New DES Drug Carrier Systems: Biostable, Bioabsorbable, and No Polymers, Elution Kinetics and Beyond

Martin B. Leon, MD

Columbia University Medical Center
Cardiovascular Research Foundation
New York City

Angioplasty Summit TCT Asia-Pacific 2007
April 25-27, 2007; Seoul, Korea
Drug-Eluting Stents
The First Generation

Stent design and delivery system

Pharmacologic agent
Known FDA-approved drugs with approximated release kinetics

Drug-Eluting Stent

Future generation enhancements on stent and delivery system

Drug carrier vehicle
Available, FDA-approved biostable polymers
Drug-Eluting Stents…. the good, the bad, and the ugly!

Late loss = 0
48 months

BMS
DES

Delayed Healing!

Giant cells.

Angioscopy

BMS

Eos

Inflammation

Late stent thrombosis
40 mos

Incomplete apposition

Abn Vasomotion

Sirolimus
Control

*P<0.001 vs. control

Future Safe DES Platforms

The Key is the Endothelium!

active support of endothelial cell proliferation and migration after stent implantation

accelerated endothelial cell strut coverage

decreased smooth muscle activation & reduced collagen secretion

optimal healing response = accelerated functional endothelium
New DES Carrier Systems

- Biostable Polymers
- Bioabsorbable Polymers
- No Polymers
- Elution Kinetics
- ...and Beyond
New DES Carrier Systems

- Biostable Polymers
- Bioabsorbable Polymers
- No Polymers
- Elution Kinetics
- ...and Beyond
First Generation
Drug-eluting Stents in the U.S.

TAXUS
Paclitaxel Drug
Express² Stent

Cypher
Sirolimus
PEVA + PBMA blend
BX Velocity

Columbia University Medical Center
90% of phospholipids in the outer membrane of a red blood cell contain the PC (Phosphorylcholine) headgroup.

PC mimics the chemical structure of the phospholipid headgroup.
Endeavor DES System

PC Technology

Non-thrombogenic  Durable
Endeavor Zotarolimus-PC Interaction

Drug Eluted by 14 days; Only PC Basecoat Left Behind

Arterial Wall

Stent strut cross-section

90/10 Zotarolimus/PC
3-4 microns

Cross-linked PC Basecoat
1-2 microns

Lumen

Columbia University Medical Center

CARDIOVASCULAR RESEARCH FOUNDATION
Endeavor Safety Analysis
Stent Thrombosis According to Prospective HCRI CEC Definitions

1317 patients with > 2 year FU

Days Post Procedure
1 2 3 // 12 13 14 // 30 // 100 // 150 // 270 // 360 // 720 // 1080

- EI
  n=100
  = 1%

- EII
  n=598
  = 0.5%

- EII CA
  n=296
  = 0.0%

- EIII
  n=323
  = 0.0%

Overall Thrombosis = 0.3%

Columbia University Medical Center

ENDEAVOR I-III Plavix Rx for ≥ 3 months
Abbott XIENCE V
Everolimus-eluting Stent*

- Everolimus
- Durable Fluoropolymer
- ML VISION® Stent Platform
- ML VISION® Stent Delivery System
- SPIRIT Clinical Trials

*Identical to BSC Promus
Xience Durable FluoroPolymer Characteristics

**Physical Properties**
- Combination of acrylic and fluorinated polymers
  - inert
  - flexible, ductile
  - thin, with high drug loading capacity
- Rare comb of hardness and elongation

**Mechanical Integrity**
- Strong adhesion to stent and balloon

**Biocompatibility**
- Low thrombogenicity and inflammation
- History of medical use
  - bone cement (acrylic)
  - sutures (fluorinated)

