A Data-driven Therapeutic Algorithm For Choosing Among Currently Available Tools For SFA Intervention

William A. Gray MD
Director of Endovascular Services
Associate Professor of Clinical Medicine
Columbia University Medical Center
The Cardiovascular Research Foundation
Dissapointing results for non-nitinol stents

- Results of the first generation self-expanding stents (WallStent & Strecker stent) in the SFA

<table>
<thead>
<tr>
<th></th>
<th>FU</th>
<th>Lesion length</th>
<th>Primary Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Van Der Zaag et al</td>
<td>12M</td>
<td>5-15 cm</td>
<td>43%</td>
</tr>
<tr>
<td>EJVES 2004</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Conroy et al</td>
<td>24M</td>
<td>mean 13.5 cm</td>
<td>36%</td>
</tr>
<tr>
<td>J Vasc Int Radiol 2000</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gordon et al</td>
<td>12M</td>
<td>mean 14.5 cm</td>
<td>55%</td>
</tr>
<tr>
<td>Arch Surg 2001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cheng et al</td>
<td>24M</td>
<td>mean 16 cm</td>
<td>35%</td>
</tr>
<tr>
<td>Ann Vasc Surg 2003</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
TASC classifications of SFA lesions

Type A lesions
- Single stenosis ≤10 cm in length
- Single occlusion ≤5 cm in length

Type B lesions:
- Multiple lesions (stenoses or occlusions), each ≤5 cm
- Single stenosis or occlusion ≤15 cm not involving the infrageniculate popliteal artery
- Single or multiple lesions in the absence of continuous tibial vessels to improve inflow for a distal bypass
- Heavily calcified occlusion ≤5 cm in length
- Single popliteal stenosis

Type C lesions
- Multiple stenoses or occlusions totaling >15 cm with or without heavy calcification
- Recurrent stenoses or occlusions that need treatment after two endovascular interventions

Type D lesions
- Chronic total occlusions of CFA or SFA (>20 cm, involving the popliteal artery)
- Chronic total occlusion of popliteal artery and proximal trifurcation vessels
### Levels of evidence

**Source:** US Preventive Services Task Force

<table>
<thead>
<tr>
<th>Level</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Level I</strong></td>
<td>well-designed, prospective, randomized, controlled trials</td>
</tr>
<tr>
<td><strong>Level IIa</strong></td>
<td>well-designed, prospective, non-randomized, controlled trials</td>
</tr>
<tr>
<td><strong>Level IIb</strong></td>
<td>well-designed, prospective, non-randomized, non-controlled cohort or case-control analytic studies</td>
</tr>
<tr>
<td><strong>Level IIc</strong></td>
<td>retrospective, non-randomized, non-controlled multiple time series</td>
</tr>
<tr>
<td><strong>Level III</strong></td>
<td>expert opinions, based on clinical experience, descriptive studies or reports of expert committees</td>
</tr>
</tbody>
</table>
### Summary of non-randomized trial results

