Angioplasty

Serial Observation of Drug-Eluting Absorbable Metal Scaffold
Multi-Imaging Modality Assessment

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Background—The drug-eluting absorbable metal scaffold has demonstrated feasibility, safety, and promising clinical and angiographic outcomes at 12 months in human coronary arteries. This study aimed to evaluate the degradation rate and long-term vascular responses to drug-eluting absorbable metal scaffold.

Methods and Results—BIOSOLVE-I was a multicenter, single-arm, first-in-man trial assessing the safety and performance of drug-eluting absorbable metal scaffold in 46 patients with coronary artery disease. Patients who underwent serial invasive imaging, such as quantitative coronary angiography, intravascular ultrasound, and optical coherence tomography, at 6 and 12 months were included in this study. From postimplantation to follow-up, arterial curvature and angulation were significantly increased by the degradation process. The greatest increase was seen from postimplantation to 6 months. The systolic–diastolic changes of the curvature and angulation gradually improved throughout the follow-up period. At the site of implantation, vasoconstriction (~10% mean reduction) was observed during the acetylcholine test at 6 months. The average percent hyperechogenicity of the scaffolded segments showed a continuous decrease over time, with the most pronounced changes within the first 6 months (from 22.1±7.0% to 15.8±3.7%; P<0.001). Struts discernible on optical coherence tomography at 6 and 12 months showed full neointimal coverage, with stabilization of the mean scaffold area from 6 to 12 months. Furthermore, the mean neointimal area (1.55±0.51 versus 1.58±0.34 mm²; P=0.794) remained unchanged from 6 to 12 months.

Conclusions—This serial analysis of drug-eluting absorbable metal scaffold confirmed the safety and efficacy of this new device, with vasomotion restoration and continued degradation over time demonstrated by multi-invasive imaging modalities.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT01168830.


Key Words: bioabsorbable magnesium scaffold ◼ coronary geometry ◼ echogenicity ◼ neointima ◼ vasomotion

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WHAT IS KNOWN
• The poly-L-lactic acid–based bioabsorbable scaffold has demonstrated clinical efficacy with an acceptable safety profile.
• Clinical event rates seen with the magnesium–based scaffold coated with a bioabsorbable polymer and paclitaxel are comparable to those seen with the poly-L-lactic acid bioabsorbable scaffold.

WHAT THE STUDY ADDS
• Degradation of the magnesium–based scaffold influences angiographic vascular geometry and vascular remodeling.
• Optical coherence tomography is a valuable imaging modality to demonstrate a decrease in the stent scaffold area and an increase in neointima coverage between 6 and 12 months.
• Degradation of the magnesium–based scaffold resulted in a vascular reactivity response to acetylcholine and nitroglycerine that was similar to nonscaffolded segments of the vessel at 6 and 12 months.

The study design, clinical outcomes at 12 months, and initial results of quantitative coronary angiography, intravascular ultrasound (IVUS), and optical coherence tomographic (OCT) analyses have recently been reported.7 The present study reports the subanalysis results of serial imaging assessment after DREAMS implantation. The study was approved by an institutional review committee, and the subjects gave informed consent.

Methods
Study Population
BIOSOLVE-I is a single-arm trial that included 46 patients with 47 lesions treated with DREAMS. The study design, clinical outcomes at 12 months, and initial results of quantitative coronary angiography, intravascular ultrasound (IVUS), and optical coherence tomographic (OCT) analyses have recently been reported.7 The present study reports the subanalysis results of serial imaging assessment after DREAMS implantation. The study was approved by an institutional review committee, and the subjects gave informed consent.

Study Device
DREAMS is made of a magnesium alloy, coated with a 1-µm matrix of the absorbable polymer carrier poly(lactic-co-glycolic) acid and the antiproliferative drug paclitaxel (0.07 µg/mm²). The details of the device have been described previously.7

Study Procedure
Target lesions were scaffolded (3.25 or 3.5 mm in diameter and 16 mm in length) after mandatory predilation. Postdilation with a noncompliant balloon was left to the operator’s discretion in case of incomplete expansion of the scaffold or residual stenosis. After the procedure, patients were recommended, per protocol, to receive ≥75 mg aspirin daily indefinitely and 75 mg clopidogrel daily (or alternatively 500 mg ticlopidine or 5–10 mg prasugrel) for ≥12 months.

Quantitative Coronary Angiographic Analysis of Vessel Geometric Parameters
Operators were requested to select an angiographic view with minimal foreshortening of the lesion and limited overlap with other arteries, with matching projections at baseline (before and after implantation) and follow-up.

