Current developments in SFA treatment and future opportunities: The Alvimedica DES project

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Disclosure

Speaker’s name: Dierk Scheinert

I have the following potential conflicts of interest to report:

Advisory Board /Consultant:
Abbott, Biotronik, Boston Scientific, Cook Medical, Cordis, CR Bard, Gardia Medical/Allium, Medtronic, TriReme Medical, Trivascular, Upstream Peripheral Technologies
As of today the treatment of SFA lesions could be made with different devices which have provided different clinical outcomes:

- Drug Coated Balloons (DCB) or “Atherectomy + DCB” (in case of high calcifications)

- Bare Metal Stent (BMS)

- Drug Eluting Stent (DES)
EFFICACY: DCB results

DCBs have shown good results in terms of Primary patency rates/TLRs, in case of simple lesions, @ 12 and @ 24 months.
EFFICACY: DCB results - II

In case of calcifications, DCB efficacy is affected. Adjunctive use of Atherectomy provides improved outcome in calcified lesions.
EFFICACY: DCB results - III

Medium-Long term results of DCBs in complex SFA lesions show a trend of worse primary patency continuing beyond 1 and 2 years.

2-year results DCB in complex SFA-Lesions

- 288 fempop-lesions
- Lesion-length 24.0 cm
- In.Pact DCB
  + BMS in 23.3 %

Kaplan-Meier primary patency

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<th>Days FU</th>
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<td>0</td>
<td>288</td>
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<td>540</td>
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1 year 79.2 %
2 years 55.4 %

Schmidt A et al JACC Cardiovasc Interv 2016
EFFICACY: DCB results - IV

Is the restenosis pattern different between BMS and DCB?

While DCBs results are better at Short-Medium term...

...BMS show tendency for a patency stabilization which provides advantages at medium-Long term

BMS patency results in a “stable plateau” after 1 year!
EFFICACY: BMS results

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

How can BMS short-medium term results be improved?
EFFICACY: Fast drug elution DES

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)

EFFICACY: Fast drug elution DES results

First generation fast elution polymer free DES has shown a moderate patency improvement with a reduction of events at 1 year versus BMS.
EFFICACY: Fast drug elution DES results - II

The patency improvement at 1 year is kept at long-term follow-up maintaining the patency stabilization seen with BMS.

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**Primary Patency**

- **Zilver PTX**: 66.4%
- **Optimal PTA + BMS**: 43.4%

**Years**

- **Enrollment**
- **Primary Randomization**
- **Secondary Randomization**
- **PTA**: Suboptimal PTA, Optimal PTA
- **BMS**, Zilver PTX
EFFICACY: Fast drug elution DES results

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

C. Can we further improve “drug” contribution to increase short-medium term patency rates?
EFFICACY: Slow drug elution DES through permanent polymer

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

RESULTS
- Improved efficacy at 1st year* but dropped in the 2nd year**

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

* CIRSE 2015 ** CIRSE 2016
EFFICACY: **Slow drug elution DES through permanent polymer**

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.
EFFICACY: Slow drug elution DES long-term results

Good patency at 1 year... but NO “patency plateau” is maintained at 2 years (~20% reduction vs. 1 year results): Is this due to the permanent presence of the inflammatory polymer?

Same negative LONG-TERM polymeric impact as seen in previous Sirocco trials???
Alvimedica patented polymer-free controlled drug elution technology:

- Maximum short-medium term efficacy
- Stable Polymer-free DES medium-long term “patency plateau”
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 + fatty 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

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

* Implants in rabbit model
The Amphilmus™ formulation

**Sirolimus**

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

**Fatty acid**

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

**Proprietary technology**

**Sirolimus and Fatty Acid are eluted together**

**Combined effect!!!**
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: Non-Diabetics vs. Diabetics

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

Common DES Releasing Pure Drug:

- Taxus: Overall 0.34, Diabetics 0.39
- Resolute: Overall 0.22, Diabetics 0.34
- Cypher: Overall 0.21, Diabetics 0.39
- Xience: Overall 0.14, Diabetics 0.24

**High LLL Increase in DIABETICS**

VS

Cre8™ DES Releasing a Formulation:

- Next: Overall 0.14, Diabetics 0.12
- Particip8: Overall 0.14, Diabetics 0.16
- Reservoir: Overall 0.14, Diabetics 0.14

**No decreased efficacy in DIABETICS**

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* Carrié et al. JACC, 2012, 59, 1371-76
** Presented at TCT2015
*** Romaguera et al. JACC: CARDIOVASCULAR INTERVENTIONS VOL.9,NO.1,2016:42-50
Clinical efficacy at 1 year: Non-Diabetics vs. Diabetics

AMPHILIMUS™ eluting stent (AES) vs BIOLIMUS A9 eluting stent (BES)

Sources: ASTUTE study (1216 patients) and INSPIRE study (1066 patients)

Propensity score matching 1:1
Innovative sirolimus self expanding drug-eluting stent for the treatment of peripheral disease: evaluation of safety and efficacy.

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

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.

Clinical FU
(Duplex ultrasound)

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 - Participating centers

#### Coordinating Clinical Investigator: Dierk Scheinert

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<td>Centre Privé Claude Galien</td>
<td>Quincy</td>
<td>Philippe Garot</td>
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Expected enrolment chart

Actual enrolment at 18/01/2017: 89 patients
CONCLUSIONS

1. As of today the treatment of SFA lesions can be made with different devices. The drug contribution, “DCB vs PTA” or “DES vs BMS”, have shown to improve primary patency at medium and long-term.

2. BMS stenting, when effective, seems to change restenosis pattern in complex lesions leading to a “plateau” after 1 year. The same results have been seen with fast eluting DES.

3. The patented polymer-free Abluminal Reservoir Technology coupled with the innovative Amphiliimus™ formulation (Sirolimus + fatty acid) allows for targeted and prolonged drug elution to the vessel wall without utilizing any element possibly cause of an inflammatory stimulus at long-term (i.e. polymer)

4. The ILLUMINA trial has been designed to prove NitiDES device safety and efficacy at medium and long-term.
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