Biodegradable Stents: Future or Fancy...

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Why Degradable Stents?

• No late adverse events
  – Late thrombosis
  – Hypersensitivity reactions (chronic inflammation)
  – Stent fractures
• Does not restrict arterial remodeling
• Permits non-invasive imaging of artery
• Permits bypass surgery in future
# Materials Applied for Development of Biodegradable Stents

<table>
<thead>
<tr>
<th>Material</th>
<th>Stent</th>
<th>Status</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymers</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLA</td>
<td>Thermal balloon expandable, ring</td>
<td>4-year clinical data</td>
<td>Tamai et al. CCT 2004</td>
</tr>
<tr>
<td></td>
<td>(Igaki-Tamai)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLA</td>
<td>Balloon expandable, tubular (Abbott</td>
<td>Phase I Clinical trial</td>
<td>Stack RS. TCT 2005</td>
</tr>
<tr>
<td></td>
<td>Vascular, Inc.)</td>
<td>(Absorb)</td>
<td>Ormiston J. TCT 2006</td>
</tr>
<tr>
<td>Tyrosine-</td>
<td>Balloon expandable, tubular (REVA</td>
<td>Pre-clinical</td>
<td>Kaluza G. TCT 2006</td>
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<tr>
<td>polycarbonate</td>
<td>Medical)</td>
<td></td>
<td></td>
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<tr>
<td>PAE-Salicylate</td>
<td>Balloon expandable, tubular</td>
<td>Pre-clinical</td>
<td>Robinson KA. TCT 2006</td>
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<tr>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td><strong>Metallic</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Magnesium</td>
<td>Balloon expandable, tubular (Biotronik)</td>
<td>Phase I Clinical</td>
<td>Heublein B et al. Heart 2003;89:651-656</td>
</tr>
</tbody>
</table>
Bioresorbable Stents

- Igaki-Tamai
- BVS
- REVA
- BIT
- Biotronik

PLA
PLA
Tyrosine-Polycarbonate
PAE-Salicylate
Magnesium
PLA Metabolic Pathway

1. PLA
2. Hydrolysis
3. Molecular Weight
4. Lactic Acid
5. Mass Loss
6. Mass Transport
7. Krebs Cycle
8. CO₂ + H₂O

Generalized Degradation Curves

Molecular Weight
Strength
Mass

References:
Biodegradable Stents: Time Course

Diffusion → Bulk Erosion → Isolation
### Bioabsorbable Stents

<table>
<thead>
<tr>
<th>Bioabsorbable material</th>
<th>Degradation period</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. polyglycolic acid (PGA)*</td>
<td>2~3 months</td>
</tr>
<tr>
<td>2. poly-l-lactic acid (PLLA)*</td>
<td>12~18 months</td>
</tr>
<tr>
<td>3. Poly (d,l-lactide/glycolide) co-polymer (PGLA)</td>
<td>2~3 months</td>
</tr>
<tr>
<td>4. Polyorthoester (POE)</td>
<td>10 months</td>
</tr>
<tr>
<td>5. Mg Alloy</td>
<td>2-3 months</td>
</tr>
<tr>
<td>6. polycaprolactone (PCL)</td>
<td>36 months~</td>
</tr>
</tbody>
</table>
Challenges with Bioabsorbable Stents

- Scaffolding and radial force
- Time of degradation
- Rate of degradation
- Biocompatibility
- Recoil: early and late
- Biodegradable products
- Remaining polymer
- Elution of the drug from a biodegradable stents
- Radioopacity of the stents
Biodegradation and Biocompatibility
Igaki-Tamai PLLA Bioabsorbable Stent

- 63 lesions in 50 patients, 84 stents
- Non drug eluting stent
- Four year follow-up data demonstrated no unusual findings

Long Term (3-years)

<table>
<thead>
<tr>
<th>Event</th>
<th>6 mo</th>
<th>12 mo</th>
<th>36 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>QMI</td>
<td>1/50* (2.0%)</td>
<td>7/50 (14%)</td>
<td>8/50 (16%)</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>1/50* (2.0%)</td>
<td>7/50 (14%)</td>
<td>8/50 (16%)</td>
</tr>
</tbody>
</table>

