Editorial

The Disappearing Stent
When Plastic Replaces Metal

Ron Waksman, MD

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, in comparison with balloon angioplasty, the use of metallic stents was associated with a significant reduction in restenosis rates. It was not 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.

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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.

Considering the complications of both bare metal stents 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, biodegradable 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 9 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 antiproliferative 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, with use of 30-second inflations at 6 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 2 to 4 years.

When assessing biodegradable 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?

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

First, complete degradation occurs at 2 to 4 years based on the PLLA crystallization, and the scaffold indeed disappears. Serial intravascular ultrasound analysis in this study detected continued strut degradation over 3 years; most of the struts had disappeared by then. However, a single histological specimen taken after directional atherectomy, at 42 months postimplantation, detected remnants of the polymeric struts. Angiographic follow-up and optical coherence tomography assessment 10 years after 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, 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 rates were 26%. These rates support the claim that, to obtain efficacy similar to DES, the PLLA polymer-based scaffold requires the addition of an antiproliferative drug. As shown in the ABSORB studies, drug-eluting PLLA scaffolds have target lesion revascularization rates similar to those reported with the Xience V DES. For comparative stent scaffold properties and outcomes, see the Table.

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 3 years. In addition, these imaging studies also demonstrated neointima reduction from year 1 to year 2. 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/poly-DL-lactic acid 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

After 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 6 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 2 scaffolds, each with a strut thickness of 150 μm, will result in a 300-μm thickness, which is not warranted in small coronary arteries.

In addition, the optimal duration of dual-antiplatelet therapy with PLLA is unknown, but a complete degradation duration of >3 years rules out a shorter dual-antiplatelet therapy duration in comparison with 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 metallic, balloon-expandable, bioresorbable scaffolds is their mechanical similarity to permanent metal stents. Acutely, they behave similarly to permanent metal stents.

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**Table. 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>Polymmer/alloy</td>
<td>PLLA</td>
<td>PLLA</td>
<td>Magnesium</td>
<td>Cobalt chromium</td>
</tr>
<tr>
<td>Strut thickness, μm</td>
<td>170</td>
<td>150</td>
<td>150</td>
<td>86</td>
</tr>
<tr>
<td>Size and length, mm</td>
<td>3.0–4.0×12</td>
<td>3.0×12, 18</td>
<td>3.25/3.5×10, 16</td>
<td>2.25–4.0×8–38</td>
</tr>
<tr>
<td>Total absorption, y</td>
<td>3–4</td>
<td>4</td>
<td>1</td>
<td>None</td>
</tr>
<tr>
<td>Drug dosage</td>
<td>None</td>
<td>100 μg/cm²</td>
<td>8 μg</td>
<td>100 μg/cm²</td>
</tr>
<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</td>
<td>0.91</td>
<td>Absorb A, 0.44</td>
<td>0.64</td>
<td>0.10</td>
</tr>
<tr>
<td>loss at 6 mo, mm</td>
<td>Absorb B, 0.19</td>
<td>Absorb A, 3.3</td>
<td>4.3</td>
<td>3.8</td>
</tr>
<tr>
<td>TLR at 6 mo, %</td>
<td>10.5 at 6 mo</td>
<td>Absorb A, 3.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>26 at 10 y</td>
<td>Absorb B, 3.6</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

PLLA indicates poly-L-lactic acid; PDLLA, poly-DL-lactic acid; TLR, target lesion revascularization; and PLGA, polylactic-co-glycolic acid.
Two alloys are identified as candidates for absorbable metallic scaffolds: magnesium and iron. Studies have reported complete magnesium degradation within 4 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 to 5.3 mm without breakage of the scaffold struts.

The initial clinical experience with magnesium was mixed. 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, 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 drug-eluting absorbable metal scaffold (DREAMS) project, albeit with the following iterations: Changes were made in the alloy composition, scaffold design, and magnesium coating with paclitaxel eluted from a poly(lactic-co-glycolic acid polymer. These changes resulted in significant angiographic late loss improvement with a low target revascularization rate at 6 months.

A future development in the DREAMS technology includes the addition of a bioresorbable 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 bioresorbable 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 BRS Replace Metallic Stents?
The development of BRS was initiated >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 in comparison with bare metal stents,13 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. Although the efficacy and safety profiles of BRS are similar to best-in-class DES in the first 2 years after implantation, and with slow progression of target lesion revascularization and the low continued hazard of late stent thrombosis of second-generation DES, it is possible that after 5 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, neointimal hyperplasia, and narrowing of the lumen, BRS allows the vessel to expand and enlarge the lumen over time.

In addition, 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. Furthermore, as recently demonstrated in imaging studies including optical coherence tomography and virtual histology, plaque thinning, morphology changes, and vessel panning,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 PLAGA stent are encouraging. These preliminary results demonstrate that the PLAGA stent can disappear without any related adverse events. Ten years from now, we will look back and laugh at the days when we left a permanent metallic stent in our patients’ coronary arteries.

Disclosures
None.

References


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