**Manufacturability**
- High stability

**Controlled Release**
DES Strut and Polymer Thickness
3.0 mm diameter stents, 500x magnification

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Strut Thickness</th>
<th>Polymer Thickness</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>CYPHER®</td>
<td>140 µm</td>
<td>12.6 µm</td>
<td>152.6 µm</td>
</tr>
<tr>
<td>TAXUS®</td>
<td>132 µm</td>
<td>16.0 µm</td>
<td>148 µm</td>
</tr>
<tr>
<td>ENDEAVOR™</td>
<td>91 µm</td>
<td>5.3 µm</td>
<td>96.3 µm</td>
</tr>
<tr>
<td>XIENCE™ V</td>
<td>81 µm</td>
<td>7.6 µm</td>
<td>88.6 µm</td>
</tr>
</tbody>
</table>

Data on file at Abbott Vascular. Strut thickness per manufacturer’s published specifications.
DES Re-endothelialization: 14-Day Rabbit Iliac Study

Xience thin fluoropolymer + everolimus

Data on file at Abbott Vascular
DES Functional Endothelium:
Rabbit Iliacs, CD-31 Staining @ 14-day

Xience thin fluoropolymer + everolimus

% CD-31 Over Stent Struts

14-day

28-day

GREATER HEALING

LESS HEALING
Endeavor Resolute

Retains three components of the Endeavor Coronary Stent System

- Driver: Cobalt Alloy Stent
- Stent Delivery System
- Drug: ABT-578

Novel Features:
- Medtronic proprietary polymer design
- Extended release kinetics
- Biocompatibility equivalent to PC
- Ability to add multiple drugs with release kinetics
The BioLinx Polymer System

**C10 Polymer**
- Based primarily on hydrophobic butyl methacrylate to provide adequate hydrophobicity for zotarolimus

**C19 Polymer**
- Manufactured from a mixture of hydrophobic hexyl methacrylate and hydrophilic vinyl pyrrolidinone and vinyl acetate to provide enhanced biocompatibility

**Polyvinyl Pyrrolidinone (PVP)**
- Hydrophilic polymer increases initial drug burst and enhances biocompatibility
Endeavor Resolute

BioLinx Polymer System

Hydrophilic

Zotarolimus

Hydrophobic

Durable

Non-inflammatory
Reduced Monocytic Adhesion to BioLinx Polymer System

Hydrophobic polymer (C10) induces the greatest inflammatory response.

Hydrophilic polymer (C19) does not provoke an inflammatory response.

The BioLinx polymer system (with a hydrophilic surface) maintains the favorable biocompatibility feature of the hydrophilic C19 (see Table below).

### Polymer Contact Angle

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Contact Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>C10</td>
<td>118°</td>
</tr>
<tr>
<td>C19</td>
<td>91°</td>
</tr>
<tr>
<td>C10 + C19 (30:70)</td>
<td>84°</td>
</tr>
<tr>
<td>BioLinx</td>
<td>94°</td>
</tr>
</tbody>
</table>

Activated monocytes do not bind to polymer blends containing C19.
Monocytes cultured on polymer blends containing the hydrophilic C19 release low levels of inflammatory cytokines into the cell culture media.

* TC = Tissue Culture Polystyrene
Biocompatibility of the BioLynx Polymer

Inflammation score
0.10 ± 0.21

Inflammation score
0.11 ± 0.38

Porcine coronary artery implants at 28 days
Endeavor Resolute

28 Day Results in Porcine Coronaries

Control

Endeavor Resolute

Endeavor Resolute

Reduced neointimal hyperplasia compared with control bare metal stents
New DES Carrier Systems

Biostable Polymers

- 1st generation DES biostable polymers have been suboptimal due to increased thickness (polymer burden), mechanical surface defects, increased inflammatory responses, and idiosyncratic hypersensitivity reactions.

