Drug Eluting Stents in the SFA: A Long Way Off?

John R. Laird
Cardiovascular Research Institute
Washington Hospital Center
METHODS OF STENT-MEDIATED DELIVERY

Stent

- COOK
- CORDIS
- GUIDANT

Top-coat

Sub-layer

2µm
5µm

Bio
divYsio

Matrix H1

Boston Scientific

BiodivYsio Matrix LO

Degradable inlays

Degradable polymer

JOMED

Degradable stent

Nanoporous ceramic

SORIN

CONOR-Medsystems

Biosensor

PC coating

1µm

1µm

1µm

+++

1µm
SFA Intervention - Nature of the Problem

- Occlusion predominates over stenosis
- Diffuse disease common
- Adductor canal
- Low flow/high resistance
- Coexistant disease of distal run-off vessels
SFA Drug Eluting Stents

Issues to be Resolved

- Proper dose
- Ideal release kinetics
- Applying drug with or without a polymer to self-expanding stents that are implanted in a dynamic environment
- Stent fractures
- Cost
What is the Proper Dose?

Dose of Sirolimus in SIROCCO Trial:
1 mg per 6 x 80 cm SMART stent
## SIROCCO I
### Six Month Angiographic Results

<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>MLD (mm)</td>
<td>4.31</td>
<td>3.47</td>
<td>3.28</td>
</tr>
<tr>
<td>Late Loss (mm)</td>
<td>0.39</td>
<td>0.72</td>
<td>1.03</td>
</tr>
<tr>
<td>Restenosis Rate</td>
<td>0%</td>
<td>0%</td>
<td>17.6%</td>
</tr>
</tbody>
</table>
# SIROCCO II
## Six Month Angiographic Results

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus (N=24)</th>
<th>Control (N=26)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MLD (mm)</td>
<td>3.91±0.72</td>
<td>3.62±0.91</td>
</tr>
<tr>
<td>Late Loss (mm)</td>
<td>0.38±0.64</td>
<td>0.68±0.97</td>
</tr>
<tr>
<td>Restenosis Rate</td>
<td>0%</td>
<td>7.7%</td>
</tr>
</tbody>
</table>
Zilver® PTX™ Coating

- Paclitaxel only (no polymer or binder)
- Thin coating (less than 5 microns)
- 3 microgm/mm² dose density
  (maximum 880 microgm total dose, largest stent)
What are the Optimal Release Kinetics?

Is the time course of restenosis the same in the SFA?
SFA Wallstents

61% Primary Patency @ one year

6 mo patency: < 10 cm=83%
> 10 cm=59%  p=0.38

Martin, etal., JVIR 1995;6:843-849
SFA Stenting – Nitinol Stents

- 137 limbs in 122 patients
- Cordis SMART stent (n=246, 1.8 stents/limb)
- Mean lesion length: 12.6 cm
- Technical Success 98%
- No acute (<30 day) occlusion
- Mean follow-up 302 days
- Primary Patency:
  - 6 month: 92%
  - 12 months: 76%

Mewissen, Endovascular Today 2003
FP Primary Stenting Results

50-99% Stenosis Free Survival

PP% SE%

Months

24m 18m 12m 6m 60 66 76 92 2 3.5 4 5

13 6 4 2 13

0.00 0.20 0.40 0.60 0.80 1.00
The SIROCCO Studies: Stent Binary Restenosis Rates

<table>
<thead>
<tr>
<th>Follow up</th>
<th>6 months</th>
<th>18 months</th>
<th>24 months</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Angiographic</td>
<td>Duplex Ultrasound</td>
<td>Duplex Ultrasound</td>
</tr>
<tr>
<td>SIROCCO I</td>
<td>17.6% (n=17)</td>
<td>24% (n=17)</td>
<td>47.1% (n=17)</td>
</tr>
<tr>
<td>Lesion Length (mm)</td>
<td>88.6mm</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIROCCO II</td>
<td>7.7% (n=26)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lesion length (mm)</td>
<td>76.3 ± 45.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>SIROCCO I &amp; II</td>
<td>11.6% (n=43)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(Pooled data)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Are the Current DES Release Kinetics Going to Work?
Late Failures in SIROCCO I
18 Month Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Slower Eluting</th>
<th>Fast Eluting</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n=5</td>
<td>n=9</td>
</tr>
<tr>
<td>Binary Restenosis</td>
<td>0</td>
<td>33%</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLR</td>
<td>0</td>
<td>11% (1)</td>
</tr>
</tbody>
</table>
Late Failures in SIROCCO I
24 Month Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Slower Eluting n=5</th>
<th>Fast Eluting n=9</th>
</tr>
</thead>
<tbody>
<tr>
<td>Binary Restenosis</td>
<td>40% (2)</td>
<td>44% (4)</td>
</tr>
<tr>
<td>Total Occlusion</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>TLR</td>
<td>0</td>
<td>11% (1)</td>
</tr>
</tbody>
</table>
## SIROCCO II – 24 Months
Duplex Restenosis/Reocclusion

