Bioabsorbable technology “the current players”

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Oxford
MY CONFLICTS OF INTEREST ARE

Advisory Boards - Medtronic, Boston, Cordis
Research funding - Boston
Oxford Live sponsors - Boston, Elli lilly, Edwards
Concept:
Vessel scaffolding is only needed transiently........... (temporarily)

- Revascularize with DES performance, then be completely absorbed

- Leave no permanent implant
  - No permanent scaffold – restore vascular response
  - No stimulus for chronic inflammation – potentially reduces the need for long-term dual antiplatelet therapy
  - Future re-intervention (PCI and CABG) is facilitated.

- Provide compatibility with non-invasive diagnostic imaging (MR/MSCT), allowing non-invasive follow-up.
As technology advances we will increasingly recognise the utility of our current technology!!
Remember what stents do!

- Prevent recoil over the initial 3 months
  - Glagov
- Scaffold providing round lumen
  - prevent tissue prolapse through struts
- Minimal shortening during expansion
- Low profile and flexibility to allow delivery
- Drug delivery
The current players

- Igaki-Tomai
- Biotronik
- Reva (Boston)
- Medtronic
- Orbus Neich
- Abbott
The future players?

- **ART**
  PLLA stent amorphous polymer Balloon-expandable positive remodeling?

- **BIT**
  Salicylic acid-based surface eroding stent, Sirolimus eluting

- **Endovascular Tissue Gen**
  PLLA stent Spiral helical design Claim of growth factors/enzymes delivery

- **Tepha**
  Combination of polyester based-“TephaFLEX” and PLLA

- **Sehajanand**
  PLLA and heparinized PLLA stent with genistein drug Balloon-expandable

- **Amaranth**
  PLLA stent, Self-expanding stent, Multiple drug delivery, Peripheral
Igaki-Tomai

Poly-L-lactic acid zig-zag helical coil design with straight bridges.

Strut thickness is 170 μm, coverage of the artery by stent is 24%. No drug.

Self-expansion is hastened by balloon inflation with heated contrast.

Gold radio-opaque markers at its ends.
Biotronik

Figure 1: Biodegradable magnesium stent (BIOTRONIK, Berlin, Germany)
(A) after expansion, (B) before expansion, and (C) in an electron microscopy magnification.
DREAMS is based on BIOTRONIK’s proprietary Magnesium technology

**Requirements**

- Biocompatibility
- Absorbable scaffolds
- Absorption
- Mechanics

**Absorbable materials**

<table>
<thead>
<tr>
<th>BIOTRONIK: Magnesium-based alloy</th>
<th>Polymers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron</td>
<td></td>
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</table>

For coronary scaffolds, tailor-made Magnesium alloys provide the best balance between biocompatibility, mechanical properties and absorption characteristics.
Previous bare AMS devices demonstrated safety but failed to show sufficient efficacy

- Safe in human coronary and peripheral arteries (150 patients)
  - No death, no MI, no scaffold thrombosis, no distal embolization, no excessive inflammation
  - Device success rate of 99.4%
- Absorbed as intended in several months
- Fully CT/MRI compatible

- High TLR in coronary indication, compared with DES due to
  - Loss of scaffolding too early
  - Missing inhibition of neointimal proliferation

BIOTRONIK decided to enhance the device with an anti-proliferative drug
Results PROGRESS 1 - IVUS

Post implantation

Contribution to lumen loss

Negative remodeling/recoil: 42%
Thickening of extra-stent tissue: 13.5%
In-stent neointima: 41%

4 months follow-up
DREAMS provides scaffolding and Paclitaxel release up to 3 months

- **Mg alloy**
- **Mg degradation product**
- **Polymer**

**Scaffolding**

- **Acute**
  - Mg degradation (conversion)
  - Stable drug carrier layer
  - Diffusion controlled drug release

- **3 months**
  - Mg degradation completed
  - Drug release completed
  - Degradation of polymer

- **6 months**
  - Drug carrier layer degradation completed
  - Beginning disintegration of Mg degradation product

- **9 months**
The BIOTRONIK clinical program has resumed with a DREAMS first in man study.

