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Incidence and Short-Term Clinical Outcomes of Small Side Branch Occlusion After Implantation of an Everolimus-Eluting Bioresorbable Vascular Scaffold

An Interim Report of 435 Patients in the ABSORB-EXTEND Single-Arm Trial in Comparison With an Everolimus-Eluting Metallic Stent in the SPIRIT First and II Trials

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Objectives The aim of this study was to investigate the incidence and clinical sequelae of small side branch occlusion (SBO) after Absorb (Abbott Vascular, Santa Clara, California) bioresorbable vascular scaffold (BVS) implantation.

Background The thicker strut of metallic stents potentially contributes to a higher incidence of SBO.

Methods We performed a post-hoc angiographic assessment of 1,209 side branches in 435 patients enrolled in the ABSORB-EXTEND single-arm trial (ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold [BVS] System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions), in comparison with 682 side branches in 237 patients treated with the everolimus-eluting metallic stent (EES) in the SPIRIT (A Clinical Evaluation of an Investigational Device. The Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) first and II trials. Any visible side branches originating within the device implantation site or the 5-mm proximal and distal margins were included in the angiographic assessment. The SBO was defined as a reduction in Thrombolysis In Myocardial Infarction flow grade 0 or 1.

Results Post-procedural SBO was observed in 73 side branches (6.0%) in BVS group and 28 side branches (4.1%) in EES group ($p = 0.09$). Patients with post-procedural SBO were significantly associated with an increased incidence of in-hospital myocardial infarction (6.5% in SBO group vs. 0.5% in non-SBO group, $p < 0.01$). Multivariable analysis revealed that BVS was an independent predictor of post-procedural SBO (odds ratio: 2.09; 95% confidence interval: 1.18 to 3.68). By stratified analysis, BVS demonstrated a higher incidence of post-procedural SBO compared with EES only in small side branches with a reference vessel diameter ≤0.5 mm (10.5% vs. 3.9%, $p = 0.03$ between the groups, p for interaction = 0.08).

Conclusions Bioresorbable vascular scaffold was associated with a higher incidence of post-procedural SBO compared with EES. This effect was more pronounced with small side branches with a reference vessel diameter ≤0.5 mm. (ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold [BVS] System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions: NCT01023789) (J Am Coll Cardiol Intv 2013;6:247–57) © 2013 by the American College of Cardiology Foundation

Side branch occlusion (SBO) has been implicated as a contributing factor to the development of periprocedural myocardial infarction (MI) after percutaneous coronary intervention (1–3). Periprocedural MI has been associated with unfavorable late clinical outcomes, including an increased risk of cardiac mortality (4–6). Mechanisms to explain the incidence of SBO after the metallic platform stent implantation have included mechanical vessel straightening and enlargement of the stented vessel, bifurcation carina shift, and/or coronary plaque shift into the orifice of side branch (7–9). In addition, the increased strut thicknesses of the first-generation drug-eluting stents (DES) has been implicated in contributing to a higher incidence of SBO compared with the thinner strut second-generation DES (10,11).

Abbreviations and Acronyms

BVS = bioresorbable vascular scaffold(s)
CK = creatine kinase
CK-MB = creatine kinase myocardial band
DES = drug-eluting stent(s)
DS = diameter stenosis
EES = everolimus-eluting metallic stent(s)
MI = myocardial infarction
NQMI = non–Q-wave myocardial infarction
PES = paclitaxel-eluting stent(s)
QCA = quantitative coronary angiography
ROI = region of interest
RVD = reference vessel diameter
SBO = side branch occlusion
TIMI = Thrombolysis In Myocardial Infarction
ZES = zotarolimus-eluting stent(s)

Fully bioresorbable vascular scaffolds (BVS) are a novel approach to the treatment of coronary lesions, in that they provide transient vessel support and drug delivery to the vessel wall, without the potential long-term limitations of conventional metallic DES, such as stent thrombosis and prevention of future surgical revascularization (12–14). In addition, the BVS has the potential to restore a more normal vascular physiology of the treated vessel (13,14). Early studies investigating the current generation of the everolimus-eluting BVS system (Absorb, Abbott Vascular, Santa Clara, California) have been shown to have excellent angiographic and clinical outcomes (12,15–17). The strut thickness of Absorb BVS is 157 μm, which is comparable to the first-generation DES (e.g., Cypher [Cordis Corporation, Johnson & Johnson, Warren, New Jersey], 153 μm; Taxus Express2 [Boston Scientific, Natick, Massachusetts], 148 μm) and thicker than newer-generation DES (e.g., Xience V [Abbott Vascular, Santa Clara, California], 89 μm) (18). The increased strut thickness of the Absorb BVS is to allow for sufficient radial strength and prevent acute vessel recoil (19,20). Given the increased strut thickness of the Absorb BVS, a potential concern exists that it might be associated with a higher incidence of SBO compared with newer-generation DES. The aim of this study is to assess the incidence and clinical impact of SBO after Absorb BVS implantation in a prospective, multicenter, single-arm trial. To allow for comparisons between the Absorb BVS and newer-generation DES, the SPIRIT (A Clinical Evaluation of an Investigational Device. The Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) first and II trials investigating the everolimus-eluting metallic stent (EES) will act as a historical control (21,22).

Methods

Study population. We studied patients enrolled in the ABSORB-EXTEND single-arm trial (ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold [BVS] System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions). This trial is prospectively assessing the safety and feasibility of the Absorb BVS (see trial registry information after abstract). In brief, patients older than 18 years who have 1 or 2 de novo lesions located in different native coronary arteries were enrolled. Target lesions must have been located in a major epicardial vessel or side branch with a visually estimated stenosis of ≥50% and <100% and a Thrombolysis In Myocardial Infarction (TIMI) flow grade of ≥1. The target lesions must have a diameter of 2.0 to 3.3 mm and a lesion length of ≤28 mm, both assessed by online quantitative coronary angiography (QCA). Exclusion criteria included aorto-ostial lesions, left main coronary artery lesions, total occlusions, lesions with visible thrombus, heavily calcified lesions, and bifurcation lesions involving a side branch ≥2 mm in diameter and ostial lesions >40% stenosed by visual estimation or a side branch requiring pre-dilation.

