What are the many variables in drug eluting technologies which may influence their ability to prevent restenosis? Where are they today and where are they going?

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DISCLOSURES
- Consultant: Medtronic, Boston Scientific, Abbott Vascular, Mercator

DES outcomes in the SFA lag behind those of the coronary arteries

What is the key element to drug elution efficacy?

Tissue. Residence. Time.

The ability of the drug to be delivered in adequate dosing and then to reside in tissue for the requisite duration of time to quell restenosis

Mechanism of action for DCB

Timing of disease progression much longer in the SFA vs. coronary artery
Variables in drug-eluting technologies which may limit their effectiveness

- Four categories:
  - Environmental
  - Drug
  - Delivery vehicle
  - Operator intransigence

Environmental
- Calcium
  - Especially in DCB technologies, but DES also

Calcium distribution evaluation by CTA (circumferential) and DSA (longitudinal)


Dissections are worse than we think

SFA Dissections Affect Long-Term Outcomes

THUNDER Study
- Overall Dissection Rate = 31.1%
  - 11% at 6m
  - 17% at 24m

- No Post-PTA Dissection: 10.5%
- Grade A-B: 33% (43%)
- Grade C-D-E: 43% (78%)

Rates of TLR for A/B SFA dissections reported worse than C/D/E dissections at 12 months

Fulihan et al.
- Overall Dissection Rate = 84.6%
  - 14% at 6m
  - 14% at 12m

- No Post-PTA Dissection: 14%
- Grade A-B: 14%
- Grade C-D-E: 34%

Small diameter, long lesion and vessel occlusion were predictive of high risk for dissection in the SFA

SFA Dissections Affect Long-Term Outcomes
Paclitaxel drug polymorphs

- Anhydrous Crystal PTX
- Crystalline Coating
- Amorphous Coating
- Hybrid Coating

Paclitaxel Processing

<table>
<thead>
<tr>
<th>Particles Released</th>
<th>Crystalline</th>
<th>Amorphous</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uniform Coating</td>
<td>++</td>
<td>++</td>
</tr>
<tr>
<td>Drug Transfer to Vessel</td>
<td>+++</td>
<td>+++</td>
</tr>
<tr>
<td>Drug Retention vs. Time</td>
<td>+++</td>
<td>+</td>
</tr>
<tr>
<td>Biological Effectiveness</td>
<td>+++</td>
<td>++</td>
</tr>
<tr>
<td>Vascular Toxicity</td>
<td>+++</td>
<td>++</td>
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</tbody>
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Nano-encapsulation of ‘limus using phospholipids

ADVANTAGES:
- Bilayer structure for encapsulation
- Prevents degradation of drug
- Reduces unintended effects of byproducts
- Targeted drug action

LIMITATIONS:
- Encapsulation efficiency
- Rapid leak of water soluble drugs
- Poor stability for storage

Delivery vehicle: balloon, excipient, phase, polymer coating

- Balloon surface energy can affect the ability of drug:excipient combination to be released into tissue
- Excipient: Solubility, drug-carrying capacity, etc.
- Phase: solid (crystalline vs. amorphous), liquid, nanoencapsulated
- Polymer coating

Eluvia coating design

- Primer layer (PBMA) promotes adhesion of active layer to stent
- Active layer (PTx/PVDF-HFP) provides release of Paclitaxel

Polymer coating sustains drug release to reduce restenosis

Design Difference: Elution Profiles

Operator intransigence

- Balloon sizing
- Geographic miss
- Vessel preparation
- Balloon handling
  - Wetting the balloon, damaging thru valve, long transit time to lesion, etc.
- Inadequate inflation time
Summary

• A host of factors related to drug formulation, carrier qualities, environmental (fate) factors, and operator behavior will affect outcomes for DCB and DES

• Next generation drug-delivery technologies will address some, but not all (see: operator behavior), of these issues