**Levels IIa, IIb, IIc**

<table>
<thead>
<tr>
<th>Reference</th>
<th>stent name</th>
<th>lesion length (cm)</th>
<th>prim patency @12-months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jahnke 2002</td>
<td>IntraCoil</td>
<td>3.6</td>
<td>86.2%</td>
</tr>
<tr>
<td>Wiesinger 2005</td>
<td>Covered SMART</td>
<td>5</td>
<td>89.8%</td>
</tr>
<tr>
<td>Henry 1996</td>
<td>VascuCoil</td>
<td>&lt; 4</td>
<td>89 %</td>
</tr>
<tr>
<td>Sabeti 2004</td>
<td>any</td>
<td>5</td>
<td>75 %</td>
</tr>
<tr>
<td>Lugmayr 2002</td>
<td>Symphony</td>
<td>&lt; 6</td>
<td>87 %</td>
</tr>
<tr>
<td>Lenti 2007</td>
<td>aSpire</td>
<td>unk</td>
<td>64 %</td>
</tr>
<tr>
<td>Schillinger 2001</td>
<td>any</td>
<td>10.1</td>
<td>63 %</td>
</tr>
<tr>
<td>Fischer 2006</td>
<td>Hemobahn/Viabahn</td>
<td>10.7</td>
<td>80 %</td>
</tr>
<tr>
<td>Jahnke 2003</td>
<td>Hemobahn</td>
<td>10.9</td>
<td>78.4%</td>
</tr>
<tr>
<td>Schlager 2005</td>
<td>any</td>
<td>12.5</td>
<td>80 %</td>
</tr>
<tr>
<td>Lammer 2000</td>
<td>Hemobahn</td>
<td>13.1</td>
<td>78.7%</td>
</tr>
<tr>
<td>Cheng 2001</td>
<td>any</td>
<td>13.8</td>
<td>62.6%</td>
</tr>
<tr>
<td>Daenens 2005</td>
<td>Hemobahn</td>
<td>15</td>
<td>66 %</td>
</tr>
<tr>
<td>Cheng 2003</td>
<td>any</td>
<td>16</td>
<td>56 %</td>
</tr>
<tr>
<td>Bray 2005</td>
<td>Hemobahn</td>
<td>17.8</td>
<td>60.8%</td>
</tr>
<tr>
<td>Biamino 2002</td>
<td>SMART</td>
<td>20.8</td>
<td>55 %</td>
</tr>
</tbody>
</table>
WL Gore Hemobahn vs. PTA

Study description:

- Single-center experience as part of a US prospective, randomized, controlled, multi-center study

- Balloon angioplasty vs. Hemobahn (Gore) ePTFE-covered endoprosthesis placement


Saxon et al. J Vasc Interv Radiol 2003;14:303-311
28 patients

Randomization

PTA (n = 13)

Hemobahn (n = 15)

Saxon et al. J Vasc Interv Radiol 2003;14:303-311
<table>
<thead>
<tr>
<th>Lesion information</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PTA</strong></td>
<td><strong>Hemobahn</strong></td>
</tr>
<tr>
<td>Average lesion length</td>
<td>6.32cm (4.44-8.20)</td>
</tr>
<tr>
<td>TASC A</td>
<td>1</td>
</tr>
<tr>
<td>TASC B</td>
<td>8</td>
</tr>
<tr>
<td>TASC C</td>
<td>3</td>
</tr>
<tr>
<td>TASC D</td>
<td>1</td>
</tr>
</tbody>
</table>

Saxon et al. J Vasc Interv Radiol 2003;14:303-311
WL Gore Hemobahn vs. PTA

Survival Plot for Treatment Site

<table>
<thead>
<tr>
<th>Months</th>
<th>Patency Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.0</td>
</tr>
<tr>
<td>5</td>
<td>0.9</td>
</tr>
<tr>
<td>10</td>
<td>0.8</td>
</tr>
<tr>
<td>15</td>
<td>0.7</td>
</tr>
<tr>
<td>20</td>
<td>0.6</td>
</tr>
<tr>
<td>25</td>
<td>0.5</td>
</tr>
<tr>
<td>30</td>
<td>0.4</td>
</tr>
<tr>
<td>35</td>
<td>0.3</td>
</tr>
<tr>
<td>40</td>
<td>0.2</td>
</tr>
<tr>
<td>45</td>
<td>0.1</td>
</tr>
<tr>
<td>50</td>
<td>0.0</td>
</tr>
</tbody>
</table>

Hemobahn 87%

Angioplasty 23%

Dotted lines provide 95% confidence intervals.

P-value 0.0019

Saxon et al. J Vasc Interv Radiol 2003;14:303-311
Conclusions for medium length lesions

- Patency rates after Hemobahn implantation were significantly better than those after balloon angioplasty.

- Clinical success rate was significantly higher in the Hemobahn group.