For the current analysis, patients treated with EES (Xience V) in the SPIRIT first and II trials were used as a historical control. The SPIRIT first and II trials compared the EES with either the bare-metal stent (SPIRIT first trial, NCT00180453) or with the paclitaxel-eluting stent (SPIRIT II trial, NCT00180310). The details of the SPIRIT first and II trials have previously been described (21,22). The SPIRIT first trial included patients with single de novo lesion that was 3.0 mm in diameter and that could be covered by an 18-mm stent. The SPIRIT II trial allowed for the inclusion of patients with 1 or 2 lesions in different

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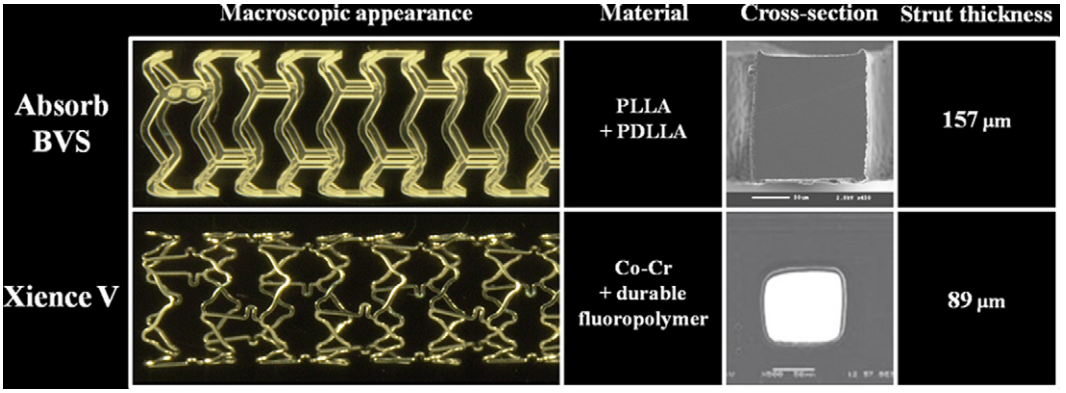

Figure 1. Features of Absorb BVS and Xience V

Absorb BVS (Abbott Vascular, Santa Clara, California) and Xience V (Abbott Vascular, Santa Clara, California). Co-Cr = cobalt–chromium; PLLA = poly-L-lactide; PDLLA = poly-D,L-lactide.

major epicardial vessels that were 2.5 to 4.25 mm in diameter and ≤28 mm in lesion length. Exclusion criteria were similar to that in the ABSORB-EXTEND trial. All trials were approved by the institutional review board, and written informed consent was obtained from each patient before inclusion.

Study devices. The backbone of the Absorb BVS is made of semi-crystalline poly-L-lactide (12). The coating consists of

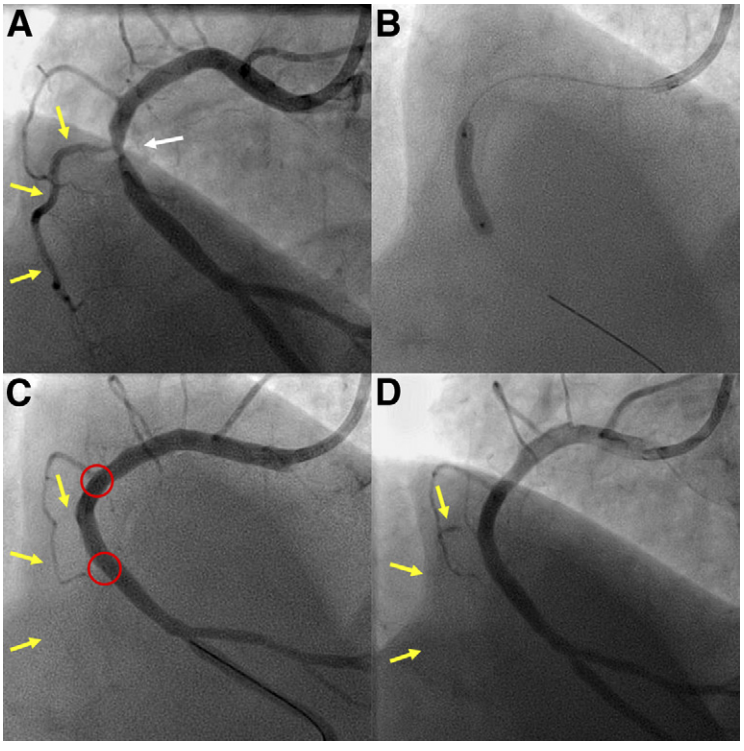

Figure 2. Representative Case of Side Branch Occlusion

Pre-procedure angiography showed a focal stenosis **(A, white arrow)** and a side branch in the mid-segment of the right coronary artery **(A, yellow arrows)**. Immediately after Absorb bioresorbable vascular scaffold (BVS) implantation **(B)**, a jailed side branch was occluded at the ostium (**C, yellow arrows; red circles** indicate the proximal and distal markers of the Absorb BVS). This side branch continued to be occluded at the post-procedural angiography **(D, yellow arrows)**.

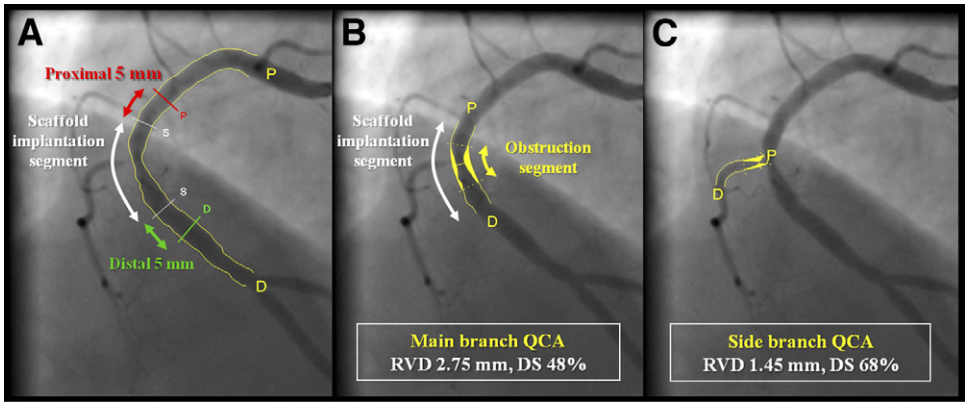

Figure 3. Assessment of QCA

Pre-procedural quantitative coronary angiography (QCA) analyses are shown. The QCA analysis delineates 5-mm proximal **(A, red double arrow)** and distal segment **(A, green double arrow)** to the intended device implantation site **(A, white double arrow)**. Any visible side branches originating from this region of interest were analyzed. The conventional QCA analysis automatically delineates an obstruction segment in the main branch **(yellow double arrow)**. An example of side branch analysis is shown in **C**. The results of QCA analysis are shown in the white-outlined box. DS = diameter stenosis; RVD = reference vessel diameter.

poly-D,L-lactide which controls the release of the antiproliferative drug everolimus. Both poly-L-lactide and poly-D,L-lactide are fully bioresorbable and degrade to lactic acid, which is metabolized via the Krebs cycle. The Absorb BVS has struts with a thickness of 157 μm and zigzag hoops connected by 3 links, similar to the Xience V design. The Xience V is an everolimus-eluting metallic stent with a platform of cobalt-chromium alloy and the durable fluoropolymer coating (23). The overall strut thickness of the Xience V is 89 μm (Fig. 1).

