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In vivo serial invasive imaging of the second-generation drug-eluting absorbable metal scaffold (Magmaris — DREAMS 2G) in de novo coronary lesions: Insights from the BIOSOLVE-II First-In-Man Trial

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ABSTRACT

Rationale: Bioresorbable scaffolds may confer clinical benefit in long-term studies; early mechanistic studies using intravascular imaging have provided insightful information about the immediate and mid-term local serial effects of BRS on the coronary vessel wall.
Objectives: We assessed baseline, 6- and 12-month imaging data of the drug-eluting absorbable metal scaffold (DREAMS 2G).
Methods and results: The international, first-in-man BIOSOLVE-II trial enrolled 123 patients with up to 2 de novo lesions (in vessels of 2.2 to 3.7 mm). Angiographic based vasomotion, curvature and angulation were assessed; intravascular ultrasound (IVUS) derived radiofrequency (RF) data analysis and echogenicity were evaluated; optical coherence tomography (OCT) attenuation and backscattering analysis were also performed.
There was hardly any difference in curvature between pre-procedure and 12 months (−0.0019; $p = 0.48$). The change in angulation from pre- to 12 months was negligible (−3.58°; 95% CI [−5.97, −1.20]), but statistically significant. At 6 months, the change in QCA based minimum lumen diameter in response to high dose of acetylcholine and IVUS-RF necrotic core percentage showed an inverse relationship (estimate of −0.489; $p = 0.055$) and with fibrous volume a positive relationship (estimate of 0.53, $p = 0.035$). Bioresorption analysis by OCT showed that the maximum attenuation values decreased significantly from post-procedure at 6 months (Δ 6 months vs. post-proc. is −13.5 [95% CI −14.6, −12.4]) and at 12 months (Δ 12 months vs. post-proc. is −14.0 [95% CI −15.4, −12.6]). By radiofrequency data, the percentage of dense calcium decreased significantly from post-procedure at 6 months and at 12 months. Likewise, by echogenicity, hyperechogenic structures decreased significantly from post-procedure at 6 months; thereafter, they remained unchanged.
Conclusion: Following implantation of DREAMS 2G, restoration of the vessel geometry, vasomotion and bioresorption signs were observed at up to 12 months; importantly, these changes occurred with preservation of the lumen size between 6 and 12 months.
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1. Introduction

Bioresorbable scaffolds (BRS) are newly approved devices in Europe for treating stable patients with obstructive coronary lesions. Since these devices are fully resorbable, they might overcome some of the

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problems related to the everlasting presence of metallic stents in coronary arteries. While it is expected that BRS may confer clinical benefit in long-term studies, early mechanistic studies using intravascular imaging have provided insightful information about the immediate and mid-term local serial effects of BRS on the coronary vessel wall [1].

The BIOSOLVE-II study assessed a newly redesigned second-generation drug-eluting absorbable metal scaffold (Magmaris — DREAMS 2G). The magnesium backbone of DREAMS 2G has been improved and it has a drug-polymer combination composed of sirolimus/poly-L-lactide (Biotronik AG, Buelach, Switzerland) [2,3]. The clinical reports showed a continuous favorable safety profile and stable performance outcomes up to 12 months [4]; however, the mechanistic explanation of these optimal results is uncertain.

We therefore assessed, the baseline, 6-month and 12-month imaging performance of DREAMS 2G with regard to the serial geometrical changes in angiographic curvature, angulation and vasomotion, as well as to the temporal changes in bioresorption process as assessed by optical coherence tomography (OCT) attenuation and backscattering analyses, and intravascular ultrasound (IVUS) derived-radiofrequency (RF) data analysis and -echogenicity.

2. Methods

2.1. Study design and population

BIOSOLVE-II is a prospective, multi-center, first-in-man study which evaluates the safety and performance of DREAMS 2G (drug-eluting absorbable metal scaffold system — Biotronik AG, Buelach, Switzerland) in 123 patients (Fig. 1 supplement online). Key inclusion criteria: patients with stable or unstable angina or documented silent ischemia, a maximum of 2 single de novo lesions (length of ≤21 mm) in 2 separate coronary arteries (with a reference vessel diameter between 2.2 and 3.7 mm). Exclusion criteria included: thrombotic lesions, severe calcification, ostial lesion, bifurcation lesion involving a side branch >2.0 mm in diameter, target lesion located in or supplied by an arterial or venous bypass graft, and unsuccessful pre-dilatation. The full list of inclusion and exclusion criteria can be accessed at clinicaltrials.gov (NCT01960504).

Clinical follow-up was planned at 1, 6, 12, 24 and 36 months. Angiographic follow-up was scheduled at 6 months for all patients; a subgroup of evaluable patients underwent IVUS, OCT and vasomotion testing at 6 months per protocol and additional imaging follow up was scheduled at 12 months, if subjects consented. The respective number of patients investigated per modality in each phase are as follows: curvature and angulation (Δ pre-proc. vs post-proc., $n = 103$; Δ 6 months vs post-proc., $n = 103$; Δ 12 vs post-proc., $n = 38$; Δ 6 months vs pre-proc., $n = 101$; Δ 12 vs pre-proc., $n = 37$). OCT (Δ 6 months vs post-proc., $n = 65$; Δ 12 vs post-proc., $n = 25$; Δ 12 vs 6 months, $n = 22$). IVUS (19 cases for all comparisons) and vasomotion assessment in 25 (6 months) and 14 (12 months) patients (Fig. 1 supplement online).