Vessel geometric parameters were assessed as curvature and angulation of the in-scaffold segment. Both parameters were analyzed by an independent core laboratory (MedStar Cardiovascular Research Network, Washington, DC). Curvature and angulation were measured before and after implantation and at follow-up with the same angiographic views (maximum difference of 10°) using the CAAS analysis system (CAAS 5.9 research version; Pie Medical Imaging BV, Maastricht, The Netherlands).8 In brief, curvature is defined as the infinitesimal rate of change in the tangent vector at each point of the centerline. The software automatically detects the lumen contours of the selected segment and configures the centerline. A perfect circle was fitted through the centerline of the vessel, calculating the radius of the circle. The curvature value is calculated as 1/radius of the circle in cm−1. Angulation is defined as the angle in degrees that the tip of an intracoronary guidewire would need to reach the distal part of a coronary bend. The cardiac contraction–induced cyclic changes in vessel curvature and angulation were estimated as absolute differences between curvature/angle at the end diastole and curvature/angle at the end systole. End-diastolic curvature/angulation was assessed in the still angiographic view corresponding to the peak of the QRS complex of the ECG, and end-systolic curvature/angulation was assessed in the still angiographic view corresponding to the peak of the T wave of the ECG. Relative differences between before and after implantation and follow-up were also estimated at the end diastole. Because intracoronary guidewires straighten the coronary arteries, all lesions without any angiographic view (before and after implantation and at follow-up) without the intracoronary wire were excluded.9

Vasomotion Test
Vasomotion in the scaffolded vessel segment was tested in a subgroup of patients at 6- and 12-month follow-up. All antiangiinal agents that influence vasomotor tone, including long-acting nitrates, calcium channel blockers, and β-blockers, were withheld for 48 hours before coronary angiography save for sublingual nitroglycerin as needed. The test was performed after IVUS and OCT assessment. The endothelium-dependent vasoreactive agent acetylcholine (Miochol, Ciba Vision, Basel, Switzerland) was administered in incremental doses of 0.36, 3.6, and 18 µg/mL. Vasomotion was assessed by measuring changes in mean lumen diameter in the scaffolded segment and in the 5-mm proximal and 5-mm distal adjacent segments by quantitative coronary angiography after intracoronary infusion of acetylcholine at different concentrations and finally after bolus injection of 200 µg nitroglycerin.10 Vasomotion analysis was conducted by an independent angiographic core laboratory (Medstar Cardiovascular Research Network, Washington, DC).

IVUS Echogenicity Analysis
IVUS was performed before and after implantation and at 6-, 12-, and 18-month follow-up. A 45-MHz rotational imaging catheter
(Revolution; Volcano Rancho Cordova, CA), a 20-MHz imaging catheter (Eagle Eye Gold; Volcano Rancho Cordova, CA), or a mechanical rotating element 40-MHz transducer (Atlantis; Boston Scientific, Natick, MA) was used in the BIOSOLVE-I trial. To analyze and compare the IVUS data consistently, however, IVUS images were acquired with the same type of catheter and ultrasound consoles at baseline and follow-up. The speed of an automated pullback was 0.5 mm/s.

The IVUS data were retrospectively ECG-gated by the previously validated Intelligate method before quantitative IVUS echogenicity analysis was performed. This method selects fully automatic near end-diastolic IVUS cross-sectional images from nongated acquired IVUS studies. This process allows for a smoother appearance of the coronary vessel wall, which results in accurate matching between baseline and follow-up studies, longitudinal contouring, and finally echogenicity analysis. Of note is that low frame rates, <10 frames/s instead of the optimal setting of 30 frames/s, do not allow accurate detection of near end-diastolic acquired frames.

The pre- and postprocedural and follow-up IVUS images were analyzed side by side comparing the matched segments, as previously described. The scaffolded segments, identified by the scaffolds themselves when visible and with the help of anatomic landmarks in case the scaffold was not visible (eg, by preimplantation), were analyzed. The lumen, scaffold, and external elastic membrane contours were detected using previously validated IVUS analysis software (CURAD Vessel Analysis, Curad BV, Wijk bij Duurstede, The Netherlands) in longitudinal reconstructed views of the coronary vessels. Fully automated quantitative echogenicity analysis software, previously developed in-house and validated, was used to quantify the hyperechogenicity changes in the scaffolded segment, as previously applied in the ABSORB trials and the Igaki-Tamai study. In brief, the mean gray value of the adventitia tissue is used to classify tissue components as either hypo- or hyperechogenic. The adventitia

