The Disappearing Stent: When Plastic Replaces Metal

Running title: Waksman; Igaki-Tamai stents

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When metallic stents were first introduced in 1986 they offered immediate promise. Vessel scaffolding, which created a wide patent lumen, was conceived as an attractive solution to dissection, acute recoil, and abrupt closure, which were the main shortcomings of balloon angioplasty. Furthermore, when compared to balloon angioplasty, the use of metallic stents was associated with a significant reduction in restenosis rates. It wasn’t long after their introduction that metal stents became the default device for coronary intervention; nearly every lesion in the coronary artery that could accommodate a stent, received one, and the phrase “Full Metal Jacket” became jargon in the interventional cardiology field.

With the heavy use of metallic stents, however, certain problems arose; specifically, the emergence of stent thrombosis and late restenosis. It took nearly a decade to develop drug-eluting stents (DES) with the potential to reduce restenosis rates. DES, however, also had their shortcomings and were associated with higher rates of subacute and late stent thrombosis. This in turn mandated long-term (≥12 months) dual antiplatelet therapy (DAPT).

Considering the complications of both bare metal- and DES, the following question arose: “Why is a permanent prosthesis needed to fix a temporary problem?” This gave rise to a new field dedicated to developing a temporary, bioresorbable stent that would disappear after its job was done. Zidar et al. were the first team to successfully implant such a device, made of poly-L-lactic acid (PLLA), into the canine femoral arteries, and reported significant stent degradation with low grade inflammation at nine months.

In 2000, the late Hideo Tamai reported the 6-month results of 15 patients who underwent Igaki-Tamai PLLA stent implantation for the treatment of coronary artery stenosis. This stent was unique in that it had a zig-zag helical coil design and its strut thickness was 0.17 mm; however, it lacked an anti-proliferative drug. One of the first challenges with the PLLA stent was
its deployment in the coronary artery. For optimal deployment, the Igaki-Tamai PLLA stent requires a balloon expandable system with contrast heated at 80°C, using 30-second inflations at six and 14 atmospheres.

In this issue of Circulation, Nishio et al. report beyond 10 years’ clinical outcome of the first 50 patients with coronary artery disease who were treated with 84 Igaki-Tamai stents. This long-term report provides the unique opportunity to understand what the future holds for PLLA technology as a pivotal polymer for biodegradable scaffolds. PLLA is a biodegradable, thermoplastic, aliphatic polyester that undergoes self-catalyzed hydrolytic degradation to lactic acid, which finally metabolizes to carbon dioxide and water. The duration of the degradation process depends on the crystallization of the polymer and varies from two to four years.

When assessing bioresorbable scaffold (BRS) technology there are important questions to be asked:

- How long of a scaffold is essential for the prevention of vessel recoil?
- What is the optimal rate of degradation? Does the polymer completely degrade? If so, at what time points?
- What happens to the degraded products?
- What is the vessel composition following complete degradation?
- Are there any safety concerns?
- Are there any potential utility advantages of BRS over permanent metal stents? Will BRS ever be the workhorse stent to replace best-in-class DES?

While the present manuscript does, in part, address some of these questions, continued investigation and experimental data derived from preclinical testing (including the use of multi imaging modalities) will shed some clarity on the future of this technology and its place in
clinical practice. Based on the information provided in the manuscript, and that from the continuing investigations of the BRS technology, several assumptions can be made:

First, complete degradation occurs at two to four years based on the PLLA crystallization and the scaffold indeed disappears. Serial intravascular ultrasound (IVUS) analysis in this study detected continued strut degradation over three years; most of the struts had disappeared by then. However, a single histological specimen taken after directional atherectomy, at 42 months post-implantation, detected remnants of the polymeric struts. Angiographic follow-up and optical coherence tomography (OCT) assessment 10 years’ post stent implantation demonstrated absence of the struts with endoluminal lining of the vessel wall.

The 10-year outcomes of patients who received the PLLA stent reassured the biocompatibility of the polymer in human coronary arteries without apparent inflammation and no unexpected, adverse angiographic, intravascular, and clinical findings, although the number of patients investigated was quite small. The single patient’s histological specimen supports these findings, showing healing with thickened neointima at the previously stented segment without inflammatory cell infiltration or foreign body reactions.

Restenosis rates seen with PLLA stents, however, are similar to those reported with bare metal stents. Overall late loss at 6 months was 0.91 mm and overall long-term target lesion revascularization (TLR) rates were 26%. These rates support the claim that in order to obtain efficacy similar to DES, the PLLA polymer-based scaffold requires the addition of an anti-proliferative drug. As shown in the ABSORB studies, drug-eluting PLLA scaffolds have similar TLR rates to those reported with the Xience V DES. For comparative stent scaffold properties and outcomes, please see Table 1.