Saxon et al. J Vasc Interv Radiol 2003;14:303-311
Absolute stent vs. PTA

- Prospective, randomized, controlled, single-center
- Balloon angioplasty vs. nitinol stent implantation
- Inclusion period: Jun 2003 – Aug 2004

Schillinger et al. NEJM 2006;354:1879-1888
Absolute stent vs. PTA

Randomization scheme
“on treatment” basis

104 patients

PTA
(n = 53)

Stent
(n = 51)

Crossover
due to insufficient PTA result
(n = 17 [32%])

Schillinger et al. NEJM 2006;354:1879-1888
Absolute stent vs. PTA

Randomization scheme
“on treatment” basis

104 patients

Randomization

PTA (n = 53)

Stent (n = 51)

Crossover due to insufficient PTA result (n = 17 [32%])

PTA (n = 36)

Stent (n = 68)

← “on treatment” →

Schillinger et al. NEJM 2006;354:1879-1888
Absolute stent vs. PTA

Lesion information

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>Nitinol stent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average lesion length</td>
<td>9.2cm (±6.4)</td>
<td>10.1cm (±7.5)</td>
</tr>
<tr>
<td>Occlusions</td>
<td>19% (±10)</td>
<td>17% (±10)</td>
</tr>
</tbody>
</table>

Schillinger et al. NEJM 2006;354:1879-1888
Absolute stent vs. PTA

“intention to treat”

- PTA (30/53) 57%
- Stent (39/51) 66%

p=0.05 (significant)

“on treatment”

- PTA (18/36) 50%
- Stent (51/68) 75%

p=0.03 (significant)

Schillinger et al. NEJM 2006;354:1879-1888
Absolute stent vs. PTA

Based on “intention to treat” principle

After 6 months

- PTA (29/53): 55%
- Stent (38/51): 75%

p = 0.06 (not significant)

After 12 months

- PTA (19/52): 37%
- Stent (31/49): 63%

p = 0.01 (significant)

Schillinger et al. NEJM 2006;354:1879-1888
Conclusion for medium length lesions

- Angiography showed significantly better restenosis rates for the stent group at 6 months
- Duplex sonography confirmed significantly better restenosis rates at 12 months
- Clinical worsening was rare in either group
- Reintervention rates were similar in both groups

Schillinger et al. NEJM 2006;354:1879-1888
PTA vs. Lumunexx Stent

- Prospective, randomized, controlled
- Balloon angioplasty vs. Luminexx nitinol stent
- Femoral Artery Stenting Trial
- SFA lesions between 1 and 10cm in length
- Only 1 stent per treated lesion

PTA vs. Lumunexx Stent

Randomization scheme
“on treatment” basis

- 244 patients

Randomization

- PTA (n = 121)
- Stent (n = 123)

Crossover due to insufficient PTA result
(n = 13 [11%])

PTA vs. Lumunexx Stent

Randomization scheme
“on treatment” basis

244 patients

Randomization

PTA (n = 121)

Stent (n = 123)

Crossover due to insufficient PTA result (n = 13 [11%])

PTA (n = 108)

Stent (n = 136)

← “on treatment” →

## PTA vs. Luminexx Stent

### Lesion information: short to medium length lesions

<table>
<thead>
<tr>
<th></th>
<th>PTA</th>
<th>Luminexx stent</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Average lesion length</td>
<td>44.5mm</td>
<td>45.2mm</td>
<td>not significant</td>
</tr>
<tr>
<td>Occlusions</td>
<td>25%</td>
<td>37%</td>
<td>not significant</td>
</tr>
</tbody>
</table>

*Krankenberg H et al. Circulation 2007;116;285-292*
PTA vs. Lumunexx Stent

"intention to treat"

PTA (62/101) Stent (69/101)

61.4% 68.3%

p=0.377 (not significant)

"on treatment"

PTA (56/90) Stent (75/112)

62.2% 67%

p=0.554 (not significant)