Treatment procedure. Lesions were treated with standard interventional techniques, with mandatory pre-dilation and

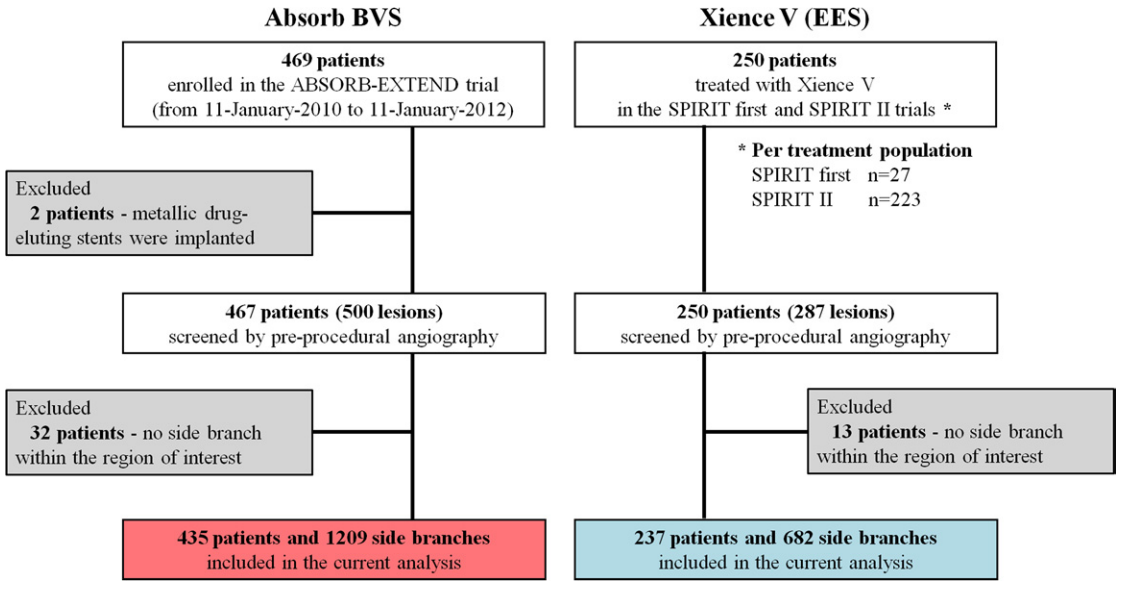

Figure 4. Flow Diagram of Study

Absorb BVS (Abbott Vascular, Santa Clara, California); ABSORB-EXTEND single-arm trial (ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold [BVS] System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions); SPIRIT (A Clinical Evaluation of an Investigational Device. The Abbott XIENCE V Everolimus Eluting Coronary Stent System in the Treatment of Patients With de Novo Native Coronary Artery Lesions) first and II trials; Xience V (Abbott Vascular, Santa Clara, California).

scaffold/stent implantation at a pressure not exceeding the burst pressure rate. Post-dilation was left to the discretion of the operator and only permitted with balloons sized to fit within the boundaries of the scaffold/stent. The Absorb BVS was available in diameters of 2.5 and 3.0 mm and lengths of 18 and 28 mm, in the ABSORB-EXTEND trial. A single 3.0 × 18 mm EES was used in the SPIRIT first trial, whereas the EES in diameters of 2.5, 3.0, 3.5, and 4.0 mm and lengths of 8, 18, and 28 mm were used in the SPIRIT II trial.

Definition of SBO and clinical outcomes. Side branch occlusion was defined as a reduction in TIMI flow to grade 0 or 1. Accordingly, side branches with pre-procedural TIMI flow grade 0 or 1 were excluded. In the current analysis, the primary clinical outcome was evaluated by in-hospital Q-wave MI or non–Q-wave myocardial infarction (NQMI). In-hospital events were defined as those occurring during hospital stay ≤7 days post-procedure. Per protocol definition of MI was an increase in the creatine kinase (CK) level to more than twice the upper limit of the normal, accompanied by an increased level of creatine kinase myocardial band (CK-MB) (24). Per protocol CK-MB assessment was a mandatory requirement if the CK was greater than upper limit of the normal. Within study sites where troponin is routinely used in the clinical practice, CK, and CK-MB assessments were obligatory if the troponin level was elevated. All clinical outcomes were adjudicated by an independent Clinical Events Committee.

Angiographic assessment and QCA. The region of interest (ROI) was defined as the study device implantation site and the 5-mm proximal and distal margins in the main branch. All pre-procedural visible small side branches originating within ROI were included in the angiographic assessment. All side branches were assessed in at least 2 different projections, with angiographic assessment for each side branch performed at 5 time points during the procedure (i.e., pre-procedure, after pre-dilation, after study device implantation, after post-dilation and post-procedure). A case example of SBO in the ABSORB-EXTEND trial is shown in Figure 2.

The main branch and side branch were evaluated separately by conventional 2-dimensional, single-vessel, off-line QCA analysis (25). The obstruction segment was automatically delineated by main branch QCA analysis within the scaffold/stent implantation segment, as defined by radiopaque markers for the Absorb BVS, or by the stent borders identified on the positioning/implantation cine-runs for the EES (26). The ostial side branch location was classified into 3 subsegments: 1) obstruction segment, 2) the scaffold/stent implantation segment outside obstruction, and 3) the 5-mm proximal and distal margins of the scaffold/stent implantation site (Fig. 3). A QCA analyses of small side branches, with a reference vessel diameter (RVD) of ≤0.5 mm, could not be undertaken because the angiographic analysis system was not validated for the vessels with this size (CAAS 5.10, Pie Medical, Maastricht, the Netherlands) (27,28). Therefore, such small side branches were assessed only for TIMI flow grade during the procedure.

