DCB Potential Beyond the Selected SFA Lesions Types Studied in Trials to Date

What We Know About the ‘Real World’

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Revisiting “Nothing Left Behind”

Defining DCB Efficacy in Complex Disease

• DCB technologies enter into a new era of ‘data evolution’ to define their role in the management of complex FPA disease

• Beyond RCTs, robust adjudicated ‘real world’ multicenter registries are essential to that ‘data evolution’

• Importantly, a uniform definition of terms of what constitutes a “complex FPA lesions”, how ‘vessel preparation’ is used and assessed requires collaboration between physicians, industry and regulators
Real World Registries: Exploring Alternate Realities

RCT

MULTI-CENTER REGISTRIES:
ALL-COMERS, DEFINED I/E,
CORE LAB AND CEC
ADJUDICATION WITH MEANINGFUL
LONG-TERM FOLLOW-UP

PROSPECTIVE MULTI-CENTER
UNADJUDICATED
UN-MONITORED REGISTRIES
LIMITED FOLLOW-UP

SINGLE-CENTER
UNADJUDICATED CASE STUDIES
## IN.PACT SFA Trial: 3-Yr Follow-Up Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th></th>
<th>IN.PACT ( n = 220 ) subjects</th>
<th>PTA ( n = 111 ) subjects</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, Y ± SD</strong></td>
<td>67.5 ± 9.5</td>
<td>68.0 ± 9.2</td>
<td>0.612</td>
</tr>
<tr>
<td><strong>Male, % (n)</strong></td>
<td>65.0% (143/220)</td>
<td>67.6% (75/111)</td>
<td>0.713</td>
</tr>
<tr>
<td><strong>Diabetes, % (n)</strong></td>
<td>40.5% (89/220)</td>
<td>48.6% (54/111)</td>
<td>0.161</td>
</tr>
<tr>
<td><strong>Hypertension, % (n)</strong></td>
<td>91.4% (201/220)</td>
<td>88.3% (98/111)</td>
<td>0.431</td>
</tr>
<tr>
<td><strong>Current smoker, % (n)</strong></td>
<td>38.6% (85/220)</td>
<td>36.0% (40/111)</td>
<td>0.719</td>
</tr>
<tr>
<td><strong>Rutherford class, % (n)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37.7% (83/220)</td>
<td>37.8% (42/111)</td>
<td>0.898</td>
</tr>
<tr>
<td>3</td>
<td>57.3% (126/220)</td>
<td>55.9% (62/111)</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>5.0% (11/220)</td>
<td>5.4% (6/111)</td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>0.0% (0/220)</td>
<td>0.9% (1/111)</td>
<td></td>
</tr>
<tr>
<td><strong>ABI / TBI, ± SD</strong></td>
<td>0.769 ± 0.228</td>
<td>0.744 ± 0.189</td>
<td>0.308</td>
</tr>
</tbody>
</table>

1. TBI allowed in cases of incompressible vessels in IN.PACT SFA II phase

P. Krishnan VIVA 2016
IN.PACT SFA Trial: 3-Year Outcomes
Primary Patency\(^1\)

1. Freedom from core laboratory-assessed restenosis (duplex ultrasound PSVR ≤2.4) and clinically-driven target lesion revascularization through 36 months (adjudicated by a Clinical Events Committee blinded to the assigned treatment)
2. Number at risk represents the number of evaluable subjects at the beginning of the each 30-day window
Number at risk represents the number of evaluable subjects at the beginning of each 30-day window.
IN.PACT Global Study Architecture

NEEDED: Expanded clinical evidence of the IN.PACT™ Admiral™ DCB in the treatment of a real-world patient population

Outcome data on the 1406 ITT subjects who compose the IN.PACT Global Clinical Cohort

M. Jaff VIVA 2016
# IN.PACT™ Admiral™ DCB Studies
## Comparison of 12-month Outcomes

<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>
</tbody>
</table>

*M. Jaff VIVA 2016*
## IN.PACT Global Long Lesion Imaging Cohort: Lesion/Procedural Characteristics

<table>
<thead>
<tr>
<th>Lesions (N)</th>
<th>164</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Lesion Type:</strong></td>
<td></td>
</tr>
<tr>
<td>de novo</td>
<td>83.2% (134/161)</td>
</tr>
<tr>
<td>restenotic (no ISR)</td>
<td>16.8% (27/161)</td>
</tr>
<tr>
<td>ISR</td>
<td>0.0% (0/161)</td>
</tr>
<tr>
<td><strong>Lesion Length</strong></td>
<td>26.40 ± 8.61 cm</td>
</tr>
<tr>
<td>Total Occlusions</td>
<td>60.4% (99/164)</td>
</tr>
<tr>
<td>Calcification</td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>71.8% (117/163)</td>
</tr>
<tr>
<td></td>
<td>19.6% (32/163)</td>
</tr>
<tr>
<td>RVD (mm)</td>
<td>4.594 ± 0.819</td>
</tr>
<tr>
<td>Diameter Stenosis (pre-treatment)</td>
<td>90.9% ± 14.2</td>
</tr>
<tr>
<td>Dissections: 0</td>
<td>37.9% (61/161)</td>
</tr>
<tr>
<td>A-C</td>
<td>47.2% (76/161)</td>
</tr>
<tr>
<td>D-F</td>
<td>14.9% (24/161)</td>
</tr>
</tbody>
</table>

