Head-to-Head Comparison of a Drug-Free Early Programmed Dismantling Polylactic Acid Bioresorbable Scaffold and a Metallic Stent in the Porcine Coronary Artery
Six-Month Angiography and Optical Coherence Tomographic Follow-up Study

Eric Durand, MD, PhD; Tahmer Sharkawi, PhD; Guy Leclerc, MD; Marine Raveleau, MSc; Machiel van der Leest, MSc; Michel Vert, PhD; Antoine Lafont, MD, PhD

Background—We aimed to evaluate a new drug-free fully bioresorbable lactic acid–based scaffold designed to allow early dismantling synchronized with artery wall healing in comparison with a bare metal stent (BMS).

Methods and Results—Twenty-three BMS (3.0×12 mm) and 36 lactic acid–based bioresorbable scaffolds (BRS, 3.0×11 mm) were implanted in porcine coronary arteries. QCA and optical coherence tomographic analyses were performed immediately after implantation and repeated after 1, 3, and 6 months. Microcomputed tomography was used to detect scaffold dismantling. Polymer degradation was evaluated throughout the study. The primary end-point was late lumen loss, and the secondary end-points were scaffold/stent diameter and acute recoil. Acute recoil was low and comparable between the BRS and the BMS groups (4.6±6.7 versus 4.6±5.1%; P=0.98). BRS outer diameter increased significantly from 1 to 6 months indicating late positive scaffold remodeling (P<0.0001), whereas BMS diameter remained constant (P=0.159). Late lumen loss decreased significantly from 1 to 6 months in the BRS group (P=0.003) without significant difference between BRS and BMS groups at 6 months (P=0.68). Microcomputed tomography identified BRS dismantling starting at 3 months, and weight-average molar masses of scaffold parts were 20% and 14% of their initial values at 3 and 6 months.

Conclusions—BRS and BMS have similar 6-month outcomes in porcine coronary arteries. Interestingly, BRS dismantling was detected from 3 months and resulted in late lumen enlargement by increased scaffold diameter at 6 months. (Circ Cardiovasc Interv. 2014;7:00-00.)

Key Words: bioabsorbable implants • coronary restenosis • polymers • stent

The concept of bioresorbable scaffolding is now perceived as an effective alternative to metallic stenting for several reasons1-2: (1) metallic stenting inhibits lumen enlargement, (2) metallic drug–eluting stents require long-term dual anti-platelet therapy, complicate surgical revascularization, permanently jail sides branches, and preclude the use of noninvasive follow-up of the fate of coronary arteries with multislice computed tomography and MRI.2 Moreover, the ad vitam presence of metallic stents is not coherent with the rather short healing time of an artery wall.3-5 Ideally, coronary artery healing requires scaffolding for not >3 months.6 A temporary scaffold must provide radial support during the healing phase and exhibit conformability to match the vessel geometry without imposing excessive mechanical stress. It should dismantle after 3 months and undergo resorption once scaffolding is no longer required.2,6

Although various types of temporary metallic or polymeric bioresorbable stents are currently under investigation,2 those based on lactic acid–derived polymers are the most extensively advanced in the cardiovascular field because of their biocompatibility and their hydrolytic degradability. The principal member of the family is composed of the repetition of the sole L-lactyl unit, known as poly-L-lactic acid (PLLA).7 PLLA of different sources have been used to make either bare

Received February 27, 2013; accepted November 21, 2013.

From the Cardiology Department, European Georges Pompidou Hospital, Paris Centre de Recherche Cardiovasculaire, INSERM U 970, Université Paris-Descartes, Paris, France (E.D., M.R., A.L.); Faculty of Pharmacy, Institut Charles Gherardt, MACS (T.S.) UMR CNRS 5253 and Faculty of Pharmacy, Research Center for Artificial Biopolymers, Institut de Biomolecules Max Mousseron, University Montpellier 1-CNRS, Montpellier, France (M.V.); AccelLAB Inc, Boisbriand, Quebec, Canada (G.L.); and Arterial Remodeling Technologies, Noisy le Roi, France (M.v.d.L.).

The online-only Data Supplement is available at http://circinterventions.ahajournals.org/lookup/suppl/doi:10.1161/CIRCINTERVENTIONS.113.000738/-/DC1.

Correspondence to Eric Durand, MD, PhD, Hôpital Européen Georges Pompidou, Service de cardiologie, 20, rue Leblanc, 75340 Paris Cedex 07, France. E-mail eric.durand@egp.aphp.fr

© 2013 American Heart Association, Inc.