\( N=57 \)

<table>
<thead>
<tr>
<th></th>
<th>6 Months</th>
<th>9 Months</th>
<th>18 Months</th>
<th>24 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus Coated</td>
<td>0%</td>
<td>10.3%</td>
<td>20.7%</td>
<td>24.1%</td>
</tr>
<tr>
<td>( N=29 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bare Metal</td>
<td>7.7%</td>
<td>14.3%</td>
<td>17.9%</td>
<td>25.0%</td>
</tr>
<tr>
<td>( N=28 )</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SIROCCO Cases (Pt. #11, sirolimus)
Polymer vs. No Polymer?
What Happens to the Polymer?

Drug-Eluting Stent
U.S. Approved Coronary DES (Ormiston, et al., TCT2004)
Mechanical Forces Applied to the SFA
Polymer-free Coating Rationale

• Paclitaxel is hydrophobic, lipophilic and highly protein bound
  – Minimal washout during stent delivery (also protected within sheath)
  – Long tissue residence time (>2 months)
• All known stent coatings have imperfections
What is the impact of stent fracture in the SFA?
Results of X-Ray Screening – FESTO Trial
10.7 Month Follow-up

• Fractures in 45 of 121 treated legs: 37.2%

• Fractures in 64 of 261 implanted stents: 24.5%
Results of X-Ray Screening

- Minor (single strut fracture)
  - In 31 cases
  - 48.4%
- Moderate (>one strut fracture)
  - In 17 cases
  - 26.6%
- Severe (separation of segments)
  - In 16 cases
  - 25.0%

D. Scheinert
Stent Fracture
Femoropopliteal Stent-Fracture

D. Scheinert
What will it cost?
SFA DES – Where do we Stand?

- SIROCCO II confirmed the short term efficacy of the slower release formulation identified in SIROCCO I.

- Good outcomes in the bare SMART stent arm of the trial with an overall 6 month angiographic pooled restenosis rate of 11.6% (n=43) and an 18 month rate of 22.2% (n=45).

- Slower eluting data pooled from SIROCCO I and II resulted in an early statistically significant difference in the primary endpoint (mean stent diameter), however, this advantage was lost by 18 months.

- The DESTINY trial using the Cook Zilver PTX devices with Paclitaxel recently completed Phase 1 - enrolling 60 patients with SFA disease <7cm long.
Study Design – Phase 2

- Controlled, randomized, multicenter study
- Up to two lesions, one in each limb, may be treated and up to two stents (one stent in Phase 1) may be used per lesion

![Study Design Diagram]

- **Total = 480 patients**
  - **Lesions ≤ 7 cm**
    - Phase 1: Randomized (single DES per lesion versus PTA)
  - **Lesions 7-14 cm**
    - Phase 2: Randomized (up to two, overlapping DES per lesion versus PTA)
Substudies

• Angiographic Substudy
  – 6 months in Phase 1 (plus IVUS)
  – 12 months in Phase 2
• Long-term Duplex Ultrasound Substudy
  – 2, 3, 4, and 5 years
  – All DES patients
  – Subgroup of PTA patients
• Pharmacokinetic Substudy (DES group)
Summary

- Still many reasons for optimism given the excellent results with DES in the coronary arteries.
- No guarantee that DES will work in the SFA.
- Many unanswered questions.
- Given the current pace of investigation, commercially available DES for the SFA is several years away (at least!)