The study is in compliance with the Declaration of Helsinki, Good Clinical Practice, ISO14155, and was approved by the institutional ethics committees at the participating 13 institutions in Europe, South-America and Asia. All patients provided written informed consent.

2.2. Procedure

The device sizes were 2.5 × 20 mm, 3.0 × 20 mm, or 3.5 × 25 mm. Only one study device per lesion was allowed, although in bailout situations, a second DREAMS 2G could be used, and, in case of failure, an Orsiro DES [1].

2.3. Quantitative coronary angiographic (QCA) analysis of conformability

Angiographically, conformability of the device can be assessed by evaluating the geometric changes in curvature and angulation of the treated segment (in-scaffold). "Curvature" is defined as the infinitesimal rate of change in the tangent vector at each point of the center line. This measurement has a reciprocal relationship with the radius of the perfect circle defined by the curve at each point. 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 [1].

Both parameters were analyzed by an independent core laboratory (MedStar Cardiovascular Research Network, Washington, DC, USA).

2.4. Angiographic assessment of vasomotion

For vasomotion testing, acetylcholine was infused via a microcatheter that was placed 8–12 mm proximal to the scaffold. Incremental doses of acetylcholine – Ach – (0.36 μg/mL, 3.6 μg/mL, and 18 μg/mL) were applied into the coronary artery at a rate of 2 mL/min for 5-min per dose. The highest possible dose was assessed. After the maximum dose of acetylcholine, an intracoronary bolus injection of nitroglycerine (200 μg) was administered.

Mean lumen diameters in the scaffolded, proximal and distal segments are measured by QCA after infusion or injection of the Ach maximum dose.

2.5. Optical coherence tomography acquisition and analysis

Analysis of contiguous cross-sections at 1 mm longitudinal intervals within the scaffolded segment was performed using offline software QIVUS (MEDIS, Leiden, the Netherlands). At post-PCI, the scaffold and lumen areas were drawn. However, at follow-up, the scaffold was no more visible and therefore no scaffold area was drawn.

At post-PCI, the number of stent struts was determined in each cross section. Struts were classified as apposed (when the strut was in contact with the vessel wall) or malapposed if protruding into the lumen at a distance greater than the strut thickness.

2.5.1. Attenuation and backscatter analysis

In each analyzed OCT cross section, the attenuation and backscatter indices were estimated using a module developed by QCU-CMS (LKEB, Leiden, the Netherlands) [5]. In order to ensure inclusion of the attenuation and backscatter changes due to the strut, in each cross section, a contour was drawn 500 μm outside the stent border and the region of interest was defined by this contour and the lumen border. The guidewire artifact was also removed in each frame. The output of this analysis was color coded and displayed in each cross section and in spread-out scaffold plots (Fig. 1). Struts are anticipated to have a very high attenuation and backscatter indices. We compared these values between post-procedure, 6 and 12 months.

2.6. IVUS acquisition and analysis

Only after checking the availability of the serial IVUS recordings and selecting the matched region of interest, using computerized planimetry, the lumen and external elastic membrane were measured every 1 mm with a validated software (QIVUS, Medis, Leiden, the Netherlands).

2.6.1. Automatic quantitative echogenicity analysis

Echogenicity uses the grey-scale IVUS data to further evaluate the distribution of the grey values within the lumen and vessel boundaries [6]. Here we quantified 5 tissue types:

1. Calcified plaque is typically identified in B-mode IVUS images as a highly echogenic area, with a grey-level intensity higher than the high intensity threshold, creating an acoustic shadow.
2. Upper echogenic: highly echogenic areas with a grey-level intensity higher than the high-intensity threshold but without acoustic shadow behind them are classified as upper echogenic.
3. Hyperechogenic: highly echogenic areas with a grey-level intensity higher than the median value of the global reference adventitia.
4. Hypoechogenic: low echogenic areas with a grey-level intensity lower than median value of the adventitia.
5. Lower echogenic: lower echogenic areas with a grey-level intensity lower than the low-intensity threshold but without acoustic shadow behind them are classified as lower echogenic.
6. Unknown: shadows, etc.

The analysis was performed using QCU-CMS (developed by the Leiden University Medical Center).

2.6.2. Automatic quantitative IVUS-derived radiofrequency data analysis

The external elastic membrane and luminal borders were contoured for each frame (median interslice distance, 0.40 mm). The composition of atherosclerotic plaque was characterized into 4 different tissue types: fibrous, fibro-fatty, dense calcium and necrotic core [7].

2.7. Statistical analysis

Descriptive statistical methods were used. Means and standard deviations, medians and interquartile ranges (IQR), and 95% CIs were calculated as appropriate. For categorical data, absolute and relative frequencies were calculated and 95% CIs for proportions. *P*-values were calculated using paired *t*-test, Fisher's Exact test, and Chi-squared test where applicable. All statistical analyses were performed with SAS (version 9.3).

3. Results

Between October 2013 and May 2015, 123 subjects were enrolled. Baseline parameters are listed in Table 1 supplement online. In 2 lesions, DREAMS 2G could not be implanted due to insufficient pre-dilatation; follow-up of these 2 subjects was consequently not included in this analysis. Most patients were male and had stable angina (71.5%) at baseline. At 12-months follow-up, 100 (86.2%) patients were symptom-free. Detailed 12-month clinical follow-up has been previously reported [4].

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