Importance of Polymer Biocompatibility for Drug Eluting Stent (DES) Outcomes

Josiah N. Wilcox, Ph.D.
Vice President, Resident Scholar
Science & Technology, Medtronic CardioVascular
Santa Rosa, CA

BioInterface Conference 2010
October 17-19
Conflict of Interest

• Josiah N. Wilcox is a full time employee of Medtronic CardioVascular which makes the Endeavor and Resolute stents
Number of Different DES Available

- Cypher®
  Sirolimus-eluting Coronary Stent

- Endeavor®
  Zotarolimus-eluting Coronary Stent System

- TAXUS® Liberté®
  Paclitaxel-eluting Coronary Stent System

- XIENCE/PROMUS®
  Everolimus-Eluting Coronary Stent System
Results come from separate clinical trials. Data may differ in a head-to-head comparison.

Xience V: No Pooled Data Available Beyond 3 Years

Stent thrombosis is a low-frequency event that current drug-eluting stent (DES) clinical trials are not adequately powered to fully characterize. The true rate of VLST is unknown, however pooled data exist from the various DES programs that are shown here.

Endeavor IV – Three Year Results

Significant Risk Reduction in VLST

ARC Definite/Probable ST 12–36 Months (VLST)

<table>
<thead>
<tr>
<th>Time After Initial Procedure (days)</th>
<th>Endeavor</th>
<th>Taxus</th>
</tr>
</thead>
<tbody>
<tr>
<td>360</td>
<td>732</td>
<td>734</td>
</tr>
<tr>
<td>450</td>
<td>732</td>
<td>734</td>
</tr>
<tr>
<td>540</td>
<td>719</td>
<td>721</td>
</tr>
<tr>
<td>630</td>
<td>716</td>
<td>718</td>
</tr>
<tr>
<td>720</td>
<td>710</td>
<td>714</td>
</tr>
<tr>
<td>810</td>
<td>699</td>
<td>701</td>
</tr>
<tr>
<td>900</td>
<td>688</td>
<td>690</td>
</tr>
<tr>
<td>990</td>
<td>684</td>
<td>681</td>
</tr>
<tr>
<td>1080</td>
<td>680</td>
<td>674</td>
</tr>
</tbody>
</table>

*p*-Values were calculated by logrank test. *p*-Values for outcome differences are unadjusted for multiple comparisons.

ENDEAVOR IV was not specifically designed or powered to individually compare VLST.

RRR = Relative Risk Reduction

Leon TCT 2009
Pivotal Trials TLR: DES Arms

Rates of TLR Overtime

Sirius
(n=525)

Taxus IV
(n=650)

SPIRIT III
(n=669)

Results come from separate clinical trials. Data may differ in a head-to-head comparison.

5 Year Clinical Results of TAXUS IV, Stone, TCT 2009
5 year Outcomes in the Sirius Trial, Leon, TCT 2008
4 year Outcomes in SPIRIT III, TCT 2010
Clinical Event Late Catch Up With DES
SIRTAX Late: 5-year TLR results

Target Lesion Revascularization @ 5 Years

1 year HR
0.54 [0.34 – 0.84]
P<0.01

5 year HR
0.80 [0.59 – 1.52]
P=0.16

10.4% Δ 4.6%
5.8%

17.9% Δ 3.0%
14.9%

Cumulative Incidence of target lesion (%)

Years
0 1 2 3 4 5

SES n=503
PES n=509

TCT 2009
Late Catch-Up Trend Different Than BMS

**j-Cypher: 3-year results**

### Total Lesion Revascularization (TLR)

<table>
<thead>
<tr>
<th></th>
<th>1 Yr</th>
<th>2 Yr</th>
<th>3 Yr</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Cypher</strong></td>
<td>5.7%</td>
<td>8.1%</td>
<td>10.0%</td>
</tr>
<tr>
<td><strong>BMS</strong></td>
<td>14.2%</td>
<td>15.5%</td>
<td>15.5%</td>
</tr>
</tbody>
</table>

