The latest treatment approach and current developments in SFA

Dierk Scheinert, MD
Department for Interventional Angiology
University-Hospital Leipzig, Germany
Disclosure Statement of Financial Interest

Within the past 12 months, I or my spouse/partner have had a financial interest/arrangement or affiliation with the organization(s) listed below.

Advisory Board /Consultant:

Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical, Medtronic/Covidien, TriReme Medical, Trivascular, Upstream Peripheral Technologies
1st approach to Drug Elution from a SX stent in SFA (Sirocco study)

TECHNOLOGY
PURE DRUG placed into a PERMANENT POLYMERIC matrix:
- Drug = SIROLIMUS (cytostatic)
- Release = Prolonged drug elution (1-2months)

RESULTS & LIMITATIONS
- Efficacy at short term*
- Decreasing efficacy with the time passing (medium and long-term follow-ups)* due to the presence of the inflammatory permanent polymer

* J Endovasc Ther. 2006 Dec;13(6):701-10
Current “polymer-free” approach to Drug Elution from a SX stent in SFA (Zilver PTX)

TECHNOLOGY

PURE DRUG deposited on the bare Nitinol stent surface:
- Drug = PACLITAXEL (cytotoxic)
- Release = Fast drug elution (days)

RESULTS
- Improved efficacy at short term maintained at longer follow-ups*

Possible LIMITATIONS
- High portion of drug lost into the blood stream during stent placement
- Fast drug elution (drug contribution to clinical results only during the very first days)

Current “polymeric” approach to Drug Elution from a SX stent in SFA (Eluvia)

TECHNOLOGY
PURE DRUG placed into a PERMANENT POLYMERIC matrix:
- Drug = PACLITAXEL (cytotoxic)
- Release = Long lasting drug elution (1 year)

RESULTS
- Improved efficacy at medium term (1 year data)*

Possible LIMITATIONS
- Permanent presence of a polymer in contact with the vessel wall/ blood stream in a complex setting (inflammatory trigger?)

* CIRSE 2015
A. Latest generation BMS provide good results in terms of Primary patency rates/ TLRs

B. “Fast eluting” DES provide better efficacy results due to the contribution of the anti-proliferative drug

C. The very first result of the “Slow eluting” DES shows that there may be a further improved short/medium term efficacy due to controlled drug elution
Alvimedica patented polymer-free controlled drug elution technology
Polymer-Free platform

Avoids all the well known drawbacks due to the presence of a polymer interface with blood flow or vessel wall

Abluminal Reservoir Technology

Controlled and directed elution to the vessel wall

Bio Inducer Surface (BIS)

2nd generation pure carbon coating
Optimal haemo-compatibility vs. lumen blood flow

Amphilimus Formulation = Sirolimus + organic acid
Enhanced drug bioavailability, permeability and maximized product overall safety and efficacy
Abluminal Reservoir Technology

Proprietary polymer-free drug release system (Abluminal Reservoir Technology) constituted by reservoirs on the stent's outer surface

**Fick's law**

\[
\frac{\Delta m}{\Delta t} = -D \cdot A \cdot \frac{\Delta C}{\Delta x}
\]

- Drug diffusion coefficient
- Drug amount released over time
- Area of the drug-vessel contact surface
- Drug concentration gradient

**Drug release kinetic:**
- Peak tissue concentration during the first days
- 50% drug elution in approximately 18 days
- 65%-70% drug elution within 30 days
- Complete drug elution within 90 days

**AR TERIAL WALL**
Controlled and directed Drug elution

**BLOOD FLOW**
Lack of any polymer and any drug

*Implants in rabbit model*
A **REAL** innovative approach in drug elution to the vessel wall: Alvimedica patented AMPHILIMUS formulation
What is known #1: Direct resistance of diabetic VSMCs to -olimus drugs

10 times higher “-olimus” concentration is needed in the diabetic cell to achieve similar inhibition seen in non-diabetic one.
What is known #2: diabetic patients can be correlated to up-regulation of leptin

Reduced sensitivity of diabetic patients to DES releasing mTOR inhibitors (-olimus drugs) can be correlated to **up-regulation of leptin**.

- Following balloon injury, **Leptin activates VSMCs proliferation** and increases neointimal hyperplasia.

- **9 times higher “-olimus” drug concentration is needed** to block leptin-induced hyperplasia.
The Amphilimus™ formulation

**Sirolimus**

**Organic acid**

- Proprietary technology
  - Sustained drug elution timing
  - Modulated drug bioavailability
  - Raised homogeneous drug distribution
  - Enhanced drug stability

- Immunosuppressant
- Anti-proliferative action
- Anti-microbial
- Inhibitor of inflammatory cell activities
- High potency

**Sirolimus and Organic Acid are eluted together**

**Combined effect!!!**
For ALL the patients: Homogeneous drug distribution in the vessel wall

Fatty acid small molecules are characterized by an excellent permeability through cell membrane that allows an homogeneous Sirolimus distribution and action on the whole vessel tissue.
For DIABETIC patients: Higher Sirolimus concentration inside the cell

Diabetic cells have membrane protein overexpression (to compensate lack of Glucose pathway).

