Serial 3-Dimensional Optical Coherence Tomography Assessment of Jailed Side-Branch by Second-Generation Drug-Eluting Absorbable Metal Scaffold (from the BIOSOLVE-II Trial)

Yuichi Ozaki, MD, PhD[a,b], Hector M. Garcia-Garcia, MD, PhD[a,b,*], Alexandre Hideo-Kajita, MD[a,b], Kayode O. Kuku, MD[b], Michael Haude, MD, PhD[c], Hüseyin Ince, MD, PhD[d], Alexandre Abizaid, MD, PhD[e], Ralph Tölg, MD, PhD[f], Pedro Alves Lemos, MD, PhD[g], Clemens von Birgelen, MD, PhD[h], Evald Høj Christiansen, MD, PhD[i], William Wijns, MD, PhD[j], Javier Escaned, MD, PhD[k], and Ron Waksman, MD[a]

Second-generation drug-eluting absorbable metal scaffold (DREAMS 2G) is used for treating coronary lesions. However, the natural history of the jailed side-branch (SB) after DREAMS 2G implantation remains to be elucidated. The aim of this study is to investigate the effect of scaffold struts on jailed SBs as assessed by 3-dimensional (3D) optical coherence tomography (OCT) after implantation of DREAMS 2G. We enrolled the patients who received a DREAMS 2G implantation and where OCT was performed at postprocedure and 12-month follow-up in the BIOSOLVE-II trial. The area of the ostium of jailed SBs and number of compartments divided by scaffold struts were assessed by cut-plane analysis using 3D OCT. A total of 24 patients with 61 jailed SBs were analyzed in this study. The number of compartments was significantly decreased (postprocedure; 1.98 ± 0.84 vs 12 months; 1.10 ± 0.30, p <0.001) during the 12 months. Since most of the struts disappeared, the ostium area was increased in 62% of jailed SBs at 12 months, however, not significantly different from postprocedure (postprocedure; 0.74 [0.34 to 1.46] mm^2 vs 12 months; 0.78 [0.41 to 1.68] mm^2, p = 0.055). The number of compartments created by scaffold struts and branching angle at postprocedure had no effect on the changes of SB ostium area. DREAMS 2G has a favorable absorption process in the jailed SBs up to 12 months and may be considered as an optional therapy for treating lesions that involve SBs. **(Am J Cardiol 2019;123:1044−1051)**

The feasibility with favorable safety and performance of the second-generation drug-eluting absorbable metal scaffold (DREAMS 2G; Biotronik AG, Buelach, Switzerland) have been demonstrated in the BIOSOLVE-II trial.[1−3] Restoration of the vessel geometry and bioresorption signs were confirmed up to 12 months using intracoronary optical coherence tomography (OCT), with the halting of the neointimal growth.[4] Furthermore, irrespective of the implantation technique, excellent healing was verified in the scaffolded segment up to 12 months assessed by OCT.[5] Bioabsorbable vascular scaffolds have revealed favorable outcomes with jailed side-branches (SBs),[6] but they have a very slow absorption process. The absorption process of absorbable metal scaffolds is much faster; however, the specific behavior of DREAMS 2G in bifurcations has never been previously described. OCT can evaluate the details of stent struts and also absorbable scaffolds with its high resolution. Frequency domain OCT enables 3-dimensional (3D) reconstruction of the coronary artery and permits a direct visualization of the jailed SBs and struts in vivo.[7] 3D OCT reconstruction is feasible with respect to the evaluation of the orifices of the jailed SB.[8] We therefore evaluated the effect of scaffold struts on jailed SBs in terms of patency and orifice area as assessed by 3D OCT at 12 months after implantation of DREAMS 2G.

Methods

The present analysis is a substudy of the BIOSOLVE-II trial. We enrolled the patients who received a DREAMS

[a]Section of Interventional Cardiology, MedStar Washington Hospital Center, Washington, District of Columbia; [b]MedStar Cardiovascular Research Network, MedStar Washington Hospital Center, Washington, District of Columbia; [c]Medical Clinic I, Städtische Kliniken Neuss, Lukaskrankenhaus GmbH, Neuss, Germany; [d]Department of Cardiology, Vivantes Klinikum im Friedrichschain and Am Urban, Berlin, Germany; [e]Instituto de Cardiologia Dante Pazzanese, Sao Paulo, Brazil; [f]Herzzentrum Segeberger Kliniken GmbH, Bad Segeberg, Germany; [g]Instituto do Coração − HCFMUSP, University of Sao Paulo, São Paulo, Brazil; [h]Department of Cardiology, Medisch Spectrum Twente, Thoraxcentrum Twente, Enschede, the Netherlands; [i]Department of Cardiology, Aarhus University Hospital, Aarhus, Denmark; [j]Cardiology Department, Cardiovascular Research Center Aalst, OLV Hospital, Aalst, Belgium; and [k]Department of Cardiology, Hospital Clinico San Carlos, Madrid, Spain. Manuscript received October 3, 2018; revised manuscript received and accepted December 20, 2018.

