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Randomized Comparison Between Everolimus-Eluting Bioresorbable Scaffold and Metallic Stent

Multimodality Imaging Through 3 Years

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ABSTRACT

OBJECTIVES The aim of this study was to investigate the vascular responses and fates of the scaffold after bioresorbable vascular scaffold (BVS) implantation using multimodality imaging.

BACKGROUND Serial comprehensive image assessments after BVS implantation in the context of a randomized trial have not yet been reported.

METHODS In the ABSORB Japan trial, 400 patients were randomized to a BVS (n = 266) or a cobalt-chromium everolimus-eluting stent (n = 134). Through 3 years, patients underwent serial angiography and intravascular ultrasound or optical coherence tomography (OCT).

RESULTS Luminal dimension at 3 years was consistently smaller with the BVS than with the cobalt-chromium everolimus-eluting stent (mean angiographic minimal luminal diameter 2.04 ± 0.63 mm vs. 2.40 ± 0.56 mm, mean difference −0.37 mm [95% confidence interval: −0.50 to −0.24 mm]; $p < 0.001$), mainly because of smaller device area (6.13 ± 2.03 mm^2 vs. 7.15 ± 2.16 mm^2, mean difference −1.04 mm^2 [95% confidence interval: −1.66 to −0.42 mm^2]; $p < 0.001$), and larger neointimal area (2.10 ± 0.61 mm^2 vs. 1.86 ± 0.64 mm^2, mean difference 0.24 mm^2 [95% confidence interval: 0.06 to 0.43 mm^2]; $p = 0.01$) by OCT. BVS-treated vessels did not show previously reported favorable vessel responses, such as positive vessel remodeling, late luminal enlargement, and restoration of vasomotion, although the OCT-based healing score was on average zero (interquartile range: 0.00 to 0.00). At 3 years, intraluminal scaffold dismantling (ISD) was observed in 14% of BVS. On serial OCT, ISD was observed in 6 lesions at 2 years, where the struts had been fully apposed at post-procedure, while ISD was observed in 12 lesions at 3 years, where 8 lesions were free from ISD on 2-year OCT. In 5 cases of very late scaffold thrombosis, strut discontinuities were detected in all 4 cases with available OCT immediately before reintervention.

CONCLUSIONS In this multimodality serial imaging study, luminal dimension at 3 years was smaller with the BVS than with the cobalt-chromium everolimus-eluting stent. ISD, suspected to be one of the mechanisms of very late BVS thrombosis, was observed in a substantial proportion of cases at 3 years, which developed between post-procedure and 2 years and even beyond 2 years. (AVJ-301 Clinical Trial: A Clinical Evaluation of AVJ-301 [Absorb™ BVS] in Japanese Population [ABSORB JAPAN]; NCT01844284) (J Am Coll Cardiol Intv 2020;13:116–27) © 2020 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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A drug-eluting stent (DES) prevents repeat revascularization more efficiently than a bare-metal stent and is currently a standard treatment device in percutaneous coronary intervention (1). However, the permanent presence of metallic foreign material could cause late complications such as metallic stent fractures, late restenosis, and neoatherosclerosis (2,3), resulting in a steady increase of stent-related events in the long term (4).

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Fully bioresorbable scaffolds were designed to mitigate the potential long-term adverse effect of metallic DES (5). The device offers transient scaffolding of the dilated coronary vessel to prevent acute recoil and abrupt vessel closure, elutes an antiproliferative drug to prevent neointimal hyperplasia, and ultimately disappears through bioresorption. After bioresorption, the vessel may recover physiological functions such as mechanotransduction, cyclic strain, and vasomotion, which theoretically could lower the risk for long-term event (6,7).

The polylactic bioresorbable everolimus-eluting Absorb vascular scaffold (Abbott Vascular, Santa Clara, California) received its Conformité Européenne mark in 2010 and was approved by the U.S. Food and Drug Administration in the United States and the Pharmaceuticals and Medical Devices Agency in Japan on the basis of the reported noninferiority of the bioresorbable vascular scaffold (BVS) to the cobalt-chromium everolimus-eluting stent (CoCr-EES) at 1 year in the pivotal trials (8,9). However, long-term clinical results from these pivotal trials demonstrated that there were higher risks for device thrombosis with the BVS than with the CoCr-EES during the time period when bioresorption was still ongoing (10). The safety concerns raised by these results and the low market share of the device forced the manufacturer to discontinue marketing the device. Nevertheless, to improve bioresorbable scaffolds further, it is essential to investigate the long-term behavior of the BVS using intravascular imaging and to identify potential mechanisms of late failures of the current BVS such as device thrombosis. Previous imaging studies up to 5 years after BVS implantation have suggested favorable vascular responses, including restoration of vasomotion and endothelium-dependent vasodilation, late luminal enlargement with plaque regression, and positive vessel remodeling, and the formation of a stable-appearing neointima (11–13). However, these studies were single-arm studies including relatively small numbers of patients, and no previous imaging study has compared vessel responses after BVS implantation with those after metallic DES implantation. Therefore, we conducted a comprehensive serial imaging study using angiography, optical coherence tomography (OCT) and intravascular ultrasound (IVUS) up to 3 years after BVS compared with CoCr-EES implantation in the randomized ABSORB Japan trial.