**DIABETIC** cell

The fatty acid transmembrane concentration gradient favors higher Sirolimus presence inside the cell (bioavailability).
Success story:
The coronary evidence
Late Lumen Loss at 6-9 months: NonDiabetics vs. Diabetics

**LATE LUMEN LOSS AT 6/9 MONTHS**

Common DES Releasing Pure Drug: (LIMUS)

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<th>Overall</th>
<th>Diabetics</th>
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<tr>
<td>Taxus</td>
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<td>Cypher</td>
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<tr>
<td><strong>Xience</strong></td>
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High LLL Increase in DIABETICS

Creat8™ DES Releasing a Formulation: (LIMUS + Fatty Acid)

<table>
<thead>
<tr>
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<th>Overall</th>
<th>Diabetics</th>
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<tbody>
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<tr>
<td><strong>Reservoir</strong></td>
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<td>0.14</td>
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</tbody>
</table>

No decreased efficacy in DIABETICS

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Carrié et al JACC, 2012, 59, 1371-76
Presented at TCT2015
Romagero et al JACC: CARDIOVASCULAR INTERVENTIONS VOL 9, NO 1, 2016:42-50
Polymer-free Amphilimus elution from SX stent: In-Vivo study
Biocompatibility and Safety in Pigs

Animal Model: Pig (Sus scrofa) (n = 11)
Project Device: NITIDES
N° stents: 42
Follow-up: 7, 30 and 90 days
Evaluation: SEM, histopathology and histomorphometry

Aim of the study:
- Endothelialization at 7 days
- Histological evaluation at 30 and 90 days
- Histomorphometric analysis at 30 and 90 days
**Neointima** from thin to very thin and regular, blood clots are present around struts especially in overlapped areas, endothelium continuous, no inflammatory cells.

Endothelium continuous, neointima thin and regular, no signs of inflammation, necrosis and most of blood clots and fibrin traces have been reabsorbed.
Innovative siroLimus seLf expanding drUg-eluting stent for the treatMent of peripheral disease: evaluation of safety aNd efficAcy.

The ILLUMINA Study
ILLUMINA - Clinical Study Design

Patients over 18 years with ischemic obstruction of SFA and proximal popliteal arteries due to de novo or restenotic lesion(s) and no prior stent in the target lesion.

Prospective, Single arm
14 centers in Europe (n= 100 pts)
Prof. Dierk Scheinert (Coordinating Clinical Investigator, Leipzig-Germany)
eCRFs; Core Lab; CEC

Primary Endpoint:
- **SAFETY:** Composite event –free survival at 12 months
- **EFFICACY:** Primary patency at 12 months

Secondary Endpoints:
Technical Success/ Death within 30 days / Composite event –free survival and primary patency rate at 6, 12 and 24m/ Target limb ischemia requiring surgical intervention at 6, 12 and 24m/ Rutherford class, Walking impairment test and ABI at 6, 12 and 24m
ILLUMINA – Investigator Centers

GERMANY
1. Prof. Scheinert (Study Coordinator), Universitätsklinikum, Leipzig
2. Prof. Zeller, Herz Zentrum, Bad Krozingen
3. Dr. Langhoff, St. Gertrauden Krankenhaus, Berlin
4. Dr. Euringer, Herz- und Gefäßzentrum, Bad Bevensen
5. Dr. Thieme, Regiomed Gefäßzentrum, Sonneberg

ITALY
1. Prof. Cremonesi, GVM, Cotignola
2. Prof. Chiesa, Ospedale San Raffaele, Milan
3. Prof. Marone, Ospedale San Matteo, Pavia
4. Prof. Carrafiello, Ospedale di Circolo, Varese
5. Dr. Micari, Ospedale Maria Eleonora, Palermo
6. Dr. Silingardi, Ospedale S. Agostino Estense, Modena

FRANCE
1. Dr. Sauguet, Clinique Pasteur, Toulouse
2. Dr. Commeau, Polyclinique Les Fleurs, Ollioules
3. Dr. Garot, Centre Privé Claude Galien, Quincy Sous Sénart
ILLUMINA – Study Flowchart

To Inform and consent of patient

CLINICAL SCREENING:
Clinical inclusion & exclusion criteria

One or more exclusion criteria fulfilled: PATIENT EXCLUDED

All clinical inclusion criteria fulfilled

ANGOIOGRAPHIC SCREENING:
Angiographic inclusion & exclusion criteria

One or more exclusion criteria fulfilled: PATIENT EXCLUDED

All angiographic inclusion criteria fulfilled and guidewire has successfully passed the lesion

Procedure = time of enrollment

CLINICAL FOLLOW-UP
1 month: phone call
6, 12 and 24 months: Duplex Ultrasound assessment
CONCLUSIONS

1. The polymer-free Abluminal Reservoir Technology allows for targeted and prolonged drug elution to the vessel wall without utilizing any element possibly cause of an inflammatory stimulus (i.e. polymer)

2. The innovative Amphilimus\textsuperscript{TM} formulation (Sirolimus + organic acid) enhances drug bioavailability and permeability for improved efficacy in challenging patients like DIABETICS

3. The ILLUMINA trial has been designed to prove NITIDES device safety and efficacy
The latest treatment approach and current developments in SFA

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