- Newer (2nd) generation biostable polymers are thinner, have improved mechanical integrity, have more versatile kinetic release properties, and are more "biocompatible" with improved early healing and reduced inflammation.
New DES Carrier Systems

- Biostable Polymers
- *Bioabsorbable Polymers*
- No Polymers
- Elution Kinetics
- ...and Beyond
Biodegradable Polymers can be very **TRICKY**!

marked inflammatory responses

polymer swelling and physical degradation
BioMatrix® II Stent Platform Design

**Biodegradable Drug/Carrier:**
- Biolimus A9® / Poly (Lactic Acid) 50:50 mix
- abluminal surface only (contacts vessel wall)
- 15 μmeter coating thickness
- degrades in 9 months releasing CO₂ + water

**Stent Platform:**
- stainless steel (112 μm)
- corrugated ring, quadrature-link™ design
- radius link enhances axial fatigue life

**Parylene Durable Primer Coating:**
- 5 μmeter thick, encapsulates stent
- prevents surface metal ion migration
- biostable + athrombogenic*

* Data per NHLBI sponsored study, available from BSI
CoStar® Paclitaxel-Eluting Coronary Stent System

A Stent Specifically Designed for Controlled Drug Delivery from a Bioresorbable PLGA Polymer

Reservoir inlays with PLGA bioresorbable polymers; reduced tissue-polymer contact area
CoStar Bioresorbable Polymer Reservoir System

- **PLGA bioresorbable polymer**
  - Fully resorbable in ~ 6 mos (current formulation)
  - Degrades into naturally occurring products: lactate and glycolate
  - Used in medical implants for several decades (e.g. sutures)
  - Different co-monomer ratios permit variable resorption times (few weeks to many months)

Images showing the polymer at different stages:
- 7 days
- 30 days
- 180 days
The Versatility of Reservoirs

Bi-Directional

Single Drug Structure

Uni-Directional

Drug Delivery Reservoirs

Adjacent

Multiple Drug Structures
The Versatility of Reservoirs

- Reduced polymer-tissue contact
- Non-deformable (no surface damage)
- Increased polymer volume (3-10X current encapsulated polymers)
- Directional control (mural vs. bi-directional)
- Precise kinetic release patterns
- Ideal for dual drugs (increased capacity, independent release kinetics, hydrophilic drugs, directional specificity)
Supralimus-Eluting Stents

Supralimus™
Biodegradable Polymer Based Sirolimus Eluting Stent

Platform
- Millennium Matrix
- ‘Intermediate Cell Geometry’, Slotted Tube Design
- 0.0032” strut thickness

- Drug: Sirolimus
- Drug Dosage: 102μg-16mm
- Unique Biodegradable Polymeric Blend
- Single layer of coating with drug free top coat
- 4-5 μm coating thickness
Synchronium Sirolimus-Heparin Eluting Stent

- Drug Dose: **Sirolimus**-1.19 μg/mm², **Heparin**-0.28 μg/mm²
  (89 μg Sirolimus and 21 μg Heparin content on 16 mm stent)

- Unique Biodegradable Polymeric Blend includes-Poly L-Lactide, 50/50 Poly DL-Lactide-co-Glycolide and Polyvinyl pyrrolidone)
New DES Carrier Systems

Bioabsorbable Polymers

- Bioabsorbable polymers for DES systems have potential advantages, including diminished polymer burden and effects over time, which may improve long-term safety. *THE NEXT WAVE?*

- However, inflammatory responses due to polymer breakdown may be problematic and must be optimized.

- Several bioabsorbable polymer DES systems have been developed with acceptable characteristics and favorable early clinical outcomes.
New DES Carrier Systems

- Biostable Polymers
- Bioabsorbable Polymers
- *No Polymers*
- Elution Kinetics
- ...and Beyond
Nanoporous Ceramic Coating

- Nanoporous ceramic layer of aluminium oxide (300nm thickness) developed by AlCove Surfaces, Essen
- High mechanical stability
- No heavy metal ion dissolution
- Good tissue compatibility
- Anti-restenotic properties
- Suitable for drug release

Jomed Tacrolimus DES
# Comparison of Several Non-Polymeric Drug Delivery Stent Technologies