ABBREVIATIONS AND ACRONYMS

BVS = bioresorbable vascular scaffold(s)

CoCr-EES = cobalt-chromium everolimus-eluting stent(s)

DES = drug-eluting stent(s)

IVUS = intravascular ultrasound

OCT = optical coherence tomography

PSP = pre-dilatation, appropriate sizing, and post-dilatation

QCA = quantitative coronary angiographic

TLF = target lesion failure

TLR = target lesion revascularization

METHODS

STUDY DESIGN AND POPULATION. ABSORB Japan was a prospective, multicenter, randomized, single-blind, active-controlled clinical trial randomizing 400 patients in a 2:1 ratio to treatment with the BVS (n = 266) or the CoCr-EES (n = 134). The details of the trial have been published elsewhere (9). The primary endpoint of the present study was target lesion failure (TLF) at 12 months, whereas the imaging investigations and analysis at 3 years were pre-specified per protocol (9). The patients were subrandomized into 3 imaging groups: the OCT-1 subgroup (n = 125) with serial OCT at post-implantation, 2 years, and 3 years; the OCT-2 group (n = 125) with OCT only at 3 years; and the IVUS subgroup (n = 150) with IVUS at post-implantation and 3 years. Quantitative coronary angiographic (QCA) analysis was performed at

Medical Center, Boston, Massachusetts; [p]Columbia University Medical Center, NewYork-Presbyterian Hospital, and the Cardiovascular Research Foundation, New York, New York; and the [q]International Centre for Circulatory Health, National Heart and Lung Institute, Imperial College London, London, United Kingdom. The sponsor (Abbott Vascular) was involved in study design, data collection, data analysis, data interpretation, and writing of this report. The corresponding author had full access to the analyzed data in the study and accepts full responsibility for the integrity of the study and the decision to submit for publication. Drs. Onuma and Serruys are members of the advisory board of Abbott Vascular. Dr. Stone is chairman of the advisory board of Abbott Vascular; and is a consultant to Reva. Dr. Popma has received grants and personal fees from Abbott Vascular. Drs. Namiki, Ueno, Ando, Igarashi, Kozuma, Tanabe, and Kimura have received personal fees for advisory agreements with Abbott Vascular Japan. Drs. Kusano, Rapoza, and Simonton are employees of Abbott Vascular. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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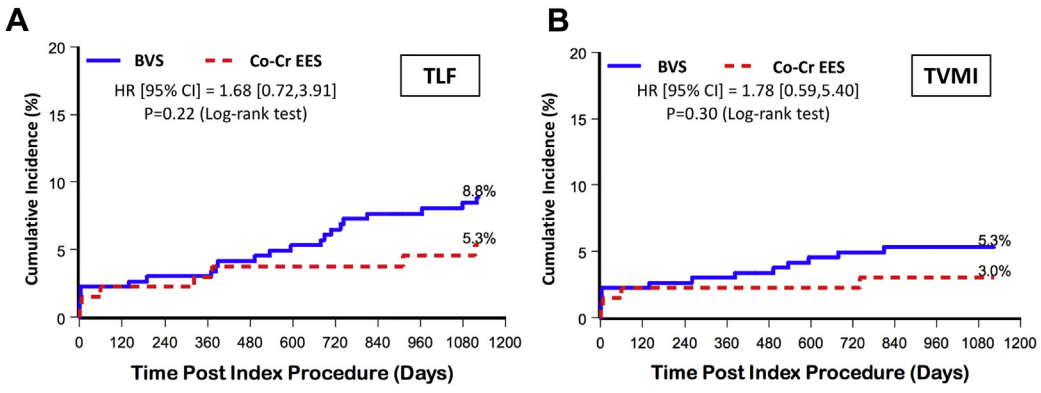
FIGURE 1 Kaplan-Meier Curves Representing the Estimated Cumulative Incidences of Clinical Endpoints



Time After Index Procedure (days)	0	37	208	393	758	1123
BVS N of patients at risk	266	259	256	251	239	225
N of patients with event	3	6	8	9	15	17
Cumulative incidence (%)	1.1	2.3	3	4.2	7.3	8.8
Co-Cr EES N of patients at risk	134	131	130	128	124	119
N of patients with event	1	2	3	5	5	7
Cumulative incidence (%)	0.7	1.5	2.3	3.8	3.8	5.3

Time After Index Procedure (days)	0	37	208	393	758	1123
BVS N of patients at risk	266	259	257	253	244	232
N of patients with event	3	6	7	9	13	14
Cumulative incidence (%)	1.1	2.3	2.6	3.4	4.9	5.3
Co-Cr EES N of patients at risk	134	131	130	130	125	122
N of patients with event	1	2	3	3	4	4
Cumulative incidence (%)	0.7	1.5	2.3	2.3	3.0	3.0

(A) Target lesion failure (TLF), **(B)** target vessel myocardial infarction (TV-MI), **(C)** ischemia-driven target lesion revascularization (ID-TLR), and **(D)** device (stent/scaffold) thrombosis. BVS = bioresorbable vascular scaffold; CI = confidence interval; Co-Cr EES = cobalt-chromium everolimus-eluting stent; HR = hazard ratio.

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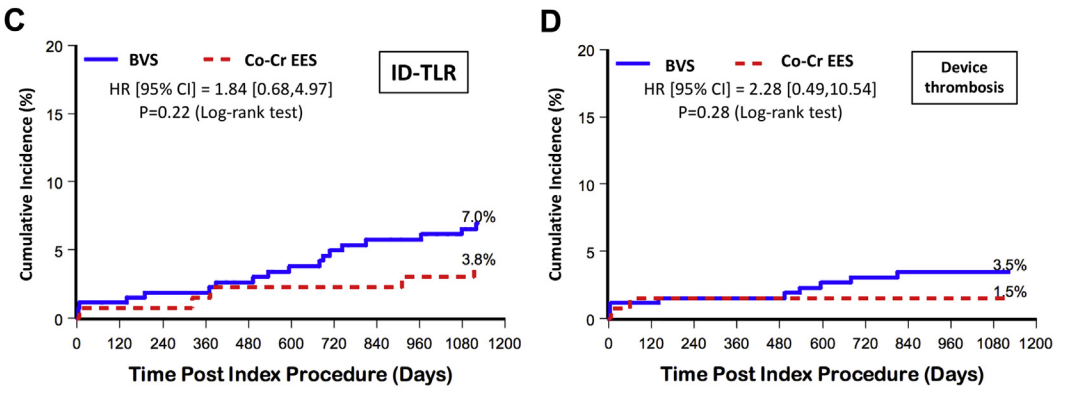
baseline, 13 months, and 3 years in all patients and at 2 years in the OCT-1 subgroup (Online Figure S1). The ethics committees approved the protocol at all participating institutions. All patients provided written informed consent and were blinded to their treatment assignment through 5-year follow-up. All patients were maintained on a thienopyridine for at least 12 months and aspirin indefinitely.

