Patterns of Restenosis:  
A Core Lab-driven Assessment of SFA Restenosis and a Potential Shift to Unify Various Trials

Lawrence A. Garcia, MD  
St. Elizabeth’s Medical Center  
Boston, MA, USA
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

<table>
<thead>
<tr>
<th>Affiliation/Financial Relationship</th>
<th>Company</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grant/Research Support</td>
<td>Abbott, Medtronic</td>
</tr>
<tr>
<td>Consulting (non-compensated)</td>
<td>Medtronic, Boston Scientific, Abbott</td>
</tr>
<tr>
<td>Major Stock Shareholder/Equity</td>
<td>Arsenal, Primacea, TissueGen, CV Ingenuity, Spirox, Scion Cardiovascular, Syntervention, Essential Medical</td>
</tr>
<tr>
<td>Royalty Income</td>
<td>None</td>
</tr>
<tr>
<td>Ownership/Founder</td>
<td>None</td>
</tr>
<tr>
<td>Intellectual Property Rights</td>
<td>None</td>
</tr>
<tr>
<td>Other Financial Benefit</td>
<td>None</td>
</tr>
</tbody>
</table>

Challenge of Femoropopliteal Artery Disease

- Peripheral Artery Disease (PAD) affects up to 200 million people worldwide\(^1\) and prevalence of PAD is increasing with an aging population and increasing prevalence of diabetes\(^2\) and increasingly more endovascular therapy
- *No single endovascular therapy has emerged as a “gold standard”*
- Multiple factors influence operator selection of device treatment to include morphology, lesion length, calcification
- All devices have primary patency, CD-TLR rates that on average seem similar from device to device
- However, to date we still do not understand the failure mode and restenotic pattern on any one device
- Therefore, characterizing “the restenotic pattern” remains a critical component in advancing PAD standard of care and device specific treatment choices and may impact healthcare economics

**Background: Coronary**

- Mehran, et al: Retrospective review of 245 in-stent restenosis (ISR) subjects (288 ISR lesions) at single center\(^1\)
- Four ISR Types
  - Type I: Focal (≤10mm in length)
  - Type II: Diffuse Intra-stent (>10mm)
  - Type III: Diffuse Proliferative (>10mm extending beyond stent)
  - Type IV: Occlusive (CTO)
- Target lesion revascularization (TLR) increased with increasing ISR Type

---

**One-Year Results**

<table>
<thead>
<tr>
<th>Patterns of ISR</th>
<th>Focal</th>
<th>Intrastent</th>
<th>Proliferative</th>
<th>Total Occlusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>2.5</td>
<td>2.6</td>
<td>3.3</td>
<td>0.0</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>1.2</td>
<td>2.6</td>
<td>0.0</td>
<td>0.0</td>
</tr>
<tr>
<td>TLR*</td>
<td>19.1</td>
<td>34.5</td>
<td>50.0</td>
<td>83.4</td>
</tr>
<tr>
<td>PTCA*</td>
<td>14.8</td>
<td>26.3</td>
<td>36.3</td>
<td>66.7</td>
</tr>
<tr>
<td>CABG*</td>
<td>4.3</td>
<td>8.2</td>
<td>13.7</td>
<td>16.7</td>
</tr>
</tbody>
</table>

Values are expressed as percentages. CABG indicates coronary artery bypass surgery.