PTA vs. Luminexx Stent

Conclusion

- The Femoral Artery Stenting Trial failed to demonstrate the superiority of the Luminexx nitinol stent over stand-alone PTA in the treatment of patients with superficial femoral artery (SFA) lesions 1-10cm in length.
SIROCCO I & II: SES vs. BMS

• Double-blind, randomized, prospective (sirolimus vs. bare stent)
• SIROLimus Coated Cordis SMART Nitinol Self-expanding stent for the treatment of Obstructive SFA disease

• Phase 1: 36 patients
  - max 3 stents → >70% stenosis >7cm to <20cm
    → occlusion >4cm to <20cm

• Phase 2: 57 patients
  - max 2 stents → lesion length >7cm to <14.5cm
    → occlusion >4cm to <14.5cm
### SIROCCO I & II

#### Baseline Lesion Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus (n=29)</th>
<th>Control (n=28)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thrombus (%)</td>
<td>3.6</td>
<td>0</td>
<td>0.42</td>
</tr>
<tr>
<td>Moderate/Severe Calcification (%)</td>
<td>44.8</td>
<td>32.3</td>
<td></td>
</tr>
<tr>
<td>Total Occlusion (%)</td>
<td>75.9</td>
<td>57.1</td>
<td>0.17</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>86.5 ±36.6</td>
<td>76.3 ±45.7</td>
<td>0.39</td>
</tr>
<tr>
<td>Reference Vessel Diameter (mm)</td>
<td>4.92 ±0.77</td>
<td>4.61 ±0.72</td>
<td>0.12</td>
</tr>
<tr>
<td>Pre – Percent Diameter Stenosis (%)</td>
<td>95.8 ±7.82</td>
<td>89.1 ±14.8</td>
<td>0.09</td>
</tr>
</tbody>
</table>
### SIROCCO I & II

#### Duplex Ultrasound @ 24-month

<table>
<thead>
<tr>
<th></th>
<th>Slower Eluting (n=5)</th>
<th>Fast Eluting (n=11)</th>
<th>Control (n=17)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Binary Restenosis Rate</strong></td>
<td>% (n)</td>
<td>40.0 (2)</td>
<td>44.4 (4)</td>
</tr>
<tr>
<td><strong>Total Occlusion</strong></td>
<td>% (n)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td><strong>Total Restenosis/Occlusions</strong></td>
<td>% (n)</td>
<td>40.0 (2)</td>
<td>44.4 (4)</td>
</tr>
<tr>
<td><strong>Target Lesion Revascularization</strong></td>
<td>% (n)</td>
<td>0</td>
<td>11.1 (1)</td>
</tr>
</tbody>
</table>
## SIROCCO I & II

### Angiography @ 24-month

<table>
<thead>
<tr>
<th></th>
<th>Pooled SR</th>
<th>Control</th>
<th>( p ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SIROCCO I-II</td>
<td>SIROCCO I-II</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(n=16)</td>
<td>(n=14)</td>
<td></td>
</tr>
<tr>
<td><strong>Minimum Lumen Diameter</strong></td>
<td>2.15mm</td>
<td>2.15mm</td>
<td>0.941</td>
</tr>
<tr>
<td><strong>Stent Mean Diameter</strong></td>
<td>3.42mm</td>
<td>3.35mm</td>
<td>0.995</td>
</tr>
<tr>
<td><strong>In-stent restenosis</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>- unreadable</td>
<td>3 (18.8%)</td>
<td>2 (14.3%)</td>
<td>0.370</td>
</tr>
<tr>
<td>- patent</td>
<td>9 (56.3%)</td>
<td>8 (57.1%)</td>
<td></td>
</tr>
<tr>
<td>- ≥50% and &lt;70%</td>
<td>4 (25.0%)</td>
<td>2 (14.3%)</td>
<td></td>
</tr>
<tr>
<td>- ≥70% and &lt;100%</td>
<td>-</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
<tr>
<td>- occlusion</td>
<td>-</td>
<td>1 (7.1%)</td>
<td></td>
</tr>
</tbody>
</table>
Fractures associated with
- Multiple stents
- Longer stented lengths
- Frequently adjacent to the overlaps (not in the overlap areas themselves)