Table 1. Coronary Geometric Changes at Baseline and Follow-up

<table>
<thead>
<tr>
<th></th>
<th>Preimplantation (n=38)</th>
<th>Postimplantation (n=38)</th>
<th>6 mo (n=25)</th>
<th>12 mo (n=25)</th>
<th>Relative Change Post-Pre, %</th>
<th>p 1</th>
<th>Relative Change (6 mo-Post) %</th>
<th>p 2</th>
<th>Relative Change (12 mo-6 mo %)</th>
<th>p 3</th>
<th>Relative Change (12 mo-Pre %)</th>
<th>p 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Curvature, cm⁻¹</td>
<td>0.414</td>
<td>0.309</td>
<td>0.453</td>
<td>0.409</td>
<td>−32.1 &lt;0.0001</td>
<td>39.0 &lt;0.0001</td>
<td>7.5 0.56</td>
<td>2.7 0.97</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic changes in curvature, cm⁻¹</td>
<td>0.133</td>
<td>0.084</td>
<td>0.097</td>
<td>0.108</td>
<td>−31.5 0.0024</td>
<td>5.1 0.63</td>
<td>19.5 0.25</td>
<td>−13.8 0.22</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Angle, °</td>
<td>40.21</td>
<td>22.38</td>
<td>33.44</td>
<td>43.41</td>
<td>−40.5 &lt;0.0001</td>
<td>38.2 &lt;0.0001</td>
<td>2.6 0.60</td>
<td>−7.4 0.0264</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cyclic changes in angle, °</td>
<td>7.62</td>
<td>4.53</td>
<td>4.16</td>
<td>6.37</td>
<td>−35.6 0.0114</td>
<td>−14.8 0.95</td>
<td>24.2 0.12</td>
<td>−19.6 0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values presented are median and interquartile range. p1 indicates paired comparison between pre- and postimplantation; p2, paired comparison between postimplantation and 6-mo follow-up; p3, paired comparison between 6- and 12-mo follow-up; and p4, paired comparison between preimplantation and 12-mo follow-up.

Figure 1. Geometric changes in curvature and angulation in a patient treated with drug-eluting absorbable metal scaffold (DREAMS) and followed at both 6 and 12 months. This patient had a significant stenotic lesion in the mid left circumflex artery. Curvature and angulation significantly decreased from pre- to post-drug-eluting absorbable metal scaffold (DREAMS) implantation. From postimplantation to 6 months’ follow-up, the patient presented with a large increase in curvature and angulation. Between 6 and 12 months, the patient demonstrated similar values of curvature and angulation. Bottom, Corresponding 3-dimensional (3D) quantitative coronary angiographic images at each time point. Maximum bending angle in the scaffolded segment was significantly reduced from pre- to post-DREAMS implantation. At follow-up, DREAMS showed a large increase in bending angle, with similar values seen from 6 to 12 months.
circumventing the coronary artery is defined as a layer extending from 0.2 to 0.5 mm outside of the external elastic membrane. To avoid artifacts, tissue within acoustic shadowed areas is excluded. After the tissue identification process, the relative fraction of hypo- versus hyperechogenic tissue volumes is calculated for the scaffolded segment. At the various follow-up time points, echogenicity was calculated between the lumen and the external elastic membrane contours. The echogenicity software calculates the relative fraction of hypo- and hyperechogenic tissue components (together set to be 100%).

OCT Analysis

Intracoronary OCT imaging after implantation and at follow-up was performed using a frequency domain system (C7XR; LightLab Imaging, Westford, MA) at 100 frames/s and a pullback speed of 20 mm/s. Frequency-domain OCT images were calibrated with adjustment for the Z-offset before image acquisition to obtain accurate measurements. OCT images were digitally recorded and independently analyzed by a validated core laboratory (Rome Heart Research, Rome, Italy), and proprietary software for offline analysis was used (Saint Jude Console, Westford, MA). Analyses were performed at each 0.20 mm longitudinal interval in the scaffolded segment. Using landmarks such as side branches, calcium deposits, or luminal areas with particular shapes, all OCT images were matched correctly along the whole scaffold length between baseline and follow-up.

To depict the degradation process for any strut and to specify whether strut components can be visualized at different time points, scaffold struts were evaluated postimplantation and at 6 and 12 months by visual inspection. Lumen and scaffold areas were measured for each cross section. Neointimal area was estimated as scaffold area minus lumen area. The percentage neointimal area was calculated as follows: neointimal area/scaffold area×100 (%). Coverage thickness was measured for every strut if discernible between the endoluminal side of the strut and the lumen. Struts without distinct overlying tissue were defined as uncovered.16

Statistical Analysis

The Kolmogorov–Smirnov test was used to verify the distribution normality of the variables. Continuous variables were expressed as mean±SD or median with interquartile range according to their distribution. Paired comparisons of continuous variables between different time points were estimated by a paired t test or the Wilcoxon test, as appropriate. Nonserial data were compared by applying the Mann–Whitney test.

Values of P<0.05 were considered statistically significant. Statistical analyses were performed using the SAS version 9.1 (SAS Institute, Cary, NC) or SPSS version 16.0 software (SPSS Inc, Chicago, IL).