Statistical analysis. Data were analyzed on a patient-level basis. Continuous variables are expressed as means ± SD and were compared by *t* test. Categorical variables are presented as proportions (percentage) and compared by Fisher exact test. Univariable and multivariable logistic regression models were applied to determine the predictors of post-procedural SBO. The logistic regression model was performed on a patient-level basis, including the following variables; age, male sex, current smoking, hypertension requiring treatment, dyslipidemia requiring treatment, any diabetes, unstable angina, family history of coronary artery disease, prior MI, number of diseased vessels (single or

Table 1. Baseline Demographic Data and Angiographic Characteristics in Patients With Side Branches

Variables	Absorb BVS (n = 435)	EES (n = 237)	p Value
Age (yrs)	61.4 ± 10.6	62.2 ± 10.4	0.35
Male (%)	75.2	70.0	0.17
Hypertension	65.5	68.4	0.49
Diabetes mellitus	26.2	22.4	0.30
Dyslipidemia	62.3	68.8	0.11
Current smoker	21.8	32.6	<0.01
Unstable angina	31.3	26.2	0.18
Family history of coronary artery disease	34.1	45.0	0.01
Prior history of myocardial infarction	28.7	33.9	0.19
Number of diseased vessels			
1-vessel disease	80.0	69.2	<0.01
2-vessel disease	16.3	26.2	<0.01
3-vessel disease	3.7	4.6	0.54
Number of lesions/patient	1.07 ± 0.26	1.13 ± 0.34	0.02
Lesion location			
Right coronary artery	28.5	28.7	1.00
Left anterior descending artery	45.8	42.9	0.49
Left circumflex artery	25.7	28.4	0.44
ACC/AHA lesion complexity			
A	2.6	0.8	0.10
B1	59.2	23.5	<0.01
B2	34.8	63.8	<0.01
C	3.5	11.9	<0.01
Angulation ≥45°	3.2	7.3	0.02
Calcification (moderate/severe)	12.6	29.5	<0.01
Eccentric lesion	96.3	98.9	0.06
Thrombus	2.2	0.8	0.23
Reference vessel diameter (mm)	2.62 ± 0.35	2.69 ± 0.52	0.04
Percentage diameter stenosis	58.6 ± 10.6	60.9 ± 11.0	0.01
Lesion length (mm)	11.7 ± 4.9	12.8 ± 5.6	0.01

Values are mean ± SD or %.

ACC/AHA = American College of Cardiology/American Heart Association; BVS = bioresorbable vascular scaffold(s); EES = everolimus-eluting metallic stent(s).

multivessel disease), angulation (≥45°), calcification (moderate/severe), eccentric lesion, pre-procedural visible thrombus, lesion classification (type B2/C), main branch lesion length, main branch pre-procedural RVD, main branch pre-procedural percentage diameter stenosis (DS), number of side branches within ROI, location of side branch (obstruction segment), size of side branch (RVD >1.0 mm), ostial stenosis of side branch (DS >50%), post-dilation, number of study devices implanted, 2.5-mm scaffold/stent implanted, and device type (Absorb BVS or EES). In patients with 2 lesions treated with the study device (6.7% in total population), we took the patients who had at least 1 lesion that met the condition described in the preceding text, and the greater main branch DS and lesion length and smaller main branch RVD were applied in such cases. In patients with multiple side branches within ROI, we took the patients who had at least 1 side branch that met the condition. The multivariable model was created with a stepwise elimination procedure, where the independent variables were entered into the model at the 0.20 significance level and removed at the 0.05 level. If some variables were highly correlated with each other ($r > 0.5$ and $p < 0.05$), the variables that had a higher level of significance were eligible for inclusion in the multivariable model. A 2-sided p value <0.05 was considered statistically significant.

Results

Study population. A total of 469 consecutive patients were enrolled in the ABSORB-EXTEND trial from January 11, 2010 to January 11, 2012. Two patients treated with DES implantation were excluded. In the first patient, the Absorb BVS failed to be delivered to the lesion. In the second patient, the appropriate size of the Absorb BVS for the lesion was not available. In addition, 32 patients without any visible side branches within ROI and 4 side branches with pre-procedural TIMI flow grade 0 or 1 were excluded. Conversely, 27 patients in the SPIRIT first and 223 patients in the SPIRIT-II trial were treated with EES at the baseline procedure. Among the total 250 patients in both trials, 13 patients were without any visible side branches within ROI, and 6 side branches with pre-procedural TIMI flow grade 0 or 1 were excluded. In total, 435 patients and 1,209 side branches in the Absorb BVS group and 237 patients and 682 side branches in the EES group were included in the current analysis (Fig. 4).

Table 2. Angiographic Assessment of Side Branches

Variables	Absorb BVS	EES	p Value
Total number of analyzed side branches	1,209	682	
Mean number/patient	2.8 ± 1.5	2.9 ± 1.5	0.37
Mean number/lesion	2.6 ± 1.2	2.6 ± 1.2	0.69
Location of the side branch			
Obstruction segment	36.3% (439/1,209)	36.2% (247/682)	0.97
Device implantation segment outside obstruction	49.1% (594/1,209)	47.9% (327/682)	0.63
Outside device implantation segment (5-mm proximal or distal)	14.6% (176/1,209)	15.8% (108/682)	0.46
Pre-procedure QCA analysis			
RVD (mm)	1.18 ± 0.39	1.19 ± 0.39	0.81
Percentage diameter stenosis (%)	20.1 ± 13.5	19.8 ± 12.2	0.74
Pre-procedure TIMI flow grade			
Grade 2	0.7% (8/1,209)	0.9% (6/682)	0.59
Grade 3	99.3% (1,201/1,209)	99.1% (676/682)	0.59
Non-hierarchical incidence of SBO*			
After pre-dilation	0.3% (4/1,204)	0.7% (5/672)	0.30
After scaffold/stent implantation	6.0% (73/1,209)	5.3% (36/682)	0.54
After post-dilation	6.7% (53/787)	5.1% (15/293)	0.40
Hierarchical incidence of SBO			
After pre-dilation	0.3% (4/1,209)	0.7% (5/682)	0.30
After scaffold/stent implantation	5.8% (70/1,209)	4.7% (32/682)	0.34
After post-dilation	0.3% (4/1,209)	0.3% (2/682)	1.00
Post-procedural SBO	6.0% (73/1,209)	4.1% (28/682)	0.09

Values are n, mean ± SD, or %(n/N). *Side branch occlusion (SBO) is defined as a reduction in Thrombolysis In Myocardial Infarction (TIMI) flow to grade 0 or 1.

QCA = quantitative coronary angiography; RVD = reference vessel diameter.

Other abbreviations as in Table 1.

Patient demographic data and lesion characteristics. Patient demographic data in patients with side branches were comparable in both groups, except for current smoker and family history of coronary artery disease, which were significantly higher in the EES group (Table 1). In addition, single vessel disease was more prevalent in the Absorb BVS group. With regard to the lesion characteristics, the EES group demonstrated a significantly higher prevalence of type B2/C lesions, angulation ≥45°, and moderate/severe calcification, compared with the Absorb BVS group. Comparisons of QCA measurements in the main branch indicated that the RVD was significantly greater in the EES group compared with the Absorb BVS group (2.62 ± 0.35 mm vs. 2.69 ± 0.52 mm, p = 0.04). In addition, percentage DS was greater and the lesion length was longer in the EES group compared with the Absorb BVS group (58.6 ± 10.6% vs. 60.9 ± 11.0%, p = 0.01; 11.7 ± 4.9 mm vs. 12.8 ± 5.6 mm, p = 0.01; respectively).

