New Drugs and Technologies

Bioresorbable Scaffold

The Advent of a New Era in Percutaneous Coronary and Peripheral Revascularization?

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The invention of balloon angioplasty as a percutaneous treatment for obstructive coronary disease by Andreas Gruntzig in 1977 was a huge leap forward in cardiovascular medicine and undoubtedly will always be remembered as a revolution in the field of revascularization. However, this technique was plagued by multiple problems, including the risk of acute vessel closure secondary to occlusive coronary dissection, sometimes necessitating emergency coronary artery bypass surgery. Although late luminal enlargement and vascular remodeling could take place, more often restenosis would occur instead. The restenosis would essentially be caused by constrictive remodeling and, to a lesser extent, by elastic recoil or the neointimal hyperplastic healing response.

The advent of bare metal stenting (BMS) and the landmark Belgian-Netherlands Stent Study (BENESTENT) and Stent Restenosis Study (STRESS) trials have established BMS as the second revolution in interventional cardiology. This technology provided a solution to acute vessel occlusion by sealing the dissection flaps and preventing recoil. The rate of subacute occlusion was reduced to 1.5%, making emergency bypass surgery a rare occurrence. Restenosis rates were further reduced from 32% to 22% at 7 months, but this rate was still high, and neointimal hyperplasia inside the stent was even more prominent than with angioplasty, necessitating repeat treatment in numerous patients.

Because the vessel was now caged with metal, late luminal enlargement and advantageous vascular remodeling could no longer occur. Another problem, namely late stent thrombosis (ST), was also first described. To solve the problem of in-stent restenosis, after the historic failure of brachytherapy to resolve this problem, drug-eluting stents (DES) were introduced. The first 45 patients implanted with the sirolimus-eluting Bx velocity stent (Cordis, Johnson & Johnson, Warren, NJ) were found to have negligible neointimal hyperplasia over 4 years. In the Arterial Revascularization Therapies Study II (ARTS II) trial, which enrolled patients with complex multivessel disease, the rate of combined definite, probable, and possible ST was as high as 9.4% at 5 years, accounting for 32% of major adverse cardiovascular events (MACEs). In addition, postmortem pathological specimens of DES revealed significant numbers of uncovered struts with evidence of a persistent inflammatory reaction around the stent struts. Vasomotion testing demonstrated abnormal vasoconstriction responses to acetylcholine distal to the deployed stent, suggesting that the structure and function of the endothelium remained abnormal. All these problems promise to be solved with the advent of fully biodegradable scaffolds. This new technology, heralded as the fourth revolution in interventional cardiology, offers the possibility of transient scaffolding of the vessel to prevent acute vessel closure and recoil while transiently eluting an antiproliferative drug to counteract the constrictive remodeling and excessive neointimal hyperplasia. In the pilot ABSORB cohort A study, optical coherence tomography (OCT) revealed 100% of the scaffold struts to be fully tissue covered and apposed. After 2 years, the stent struts were resorbed with complete integration of the scaffold into the vessel wall and infiltration by functional smooth muscle cells. In addition, it appeared that the vessel lumen enlarged and the plaque/media diminished. Vasomotion testing suggested that the endothelial structure and function were fully restored with a normal vasodilatory response to both acetylcholine and nitroglycerine within the previously scaffolded area of the vessel. Thus, this new era in interventional cardiology could be viewed as the era of vascular restoration therapy with fully bioresorbable devices.

Fully Bioresorbable Scaffold: The Fourth Revolution in Interventional Cardiology?

Bioresorbable scaffolds have obvious potential advantages over current metallic DES technology (Table 1). These include the following:
Table 1. Potential Advantage of BRS

<table>
<thead>
<tr>
<th></th>
<th>Balloon Angioplasty</th>
<th>Metallic DES</th>
<th>Bioresorbable Scaffold</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute occlusion</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Acute ST/scaffold thrombosis</td>
<td>NA</td>
<td>–</td>
<td>+/-</td>
</tr>
<tr>
<td>Subacute ST/scaffold thrombosis</td>
<td>NA</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Acute recoil</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Constrictive remodeling</td>
<td>–</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Neointimal hyperplasia</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Expansive remodeling</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Late luminal enlargement</td>
<td>+</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Late ST/scaffold thrombosis</td>
<td>NA</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

+ implies prevented or not restricted; –, not prevented or restricted; and NA, not applicable because of absence of stent.

1. A reduction in adverse events such as ST. Because drug elution and scaffolding are temporary and are provided by the device only until the vessel has healed, no foreign material such as nonendothelialized struts and drug polymers (potential triggers for ST) can persist long term.

2. The removal, through bioabsorption, of the rigid caging of the stented vessel. This can facilitate the return of vessel vasomotion, adaptive shear stress, late luminal enlargement, and late expansive remodeling. Furthermore, this might reduce the problems of jailing of the ostium of side branches as seen with permanent metallic stent struts.

3. A reduction in bleeding complications. Once bioabsorption of the temporary scaffold has been completed, there will potentially be no requirement for long-term dual antiplatelet therapy. This is particularly pertinent given that the elderly, who are at the greatest risk of bleeding, are increasingly receiving invasive treatment for ischemic heart disease. Furthermore, early discontinuation of dual antiplatelet therapy with current metallic DES, for whatever indication, has consistently been shown to be an independent predictor of ST.

4. An improvement in future treatment options. The treatment of complex multivessel disease frequently results in the use of multiple long DES; for example, in the synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial, the average number of stents was 4, and one third of patients had >100 mm of stent implanted. In such cases, repeat revascularization, by means of either percutaneous or surgical revascularization, is potentially challenging because of the metallic cages formed by previously implanted DES. The use of a BRS would mean that there would potentially be no restriction on any future percutaneous or surgical revascularization should they be needed.

5. Allowing the use of noninvasive imaging techniques such as computed tomography (CT) angiography or magnetic resonance imaging for follow-up. Presently, metallic stents can cause a blooming effect with these imaging modalities, making interpretation more difficult. The poly-l-lactic acid (PLLA) scaffold should not restrict the use of CT or magnetic resonance imaging because it is nonmetallic; once bioabsorption has been completed with a metallic BRS, it should also not restrict the use of CT or magnetic resonance imaging. Noninvasive imaging follow-up could therefore become an alternative to invasive imaging follow-up.

6. Reservoir for the local delivery of drugs and genes. Because the duration of bioresorption is modifiable, according to the type of polymers/copolymers, a tuned elution of multiple drugs can potentially be achievable (eg, early elution of antiproliferative agent from a coated polymer and long-term elution of an antiinflammatory or other agent from the backbone polymer).

7. Elimination of the concern that some patients have at the thought of having an implant in their bodies for the rest of their lives.