CLINICAL ENDPOINTS AND DEFINITIONS. Death, myocardial infarction, target lesion revascularization (TLR) or target vessel revascularization and stent or scaffold thrombosis were adjudicated by an independent blinded clinical events committee (Harvard Clinical Research Institute, Boston, Massachusetts). Independent study monitors verified all case report forms on site. A Data and Safety Monitoring Board monitored patient safety. Definitions of stent or scaffold thrombosis and other endpoints were based on the Academic Research Consortium criteria (14). TLF was defined as a composite of cardiac death, target vessel myocardial infarction, and ischemia-driven TLR. A complete list of endpoints is provided elsewhere (9).

DEVICE IMPLANTATION AND IMAGING FOLLOW-UP. The details of the implantation technique were previously described (9). The proportion of optimal implantation technique, so-called PSP (a combination of pre-dilatation, appropriate sizing, and post-dilatation) was evaluated stratified to each imaging subgroup. At follow-up, coronary angiography was repeated in the same angiographic views as at post-procedure. IVUS and OCT were performed in the target lesion including 5 mm distal and proximal to the stent or scaffold. The imaging data were analyzed by the independent core laboratories (quantitative coronary angiography: Beth Israel Deaconess Medical Center, Boston, Massachusetts; IVUS: Stanford University, Stanford, California; and OCT: Cardialysis, Rotterdam, the Netherlands). In patients with interim TLR, pre-TLR QCA data were carried forward up to the 3-year follow-up QCA study for the nonserial analysis, while for the serial analysis, pre-TLR QCA

FIGURE 1 Continued



Time After Index Procedure (days)	0	37	208	393	758	1123
BVS N of patients at risk	266	262	259	255	243	229
N of patients with event	0	3	5	7	14	18
Cumulative incidence (%)	0.0	1.1	1.9	2.7	5.4	7.0
Co-Cr EES N of patients at risk	134	132	132	130	126	121
N of patients with event	0	1	1	3	3	5
Cumulative incidence (%)	0.0	0.8	0.8	2.3	2.3	3.8

Time After Index Procedure (days)	0	37	208	393	758	1123
BVS N of patients at risk	266	262	260	257	248	236
N of patients with event	0	3	4	4	8	9
Cumulative incidence (%)	0	1.1	1.5	1.5	3.1	3.5
Co-Cr EES N of patients at risk	134	132	131	131	127	124
N of patients with event	0	1	2	2	2	2
Cumulative incidence (%)	0.0	0.8	1.5	1.5	1.5	1.5

data were carried forward only to the next follow-up QCA study.

The details of IVUS and optical coherence tomographic analysis methods are described in the Online Appendix. In serial IVUS and optical coherence tomographic analysis, cases with interim TLR were excluded because of the presence of a nonstudy device.

OCT endpoints included the mean and minimal in-device luminal area, the mean and maximum neointimal hyperplasia area, the mean device area, and the percentage of malapposed struts (15). IVUS endpoints included mean areas of vessel, stent or scaffold, and neointima and mean and minimal areas of the lumen, which were measured in the device segment using validated software (echoPlaque, Indec Systems, Los Altos, CA). At 3 years, scaffold area of the BVS was not measured, because of limited visibility of struts due to bioresorption of the device. Strut discontinuities were assessed on OCT as the presence of overhang or stacked struts, categorized into 4 groups from high to low ranking: "uncovered and malapposed," "uncovered and apposed," "covered and malapposed," and "covered and apposed." If more than 1 condition was present in 1 lesion, the lesion was classified with the worst ranking.

STATISTICAL ANALYSIS. The clinical endpoint was evaluated in the intent-to-treat population, whereas the imaging endpoint was evaluated specifically in a population excluding patients who did not receive the assigned treatment. For binary variables, counts, percentages, and 95% confidence intervals were calculated. Pearson's chi-square test or the Fisher exact test were performed as appropriate. Continuous variables are presented as mean ± SD or as median (interquartile range) and were compared using Student's *t*-test or a Wilcoxon rank sum test on the basis of the distributions. Paired numeric data obtained in the serial imaging studies were compared using the paired *t*-test. For time-to-event variables, survival curves were constructed using Kaplan-Meier estimates to demonstrate the cumulative incidences and were compared using the log-rank test. All statistical analyses were performed using SAS versions 9.2 and 9.3 (SAS Institute, Cary, North Carolina).

TABLE 1 Nonserial Results of Quantitative Coronary Angiography, Intravascular Ultrasound, and optical Coherence Tomography at Baseline and at 3 Years

