Can Biodegradable Polymer DES Be Better than 2nd Generation DES?

G. Nakazawa, MD
Tokai Univ. Japan
CV-HILLs
Receiving Research Grant From
Abbott Vascular Japan
Boston Scientific Japan
Medtronic Vascular Japan
Cordis Johnson & Johnson
Terumo Corp.
Biosensors Japan

Advisory Contract With
Abbott Vascular Japan
Terumo Corp.
Components of DES

Metal/Design

Thick struts ~ 81-140 microns

Inflammatory reaction

Incomplete healing

Polymer

Drug and Release kinetics

Determining Antiproliferative effects

Drugs

Sirolimus-135 µg
Everolimus – 100 µg
Paclitaxel- 80 µg
Biolimus A9 – 225 µg
Localized Hypersensitivity Reaction in Cypher

LAD: Cypher (17 months)

RCA: Cypher (17 months)

Long Term Safety : Future Directions

Long-Term Safety of DES: Future Directions

Asymmetric Biodegradable Polymer

No Polymer
No Drug
General criteria for selecting a polymer for use as biomaterial

- Does not evoke an inflammatory/toxic response, disproportionate to its beneficial effect
- Is metabolized in the body after fulfilling its purpose, leave no trace
- Is easily processed into the final product form
- Has acceptable shelf life
- Is easily sterilized

Middleton JC and Tipton AJ. Biomaterials 2000; 21:2335
Synthetic Biodegradable Polymers

- Poly(lactide) (PLA)
- Poly(glycolide) (PGA)
- Poly(glycolic-co-lactic acid) (PLGA)
- Poly(e-caprolactone) (PCL)
- Poly(dioxanone) (PDS)
- Poly(glycolide-co-trimethylene carbonate) (PGA-TMC)
Degradation Speed in Various Biodegradable Polymers

<table>
<thead>
<tr>
<th>Material</th>
<th>Degradation Period</th>
</tr>
</thead>
<tbody>
<tr>
<td>Polylactic acid (PLA)</td>
<td>9 months</td>
</tr>
<tr>
<td>Polyglycolic acid (PGA)</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Poly-L-lactic acid (PLLA)</td>
<td>12-18 months</td>
</tr>
<tr>
<td>Poly(d,l-lactide/glycolide) copolymer (PGLA)</td>
<td>2-3 months</td>
</tr>
<tr>
<td>Polyorthoester (POE)</td>
<td>10 months (60%)</td>
</tr>
<tr>
<td>Poly(hydroxybutyrate/hydroxyvalerate) copolymer (PHBV)</td>
<td>6 months</td>
</tr>
<tr>
<td>Polycaprolactone (PCL)</td>
<td>36 months</td>
</tr>
</tbody>
</table>
The degradation-absorption mechanism is the result of many interrelated factors, including:

- The chemical stability of the polymer backbone
- The presence of catalysts
- Additives
- Impurities or plasticizers
- Geometry of the device
- Location of the device

Factors which accelerate polymer degradation are the following:

- More hydrophilic monomers
- More hydrophilic, acidic endgroups
- More reactive hydrolytic group in the backbone
- Less crystallinity
- Small device size

Middleton JC and Tipton AJ. Biomaterials 2000;
PLA Metabolic Pathway

PLA → H₂O

Hydrolysis

↓Molecular weight → Mass loss → Lactic acid → Mass transport of lactic acid → Krebs cycle → CO₂ + H₂O

Fig. 10. Generic curves showing the sequence of polymer-molecular weight, strength, and mass-reduction over time [19].
Bioerodible polymer breaks down into Polymer degradation products and side products. The side products, mostly responsible for toxic effects.