Circ Cardiovasc Interv is available at http://circinterventions.ahajournals.org DOI: 10.1161/CIRCINTERVENTIONS.113.000738

113.000738/DC1.
WHAT IS KNOWN

• The concept of a bioresorbable coronary scaffold is now perceived as an attractive alternative to a metallic stent.
• The Igaki-Tamai stent and the everolimus-eluting bioresorbable stent, which are made of poly-L lactic acid, have shown safety and efficacy with complete resorption by 3 years.

WHAT THE STUDY ADDS

• Evaluates a drug-free coronary bioresorbable scaffolds (BRS) made of poly-DL lactic acid in a swine model.
• The poly-DL lactic acid composition allows for faster degradation with early dismantling of the BRS at 3 months with concomitant lumen enlargement as a result of increased BRS diameter at 6 months.

or drug-eluting bioresorbable stents already tested in humans like Abbott's bioresorbable vascular scaffold (BVS) and Igaki-Tamai's stent. BVS, an everolimus-eluting PLLA scaffold, was evaluated in the ABSORB (clinical evaluation of the bioabsorbable everolimus coronary stent system in the treatment of patients with de novo coronary artery lesions) trials showing the feasibility with a low rate of restenosis. Both the BVS and the Igaki-Tamai stent were made of PLLA and showed similar degradation characteristics with a scaffolding period of 12 months and a complete resorption estimated in the range of 4 years after implantation according to various imaging data and their extrapolation. Ideally, the required temporary scaffolding period can be reasonably assumed to be 3 months with the aims of avoiding acute recoil and constrictive remodeling, and complete resorption should follow thereafter. Biodegradation is a secondary requirement aimed at clearing any foreign materials while keeping the presence of inflammatory crystalline residues as low as possible.

One means to shorten the scaffolding time of PLLA-based bioresorbable stents is to take advantage of stereocopolymers composed of L- and D-lactyl units instead of only L-lactyl ones. We previously showed that biological, mechanical, and biore sorption properties of prototypes of lactic acid stereocopolymers could be tunable to match the short healing time of coronary arteries by varying the percentage of D-lactyl units. Unlike the crystalline PLLA, the insertion of a few D-lactyl units within the poly-L chains increases the proportion of amorphous domains resulting in faster water penetration.

A new drug-free coronary bioresorbable scaffold (BRS) is currently under development by Arterial Remodeling Technologies (Noisy le Roi, France). It is made of a specific poly(lactic acid stereocopolymer that provides effective scaffolding for 3 months, followed by progressive dismantling, and complete monomer resorption in 18 to 24 months. The selected stereocopolymer has 2 major differences compared with commercial PLLA used to date for bioresorbable scaffolds: the presence of a small proportion of D-lactyl units and the use of zinc lactate instead of stannous octoate as initiator of polymerization. These particularities lead to faster water absorption and therefore faster degradation necessary for earlier dismantling, and shorter resorption time than reported for PLLA-based bioresorbable implantable devices.

No drug is incorporated in this first-generation BRS for the following reasons: (1) to promote rapid stent coverage and avoid delayed re-endothelialization; (2) to test the hypothesis that neo-intimal development is required for the occurrence of positive arterial remodeling. We recently showed 100% re-endothelialization at 1 month, low and stable inflammation score circumscribed around the struts for a prototype lactic acid–based stereocopolymer scaffold in the rabbit iliac artery model.

The aim of this study was to compare the transitory scaffolding capability of the specific lactic acid–based stereocopolymer scaffold with a drug-free metallic stent taken as reference. The comparison was based on the monitoring of the fate of the BRS and the specific consequences of the degradation of polymeric struts on the evolution of the BRS and the stented sites.

Methods

The evaluated BRS was made of a specific synthesized lactic acid–based stereocopolymer. Briefly, the polymer was synthesized by ring opening polymerization using zinc lactate as initiator of a feed composed of 96/4 L/DL lactides. After purification and characterization, the polymer was injection-molded at suitable temperatures to form tubes. Commercial PLLA (Purasorb PL-24) was purchased from Purac (Gorinchem, The Netherlands) and processed similarly for in vitro comparison purposes. The tubes were laser-cut to create struts according to a proprietary design showed in Figure 1. The design of the stent took into consideration the viscoelasticity of the polymer, the distribution of mechanical stress levels in the hinge and central regions of the struts, thus providing effective radial strength. The 3.0×11 mm BRS
were crimped on standard 3.0 mm diameter balloon catheters, and in vitro deployment of all BRS was successful without any strut rupture.

Study Design and Animal Experiments

The protocol was reviewed, approved, and performed by the AccelLAB (Montreal, Canada) Institutional Animal Care and Use Committee (IACUC) and was performed in accordance with Canadian Council on Animal Care regulations.