Results

Quantitative Coronary Angiographic Analysis of Coronary Geometry

In the BIOSOLVE-I study, 46 patients were consecutively assigned to angiographic follow-up at 6 or 12 months as follows: 22 patients in the 6-month group were assigned to mandatory angiography at 6 months and to voluntary angiography at 6 and 12 months by visual inspection. Lumen and scaffold areas were measured for each cross section. Neointimal area was estimated as scaffold area minus lumen area. The percentage neointimal area was calculated as follows: neointimal area/scaffold area×100 (%). Coverage thickness was measured for every strut if discernible between the endoluminal side of the strut and the lumen. Struts without distinct overlying tissue were defined as uncovered.16

Figure 2. Geometric changes in curvature and angulation in patients with serial follow-up. Individual changes in artery curvature and angulation in patients with both 6- and 12-month angiographic follow-up (FU; n=16) are shown. The thick line represents the median value. *P=comparison of the relative differences from postimplantation to 6 months’ FU and 6 to 12 months’ FU.

Figure 3. Vasomotion test results at 6 (n=26) and 12 months (n=18). Acetylcholine (ACH): presents the % change in mean lumen diameter between pre- and post-ACH. Nitroglycerin (NTG): presents the % change in mean lumen diameter between post-ACH and NTG. FU indicates follow-up.
assigned to mandatory angiography at 12 months and to voluntary angiography at 6 months. At follow-up, 2 patients from the 6-month group and 4 patients from the 12-month group withdrew from follow-up angiogram. As a result, 36 (20 mandatory and 16 voluntary) of 46 patients underwent coronary angiography at 6-month follow-up and 33 (20 mandatory and 13 voluntary) at 12-month follow-up. Of the original 46 patients, 8 patients were excluded as a result of different angiographic views between pre- and poststent implantation and the presence of intracoronary wire. Thus, a total of 38 patients were available for the baseline (pre- and postimplantation) analysis (Table 1). After excluding an additional 11 patients at 6 months and 8 patients at 12 months as a result of different angiographic views between baseline and follow-up or target lesion revascularization, the study cohort available for analysis consisted of 25 patients with qualifying 6-month angiographic follow-up and 25 patients with qualifying 12-month angiographic follow-up. Of these, only 16 patients had complete serial angiographic follow-up (baseline, 6- and 12-month follow-up) with the same orthogonal views.

Angiographic findings related to coronary geometry are summarized in Table 1. Median values of curvature and angulation before implantation were 0.414 cm\(^{-1}\) and 40.2\(^°\), respectively. Cyclic changes in curvature and angulation were 0.133 cm\(^{-1}\) and 7.6\(^°\), respectively. From pre- to postimplantation, both curvature (32.1\% reduction; \(P<0.0001\)) and angulation (40.5\% reduction; \(P<0.0001\)) decreased significantly. Cyclic changes in curvature (31.5\% reduction; \(P=0.0024\)) and angulation (35.6\% reduction; \(P=0.0114\)) also decreased significantly.

From postimplantation to 6-month follow-up, the curvature showed a 39.0\% increase and the angulation showed a 38.2\% increase (\(P<0.0001\) for both), whereas the cyclic changes in curvature and angulation observed at 6 months were similar to those observed after implantation, with no statistical differences (\(P=0.63\) for curvature and \(P=0.95\) for angulation). From 6- to 12-month follow-up, DREAMS presented with a small increase in curvature (7.5\% increase; \(P=0.56\)) and angulation (2.6\% increase; \(P=0.60\)). The cyclic changes in coronary curvature and angulation showed an increase of 19.5\% and 24.2\%, but they did not reach statistical significance (\(P=0.25\) for curvature and \(P=0.12\) for angulation).

From preimplantation to 12-month follow-up, DREAMS demonstrated a similar value in artery curvature but a significant reduction in angulation of 7.4\% (\(P=0.0264\)). DREAMS experienced fewer systo-diastolic changes in curvature (13.8\% reduction; \(P=0.22\)) and angulation (19.6\% reduction; \(P=0.25\)) than the relative changes in those from pre- to postimplantation. A representative case is shown in Figure 1. Figure 2 shows the individual data of 16 patients with both 6- and 12-month angiographic follow-up. Curvature (63.3\% versus 7.5%; \(P=0.0027\)) and angulation (40.3\% versus 2.6%; \(P<0.0001\)) between postimplantation and 6-month follow-up had greater changes compared with those between 6- and 12-month follow-up.

**Vasomotion**

Vasomotion tests were performed in 26 patients at 6 months and in 18 patients at 12 months. Serial vasomotion tests were available in 13 patients. As shown in Figure 3, the treated segment showed changes in the mean lumen diameter similar to those in the proximal and distal adjacent segments after acetylcholine and nitroglycerin at 6 months. These observations in the scaffolded segments at 6 months did not demonstrate significant further changes at 12-month follow-up (Figures 3 and 4).

