Safety and performance of the second-generation drug-eluting absorbable metal scaffold in patients with de-novo coronary artery lesions (BIOSOLVE-II): 6 month results of a prospective, multicentre, non-randomised, first-in-man trial

Michael Haude, Hüseyin Ince, Alexandre Abizaid, Ralph Toelg, Pedro Alves Lemos, Clemens von Birgelen, Evald Høj Christiansen, William Wijns, Franz-Josef Neumann, Christoph Kaiser, Eric Eeckhout, Soo Teik Lim, Javier Escaned, Hector M Garcia-Garcia, Ron Waksman

Summary

Background Absorbable scaffolds were designed to overcome the limitations of conventional, non-absorbable metal-based drug-eluting stents. So far, only polymeric absorbable scaffolds are commercially available. We aimed to assess the safety and performance of a novel second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) in patients with de-novo coronary artery lesions.

Methods We did this prospective, multicentre, non-randomised, first-in-man trial at 13 percutaneous coronary intervention centres in Belgium, Brazil, Denmark, Germany, Singapore, Spain, Switzerland, and the Netherlands. Eligible patients had stable or unstable angina or documented silent ischaemia, and a maximum of two de-novo lesions with a reference vessel diameter between 2·2 mm and 3·7 mm. Clinical follow-up was scheduled at months 1, 6, 12, 24, and 36. Patients were scheduled for angiographic follow-up at 6 months, and a subgroup of patients was scheduled for intravascular ultrasound, optical coherence tomography, and vasomotion assessment. All patients were recommended to take dual antiplatelet treatment for at least 6 months. The primary endpoint was in-segment late lumen loss at 6 months. We did analysis by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT01960504.

Findings Between Oct 8, 2013, and May 22, 2015, we enrolled 123 patients with 123 coronary target lesions. At 6 months, mean in-segment late lumen loss was 0·27 mm (SD 0·37), and angiographically discernable vasomotion was documented in 20 (80%) of 25 patients. Intravascular ultrasound assessments showed a preservation of the scaffold area (mean 6·24 mm² [SD 1·15] post-procedure *vs* 6·21 mm² [1·22] at 6 months) with a low mean neointimal area (0·08 mm² [0·09]), and optical coherence tomography did not detect any intraluminal mass. Target lesion failure occurred in four (3%) patients: one (<1%) patient died from cardiac death, one (<1%) patient had periprocedural myocardial infarction, and two (2%) patients needed clinically driven target lesion revascularisation. No definite or probable scaffold thrombosis was observed.

Interpretation Our findings show that implantation of the DREAMS 2G device in de-novo coronary lesions is feasible, with favourable safety and performance outcomes at 6 months. This novel absorbable metal scaffold could be an alternative to absorbable polymeric scaffolds for treatment of obstructive coronary disease.

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Medical Clinic I, Städtische Kliniken Neuss, Lukaskrankenhaus GmbH, Neuss, Germany (Prof M Haude MD); **Department of Cardiology, Vivantes Klinikum im Friedrichshain and Am Urban, Berlin, Germany** (Prof H Ince MD); **Instituto de Cardiologia Dante Pazzanese, São Paulo, Brazil** (A Abizaid MD); **Herzzentrum Segeberger Kliniken GmbH, Bad Segeberg, Germany** (R Toelg MD); **Instituto do Coração–HCFMUSP, University of São Paulo, São Paulo** (P A Lemos MD); **Department of Cardiology, Medisch Spectrum Twente, Thoraxcentrum Twente, Enschede, Netherlands** (Prof C von Birgelen MD); **Department of Cardiology, Aarhus University Hospital, Skejby, Aarhus, Denmark** (E H Christiansen MD); **Cardiology Department, Cardiovascular Research Center Aalst, OLV Hospital, Aalst, Belgium** (W Wijns MD); **Klinik für Kardiologie und Angiologie II, Universitäts-Herzzentrum Freiburg-Bad Krozingen, Bad Krozingen, Germany** (Prof F-J Neumann MD); **Department of Cardiology, University Hospital, Basel, Switzerland** (C Kaiser MD); **Department of Cardiology, Lausanne University Hospital, Switzerland** (Prof E Eeckhout MD); **Department of Cardiology, National Heart Center Singapore, Singapore** (Prof S T Lim MD); **Division of Cardiology, Hospital Clinico San Carlos, Madrid, Spain**

Introduction

Drug-eluting stents reduce restenosis rates compared with bare-metal stents and are the present default device for percutaneous coronary intervention.[1] However, concerns have been raised about the use of drug-eluting stents, such as the risks of delayed arterial healing, late and very late stent thrombosis, hypersensitivity reactions to polymers, and accelerated in-stent formation of neoatherosclerosis. Furthermore, a vessel that is permanently caged by a metal stent has some restrictions: compensatory vascular remodelling is prevented by the stent, non-invasive imaging options are limited by the presence of the metal, and struts might interfere with future treatment options, including coronary bypass surgery.[2–4] These drawbacks motivated scientists to develop absorbable vascular scaffolds, which are designed to free the vessel from a permanently implanted metal stent.

