Intravascular Lithotripsy for Peripheral Artery Calcification

The Disrupt PAD III Randomized Controlled Trial
30-day Outcomes

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Faculty Disclosure

William A. Gray, MD

For the 12 months preceding this CME activity, I or my spouse/partner disclose the following types of financial relationships:

- Honoraria received from: None
- Consulted for: Shockwave Medical
- Held common stock in: None
- Research, clinical trial, or drug study funds received from: Shockwave Medical

I will not be discussing products that are investigational or not labeled for use under discussion.
Endovascular Treatment for Calcified PAD

• The presence of calcified PAD*:  
  • Restricts arterial compliance  
  • Results in poor balloon expansion, dissections and acute procedural failure  
  • May impair effectiveness of DCBs by limiting drug uptake  
  • Stents to address PTA failure may fracture and complicate future revascularization

• Distal embolization, dissection and perforation remain a concern with atherectomy treatment

• Patients with moderate-severe calcification are often excluded from endovascular treatment trials resulting in little available evidence to provide treatment guidance in this challenging patient population

*Rocha-Singh et al., Catheter Cardiovas Interv 2014; Tosaka et al, JACC 2012; Walker et al., J. Vasc Surg 2015
Intravascular Lithotripsy

Deliver catheter and inflate to low pressure
Generate sonic pressure waves using lithotripsy
Crack calcium
Safely expand the vessel

IVL
- Delivers 1 pulse/sec at effective pressure of ~50 atm
- At low balloon inflation pressure
- Fractures both superficial and deep calcium

Pre-IVL Treatment*

Post-IVL Treatment*

*Micro-CT scan analysis: R. Virmani, CV Path Institute
IVL treatment at low balloon pressure resulted in marked improvement in diameter stenosis with no stent implantation.
# Peripheral IVL Clinical Programs

<table>
<thead>
<tr>
<th></th>
<th>Disrupt PAD I</th>
<th>Disrupt PAD II</th>
<th>Disrupt BTK</th>
<th>Disrupt PAD III RCT</th>
<th>Disrupt PAD III OS</th>
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<td>Status</td>
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<td>Enrollment completed</td>
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<td>ACL</td>
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<td>ACL</td>
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<tr>
<td># of patients</td>
<td>35</td>
<td>60</td>
<td>20</td>
<td>306</td>
<td>Up to 1,500</td>
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<td># of sites</td>
<td>3</td>
<td>8</td>
<td>3</td>
<td>45</td>
<td>32</td>
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<td>NZ, EU</td>
<td>NZ, EU</td>
<td>U.S., NZ, EU</td>
<td>U.S., NZ, EU</td>
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</tbody>
</table>

*CEC: Independent clinical events committee; ACL: Angiographic core lab
**Objective**
Assess the safety and effectiveness of IVL + DCB versus PTA + DCB to treat moderately and severely calcified femoropopliteal arteries

**Statistics**
Superiority analysis performed for primary and powered secondary endpoint

**Study Design**
Prospective, multicenter, single-blind, randomized controlled trial

NCT02923193

**Moderate-severe calcium de novo femoropopliteal arteries**
N = 306, 45 global sites

**Randomized Cohort 1:1**

- **IVL**
  - N = 153
  - IN.PACT DCB +/- stent
  - 30-day Follow-up
  - 6-month, 1-year, 2-year Follow-up

- **PTA**
  - N= 153
Study Endpoints

Primary Endpoint: **Procedural success**
- Residual stenosis ≤ 30% without flow-limiting dissection (≥ grade D) prior to DCB +/- stenting by angiographic core lab

Secondary Endpoints at 30 days:
- Major Adverse Events*
- CD-TLR
- ABI, RC, WIQ

Powered Secondary Endpoint at 12 months: **Primary patency**
- Acute PTA failure† requiring a stent at any time during the index procedure will be counted as a loss of primary patency
- Freedom from CD-TLR and freedom from restenosis determined by DUS or angiogram ≥50% stenosis

*MAE: Need for emergency surgical revascularization of target limb, unplanned target limb major amputation, thrombus or distal emboli requiring intervention to improve flow, perforations that require intervention including bail-out stenting.
†PTA failure defined as residual stenosis ≥50% by visual estimate, or unresolved flow-limiting (≥grade D) dissection, and trans-lesional gradient >10mmHg.
Key Clinical and Angiographic Eligibility Criteria