Biodegradation, Bioabsorption, and Bioresorption

The first commercially available therapeutic polymer (surgical sutures made from glycolic and lactic acid) was referred to as “absorbable sutures” and biodegradable medical devices were frequently dubbed “bioabsorbable.” This in general reflected the disappearance of the compound into another substance. However, the term “bioabsorbable” appears not to be appropriate because bioabsorption does not necessarily imply degradation and, even less, elimination of the polymer from the body. For example, even if the bioabsorbable polymeric suture thread was not visible as a result of dissolution (bioabsorption), high-molecular-mass molecules can still be trapped between skin and mucosa without passing through physiological barriers and be eliminated. Bioabsorption therefore does not necessarily indicate complete cleavage of macromolecules up to small molecules that can be eliminated from the body through natural pathways, namely kidney or lungs. To indicate the total elimination of polymers by dissolution, assimilation, and excretion, the concept of “biore sorption” was introduced.

The words “degradation” and “biodegradation” are also confusing. “Degradation” is to be used in the case of unknown or ex vivo mechanisms, whereas the use of “biodegradation” should be restricted to cell-mediated in vivo mechanisms.

Development of BRS

The efforts to create BRS started ≈20 years ago. The first experimental studies using a nonbiodegradable polyethylene-terephthalate braided mesh stents in porcine animal models were published by our group in 1992. In 1996, our group, in collaboration with the Mayo Clinic and Cleveland Clinic, reported in porcine coronary arteries negative consequences after implantation of the Wiktor stent coated with 5 different types of biodegradable polymers (polyglycolic acid/polyactic acid copolymer, polycaprolactone, polyhydroxy-butylate/-valerate copolymer, polycaprolactone, and polyethyleneoxide/polybutylene terephthalate), all resulting in marked inflammation leading to neointimal hyperplasia and/or thrombus formation. Subsequently, Lincoff et al demonstrated that in a porcine model a stent coated with high-molecular-weight...
PLLAs were well tolerated and effective, whereas a stent coated with low-molecular-weight (80 kDa) PLLA was associated with an intense inflammatory neo-intimal response. They also proved the feasibility of drug elution from the PLLA, although no suppression of neo-intimal hyperplasia was reported. In 1998, Yamawaki et al. reported that in the porcine model the fully biodegradable PLLA stent with tyrosine kinase inhibitor efficiently suppressed proliferative stimuli caused by balloon injury. These pioneering experiments with high-molecular-weight PLLA further supported the investigations in human. However, despite the impressive results of these early stents, the technology failed to develop, primarily because of an inability to manufacture an ideal polymer that could limit inflammation and restenosis and secondarily because of the growing interest in metallic DES.

The current BRS are composed of either a polymer or bioresorbable metal alloy. Numerous different polymers are available, each with different chemical compositions, mechanical properties, and subsequently bioabsorption times (Tables 2 and 3). The most frequently used polymer in the current generation of BRS is PLLA. PLLA is already in widespread clinical use with applications such as resorbable sutures, soft-tissue implants, orthopedic implants, and dialysis media. The key mechanical traits for candidate material in coronary indications include high-elastic moduli to impart radial stiffness, large-break strains to impart the ability to withstand deformations from the cramped to expanded states, and low-yield strains to reduce the amount of recoil and overinflation necessary to achieve a target deployment. Stent developers look to increase stent strut dimensions to compensate for mechanical shortcomings of bioresorbable materials. As the thickness of these struts increases, strain levels imposed on a material increase proportionally.

### Bioresorption Process of PLLA

In the PLA family of polymers, molecular-weight degradation occurs in vivo predominantly through hydrolysis, which is a bimolecular nucleophilic substitution reaction that can be catalyzed by the presence of either acids or bases. The schematic shown in Figure 1A describes the hydrolysis reaction in which water catalyzes a chain scission event at an ester bond.

Poly-L-lactide is a semicrystalline polymer. The ordered polymer chains constitute the crystalline component of the semicrystalline polymer, and the random polymer chains form the amorphous segment (Figure 1B).53 In other words, the semicrystalline PLLA polymer is made of crystal lamella (regions with high concentrations of polymer with crystalline structure) interconnected by amorphous tie chains binding the lamellae together (middle), and semicrystalline polymer (right).

### Table 2. Leading Compounds and Degradation End Products According to Type of Polymer Family

<table>
<thead>
<tr>
<th>Polymer Family</th>
<th>Leading Compounds</th>
<th>Degradation End Products</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aliphatic polyesters</td>
<td>Poly (lactic acids and copolymers)</td>
<td>Lactic acid and glycolic acid (metabolites)</td>
</tr>
<tr>
<td>Poly (tyrosine carbonate)s</td>
<td>Undefined</td>
<td>Chemicals, metabolites, and oligomers</td>
</tr>
<tr>
<td>Poly-anhydrides</td>
<td>Undefined (eg, salicylic acid and adipic acid)</td>
<td>Chemicals</td>
</tr>
<tr>
<td>Poly (orthoesters)</td>
<td>Undefined</td>
<td>Chemicals</td>
</tr>
</tbody>
</table>

### Table 3. Mechanical Properties and Degradation Time for Different Polymers

<table>
<thead>
<tr>
<th>Polymer Composition</th>
<th>Tensile Modulus of Elasticity, GPa</th>
<th>Tensile Strength, MPa</th>
<th>Elongation at Break, %</th>
<th>Degradation Time, mo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Poly (L-lactide)</td>
<td>3.1–3.7</td>
<td>60–70</td>
<td>2–6</td>
<td>&gt;24</td>
</tr>
<tr>
<td>Poly (D,L–lactide)</td>
<td>3.1–3.7</td>
<td>45–55</td>
<td>2–6</td>
<td>12–6</td>
</tr>
<tr>
<td>Poly (glycolide)</td>
<td>6.5–7.0</td>
<td>90–110</td>
<td>1–2</td>
<td>6–12</td>
</tr>
<tr>
<td>50/50 L–lactide/glycolide</td>
<td>3.4–3.8</td>
<td>40–50</td>
<td>1–4</td>
<td>1–2</td>
</tr>
<tr>
<td>82/18 L-lactide/glycolide</td>
<td>3.3–3.5</td>
<td>60–70</td>
<td>2–6</td>
<td>12–18</td>
</tr>
<tr>
<td>70/30 L-lactide/caprolactone</td>
<td>0.02–0.04</td>
<td>18–22</td>
<td>&gt;100</td>
<td>12–24</td>
</tr>
<tr>
<td>Cobalt chromium</td>
<td>210–235</td>
<td>1449</td>
<td>~40</td>
<td>Biostable</td>
</tr>
<tr>
<td>Stainless steel 316L</td>
<td>193</td>
<td>668</td>
<td>40+</td>
<td>Biostable</td>
</tr>
<tr>
<td>Nitinol</td>
<td>45</td>
<td>700–1100</td>
<td>10–20</td>
<td>Biostable</td>
</tr>
<tr>
<td>Mg alloy</td>
<td>40–45</td>
<td>220–330</td>
<td>2–20</td>
<td>1–3</td>
</tr>
</tbody>
</table>
For objects with a smallest dimension of O (100 μm), hydrolysis byproducts cannot readily diffuse out of the object, and bulk degradation controls the process. The object degrades more or less from the inside out. In this case, the third-order kinetics theory of Pitt et al. predicts that the hydrolysis rate depends on the concentration of ester bonds, water, and carboxylic acid end groups; the carboxylic acid end groups are generated by each hydrolysis reaction. This so-called autocatalytic model for aliphatic polyesters like PLA is based on the third-order rate equation given by