Absorbable scaffold designs should ensure sufficient but temporary scaffolding with a performance similar to metal drug-eluting stents with respect to recoil, healing, and restenosis rates, followed by safe degradation and absorption, enabling restoration of vasomotion and prevention of late unfavourable effects of metal stents. So far, only two drug-eluting absorbable polymeric scaffolds have received CE-mark approval—the Absorb bioresorbable vascular scaffold system (ABSORB BVS;

(J Escaned MD); **Cardialysis BV, Rotterdam, Netherlands** (H M Garcia-Garcia MD); **and Interventional Cardiology, MedStar Washington Hospital Center, Washington, DC, USA** (R Waksman MD)

Correspondence to: Prof Michael Haude, Medical Clinic I, Städtische Kliniken Neuss, Lukaskrankenhaus, Neuss 41464, Germany **mhaude@lukasneuss.de**

Research in context

Evidence before this study

We searched PubMed between Sept 8, 2005, and Sept 8, 2015, for trials with absorbable scaffolds that included 6 month data for late lumen loss (LLL). Our keywords were "drug-eluting coronary scaffold". We knew of publications of precursor products of DREAMS 2G. Our search retrieved 172 hits, from which we selected three trials with 91 patients (ABSORB cohort A and B, and DESolve). The findings of these studies showed an in-segment late lumen loss of 0·11–0·37 mm and an in-scaffold loss of 0·19–0·44 mm.

Added value of this study

Compared with DREAMS 1G, the DREAMS 2G novel absorbable metal scaffold showed substantially improved performance measures, with a sustained favourable clinical and safety profile up to 6 months. No definite or probable scaffold thrombosis was noted for DREAMS 2G or any of the precursor devices, and the rates of target lesion failure and revascularisation were low. Vasomotion was restored at 6 months.

Implications of all the available evidence

DREAMS 2G could be an alternative to current absorbable polymeric scaffolds for the treatment of obstructive coronary disease.

Abbott Vascular, Santa Clara, CA) and the DESolve bioresorbable scaffold (Elixir Medical, Sunnyvale, CA).[3,4]

The absorbable metal scaffold was developed as an alternative to polymeric scaffolds. Findings from early animal studies with magnesium alloy scaffolds in porcine coronary arteries showed good biocompatibility of this material.[5,6] First devices showed a good safety profile, but angiographic performance measures of these early devices were inferior to those of contemporary drug-eluting stents.[7,8] Device iterations led to development of the second-generation drug-eluting absorbable metal scaffold (DREAMS 2G; Biotronik AG, Buelach, Switzerland). We did the BIOSOLVE-II study to assess the safety and performance of this novel absorbable metal scaffold in symptomatic patients with de-novo coronary artery lesions.

Methods

Study design and patients

We did this prospective, multicentre, non-randomised, first-in-man trial at 13 percutaneous coronary intervention centres in Belgium, Brazil, Denmark, Germany, Singapore, Spain, Switzerland, and the Netherlands. Eligible patients were older than 18 years and younger than 80 years and had stable or unstable angina or documented silent ischaemia. A maximum of two de-novo lesions in two separate coronary arteries were allowed to be treated per patient, with a reference vessel diameter between 2·2 mm and 3·7 mm, a lesion length of 21 mm or less, and a stenosis of between 50% and 99% in diameter. Exclusion criteria included left ventricular ejection fraction of less than 30%, thrombus in the target vessel, severe calcification, three-vessel disease, ostial lesion, target lesion involving a side branch of more than 2·0 mm in diameter, target lesion located in or supplied by an arterial or venous bypass graft, and unsuccessful predilatation. The full list of inclusion and exclusion criteria can be accessed at ClinicalTrials.gov (number NCT01960504).

The study was done in accordance with the Declaration of Helsinki, good clinical practice, and the International Organization for Standardization standard 14155. The protocol was approved by the institutional ethics committees at the participating institutions. All patients provided written informed consent. Completeness and quality of data were assured by 100% source document verification. An independent data monitoring committee adjudicated all adverse clinical events.

Procedures

DREAMS 2G is a balloon-expandable sirolimus-eluting scaffold on a rapid-exchange delivery system. The scaffold backbone is made from an absorbable magnesium alloy with two permanent x-ray markers made from tantalum at the distal and proximal scaffold end. Degradation of the alloy includes two steps: first, the magnesium alloy is converted to hydrated magnesium oxide. Second, magnesium oxide is converted to magnesium phosphate, which is consecutively replaced by amorphous calcium phosphate. During this process, metallic magnesium is removed by diffusion from the amorphous matrix and is absorbed by the body. The amorphous calcium phosphate remains in the tissue together with the other elements of the alloy and the markers. About 95% of the magnesium is converted at 12 months. The surface of the scaffold backbone is completely coated with bioresorbable poly-L-lactide acid, which incorporates sirolimus. The sirolimus load is 1·4 µg/mm² scaffold surface. Poly-L-lactide acid is highly biocompatible and undergoes self-catalysed hydrolytic degeneration to lactic acid, which eventually metabolises and is transformed into CO_2 and H_2O.[3]

Target lesions were treated with standard interventional techniques, including a mandatory predilatation of the lesion. A 2·5×20 mm, 3·0×20 mm, or 3·5×25 mm DREAMS 2G was then implanted. Scaffold implantation and sizing was done in accordance with the instructions-for-use document. The scaffold

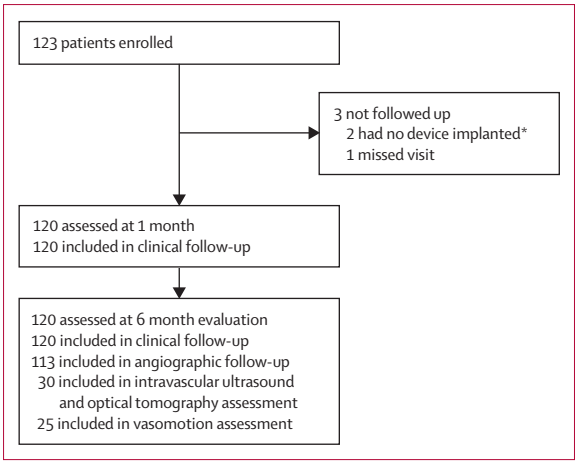

***Figure 1*: Patient flow chart**
*Two patients who did not receive an implant were included in calculation of device and procedural success only.

