Vessel Preparation Has DEFINITIVE LE and DEFINITIVE AR Results Influenced Current Practice?

Lawrence Garcia, MD
St. Elizabeth’s Medical Center
Boston, MA, USA
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abbott, Covidien/Medtronic</td>
</tr>
<tr>
<td>Consulting (non-compensated)</td>
<td>Covidien/Medtronic, Boston Scientific, Abbott</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity</td>
<td>Arsenal, Primacea, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical</td>
</tr>
<tr>
<td>Royalty Income</td>
<td>None</td>
</tr>
<tr>
<td>Ownership/Founder</td>
<td>None</td>
</tr>
<tr>
<td>Intellectual Property Rights</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td>None</td>
</tr>
</tbody>
</table>
Vessel Prep: What Does It Mean?

Vessel prep is improving the local environment of the vessel prior to leaving something behind, whether that something is a stent or a non-stent anti-proliferative agent.

Vessel Compliance and/or Lumen Gain

Drug Transfer and Uptake

Directional Atherectomy achieves lumen gain by reducing plaque burden through debulking.
## Available Solo Atherectomy Data

<table>
<thead>
<tr>
<th>Study (*Core Lab)</th>
<th>Type</th>
<th>Patients</th>
<th>Lesions</th>
<th>Dissection (≥Grade D)</th>
<th>BO Stent</th>
<th>30-day MAE</th>
<th>Patency 1-year</th>
<th>Patency &gt;1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DEFINITIVE LE(^1)</td>
<td>DA</td>
<td>598 (RCC 1-3) 201 (RCC 4-6)</td>
<td>743 279</td>
<td>2.2% (13/598) 2.5% (5/201)</td>
<td>3.2% (33/1022)</td>
<td>1.0% (6/598) 3.5% (7/201)</td>
<td>78% 71%</td>
<td>?</td>
</tr>
<tr>
<td>*DEFINITIVE CA(^2)</td>
<td>DA</td>
<td>133</td>
<td>168</td>
<td>0.8% (1/131)</td>
<td>4.1% (7/169)</td>
<td>6.9% (9/131)</td>
<td>NR</td>
<td>?</td>
</tr>
<tr>
<td>VISION-IDE(^3)</td>
<td>DA</td>
<td>130</td>
<td>130</td>
<td>NR</td>
<td>4.0%</td>
<td>17.6% (6-mo)</td>
<td>NR</td>
<td>?</td>
</tr>
<tr>
<td>OASIS(^4)</td>
<td>OA</td>
<td>124</td>
<td>201</td>
<td>NR</td>
<td>2.5% (5/201)</td>
<td>3.2% (4/124)</td>
<td>NR</td>
<td>?</td>
</tr>
<tr>
<td>COMPLIANCE 360(^5)</td>
<td>OA</td>
<td>25</td>
<td>38</td>
<td>NR</td>
<td>5.3% (2/38)</td>
<td>NR</td>
<td>81.2%</td>
<td>?</td>
</tr>
<tr>
<td>CALCIUM 360(^6)</td>
<td>OA</td>
<td>25</td>
<td>29</td>
<td>3.5% (1/29)</td>
<td>6.9% (2/29)</td>
<td>0%</td>
<td>NR</td>
<td>?</td>
</tr>
<tr>
<td>*PATHWAY PVD(^7)</td>
<td>RA</td>
<td>172</td>
<td>210</td>
<td>9% (15/172)</td>
<td>7% (14/210)</td>
<td>1.0% (2/172)</td>
<td>61.8%</td>
<td>?</td>
</tr>
<tr>
<td>*CELLO(^8)</td>
<td>Las</td>
<td>65</td>
<td>65</td>
<td>NR</td>
<td>23.2% (15/65)</td>
<td>0%</td>
<td>54.3%</td>
<td>?</td>
</tr>
<tr>
<td>*EXCITE-ISR(^9)</td>
<td>Las</td>
<td>169</td>
<td>169</td>
<td>2.4% (≥Grade C)</td>
<td>4.1% (7/169)</td>
<td>5.8% (9/155)</td>
<td>71.1% (6-mo)</td>
<td>?</td>
</tr>
</tbody>
</table>

DEFINITIVE LE: Trial Overview

**DESIGN**
- Prospective, multinational, single-arm study
- Clinical events committee (CEC) adjudicated adverse events
- Largest Core Lab\(^1\) adjudicated atherectomy trial

**OBJECTIVE**
To evaluate the effectiveness of standalone SilverHawk™ and TurboHawk™ Peripheral Plaque Excision Systems for endovascular treatment of peripheral arterial disease in the femoropopliteal and tibioperoneal arteries

**PATIENTS**
- 800 PATIENTS
- Pre-specified comparison of patients with / without diabetes

**SITES**
47 total sites in EU and US

---

1. VasCore DUS Core Laboratory, Boston, MA and SynvaCor Angiographic Core Laboratory, Springfield, IL.
DEFINITIVE LE: Design & Endpoints