<table>
<thead>
<tr>
<th>Year</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>2004</td>
<td>Bare AMS</td>
</tr>
<tr>
<td>2005</td>
<td>PROGRESS (N=63)</td>
</tr>
<tr>
<td>2006</td>
<td>BIOSOLVE-I</td>
</tr>
<tr>
<td>2007</td>
<td>Drug eluting scaffold (DREAMS)</td>
</tr>
<tr>
<td>2008</td>
<td></td>
</tr>
<tr>
<td>2009</td>
<td></td>
</tr>
<tr>
<td>2010</td>
<td></td>
</tr>
<tr>
<td>2011</td>
<td></td>
</tr>
</tbody>
</table>

**Coronary**

- BEST-BTK (N=20)
- INSIGHT (N=117)

**Peripheral**

- PROGRESS (N=63)
- BIOSOLVE-I

**References**

- INSIGHT: Bosiers et al. Cardiovascular and Interventional Radiology 2008
Bioabsorbable Stent

**Mechanical properties**

Polymer properties that enable radial strength & deliverability

- CoCr
- Mg
- PLA

50% 
240%

**Figure 2.** Stent mechanical properties. A) Relative comparisons between polylactides (PLA), cobalt chromium (CoCr) and magnesium (Mg) mechanical properties. B) Effect of crimping and deployment dynamics on mechanical deformation.

**Figure 1.** Polymer chain orientation, crush recovery and relaxation. A) The orientation, as well as average length and average molecular weight can affect mechanical properties. B) Self-expanding stent recovery properties. C) Post-deployment relaxation properties.
Bioabsorbable Stent

Figure 3. Polymer degradation. A) Long chain monomer units absorb water, followed by B) cleavage at random location to generate two chains. C) Chains reach point of physical disentanglement resulting in loss of mechanical strength. D) As hydrolysis continues, the concentration of acidic end groups increases such that E), the chains become short enough to become soluble and actively resorbed by inflammatory cells.
## Bioabsorbable Options

**Design Goal:** The drug & stent gone within 12 months  
*“Leave Nothing Behind”*

<table>
<thead>
<tr>
<th>BSC’s Bioabsorbable Stent Projects</th>
<th>Bioabsorbable</th>
<th>Absorbed within</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioabsorbable Metal Stent</td>
<td>Magnesium</td>
<td>6 - 12 months</td>
</tr>
<tr>
<td>Bioabsorbable Metal Stent</td>
<td>Iron</td>
<td>+24 months</td>
</tr>
<tr>
<td>Bioabsorbable Polymer Stent</td>
<td>PLLA</td>
<td>+24 months</td>
</tr>
<tr>
<td>Bioabsorbable Polymer Stent</td>
<td>(Poly DTE carbonate)</td>
<td>+24 months</td>
</tr>
<tr>
<td>Bioabsorbable Polymer Stent</td>
<td>POSS</td>
<td>6 - 12 months</td>
</tr>
</tbody>
</table>


Source: Boston Scientific
Challenges Exist for Current FULLY Bioabsorbable Stent Solutions

All bioabsorbable materials have potential drawbacks

<table>
<thead>
<tr>
<th>Performance Attributes (Prioritized)</th>
<th>Polymer (PLLA)</th>
<th>Metallic (Iron-based)</th>
<th>Metallic (Magnesium)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time to Full Degradation (less than 12 months)</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td>Acute Performance (Deliverability, Recoil, etc)</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td>Strength (≥3 months)</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td>Vascular Compatibility</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td>Drug Compatibility</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
<tr>
<td>Strut Thickness</td>
<td>⬜️</td>
<td>⬜️</td>
<td>⬜️</td>
</tr>
</tbody>
</table>

- ⬜️: Optimal
- ⬜️: Acceptable
- ⬜️: Unacceptable

Data on file Boston Scientific.
REVA- Boston

Tyrosine-derived polycarbonate polymer impregnated with iodine for radio-opacity.

Struts are thick at 200 μm and crossing profile is 1.7 mm.

Balloon expandable with a slide and lock (ratchet) design that allows stent expansion and high initial radial strength without material deformation.