	Baseline data
All patients (n=123)	
Age (years)	65·2 (10·3)
Sex	
Male	78 (63%)
Female	45 (37%)
Hypertension	101 (82%)
Hyperlipidaemia	74 (60%)
Diabetes	36 (29%)
History of smoking	67 (54%)
Previous percutaneous coronary interventions	44 (36%)
Coronary artery bypass graft	8 (7%)
History of myocardial infarction	29 (24%)
Renal failure*	4 (3%)
Congestive heart failure	8 (7%)
History of stroke or transient ischaemic attack	7 (6%)
Stable angina	88 (72%)
Unstable angina	17 (14%)
Silent ischaemia	18 (15%)
All lesions (n=123)	
Lesion length (mm; n=120)†	12·61 (4·53)
Reference vessel diameter (mm^2; n=120)†	2·68 (0·40)
Target vessel	
Left anterior descending artery	47 (38%)
Left circumflex artery	29 (24%)
Right coronary artery	45 (37%)
Intermediate branch	2 (2%)
AHA/ACC classification (n=122)‡	
Type A	1 (<1%)
Type B1	68 (56%)
Type B2	51 (42%)
Type C	2 (2%)
Calcification	
Moderate to severe	13 (11%)
Thrombus present	3 (2%)

Data are mean (SD) or n (%), unless otherwise specified. AHA/ACC=American Heart Association/American College of Cardiology. *Defined as patients undergoing dialysis or those with elevated creatinine values. †Images were not analysable in three patients. ‡One patient not analysable.

***Table 1*: Baseline characteristics**

length had to cover the entire target lesion and only one study device should be used per lesion (planned overlapping scaffolds were not permitted). Post-dilatation was done at the operator's discretion. In bailout situations, a second DREAMS 2G could be used, or, in case of failure, a sirolimus-eluting stent (Orsiro; Biotronik AG, Buelach, Switzerland) was allowed. Dual antiplatelet treatment was recommended for a minimum of 6 months after the procedure.

Clinical follow-up was scheduled at months 1, 6, 12, 24, and 36, and imaging follow-up at 6 months in a subgroup of patients undergoing intravascular ultrasound, optical coherence tomography, and vasomotion testing. All patients were assigned to angiographic follow-up at 6 months. An independent core laboratory (Cardialysis BV; Rotterdam, Netherlands) did the quantitative coronary angiography, intravascular ultrasound, and optical coherence tomography analyses. Angiograms were recorded in two orthogonal views after intracoronary injection of nitroglycerine (200 μg), with matching projections taken before and after the procedure and at follow-up.

For intravascular ultrasound assessment, either a 20 MHz ultrasound catheter (Eagle Eye; Volcano Cooperation, Rancho Cordova, CA) or a 45 MHz catheter (Revolution; Volcano Cooperation, Rancho Cordova, CA) was advanced beyond a distal landmark and, after intracoronary administration of nitroglycerine, a motorised pullback was done at a speed of 0·5 mm/s. In the pre-percutaneous coronary intervention intravascular ultrasound, dimensions of the lumen and external elastic membrane were measured every 1 mm with validated analysis software (QIVUS; Medis, Leiden, Netherlands). After percutaneous coronary intervention and at follow-up, the contours of scaffold, lumen, and external elastic membrane were drawn. Neointima was calculated as scaffold minus lumen measures. Incomplete scaffold apposition was defined as one or more scaffold struts clearly separated from the vessel wall with evidence of blood speckles behind the strut without overlapping side branches.

Optical coherence tomography of the scaffolded segment was done with the frequency domain Ilumien system (St Jude Medical, Westford, MA, USA) with a non-occlusive imaging technique following the administration of nitroglycerine.[9] Analysis of contiguous cross-sections at 1 mm longitudinal intervals within the scaffolded segment was done offline with dedicated software (QIVUS; MEDIS, Leiden, Netherlands). The contours of scaffold, lumen, and external elastic membrane were drawn post-percutaneous coronary intervention. The number of scaffold struts was

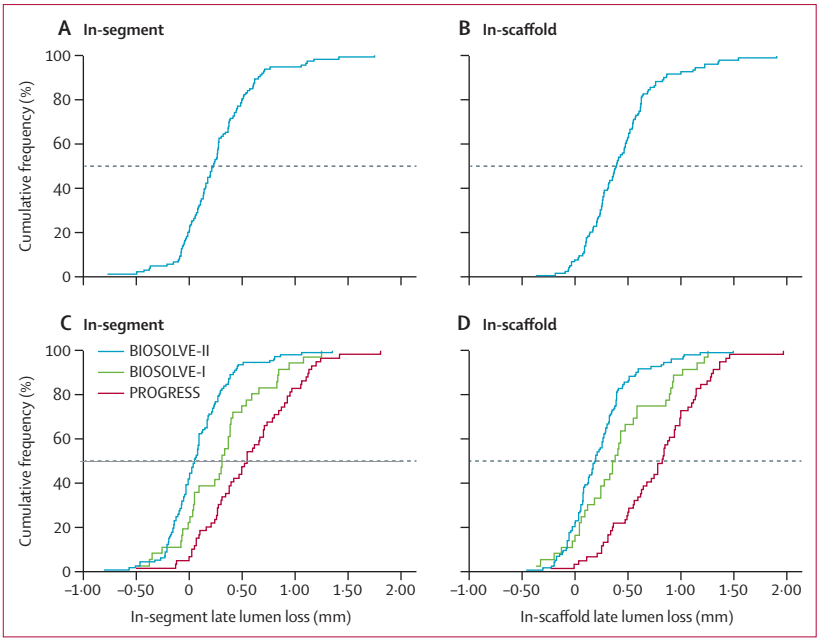

***Figure 2*: Cumulative frequency curves for late lumen loss**
In-segment late lumen loss (A). In-scaffold late lumen loss (B). In-segment (C) and in-scaffold (D) late lumen loss by comparison with PROGRESS[7] and BIOSOLVE-I.[8]

