr>
</tbody>
</table>

* Kaplan Meier
† One 12 M stent fracture occurred in non-lased stent deployed post treatment. Four other minor stent fractures occurred at 6 and 12 M in The ELA+PTA arm. Three minor stent fractures occurred at 12 M in the PTA arm.
Freedom from TLR

Product-Limit Survival Estimates
With number of subjects at risk

p < 0.003

Dippel et al. JACC Cl. 2015;8:92-101
Freedom from MAE

Product-Limit Survival Estimates
With number of subjects at risk

Internal Field - randomization group:
1: Excimer Laser Atherectomy + PTA
2: PTA Alone

Days from Index Procedure
Survival Probability

$p < 0.001$

Dippel et al. JACC CI. 2015;8:92-101
Lesion Length and TLR

<table>
<thead>
<tr>
<th>Variable (Lesion Length)</th>
<th>Estimate</th>
<th>Lower CL</th>
<th>Upper CL</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 cm</td>
<td>0.96</td>
<td>0.43</td>
<td>2.14</td>
</tr>
<tr>
<td>15 cm</td>
<td>0.66</td>
<td>0.39</td>
<td>1.12</td>
</tr>
<tr>
<td>25 cm</td>
<td>0.46</td>
<td>0.29</td>
<td>0.70</td>
</tr>
<tr>
<td>35 cm</td>
<td>0.31</td>
<td>0.17</td>
<td>0.58</td>
</tr>
</tbody>
</table>

Dippel et al. JACC CI. 2015;8:92-101
EXCITE ISR Conclusions

EXCITE

• Laser + PTA is **superior** to PTA alone for the treatment of femoropopliteal ISR

• 1st FDA approved IDE randomized control study demonstrating the **benefits of laser atherectomy** in the lower extremities

• Laser+ PTA is the **only atherectomy treatment FDA indicated** for femoropopliteal ISR
In-Stent Restenosis

- 2.0 Turbo Elite Pilot Channel
- 8 Fr Turbo Booster
- 6.0x300 VascuTrak balloon
Before

After Laser Atherectomy

Craig Walker, MD
 Turbo-Power® Laser Catheter
DEB Experience in SFA ISR

• 3 Prospective Registries
  • IN.PACT SFA ISR
  • DEBATE-ISR
  • PLAISIR

• 4 Prospective Randomized Control Trials
  • PACUBA
  • FAIR
  • COPA CABANNA
  • ISAR-PEBIS—ongoing
IN.PACT SFA ISR

- Prospective
- Single center
- N = 39
- IN.PACT balloon
- 12 mth primary patency 92.1%
- Ave length 82.9mm

DEBATE-ISR registry

- Prospective
- Single center
- Diabetics only
- PTA historical control
- \( N = 44 \)
- IN.PACT balloon
- Restenosis
  - 18% DEB
  - 72% PTA
- Ave length 132 mm

PLAISIR registry

- Prospective
- Multi-center
- N = 45
- IN.PACT balloon
- Freedom TLR 90.5%
- Ave length 91 mm
**PACUBA study**

- Prospective
- Randomized 1:1
- Single center
- \( N = 60 \) (planned)
- EuroCor balloon
- No core lab

<table>
<thead>
<tr>
<th></th>
<th>POBA</th>
<th>DEB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients</td>
<td>15</td>
<td>21</td>
</tr>
<tr>
<td>Age (years)</td>
<td>70</td>
<td>68</td>
</tr>
<tr>
<td>Lesion length (cm)</td>
<td>8.1</td>
<td>8.5</td>
</tr>
<tr>
<td>Total occlusion</td>
<td>5</td>
<td>5</td>
</tr>
<tr>
<td>6 months PP rate</td>
<td>37%</td>
<td>78%</td>
</tr>
</tbody>
</table>
FAIR study

- Prospective
- Multi-center
- Primary end pt binary restenosis
- N = 119
- IN.PACT balloon
- Ave length 82 mm
- Core lab

*Krankberg H, et al. LINC 2015*
COPA COBANNA study

- Prospective
- Multi-center
- Primary end point LLL by DSA
- N = 88
- Cotavance balloon
- Ave length 119 mm
- Core lab

*Krankberg H, et al. LINC 2015*
Laser proven with DCBs in ISR

Van den Berg et al. n=14

- Mean lesion length: 13cm
- Technical success: 100%
  - Distal embolization occurred in 2 cases - treated successfully
- Patency at follow up
  - Primary Patency at 12 months: 100%
  - Primary Patency for duration of follow-up:
    - Average 19 months: 91.7%
    - 1 restenosis 36 months post-procedure
Laser + DCB vs. DCB Alone

• RCT laser+DCB (n=24) vs. DCB n=24
• All diabetic CLI and total occlusions
• Treated stent length and lesion length >20cm
• 100% crossing success
• Complications:
  • Distal embolizations 3:
  • Laser+DCB: 1 (4%), DCB: 2 (8%)
• Zero perforations
• Zero dissections

Gandini R et al, JET 2013;20:805-813
12 months result: Laser + DCB had much better outcomes

<table>
<thead>
<tr>
<th></th>
<th>DCB</th>
<th>Laser + DCB</th>
<th>P</th>
<th>Freedom from TLR</th>
<th>Limb Salvage</th>
<th>Freedom from amputation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patency</td>
<td>37.5%</td>
<td>66.7%</td>
<td>≤ 0.01</td>
<td>50.0%</td>
<td>83.3%</td>
<td>91.7%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.01</td>
<td>P = 0.03</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>54.2%</td>
<td>54.0%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>P = 0.03</td>
<td>P ≤ 0.03</td>
</tr>
</tbody>
</table>

Gandini R et al, JEVT 2013;20:805-813
Conclusions

- A new paradigm is emerging for the treatment of FemPop ISR
- PTA alone has failed against 3 different treatment strategies
- DCB is effective for lesions less than 10cm
  - More data is needed for Tosaka 3, cost effectiveness
- Both laser atherectomy and Viabahn are effective for long lesions
  - Both are FDA approved for ISR
- Combination therapy needs further investigation