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*Corresponding author: Tel: (202) 877-2812.

E-mail address: hector.m.garciagarcia@medstar.net (H.M. Garcia-Garcia).

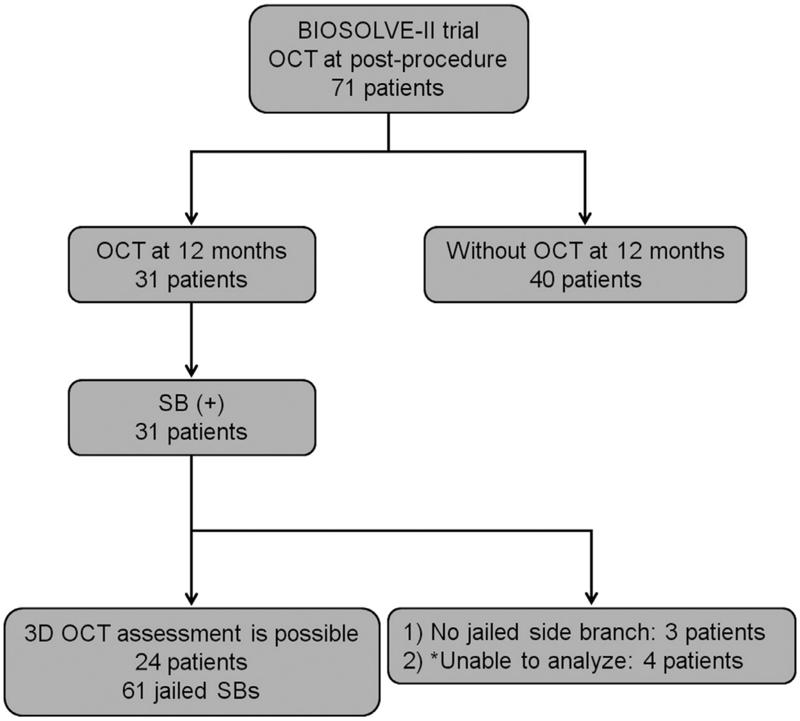

Figure 1. Flow chart of patient selection. A total of 71 patients underwent OCT postprocedure in BIOSOLVE-II. Forty patients were excluded as no OCT was available at 12-month follow-up and the remaining 31 patients were evaluated for eligibility for analysis. Additionally, 3 patients with no jailed SB and 4 patients with poor imaging quality due to an insufficient flushing, guide-wire, or motion artifact were excluded. Ultimately, a total of 24 patients with 61 jailed SBs were assessed using 3-dimensional OCT.
*Due to insufficient flushing, guide-wire or motion artifact.
3D = 3-dimensional; OCT = optical coherence tomography; SB = side-branch.

2G implantation in the lesion with SB and where OCT was performed at postprocedure and 12-month follow-up in the BIOSOLVE-II trial. Figure 1 shows the flow chart of the patient selection for this OCT substudy.

BIOSOLVE-II was a prospective, multicenter, first-in-man study assessing the safety and performance of DREAMS 2G in patients with de-novo coronary artery lesions between October 2013 and May 2015. In this study, eligible patients were older than 18 years, younger than 80 years, and had stable or unstable angina or documented silent ischemia. A maximum of 2 single de-novo lesions in 2 separate coronary arteries were allowed to be treated per patient (reference vessel diameter between 2.2 and 3.7 mm, lesion length of ≤21 mm, and a diameter stenosis between 50% and 99%). Patients with a left ventricular ejection fraction of less than 30%, thrombus in the target vessel, severe calcification, three-vessel disease, ostial lesion, target lesion involving a SB of >2.0 mm in diameter, target lesion located in or supplied by an arterial or venous bypass graft, and unsuccessful predilatation were excluded. The full list of inclusion and exclusion criteria can be accessed at clinicaltrials.gov (NCT01960504).

The study was in compliance with the Declaration of Helsinki, Good Clinical Practice, and ISO14155 and was approved by the institutional ethics committees at each participating institutions in Europe, South America, and Asia and all patients gave written informed consent before inclusion.