	Preprocedure* (n=112)	Post-procedure (n=112)	6 months (n=112)	p value†
Reference vessel diameter (mm)				
In-segment	2·70 (0·39; 2·63–2·78)	2·70 (0·38; 2·63–2·77)	2·55 (0·41; 2·48–2·63)	<0·0001
In-scaffold	NA	2·80 (0·37; 2·73–3·86)	2·59 (0·40; 2·52–2·67)	<0·0001
Minimum lumen diameter (mm)				
In-segment	1·20 (0·31; 1·14–1·26)	2·18 (0·40; 2·63–2·77)	1·89 (0·43; 1·81–1·97)	<0·0001
In-scaffold	NA	2·46 (0·33; 2·40–2·52)	2·00 (0·44; 1·92–2·08)	<0·0001
Acute gain (mm)				
In-segment	NA	0·97 (0·41; 0·89–1·05)	NA	NA
In-scaffold	NA	1·26 (0·36;1·19–1·32)	NA	NA
Diameter stenosis (mm)				
In-segment	55·3 (10·4; 53·3–57·2)	19·2 (7·5; 17·8–20·6)	25·9 (12·3; 23·6–28·2)	<0·0001
In-scaffold	NA	11·8 (5·1; 10·8–12·7)	22·6 (12·9; 20·2–25·0)	<0·0001
Binary restenosis (%)				
In-segment	NA	NA	6 (5%)	NA
In-scaffold	NA	NA	6 (5%)	NA
Late lumen loss (mm)				
In-segment	NA	NA	0·27 (0·37; 0·20–0·33)	NA
In-scaffold	NA	NA	0·44 (0·36; 0·37–0·50)	NA

Data are mean (SD; 95% CI) or n (%), unless otherwise specified. NA=not applicable. *For one patient, image was not analysable. †Post-procedure versus 6 months.

***Table 2*: Paired angiographic analysis**

determined in each cross section. Struts were classified as apposed (if the strut was in contact with the vessel wall) or malapposed (if protruding into the lumen at a distance greater than the strut thickness). At follow-up, the scaffold was no more visible and therefore no scaffold contour was drawn.

For vasomotion testing, acetylcholine was infused via a microcatheter that was placed 8–12 mm proximal to the scaffold. Incremental doses of acetylcholine (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.

We defined vasoconstriction or vasodilation to acetylcholine or nitroglycerine as a change of 3% or more to the mean in-segment lumen diameter after infusion or injection of the maximum dose.[10]

Outcomes

Our primary endpoint was in-segment late lumen loss at 6 month follow-up. Secondary clinical endpoints were the rate of target lesion failure, defined as a composite of cardiac death, target vessel myocardial infarction, coronary artery bypass graft surgery, and clinically driven target lesion revascularisation; the rate of scaffold thrombosis; and device and procedure success. We defined cardiac death, clinically driven target lesion revascularisation, and scaffold thrombosis in accordance with Academic Research Consortium guidelines.[11] We defined myocardial infarction in accordance with the most recent definition of the Society for Cardiovascular Angiography and Interventions.[12] We defined device success as a final residual diameter stenosis of 30% or more by quantitative coronary angiography, with use of the assigned device only; successful delivery of the scaffold to the target lesion site; appropriate scaffold deployment; and successful removal of the delivery system. Procedure success was defined as achievement of a final diameter stenosis of less than 30% by quantitative coronary angiography, using any percutaneous method, without the occurrence of death, myocardial infarction, or target lesion revascularisation during the hospital stay.

Secondary angiographic parameters were in-scaffold and in-segment binary restenosis, diameter stenosis, and in-scaffold late lumen loss. Measurements within the scaffolded segment were defined as in-scaffold and the in-scaffold segment plus 5 mm proximal or distal was defined as in-segment.[13,14] We also assessed the drug-induced vasomotion in the scaffolded segment. Secondary intravascular ultrasound and optical coherence tomography endpoints included a descriptive analysis of vessel morphology, lesion composition, and scaffold strut data.

Statistical analysis

The sample size was calculated for the primary endpoint of late lumen loss. A late lumen loss of 0·5 mm leads to a binary restenosis rate of about 5% and an in-segment loss of 0·5 mm or less is associated with a low probability of target lesion revascularisation.[15,16] Assuming an expected in-segment late lumen loss of 0·45 mm, a

