Latest advancements in diabetic patients:
May drug elution technologies improve clinical outcome?

**Focus on SFA:**
When should we use DESs?
Why?

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Disclosure statement

- Investigator for trials sponsored by Alvimedica, Boston Scientific, Cook Medical, Medtronic, Cordis, W.L. Gore, Bolton Medical

- Lecturer at courses/symposia hosted by Alvimedica, Boston Scientific, Cook Medical, Medtronic, W.L. Gore, Terumo, Biovascular, Abbott

- Proctorship for W.L. Gore
BMS vs DES: the role of the drug

Results @ 1 year

<table>
<thead>
<tr>
<th></th>
<th>COOK*</th>
<th>Zilver Flex</th>
<th>Zilver PTX</th>
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<tbody>
<tr>
<td>Diabetic</td>
<td>42.0</td>
<td>49.6</td>
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<tr>
<td>Occlusion (%)</td>
<td>25.0</td>
<td>30.0</td>
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<tr>
<td>Calcification (%)</td>
<td>57.0</td>
<td>72.6</td>
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<tr>
<td>Primary Patency (%)</td>
<td>73.0</td>
<td>83.1</td>
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* COOK Zilver PTX clinical data guide 2010-2011

+14%
### Results @ 1 year

<table>
<thead>
<tr>
<th>BOSTON**</th>
<th>superNOVA</th>
<th>Majestic</th>
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<tbody>
<tr>
<td>Diabetic</td>
<td>40.5</td>
<td>35.1</td>
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<tr>
<td>Occlusion (%)</td>
<td>...</td>
<td>46.0</td>
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<tr>
<td>Calcification (%)</td>
<td>70.2</td>
<td>78.9</td>
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<tr>
<td>Primary Patency (%)</td>
<td>66.4</td>
<td>96.1</td>
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</table>

+45%
BMS vs DES: the role of the drug

Results @ 5 years

41% reduction in restenosis rate

Dake et al, Circulation 2016
The role of the drug on balloons

DCB US Pivotal + EU Multicenter RCTs for the SFA

Primary Patency at 1 year

- Lutonix II: Δ 16.7%, P < 0.001
- IN.PACT SFA: Δ 31.7%, P < 0.001
- Stellarex-EU: Δ 24.0%, P < 0.001
- Stellarex-Pivotal: Δ 11.4%, P = NR
- Ranger: Δ 30.0%, P < 0.001

4. Lyden S, presented at TCT DC 2016. PSVR ≤ 2.5 and freedom from CD-TLR. Not yet published.

5. Scheinert, D. Charing Cross 2017. Ranger-SFA Study
The role of the drug on balloons

DCB US Pivotal + EU Multicenter RCTs for the SFA

Freedom from TLR at 1 year

- Lutonix II: DCB, 87.7% (Δ 4.5%, P = NSS)
- IN.PACT SFA: PTA, 83.2% (Δ 18.2%, P < 0.001)
- Stellarex-EU: DCB, 94.8% (Δ 9.5%, P = 0.010)
- Stellarex-Pivotal: DCB, 93.6% (Δ 6.3%, P = NR)
- Ranger: DCB, 91.0% (Δ 21.0%, P = 0.010)

2. Tepe G, et al. Circ 131:495-502 (2015). Reintervention at target lesion due to symptoms or drop of ABI of ≥20% or >0.15 compared to baseline.
3. Brodman M, presented at AMP Chicago 2016. Reintervention at target lesion due to an increase in RCC >1 category or deterioration in the ABI by >0.15 compared to baseline.
4. Lyden S, presented at TCT DC 2016. Reintervention at target lesion due to an increase in RCC >1 category or deterioration in the ABI by >0.15 compared to baseline.
DCB: what about bail-out stenting?