\[
d[E]/dt = -d[COOH]/dt = -k[COOH][H_2O][E]
\]

where \([E]\), \([COOH]\), and \([H_2O]\) represent the concentrations of ester bonds, carboxylic acid end groups, and water, respectively, and \(k\) is the hydrolytic degradation rate constant. Assuming that the concentrations of ester bonds and water are approximately constant throughout the degradation process and that the concentration of carboxylic acid end groups is inversely proportional to the number-average molecular weight (\(M_n\)) of the polymer (ie, \([COOH] = 1/M_n\)). Weir and coworkers showed that

\[
M_n(t) = M_n(0)e^{kt}
\]

where \(M_n(t)\) is the number-average molecular weight after degradation time \(t\), and \(M_n(0)\) is the number-average molecular weight at time \(t = 0\) (before degradation). The assumptions inherent to the model are reasonable if mass loss does not occur because mass loss would affect the concentrations of water and carboxylic end groups in the sample. Equation 2 can be rewritten as

\[
\ln\left(\frac{M_n(t)}{M_n(0)}\right) = -kt
\]

By representing data for \(M_n(t)/M_n(0)\) versus \(t\) on a log-linear plot, one may infer the hydrolytic degradation rate from the slopes of the line connecting the points (Figure 2A).

From a chemical standpoint, it is considered that resorbable implants undergo 5 stages that are not discrete and can overlap. The first stage is hydration of the polymer. After implantation of the polymeric resorbable device, the poly-
mers begin to absorb water from surrounding tissue. In general, polylactides are relatively hydrophobic and increasingly so the molecular weight of the polymer chain increases. The chain, however, are hydrophilic due to the carboxylic acid end group. Chain ends cannot participate in an crystal lattice; therefore, the hydrophilic chain ends are relegated to the amorphous phase, rendering it more hydrophilic than the bulk. The second phase is depolymerization by hydrolysis (Figure 1A). This is observed first by a reduction in molecular weight. A loss of mass (third stage) occurs when the implant no longer has cohesive strength and the polymer starts to fragment into segments of low-weight polymer (Figure 1B). Subsequently, radial strength reduces as a result of the scission of amorphous tie chains linking the crystalline regions (Figure 2B). At this time, cracks and structural discontinuities are normal and entirely expected because the device is designed to degrade and be physiologically processed over time. Finally, polymer chains have been hydrolyzed to sufficiently short lengths so that they are increasingly hydrophilic (and hence soluble in an aqueous environment) and able to diffuse out of the device and be resorbed into the body (loss of mass; Figure 2C). The fourth phase is assimilation or dissolution of the monomer. Phagocytes can assimilate small particles and lead to soluble monomeric anions. Lastly, the soluble monomer (eg, L-lactate) is changed into pyruvate, which eventually enters the Krebs cycle and is further converted into carbon dioxide and water. These final products are excreted from the body through the kidneys or lungs, which results in complete bioresorption of the implant.

Because of the described properties of semicrystalline polymers, they are used predominantly for the purposes of mechanical support (ie, the scaffold), whereas amorphous polymers allow a more uniform dispersion of the drug and are therefore preferred for use in controlled drug release systems (eg, coating of the BVS system).

**Bioresorption in a Porcine Model**

Recently, in a porcine coronary model, long-term histological findings after implantation of everolimus-eluting PLLA BRS have been reported." Fifty-five polymeric everolimus-eluting PLLA BRS (BVS; 3.0×12.0 mm) were singly implanted in the main coronary arteries of 17 pigs that underwent OCT and were then euthanized immediately (n = 2), 2 years (n = 3), 3 years (n = 5), or 4 years (n = 5) after implantation. All BVS-implanted arteries in these animals were evaluated by histology except for 5 arteries examined at 2 years with gel permeation chromatography to assess the biodegradation of the PLLA. Fourteen arteries with BVS from an additional 6 pigs were examined by gel permeation chromatography at 1 (n = 1), 1.5 (n = 2), and 3 (n = 3) years. Corresponding OCT and histology images were selected using the distal and proximal radiopaque markers as landmarks.

OCT at 28 days showed sharply defined, bright reflection borders, best described as a box-shaped appearance, in 82% of the struts. Histologically, all struts appeared intact with no evidence of resorption (Figure 3A through 3C). OCT at 2 years revealed 60±20 struts to be discernible in each BVS with 80.4% strut sites showing a box-shaped appearance. Despite their similar appearances on OCT, histological analysis revealed that these structures appeared to be composed of proteoglycan, with polylactide residue being at such a low level as to be no longer quantifiable by chromatography (Figure 3D through 3F). OCT at 3 years demonstrated that the recognizable struts decreased to 28±9 struts per BVS. Histology shows that connective tissue cells within a proteoglycan-rich matrix replaced the areas previously occupied by the polymeric struts and coalesced into the arterial wall (Figure 3G through 3I). OCT at 4 years showed that only 10±6 struts per BVS were still recognizable. Histological analysis demonstrated that these struts were minimally discernible as foci of low-cellular-density connective tissue (Figure 3J through 3L). In conclusion, struts still discernible by OCT at 2 years were compatible with complete bioresorption of the polylactide struts as demonstrated by histological and gel permeation chromatography analyses, whereas at 3 and 4 years, both OCT and histology confirmed complete bioresorption of the struts into the arterial wall.

**Clinically Tested BRS**

BRS technologies that have already been tested in clinical studies are summarized in Table 4. The other BRS technologies in preclinical phases are described in the online-only Data Supplement.

**Igaki-Tamai Stent**

The Igaki-Tamai PLLA coronary stent was the first fully bioresorbable stent to be implanted in humans, with complete degradation taking 18 to 24 months. The stent had a helical zigzag design, which differed from previous knitted patterns (Figure 4). This resulted in less vessel wall injury during implantation and therefore less initial thrombus formation and reduced intimal hyperplasia. The stent was mounted on a standard angioplasty balloon and was both thermal self-expanding and balloon expandable. Self-expansion occurred in response to heating the PLLA, which was achieved by the use of heated contrast (up to 70°C) to inflate the delivery balloon. Stent expansion was further optimized by inflating the delivery balloon to 6 to 14 atm for 30 seconds, and the nominal size of the stent was ultimately achieved by continued self-expansion at 37°C in the 20 to 30 minutes after stent deployment. The stent had a standard length of 12 mm and was available in diameters of 3, 3.5, and 4 mm; the stent strut thickness was 0.17 mm. An 8F guiding catheter was required because the stent was initially constrained by a sheath that was removed once it was across the lesion. At either end of the stent, to aid visualization, were 2 radiopaque cylindrical gold markers (0.6 mm high by 0.18 mm in diameter; Figure 4). The first-in-humans study of the Igaki-Tamai stent (15 patients, 19 lesions, 25 stents) demonstrated no MACEs or ST within 30 days and 1 repeat percutaneous coronary intervention at the 6-month follow-up. Encouragingly, the loss index (late loss/acute gain) was 0.48 mm, which was comparable to BMS, and demonstrated for the first time that BRS did not induce an excess of intimal hyperplasia. Furthermore, intravascular ultrasound (IVUS) imaging demonstrated no significant stent recoil at day 1, and continued stent...
expansion was observed in the first 3 months of follow-up. The mean stent cross-sectional area increased from $7.42 \pm 1.51$ mm$^2$ at baseline to $8.18 \pm 2.42$ mm$^2$ ($P=0.086$) at 3 months and $8.13 \pm 2.52$ mm$^2$ at 6 months. A second, larger study of 50 elective patients (63 lesions, 84 stents) also showed promising results. IVUS performed at the 3-year follow-up demonstrated the complete absence of stent struts, and angiographic analysis demonstrated a mean diameter stenosis of 25% compared with 38%, 29%, and 26% at 6, 12, and 24 months, respectively. Clinical outcomes at 4-year follow-up showed rates of overall and MACE-free survival rates of 97.7% and 82.0%, respectively.