800 Patients | 47 Centers

Claudication
598 Patients

Primary Patency by
Duplex US at 12 months

Critical Limb Ischemia
201 Patients

Freedom From Major Unplanned Amputation at 12 months

1. Censored due to informed consent violation.
### Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th>Lesion Characteristic</th>
<th>Claudicant  n = 598</th>
<th>CLI  n = 201</th>
<th>P value</th>
<th>All Patients  n = 799</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Number of Lesions</strong></td>
<td>743</td>
<td>279</td>
<td>n/a</td>
<td>1022</td>
</tr>
<tr>
<td><strong>Mean Length (cm ± SD)</strong></td>
<td>7.5 ± 5.3</td>
<td>7.2 ± 5.5</td>
<td>0.381</td>
<td>7.4 ± 5.3</td>
</tr>
<tr>
<td><strong>Baseline Stenosis ± SD</strong></td>
<td>72.7% ± 18.1</td>
<td>75.9% ± 20.0</td>
<td>0.015</td>
<td>73.6% ± 18.7</td>
</tr>
<tr>
<td><strong>Oclusions</strong></td>
<td>17.4%</td>
<td>29.9%</td>
<td>&lt;0.001</td>
<td>20.8%</td>
</tr>
<tr>
<td><strong>Calcification</strong></td>
<td>37.1%</td>
<td>37.1%</td>
<td>1.000</td>
<td>37.1%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Lesion Location</th>
<th>Claudicant  n = 743 lesions</th>
<th>CLI  n = 279 lesions</th>
<th>P value</th>
<th>All Patients  n = 1022 lesions</th>
</tr>
</thead>
<tbody>
<tr>
<td>SFA</td>
<td>72.1%</td>
<td>48.4%</td>
<td>&lt;0.001</td>
<td>65.7%</td>
</tr>
<tr>
<td>Popliteal</td>
<td>15.3%</td>
<td>17.2%</td>
<td>0.501</td>
<td>15.9%</td>
</tr>
<tr>
<td>Infrapopliteal</td>
<td>12.5%</td>
<td>34.4%</td>
<td>&lt;0.001</td>
<td>18.5%</td>
</tr>
</tbody>
</table>

---

## DEFINITIVE LE:
Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Claudicant n = 598</th>
<th>CLI n = 201</th>
<th>P value</th>
<th>All Patients n = 799</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Device Success</strong></td>
<td>75.9%</td>
<td>72.1%</td>
<td>0.218</td>
<td>74.9%</td>
</tr>
<tr>
<td><strong>Post-device stenosis ± SD</strong></td>
<td>23.9% ± 13.1</td>
<td>25.6% ± 13.8</td>
<td>0.073</td>
<td>24.3% ± 13.3</td>
</tr>
<tr>
<td><strong>Adjunctive therapy</strong></td>
<td>38.0%</td>
<td>30.2%</td>
<td>NR</td>
<td>35.3%</td>
</tr>
<tr>
<td><strong>Procedure Success</strong></td>
<td>91.3%</td>
<td>83.0%</td>
<td>&lt;0.001</td>
<td>89.1%</td>
</tr>
<tr>
<td><strong>Post-adjunctive stenosis ± SD</strong></td>
<td>18.0% ± 11.0</td>
<td>20.9% ± 12.3</td>
<td>0.045</td>
<td>18.6% ± 11.4</td>
</tr>
</tbody>
</table>

### Flow-limiting dissections
- 598 (RCC 1-3) = 2.2%
- 201 (RCC 4-6) = 2.5%

### Additional interventions
- Pre-dilatation: 9%
- Post-dilatation: 33%
- Bail-out stenting: 3%

---

2. Core lab adjudicated device success: ≤30% angiographic residual stenosis after directional atherectomy without adjunctive interventions
3. Core lab adjudicated adjunctive therapy: PTA, stent
4. Core lab adjudicated procedure Success: ≤30% angiographic residual stenosis after directional atherectomy and adjunctive interventions
While directional atherectomy demonstrates compelling 12-mo outcomes, adjunctive value may come in the form of low dissection and bail-out stent rates.

2. Kaplan-Meier estimate of primary patency by duplex ultrasound at 12 months (PSVR ≤2.4 with no clinically-driven reintervention).
DCB Data Synopsis

- DCBs demonstrate safety and effectiveness in RCTs and registries
- DCB use in real-world registries enrolling more complex disease is associated with increased provisional stenting

Patient demographics, lesion morphologies, patency definitions, and follow-up vary across trials.

5. IN.PACT™ Admiral Instructions for Use, M052624T001_Rev1F_EN, Figure 10.
8. Lutonix™ 035 Instructions for Use, BAW 1387400r3 Section 10.5.

