Understanding the Challenges in Assessing Calcium in Clinical Trials

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- Research Grants
  - MDT
- Consultant/Advisory Board
  - Medtronic
  - Alucent Medical
  - SoundBite Medical
  - ROX Medical
  - Abbott Medical
- Royalties/Financial Interest
  - None
- Speaker’s Bureau
  - None
- VIVA Board Member
- I will discuss ‘off-label’ DCB use (outside the US IFU).
Background

- DCBs enter into a new era of ‘data evolution’ which will define their safety/effectiveness in more complex FPA disease

- A uniform definition of what constitutes a ‘complex’ FPA lesion and ‘vessel preparation’ prior to DCB use requires collaboration between physicians, industry and regulators

- Example: What constitutes ‘severe calcium’ has emerged as an important issue in the evolution and clinical acceptance of DCB treatment in complex FP lesions
The Next Hurdle for DCBs: Complex Lesions (Long lesions, Ca++ and CTOs):

<table>
<thead>
<tr>
<th>Follow-up</th>
<th>LUTRONIX Global</th>
<th>ILLUMENATE Global</th>
<th>IN.PACT Global Full Clinical Cohort</th>
<th>IN.PACT Global Long Lesion</th>
<th>IN.PACT Global CTO</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>691 subjects Complete follow-up Site-reported</td>
<td>Interim Core Lab-adjudicated</td>
<td>1406 subjects Complete follow-up Core Lab-adjudicated</td>
<td>157 subjects Complete follow-up Core Lab-adjudicated</td>
<td>126 subjects Complete follow-up Core Lab-adjudicated</td>
</tr>
</tbody>
</table>

Key Lesion Characteristics

<table>
<thead>
<tr>
<th>Length (cm)</th>
<th>CTO (%)</th>
<th>Ca++ (%)</th>
<th>Primary Patency FF TLR/CD-TLR</th>
<th>Bail-out Stent (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>10.12 cm</td>
<td>31.2%</td>
<td>50.2%</td>
<td>85.4%</td>
<td>25.2%</td>
</tr>
<tr>
<td>7.2 cm</td>
<td>28.3%</td>
<td>62%</td>
<td>86.5%</td>
<td>15.0%</td>
</tr>
<tr>
<td>12.1 cm</td>
<td>35.5%</td>
<td>68.7%</td>
<td>92.6%</td>
<td>25.3%</td>
</tr>
<tr>
<td>26.4 cm</td>
<td>60.4%</td>
<td>71.8%</td>
<td>91.1%</td>
<td>40.4%</td>
</tr>
<tr>
<td>22.9 cm</td>
<td>100.0%</td>
<td>71.2%</td>
<td>84.4%</td>
<td>46.8%</td>
</tr>
</tbody>
</table>

What drove the marked increase in provisional stenting?
Examples of “Severe” Calcium Definitions

Can different core labs applying different definitions obscure our interpretation of clinical data and its implications for patient care?

Defining the ‘Real World’: Four Peer-reviewed CA++ Grading Systems...and SEVERAL OTHERS UNREPORTED

<table>
<thead>
<tr>
<th>Fanelli et al. [1]</th>
<th>1a</th>
<th>1b</th>
<th>2a</th>
<th>2b</th>
<th>3a</th>
<th>3b</th>
<th>4a</th>
<th>4b</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumf.</td>
<td>0-90°</td>
<td>0-90°</td>
<td>90-180°</td>
<td>90-180°</td>
<td>180-270°</td>
<td>270-360°</td>
<td>270-360°</td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>&lt;3 cm</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
<td>&gt;3 cm</td>
<td>&lt;3 cm</td>
<td>&gt;3 cm</td>
</tr>
<tr>
<td>Compliance 360 [2]</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumf.</td>
<td>NO calcium</td>
<td>&lt;180°</td>
<td>&lt;180°</td>
<td>(both sides of vessel)</td>
<td>(both sides of vessel)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>NO calcium</td>
<td>&lt;50%</td>
<td>≥50%</td>
<td>of lesion length</td>
<td>of lesion length</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PACSS [3]</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
<td>4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumf.</td>
<td>NO calcium</td>
<td>unilateral</td>
<td>unilateral</td>
<td>bilateral</td>
<td>bilateral</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>NO calcium</td>
<td>&lt;5 cm</td>
<td>≥5 cm</td>
<td>&lt;5 cm</td>
<td>≥5 cm</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>location</td>
<td>a) intimal calcification; b) medial calcification; c) mixed type</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PARC [4]</td>
<td>Focal</td>
<td>mild</td>
<td>moderate</td>
<td>severe</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Circumf.</td>
<td>&lt;180°</td>
<td>&lt;180°</td>
<td>≥180°</td>
<td>&gt;180°</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Length</td>
<td>&lt;1/2</td>
<td>&gt;1/2</td>
<td>&lt;1/2</td>
<td>&gt;1/2</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Fanelli LINC 2017
Recent Severe Calcium Grading Scale Validation Studies

Tepe G et al; JVET 2015; Yin D et al; JVET 2017; Okuno S et al; JVET 2016
Why We Need an Accepted Uniform Calcium Grading Scale

- **Clinicians:** Understand the potential impact of various calcium grades on acute procedural results and long-term DCB effectiveness...make better care decisions
- **Industry:** To clinical trials using the identical Ca++ definitions, develop new devices and pursue potential labeling claims
- **Regulators:** Better assess potential device safety and effectiveness claims in treating severe Ca++

Ca++ definitions, develop new devices and pursue potential labeling claims
- **Regulators:** Better assess potential device safety and effectiveness claims in treating severe Ca++
Requirements of Relevant Calcium Grading System

• Imaging modality: Must be widely available and adopted across physician specialties
• Grading scale: Data-driven, not hypothesis driven
• Grading scale: Derived from adjudicated patient level demographic and angiographic datasets, inclusive of hard clinical endpoints, assessed through clinically relevant time points (i.e., one year)

The grading scale must be peer-reviewed

Yin D et al; JVET 2017
Limitations of a DCB Calcium FPA Grading Scale

- Other imaging assessments (i.e., IVUS) are more sensitive than fluoroscopy...and could be used to validate fluoroscopy in follow-up studies as a adequate imaging modality

- The grading scale will be germane only to DCB technologies used in the FPA segment

- Cannot be generalized to other technologies (i.e., DES) or other vascular beds (i.e., BTK) without additional validation
The VIVA Calcium Scale Unification Project: Proposed Investigational Plan

Develop a statistical model, using vascular calcification as a continuous variable, which predicts both acute procedural success and clinical results through one-year.

- Baseline DCB/PTA procedure angiograms
- Core lab collects patient demographic/procedural data from industry partners; analysis & de-identification
- Procedural (≤30d) & CD-TRL thru one-year
- Determine parameters affecting outcomes
- Proposed definition
- Peer review
- Retrospective cohorts
- Ongoing studies
- A future standard for DCB trials±atherectomy or PTA adjuncts
The VIVA Calcium Scoring Unification Project: A *Data Driven* Scoring System

Diagram showing the relationships between Statisticians, VIVA/Investigators, Industry Partners, FDA, and Angiographic Core Lab.
The Challenges of Assessing Calcium in Clinical Trials

- A core lab-driven statistical analysis of patient level demographic/angiographic outcomes will ensure this metric is indicative of acute and long-term DCB outcomes in the FP Artery
- More importantly, a standardized calcium scale will facilitate the advancement of new FPA DCB technologies and combined treatment strategies (i.e., vessel preparation) to promote the care of patients with more complex FP disease
THE END
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