### Device Success [1]
99.5% (442/444)

### Procedure Success [2]
99.4% (155/156)

### Clinical Success [3]
99.4% (155/156)

### Pre-dilatation
89.8% (141/157)

### Post-dilatation
39.1% (61/156)

### Provisional Stent
- LL 15-25 cm: 40.4% (63/156)
- LL > 25 cm: 33.3% (33/99)
- 52.6% (30/57)

1. **Device success**: successful delivery, inflation, deflation and retrieval of the intact study balloon device without burst below the RBP.
2. **Procedure success**: residual stenosis of ≤ 50% (non-stented subjects) or ≤ 30% (stented subjects) by core lab (if core lab was not available then the site reported estimate was used).
3. **Clinical success**: procedural success without procedural complications (death, major target limb amputation, thrombosis of the target lesion, or TVR) prior to discharge.

M. Jaff VIVA 2016
"Severe calcification has been viewed as the Achilles heel of drug coated balloons. Our U.S. Pivotal Trial data provides compelling evidence that Stellarex achieves top tier patency even in very complex patients. These outcomes are a significant step forward in our effort to improve patient care and lead the way in clinical science."

*VasCore (Boston, MA); PSVR: 2.5, KM estimates at day 365 (360 for IN.PACT SFA)
The Need to Align the Definition of ‘Severe’ Calcification

Medtronic IN.PACT SFA core lab definition of Severe Calcification:

“Calcium is visible along both sides of the arterial wall, covers 2 cm or greater of the target lesion area, encompasses greater than 50% of the total target lesion treatment area by visual estimate and/or the calcium is circumferential (360°) in nature (i.e. on both sides of the vessel lumen extending 2 cm or greater on a single AP view) or classified as exophytic calcification, which significantly impedes blood flow in the vessel.

<table>
<thead>
<tr>
<th>Baseline diameter stenosis (%)</th>
<th>79.6 ± 17.5 (244)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Eccentric lesion</td>
<td>59.8% (146/244)</td>
</tr>
</tbody>
</table>

1. Site reported

2. Defined as: Radiopacities noted on both sides of the arterial wall and extending more than one cm of length prior to contrast injection or digital subtraction.
‘Leave Nothing Behind’: What About Long, Calcified Lesions?

Vessel Preparation and Complex FPA Disease Prior to DCB: An Emerging Paradigm
Treating Complex FPA Disease: What is the REALITY?
The REALITY Study: Rational and Hypotheses

Could “vessel preparation” using directional atherectomy in LONG, CALCIFIED FPAs PRIOR to DCB use:

A. Reduce vessel recoil and high grade dissections and provisional stent rates
B. Remove athermanous barrier to promote PTX vessel uptake
C. Reduce re-intervention rates through 2-Yr follow-up
Why the REALITY Study?

Questions to be Explored:

- Evaluated the clinical safety/effectiveness "vessel preparation" with DA prior to IN.PACT Admiral DCB use in long (8-25 cm), severely calcified FPA lesions in up to 250 RC 2-4 claudicants in the US and Germany.
  -- Duplex Ultrasound core lab to assess 12 mo. patency
  -- Angiographic core lab to assess technical success after DA and DCB; adjudicate dissection grade and provisional stenting
  -- PACSS Calcium grading scale to be validated
Why the REALITY Study?

**Questions to be Explored:**

- IVUS core lab evaluation of vessel metrics and calcification at baseline, after DA and post-DCB
- Histology core lab to fully quantify and analyze all tissue extracted from the FPA using H&E, elastin and calcium stains
- Global CRO to perform 100% source documentation
- Independent CEC to adjudicate all clinical events through 2-Yr follow-up
REALITY:
Assessing Lesion Complexity

Angio Core Lesion Assessment

Core Lab Assessment of Ca++
REALITY: Assessing Lesion Complexity

IVUS Core Lab Assessment

- IVUS metrics: lumen diameter, CSA, plaque burden, dissection, Ca++ are assessed at baseline, post-DA, post-DCB

- All investigator are blinded to IVUS images
REALITY:
Assessing Lesion Complexity

Histology Core Lab analysis of all tissues extracted

Dysplastic bone formation
Finally, We Must Avoid Our Natural Tendency of ‘Irrational Exuberance’

- Regardless of the device combinations evaluated, all stakeholders should openly collaborate, align definitions, and disclose outcomes.
- While a RCT to evaluate the “best” device combinations to treat complex disease is impractical, robust/adjudicated registries provide important insights.
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