No relationship between fracture and restenosis

Sirolimus-eluting stents are safe for SFA treatment

Excellent results with bare SMART stent
- In-stent binary restenosis rate: 28.5% @ 24 months (angiographically)
Zilver PTX: PES vs. BMS

- Randomized Study (480 pts)
  - Phase 1: 60 patients
    - lesions ≤ 7 cm, up to 1 stent per limb
    - enrollment complete
  - Phase 2: 420 patients
    - Lesions ≤ 14 cm, up to 2 stents per limb
    - Currently enrolling

- Registry Study (760 pts)
  - Up to 4 Zilver® PTX™ stents per patient
  - Currently enrolling:
    - more than 700 patients enrolled/approximately 2500 stents implanted
### PTX: Baseline angiographic data

<table>
<thead>
<tr>
<th></th>
<th>Randomized Study (Phase 1)</th>
<th>Registry Study</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>PTA (N = 33 lesions)</td>
<td>ZPTX (N = 29 lesions)</td>
</tr>
<tr>
<td>Lesion Length (cm)</td>
<td>3.6 ± 2.0 (range 1 to 7)</td>
<td>4.1 ± 3.1 (range 1 to 10)</td>
</tr>
<tr>
<td>Proximal RVD (mm)</td>
<td>5.2 ± 1.0</td>
<td>5.0 ± 1.1</td>
</tr>
<tr>
<td>Distal RVD (mm)</td>
<td>5.3 ± 1.0</td>
<td>4.9 ± 1.1</td>
</tr>
<tr>
<td>MLD in lesion (mm)</td>
<td>1.3 ± 0.8</td>
<td>1.1 ± 0.7</td>
</tr>
<tr>
<td>% Diameter Stenosis</td>
<td>76 ± 15</td>
<td>78 ± 14</td>
</tr>
</tbody>
</table>
# Zilver PTX: 6-month effectiveness

<table>
<thead>
<tr>
<th>Study</th>
<th>Freedom from TLR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Phase 1 of the randomized study</td>
<td></td>
</tr>
<tr>
<td>PTA</td>
<td>52% [17/33]</td>
</tr>
<tr>
<td>No PTA failure</td>
<td>100% [17/17]</td>
</tr>
<tr>
<td>PTA acute failure → BMS Zilver</td>
<td>75% [6/8]</td>
</tr>
<tr>
<td>PTA acute failure → PTX Zilver</td>
<td>100% [8/8]</td>
</tr>
<tr>
<td>Zilver PTX</td>
<td>90% [26/29]</td>
</tr>
<tr>
<td>Registry Zilver PTX</td>
<td>90% [82/91]</td>
</tr>
</tbody>
</table>

48% [16/33]
RESILIENT: LifeStent vs. PTA

Phase I: Feasibility @ 6 sites
- n=20 PTA + LifeStent
- n=20 roll-in PTA + LifeStent

Phase II: Pivotal @ 24 sites
- n=206 randomly allocated 1:2

PTA Only Control Arm n=69
PTA + LifeStent Test Arm n=137

RESILIENT: Bail-out lesion characteristics

Lesion Length/patient (mm)

- PTA only (n=43): 52.0 ± 38.2
- PTA-Bailout-Stent (n=29): 70.5 ± 44.3
- LifeStent (n=134): 82.8 ± 37.8

* = Visual Estimate
+ = t-test for Equality of Means

RESILIENT Results: 12-Month

*Data from Kaplan-Meier Survival Analysis

- Freedom from MACE*: 86% (PTA) vs. 86% (PTA+LifeStent, p=.91)
- Prim. Patency (duplex)*: 80% (PTA) vs. 38% (PTA+LifeStent, p<.0001)
- Freedom from TLR*: 87% (PTA) vs. 46% (PTA+LifeStent, p<.0001)
- Clinical success: 72% (PTA+LifeStent, p<.0001)