12-mo Primary Patency Rates
[and mean lesion lengths (cm); Core Lab-Adjudicated]
Known Limitations of DCB

- Calcium distribution and severity may affect late lumen loss (LLL) and primary patency
- Calcium may represent a barrier to optimal drug absorption

Existing Atherectomy + DCB Data

Few reports – Two single-center studies and one randomized feasibility study

<table>
<thead>
<tr>
<th>Study (* Core Lab)</th>
<th>Type</th>
<th>Patients</th>
<th>Lesions</th>
<th>Dissection(^6)</th>
<th>BO Stent</th>
<th>30-day MAE</th>
<th>Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DEFINITIVE AR(^1)</td>
<td>DCB(^\dagger) DAART(^\dagger) DAART-Ca</td>
<td>54 48 19</td>
<td>54 48 19</td>
<td>19% (10/54) 2% (1/48) 0%</td>
<td>3.7% (2/54) 0% 5.3% (1/19)</td>
<td>NR</td>
<td>89.6% 93.4% ---</td>
</tr>
<tr>
<td>Cioppa(^2)</td>
<td>DAART</td>
<td>30</td>
<td>30</td>
<td>6.7% (2/30)</td>
<td>6.7% (2/30)</td>
<td>13% (4/30) (1-year)</td>
<td>90%</td>
</tr>
<tr>
<td>Stavroulakis(^3) (Popliteal)</td>
<td>DAART</td>
<td>21</td>
<td>26</td>
<td>NR</td>
<td>NR</td>
<td>14% (3/21)</td>
<td>95% 90% (18-mo)</td>
</tr>
<tr>
<td>Foley(^4)</td>
<td>DCB OA+DCB</td>
<td>61 28</td>
<td>99 40</td>
<td>14% (14/99) 13% (5/40)</td>
<td>39% (39/99) 18% (7/40)</td>
<td>NR</td>
<td>81% 77%</td>
</tr>
<tr>
<td>Stavroulakis(^4) (CFA)</td>
<td>DCB DAART</td>
<td>26 21</td>
<td>26 21</td>
<td>31% (8/26) 5% (1/21)</td>
<td>4% (1/26) 5% (1/21)</td>
<td>NR</td>
<td>68% 88%</td>
</tr>
</tbody>
</table>

---

6. Zeller, et al., defined dissection as ≥ Grade C while Cioppa, et al., defined dissection via chroma-flow involving more than 60% of cross-sectional diameter with blood flow in the false lumen.
DEFINITIVE AR\textsuperscript{1}

Prospective, multicenter, randomized (DAART v DCB); plus non-randomized DAART arm for severely calcified lesions

- 121 subjects enrolled at 10 sites
- RCC 2-4; lesion lengths 7-15cm [excluding ISR, aneurysmal target sites and multi-lesion limbs]
- Independent CEC, and angiographic and DUS core labs
- Pilot study designed to assess effect of DAART v DCB
  - Not statistically powered
  - Motivated by determining trends that may foster development of future studies

\textsuperscript{1} “DEFINITIVE AR: A Pilot Study of Antirestenosis Treatment. 12-month Results: Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency” presented by Zeller T, VIVA Las Vegas 2014.
“DEFINITIVE AR: A Pilot Study of Antirestenosis Treatment. 12-month Results: Directional Atherectomy Followed by a Paclitaxel-Coated Balloon to Inhibit Restenosis and Maintain Vessel Patency” presented by Zeller T, VIVA Las Vegas 2014.
DEFINITIVE AR¹

- Patency rates generally favorable
- Lower residual stenosis trended toward higher patency rates

DEFINITIVE AR: 2-year Extension

DEFINITIVE AR was extended beyond its originally-designed 1-year follow-up to 2 years. 

Extended endpoints included:
- Major Adverse Event Rate at 2 Years: Defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
- Change in WIQ/EQ-5D Score at 2 Years
- Target Lesion Revascularization (TLR) at 2 Years

121 Patients
1 year

53 Patients
2 years

DEFINITIVE AR: 2-year Extension

2. MAE (Major Adverse Event) defined as major unplanned amputation of the treated limb, all-cause mortality or clinically-driven target lesion revascularization.
3. Clinically-driven TLR (target lesion revascularization) defined as any reintervention or artery bypass graft surgery involving the target lesion in which the subject has a ≥ 70% diameter stenosis (Peak Systolic Velocity Ratio (PSVR) > 3.5 may substitute if a pre-intervention angiogram is not available) and at least two of the following: worsening RCC, worsening WIQ score, or an ABI drop > 0.15 from baseline.
DEFINITIVE AR: 2-year Extension

Impact of lumen gain at 2 years: trend towards lower TLR with ≤30% residual stenosis after DA

Summary

• Vessel preparation is a critical step in enhancing outcomes independent of a drug, a stent, or both being “left behind”
• Directional atherectomy has demonstrated low dissection and bailout stent rates in the 800-subject DEFINITIVE LE study
• Since calcium may be a potential barrier to DCB effectiveness, atherectomy enhance DCB outcomes by establishing lumen gain and potentially increasing drug uptake
• The promise of atherectomy + DCB for femoropopliteal artery lesions is demonstrated in only a few studies, of which one is a multi-center core lab-adjudicated pilot study
• The marriage of atherectomy and DCB may bring together the best of two worlds – effective plaque modification/debulking paired with sustained drug presence
• While limited data show promise, understanding “what is optimal vessel prep” prior to DCB or DES use requires more comprehensive data and longer follow-up
Vessel Preparation
Has DEFINITIVE LE and DEFINITIVE AR Results Influenced Current Practice?

Lawrence Garcia, MD
St. Elizabeth’s Medical Center
Boston, MA, USA