Drug-Eluting Stent Implantation for the Treatment of CLI

Ramzan M. Zakir, MD, FACC, FSCAI

Director of Peripheral Vascular Program
Saint Peter’s University Hospital
Clinical Assistant Professor Of Medicine
Rutgers: Robert Wood Johnson Medical School
New Brunswick, New Jersey
Disclosures

Speaker’s Bureau:
• Abbott Vascular
• Medtronic

Honorarium:
• AstraZeneca

Consultant:
• CSI
• Terumo Medical
• Spectranetics
• Bard
• Avinger

Stockholder:
• Avinger
Critical Limb Ischemia

- Goal of Therapy is functional limb preservation

  - Optimal
    - Revascularization
    - Extravascular Care
  - Durable
    - Surveillance
PTA in BTK: CLI Patients

Up to 50% post-PTA TLR rate in real world CLI pts

- 101 Patients 12m Angio
- 60 Patients 10m Angio
- 33 Patients 6m Angio
- 11 Patients 12m Angio
- 67 Patients 12m Angio
- 77 Patients 3m Angio

Restenosis Rate, TLR, Tot Occlusions (%), lesion length (cm)

Zeller T, LINC 2013
Restenotic Cascade

Balloon inflation or stent deployment in atherosclerotic vessel
- Crush plaque
- Stretch artery
- De-endothelialization

Platelets and fibrin deposited at injured site
- Signaling cascades
- Inflammatory response

Neointimal proliferation
- Smooth muscle cell (SMC) migration
- Cellular division

Restenosis
- Extracellular matrix production
- Re-endothelialization

Antiproliferative Agents
- Reduce inflammation
- Arrest mitosis
- Inhibit SMC migration

Immediate
- Days
- Weeks
- Months
DES for Peripheral Applications: Intended Clinical Benefit

Minimize negative vessel remodeling and proliferative response¹

- Scaffolding prevents vessel shrinkage
- Anti-proliferative drugs (e.g., paclitaxel) counteract neointimal response to stenting

Clinical trials of drug-eluting stents have shown improved stent patency following treatment of femoropopliteal² and below-the-knee³,⁴ lesions

Prolong stent patency

## SFA Stent Patency
### Recent Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Stent</th>
<th>Subjects</th>
<th>Avg. Lesion Length (cm)</th>
<th>% CTO</th>
<th>Freedom from TLR</th>
<th>Fracture Rate (%)</th>
<th>12 M Primary Patency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Leipzig</td>
<td>SUPERA</td>
<td>107*</td>
<td>10.9</td>
<td>30</td>
<td>-</td>
<td>0</td>
<td>86</td>
</tr>
<tr>
<td>Zilver Trial</td>
<td>Zilver PTX</td>
<td>489</td>
<td>6.6</td>
<td>-</td>
<td>-</td>
<td>.9</td>
<td>83</td>
</tr>
<tr>
<td>Sirocco II</td>
<td>SMART (DES)</td>
<td>57</td>
<td>8.1</td>
<td>-</td>
<td>91</td>
<td>8</td>
<td>82**</td>
</tr>
<tr>
<td>Resilient</td>
<td>LifeStent</td>
<td>134</td>
<td>6.2</td>
<td>17</td>
<td>83</td>
<td>3.4</td>
<td>80</td>
</tr>
<tr>
<td>Saxon</td>
<td>Viabahn</td>
<td>76</td>
<td>14.2</td>
<td>42</td>
<td>87</td>
<td>0</td>
<td>76</td>
</tr>
<tr>
<td>Durability</td>
<td>Everflex</td>
<td>151</td>
<td>9.6</td>
<td>40</td>
<td>79</td>
<td>8.1</td>
<td>72</td>
</tr>
<tr>
<td>FAST</td>
<td>Luminexx</td>
<td>244</td>
<td>4.5</td>
<td>37</td>
<td>85</td>
<td>12</td>
<td>67</td>
</tr>
<tr>
<td>Super-SL</td>
<td>SMART</td>
<td>96</td>
<td>13.4</td>
<td>-</td>
<td>75</td>
<td>23</td>
<td>65</td>
</tr>
<tr>
<td>Vienna</td>
<td>Absolute</td>
<td>104</td>
<td>13</td>
<td>37</td>
<td>54.3</td>
<td>2</td>
<td>63</td>
</tr>
<tr>
<td>Vibrant</td>
<td>BMS Arm</td>
<td>76</td>
<td>16</td>
<td>50+</td>
<td>-</td>
<td>&gt;30</td>
<td>58</td>
</tr>
<tr>
<td>Vibrant</td>
<td>Viabahn Arm</td>
<td>72</td>
<td>20</td>
<td>50+</td>
<td>-</td>
<td>2</td>
<td>53</td>
</tr>
</tbody>
</table>