	BVS		CoCr-EES		
	Number of Lesions		Number of Lesions		p Value
QCA					
Lesion length, mm					
Pre-procedure	272	13.5 ± 5.28	137	13.3 ± 5.52	0.78
Reference vessel diameter, mm					
Pre-procedure	272	2.72 ± 0.44	137	2.79 ± 0.46	0.11
Post-procedure	272	2.76 ± 0.42	137	2.85 ± 0.43	0.04
At 13 months	260	2.70 ± 0.42	129	2.80 ± 0.44	0.046
At 3 yrs	238	2.70 ± 0.43	119	2.81 ± 0.45	0.03
MLD, mm					
Pre-procedure	272	0.96 ± 0.33	137	0.99 ± 0.36	0.42
Post-procedure*	272	2.42 ± 0.38	137	2.64 ± 0.40	<0.0001
At 13 months*	260	2.23 ± 0.47	129	2.48 ± 0.53	<0.0001
At 3 yrs*	238	2.04 ± 0.63	119	2.40 ± 0.56	<0.0001
DS, %					
Pre-procedure	272	64.6 ± 11.2	137	64.7 ± 10.9	0.93
Post-procedure*	272	11.8 ± 7.4	137	7.1 ± 8.0	<0.0001
At 13 months*	260	17.4 ± 12.8	129	11.7 ± 12.3	<0.0001
At 3 yrs*	238	24.9 ± 19.0	119	14.7 ± 14.8	<0.0001
Late lumen loss (in-device), mm					
At 13 months*	260	0.19 ± 0.31	129	0.16 ± 0.33	0.35
At 3 yrs*	238	0.39 ± 0.55	119	0.23 ± 0.42	0.003
Nitrate vasoreactivity test at 3 yrs, mm					
Mean luminal diameter pre-NTG*	219	2.48 ± 0.52	110	2.82 ± 0.49	<0.001
Mean luminal diameter post-NTG*	220	2.54 ± 0.52	112	2.88 ± 0.48	<0.001
Absolute change*	218	0.06 ± 0.15	110	0.06 ± 0.11	0.70
IVUS					
Mean vessel area, mm^2					
Post-procedure	77	13.69 ± 4.51	41	14.61 ± 5.04	0.33
At 3 yrs	70	13.42 ± 4.49	37	14.95 ± 4.99	0.12
Mean scaffold/stent area, mm^2					
Post-procedure	97	6.48 ± 2.00	47	7.33 ± 2.12	0.02
At 3 yrs	–	NA	43	7.70 ± 2.37	NA
Mean total plaque area, mm^2					
Post-procedure	77	7.29 ± 2.72	41	7.36 ± 3.13	0.91
At 3 yrs	70	7.49 ± 2.33	37	8.14 ± 3.09	0.27
Mean luminal area, mm^2					
Post-procedure	97	6.49 ± 2.00	47	7.35 ± 2.14	0.02
At 3 yrs	86	6.13 ± 2.41	43	6.83 ± 2.29	0.11
Absolute change	83	−0.45 ± 1.28	41	−0.67 ± 0.98	0.30
Minimum luminal area, mm^2					
Post-procedure	97	5.39 ± 1.80	47	6.32 ± 2.04	0.009
At 3 yrs	86	4.56 ± 2.06	43	5.23 ± 2.11	0.09

Continued on the next page

RESULTS

BASELINE CHARACTERISTICS AND CLINICAL OUTCOMES. The study flowchart for clinical follow-up and the baseline characteristics are presented in Online Figure S1 and Online Tables S1, S2, and S3. Eight patients in BVS arm and 4 patients in CoCr-EES arm withdrew their consent. In total, 96.5% had 3-year clinical follow-up (median 1,098 days; interquartile range: 1,085 to 1,110 days). At 3 years, 40.5% of patients were on dual-antiplatelet therapy (BVS 41.7% vs. CoCr-EES 38.1%). Clopidogrel was predominantly used as a $P2Y_{12}$ inhibitor, while prasugrel was used in 7 and 6 patients in the BVS and CoCr-EES arms, respectively.

The PSP criteria were achieved in only 16 lesions (5.8%) in the BVS arm at the time of the procedure (7 lesions [8.1%] in the IVUS subgroup and 8 lesions [6.1%] in the OCT subgroup).

The cumulative 3-year incidence of TLF was numerically higher in the BVS arm than in the CoCr-EES arm (8.9% vs. 5.5%; p = 0.23) (**Figure 1**, Online Table S4). The cumulative 3-year incidence of stent or scaffold thrombosis was also numerically higher in the BVS arm than in the CoCr-EES arm (3.6% vs. 1.6%; p = 0.17): there were 4 BVS thromboses and 2

TABLE 1 Continued

	BVS		CoCr-EES		
	Number of Lesions		Number of Lesions		p Value
OCT					
Minimum scaffold/stent area (abluminal), mm^2					
Post-procedure	81	6.55 ± 1.99	43	6.90 ± 2.44	0.4
At 2 yrs	77	6.31 ± 2.05	38	7.11 ± 2.42	0.07
At 3 yrs	131	6.13 ± 2.03	66	7.15 ± 2.16	<0.001
Neointimal area (on top of/in-between strut), mm^2					
At 2 yrs	77	2.08 ± 0.66	38	1.82 ± 0.67	0.05
At 3 yrs	131	2.10 ± 0.61	66	1.86 ± 0.64	0.01
Minimum flow area, mm^2					
Post-procedure	81	5.60 ± 1.81	43	5.95 ± 2.23	0.35
At 2 yrs	77	4.10 ± 1.79	38	5.05 ± 1.97	0.01
At 3 yrs	131	4.02 ± 1.74	66	5.10 ± 2.03	<0.001
Late strut discontinuities					
At 2 yrs	77	19 (24.7)	38	0 (0)	NA
At 3 yrs	130†	70 (53.8)	64‡	3 (4.7)	<0.001
Healing score					
At 2 yrs	77	0.00 (0.00-1.35)	38	0.00 (0.00-1.04)	0.66
At 3 yrs	131	0.00 (0.00-0.00)	66	0.00 (0.00-0.62)	0.06
Lesion with ISA					
Post-procedure	81	67 (82.7)	43	40 (93.0)	0.17
At 2 yrs	77	6 (7.8)	38	6 (15.8)	0.19
At 3 yrs	131	13 (9.9)	66	15 (22.7)	0.02
Covered struts, %					
At 2 yrs	77	100.0 (99.4-100)	38	100 (99.7-100)	0.44
At 3 yrs	131	100 (100-100)	66	100 (100-100)	1.00

Values are mean ± SD, n (%), or median (interquartile range), unless otherwise indicated. *In-device analysis. †One lesion was not analyzable because of incomplete pull-back length. ‡Two lesions were not analyzable because of artifact.

BVS = bioresorbable vascular scaffold; CoCr-EES = cobalt-chromium everolimus-eluting stent; DS = diameter stenosis; ISA = incomplete strut apposition; IVUS = intravascular ultrasound; MLD = minimum luminal diameter; NTG = nitroglycerin; NA = not available; OCT = optical coherence tomography; QCA = quantitative coronary angiography.