**Quantitative Echogenicity Analysis**

Immediate postimplantation IVUS examinations suitable for echogenicity analyses were available in 38 patients: 19 at 6 months', 15 at 12 months', and 4 at 18 months' follow-up. Several examinations could not be analyzed because of use of another catheter and ultrasound catheter combination, which cannot be mixed for this kind of analysis. In addition, several cases were recorded with a frame rate of <10 frames/s, which makes retrospective gating impossible.

![Figure 4. Serial change in vasomotion in the scaffolded segment from 6 to 12 months (n=13). Individual changes in mean lumen diameter of the scaffolded segment during acetylcholine test and intracoronary nitroglycerin. Acetylcholine (ACH): presents the % change in mean lumen diameter between pre- and post-ACH. Nitroglycerin (NTG): presents the % change in mean lumen diameter between post-ACH and NTG. FU indicates follow-up.](Image)

![Figure 5. Intravascular ultrasound echogenicity gray-scale images and with echogenicity overlay at postimplantation and 6- and 12-month follow-up (FU). The stent struts appear as bright white spots on the gray-scale images (top), which are identified as hyperechogenic tissue, and as green onto the color overlay (bottom). The diminished appearance over time can be clearly appreciated.](Image)
Magnesium struts appeared as hyperechogenic spots within the scaffolded area; yet, unlike areas of severe calcification, they did not cause acoustic shadowing. Their appearance seems to be close to that of normal permanent metallic implanted stents (Figure 5), at least at postimplantation. The implantation of DREAMS significantly increased the % hyperechogenic tissue in the scaffolded segments (Table 2), at least at postimplantation. The implantation of DREAMS significantly increased the % hyperechogenic tissue in the scaffolded segments (Table 2, Figure 6). The average percent hyperechogenicity of the scaffolded segments showed a continuous decrease throughout the follow-up period, with the most pronounced changes within the first 6 months (Figure 6).

Analysis of patients for whom IVUS was available at all time points (n=10, true serial analysis) showed a significant decrease in percent hyperechogenicity between postimplantation, 6-month follow-up, and 12-month follow-up (P<0.001, P=0.001, and P=0.009, respectively; Table 3).

At 18 months, the analysis, although limited to only 4 data sets, showed a further, albeit small, decrease in percent hyperechogenicity in the area between the lumen and the external elastic membrane; this was not significant compared with the 12-month analyses. Comparison of the area between the lumen and the outer scaffold at the 12- and 18-month time points showed no change in percent hyperechogenicity.

**OCT Analysis**

Because OCT was not available at all centers during the index procedure, serial analysis was performed in only 7 patients (Table 4). Discernible struts of DREAMS decreased over time, especially from 6 to 12 months. The mean scaffold area significantly decreased from 7.94±1.29 mm² postprocedure to 6.79±1.51 mm² at 6 months (P=0.0058), whereas it did not change significantly from 6 to 12 months (6.79±1.51 versus 6.49±1.52 mm²; P=0.21). The serial analysis of the mean lumen area showed a progressive decrease from 7.90±1.24 mm² postprocedure to 5.70±0.99 and 5.34±1.14 mm² at 6 and 12 months, respectively, with small differences seen from 6 to 12 months. The mean neointimal area (1.55±0.51 versus 1.58±0.34 mm²; P=0.79) and maximum neointimal thickness (0.32±0.05 versus 0.30±0.04 mm; P=0.20) remained comparable from 6 to 12 months. Furthermore, to evaluate strut coverage, we analyzed 15,584 struts of 27 scaffolds at 6 months and 11,311 struts of 21 scaffolds at 12 months. All struts evaluated at 6 and 12 months after implantation were completely covered by neointima. Representative OCT images in the same cross-section level at baseline and at follow-up are shown in Figures 7 and 8.

**Coronary Geometry**

A temporary metallic scaffold is attractive because of an acute result that is similar to a conventional metallic stent. However, coronary stenting has previously been shown to modify coronary geometry, such as curvature and angulation, from pre- to postimplantation. From postimplantation to follow-up, DREAMS significantly increased the artery curvature and angulation, with a slower increase from 6 to 12 months. The systo-diastolic changes in curvature and angulation gradually improved during the follow-up period.

The vasomotion test with intracoronary acetylcholine showed vasoconstriction of the scaffolded segment at 6 months, suggesting restoration of vasomotor tone. On IVUS, DREAMS demonstrated a significant reduction in hyperechogenicity over time, particularly during the first 6 months of follow-up.

Serial OCT analysis confirmed the stabilization of the mean scaffold area from 6 to 12 months. The neointimal area on OCT remained comparable from 6 to 12 months. At 6 months, all the struts were covered. Although the struts were still discernible on OCT at 12 months, the number of discernible struts significantly decreased over time, reflecting bioabsorption of the struts.