*B Data available from 91 patients.
**18 month data. BMS arm patency 82%, DES arm 79%.

Results from different clinical investigations are not intended for direct comparison. Provided for educational purposes only.

Drug eluting stents
## 12-Month Follow-Up

**Drug-Eluting Stent Randomized Trials**

<table>
<thead>
<tr>
<th></th>
<th>YUKON-BTK SES/BMS</th>
<th>DESTINY EES/BMS</th>
<th>ACHILLES† SES/PTA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients (n)/lesions (n)</td>
<td>161/161</td>
<td>140/154</td>
<td>200/228</td>
</tr>
<tr>
<td>Rutherford-Becker class</td>
<td>2 to 5</td>
<td>4 and 5</td>
<td>3 to 5</td>
</tr>
<tr>
<td>Mean lesion length (mm)</td>
<td>30±8/31±9†</td>
<td>15.9/18.9†</td>
<td>26.9±21/27.5±22†</td>
</tr>
<tr>
<td>Follow-up (months)</td>
<td>12</td>
<td>12</td>
<td>12</td>
</tr>
<tr>
<td>TLR (%)</td>
<td>9.7/17.5†</td>
<td>7.5/34.7*</td>
<td>10/16.5†</td>
</tr>
<tr>
<td>Limb salvage rate (%)</td>
<td>98.4/96.8†</td>
<td>98.7/97.1†</td>
<td>86.2/80†</td>
</tr>
<tr>
<td>Death (%)</td>
<td>17.1/13.9†</td>
<td>18.5/16.3†</td>
<td>10.1/11.9†</td>
</tr>
</tbody>
</table>
YUKON-BTK Trial: Event-Free Survival at 24 Months
Survival Free from TVR, Major and Minor Amputation, Myocardial Infarction and Death Was Compared by Kaplan-Meier Analysis with the Use of the Mantel-Cox Log-Rank Test

No. at risk

<table>
<thead>
<tr>
<th>Group</th>
<th>Risk</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Sirolimus Stent</td>
<td>82</td>
<td>62</td>
<td>59</td>
</tr>
<tr>
<td>Bare-metal Stent</td>
<td>79</td>
<td>63</td>
<td>57</td>
</tr>
</tbody>
</table>
## Yukon Trial

### MAE and Limb Salvage at 2-Year FU in CLI Patients

*DES vs BMS (YUKON Trial)*

<table>
<thead>
<tr>
<th>CLI Cohort</th>
<th>Sirolimus Stent (N=38)</th>
<th>Bare Metal Stent (N=31)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10 (26.3%)</td>
<td>10 (30.3%)</td>
<td>0.60</td>
</tr>
<tr>
<td>Major/minor amputation</td>
<td>1/1 (5.3%)</td>
<td>4/3 (22.6%)</td>
<td>0.04</td>
</tr>
<tr>
<td>TVR</td>
<td>4 (10.5%)</td>
<td>4 (12.9%)</td>
<td>0.70</td>
</tr>
<tr>
<td>Myocardial infraction</td>
<td>0 (0%)</td>
<td>2 (6.4%)</td>
<td>0.20</td>
</tr>
<tr>
<td>Limb salvage</td>
<td>37 (97.4%)</td>
<td>27 (87.1%)</td>
<td>0.10</td>
</tr>
</tbody>
</table>
Achilles Trial

DES vs PTA in BTK (RCT)

ACHILLES\textsuperscript{1-2} trial – Cypher Select vs PTA

- Lesion length 2.7 cm (DES)/2.7 cm (PTA)
- 12-m TLR = 10.0% (DES) vs 16.5% (PTA) (p=0.257)
- 12-m wound heal rate (WHR): 61.7% (DES) vs 41.3% (PTA) (p=0.0628)

39% TLR \quad p=0.257

49% WHR \quad p=0.0628

Randomized Comparison of Everolimus-Eluting vs. Bare-Metal Stents in Pts with Critical Limb Ischemia and Infrapopliteal Arterial Occlusive Disease

Multicenter European study of 140 pts.

