First Human Experience with a PC-coated Angiopeptin-eluting Stent

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Interventional Cardiologist VS Cardiac Surgeon

Today

21% reduction in referrals for cardiac surgery

**Targets for Restenosis Prevention after Coronary Stenting**

**PROLIFERATION**
- Radiation
- Sirolimus
- Paclitaxel
- Angiopeptin
- Everolimus
- ABT-578
- Tacrolimus
- MPA/MMF
- Cyclosporin
- Resten NG
- c-myc Anti-sense
- Actinomycin D

**MIGRATION**
- MMPI (Batimastat)

**PLATELET ACTIVATION**
- αvβ3

**INFLAMMATION**
- Dexamethasone
- Bisphosphonate

**HEALING**
- VEGF
- 17-β estradiol
- EPCs

**The Cell Cycle**
- G1
- S-Phase (DNA Synthesis)
- G2

**Targets**:
- Endothelial cells
- Intima
- Internal elastic lamina
- Media
- Adventitia
DES-Three Component System

**Stent design**

**Drug-eluting Stent**

**Pharmacologic agent**

**Drug carrier vehicle**
Phosphorylcholine is a synthetic copy of the outer membrane of a red blood cell. Over 90% of the phospholipid bilayer in the outer membrane contain the PC headgroup.
Phosphorylcholine LDD “sponge” coating

Advantages of PC-Coating

- Does not elicit an inflammatory response
- Acts as a reservoir for drug elution
- “On-site” loading of novel agents
- Elution duration over two weeks
DES Trials Using the PC Platform

- Batimastat-Matrix Metalloproteinase Inhibitor (MMPI): BRILLANT & BATMAN Trials
- Dexamethasone: STRIDE study in Belgium
- Angiopeptin: Pilot Study in Hong Kong
- 17-Beta Estradiol: EASTER Trial
- ABT-578 (Medtronic AVE PC-coated Driver Stent): Endeavor Trial
**Structure of Angiopeptin**

*Synthetic Cyclic Octapeptide Analogue of Somatostatin*

D-Nal-Cys-Tyr-D-Trp-Lys-Val-Cys-Thr-NH₂

- Plasma half-life = 90 minutes
- Molecular weight = 1096 daltons
- Both hydrophilic and lipophilic

**Generic:**

*Lanreotide (Beaufour Ipsen, UK)*
Mechanism(s) of Action

- Inhibits VSMC proliferation through altering the production and release of several growth factors including IGF, PDGF, b-FGF and EGF
- Activation of a membrane-bound phosphatase, which dephosphorylates tyrosine kinase
- Inhibits VSMC migration through G-protein mediated pathway
- Promotion of neo-endothelial function
- CYTOSTATIC-inhibits mitogen-induced cellular proliferation at G1 checkpoint
- Lack of local toxicity
Postulated Sites of Action by Angiopeptin

Hong et al. Circulation 1997; 95: 449-454
Angiopeptin:
- Lowers GF release
- Alters GF binding
- Affects GF Signal Transduction
Comparative Release Studies (In-vitro)
In-Vivo Delivery Efficacy of Angiopeptin from BiodivYsio DD PC Stent

- Radio-labelled Angiopeptin ($I^{125}$)
- Loaded from 1mg/ml solution - 10µg/stent
- Porcine (LAD) coronary model (NGH Sheffield)
- 1 hour, 24 hours, 7 days & 28 days, two animals per time point
- Angiopeptin ($I^{125}$) levels determined in blood, urine and tissue
- LAD sectioned for histology and auto-radiography
\[ ^{125}\text{I} \]-Angiopeptin Concentration within the Central Region of the Left Coronary Artery

![Graph showing Angiopeptin Concentration](image)
Histology and Autoradiography of Angiopeptin Loaded BiodivYsio DD PC Stent

Histological section

Autoradiograph

Superimposition

28 Days
Summary of In-vivo Findings

• Angiopeptin was locally delivered to the LAD in the porcine model at time-points up to 28 days from the BiodivYsio DD stent

• Angiopeptin was detected in blood at 1 and 24 hours, however, after 7 days none was detected