At the 10-year clinical follow-up, freedom from cardiac death, noncardiac death, and MACEs was 98%, 87%, and 48%, respectively. In the limited cases with serial angiographic follow-up, the minimum lumen diameter was stable: the mean minimum lumen diameter was 2.01 mm at 1 year and 2.06 mm at 10 years. There were 2 ST events: 1 subacute event occurring at day 5 possibly as a result of inadequate heparinization at the time of percutaneous coronary intervention and 1 very late ST event occurring in the sirolimus-eluting metallic stent that was later implanted proximal to the previously placed Igaki-Tamai stent. Serial angiographic and OCT images of the stent struts out to the 10-year follow-up in 1 anecdotal case are shown in Figure 4.

Despite these impressive results, the failure of the stent to progress was related primarily to the use of heat to induce self-expansion. There were concerns that this could cause necrosis of the arterial wall, leading to excessive intimal hyperplasia or increased platelet adhesion, leading to ST. None of these concerns were substantiated in the initial studies; however, only low-risk patients were enrolled. After completion of the Biodegradable peripheral Igaki-Tamai stents PERSEUS study, the stent became available in Europe for peripheral use; however, there are plans to review its use in coronary arteries. At present, the stent has no drug elution, although preclinical studies of the polymeric stent eluting the tyrosine kinase antagonist ST 638 showed promising results.

Magnesium Alloy
Magnesium (Mg) is the fourth-most-common cation within the human body; the total body content is $\approx 20$ g, with 350 mg...
required daily. It is essential for the synthesis of >300 enzymes and is a cofactor for ATPase. A high-dose infusion of Mg can cause vasodilatation and the promotion and recruitment of collaterals during ischemia and can function as a direct inhibitor ST.

The absorbable metallic stent (AMS-1; Biotronik, Berlin, Germany) is the first metallic biodegradable stent, composed of 93% magnesium (approximate size, 3.0 mm and 3 mg) and 7% rare earth metals. The first-generation AMS-1 stent, which is balloon expandable, is available in diameters of 3.0 to 3.5 mm and lengths of 10 to 15 mm. It has a high mechanical strength and properties comparable to stainless steel stents in terms of its low elastic recoil (<8%), high collapse pressure (0.8 bar), and minimal shortening after inflation (<5%).70 The degradation of Mg produces an electronegative charge that results in the stent being hypo-thrombogenic.71 In the porcine model, the AMS-1 has been shown to be rapidly endothelialized, and within 60 days it is largely degraded into inorganic salts with little associated inflammatory response.72 After promising initial preclinical trials and successful deployment in 20 patients with critical limb ischemia,73 the Clinical Performance and Angiographic Results of Coronary Stenting (PROGRESS AMS) trial was performed. This multicenter, nonrandomized, prospective study assessed the efficacy and safety of the stent in 63 patients (71 stents) with single de novo lesions.

Table 4. Currently Available BRS Tested in Clinical Trials

<table>
<thead>
<tr>
<th>Scaffolds</th>
<th>Strut Material</th>
<th>Coating Material</th>
<th>Design</th>
<th>Absorption Products</th>
<th>Drug Elution</th>
<th>Stent Radiopacity</th>
<th>Deployment</th>
<th>Total Strut Thickness (Strut + Coating), μm</th>
<th>Cross Linking Profile, mm</th>
<th>Stent-to-Artery Coverage, %</th>
<th>Duration</th>
<th>Radial Support</th>
<th>Absorption Time</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igaki-Tamai PLLA</td>
<td>Nil</td>
<td>Zigzag helical coils with straight bridges</td>
<td>Lactic acid, CO₂, H₂O</td>
<td>Nil</td>
<td>Gold markers</td>
<td>Self-expanding with heated balloon</td>
<td>170</td>
<td>7</td>
<td>24</td>
<td>6 mo</td>
<td>2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMS-1 Metal-Mg alloy</td>
<td>Nil</td>
<td>Sinuous in-phase hoops linked by straight bridges</td>
<td>Not applicable</td>
<td>Nil</td>
<td>Nil</td>
<td>Balloon</td>
<td>165</td>
<td>1.2</td>
<td>10</td>
<td>Days or weeks</td>
<td>&lt;4 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AMS-2 Metal-Mg alloy</td>
<td>Nil</td>
<td>Sinuous in-phase hoops linked by straight bridges</td>
<td>Not applicable</td>
<td>Nil</td>
<td>Nil</td>
<td>Balloon</td>
<td>125</td>
<td>1.2</td>
<td>10</td>
<td>Weeks</td>
<td>&gt;4 mo</td>
<td></td>
<td></td>
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<tr>
<td>AMS-3 Metal-Mg alloy</td>
<td>Nil</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>Yes</td>
<td>Nil</td>
<td>Balloon</td>
<td>125</td>
<td>1.2</td>
<td>10</td>
<td>Weeks</td>
<td>&gt;4 mo</td>
<td></td>
<td></td>
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<tr>
<td>REVA Poly-tyrosine-derived polycarbonate polymer</td>
<td>Nil</td>
<td>Side and lock</td>
<td>Amino acid, ethanol, CO₂</td>
<td>Nil</td>
<td>Iodine impregnated</td>
<td>Balloon</td>
<td>200</td>
<td>1.7</td>
<td>55</td>
<td>3-6 mo</td>
<td>2 y</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BTI Polymer salicylate + linker</td>
<td>Salicylate + different linker</td>
<td>Tube with laser-cut voids</td>
<td>Salicylate, CO₂, H₂O</td>
<td>Sirotinus salicylate</td>
<td>Nil</td>
<td>Balloon</td>
<td>200</td>
<td>2</td>
<td>65</td>
<td>3 mo</td>
<td>6 mo</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BVS 1.0 PLL</td>
<td>Poly-γ- lactide</td>
<td>Out-of-phase sinusoidal hoops with straight and direct links</td>
<td>Lactic acid, CO₂, H₂O</td>
<td>Everolimus salicylate</td>
<td>Platinum markers</td>
<td>Balloon</td>
<td>156</td>
<td>1.4</td>
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<td>BVS 1.1 PLL</td>
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Adapted from Garg and Serruys.64

Figure 4. Macroscopic view (left) of the Igaki-Tamai PLLA stent, which has zig-zag helical coils with straight bridges and golden markers at both ends of the strut. The coronary angiography performed 10 years after implantation showed the patency and curved trajectory of the previously stented lesion in the proximal right coronary artery (bottom right). Stent markers of the overlapping Igaki-Tamai stents are clearly visible in the vessel wall. On OCT, endoluminal surface of the stent was smooth and struts were no longer visible, whereas radiopaque markers remained detectable (white arrows). OCT cross sectional images (panel A–E) correspond to the yellow lines (A–E) in the angiography (bottom right).
The study reached the primary end point, a composite of cardiac death, nonfatal myocardial infarction, and clinically driven target lesion revascularization (TLR; equal to MACEs) at 4 months, by achieving a MACE rate of 23.8%; the MACE rate at 12 months was 26.7%. The study demonstrated the safety of the AMS-1 with no reported death, myocardial infarction, or ST during 12 months of follow-up; in addition, there was a return of vessel vasoreactivity.

