Gain lumen, maintain patency: The power of adjunctive therapy with directional atherectomy and DCB

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Faculty Disclosure

**Thomas Zeller, MD**

For the 12 months preceding this presentation, I disclose the following types of financial relationships:

- **Honoraria received from:** Abbott Vascular, Bard Peripheral Vascular, Veryan, Biotronik, Boston Scientific Corp., Cook Medical, Cordis Corp., Gore & Associates, Medtronic, Spectranetics, Straub Medical, TriReme

- **Consulted for:** Abbott Vascular, Bard Peripheral Vascular, Boston Scientific Corp., Cook Medical, Gore & Associates, Medtronic, Spectranetics

- **Research, clinical trial, or drug study funds received from:**
  480 biomedical, Bard Peripheral Vascular, Veryan, Biotronik, Cook Medical, Cordis Corp., Gore & Associates, Abbott Vascular, Medtronic, Spectranetics, Terumo, TriReme, Volcano
Current long-term DCB data is promising

LONG-TERM PRIMARY PATENCY FROM PIVOTAL DCB RCTs

12 months

- **IN.PACT DCB Arm**: 87.5%
- **LEVANT DCB Arm**: 73.5%
- **ILLUMENATE Pivotal DCB arm**: 82.3%

24 months

- **IN.PACT DCB Arm**: 78.9%
- **LEVANT DCB Arm**: 58.6%
- **ILLUMENATE Pivotal DCB arm**: Not available

36 months

- **IN.PACT DCB Arm**: 69.5%
- **LEVANT DCB Arm**: Not available
- **ILLUMENATE Pivotal DCB arm**: Not available

Primary patency rates may be calculated differently, and therefore may not be directly comparable; chart is for illustration purposes only.

... but the bailout-stent rate is increasing with lesion length

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT SFA (DCB ARM) (N=220)</th>
<th>IN.PACT Global Long Lesion Imaging Cohort (N=157)</th>
<th>IN.PACT Global ISR Imaging Cohort (N=131)</th>
<th>IN.PACT Global CTO Imaging Cohort (N=126)</th>
<th>IN.PACT Global Clinical Cohort (N=1406)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion Length (Mean ± SD, cm)</td>
<td>8.94 ± 4.89</td>
<td>26.40 ± 8.61</td>
<td>17.17 ± 10.47</td>
<td>22.83 ± 9.76</td>
<td>12.09 ± 9.54</td>
</tr>
<tr>
<td>Primary Patency (KM @ 360 days)</td>
<td>86.6%*</td>
<td>91.1%</td>
<td>88.7%</td>
<td>85.3%</td>
<td>N/A</td>
</tr>
<tr>
<td>CD-TLR</td>
<td>2.4%</td>
<td>6.0%</td>
<td>7.3%</td>
<td>11.3%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Thrombosis</td>
<td>1.4%</td>
<td>3.7%</td>
<td>0.8%</td>
<td>4.3%</td>
<td>2.9%</td>
</tr>
<tr>
<td>Major Amputation Target Limb</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.0%</td>
<td>0.2%</td>
</tr>
<tr>
<td>Provisional stent rate</td>
<td>7.3%</td>
<td>40.4%</td>
<td>14.5%</td>
<td>46.8%</td>
<td>25.3%</td>
</tr>
</tbody>
</table>

IN.PACT excellent outcomes come with **high** bailout stent rate especially in complex lesions (CTO and LL)
How can we optimize DCB outcomes?

Limitations of DCB angioplasty...

DCB is based on Angioplasty

Provisional Stent Rate increases with Lesion Length

Calcium May Limit Drug Effect

..addressed by Directional Atherectomy

Mechanically re-canalinze the vessel without overstretch

Reduce likelihood of bail-out stent & preserve native vessel

Removes potential barriers for drug uptake
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>1-year</th>
<th>&gt;1-year</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%</td>
<td>?</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</td>
<td>?</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</td>
<td>?</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2.5%</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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

<table>
<thead>
<tr>
<th>Study (* Core Lab)</th>
<th>Type</th>
<th>Patients</th>
<th>Lesions</th>
<th>Dissection (≥Grade C)</th>
<th>BO Stent</th>
<th>30-day MAE</th>
<th>1-year</th>
<th>&gt;1-year</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</td>
<td>?</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%</td>
<td>?</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%</td>
<td>?</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% (6-mo)</td>
<td>?</td>
</tr>
</tbody>
</table>

DEFINITIVE Ca++ demonstrated calcified disease can be treated with DA and embolic protection