Bail-out stenting (crossover) in the PTA group occurred 40.2% (29/72) for:
- Major flow-limiting dissection (38%)
- Residual stenosis >30% (62%)

Confirmed as acceptable by Core Lab and CEC

Procedural crossover to stenting in the PTA group was defined as a TLR and counted as a primary endpoint and patency failure

Clinical trial comparison using the reported rates of TLR
Clinical trial comparison using the RESILIENT/ZILVER PTX definitions of TLR

freedom from TLR (%)

- ABSOLUTE VIENNA (12 mos., 10.1 cm)
- RESILIENT (12 mos., 7.1 cm)
- ZILVER PTX (6 mos., 4.1 cm)

Freedom from TLR @1-day

Freedom from TLR @8-12 mos.
Clinical trial comparison using the ABSOLUTE/VIENNA definitions of TLR

Freedom from TLR @1-day

Freedom from TLR @6-12 mos.

PTA

STENT

PTA

STENT

ABSOLUTE VIENNA
(12 mos., 10.1 cm)

RESILIENT
(12 mos., 7.1 cm)

ZILVER PTX
(6 mos. 4.1 cm)
SFA Challenges: Data collection

- Data collection
  - Endpoint definitions of success
    - Anatomic
      - Binary restenosis (>50%)
      - Discrete vs. diffuse vs. volume definitions
    - Clinical
      - Walking distance
      - ABI
  - Quantifying (and understanding) restenosis
    - Angiographic
    - Duplex
    - Intravascular ultrasound
  - Time course defining durability of intervention
  - Consistent and standardized reporting structure
Patient factors with unclear influence on interventional outcomes

- Inflow/Run-off status
- Length of disease
- Vessel diameter
- Occlusion vs. stenosis
- Diabetic status
- Tobacco status
- Atheroma volume
- Calcification
- Gender
Procedural factors with unclear influence on interventional outcomes

- Stents
  - Number
  - Degree of overlap
  - Compression or stretch during implant
  - Significant oversizing or undersizing
- Adjunctive debulking
SFA: Design challenges

- This arterial territory response to intervention is poorly understood
  - There are no large-scale data sets from which to establish design goals
  - Such data was critical to the understanding of coronary stent behavior and the opportunity to improve the technology in a focused direction
Late Loss in Bare Metal Stents

6-mo Follow-Up

QCA Late Loss (mm)

- Multi-Link, .0022", 0.90mm
- Multi-Link Vision*, .0032", 0.83mm
- Multi-Link Penta*, .0036"-.0049", 0.90mm
- BiodivYsio®, .0040", 0.80mm
- NIR*, .0040", 0.80mm
- Bx VELOCITY®, .0055", 0.97mm
- Bx VELOCITY®, .0055", 0.80mm
- Bx VELOCITY®, .0055", 0.70mm
- RAVEL Ctrl, .0055", 0.80mm
TAXUS IV – Impact of Vessel Size & Lesion Length

TLR (12-month)

Control

TAXUS

Lesion Length (mm)

RVD (mm)

< 2.5

2.5-3.0

≥ 3.0

TLR (%)
Result of lack of outcome data

- Current efforts at designing successful devices which will have improved outcomes are at best estimates of the causal relationships.

- In the typically small clinical trials testing in SFA therapies, these devices are subject to variation in subject/vessel characteristics.
Conclusions

• Stents are better than PTA (I think) for limited lesion length
• Long stents are worse than short stents
• Not all stent fractures are created equal
  ▪ FESTO results not borne out in later trials
• Alternative therapies (photodynamic, adventitial injection, adjunctive atherectomy, etc.,) may be useful but as yet untested
• Drug-eluting balloon looks interesting in spite of lack of clear mechanism
• VIBRANT trial data will be interesting