Yoshihisa Nakagawa, “The Incidence and Predictors of Late (Beyond 1 Year) Target Lesion Revascularization After Sirolimus-eluting Stent Implantation: From Three-year Follow-up of the j-Cypher Registry”, AHA 2009.
Endeavor Trials TLR

Rates of TLR Overtime

Endeavor II
(n=598)

Endeavor III
(n=323)

Endeavor IV
(n=773)

Results come from separate clinical trials. Data may differ in a head-to-head comparison.
## Target Lesion Revascularization to 5 Years

**Cumulative Incidence of TLR to 5 Years**

- **Endeavor DES**
- **Driver® BMS**

### Time After Initial Procedure (days)

<table>
<thead>
<tr>
<th>Time (days)</th>
<th>Endeavor</th>
<th>CI (%)</th>
<th>Driver</th>
<th>CI (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2132</td>
<td>0.09</td>
<td>596</td>
<td>0.17</td>
</tr>
<tr>
<td>360</td>
<td>2130</td>
<td>5.43</td>
<td>595</td>
<td>13.16</td>
</tr>
<tr>
<td>720</td>
<td>1908</td>
<td>6.23</td>
<td>489</td>
<td>14.23</td>
</tr>
<tr>
<td>1080</td>
<td>1842</td>
<td>6.75</td>
<td>474</td>
<td>14.78</td>
</tr>
<tr>
<td>1440</td>
<td>1552</td>
<td>6.83</td>
<td>456</td>
<td>15.91</td>
</tr>
<tr>
<td>1800</td>
<td>1100</td>
<td>7.00</td>
<td>445</td>
<td>16.49</td>
</tr>
</tbody>
</table>

*CI (%)*: Cumulative Incidence of TLR (%)

- **p**-Values are unadjusted for multiple comparisons.
- **p**-Values were calculated by logrank test.

ENDEAVOR Pooled Analysis: E I 5-year, E II 5-year, E II CA 5-year, E III 5-year, E IV 3-year, E pK 3-year.
Hypothesis
Polymers are permanent and may have continued impact long term after the drug is exhausted.

Drug is exhausted by 6 months to 1 year
Bare metal stents have minimal long term impact on the vessel.

Potential Vessel Impact

Low level inflammation due to lack of complete polymer biocompatibility may contribute to late TLR catch-up and very late stent thrombosis.
DES Polymers Must be Designed with Biocompatibility in Mind

“Once the drug is eluted from the stent the remaining polymer if not biocompatible may stimulate inflammation and late intimal development.”

Lafont, A. Cardiovas. Res. 63:575;2004
Long-term effects of polymer-based, slow-release, sirolimus-eluting stents in a porcine coronary model

Andrew J. Carter\textsuperscript{a,*}, Meenakshi Aggarwal\textsuperscript{b}, Gregory A. Kopia\textsuperscript{c}, Fermin Tio\textsuperscript{d}, Philip S. Tsao\textsuperscript{b}, Ron Kolata\textsuperscript{c}, Alan C. Yeung\textsuperscript{b}, Gerald Llanos\textsuperscript{c}, John Dooley\textsuperscript{c}, Robert Falotico\textsuperscript{c}

Increased Inflammation Over Time

“the vascular response to ongoing injury and inflammation induced by the stent with residual polymer may simply overwhelm the biological effects of the drug in this model and result in the late formation of neointima.”

Localized Hypersensitivity and Late Coronary Thrombosis Secondary to a Sirolimus-Eluting Stent
Should We Be Cautious?