Furthermore, long-term imaging studies of the Igaki-Tamai stent have shown continued
polymer degradation with enlargement of the vessel wall and lumen. As measured by quantitative coronary angiography, late lumen loss decreased from 0.91 mm at 6 months to 0.59 at three years, and, as measured by IVUS, minimum lumen area markedly increased from 3.64 mm at six months to 5.18 at three years. In addition, these imaging studies also demonstrated reduction of the neointima from year one to year two. These findings suggest that the artery restored its capability to respond to positive remodeling once the scaffold degraded. The vessel remodeling features at the scaffold site are unique to the PLLA stent and cannot be seen in conventional metallic stents, which act like a permanent metal cage once implanted.

**Promises and Challenges of the PLLA Absorbable Scaffold**

A decade after the first deployment of the Igaki-Tamai PLLA stent we are in the midst of an intensive clinical investigation of a fully bioresorbable DES: ABSORB. ABSORB, a bioresorbable eluting scaffold composed of a PLLA polymer ‘backbone’ and an everolimus/PDLLA matrix coating, demonstrated similar efficacy and safety to the everolimus-eluting metal stent in its first human study with 5-year follow-up. Interesting observations of the BRS technology are vessel lumen enlargement during follow-up, and the ability of the vessel to restore its vasoreactivity capabilities in response to stimuli with vasoconstrictors and vasodilators.8,9

Following the first human experience, ABSORB was developed into a global registry, and ultimately renamed ABSORB EXTEND. The ABSORB EXTEND global registry plans to enroll 1000 patients; reports on the first 200 patients are encouraging, with low event rates of 2.5% at six months.10 To date, the number of patients to have undergone clinical exposure to the BRS technology is nearly 700; however, exposure has been limited to simple and focal lesions.

Despite its initial promise, BRS technology has major challenges. By its nature, the
plastic PLLA polymer is limited in expansion and optimal scaffold apposition. Overexpansion of
the scaffold may result in fractures that can lead to target vessel failure. Furthermore, it is not
clear how the PLLA scaffold will behave in calcified lesions, bifurcations, long lesions, or when
overlapping of additional PLLA scaffolds is required. Overlapping two scaffolds, each with a
strut thickness of 150μm, will result in a 300 μm thickness, which is not warranted in small
coronary arteries.

Additionally, the optimal duration of DAPT with PLLA is unknown; but a complete
degradation duration of >3 years rules out a shorter DAPT duration when compared to metal
stents. Finally, manufacturing the PLLA BRS is complex, and the availability of a broad
spectrum of vessel sizes and lesion lengths is currently limited. The question is whether PLLA
limitations and the additional cost to patients will prevent the ABSORB device from becoming a
workhorse in the treatment of coronary artery disease and ultimately replace permanent metal
DES.

**Can an Absorbable Metallic Scaffold be the Alternative to PLLA?**

An alternative to the plastic PLLA polymeric scaffold is the bioresorbable metallic alloy. The
attraction of a metallic, balloon expandable,bioresorbable scaffold is their mechanical similarity
to permanent metal stents. Acutely, they behave similar to permanent metal stents.

Two alloys are identified as candidates for absorbable metallic scaffolds: magnesium and iron.
Studies have reported complete magnesium degradation within four to 12 months, and complete
iron degradation at >4 years. Furthermore, the recent iteration on the magnesium scaffold allows
the expansion of the scaffold from 3.0 mm to 5.3 mm without breakage of the scaffold struts.
The initial clinical experience with magnesium was mixed.11 The fast degradation of the
magnesium alloy (within 2-4 weeks) used in the first clinical trial led to early loss of radial force
and resulted in early recoil and neointima formation, leading to a higher restenosis recurrence rate. Lessons from the first human experience with the bare magnesium scaffold showed that degradation should be slowed by modification of the alloy and scaffold design, and that in order to obtain high patency rates, there must be antiproliferative drug elution from the magnesium to attenuate intima formation. These issues were addressed in the recent DREAMS project, albeit with the following iterations: Changes were made in the alloy composition, scaffold design, and magnesium coating with paclitaxel eluted from a PLGA polymer. These changes resulted in significant angiographic late loss improvement with a low target revascularization rate at six months.