DREAMS 2G is a drug-eluting absorbable metal scaffold system comprised of a magnesium alloy with 2 permanent radiopaque markers made from tantalum at the distal and proximal scaffold end, premounted on a balloon-expandable delivery system. The struts are 150 μm thick, have a width of 150 μm, and are laser-polished, and their surface is completely coated with bioresorbable poly-L-lactide acid, which incorporates sirolimus.[1]

The lesions were treated with standard interventional techniques using DREAM 2G after a mandatory predilatation, and postdilatation was performed at the operator's discretion. The size of the predilatation balloon had to be ≤0.5 mm smaller than the reference vessel diameter and the length had to be shorter than or the same as the lesion length. DREAMS 2G implantation and sizing was done in accordance with the instructions-for-use document. The postballoon size was not permitted to exceed the maximum inner diameter of the DREAMS 2G and the length had to be shorter than the scaffold. A 2.5 × 20 3.0 × 20 mm, or 3.5 × 25 mm DREAMS 2G was available to operators.[1]

Intracoronary OCT imaging was performed after DREAMS 2G implantation and 12-month follow-up. A frequency domain ILUMIEN system (St. Jude Medical, Westford, MA) with a nonocclusive imaging technique following the administration of nitroglycerine was used.[9] Frequency-domain OCT images were calibrated with adjustment for the Z-offset before image acquisition to obtain accurate measurement. Analysis of contiguous cross

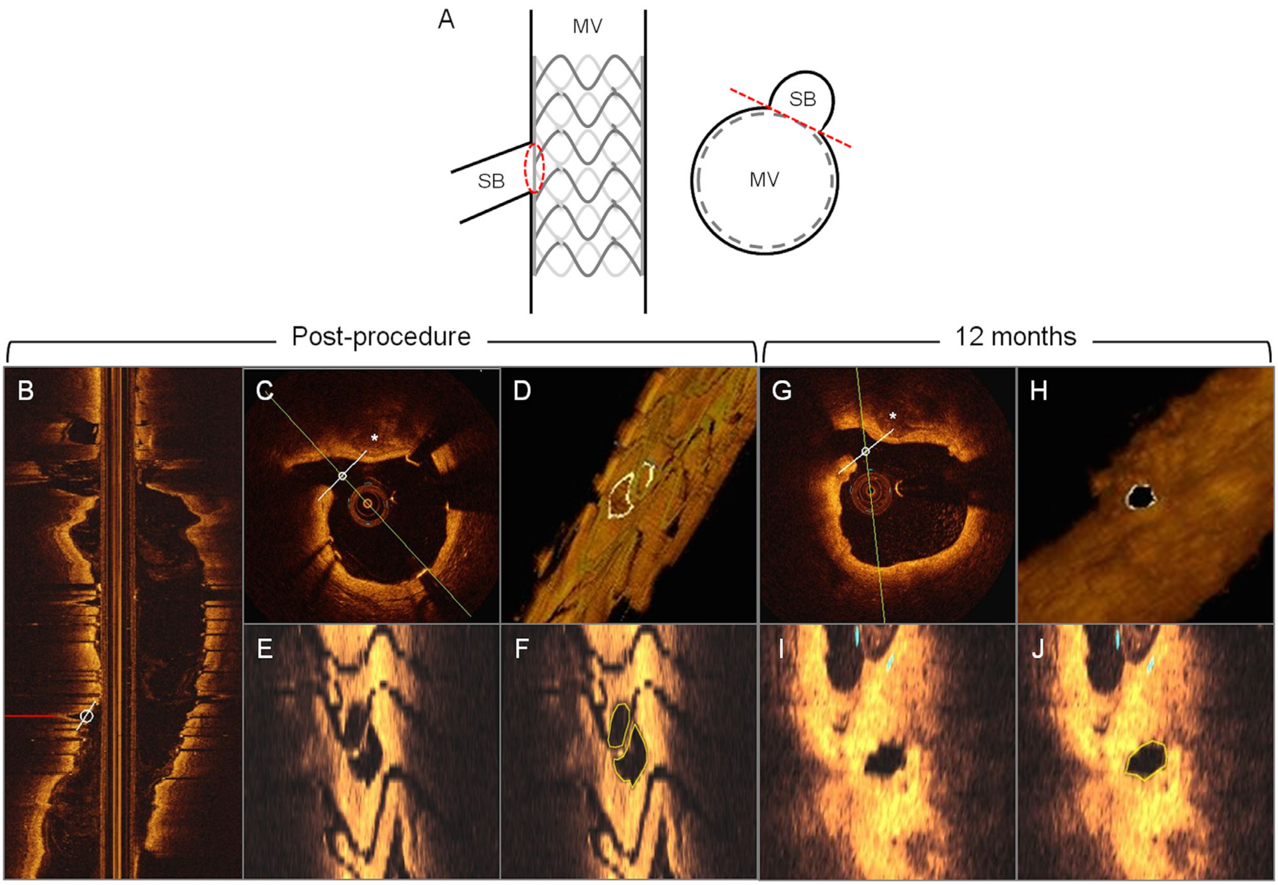

Figure 2. Methodology of the cut-plane analysis. (A) The scheme of the cut-plane line. In the cross-sectional image, the cut-plane line, indicated by the red dotted line, was adjusted vertical to the lumen center, through the jailed struts at the SB ostium. In the longitudinal image, the cut-plane line, indicated by the red dotted circle, was rotated parallel to the longitudinal strut line. (B, C) The images of the cut-plane line in the cross-sectional and longitudinal in QAngioOCT, respectively. (D, H) The corresponding 3D rendering images. (E) The cut-plane image at the ostium of jailed SB at postprocedure. The area was divided into 2 compartments by the scaffold. (F) The scaffold was visible at the SB orifice and the area was excluded from the traced area. (G) The corresponding cross-sectional image at 12 months. (I, J) The cut-plane image at the ostium of jailed SB at 12 months. The scaffolds have completely disappeared and the area was traced. Calcium marked by *.
3D = 3-dimensional; MV = main vessel; OCT = optical coherence tomography; SB = side-branch.

