Bioabsorbable Stents

Ron Waksman, MD, FACC, FSCAI
Professor of Medicine, Georgetown University, Associate Chief of Cardiology, Washington Hospital Center, Washington DC
Why absorbable stents?

- Short duration of Plavix post stenting
- Avoid chronic inflammatory processes
- Problem of re-intervention with traditional techniques
- Ability of the vessel to perform positive remodeling
- Peripheral application: no longer crushing issue after absorption
- CT and MR – (follow up) compatibility

Why permanent stents?

Vessel scaffolding is necessary only for a certain, limited time, than the permanent implant has no known advantage.
# Bioabsorbable Stent Programs

<table>
<thead>
<tr>
<th>Company</th>
<th>Picture</th>
<th>Polymer/Drug</th>
<th>Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bioabsorbable Vascular Solutions (BVS) [Guidant]</td>
<td></td>
<td>All biodegradable polymers (PLLA) with everolimus</td>
<td>Self expanding and balloon expandable designs.</td>
</tr>
<tr>
<td>Igaki-Tamai</td>
<td></td>
<td>PLLA; Transilast</td>
<td>Zig-zag design which is deployed using a heated balloon FIH Trial with 50 patients</td>
</tr>
<tr>
<td>Reva Medical</td>
<td></td>
<td>Poly (DTE carbonate) with iodine on the backbone to make the stent radio opaque</td>
<td>Design do not require heat to expand the stent…by ratchet links</td>
</tr>
<tr>
<td>Biotronik</td>
<td></td>
<td>Mg Alloy</td>
<td>Balloon expanding stent with a delivery catheter</td>
</tr>
</tbody>
</table>
Igaki-Tamai PLLA Bioabsorbable Stent 4 Years Follow-up

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

**Long Term (4-year results)**

<table>
<thead>
<tr>
<th>Event</th>
<th>6 mo</th>
<th>12 mo</th>
<th>48 mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>1/50</td>
<td>1/50**</td>
<td>1/50**</td>
</tr>
<tr>
<td>QMI</td>
<td>1/50**</td>
<td>1/50**</td>
<td>1/50**</td>
</tr>
<tr>
<td>CABG</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Stent Thrombosis</td>
<td>1/50**</td>
<td>1/50**</td>
<td>1/50**</td>
</tr>
<tr>
<td>TLR</td>
<td>9/50</td>
<td>9/50</td>
<td>9/50</td>
</tr>
</tbody>
</table>

**ABRR***

- 6/50 (12%) 6 mo
- 7/50 (14%) 12 mo
- 9/50 (18%) 48 mo

**Repeat PCI**

- 12/60 (20%) 6 mo
- 9/53 (17%) 12 mo

**Behaves similar to bare metal stents**

Hideo Tamai CCT 2004.
Serial Changes in Stent CSA and Neointimal Area (IVUS)

<table>
<thead>
<tr>
<th></th>
<th>post</th>
<th>3 months</th>
<th>6 months</th>
<th>12 months</th>
</tr>
</thead>
<tbody>
<tr>
<td>stent CSA</td>
<td>n.s.</td>
<td>n.s.</td>
<td>n.s.</td>
<td>9.12</td>
</tr>
<tr>
<td>neointimal area</td>
<td>7.61</td>
<td>8.76</td>
<td>8.86</td>
<td>2.51</td>
</tr>
</tbody>
</table>

*p<0.05, n.s.*
### Igaki-Tamai PLLA Bioabsorbable Self expanding stent for the SFA

<table>
<thead>
<tr>
<th>Material composition</th>
<th>PLLA (poly-L-lactic acid) medical grade</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stent design</td>
<td>Zig zag helical coil</td>
</tr>
<tr>
<td>Strut thickness</td>
<td>0.009 inch (0.24 mm)</td>
</tr>
<tr>
<td>Radio-opaque markers</td>
<td>2 gold markers</td>
</tr>
<tr>
<td>Currently available diameters</td>
<td>5, 6, 7, 8 mm</td>
</tr>
<tr>
<td>Currently available length</td>
<td>36 mm</td>
</tr>
</tbody>
</table>
BVS Fully Bioabsorbable Drug Eluting Stent