• Negligible amounts of angiopeptin were detected in tissues outside of the heart
# Animal Studies (POSITIVE)

<table>
<thead>
<tr>
<th>Animal model</th>
<th>Injury</th>
<th>Reference</th>
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</thead>
</table>
## Animal Studies (POSITIVE)

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<th>Animal model</th>
<th>Injury</th>
<th>Reference</th>
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</thead>
</table>
Reduction of In-Stent Restenosis

- **Stent:** Palmaz-Schatz
- **Design:**
  1. Controls (no Angiopeptin Rx);
  2. Local AP Rx (200ug) via Dispatch catheter;
  3. Systemic AP Rx (200ug/kg via Alza minipump);
  4. Combined local and systemic Rx
- **Animal model:** Porcine coronary overstretch in-stent restenosis model (N= 10/group)
- **Results:** Continuous systemic treatment significantly reduced in-stent neointima (~50%) compared with the controls

*Hong et al. Circulation 1997:95:449-454*
Hong et al. Circulation 1997; 95: 449-454
IVUS: Mechanisms of Restenosis

Systemic administration of angiopeptin is capable of reducing intimal hyperplasia volume within stents by >50%
Reduction of In-Stent Restenosis

- Stent: Palmaz-Schatz
- Design: (1) Controls (no Angiopeptin Rx); (2) Slow-release systemic AP Rx (20mg IM) (3) Systemic AP Rx (200ug/kg SC via Alza minipump)
- Animal model: Porcine coronary overstretch in-stent restenosis model (N=10/group)
- Results: Both treatment groups had significantly reduced in-stent neointima (~60%) compared with the controls

Hong et al. Coron Artery Dis 1997:8:101-104
Angiopeptin-Coated Stent

- Stent: Wiktor stent
- Polymer: Poly(organo)phosphazene
- Angiopeptin: 250 ug/stent
- Release kinetics: > 1-week
- Animal model: Overstretch in-stent restenosis in porcine coronary arteries
- Results: Significant reduction in neointima by Angiopeptin (2.2 ± 0.6 vs 1.6 ± 0.7 mm, p<0.01 and 1 ± 0.5 mm² vs 0.4 ± 0.3 mm², p<0.01)

Negative study

Angiopetin-eluting stents: observations in human vessels and pig coronary arteries.


- Delivery of angiopetin from drug delivery PC-coated stents is safe, but does not lead to a significant reduction in neointimal growth at 28 days within the parameters of the study

Limitations:

- Non-overstretched Porcine Coronary Model:
  - unable to bring out the difference of NIH between treatment and control groups
- ex-vivo human SVG: may not be a relevant surrogate
FIM study of Angiopeptin-eluting PC-coated stent

- 14 patients (16 lesions) underwent Angiopeptin-eluting stent implantation
- The mean age was 63.2±8.5 yrs (47-75 yrs)
- 50% of the patients were diabetic
- Clinical follow-up: 30 Days, 3, 6, 9, 12 and 24 months
- Angiographic & IVUS follow-up at 6 months

N.B. Physician-driven program
Primary (Clinical) Endpoint:

• 6 months Target Vessel Failure (TVF)

Secondary Endpoints:

• Angiographic:
  6 months binary restenosis, late lumen loss and late loss index

• Volumetric Intravascular Ultrasound (IVUS)
  6 months neointimal volume

• Safety Endpoints:
  6 –12 months MACE, up to 2 years
Major Inclusion Criteria

• Age > 30 and < 80 years of age

• Native de novo coronary artery lesion of ≥70% diameter stenosis by QCA.

• Target lesion must be located in a de novo native coronary artery between 3.0 and 4.0 mm in diameter and < 18 mm in length.

• The patient is hemodynamically stable before the treatment.