section at 0.2 mm longitudinal intervals within the scaffolded segment was performed. The 3D OCT images were reconstructed using QAngioOCT (MEDIS, Leiden, the Netherlands). Offline OCT data analysis was performed by an independent core laboratory (MedStar Cardiovascular Research Network, Washington, DC). The number of compartments divided by scaffolds was counted under 3D OCT construction (Figure 2). Furthermore, the area of the ostium of jailed SBs was measured by cut-plane analysis as previously described.[10] The position and orientation of the cut-plane line at the SB orifice was set based on the cross sectional and longitudinal images. In the cross-sectional image, the cut-plane line was adjusted vertical to the lumen center, through the jailed scaffolds at the SB ostium. In the longitudinal image, the cut-plane angle was arranged parallel to the longitudinal scaffold line. The position of the created cut-plane was confirmed in the 3D renderings. If the scaffold with or without tissue was visible at the SB orifice, we excluded its area from the traced area. Branching angle was measured with the specific longitudinal OCT image where both the carina and the SB ostium could be identified clearly with the narrowest carina angle. On the basis of the selected longitudinal image, branching angle was defined as the angle between the main vessel lumen contour line and the SB lumen contour line at the surface of the carina (Figure 3).[11]

Categorical variables are presented as number (percentage) with comparison using chi-square or Fisher's exact test (for an expected cell value <5). Continuous variables were presented as mean ± standard deviation or median (interquartile range) and compared using Student's *t* test or Mann-Whitney *U* test (between-group comparison) or Wilcoxon signed rank test (if variables were compared between postprocedure and 12-month follow-up) (according to Shapiro-Wilk test). Bivariate correlation was assessed with Pearson's method or alternatively with Spearman's method if the variable values were not normally distributed. All statistical analyses were performed with JMP Pro software version 12.2 (SAS Institute, Inc., Cary, NC). A p value <0.05 was considered statistically significant.

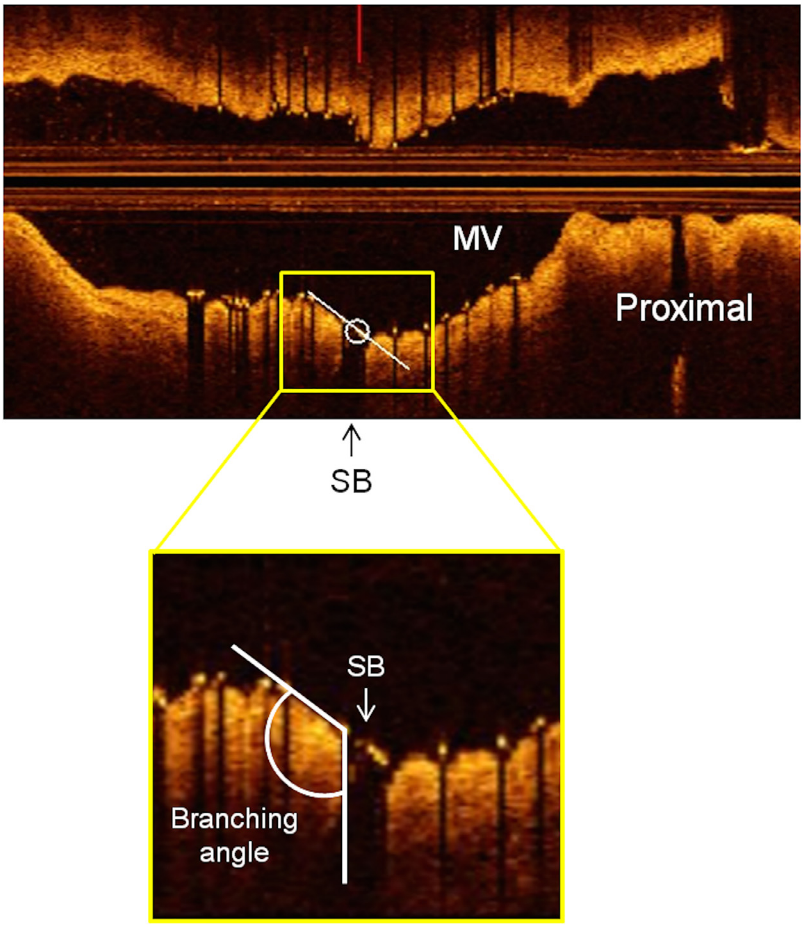

Figure 3. Measurements of branching angle. Branching angle was defined as the angle between the main vessel lumen contour line and the SB lumen contour line at the surface of the carina using longitudinal reconstruction OCT image.
MV = main vessel; OCT = optical coherence tomography; SB = side-branch.

