Why, when and where: the DES role in SFA treatment

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Disclosure

Speaker name:
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I have the following potential conflicts of interest to report:

☒ Consulting: Terumo, Boston Scientific, Eurocor Tech, Alvimedica
  o Employment in industry
  o Stockholder of a healthcare company
  o Owner of a healthcare company
  o Other(s)

  o I do not have any potential conflict of interest
Today’s DES role in SFA treatment

Drug added value in Drug Eluting Technologies

DES main position in SFA lesion treatment

Currently available DES technologies

The Paclitaxel issue and devices drug dose released

Expected DES features for the near future

Conclusions
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Drug added value in Drug Eluting Technologies

➢ The added value provided by a Drug, eluted from a Balloon or from a Stent, has been an increased device effectiveness over time.

➢ Although both DCB and DES have provided better outcomes vs respective comparators without drug, some considerations have to be made for both devices.

Circulation. 2016;133:1472-1483
DCB & DES limitations

➢ DCB: its efficacy is reduced by higher calcium content, and “DCB use only strategy” is less feasible when lesion complexity is higher.

➢ DES: Popliteal p2 stenting provides mechanical challenges to the device that may interfere with the procedural outcome in the mid-long term.

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Indications for SX stenting:

➢ Lesions with calcium content or very complex lesions (lesions needing stenting to maximize MLD)

➢ Flow limiting dissections or high vessel elastic recoiling

Indications for SX DES:

➢ “All the above” + “lesions at high restenosis risk”
DES main position in SFA lesion treatment

While DCB efficacy benefits over PTA seem to slowly vanish with the time passing, this is not what has been seen for DES efficacy benefits over optimal PTA.

3 years results of the ILLUMENATE EU RCT (Stellarex DCB vs PTA)

5 years results of the ZILVER PTX RCT (ZILVER PTX DES vs PTA)

Circulation. 2016;133:1472-1483
DES main position in SFA lesion treatment

➢ Recently published studies* show that medium/complex lesions (where Ca2+/recoiling/dissection... are more often present) may benefit from DES over DCB to reduce restenosis.

REAL PTX study:
Zilver® PTX® vs. In.Pact Admiral/In.Pact Pacific/Lutonix
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Currently available DES on the market

Zilver PTX (Cook) provides a “polymer-free fast elution approach” to deliver the drug from a Self-Expanding nitinol platform.

Crystals of pure drug are deposited on the bare Nitinol stent surface and quickly released:

- Drug = PACLITAXEL (cytotoxic)
- Release = Polymer-free fast drug elution (days)

- Drug elution → Better EFFICACY at Short-Term
- Lack of inflammatory trigger → STABILITY at long-term
Currently available DES on the market

**Eluvia** (Boston Sc.) provides a “slow release approach” utilizing a durable polymer to deliver drug from a Self-Exp nitinol platform.

Pure drug is deposited within a permanent polymeric matrix:
- Drug = PACLITAXEL (cytotoxic)
- Release = Durable polymeric slow drug elution (1y)

- **Effective PACLITAXEL release**
- **Integral polymer coating**
- **Elution in the blood**
- **Nitinol strut cross section**

- Drug release from the Eluvia system is sustained over time
  - >90% of drug is released at 1 year
  - Drug release coincides with the restenotic cascade

- **Slow eluting polymeric DES**
- **Freedom from TLR**
  - Slow drug elution → Much Better EFFICACY at Short-Term
  - Permanent polymeric presence → STABILITY at long-term???
**IMPERIAL - TLR @ 2 Years:**
Slower drug elution provides higher efficacy

*Eluvia™ 12.9% vs. Zilver® PTX® 20.5% (p=0.0472)*

Consistent clinical benefit with Eluvia DES in all high-risk subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>MAJESTIC (N=57)</th>
<th>IMPERIAL RCT (N=310)</th>
<th>Diabetic (n=116)</th>
<th>CTO (n=96)</th>
<th>Mod/Sev Ca (n=194)</th>
<th>Long Lesions (N=50)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MAJESTIC (N=57)</td>
<td>7.1%</td>
<td>12.9%</td>
<td>11.2%</td>
<td>16.1%</td>
<td>9.5%</td>
<td>13.6%</td>
</tr>
</tbody>
</table>