BVS Bioabsorbable Stent Platform

ML VISION® Balloon SDS

Everolimus

Champion™ Bioabsorbable Polymeric Drug Release
Poly Lactic Acid (PLA)

- PLA safely used in numerous medical applications since the 1960s
  - Approx. 200 products made from PLA or co-polymer containing PLA
- Breaks down to lactic acid, a natural metabolite
- BVS stent has a tailored bioabsorption rate
- Fully bioabsorbed – no drug left behind

Data on file at Guidant.
Bioabsorbable Everolimus Eluting Coronary Stent Surface

Uncoated

Coated

Photos on file at Guidant.
Representative Photomicrographs (10x): Porcine Coronary Studies

28 Day

90 Day

180 Day

BVS

CYPHER®

Photos on file at Guidant.

Pipeline DES products are currently in development at Guidant. Not available for sale.
BVS Intracoronary, *In-vivo* OCT Imaging

- Periprocedural Rx:
  - Heparin
- Target vessel: RCA
- BVS stent 3.0/12mm
- OCT imaging

Strut dimension 0.52mm X 0.10mm
REVA Bioresorbable Stent

- Fully bioresorbable coronary stent system
- Integral bioresorbable drug-elution coating
- Paclitaxel-eluting
Design Enables Material
- Expansion based upon sliding, locking parts rather than material deformation
  - Facilitates the use of polymers

Enables Performance
- Negligible recoil
- Comparable radial strength & flexibility
- Equivalent sizing to current metal stents
- Standard balloon deployment
Metalic stents provide temporary scaffolding, that will *Disappear at 60-90 days after deployment* and may reduce restenosis! and will be compatible with cardiac imaging MRI or CT.

**Magnesium Based Alloys – Bioabsorbable Stents**
In-vivo results animal trials

Quick endotheliasation and gradual absorption

Stent immediately after implant

Ingrowth stent in vessel wall

Gradual absorption Mg-alloy by vessel wall

procedure → +/- 10 days → +/- 30 days → +/- 60 days
Magnesium Stent: Visibility

- IVUS

- MR

316L  Mg alloy
Reduced Proliferation of SMCs & ECs

Proliferation / % (316L)

<table>
<thead>
<tr>
<th>Alloy</th>
<th>hEC</th>
<th>hSMC</th>
</tr>
</thead>
<tbody>
<tr>
<td>C</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>E</td>
<td>30</td>
<td>15</td>
</tr>
<tr>
<td>D</td>
<td>20</td>
<td>10</td>
</tr>
</tbody>
</table>

α-actin straining after 35d
Heublein, et al., MHH

Proliferation (BrdU) test of aterial hSMC and hEC in eluates.
Heublein, et al., MHH
Structural Integrity

Testing after 3 days of implantation (minipig)
Stent structure is completely intact

Micro CT and Light optical microscope images of Mg-stents 3 days after implantation
Mean neointima in minipig coronary arteries adjusted for injury score and media reference (ANCOVA)
Heublein, et al., MHH
Control and Mg – minipig coronary arteries; 8 weeks fu

<table>
<thead>
<tr>
<th>Control</th>
<th>Mg Alloy</th>
</tr>
</thead>
<tbody>
<tr>
<td>LAD</td>
<td>LAD</td>
</tr>
<tr>
<td>Cx</td>
<td>Cx</td>
</tr>
<tr>
<td>Cx</td>
<td>Cx</td>
</tr>
<tr>
<td>RCA</td>
<td>RCA</td>
</tr>
<tr>
<td>RCA</td>
<td>RCA</td>
</tr>
</tbody>
</table>

Image descriptions of control and Mg alloy samples for LAD, Cx, and RCA coronary arteries.
Mg versus Control at 30 days

Mg

Conrtol L316
Neointimal Thickness of AMS Decreases in Minipig

n=33

1 Month 3 Months 6 Months 12 Months

Neointima AMS Neointima Control
AMS-Animal Study, 6 months follow up

Histological Findings

Animal 1, RCA pos.2, (HE 25x magnification)