Results

A total of 71 patients underwent OCT postprocedure in BIOSOLVE-II. Forty patients were excluded as no OCT was available at 12-month follow-up and the remaining 31 patients were evaluated for eligibility for analysis. An additional 7 patients were excluded as following: 3 patients had no jailed SB and 4 patients were unable to be analyzed due to poor imaging quality with an insufficient flushing, guide-wire, or motion artifact. Ultimately, the present study population comprises of a total of 24 patients with 24 lesions who had OCT at both postprocedure and 12-month follow-up in the BIOSOLVE-II trial. A total of 61 jailed SBs were analyzed using 3D OCT in this study. Baseline clinical and lesion characteristics are summarized in Table 1.

Table 2 shows the characteristics and quantitative analysis of jailed SBs. Of 61 jailed SBs, 20 SBs which had no struts at the orifice were classified into nonscaffold type and 41 SBs were classified into I type, V type, or Y type according to the layout of the struts at the SB orifice. Most of the scaffolds jailing SBs at postprocedure have disappeared at 12 months (Figure 4). On the other hand, a few of them remained and continued jailing SBs as shown in Figure 5. Two jailed SBs that were occluded during DREAMS 2G implantation opened and were detected at 12-month follow-up. Along with the disappearance of the struts, the number of compartments significantly decreased (postprocedure; 1.98 ± 0.84 vs 12 months; 1.10 ± 0.30, $p < 0.001$) at 12-month follow-up. The area of SB ostium tended to increase but not significantly at 12 months (postprocedure; 0.74 [0.34 to 1.46] mm^2 vs 12 months; 0.78 [0.41 to 1.68] mm^2, $p = 0.055$). The ostium area increased in 38 jailed SBs (62%) as shown in Figure 6. Furthermore, the changes of ostium area of SBs during the 12 months had no significant correlation with both the ostium area ($r = -0.061$, $p = 0.642$) and number of strut jailed SB at postprocedure ($r = -0.229$, $p = 0.075$).

No significant differences were observed between the SBs with increased ostium area and those with decreased ostium area in terms of procedure characteristics including target vessel, position of SB within the scaffold, scaffold diameter, postballoon diameter, and postballoon inflation pressure (Table 3). Moreover, the number of compartments created by scaffold struts (increase; 2.1 ± 0.8 vs decrease; 1.9 ± 0.9, $p = 0.296$) and branching angle (increase; 86 [85

Table 1
Baseline clinical and lesion characteristics

All patients (n = 24)	
Age (years)	66.3 ± 9.5
Men	16 (67%)
Women	8 (33%)
Hypertension[†]	18 (75%)
Hyperlipidemia[#]	14 (58%)
Diabetes mellitus	4 (17%)
History of smoking	14 (58%)
Previous PCI	7 (29%)
Previous coronary bypass	4 (17%)
History of myocardial infarction	4 (17%)
Renal failure*	0 (0%)
Congestive heart failure	2 (8%)
Prior stroke or TIA	1 (4%)
Stable angina pectoris	16 (67%)
Unstable angina pectoris	5 (21%)
Silent myocardial ischemia	1 (4%)
All lesions (n = 24)	
Target coronary artery	
Left anterior descending	11 (46%)
Left circumflex	6 (25%)
Right	6 (25%)
Intermediate branch	1 (4%)
AHA/ACC classification (Type)	
A	0 (0%)
B1	14 (58%)
B2	9 (38%)
C	1 (4%)

Data are mean ± SD (standard deviation) or n (%).
† Defined as patients taking any antihypertensive treatments.
# Defined as patients taking any antilipidemic treatments.
* Defined as patients undergoing dialysis or those with elevated creatinine values.AHA/ACC = American Heart Association/American College of Cardiology; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

to 98] degree vs decrease; 93 [85 to 99] degree, p = 0.461) at postprocedure showed no significant difference between the SBs with increased and decreased ostium area.

Discussion

The main finding in this substudy of BIOSOLVE-II was that DREAMS 2G has a favorable absorption process at jailed SBs up to 12 months regardless of the number of compartments divided by scaffolds and branching angle. This study is the first demonstrating the serial assessment of SBs jailed by DREAMS 2G using 3D OCT.