Unfortunately, the rate of any TLR was a disappointing 23.8% at 4 months and 45% at 12 months. Quantitative coronary angiography (QCA) and IVUS have both provided important data on the mechanism of this restenosis, all of which have had important implications on future stent designs. QCA showed an acute gain after stenting of 1.41 mm (SD, 0.46 mm) and a reduction in the mean diameter stenosis from 61.5% before stenting (SD, 13.1%) to 12.7% (SD, 5.6%) after stenting. At the 4-month follow-up, the mean diameter stenosis was 48.4% (SD, 17.0%) and the in-stent late loss was 1.08 mm (SD, 0.49 mm). Immediately after poststenting balloon dilatation, which was required in 42 patients, IVUS demonstrated that both the mean stent cross-sectional area (6.2±1.5 mm²), and mean stent volume (116.5±40.2 mm³) were lower than that seen with standard metallic stents deployed in similarly sized vessels. These results were consistent with QCA results and were probably related to both the lower radial force of the Mg alloy compared with stainless steel and immediate vessel recoil after stent implantation.

At the 4-month follow-up, IVUS demonstrated that both the mean stent cross-sectional area (6.2±1.5 mm²), and mean stent volume (116.5±40.2 mm³) were lower than that seen with standard metallic stents deployed in similarly sized vessels. These results were consistent with QCA results and were probably related to both the lower radial force of the Mg alloy compared with stainless steel and immediate vessel recoil after stent implantation. At the 4-month follow-up, IVUS demonstrated that only small remnants of the original struts were visible, which were all well embedded in the intima. IVUS also showed a 42% reduction in the area delineated by the external elastic membrane, suggesting that early vessel recoil was indeed the primary cause of the high late loss and restenosis. This vessel recoil was attributable to the loss of radial force from the early, rapid AMS-1 stent degradation, so no stent support was available to oppose constrictive remodeling, a natural response of the vessel to injury. Exacerbating the problem was evidence to suggest that stent degradation was possibly faster than previously anticipated. A repeat IVUS in 1 patient only 3 weeks after AMS-1 implantation showed that 50% of struts were already degraded.74 Other factors besides constrictive recoil contributing to the luminal loss seen at follow-up were intrastent tissue growth (intrastent neointima; 41%) and tissue growth behind the stent struts (extrastent neointima; 13.5%; Figure 5E). Reassuringly, long-term data from angiographic and IVUS performed in the 8 patients who did not experience an event at 4 months have shown that there was no evidence of either later recoil or late development of neointima. In fact, in some patients, evidence of neointimal regression and/or an increase in vessel and lumen volume was seen.74 Of note, the AMS stent is proven to be compatible with magnetic resonance imaging;75 furthermore, the vasodilator function after nitroglycerin injection was restored in the treated segment at follow-up.

The results from the patients enrolled in studies of the AMS-1 stent demonstrated that it was safe for use in both coronary and peripheral vessels.70,73,77 The stent was resorbed as intended with no undue safety concerns. The disappointingly high TLR rate compared with standard BMS and DES has led to modifications in the design of future stents. These modifications aim to prolong degradation and enable drug elution, thereby reducing restenosis, which was due partly to negative remodeling and partly to an excessive healing response. Two new stents have been developed: AMS-2 and AMS-3 (Figure 5B through 5D). The AMS-2 stent is designed to overcome some of the problems of excessive vessel recoil seen with AMS-1. It provides prolonged mechanical stability, which has been achieved by using a different magnesium alloy that has not only a higher collapse pressure of 1.5 bar compared with 0.8 bar for AMS-1 but also a slower degradation time. In addition, the stent surface has been modified; the stent strut thickness has been reduced from 165...
to 125 μm, and the shape of the strut in cross section has been altered from rectangular to square (improving radial strength). These changes have prolonged scaffolding and stent integrity, improved radial strength, and reduced neointima proliferation in animal models.

The AMS-3 stent (drug-eluting AMS) is designed to reduce neointimal hyperplasia by incorporating a bioresorbable matrix for controlled release of an antiproliferative drug onto the AMS-2 stent. Research is currently focused on establishing the ideal drug kinetics; initial animal trials have demonstrated a sustained antiproliferative effect at 1 month. A new clinical program resumed in July 2010.

**Tyrosine Polycarbonate: The REVA Stent**

The REVA stent (Boston Scientific, Natick, MA) is a tyrosine poly (desaminotyrosyltyrosine ethyl ester) carbonate stent that is both resorbable and radiopaque after the chemical modification of tyrosine to incorporate iodine molecules. The polymer degrades, as summarized in Figure 6A, into water, carbon dioxide, and ethanol; in addition, tyrosine is metabolized by the Krebs cycle. The resorption time of the stent is dependent on the mass of the polymer, with reported times of >18 months or <12 months for the high- and low-molecular-weight polymers, respectively. In addition to its radiopacity, the REVA stent also has a distinctive slide-and-lock design that provides both flexibility and strength. During the deployment of a standard deformable stent, significant strain is concentrated at hinge points; the consequence of straining a polymer beyond its yield point is a significant loss of mechanical strength. The slide-and-lock design eliminates hinge points and therefore minimizes polymer strain by >75% over a wide range of deployment diameters, thereby preventing deformation and weakening of the polymer during stent deployment. The locking mechanism maintains the acute lumen gain after stent deployment and provides additional support to the stent during vessel remodeling. Company data report negligible recoil and a radial force that is superior to the MULTI-LINK VISION BMS (Abbott Vascular, Santa Clara, CA). Preclinical data from 600 stents in 300 animals showed encouraging results. Histological samples taken at day 5 demonstrated minimal injury, a nonthrombogenic response, and low inflammation. Electron microscopy at 30 days confirmed complete endothelialization with histology at 6 months, confirming complete encapsulation. Inflammation was noted to be higher with the REVA stent compared with BMS at 1 month but comparable by 12 months; a similar trend was noted for area stenosis. Notably, IVUS data demonstrated an increase in the luminal area with the REVA stent from 3.65 mm² at 1 month to 8.28 mm² at 12 months, whereas only a minimal rise was observed over the...
same period in the BMS control (5.84 to 6.28 mm²). The 30-patient multicenter first-in-humans clinical study of the REVA stent, the REVA Endovascular Study of a Bioresorbable Coronary Stent (RESORB) study, began enrollment in June 2007. The study was designed to evaluate the safety of the stent in de novo lesions \( \approx 12 \) mm in length and between 3.0 to 3.5 mm in diameter. The primary end point was MACEs at 30 days; the secondary end point was IVUS- and QCA-derived parameters at the 6-month follow-up. The strength of the stent was demonstrated by prestenting and poststenting mean minimum lumen diameters of 0.88 ± 0.39 and 2.76 ± 0.36 mm, respectively, whereas the respective mean diameter stenosis prestenting and poststenting was 70% and 5.9%. Follow-up at 6 months showed the absence of any significant vessel recoil as indicated by the external elastic lamina, which went from 15.5 ± 4.0 to 15.3 ± 3.1 mm². Unfortunately, focal mechanical failures driven by polymer embrittlement led to a higher-than-anticipated rate of TLR (66.7%) between 4 and 6 months of follow-up. Interestingly, the degree of neointimal hyperplasia was similar to that of a BMS. Redesign of the stent has ensued, resulting in the second-generation ReZolve stent. This stent has a more robust polymer, a spiral slide-and-lock mechanism to improve clinical performance, and a coating of sirolimus (Figure 6). The sirolimus elution is such that 80% is eluted by 30 days and 95% by 90 days. Successful preclinical trials have been performed, and clinical trials are anticipated in 2011.