Renu Virmani, MD; Giulio Guagliumi, MD; Andrew Farb, MD; Giuseppe Musumeci, MD; Niccolo Grizzi, MD; Teresio Motta, MD; Laurenian Mihalesik, MD; Maurizio Testa, MD; Orazio Valsecchi, MD; Frank D. Kolodgie, PhD

A. Proximal Stent
B. Distal Stent

Luna Stain (K and L) T-cells (CD45Ro) B-cells (CD20) Macrophages (CD68)

Requirements for DES Coating Polymers

- Biocompatibility
- Biodegradation Kinetics / Products
- Hydrophobicity / Hydrophilicity
- Sterilizability
- Thermal Properties
- Stability
- Molecular Weight and Distribution
- Polymer Blend Compatibility
- Packaging Requirements

- Durability
- Solubility in Volatile Solvents

- Drug Elution Rate

In vitro Cumulative Release (%) of a Drug from Different Polymers
Parameters affecting polymer biocompatibility

1. Polymer Mass
2. Surface architecture
3. Hydrophilicity / hydrophobicity
   - Hydrophilic surfaces better
4. Net surface charges
   - Certain blood coagulation factors are activated in the presence of negatively charged surfaces

Ultimately these factors influence the nature of the protein layer found at the tissue / material interface.
Endeavor Drug Elution

Drug Eluted by 14 days only PC Basecoat Left Behind
Hydrophilic vs Hydrophobic

Contact Angle

- Angle formed when water drop applied to polymer surface
- Smaller angle = more hydrophilic

<table>
<thead>
<tr>
<th>Hydrophilic Polymer</th>
<th>Contact Angle</th>
<th>Hydrophobic Polymer</th>
</tr>
</thead>
<tbody>
<tr>
<td>PC (Endeavor)</td>
<td>81°</td>
<td>PBMA (Cypher)</td>
</tr>
<tr>
<td>BioLinx (Resolute)</td>
<td>94°</td>
<td>SIBS (Taxus)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>PVDF-HFP (Xience V)</td>
</tr>
</tbody>
</table>

Water-loving

Water-hating

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
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.

*Hayward JA & Chapman D; Biomaterials 5, 135, 1984.

PC Technology is licensed under patents or patent applications owned by Biocompatibles.
BioLinx Polymer Shows Low Inflammation Scores and Allows for Extended Drug Elution

Preclinical results may not be indicative of clinical performance of DES

1 Preclinical porcine data on file at Medtronic, Inc.

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
BioLinx Polymer System

*Composed of Hydrophilic and Hydrophobic Polymers*

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

- **C19 polymer** *(Hydrophilic)*
  Manufactured from a mixture of hydrophobic hexyl methacrylate and hydrophilic vinyl pyrrolidinone and vinyl acetate monomers to provide enhanced biocompatibility

- **PVP** *(Hydrophilic)*
  Hydrophilic polyvinyl pyrrolidinone polymer increases initial drug burst and enhances biocompatibility

Overall the BioLinx polymer blend displays a very hydrophilic surface *(94° contact angle)* to the body for biocompatibility

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
BioLinx Polymer System
Composed of Hydrophilic and Hydrophobic Polymers

C10
Hydrophobic

C19
Hydrophilic

Zotarolimus
Hydrophobic

PVP
Hydrophilic

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
BioLinx Polymer System
Composed of Hydrophilic and Hydrophobic Polymers

C10, C19, PVP and Zotarolimus are mixed together in a common solvent

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
BioLinx Polymer System
*Composed of Hydrophilic and Hydrophobic Polymers*

The mixture of C10, C19, PVP and zotarolimus are sprayed as a uniform layer onto the stent (no specific orientation all three components show a uniform distribution)

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
BioLinx Polymer System
*Composed of Hydrophilic and Hydrophobic Polymers*

In the presence of water the polymer blend self-orient such that the hydrophilic PVP groups in C19 will be on the surface and the long chain hydrocarbons will form a hidden hydrophobic domain where the drug will be sequestered.