**Discussion**

The major findings of the present study support DREAMS degradation at 6 and 12 months by multi-imaging modalities as follows: On quantitative coronary angiographic analysis of coronary geometry, DREAMS decreased the vessel curvature, angulation, and their cyclic changes from pre- to postimplantation. From postimplantation to follow-up, DREAMS significantly increased the artery curvature and angulation, with a slower increase from 6 to 12 months. The systo-diastolic changes in curvature and angulation gradually improved during the follow-up period.

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**Table 2. Echogenicity Analysis After DREAMS Implantation, 6, 12, and 18 Months**

<table>
<thead>
<tr>
<th>% Hyperechogenicity</th>
<th>Preimplantation (n=9)</th>
<th>Postimplantation (n=38)</th>
<th>6 mo (n=19)</th>
<th>12 mo (n=15)</th>
<th>18 mo (n=4)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen stent, %</td>
<td>32.1±5.3</td>
<td>19.1±3.7</td>
<td>15.8±3.9</td>
<td>15.8±3.1</td>
<td></td>
</tr>
<tr>
<td>Lumen media, %</td>
<td>9.2±5.0</td>
<td>22.1±7.0</td>
<td>15.8±3.7</td>
<td>12.9±3.3</td>
<td>11.6±4.3</td>
</tr>
<tr>
<td>Media stent, %</td>
<td>17.4±9</td>
<td>14.4±5.5</td>
<td>11.6±4.4</td>
<td>9.9±5.5</td>
<td></td>
</tr>
<tr>
<td>Lumen stent, mm²</td>
<td>18.0±6.2</td>
<td>12.2±3.2</td>
<td>8.5±2.8</td>
<td>7.8±1.6</td>
<td></td>
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</table>

DREAMS indicates drug-eluting absorbable metal scaffold.
to follow-up in metallic scaffold segments. From pre- to postimplantation, both curvature (32.1% reduction) and angulation (40.5% reduction), which are similar to those observed in the metallic platform EES (21.9% reduction for curvature and 31.8% reduction for angulation),9 decreased significantly. However, the differences in these values are somewhat high. This may be explained, in part, by the difference in the strut thickness between DREAMS (120 µm) and EES (81 µm). Another explanation might be that the curvature and angulation before implantation were greater in our study than in the previous study.

The cyclic changes in curvature (31.5% reduction) and angulation (35.6% reduction) also decreased significantly from pre- to postimplantation. Notably, these values were consistent with those observed in the BVS 1.1 (23.1% reduction for curvature and 29.6% reduction for angulation).8 From postimplantation to follow-up, DREAMS significantly increased the artery curvature and angulation, with the greatest increase seen from postimplantation to 6 months. Thus, bioabsorption of DREAMS over time potentially allows the restoration of coronary artery to its original coronary anatomic configuration seen before implantation, with the most pronounced changes from postimplantation to 6 months of follow-up. Furthermore, the conformability of DREAMS could minimize disturbed flow patterns after implantation; returning to the original geometry of the vessel curvature may attenuate the stent-induced adverse changes in the endothelial shear stress that can be associated with a possible increase in neointima formation.

Vasomotion
Acetylcholine was used as a vasomotor drug. Vasoconstriction has been defined as a ≥3% change in the mean vessel diameter between baseline and vasomotor tone, measured after the infusion of the maximum acetylcholine dosage.10 In this series, vasoconstriction of the scaffolded segment was already observed at 6 months (−10±20.3%), without further changes at 12-month follow-up. This suggests that the return of coronary vasoreactivity might be achieved 6 months after DREAMS implantation. Although vasomotion has been demonstrated with the poly-l-lactic acid–based scaffold, it was at 12 months only.5 Because it has been demonstrated that coronary endothelial dysfunction predicts adverse cardiovascular events,18 DREAMS may present an advantage because of the earlier restoration of the vasomotor functions compared with the poly-l-lactic acid scaffold.

Metal Absorption by IVUS and OCT
One of the challenges evaluating bioabsorbable scaffolds is the measurement of degradation/absorption of the scaffold material in human coronary arteries. Imaging possibilities available preclinically, such as histology micro-computed tomography and measurements at the bench of radial strength and mass loss, are impossible in the clinical catheterization laboratory setting. Currently, angiography, IVUS, and IVUS-derived methods, such as virtual histology IVUS (VH-IVUS), echogenicity, and OCT, are available. Visual assessment of the IVUS images over time shows that for different bioabsorbable scaffolds, their ultrasound appearance changes (ie, they become less visible). At first, they show up after implantation as bright spots whose effects diminish over time. This effect can be measured and quantified for whichever 2 methods have been applied (eg, differential quantitative echogenicity and VH-IVUS).13,19–21

The results of the DREAMS serial VH-IVUS analysis have been previously reported.7 In brief, serial VH-IVUS analysis showed a significant decrease in dense calcium at 6 and 12 months compared with postprocedure (15.4% reduction between 6 months and after procedure, P=0.0015; 12.9% reduction between 12 months and after procedure, P=0.0029), with no significant changes in necrotic core over time. VH-IVUS was also used in the ABSORB study. Serruys et al