• The patient must agree to come for a 6-month angiographic follow-up and be available for clinical follow-up for at least 2 years.
Major Exclusion Criteria

- Imminent comorbid illness (i.e. life expectancy < 2 yrs)
- Acute coronary syndrome requiring emergent procedure.
- Acute myocardial infarction within 72 hours.
- Visualized thrombus by angiographic criteria.
- Left ventricular function < 20%.
- Unprotected left main disease
- Anticipated use of glycoprotein IIb/IIIa antagonist.
- Known allergy to aspirin, ticlid or plavix. OR unable to comply with prolonged combination anti-platelet treatment
Patients Demographics

- **SEX**: 71.4%
- **AGE**: 63.2±8.5 yrs
- **DIABETES**: 50%
  - Insulin-requiring: 21.4%
- **HYPERTENSION**: 71.4%
- **HIGH CHOLESTEROL**: 50.0%
- **HISTORY OF MI**: 14.3%
- **Current smoker**: 14.3%
Informed consent obtained & patients deemed potentially eligible for procedure

Predilation of the de novo target lesion with an under-sized balloon (preferably shorter than the anticipated stent length). Record the peak inflation pressure.

Patient enrolled when all criteria, including angiographic, met

Deploy Angiopeptin-coated stent. (Peak pressure recorded).
Perform Volumetric automatic pullback IVUS (Boston Scientific Atlantis 40MHz). If stent was not well apposed, further expand the stent with a non-compliant balloon, guided by IVUS

1 month clinical follow-up

6±1 months angiographic and volumetric IVUS follow-up

1 and 2 year clinical follow-up

Adjunctive pharmacotherapy:
ALL patients receive Front-loaded Clopidogrel (Plavix®) 300mg p.o. at least 2 hours before the procedure followed by Clopidogrel 75mg QD for 90 days and Aspirin 100-325mg QD for life.
Lesion Location

AHA/ACC Lesion Morphology

Type B1  56.2%
Type B2  43.8%
**Dosimetry**

- **Low dose:** 22 μg/stent  13 lesions

- **High dose:** 126 μg/stent  3 lesions

†High dose: Experimental data suggested that the local tissue concentration detected using the 126 μg angiopeptin-eluting PC-coated stent in a porcine coronary model was over 100-fold that seen in the study performed by De Scheerder et al. in which significant reduction of neointima was observed.
In-Hospital Outcomes

Any MACE, % 0
Death, % 0
All MI, % 0
Q-wave 0
Non-Q-wave 0
Emergent CABG, % 0
TLR, % 0
Vascular Compl, % 0
Clinical Outcomes up to 1 year

Any MACE 0
Death 0
Q wave MI 0
TLR 0
TVF 0
SAT 0
### Off-line Quantitative Coronary Angiographic Analysis

*(CAAS II QCA, Pie Medical, Netherlands)*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Low Dose (22µg) Angiopeptin-eluting stents</th>
<th>High Dose (126µg) Angiopeptin-eluting stents</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><em>N</em>=13 lesions</td>
<td><em>N</em>=3 lesions</td>
</tr>
<tr>
<td><strong>Pre-procedure</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reference vessel diameter</td>
<td>2.84±0.66mm</td>
<td>2.91±0.41mm</td>
</tr>
<tr>
<td>MLD</td>
<td>0.79±0.52mm</td>
<td>0.72±0.36mm</td>
</tr>
<tr>
<td>DS%</td>
<td>72.5±10.4%</td>
<td>76.2±8.6%</td>
</tr>
<tr>
<td>Lesion length</td>
<td>12.4±4.3mm</td>
<td>13.2±3.2mm</td>
</tr>
</tbody>
</table>
### Off-line Quantitative Coronary Angiographic Analysis

(CAAS II QCA, Pie Medical, Netherlands)

<table>
<thead>
<tr>
<th></th>
<th>Low-Dose</th>
<th>High-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Final MLD</strong></td>
<td>2.88±0.52mm</td>
<td>2.97±0.33mm</td>
</tr>
<tr>
<td>Analysis segment</td>
<td>2.75±0.46mm</td>
<td>2.84±0.48mm</td>
</tr>
<tr>
<td>In-stent</td>
<td>2.82±0.49mm</td>
<td>2.89±0.36mm</td>
</tr>
<tr>
<td><strong>Final DS%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis segment</td>
<td>4.0±8.2%</td>
<td>4.2±5.3%</td>
</tr>
<tr>
<td>In-stent</td>
<td>3.4±8.9%</td>
<td>3.2±7.7%</td>
</tr>
<tr>
<td><strong>In-stent acute gain</strong></td>
<td>1.97±0.52mm</td>
<td>1.99±0.47mm</td>
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</table>
### Off-line Quantitative Coronary Angiographic Analysis