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
BioLinx Polymer System
Composed of Hydrophilic and Hydrophobic Polymers

Overall the combined BioLinx polymer blend is hydrophilic

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
Surface Analysis of BioLinx Polymers

**Hydrophilic C19 Predominates at the Surface of the Final Blend**

<table>
<thead>
<tr>
<th>Polymer</th>
<th>%N</th>
<th>%C</th>
<th>%O</th>
</tr>
</thead>
<tbody>
<tr>
<td>C19</td>
<td>1.6</td>
<td>81.5</td>
<td>16.9</td>
</tr>
<tr>
<td>C10</td>
<td>0</td>
<td>79.7</td>
<td>20.3</td>
</tr>
<tr>
<td>C10:C19</td>
<td>1.4</td>
<td>81.4</td>
<td>17.2</td>
</tr>
<tr>
<td>BioLinx</td>
<td>1.3</td>
<td>81.2</td>
<td>17.5</td>
</tr>
</tbody>
</table>

Surface characterization by X-ray Photoelectron Spectroscopy (XPS) suggests that the Nitrogen-rich C19 predominates on the surface of Endeavor Resolute polymer blends.

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
Phosphorylcholine (PC) Headgroup

Hydrophilic outer surface

Drug Elution 28 Days

Phosphorylcholine (PC) Headgroup

Similar Inflammatory profiles and vascular biocompatibility

BioLinx

Hydrophilic outer surface

Drug Elution 6 Months

Vinyl pyrrolidinone groups

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
In vitro and in vivo analysis of inflammation associated with DES polymers
Monocyte Adhesion Correlates With Polymer Hydrophobicity

Contact Angle:

Hydrophobic:
- C10: 118\(^0\)
- SIBS: 118\(^0\)
- PBMA: 112\(^0\)
- PVDF-HFP: 129\(^0\)

Hydrophilic:
- PC: 81\(^0\)
- C19: 91\(^0\)
- C10/C19: 84\(^0\)
- BioLinx: 94\(^0\)

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in Japan.
Monocytic Adhesion to Commercial DES

Differential Monocytic Adhesion To Various DES In-Vitro

24 hr incubation with activated monocytes
Followed by PBS wash and calcein staining

FACS analysis

Increased adhesion of monocytes to DES with hydrophobic polymeric coatings

Hezi-Yamit et al. TCT 2008
## Relative Gene Expression

**Hydrophobic polymers stimulate inflammatory and pro-coagulant genes**

<table>
<thead>
<tr>
<th>POLYMER CONTACT ANGLE</th>
<th>C19 91°C</th>
<th>BioLinx 94°C</th>
<th>Fluoro 129°C</th>
<th>C10 118°C</th>
<th>SIBS 118°C</th>
<th>PBMA 115°C</th>
</tr>
</thead>
<tbody>
<tr>
<td>+</td>
<td>1-5 fold</td>
<td>EC SMC</td>
<td>EC SMC</td>
<td>EC SMC</td>
<td>EC SMC</td>
<td>EC SMC</td>
</tr>
<tr>
<td>++</td>
<td>6-10 fold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+++</td>
<td>&gt;10 fold</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>TF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PAR-2</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>PAI-1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>IL-8</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>MCP-1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td>TNF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Endothelin-1</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>TSP-1</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>CTGF</td>
<td>-</td>
<td>-</td>
<td>-</td>
<td>+</td>
<td>-</td>
<td>+</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>0</strong></td>
<td><strong>1</strong></td>
<td><strong>0</strong></td>
<td><strong>1</strong></td>
<td><strong>10</strong></td>
<td><strong>4</strong></td>
</tr>
</tbody>
</table>

*Hezi-Yamit et al. Comb. Chem & High Throughput Screening 12;2009*

**Caution:** Resolute utilizing the BioLinx polymer is an investigational device, not approved for US sale or commercial use.
Tissue factor is a key regulator of the coagulation cascade

- TF is produced by macrophages, endothelial cells, and SMC
- TF is over-expressed in atherosclerotic plaques
- TF triggers thrombosis formation associated with plaque rupture in acute coronary syndrome

Steffel, J. et al. Circulation 2006;113:722-731
Monocytic TF Activation by DES Polymers Correlates with Relative Polymer Hydrophobicity

Contact Angle:

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Hydrophobic Contact Angle</th>
<th>Hydrophilic Contact Angle</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fluoro</td>
<td>129°</td>
<td>118°</td>
</tr>
<tr>
<td>SIBS</td>
<td>115°</td>
<td></td>
</tr>
<tr>
<td>PBMA</td>
<td>94°</td>
<td>83°</td>
</tr>
<tr>
<td>BioLinx</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PC</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
Upregulation of TF by Hydrophobic Polymers