<table>
<thead>
<tr>
<th>1-Year Follow-up</th>
<th>EES</th>
<th>BMS</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Patency</td>
<td>85%</td>
<td>54%</td>
<td>0.0001</td>
</tr>
<tr>
<td>Freedom from TLR</td>
<td>91%</td>
<td>66%</td>
<td>0.001</td>
</tr>
<tr>
<td>In-Stent Late Lumen Loss, mm</td>
<td>0.78</td>
<td>1.41</td>
<td>0.001</td>
</tr>
</tbody>
</table>

**Conclusion:** Treatment of infrapopliteal occlusive lesions in pts with critical limb ischemia using EES improves primary patency and lowers need for reintervention compared with BMS.
In infrapopliteal DES – Meta Analysis
Risk Estimates for DES Therapy versus Control Therapy

- In patients with focal disease of infrapopliteal arteries, DES therapy:
  - Reduces the risk of reintervention and amputation compared with plain balloon angioplasty or BMS therapy without impact on mortality and RC at 1-year follow-up

 Trials included in analysis:
ACHILLES = Comparing Angioplasty and DES in the Treatment of Subjects With Ischemic Infrapopliteal Arterial Disease;
BELOW = Balloon angioplasty or Stents With ReoPro for Prevention of Subacute Reocclusion in Arteries Below the Knee Angioplasty; DESTINY = Drug Eluting Stents In The Critically Ischemic Lower Leg; Falkowsky et al. = Evaluation of prim. Stenting of SES vs BMS in the treatement of atherosclerotic lesions of crural arteries; YUKON-BTK = YUKON-Drug Eluting Stent Below The Knee

• Prospective, non-randomized, multi-center study

• Study Objective:
  • To evaluate the immediate and long-term (up to 12 months) outcome of the Xience Prime in a controlled prospective investigation for lesions between 30mm and 100mm

• Main Inclusion Criteria
  • Rutherford Classification 4 or 5
  • De novo lesion or restenotic lesion after PTA
  • Total target lesion length minimally 30mm and maximally 100mm

• Primary Endpoint
  • Absence of restenosis (>50%) or occlusion within the originally treated lesion based on angiography, verified by core lab
## Destiny 2: Lesion characteristics

<table>
<thead>
<tr>
<th></th>
<th>N= 60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left/Right Limb</td>
<td>31/28</td>
</tr>
<tr>
<td>Lesion Length</td>
<td>47.4 mm</td>
</tr>
<tr>
<td>Reference vessel diameter</td>
<td>3.09 mm</td>
</tr>
<tr>
<td>Mean lumen diameter</td>
<td>0.32 mm</td>
</tr>
<tr>
<td>Occlusion (%)</td>
<td>32</td>
</tr>
<tr>
<td>Calcified Lesion (%)</td>
<td>27</td>
</tr>
</tbody>
</table>
DESTINY 2 study: 
12 Month Primary Patency

<table>
<thead>
<tr>
<th>time</th>
<th>baseline</th>
<th>1MFU</th>
<th>6MFU</th>
<th>12MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk</td>
<td>60</td>
<td>57</td>
<td>43</td>
<td>37</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>98.3</td>
<td>83.4</td>
<td>75.4</td>
</tr>
</tbody>
</table>

75.4 %
DESTINY 2 study:
12 Month Freedom from TLR

![Graph showing Freedom from Target Lesion Revascularization over time]

<table>
<thead>
<tr>
<th>time</th>
<th>baseline</th>
<th>1MFU</th>
<th>6MFU</th>
<th>12MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk</td>
<td>60</td>
<td>58</td>
<td>50</td>
<td>42</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>100</td>
<td>94.5</td>
<td>84.9</td>
</tr>
</tbody>
</table>
DESTINY 2 study: 12 Month Limb salvage