Abbreviations:
- ABRR (Angiographic Binary Restenosis Rate)

**ABRR**

- 6 mo: 12/60 (20%)
- 12 mo: 9/53 (17%)
- 36 mo: 8/50 (16%)

Repeat PCI

- 6 mo: 6/50 (12%)
- 12 mo: 7/50 (14%)

* = same patient

**Biodegradable Stents An update and work-in-progress** Presentation, Hideo Tamai CCT 2003

**ABRR (Angiographic Binary Restenosis Rate) per lesion.**
Igaki-Tamai PLLA Bioabsorbable Stent: 3-year Angiographic Analysis

MLD (mm)

% Diameter Stenosis

Pre Post 6-mos 12-mos 24-mos 36-mos

MLD (mm)

% Diameter Stenosis

0 0.5 1 1.5 2 2.5 3

0 20 40 60 80 100

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Tamai CCT 2004
Peripheral Stent Delivery System

Balloon-expandable system covered with a protective sheath

<table>
<thead>
<tr>
<th>Protective sheath:</th>
<th>Outer diameter; 8F</th>
</tr>
</thead>
<tbody>
<tr>
<td>System length:</td>
<td>60 cm and 120 cm</td>
</tr>
<tr>
<td>Balloon length:</td>
<td>4 cm (Stent length 36 mm)</td>
</tr>
<tr>
<td>Balloon size:</td>
<td>6.0, 7.0, 8.0 mm</td>
</tr>
</tbody>
</table>
Study Results

- Primary success rate 100%
- No serious adverse event

6-Month Angiographic Follow up

- No reocclusions or thrombosis
- 9 symptomatic restenoses (20%), all successfully retreated
- Asymptomatic angiographic restenosis (< 50%) in 3 cases (6.6%)
Poly Lactic Acid (PLA)

PLA safely used in numerous medical applications since the 1960s

Everolimus

ML VISION® Balloon SDS

Champion™ Bioabsorbable Polymeric Drug Release
**Material Characteristics of the BVS**

**Bioabsorbable Polymeric DES**

**Everolimus/PLA Matrix Coating**
- Thin coating layer
- 1:1 ratio of Everolimus/PLA matrix
- Controlled drug release

**PLA Stent**
- Laser cut, tubular
- Processed for increased radial strength
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Foundation for Cardiovascular Medicine

ABSORB TRIAL
FIM Trial of A Fully Bioabsorbable Drug-eluting Coronary Stent

Assess the Safety and Performance of the BVS Everolimus-Eluting Coronary Stent System in the Treatment of Patients with Single, De Novo, Native Coronary Artery Disease.
ABSORB Study Design

Single, de-novo lesion

3.0 mm
n = 30

BVS Stent

• Sponsor: Abbott Vascular
• Primary Investigators:
  - J Ormiston MD
  - PW Serruys MD, PhD
• DSMB: J Tijssen PhD, T Lefèvre MD, P Urban MD
• CEC: C Hanet MD, D McClean MD, V Umans MD
• Angiographic and IVUS Corelab: Cardialysis (Rotterdam, NL)

• Prospective, open label, FIM
• 3.0 x 12mm stents (3.0 x 18mm* stents available after enrolment start and used in 2 pts)
• 6 sites EU, NZ

Rotterdam, NL, Patrick Serruys (16)
Krakow, PL, Dariusz Dudek (6)
Auckland, NZ, John Ormiston (5)
Arhus, DN, Leif Thuesen (3)
Aalst, BE, Bernard de Bruyne
St Denis, F, Bernard Chevalier
BMS loss from SPIRIT FIRST (n=27)

Mean: 0.85 ± 0.36mm, 95%CI [0.71, 1.00mm]
Median: 0.85mm, 25, 75% percentile [0.55, 1.14mm]
Diameter stenosis at follow-up (26pts)

Mean: 27 ± 14%,
95%CI [22, 33%]
Median: 25%
25, 75% percentile [19, 37%]

Binary restenosis: 11.5 % (3/26)
No TLR
### ABSORB: IVUS results (24 pts)

<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 area (mm²)</td>
<td>0</td>
<td>0.30</td>
<td>NA</td>
<td>NA</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>
What is Contributing to Late Loss?