Table 3. Serial Echogenicity Analysis Postimplantation and at 6- and 12-Month Follow-up (n=10)

<table>
<thead>
<tr>
<th>% Hyperechogenicity</th>
<th>Postimplantation</th>
<th>6 mo</th>
<th>12 mo</th>
<th>P Value (Post vs 6 mo)</th>
<th>P Value (Post vs 12 mo)</th>
<th>P Value (6- vs 12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lumen stent, %</td>
<td>30±2.28</td>
<td>19±3.2</td>
<td>15.6±3.6</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
<tr>
<td>Lumen media, %</td>
<td>22.6±4.4</td>
<td>15.6±3.5</td>
<td>12.8±3.4</td>
<td>&lt;0.001</td>
<td>0.001</td>
<td>0.009</td>
</tr>
<tr>
<td>Media stent, %</td>
<td>18.9±6.4</td>
<td>14.3±5.7</td>
<td>11.7±4.9</td>
<td>0.04</td>
<td>0.006</td>
<td>0.04</td>
</tr>
<tr>
<td>Lumen stent volume, mm³</td>
<td>19.2±4.9</td>
<td>12.7±3.6</td>
<td>7.7±1.3</td>
<td>0.002</td>
<td>&lt;0.001</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Table 4. Serial OCT Analysis Postimplantation and at 6- and 12-Month Follow-up (n=7)

<table>
<thead>
<tr>
<th>Discernable struts</th>
<th>Postimplantation</th>
<th>6 mo</th>
<th>12 mo</th>
<th>P Value (Baseline vs 6 mo)</th>
<th>P Value (6 vs 12 mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean lumen area, mm²</td>
<td>7.90±1.24</td>
<td>5.70±0.99</td>
<td>5.34±1.14</td>
<td>&lt;0.0001</td>
<td>0.04</td>
</tr>
<tr>
<td>Mean scaffold area, mm²</td>
<td>7.94±1.29</td>
<td>6.79±1.51</td>
<td>6.49±1.52</td>
<td>0.0058</td>
<td>0.21</td>
</tr>
<tr>
<td>Neointima area, mm²</td>
<td>0.00±0.00</td>
<td>1.55±0.51</td>
<td>1.58±0.34</td>
<td>0.0002</td>
<td>0.79</td>
</tr>
<tr>
<td>Percent neointima area, %</td>
<td>0.00±0.00</td>
<td>23.91±8.22</td>
<td>25.51±5.40</td>
<td>0.0003</td>
<td>0.28</td>
</tr>
<tr>
<td>Minimal neointima thickness, mm</td>
<td>N/A</td>
<td>0.09±0.04</td>
<td>0.10±0.04</td>
<td>N/A</td>
<td>0.13</td>
</tr>
<tr>
<td>Maximal neointima thickness, mm</td>
<td>N/A</td>
<td>0.32±0.05</td>
<td>0.30±0.04</td>
<td>N/A</td>
<td>0.20</td>
</tr>
</tbody>
</table>

N/A indicates not applicable; and OCT, optical coherence tomography.
reported that VH-IVUS measurements showed a significant increase in calcium and necrotic tissue components between pre- and post-BVS and a significant decrease in these 2 tissue components at 6 months of follow-up. Thus, the decrease in dense calcium was interpreted as a surrogate measure for the bioabsorption of DREAMS.

Figure 7. Representative optical coherence tomographic images after implantation of drug-eluting absorbable metal scaffold (DREAMS; A) and at 6 months (B) and 12 months (C). The appearance of DREAMS immediately after implantation looks like a permanent metallic stent on optical coherence tomographic images. The stent struts after implantation were well expanded and apposed, save for 1 incomplete strut apposition (5 o’clock position). At 6 months, remnants are completely covered, and the former strut malapposition was resolved. The change from a metallic stent-like appearance to struts after magnesium absorption is shown. At follow-up (FU), the strut is recognized as a bright region with diffuse border and shadow behind (white arrow).