**DEFINITIVE LE and Ca\(^{2+}\): Outcomes**

*SilverHawk, TurboHawk (Medtronic)*

<table>
<thead>
<tr>
<th>Patient #</th>
<th>598 (RCC 1-3)</th>
<th>201 (RCC 4-6)</th>
<th>133</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion #</td>
<td>743</td>
<td>279</td>
<td>168</td>
</tr>
<tr>
<td>Bail-out Stent</td>
<td>3.2% (33/1022)</td>
<td>4.1% (7/169)</td>
<td></td>
</tr>
<tr>
<td>MAE (30d)</td>
<td>1.0% (6/598)</td>
<td>3.5% (7/201)</td>
<td>6.9% (9/131)</td>
</tr>
<tr>
<td>1° Patency (1y)</td>
<td>78.0%</td>
<td>71.0%</td>
<td>NR²</td>
</tr>
<tr>
<td>1° Patency Def</td>
<td>PSVR ≤ 2.4 by DUS</td>
<td>NR²</td>
<td></td>
</tr>
<tr>
<td>TLR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

NR = Not Reported. Boldfaced values indicate statistical significance (p < 0.05).

1. Site-reported lesions totaled 169 while Core Lab evaluated lesions totaled 168 (two site-reported lesions were considered one diffuse lesion by the Core Lab). Provisional stent rate was reported by Roberts, et al., with respect to the site-reported lesion number, i.e. 169 not 168.

2. Primary endpoint for DEFINITIVE Ca\(^{2+}\) was safety; patency was not evaluated.

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Rationale for Plaque Excision and Drug-Delivery as an Essential Combination

- Mechanically recanalize the vessel without overstretch
- Remove the perfusion barrier – better and more homogenous drug uptake?
- Reduce the likelihood of bail-out stenting and preserve the native vessel
DA+DCB combination therapy can overcome main limitations of stand-alone SFA therapies

<table>
<thead>
<tr>
<th>Unmet Need</th>
<th>PTA</th>
<th>BMS</th>
<th>DES</th>
<th>DCB</th>
<th>DA</th>
<th>DA+DCB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Address recoil, dissections and Ca²⁺</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Prevent Neointimal Proliferation/ Restenosis</td>
<td></td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
<tr>
<td>Minimize permanent implants + preserve future options</td>
<td>✔️</td>
<td></td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
<td>✔️</td>
</tr>
</tbody>
</table>
Prospective, single-center study to characterize conjunctive DA + DCB use in severely calcified lesions

Design and Inclusion
- Prospective, single-center study
- N = 30 patients (RCC 3-6)
- Enrolled only heavily calcified lesions (Ca2+ on both sides of vessel wall > 1 cm in length)

Specific Technical Details
- All procedures included distal protection with SpiderFX™ embolic protection device and IVUS-guided atherectomy with TurboHawk™ peripheral plaque excision system
- Once < 30% residual stenosis was achieved (via IVUS and Angio) a DCB was used for post-dilation

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)

Authors note DA+DCB may be a strategy for treating severely calcified lesions of the femoropopliteal artery

Stavroulakis, et al., DAART Study

Prospective, single-center study to characterize conjunctive DA + DCB use in isolated popliteal artery lesions

**Design and Inclusion**
- Prospective, single-center study
- N = 21 patients (26 lesions)
  - RCC 3: 18 (85%)
  - RCC 4: 1 (5%)
  - RCC 5: 2 (10%)
- Enrolled only PA lesions
  - P1: 9 (42% of patients)
  - P2: 17 (81% of patients)

**Specific Technical Details**
- All procedures included distal protection with SpiderFX™ embolic protection device and directional atherectomy
- Silver- / TurboHawk used in all cases
- IN.PACT Admiral (MDT) and Freeway (Eurocor) DCBs were used
- Aim of DA was to reduce stenosis to ≤50% and combined treatment (“technical success”) to ≤30%

Stavroulakis, et al., DAART Study

Prospective, single-center study to characterize conjunctive DA + DCB use in isolated popliteal artery lesions

Procedural Characteristics (n=21)
- Post-DA mean lumen: 4.8mm
- Post-DCB mean lumen: 5.9mm
- Technical success: 90%
- Complications: 3 (15%)  
  2 PA perforations  
  1 flow-limiting dissection (stented)

Follow-up Results (mean 18mo)
- 12-mo Restenosis (PSVR>2.5): 95%
- 18-mo Restenosis (PSVR>2.5): 90%

Authors note DA+DCB for isolated PA lesions is effective, though frequency of these types of lesions scarce and small study

DEFINITIVE AR 1 Year Outcomes

**Duplex Ultrasound Patency at 12 Months**
*Emerging Advantage in Long and Severely Calcified Lesions*

- **All Patients**
  - N = 48
  - DAART: 93.4%
  - DCB: 89.6%
- **Lesions > 10 cm**
  - N = 31
  - DAART: 96.8%
  - DCB: 85.9%
- **All Severe Ca++**
  - N = 27
  - DAART: 70.4%
  - DCB: 62.5%

**Angiographic Patency at 12 Months**
*Angiographic Patency shows similar pattern*

- **All Patients**
  - N = 34
  - DAART: 82.4%
  - DCB: 71.8%
- **Lesions > 10 cm**
  - N = 22
  - DAART: 90.9%
  - DCB: 68.8%
- **All Severe Ca++**
  - N = 24
  - DAART: 58.3%
  - DCB: 42.9%

*Per Core Lab Assessment.*
*All Severe Ca++* group includes all patients with severe calcium (including randomized and non-randomized).