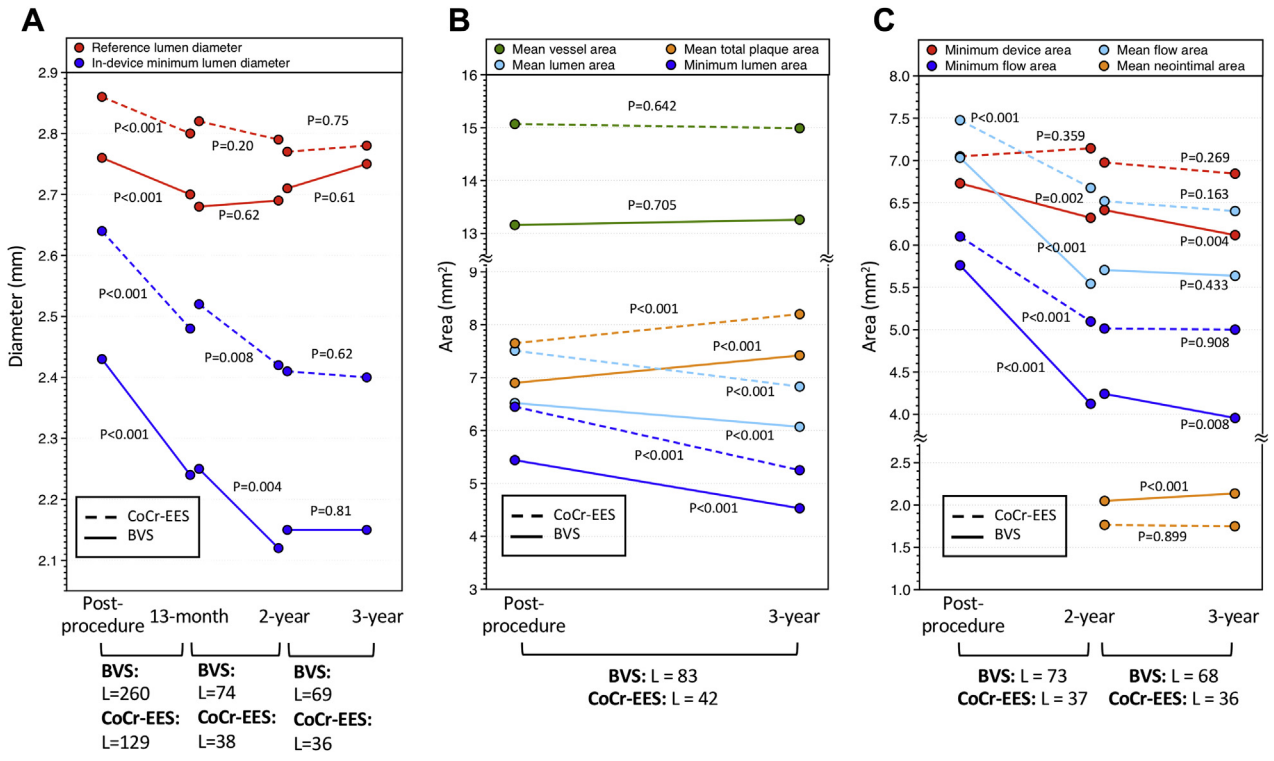
CoCr-EES thromboses in the first year, 4 BVS thromboses between 1 and 2 years (16), and 1 BVS thrombosis on day 810 in the third year (**Figure 1**, Online Table S4, Online Figure S2).

OPTICAL COHERENCE TOMOGRAPHIC FINDINGS. OCT was performed and analyzable in 124 patients (BVS, n = 81; CoCr-EES, n = 43) at post-procedure, in 110 patients (BVS, n = 73; CoCr-EES, n = 37) at 2 years, and in 192 patients (BVS, n = 126; CoCr-EES, n = 66) at 3 years (Online Figure S1). Minimum flow area was numerically smaller at post-procedure and significantly smaller at 2 and 3 years in the BVS arm than in the CoCr-EES arm (**Table 1**, Online Table S5). In the serial analysis, minimum flow area decreased significantly between 2 and 3 years in the BVS arm but not in the CoCr-EES arm (**Figure 2**, Online Table S6). Minimum scaffold or stent area was also numerically smaller at post-procedure and significantly smaller at 2 and 3 years in the BVS arm than in the CoCr-EES arm (**Table 1**, Online Table S5). In the serial analysis, minimum scaffold or stent area decreased significantly between post-procedure and 2 years and between 2 and 3 years in the BVS arm but not in the CoCr-EES arm (**Figure 2**). Neointimal area was significantly larger in the BVS arm than in the CoCr-EES arm at 3 years (**Table 1, Figure 3**, Online Table S5). In the serial analysis, neointimal area in the BVS arm, but not in the CoCr-EES arm, significantly increased between 2 and 3 years (**Figure 2**). The decreased luminal area at follow-up in the BVS arm should be attributed more to an increase in neointimal area rather than a decrease in scaffold area (Online Table S7).

At 3 years, the coverage of struts was complete in both arms, whereas lesions with incomplete strut apposition were less frequent in the BVS arm than in the CoCr-EES arm (**Table 1**, Online Table S5). Qualitative light intensity analysis of neointima demonstrated that homogeneous neointima was more frequently observed in the BVS arm than in the CoCr-EES arm at 3 years (Online Table S5). The healing score was optimal in both arms (**Table 1, Figure 3**, Online Table S5).

At 3 years, strut discontinuities were found in 70 cases (54%) in the BVS arm, 52 of which were covered and apposed. There were 3 cases with strut discontinuities in the CoCr-EES arm, which were presumably

FIGURE 2 Serial Imaging Observations After Bioresorbable Vascular Scaffold and Cobalt-Chromium Everolimus-Eluting Stent Implantation



(A) Quantitative coronary angiography (QCA), **(B)** intravascular ultrasound (IVUS), and **(C)** optical coherence tomography (OCT). Device areas are derived from abluminal contours. Neointimal areas are presented as on-top of or in-between struts. Only those lesions with paired study were included in this serial analysis. In patients with interim target lesion revascularization (TLR), pre-TLR quantitative coronary angiography data were carried forward only to the nearest follow-up quantitative coronary angiographic study for this serial analysis. In serial IVUS and optical coherence tomography analysis, cases with interim TLR were excluded because of the presence of a nonstudy device. BVS = bioresorbable vascular scaffold; CoCr-EES = cobalt-chromium everolimus-eluting stent; IVUS = intravascular ultrasound.

due to deformation of proximal edge of stent caused by guiding catheter or other interventional devices (Online Figure S3). In 18 cases (14%), discontinued struts were either uncovered and/or malapposed (intraluminal scaffold dismantling). Of 5 cases with very late scaffold thrombosis of BVS, strut discontinuities were detected in all 4 cases by OCT performed just before reintervention (Figure S2, Online Table S8) (15).