Implantation of polymer only stents in porcine coronary arteries

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
Upregulation of TF Protein by SES/PES 90 days after stenting in porcine coronary arteries

Haraguchi et al. TCT. 2007
Inflammation scores

Porcine Coronary Artery Implants

Low inflammation scores seen with Endeavor and Resolute DES
Higher inflammation scores (>1) seen with Xience and Cypher DES

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
Study design for Atherosclerosis

New Zealand White Rabbits, n=45

Blood Collection for Cholesterol measurements

0 5 w 9 w 13 w

Study duration

5 wks.
Balloons injury after 1 week

1 2 3 4 5

Study duration

Groups:
Diver
Endeavor
Xience V
Cypher

1% Atherogenic Diet
0.025% Atherogenic diet
Stent Implantation
Euthanasia

Blood Collection for Cholesterol measurements

0 5 w 9 w 13 w
Pre-Clinical Evaluation

Healing in Atherosclerotic Rabbit Model

Representative healing at 28 days

Virmani et al. CRT 2008
Nakazawa et al PCR 2009
Pre-Clinical Evaluation

Healing in Atherosclerotic Rabbit Model

Neointimal Area

%Stenosis

Neointimal Thickness

Cypher
Xience V
Endeavor
Driver

*significant vs. Driver

Nakazawa et al PCR 2009
Pre-Clinical Evaluation

*Healing in Atherosclerotic Rabbit Model*

- %Struts with Giant cell: Red bars, *P<0.0001*
- %Struts with Fibrin: Orange bars, *P=0.0005*
- Uncovered Struts: Red bars, *P<0.0001*
- Number of Luminal Inflammatory cell: Red bars, *P=0.0002*

*significant vs. Driver

Nakazawa et al PCR 2009
Tissue Factor
*Thrombosis/ Inflammation*

Hezi-Yamit et al. PCR 2010

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
Endothelin 1

Inflammation/Late proliferation catch-up

---

Hezi-Yamit et al. PCR 2010

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
NADPH oxidase 3
Pro-Healing (low is bad)

Hezi-Yamit et al. PCR 2010

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
**HO1 – Day 28**

*Protection from Inflammation and Oxidative stress*

---

*Low - Undesirable*

Hezi-Yamit et al. PCR 2010

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
Incomplete Healing of Cypher Stents

Angioscopy 3-6 months post-stenting

Kotani et al. JACC 2006;47:2008
Serial Angioscopy Cypher vs. BMS

*Persistent Lack of Healing – Role of Polymers?*

Clinical Evaluation: Vessel Coverage

Coverage Grade: ZES vs SES at 8 months

Grade 0: struts were exposed similarly to the time of implantation
Grade 1: struts were covered, but not embedded
Grade 2: struts were embedded by the neointima, but no translucency seen
Grade 3: struts were fully embedded and invisible by angioscopy

\[ P = 0.0004 \]

Awata et al. JACC 2008;52:789
Representative Cases

Grade 1
SES 3.5x23mm

Grade 3
ZES 3.5x23mm

Awata et al. JACC 2008;52:789
OCT Studies Verify Endeavor Strut Coverage

Uncovered Struts (%)

<table>
<thead>
<tr>
<th>Time</th>
<th>ZES (N=32)</th>
<th>SES (N=36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>9-Months</td>
<td>0.3%</td>
<td>12.2%</td>
</tr>
<tr>
<td>6-Months</td>
<td>0.01%</td>
<td>1.6%</td>
</tr>
<tr>
<td>3-Months</td>
<td>0.0%</td>
<td>0.0%</td>
</tr>
</tbody>
</table>

1 Kim et al., Heart, 2009: 95 1907-1912.
2 Guagliumi et al. TCT 2008.
Functional Endothelial Healing
Biological Functions of Nitric Oxide

eNOS (Endothelial Nitric Oxide Synthase) is the protein that helps produce NO and is a marker of endothelial cell function.
Clinical Data Indicate SES and PES are Associated with EC Dysfunction Proximal and Distal to Stent