**Poly (Anhydride Ester) Salicylic Acid: The IDEAL Stent**

The IDEAL biodegradable stent (Bioabsorbable Therapeutics, Inc, Menlo Park, CA) consists of a backbone of polyanhydride ester based on salicylic acid and adipic acid anhydride and an 8.3-μg/mm coating of sirolimus (Figure 7), potentially giving the stent both antiinflammatory and anti-proliferative properties. The vascular compatibility and efficacy of this biodegradable salicylate-based polymer have previously been demonstrated in the porcine model. Most notably, the polymer was associated with reduced inflammation compared with a standard BMS and Cypher stent. This was very likely due to the antiinflammatory properties of salicylic acid following absorption by the vessel wall after its release. Drug elution was found to be complete after 30 days, and complete stent degradation occurred over a 9- to 12-month period. The 8F-compatible, balloon-expandable stent is radiopaque and does not require any special storage. Its
radial strength is greater than that of a BMS but considerably less than the Cypher stent. Histological analyses from preclinical studies of the IDEAL stent in pigs have confirmed the absence of excessive thrombosis or inflammatory reaction and satisfactory healing of the vessel. Furthermore, the promising mechanical properties of the stent were confirmed, with well-apposed stent struts observed at follow-up. In July 2009, the 11 patients enrolled in the multicenter first-in-humans Whisper trial completed their 12 month follow-up. Primary results have shown stent safety and confirmed structural integrity of the stent with no evidence of acute or chronic recoil. Unfortunately, insufficient neointimal suppression has been demonstrated. This is likely to be the consequence of inadequate drug dosing, particularly considering that the surface area dose of sirolimus is only a quarter of that found on the Cypher stent. The rapid elution of sirolimus may also be a contributing factor.

A second-generation stent has been developed with a higher dose of sirolimus and a slower drug release pattern. Furthermore, the stent design has been optimized, which has resulted in a reduced crossing profile (6F compatible) and thinner struts (175 \( \mu \)m). Although the program was on hold in early 2009, it will resume in 2011, and the results of preclinical porcine coronary implants and a first-in-human implantation are anticipated in 2011.

### Everolimus-Eluting PLLA Stent: BVS Scaffold

The BVS stent design is characterized by a crossing profile of 1.4 mm with circumferential hoops of PLLA. The struts are 150 \( \mu \)m thick and are either directly joined or linked by straight bridges (Figure 8). Both ends of the stent have 2 adjacent radiopaque platinum markers. The radial strength, measured in a water bath at 37°C using IVUS and by flat-plate compression of 10%, 15%, and 25%, is 0.048±0.007, 0.070±0.008, and 0.106±0.009 N/mm²; comparative values for a contemporary BMS (Vision coronary stent; Abbott Vascular) is 0.073±0.011, 0.114±0.012, and 0.155±0.012 N/mm², respectively.

The backbone of the BVS device is made of semicrystalline polymer called PLLA. The coating consists of poly DL-lactide acid (PDLLA), which is a random copolymer of D- and L-lactic acid with lower crystallinity than the BVS backbone. The coating contains and controls the release of the antiproliferative drug everolimus. Both PLLA and PDLLA are fully bioresorbable. During bioresorption, the long chains of PLLA and PDLLA are progressively shortened as ester bonds between lactide repeat units are hydrolyzed, and small particles <2 \( \mu \)m in diameter are phagocytosed by macrophages. Ultimately, PLLA and PDLLA degrade to lactic acid, which is metabolized via the Krebs cycle. In a porcine coronary artery model, mass decreased with time: 30% at 12 months increasing to 60% at 18 months and to 100% at 24 months after implantation.

### Study Design of the ABSORB Cohort A Trial

The ABSORB trial was a single-arm, prospective, open-label, first-in-humans study with safety and imaging end points. Between March and July 2006, 30 patients were enrolled at 4 participating sites. Inclusion criteria included age ≥18 years; a diagnosis of stable, unstable, or silent ischemia; and a single de novo lesion in a native coronary artery of 3.0 mm, <8 mm for the 12-mm BVS or <14 mm for the 18-mm BVS (only 2 patients received the latter stent). Of the 30 patients enrolled, 4 were excluded from the per-treatment evaluable population because they received a non-BVS stent in addition to a BVS. Clinical end points were assessed at 6 months and 1 and 2 years; angiography, IVUS, and derived morphology parameters (virtual histology [VH], palpography, and echogenicity)
were assessed at 6 months and repeated at 2 years. Noninvasive coronary angiography with multislice CT (MSCT) was performed at the 18-month follow-up. This trial sought to answer the following questions.

Is Noninvasive Evaluation of the Treated Vessel Feasible?
In contrast to the radiopaque metallic stents that hinder in-stent luminal assessment with MSCT because of blooming artifacts, the polymeric BVS stent is radiolucent except for 2 metallic markers located at both extremities of the stent that facilitate the luminal and length assessment of the scaffold with MSCT (Figure I in the online-only Data Supplement). Because of the noninvasive nature of MSCT, 25 patients underwent MSCT imaging 18 months after the index procedure, which represents a larger number of patients compared with the patients who underwent conventional coronary angiography at 24 months (n=19). Of the 25 patients who underwent MSCT, quantitative analysis was feasible in 24. According to MSCT measurements, the mean luminal area was 5.2±1.3 mm², the minimal lumen area was 3.6±0.9 mm², and the mean area stenosis was 34±15%. The calculated mean diameter stenosis was 19.9% and was in fact not too much at variance with the results of invasive QCA (percent diameter stenosis, 27±11%). The feasibility and accuracy of the use of MSCT in analyzing radiolucent biodegradable stents in a multicenter study may therefore usher in a new era of noninvasive evaluation of patients treated with radiolucent stents.40,84

Does Plaque Deformability Remain Scaffolded at Follow-Up?
The underlying principle of palpography is that softer tissue is more readily deformed than harder or scaffolded tissue when pulsatile arterial pressure is applied.84–86 The rationale of this analysis in the present study was to detect some subtle changes in strain resulting from scaffolding and late bioresorption of the stent. The deformability of a vessel wall is quantified with analysis in the present study was to detect some subtle changes in strain resulting from scaffolding and late bioresorption of the stent. The deformability of a vessel wall is quantified with

Virtual Histology
IVUS backscattering radiofrequency analysis (VH) was also applied to assess the absorption of the polymeric struts. Because polymeric struts are misclassified as pseudodense calcium on VH immediately after implantation, it was hypothesized that bioresorption of struts would be reflected by a reduction of pseudodense calcium at follow-up (Figure 9).