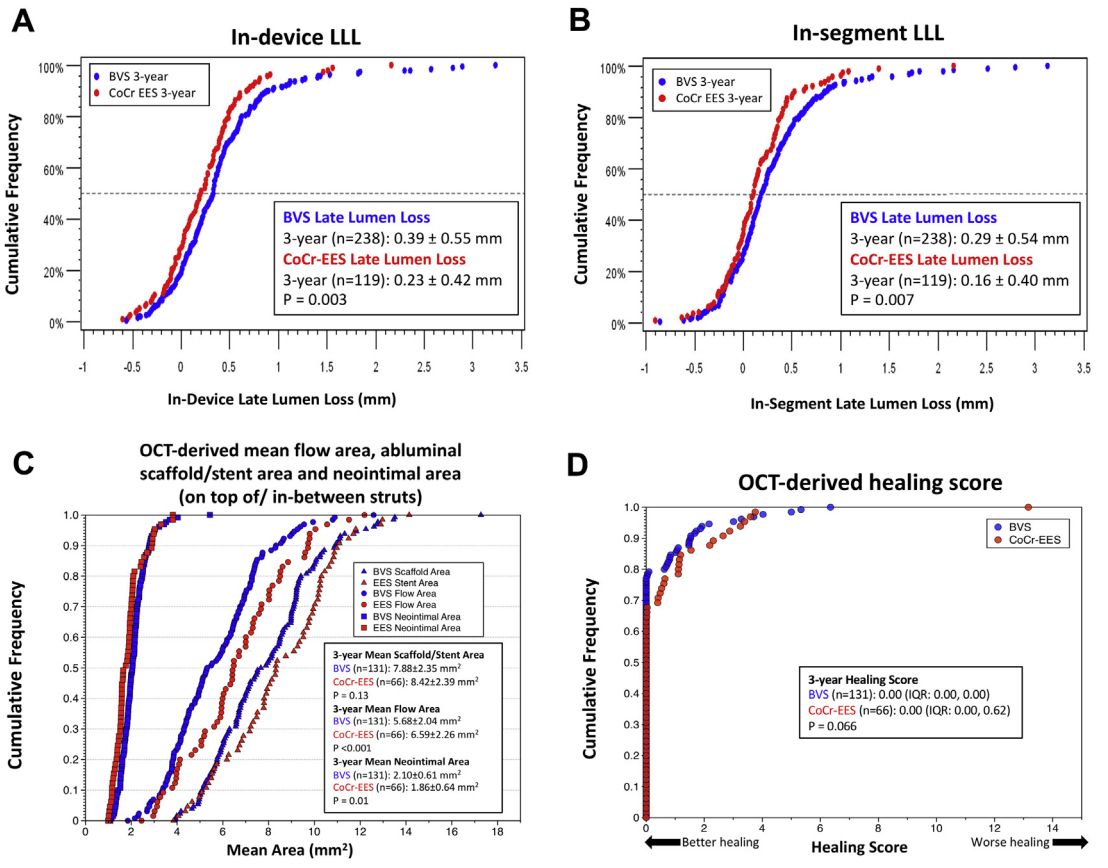
In the serial analysis in the OCT-1 group, there were 6 lesions (8%) with intraluminal scaffold dismantling at 2 years, in all of which struts were fully apposed at post-procedure (Online Figure S4). At 3 years, there were 12 lesions (18%) with intraluminal scaffold dismantling, in 8 of which there were no discontinuities or only covered and apposed discontinuities at 2 years, suggesting that new intraluminal scaffold dismantling occurred between 2 and 3 years even from struts without any discontinuity (**Central Illustration**, Online Tables S5 and S9).

QCA AND IVUS FINDINGS. The details of QCA and IVUS findings are presented in **Table 1, Figures 2 and 3**, and the Online Tables S10 and S11. On quantitative coronary angiography, change in mean luminal diameter after intracoronary injection of nitrate was not significantly different between the 2 arms (BVS 0.06 ± 0.11 mm vs. CoCr-EES 0.06 ± 0.11 mm; p = 0.69) (Online Table S10). In the serial IVUS analysis, mean vessel area was unchanged not only in the CoCr-EES arm but also in the BVS arm, suggesting no positive vessel remodeling in the BVS arm (**Figure 2**). There were also few cases with expansive vessel remodeling in the BVS arm (9.7%) (Online Figure S5).

DISCUSSION

The main findings in the ABSORB Japan 3-year multimodality serial imaging assessment were the following: 1) Luminal dimension at 3 years was smaller in the BVS arm than in the CoCr-EES arm

FIGURE 3 **Cumulative Distribution Function Curves of Angiographic Late Lumen Loss and Optical Coherence Tomographic Parameters at 3-Year Follow-Up**