Angiographic findings of side branches. Pre-procedural angiographic characteristics of the side branches were comparable between both study groups (Table 2). The mean number of analyzed side branches/patient was 2.8 ± 1.5 in the Absorb BVS group and 2.9 ± 1.5 in the EES group (p = 0.37). Side branch occlusion occurred predominantly after the implantation of the study device in both groups. The incidence of post-procedural SBO demonstrated a trend toward being higher in the Absorb BVS group compared with the EES group (6.0% vs. 4.1%, p = 0.09).

Cardiac enzymes and incidence of periprocedural MI. Post-procedurally any cardiac enzymes were obtained from 424 patients (98%) in the Absorb BVS group and from 219 patients (92%) in the EES group (Online Fig. S1). There was no significant difference in the incidence of post-procedural CK-MB elevation between the 2 treatment groups (Fig. 5A). A significantly higher incidence of post-procedural CK-MB elevation was observed in patients with angiographic evidence of SBO (SBO group) compared with those without SBO (non-SBO group) in each cutoff level (Fig. 5B). Cardiac troponin was assessed in 360 patients post-procedurally. Similarly to CK-MB, there was no significant difference in the peak level between the 2 treatment groups (Fig. 6A), whereas the SBO group had a significantly greater release of cardiac troponin compared with the non-SBO group (Fig. 6B).

In-hospital and 30-days clinical outcomes after the procedure are shown in Table 3. Of 92 patients in the SBO group, 6 (6.5%) were adjudicated to have experienced in-hospital NQMI, whereas 3 of 580 patients in the non-SBO group (0.5%) developed an in-hospital NQMI (p < 0.01).

Predictors of SBO. Multivariable analyses indicated several factors to be significantly associated with post-procedural SBO, including the main branch lesion length, main branch pre-procedural percentage DS, location of side branch (obstruction segment), ostial stenosis of side branch (DS >50%), and device type (Absorb BVS vs. EES; odds ratio: 2.09, 95% confidence interval: 1.18 to 3.68, p = 0.01) (Table 4). By stratified analysis, the Absorb BVS demonstrated a higher incidence of post-procedural SBO compared with the EES, only in side branches with an RVD of ≤0.5 mm (10.5% vs. 3.9%, p = 0.03 between the groups, p for interaction = 0.08) (Fig. 7).

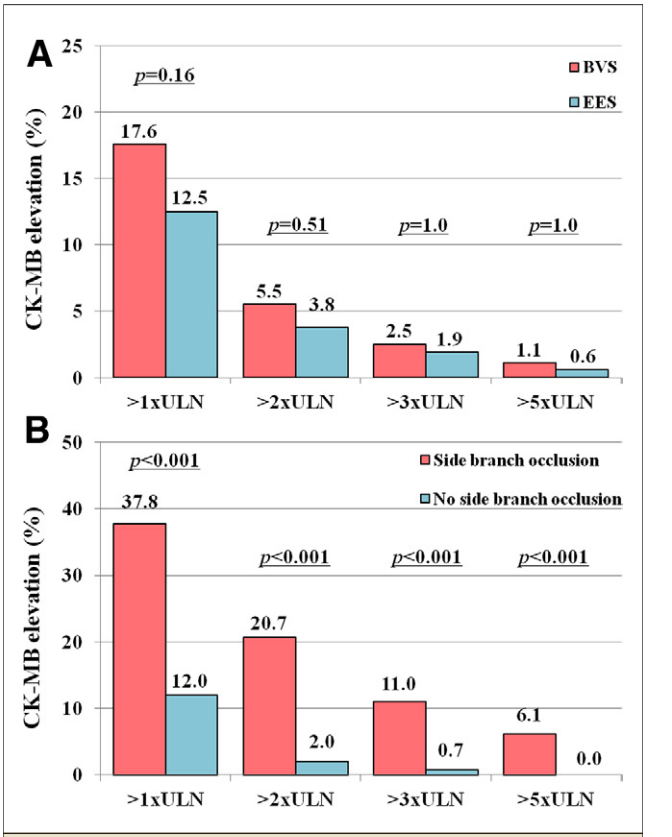

Figure 5. Magnitude of Post-Procedural CK-MB Elevation

(A) Comparisons between the patients treated with the Absorb BVS **(red bars)** and those treated with the EES **(blue bars)**. **(B)** Comparisons between the patients with post-procedural side branch occlusion **(red bars)** and those without side branch occlusion **(blue bars)**. BVS = bioresorbable vascular scaffold(s); CK-MB = creatine kinase myocardial band; EES = everolimus-eluting metallic stent(s); ULN = upper limit of the normal.

Discussion

The present study is the first demonstrating the angiographic incidence of small SBO after Absorb BVS implantation and the impact of post-procedural SBO on short-term clinical outcomes. The main findings of this study are: 1) post-procedural SBO after Absorb BVS implantation was observed in 6.0% of all visible side branches; 2) patients with post-procedural SBO were significantly associated with a higher incidence of in-hospital MI compared with

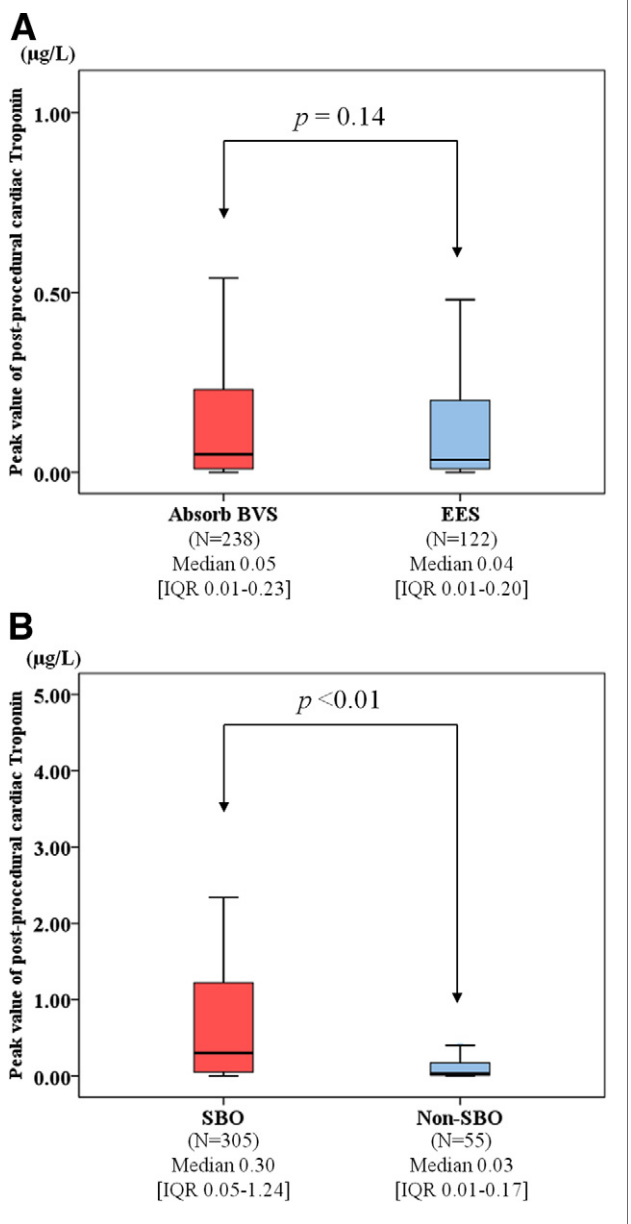

Figure 6. Peak Value of Post-Procedural Cardiac Troponin

(A) Comparisons between the patients treated with the Absorb bioresorbable vascular scaffold(s) (BVS) **(red bar)** and those treated with the everolimus-eluting metallic stent (EES) **(blue bar)**. **(B)** Comparisons between the patients with post-procedural side branch occlusion (SBO) **(red bar)** and those without SBO **(blue bar)**. IQR = interquartile range.