Animal 1, RCA pos.4, (HE 25x magnification)

Animal 26, RCA pos.2 (EvG 25x magnification)

Animal 15, LAD pos.2, (EvG 63x magnification)

Animal 15, RCA pos.2, (EvG 63x magnification)

Animal 1, RCA pos.4, (EvG 63x magnification)

HE = hematoxylin-eosin staining;  EvG = Elastica van Giesson staining
PROGRESS AMS I Clinical Study

Preliminary Data Analysis

March 2006

Late Breaking Trials ACC
To evaluate the clinical feasibility of the Absorbable Metal Stent in the treatment of a single de novo lesion in a native coronary artery

Prospective, multi-center, consecutive, non-randomized FIM (First In Man – coronary) study

The study included 63 patients at 8 international clinical sites
The PROGRESS-AMS study designed to yield first data on the clinical safety and efficacy of the absorbable metal stent in the coronary artery application.

**Primary Hypothesis**

To demonstrate feasibility and safety being in the range of currently available stent systems. With MACE rate after 4 months <30 % (max. 18 events)
The primary endpoint of PROGRESS-AMS is Major Adverse Cardiac Events (MACE) at 4 months defined as:

- Cardiac death
- Nonfatal myocardial infarction
- Ischemia driven TLR

Early primary endpoint as basis for starting subsequent clinical trials with Absorbable Metal Stent
# PRELIMINARY RESULTS

## Demographics

<table>
<thead>
<tr>
<th>Age, yrs</th>
<th>61.3 ± 9.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>Males, % (n)</td>
<td>69.8</td>
</tr>
<tr>
<td>Diabetes, % (n)</td>
<td>17.4</td>
</tr>
<tr>
<td>Insulin Dependent, % (n)</td>
<td>4.8</td>
</tr>
<tr>
<td>Smoking History, % (n)</td>
<td>47.6</td>
</tr>
<tr>
<td>Hypercholesterolemia, % (n)</td>
<td>61.9</td>
</tr>
<tr>
<td>Hypertension , % (n)</td>
<td>65.1</td>
</tr>
<tr>
<td>Prior MI, % (n)</td>
<td>41.3</td>
</tr>
<tr>
<td>Unstable Angina, % (n)</td>
<td>9.5</td>
</tr>
<tr>
<td>Prior CVA, % (n)</td>
<td>1.6</td>
</tr>
<tr>
<td>Prior PCI, % (n)</td>
<td>23.8</td>
</tr>
</tbody>
</table>
### Preliminary Results

<table>
<thead>
<tr>
<th>Event Description</th>
<th>In Hospital Events</th>
<th>30-Day Events</th>
<th>4-Month Events</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>%</td>
<td>n</td>
<td>%</td>
</tr>
<tr>
<td>MACE (Cardiac death, nonfatal MI, ischemia driven TLR)</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
<tr>
<td>Death</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
<tr>
<td>Q-wave MI (new pathol. Q-waves with CK or CK-MB elevated)</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
<tr>
<td>Non Q wave MI (CK 2 times above normal with CK-MB elevated)</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
<tr>
<td>Ischemic Driven TLR</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
<tr>
<td>TLR (Any)</td>
<td>0.00%</td>
<td>0.00</td>
<td>0.00%</td>
</tr>
</tbody>
</table>
Multislice CT (16 row) imaging of coronary arteries

Stent not visible, but optimal vessel lumen opacification
### Preliminary Results – QCA Brief Summary

<table>
<thead>
<tr>
<th>Metric</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diameter Stenosis (%) Post</td>
<td>12.4 ± 5.6</td>
</tr>
<tr>
<td>MLD POST, mm</td>
<td>2.46 ± 0.37</td>
</tr>
<tr>
<td>Follow-up QCA at 4 months</td>
<td></td>
</tr>
<tr>
<td>N = 57 lesions</td>
<td></td>
</tr>
<tr>
<td>Diameter Stenosis (%)</td>
<td>48.2 ± 17.2</td>
</tr>
<tr>
<td>Binary Restenosis (%)</td>
<td>31/57 (54.4%)</td>
</tr>
<tr>
<td>MLD, mm</td>
<td>1.37 ± 0.52</td>
</tr>
<tr>
<td>Late Loss, mm</td>
<td>1.09 ± 0.51</td>
</tr>
</tbody>
</table>