<table>
<thead>
<tr>
<th></th>
<th>Compatibility with Drugs</th>
<th>Low-Residue Process</th>
<th>Surface Topography</th>
<th>Same Material as Stent</th>
<th>In vivo Drug Release Kinetics</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Setagon</td>
<td>High</td>
<td>Yes</td>
<td>Smooth</td>
<td>Yes</td>
<td>Days*</td>
<td>Nanoporous metal</td>
</tr>
<tr>
<td>Translumina</td>
<td>High</td>
<td>Yes</td>
<td>Rough</td>
<td>Yes</td>
<td>Hours*</td>
<td>Roughened surface, on site surface drug application</td>
</tr>
<tr>
<td>Blue Membranes</td>
<td>High</td>
<td>Yes</td>
<td>Rough</td>
<td>No</td>
<td>Days*</td>
<td>Micro- to macro-porous carbon/carbon composite</td>
</tr>
<tr>
<td>MIV Therapeutics</td>
<td>High</td>
<td>Yes</td>
<td>Smooth</td>
<td>No</td>
<td>Hours*</td>
<td>Thin hydroxyapatite coating</td>
</tr>
<tr>
<td>Electroformed Stents Inc.</td>
<td>High</td>
<td>No</td>
<td>Rough</td>
<td>No</td>
<td>Days*</td>
<td>Electroplated coating</td>
</tr>
<tr>
<td>Medlogics/NTI</td>
<td>Low</td>
<td>No</td>
<td>Rough</td>
<td>No</td>
<td>Days*</td>
<td>Electrolysis co-deposition</td>
</tr>
</tbody>
</table>

* KDRs for can be extended to weeks/months with thin biodegradable top coats.

+ Predicted KDRs based on diffusion modeling analyses.
Setagon No Polymer System: Porosity & Elution Kinetics

Nanoporous DES with thin bioabsorbable topcoat
Setagon Nanoporous Surface Enhances Adhesion and Growth of Cultured Human Endothelial Cells Compared to Bare Metal (4-days)

- Poor Re-endothelialization on L605 bare metal.
- Complete Re-Endothelialization on CES.
ESI DES System... Microporous

Gold ESI Stent with Microporous Coating
Translumina YUKON Stent (with sirolimus)

Stent Coating Machine & Stent Cartridge
Translumina YUK

(microporous with)

before

after
ISAR - TEST

450 Patients

Polmyer-free
Rapamycin stent

No. of patients 225
Yukon DES stent+Rapamycin

Polmyer-based
Paclitaxel stent

225
Taxus Express²
ISAR - TEST

Late Lumen Loss

Late lumen loss (in-stent)

- Polymer-Free Rapamycin Stent
- Polymer-Based Paclitaxel Stent

Late lumen loss (in-segment)

- Polymer-Free Rapamycin Stent
- Polymer-Based Paclitaxel Stent

P = 0.98
P = 0.09

mm
BioMatrix Polymer-Free Freedom™ Stent

Selectively micro-structured surface holds drug in ablumenal pores or cavities; Pure Biolimus A9 impregnated within textured porous surface
# BioMatrix Freedom DES vs. microstructured control in 28-day Porcine Overstretch Model

<table>
<thead>
<tr>
<th>Histomorphometry Results</th>
<th>Arterial Area mm²</th>
<th>Lumen/Artery Ratio</th>
<th>Injury Score</th>
<th>Lumen Area mm² @28 day f/u</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bare Stent- Textured Abl. surface</td>
<td>7.76 mm²</td>
<td>1.08</td>
<td>0.57</td>
<td>3.35 ±0.66</td>
</tr>
<tr>
<td>BioMatrix Freedom Textured surf. 225μg BA9</td>
<td>8.49 mm²</td>
<td>1.08</td>
<td>0.50</td>
<td>5.68 ±0.68</td>
</tr>
</tbody>
</table>

![Percentage Area Occlusion Chart](chart.png)

- **No Drug**
- **225 micrograms BA9**

**Histological Images:**
- Biomatrix Freedom B9
- Bare - Microstruct. Surf
BioMatrix Polymer-Free Freedom Stent

Rabbit iliac arteries @ 14 days

Bare

DES

Similar EC coverage & function
New DES Carrier Systems

No Polymer

- Polymer-free DES systems are attractive as they eliminate all patho-biologic responses associated with artificial polymers and provide the possibility of short-term dual anti-platelet therapy.