Expanded, covers 55% of arterial wall. FIM no drug coating.
Bioabsorbable Polymer Material

The issued patent covers material compositions fabricated from:

A crystallized bioabsorbable polymer composition, comprising a base polymer poly (L-lactide) moiety, and/or a poly (D-lactide) moiety, linked with a modifying copolymer thereof, comprising poly (L-lactide-co-Tri-methylene-carbonate) or poly (L-lactide-co-ε-caprolactone) in the form of block copolymers.
Absorbable Stent Overview

**Mechanical / Structural:**
- Stent retention
- Radial strength
- Flexible and conformable
- Side Branch, tapered and long stents

**Polymer Materials:**
- Radial strength and minimize “Creep” movement
- Controlled degradation / absorption

**Clinical Utility:**
- Combination of materials, design and coating
- Enables a full product portfolio
Bioabsorbable Polymer Material

The stent is fabricated from:

- A blend of three (3) lactide based polymer alloys
- All with known degradation roadmap
- Unique blend enables polymer mechanics and crystalline orientation
  - Tube or Sheet (Alpha)
  - Post Processing (Eta)
  - Strain induced (Beta)
Expansion of Nested Ring Modules

Crimped  3.0 mm  3.5 mm  4.0 mm
Flexibility and Deliverability

Highly flexible SDS
5-Fr compatible

3.5x13/15mm CoCr Blazer Stent

3.5x18/20mm Polymer R Stent
Scaffolding to resist remodeling for min of 6 months

Full degradation with no chronic adverse response
Stent Retention Features

When the platform is crimped…

it locks!

Mechanism releases at expansion
First In Man Clinical Trial

Cohort A: 30 patients enrolled March – July 2006
Cohort B: 101 patients enrolled March – November 2009
Polylactide Degradation by Hydrolysis

- Primary mode of degradation is by hydrolysis of ester bonds
- Water preferentially penetrates amorphous regions of the polymer matrix
- Hydrolysis initially results in a loss of molecular weight, but not radial strength, as the strength comes from crystalline domains
- Once crystalline domains are hydrolyzed, there is mass loss

\[ R-O-R' + H_2O \rightarrow R-COOH + HO-R' \]

\[ \text{carboxylic acid} \quad \text{alcohol} \]

Polylactide Degradation & Lactate Metabolism

Lactate Shuttle
Lactate serves as a carbohydrate fuel source for multiple metabolic pathways

Late lumen loss at 6 months mainly due to reduction in scaffold area

Very late lumen enlargement noted from 6 months to 2 years

BVS Device Optimization Objectives

- More uniform strut distribution
- More even support of arterial wall
- Lower late scaffold area loss
  - Maintain radial strength for at least 3-4 months
- Storage at room temperature
- Improved device retention
- Unchanged:
  - Material, coating and backbone
  - Strut thickness
  - Drug release profile
  - Total degradation Time

Photos taken by and on file at Abbott Vascular.

The ABSORB Family of Trials

ABSORB

3 year F/U

Cohort A

Safety and Performance

International
N=30
4 sites

Single de novo lesion

9 month F/U

Cohort B

Safety and Performance after assessing safety at 180 days in the Cohort A patients

International
N=101
12 sites

Up to two de novo lesions

ABSORB EXTEND

Enrolling

Continuation of assessment of Safety and Performance

N=1,000
100 sites

Up to two de novo lesions, longer lesions, overlapping stents

Gentleman or players??
Fully Bioabsorbable Stents

Clinical Pathways

FIM (n<50)
3-yr data

FIM II (n~100)
Enrollment Complete

Registry (n~1,000)

Registry
1-yr data

IDE Pivotal Trial
Enrollment

Pivotal Trial Clinical Follow-up
18-mo min

File PMA,
FDA Review

CE-mark

FDA Approved

Boston Scientific Corporation internal estimates.

See Glossary for general and prescribing information. Presentation for Information Purposes Only
Can the UK “afford” scaffolds?

Fixed DES price – around £350
Scaffolds…..

Same (ish) indications

– need to prove superiority for a price premium

Same dual anti-platelet requirements
Possible initial increase implant costs
- limited length, IVUS etc

Just because they appeal to us conceptually – doesent mean we will be able to buy them!!