Background: Peripheral

- Tosaka, et al: Retrospective review of 116 ISR subjects (133 ISR lesions) at multicenter\(^1\)
- Three ISR Classes
  - Class I: Focal ($\leq 50$mm in length)
  - Class II: Diffuse ($>50$mm; including stent body through the edges)
  - Class III: Occlusive (CTO)
- Class III ISR was associated with higher rates of ISR & re-occlusion than Classes I and II

Motivation

• Benefits of existing scoring systems
  – Mehran, et al., developed a pragmatic and easily-applied system for stent-based restenosis classification\(^1\)
  – Tosaka, et al., applied a similar system to the periphery\(^2\)
  – Both systems have demonstrated associations of restenosis type or class to outcomes

• Limitations of existing scoring systems
  – Limited to in-stent restenosis (ISR) classification, thus not applicable to PTA-, DCB- and Atherectomy-based approaches
  – May lack descriptive value in long, complex femoropopliteal artery (FPA) lesions commonly confronting operators

• We have developed a scoring system agnostic to treatment modality and applicable by both operators and core labs

Multidisciplinary Team

Oversight/Steering Board

– Lawrence Garcia, MD Interventional Cardiologist
  St. Elizabeth’s Medical Center, Boston, MA, USA
– Krishna Rocha-Singh, MD, Interventional Cardiologist
  St. John’s Hospital, Springfield, IL, USA
– Prakash Krishnan, MD, Interventional Cardiologist
  Mt. Sinai Medical Center, New York, NY, USA
– Thomas Zeller, MD, Angiologist
  Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany
– Gunnar Tepe, MD, Angiologist
  RoMed Klinikum, Rosenheim, Germany
– Mark Fleming, MD, Vascular Surgeon
  Mayo Clinic, Rochester, MN, USA
– Juan Granada, MD, Interventional Cardiologist
  CRF-Skirball Center for Innovation, Orangeburg, NY, USA
– Michael Jaff, DO, Vascular Medicine
  Newton-Wellesley Hospital, Newton, MA, USA

Industry Representatives (Medtronic)

– Mark Turco, MD
– Chris Tieché, PhD
– Lynn Oster, RN
– Simona Zannetti, MD

Core Labs

– SynvaCor, Springfield, IL, USA
– Beth Israel Deaconess Medical Center, Boston, MA, USA
Methods: Study Scope

Inclusion Criteria
– Medtronic Peripheral trials and registries
– TLRs ≤12mo of index procedure

Exclusion Criteria
– Unevaluable or absent angiographic studies
– Below-knee TLRs (as part of DEFINITIVE LE)

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment Cohort</th>
<th>Total Subjects</th>
<th>Target Lesion Revascularizations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IN.PACT SFA</td>
<td>PTA</td>
<td>111</td>
<td>22</td>
</tr>
<tr>
<td>IN.PACT SFA</td>
<td>DCB</td>
<td>220</td>
<td>6</td>
</tr>
<tr>
<td>IN.PACT Global - Interim analysis</td>
<td>DCB</td>
<td>655</td>
<td>46</td>
</tr>
<tr>
<td>DEFINITIVE LE - Above-knee</td>
<td>Atherectomy</td>
<td>655</td>
<td>106</td>
</tr>
<tr>
<td>DEFINITIVE AR</td>
<td>Atherectomy + DCB</td>
<td>121</td>
<td>22</td>
</tr>
<tr>
<td>DURABILITY II</td>
<td>Bare metal stent</td>
<td>287</td>
<td>35</td>
</tr>
<tr>
<td>Complete SE SFA</td>
<td>Bare metal stent</td>
<td>196</td>
<td>17</td>
</tr>
<tr>
<td>IN.PACT Global ISR</td>
<td>Bare metal stent</td>
<td>131</td>
<td>149</td>
</tr>
</tbody>
</table>

2376 403
Methods: Index Treated Length

The index treated length (ITL) for stent cases, was defined by the margins of stent
Methods: Index Treated Length

The index treated length (ITL) for non-stent cases, was determined by the angiographic core lab.
Methods: Qualified Lesions

Stenosis qualifications

- >50% restenosis (Figure A)
- Within ITL (Figure B)
Methods: Validation

Validation Process

- 32 TLR cases representing a selection of all treatment modalities were chosen for validation
- Physician panel scored the cases by consensus
- Angiographic core lab independently scored cases

Validation Results

- 1 TLR case excluded due to incomplete imaging needed by core lab
- 3 TLR cases disqualified due to restenosis <50%
- Remaining 28 cases achieved 100% correlation with physician panel

