ACHILLES-Study (DES for BTK)

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The ACHILLES Study

A Prospective, Randomized, Multicentre Comparison of Balloon Angioplasty and the CYPHER SELECT® Plus Coronary and Infrapopliteal Stent in the Treatment of Infrapopliteal Arterial Disease
The ACHILLES Study

Background

• Several single-centre studies have shown the safety and efficacy of the sirolimus-eluting stent in BTK-lesions.

• The sirolimus-eluting stent (Cypher™, Cordis) has received CE-mark approval in 2006 for use in infrapopliteal arteries.

• ACHILLES was designed to compare for the first time the performance of a drug-eluting stent with balloon angioplasty (PTA) for lesions in infrapopliteal arteries in a randomized trial using an angiographic primary endpoint.
ACHILLES: Investigators and Study Sites

Germany
- D. Scheinert, MD, Leipzig – Coordinating Investigator
- V. Geist, MD, Bad Segeberg
- P. Huppert, MD, Darmstadt
- H. Krankenberg, MD, Hamburg
- K. Brechtel, MD, Tübingen
- T. Zeller, MD, Bad Krözingen

Austria
- J. Lammer, MD and R. Koppensteiner, MD, Vienna

Belgium
- M. Bosiers, MD, Dendermonde
- W. Lansink, MD, Genk

Switzerland
- I. Baumgartner, MD, Bern
- J. Peregrin, MD, Prague

Czech Republic
- J. Peregrin, MD, Prague

France
- P. Commeau, MD, Ollioules
- P.E. Magnan, MD, Marseille

Greece
- D. Siablis, MD, Rion

Italy
- P. Rubino, MD, Mercogliano

UK
- P. Sidhu, MD, London
ACHILLES: Study Design

• **Design:** Prospective, randomized, multicentre trial

• **Primary endpoint:** in-segment binary restenosis at 12 months by quantitative angiographic analysis

• **Secondary endpoints:** technical success rates, TLR, TVR, death, amputation, Rutherford status, stent fracture, and wound status

• **Clinical follow-up:** 6 weeks, 6 months, 12 months

• **Event adjudication:** independent CEC and DSMB

• **Wound analysis:** independent clinical reviewer, blinded to treatment assignment

• **Anti-platelet regimen:** Aspirin/Clopidogrel at least for 6 months

• **Sponsor:** Cordis, Johnson&Johnson
ACHILLES: Inclusion Criteria

- Symptomatic CLI **(Rutherford 3 - 5)**
- *De novo* or restenotic (after PTA only) lesion(s) in the tibial arteries
- Target vessel diameter $\geq 2.5$ and $\leq 3.5$ mm
- Target lesion stenosis > 70% DS
- Maximum of 2 vessels in 1 limb (each 1 lesion) with a maximum lesion length of 120 mm
- **Maximum of 4 stents within 1 vessel, or in total for 2 lesions**

*Additional non-TL in a non-TV could be treated at investigators discretion by PTA (or bailout stenting if needed)*
ACHILLES: Study Flowchart

Total Patient Population
n = 200
1:1 randomization

CYPHER SELECT® Plus
n = 99 patients
n = 113 lesions
Stent(s) implanted (99 patients)
Stents/patient: 1.8 on avg.

Balloon Angioplasty
n = 101 patients
n = 115 lesions
PTA (93 patients)
Cross-over to Stent (8 patients)

12 months follow-up:
Pts. comp. clinical f/u: n=74 (74.7%)
- Deceased (n = 11)
- Withdrew consent (n = 4)
- Lost to FU (n = 10)
Lesions eval. angio f/u : n=67 (59.3%)

12 months follow-up:
Pts. Comp. clinical f/u: n=80 (79.2%)
- Deceased (n = 12)
- Withdrew consent (n = 3)
- Lost to FU (n = 6)
Lesions eval. angio f/u : n=74 (64.3%)
## ACHILLES: Patient Demographics - ITT