Yucatan miniswine were implanted via femoral access according to standard procedures. Each porcine received at random either a single 3.0x11 mm BRS (Arterial Remodeling Technologies [ART], Noisy le roi, France) or a control bare metal stent (BMS, Multi link Vision, Abbott, 3.0x12 mm) in 1 to 3 of the main coronary arteries with a stent-to-artery ratio between 1.1:1 and 1.2:1. Stent thickness was 170 μm for the BRS and 81 μm for the BMS.

Twenty-three BMS and 36 BRS were implanted in 23 Yucatan female or castrated miniswine (27.0–38.5 kg) according to the online-only Data Supplement. Protocols were designed to collect information by optical coherence tomographic (OCT) and quantitative coronary angiography (QCA) analyses from the same sites at 1 and 3 months and between 3 and 6 months, and by size exclusion chromatography (SEC) at the time of euthanizing. Microcomputed Tomography (μCT) was applied to 7 BRS from the 3-month cohort and 4 BRS of the 6-month cohort.

Two animals died during the study (1 in the 3-month cohort implanted with 2 BMS and 1 in the 6-month cohort implanted with 2 BRS and 1 BMS). Two animals died at stent implantation during OCT runs related to refractory ventricular fibrillation, and 1 animal was euthanized 100 days after stent implantation for refractory lung infection.

Angiographic Analysis

Angiography was performed before and immediately after BRS/BMS implantation (preimplantation angiography, balloon angiography, and postimplantation angiography) and at follow-up time points, and at explantation (final angiography). All coronary angiograms were performed separately after BRS and BMS implantation. Repeat measurements were analyzed overtime in the same artery in the 3- and 6-month cohorts. Correlations between pairs of factors were evaluated separately after BRS and BMS implantation. Repeat measurements were analyzed at baseline and 1 month later. Data were expressed with respect to polystyrene standards.

OCT Analysis

OCT analysis was performed with a commercially available OCT system (LightLab imaging, Westford, MA), as previously described.16 Three in-stent/scaffold sections were analyzed (3-mm distal and proximal ends, and at the middle of the BMS/BRS). Qualitative analyses were performed at 1-mm intervals in the implanted segment, which was defined as the region between the metallic radiopaque markers. The struts sites were categorized according to the 4 morphological categories, as previously described.16,17 Details methods are shown in the online-only Data Supplement.

In Vitro Polymer Degradation

To investigate the in vitro degradation, BRS were placed in vials containing sterile 0.13 mol/L iso-osmolar phosphate buffer (pH 7.4) at 37°C. The pH was monitored regularly to make sure of constancy throughout the study. At each degradation time point, 6 specimens were recovered and washed with purified water. The samples were then wiped with an absorbing paper, weighed, and vacuum-dried before being subjected to analysis. Water absorption was deduced from the weight of wiped BRS/initial dry weight ratio. Mass loss was deduced from the weight of the vacuum-dried residue/initial weight ratio. The appearance of lactic acid in the degradation medium was assessed throughout the study using an enzymatic assay kit (K-DLATE, Libios, France).

Enzymatic Digestion

For in vivo degradation, the embedded polymeric residues had to be separated from the retrieved arterial tissues to allow molar mass determination. A pH 7.5 enzymatic digestion solution was prepared by dissolving 1 g of collagenase Type H in 500 mL of Tris base and CaCl2 buffer solution. Typically, 4 mL of this enzymatic digestion solution was introduced in a vial together with an explanted stented artery. Vials were put in a thermostated agitator during 7 hours at 37°C with an agitation of 200 rpm. On collagen digestion, and arterial tissue softening, the stent remainings were gently removed from the artery tissues, rinsed with purified water, and wiped with an absorbing paper before SEC analysis.

Size Exclusion Chromatography

Mass-average molecular weight (Mw) of initial BRS and partially degraded BRS residues were determined using a VE2001 GPC Max system (Viscotec, Malvern Instruments, Worcestershire, UK) equipped with a VE3580 RI detector (Viscotec, Malvern Instruments) and a mixed-C PL gel column (Agilent Technologies, Les Ulis, France). Tetrahydrofuran was used as the mobile phase at a flow rate of 1 mL/min. In parallel, chemical analysis was also performed in vitro at baseline (n=6) and 1 (n=6) and 3 (n=6) months later. Data were expressed with respect to polystyrene standards.

Differential Scanning Calorimetry

Thermal properties and crystallinity were determined by differential scanning calorimetry with a thermostated differential scanning calorimeter (Netzsch, Germany). Accurately weighed samples were placed in sealed aluminum pans. Readings of thermal transitions were taken from the first heating ramp performed from 0°C to 200°C at 10°C/min.

