Biodegradable Stents

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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
Mechanism of Restenosis

- Acute Recoil
- Intimal Hyperplasia
- Chronic Recoil
Intimal Hyperplasia

- Acute Recoil
- Intimal Hyperplasia
- Chronic Recoil

( % Response )

Days Post Injury

- Thrombosis
- Inflammation
- Proliferation
- Extracellular Matrix Production
# Materials Applied for Development of Biodegradable Stents

<table>
<thead>
<tr>
<th>Material</th>
<th>Stent</th>
<th>Status</th>
<th>References</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 (Igaki-Tamai)</td>
<td>4-year clinical data</td>
<td>Tamai et al. CCT 2004</td>
</tr>
<tr>
<td>PLA</td>
<td>Balloon expandable, tubular (REVA Medical)</td>
<td>Pre-clinical</td>
<td>Kaluza G. TCT 2006</td>
</tr>
<tr>
<td>PLA</td>
<td>Balloon expandable, tubular</td>
<td>Pre-clinical</td>
<td>Robinson KA. TCT 2006</td>
</tr>
<tr>
<td>Tyrosine-polycarbonate</td>
<td>Balloon expandable, (REVA Medical)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAE-Salicylate</td>
<td>Balloon expandable, tubular</td>
<td></td>
<td></td>
</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

Materials:
- PLA
- Tyrosine-Policarbonate
- PAE-Salicylate
- Magnesium
PLA Metabolic Pathway

- PLA
- Hydrolysis
- Lactic Acid
- Mass Loss
- Mass Transport
- Krebs Cycle
- $\text{CO}_2 + \text{H}_2\text{O}$

Generalized Degradation Curves

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>Death</th>
<th>QMI</th>
<th>CABG</th>
<th>Stent Thrombosis</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0</td>
<td>1/50* (2.0%)</td>
<td>0</td>
<td>1/50* (2.0%)</td>
</tr>
</tbody>
</table>

* = same patient

### ABRR** & Repeat PCI

<table>
<thead>
<tr>
<th>Time</th>
<th>ABRR**</th>
<th>Repeat PCI</th>
</tr>
</thead>
<tbody>
<tr>
<td>6 mo</td>
<td>12/60 (20%)</td>
<td>6/50 (12%)</td>
</tr>
<tr>
<td>12 mo</td>
<td>9/53 (17%)</td>
<td>7/50 (14%)</td>
</tr>
<tr>
<td>36 mo</td>
<td>8/50 (16%)</td>
<td></td>
</tr>
</tbody>
</table>

*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

0 0.5 1 1.5 2 2.5 3

0 20 40 60 80 100

69 2.68 1.76 2.01 2.08 2.22

12 38 29 26 25

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Tamai CCT 2004
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
**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

Serruys at al. ACC 2007
ABSORB
Late Loss (26 pts)

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>
• 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
Magnesium and the Human Body

- Essential element for human body involved in the synthesis of more than 300 enzymes (4th most common mineral)
- Quantity in human body: ~ 20 g
- Daily need (adult): ~ 350 mg
- Quantity in the intracellular space: > 40%

- Degradation by replacement with Calcium and Phosphorous (2 months)

AMS, Biotronik
Magnesium Alloy Biodegradable Stent

3.0 x 10 mm stent: ~ 3 mg
• **Anti-inflammatory:**
  - Salicylic acid (active ingredient in aspirin) chemically incorporated into polymer backbone

• **Combination therapy:**
  - Anti-neoplastic (sirolimus)
  - Plus anti-inflammatory (salicylic acid)
  - Elution over first month post-implant
### Polyanhydride Polymers (PAE)

**Polymer A:**

<table>
<thead>
<tr>
<th>Salicylic acid</th>
<th>Polylactide Anhydride (Linker)</th>
<th>Salicylic acid</th>
</tr>
</thead>
</table>

**Polymer B:**

<table>
<thead>
<tr>
<th>Salicylic acid</th>
<th>Adipic acid</th>
<th>Salicylic acid</th>
</tr>
</thead>
</table>

Poly(anhydride based on salicylic acid and adipic acid anhydride)
Bioabsorbable Stent Design

- Core: Polymer A
- Undercoat: Polymer B
- Drug Layer: Polymer B + Sirolimus
- Topcoat: Polymer B

Coating Layers
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
Radial Strength

Atmospheres (10% Compression)

- BTI: 1.17
- MultiLink: 0.91
- Cypher: 1.96
## 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

- **BMS**: 15% mean stenosis, intimal thickness 0.23 mm
- **Salicylate only**: 16% mean stenosis, intimal thickness 0.23 mm
- **Cypher**: 5% mean stenosis, intimal thickness 0.13 mm
- **Salicylate with Sirolimus**: 6% mean stenosis, intimal thickness 0.14 mm

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30-Day Histology
Day 3 Flow Cytometry

- All Leukocytes
  - CD45: 8.38 PAE, 9.63 PLA

- Activated Lymphocytes and Macrophages
  - CD25: 0.50 PAE, 0.88 PLA

- Prolif Endothelial Cells
  - CD31: 2.63 PAE, 2.06 PLA

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Day 30 Inflammation Scores

Mean Inflammation Score

- BMS: 1.3
- Cypher: 1.3
- Salicylate only: 1.0
- Salicylate with Sirolimus: 1.0
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 infarct repair and angiogenesis.....
“Biodegradable Stents: They Do Their Job and Disappear”

- Ron Waksman