Both SES and TES implantation have been shown to have adverse effects on local endothelium-dependent vasomotor responses in response to ACH or exercise stress six months after implantation

Tongi et al. JACC 2005;46:231
Hofma et al. Eur Heart J 2006;27:166
Tongi et al. Int. J. Cardiol. 2007;120:212
Kim, J. W. et al. JACC Intv 2008;1:65-71
EC Dysfunction Associated with PES

Tongi et al. Int. J. Cardiol. 2007;120:212
EC Dysfunction Associated with PES

Baseline

Exercise

Tongi et al. Int. J. Cardiol. 2007;120:212
EC function after SES or ZES Implants
Clinical evaluation of ACH six-nine months post-stenting

“SES implantation may induce significant impairment of long-term coronary endothelial function, while ZES implantation may not”

Shin et al. Int Heart J 49(639) 2008
EC function after SES or ZES Implants
Clinical evaluation of ACH six months post-stenting

Kim et al. JACC 53(1653) 2009
Comparison of EC function by Atrial Pacing

Percent change in vessel diameter from baseline at 9-12 months follow-up

<table>
<thead>
<tr>
<th></th>
<th>PES</th>
<th>SES</th>
<th>BES</th>
<th>ZES</th>
<th>BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>10</td>
<td>17</td>
<td>23</td>
<td>9</td>
<td>12</td>
</tr>
</tbody>
</table>

Hamilos Circ Cardiovas Intervent 1(193)2008
Acetylcholine challenge response
*Proximal to stents implanted in porcine coronary arteries*

**Vasodilation**

**Vasoconstriction**

Endeavor and Resolute stents show high eNOS levels, suggesting good NO production and a functional endothelium.

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
EC Function Assessed by ACH Challenge
28 Days After Stenting in Porcine Coronary Arteries

**RESOLUTE (n=8)**

<table>
<thead>
<tr>
<th>Ach (10^{-6}M)</th>
<th>Baseline</th>
<th>Relative eNOS Expression</th>
<th>Inflammation Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2.06 ± 0.58</td>
<td>0.27 ± 0.26</td>
<td>1.89 ± 1.95</td>
</tr>
</tbody>
</table>

**Xience (n=8)**

<table>
<thead>
<tr>
<th>Ach (10^{-6}M)</th>
<th>Baseline</th>
<th>Relative eNOS Expression</th>
<th>Inflammation Scores</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.67 ±1.52</td>
<td>1.89 ± 1.95</td>
<td></td>
</tr>
</tbody>
</table>

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan.
Hypothesize that inflammation exerts paracrine actions by releasing cytokines and ROS that affect the adjacent segments.

Inflammation only found in the stented region.

Why is this associated with vasomotor changes proximally and distally?
Polymer Related Oxidative Stress
Human peripheral blood monocytes

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
Superoxide Production in Porcine Coronary Artery

Comparison of PES vs BMS by lucigenin assay

* P<0.05 PES vs. BMS
# P<0.05 PES vs. Naive

Keith Robinson, LDDR 2008
Superoxide Production in Porcine Coronary Artery

Comparison of BMS, ZES and SES by lucigenin assay

Nakamura PCR 2010
**Contributors to Late Stent Thrombosis**

Inflammation and Vasomotor Dysfunction may be Relevant

**DES Exposure**

- Chronic inflammation,
- Hypersensitivity to polymer
- Expression of Prothrombotic Genes

**Endothelial dysfunction**

Vasospasm (conduit ± resistance)

Reduced blood flow, Stasis & turbulence

Leukocyte adherence

Leukocyte activation

Platelet recruitment

**Late Stent Thrombosis**

K. Robinson LDDR 2008

Flow disturbance associated with EC dysfunction

Proximal Vasoconstriction.
Potential to create areas of disturbed flow within the stent segment leading to further EC injury and platelet activation.