Table 2
OCT findings

Jailed SBs (n = 61)	Postprocedure	12 months	p value
Jailed type*			
Non-scaffold type	20 (32%)	55 (90%)	–
I	16 (26%)	4 (7%)	–
V	18 (29%)	2 (3%)	–
Y	8 (13%)	0 (0%)	–
N of struts jailed SB	7.62 ± 6.37	0.34 ± 1.02	<0.001
N of compartments	1.98 ± 0.84	1.10 ± 0.30	<0.001
Area of SB ostium (mm^2)	0.74 (0.34 to 1.46)	0.78 (0.41 to 1.68)	0.055
Branching angle (degree)	93 (85 to 98)	92 (85 to 100)	0.618

Data are mean ± SD (standard deviation), median (interquartile range), or n (%).
* One case included type I and V at postprocedure.N = number; OCT = optical coherence tomography; SB = side-branch.

Table 3
Comparison of procedural characteristics between the SBs with increased and decreased ostium area

Jailed SBs (n = 61)	Decrease (n = 23)	Increase (n = 38)	p value
Target coronary artery			0.403
Left anterior descending	9 (39%)	19 (50%)	
Left circumflex	5 (22%)	11 (29%)	
Right	8 (35%)	6 (16%)	
Intermediate branch	1 (4%)	2 (5%)	
Position of SB within scaffold			0.801
Distal	8 (35%)	12 (32%)	
Middle	9 (39%)	13 (34%)	
Proximal	6 (26%)	13 (34%)	
Scaffold diameter (mm)	3.20 ± 0.25	3.12 ± 0.22	0.225
Post balloon dilatation	16 (70%)	27 (71%)	0.902
Post balloon diameter (mm)	3.31 ± 0.42	3.27 ± 0.43	0.474
Inflation pressure of post balloon (atm)	15.9 ± 4.0	17.6 ± 3.9	0.182

Data are mean ± SD (standard deviation) or n (%).
SB = side-branch.

In the clinical setting, SB orifices would be usually occluded or narrowed after stent implantation. The possible mechanism for this occlusion is involved in plaque shift, plaque embolization, spasm and dissection at the ostium, and interference by the stent struts.[12] In a previous report about the assessment of stent struts across SBs, uncovered stent struts across the SBs were more common with first-generation drug-eluting stents (DES).[13] Similar findings were observed in second-generation DES as well.[14] As previously described, neointimal coverage with bare metal stents is higher compared with that with DES.[15] The neointimal proliferation on the jailed struts would have an effect on the ostium area of jailed SBs at follow-up. In terms of bioabsorbable scaffolds, especially polymer scaffolds, most of the scaffolds would be absorbed and disappear within 5 years after implantation.[16] Onuma et al reported that in the subgroup analysis of the ABSORB cohort B trial, the SB ostial area initially decreased; however, the ostial area increased between 2 to 3 years and 5 years with full scaffold bioresorption in the most of patients.[17] The same mechanism supposedly occurred after DREAMS 2G implantation. At first, tissue growth surrounding the jailed struts decreases the SB ostial area, and the area increases after complete bioresorption of metal scaffolds. The different point is bioresorption period between polymer scaffolds (i.e., bioresorbable vascular scaffolds) and DREAMS 2G. For absorbable metallic scaffolds, the resorption period is less than 12 months. In our previous study, most of the scaffolds have disappeared and OCT findings demonstrated the excellent healing of dissection, incomplete scaffold apposition, and intraluminal mass at 6 months.[5]

The lumen area and diameter of the SB ostium measured by OCT increased at follow-up in patients treated with DES.[18] Some of the most probable explanations for this