Validation results confirm the scoring algorithm could be practically applied with minimal instruction to an experienced angiographic core lab.
**Results: Scoring System**

**Type 1: Focal lesions <20% ITL**
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

*ITL = Index Treated Length*
Results: Scoring System

**Type 1: Focal lesions**  <20% ITL
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

**Type 2: Multifocal lesions**
- Multiple lesions combining to <50% ITL but with ≥3cm separation
- Edge bilateral within 2cm of both ITL margins

Blue arrow denotes ITL  

ITL = Index Treated Length
Results: Scoring System

**Type 1: Focal lesions** <20% ITL
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

**Type 2: Multifocal lesions**
- Multiple lesions combining to <50% ITL but with ≥3cm separation
- Edge bilateral within 2cm of both ITL margins

**Type 3: Moderate lesions**
- Lesions ≥20% but <50% of the ITL
- Multiple lesions with <3cm separation

ITL = Index Treated Length
Results: Scoring System

**Type 1: Focal lesions <20% ITL**
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

**Type 2: Multifocal lesions**
- Multiple lesions combining to <50% ITL but with ≥3cm separation
- Edge bilateral within 2cm of both ITL margins

**Type 3: Moderate lesions**
- Lesions ≥20% but <50% of the ITL
- Multiple lesions with <3cm separation

**Type 4: Diffuse lesions**
- Lesions ≥50% ITL regardless of separation

ITL = Index Treated Length
Results: Scoring System

**Type 1: Focal lesions <20% ITL**
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

**Type 2: Multifocal lesions**
- Multiple lesions combining to <50% ITL but with ≥3cm separation
- Edge bilateral within 2cm of both ITL margins

**Type 3: Moderate lesions**
- Lesions ≥20% but <50% of the ITL
- Multiple lesions with <3cm separation

**Type 4: Diffuse lesions**
- Lesions ≥50% ITL regardless of separation

**Type 5: Occlusive lesions**

ITL = Index Treated Length
Results: Scoring System

Type 1: **Focal lesions** <20% ITL
- Edge proximal <2cm of proximal ITL margin
- Edge distal <2cm of distal ITL margin

Type 2: **Multifocal lesions**
- Multiple lesions combining to <50% ITL but with ≥3cm separation
- Edge bilateral within 2cm of both ITL margins

Type 3: **Moderate lesions**
- Lesions ≥20% but <50% of the ITL
- Multiple lesions with <3cm separation

Type 4: **Diffuse lesions**
- Lesions ≥50% ITL regardless of separation

Type 5: **Occlusive lesions**

ITL = Index Treated Length
Limitations

• Only MDT devices evaluated
  - Atherectomy cases were only directional atherectomy (SilverHawk and TurboHawk)
  - Laser-cut nitinol stents
    • No interwoven stents
  - DCB cases were only IN.PACT Admiral
  - No peripheral stent-grafts
  - No peripheral drug-eluting stents

• Only complete / high-quality imaging studies were evaluable

• Procedural and technical variables, such as catheter placement and remote device complications, are not part of the analysis
Summary

- Existing restenosis scoring systems lack descriptive value for non-stent treatments and long, complex FPA lesions
- We currently do not have a single system detailing PV interventional failures
- Proposed system provides all-inclusive nomenclature with more description of failure morphologies
  - These may provide for more information regarding subsequent therapy (ies)
  - Potential determinant for index procedural technology
- The proposed “patterns of restenosis” may unify previous and future device trials regardless of technology
- Current team will continue to explore factors influencing restenosis patterns, including treatment modality, index lesion morphology, and time-to-failure
Patterns of Restenosis:  
A Core Lab-driven Assessment of SFA Restenosis and a Potential Shift to Unify Various Trials

Lawrence A. Garcia, MD  
St. Elizabeth’s Medical Center  
Boston, MA, USA