**SPIRIT-First ML Vision Stent**
- Δ Vessel Area (mm²) = -0.29 (-1.9%)
- Δ Stent Area (mm²) = -0.14 (-2.0%)
- Δ Lumen Area (mm²) = -2.12 (-29.4%)
- NIH Area (mm²) = 1.98
- % VO = 28.1%

Late Loss = 0.87mm*

**SPIRIT-First Xience V Stent**
- Δ Vessel Area (mm²) = 0.19 (+1.2%)
- Δ Stent Area (mm²) = -0.02 (-0.3%)
- Δ Lumen Area (mm²) = -0.51 (-7.2%)
- NIH Area (mm²) = 0.50
- % VO = 8.0%

Late Loss = 0.10mm**

**ABSORB BVS Stent**
- Δ Vessel Area (mm²) = -0.06 (-0.4%)
- Δ Stent Area (mm²) = -0.71 (-11.7%)
- Δ Lumen Area (mm²) = -1.01 (-16.6%)
- NIH Area (mm²) = 0.30
- % VO = 5.5%

Late Loss = 0.44mm

• Steel-like performance in a polymer stent
• Low recoil (<1%)
• High radial strength
• Flexible and conformable

Deploys (expands) in artery with sliding, locking parts rather than material deformation
REVA
Bioresorbable Polymer Material

- Developed for stent performance
- Tunable resorption rate
- Benign breakdown products
- X-ray visibility
- MRI/CT compatibility

Tyrosine-derived Polycarbonate Stent
RESORB Clinical Trial

The REVA Endovascular Study of a Bioresorbable Coronary Stent
RESORB Trial
Endpoints and Follow-Up

• Endpoints
  – Primary – 30 day MACE
  – Secondary – 6 month QCA & IVUS derived parameters (restenosis)

• Clinical Follow-up
  – Discharge, 2 weeks, 1, 6, 12*, 24*, 36, 48 and 60 months
  – * Subset of patients returning for long term angiographic follow-up

• FIM initiated and currently on Hold
Multi-Layer, Combination Drug Delivery
Stent Design

- Balloon expandable
- No foreshortening
- Suitable for primary stenting
- Radiopaque
- Good scaffolding and mechanical properties
- Excellent side branch access
- Full range of diameters and lengths
- No special storage required
# Pre-Clinical Results

<table>
<thead>
<tr>
<th>Study</th>
<th>Arm 1</th>
<th>Arm 2</th>
<th>Arm 3</th>
<th>End points</th>
</tr>
</thead>
<tbody>
<tr>
<td>PAE Vascular Compatibility</td>
<td>BMS (no coating)</td>
<td>PLA coated metal stent</td>
<td>PAE coated metal stent</td>
<td>3D: FC, 30D: A/H</td>
</tr>
<tr>
<td>PAE + Sirolimus Efficacy</td>
<td>Cypher</td>
<td>PLA + sirolimus coated BX Velocity</td>
<td>PAE + sirolimus coated BX Velocity</td>
<td>3D: FC, 30D: A/H, 90D: A/H</td>
</tr>
</tbody>
</table>
Mean Percent Stenosis in Pig Coronary Arteries
One Month after Stent Implant

<table>
<thead>
<tr>
<th>Intimal thickness (mm)</th>
<th>BMS</th>
<th>Salicylate only</th>
<th>Cypher</th>
<th>Salicylate with Sirolimus</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.23</td>
<td>0.23</td>
<td>0.13</td>
<td>0.14</td>
</tr>
</tbody>
</table>
Day 3 Flow Cytometry