Microcomputed Tomography

Fixed BRS were scanned using a Skyscan 1172 μCT model. Scan settings were first set-up using 1 BRS. After determination of appropriate settings, 7 BRS of the 3-month cohort and 4 BRS of the 6-month Cohort subset 1 were scanned. Details methods are shown in the online-only Data Supplement.

Statistical Analysis

Continuous variables are expressed as mean±SD or median (25th to 75th interquartile range [IQR]) depending on variable distribution. Normality of the distributions was assessed graphically and with the Shapiro–Wilk test. BRS and BMS group comparisons for continuous variables were analyzed using the Student t test or Shapiro–Wilk test, according to the variable distribution. General linear model for repeat measurements analysis was used to compare QCA and OCT variables poststenting at 1 and 3 months in the 3-month cohort and poststenting at 3 and 6 months in the 6-month cohort. Analyses were performed separately after BRS and BMS implantation. Repeat measurements were analyzed overtime in the same artery in the 3- and 6-month cohorts. Correlations between pairs of factors were evaluated with a Spearman’s rank correlation. All the statistical tests assumed that multiple stents implanted within the same animal are independent of each other. A value of P<0.05 was considered statistically significant. Statistical analysis was performed using SPSS software (version 17.0, SPSS Inc, Chicago, IL).
Results

QCA Analysis
Results are listed in Tables 1 and 2 for the 3-month and the 6-month cohorts, respectively, and for all animals in Figure 2.

Mean lumen diameter before stenting and scaffold/artery ratio were significantly lower in the BRS group than those in the BMS group.

Acute recoil was small for the BRS and similar to that for the BMS group in both cohorts (Figure 2A).

MLD was significantly lower in the BRS group than that in the BMS group at 1, 3, and 6 months (Figure 2B). In the BRS group, MLD increased significantly from 1 to 3 months (P<0.0001) and from 3 to 6 months (P<0.0001). In contrast, in the BMS group, MLD remained unchanged from 1 to 3 months (P=0.304) and from 3 to 6 months (P=0.143).

Diameter stenosis was significantly greater in the BRS group than that in the BMS group at 1 and 3 months (Figure 3C). However, at 6 months, the difference vanished (P=0.192). In the BRS group, diameter stenosis decreased from 1 to 3 months (P=0.05) and from 3 to 6 months (P=0.05). In contrast, in the BMS group, diameter stenosis remained unchanged from 1 to 3 months (P=0.199) and from 3 to 6 months (P=0.322).

LLL was significantly greater in the BRS group than in the BMS group at 1 and 3 months (Figure 2D). However, at 6 months, the difference vanished (P=0.68). In the BRS group, LLL decreased from 1 to 3 months (P=0.009) and from 3 to 6 months (P=0.003). In contrast, in the BMS group, LLL remained unchanged from 1 to 3 months (P=1.0) and from 3 to 6 months (P=0.192).

OCT Analysis
The results are summarized in Figures 3 and 4 with an example of BRS OCT picture shown in Figure 5.

Immediately after implantation, OCT demonstrated that all the BMS and BRS were adequately deployed without malapposition (Figure 5).

In-scaffold/stent area was significantly lower in the BRS group than that in the BMS group immediately (poststent) and at 1 and 3 months (Figure 3A). However, at 6 months, the difference vanished (P<0.0001) and from 3 to 6 months (P<0.0001). In contrast, in the BMS group, in-scaffold area remained unchanged from 1 to 3 months (P=0.143) and from 3 to 6 months (P=0.81).

Table 1. QCA Analysis (3-Month Cohort)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BRS (n=25)</th>
<th>BMS (n=12)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter poststent (mm), mean±SD</td>
<td>2.48±0.18</td>
<td>2.72±0.21</td>
<td>0.002</td>
</tr>
<tr>
<td>Mean luminal diameter prestent (mm), mean±SD</td>
<td>2.54±0.14</td>
<td>2.69±0.14</td>
<td>0.006</td>
</tr>
<tr>
<td>Stent-to-artery ratio, mean±SD</td>
<td>1.02±0.09</td>
<td>1.09±0.08</td>
<td>0.024</td>
</tr>
<tr>
<td>Acute recoil, %, mean±SD</td>
<td>5.3±6.6</td>
<td>5.5±6.0</td>
<td>0.916</td>
</tr>
<tr>
<td>MLD poststent, mm, median (IQR)</td>
<td>2.37 (0.19)</td>
<td>2.57 (0.16)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MLD 1-month, mm, median (IQR)</td>
<td>1.80 (0.35)</td>
<td>2.54 (0.34)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MLD 3-month, mm, median (IQR)</td>
<td>1.88 (0.51)</td>
<td>2.53 (0.14)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diameter stenosis 1-month, %, median (IQR)</td>
<td>18.4 (15.9)</td>
<td>4.4 (12.5)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Diameter stenosis 3-month, %, median (IQR)</td>
<td>17.5 (13.0)</td>
<td>8.0 (6.0)</td>
<td>0.002</td>
</tr>
<tr>
<td>Late loss 1-month, mm, median (IQR)</td>
<td>0.55 (0.35)</td>
<td>0.08 (0.42)</td>
<td>0.003</td>
</tr>
<tr>
<td>Late loss 3-month, mm, median (IQR)</td>
<td>0.47 (0.53)</td>
<td>0.07 (0.27)</td>
<td>0.028</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; BRS, bioresorbable scaffolds; IQR, interquartile range; MLD, minimal luminal diameter; and QCA, quantitative coronary angiography.

