Vascular Calcium: detection, classification and implications in DCB treatment

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Disclosure

- Consultant / Speaker / Proctor / Advisory Board
  - AstraZeneca
  - Bayer
  - Bolton
  - Boston Scientific
  - Cook
  - Cordis
  - CR Bard
  - Ev3-Covidien
  - Medtronic
  - Shockwave
  - Spectranetics
  - TriReme Medical
  - Volcano
  - W.L. Gore & Associates
Vascular Calcium

- Highly prevalent in:
  - Elderlies
  - Diabetics
  - Kidney disease

- Prevent optimal balloon dilatation, can result in stent under-expansion

- Common cause of severe dissections

- Underestimated by angiography

Calcium grading: Compliance 360 and PARC

- **Angiographic assessment**
- **4 grades** classified by circumferential and longitudinal extension
  - Longitudinal: ± 50% of lesion length
  - Circumferential: >/< 180° (bilateral / unilateral)

Calcium grading: Fanelli et al.
Cardiovasc Intervent Radiol. 2014

<table>
<thead>
<tr>
<th>GROUP</th>
<th>GRADE</th>
<th>LENGTH</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 a</td>
<td>0 – 90°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>1 b</td>
<td></td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>2 a</td>
<td>90 – 180°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>2 b</td>
<td></td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>3 a</td>
<td>180 – 270°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>3 b</td>
<td></td>
<td>&gt; 3 cm</td>
</tr>
<tr>
<td>4 a</td>
<td>270 – 360°</td>
<td>&lt; 3 cm</td>
</tr>
<tr>
<td>4 b</td>
<td></td>
<td>&gt; 3 cm</td>
</tr>
</tbody>
</table>

Fig. 3 Groups classification according to the grade and length of the calcified portion of the lesion

- **Angiographic assessment (longitudinal) + CTA (circumferential)**
- **8 grades classified by incremental circumferential extension (1 to 4 sectors) and length >/< 3 cm**

Calcium grading: PACSS

- **Angiographic assessment**
  - **5 grades** classified by:
    - unilateral / bilateral
    - length >/< 5 cm
  
- **Additional characterization**
  - Based on calcium location:
    - a) intimal
    - b) medial
    - c) mixed

**TABLE I. Proposed Peripheral Arterial Calcium Scoring System (PACSS)**

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No visible calcium at the target lesion site</td>
</tr>
<tr>
<td>1</td>
<td>Unilateral calcification &lt; 5 cm; a) intimal calcification; b) medial calcification; c) mixed type</td>
</tr>
<tr>
<td>2</td>
<td>Unilateral calcification ≥ 5 cm; a) intimal calcification; b) medial calcification; c) mixed type</td>
</tr>
<tr>
<td>3</td>
<td>Bilateral calcification &lt; 5 cm; a) intimal calcification; b) medial calcification; c) mixed type</td>
</tr>
<tr>
<td>4</td>
<td>Bilateral calcification ≥ 5 cm; a) intimal calcification; b) medial calcification; c) mixed type</td>
</tr>
</tbody>
</table>

Summary: 4 peer-reviewed grading systems

Bilateral / Circumferential Calcium = common marker of Calcium severity

<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>180-270°</td>
<td>270-360°</td>
<td>270-360°</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>&lt;3 cm</td>
<td>&gt;3 cm</td>
<td>&gt;3 cm</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compliance 360 [2]</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumf. NO calcium</td>
<td>&lt;180° (1 side of vessel)</td>
<td>&lt;180° (1 side of vessel)</td>
<td>≥180° (both sides of vessel)</td>
<td>≥180° (both sides of vessel)</td>
<td></td>
</tr>
<tr>
<td>Length NO calcium</td>
<td>&lt;50% of lesion length</td>
<td>≥50% of lesion length</td>
<td>&lt;50% of lesion length</td>
<td>≥50% of lesion length</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PACSS [3]</th>
<th>0</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumf. NO calcium</td>
<td>unilateral</td>
<td>unilateral</td>
<td>bilateral</td>
<td>bilateral</td>
<td></td>
</tr>
<tr>
<td>Length NO calcium</td>
<td>&lt;5 cm</td>
<td>≥5 cm</td>
<td>&lt;5 cm</td>
<td>≥5 cm</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>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PARC [4]</th>
<th>Focal</th>
<th>mild</th>
<th>moderate</th>
<th>severe</th>
</tr>
</thead>
<tbody>
<tr>
<td>Circumf. &lt;180° (1 side of vessel)</td>
<td>&lt;180° (1 side of vessel)</td>
<td>≥180° (both sides of vessel)</td>
<td>&gt;180° (both sides of vessel)</td>
<td></td>
</tr>
<tr>
<td>Length &lt;1/2 of lesion length</td>
<td>&gt;1/2 of lesion length</td>
<td>&lt;1/2 of lesion length</td>
<td>&gt;1/2 of lesion length</td>
<td></td>
</tr>
</tbody>
</table>

DCB and Calcium

Calcium: potential barrier to optimal drug absorption

Circumferential distribution strongest influencing factor

N=60

- SFA lesions ~ 6 cm (de-novo)
- CTO: 31.7%
- DCB with standard pre-dilatation

DCB and Calcium

Not length, nor location but bilateral Calcium observed as strongest predictor of outcome

N=91 (retrospective)
- SFA lesions ~ 5.7 cm
- Restenotic: 45.1%
- CTO: 33.0%
- 6-month LLL (primary endpoint) by Angio Core lab adjudication

