Vessel Preparation:
What does it mean and what are the current tools?

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# Disclosure Statement of Financial Interest

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<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
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<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>
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<tr>
<td>Major Stock Shareholder/Equity</td>
<td>Arsenal, Primacea, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical</td>
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<tr>
<td>Royalty Income</td>
<td>None</td>
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<tr>
<td>Ownership/Founder</td>
<td>None</td>
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<tr>
<td>Intellectual Property Rights</td>
<td>None</td>
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<tr>
<td>Other Financial Benefit</td>
<td>None</td>
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</tbody>
</table>
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.
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

Vessel Prep: What Does It Mean?

- Debulking to increase luminal gain prior to DCB use?¹,²
- Plaque modification to enhance drug uptake?³,⁴
- Plaque modification to combat flow-limiting dissections?⁵

_Honestly…no one knows_
Tools for Vessel Preparation

Balloons
- Plain Old Balloon Angioplasty
- Cutting Balloons
- Scoring Balloons
- Controlled-inflation Balloon

Atherectomy Devices
- Directional
- Orbital
- Rotational
- Photoablative
Optimal PTA: Effect of Short vs Long Balloon Inflation Times on the Morphologic Results

- Inflation times of 180s improve immediate infrainguinal PTA results vs. 30s dilations
- Significantly fewer major dissections and a modest reduction of residual stenoses are observed
- Significantly fewer continued interventions (e.g. provisional stenting)

<table>
<thead>
<tr>
<th>Inflation Time (sec)</th>
<th>30</th>
<th>180</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major dissection (grades 3 or 4)</td>
<td>16</td>
<td>5</td>
<td>.010</td>
</tr>
<tr>
<td>Minor or no dissection (grades 1 and 2)</td>
<td>21</td>
<td>32</td>
<td>.010</td>
</tr>
<tr>
<td>Further interventions (Stent, repeat dilatation, dilation with larger diameter)</td>
<td>20</td>
<td>9</td>
<td>.017</td>
</tr>
<tr>
<td>Residual stenosis (&gt;30%)</td>
<td>12</td>
<td>5</td>
<td>.097</td>
</tr>
<tr>
<td>Complication (embolization, thrombosis)</td>
<td>1</td>
<td>1</td>
<td>-</td>
</tr>
<tr>
<td>Mean ankle-brachial index (before, after intervention)</td>
<td>0.66, 0.87</td>
<td>0.65, 0.84</td>
<td></td>
</tr>
</tbody>
</table>
Specialty Balloons

• Specialty balloons aim at modifying/dilating plaque to achieve luminal gain during dilatation and potentially reduce dissections or bail-out stenting
  – In cutting / scoring balloons, blades create fissures in plaque that are intended to facilitate expansion during dilatation
  – In controlled-inflation angioplasty, constraining wire cage is designed to reduce potential dissection points, e.g. ends of balloon (dog-boning) and throughout the contact of the balloon surface with intima

• Very limited data are available describing the use of these devices in conjunction with DCB
<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>*DEFINITIVE LE¹</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% 71%</td>
</tr>
<tr>
<td>*DEFINITIVE CA²</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 78% 71%</td>
</tr>
<tr>
<td>VISION-IDE³</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 78% 71%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.5%</td>
<td></td>
<td>2.2%</td>
<td></td>
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</tbody>
</table>

It’s possible that atherectomy may complement DCB use in real-world lesions by reducing dissection rate and bail-out stenting.

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<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</th>
</tr>
</thead>
<tbody>
<tr>
<td>CALCIUM 360⁶</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 78% 71%</td>
</tr>
<tr>
<td>*PATHWAY PVD⁷</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% 71%</td>
</tr>
<tr>
<td>*CELLO⁸</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% 71%</td>
</tr>
<tr>
<td>*EXCITE-ISR⁹</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% 71%</td>
</tr>
</tbody>
</table>