Table 2. QCA Analysis (6-Month Cohort)

<table>
<thead>
<tr>
<th>Variables</th>
<th>BRS (n=11)</th>
<th>BMS (n=8)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Reference vessel diameter poststent (mm), mean±SD</td>
<td>2.43±0.23</td>
<td>2.81±0.30</td>
<td>0.012</td>
</tr>
<tr>
<td>Mean luminal diameter prestent (mm), mean±SD</td>
<td>2.49±0.14</td>
<td>2.73±0.19</td>
<td>0.01</td>
</tr>
<tr>
<td>Stent-to-artery ratio, mean±SD</td>
<td>1.03±0.06</td>
<td>1.10±0.05</td>
<td>0.013</td>
</tr>
<tr>
<td>Acute recoil, %, mean±SD</td>
<td>2.6±7.0</td>
<td>3.2±3.3</td>
<td>0.823</td>
</tr>
<tr>
<td>MLD poststent, mm, median (IQR)</td>
<td>2.30 (0.28)</td>
<td>2.74 (0.31)</td>
<td>0.002</td>
</tr>
<tr>
<td>MLD 3-month, mm, median (IQR)</td>
<td>1.85 (0.39)</td>
<td>2.61 (0.47)</td>
<td>0.004</td>
</tr>
<tr>
<td>MLD 6-month, mm, median (IQR)</td>
<td>2.36 (0.38)</td>
<td>2.69 (0.27)</td>
<td>0.016</td>
</tr>
<tr>
<td>Diameter stenosis 3-month, %, median (IQR)</td>
<td>14.1 (19.2)</td>
<td>8.9 (17.7)</td>
<td>0.124</td>
</tr>
<tr>
<td>Diameter stenosis 6-month, %, median (IQR)</td>
<td>11.4 (4.9)</td>
<td>10.1 (8.2)</td>
<td>0.386</td>
</tr>
<tr>
<td>Late loss 3-month, mm, median (IQR)</td>
<td>0.58 (0.49)</td>
<td>0.11 (0.42)</td>
<td>0.067</td>
</tr>
<tr>
<td>Late loss 6-month, mm, median (IQR)</td>
<td>0.03 (0.23)</td>
<td>0.06 (0.34)</td>
<td>0.677</td>
</tr>
</tbody>
</table>

BMS indicates bare metal stent; BRS, bioresorbable scaffolds; IQR, interquartile range; MLD, minimal luminal diameter; and QCA, quantitative coronary angiography.
In contrast, in the BMS group, in-stent area remained unchanged from poststent to 6 months ($P=0.256$).

The lumen area was significantly lower in the BRS group than that in the BMS group immediately and 1 and 3 months after implantation. However, the value was no longer significantly different at 6 months (Figure 3B). In the BRS group, lumen area increased from poststent to 3 months ($P=0.001$) and from poststent to 6 months ($P<0.0001$). In contrast, in the BMS group, lumen area decreased from poststent to 3 months ($P<0.0001$) and from poststent to 6 months ($P=0.015$).

The increases of the in-scaffold and lumen areas were associated to a vessel enlargement remodeling because total area was higher in the BRS group than that in the BMS group 3 and 6 months after implantation (Figure 3D). In the BRS group, total area increased from poststent to 3 months ($P=0.024$) and from poststent to 6 months ($P<0.0001$). In contrast, in the BMS group, total area remained unchanged from poststent to 3 months ($P=0.895$) and from poststent to 6 months ($P=0.663$).

For both BRS and BMS groups, neointimal hyperplasia remained low during the investigated period and not significantly different at 1 and 6 months (Figure 3C). However, neointimal area was significantly higher in the BRS group than that in the BMS group at 3 months (Figure 3C).

Diameter data are shown in Figures 4A–D and 6A–D. They are consistent with area data. The BRS outer diameter increased from poststent to 3 months ($P<0.0001$) and from poststent to 6 months ($P<0.0001$). In contrast, the BMS inner diameter remained unchanged from poststent to 3 months ($P=0.589$) and from poststent to 6 months ($P=0.159$).