**N = 60 lesions**
All TLR Preliminary Summary

Occurrence of TLR

TLR Occurrence

Days Post Intervention

Occurrence of TLR

4-month ANGIO
IVUS of Heavily Calcified RCA (Pre)

Lesion @ severe narrowing

Proximal Reference

Distal Reference

Bonnier Waksman, Eindhoven May 21, 2004
Full expansion after second proximal stent
IVUS at Follow-up
Conclusions

The FIM coronary study showed:

- Feasibility
- Safety: no death, no MI, no stent thrombosis
- The study met the primary endpoint < 30% of MACE
- The Absorbable Metal Stent (AMS):
  - The AMS technology platform is proven
  - Was successfully delivered to the lesion (100% device success)
  - Was MRI / CT compatible
- Was absorbed as intended
Absorbable Metal Stent Platform:

- Fully absorbable platform
- Proven biocompatibility throughout the entire absorption process*
- Effective scaffolding properties**

* = Animal data available at Biotronik / ** = In vitro data available at Biotronik

Controlled Drug Eluting Stent Design:

- Precise drug release kinetic and direction
- Resorbable polymer with minimal tissue/polymer contact area
- Protected non-deforming reservoirs

* = Animal data available at Biotronik / ** = In vitro data available at Biotronik
Complete occlusion of the left pulmonary artery after de-bandning and closure of the arterial duct with a clip (the device with three markers is for calibration purposes)
Crossing the stenosis with a guide wire
angiography revealed reperfusion

Peter Zartner, M. D., Pediatric Cardiology
University of Erlangen-Nuremberg, Germany
Implantation procedure of Mg Stent 3.0/10mm with a contrast filled balloon catheter

Peter Zartner, M. D., Pediatric Cardiology, University of Erlangen-Nuremberg, Germany
At one week follow up after Mg Stent the left lung was reperfused.
• 20 CLI patients (Rutherford 4-5) with BTK pathology

1. Improving inflow limiting ATK lesions

2. Lekton Mg implant if short (max 30mm) BTK stenoses
   • Suboptimal angiographic result after PTA
     – ≥50% stenosis post-treatment
   • At the physician’s discretion
     – flow-limiting dissection
     – threatened or acute closure

• Implants performed between December ‘03 – January ‘04
Patient demographics (N=20)

- Male: 10 (50%)
- Female: 10 (50%)
- Average age: 76 yrs (59 - 96)
- Clinical vascular status:
  - Rutherford Class IV: 9 (45%)
  - Rutherford Class V: 11 (55%)
**Lesion description**

(N=20)

- **Average lesion length**: 11 mm (2 mm – 20 mm)
- **Average vessel diameter**: 2.7 mm (2.5 mm – 3 mm)
- **Average stenosis**: 84% (75% – 95%)
- **Dissection**: 0 0%
- **Ulceration**: 1 5%
- **Thrombus**: 3 15%
- **Calcification**: 14 70%
High Patency Rate Below The Knee

- Primary Clinical Patency

时间 (天)

- 3M 89.5%
- 6M 84.2%
- 9M 78.9%
- 12M 72.4%

Bosiers M, Dendermonde, Belgium; Peeters P, Bonheiden, Belgium
94.7% Limb Salvage After One Year

- Limb Salvage Rate

- 3M 100.0%
- 6M 94.7%
- 9M 94.7%
- 12M 94.7%

Bosiers M, Dendermonde, Belgium; Peeters P, Bonheiden, Belgium
Main challenges

- Rate of degradation
- Time to complete degradation
- Radial force and elimination of recoil
- Bioabsorbable DES

Future Applications

- Coronary, Workhorse stent Vulnerable Plaque
- Peripheral, SFA, tibial
- Pediatric pulmonary coarctation of aorta biliary, etc.