Results for all patients who returned for angiographic follow-up.
DEFINITIVE AR: The value of lumen gain

What is the Impact of Lumen Gain with DAART?
Post Procedure MLD (DAART vs DCB alone)

DAART resulted in a significantly larger minimum lumen diameter (MLD) following the protocol-defined treatment in DEFINITIVE AR.

12-Month Patency: DAART RCT Patients
Increased lumen gain with DA before DCB may result in improved 12-month patency.
DEFINITE AR:
Sub-optimal debulking in DAART arm

Baseline

59% residual stenosis - post atherectomy
DEFINITE AR: Sub-optimal debulking in DAART arm

34% residual stenosis Post DAART
DEFINITE AR:
Sub-optimal debulking in DAART arm

Clinically-driven TLR 349 days post DAART procedure
Occlusion begins at site of sub-optimal debulking
DEFINITIVE AR DCB Arm Case Example Severe Ca^{++}
DEFINITIVE AR DCB Arm Case Example Severe Ca^{++}
DEFINITIVE AR DCB Arm Case Example Severe Ca^{++}
DEFINITIVE AR DCB Arm
Case Example Severe Ca^{++}: 12-Month Angio
The REALITY Study evaluates patient outcomes with adjutice use of Medtronic HawkOne™ or Medtronic TurboHawk™ and Medtronic IN.PACT™ Admiral™ drug-coated balloon.

The multi-center, international, prospective, single-arm study will enroll up to 250 subjects at up to 15 sites.

The study includes angiographic and duplex ultrasound core lab adjudication. Primary patency is assessed by duplex ultrasound at 12-months.

Patients are followed up to 24 months to determine clinically driven target lesion revascularization (CD-TLR).

The study is sponsored and managed by VIVA physicians with support from Medtronic through an external research project grant.

ClinicalTrials.gov Identifier: NCT02850107
Co-Principal Investigators

Krishna Rocha-Singh, MD
Chief Scientific Officer
Prairie Heart Institute of Illinois

Brian DeRubertis MD, FACS
Associate Professor of Surgery
UCLA Division of Vascular Surgery

- Consent 250 subjects
- Goal Enrollment 150 subjects
- 10 U.S. Sites
  - Lesion length 8-18cm
  - Occlusion length 6-10cm
- 3 German Sites
  - Lesion length up to 25cm

Primary Effectiveness Endpoint:
Primary patency (PSVR ≤ 2.4) and freedom from CD-TLR at one-year in subjects with long, moderate and severely calcified symptomatic femoropopliteal lesions and/or occlusions after treatment with DA + DCB

Primary Safety Endpoint:
Freedom from (MAEs) defined as freedom from flow-limiting dissections (D-F), vessel perforations requiring stenting or stent-grafts, unplanned amputation, intra-procedure distal atheroembolization and clinically-driven TVR in subjects with long, moderate and severely calcified FP lesions and/or occlusions through 30-day follow-up visit.

REALITY Trial Enrolls First Patient in Study Evaluating Medtronic Directional Atherectomy and Drug-Coated Balloon in PAD Treatment
July 27, 2016 2:15 PM CT

VIVA Sponsored REALITY Study Assessing Vessel Preparation and Treatment in Severe Calcified Lesions Expands to Germany: Principal Investigators Named: First Patient Enrolled

Dublin and San Jose, Calif. - July 27, 2016 - Medtronic plc (NYSE: MDT) and VIVA Physicians today report the first patient enrolled in the REALITY Study. The VIVA sponsored study is assessing outcomes for patients with significantly calcified and symptomatic femoropopliteal peripheral artery disease (PAD), following adjunctive use of directional atherectomy and drug-coated balloon (DCB). Krishna Rocha-Singh, M.D., chief scientific officer, Prairie Heart Institute of Illinois, and Brian DeRubertis, M.D., FACS, associate professor of surgery, UCLA Division of Vascular Surgery, are co-principal investigators. The study will include investigative sites both within the U.S. and in Germany.

ClinicalTrials.gov Identifier: NCT02850107
Is the Gain-Maintain approach effective?

- Some DCB offer excellent durability in TASC A & B lesions
- However, limitations exist in complex lesion morphologies such as:
  - Lesions $\geq$10 cm
  - Severely calcified lesions
  - CTOs
  - Acute residual stenosis $> 30$
- DEFINITIVE AR and small independent studies resulted in better outcomes in those challenging lesion subsets for the combination of DA + DCB
- The REALITY study will provide more evidence towards establishing the benefit of preparing the vessel with DA prior to DCB treatment and further refine the SFA treatment algorithm
Gain lumen, maintain patency: The power of adjunctive therapy with directional atherectomy and DCB

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