In the BRS group, a negative correlation was found between diameter stenosis and scaffold diameters ($r=-0.66; P=0.015$; Figure 6A) and the total artery diameter ($r=-0.51; P=0.04$; Figure 6B), whereas there was no correlation between diameter stenosis and neointimal hyperplasia thickness ($r=0.39; P=0.24$). In the BMS group, there was no correlation between diameter stenosis and stent diameter ($r=0.23; P=0.41$; Figure 6C) or total artery diameter ($r=0.32; P=0.35$; Figure 6D), whereas there was, as expected, a positive correlation between diameter stenosis and neointimal hyperplasia thickness ($r=0.64; P=0.02$).

Qualitative analysis of BRS OCT images was made according to the classification of Onuma et al\textsuperscript{16} every 1 mm for each strut after 1, 3, and 6 months (Table 3). The evolution reflected a clear modification of the struts of the BRS between 3 and 6 months likely related to polymer degradation (Figure 5).
Polymer Degradation
The initial mass-average molecular weight (Mw) and polydispersity index (I=Mw/Mn) of the BRS polymer were 365,000 g/mol and 1.9, respectively. A decrease of 80% of Mw was found at 3 months and that of 86% at 6 months. These values are in good agreement with in vitro degradation data collected for the initial stereocopolymer (Figure 7). The degradation of macromolecules was well advanced at 3 months with degradation slowing down thereafter because of enrichment in hydrolysis-resistant crystalline residues. The content in crystalline domains of partially degraded lactic acid stereocopolymers is always much lower than in the case of the PLLA homopolymer, the length of the stereoregular segments being dramatically decreased even by 1 or 2% D-units only. Table 4 shows that for BRS the content in water was undetectable before implantation, but it increased rapidly soon after from 0 to 1%, 3.5%, and 6.9% at 1, 3, and 6 months, respectively. In contrast, there was no detectable water absorption for the commercial PLLA.

Discussion
In this study, we aimed to evaluate a new concept of fully bioresorbable scaffold based on early dismantling and respect of the healing process. Indeed, it has been shown that after balloon angioplasty, restenosis is mainly because of constrictive remodeling. Our goal was to prevent this process by scaffolding the arterial wall during a limited time (ie, 3 months) and then to unjail the artery to allow positive remodeling occurring in response to increased flow. Neointimal formation resulted in rapid BRS coverage and was associated with positive remodeling, as shown earlier. Eventually, the scaffold resorption was designed to occur between 18 and 24 months.
The ability of lactic acid-based polymers to degrade has been known for more than 40 years and is well documented in literature. If ultimately, degradation by-products can be bioasimilated or excreted, the early stages of degradation that steer scaffold dismantling depend on a great number of more or less related factors but primarily on the ability of the involved polymer matrix to absorb water. It has been clearly demonstrated that high molecular weight lactic acid stereocopolymers degrade much faster than high molecular weight pure poly(L-) homopolymers, even if the content in D-lactyl units is small.18

Figure 4. Optical coherence tomographic diameter analysis. A–D, Box plot of outer bioresorbable scaffolds (BRS) and inner bare metal stent (BMS; A), luminal (B), neointimal (C), and total (D) diameters in BRS (blue) and BMS (red) groups.

Figure 5. Optical coherence tomographic (OCT) images of bioresorbable scaffolds (BRS). Example of OCT images of the same porcine artery immediately after BRS implantation, and at 3- and 6-month follow-up. White arrows indicate struts of the BRS. Note BRS enlargement at 3 and 6 months, and BRS dismantling at 6 months.
Both BRS and BMS were successfully introduced in the tested arteries and deployed with similar, low acute recoil. This is a mandatory and essential feature because it was one of the major drawbacks of biodegradable scaffolds and source of in-stent restenosis.20–22 Rapid degradation was demonstrated after coherent in vitro and in vivo molar mass decreases provided by SEC (Figure 7), and imagings were obtained by OCT and μCT (Figures 5 and 8). The latter technique conclusively showed that the dismantling subsequent to polymer degradation and weakening of the strut matrix was effective after 3 months and was in the 3-month period presently admitted as suitable range. This feature represents the major difference with the other biodegradable stents.

In parallel to the advancing degradation, the neointimal formation resulted in rapid BRS coverage as previously described.9 LLL was the first indicator used to monitor the fate of the scaffolds throughout the healing phase. A 6-month experiment period was selected for the comparison of the BRS and BMS because the scaffold degradation was expected to be well advanced at the end of the period according to preliminary data in rabbits.9 Contrary to what was observed for BMS, the BRS lumen loss decreased between 1 and 6 months. Resulting late lumen gain has already been described in other studies but with occurrence at 1 or to 2 years after deployment.23 The source of early lumen recovery in the scaffold case was definitely because of the polymer degradation and scaffold dismantling as visually shown by OCT and μCT, respectively.