those without SBO; 3) lesion length and pre-procedural percentage DS in the main branch and location and ostial stenosis of side branch were all independent predictors of post-procedural SBO; and 4) the treatment with the Absorb BVS was a significant independent predictor of post-procedural SBO compared with EES in the study population.

Side branch occlusion is well recognized as a contributing factor toward periprocedural MI and resultant clinical outcomes (4–6). Previous studies have suggested several potential mechanisms for SBO after metallic stent implantation, including the presence of coronary spasm, coronary dissection, thrombus formation, embolization of plaque debris, and the bifurcation carina shift and/or plaque shift into the orifice of side branch (7–9,29,30). Notably, intracoronary nitroglycerin was administered before angiography, and the patients principally had stable and noncomplex lesion characteristics in keeping with the protocol of the ABSORB-EXTEND and SPIRIT trials. Although unplanned bailout stenting was performed in 7 patients in the Absorb BVS group and 6 patients in the EES group because of edge dissection, it did not affect the consequences of side branches originating within the ROI. In addition, post-procedural intraluminal defects, suggestive of plaque prolapse or thrombus, could not be detected. In the present study, multivariable analyses demonstrated both the location (i.e., obstruction segment) and ostial stenosis (DS >50%) of side branch to be independent predictors of post-procedural SBO. This finding is consistent with a previous study suggesting the lesion morphology at the origin of side branch to be an angiographic predictor of SBO (31). Although we cannot clearly ascertain the exact mechanism of SBO after Absorb BVS implantation because of the lack of intracoronary imaging data, the generally accepted view is that small side branch compromise and occlusion is secondary to plaque shift from the main branch into the orifice of small side branch, although carina shift might play a further role, potentially dependent on the bifurcation angle (9,32,33).

There have been 2 publications addressing the incidence of SBO with 2 different metallic platform DES. Lansky et al. (11) performed a post hoc angiographic analysis of side branches in 606 patients treated with the EES (strut thickness 89 μm) and 304 patients treated with

Table 3. Short-Term Clinical Outcomes for Patients With or Without Post-Procedural SBO

Clinical Events	SBO (n = 92)	Non-SBO (n = 580)	p Value
In-hospital events*			
Myocardial infarction	6.5% (6/92)	0.5% (3/580)	<0.01
Q-wave	0.0% (0/92)	0.0% (0/580)	N/A
Non–Q-wave	6.5% (6/92)	0.5% (3/580)	<0.01
Ischemia driven TLR	0.0% (0/92)	0.2% (1/580)	1.0
Cardiac death	0.0% (0/92)	0.0% (0/580)	N/A
30-days events			
Myocardial infarction	6.5% (6/92)	1.2% (7/580)	<0.01
Q-wave	0.0% (0/92)	0.7% (4/580)	1.0
Non–Q-wave	6.5% (6/92)	0.5% (3/580)	<0.01
Ischemia-driven TLR	0.0% (0/92)	0.2% (1/580)	1.0
Cardiac death	0.0% (0/92)	0.0% (0/580)	N/A

*In-hospital is defined as hospital stay ≤7 days post-procedure.
N/A = not available; SBO = side branch occlusion; TLR = target lesion revascularization.

Table 4. Univariable and Multivariable Analyses for Predictors of Post-Procedural Side Branch Occlusion

Covariates	Univariable p Value	Odds Ratio (95%)	Multivariable p Value	Odds Ratio (95%)
Patient-related factors				
Age (yrs)	0.46	1.01 (0.99–1.03)	—	—
Male	0.16	0.71 (0.44–1.15)	—	—
Current smoker	0.25	0.72 (0.42–1.25)	—	—
Hypertension requiring treatment	0.09	0.68 (0.43–1.06)	—	—
Dyslipidemia requiring treatment	0.86	0.96 (0.61–1.52)	—	—
Any diabetes mellitus	0.07	1.56 (0.97–2.52)	—	—
Unstable angina	0.15	1.41 (0.89–2.23)	—	—
Family history of coronary artery disease	0.86	1.04 (0.65–1.68)	—	—
Prior myocardial infarction	0.64	1.12 (0.70–1.79)	—	—
Number of diseased vessels (single vessel disease vs. multivessel disease)	0.42	0.81 (0.49–1.34)	—	—
Lesion-related factors				
Angulation ≥45°	0.19	0.38 (0.09–1.61)	—	—
Moderate/severe calcification	0.91	0.97 (0.55–1.71)	—	—
Eccentric lesion	CS	CS	—	—
Pre-procedural visible thrombus	0.59	0.57 (0.07–4.43)	—	—
Type B2/C lesion	0.47	1.18 (0.76–1.84)	—	—
Main branch lesion length (mm)	<0.01	1.07 (1.03–1.12)	0.02	1.05 (1.01–1.11)
Main branch pre-procedural RVD (mm)	0.24	0.72 (0.41–1.26)	—	—
Main branch pre-procedural DS (%)	<0.01	1.03 (1.01–1.05)	0.02	1.03 (1.00–1.06)
Number of side branches	<0.01	1.30 (1.13–1.48)	—	—
Location of side branch (obstruction segment)	<0.01	28.91 (7.05–118)	<0.01	22.40 (5.41–92.73)
Size of side branch (RVD ≥1.0mm)	0.43	0.81 (0.48–1.37)	—	—
Ostial stenosis of side branch (DS >50%)	<0.01	7.08 (3.50–14.3)	<0.01	4.30 (1.95–9.47)
Treatment-related factors				
Treatment with ≥2 study devices	0.64	1.17 (0.60–2.26)	—	—
2.5mm device implanted	0.32	0.66 (0.29–1.50)	—	—
Post-dilation	0.15	1.41 (0.88–2.24)	—	—
Device type (BVS vs. EES)	0.09	1.54 (0.94–2.52)	0.01	2.09 (1.18–3.68)