<table>
<thead>
<tr>
<th>time</th>
<th>baseline</th>
<th>1MFU</th>
<th>6MFU</th>
<th>12MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk</td>
<td>60</td>
<td>57</td>
<td>52</td>
<td>49</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>96.6</td>
<td>96.6</td>
<td>96.6</td>
</tr>
</tbody>
</table>

96.6%
PES BTK-70 study

• Prospective, non-randomized, multi-center study

• To evaluate the immediate and long term (up to 12 month) outcomes of the Paclitaxel-Eluting Stent (Stentys) in < 50 mm lesions

• Stentys Stent System
  • Dedicated BTK self-expanding nitonol stent platform
  • Biostable, hemocompatible, polysulfone polymer which elutes paclitaxel
PES BTK-70 study
cfr. Apposition II trial
Main inclusion criteria

- Rutherford classification 4 & 5
- De novo lesion or restenotic lesion after PTA in the infrapopliteal arteries
- Total target lesion length ≤ 50mm

Primary endpoint

- Primary patency at 6 and 12 months, defined as:
  absence of restenosis (≥50% stenosis) or occlusion within the originally treated lesion based on angiography, verified by Core Lab.
PES BTK-70 Study: 12 month Primary Patency

Survival Function

<table>
<thead>
<tr>
<th>time</th>
<th>baseline</th>
<th>6MFU</th>
<th>12MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk</td>
<td>70</td>
<td>54</td>
<td>43</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>87.6</td>
<td>72.6</td>
</tr>
</tbody>
</table>

72.6%
PES BTK Study: 12-month Amputation

98.5 %

<table>
<thead>
<tr>
<th>time</th>
<th>baseline</th>
<th>6MFU</th>
<th>12MFU</th>
</tr>
</thead>
<tbody>
<tr>
<td>at risk</td>
<td>70</td>
<td>62</td>
<td>55</td>
</tr>
<tr>
<td>%</td>
<td>100</td>
<td>98.5</td>
<td>98.5</td>
</tr>
</tbody>
</table>
Comparison other trials

1 year patency rates

<table>
<thead>
<tr>
<th>Trial</th>
<th>BMS/PTA</th>
<th>SES</th>
<th>PES</th>
</tr>
</thead>
<tbody>
<tr>
<td>YUKON</td>
<td>55.6</td>
<td>80.6</td>
<td></td>
</tr>
<tr>
<td>DESTINY</td>
<td>54.4</td>
<td>82.5</td>
<td></td>
</tr>
<tr>
<td>ACHILLES</td>
<td>57.0</td>
<td>75</td>
<td></td>
</tr>
<tr>
<td>PES BTK 70</td>
<td>72.6</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
BIO-RESORBABLE VASCULAR SCAFFOLD
STUDY DESIGN

• Single centre
• 3 Implanters under special access conditions
• Chronic lower limb ischemia: RC 3-6

• Direct replacement for DES
• De novo lesions; length ≤50mm, diameters 2.5-4.0mm
• Tibial arteries (+P3)
• Sample size: ≥15 patients
• 100% Procedural success
• 1 death (6mo)
• 1 lost to follow up (panc. Ca)
• 1 Acute occlusion
  (day 1: no DAPT)

• Clinical Improvement 88%
• Primary patency 94.4%
• Assisted primary/secondary patency 100%
• Limb salvage 100%
• TLR 5.6%
• TVR 5.6%
CLI Case

TP Trunk and AT Occlusion

PTA
<table>
<thead>
<tr>
<th>Post PTA</th>
<th>Post DES</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions

• DES compared to PTA and POBA results in significant TLR reduction and higher wound healing rates

• Initial data with self-expanding DES and Bio-resorbable Vascular Scaffolds are encouraging

• Can be a cost effective initial management for patients with CLI
Closing Remarks / Thank You
Drug-Eluting Stent Implantation for the Treatment of CLI

Ramzan M. Zakir, MD, FACC, FSCAI

Director of Peripheral Vascular Program
Saint Peter’s University Hospital
Clinical Assistant Professor Of Medicine
Rutgers: Robert Wood Johnson Medical School
New Brunswick, New Jersey