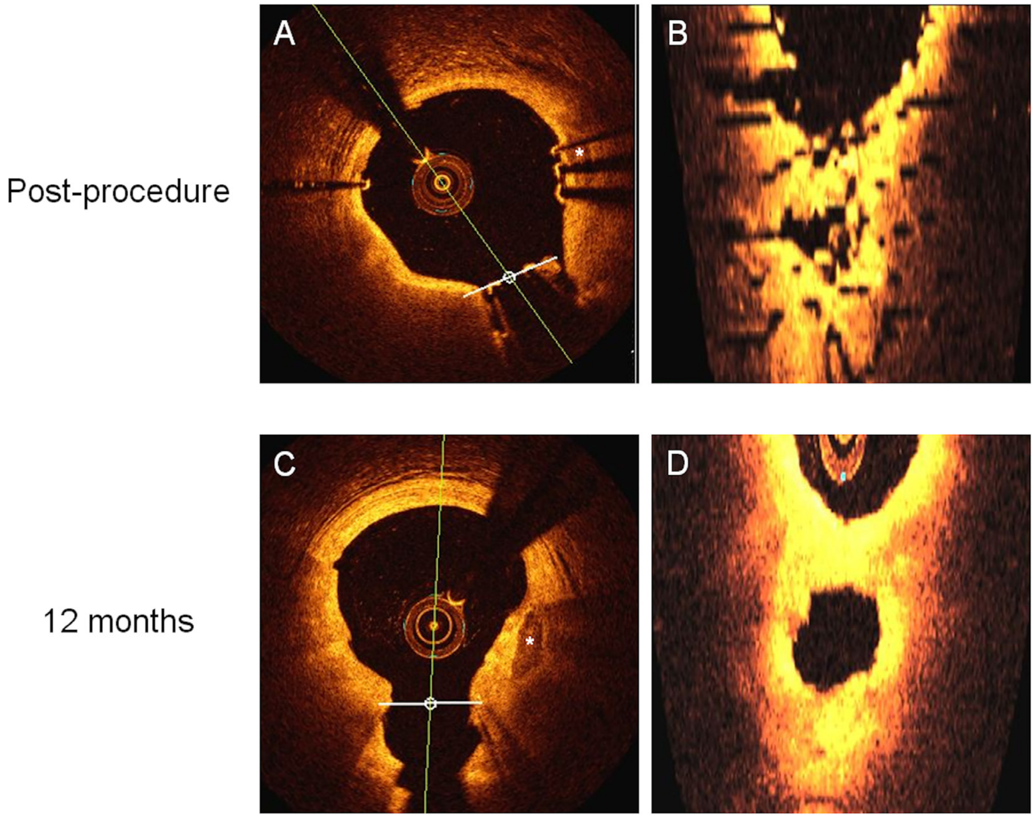

Figure 4. Representative case of disappeared scaffolds at 12 months.
(A) SB was jailed by some scaffolds at postprocedure. (B) The cut-plane image shows the ostium area is divided by the scaffold. (C) In the corresponding frame at 12 months, scaffolds jailed SB have completely disappeared. (D) The cut-plane image shows no scaffolds jail SB. Calcium marked by *.
SB = side-branch.

phenomenon are as follows: (1) regression of the plaque at the origin of SB after increase of the coronary flow in the main vessel following scaffold implantation; (2) release of a spasm after implantation; (3) healing of the injury such as dissection; and (4) disappearance of tissue protrusion and thrombus.[19,20] In the case of absorbable metallic scaffolds, this increase might be due to the resorption of scaffold struts that jailed SBs in addition to the regression of the plaque, release of a spasm, healing of the injury, and disappearance of tissue protrusion and thrombus at the SBs.

Watanabe et al demonstrated that branching angle influenced the neointimal coverage over DES struts at coronary bifurcation lesions.[11] Another report assessing jailed SB ostium by second-generation DES showed that the number of compartments was significantly decreased at follow-up. The authors also demonstrated that the changes in SB area depend on jailed types; the area with a more complex jail type was significantly decreased at follow-up. However, no differences were observed overall.[21] We revealed that no relationship between the branching angle and SB ostium area after implantation of DREAMS 2G was observed in this study. On the other hand, the number of compartments was significantly decreased, and the SB area was not different at 12 months. These results were concordant with the previous report.

This study has some limitations which are listed as following. First, since this is a retrospective substudy involving a small number of patients with only a small number of SBs in which serial assessment was available, there is a potential selection bias for this substudy. Second, our results may not be applicable to all patients with coronary artery disease because the BIOSOLVE-II trial was a cohort of patients with less complex lesions and excluded some patients with lower ejection fraction, severe calcification, three-vessel disease, and target lesion located in or supplied by an arterial or venous bypass graft. In the target segments with small SBs, operators did not perform SB treatment such as kissing balloon technique, and the patients with a target lesion involving a SB of >2.0 mm in diameter were also excluded. Therefore, a large clinical study of SBs with a diameter of >2.0 mm and/or requiring treatment is needed to confirm the results in the future. Finally, some small SBs might have been occluded when DREAMS 2G was implanted due to thicker and wider struts than current standard metallic stents. However, the actual percentage of small SBs that were occluded (if any) after DREAMS 2G implantation is unknown because we had only postprocedure OCT imaging (no preprocedure OCT imaging).

In conclusion, DREAMS 2G has a favorable absorption process in jailed SBs up to 12 months in the substudy of BIOSOLVE-II. These findings suggest that DREAMS 2G also may be considered as an optional therapy for lesions with small SBs.