Calcium and DCB implications: Summary

Calcium is Bad,
Circumferential Worse vs. Longitudinal

- Reduced Vessel Compliance
  - Barrier to optimal dilatation

- Reduced Tissue Permeability
  - Barrier to optimal drug absorption
A look at the data: 5 DCB Trials

1300 DCB patients, similar trial design, similar rigor

In.Pact SFA\(^1\), Levant 2\(^2\), Illumenate EU RCT\(^3\), Illumenate US Pivotal\(^4\), Illumenate Global\(^5\)

- Multicenter, fem-pop / RC 2-3-4,
- Primary endpoint: 1-year Primary Patency (2.4 or 2.5 PSVR threshold)
- Angiographic and duplex core-lab adjudication
- External monitoring with 100% source data verification

**Typical Calcium-related Exclusion Criteria:**

- Severe calcification that makes the lesion non-dilatable (or similar)
- Failed pre-dilatation (based on major flow-limiting dissection or >70% residual DS)

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1. Tepe G et al. IN.PACT SFA Trial Investigators.. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015
3. M.Brodmann - ILLUMENATE European Randomized Clinical Trial: 12-month Final Results from the Stellarex DCB – oral presentation, AMP 2016
4. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - oral presentation, TCT 2016
5. T.Zeller – Illumenate Global – oral presentation, LINC 2017
# Key Baseline Characteristics

**Enrolment:** Sep 2010 → → → → → → → → → → → → → July 2015

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Diabetes</td>
<td>40.5%</td>
<td>43.4%</td>
<td>37.4%</td>
<td>49.5%</td>
<td>33.7%</td>
</tr>
<tr>
<td>Females</td>
<td>35.0%</td>
<td>38.9%</td>
<td>27.9%</td>
<td>44.0%</td>
<td>27.0%</td>
</tr>
<tr>
<td>Renal Insuff.</td>
<td>8.3%</td>
<td>NA</td>
<td>9.0%</td>
<td>18.0%</td>
<td>7.0%</td>
</tr>
<tr>
<td>RC≥3</td>
<td>62.3%</td>
<td>70.6%</td>
<td>84.6%</td>
<td>68.5%</td>
<td>66.3%</td>
</tr>
<tr>
<td>Lesion length</td>
<td>8.9 cm</td>
<td>6.3 cm</td>
<td>7.2 cm</td>
<td>8.0 cm</td>
<td>7.5 cm</td>
</tr>
<tr>
<td>Severe Calcium*</td>
<td>8.1%</td>
<td>10.4%</td>
<td>12.7%</td>
<td>43.9%</td>
<td>40.8%</td>
</tr>
<tr>
<td>CTOs</td>
<td>25.8%</td>
<td>20.6%</td>
<td>19.2%</td>
<td>19.0%</td>
<td>31.3%</td>
</tr>
</tbody>
</table>

* different Ca++ definitions may apply across trials

1. Tepe G et al. IN.PACT SFA Trial Investigators.. Drug-coated balloon versus standard percutaneous transluminal angioplasty for the treatment of superficial femoral and popliteal peripheral artery disease: 12-month results from the IN.PACT SFA randomized trial. Circulation 2015
3. M.Brodman - ILLUMENATE European Randomized Clinical Trial: 12-month Final Results from the Stellarex DCB – oral presentation, AMP 2016
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5. T.Zeller – Illumenate Global – oral presentation, LINC 2017
1-year Primary Patency and Ca++

Context view from DCB Trials powered on a 1 year Primary Patency primary endpoint

- Core-lab (Duplex) adjudicated Primary Patency
- Core-lab (Angio) adjudicated Severe Calcium*

Core-lab adjudicated Duplex derived Primary Patency based on PSVR ≤2.4 (*) or ≤2.5 (‡) KM survival estimates at 360 (†) or 365 (‡) days.

* different Ca++ definitions may apply across trials

1. T.Zeller – Illumenate Global – oral presentation, LINC 2017
2. S.Lyden - ILLUMENATE Pivotal Stellarex DCB IDE Study 12-month Results - oral presentation, TCT 2016
3. M.Brodmann - ILLUMENATE European Randomized Clinical Trial: 12-month Final Results from the Stellarex DCB – oral presentation, AMP 2016
4. P. Krishnan, DCB show superior 3-year outcomes vs. PTA: results from In.Pact SFA randomized trial - oral presentation, VIVA 2016
Ca++ Exclusion Criteria are vague and mild

1. Angiography under-estimates calcium
2. Pre-dilatation failing to achieve at least 70% residual stenosis is a rare circumstance (non dilatable lesions)
3. Flow limiting dissections may be either subjective or just resolvable

False negative Ca++ in these trials should not surprise, neither should surprise a growing bias in enrolling Ca++ as observed in more recent trials (higher confidence in DCB)
Conclusions

• Calcium limits optimal dilatation and optimal drug absorption
• Circumferential calcium seems the biggest issue and bilateral calcium is the common marker of calcium severity in different grading systems
• Angiography underestimates calcium and makes angio-based study exclusions criteria mild and vague
• Angiographic core-lab is an important must-have to confirm calcium presence, entity and distribution
• Results from 2 ILLUMENATE Trials indicate that some DCBs can still perform very well in presence of high severe calcium rates
• Vessel prep by plaque scoring or debulking may further improve results
Interdisciplinary Endovascular Aortic Symposium
IDEAS 2017
September 17-19
Copenhagen/Denmark

Featuring:
• Expert Case Discussions and Round Table sessions
• Basic workshops on EVAR and TEVAR
• Hot Topic Symposium on EVAR/TEVAR centred on long term results
• Complications
• Controversies
• Emergencies
• And much more...

www.aorticideas.org
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