Inclusion
- Rutherford category 2, 3 or 4 of the target limb
- Target lesion is *de novo* SFA or popliteal artery
- Target lesion
  - RVD ≥ 4.0mm and ≤7.0mm
  - Stenosis ≥ 70% by visual estimate
  - Length ≤ 180mm for lesions 70-99% stenosis
  - CTO lesion length ≤ 100mm of the total ≤ 180mm target lesion
- Calcification ≥ moderate defined as presence of fluoroscopic evidence of calcification:
  - On parallel sides of the vessel and
  - Extending >50% of lesion length (if length ≥50mm) or minimum calcification of 20mm (if length <50mm)

Exclusion
- Rutherford category 0, 1, 5 and 6
- Significant stenosis (>50%) or occlusion of inflow tract before target zone not successfully treated
- Planned target limb major amputation
- Renal disease (SCr >2.5 mm/dl) or on dialysis
- In-stent restenosis within 10mm of target zone
- Lesions within 10mm of the ostium of the SFA or anterior tibial artery
# Study Support

| Principal Investigators          | William A. Gray, MD  
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|                                | Yale Cardiovascular Research Group, New Haven, CT  
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| Management and Statistics       | Clinlogix, Lower Gwynedd, PA  

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Mount Sinai West

Vince Varghese
Deborah Heart and Lung Center

Mohammad Al Madani
Einstein Medical Center
Patients enrolled from February 2017 to May 2020
N = 306

IVL
N = 153

PTA
N = 153

Primary Endpoint Analysis
Images available
N = 146

Withdrawn (n=1)

30-day Clinical Follow-up
N = 152

Primary Endpoint Analysis
Images available
N = 133

Withdrawn (n=1)

30-day Clinical Follow-up
N = 152
## Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IVL (N=153)</th>
<th>PTA (N=153)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.2 ± 8.0</td>
<td>71.5 ± 7.7</td>
<td>0.41</td>
</tr>
<tr>
<td>Male</td>
<td>69.3%</td>
<td>78.4%</td>
<td>0.07</td>
</tr>
<tr>
<td>Hypertension</td>
<td>94.8%</td>
<td>94.1%</td>
<td>0.80</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>86.3%</td>
<td>86.3%</td>
<td>0.60</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.3%</td>
<td>28.1%</td>
<td>0.05</td>
</tr>
<tr>
<td>Diabetes</td>
<td>41.8%</td>
<td>46.4%</td>
<td>0.72</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>25.5%</td>
<td>24.2%</td>
<td>0.97</td>
</tr>
<tr>
<td>Coronary artery disease</td>
<td>66.7%</td>
<td>58.2%</td>
<td>0.21</td>
</tr>
<tr>
<td>Renal insufficiency</td>
<td>24.2%</td>
<td>16.3%</td>
<td>0.13</td>
</tr>
<tr>
<td>History of CVA or TIA</td>
<td>12.4%</td>
<td>11.1%</td>
<td>0.85</td>
</tr>
<tr>
<td>ABI</td>
<td>0.74 ± 0.20</td>
<td>0.77 ± 0.25</td>
<td>0.25</td>
</tr>
<tr>
<td>WIQ – overall</td>
<td>26.0 ± 20.9</td>
<td>26.5 ± 22.0</td>
<td>0.84</td>
</tr>
</tbody>
</table>

### Rutherford Category

<table>
<thead>
<tr>
<th>Category</th>
<th>IVL (%)</th>
<th>PTA (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>RC 5</td>
<td>6%</td>
<td>8%</td>
<td>0.56</td>
</tr>
<tr>
<td>RC 4</td>
<td>77%</td>
<td>74%</td>
<td></td>
</tr>
<tr>
<td>RC 3</td>
<td>17%</td>
<td>17%</td>
<td></td>
</tr>
<tr>
<td>RC 2</td>
<td>0%</td>
<td>20%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>20%</td>
<td>40%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>60%</td>
<td>80%</td>
<td></td>
</tr>
<tr>
<td></td>
<td>100%</td>
<td></td>
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</tbody>
</table>
## Baseline Lesion Characteristics

**Core lab adjudicated**

<table>
<thead>
<tr>
<th></th>
<th>IVL N=153</th>
<th>PTA N=153</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter, mm</td>
<td>5.3 ± 0.8</td>
<td>5.4 ± 0.8</td>
<td>0.68</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>0.81 ± 0.67</td>
<td>0.83 ± 0.76</td>
<td>0.77</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>85% ± 12%</td>
<td>85% ± 14%</td>
<td>0.76</td>
</tr>
<tr>
<td>CTO</td>
<td>26%</td>
<td>31%</td>
<td>0.39</td>
</tr>
<tr>
<td>Lesion length, mm</td>
<td>101 ± 41</td>
<td>97 ± 42</td>
<td>0.37</td>
</tr>
<tr>
<td>Lesion length &gt;150mm</td>
<td>12%</td>
<td>11%</td>
<td>0.72</td>
</tr>
<tr>
<td>Calcified length, mm</td>
<td>129 ± 51</td>
<td>125 ± 48</td>
<td>0.40</td>
</tr>
</tbody>
</table>