Figure 8. The fate of struts of drug-eluting absorbable metal scaffold (DREAMS) located at a side branch ostium as assessed by 3-dimensional reconstruction of optical coherence tomography (OCT). After implantation, DREAMS was well expanded and apposed, with some struts covering the side branches. The 3-dimensional reconstruction of OCT clearly demonstrates the strut arrangement across the side branches. At 12 months, the struts were covered, and the former struts over the side branches were absorbed. At the ostium of the side branch, the stent strut of DREAMS was replaced by a neointimal membranous neocarina (white arrow). GWS indicates guidewire shadow; and *, side branch.
In the current study, from pre- to postimplantation, there was a significant increase with respect to the percent echogenicity in the lumen-media region (9.2% versus 22.1%; \(P<0.001\); Table 2 and Figure 6). The percentage of hyper-echogenic tissue was 22.1%, 15.8%, 12.9%, and 11.6% at postimplantation, 6, 12, and 18 months, respectively. The most pronounced reduction was observed within the first 6 months, which is in agreement with angiographic coronary geometric changes. Interestingly, the reduction rate in hyper-echogenicity, which reflects a degradation rate of DREAMS, was similar to that observed with the second-generation BVS 1.1.\(^{21,22}\) These results suggest that quantitative differential echogenicity is a useful method for monitoring the degradation process of absorbable metallic scaffolds. Furthermore, on OCT, 85.7% of the scaffold struts at 6 months and only 61.1% at 12 months were discernible, indicating continued resorption of DREAMS over time.

### Vascular Healing Response

A parallel increment in neointimal growth as assessed by OCT was found at 6 to 12 months (neointimal area: 1.55±0.51 versus 1.58±0.34 mm\(^2\), \(P=0.79\); percent neointimal area: 23.9±8.2% versus 25.5±5.4%, \(P=0.28\)). However, these values are considerably higher compared with those seen with the second-generation EES (1.3±0.6 mm\(^2\) and 19.1±8.9% at 6 months; 0.78±0.32 mm\(^2\) and 12.5±7.1% at 12 months)\(^{23,24}\) or the second-generation BVS 1.1 (1.25±0.36 to 1.43±0.36 mm\(^2\) at 6 months; 0.84±0.51 to 1.34±0.67 mm\(^2\) and 13.6±9.7% at 12 months)\(^{23,24}\) at the same time points. Taken together, neointimal proliferation with a magnesium-based, paclitaxel-eluting, bioabsorbable scaffold remains excessive.

Strut coverage is a powerful predictor of stent thrombosis.\(^{25}\) OCT strut coverage of various metallic drug-eluting stents seems to be heterogeneous. At 6 months, sirolimus-eluting stents showed a rate of uncovered struts from 8.7% to 15.0%.\(^{26–29}\) With paclitaxel-eluting stents, uncovered struts varied from 2.7% to 5.2%.\(^{23,26,27}\) EES demonstrated 2.3% of uncovered struts.\(^{23}\) Furthermore, uncovered struts with the second-generation BVS 1.1 were observed from 1.6% to 3.2% at 6-month follow-up.\(^{22,30}\)

In the BIOSOLVE-I trial, DREAMS presented with full strut coverage at 6 months, with 2.8% of malapposed struts. At 12 months, almost all of the malapposed struts were resolved with only 0.1% persistent incomplete strut apposition and 0.1% late acquired incomplete strut apposition.\(^{7}\) This coverage suggests that a 6-month duration of dual antiplatelet therapy may be sufficient to prevent DREAMS scaffold thrombosis.

### Study Limitations

Several potential limitations should be considered. First, the current observation is limited by the small cohort of patients enrolled in the first feasibility study with DREAMS. In addition, more data at later time points are needed to evaluate what happens >1 year after implantation. Second, 2-dimensional images were used to analyze the geometric parameters of coronary arteries. Despite the use of the least foreshortened view, it should be recognized that in 2 dimensions, geometric parameters are simple planer projections of complex structures and do not reflect the real vessel anatomic shape. Third, although the method of differential echogenicity analysis is limited by the physical properties of IVUS, such as spatial resolution and operating frequency of the ultrasound transducer, 3 different types of IVUS catheter systems were used in the BIOSOLVE-I trial, which may have affected our results. Finally, because a method to assess quantitatively the struts of magnesium platform bioabsorbable scaffold on OCT has not yet been established, we could not quantify the absorption process of DREAMS by OCT. The process was therefore based on a qualitative observation.

### Conclusions

DREAMS demonstrated significant bioabsorption of the scaffold by 6 and 12 months after implantation in diseased human coronary arteries. At 12 months’ follow-up, the coronary configuration and systolic–diastolic movements in the segments treated with DREAMS were back to those observed at preimplantation, with the restoration of the vasomotor functions at 6 months. First-generation DREAMS is associated with a low major adverse cardiac event rate and shows a safe degradation of the magnesium alloy. However, it still shows higher levels of neointimal proliferation compared with second-generation drug-eluting stents and the bioabsorbable everolimus-eluting coronary scaffold system at similar time points. An improved version of DREAMS may be mandatory to minimize neointimal tissue formation. Second-generation DREAMS, with a modified design and sirolimus drug elution instead of paclitaxel, is under intense investigation.

### Sources of Funding

The trial was funded by Biotronik.

### Disclosures

Drs Haude, Waksman, and Koolen receive grant research support and consulting fees from Biotronik. Drs Erbel and Erne receive research support and Dr Prati receives consulting fees from Biotronik. The other authors report no conflicts.

### References


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