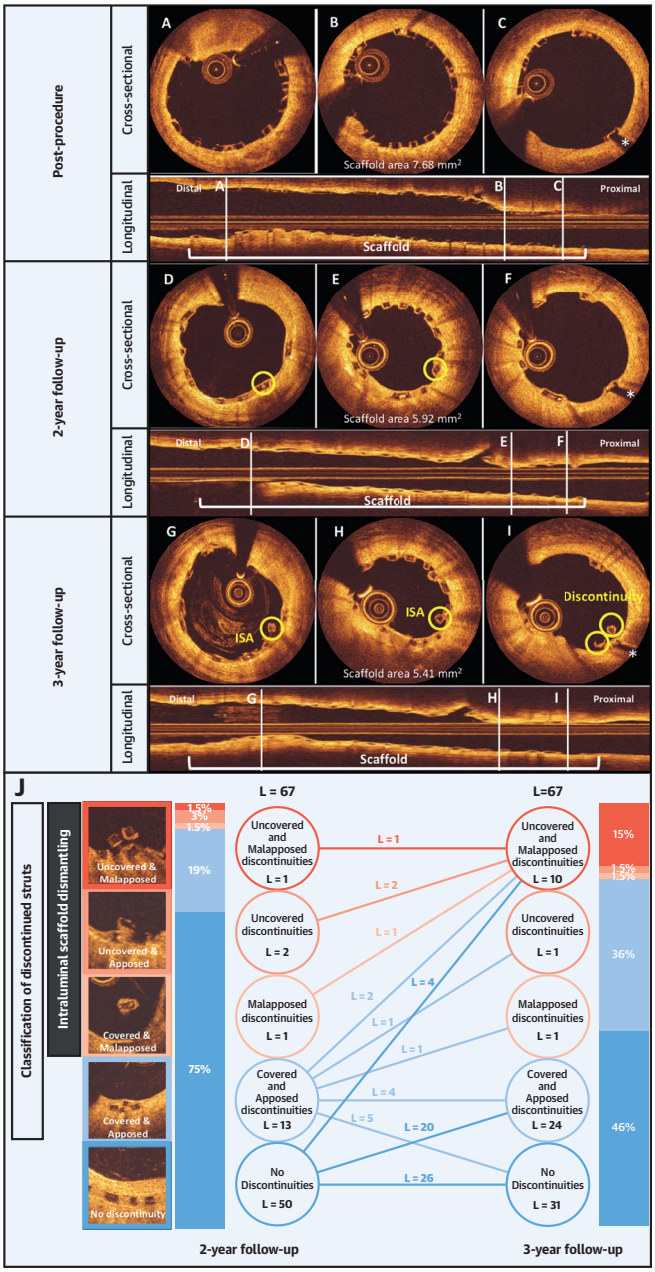


(A) Angiographic in-device late lumen loss (LLL); **(B)** angiographic in-segment LLL; **(C)** optical coherence tomography (OCT)–derived mean flow area, abluminal scaffold/stent area, and neointimal area (on top of or in between struts); and **(D)** OCT-derived healing score.
BVS = bioresorbable vascular scaffold; CoCr-EES = cobalt-chromium everolimus-eluting stent; IQR: interquartile range.

because of the combined effects of smaller device and luminal dimension at post-procedure, further decrease in scaffold dimension during follow-up, and greater neointimal formation with the BVS; 2) BVS-treated vessels did not show previously reported favorable vessel responses, such as positive vessel remodeling, late luminal enlargement, and restoration of vasomotion; and 3) intraluminal scaffold dismantling, suspected as one of the mechanisms of very late BVS thrombosis, was observed in 14% of cases at 3 years, 75% of which newly developed between 2 and 3 years.

The 3-year clinical outcomes in the present study were consistent with those of other randomized trials comparing BVS with metallic DES, demonstrating numeric excess of adverse events such as TLF and scaffold thrombosis with BVS (17–19). The strength of the present study was the extensive multimodality serial imaging assessment after BVS compared with CoCr-EES implantation in a randomized scheme. The time course of serial luminal change after device implantation was basically not different between the BVS and CoCr-EES, with progressive luminal loss until 2 years, which was somewhat stabilized beyond 2 years. However, luminal dimension was smaller in the BVS arm than in the CoCr-EES arm throughout the 3-year follow-up period. IVUS and OCT in the present study provided important information on the serial changes in device and vessel wall geometry, shedding light on the mechanisms of the different luminal dimensions between BVS and CoCr-EES. The QCA, IVUS, and optical coherence tomographic findings in the present study were generally concordant with one another, although there were some minor differences between the imaging modalities. The smaller luminal dimension with the BVS relative to the CoCr-EES was,

CENTRAL ILLUSTRATION **A Representative Case With Late Acquired Strut Malapposition and Discontinuity of Bioresorbable Vascular Scaffold and Changes in the Frequency of Late Discontinuity With Serial Optical Coherence Tomography at 2 and 3 Years**



Onuma, Y. et al. J Am Coll Cardiol Intv. 2020;13(1):116–27.

(A–I) A representative case with late acquired strut malapposition and discontinuity of bioresorbable vascular scaffold (BVS). Each cross-sectional image at 3-year follow-up was matched with a cross section at 2-year follow-up and at post-procedure **(A, D, and G; B, E, and H; and C, F, and I)**. Struts with incomplete coverage at 2-year follow-up became malapposed at 3-year follow-up **(yellow circles in G and H)**. Overhung struts were observed at 3-year follow-up **(yellow circles in I)**, whereas these findings were not observed at 2-year follow-up. Scaffold areas are calculated with abluminal contours. Asterisk denotes proximal marker. **(J)** Changes in the frequency of late strut discontinuity with serial optical coherence tomography (OCT) at 2 and 3 years in 67 scaffolds. Two lesions with malapposed and uncovered discontinuity observed at 2-year follow-up did not have analyzable OCT for the purpose of strut assessments at 3 years. These 2 lesions are not presented in these serial observations. ISA = incomplete strut apposition; L = number of lesions.

in totality, due to the combined effects of smaller device and luminal dimension at post-procedure, further decrease in scaffold dimension during follow-up, and greater neointimal formation in BVS. The smaller device area post-implantation was presumably due to the limited mechanical property of BVS (5) and/or a relatively conservative optimization strategy for BVS compared with CoCr-EES. Further improvement of BVS targeting less acute and chronic recoil would be required to optimize the luminal outcome of BVS.

Previous small single-arm imaging studies have reported positive vessel remodeling, late luminal enlargement, and restoration of vasomotion during the resorption phase of BVS (5,17,20). We did not find any of those favorable vessel responses at 3 years in this large multimodality imaging study with a randomized scheme between BVS and metallic DES, although a complete healing response and dominance of homogeneous neointimal formation were observed in the BVS arm. The possible reason for absence of positive vessel remodeling may be attributed to relatively small sample size or use of different IVUS system between baseline and follow-up.