<table>
<thead>
<tr>
<th></th>
<th>CYPHER SELECT® Plus (99 Patients)</th>
<th>PTA (101 Patients)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years</td>
<td>72.4 ± 9.4</td>
<td>74.3 ± 8.2</td>
<td>0.117</td>
</tr>
<tr>
<td>Male, %</td>
<td>67.7</td>
<td>75.2</td>
<td>0.274</td>
</tr>
<tr>
<td>History of CAD, %</td>
<td>45.5</td>
<td>44.6</td>
<td>1.000</td>
</tr>
<tr>
<td>History of PVD, %</td>
<td>66.7</td>
<td>63.4</td>
<td>0.658</td>
</tr>
<tr>
<td>Diabetes, %</td>
<td>64.6</td>
<td>64.4</td>
<td>1.000</td>
</tr>
<tr>
<td>Hyperlipidemia, %</td>
<td>77.6</td>
<td>68.3</td>
<td>0.154</td>
</tr>
<tr>
<td>Hypertension, %</td>
<td>89.9</td>
<td>91.1</td>
<td>0.813</td>
</tr>
<tr>
<td>Smoker, %</td>
<td>38.4</td>
<td>26.3</td>
<td>0.094</td>
</tr>
<tr>
<td></td>
<td>CYPHER SELECT® Plus (113 Lesions)</td>
<td>PTA (115 Lesions)</td>
<td>p-value</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------------------------</td>
<td>-------------------</td>
<td>---------</td>
</tr>
<tr>
<td>Total Lesion Length, mm</td>
<td>26.9 ± 20.9</td>
<td>26.8 ± 21.3</td>
<td>0.990</td>
</tr>
<tr>
<td>Total Occlusion, %</td>
<td>81.3</td>
<td>75.4</td>
<td>0.334</td>
</tr>
<tr>
<td>Total Length of Occlusion, mm</td>
<td>6.7 ± 19.3</td>
<td>11.0 ± 22.4</td>
<td>0.135</td>
</tr>
<tr>
<td>Reference Vessel Diameter, mm</td>
<td>2.6 ± 0.5</td>
<td>2.6 ± 0.6</td>
<td>0.991</td>
</tr>
<tr>
<td>Restenotic Lesions, %</td>
<td>5.3</td>
<td>1.8</td>
<td>0.171</td>
</tr>
<tr>
<td>Calcification (moderate, severe), %</td>
<td>15.1</td>
<td>15.2</td>
<td>1.000</td>
</tr>
</tbody>
</table>
ACHILLES: Lesion Location - ITT

CYPHER SELECT® Plus

- TPT + PA: 4%
- TPT + PTA: 1%
- TPT: 35%
- ATA: 36%
- PTA: 11%
- PA: 11%

Balloon Angioplasty

- TPT + PA: 4%
- PT + PTA: 3%
- TPT: 22%
- ATA: 32%
- PTA: 16%
- PA: 23%

P = NS
### ACHILLES: Procedural Parameters - ITT

<table>
<thead>
<tr>
<th></th>
<th>CYPHER SELECT® 113 Lesions</th>
<th>PTA 115 Lesions</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pre-procedure Stenosis, %</td>
<td>68.8 ± 19.3</td>
<td>74.0 ± 19.0</td>
<td>0.056</td>
</tr>
<tr>
<td>Post-procedure Stenosis, %</td>
<td>13.3 ± 14.3</td>
<td>25.9 ± 15.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Device Success, % residual stenosis &lt; 30% with Assigned treatment</td>
<td>95.5</td>
<td>58.2</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Lesion Success, % residual stenosis &lt; 50% with any treatment</td>
<td>100</td>
<td>96.9</td>
<td>0.103</td>
</tr>
<tr>
<td>Procedure Success, % residual stenosis &lt; 50% with any treatment without any SAE</td>
<td>94.8</td>
<td>92.9</td>
<td>0.758</td>
</tr>
</tbody>
</table>
The ACHILLES Study

Primary Endpoint
12M In-Segment Binary Restenosis by QA*

Intention to Treat (ITT): As Treated: * lesion-based analysis

CYPHER SELECT PLUS (n = 67) P=0.019

PTA (n = 74)

CYPHER SELECT PLUS (n = 75) P=0.004

PTA (n = 66)
The ACHILLES Study
12M In-Segment Binary Restenosis by QA in Diabetic Patients* - Lesion based analysis

*Post-hoc analysis
## Safety Endpoints at 12M Follow-up - ITT

<table>
<thead>
<tr>
<th>Category</th>
<th>CYPH ER SELECT®</th>
<th>PTA</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>10.1%</td>
<td>11.9%</td>
<td>0.822</td>
</tr>
<tr>
<td>TLR, clinically driven</td>
<td>10.0%</td>
<td>16.5%</td>
<td>0.257</td>
</tr>
<tr>
<td>TVR, non TLR</td>
<td>6.4%</td>
<td>2.4%</td>
<td>0.263</td>
</tr>
<tr>
<td>Index Limb Amputations</td>
<td>13.8%</td>
<td>20.0%</td>
<td>0.307</td>
</tr>
<tr>
<td>Stent fractures</td>
<td>0.9%</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td></td>
<td>CYPHER SELECT®</td>
<td>PTA</td>
<td>p-value</td>
</tr>
<tr>
<td>----------------------</td>
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</tr>
<tr>
<td>Baseline (mean ± sd)</td>
<td>4.1 ± 0.9</td>
<td>4.0 ± 0.9</td>
<td>0.641</td>
</tr>
<tr>
<td>At 6 weeks</td>
<td>2.6 ± 1.9</td>
<td>2.7 ± 2.0</td>
<td>0.701</td>
</tr>
<tr>
<td>Δ vs baseline</td>
<td>-1.5 ± 1.6</td>
<td>-1.3 ± 1.6</td>
<td>0.548</td>
</tr>
<tr>
<td>At 6 months</td>
<td>2.0 ± 1.8</td>
<td>2.5 ± 2.0</td>
<td>0.180</td>
</tr>
<tr>
<td>Δ vs baseline</td>
<td>-2.0 ± 1.7</td>
<td>-1.5 ± 1.9</td>
<td>0.098</td>
</tr>
<tr>
<td>At 12 months</td>
<td>1.9 ± 1.7</td>
<td>2.3 ± 1.8</td>
<td>0.189</td>
</tr>
<tr>
<td>Δ vs baseline</td>
<td>-2.2 ± 1.7</td>
<td>-1.6 ± 1.8</td>
<td>0.077</td>
</tr>
</tbody>
</table>