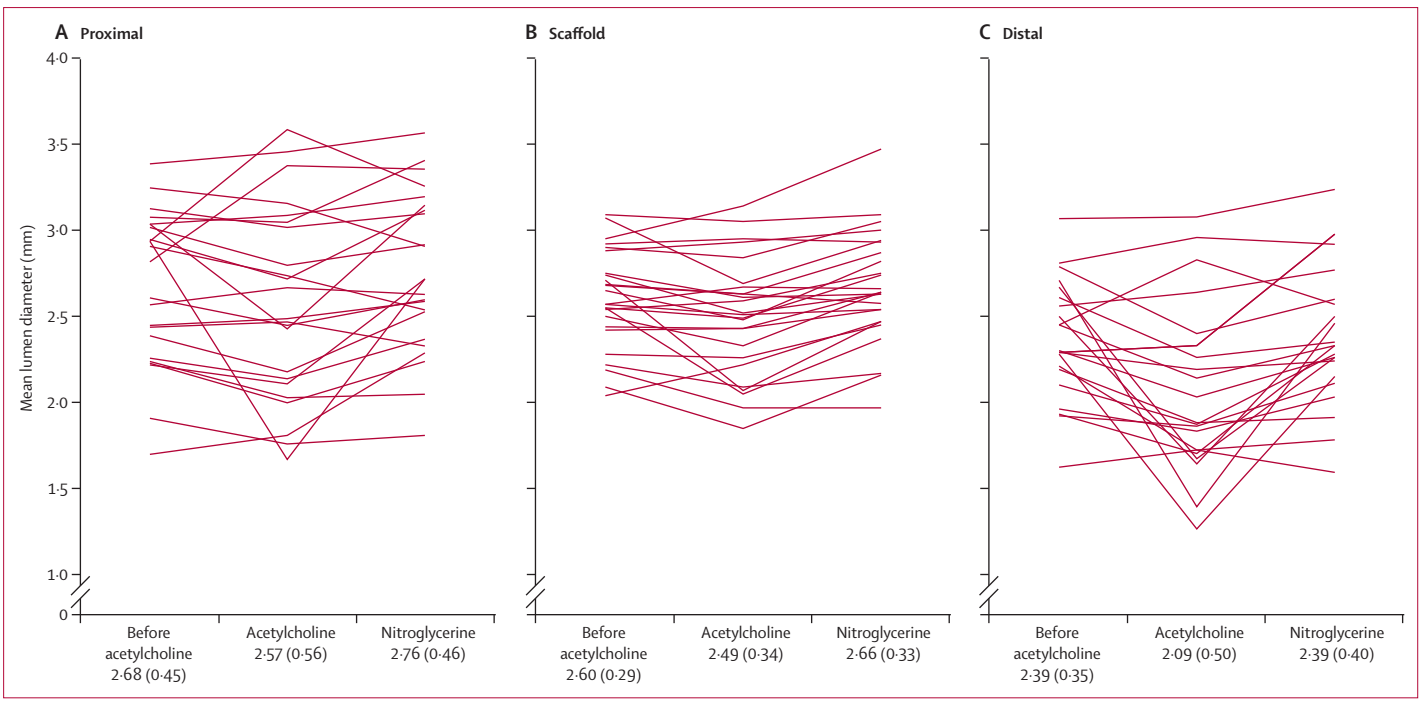

Figure 3: **Effect of acetylcholine and nitroglycerine administration at 6 month follow-up (n=25)**
Proximal (A). Scaffold (B). Distal (C). Data are mean (SD). Each line represents data of individual patient response to the highest concentration of acetylcholine, and nitroglycerine.

standard deviation of 0·2 mm, a one-sided significance level of 5%, a power of 80%, and 16·5% loss to follow-up, 121 patients needed to be enrolled.

We calculated means, SDs, and 95% CIs for descriptive statistics, and absolute and relative frequencies with 95% CIs for proportions for categorical data. We used Student's *t* test for group comparison. We did analyses in the intention-to-treat population, defined as patients for whom an investigational scaffold entered the guide catheter following the diagnostic angiogram, irrespective of whether the investigational scaffold was implanted. Patients not receiving a DREAMS 2G scaffold were included in the device and procedure success analysis, but were excluded from angiographic and clinical endpoint analysis. No interim analysis was done before the primary endpoint.

We did statistical analyses with SAS (version 9.3). This trial is registered with Clinicaltrials.gov, number NCT01960504.

Role of the funding source

The funder of the study had a role in study design, data collection, data analysis, data interpretation, and writing of the report. All authors had full access to all the data in the study and the corresponding author had final responsibility for the decision to submit for publication.

Results

Between Oct 8, 2013, and May 22, 2015, we enrolled 123 patients (figure 1). Clinical follow-up was 99% of all patients who received the study device at both 1 month and 6 months (figure 1). Although treatment of two de-novo lesions was allowed, only patients with one lesion were enrolled (n=123 lesions). The DREAMS 2G could not be implanted in two (2%) patients; in both individuals, predilatation was insufficient. Neither patient was considered for follow-up assessment according to the protocol. In another patient (1%), the lesion could not be crossed with the initial device because of insufficient predilatation, but could be crossed with a second device after an additional predilatation. A second DREAMS 2G was implanted in four (3%) patients (n=3 due to dissection and n=1 due to an underestimation of lesion length), and three (2%) patients received a non-study device (n=2 to cover dissections and n=1 because DREAMS 2G could not cover the lesion completely). Procedural success was 99% (122 of 123 patients) and device success was 93% (122 of 131 patients). Table 1 summarises baseline characteristics.

Mean in-segment late lumen loss at 6 months was 0·27 mm (SD 0·37) and in-scaffold late lumen loss was 0·44 mm (0·36) (figure 2, table 2). During 6 months of vasomotion testing in 25 patients, the mean lumen diameter of 2·60 mm (SD 0·29) in the treated segment decreased to 2·49 mm (0·3) with acetylcholine (difference –0·10 mm; p=0·014) and dilated to 2·66 mm (0·33) with nitroglycerine (difference *vs* post-acetylcholine 0·17 mm; p<0·001; figure 3). For 20 (80%) patients, we noted vasodilatation or vasoconstriction after either acetylcholine or nitroglycerine administration with a threshold of change of 3·0% or more.