From before to after stenting, there was an increase in the mean pseudodense calcium (9.8% versus 25.4%; P<0.001) and necrotic core (15.5% versus 30.5%; P=0.001; n=13).88 However, at the 6-month follow-up, VH showed a relative 30% decrease in pseudodense calcium (29.7% versus 21.2%; P<0.001) and a nearly 20% decrease in necrotic core (26.9% versus 21.9%; P=0.005; n=27). Between 6 months and 2 years, IVUS VH assessments demonstrated no significant differences in percentage of each plaque component (Figure 9).40

What Did We Learn From OCT?
Serial OCT data obtained immediately after stent implantation and at the 6-month and 2-year follow-up were available in 7 patients from the intention-to-treat population.40 One of the main findings was a reduction in the number of apparent struts over time. The total number of apparent struts decreased from 403 at baseline to 368 at the 6-month follow-up and to 264 at the 2-year follow-up (35% reduction over 2 years). Strut appearance at 2 years is shown in Figure 10.

Does Late Luminal Enlargement Occur?
The main observation provided by gray-scale IVUS was the significant increase in minimal luminal area and average luminal area/volume, together with a significant decrease in plaque area/volume between 6 months and 2 years. Except for the minimal luminal area (decreasing from 5.09 to 4.35 mm²; P=0.034), there were no apparent differences in vessel area, average luminal area, plaque area, and lumen area stenosis between the immediate postprocedure and 6-month follow-up measurements. Of note, the vessel area/volumes remained constant during follow-up, suggesting the absence of significant remodeling; however, late enlargement of the lumen was observed in OCT analysis (n=7). In summary, minimal and mean luminal areas decreased significantly between postprocedure and 6-month assessments but enlarged significantly between 6 months and 2 years.

This observed phenomenon needs to be confirmed. The volumetric reduction in struts induced by bioresorption might explain this phenomenon. Otherwise, it could be hypothesized that everolimus exerts a specific autophagic effect on the plaque with a reduction in plaque size between 6 and 24 months.89
Is Vasomotion Restored?

To study vasomotion, either the endothelium-independent vasoconstrictor methylergonovine maleate (methergin) or the endothelium-dependent vasoactive agent acetylcholine was administered at the 2-year angiographic follow-up. Mean lumen diameters were measured by QCA after baseline saline infusion and after administration of methergin/acetylcholine. Both tests were terminated by intracoronary administration of 200 μg nitroglycerin.

In the methergin group \( (n=7) \), there was significant vasoconstriction in proximal \( (\text{before methergin}, 2.70 \pm 0.43 \text{ mm}; \text{after methergin}, 2.49 \pm 0.46 \text{ mm}; P=0.02) \) and scaffolded \( (\text{before methergin}, 2.64 \pm 0.22 \text{ mm}; \text{after methergin}, 2.44 \pm 0.33 \text{ mm}; P=0.03) \) segments. In the acetylcholine group \( (n=9) \), 5 patients exhibited vasodilation in the scaffolded segment (Figure II in the online-only Data Supplement). These results suggested that vasomotor function was restored in the scaffolded segment, an observation that had obviously never been made after metallic stent implantation.

The reappearance of vasomotion of the scaffolded and periscaffold segments in response to methergin or acetylcholine indicates that vessel vasoreactivity has been restored and that a physiological response to vasoactive stimulus may occur anew. Furthermore, 5 of 9 patients tested with acetylcholine exhibited vasodilatation (at least 3% of the mean diameter) during the highest infused doses, further suggesting flow-mediated response to acetylcholine and thus the presence of functionally active endothelium at the site of the stent implantation.

How About Clinical Outcomes?

At 3 years, clinical follow-up was obtained from 29 of 30 enrolled patients. There was only 1 non-Q-wave myocardial infarction (peak troponin, 2.21 ng/mL) related to the treatment of a non-flow-limiting stenosis (QCA diameter stenosis, 42%) in a patient implanted with the BVS 46 days earlier. Furthermore, this patient experienced a single episode of angina at rest without any ECG evidence of ischemia.
Otherwise, there were no new MACEs between 6 months and 3 years and no instances of ST as defined by the protocol or Academic Research Consortium definitions. In total, the MACE rate at 3 years was 3.4%.91

Discovered Challenges and Future Perspectives

During the ABSORB trial, the mechanical properties of the polymeric stent were assessed. The acute recoil was evaluated in angiography as the difference between the mean luminal diameter of the scaffolded vessel and the diameter at maximal balloon inflation. The mean percent acute recoil was 6.85 ± 6.96% for BVS in the ABSORB cohort A trial and 4.27 ± 7.08% for Xience V stent (Abbott Vascular, Santa Clara, USA) in the SPIRIT I trial. This suggests that the scaffolding properties of the BVS are slightly weaker than in the Xience V stent.

The late recoil assessed by means of IVUS was defined as a reduction in stent area from after the procedure to the 6-month follow-up. At 6 months, the lumen area was reduced by 16.6% and late recoil was 11.7%. This suggested that approximately two thirds of the luminal area reduction was caused by late recoil.

Modification of Strut Design

To enhance the mechanical strength of the struts and to reduce early and late recoil, the strut design and the manufacturing process of the polymer were modified in the revised version, BVS 1.1. First, the new design has in-phase zigzag hoops linked by bridges that allow a more uniform strut distribution, reduce maximum circular unsupported surface area, and provide more uniform vessel wall support and drug transfer (Figure 8). Second, a modified manufacturing process has resulted in a slower hydrolysis (in vivo degradation) rate of the polymer, thus preserving its mechanical integrity for a longer period of time.95

The BVS 1.1 was tested in 101 patients of the ABSORB cohort B study. This cohort was subdivided in 2 subgroups of patients: the first group (B1) had to undergo invasive imaging with QCA, IVUS, IVUS VH, and OCT at 6 and 24 months; the second group (B2) will undergo invasive imaging at 12 and 36 months.