Personal communication Dr. Peter Davies
Late Loss Changes Over Time
Factors contributing to late loss changes
SMC proliferation and changes in extracellular matrix

**Smooth Muscle Cell Migration/Proliferation**

**Extracellular Matrix Production**

**Extracellular Matrix Reabsorption**

---

Time after stenting (days)

3

14

90

440

1000

Growth of neointima
Increased late loss
Luminal narrowing

Intimal remodeling
Reduced late loss
Increase in lumen diameter

Seen in BMS but not all DES
BMS Demonstrate LL Regression

Hypothesize associated reabsorption of ECM proteins

THREE-YEAR FOLLOW-UP AFTER IMPLANTATION OF METALLIC CORONARY-ARTERY STENTS

Takeshi Kimura, M.D., Hiroyoshi Yokoi, M.D., Yoshihisa Nakagawa, M.D., Takashi Tamura, M.D., Satoshi Kaburagi, M.D., Yoshihiro Sawada, M.D., Yasukazu Sato, M.D., Hiroatsu Yokoi, M.D., Naoya Hamasaki, M.D., Hideyuki Nosaka, M.D., and Masakiyo Nobuyoshi, M.D.

Figure 3. Serial Changes in the Mean (±SD) Minimal Luminal Diameter of 72 Lesions for Which Sequential Studies over a Three-Year Period. Were Completed (●), as Compared with a Reference Diameter (○).

There was significant improvement in minimal luminal diameter during the period from one year to three years after implantation of the stent. P<0.001 for the comparison between the points linked by brackets.

Kimura et al. NEJM 1996;334:561
Cypher Late “Catch-up” vs. BMS
Decreased MLD/Increased Late Loss over 3yrs

Shiode et. al. Late Progression After Sirolimus-Eluting Stent Implantation: Comparison with Bare Metal Stent Implantation. ACC 2009 Abstract 2501-523/523
LL Progression and ABR Changes

*Taxus and Cypher LL progressed between 6-8 months and 2 years in a paired analysis of 1,331 patients*


**Figure 2. Primary End Point: LLL**

Data are displayed as mean ± standard error of mean. LLL = late luminal loss; PES = paclitaxel-eluting stent; RES = rapamycin-eluting stent.

**Figure 3. Secondary End Point: Binary Angiographic Restenosis**

Shaded bars represent restenosis at 6 to 8 months. Full-color bars represent delayed (interval) restenosis at 2 years in patients who did not undergo revascularization at 6 to 8 months. $P_{\text{interval}}$ represents $p$ value for differences in interval progression between 6 to 8 months and 2 years. Abbreviations as in Figure 2.
In-stent Late Loss in Spirit II
Serial 6 Month and 2 Year Angio FU

**6 Months**
- **XIENCE™ V:** 0.17 ± 0.32 (nL=97)
- **TAXUS®:** 0.33 ± 0.32 (nL=35)
- \[ P=0.0037 \]

**2 Years**
- **XIENCE™ V:** 0.33 ± 0.37 (nL=97)
- **TAXUS®:** 0.34 ± 0.34 (nL=35)
- \[ P=0.6026 \]

In this serial analysis, for patients having TLR, values of loss and neo-intimal hyperplasia observed prior to 6 month or 2 year FU were imputed at 6 months and 2 years respectively.
Spirit II Paired Changes in In-Stent Late Lumen Loss from 6 to 24 Months

**TAXUS®** (nL=35)
Mean Δ
0.01 mm ± 0.24

**Xience™ V** (nL=97)
Mean Δ
0.16 mm± 0.32

*P<0.0001*
ISAR Test 4 – EES vs SES

Late Lumen Loss to 2 Years

n=805 lesions

With paired angiographic FU

P=0.59
SES 0.31±0.58

P=0.15
SES 0.17±0.33

EES 0.14±0.41

EES 0.29±0.51

Post-PCI  6-8-month  Data are mean ± SEM  2-year

XXX TCT 2010
Serial angiographic follow-up after successful implantation of sirolimus, paclitaxel and everolimus-eluting stent for chronic total occlusions: multicenter registry in Asia