**Calcification**

- None/Mild: 0.7% IVL, 0.7% PTA, P=0.23
- Moderate: 16.4% IVL, 9.8% PTA
- Severe: 82.9% IVL, 89.5% PTA
- Eccentric: 22.4% IVL, 17.6% PTA, P=0.30

*PARC definition of calcium severity

### Arterial Segment

<table>
<thead>
<tr>
<th>Arterial Segment</th>
<th>IVL</th>
<th>PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA - Proximal</td>
<td>18%</td>
<td>10%</td>
</tr>
<tr>
<td>SFA - Mid</td>
<td>35%</td>
<td>40%</td>
</tr>
<tr>
<td>SFA - Distal</td>
<td>39%</td>
<td>48%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>7%</td>
<td>3%</td>
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P=0.03
### Procedural Characteristics

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<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Contrast volume, ml</td>
<td>138 ± 73</td>
<td>129 ± 61</td>
<td>0.26</td>
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<tr>
<td>Fluoroscopy time, min</td>
<td>16.6 ± 11.0</td>
<td>13.5 ± 10.1</td>
<td>0.01</td>
</tr>
<tr>
<td>Embolic protection used</td>
<td>1.3%</td>
<td>4.6%</td>
<td>0.09</td>
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<td>Pre-dilatation</td>
<td>17.6%</td>
<td>15.0%</td>
<td>0.54</td>
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<tr>
<td>Post-dilatation*</td>
<td>5.2%</td>
<td>17.0%</td>
<td>0.001</td>
</tr>
<tr>
<td>Stent placed†</td>
<td>4.6%</td>
<td>18.3%</td>
<td>0.0002</td>
</tr>
<tr>
<td>Number of treatment balloons</td>
<td>1.6 ± 0.8</td>
<td>1.3 ± 0.6</td>
<td>0.005</td>
</tr>
<tr>
<td>Total number of pulses</td>
<td>228 ± 115</td>
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Significantly lower maximum inflation pressure used with a 75% relative risk reduction for stent placement with IVL

*Performed with semi or NC PTA balloon if: RS >30% by visual estimate, or presence of ≥type D dissection and trans-lesional gradient > 10 mmHg
†Provisional stent placed if: RS ≥50% by visual estimate, or unresolved ≥ type D dissection and trans-lesional gradient > 10 mmHg
Post-treatment % Diameter Stenosis
Core lab adjudicated

Significant reduction in post-treatment diameter stenosis in IVL group
Post-treatment Angiographic Complications
Core lab adjudicated

<table>
<thead>
<tr>
<th>Type</th>
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<th>PTA</th>
<th>P-value</th>
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<tr>
<td>A</td>
<td>2.1%</td>
<td>4.5%</td>
<td>0.31</td>
</tr>
<tr>
<td>B</td>
<td>13.0%</td>
<td>12.8%</td>
<td>1.0</td>
</tr>
<tr>
<td>C</td>
<td>8.3%</td>
<td>6.8%</td>
<td>0.03</td>
</tr>
<tr>
<td>D</td>
<td>1.4%</td>
<td>1.0</td>
<td>0.03</td>
</tr>
</tbody>
</table>

Freedom from any dissection
IVL = 81.5%
PTA = 67.7%

Dissection ≥ Grade C
IVL = 3.5%
PTA = 15.1%
↓ 77% Relative Risk

Significant reduction in the frequency and severity of dissections with IVL

*No occurrence of thrombus, abrupt closure, no-reflow, distal emboli or perforation in both study arms
Primary Endpoint

Procedural success: Residual stenosis ≤ 30% without flow-limiting dissection (≥ grade D) prior to DCB +/- stenting by ACL

**Site Reported**

- **Procedural success (%)**
  - IVL: 90.1%
  - PTA: 64.5%

  Treatment effect: 25.6% [16.5%, 34.4%]

  **P<0.0001**

**Angiographic Core Lab**

- **Procedural success (%)**
  - IVL: 65.8%
  - PTA: 50.4%

  Treatment effect: 15.4% [3.9%, 26.8%]

  **P=0.0065**

Superior procedural success with IVL by Site and Core Lab adjudication.
### Final Angiographic and Clinical Outcomes