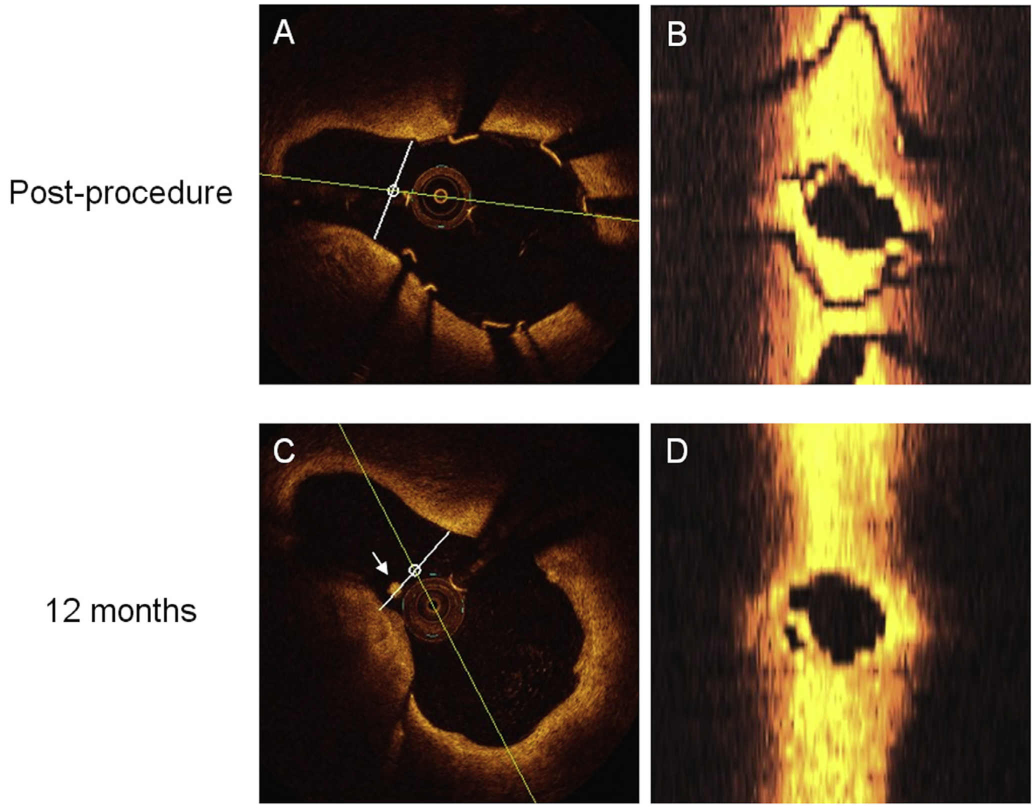

Figure 5. Representative case of a persistent strut jailed SB at 12months.
(A) The cross-sectional image at the SB ostium. (B) The cut-plane image shows the area is divided into 3 compartments by the scaffold. (C) The strut (white arrow) remains in the corresponding frame at 12 months. (D) The cut-plane image shows that the area is still divided by the strut.
SB = side-branch.

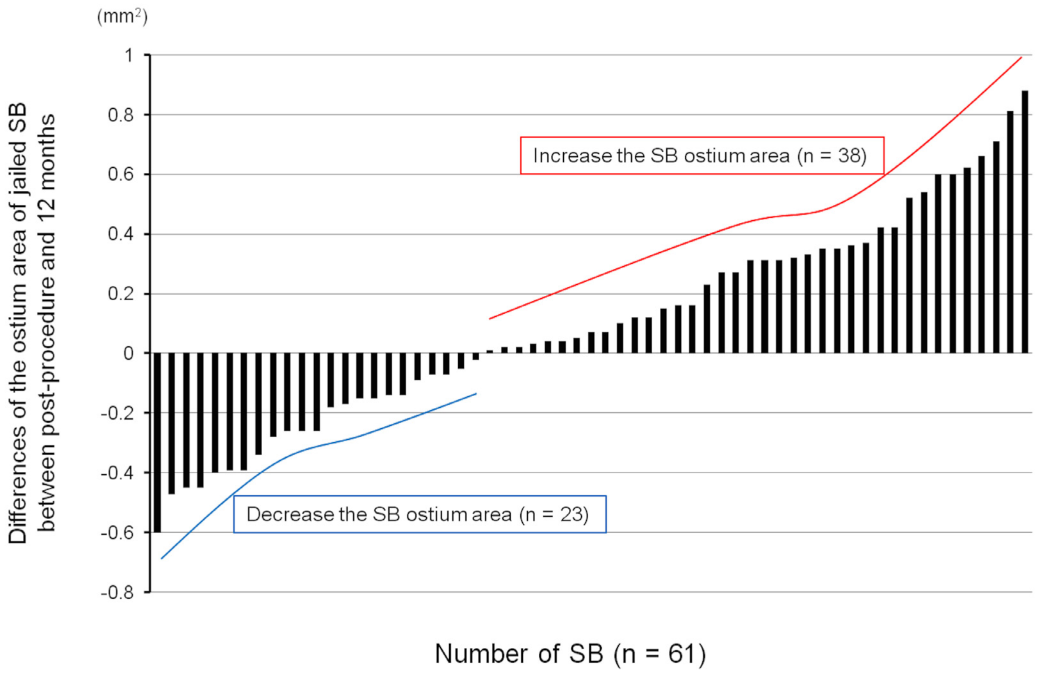

Figure 6. Differences of the ostium area of jailed SB between postprocedure and 12 months.
The ostium area was increased in 38 SBs (62%) and decreased in 23 SBs, respectively.
SB = side-branch.

Disclosures

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