There was a significant difference in the change from baseline to 12 months in the “As Treated” population: -2.2±1.6 vs. -1.6±1.8, p=0.044
The ACHILLES Study

Closed Wound By Visit* - Independent Blinded Evaluation

*Any amputation (major or minor) considered as wound failure

<table>
<thead>
<tr>
<th></th>
<th>Stent</th>
<th>PTA</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>n=53 wounds</td>
<td>n=57 wounds</td>
</tr>
<tr>
<td>6 weeks</td>
<td>18.9%</td>
<td>12.3%</td>
</tr>
<tr>
<td>6 Months</td>
<td>40.8%</td>
<td>29.4%</td>
</tr>
<tr>
<td>12 Months</td>
<td>57.1%</td>
<td>39.1%</td>
</tr>
</tbody>
</table>

*Preliminary Data
The ACHILLES Study - Summary

• The Achilles study achieved its primary endpoint and documented superiority of the Cypher™ sirolimus eluting stents in reducing rates of angiographic restenosis compared to PTA in infrapopliteal arteries at 12 months follow-up.

• There was a significant difference in device success and residual stenosis in favor of the Cypher™ arm, supporting the feasibility of stent implantation in the infrapopliteal territory.

• Rates of TLR, amputation or death were similar, however, the study was not powered for clinical endpoints.

• The rate of healed wounds – as assessed by an independent reviewer blinded to treatment allocation – showed a trend in favor of the stent arm at any follow-up time point.

• Implantation of sirolimus-eluting stents are a potentially promising therapeutic option to enhance interventional treatment of infrapopliteal arteries.
Randomized Trials DES BTK

- **YUKON:**
  - Yukon BMS vs. Sirolimus coated stent (no polymer)

- **DESTINY:**
  - BMS (Multilink Vision) vs. Xience V (Everolimus)

- **ACHILLES:**
  - Balloon vs. Cypher Select (Sirolimus)
DESTINY-Trial DES vs. BMS

Primary patency (angiographical at 12 months)

- 85.2% for DES (Xience V)
- 54.3% for BMS (Multilink Vision)

P < 0.001

Bosiers et al. LINC 2011
Standard-Treatment BTK

- Standard-treatment BTK is plane balloon-angioplasty, not BMS-implantation.

- If improvement of patency is the goal, comparison of DES to standard-treatment (POBA) is reasonable.

- The Achilles-trial design is therefore the appropriate concept, not the Destiny- and Yukon-design.
Drug-Eluting Stents Below-The-Knee

52 years, DM, Rutherford 5

Cypher 3.5/33mm
Angioplasty with Uncoated Balloons (POBA)

Occlusion ATA, Stenosis PA

After POBA both arteries

3-mo re-occlusion
Leipzig Experience with DEB BTK
Leipzig Experience with DEB BTK
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Leipzig Experience with DEB BTK

3-months follow-up angiography
Leipzig Experience with DEB BTK

<table>
<thead>
<tr>
<th></th>
<th>POB BTK</th>
<th>DEB BTK</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesion-length</td>
<td>183 mm</td>
<td>173 mm</td>
</tr>
<tr>
<td>Restenosis &gt;50 % @ 3 Mo</td>
<td>69 %</td>
<td>27 %</td>
</tr>
</tbody>
</table>

61% restenosis reduction
Use of Cypher BTK in Daily Practice

- Often as primary treatment, not only for bailout
- Short BTK lesions
- Younger patients
- When long wound-healing time is expected
- Calcified lesions

Is dual anticoagulation for 6 mo possible?

Always full-lesion coverage!
Problem of Long BTK-Lesions

- Residual stenosis
- Balloon-angioplasty
- Focal stenting with DES

Follow-up
## Long-Term Patency Cypher BTK

<p>| | |</p>
<table>
<thead>
<tr>
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</thead>
<tbody>
<tr>
<td>Patients</td>
<td>150</td>
</tr>
<tr>
<td>Treated limbs</td>
<td>158</td>
</tr>
<tr>
<td>Mean clinical follow up</td>
<td>30.1 months</td>
</tr>
<tr>
<td>Deaths</td>
<td>26 (21%)</td>
</tr>
<tr>
<td>Limb amputations</td>
<td>3 (2%)</td>
</tr>
<tr>
<td>Mean angiographical follow up</td>
<td>21.9 months</td>
</tr>
<tr>
<td>Patients available for FU</td>
<td>100 (67%)</td>
</tr>
</tbody>
</table>
Clear Case for Cypher-Stents

- 54 years, male pat.
- Severe claudication left calf
- Walking-capacity 100m
- Sustained relieve of symptoms after DES-implantation