- An added benefit may be improved endothelial cell adhesion and coverage due to the micro-structured surface; accelerated early healing.

- Problems abound including optimizing kinetic drug release patterns, inconsistent manufacturing and reduced drug loading capabilities.
New DES Carrier Systems

- Biostable Polymers
- Bioaborbable Polymers
- No Polymers
- *Elution Kinetics*
- ...and Beyond
Controlled Sirolimus Elution from Cypher™

Basecoat = polymer/sirolimus +
Topcoat = polymer only (diffusion barrier)

In Vivo Release Kinetics

Sirolimus is released in a controlled manner from a polymer matrix (PEVA + PBMA) bound to the stent; ALL of the drug is released within 3 months.
PISCES Trial Release Profiles

2 doses (10 and 30 µg); 3 rates (5, 10 and 30 days); mural or bi-directional

Release \textit{in vitro} under infinite sink conditions

Columbia University Medical Center
Cardiovascular Research Foundation
PISCES: In-Stent (Non-Paired) QCA

Late Loss (mm)

<table>
<thead>
<tr>
<th></th>
<th>4 Months</th>
<th>12 Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>D1</td>
<td>0.72</td>
<td>0.76</td>
</tr>
<tr>
<td>D2</td>
<td>0.70</td>
<td>0.61</td>
</tr>
<tr>
<td>D3</td>
<td>0.67</td>
<td>0.75</td>
</tr>
<tr>
<td>D4</td>
<td>0.48</td>
<td>0.68</td>
</tr>
<tr>
<td>D5</td>
<td>0.38</td>
<td>0.52</td>
</tr>
<tr>
<td>D6</td>
<td>0.37</td>
<td>0.36</td>
</tr>
</tbody>
</table>

N=29 N=20
N=28 N=19
N=28 N=19
N=30 N=26
N=38 N=32
N=26 N=17
Comparison of \textit{in vivo} Elution Rates

Rabbit iliac models

\begin{itemize}
\item \textbf{Endeavor}™:
  \begin{itemize}
  \item \textbf{LL} = 0.6mm
  \end{itemize}
  \begin{itemize}
  \item \textbf{\~75\%} elution in 2 days
  \item \textbf{100\%} elution in 10 days
  \end{itemize}

\item \textbf{Cypher}™:
  \begin{itemize}
  \item \textbf{LL} = 0.2mm
  \end{itemize}
  \begin{itemize}
  \item \textbf{\~75\%} elution in 10 days
  \item \textbf{100\%} elution in 30 days
  \end{itemize}
\end{itemize}

Cypher data from B. Chevalier, EuroPCR 2004
Endeavor data from G. Laarman, EuroPCR 2004
BioLinx Polymer System

Drug Elution Control

- C10 polymer is lipophilic and aids in control of drug release. Alone it locks in the drug.
- C19 polymer is primarily hydrophilic making it more biocompatible and aids in drug elution.
- PVP is hydrophilic, increases the initial drug burst and enhances the elution rate.

The BioLinx Polymer System blends C10, C19 and PVP for optimum elution.

LL < 0.2mm
BioMatrix Polymer-Free Freedom™ Stent

Drug Elution is much faster from polymer-free vs. bioresorbable polymeric DES

Biolimus A9 drug elution

Polymer-free

PLA resorbable polymer

Cumulative Release (%) vs. Time (Hrs)
New DES Carrier Systems

Elution Kinetics

- Kinetic drug release can be modulated from polymers and polymer-free DES by changing the thickness, composition, and internal architecture of the drug carrier system.