**IMPERIAL RCT Subgroups**

- **65%** High risk lesions, non-drug therapy
- **25.6%** FDA PTA Reference (pivotal trials)

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Dr. Katsanos presented a meta-analysis of the 28 most important and rigorous randomized controlled trials done with DCB (27) and DES (1 - Cook) in femoropopliteal lesions.

While both patients treated with the PTX and control devices showed equivalent all-cause mortality at 1 year, a high change (worsening) occurred beyond that time point (2 & 5 years) only for the patients where the drug eluting devices were used.
Analysis on mortality for Paclitaxel-Containing Devices: Key Events

- Meta-analysis by Katsanos et al. published in J Am Heart Assoc
- FDA Letter to Health Care Providers #1
- FDA Advisory Committee meeting of the Circulatory System Devices Panel
- VIVA Vascular Leaders Forum Convened
- FDA Letter to Health Care Providers #2
- BfArM Letter to Health Care Providers in Germany (equal to FDA Letter #2)
- FDA Letter to Health Care Providers #3

... accompanied by society recommendations and scientific publications
Predictors of 2y mortality in Majestic & Imperial trials

List of predictors for Eluvia/Zilver PTX pts included into Majestic & Imperial trials

Multivariable Model with Dose Variable \((N=540\) Eluvia & Zilver PTX)

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Coefficient</th>
<th>Standard Error</th>
<th>Odds Ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>PTX Dose (100µg)</td>
<td>0.04</td>
<td>0.04</td>
<td>1.04 (0.96, 1.00)</td>
<td>0.3543</td>
</tr>
<tr>
<td>Diabetes</td>
<td>1.12</td>
<td>0.36</td>
<td>3.07 (1.52, 6.20)</td>
<td>0.0018</td>
</tr>
<tr>
<td>Age /year</td>
<td>0.06</td>
<td>0.02</td>
<td>1.06 (1.02, 1.10)</td>
<td>0.0029</td>
</tr>
</tbody>
</table>

• Diabetes and Age resulted significant predictors, typical for PAD patients
• Paclitaxel didn’t result a significant predictor

Significant comorbidities in pts with PAD are not fully accounted for in the meta-analyses
RCT Actual Treatment with ZilverPTX

- 5-year vital status for 94% of patients
- All patients analyzed by actual treatment
- No mortality signal

Cox proportional hazard models revealed that age, tissue loss, and congestive heart failure were significantly associated with mortality in the RCT

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Expected DES features for the near future

- Controlled drug elution for maximized DES efficacy in the short-medium term.
- Release of a non-Cytotoxic drug to avoid possible long term safety issues
- SX BMS platform without any inflammatory trigger which could elicit long-term restenotic events (polymer-free platform?)

### Graph

- **Slow eluting polymer-free DES**
- **Standard SX BMS**

- Slow drug elution → Much Better EFFICACY at Short-Term
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➢ DES, in selected patient populations, provide better reduction in both primary patency & TLR compared with DCB;

➢ Current DES slowly releasing Paclitaxel - Eluvia™ - demonstrated superior patency and reduced TLR rates compared to DES fast releasing Paclitaxel - Zilver® PTX®;

➢ Paclitaxel didn’t result being a significant predictor of mortality for both DES (Eluvia™ and Zilver® PTX®) at 2 years, and its efficacy benefits seem to outweigh the theoretical and currently uncertain higher risk of death;

➢ The availability of an alternative DES - able to slowly elute a non-cytotoxic drug which result in equivalent efficacy - is warranted, as it’s worth to invest in innovative research in order to improve patient’s clinical outcome.
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