Very late scaffold thrombosis beyond 1 year is a major safety issue with BVS; however, its causative mechanism is still unclear. Previous optical coherence tomographic studies have suggested a high prevalence of intraluminal scaffold dismantling at the time of very late BVS thrombosis (21,22). In the present study, OCT also revealed the structural discontinuities (either covered or uncovered) in all cases at the time of very late BVS thrombosis. Malapposed, uncovered, and disrupted struts in direct contact with blood flow might have a major bearing on the occurrence of very late BVS thrombosis (23). In the present study, intraluminal scaffold dismantling was observed in 14% of cases at 3 years. It is currently unknown whether the intraluminal scaffold dismantling observed beyond 1 year stems from persistently malapposed struts at post-implantation or from late acquired malapposition. Importantly, the present serial optical coherence tomographic analysis demonstrated that intraluminal scaffold dismantling developed at 2 years even if struts were fully apposed at post-procedure, and it newly developed between 2 and 3 years, suggesting that optimizing struts apposition at time of implantation could not eliminate late intraluminal scaffold dismantling. To prevent very late BVS thrombosis, it is therefore of paramount importance to reduce intraluminal scaffold dismantling by enhancing early tissue encapsulation of the struts before the structure lose mechanical integrity during bioresorption. Those findings would also support prolonged dual-antiplatelet therapy at least up to 3 years in patients with BVS implantation, except in patients with high bleeding risk.

In the previous ABSORB Cohort A trial, late discontinuities and dismantling were not observed and were likely underestimated because of: 1) low image quality of time-domain OCT; 2) no established method to detect discontinuities and dismantling; 3) a limited number of serial optical coherence tomographic imaging studies; and 4) suboptimal timing of OCT in relation to the bioresorption duration. To avoid any underestimation of late discontinuities and dismantling, systematic serial intracoronary OCT up to the end of bioresorption is indispensable. Such imaging should be applied to early clinical investigation of a new bioresorbable scaffold.

These observations may entail further iteration of polymeric bioresorbable scaffolds. Scaffold discontinuities themselves are an inevitable phenomenon associated universally with bioresorption process (24), but early encapsulation of struts could be achieved by making struts smaller and biodegradation time shorter. For example, a new bioresorbable scaffold made from post-processed polymer with improved tensile strength has stronger and thinner struts and may achieve better embedment and earlier strut encapsulation without compromising acute and late recoil (5). As dismantling occurs in the final phase of bioresorption, future pivotal trials of new bioresorbable scaffolds would need long-term follow-up until the device completely biodegrades, to ensure that the intraluminal dismantling does not exist at the end of bioresorption process (25).

The impact of implantation technique was recently investigated in the pooled population (n = 2,973) of the ABSORB trials, including the ABSORB Japan cohort. BVS implantation in properly sized vessels was an independent predictor of freedom from scaffold thrombosis through 1 year (hazard ratio: 0.36; $p = 0.004$), whereas aggressive pre-dilation was an independent predictor of freedom from scaffold thrombosis between 1 and 3 years (hazard ratio: 0.44; $p = 0.03$). Because of the lack of prospective instruction for the PSP technique, the PSP was optimally performed in only 155 of 3,096 lesions (5.0%), as in the present study (5.8%). Recently in the AIDA trial, including an all-comers population treated with ABSORB, the lesion-level event rate of PSP-treated lesions did not differ from that of non-PSP-treated lesions (5.6% vs. 7.1%; $p = 0.492$). Without prospective implementation of the PSP strategy, these results from retrospective analyses preclude drawing definite conclusions. In addition, the presence of late

acquired strut malapposition demonstrated in the present study suggests that even optimal post-procedural results by PSP may not guarantee freedom from future scaffold dismantling.

STUDY LIMITATIONS. First, the study was underpowered to detect difference in clinical outcomes between the BVS and CoCr-EES. Second, post-procedure OCT and IVUS were performed primarily for documentary purpose, but not for optimization of scaffold expansion. Third, the included patients had mainly stable coronary artery disease and noncomplex lesions, precluding the generalizability of the study findings to patients with complex lesions. Fourth, use of multiple types of IVUS and optical coherence tomographic devices could confound the absolute measurement of area, although the same system was used for serial follow-up. Because of the bioresorption, IVUS could not differentiate the struts, so that scaffold area was not delineated. Fifth, lesions with interim TLR were excluded from the serial IVUS and optical coherence tomographic analysis because of the presence of a nonstudy device, whereas pre-TLR QCA data were carried forward up to the 3-year follow-up QCA study for the nonserial analysis, which might lead to overestimation of luminal dimensions in IVUS and optical coherence tomographic analysis. Last, this was an interim analysis at 3 years; the planned 5-year follow-up will provide further information on the long-term clinical outcomes of the BVS.

CONCLUSIONS

In this multimodality serial imaging study, luminal dimension at 3 years was smaller with the BVS than with the CoCr-EES because of the combined effects of smaller device and luminal dimension at post-procedure, further decrease in scaffold dimension during follow-up, and greater neointimal formation in the BVS. Intraluminal scaffold dismantling, suspected as one of the mechanisms of very late BVS thrombosis, was observed in a substantial proportion of cases at 3 years, which could newly develop between post-procedure and 2 years and even beyond 2 years.

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PERSPECTIVES

WHAT IS KNOWN? In the ABSORB Japan trial, randomizing 400 patients in a 2:1 ratio to treatment with a BVS or a CoCr-EES, 3-year serial comprehensive imaging with IVUS and OCT demonstrated that luminal dimension at 3 years was consistently smaller with the BVS than with the CoCr-EES.

WHAT IS NEW? New occurrence of intraluminal dismantling between 2 and 3 years was observed by serial OCT after percutaneous coronary intervention with the BVS.

WHAT IS NEXT? The development of a new-generation bioresorbable scaffold with thinner and narrower struts is ongoing. Any new scaffold should eliminate late dismantling, in reference to the present data.

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KEY WORDS bioresorbable scaffold, optical coherence tomography, percutaneous coronary intervention, stable angina

APPENDIX For a list of investigators and committee members, supplemental methods, tables, and figures, please see the online version of this paper.