	Preprocedure (n=28)*	Post-procedure (n=30)	6 months (n=30)	Mean difference (95% CI)†	p value†
Intravascular ultrasound					
Vessel area (mm²)	12·10 (3·02)	14·06 (3·17)	14·21 (3·14)	0·15 (–0·13 to 0·42)	0·289
Mean scaffold area (mm²)	NA	6·24 (1·15)	6·21 (1·22)	–0·03 (–0·29 to 0·23)	0·803
Minimum scaffold area (mm²)	NA	5·41 (1·16)	4·62 (0·99)	–0·79 (–1·06 to –0·51)	<0·0001
Neointimal hyperplasia area (mm²)	NA	NA	0·08 (0·09)	NA	NA
Mean lumen area (mm²)	5·24 (1·14)	6·30 (1·16)	6·15 (1·23)	–0·15 (–0·40 to 0·10)	0·231
Minimum lumen area (mm²)	2·58 (0·62)	5·37 (1·15)	4·54 (1·02)	–0·83 (–1·14 to –0·52)	<0·0001
Total plaque area (mm²)	6·86 (2·64)	7·76 (2·41)	8·06 (2·23)	0·29 (0·11 to 0·47)	0·002
Patients with incomplete strut apposition	NA	9 (30%)	11 (37%)	NA	0·785
Malapposition area (mm²)	NA	0·06 (0·14)	0·02 (0·05)	–0·04 (–0·08 to 0·00)	0·039
Optical coherence tomography					
Number of analysed struts	NA	195·67 (15·49)	NA‡	NA	NA
Scaffold area (mm²)	NA	7·21 (1·15)	NA‡	NA	NA
Mean lumen area (mm²)	NA	7·28 (1·14)	6·26 (1·38)	–1·02 (–1·43 to –0·61)	<0·0001
Minimum lumen area (mm²)	NA	6·00 (1·19)	4·35 (1·20)	–1·65 (–2·11 to –1·19)	<0·0001
Malapposed struts (%)	NA	7·67 (7·06)	NA‡	NA	NA
Mean incomplete strut apposition area (mm²)	NA	0·16 (0·16)	NA‡	NA	NA
Mean intraluminal mass area (mm²)	NA	0·00 (0·00)	0·00 (0·00)	NA	NA
Mean prolapse area (mm²)	NA	0·07 (0·06)	NA‡	NA	NA

Data are mean (SD) or n (%), unless otherwise specified. NA=not applicable. *Preprocedure intravascular ultrasound could not be analysed in two patients because of an inconsistent pullback speed. †6 months versus post-procedure. ‡Could not be assessed at 6 months' follow-up because of degradation of the scaffold.

***Table 3*: Intravascular ultrasound and optical coherence tomography measurements per lesion**

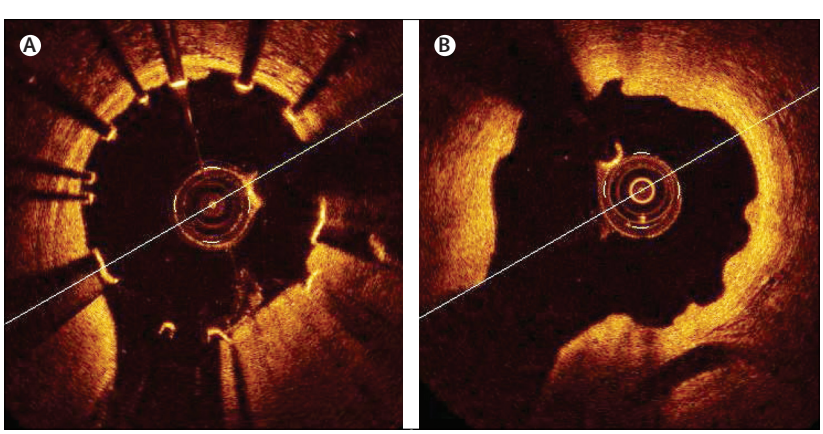

***Figure 4*: Optical coherence tomographs after implantation of the second-generation drug-eluting absorbable metal scaffold (A) and at 6 months (B)**
Immediately after implantation, struts are well apposed to the vessel wall. At 6 months, scaffold remnants have lost their metallic stent-like appearance during the magnesium absorption process.

See Online for appendix

Intravascular ultrasound and optical coherence tomography were done in a subgroup consisting of the first consecutive 30 patients with preprocedure, post-procedure, and 6 month recordings. Intravascular ultrasound assessment showed a preservation of the scaffold area, with a low neointimal area (table 3). 6 month optical coherence tomography showed no malapposed struts, because the scaffold struts were embedded into the vessel wall (figure 4). We observed no intraluminal mass at any time.

Target lesion failure at 6 months occurred in four patients (3%, 95% CI 1·3–8·3). One death of unknown cause (<1%, 0·0–3·0) on day 134 post-procedure was classified as cardiac death and possible scaffold thrombosis. One patient (<1%, 0·0–3·0) had a target vessel myocardial infarction. This patient had temporary no-reflow after scaffold implantation in the right coronary artery with clinical symptoms and electrocardiogram changes. Two patients (2%, 95% CI 0·2–5·9) needed clinically driven target lesion revascularisation: one patient had unstable angina and a stenosis of 81% in diameter on day 84 and one had Canadian Cardiovascular Society class II angina and a stenosis of 54% in diameter at 6 month control angiography. The decision for revascularisation was operator driven. No definite or probable scaffold thrombosis was observed nor was any additional clinically driven target vessel revascularisation. One patient (<1%, 95% CI 0·0–3·0) died of non-cardiac causes (cancer) before 6 month follow-up. The appendix provides additional data for 30 day and 6 month safety outcomes, and a detailed analysis of post-procedure creatinine kinase-MB and troponin values.