The multivariable model was created with a stepwise elimination procedure, where the independent variables were entered into the model at the 0.20 significance level and removed at the 0.05 level.
BVS = bioresorbable vascular scaffold(s); CS = complete separation; CI = confidence interval; DS = diameter stenosis; EES = everolimus-eluting metallic stent; RVD = reference vessel diameter.

the paclitaxel-eluting stent (PES) (Taxus Express2) (strut thickness 148 μm) in the SPIRIT-III substudy. Post-procedural SBO was observed in 2.7% of analyzed side branches in the EES group and 4.3% in the PES group (p = 0.06). Similarly, Popma et al. (10) assessed side branches with an RVD of >1.0 mm in 597 patients treated with the zotarolimus-eluting stent (ZES) (Endeavor; Medtronic Cardio Vascular, Santa Rosa, California) (strut thickness 96 μm) and 619 patients treated with the PES in the ENDEAVOR-IV (Randomized Comparison of Zotarolimus- and Paclitaxel-Eluting Stents in Patients With Coronary Artery Disease) substudy. Post-procedural SBO was observed in 2.0% of the analyzed side branches in the ZES group and 3.4% in the PES group (p = 0.07). Both studies suggested that strut thickness was a potential contributing factor toward SBO, on the basis of the findings of PES to be an independent predictor of SBO in both studies (10,11). In the present study, the Absorb BVS (strut thickness 157 μm) showed a trend toward higher incidence of post-procedural SBO compared with the EES (6.0% vs. 4.1%, p = 0.09). By multivariable analysis, the Absorb BVS seemed to be an independent predictor of post-procedural SBO. These results are in line with the previous studies, despite the differences between the polymeric and metallic platform devices. It is, however, noteworthy that a smaller RVD and larger number of analyzed side branches/lesion (mean 1.18 mm and 2.6, respectively) were evident in the present study when compared with those in the SPIRIT-III (mean 1.61 mm and 2.0, respectively) and in the ENDEAVOR-IV substudies (mean 1.52 mm and 1.6, respectively) and that this might partially contribute to the higher incidence rates of SBO reported in the present study. When only side branches with an RVD of >1.0 mm were considered, according to the methodology used in the ENDEAVOR-IV substudy, the incidence rates of post-procedural SBO were 1.7% in the Absorb BVS group and 2.2% in the EES group and comparable to the ZES (2.0%). This result prompts the question of how small side branches were more likely to be affected by the devices with different strut thickness. By stratified analysis, the incidence of

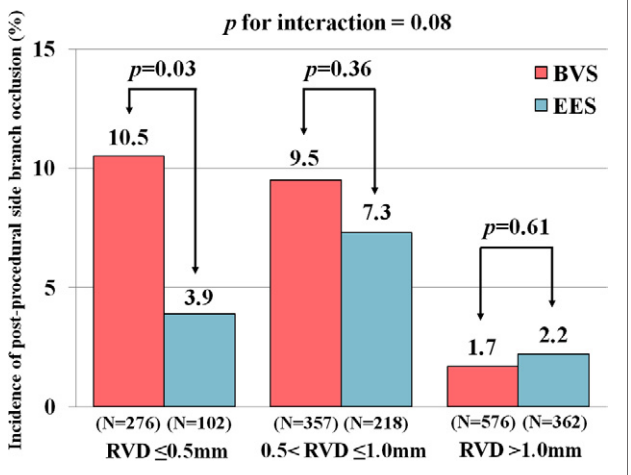

Figure 7. Incidence of Post-Procedural SBO Stratified by RVD of Side Branches

BVS = bioresorbable vascular scaffold(s); EES = everolimus-eluting metallic stent(s); RVD = reference vessel diameter.

post-procedural SBO was higher in the Absorb BVS group compared with the EES group, only in small side branches with an RVD ≤0.5 mm, despite the borderline significant interaction. Furthermore, when taking only side branches with an RVD >1.0 mm into account, multivariable analyses indicated that the Absorb BVS was no longer an independent predictor of post-procedural SBO (data not shown). Considering the greater vessel wall area covered by the Absorb BVS strut (26%) compared with the EES (12%), there is a greater probability of covering the orifice of side branches with the Absorb BVS. Thus, these findings might suggest that such small side branches are more likely to be compromised by the thicker strut of the Absorb BVS.

In the current analysis, patients with post-procedural SBO had a significantly greater release of CK-MB and cardiac troponin and also a higher risk of in-hospital MI, compared with those without SBO. There were, however, no significant differences between the 2 treatment groups with respects to the incidence of post-procedural CK-MB elevation and the peak level of cardiac troponin. A potential explanation is that the Absorb BVS was associated with a higher risk of SBO compared with the EES only in small side branches with an RVD of ≤0.5 mm, resulting in minimal impact on periprocedural myocardial necrosis. Because bioresorbable scaffolds are programmed to be completely resorbed between 2 and 3 years after implantation, the impact of SBO on long-term clinical outcomes might differ from that caused by permanent metallic endoluminal prosthesis (34). Further investigations are required to elucidate this issue.

Study limitations. The present study relies on a nonrandomized comparison of different study populations. Consequently, there were significant differences in several baseline characteristics, and the possibility of results being affected by unknown confounding factors cannot be excluded. Second, these trials principally included patients with stable coronary artery disease and excluded patients with complex lesion characteristics, such as total occlusions, thrombotic lesions, and bifurcation lesions with side branch ≥2 mm in diameter. The incidence of SBO would be expected to be higher in more complex lesions.

Conclusions

Absorb BVS implantation was associated with a 6.0% incidence of post-procedural SBO in 435 patients with 1,209 side branches. Absorb BVS was related to a higher incidence of post-procedural SBO compared with the EES, and this effect was more pronounced with small side branches with an RVD ≤0.5 mm. Further investigation is required in a pivotal randomized controlled trial.