**Complex lesions**: Increasing use of DCBs **AND** increasing use of bail-out stents
Drug Coated Balloons

- No permanent implants (*leave no metal behind*)
- Reduced requirement for DAPT

- Procedural effectiveness similar to simple PTA (recoil, calcium dissection)
- Increased provisional stent placement with increasing lesion length
The role of DESs in the daily practice

When and why?
1) Bail-out after PTA
1) Bail-out after PTA
1) Bail-out after PTA
2) Restenosis/occlusion after DCB
3) Complex lesions
(> 20 cm occlusions and/or heavily calcified)
3) Complex lesions
(> 20 cm occlusions and/or heavily calcified)
Marketed DES drug release approaches

Currently 2 different approaches in the release of a drug from a stent:

1) “Simple” Polymer-free release-controller (e.g. Cook Zilver PTX)

Pro safety: no-inflammatory trigger

Con efficacy: fast elution

Relative paclitaxel levels remaining on the stent

Marketed DES drug release approaches

Currently 2 different approaches in the release of a drug from a stent:

2) Polymer-based drug delivery (e.g. Boston Sc. Eluvia)

Pro efficacy: sustain elution

Con safety: possible negative (inflammatory) long-term effect of the polymer
Other new solutions for DES

Polymer-free

but

controlled and sustained elution

“maximize the efficacy avoiding polymer’s drawbacks “
Other new solutions for DES

NiTiDES (Alvimedica)
patented technology of abluminal reservoir
sustained release but polymer-free platform

Reservoir section
Drug/formulation without polymers
Amphilimus™ formulation (NiTiDES)

Drug formulation = Sirolimus + permeation enhancer (fatty acid)

Fatty Acids are used to improve delivery of many different drugs.*

Fatty Acid uptake is double in diabetic mice model.**

For all patients:

**Cardiac fatty acid uptake and metabolism in db/+ and db/db mice. Curr Cardiol Rev. 2008 February; 4(1): 12-21

Increased drug concentration (diabetes)
ILLUMINA study

FIH study of NiTiDES stent

100 patients enrolled in 10 European centers (Germany, Italy, France) - Coord. P.I. Dierk Scheinert

<table>
<thead>
<tr>
<th>Baseline Characteristics</th>
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<tbody>
<tr>
<td>Patients enrolled (n)</td>
<td>100</td>
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<tr>
<td>Mean age (y)</td>
<td>67</td>
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<tr>
<td>Male (n)</td>
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<tr>
<td>Smoker (n)</td>
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<tr>
<td>Diabetic (n)</td>
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<td>Hypertension (n)</td>
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<td>Hypercholesterolemia (n)</td>
<td>54</td>
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<tr>
<td>Reference Vessel Diameter (mm): Mean (SD)</td>
<td>5.11 ± 0.72</td>
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<tr>
<td>Average lesion length (mm)</td>
<td>72.54 ± 37.99</td>
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<table>
<thead>
<tr>
<th>Calcifications</th>
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<tr>
<td>None (%)</td>
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</tr>
<tr>
<td>Little (%)</td>
<td>20</td>
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<tr>
<td>Moderate (%)</td>
<td>35</td>
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<tr>
<td>Heavy (%)</td>
<td>20</td>
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<table>
<thead>
<tr>
<th>Lesions Location</th>
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<tbody>
<tr>
<td>Proximal SFA (%)</td>
<td>8</td>
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<tr>
<td>Middle SFA (%)</td>
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<td>Distal SFA (%)</td>
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<tr>
<td>Popliteal P1 (%)</td>
<td>5</td>
<td></td>
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</tbody>
</table>
ILLUMINA study

1 year results

• Excellent Safety (3% MAE)
• Excellent Efficacy (Primary Patency -87%; TLR – 2%)

Freedom from TLR
98% @1y

Primary patency
97% @1y

Data firstly presented @ CIRSE 2018
Conclusions

Drug elution has proved to increase patency rates of both balloons and stents up to 5 years.

Stenting with DES has elective indications in complex lesions, bail-out situations, restenosis and occlusions after DCB.

It’s time to investigate the role of DES in subgroups of patients considered at high-risk.
Focus on SFA: When should we use DESs? Why?

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