Discussion

Our findings show that DREAMS 2G improves late lumen loss compared with its precursor devices while maintaining a favourable clinical and safety profile.

DREAMS 2G is built on continuous improvements of previous generations of absorbable metal scaffolds.[7,8,17,18] Advantages of metal scaffolds are a good radial strength, low acute recoil, and high compliance to the vessel geometry.[3] Furthermore, metal scaffolds can be implanted via a single-step inflation, hence providing the advantage that they can be implanted in a similar way to a permanent metal stent. Furthermore, they can be electropolished, which results in soft, rounded edges that can improve trackability and deliverability.

The first magnesium scaffold investigated in human coronary arteries was a bare absorbable metal scaffold tested in the PROGRESS study.[7,17] This scaffold had a good safety profile, but measures of performance, such as in-scaffold late lumen loss, were not satisfactory, suggesting a need for slower scaffold absorption together with an antiproliferative drug-elution concept.[7,17] Refinement of the absorbable metal scaffold led to development of the DREAMS 1G device, with an improved alloy composition and strut geometry for better scaffolding properties and addition of a drug-polymer matrix with paclitaxel to counteract the neointimal proliferative response.[18] DREAMS 1G was tested in the first-in-man BIOSOLVE-I study[8] and showed a favourable clinical safety profile and significantly improved angiographic performance measures compared with its bare absorbable metal scaffold precursor. However, BIOSOLVE-I findings still showed a substantial in-segment late lumen loss of 0·52 mm (SD 0·48) and an in-scaffold loss of 0·65 mm (0·50) at 6 months. These results were not competitive with newer generation drug-eluting stents, showing a need for further iterations to the device.

Compared with DREAMS 1G, DREAMS 2G has a more flexible and stronger scaffold backbone design, higher bending flexibility, and higher radial force. Additionally, the drug-polymer coating has changed to sirolimus in combination with a bioresorbable poly-L-lactide acid polymer to more effectively decrease neointimal formation. The same coating is successfully used in the commercially available Orsiro drug-eluting stent.[9]

Findings from the present study show that the iterations in DREAMS 2G met the expectations for scaffold performance, with continued improvement of late lumen loss. Specifically, in-segment late lumen loss decreased by 0·31 mm (relative difference 37·4%, from 0·83 mm to 0·52 mm) from PROGRESS,[7] with absorbable metal scaffold, to BIOSOLVE-I,[8] with DREAMS 1G, and by 0·25 mm (48·1%, from 0·52 mm to 0·27 mm) from BIOSOLVE-I to BIOSOLVE-II with DREAMS 2G; among these studies, in-scaffold late lumen loss decreased by 0·43 mm (39·8%, from 1·08 mm to 0·65 mm) and 0·21 mm (32·3%, from 0·65 mm to 0·44 mm), respectively. The in-segment late lumen loss of DREAMS 2G is similar to that of polymeric scaffolds, ranging from 0·11 mm to 0·37 mm, whereas the in-scaffold loss is within the upper range of late lumen loss in polymeric scaffolds (0·19–0·44 mm) and slightly higher than the loss with the latest iterations of ABSORB and DESolve.[14,19,20]

Notably, late lumen loss is probably a moving target in absorbable scaffolds and has low relevance for prediction of long-term outcomes, because in absorbable scaffolds late lumen enlargement (beyond 1 year) was reported.[17,21] Moreover, in the ABSORB cohort A trial, despite an in-scaffold late lumen loss of 0·44 mm at 6 months, 5 year outcomes were excellent without any additional major adverse cardiac events beyond 6 months.[19,22]

Similar to DREAMS 1G,[23] we recorded drug-induced vasomotion at 6 months with DREAMS 2G, showing that vessels were uncaged, but the response to acetylcholine within the scaffolded segment showed that in most cases the endothelial function was still abnormal.

In the present assessment of intravascular ultrasound, similar to in BIOSOLVE-I,[8] the vessel area did not change significantly between the post-procedure assessment and 6 month follow-up. However, the degradation process seemed to be more favourable for the DREAMS 2G device in the BIOSOLVE-II study: in BIOSOLVE-I, mean scaffold and mean lumen areas decreased faster than in BIOSOLVE-II (mean scaffold area –11·1% *vs* –0·5%; mean lumen area –15·3% *vs* –2·4%), which could be a sign of a too-fast degradation of DREAMS 1G, whereas degradation of DREAMS 2G seems to be more balanced.

The neointimal hyperplasia area decreased from 0·30 mm² in BIOSOLVE-I[8] to only 0·08 mm² in BIOSOLVE-II. Notably, the area of BIOSOLVE-II is identical to that recorded in ABSORB cohort B (0·08 mm²) and lower than that in ABSORB cohort A (0·30 mm²) and in DESolve (0·4 mm²).[14,19,20] The discordance between late lumen loss and neointimal hyperplasia in our study might be due to decreasing radial strength in the context of the absorption process. Furthermore, intravascular ultrasound was only done in a subset of 30 patients and anatomic variations cannot be ruled out.