- **All Leukocytes**
  - CD45: 8.38 (PAE) 9.63 (PLA)
  - CD25: 0.50 (PAE) 0.88 (PLA)
  - CD31: 2.63 (PAE) 2.06 (PLA)

- **Activated Lymphocytes and Macrophages**
  - CD45: 8.38 (PAE) 9.63 (PLA)
  - CD25: 0.50 (PAE) 0.88 (PLA)

- **Prolif Endothelial Cells**
  - CD45: 8.38 (PAE) 9.63 (PLA)
  - CD31: 2.63 (PAE) 2.06 (PLA)
Day 30 Inflammation Scores

- BMS: 1.3
- Cypher: 1.3
- Salicylate only: 1.0
- Salicylate with Sirolimus: 1.0
Stent Thrombosis in Baboons

Mean ± sem

Platelet Deposition ($x10^9$) vs. Time (min)

Blue group (N=7) - Blue: Bare Metal
Red group (N=7) - Red: Polymer + Drug
Yellow group (N=7) - Yellow: Polymer Only
### 3-month

<table>
<thead>
<tr>
<th>animal #</th>
<th>vessel</th>
<th>% stenosis</th>
<th>OCT DS%</th>
<th>OCT AS%</th>
</tr>
</thead>
<tbody>
<tr>
<td>4106</td>
<td>RCA</td>
<td>26%</td>
<td>23</td>
<td>26</td>
</tr>
<tr>
<td>4106</td>
<td>LAD</td>
<td>27%</td>
<td>17</td>
<td>26</td>
</tr>
<tr>
<td>4106</td>
<td>LCX</td>
<td>31%</td>
<td>37</td>
<td>59</td>
</tr>
<tr>
<td>4107</td>
<td>RCA</td>
<td>29%</td>
<td>23</td>
<td>42</td>
</tr>
<tr>
<td>4107</td>
<td>LAD</td>
<td>22%</td>
<td>28</td>
<td>40</td>
</tr>
<tr>
<td>4107</td>
<td>LCX</td>
<td>19%</td>
<td>29</td>
<td>54</td>
</tr>
<tr>
<td>4108</td>
<td>RCA</td>
<td>23%</td>
<td>20</td>
<td>48</td>
</tr>
<tr>
<td>4108</td>
<td>LAD</td>
<td>18%</td>
<td>21</td>
<td>40</td>
</tr>
<tr>
<td>4108</td>
<td>LCX</td>
<td>24%</td>
<td>35</td>
<td>53</td>
</tr>
</tbody>
</table>

**Mean**

- % stenosis: 24%
- OCT DS%: 26%
- OCT AS%: 43%

**SD**

- 4%
- 7%
- 12%
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**BTI**
completely absorbable stent
eluting sirolimus

**Histology of pig coronary artery implants**
VM stain 20X
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Foundation for Cardiovascular Medicine

BTI completely absorbable stent
eluting sirolimus

one week
two weeks

histology of pig coronary artery implants
H&E stain 200X

four weeks
**BTI STENT**
1-mo implant

inflammation is minimal, consisting mostly of multinucleated foreign-body giant cells

*H&E, 400X*
3-month
Ongoing & Upcoming Studies *(BTI STENT)*

- Preclinical - porcine coronary implants
  - Efficacy: 1, 3, 6 and 9 months follow up including IVUS and OCT
  - In vivo degradation (*^{14}C label*)
  - In vivo drug release pharmacokinetics
  - Flow cytometry (inflammatory & other markers)
  - Assay for inflammatory mediators (ROS, IL-1, etc.)
  - Thrombogenicity studies in baboon ex-vivo shunt
  - Vascular function proximal and distal to the stent
- First-in-man studies outside USA has been initiated
Conclusion

• Though biodegradable polymer stents seem to be the ultimate candidate for the “ideal stent” further evaluation is needed to understand their role as a substitute for bare metal or present generation metallic drug eluting stents.

• They could also be the ideal vehicle for several other applications: non-obstructive vulnerable plaque, gene transfer for infract repair and angiogenesis.....