#### 6 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>Low-Dose</th>
<th>High-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter</td>
<td>2.83±0.45mm</td>
<td>2.89±0.42mm</td>
</tr>
<tr>
<td><strong>MLD</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis segment</td>
<td>2.36±0.67mm</td>
<td>2.59±0.46mm</td>
</tr>
<tr>
<td>In-stent</td>
<td>2.39±0.52mm</td>
<td>2.62±0.35mm</td>
</tr>
<tr>
<td><strong>DS%</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis segment</td>
<td>17.6±12.4%</td>
<td>10.2±5.8%</td>
</tr>
<tr>
<td>In-stent</td>
<td>15.6±12.0%</td>
<td>10.0±7.3%</td>
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<tr>
<td><strong>Late loss</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Analysis segment</td>
<td>0.36±0.42mm</td>
<td>0.23±0.16mm</td>
</tr>
<tr>
<td>In-stent</td>
<td><strong>0.46±0.32mm</strong></td>
<td><strong>0.26±0.14mm</strong></td>
</tr>
<tr>
<td><strong>Late Loss in DISTINCT:</strong></td>
<td>0.94 ±0.61mm</td>
<td></td>
</tr>
<tr>
<td><strong>Late Loss in TAXUS IV:</strong></td>
<td>0.39 ±0.50mm</td>
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Late Loss as A Predictor of Restenosis

Late Loss of 1.2mm associated with a 50% chance of binary restenosis

Late Loss < 0.6mm associated with single-digit binary restenosis

Logistic regression combining all patients
Patient No. DD2

Pre

Post

6 months
### Echo Plaque Volumetric IVUS

#### 3D-IVUS follow-up

<table>
<thead>
<tr>
<th></th>
<th>Low-Dose</th>
<th>High-Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent volume</td>
<td>$185.3 \pm 102.6\text{mm}^3$</td>
<td>$188.4 \pm 64.6\text{mm}^3$</td>
</tr>
<tr>
<td>% neointimal hyperplasia volume</td>
<td>$18.4 \pm 22.5%$</td>
<td>$10.2 \pm 5.8%$</td>
</tr>
</tbody>
</table>

- No Late stent mal-apposition. No aneurysm.

**N.B.** In BMS, the % NIH is consistently around 30% by volumetric IVUS at 6-9 months.
F/52

- Insulin-Dependent DM

- 3.5x18mm Angiopeptin-eluting stent (126μg) in mid-LCx

6-month FU

- Late Lumen Loss=0.22mm (QCA)

- % Volume Obstruction=10.2% (3D-IVUS)
Study Limitations and Future Directions

• The sample size was too small to draw any conclusion on the efficacy of Angiopeptin-eluting stents in reducing restenosis.

• By modifying the physical property of the PC polymer, the coating could be tailored to achieve better loading, release and less ‘wash-out’ of the drug. Pre-loading the drug with spray-loader by the industry would ensure more reliable and reproducible dosimetry.

• There are at least 5 known Somatostatin receptor subtypes, SSTR1-SSTR5. Human blood vessels express high levels of SSTR-1 after injury. Research on SSTR-1 specific agonist is underway.
Conclusions

• Angiopeptin-eluting BiodivYsio™ DD PC stent appears feasible and safe in treating native de novo coronary lesions.

• Angiopeptin-eluting stents resulted in modest degree of neointimal hyperplasia and zero binary restenosis in this small cohort of patients (half DM). High-dose (126 µg) Angiopeptin-eluting stent appears more promising.

• The preliminary results warrant further confirmation by randomized, controlled trials.
Acknowledgement

• On behalf of all the co-investigators, I would like to thank Dr. Mun K. Hong for his invaluable advice and pioneer work in the research.

• We would also like to thank Beaufour Ipsen, UK, for providing free samples of generic Lanreotide for our study.