Sirolimus Drug Eluting Stent with Heparin Surface Using RES TECHNOLOGY™

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Reservoir Based Drug Eluting Stents

- CoCr thin-strut, open cell design
- Low profile delivery system
- Drug delivery through reservoirs
- Anti-restenotic sirolimus
- Biodegradable polymer

Reservoirs
Advantages of Reservoirs

- Directional control of drug release (abluminal or luminal)
- Multiple drug delivery (single- or bi-directional)
- Independent control of release kinetics
- Turns a DES to a BMS after 90 days
- Potential to add surface treatments to bare metal stent

Potential controlled release options
Fully biodegradable PLGA polymer

- Complete degradation in ~ 90 days
- Fully metabolizable and highly biocompatible
- Controlled drug release without a polymer coating
- Drug delivered over a period of ~ 90 days (*in vivo*)
Future Dual Drug Eluting Stents

Thrombosis
Reduce stent thrombosis and Plavix dependence

Acute MI
Reduce reperfusion injury and prevent “no-reflow”

Diabetes
Further reduce restenosis and improve clinical outcomes
Objectives for Anti-thrombotic Stent

✓ Retain anti-restenotic efficacy of sirolimus
✓ Improve stent thromboresistance
✓ Reduce long-term dual anti-platelet therapy dependence
✓ Reduce subacute and late stent thrombosis
✓ Address thrombosis concerns in key patient subgroups: AMI, diabetics, bifurcation and small vessel diseases, etc.
Heparin-Coated Reservoir Stent

- CoCr stent with anti-restenotic sirolimus
- Addition of surface bound heparin coating
  - Excellent coating uniformity
  - Consistent surface density and activity

Toludine blue stained heparin coated stent
Characterization of Heparin Coating

- Surface characterization
  - Uniform thickness of ~ 330 nm

- Heparin density and activity
  - Surface density: 10 - 20 µg/cm²
  - Anti-thrombin uptake: 50 - 150 pmol/cm²
  - Anti-factor Xa: 1 - 5 IU/cm²
Unique Combination of Heparin Coating and Reservoir Based DES

✓ CoCr stent with drug/polymer reservoirs
✓ Ultra-thin covalent bound heparin coating
✓ Non-elutable thromboresistant action
✓ Better hemocompatibility
✓ Reliable anti-restenotic efficacy with sirolimus
In Vivo Sirolimus Release Study

Sirolimus Release

- Heparin Coated
- NEVO

Sirolimus Release (%) vs. Days
Histology Data at Day 90

- Complete stent re-endothelialization
- Minimal strut inflammation (similar to BMS)
Flow Loop Thrombus Reduction Study

Reduction of $\text{In}^{111}$ Labeled Platelet Deposition

* $p < 0.0001$
Overlapped Thrombosis Model

- 50% stent overlap in porcine coronary artery
- No post-procedural anti-platelet regimen
- Necropsy time point: 7 days

Thrombus Quantitative Analysis

<table>
<thead>
<tr>
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<th>% Area Covered by Clot</th>
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<tbody>
<tr>
<td>Polymer Control</td>
<td>N=7</td>
</tr>
<tr>
<td>Heparin Coated</td>
<td>N=7</td>
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71% Reduction vs. Control, *p < 0.05
RES TECHNOLOGY™ can accommodate multiple drugs and surface modification in a single device.

Heparin coated stents consistently showed effective thromboresistant activities in vitro and in vivo.

Heparin coating process had a good control of coating uniformity & thickness, and heparin density & activity.

Heparin coating process is compatible with downstream drug-filling processes.
Thank You