Endeavor Late Loss Stability/Regression

Change in Late Lumen Loss between 6 and 36 months

Three Year Follow-up E Five

Courtesy of Dr. Fausto Feres
MLD Pre PCI: 0.77 ± 0.29
MLD Post PCI: 2.69 ± 0.52
6-Month MLD: 2.11 ± 0.60
3-Year MLD: 2.16 ± 0.52

Endeavor -3 years
MLD pre, post, 6-month and 3 years
(17 matched lesions)
Endeavor- 3 years

Late loss at 6-months and 3 years (17 matched lesions)

Luminal Late Loss, mm

Percent of Lesions, %

6-month Late Loss: 0.58 ± 0.31
3-Year Late Loss: 0.53 ± 0.33
Pivotal Trials TLR: DES Arms

Rates of TLR Overtime

Results come from separate clinical trials. Data may differ in a head-to-head comparison.

5 Year Clinical Results of TAXUS IV, Stone, TCT 2009
5 year Outcomes in the Sirius Trial, Leon, TCT 2008
4 year Outcomes in SPIRIT III, TCT 2010

Sirius (n=525)  R² = 0.9762
1 yr 2 yrs 3 yrs 4 yrs 5 yrs
4.9 6.3 6.8 7.9 9.4

Taxus IV (n=650)  R² = 0.9973
1 yr 2 yrs 3 yrs 4 yrs 5 yrs
4.4 5.6 6.9 7.8 9.1

SPIRIT III (n=669)  R² = 0.9915
1 yr 2 yrs 3 yrs 4 yrs 5 yrs
3.3 4.4 5.4 7.6

Endeavor II (n=598)  R² = 0.9665
1 yr 2 yrs 3 yrs 4 yrs 5 yrs
5.9 6.5 7.2 7.2 7.5

Endeavor III (n=323)  R² = 0.9256
1 yr 2 yrs 3 yrs 4 yrs 5 yrs
6.6 6.9 7.3 7.7 8.1

Endeavor IV (n=773)  R² = 0.9995
1 yr 2 yrs 3 yrs
4.5 5.8 6.5
Long-Term Results with RESOLUTE Using the Hydrophilic BioLinx Polymer Blend

RESOLUTE 3-year data show very low rate of events at 3 years

**TLR 1-3 Years**

<table>
<thead>
<tr>
<th>RESOLUTE (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 events 2–3 Years</td>
</tr>
<tr>
<td>1 event 1 Year  0.8%</td>
</tr>
<tr>
<td>2 events 2 Years 1.5%</td>
</tr>
<tr>
<td>2 events 3 Years 1.6%*</td>
</tr>
</tbody>
</table>

**ST (ARC Def/Prob) 1-3 Years**

<table>
<thead>
<tr>
<th>RESOLUTE (n = 130)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 events 12–24 months 0.0</td>
</tr>
<tr>
<td>0 events 24–36 months 0.0</td>
</tr>
</tbody>
</table>

*n=129, missing data from one patient.

Three Year Follow-up with Zotarolimus-eluting Stent, Resolute DES, Ian Meredith, TCT 2009. RESOLUTE had single de novo native coronary artery lesions. Lesion length: 14–27 mm. Stent diameters: 2.5, 3.0, 3.5 mm. Stent lengths: 18, 24, 30 mm (8/9 mm bailout).

Caution: Resolute utilizing the BioLinx polymer is an investigational device, not approved for sale or commercial use in US or Japan
We hypothesize that hydrophilic polymers are more biocompatible for DES applications

- Healthy Healing
- Less Inflammation
- Reduced cytokine and procoagulant production
- Restoration and maintenance of endothelial function

Hypothesize that polymer biocompatibility is important for long-term outcomes
Thanks to the team that contributed to this work

Kishore Udupi
Ayala Hezi-Yamit
Mingfei Chen
Peiwen Cheng
David Shumaker
Carol Sullivan
Robert Melder

Go Haraguchi
Andrew Carter
Thank You!