**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 1-year</th>
<th>&gt;1-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>*<strong>DEFINITIVE AR</strong>(^1)</td>
<td>DCB(^†)</td>
<td>54</td>
<td>54</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>
<td>?</td>
</tr>
<tr>
<td></td>
<td>DAART(^†)</td>
<td>48</td>
<td>48</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>DAART-Ca</td>
<td>19</td>
<td>19</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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>
<td>?</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%</td>
<td>90% (18-mo)</td>
</tr>
<tr>
<td>Foley(^4)</td>
<td>DCB</td>
<td>61</td>
<td>99</td>
<td>14% (14/99) 13% (5/40)</td>
<td>39% (39/99) 18% (7/40)</td>
<td>NR</td>
<td>81% 77%</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>OA+DCB</td>
<td>28</td>
<td>40</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stavroulakis(^4) (CFA)</td>
<td>DCB</td>
<td>26</td>
<td>26</td>
<td>31% (8/26) 5% (1/21)</td>
<td>4% (1/26) 5% (1/21)</td>
<td>NR</td>
<td>68% 88%</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td>DAART</td>
<td>21</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></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}

- 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\(^1\)

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

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

Cioppa, et al., DAART Study

Prospective, single-center study to characterize conjunctive DA + DCB use in severely calcified lesions

Procedural Characteristics (n=30)
- Mean lesion length: 115mm
- Total occlusion: 13.3% (4)
- < 30% residual stenosis achieved in all cases
- No procedure-related AEs
- Provisional stenting rate: 6.7% (2) [due to flow limiting dissections]

12-mo Results (n=30)
- 1° patency (PSVR<2.5): 90% (27)
- TLR: 10% (3)
- Limb salvage: 100% (12 CLI Pts)

Calcium defined as 1 cm on both sides of lesion

Foley, et al., OA+DCB Study

*Retrospective*, single-center study comparing DCB outcomes in subjects treated with or without adjunctive orbital atherectomy (OA)

**Procedural Characteristics (n=89)**
- 28 patients treated with OA (40 lesions); 61 patients treated with OA+DCB (99 lesions)
- Lesion length: 13.5cm in OA+DCB group and 13.9cm in DCB group
- Scoring balloon utilization was statistically higher and stent placement statistically lower in the OA+DCB cohort versus the DCB-only cohort

**Outcomes**
- Calcium severity was statistically significantly higher in the OA+DCB group versus the DCB-only group
  - Longer and more circumferential calcium in the combination group
- 12-mo results
  - Freedom from TLR was 82% in both groups
  - Primary patency rate was 77% in OA+DCB and 81% in DCB-alone

Stavroulakis, et al., CFA Study

Prospective, single-center study to characterize conjunctive DA (SH or PTh) + DCB use in common femoral artery lesions

Procedural Characteristics (n=47)
- Lesion lengths averaged 3.9cm and 3.4cm in the DCB and DAART groups, respectively
- Four occlusion were present in the DAART arm (none in the DCB group)
- Technical success: 88% and 95% in the DCB and DAART groups, respectively
- Bail-out stenting occurred once in each arm (not statistically different)
- Flow-limiting dissection more frequent in the DCB arm versus the DAART arm (8 versus 1, p=0.02)

Follow-up Results (12-mo)
- Primary Patency (PSVR≤2.0 and freedom from TLR or occlusion):
  DCB = 68%
  DAART = 88% (p=0.40)
- 12-mo freedom from TLR:
  DCB = 75%
  DAART = 89% (p=0.98)
- 12-mo Secondary Patency
  DCB = 81%
  DAART = 100% (p=0.03)

Summary

• Vessel preparation is a critical step in enhancing DCB effectiveness
  – Though it remains ill-defined

• The marriage of atherectomy and DCB (effective plaque modification / debulking paired with sustained drug presence) may be a useful union of technologies

• DCBs generally demonstrate high 12-month patency rates, though data at 2 years and beyond are inconsistent
  – Overall, DCB use in increasingly complex and long lesions is associated with increasing provisional stent use

• Calcium is a potential barrier to DCB effectiveness, highlighting the importance of vessel prep

• Atherectomy has demonstrated effectiveness through 12 months, though long-term data remain limited
  – Now with greater data and technologies available

• 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

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