The design of the most recent trial was to demonstrate the improved performance at 6 months of this second iteration, the BVS 1.1. So far, 6-month results of the first 45 patients (B1) are available.49 Forty-five patients successfully received a single BVS. One patient had postprocedural release of myocardial enzymes without Q-wave occurrence, and another patient had OCT-diagnosed disruption of the BVS scaffold secondary to excessive postdilatation that was successfully treated 1 month later with a metallic DES. At follow-up, 3 patients declined recatheterization, 42 patients had QCA, 37 had quantitative IVUS, and 25 had OCT. QCA disclosed 1 edge restenosis (1 of 42; in-segment binary restenosis, 2.4%). At variance with the ultrasonic changes seen with the first generation of BVS at 6 months, the backscattering of the polymeric struts did not decrease over time, and the scaffold area was reduced by only 2.0% with IVUS without change on OCT (Figure 11). On an intention-to-treat basis, the late lumen loss amounted to 0.19 ± 0.18 mm (Figure 12) with a limited relative decrease in minimal luminal area of 5.4% on IVUS. OCT at follow-up showed that 96.9% of the struts were covered and that malapposition of at least 1 strut, initially observed in 12 scaffolds, was detected at follow-up in only 3 scaffolds. Mean neointimal growth measured by OCT between and on top of the polymeric struts equaled 1.25 mm², or 16.6% of the scaffold area. Modified manufacturing processes of the polymer and geometric changes in the polymeric platform have substantially improved the medium-term performance of this new generation of drug-eluting scaffold so that it has become comparable to current-generation DES.
The promising results at 6 months of this second-generation bioresorbable drug-eluting scaffold (BVS 1.1) constitute proof of concept that this device can adequately revascularize coronary vessels and prevent restenosis. Considering the favorable outcomes at 2 years of the first generation (BVS 1.0), it is deemed appropriate and timely to initiate a randomized pivotal trial comparing a metallic DES with this drug-eluting bioresorbable vascular scaffold. In the meantime, the BVS 1.1 is being tested in the extended registry of ABSORB EXTEND, which will enroll ~1000 patients.

Future Perspectives

Although the BRS technology is still in its infancy, some initial clinical results are promising. For further development of this technology, some issues need to be addressed. First, the optimal duration of scaffolding with drug-elution should be further elucidated. In both AMS-1 magnesium stent and BVS 1.0 scaffolds, late scaffold shrinkage was one of major contributors to luminal loss. In a previous study with serial IVUS imaging after angioplasty or directional coronary atherectomy,9 some positive remodeling occurred early after the procedure up to 1 month, whereas the negative remodeling (eg, decrease in external elastic lamina) occurred at 1 to 6 months. This suggests that the need to prevent negative remodeling is necessary at least until 6 months. This could be achieved by tuning the biodegradation speed in changing the molecular weight of the polymer and increasing its crystallinity, thereby prolonging the mechanical integrity of the scaffold.

So far, the BRS technologies without drug elution such as REVA and AMS-1 were associated with high TLR rates. More specifically, in the AMS-1 trial, 45% of late luminal reduction was attributed to neointimal hyperplasia at 6 months.70 These results suggest that the elution of antiproliferative agents might be indispensable to make the BRS clinically applicable and efficient at medium term.

Second, the clinical advantage of BRS technology over the currently available DES needs to be further investigated. BVS and Mg stents showed the recovery of responsiveness of the treated vessel to vasoactive agents such as nitroglycerin. The restoration of vasomotion can indirectly stand for the completeness of vessel healing; however, it is still unclear what the real clinical advantage of this phenomenon is. A number of studies have shown that the neointimal hyperplasia area and percent volume obstruction (VO) in Xience V everolimus-eluting metallic stent (EES; left), BVS 1.0 scaffold (middle), and BVS 1.1 scaffold (right). In the SPIRIT I trial, Xience V showed a 6-month late loss of 0.10 mm, and the main contributor of luminal loss was neointimal hyperplasia in the stent. In the ABSORB cohort A, BVS 1.0 was associated with the late loss of 0.44 mm, which was caused mainly by a scaffold area shrinkage (relative reduction, 11.7%) and, to a lesser extent, by neointimal hyperplasia. In the ABSORB cohort B trial, BVS 1.1 demonstrated an angiographic loss of 0.19 mm at 6 months. Shrinkage of scaffold area was almost eliminated (relative reduction, 2.9%), and a minimal amount of neointimal hyperplasia was observed.
of studies using metallic DES have reported the abnormal vasomotion in the distal segment to the DES. Some consider that this abnormality might restrict the distal flow and therefore predispose to the occurrence of late ST; however, the clinical consequences of these findings are still not clear. In patients with early atherosclerosis, the presence of abnormal endothelial function was associated with poor outcomes or more frequent angina.

To elucidate these issues further, larger studies with specific end points such as anginal status, functional exercise testing or flow reserve, radioisotopic investigation flow, and myocardial metabolism may be necessary. Similarly, the feasibility that MSCT/magnetic resonance imaging has shown in the initial clinical trials, in terms of comparability with other modalities, needs to be further investigated.

A potential drawback of this new technology is strut fracture. Unlike metallic stents, the polymeric devices have inherent limit of expansion and can break as a result of overdilatation. In an anecdotal case from the ABSORB cohort A, a 3.0-mm scaffold was overexpanded with 3.5-mm balloon, which resulted in strut fracture as documented with OCT. Because of the recurrence of limited anginal symptoms, this patient underwent TLR despite an angiographically nonsignificant stenosis by QCA (diameter stenosis, 42%). The clinical significance of such a case, evidenced only by OCT, needs to be further elucidated, but undoubtedly fracture should be avoided by respecting the nominal size of the scaffold.

Another issue is whether the metallic stents with thin struts covered by a thin biodegradable polymer or metallic DES without polymer can succeed in minimizing ST. So far, the evidence shows that late ST can occur with BMS, Considering the deadly consequence of ST, we should aim at eradicating this complication, and BRS technology theoretically seems closer to achieving this goal, in addition to eliminating the deleterious caging effect of the permanent metallic endoluminal prosthesis.

Data transferability might be another issue from the regulatory perspective. In conventional metallic stents, the essential component was platform, coating, and drug. When it comes to BRS polymeric stents, even with the same PLLA and design, the speed of biodegradation/bioresorption can be different according to the manufacturing process of PLLA. For example, molecular weight can influence the degree of inflammation, as shown in a previous preclinical study. Although the safety of PLLA is inferred from other medical application such as orthopedics, orbital floor defects, and spinal surgery, each scaffolding device implanted in the coronary circulation still needs to be tested in terms of biocompatibility.

Conclusion

There is no doubt that after percutaneous coronary intervention the injured vessel requires scaffolding; however, there is no consensus on how long this scaffolding is required. The currently available metallic DES have demonstrated their ability to provide a permanent scaffolding and to prevent restenosis, but legitimate safety concerns have emerged. These concerns have led to improvements in conventional DES with the use of novel, more biocompatible polymers. However, they have also provided the impetus for the development of stents that provide only a temporary scaffold, ie, biodegradable stents. This technology is currently still in its infancy. However, the return of normal vascular function after bioabsorption has opened a new horizon aimed at promoting “vascular restoration therapy.” This therapy is an exciting development and certainly worthy of the accolade of being the fourth revolution in interventional cardiology.

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Disclosures

None.

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