Interestingly, the neointimal formation was maximal at 3 months in scaffolded arteries before decrease between 3 and 6 months, a feature that suggested near complete healing phase. Neointimal formation was slightly greater for the scaffolded arteries probably because they were thicker than the BMS.

At this point, it is important to emphasize the fundamental difference between scaffold degradation and biodegradation.
Scaffold degradation is necessary and must occur, whereas the tissue healing process is still active and dependent on blood flow pulsation and artery contractility. Therefore, it was essential to shorten the PLLA lifetime and allow remodeling under natural physiological conditions (ie, free of scaffolding effect). This was performed by selecting a specific lactic acid stereocopolymer after preliminary prospection.9 Bioresorption is a secondary function only aimed to eliminate the residual foreign material. It occurs at the later stages of the degradation when polymer chains have been sufficiently cleaved to generate polymer chain shortened enough to become soluble in physiological fluids or if the polymer is completely hydrolyzed in lactic acid.

The rapid molecular weight decrease observed for the 3-month BRS cohort was sufficient to induce early dismantling and release of arteries from scaffold caging effects. This release was essential for lumen enlargement.

As well documented in literature, the rather fast degradation exhibited by the studied BRS compared with Abbott’s BVS for instance was because of the relatively high content in amorphous domains (c.a. 80%) and also because the stereocopolymer-based precursor was made by ring opening polymerization of the lactide mixtures using zinc lactate. Indeed, zinc lactate leaves a lactyl unit at chain end, whereas other initiators and catalysts can leave more or less hydrophobic elements either attached to chain ends or as embedded small molecules because it is the case for tin octoate with the alcohols used to limit molar masses of some PLLA.

Data collected from the BRS-BMS comparison suggested that scaffolding limited to a couple of months allowed wall positive remodeling. Accordingly the healing phase associated with neointimal formation should not be inhibited because we previously showed that neointimal formation is associated with positive remodeling after balloon angioplasty.24 Allowing neointima formation constitutes a complete change concerning the strategy proposed for the past 10 years, that is, targeting the neointimal formation using antiproliferative drugs. In other words, neointima is no more an enemy. It could be actually an ally to promote positive remodeling. Before dismantling, BRS struts embedded within the neointima act as a kind of composite material that contribute to the local mechanical balance. The effect is likely to be sustained by the partial dismantled BRS. The fact that, for the BRS, the lumen diameter increased with the weakening of the scaffolding function suggests that 3-month preservation of the struts should be enough to help the healing of damaged artery wall including in human. Dismantling means that the respect of the healing phase, that is, the neointimal formation, confirms the timing of the stent scaffolding.

This head-to-head study confirmed the positive effect of the rapid degradation and early dismantling related to the particular stereocomposition of the BRS on the LLL, scaffold diameter, and neointimal thickness compared with a metallic reference stent.

### Conclusions

This study showed that a lactic acid–based drug-free BRS behaved like the reference BMS in terms of scaffolding function but differently in terms of healing because it exhibited dismantling 3 months postimplantation, a feature that promoted positive remodeling when BMS did not. This

### Table 4. Crystallinity and Time-Dependent Water Absorption for ART Specific PLA Compared With Commercial PLLA

<table>
<thead>
<tr>
<th>Polymer</th>
<th>Feed Composition</th>
<th>Initiator</th>
<th>Crystallinity (%)</th>
<th>Day 0</th>
<th>Day 30</th>
<th>Day 60</th>
<th>Day 90</th>
</tr>
</thead>
<tbody>
<tr>
<td>Commercial PLLA</td>
<td>100% L-Lactide</td>
<td>Tin octoate</td>
<td>52</td>
<td>0</td>
<td>0.5</td>
<td>0.6</td>
<td>0.5</td>
</tr>
<tr>
<td>ART-specific PLA</td>
<td>98% L-Lactide 2% D-Lactide</td>
<td>Zinc lactate</td>
<td>22</td>
<td>0</td>
<td>1</td>
<td>3.5</td>
<td>6.9</td>
</tr>
</tbody>
</table>

ART indicates Arterial Remodeling Technologies; PLA, polylactic acid; and PLLA, poly-L lactic acid.
conclusion was based on coherent data on the fate of the polymeric matrix of the BRS and on the evolution of the artery itself by QCA and images issued from complementary techniques such as OCT and µCT. OCT and QCA analyses of the BRS indicated favorable 6-month outcome as compared with BMS. The BRS presented early positive remodeling resulting in late lumen gain and increased BRS area at 6 months.