<table>
<thead>
<tr>
<th></th>
<th>IVL N=153</th>
<th>PTA N=153</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td>Final angiographic outcomes’</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter, mm</td>
<td>5.4 ± 0.8</td>
<td>5.4 ± 0.8</td>
<td>0.62</td>
</tr>
<tr>
<td>Minimum lumen diameter, mm</td>
<td>4.2 ± 0.7</td>
<td>4.3 ± 0.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Diameter stenosis</td>
<td>22% ± 8%</td>
<td>21% ± 9%</td>
<td>0.39</td>
</tr>
<tr>
<td>Acute gain, mm</td>
<td>3.4 ± 0.8</td>
<td>3.5 ± 0.9</td>
<td>0.63</td>
</tr>
<tr>
<td>Dissection</td>
<td></td>
<td></td>
<td>0.47</td>
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<tr>
<td>None</td>
<td>83.9%</td>
<td>77.2%</td>
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<tr>
<td>Type A/B/C</td>
<td>16.1%</td>
<td>22.8%</td>
<td></td>
</tr>
<tr>
<td>Type D</td>
<td>0.0%</td>
<td>0.0%</td>
<td></td>
</tr>
<tr>
<td>30-day clinical outcomes</td>
<td></td>
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</tr>
<tr>
<td>ABI</td>
<td>0.97 ± 0.18</td>
<td>0.99 ± 0.16</td>
<td>0.33</td>
</tr>
<tr>
<td>WIQ – overall</td>
<td>51.2 ± 30.3</td>
<td>52.9 ± 31.5</td>
<td>0.64</td>
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</tbody>
</table>

*Radiographic core lab adjudicated

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**Rutherford Category**

```
<table>
<thead>
<tr>
<th>Category</th>
<th>IVL</th>
<th>PTA</th>
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<tbody>
<tr>
<td>RC 5</td>
<td>10%</td>
<td>6%</td>
</tr>
<tr>
<td>RC 3</td>
<td>12%</td>
<td>10%</td>
</tr>
<tr>
<td>RC 2</td>
<td>63%</td>
<td>59%</td>
</tr>
<tr>
<td>RC 1</td>
<td>15%</td>
<td>25%</td>
</tr>
<tr>
<td>RC 0</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>
```

P=0.69

---

William A. Gray, MD

CME Accredited
## 30-Day Safety Endpoints

CEC adjudicated

<table>
<thead>
<tr>
<th></th>
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<th>PTA</th>
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<tbody>
<tr>
<td><strong>MAE</strong></td>
<td>0.0%</td>
<td>1.3%</td>
</tr>
<tr>
<td><strong>Emergency Revascularization</strong></td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Major Amputation</strong></td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
<tr>
<td><strong>Thrombus/ Distal emboli</strong></td>
<td>0.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>Perforation</strong></td>
<td>0.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td><strong>CD-TLR</strong></td>
<td>0.7%</td>
<td>0.7%</td>
</tr>
</tbody>
</table>

*P = NS for all endpoints*
PAD III Observational Study
Core lab adjudicated

Diameter Stenosis (%)

<table>
<thead>
<tr>
<th></th>
<th>PAD III RCT</th>
<th>PAD III OS*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter Stenosis (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pre-procedure</td>
<td>85.0%</td>
<td>80.7%</td>
</tr>
<tr>
<td>Post-IVL</td>
<td>27.3%</td>
<td>30.8%</td>
</tr>
<tr>
<td>Final</td>
<td>21.5%</td>
<td>23.6%</td>
</tr>
</tbody>
</table>

Consistent outcomes from clinical trial to real world environment

Final Angiographic Complications

<table>
<thead>
<tr>
<th></th>
<th>PAD III RCT</th>
<th>PAD III OS*</th>
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<tbody>
<tr>
<td>Dissection (Type D-F)</td>
<td>0%</td>
<td>1.1%</td>
</tr>
<tr>
<td>Perforation</td>
<td>0%</td>
<td>0.5%†</td>
</tr>
<tr>
<td>Embolization</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Thrombus</td>
<td>0%</td>
<td>0%</td>
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<tr>
<td>No reflow</td>
<td>0%</td>
<td>0%</td>
</tr>
<tr>
<td>Abrupt closure</td>
<td>0%</td>
<td>0%</td>
</tr>
</tbody>
</table>

†Following DCB inflation; unrelated to IVL

Conclusions

• Disrupt PAD III RCT provides the largest level I evidence for the treatment of heavily calcified femoropopliteal arteries, a cohort often excluded from trials

• IVL was superior to PTA in acute procedural success and demonstrated atraumatic treatment:
  • Reduction in % diameter stenosis prior to DCB or stent placement
  • Lower maximum inflation pressure
  • Reduction in frequency and severity of dissections
  • Lower post-dilatation and stent implantation rate

• RCT outcomes are similar to PAD III registry in multiple vessel beds highlighting the consistency of IVL treatment in complex anatomy

• Powered secondary endpoint of primary patency at 12 months will be analyzed following appropriate follow-up for all enrolled patients