Commandeur S, J Interven Cardiol 2006
NOBORI Stent Platform

S-Stent™ Platform:
- Stainless steel (129 µm)
- Open cell design
- Quadrature-link™ connectors
- Different models for small and large vessels

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

Drug: Biolimus A9
15.6 µg/mm-stent length

2.5-3.0mm (6 crown 2 link)
3.5mm (10 crown 2 link)
### NOBORI—Strut and polymer thickness

<table>
<thead>
<tr>
<th>DES</th>
<th>Xience Stent</th>
<th>ENDEAVOR® Stent</th>
<th>NOBORI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent Material</td>
<td>Cobalt Chromium</td>
<td>Cobalt Chromium</td>
<td>Stainless Steel</td>
</tr>
<tr>
<td>BMS Strut Thickness (in.)</td>
<td>0.0032”</td>
<td>0.0036”</td>
<td>0.0053”</td>
</tr>
<tr>
<td>BMS Strut Thickness (µm)</td>
<td>81µm</td>
<td>91µm</td>
<td>130µm</td>
</tr>
<tr>
<td>Polymer Thickness (µm)</td>
<td>7µm</td>
<td>6µm</td>
<td>18µm</td>
</tr>
</tbody>
</table>
Drug Dose in various DES

- **XIENCE V™** 3.0x 18 mm: 88 µg
- **Cypher** 3.0x 18 mm: 150 µg
- **Endeavor** 3.0x 18 mm: 180 µg
- **NOBORI** 3.0x 18 mm: 280 µg
Percent Stenosis in Single DES in Rabbit Iliac Arteries following Deployment of Cypher, Taxus and Nobori stents at 28-days

Data from CVPath Institute, Inc.
Fibrin Deposition in Single DES in Rabbit Iliac Arteries at 28-days

Cypher

Taxus

Nobori

Data from CVPath Institute, Inc.
Inflammation in Single DES

![Images of tissue samples labeled Cypher, Taxus, Nobori]

Bar charts showing:
- No. Lumen Eosinophils/Neutrophils
- No. Giant Cells

Data from CVPath Institute, Inc.
Overlapping Drug-Eluting Stents (Cypher, Taxus and Nobori) at 28-day

Proximal | Middle | Distal
---|---|---
Cypher
Taxus
Nobori

Neointimal Thickness (mm)

Data from CVPath Institute, Inc.
Fibrin Deposition in Overlapped DES at 28 days

Cypher™

Taxus™

Nobori™

Data from CVPath Institute, Inc.
Giant cells in Overlapped DES at 28-Days

Cypher™

Taxus™

Nobori™

Data from CVPath Institute, Inc.
Comparison of Various BMS and DES In Rabbit Iliac Arteries at 28-days
28 Day Endothelialization

Data from CVPath Institute, Inc.
Endothelial Function in NOBORI

Hamilos, MI et al. J Am Coll Cardiol 2008;51:2123–9
Is the biodegradable polymer really better than durable ones?
**Study Title:** Comparison of long-term safety following new generation drug eluting stents implantation in porcine coronary artery

**Purpose:** Hypersensitivity reaction due to lack of biocompatibility has emerged as one of the major concerns in 1st generation drug-eluting stents (DES). Newer generation DES has applied better polymer but the long-term safety is still unclear. The aim of this study is to evaluate the long-term safety following Xience V, Cypher, and Nobori DES in porcine coronary artery model.

**Test Articles:**
1. Xience V everolimus eluting stent
2. Cypher Select sirolimus eluting stent
3. Nobori Biolimus eluting stent
Collaborators

Kobe University Graduate School of Medicine
Toshiro Shinke, MD (Study Co-Director)
Daisuke Matsumoto, MD
Hiromasa Otake, MD
Junya Shite, MD

Tokai University School of Medicine
Takeshi Ijichi, MD

Abbott Vascular Japan
Masaharu Osa
Masaru Uchiyama
Akiji Kato
Yoshihiro Odagawa

GOODMAN CO., LTD.
Kentaro Asada
Toshio Kimura
Study Design

Implantation of DES
Animal N=12
Each animal receives 3 DESs (XV, CS, and NB)

Sacrifice 6 animals for Histo
• Ach challenge test
• OCT observation
Before sacrifice

N=6
0 3M
1M
6M

• Acetylcholine challenge test
• OCT observation
6 animals for 6M

Sacrifice 6 animals for Histo
• Ach challenge test
• OCT observation
Before sacrifice
Protocol for Acetylcholine challenge test