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REFERENCES

1. Meier B, Gruentzig AR, King SB III, et al. Risk of side branch occlusion during coronary angioplasty. Am J Cardiol 1984;53:10–4.
2. Holmes DR Jr., Holubkov R, Vlietstra RE, et al. Comparison of complications during percutaneous transluminal coronary angioplasty from 1977 to 1981 and from 1985 to 1986: the National Heart, Lung, and Blood Institute percutaneous transluminal coronary angioplasty registry. J Am Coll Cardiol 1988;12:1149–55.
3. Porto I, Selvanayagam JB, Van Gaal WJ, et al. Plaque volume and occurrence and location of periprocedural myocardial necrosis after percutaneous coronary intervention: insights from delayed-enhancement magnetic resonance imaging, thrombolysis in myocardial infarction myocardial perfusion grade analysis, and intravascular ultrasound. Circulation 2006;114:662–9.
4. Califf RM, Abdelmeguid AE, Kuntz RE, et al. Myonecrosis after revascularization procedures. J Am Coll Cardiol 1998;31:241–51.
5. Prasad A, Singh M, Lerman A, Lennon RJ, Holmes DR Jr., Rihal CS. Isolated elevation in troponin T after percutaneous coronary intervention is associated with higher long-term mortality. J Am Coll Cardiol 2006;48:1765–70.
6. Jensen LO, Maeng M, Kaltoft A, et al. Stent thrombosis, myocardial infarction, and death after drug-eluting and bare-metal stent coronary interventions. J Am Coll Cardiol 2007;50:463–70.
7. Fischman DL, Savage MP, Leon MB, et al. Fate of lesion-related side branches after coronary artery stenting. J Am Coll Cardiol 1993;22:1641–6.
8. Mazur W, Grinstead WC, Hakim AH, et al. Fate of side branches after intracoronary implantation of the Gianturco-Roubin flex-stent for

acute or threatened closure after percutaneous transluminal coronary angioplasty. Am J Cardiol 1994;74:1207–10.
9. Farooq V, Serruys PW, Heo JH, et al. New insights into the coronary artery bifurcation hypothesis-generating concepts utilizing 3-dimensional optical frequency domain imaging. J Am Coll Cardiol Intv 2011;4:921–31.
10. Popma JJ, Mauri L, O'Shaughnessy C, et al. Frequency and clinical consequences associated with sidebranch occlusion during stent implantation using zotarolimus-eluting and paclitaxel-eluting coronary stents. Circ Cardiovasc Interv 2009;2:133–9.
11. Lansky AJ, Yaqub M, Hermiller JB, et al. Side branch occlusion with everolimus-eluting and paclitaxel-eluting stents: three-year results from the SPIRIT III randomised trial. EuroIntervention 2010;6:J44–52.
12. Ormiston JA, Serruys PW, Regar E, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008; 371:899–907.
13. Serruys PW, Garcia-Garcia HM, Onuma Y. From metallic cages to transient bioresorbable scaffolds: change in paradigm of coronary revascularization in the upcoming decade? Eur Heart J 2012;33:16–25b.
14. Onuma Y, Serruys PW. Bioresorbable scaffold: the advent of a new era in percutaneous coronary and peripheral revascularization? Circulation 2011;123:779–97.
15. Serruys PW, Ormiston JA, Onuma Y, et al. A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373:897–910.
16. Onuma Y, Serruys PW, Ormiston JA, et al. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2010;6:447–53.
17. Dudek D, Onuma Y, Ormiston JA, Thuesen L, Miquel-Hebert K, Serruys PW. Four-year clinical follow-up of the ABSORB everolimus-eluting bioresorbable vascular scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2012;7:1060–1.
18. Oberhauser JP, Hossainy S, Rapoza RJ. Design principles and performance of bioresorbable polymeric coronary scaffolds. EuroIntervention 2009;5:F15–22.
19. Onuma Y, Serruys PW, Gomez J, et al. Comparison of in vivo acute stent recoil between the bioresorbable everolimus-eluting coronary scaffolds (revision 1.0 and 1.1) and the metallic everolimus-eluting stent. Catheter Cardiovasc Interv 2011;78:3–12.
20. Farooq V, Gomez-Lara J, Brugaletta S, et al. Proximal and distal maximal luminal diameters as a guide to appropriate deployment of the ABSORB everolimus-eluting bioresorbable vascular scaffold: a sub-study of the ABSORB cohort B and the on-going ABSORB EXTEND single arm study. Catheter Cardiovasc Interv 2012;79:880–8.
21. Serruys PW, Ong AT, Piek JJ, et al. A randomized comparison of a durable polymer everolimus-eluting stent with a bare metal coronary stent: the SPIRIT first trial. EuroIntervention 2005;1:58–65.
22. Serruys PW, Ruygrok P, Neuzner J, et al. A randomised comparison of an everolimus-eluting coronary stent with a paclitaxel-eluting coronary stent: the SPIRIT II trial. EuroIntervention 2006;2:286–94.
23. Garg S, Serruys PW. Coronary stents: current status. J Am Coll Cardiol 2010;56:S1–42.
24. Vranckx P, Cutlip DE, Mehran R, et al. Myocardial infarction adjudication in contemporary all-comer stent trials: balancing sensitivity and specificity. Addendum to the historical MI definitions used in stent studies. EuroIntervention 2010;5:871–4.
25. Foley DP, Escaned J, Strauss BH, et al. Quantitative coronary angiography (QCA) in interventional cardiology: clinical application of QCA measurements. Prog Cardiovasc Dis 1994;36:363–84.
26. Gronenschild E, Janssen J, Tijdens F. CAAS. II: A second generation system for off-line and on-line quantitative coronary angiography. Cathet Cardiovasc Diagn 1994;33:61–75.
27. Haase J, Escaned J, van Swijndregt EM, et al. Experimental validation of geometric and densitometric coronary measurements on the new generation cardiovascular angiography analysis system (CAAS II). Cathet Cardiovasc Diagn 1993;30:104–14.
28. Tsuchida K, van der Giessen WJ, Patterson M, et al. In vivo validation of a novel three-dimensional quantitative coronary angiography system (CardiOp-B): comparison with a conventional two-dimensional system (CAAS II) and with special reference to optical coherence tomography. EuroIntervention 2007;3:100–8.
29. Aliabadi D, Tilli FV, Bowers TR, et al. Incidence and angiographic predictors of side branch occlusion following high-pressure intracoronary stenting. Am J Cardiol 1997;80:994–7.
30. Morimoto S, Hiramitsu S, Yamada K, Uemura A, Kubo N, Mizuno Y. Lesions in side branches of arteries having undergone percutaneous transluminal coronary angioplasty: a histopathologic study. Am Heart J 1990;120:864–72.
31. Tanabe K, Serruys PW, Degertekin M, et al. Fate of side branches after coronary arterial sirolimus-eluting stent implantation. Am J Cardiol 2002;90:937–41.
32. Farooq V, Okamura T, Onuma Y, Gogas BD, Serruys PW. Unravelling the complexities of the coronary bifurcation: is this raising a few eyebrows? EuroIntervention 2012;7:1133–41.
33. Diletti R, Farooq V, Muramatsu T, et al. Serial 2- and 3-dimensional visualization of side branch jailing after metallic stent implantation. J Am Coll Cardiol Intv 2012;5:1089–90.
34. Okamura T, Serruys PW, Regar E. The fate of bioresorbable struts located at a side branch ostium: serial three-dimensional optical coherence tomography assessment. Eur Heart J 2010;31:2179.

Key Words: bioresorbable vascular scaffold ■ complications ■ drug-eluting stent(s) ■ myocardial infarction ■ side branch occlusion

APPENDIX

For a supplementary figure, please see the online version of this article.