Post-procedure assessment of optical coherence tomography showed a similar incomplete strut apposition area for DREAMS 2G (0·16 mm²) and ABSORB cohort B (0·19 mm²; p=0·663).[14] For ABSORB cohort A, 91% of the struts were apposed post-procedure and DESolve had 14·45% cross sections with malapposition. At 6 months, we could not detect any malapposed struts with optical coherence tomography because the DREAMS 2G device was fully embedded into the vessel wall. 97% of the struts were well apposed in BIOSOLVE-I and 93% were well apposed in ABSORB cohort A; 0·04% of the optical coherence tomography cross sections showed malapposition for DESolve at follow-up.[14,19,20,24] No intraluminal mass was observed at any time in our study compared with intraluminal masses in 24% of patients at 6 months for ABSORB cohort B, in which intraluminal masses were more often associated with malapposed or uncovered struts.[24]

Whereas the angiographic performance measures improved compared with the precursor devices of DREAMS 2G, the safety profile remained good, with only one cardiac death and one target vessel myocardial infarction. Corresponding to the decrease in late lumen loss, the rate of clinically driven target lesion revascularisation declined (1·7% for DREAMS 2G in BIOSOLVE II *vs* 4·3% for DREAMS 1G in BIOSOLVE-I[8] and 23·8% at 4 months for absorbable metal scaffold in PROGRESS[7]), which consequently led to a reduced rate of target lesion failure, which was mainly driven by the two revascularisations. No definite or probable scaffold thrombosis was observed in any precursor study[7,8] or in BIOSOLVE-II.

Clinical results for DREAMS 2G compare well with the clinical outcome of polymeric scaffolds in which a similar composite endpoint (cardiac death, myocardial infarction, coronary artery bypass graft surgery, or clinically driven target lesion failure) occurred in 2–5% of patients.[3,19,25,26] The clinically driven rate of target lesion revascularisation for DREAMS 2G was 1·7%, versus 0–6·3% for polymeric scaffolds.[3,19,25,26] A meaningful comparison to the DESolve first-in-man study is hampered by the fact that the study included no more than 16 patients (one patient had a periprocedural target vessel myocardial infarction and one patient had a target lesion failure after DESolve implantation).[20] Post-procedure findings for maximum creatinine kinase-MB and troponin were similar to those recorded in the ABSORB-II trial at different cutoff values.[27]

Our present study has limitations that are inherent to a non-randomised first-in-man study. The absence of a direct comparison with other permanent stents or scaffolds restricts the interpretation of our results. This study is the first-in-man experience and included patients with straightforward de-novo lesions; thus, the results cannot be generalised to other types of lesions, such as highly calcified, complex, or restenotic lesions. The ideal follow-up time for absorbable scaffolds is, by contrast with permanent stents, still uncertain. We selected the 6 month follow-up timepoint for assessment of the primary endpoint in-segment late lumen loss for similarity with the earliest timepoint available in the BIOSOLVE-I trial. As known from the BIOSOLVE-I trial of DREAMS 1G, and from trials with polymeric scaffolds, there is a continued lumen enlargement beyond the 6 month timeframe, resulting in better results for in-segment and in-scaffold late lumen loss.[8,21]

In conclusion, in the BIOSOLVE-II trial with nearly complete angiographic and clinical follow-up, the DREAMS 2G novel absorbable metal scaffold showed substantially improved performance measures, with a favourable safety profile up to 6 months, compared with its precursor, DREAMS 1G. No definite or probable scaffold thrombosis was observed for DREAMS 2G or any of the precursor devices, and the rates of target lesion failure and revascularisation in BIOSOLVE-II were low. Vasomotion was restored at 6 months. Hence, DREAMS 2G could be an acceptable alternative to present absorbable polymeric scaffolds.

Contributors

MH, RW, and HMG-G contributed to the conception and design of the study. MH, HI, AA, RT, PAL, CvB, EHC, WW, F-JN, CK, EE, STL, and JE contributed to data collection. MH, RW, and HMG-G analysed, reviewed, and interpreted the data. All authors critically reviewed the manuscript and gave final approval.

Participating staff

Data monitoring committee: Ralf Birkemeyer (Oberndorf, Germany), Harald Rittger (University Erlangen), Bernhard Witzenbichler (Amper Kliniken AG, Dachau, Germany), Sanjay Kaul (data safety monitoring board only; Sherman Oaks, CA, USA). *Consultant medical writer:* Beatrix Doerr (Moosburg, Germany). *Steering committee:* Michael Haude (Städtische Kliniken Neuss, Neuss, Germany), Michael Joner (CVPath Institute, Gaithersburg, MD, USA), Jacques J Koolen (Catharina-Ziekenhuis, Eindhoven, Netherlands), Ron Waksman (Washington Hospital Center, Washington, DC, USA).

Declaration of interests

MH has received study grants and lecture fees from Biotronik, Abbott Vascular, Cardiac dimensions, Medtronic, Volcano, and Lilly. RT has received personal fees from Biotronik. PAL has received grants from Biotronik, Boston Scientific, and Scitech. CvB has received institutional research grants from Biotronik, Medtronic, Boston Scientific, AstraZeneca, and personal fees from Medtronic, Boston Scientific, Astra Zeneca. WW has received grants from Abbott Vascular, Biotronik, and Terumo, and is a non-executive board member and shareholder of Argonauts Partners (Celyad). F-JN has received grants from Biotronik, and personal fees and non-financial support from Abbott Vascular, Boston Scientific, Medtronic, and Biotronik. EE has received speakers honoraria and research grants from Biotronik. STL has received institutional research grants from Biotronik, Medtronic, Biosensors, Bayer, Actelion, and non-financial support from Abbott Vascular, Orbus Neich, Alvimedica, Philips, Asahi Intecc, and Terumo. RW has received personal fees from Biotronik, Medtronic, Abbott Vascular; grants and personal fees from Astra Zeneca, Boston Scientific; and grants from The Medicines Company and Edwards Lifesciences. All other authors declare no competing interests.

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