Baseline Angiography

10⁻⁶mol/l of acetylcholine (1ml/min) → 2.5 mins

10⁻⁵mol/l of acetylcholine (1ml/min) ← 2.5 mins

ISDN (200-400ug)

Final Angiography

OCT Imaging
MLD following Ach Challenge@1M

Proximal

Distal

Baseline  Ach 10^-6  Ach 10^-5  ISDN  Baseline  Ach 10^-6  Ach 10^-5  ISDN  Baseline  Ach 10^-6  Ach 10^-5  ISDN

Xience  Cypher  NOBORI
Maximum Change in MLD following Ach Challenge@1M

<table>
<thead>
<tr>
<th></th>
<th>Xience</th>
<th>Cypher</th>
<th>Nobori</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Proximal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-10</td>
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<td></td>
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<tr>
<td>-20</td>
<td></td>
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</tr>
<tr>
<td>-30 (%)</td>
<td></td>
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<td></td>
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</table>

<table>
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<th></th>
<th>Xience</th>
<th>Cypher</th>
<th>Nobori</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Distal</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

(%)
- Preliminary OCT results -

1 and 3 months
1-month group OCT Analysis Status

6 pigs
18 lesions enrolled

Xience™
6 cases received
6 cases analyzed

Nobori™
6 cases received
Void: 1 case (poor image quality)
5 cases analyzed

Cypher™
6 cases received
6 cases analyzed

17 lesions available
Follow-up OCT Results

~ Neointima proliferation ~

<table>
<thead>
<tr>
<th>Stent Type</th>
<th>Average Neointimal Area (mm²)</th>
<th>Average % Neointimal Area (NIA/Stent area)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xience™</td>
<td>2.2±0.6</td>
<td>31.5±11.5</td>
</tr>
<tr>
<td>Nobori™</td>
<td>1.7±0.9</td>
<td>24.0±12.2</td>
</tr>
<tr>
<td>Cypher™</td>
<td>0.9±0.5</td>
<td>14.1±7.0</td>
</tr>
</tbody>
</table>

*Bonferoni/Dunn test*
Follow-up OCT Results

~ Neointima proliferation ~

**Average neointima thickness**

<table>
<thead>
<tr>
<th>Device</th>
<th>Average Thickness (µm)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xience™</td>
<td>269±98</td>
<td>0.006*</td>
</tr>
<tr>
<td>Nobori™</td>
<td>198±103</td>
<td></td>
</tr>
<tr>
<td>Cypher™</td>
<td>102±63</td>
<td></td>
</tr>
</tbody>
</table>

**Neointimal Unevenness Score**

<table>
<thead>
<tr>
<th>Device</th>
<th>Score (%)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Xience™</td>
<td>1.4±0.1</td>
<td>0.01*</td>
</tr>
<tr>
<td>Nobori™</td>
<td>2.5±1.3</td>
<td></td>
</tr>
<tr>
<td>Cypher™</td>
<td>3.2±1.5</td>
<td></td>
</tr>
</tbody>
</table>

* Bonferoni/Dunn test
Follow-up OCT Results

~ Neointimal coverage ~

**Number of Uncovered struts**

- Xience™: 0.5±0.8
- Nobori™: 36.4±41.3
- Cypher™: 64.7±53.3

P=0.01*

**%Uncovered Struts**

- Xience™: 24.5±23.8
- Nobori™: 41.7±27.0
- Cypher™: 0.4±0.8

P=0.004*

* Bonferoni/Dunn test
### Histogram of %Uncovered struts

(No of Uncovered struts/ total no of struts)

<table>
<thead>
<tr>
<th></th>
<th>Xience™</th>
<th>Nobori™</th>
<th>Cypher™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average %</td>
<td>N=6</td>
<td>N=5</td>
<td>N=6</td>
</tr>
<tr>
<td></td>
<td>0.4±0.8</td>
<td>24.5±23.8</td>
<td>41.7±27.0</td>
</tr>
<tr>
<td>Median</td>
<td>0</td>
<td>19.5</td>
<td>42.9</td>
</tr>
<tr>
<td>25% Quartile</td>
<td>0</td>
<td>11.6</td>
<td>23.7</td>
</tr>
<tr>
<td>75% Quartile</td>
<td>0.5</td>
<td>32.0</td>
<td>59.9</td>
</tr>
</tbody>
</table>