A future development in the DREAMS technology includes the addition of a biodegradable polymeric coating base with a thin layer of PLLA to elute sirolimus. These changes have the potential to further improve the performance of the DREAMS biodegradable scaffold, aiming to obtain better outcomes than with DES. Potential advantages of the magnesium alloy over PLLA are ease in manufacturing, overall short biodegradation time, and the ability to expand the scaffold for optimal apposition without fracturing the scaffold struts. These potential advantages and similarity in clinical outcome have yet to be demonstrated in a clinical trial.

**Will Bioresorbable Scaffolds (BRS) Replace Metallic Stents?**

The development of bioresorbable scaffolds was initiated more than 12 years ago, driven by the deficiencies of bare metal stents (namely high restenosis rates) and later by first-generation DES that were associated with 0.6% continued hazard of late stent thrombosis. With the introduction of second-generation DES that continue to improve, including a recent report of lower stent thrombosis rates when compared to bare metal stents, the following are legitimate questions,
“What is the unmet need for bioresorbable scaffold technology and when will it be ready for the market?”

Current efforts in the development of BRS technology aim to refine and optimize scaffold radial force and expansion without early fractures and to show superiority over DES in reduction of late cardiac events. Only superiority of BRS over DES will support a wide dissemination of the technology at a higher cost. While the efficacy and safety profiles of BRS are similar to best-in-class DES in the first two years after implantation, and with slow progression of TLR and the low continued hazard of late stent thrombosis of second-generation DES, it is possible that after five to 10 years, BRS will demonstrate superiority in reduction of major cardiovascular events over DES. Therefore, younger patients and those at high risk for late stent thrombosis, such as the ST-elevation myocardial infarction population, are attractive target populations for the BRS technology. In contrast to DES, which continue to carry low-grade inflammation, neo-atherosclerosis, and narrowing of the lumen, BRS allows the vessel to expand and enlarge the lumen over time.

Additionally, restoring the pulsatility and vasoreactivity of the vessel following bioabsorption of the polymer is reported to impact the mechanical conditions and may improve collagen and proteoglycan deposition via restoration of the dynamic conditions.14,15 Further, as recently demonstrated in imaging studies including OCT and virtual histology, plaque thinning, morphology changes, and vessel paving,16,17 although intriguing, should translate into clinical utility when challenging the standard of care for permanent metallic stents.

The long-term results from the first in human experience with the Igaki-Tamai PLLA stent are encouraging. These preliminary results demonstrate that the PLLA stent can disappeared
without any related adverse events. Ten years from now we will look back and laugh at the days when we left a permanent metal in our patients’ human coronaries.

Conflict of Interest Disclosures: None.

References:


**Table 1.** Comparative stent scaffold properties and outcomes

<table>
<thead>
<tr>
<th>Stent / Scaffold</th>
<th>Igaki-Tamai</th>
<th>ABSORB</th>
<th>DREAMS</th>
<th>XIENCE V</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Polymer / Alloy</strong></td>
<td>PLLA</td>
<td>PLLA</td>
<td>Magnesium</td>
<td>Cobalt Chromium</td>
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<td><strong>Polymer / Drug</strong></td>
<td>NONE</td>
<td>PDLLA / Everolimus</td>
<td>PLGA / Paclitaxel</td>
<td>Fluropoloymer / Everolimus</td>
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<td>Strut thickness</td>
<td>170 μm</td>
<td>150 μm</td>
<td>150 μm</td>
<td>86 μm</td>
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<tr>
<td>Size and length</td>
<td>3.0-4.0x12 mm</td>
<td>3.0 12, 18 mm</td>
<td>3.25/3.5 10, 16 mm</td>
<td>2.25-4.0 8-38 mm</td>
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<tr>
<td>Total absorption</td>
<td>3-4 years</td>
<td>4 years</td>
<td>1 year</td>
<td>NONE</td>
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<tr>
<td>Drug dosage</td>
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<td>8 μg</td>
<td>100 μg per cm²</td>
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<tr>
<td>First-in-Man</td>
<td>Complete</td>
<td>ABSORB A&amp;B</td>
<td>Biosolve 1</td>
<td>SPIRIT I</td>
</tr>
<tr>
<td>In-stent / scaffold late loss mm at 6 months</td>
<td>0.91 mm</td>
<td>Absorb A 0.44 mm</td>
<td>0.64 mm</td>
<td>0.10 mm</td>
</tr>
<tr>
<td>TLR at 6 months</td>
<td>10.5% at 6 months</td>
<td>Absorb A 3.3%</td>
<td>4.3%</td>
<td>3.8%</td>
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