- Short-term drug release (< 2 weeks) of sirolimus (+ analogues) from carrier systems are associated with reduced neo-intimal hyperplasia suppression (higher late loss and restenosis).

- Polymer-free drug elution systems are challenged by rapid drug release which may limit effectiveness.
New DES Carrier Systems

- Biostable Polymers
- Bioabsorbable Polymers
- No Polymers
- Elution Kinetics
- ...and Beyond
New DES Carrier Systems

- Abluminal polymer applications
- Nanoparticles
- Bioabsorbable stents
- Drug eluting balloons
Directional Drug Delivery
(ablumenal preference)

- Selective coating on the outside surface of the stent
  - Reduced drug/polymer
  - Luminal surface BMS
  - Drug only where needed

Labcoat JA™Coating Technology
Biodegradable Nano-particle Drug Elution

- Particle size plays an important role in penetration and uptake of drug into arterial layer cells.
- There is a size-dependent NP penetration into the intact vessel wall.

Biodegradable polymer:
Sustained release of drug

Hydrophobic core:
Containing drug

Targeting Functional Ligand:
Guided to target organ
Hydrophilic surface:
Avoid to RES

~ 100 microns
Porous surface loaded with biodegradable nano-particles (thin polymer coat)
Bioresorbable: The Future of Stenting?

Past...
- Bare Metal Stent
  - More efficacious than POBA

Present...
- Metal DES
  - More efficacious than BMS

Future
- Cordis
- Boston Scientific
- BVS
- REVA
- Biotronik
  - no drug
  - drug
Abbott BVS Stent Components

- BVS Bioabsorbable Stent Platform
- ML VISION® Balloon SDS
- Everolimus
- Bioabsorbable Polymer Coating
ABSORB
Angiographic Late Loss

* BMS loss from SPIRIT FIRST (n=27)
** EES loss of pts with 3.0 x 18mm for single lesion from SPIRIT FIRST and II (n=22)

EES**: 0.07 ± 0.23mm (N=22)
BVS: 0.44 ± 0.35mm (N=26)
BMS*: 0.85 ± 0.36mm (N=27)
<table>
<thead>
<tr>
<th></th>
<th>Post-PCI</th>
<th>Follow-up</th>
<th>% Difference</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Vessel area (mm²)</td>
<td>13.55</td>
<td>13.49</td>
<td>-0.4</td>
<td>NS</td>
</tr>
<tr>
<td>EEM-Stent Area (mm²)</td>
<td>7.47</td>
<td>8.08</td>
<td>+8.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Stent area (mm²)</td>
<td>6.08</td>
<td>5.37</td>
<td>-11.7</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Neointimal hyperplasia</td>
<td>0</td>
<td>0.30</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>Neointimal hyperplasia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>area (mm²)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lumen area (mm²)</td>
<td>6.08</td>
<td>5.07</td>
<td>-16.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stent area obstruction (%)</td>
<td>0</td>
<td>5.55</td>
<td>NA</td>
<td>NA</td>
</tr>
</tbody>
</table>
New DES Carrier Systems

Final Thoughts-1

- There is a dramatic multi-facted effort to develop “safer” DES drug carrier systems, validating the concern that late stent thrombosis is partly related to current generation durable polymers.

- New biostable polymers are thinner, have improved mechanical stability, favor prolonged drug release, and are more biocompatible (less inflammation).

- A clear trend has emerged to reduce and eliminate the polymer carrier, either via bioabsorption (THE NEXT WAVE) or micro-textured polymer-free drug delivery surfaces (? the future).
New DES Carrier Systems

Final Thoughts-2

- Visionary concepts...including fully bioabsorbable stents and bioerodable nano-particles for drug delivery, are promising but will require extensive further experimental and clinical investigation.

- It seems likely that this explosion of new technology directed towards improving DES safety will yield worthwhile clinical results in the near future!