(No of Uncovered struts/ total no of struts)

<table>
<thead>
<tr>
<th></th>
<th>Xience™</th>
<th>Nobori™</th>
<th>Cypher™</th>
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<td>N=6</td>
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</tr>
<tr>
<td>75% Quartile</td>
<td>0.5</td>
<td>32.0</td>
<td>59.9</td>
</tr>
</tbody>
</table>

(No of Uncovered struts/ total no of struts)
Follow-up OCT Results

~ Neointimal coverage ~

% of stents with at least 1 CS with RUST>30%

Average %CS with RUST>30%

CS: Cross-section, RUST: a ratio of uncovered struts to total struts per cross section

* Bonferroni/Dunn test
3-month group: OCT Analysis Status

18 lesions enrolled

- Xience™
  - 6 lesions received
  - 6 lesions analyzed

- Nobori™
  - 5 lesions received
  - 5 lesions analyzed
  - Void: 1 case (Occluded at FUP)

- Cypher™
  - 6 lesions received
  - 6 lesions analyzed

17 lesions available
Follow-up OCT Results @ 3 months

~ Neointima proliferation ~

**Average Neointimal Area**

<table>
<thead>
<tr>
<th></th>
<th>Xienc™</th>
<th>Nobori™</th>
<th>Cypher™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average Area</td>
<td>3.7±0.6</td>
<td>4.1±1.0</td>
<td>5.7±1.0</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td><strong>0.002</strong>*</td>
<td><strong>0.01</strong>*</td>
<td></td>
</tr>
</tbody>
</table>

**Average %Neointimal Area (NIA/Stent area)**

<table>
<thead>
<tr>
<th></th>
<th>Xienc™</th>
<th>Nobori™</th>
<th>Cypher™</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average % Area</td>
<td>50.2±12.9</td>
<td>52.3±15.7</td>
<td>78.4±8.3</td>
</tr>
<tr>
<td><strong>p-value</strong></td>
<td><strong>0.004</strong>*</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Bonferoni/Dunn test*
Follow-up OCT Results @ 3months

~ Neointima proliferation ~

**Average Neointima Thickness**

- **Xience™**: 474±123 µm
- **Nobori™**: 527±171 µm
- **Cypher™**: 836±125 µm

**Neointimal Unevenness Score**

- **Xience™**: 1.3±0.0
- **Nobori™**: 1.3±0.1
- **Cypher™**: 1.3±0.1

*p=0.0005*

*p=0.003*

*N.S*

* Bonferoni/Dunn test
1- and 3-month OCT Results

~ Neointima proliferation ~

Average neointima thickness

Neointimal Unevenness Score

<table>
<thead>
<tr>
<th></th>
<th>1M</th>
<th>3M</th>
<th>1M</th>
<th>3M</th>
<th>1M</th>
<th>3M</th>
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<tbody>
<tr>
<td>Xience™</td>
<td>269</td>
<td>474</td>
<td>198</td>
<td>527</td>
<td>836</td>
<td></td>
</tr>
<tr>
<td>Nobori™</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cypher™</td>
<td>102</td>
<td></td>
<td></td>
<td></td>
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</table>

<table>
<thead>
<tr>
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<th>1M</th>
<th>3M</th>
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<th>3M</th>
<th>1M</th>
<th>3M</th>
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<tbody>
<tr>
<td>Xience™</td>
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<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Nobori™</td>
<td>2.5</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
<td>1.3</td>
</tr>
<tr>
<td>Cypher™</td>
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</tbody>
</table>

Kobe Univ.
Results from Histologic Analysis will be coming soon...
Summary

- Improvements of DES technology allow us to treat more complex patients.
- Although we intuitively feel that DES with biodegradable polymer would be favorable, it is still not clear that those are clinically better than DESs with good durable polymers.