Limitations

The findings reported in this article were obtained using a porcine model. Extrapolation of the suitability of drug-free degradable scaffolding to the case of damaged arteries is still premature and is possible when the results of a human trial under way are available.

Sources of Funding

The study was funded by the start-up Arterial Remodeling Technologies (ART, Noisy le Roi, France).

Disclosures

Drs Lafont and Vert are cofounders of ART, M. van der Leest is CEO of ART, and Dr Sharkawi has received honoraria from ART. Other authors report no conflict of interest.

References

Head-to-Head Comparison of a Drug-Free Early Programmed Dismantling Polylactic Acid Biodegradable Scaffold and a Metallic Stent in the Porcine Coronary Artery: Six-Month Angiography and Optical Coherence Tomographic Follow-up Study
Eric Durand, Tahmer Sharkawi, Guy Leclerc, Marine Raveleau, Machiel van der Leest, Michel Vert and Antoine Lafont

Circ Cardiovasc Interv. published online December 24, 2013;
Circulation: Cardiovascular Interventions is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7640. Online ISSN: 1941-7632

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circinterventions.ahajournals.org/content/early/2013/12/23/CIRCINTERVENTIONS.113.000738

Data Supplement (unedited) at:
http://circinterventions.ahajournals.org/content/suppl/2013/12/24/CIRCINTERVENTIONS.113.000738.DC1

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Interventions can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Interventions is online at:
http://circinterventions.ahajournals.org//subscriptions/
Supplemental Methods

Angiographic analysis

- Reference vessel diameter (RVD), is a calculation of the reference diameter at the position of the obstruction (measurement obtained by a software-based iterative linear regression technique to generate an interpolation of a projected vessel without the lesion)

- Mean lumen diameter of the stented region (balloon, post-stent and final angiography) or corresponding artery region (pre-stent angiography)

- Minimal lumen diameter (MLD) of the stented region (post-stent and final angiography) or corresponding artery region (pre-stent angiography)

- Balloon-to-artery ratio (balloon/pre-stent mean luminal diameter)

- Stent-to-artery ratio (post-stent/pre-stent mean luminal diameter)

- Acute recoil ([balloon mean diameter - post-stent mean luminal diameter]/balloon mean diameter) x 100%

- Late lumen loss (post-stent MLD - MLD at follow-up or final angiogram)

- Diameter stenosis (1 – [MLD/RVD]) x 100% at follow-up or final angiogram).

Optical coherence tomography (OCT) analysis

The struts sites were categorized according to the 4 morphological categories, as previously described (#1, #2).
The first subset (preserved box) corresponded to box appearance with sharply defined borders with bright reflection, and the strut body showing low reflection. The second subset was characterized as an open box (ie, luminal and abluminal “long-axis” borders thickened with bright reflection and short-axis borders no longer visible at follow-up). The third subset was categorized as a dissolved bright box (ie, partially visible bright spot with poorly defined contours and no box-shaped appearance). The fourth subset was a dissolved black box (ie, black spot with poorly defined contours, often confluent but with no box-shaped appearance).

Quantitative area and diameter measurements included the BMS/BRS and lumen area. Using IPLabs software, the lumen area was traced and additional manual corrections were made when necessary. The inner and the outer diameters of the BRS were drawn. For BMS, the inner stent was drawn at the center of the strut blooming thickness while the outer stent was not measured because of shadow artifact from metal struts. The mean neointimal thickness was calculated by software based on the lumen area and inner stent/scaffold area. Uncovered struts were identified when the distance between the luminal surface and inner aspect of the strut was 0 µm. The neointimal area was estimated as BMS/BRS area minus lumen area. Finally, total vessel area and diameter were measured at the external elastic lamina level in the stented/scaffolded and the reference segments. All values were averaged per BMS/BRS.

**Micro-Computed Tomography (µCT)**

Fixed BRS were scanned using a Skyscan 1172 µCT model. Scan settings were first set-up using one BRS. After determination of appropriate settings, 7 BRS
of the 3-month cohort and 4 BRS of the 6-month Cohort subset 1 were scanned. Arteries were gradually immersed in ethanol, up to a concentration of at least 70%, and then imaged with µCT. The long axis of the scaffold was aligned perpendicularly to the axis of the X-ray beam. Constant settings for X-ray energy and image capture were kept for the whole study length. Projection images obtained were processed with the NRecon image reconstruction software using a convolution and back projection algorithm to produce a stack of 8 bits BMP images, each one of them representing a slice of the sample. Reconstruction images were analyzed with the Skyscan CTAn software using a series algorithms plug-ins to achieve morphometric measurements. Finally, a full 3D image was generated for visualization of the BRS.
Supplemental References